

Tethered Aminohydroxylation: Synthesis of the β -Amino Acid of Microsclerodermins A and B

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1.1 Experimental techniques

General: All non-aqueous reactions were carried out under an argon atmosphere in flame-dried glassware unless otherwise stated. All reactions were followed by analytical thin layer chromatography (TLC) and procedure times represent reaction completion as judged accordingly. Reaction temperatures (unless otherwise stated) represent bath temperatures.

Solvents: Anhydrous DMF, benzene, *tert*-butanol, cyclohexane, 1,2-dichloroethane and 1,4-dioxane were used as commercially supplied. CH₂Cl₂, Et₂O, MeCN, MeOH, THF and toluene were purified by filtration through two activated alumina purification columns. In cases where mixtures of solvents were used, the ratios refer to the component volumes. Petrol refers to petroleum ether in the boiling range 30-60 °C.

Reagents: All reagents were used as supplied commercially unless otherwise stated.

Chromatography: Flash column chromatography was carried out using silica gel 40-63 μm unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using aluminium backed pre-coated silica gel 60 F₂₅₄ plates and visualised under UV radiation at 254 nm and staining with phosphomolybdic acid in ethanol, potassium permanganate in water or vanillin in ethanol.

Optical Rotation: Specific rotations (α') were recorded on a Perkin Elmer 341 Polarimeter, with a cell pathlength (*l*) of 1.0 dm, at the stated temperature (°C) and concentration (*c*) (measured in units of g/100 mL); specific rotations were converted to optical rotations, $[\alpha]_D$, via the equation: $[\alpha]_D = (100 \cdot \alpha') / (l \cdot c)$.

Melting Points: Melting points were obtained using a Leica Galen III heated-stage microscope and are uncorrected.

Mass Spectrometry: Mass spectrometry was carried out using CI⁺ (NH₃), ES⁺ or EI⁺ and recorded using a Bruker MicroTof or Fisons Platform II spectrometer. Only molecular ions and fragments from molecular ions are reported with relative intensities of peaks quoted as a percentage value. Accurate mass (HRMS) were recorded on a Bruker MicroTof spectrometer under conditions of electrospray ionisation (ESI).

NMR Spectroscopy: ¹H NMR spectra were recorded at 200, 250, 300, 400 and 500 MHz in CDCl₃, D₆-DMSO or D₄-MeOD, on a Bruker Advance 200, 250, 300, 400 or 500 spectrometer respectively, at the stated temperature, and reported as follows; chemical shift (δ) (reported to the nearest 0.01 ppm), (number of protons, multiplicity (singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and/or broad (br.)), coupling constant, *J*

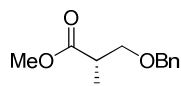
(reported in Hertz (Hz) to the nearest 0.1 Hz), assignment). Residual protic solvent was used as the internal reference: CDCl_3 ($\delta_{\text{H}} = 7.26$ ppm), $\text{D}_6\text{-DMSO}$ ($\delta_{\text{H}} = 2.50$ ppm), $\text{D}_4\text{-MeOD}$ ($\delta_{\text{H}} = 3.31$ ppm). ^{13}C NMR spectra were recorded at 75, 100 and 126 MHz, with complete proton decoupling, in CDCl_3 , $\text{D}_6\text{-DMSO}$ or $\text{D}_4\text{-MeOD}$, on a Bruker Advance 300, 400 or 500 spectrometer respectively with the chemical shift, δ , reported to the nearest 0.1 ppm. The internal reference used: CDCl_3 ($\delta_{\text{C}} = 77.0$ ppm), $\text{D}_6\text{-DMSO}$ ($\delta_{\text{C}} = 39.5$ ppm), $\text{D}_4\text{-MeOD}$ ($\delta_{\text{C}} = 49.1$ ppm). ^{19}F NMR spectra were recorded at 376 MHz on a Bruker Advance 400 spectrometer with the chemical shift reported to the nearest 0.1 ppm. All chemical shifts are quoted in parts per million relative to tetramethylsilane ($\delta_{\text{H}} = 0.00$ ppm). Assignments were based upon COSY, DEPT, HSQC and HMBC experiments, nOe enhancement experiments where appropriate, and by comparison to related compounds.

IR Spectroscopy: Infra-red spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and broad (br) signals are specified.

1.2 Experimental procedures

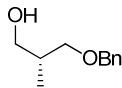
Note: The numbering system as represented for 5-21, on route to the synthesis of the β -amino acid (AMMTD) of microsclerodermin B, is in accordance with the natural product numbering system for this fragment as assigned by Faulkner¹ and may not reflect that in the systematic name, derived according to IUPAC nomenclature.

Methyl (2S)-3-(benzyloxy)-2-methylpropanoate (**2**)²



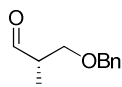
Benzyl 2,2,2-trichloroacetimidate (15.3 mL, 82.4 mmol) was added to a solution of methyl (S)-(+)-3-hydroxy-2-methylpropanoate (7.0 mL, 63.4 mmol) in cyclohexane/dichloromethane (105 mL, 2:1) at $\square 15$ °C. Trifluoromethanesulfonic acid (0.28 mL, 3.2 mmol) was then added dropwise, resulting in the formation of a white suspension. The solution was then stirred at this temperature for 2 h before being warmed to room temperature and stirred for 16 h. A further addition of benzyl 2,2,2-trichloroacetimidate (5.9 mL, 31.7 mmol) and trifluoromethanesulfonic acid (0.14 mL, 1.6 mmol) was then made and the mixture stirred for a further 20 h. The solution was then filtered over Celite, washing with petrol, and then concentrated *in vacuo*. The residue was then dissolved in EtOAc and sequentially washed with saturated aqueous NaHCO₃ and brine solutions, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-2-5% EtOAc/petrol) afforded benzyl ether **2** (12.9 g, 98%) as a colorless oil; R_f: 0.50 (10% EtOAc/petrol); $[\alpha]_D^{20} +10.3$ (*c* 0.68, CHCl₃) (lit.² $[\alpha]_D +10.2$ (*c* 3.0, CHCl₃)); δ_H (400 MHz, CDCl₃) 7.38-7.27 (5H, m, 5 x PhH), 4.54 (2H, s, OCH₂Ph), 3.71 (3H, s, OCH₃), 3.68 (1H, dd, *J* 9.2 and 7.3, 3-HH), 3.51 (1H, dd, *J* 9.1 and 5.2, 3-HH), 2.81 (1H, m, 2-H), 1.20 (3H, d, *J* 7.1, 2-(CH₃)); δ_C (100 MHz, CDCl₃) 175.2 (C(O)), 138.1 (C_(Ar)), 128.2 (CH_(Ar)), 127.5 (CH_(Ar)), 127.5 (CH_(Ar)), 73.0 (OCH₂Ph), 71.9 (3-C), 51.6 (OCH₃), 40.1 (2-C), 13.9 (2-(CH₃)). All data were in agreement with those previously reported.²

(2R)-3-(Benzyloxy)-2-methylpropan-1-ol (2a)²



Lithium borohydride (18.4 mL of a 4 M solution in THF, 73.5 mmol) was added slowly to a solution of ester **2** (5.1 g, 24.5 mmol) in THF (165 mL) at 0 °C. Methanol (3.3 mL, 80.9 mmol) was then added slowly and once the exotherm had subsided (ca. 15 mins.) the mixture was warmed to room temperature and stirred for 1.5 h. Aqueous NaOH (50 mL of a 1 M solution) was added slowly and the aqueous layer then separated and extracted with EtOAc, which was washed with saturated brine solution, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-10-20% EtOAc/petrol) afforded alcohol **2a** (4.30 g, 97%) as a colourless oil; R_f: 0.30 (20% EtOAc/petrol); [α]_D²⁰ +16.3 (c 0.80, CHCl₃) (lit.² [α]_D +11.3 (c 4.9, CHCl₃); δ_H (400 MHz, CDCl₃) 7.38-7.26 (5H, m, 5 x PhH), 4.53 (2H, s, OCH₂Ph), 3.66-3.60 (2H, m, 1-H), 3.56 (1H, dd, *J* 9.1 and 4.7, 3-HH), 3.44 (1H, dd, *J* 9.0 and 8.0, 3-HH), 2.08 (1H, m, 2-H), 0.90 (3H, d, *J* 7.1, CH₃); δ_C (100 MHz, CDCl₃) 138.0 (C_(Ar)), 128.4 (CH_(Ar)), 127.7 (CH_(Ar)), 127.6 (CH_(Ar)), 75.4 (3-C), 73.3 (OCH₂Ph), 67.8 (1-C), 35.5 (2-C), 13.4 (CH₃). All data were in agreement with those previously reported.²

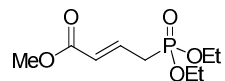
(2S)-3-(Benzyloxy)-2-methylpropanal (3)³



Method A (reduction of ester 2): Diisobutylaluminum hydride (24.0 mL of a 1 M solution in toluene, 24.0 mmol) was added dropwise to a solution of ester **2** (5.0 g, 24.0 mmol), in CH₂Cl₂ (60 mL) at -78 °C and was stirred for 1 h. MeOH (12 mL) was then added slowly at -78 °C and the mixture was stirred for 10 mins before being warmed to room temperature and quenched with saturated aqueous Rochelle salt. The solution was stirred vigorously for 30 mins before separation of the aqueous layer, which was extracted with CH₂Cl₂, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford aldehyde **3** (4.5 g (yield reported for diene **5** over two steps) as a yellow oil. The compound was used immediately and without further purification.

Method B (oxidation of alcohol 2a): Dimethyl sulfoxide (36.9 mL, 519 mmol), *N,N*-diisopropylethylamine (36.2 mL, 208 mmol) and sulfur trioxide pyridine complex (24.8 g, 156 mmol) were added sequentially to a solution of alcohol **2a** (9.35 g, 51.9 mmol) in CH₂Cl₂ (260 mL) at 0 °C and was stirred for 1.5 h. Saturated aqueous NaHCO₃ was then added and the aqueous layer was separated and extracted with CH₂Cl₂. The organic layer was then washed sequentially with saturated aqueous copper sulfate (x 2), ammonium chloride (x 3) and brine solutions and dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford aldehyde **3** (8.95 g, 97%) as a light orange oil. The compound was used immediately and without further purification; δ_{H} (200 MHz, CDCl₃) 9.73 (1H, d, *J* 1.5, CHO), 7.39-7.28 (5H, m, 5 x PhH), 4.53 (2H, s, CH₂Ph), 3.70-3.63 (2H, m, 3-H), 2.67 (1H, m, 2-H), 1.14 (3H, d, *J* 7.1, CH₃). Data was in agreement with that previously reported.³

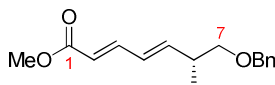
Methyl (2*E*)-4-(diethoxyphosphoryl)-but-2-enoate (**4**)⁴



Benzoyl peroxide (1.50 g of reagent damped with 20% water, 5.0 mmol) was added portionwise to a solution of methyl crotonate (26.5 mL, 249.9 mmol) and *N*-bromosuccinimide (46.7 g, 262.4 mmol) in benzene (250 mL). The mixture was then heated to reflux and stirred for 20 h. After cooling to room temperature Na₂SO₄ was added and the solution was filtered over Celite, washing with petrol. The filtrate was then concentrated *in vacuo* to afford methyl (2*E*)-4-bromo-but-2-enoate (**4a**) (43.5 g) as an orange oil; δ_{H} (200 MHz, CDCl₃) 7.02 (1H, dt, *J* 15.4 and 7.4, 3-*H*), 6.03 (1H, dt, *J* 15.4 and 1.2, 2-*H*), 4.01 (1H, dd, *J* 7.4 and 1.2, CH₂Br), 3.76 (3H, s, CO₂CH₃).⁵ Triethyl phosphite (47.1 mL, 274.9 mmol) was then added to a solution of freshly prepared allyl bromide **4a** (43.5 g) in toluene (125 mL). The mixture was then heated to reflux and stirred for 20 h. The solution was then cooled to room temperature and concentrated *in vacuo*. The residue was then redissolved in CH₂Cl₂ and concentrated onto silica gel and purified by flash column chromatography (20-50-100% EtOAc/petrol) to afford phosphonate **4** (36.4 g, 62% (2 steps)) as an orange oil; R_f: 0.40 (EtOAc); δ_{H} (300 MHz, CDCl₃) 6.84 (1H, m, 3-*H*), 5.92 (1H, dd, *J* 15.6 and 4.9, 2-*H*), 4.13-4.03 (4H, m, 2 x OCH₂CH₃), 3.69 (3H, s, CO₂CH₃), 2.71 (1H, dd, *J* 23.0 and 7.9, 4-*H*), 1.28 (6H, t, *J* 7.0, 2 x OCH₂CH₃); δ_{C} (75 MHz, CDCl₃) 165.9 (d, ⁴*J*_{C-P} 2.9, C(O)), 137.7 (d, ²*J*_{C-P} 11.1, 3-*C*), 125.3 (d, ³*J*_{C-P} 13.8, 2-*C*), 62.2 (d, ²*J*_{C-P} 6.6, OCH₂CH₃),

51.5 (CO₂CH₃), 30.5 (d, ¹J_{C-P} 138.7, 4-C), 16.3 (d, ³J_{C-P} 5.9, OCH₂CH₃). All data were in agreement with those previously reported.⁴

Methyl (2*E*,4*E*,6*R*)-7-(benzyloxy)-6-methylhepta-2,4-dienoate (**5**)



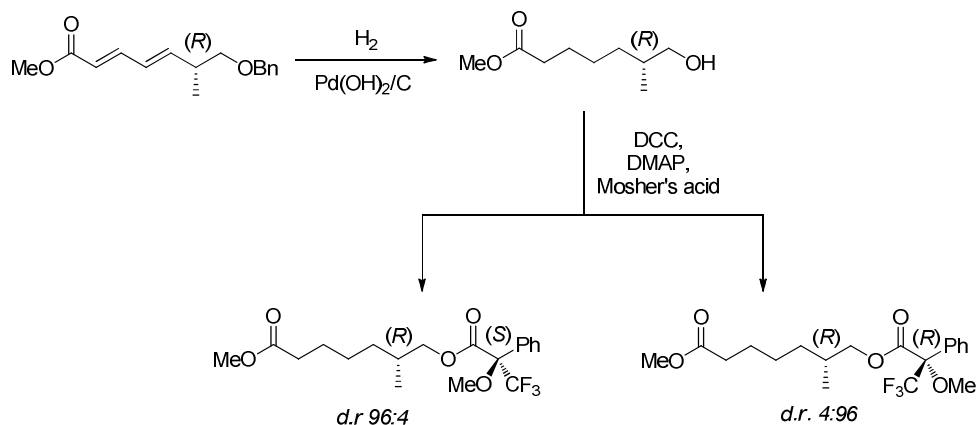
General procedure: *n*-Butyllithium (2.05 eq. of a 2.5 M solution in hexanes) was added slowly to a solution of diisopropylamine (2.05 eq.) in THF (0.4 M) at 0 °C and stirred for 30 mins. The LDA solution was then added slowly to a solution of phosphonate **4** (2.0 eq.) in THF (0.4 M) at -78 °C. The solution was slowly warmed to -20 °C and stirred for 2.5 h, before being re-cooled to -78 °C. Aldehyde **3** in THF (1 M) was then added slowly to the phosphonate solution, which was warmed to -20 °C slowly and stirred at this temperature for 3 h (internal temperature).¹ Saturated aqueous ammonium chloride solution was then added and the solution warmed to room temperature. The aqueous layer was then separated and extracted with EtOAc, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-2-5% EtOAc/petrol) afforded diene **5** as a colorless oil, with an (*E,E*)/(*E,Z*) isomeric ratio of 9:1; R_f: 0.25 (5% EtOAc/petrol); [α]_D²⁰ +1.2 (*c* 0.86, CHCl₃); ν_{max} /cm⁻¹ (neat) 2960, 2855, 1720, 1644, 1496, 1454, 1361; δ_H (400 MHz, CDCl₃ (chemical shifts reported for the major (*E,E*)-isomer only)) 7.37-7.24 (6H, m, 5 x PhH and 3-*H*), 6.22 (1H, dd, *J* 15.4 and 10.7, 4-*H*), 6.10 (1H, dd, *J* 15.3 and 7.0, 5-*H*), 5.82 (1H, d, *J* 15.4 and 7.0, 2-*H*), 4.51 (2H, s, OCH₂Ph), 3.74 (3H, s, CO₂CH₃), 3.29 (2H, dd, *J* 6.8 and 1.7, 7-*H*), 2.63 (1H, m, 6-*H*), 1.08 (3H, d, *J* 6.8, 6-(CH₃)); δ_C (100 MHz, CDCl₃ (chemical shifts reported for the major (*E,E*)-isomer only)) 167.6 (C(O)), 146.6 (5-C), 145.2 (3-C), 138.2 (C_(Ar)), 128.3 (CH_(Ar)), 127.8 (CH_(Ar)), 127.6 (4-C or CH_(Ar)), 127.6 (CH_(Ar) or 4-C), 119.4 (2-C), 74.4 (7-C), 73.0 (CH₂Ph), 51.5 (OCH₃), 37.3 (6-C), 16.5 (6-(CH₃)); *m/z* (ES⁺) 283 (MNa⁺, 100%); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₁₆H₂₀O₃Na 283.1305, observed 283.1305.

Method A (aldehyde obtained by reduction of **2**): 3.84 g scale, 68% yield from **2**.

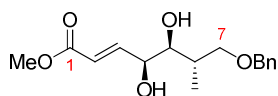
Method B (aldehyde **3** obtained by oxidation of **2a**): 10.6 g scale, 81% yield for the olefination step.

¹ Previous procedures that warmed to room temperature led to partial racemisation of the diene.

The enantiopurity of diene **5** was confirmed by removal the benzyl group under catalytic hydrogenation (with concomitant reduction of the olefins) and formation of the corresponding Mosher's esters (spectra included):



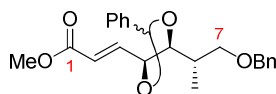
Methyl (2*E*,4*S*,5*S*,6*S*)-7-(benzyloxy)-4,5-dihydroxy-6-methylhept-2-enoate (**6**)



Potassium osmate(VI) dihydrate (112.2 mg, 0.31 mmol) was added in one portion to a solution of potassium carbonate (7.02 g, 50.8 mmol), methanesulfonamide (4.83 g, 50.8 mmol), potassium hexacyanoferrate(III) (16.72 g, 50.8 mmol) and (DHQ)₂PHAL (400 mg of a 95% purity mixture, 0.49 mmol) in *tert*-butanol/water (160 mL, 1:1) at 0 °C. The mixture was equipped with a mechanical stirrer and stirred vigorously for 20 mins. Diene **5** (4.41 g, 16.93 mmol, in 25 mL of MeCN) was then added *via* syringe pump (20 mL/hr) to the solution and stirring was then maintained at 0 °C for 16 h. Saturated aqueous sodium sulfite was then added to the mixture and stirred for 20 minutes. The aqueous layer was then separated and extracted with EtOAc, dried (Na₂SO₄), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (20-25% EtOAc/petrol) afforded diol **6** (3.76 g, 75%) as a single diastereomer; R_f: 0.30 (40% EtOAc/petrol); [α]_D²⁰ +9.5 (*c* 1.08, CHCl₃); ν_{max} /cm⁻¹ (neat) 3435, 3030, 2922, 1723, 1658, 1364; δ_H (400 MHz, CDCl₃) 7.38-7.29 (5H, m, 5 x PhH), 6.99 (1H, dd, *J* 15.6 and 4.3, 3-*H*), 6.14 (1H, dd, *J* 15.6 and 1.9, 2-*H*), 4.53 (2H, s, CH₂Ph), 4.29 (1H, m, 4-*H*), 4.76 (1H, br, OH), 3.73 (3H, s, CO₂CH₃), 3.61

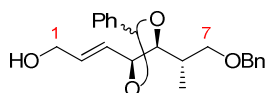
(1H, dd, *J* 9.4 and 3.8, 7-*HH*), 3.56-3.52 (2H, m, 7-*HH* and 5-*H*), 2.11 (1H, m, 6-*H*), 3.11 (1H, br, *OH*), 0.97 (3H, d, *J* 7.0, 6-(*CH*₃)); δ_C (100 MHz, CDCl₃) 166.8 (*C*(O)), 148.4 (3-*C*), 136.9 (*C*(Ar)), 128.6 (*CH*(Ar)), 128.1 (*CH*(Ar)), 127.8 (*CH*(Ar)), 121.3 (2-*C*), 78.2 (5-*C*), 74.1 (7-*C*), 73.7 (*CH*₂Ph), 71.6 (4-*C*), 51.6 (*OCH*₃), 35.4 (6-*C*), 14.4 (6-(*CH*₃)); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₁₆H₂₂O₅Na 317.1359, observed 317.1356.

(*E*)-Methyl 3-((4*S*,5*S*)-5-((*S*)-1-(benzyloxy)propan-2-yl)-2-phenyl-1,3-dioxolan-4-yl)acrylate (6a**)**



Benzaldehyde dimethyl acetal (6.6 mL, 43.8 mmol) was added dropwise to a solution of diol **6** (5.7 g, 21.9 mmol) and (±)-camphor 10-sulfonic acid (510 mg, 2.2 mmol) in CH₂Cl₂ (220 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 2 h. Saturated aqueous NaHCO₃ was then added and the aqueous layer was then separated and extracted with EtOAc, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5-10% EtOAc/petrol) afforded acetal **6a** (7.20 g, 86%) as a colourless oil, as 3:1 mixture of diastereomers; *R*_f: 0.30 (10% EtOAc/petrol); $[\alpha]_D^{20}$ -8.9 (*c* 1.58, CHCl₃); ν_{\max} /cm⁻¹ (neat) 2951, 2887 1726, 1661, 1603, 1588, 1496, 1457, 1436; δ_H (400 MHz, CDCl₃ (* denotes major diastereomer)) 7.50-7.24 (10H, m, 10 x *PhH*), 6.98* and 6.97 (1H, dd, *J* 15.6 and 5.2, 3-*H*), 6.20* and 6.19 (1H, dd, *J* 15.6 and 1.5, 2-*H*), 5.96 and 5.88* (1H, s, (RO)₂CHPh), 4.68 (1H, m, 4-*H*), 4.54-4.48 (2H, m, *CH*₂Ph), 3.96* and 3.89 (1H, t, *J* 6.7, 5-*H*), 3.77* and 3.75 (3H, s, CO₂CH₃), 3.61* and 3.67 (1H, dd, *J* 9.2 and 5.2, 7-*HH*), 3.52* and 3.49 (1H, dd, *J* 9.2 and 5.5, 7-*HH*), 2.24 (1H, m, 6-*H*), 1.11* and 1.07 (3H, d, *J* 7.0, 6-(*CH*₃)); δ_C (100 MHz, CDCl₃ (chemical shifts reported for the major diastereomer only)) 166.5 (*C*(O)), 145.3 (3-*C*), 138.2 (*C*(Ar)), 136.8 (*C*(Ar)), 129.6 (*CH*(Ar)), 128.4 (*CH*(Ar)), 128.3 (*CH*(Ar)), 127.6 (*CH*(Ar)), 127.6 (*CH*(Ar)), 126.7 (*CH*(Ar)), 121.6 (2-*C*), 103.3 ((RO)₂CHPh), 83.7 (5-*C*), 77.7 (4-*C*), 73.2 (*CH*₂Ph), 71.9 (7-*C*), 51.7 (*OCH*₃), 36.5 (6-*C*), 13.6 (6-(*CH*₃)); *m/z* (ES⁺) 405 (MNa⁺, 100%); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₂₃H₂₆O₅Na 405.1672, observed 405.1678.

(E)-3-((4S,5S)-5-((S)-1-(Benzyloxy)propan-2-yl)-2-phenyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (7)

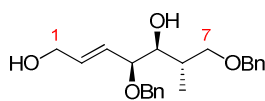


Method A (from 6a): Diisobutylaluminum hydride (37.6 mL of a 1 M solution in toluene, 37.7 mmol) was added dropwise to a solution of ester **6a** (7.2 g, 18.8 mmol) in CH₂Cl₂ (190 mL) at -78 °C. The reaction was then stirred for 1.5 h at -78 °C before the addition of saturated aqueous Rochelle's salt. The solution was then warmed to room temperature and stirred vigorously for 30 mins. The aqueous layer was separated and extracted with EtOAc, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20-30% EtOAc/petrol) afforded alcohol **7** (6.3 g, 95%) as a colourless oil, as a 3:1 mixture of diastereomers; R_f: 0.50 (40% EtOAc/petrol); [α]_D²⁰ -10.9 (c 1.41, CHCl₃); ν_{max} /cm⁻¹ (neat) 2858, 1723, 1661, 1455, 1454, 1406; δ_H (400 MHz, CDCl₃ (* denotes major diastereomer)) 7.50-7.46 (2H, m, 2 x PhH), 7.41-7.27 (8H, m, 8 x PhH), 5.88* (1H, dt, J 16.1 and 5.0, 2-H), 5.91* (1H, s, (RO)₂CHPh), 5.81 (1H, m, 3-H), 4.54-4.45 (3H, m, 4-H and CH₂Ph), 4.18-4.15 (2H, m, 1-H), 3.91* and 3.83 (1H, t, J 6.9, 5-H), 3.62* and 3.68 (1H, dd, J 9.2 and 5.1, 7-HH), 3.49 (1H, m, 7-HH), 2.20 (1H, m, 6-H), 1.80 (1H, br, OH), 1.08* and 1.04 (3H, d, J 7.0, 6-(CH₃)); δ_C (100 MHz, CDCl₃ (chemical shifts reported for the major diastereomer only)) 138.4 (C_(Ar)), 137.6 (C_(Ar)), 133.0 (2-C), 129.3 (CH_(Ar)), 128.7 (CH_(Ar)), 128.3 (CH_(Ar) and 3-C), 127.5 (CH_(Ar)), 126.7 (CH_(Ar)), 126.6 (CH_(Ar)), 102.9 ((RO)₂CHPh), 83.8 (5-C), 79.3 (4-C), 73.1 (CH₂Ph), 72.1 (7-C), 62.7 (1-C) 36.4 (6-C), 13.8 (6-(CH₃)); *m/z* (ES⁺) 377 (MNa⁺, 100%); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₂₂H₂₆O₄Na 377.1723, observed 377.1719.

Method B (two steps, one pot from 6): Benzaldehyde dimethyl acetal (5.6 mL, 40.8 mmol) was added dropwise to a solution of diol **6** (6.0 g, 20.4 mmol) and (±)-camphor 10-sulfonic acid (474 mg, 2.0 mmol) in CH₂Cl₂ (200 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 1.5 h. The solution was then cooled to -78 °C and diisobutylaluminum hydride (51 mL of a 1.2 M solution in toluene, 61.2 mmol) was added dropwise and stirred for 1.5 h. A further addition of diisobutylaluminum hydride (51 mL of a 1.2 M solution in toluene, 61.2 mmol) was then made and the reaction was stirred for a

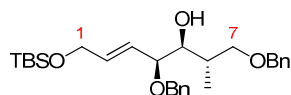
further 1 h. Methanol (50 mL) was then added slowly (caution: exotherm) at $-78\text{ }^{\circ}\text{C}$ and stirred for a further 10 mins. Copious amounts of saturated aqueous Rochelle's salt was then added and the solution was then warmed to room temperature and stirred vigorously for 30 mins. The aqueous layer was separated and extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10-20-30% EtOAc/petrol) afforded alcohol **7** (6.0 g, 83% (2 steps)) as a colourless oil, as a 3:1 mixture of diastereomers along with diol **8** (800 mg, 11%) as a colourless oil.

(4*S*,5*S*,6*S*,*E*)-4,7-Bis(benzyloxy)-6-methylhept-2-ene-1,5-diol (8)



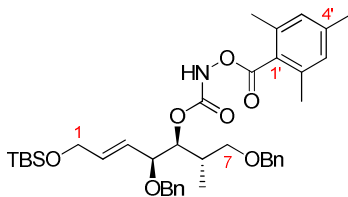
Titanium(IV) chloride (12.5 mL of a 1 M solution in CH_2Cl_2 , 12.5 mmol) was added dropwise to a solution of acetal **7** (2.96 g, 8.36 mmol) and triethylsilane (5.3 mL, 33.4 mmol) in CH_2Cl_2 (85 mL) at $-78\text{ }^{\circ}\text{C}$, resulting in the formation of a bright yellow solution. The reaction was stirred for 4 h and quenched by the addition of water at $-78\text{ }^{\circ}\text{C}$. The solution was then warmed to room temperature and the aqueous layer was separated and extracted with EtOAc, washed with saturated aqueous NaHCO_3 , dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol \rightarrow 10 \rightarrow 30% EtOAc/petrol) afforded diol **8** (2.36 g, 79%) as a colourless oil; R_f : 0.25 (45% EtOAc/petrol); $[\alpha]_D^{20} +35.4$ (c 0.82, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3405, 3030, 2923, 2856, 1497, 1454, 1364; δ_{H} (400 MHz, CDCl_3) 7.36-7.26 (10H, m, 10 x PhH), 5.87 (1H, dt, J 15.7 and 5.0, 2-H), 5.76 (1H, dd, J 15.7 and 7.6, 3-H), 4.64 (1H, d, J 11.8, 4-(OCHHPh)), 4.48 (2H, s, 7-(OCH₂Ph)), 4.34 (1H, d, J 11.8, 4-(OCHHPh)), 4.16 (2H, d, J 4.2, 1-H), 3.92 (1H, dd, J 7.5 and 4.9, 4-H), 3.58 (1H, dd, J 9.2 and 6.6, 7-HH), 3.49-3.42 (2H, m, 7-HH and 5-H), 3.02 (1H, br, OH), 2.40 (1H, br, OH), 2.11 (1H, m, 6-H), 0.90 (3H, d, J 7.0, 6-(CH₃)); δ_{C} (100 MHz, CDCl_3) 138.1 (2 x C_(Ar)), 134.0 (2-C), 128.6 (3-C), 128.3 (2 x CH_(Ar)), 127.9 (CH_(Ar)), 127.6 (CH_(Ar)), 127.6 (CH_(Ar)), 127.5 (CH_(Ar)), 79.9 (4-C), 77.5 (5-C), 73.2 (7-OCH₂Ph), 73.1 (7-C), 70.3 (4-(OCH₂Ph)), 62.7 (1-C), 35.1 (6-C), 14.6 (6-CH₃); m/z (ES⁺) 379 (MNa⁺, 100%); m/z HRMS (ES⁺) MNa⁺ calculated for $\text{C}_{22}\text{H}_{28}\text{O}_4\text{Na}$ 379.1880, observed 379.1884.

(2*S*,3*S*,4*S*,*E*)-1,4-Bis(benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-2-methylhept-5-en-3-ol (8a)



tert-Butyldimethylsilyl chloride (1.04 g, 6.89 mmol) was added to a solution of alcohol **8** (2.34 g, 6.56 mmol) and imidazole (983 mg, 14.4 mmol) in DMF (65 mL) at 0 °C. The solution was then warmed to room temperature and stirred for 16 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride and diluted with EtOAc. The organic layer was separated and washed with brine solution (x 3), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol→5→10% EtOAc/petrol) afforded silyl ether **8a** (2.82 g, 91%) as a colorless oil; R_f: 0.3 (10% EtOAc/petrol); [α]_D²⁰ +31.3 (*c* 1.12, CHCl₃); ν_{max}/cm⁻¹ (neat) 3479 br, 2955, 2929, 2856, 1497, 1455, 1378, 1362, 1253, 1208, 1093, 1068, 1028, 975, 835, 776, 733, 696; δ_H (400 MHz, CDCl₃) 7.36-7.26 (10H, m, 10 x PhH), 5.81 (1H, dt, *J* 15.6 and 4.3, 2-*H*), 5.73 (1H, ddt, *J* 15.6, 7.5 and 1.4, 3-*H*), 4.63 (1H, d, *J* 11.7, 4-(OCHHPh)), 4.47 (2H, s, 7-(OCH₂Ph)), 4.32 (1H, d, *J* 11.7, 4-(OCHHPh)), 4.22 (2H, d, *J* 4.4, 1-*H*), 3.91 (1H, dd, *J* 7.4 and 5.4, 4-*H*), 3.58 (1H, dd, *J* 9.2 and 6.4, 7-HH), 3.47-3.42 (2H, m, 7-HH and 5-*H*), 2.09 (1H, m, 6-*H*), 1.61 (1H, br, OH), 0.92 (9H, s, SiC(CH₃)₃), 0.92 (3H, d, *J* 6.9, 6-(CH₃)), 0.09 (6H, s, 2 x SiCH₃); δ_C (126 MHz, CDCl₃) 138.4 (C_(Ar)), 138.3 (C_(Ar)), 134.7 (2-C), 128.3 (CH_(Ar)), 128.3 (CH_(Ar)), 128.0 (CH_(Ar)), 127.6 (CH_(Ar)), 127.6 (CH_(Ar)), 127.5 (CH_(Ar)), 127.1 (3-C), 80.2 (4-C), 77.4 (5-C), 73.2 (7-(OCH₂Ph)), 72.8 (7-C), 70.1 (4-(OCH₂Ph)), 63.2 (1-C), 35.1 (6-C), 25.9 (SiC(CH₃)₃), 18.4 (SiC(CH₃)₃), 14.8 (6-(CH₃)), -5.1 (2 x SiCH₃); *m/z* (ES⁺) 493 (MNa⁺, 100%); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₂₈H₄₂O₄SiNa 493.2745, observed 493.2741.

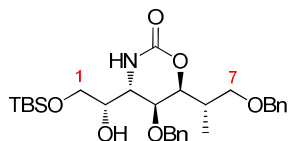
**(2*S*,3*S*,4*S*,*E*)-1,4-Bis(benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-2-methylhept-5-en-3-yl
(2,4,6-trimethylbenzoyl)oxycarbamate (9)**



1,1'-Carbonyldiimidazole (7.3 g of ca. 80% purity, 36 mmol) was added to a solution of alcohol **8a** (2.82 g, 5.99 mmol) in pyridine (40 mL) and was subsequently heated to 40 °C. After 4 h the solution was cooled to 0 °C and hydroxylamine hydrochloride (8.34 g, 120 mmol) was added in one portion. The mixture was slowly warmed to room temperature and stirred for 20 h. Water was then added and the aqueous layer was separated and extracted with EtOAc, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol→10→30% EtOAc/petrol) afforded the hydroxamic acid, (2*S*,3*S*,4*S*,*E*)-1,4-bis(benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-2-methylhept-5-en-3-yl hydroxycarbamate (2.8 g, ca. 90% purity), as a colourless oil; R_f: 0.20 (30%EtOAc/petrol); δ_H (400 MHz, CDCl₃) 7.35-7.24 (10H, m, 10 x PhH), 5.83 (1H, dt, *J* 15.5 and 4.5, 2-*H*), 5.62 (1H, dd, *J* 15.6 and 7.2, 3-*H*), 4.86 (1H, dd, *J* 7.5 and 4.5, 5-*H*), 4.61 (1H, d, *J* 11.8, 4-OCHHPh), 4.45 (1H, d, *J* 12.4, 7-(OCHHPh)), 4.40 (1H, d, *J* 12.3, 7-(OCHHPh)), 4.29 (1H, d, *J* 11.9, 4-(OCHHPh)), 4.23-4.19 (2H, m, 1-*H*), 4.05 (1H, dd, *J* 7.1 and 4.6, 4-*H*), 3.44 (1H, dd, *J* 9.2 and 5.2, 7-HH), 3.28 (1H, dd, *J* 9.1 and 6.4, 7-HH), 2.36 2.30 (1H, m, 6-*H*), 0.92-0.90 (12H, m, 6-(CH₃) and SiC(CH₃)₃), 0.08 (6H, s, 2 x SiCH₃); along with return of alcohol **8a** (417 mg, 13%). Triethylamine (1.55 mL, 11.1 mmol) and 2,4,6-trimethylbenzoyl chloride (0.88 mL, 5.29 mmol) were added sequentially to the hydroxamic acid (2.8 g, 5.29 mmol) in CH₂Cl₂ at 0 °C. The solution was then warmed to room temperature slowly and stirred for 16 h. Saturated aqueous NaHCO₃ was then added and the aqueous layer was separated and extracted with CH₂Cl₂, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol→5→10% EtOAc/petrol) afforded *O*-benzoyl hydroxamate **9** as a viscous colourless oil (2.94 g, 72% (2 steps)); R_f: 0.25 (10% EtOAc/petrol); [α]_D²⁰ +1.8 (*c* 1.87, CHCl₃); ν_{max}/cm⁻¹ (neat) 2954, 2928, 2883, 2856, 1753, 1619, 1497, 1471, 1454, 1380, 1361, 1314, 1250, 1158, 1093, 1070, 1005, 979, 950, 835, 814, 777, 736, 697; δ_H (400 MHz, CDCl₃) 8.25 (1H, s, NH), 7.34-7.25 (10H, m, 10 x PhH),

6.88 (2H, s, 3'- and 5'-H), 5.87 (1H, dt, *J* 15.5 and 4.5, 2-H), 5.68 (1H, ddt, *J* 15.5, 7.4 and 1.5, 3-H), 4.96 (1H, dd, *J* 6.9 and 4.9, 5-H), 4.64 (1H, d, *J* 11.9, 4-OCHHPPh), 4.47 (1H, d, *J* 11.9, 7-(OCHHPPh)), 4.42 (1H, d, *J* 11.9, 7-(OCHHPPh)), 4.33 (1H, d, *J* 11.9, 4-OCHHPPh), 4.23 (2H, dd, *J* 4.4 and 1.5, 1-H), 4.09 (1H, dd, *J* 7.4 and 4.9, 4-H), 3.51 (1H, dd, *J* 9.2 and 5.0, 7-HH), 3.34 (1H, dd, *J* 9.2 and 6.2, 7-HH), 2.36 (6H, s, 2'- and 6'-CH₃), 2.33 (1H, m, 6-H), 2.30 (4'-CH₃), 0.96 (3H, d, *J* 7.0, 6-(CH₃)), 0.92 (9H, s, SiC(CH₃)₃), 0.08 (6H, s, 2 x SiCH₃); δ_C (100 MHz, CDCl₃) 168.9 (C(O)), 156.4 (C(O)), 140.7 (C_(Ar)), 138.5 (C_(Ar)), (C_(Ar)), 138.0 (C_(Ar)), 136.8 (C_(Ar)), 135.3 (2-C), 128.6 (CH_(Ar)), 128.3 (CH_(Ar)), 128.2 (CH_(Ar)), 128.0 (CH_(Ar)), 127.6 (CH_(Ar)), 127.5 (CH_(Ar)), 127.4 (CH_(Ar)), 126.6 (C_(Ar)), 125.5 (3-C), 80.0 (5-C), 78.0 (4-C), 73.1 (7-(OCH₂Ph)), 71.4 (7-C), 70.2 (4-OCH₂Ph), 63.0 (1-C), 34.4 (6-C), 25.9 (SiC(CH₃)₃), 21.2 (4'-(CH₃)), 19.9 (2'- and 5'-(CH₃)), 18.3 (SiC(CH₃)₃), 14.4 (6-(CH₃)), -5.3 (2 x SiCH₃); *m/z* (ES⁺) 698 (MNa⁺, 100%); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₃₉H₅₃NO₇SiNa 698.3484, observed 698.3474.

(4*S*,5*S*,6*S*)-5-(Benzyloxy)-6-((*S*)-1-(benzyloxy)propan-2-yl)-4-((*S*)-2-((*tert*-butyldimethylsilyloxy)-1-hydroxyethyl)-1,3-oxazinan-2-one (10)

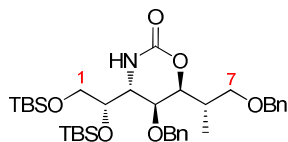


Potassium osmate(VI) dihydrate (13.8 mg, 0.04 mmol) was added in one portion to a solution of *O*-benzoyl hydroxamate **9** (510 mg, 0.75 mmol) in *t*-BuOH/MeCN/H₂O (14 mL, 4:4:1) and heated to 40 °C and maintained for 30 h. Next saturated aqueous sodium sulfite was added to quench the reaction and the solution was stirred at room temperature for 20 mins. The aqueous layer was separated and extracted with EtOAc, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20→50→100% EtOAc/petrol) afforded amino alcohol **10** as an off-white foam (302 mg, 76%) as a single diastereomer²; R_f: 0.25 (50% EtOAc/petrol); [α]_D²⁰ -37.4 (*c* 0.49, CHCl₃); ν_{max} /cm⁻¹ (neat) 3318 br, 3031, 2928, 2856, 1697, 1497, 1455, 1361, 1309, 1253, 1209, 1100, 1067, 1028, 939, 907, 835, 779, 733, 696, 669; δ_H (400 MHz, CDCl₃) 7.36-7.22 (10H, m, 10 x PhH), 6.06 (1H, s, NH), 4.69 (1H, d, *J* 11.7, 4-(OCHHPPh)), 4.52 (1H, d, *J* 12.1,

² The 1,3-*anti* relationship between 3-C and 5-C could equally be confirmed by nOe analysis.

7-OCHHPh)), 4.47 (1H, d, *J* 12.1, 7-OCHHPh)), 4.45 (1H, d, *J* 11.7, 4-OCHHPh)), 4.30 (1H, dd, *J* 9.8 and 1.0, 5-*H*), 3.77 (1H, s, 4-*H*), 3.67 (1H, m, 3-*H*), 3.67 (2H, d, *J* 4.8, 1-*H*), 3.62 (2H, d, *J* 4.4, 7-*H*), 3.51 (1H, dd, *J* 9.6 and 4.8, 2-*H*), 2.97 (1H, br, *OH*), 2.35 (1H, m, 6-*H*), 0.91 (9H, s, SiC(CH₃)₃), 0.88 (3H, d, *J* 6.9, 6-(CH₃)), 0.09 (6H, s, 2 x SiCH₃); δ_C (100 MHz, CDCl₃) 154.4 (C(O)), 138.6 (C_(Ar)), 137.0 (C_(Ar)), 128.5 (CH_(Ar)), 128.3 (CH_(Ar)), 128.1 (CH_(Ar)), 127.9 (CH_(Ar)), 127.5 (CH_(Ar)), 127.4 (CH_(Ar)), 78.0 (5-*C*), 73.1 (7-OCH₂Ph)), 72.1 (2-*C*), 71.3 (7-*C*), 71.1 (4-(OCH₂Ph)), 69.9 (4-*C*), 64.9 (1-*C*), 54.9 (3-*C*), 34.0 (6-*C*), 25.9 (SiC(CH₃)₃), 18.2 (SiC(CH₃)₃), 13.2 (6-(CH₃)), -5.4 (SiCH₃), -5.4 (SiCH₃); *m/z* (ES⁺) 552 (MNa⁺, 100%) 530 (MH⁺, 25); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₂₉H₄₃NO₆SiNa 552.2752, observed 552.2754.

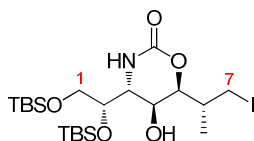
(4*R*,5*S*,6*S*)-5-(Benzyloxy)-6-((*S*)-1-(benzyloxy)propan-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (10a)



tert-Butyldimethylsilyl trifluoromethanesulfonate (1.46 mL, 6.37 mmol) was added dropwise to a solution of amino alcohol **10** (1.35 g, 2.55 mmol) and 2,6-lutidine (1.48 mL, 12.75 mmol) in CH₂Cl₂ (25 mL) at 0 °C. The solution was then stirred at this temperature for 3 h before being quenched with *i*-PrOH. Water was then added and aqueous layer was separated and extracted with CH₂Cl₂, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5→10→20% EtOAc/petrol) afforded silyl ether **10a** (1.48 g, 90%) as a viscous colourless oil; R_f 0.60 (30% EtOAc/petrol); [α]_D²⁰ -35.1 (*c* 0.74, CHCl₃); ν_{max} /cm⁻¹ (neat) 3247, 3136, 2952, 2929, 2884, 2857, 1714, 1462, 1423, 1361, 1309, 1254, 1103, 1071, 912, 832, 777, 733, 696; δ_H (400 MHz, CDCl₃) 7.37-7.225 (10H, m, 10 x PhH), 5.25 (1H, d, *J* 2.9, NH), 4.72 (1H, d, *J* 11.7, 4-(OCHHPh)), 4.52 (1H, d, *J* 12.0, 7-OCHHPh)), 4.48 (1H, d, *J* 12.0, 7-OCHHPh)), 4.47 (1H, d, *J* 11.7, 4-(OCHHPh)), 4.26 (1H, dd, *J* 10.8 and 1.0, 5-*H*), 3.87 (1H, d, *J* 0.9, 4-*H*), 3.83 (1H, m, 3-*H*), 3.71 (1H, dd, *J* 9.0 and 5.3, 7-*HH*), 3.69-3.59 (3H, m, 7-*HH* and 1-*H*), 3.54 (1H, m, 2-*H*), 2.39 (1H, m, 6-*H*), 0.94-0.91 (12H, m, SiC(CH₃)₃ and 6-(CH₃)), 0.88 (9H, s, SiC(CH₃)₃), 0.10 (6H, s, 2 x SiCH₃), 0.08 (6H, s, 2 x SiCH₃); δ_C (100 MHz, CDCl₃) 153.6 (C(O)), 138.7 (C_(Ar)), 137.2 (C_(Ar)), 128.4 (CH_(Ar)), 128.2 (CH_(Ar)), 127.9 (CH_(Ar)), 127.6 (CH_(Ar)), 127.5 (CH_(Ar)), 127.3

(CH_(Ar)), 77.7 (5-C), 73.6 (2-C), 73.0 (7-OCH₂Ph)), 71.1 (7-C), 70.9 (4-(OCH₂Ph)), 69.3 (4-C), 64.7 (1-C), 55.1 (3-C), 34.2 (6-C), 25.8 (SiC(CH₃)₃), 25.7 (SiC(CH₃)₃), 18.2 (SiC(CH₃)₃), 17.8 (SiC(CH₃)₃), 13.3 (6-(CH₃)), -4.4 (SiCH₃), -4.6 (SiCH₃), -5.4 (SiCH₃ (x 2)); *m/z* (ES⁺) 644 (MH⁺, 100%); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₃₅H₅₇NO₆Si₂Na 666.3617, observed 666.3620.

(4*R*,5*S*,6*S*)-5-Hydroxy-6-((*R*)-1-iodopropan-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (13)

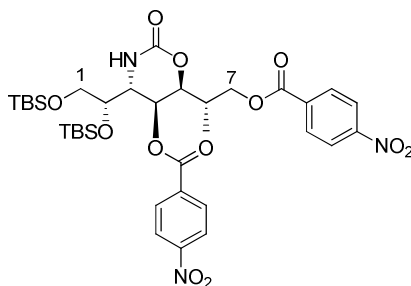


EtOAc (HPLC grade) (25 mL) was added to benzyl ether **10a** (1.56 g, 2.42 mmol) and palladium on carbon (250 mg, 20% wt.) and the mixture was stirred under an atmospheric (balloon) pressure of hydrogen for 20 h. The solution was then filtered over a plug of Celite/Na₂SO₄ (1:1), washed with EtOAc and concentrated *in vacuo* to afford diol, (4*R*,5*S*,6*S*)-5-hydroxy-6-((*S*)-1-hydroxypropan-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (**11**) (quant.) as a white solid, which was used without further purification. Iodine (277 mg, 1.09 mmol) was added in one portion to a solution of imidazole (229 mg, 3.36 mmol) and triphenylphosphine (286 mg, 1.09 mmol) in CH₂Cl₂ (3 mL) and the mixture was stirred for 10 mins. A portion of diol **11** (390 mg, 0.84 mmol) in CH₂Cl₂ (15 mL) was then added dropwise to the solution and the mixture was stirred for 3 h. Saturated aqueous Na₂SO₃ was then added and the solution stirred for 10 mins. The aqueous layer was separated and extracted with CH₂Cl₂, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20→30→60% EtOAc/petrol) afforded THF, (4*R*,4*aS*,7*S*,7*aS*)-7-methyl-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)hexahydro-2H-furo[2,3-*e*][1,3]oxazin-2-one (41.2 mg, 11%); R_f: 0.50 (60% EtOAc/petrol); and iodide **13** (403 mg, 84%) as a white foam; R_f: 0.25 (60% EtOAc/petrol); [α]_D²⁰ -59.6 (*c* 1.41, CHCl₃); ν_{max}/cm⁻¹ (neat) 3356 (br), 3247 (br), 2953, 2929, 2884, 2857, 1714, 1463, 1445, 1422, 1312, 1252, 1102, 1067, 1006, 961, 937, 832, 776, 669; δ_H (400 MHz, CDCl₃) 5.45 (1H, br s, NH), 4.10 (1H, s, 4-*H*), 4.00 (1H, d, *J* 9.6, 5-*H*), 3.67-3.57 (4H, m, 1-*H*, 2-*H* and 3-*H*), 3.51-3.48 (2H, m, 7-*H*), 1.92 (1H, m, 6-*H*), 1.05 (3H, d, *J* 6.6, 6-(CH₃)), 0.90 (18H, s, 2 x SiC(CH₃)₃),

0.11 (3H, s, SiCH₃), 0.10 (3H, s, SiCH₃); 0.08 (6H, s, 2 x SiCH₃); δ_C (100 MHz, CDCl₃) 153.9 (C(O)), 80.8 (5-C), 73.6 (2-C or 3-C), 65.3 (1-C), 63.1 (4-C), 60.9 (3-C or 2-C), 34.2 (6-C), 25.9 (SiC(CH₃)₃), 25.9 (SiC(CH₃)₃), 18.3 (SiC(CH₃)₃), 18.0 (SiC(CH₃)₃), 16.8 (6-(CH₃)), 14.8 (7-C), -4.2 (SiCH₃), -4.4 (SiCH₃), -5.4 (SiCH₃), -5.4(SiCH₃); m/z (ES⁺) 574 (MH⁺, 100%), 1147 (M₂H⁺, 100); m/z HRMS (ES⁺) MNa⁺ calculated for C₂₁H₄₄INO₅Si₂Na 596.1695, observed 596.1713.

Derivatization of **11 (for single crystal X-Ray diffraction studies (thus confirming the desired 1,3-*anti* TA stereochemistry from the TA reaction)):**

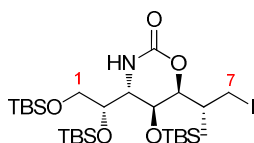
(*S*)-2-((4*R*,5*S*,6*S*)-5-((4-Nitrobenzoyl)oxy)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecan-5-yl)-2-oxo-1,3-oxazinan-6-yl)propyl 4-nitrobenzoate (12**)**



Triethylamine (24 μ l, 172 μ mol), DMAP (5.3 mg, 43 μ mol) and 4-nitrobenzoyl chloride (22.0 mg, 116 μ mol) were added sequentially to a solution of **11** (20.0 mg, 43 μ mol) in CH₂Cl₂ (0.4 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 24 h before being quenched with saturated aqueous NaHCO₃. The aqueous layer was separated and extracted with CH₂Cl₂, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-10-20% EtOAc/petrol) afforded benzoate **12** (29.6 mg, 90%) as a white solid; R_f: 0.30 (20% EtOAc/petrol); m. p. 178-180 °C; $[\alpha]_D^{20}$ -24.6 (c 0.24, CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2930, 1710, 1607, 1522, 1348, 1270, 1097, 1015, 943, 831, 778, 718, 694; δ_H (400 MHz, CDCl₃) 8.33 (2H, d, *J* 9.1, 2 x PhH), 8.29-8.24 (4H, m, 4 x PhH), 8.18 (2H, d, *J* 9.1, 2 x PhH), 5.67 (1H, s, 4-*H*), 5.43 (1H, br s, NH), 4.70 (1H, dd, *J* 11.3 and 3.7, 7-*HH*), 4.54-4.50 (2H, m, 7-*HH* and 5-*H*), 3.89 (1H, m, 2-*H*), 3.77-3.67 (3H, m, 1-*H* and 3-*H*), 2.47 (1H, m, 6-*H*), 1.10 (3H, d, *J* 7.1, 6-(CH₃)), 0.89 (9H, s, SiC(CH₃)₃), 0.88 (9H, s, SiC(CH₃)₃), 0.15 (3H, s, SiCH₃), 0.14 (3H, s, SiCH₃), 0.10 (3H, s, SiCH₃), 0.10 (3H, s, SiCH₃); δ_C (100 MHz, CDCl₃) 164.5 (C(O)), 163.9

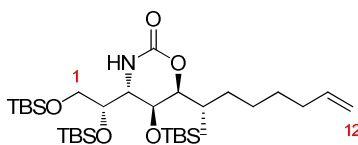
(C(O)), 152.8 (C(O)), 151.0 (C_(Ar)), 150.5 (C_(Ar)), 135.4 (C_(Ar)), 134.0 (C_(Ar)), 131.1 (CH_(Ar)), 130.7 (CH_(Ar)), 123.8 (CH_(Ar)), 123.5 (CH_(Ar)), 76.9 (5-C), 73.4 (2-C), 66.8 (4-C), 66.6 (7-C), 64.6 (1-C), 58.3 (3-C), 34.0 (6-C), 25.8 (SiC(CH₃)₃), 25.7 (SiC(CH₃)₃), 18.3 (SiC(CH₃)₃), 17.9 (SiC(CH₃)₃), 13.1 (6-(CH₃)), -4.3 (SiCH₃), -4.3 (SiCH₃), -5.4 (2 x SiCH₃); *m/z* (ES⁺) 784 (MNa⁺, 100%); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₃₅H₅₁N₃O₁₂Si₂Na 784.2903, observed 784.2909.

(4*S*,5*S*,6*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-((*R*)-1-iodopropan-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (14)



tert-Butyldimethylsilyl trifluoromethanesulfonate (2.34 mL, 10.2 mmol) was added dropwise to a solution of alcohol **13** (900 mg, 1.57 mmol) and 2,6-lutidine (1.83 mL, 15.7 mmol) in CH₂Cl₂ (16 mL) at 0 °C. The solution was then stirred at this temperature for 16 h before being quenched with *i*-PrOH. Water was then added and aqueous layer was separated and extracted with CH₂Cl₂, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol→5→10% EtOAc/petrol) afforded silyl ether **14** (978 mg, 91%) as a white solid; R_f 0.60 (15% EtOAc/petrol); m.p. 134-137 °C; [α]_D²⁰ -51.4 (*c* 0.35, CHCl₃); ν_{max} /cm⁻¹ (neat) 3447, 2954, 2927, 2884, 2855, 1698, 1454, 1419, 1360, 1303, 1252, 1109, 1074, 980, 935, 911, 876, 836, 810, 777, 724, 667; δ_H (400 MHz, CDCl₃) 5.10 (1H, d, *J* 3.2, NH), 4.15 (1H, d, *J* 0.5, 4-*H*), 3.97 (1H, d, *J* 9.4, 5-*H*), 3.64 (1H, m, 1-*HH*), 3.57-3.45 (5H, m, 3-*H*, 7-*H*, 1-*HH* and 2-*H*), 1.82 (1H, m, 6-*H*), 0.97 (3H, d, *J* 6.7, 6-(CH₃)), 0.89 (9H, s, SiC(CH₃)₃), 0.89 (9H, s, SiC(CH₃)₃), 0.87 (9H, s, SiC(CH₃)₃), 0.11 (6H, s, 2 x SiCH₃), 0.10 (3H, s, SiCH₃); 0.09 (3H, s, SiCH₃); 0.07 (6H, s, 2 x SiCH₃); δ_C (100 MHz, CDCl₃) 153.1 (C(O)), 80.4 (5-C), 73.6 (2-C), 64.9 (1-C), 63.8 (4-C), 60.2 (3-C), 34.0 (6-C), 25.9 (SiC(CH₃)₃), 25.9 (SiC(CH₃)₃), 25.6 (SiC(CH₃)₃), 18.3 (SiC(CH₃)₃), 18.0 (SiC(CH₃)₃), 17.9 (SiC(CH₃)₃), 16.9 (6-(CH₃)), 14.8 (7-C), -4.1 (SiCH₃), -4.2 (SiCH₃), -4.4 (SiCH₃), -4.7 (SiCH₃), -5.3 (SiCH₃), -5.4 (SiCH₃); *m/z* (ES⁺) 688 (MH⁺, 100%), 710 (MNa⁺, 30); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₂₇H₅₈INO₅Si₃Na 710.2560, observed 710.2548.

(4*S*,5*S*,6*S*)-5-((*tert*-Butyldimethylsilyloxy)-6-((*S*)-oct-7-en-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (15)



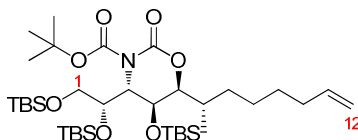
tert-Butyllithium (.98 mL of a 1.7 M solution in pentane, 8.47 mmol) was added to a solution of freshly prepared 5-iodo-1-pentene⁶ (830 mg, 4.23 mmol) in diethyl ether (4.6 mL) at -78 °C. The solution was then warmed to room temperature and stirred for 1 h. The organolithium solution was then transferred dropwise to a Schlenk tube, held at -40 °C, which was pre-loaded with copper(I) cyanide (189.6 mg, 2.12 mmol) and lithium chloride (179.4 mg, 4.23 mmol)³ in THF (7.1 mL)⁴. The organocuprate (pale yellow-to-milky white in appearance) was then allowed to stir for 30 mins. at -40 °C. Iodide **14** (224 mg, 0.326 mmol) in THF (1.2 mL) was then added dropwise to the organocuprate and the reaction was stirred for 6 h at -40 °C. The reaction was quenched by the cautious addition of saturated aqueous ammonium chloride solution. The aqueous layer was separated and extracted with EtOAc, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography over 10% silver nitrate doped silica gel (petrol→5→10% EtOAc/petrol) afforded alkene **15** (199 mg, 97%) as a white solid; *R*_f 0.40 (7% EtOAc/petrol); m.p. 85-88 °C; [α]_D²⁰ -52.9 (*c* 0.51, CHCl₃); *v*_{max}/cm⁻¹ (neat) 2955, 2927, 2855, 1692, 1457, 1389, 1361, 1309, 1253, 1111, 1069, 968, 937, 907, 875, 809, 728; δ_H (400 MHz, CDCl₃) 5.79 (1H, m, 11-*H*), 5.07 (1H, d, *J* 2.9, *NH*), 5.00-4.90 (2H, m, 12-*H*), 4.13 (1H, s, 4-*H*), 3.89 (1H, d, *J* 9.8, 5-*H*), 3.62 (1H, m, 1-*HH*), 3.56-3.48 (3H, m, 3-*H*, 1-*HH* and 2-*H*), 2.07-2.02 (2H, m, 10-*H*), 1.96 (1H, m, 6-*H*), 1.87 (1H, m, 7-*HH*), 1.45-1.34 (3H, m, 9-*H* and 8-*HH*), 1.19-1.08 (2H, m, 8-*HH* and 7-*HH*), 0.89-0.85 (30H, m, 6-(*CH*₃) and 3 x SiC(*CH*₃)₃), 0.10, 0.09, 0.08, 0.07 and 0.06 (6 x 3H, s, SiC*CH*₃); δ_C (100 MHz, CDCl₃) 154.0 (C(O)), 139.1 (11-C), 114.2 (12-C), 81.6 (5-C), 73.6 (2-C), 64.6 (1-C), 64.1 (4-C), 59.9 (3-C), 33.8 (10-C), 32.9 (6-C), 31.9 (7-C), 29.1 (9-C), 26.0 (8-C), 25.9 (SiC(*CH*₃)₃), 25.8 (SiC(*CH*₃)₃), 25.6 (SiC(*CH*₃)₃), 18.3 (SiC(*CH*₃)₃), 18.0 (SiC(*CH*₃)₃), 17.9 (SiC(*CH*₃)₃), 14.9 (6-(*CH*₃)), -4.0 (SiC*CH*₃), -4.2 (SiC*CH*₃), -4.4 (SiC*CH*₃), -4.7 (SiC*CH*₃), -5.3 (2 x SiC*CH*₃); *m/z* (ES⁺) 630 (M⁺,

³ The lithium chloride has previously been dried under high vacuum in the Schlenk tube for 16 h at 120 °C.

⁴ Note the copper(I) cyanide and lithium chloride THF solution had previously been sonicated for three minutes to ensure solubilization of copper cyanide.

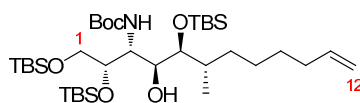
100%), 631 (MH⁺, 30); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₃₂H₆₇NO₅Si₃Na 652.4219, observed 652.4195.

(4*S*,5*S*,6*S*)-*tert*-Butyl 5-((*tert*-butyldimethylsilyl)oxy)-6-((*S*)-oct-7-en-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-2-oxo-1,3-oxazinane-3-carboxylate (15a**)**



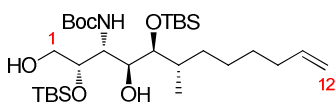
Triethylamine (110 μ L, 0.79 mmol), di-*tert*-butyl dicarbonate (0.91 mL, 3.97 mmol) and DMAP (19.2 mg, 0.157 mmol) were added sequentially to a solution of carbamate **15** (100 mg, 0.157 mmol) in CH₂Cl₂ (1.5 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 16 h. Water was added and aqueous layer was separated and extracted with CH₂Cl₂, dried (MgSO₄), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (petrol \rightarrow 1 \rightarrow 3% EtOAc/petrol) afforded *N*-Boc-carbamate **15a** (109 mg, 95%) as a viscous colourless oil; *R*_f 0.50 (2% EtOAc/petrol); $[\alpha]_D^{20}$ -55.9 (*c* 0.68, CHCl₃); ν_{\max} /cm⁻¹ (neat) 2955, 2929, 2885, 2858, 1755, 1719, 1472, 1462, 1391, 1366, 1308, 1297, 1255, 1165, 1107, 1069, 831, 775, 667; δ_H (400 MHz, CDCl₃) 5.80 (1H, m, 11-*H*), 5.01-4.91 (2H, m, 12-*H*), 4.55 (1H, dd, *J* 5.2 and 3.2, 3-*H*), 4.12 (1H, t, *J* 2.2, 4-*H*), 3.91 (1H, dd, *J* 9.8 and 1.5, 5-*H*), 3.66-3.59 (2H, m, 1-*H*), 3.56 (1H, m, 2-*H*), 2.07-2.02 (2H, m, 10-*H*), 1.95 (1H, m, 6-*H*), 1.87 (1H, m, 7-*HH*), 1.45-1.34 (3H, m, 9-*H* and 8-*HH*), 1.50 (9H, s, CO₂C(CH₃)₃), 1.23-1.08 (2H, m, 8-*HH* and 7-*HH*), 0.90, 0.87 and 0.86 (3 x SiC(CH₃)₃), 0.84 (3H, d, *J* 6.8, 6-(CH₃)), 0.13 (SiCH₃), 0.09-0.07 (15H, m, 5 x SiCH₃); δ_C (100 MHz, CDCl₃) 152.9 (C(O)), 148.4 (C(O)), 139.1 (11-*C*), 114.2 (12-*C*), 82.8 (5-*C* or CO₂C(CH₃)₃), 82.7 (CO₂C(CH₃)₃ or 5-*C*), 72.6 (2-*C*), 66.3 (1-*C*), 64.6 (4-*C*), 61.4 (3-*C*), 33.8 (10-*C*), 33.0 (6-*C*), 31.8 (7-*C*), 29.1 (9-*C*), 28.0 (CO₂C(CH₃)₃), 26.0 (SiC(CH₃)₃), 25.9 (SiC(CH₃)₃), 25.8 (8-*C*), 25.7 (SiC(CH₃)₃), 18.5 (SiC(CH₃)₃), 18.0 (2 x SiC(CH₃)₃), 14.9 (6-CH₃), -4.1 (SiCH₃), -4.4 (SiCH₃), -4.6 (SiCH₃), -4.9 (SiCH₃), -5.3 (SiCH₃), -5.4 (SiCH₃); *m/z* (ES⁺) 630 ((M-Boc)H⁺, 100%), 752 (MNa⁺, 40); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₃₇H₇₅NO₇Si₃Na 752.4744, observed 752.4730.

***tert*-Butyl ((5*S*,6*S*,7*R*,8*S*)-8-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-2,2,3,3,11,11,12,12-octamethyl-5-((*S*)-oct-7-en-2-yl)-4,10-dioxo-3,11-disilatridecan-7-yl)carbamate (**16**)**



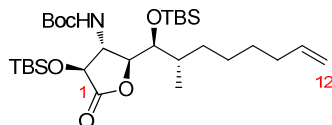
Sodium *tert*-butoxide (98.5 mg, 1.03 mmol) was added in one portion to a stirred solution of *N*-Boc-carbamate **15a** (150 mg, 0.21 mmol) in *t*-BuOH/THF (2.3 mL, 1:1) at room temperature. The reaction was stirred for 45 mins. before the addition of saturated aqueous ammonium chloride solution. The aqueous layer was separated and extracted with EtOAc, dried (MgSO₄), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (petrol→1→2% EtOAc/petrol) afforded silyl ether **16** (isolated with small amounts of inseparable regioisomeric 5-(OTBS) silyl ether) (126 mg, 87%), as a viscous colourless oil; R_f 0.55 (1% EtOAc/petrol); ν_{\max} /cm⁻¹ (neat) 3530 br, 3460, 2929, 2857, 1718, 1472, 1493, 1365, 1253, 1170, 1068, 1005, 937, 832, 776, 675; δ_{H} (400 MHz, CDCl₃ (chemical shifts reported for the major compound only)) 5.81 (1H, m, 11-*H*), 5.02-4.90 (2H, m, 12-*H*), 4.63 (1H, d, *J* 9.8, NH), 4.22 (1H, t, *J* 6.8, 2-*H*), 3.80 (1H, d, *J* 3.3, 5-*H*), 3.55 (1H, t, *J* 10.0, 3-*H*), 3.47-3.43 (2H, m, 1-*H*), 3.24 (1H, m, 4-*H*), 3.15 (1H, d, *J* 8.5, OH), 2.07-2.02 (2H, m, 10-*H*), 1.56 (1H, m, 6-*H*), 1.43 (9H, s, CO₂C(CH₃)₃), 1.39-1.27 (4H, m, 9-*H* and 8-*H*), 1.21 (1H, m, 7-*HH*), 1.08 (1H, m, 7-*HH*), 0.91-0.88 (30H, m 3 x SiC(CH₃)₃ and 6-(CH₃)), 0.21, 0.14, 0.12 and 0.10 (4 x 3H, s, SiCH₃), 0.03 (6H, s, 2 x SiCH₃); δ_{C} (100 MHz, CDCl₃ (chemical shifts reported for the major compound only)) 156.6 (C(O)), 139.0 (11-C), 114.3 (12-C), 78.6 (CO₂C(CH₃)₃), 72.3 (5-C), 70.7 (2-C), 67.0 (4-C), 64.1 (1-C), 53.2 (3-C), 39.6 (6-C), 33.6 (10-C), 32.7 (7-C), 29.2 (9-C), 28.4 (CO₂C(CH₃)₃), 26.8 (8-C), 26.1 (SiC(CH₃)₃), 26.0 (2 x SiC(CH₃)₃), 18.4 (SiC(CH₃)₃), 18.2 (SiC(CH₃)₃), 18.1 (SiC(CH₃)₃), 14.6 (6-CH₃), -4.2 (SiCH₃), -4.3 (SiCH₃), -5.0 (SiCH₃), -5.1 (SiCH₃), -5.4 (SiCH₃), -5.6 (SiCH₃); *m/z* (ES⁺) 726 (MNa⁺, 100%), 604 ((M-Boc)H⁺, 10); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₃₆H₇₇NO₆Si₃Na 726.4930, observed 726.4951.

***tert*-Butyl ((5*S*,6*R*,7*S*,8*S*)-7-hydroxy-5-(hydroxymethyl)-2,2,3,3,10,10,11,11-octamethyl-8-((*S*)-oct-7-en-2-yl)-4,9-dioxo-3,10-disiladodecan-6-yl)carbamate (**17**)**



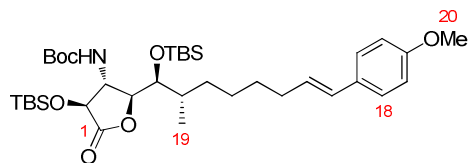
Silyl ether **16** (425 mg, 0.60 mmol) in THF (6.0 mL) at 0 °C was treated with hydrogen fluoride pyridine (304 μ L of a 70% solution, 3.02 mmol) over the course of a 30 h period, whilst slowly warming to room temperature. The reaction was quenched by the cautious addition of saturated aqueous NaHCO₃. The solution was then diluted with EtOAc and the aqueous layer was separated and extracted with EtOAc, dried (Na₂SO₄), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (petrol-2-5% EtOAc/petrol) afforded alcohol **17** (267 mg, 75%) as a colourless oil, where the minor regioisomeric 5-(OTBS) silyl ether had been removed upon purification by flash column chromatography; R_f 0.30 (5% EtOAc/petrol); [α]_D²⁰ +23.9 (*c* 0.92, CHCl₃); ν_{max} /cm⁻¹ (neat) 3553, 3403 (br), 3266 (br), 2953, 2928, 2856, 2858, 1672, 1537, 1471, 1366, 1312, 1277, 1252, 1173, 1093, 1071, 1042, 1026, 1006, 940, 896, 834, 774, 679; δ_H (400 MHz, CDCl₃) 5.81 (1H, m, 11-*H*), 5.03-4.94 (2H, m, 12-*H*), 4.44 (1H, d, *J* 10.6, *NH*), 4.27 (1H, dd, *J* 8.9 and 5.9, 2-*H*), 3.76 (1H, d, *J* 3.8, 5-*H*), 3.60 (1H, t, *J* 10.3, 3-*H*), 3.51 (1H, dd, *J* 11.5 and 5.7, 1-*HH*), 3.35 (1H, t, *J* 9.5, 4-*H*), 3.25 (1H, dd, *J* 11.4 and 9.6, 1-*HH*), 3.15 (1H, br, *OH*), 2.29 (1H, d, *J* 9.2 1-*OH*), 2.09-2.04 (2H, m, 10-*H*), 1.63 (1H, m, 6-*H*), 1.46 (9H, s, CO₂C(CH₃)₃), 1.41-1.35 (4H, m, 9-*H* and 8-*HH*), 1.31-1.21 (2H, m, 8-*HH*, 7-*HH*), 1.12 (1H, m, 7-*HH*), 0.93 (3H, d, *J* 6.9 6-(CH₃)), 0.91 (9H, s, SiC(CH₃)₃), 0.89 (9H, s, SiC(CH₃)₃), 0.13 (3H, s, SiCH₃), 0.12 (3H, s, SiCH₃), 0.09 (6H, s, 2 x SiCH₃); δ_C (100 MHz, CDCl₃) 157.4 (C(O)), 138.9 (11-C), 114.4 (12-C), 80.1 (CO₂C(CH₃)₃), 72.5 (5-C), 69.8 (2-C), 66.4 (4-C), 63.1 (1-C), 52.9 (3-C), 39.1 (6-C), 33.6 (10-C), 33.1 (7-C), 29.1 (9-C), 28.3 (CO₂C(CH₃)₃), 26.8 (8-C), 25.9 (2 x SiC(CH₃)₃), 18.2 (SiC(CH₃)₃), 18.1 (SiC(CH₃)₃), 14.7 (6-CH₃), -4.5 (SiCH₃), -4.5 (SiCH₃), -4.8 (SiCH₃), -5.0 (SiCH₃); *m/z* (ES⁺) 612 (MNa⁺, 60%), 590 (MH⁺, 40), 490 ((M-Boc)H⁺, 100); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₃₀H₆₃NO₆Si₂Na 612.4084, observed 612.4067.

***tert*-Butyl ((2*S*,3*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-((1*S*,2*S*)-1-((*tert*-butyldimethylsilyl)oxy)-2-methyloct-7-en-1-yl)-5-oxotetrahydrofuran-3-yl)carbamate (18)**



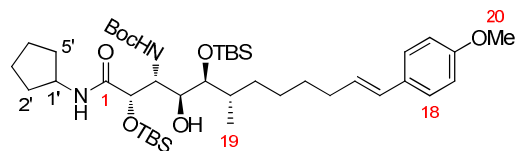
Dimethyl sulfoxide (0.28 mL, 3.99 mmol), *N,N*-diisopropylethylamine (0.28 mL, 1.59 mmol) and sulfur trioxide pyridine complex (191 mg, 1.19 mmol) were added sequentially to a solution of diol **17** (236 mg, 0.40 mmol) in CH₂Cl₂ (4.0 mL) at 0 °C. The mixture was slowly warmed to room temperature stirred for 2.5 h. Additional portions of dimethyl sulfoxide (0.28 mL, 3.99 mmol), *N,N*-diisopropylethylamine (0.28 mL, 1.59 mmol) and sulfur trioxide pyridine complex (191 mg, 1.19 mmol) were then added, and the mixture was stirred for 1 h. Saturated aqueous NaHCO₃ was then added and the aqueous layer was separated and extracted with CH₂Cl₂, dried (Na₂SO₄), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (petrol-2-5% EtOAc/petrol) afforded lactone **18** (169 mg, 72%) as a white solid; R_f: 0.60 (5% EtOAc/petrol); m. p. 81-83 °C; [α]_D²⁰ -21.3 (*c* 0.08, CHCl₃); ν_{max}/cm⁻¹ (neat) 3334, 2929, 2857, 1777, 1704, 1531, 1463, 1389, 1281, 1151, 1067, 837, 775, 661; δ_H (400 MHz, CDCl₃) 5.80 (1H, m, 11-*H*), 5.02-4.93 (2H, m, 12-*H*), 4.79 (1H, d, *J* 8.3, *NH*), 4.70 (1H, d, *J* 8.8, 2-*H*), 4.44 (1H, dd, *J* 8.6 and 5.1, 4-*H*), 3.84 (1H, ddd, *J* 8.8, 8.6 and 8.3, 3-*H*), 3.60 (1H, dd, *J* 5.1 and 3.2, 5-*H*), 2.07-2.02 (2H, m, 10-*H*), 1.68 (1H, m, 6-*H*), 1.44 (9H, s, CO₂C(CH₃)₃), 1.41-1.17 (6H, m, 9-*H*, 8-*H* and 7-*H*), 0.97 (3H, d, *J* 6.9, 6-(CH₃)), 0.91 (9H, s, SiC(CH₃)₃), 0.89 (9H, s, SiC(CH₃)₃), 0.17 (3H, s, SiCH₃), 0.12 (6H, s, 2 x SiCH₃), 0.07 (3H, s, SiCH₃); δ_C (100 MHz, CDCl₃) 172.9 (1-*C*), 154.5 (C(O)), 138.9 (11-*C*), 114.4 (12-*C*), 80.4 (CO₂C(CH₃)₃), 78.4 (4-*C*), 76.5 (5-*C*), 71.7 (2-*C*), 57.6 (3-*C*), 36.0 (6-*C*), 33.8 (10-*C*), 31.4 (8-*C*), 29.2 (9-*C*), 28.3 (CO₂C(CH₃)₃), 26.9 (7-*C*), 26.0 (SiC(CH₃)₃), 25.6 (SiC(CH₃)₃), 18.4 (SiC(CH₃)₃), 18.1 (SiC(CH₃)₃), 16.6 (6-(CH₃)), -4.3 (2 x SiCH₃), -4.7 (SiCH₃), -5.4 (SiCH₃); *m/z* (ES⁺) 608 (MNa⁺, 100%); *m/z* HRMS (ES⁺) MNa⁺ calculated for C₃₀H₅₉NO₆Si₂Na 608.3773, observed 608.3762.

***tert*-Butyl ((2*S*,3*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-((1*S*,2*S*,*E*)-1-((*tert*-butyldimethylsilyl)oxy)-8-(4-methoxyphenyl)-2-methyloct-7-en-1-yl)-5-oxotetrahydrofuran-3-yl)carbamate (**19**)**



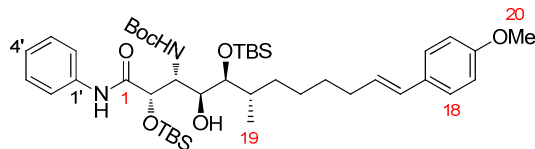
Alkene **18** (71.0 mg, 0.12 mmol) and 4-vinylanisole (81 μ L, 0.61 mmol) were added to dry degassed CH_2Cl_2 (0.4 mL). Grubbs I catalyst (5.0 mg, 6.0 μ mol) was then added to the solution and the reaction was stirred at room temperature for a total period of 48 h. Two additional injections of Grubbs I catalyst (5.0 mg, 6.0 μ mol (per injection)) were made at regular intervals over this period. After which DMSO (100 μ L) was added and the solution was stirred at room temperature for 10 mins. The mixture was then concentrated *in vacuo* onto silica gel and purified by flash column chromatography (petrol-2-5% EtOAc/petrol) to afford styrene **19** (73.3 mg, 88%) as a colourless oil; R_f : 0.25 (5% EtOAc/petrol); $[\alpha]_D^{20}$ -19.2 (c 0.13, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3393, 2929, 2857, 1788, 1719, 1510, 1463, 1366, 1249, 1153, 835, 777, 669; δ_H (400 MHz, CDCl_3) 7.28 (2H, d, J 9.3, 14- and 18-*H*), 6.85 (2H, d, J 9.3, 15- and 17-*H*), 6.33 (1H, d, J 15.9, 12-*H*), 6.08 (1H, dt, J 15.9 and 6.9, 11-*H*), 4.68 (1H, d, J 8.3, *NH*), 4.58 (1H, d, J 8.8, 2-*H*), 4.39 (1H, dd, J 8.6 and 4.9, 4-*H*), 3.38-3.81 (4H, m, 3-*H* and 20-*H*), 3.61 (1H, dd, J 4.9 and 3.2, 5-*H*), 2.23-2.18 (2H, m, 10-*H*), 1.69 (1H, m, 6-*H*), 1.50-1.39 (12H, m, $\text{CO}_2\text{C}(\text{CH}_3)_3$, 9-*H* and 7-*HH*), 1.34-1.22 (3H, m, 8-*H* and 7-*HH*), 0.98 (3H, d, J 6.9, 19-*H*), 0.91 (18H, s, 2 x $\text{SiC}(\text{CH}_3)_3$), 0.17 (3H, s, SiCH_3), 0.13 (3H, s, SiCH_3), 0.11 (3H, s, SiCH_3), 0.08 (3H, s, SiCH_3); δ_C (100 MHz, CDCl_3) 172.9 (1-*C*), 158.7 (16-*C*), 154.5 (*C*(O)), 130.5 (13-*C*), 129.2 (12-*C*), 128.7 (11-*C*), 126.9 (14- and 18-*C*), 113.9 (15- and 17-*C*), 80.4 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 78.4 (4-*C*), 76.4 (5-*C*), 71.8 (2-*C*), 57.4 (3-*C*), 55.2 (20-*C*), 36.0 (6-*C*), 33.0 (10-*C*), 31.3 (8-*C*), 29.6 (9-*C*), 28.3 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 26.9 (7-*C*), 26.0 ($\text{SiC}(\text{CH}_3)_3$), 25.5 ($\text{SiC}(\text{CH}_3)_3$), 18.4 ($\text{SiC}(\text{CH}_3)_3$), 18.1 ($\text{SiC}(\text{CH}_3)_3$), 16.6 (19-*C*), -4.3 (SiCH_3), -4.7 (SiCH_3), -5.4 (SiCH_3); m/z (ES^+) 714 (MNa^+ , 100%); m/z HRMS (ES^+) MNa^+ calculated for $\text{C}_{37}\text{H}_{65}\text{NO}_7\text{Si}_2\text{Na}$ 714.4192, observed 714.4180.

***tert*-Butyl ((5*S*,6*R*,7*S*,8*S*)-5-(cyclopentylcarbamoyl)-7-hydroxy-8-((*S*,*E*)-8-(4-methoxyphenyl)oct-7-en-2-yl)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecan-6-yl)carbamate (**20**)**



N,N'-Diisopropylethylamine (5 μ L, 30 μ mol), 2-hydroxypyridine (1.4 mg, 15 μ mol) and cyclopentylamine (4 μ L, 38 μ mol) were added sequentially to a solution of lactone **19** (10.6 mg, 15 μ mol) in CH_2Cl_2 (0.15 mL) at room temperature. The mixture was stirred for 48 h, then concentrated *in vacuo* onto silica gel and purified by flash column chromatography (petrol-5-10% EtOAc/petrol) to afford amide **20** (10.7 mg, 92%) as a colorless oil; R_f : 0.30 (10% EtOAc/petrol); $[\alpha]_D^{20}$ -7.9 (*c* 0.14, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3432, 2954, 2929, 2857, 1722, 1683, 1511, 1492, 1365, 1249, 1173, 1073, 964, 836, 779, 676; δ_{H} (400 MHz, CDCl_3) 7.28 (2H, d, *J* 8.3, 14- and 18-*H*), 6.84 (2H, d, *J* 8.3, 15- and 17-*H*), 6.37 (1H, d, *J* 8.1, NH), 6.32 (1H, d, *J* 15.7, 12-*H*), 6.08 (1H, dt, *J* 15.7 and 6.9, 11-*H*), 4.62 (1H, s, 4-*H* or 2-*H*), 4.51 (1H, d, *J* 10.3, NH), 4.25 (1H, m, 1'-*H*), 3.88 (1H, dd, *J* 10.3, 3-*H*), 3.81 (3H, s, 20-*H*), 3.74 (1H, d, *J* 3.4, 5-*H*), 3.22-3.14 (2H, m, 2-*H* or 4-*H* and OH), 2.19 (2H, dt, *J* 6.9, 10-*H*), 1.99-1.91 (2H, m, 2'-*HH* and 5'-*HH*), 1.68-1.61 (5H, m, 6-*H*, 4'-*H* and 3'-*H*), 1.46-1.08 (17H, m, $\text{CO}_2\text{C}(\text{CH}_3)_3$, 7-*H*, 8-*H*, 9-*H*, 2'-*HH* and 5'-*HH*), 0.97 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.93 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.91 (3H, d, *J* 7.1, 19-*H*), 0.26 (3H, s, SiCH_3), 0.19 (3H, s, SiCH_3), 0.12 (6H, s, 2 x SiCH_3); δ_{C} (100 MHz, CDCl_3) 171.6 (1-*C*), 158.6 (16-*C*), 154.8 (*C*(O)), 130.6 (13-*C*), 129.2 (12-*C*), 128.6 (11-*C*), 127.0 (14- and 18-*C*), 113.9 (15- and 17-*C*), 79.2 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 72.1 (4-*C* or 2-*C*), 72.1 (5-*C*), 67.0 (2-*C* or 4-*C*), 55.7 (3-*C*), 55.3 (20-*C*), 50.5 (1'-*C*), 39.3 (6-*C*), 33.5, 32.9, 32.9, 32.7, (10-*C*, 7-*C* or 8-*C*, 2'-*C* and 5'-*C*), 29.8 (9-*C*), 28.4 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 26.9 (7-*C* or 8-*C*), 25.9 ($\text{SiC}(\text{CH}_3)_3$), 25.9 ($\text{SiC}(\text{CH}_3)_3$), 23.6 (4'-*C*), 23.6 (3'-*C*), 18.2 ($\text{SiC}(\text{CH}_3)_3$), 18.1 ($\text{SiC}(\text{CH}_3)_3$), 14.6 (19-*C*), -4.3 (SiCH_3), -5.0 (SiCH_3), -5.1 (SiCH_3), -5.2 (SiCH_3); m/z (ES^+) 799 (MNa^+ , 100%); m/z HRMS (ES^+) MNa^+ calculated for $\text{C}_{42}\text{H}_{76}\text{N}_2\text{O}_7\text{Si}_2\text{Na}$ 799.5083, observed 799.5106.

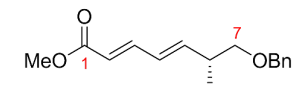
***tert*-Butyl ((5*S*,6*R*,7*S*,8*S*)-7-hydroxy-8-((*S*,*E*)-8-(4-methoxyphenyl)oct-7-en-2-yl)-2,2,3,3,10,10,11,11-octamethyl-5-(phenylcarbamoyl)-4,9-dioxo-3,10-disiladodecan-6-yl)carbamate (**21**)**



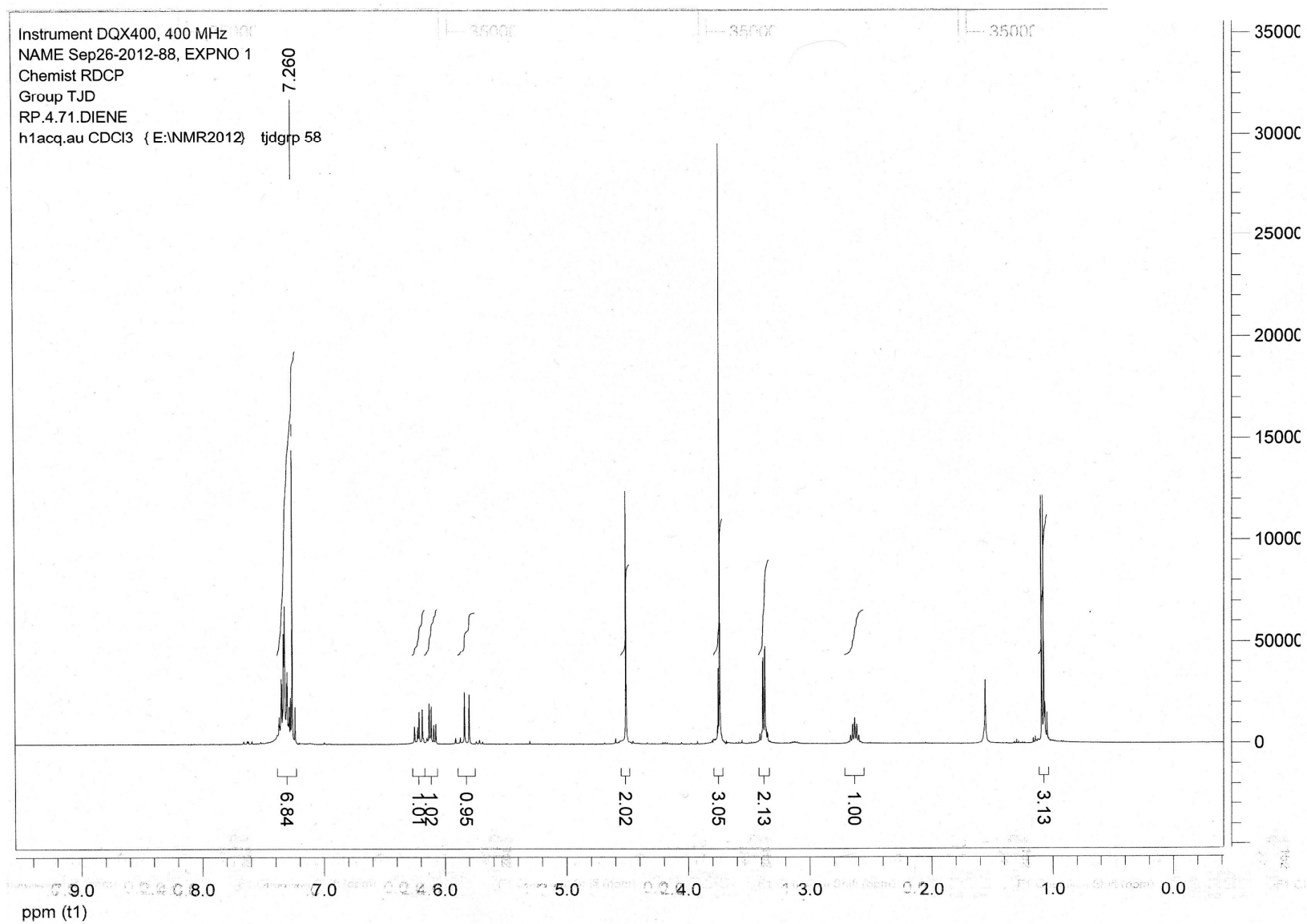
Aniline (8 μ L, 83 μ mol), trimethylaluminium (42 μ L of a 2.0 M solution in hexanes, 83 μ mol) were added sequentially to a solution of lactone **19** (23.0 mg, 33 μ mol) in dry CH_2Cl_2 (0.33 mL) at 0 $^\circ\text{C}$. The mixture was stirred for 3 h before being quenched with saturated aqueous NaHCO_3 . The aqueous layer was separated and extracted with CH_2Cl_2 , dried (Na_2SO_4), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (hexane-2-5% EtOAc/hexane) afforded amide **21** (20.2 mg, 78%) as a colorless oil; R_f : 0.30 (5% EtOAc/hexane); $[\alpha]_D^{20}$ -60.0 (c 0.08, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3404, 2954, 2929, 1722, 1698, 1603, 1511, 1442, 1248, 1172, 1075, 962, 836, 780, 691; δ_{H} (400 MHz, $(\text{CD}_3)_2\text{SO}$) 9.07 (1H, s, NH), 7.51 (2H, d, J 7.6, 2'- and 6'-H), 7.32-7.27 (4H, m, 3'- and 5'-H and 14- and 18-H), 7.05 (1H, dd, J 7.3, 4'-H), 6.85 (2H, d, J 8.8, 15- and 17-H), 6.31-6.27 (2H, m, 12-H and NH), 6.10 (1H, dt, J 15.7 and 6.9, 11-H), 4.52 (1H, d, J 2.2, 4-H or 2-H), 3.75-3.73 (4H, m, 3-H and 20-H), 3.68 (1H, d, J 3.9, 5-H), 3.48 (1H, d, J 8.6, 4-OH), 3.36 (1H, m, 2-H or 4-H), 2.15 (2H, dt, J 6.9, 10-H), 1.59 (1H, m, 6-H), 1.39-1.29 (5H, m, 7-HH, 8-H and 9-H), 1.22 (9H, s, $\text{CO}_2\text{C}(\text{CH}_3)_3$), 1.11 (1H, m, 7-HH), 0.93 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.89 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.88 (3H, d, J 6.9, 19-H), 0.14 (3H, s, SiCH_3), 0.12 (3H, s, SiCH_3), 0.09 (3H, s, SiCH_3), 0.05 (3H, s, SiCH_3); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{SO}$) 170.4 (1-C), 158.3 (16-C), 155.4 (C(O)), 138.2 (1'-C), 129.9 (13-C), 129.0 (12-C), 128.6 (3'- and 5'-C or 14- and 18-C), 128.1 (11-C), 126.9 (3'- and 5'-C or 14- and 18-C), 123.6 (4'-C), 119.7 (2'- and 6'-C), 113.9 (15- and 17-C), 77.9 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 73.0 (4-C or 2-C), 72.1 (5-C), 67.0 (2-C or 4-C), 55.5 (3-C), 55.0 (20-C), 38.4 (6-C), 32.4 (10-C and 7-C), 29.4 (9-C), 28.0 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 26.4 (8-C), 25.9 ($\text{SiC}(\text{CH}_3)_3$), 25.8 ($\text{SiC}(\text{CH}_3)_3$), 18.1 ($\text{SiC}(\text{CH}_3)_3$), 17.9 ($\text{SiC}(\text{CH}_3)_3$), 15.0 (19-C), -4.4 (SiCH_3), -5.1 (SiCH_3), -5.1 (SiCH_3), -5.2 (SiCH_3); m/z (ES^+) 808 (MNa^+ , 100%), 685 ($(\text{M}-\text{Boc})\text{H}_2^+$, 50); m/z HRMS (ES^+) MNa^+ calculated for $\text{C}_{43}\text{H}_{72}\text{N}_2\text{O}_7\text{Si}_2\text{Na}$ 807.4770, observed 807.4773.

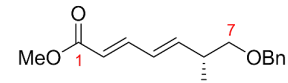
1.3 References

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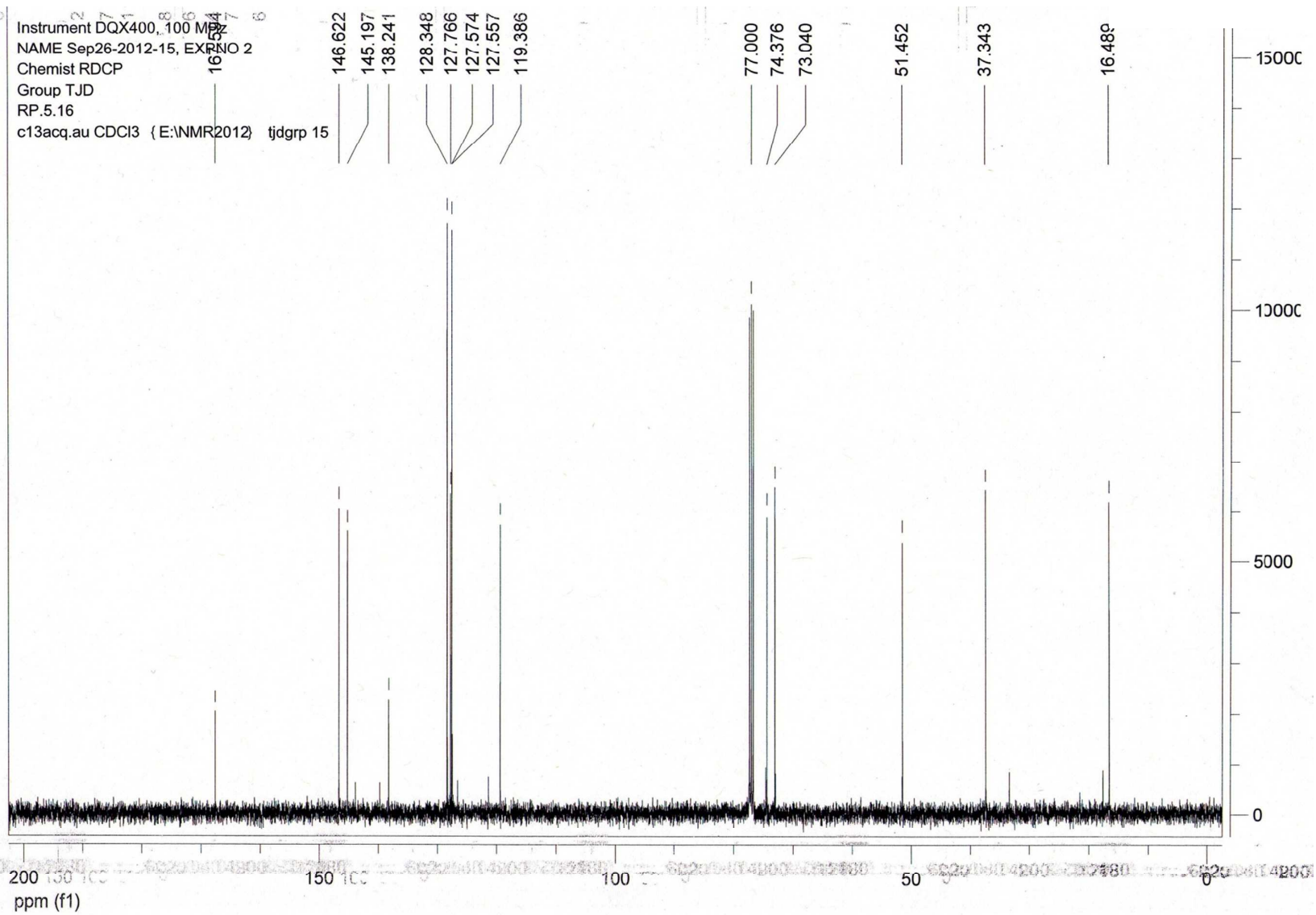


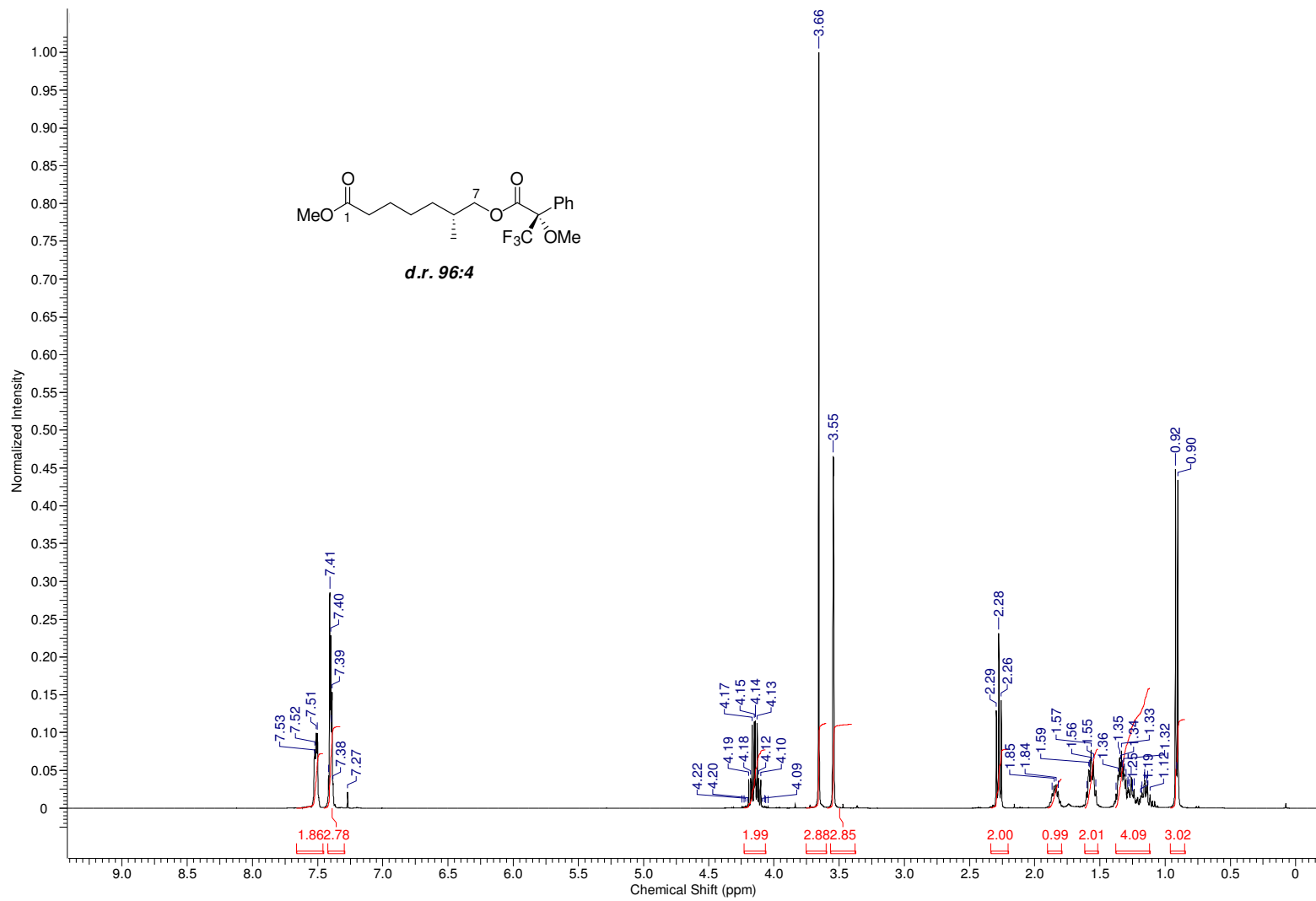
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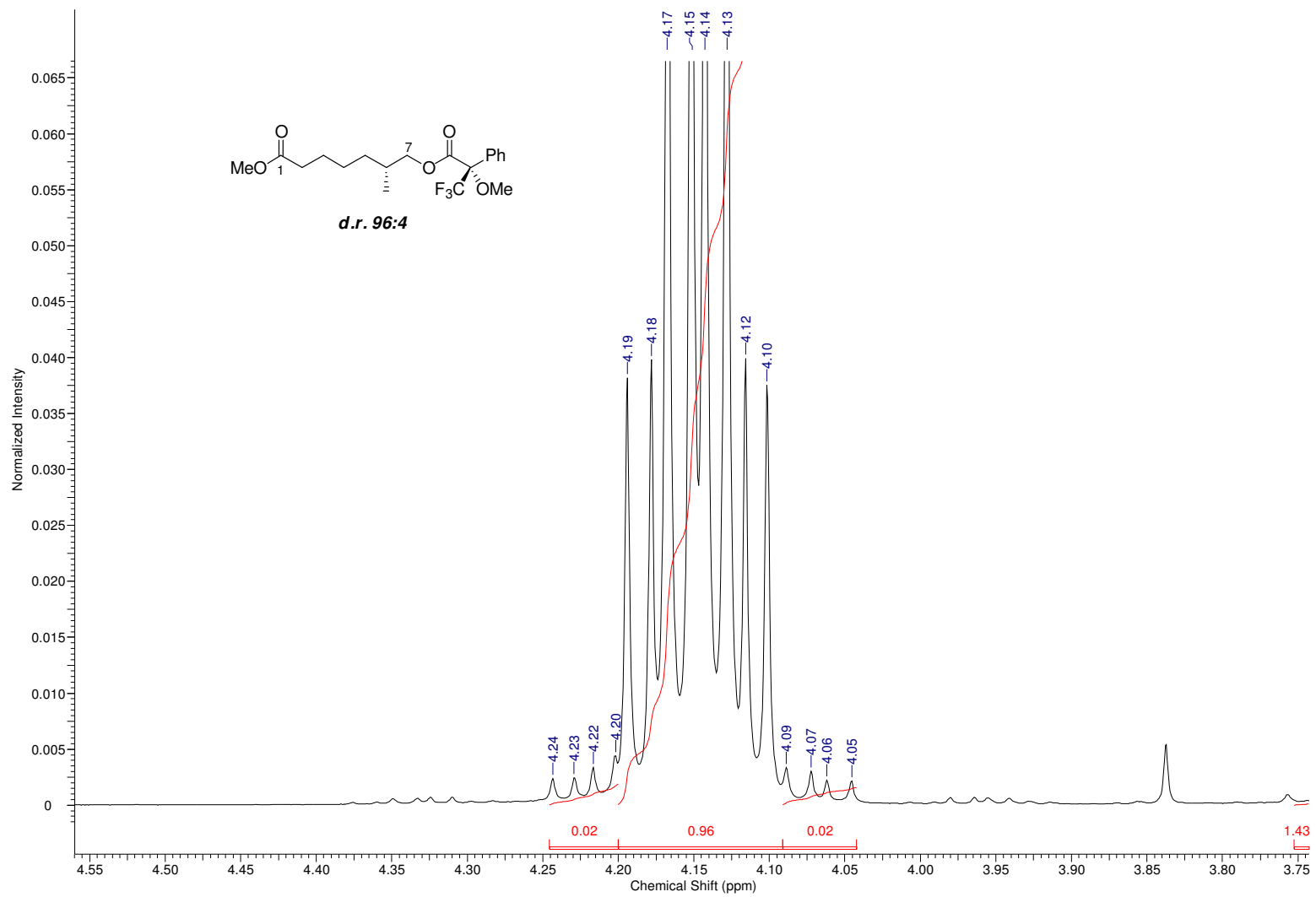


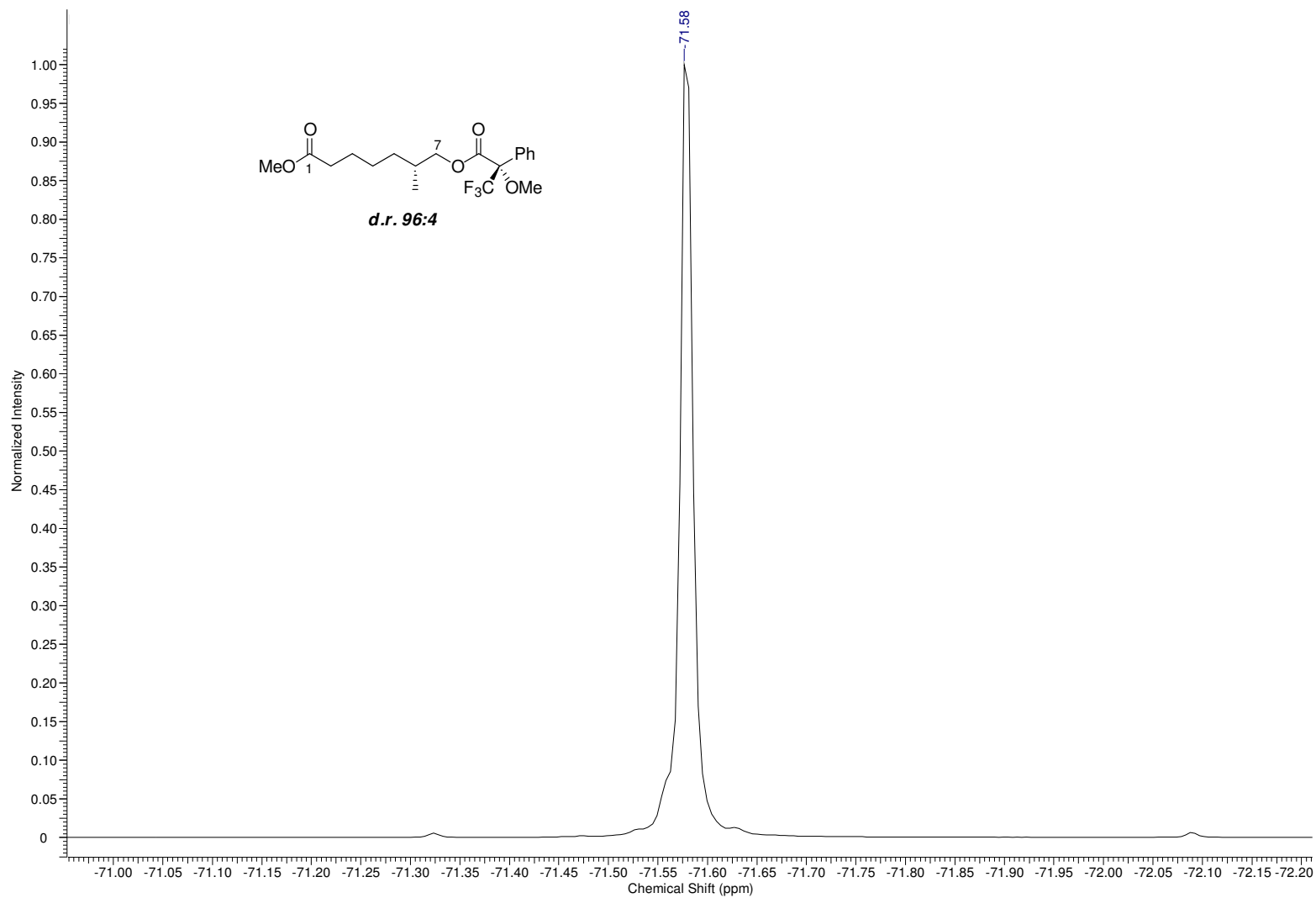


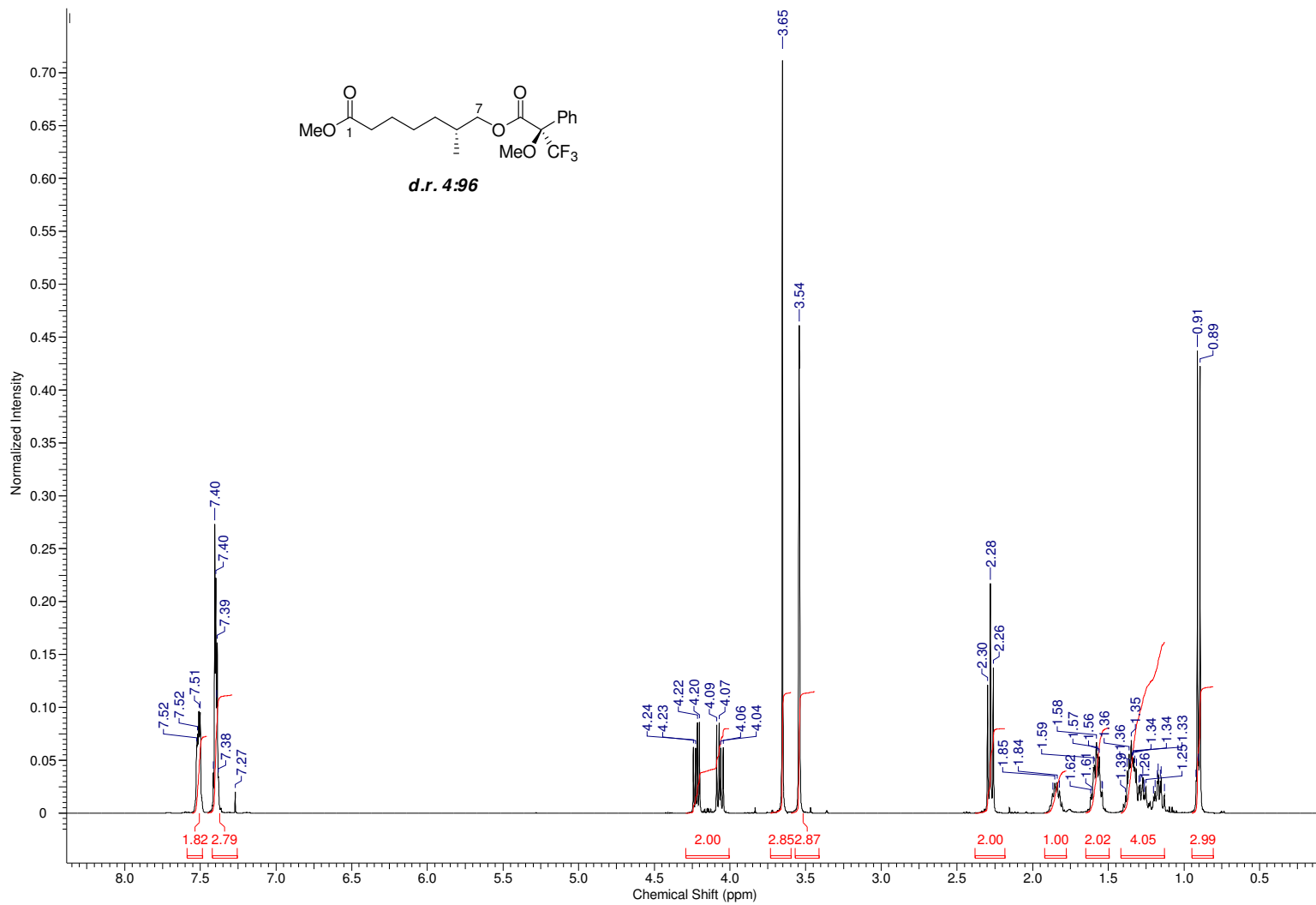
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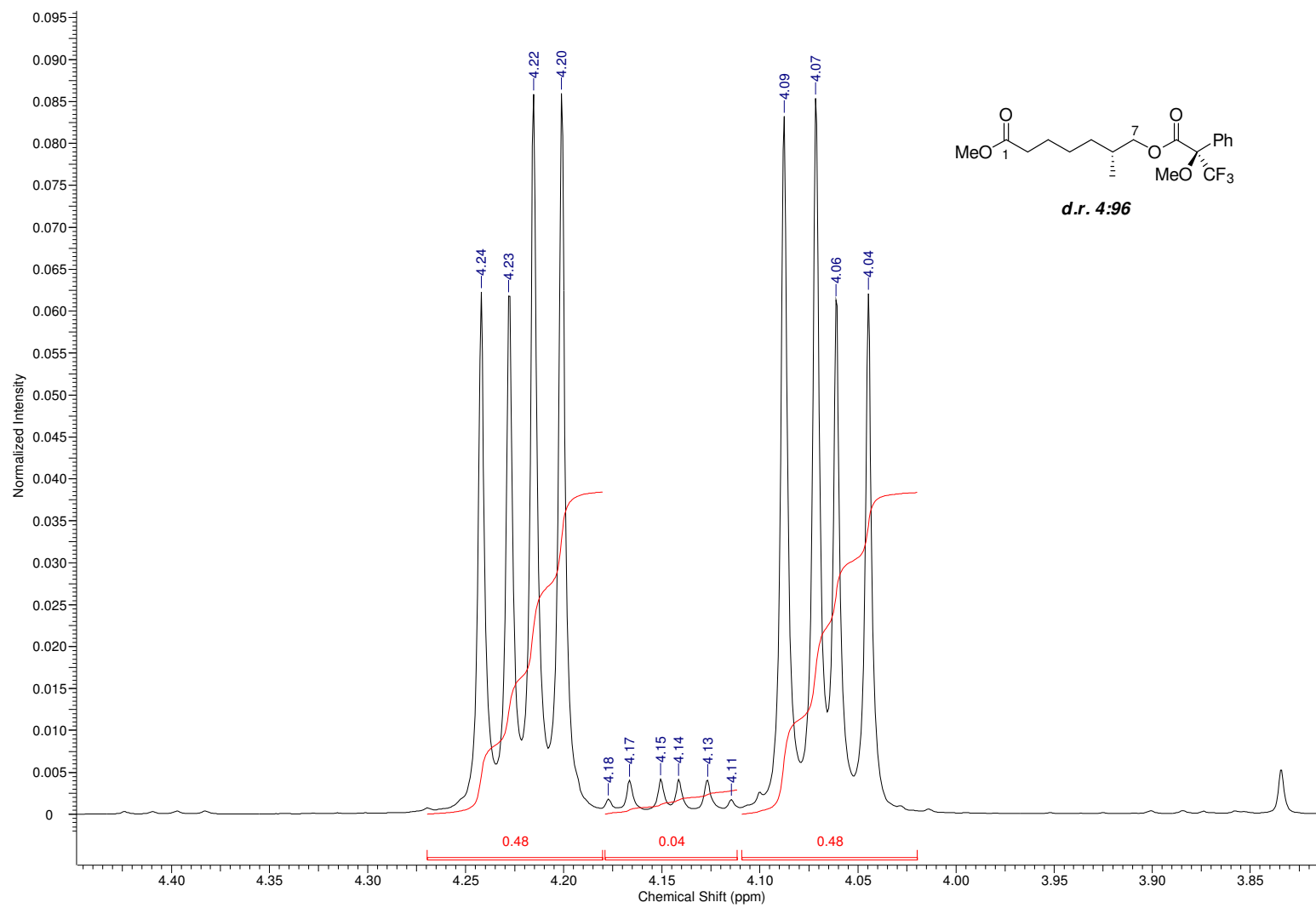


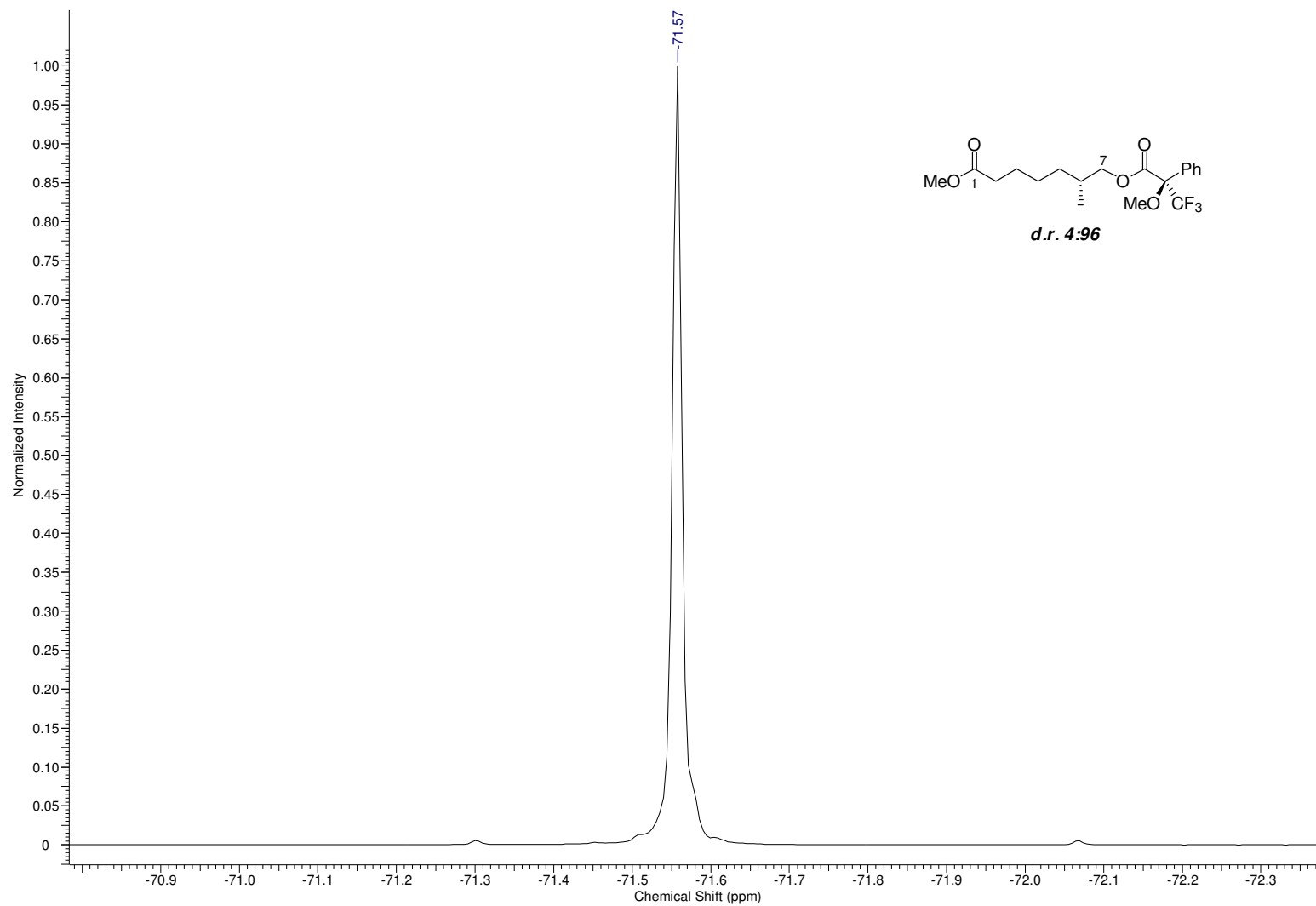


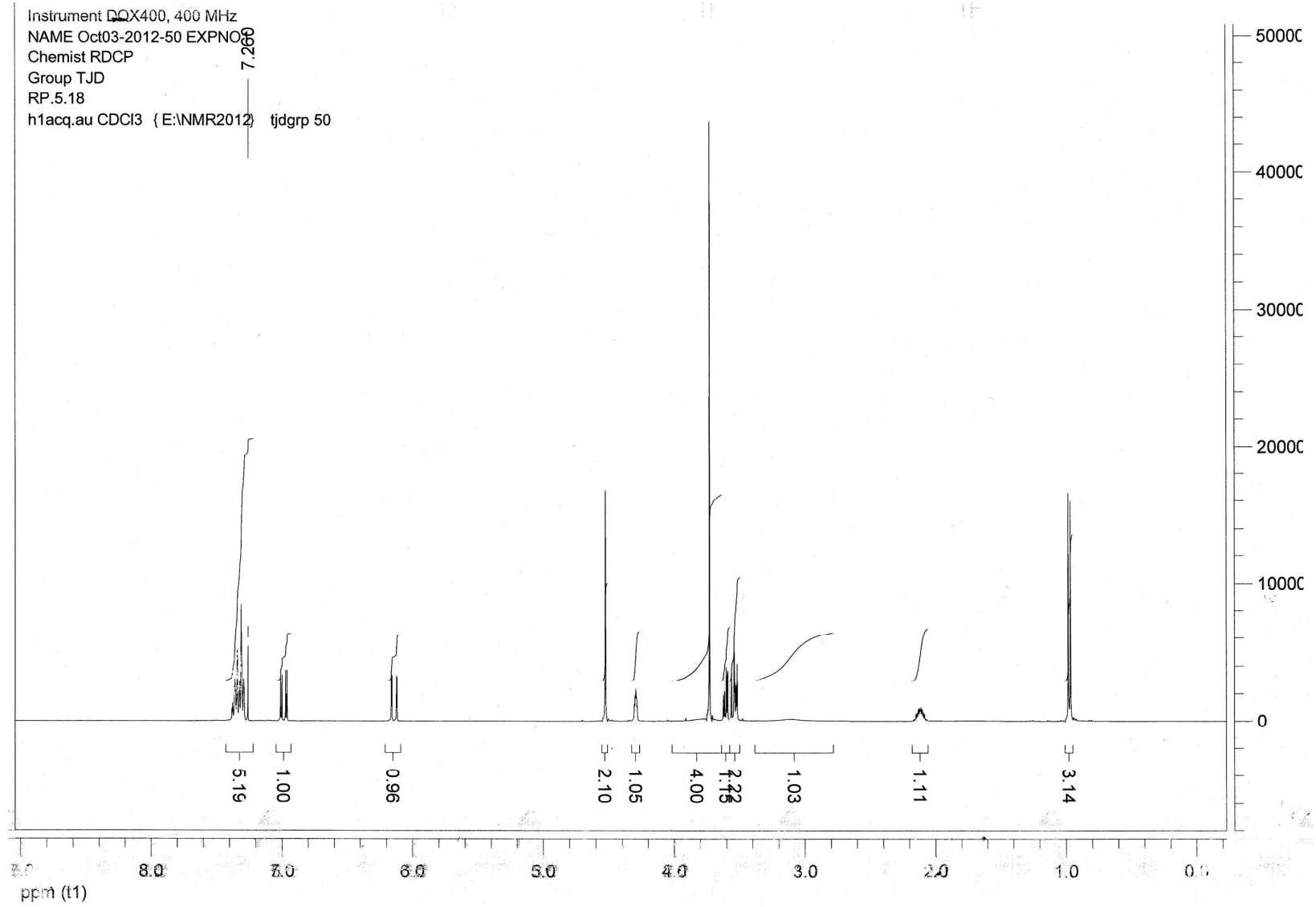
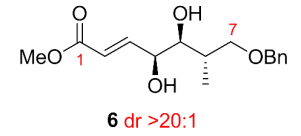


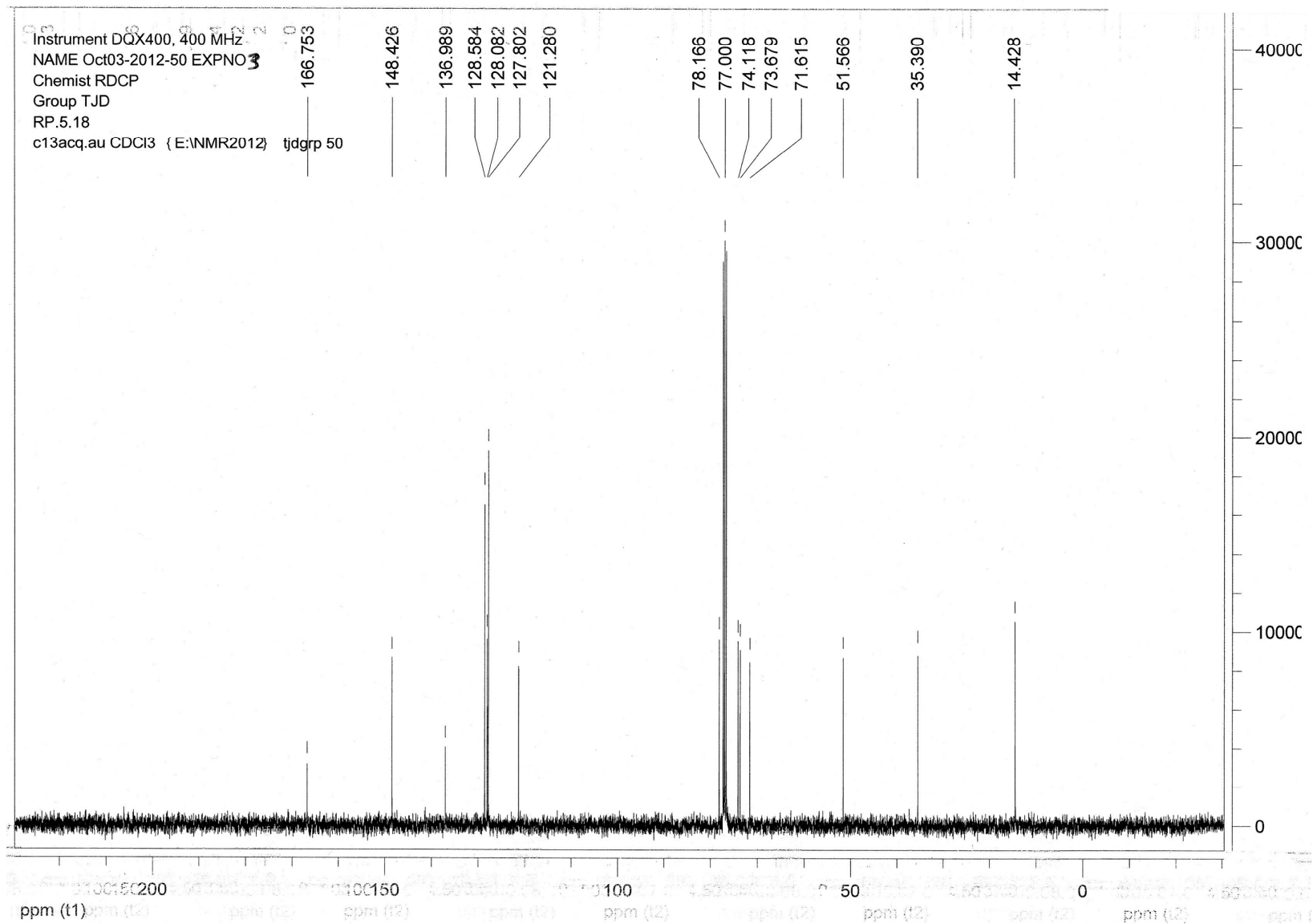
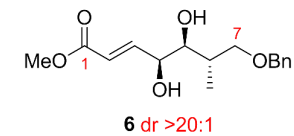


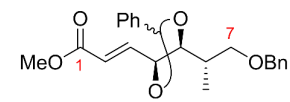




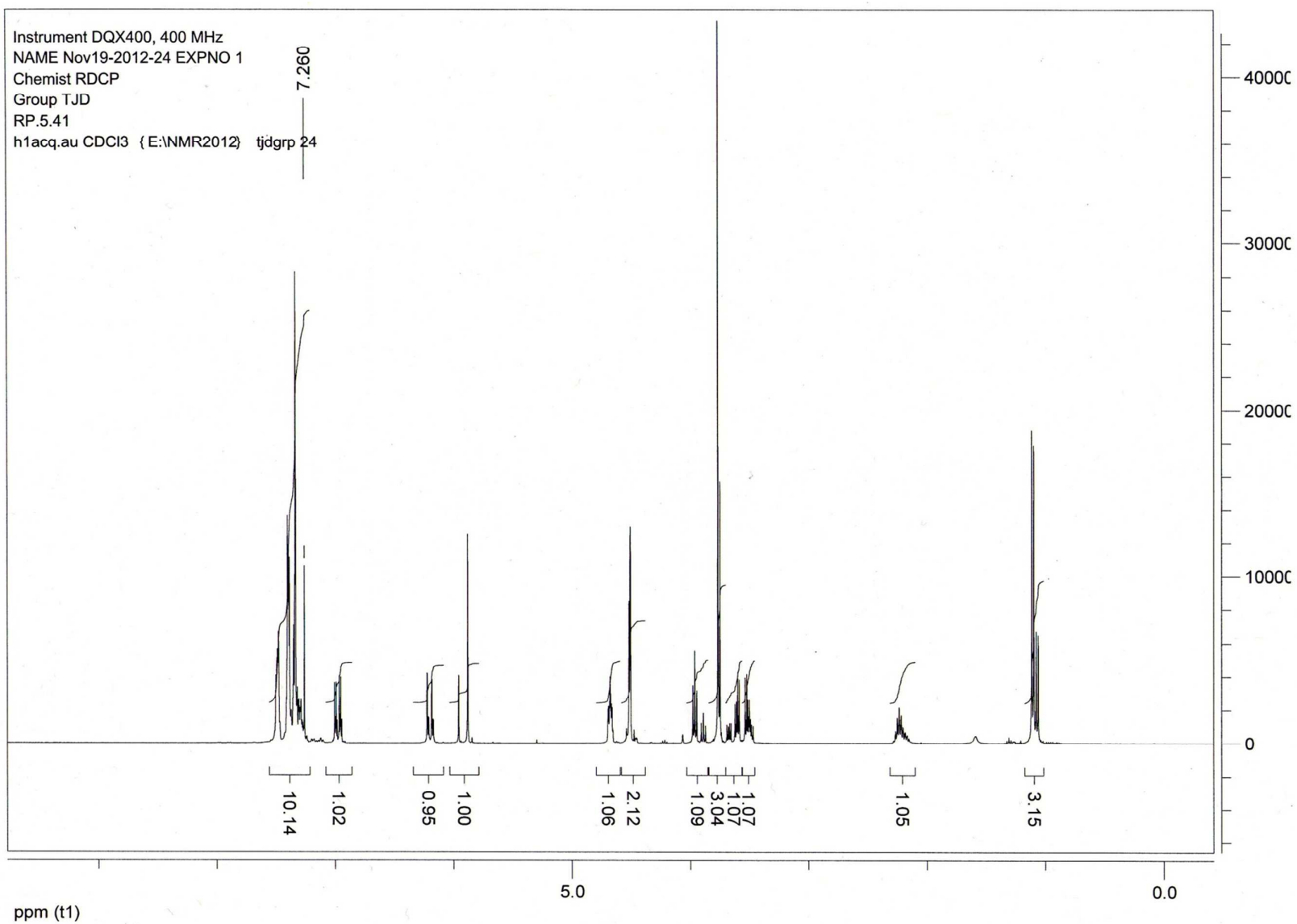


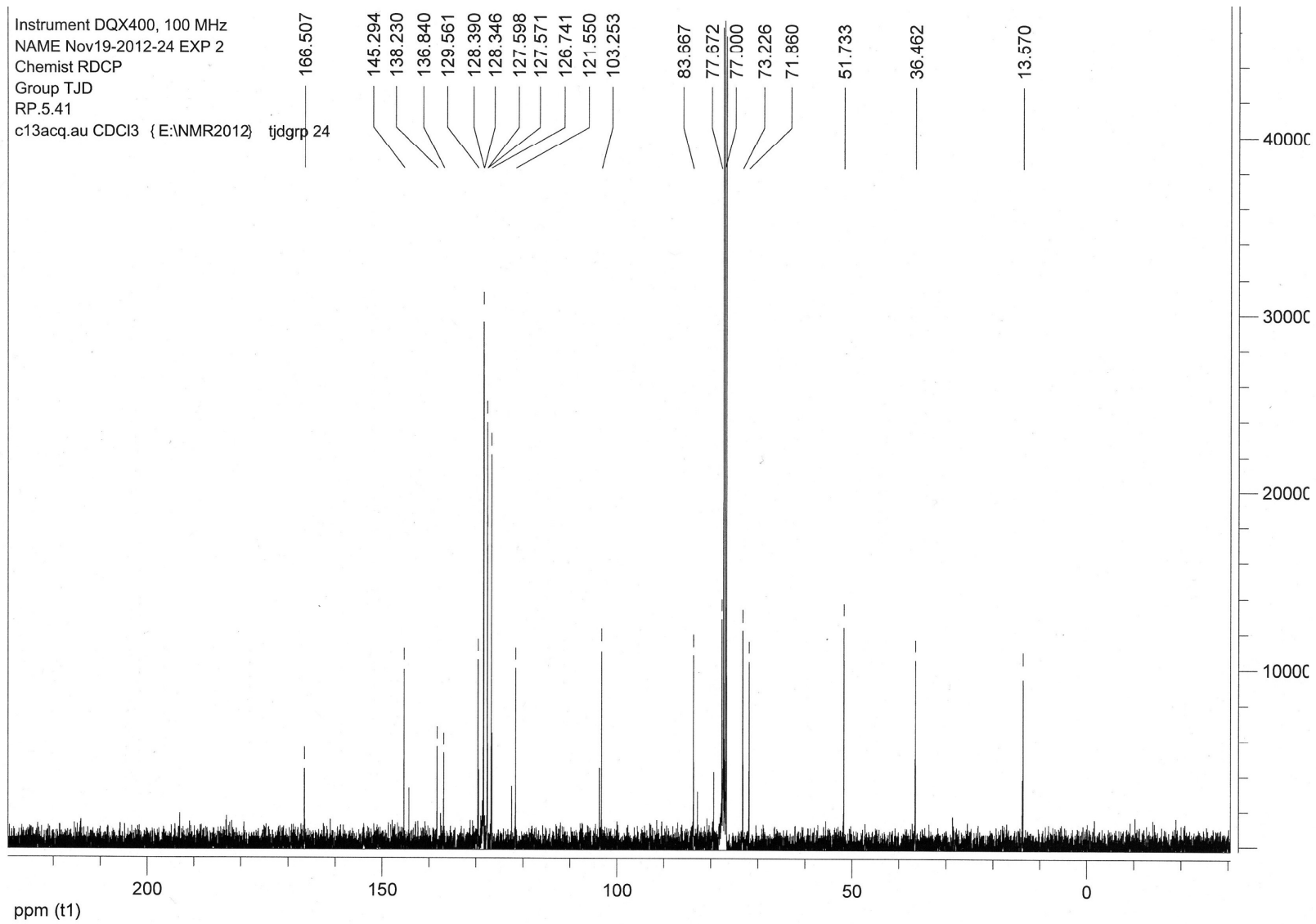
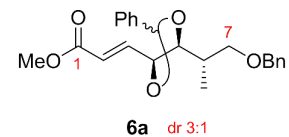


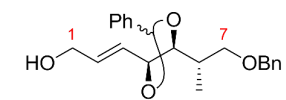




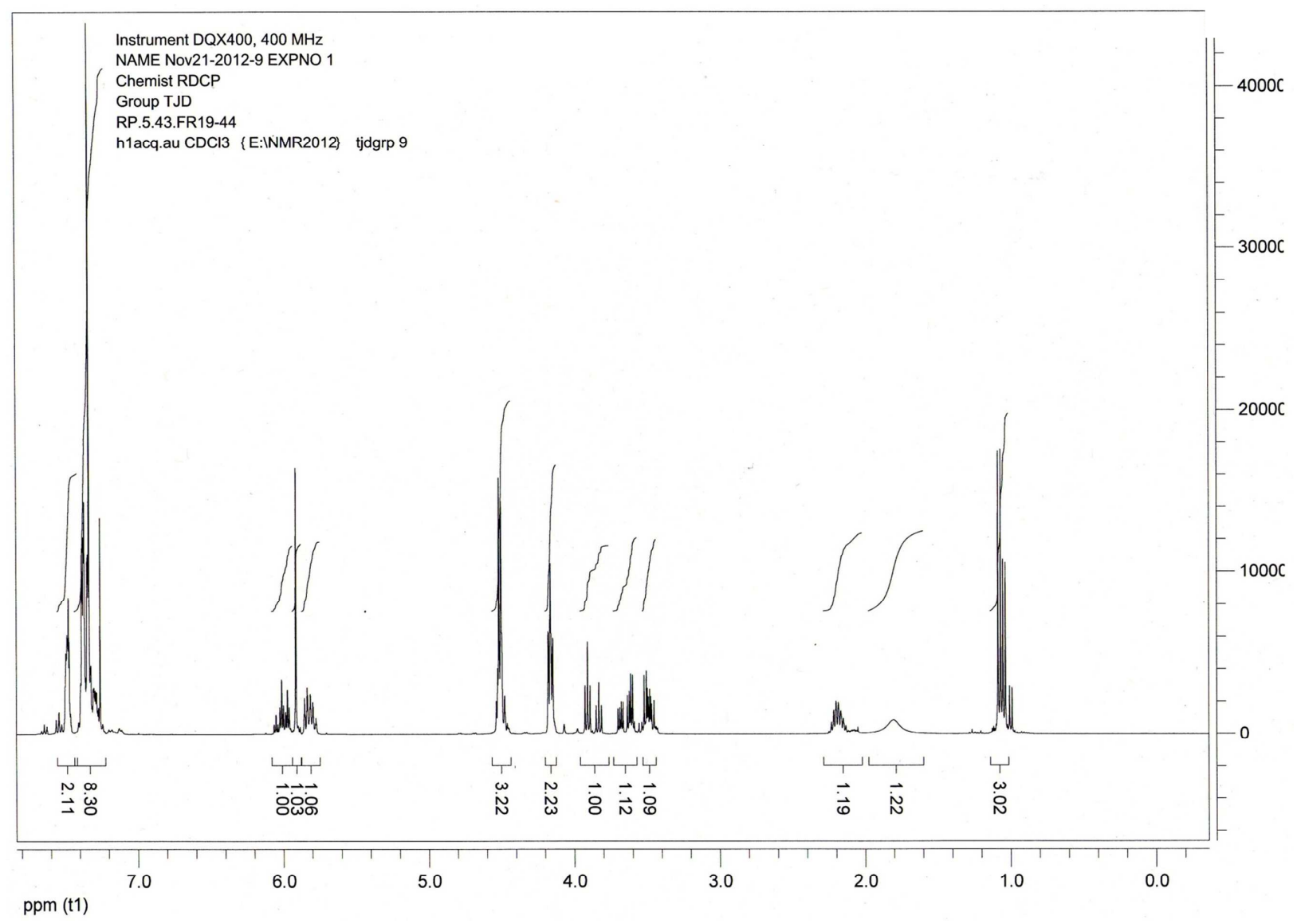
6a dr 3:1

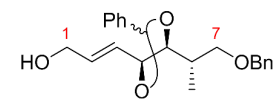




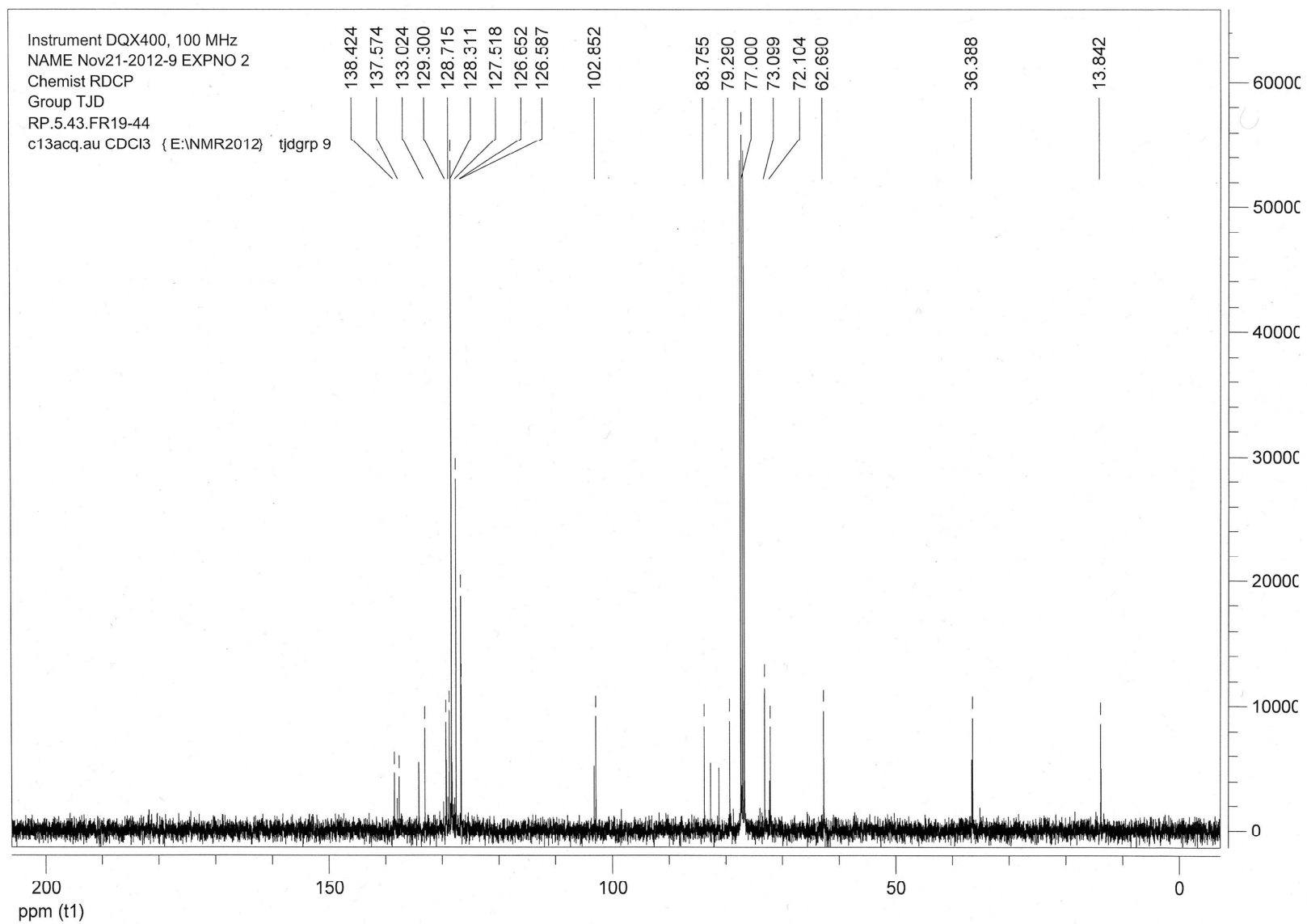


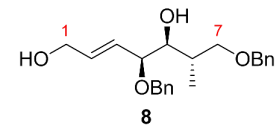
7 dr 3:1



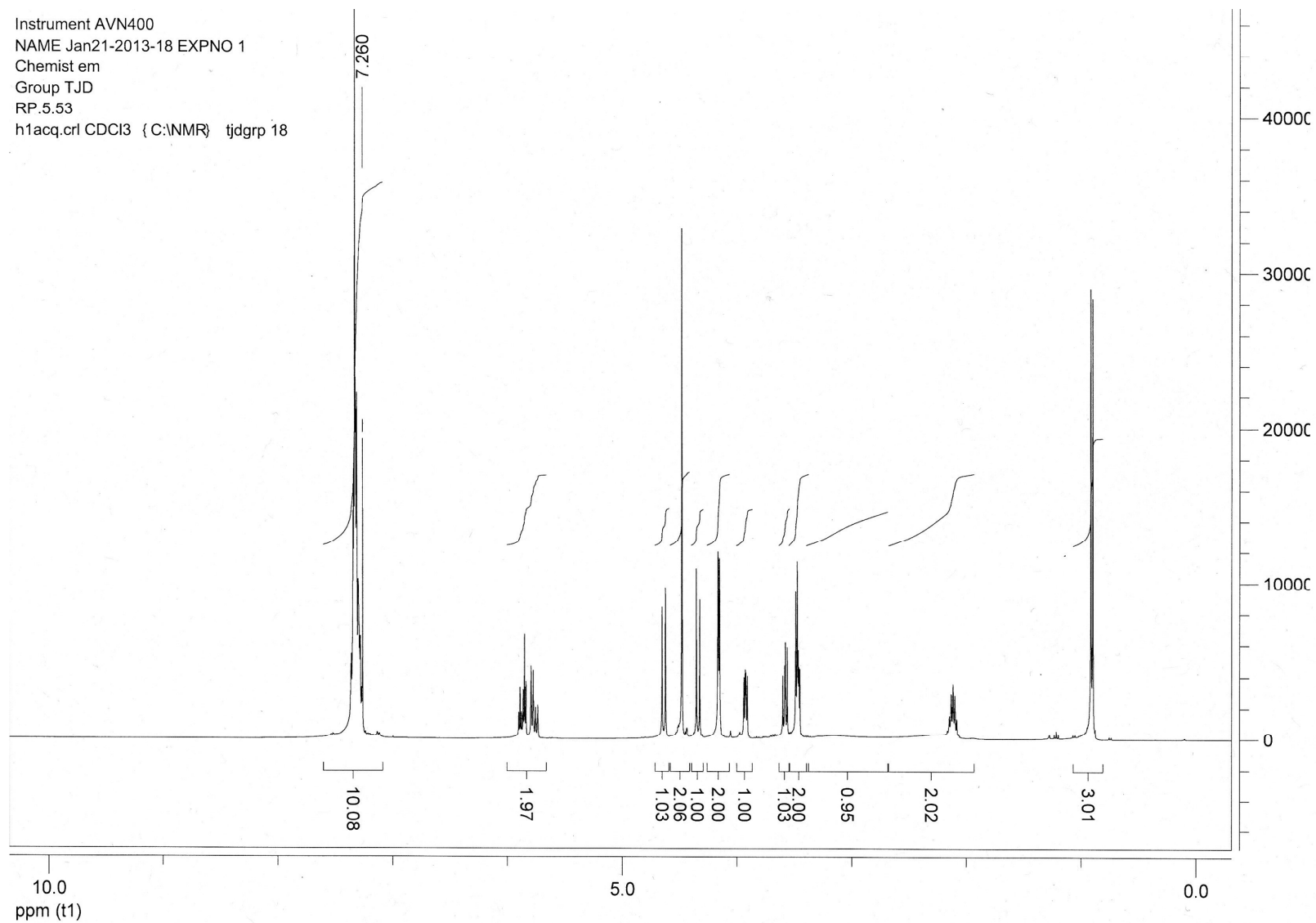


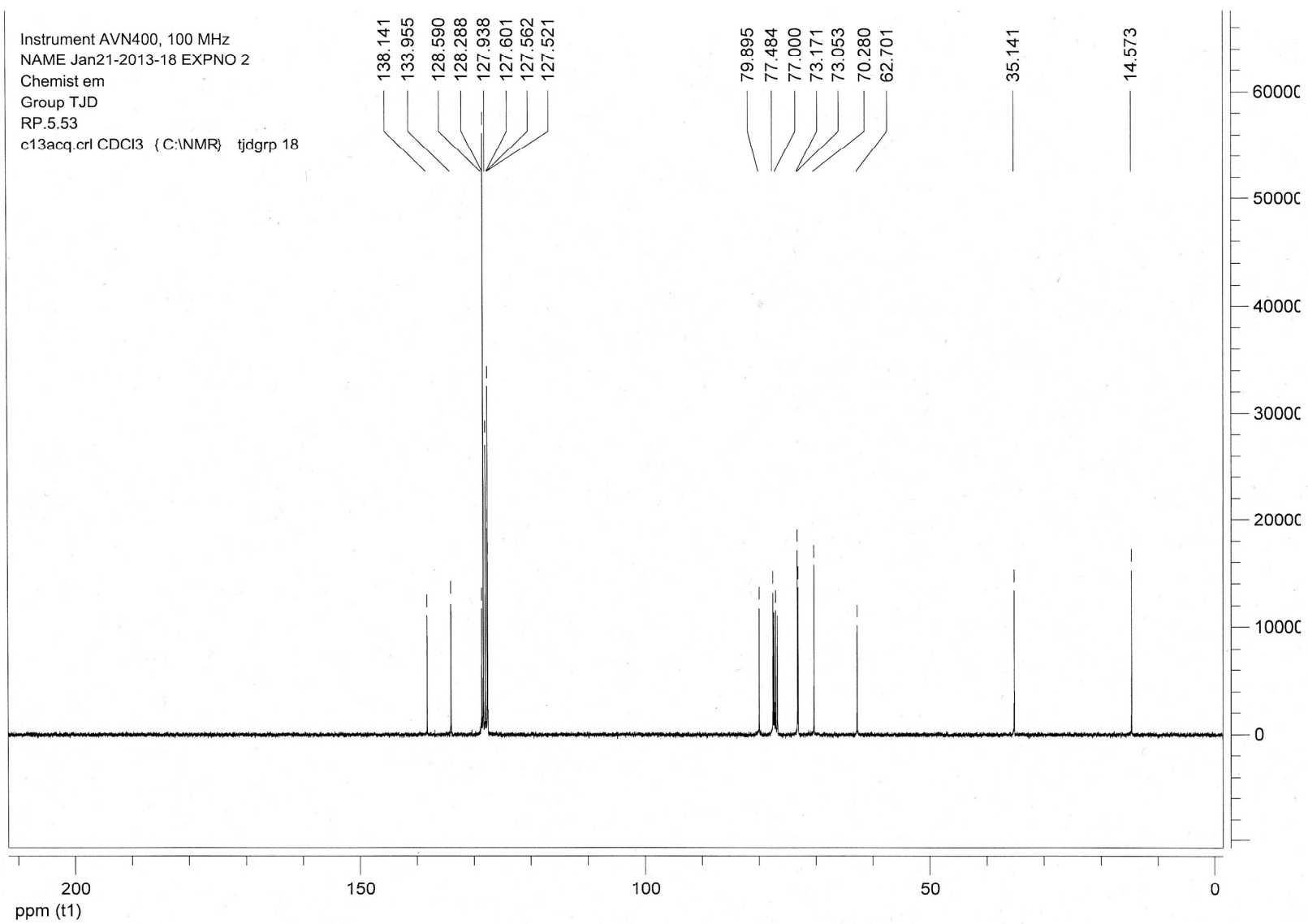
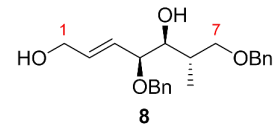
7 dr 3:1

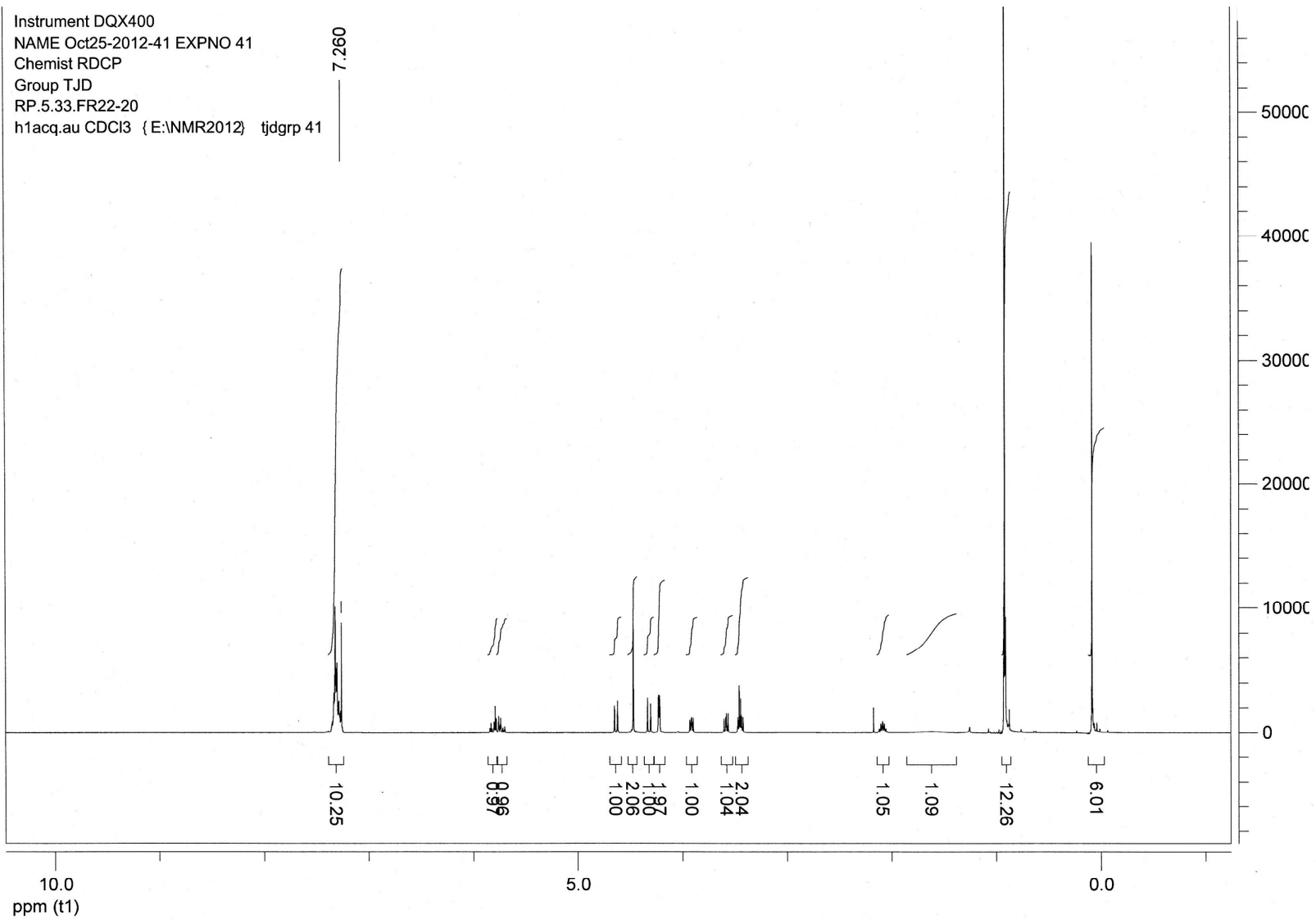
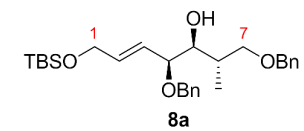


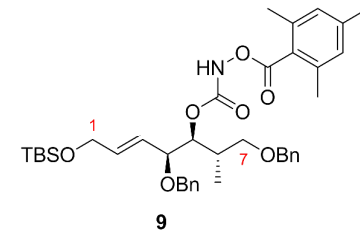


Instrument AVN400
 NAME Jan21-2013-18 EXPNO 1
 Chemist em
 Group TJD
 RP.5.53
 h1acq.crl CDCl3 {C:\NMR} tjdgrp 18

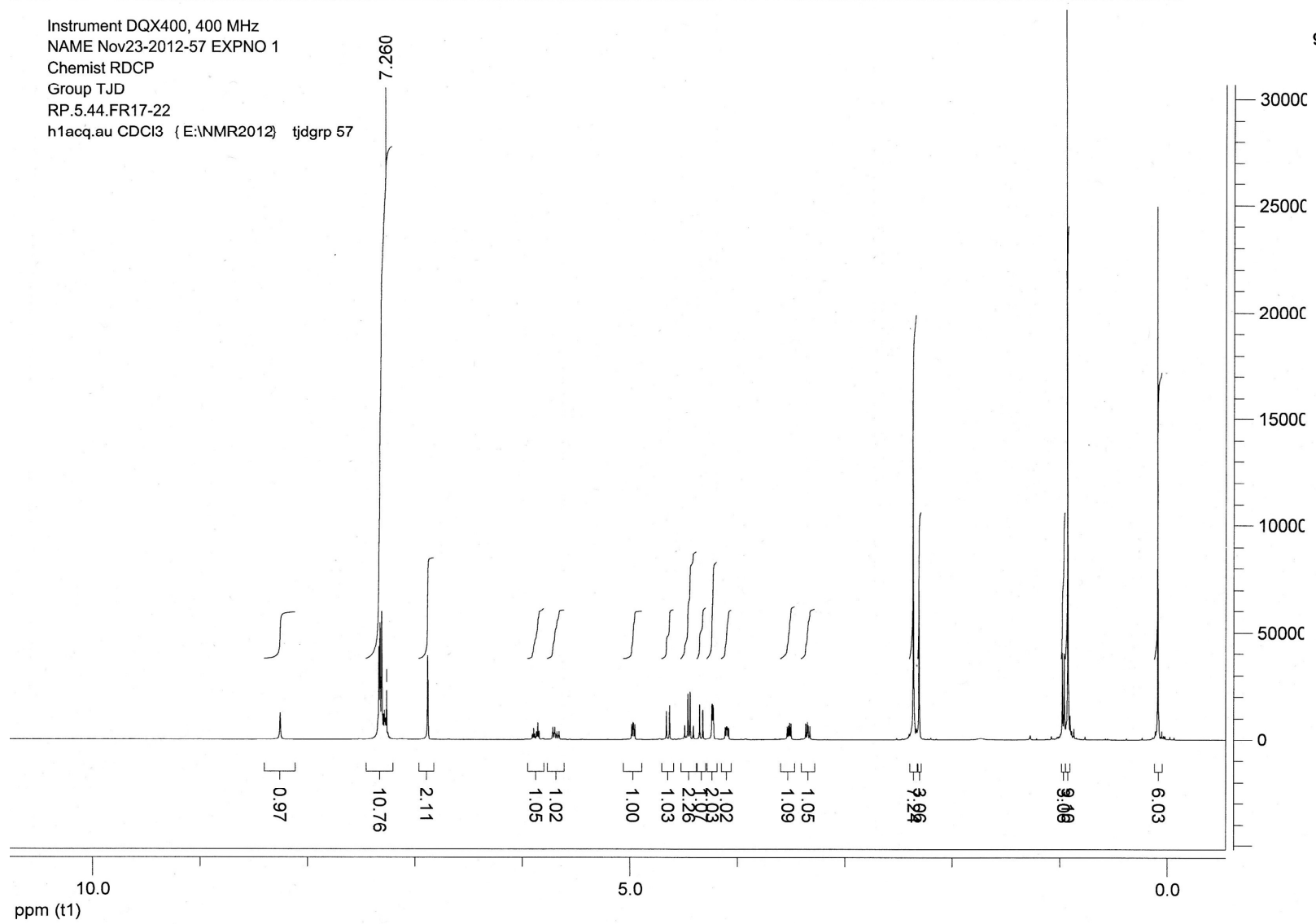


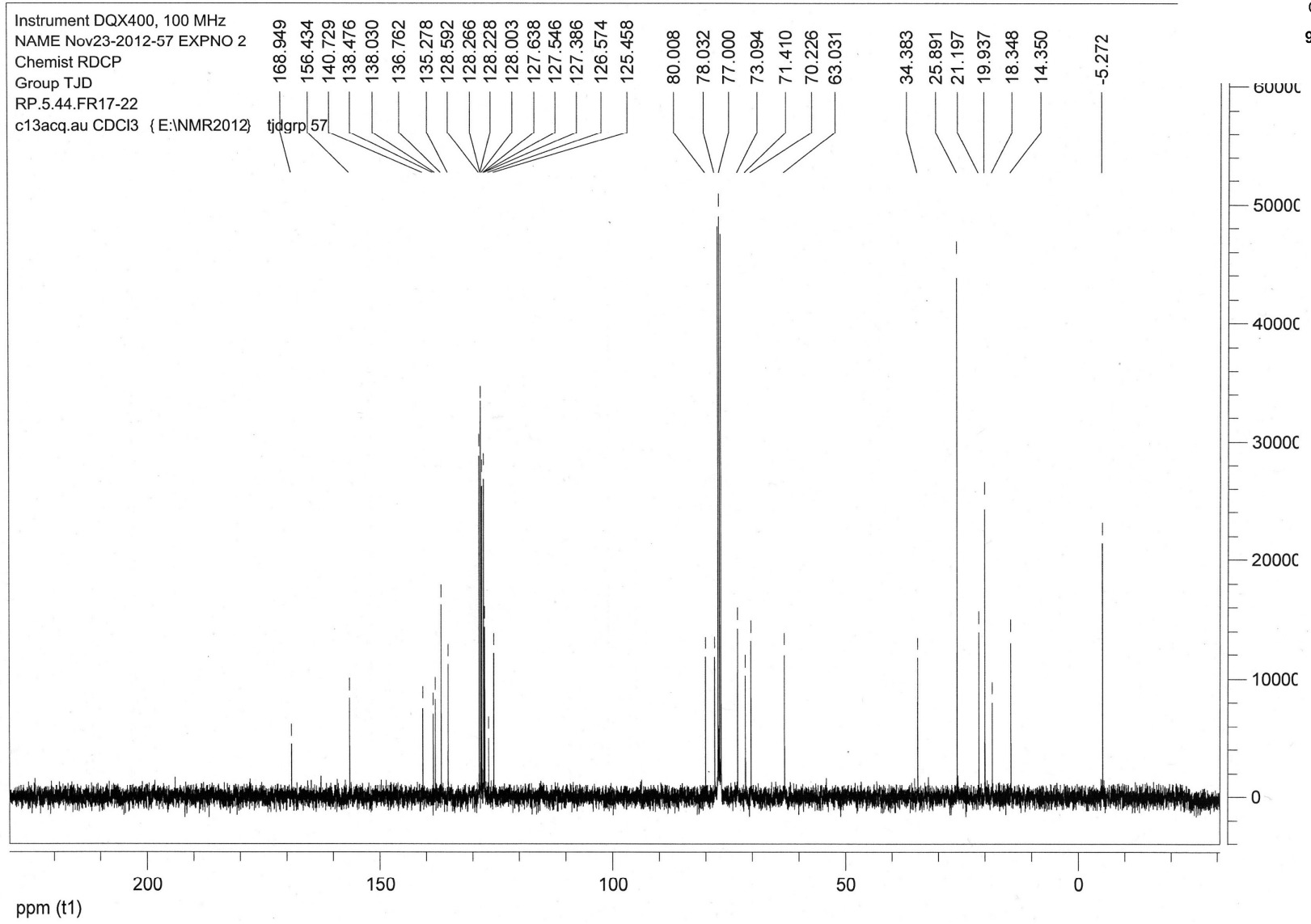
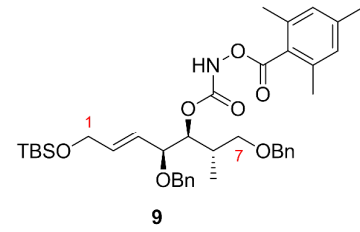


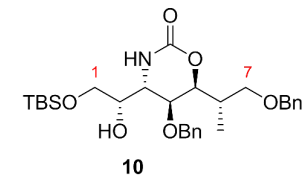




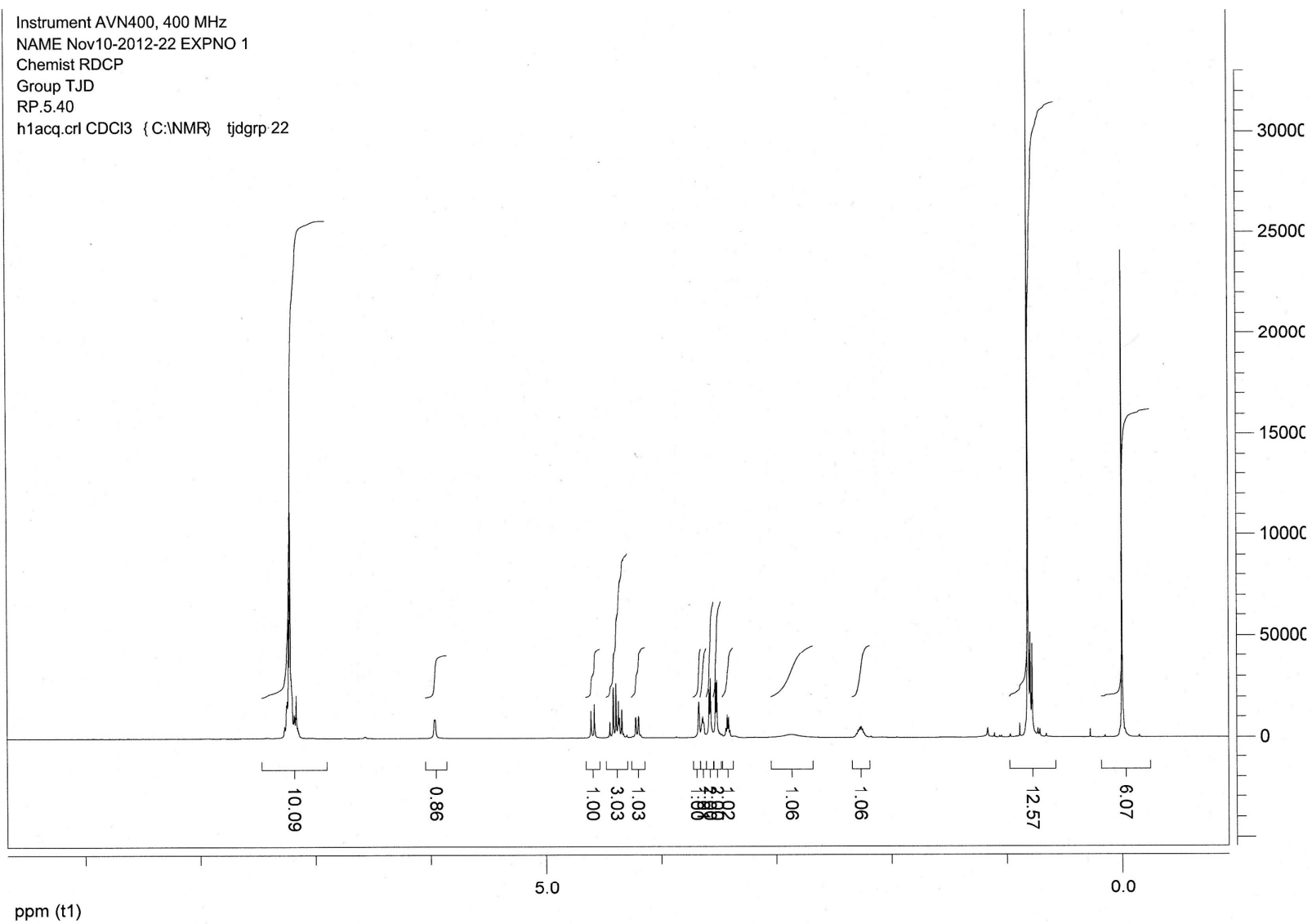
Instrument DQX400, 400 MHz
 NAME Nov23-2012-57 EXPNO 1
 Chemist RDCP
 Group TJD
 RP.5.44.FR17-22
 h1acq.au CDCI3 {E:\NMR2012} tjdgrp 57

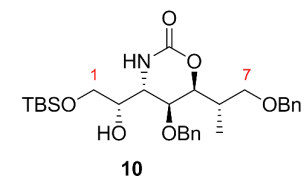




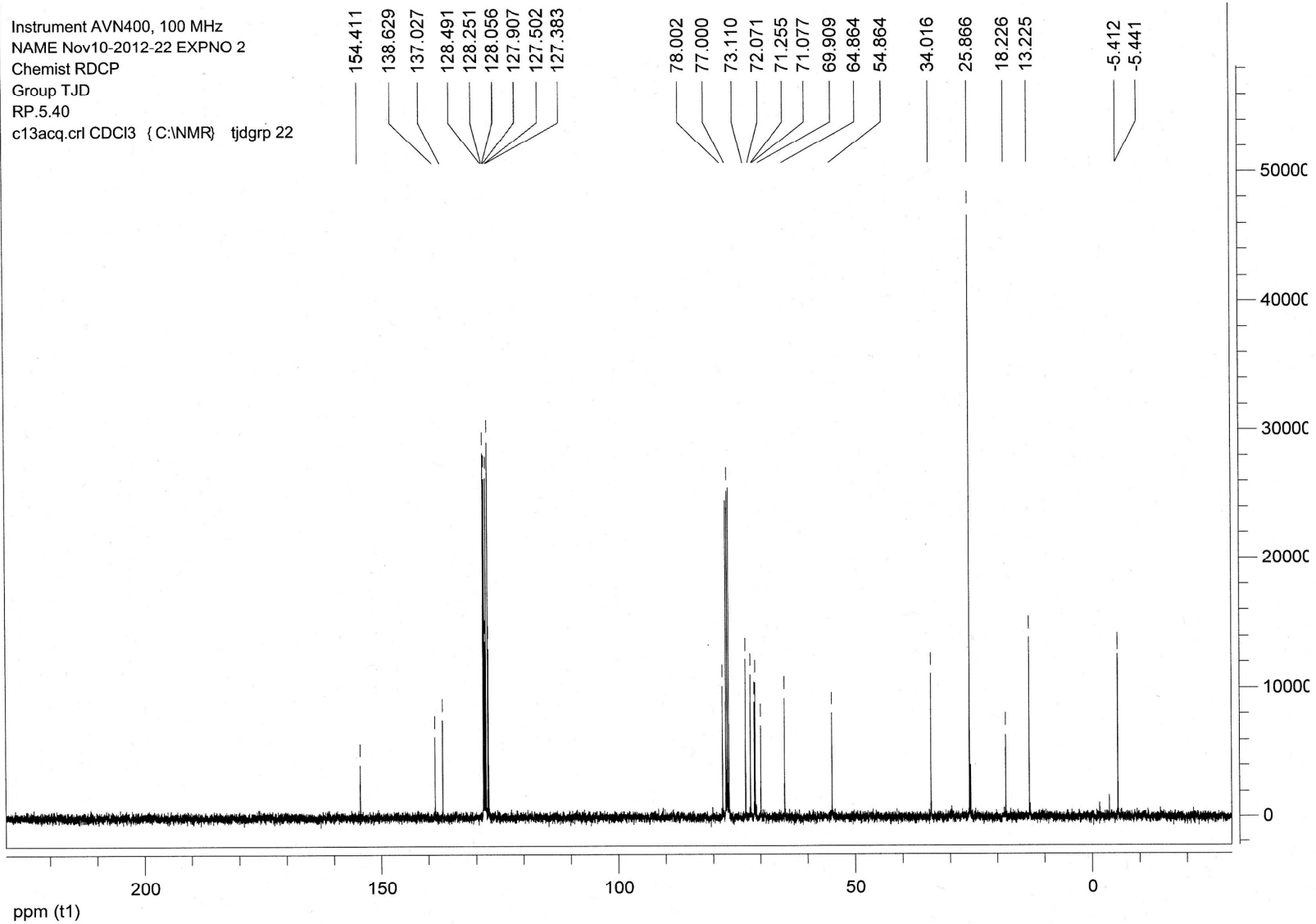


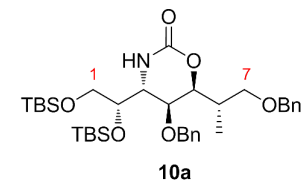
Instrument AVN400, 400 MHz
 NAME Nov10-2012-22 EXPNO 1
 Chemist RDCP
 Group TJD
 RP.5.40
 h1acq.crl CDCI3 { C:\NMR\ } tjgrp 22



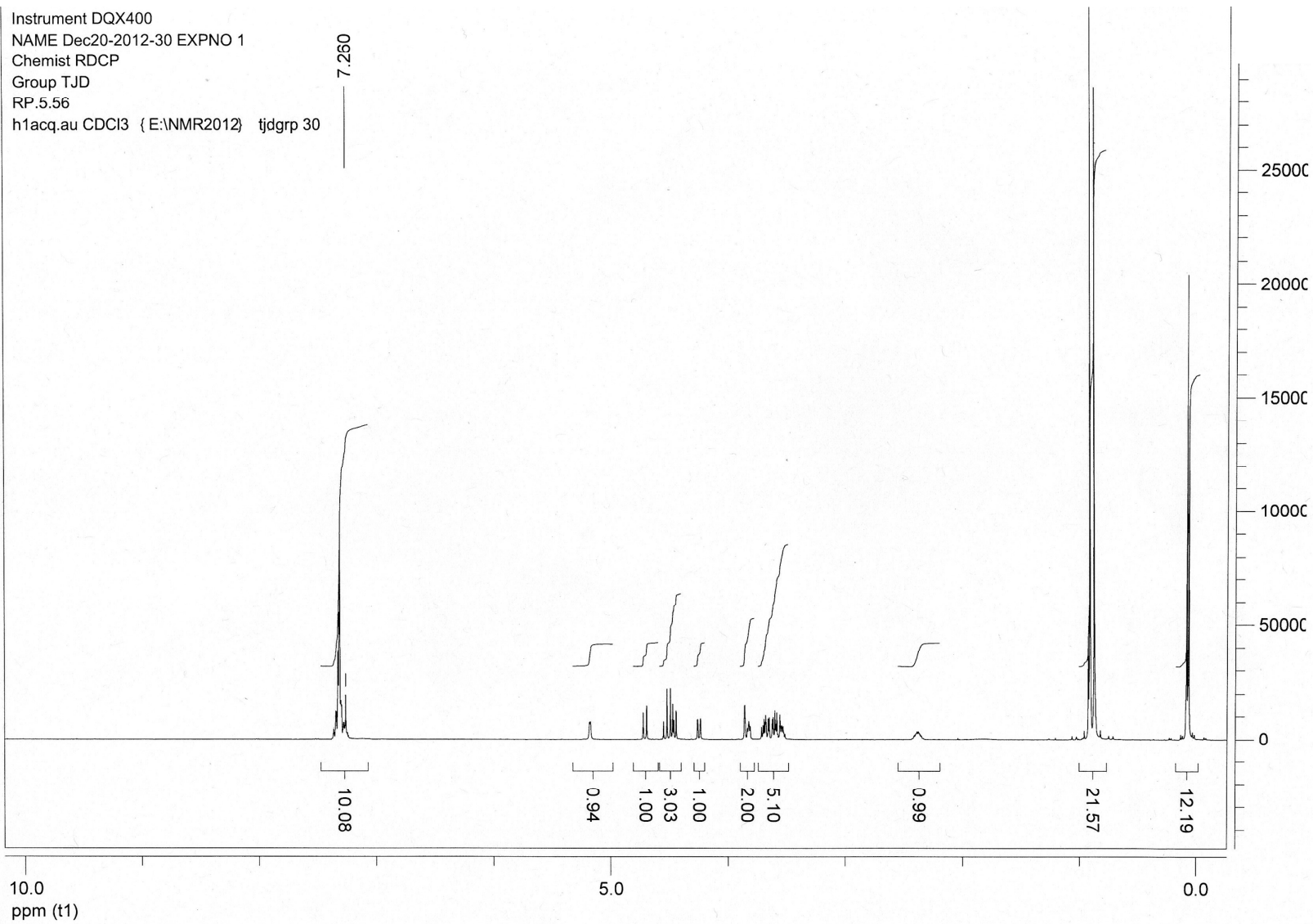


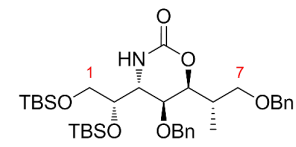
Instrument AVN400, 100 MHz
 NAME Nov10-2012-22 EXPNO 2
 Chemist RDCP
 Group TJD
 RP.5.40
 c13acq.crf CDCl3 {C:NMR} tjdgrp 22



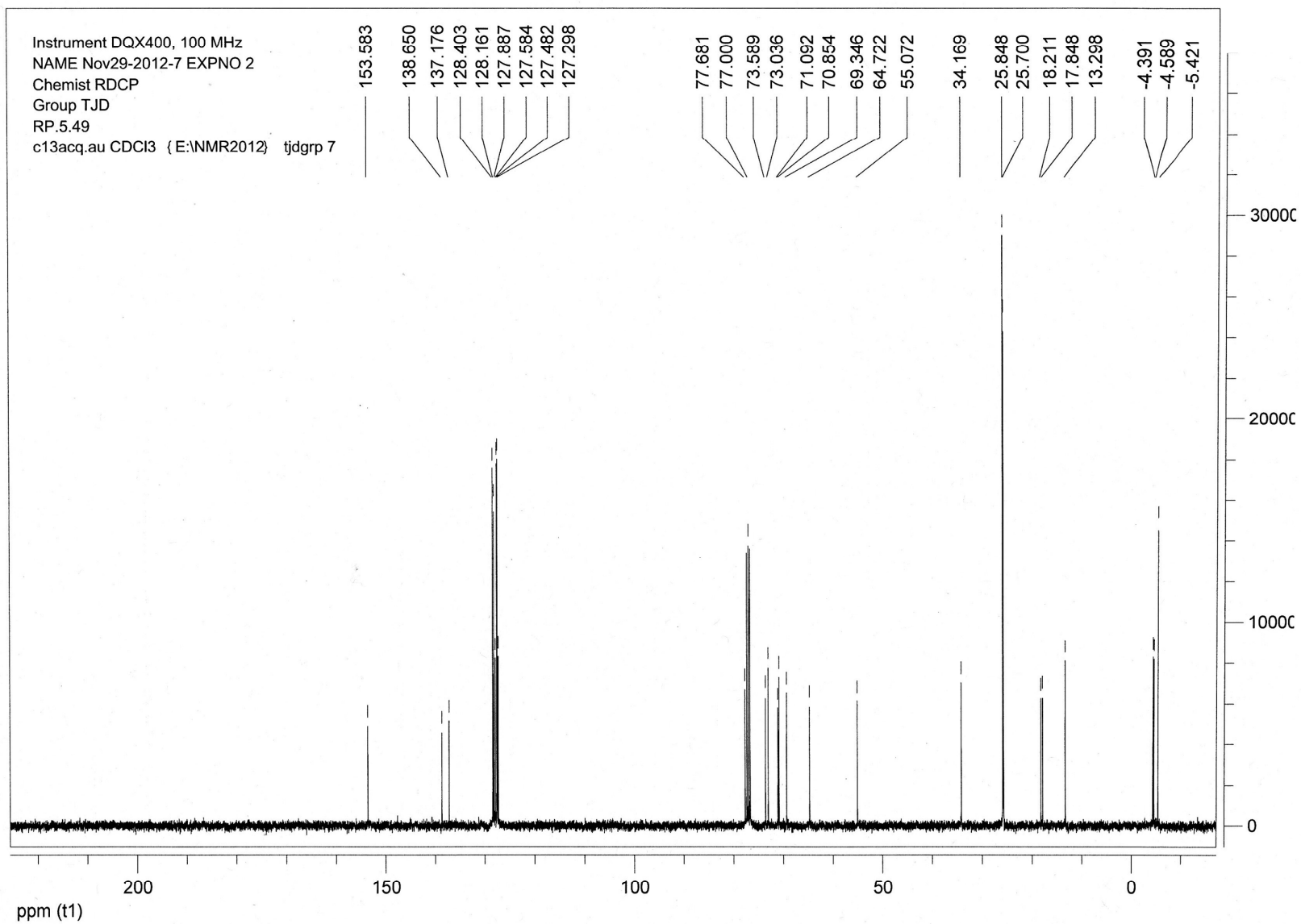


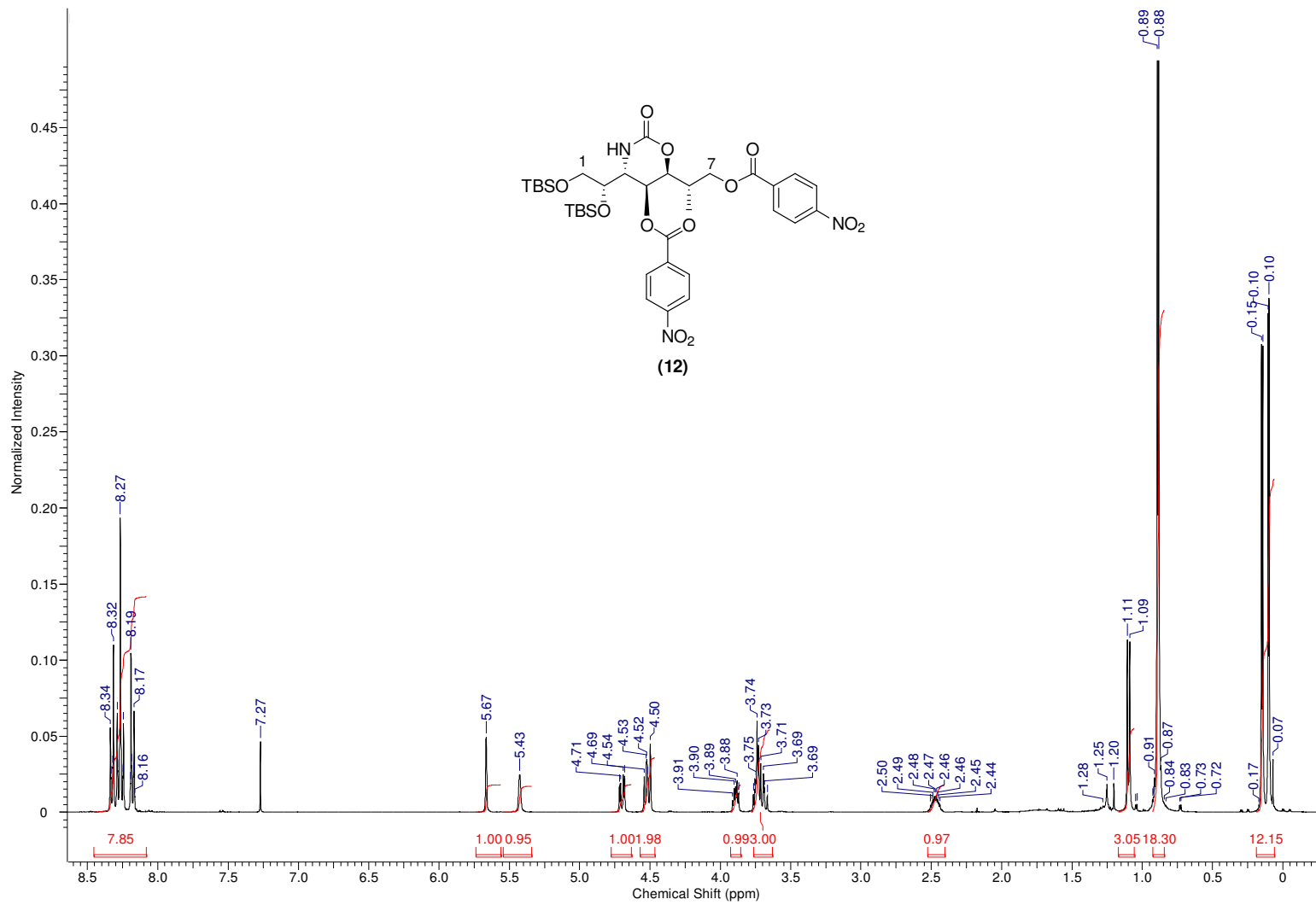
Instrument DQX400
 NAME Dec20-2012-30 EXPNO 1
 Chemist RDCP
 Group TJD
 RP.5.56
 h1acq.au CDCl3 {E:\NMR2012} tjdgrp 30

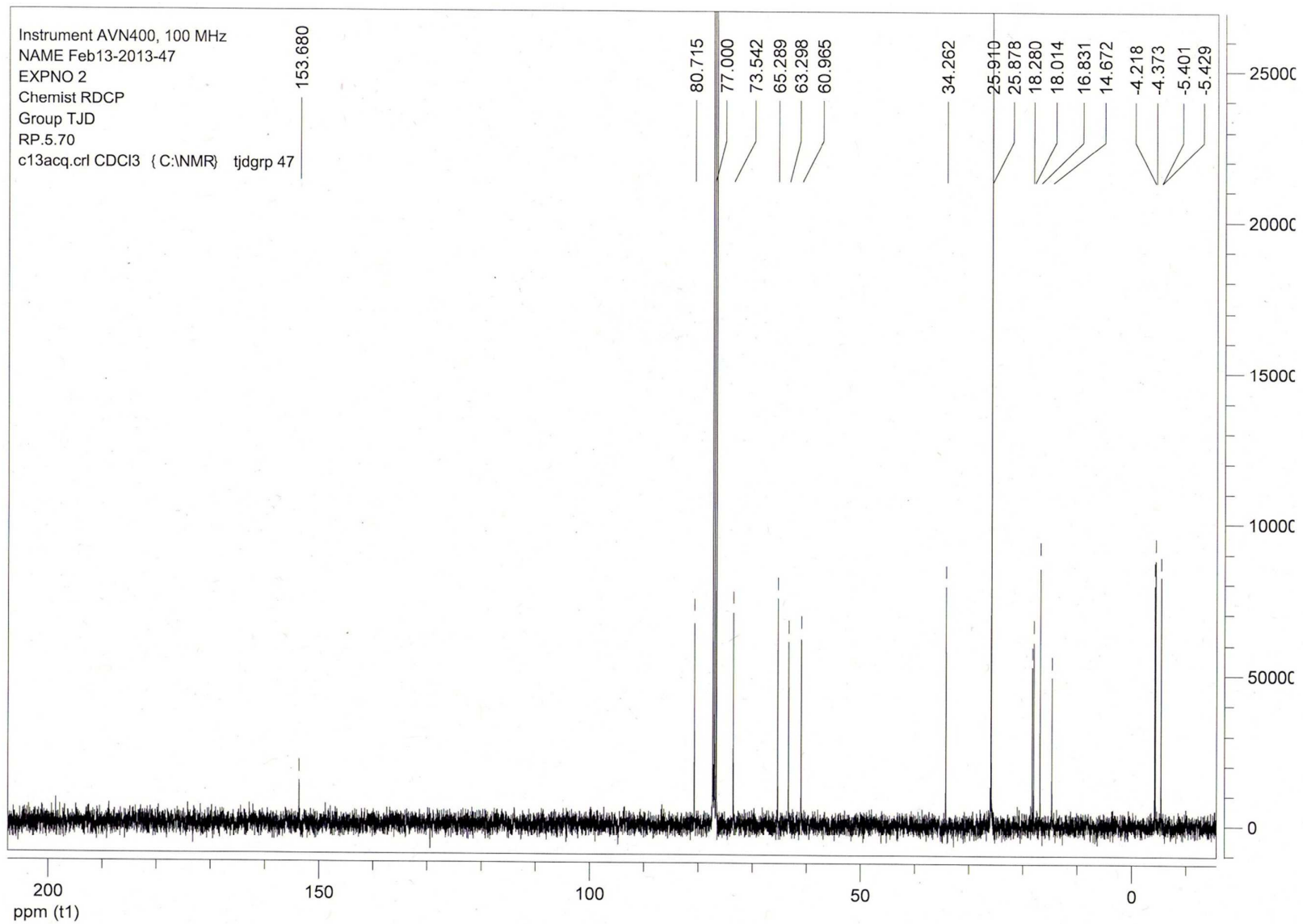
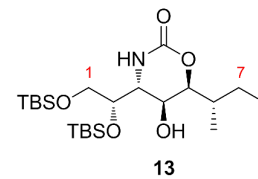




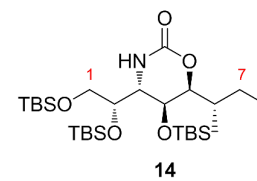
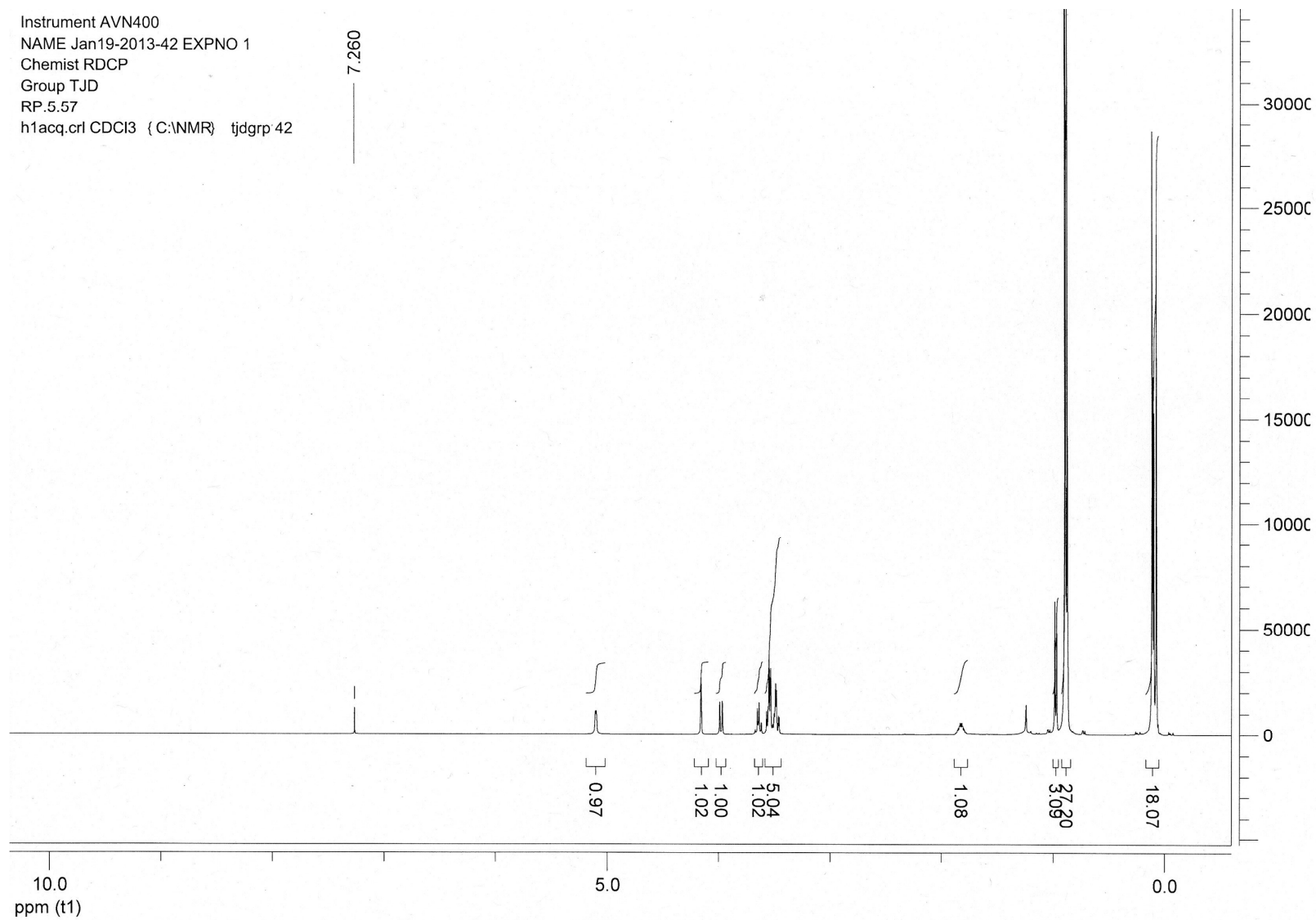
10a

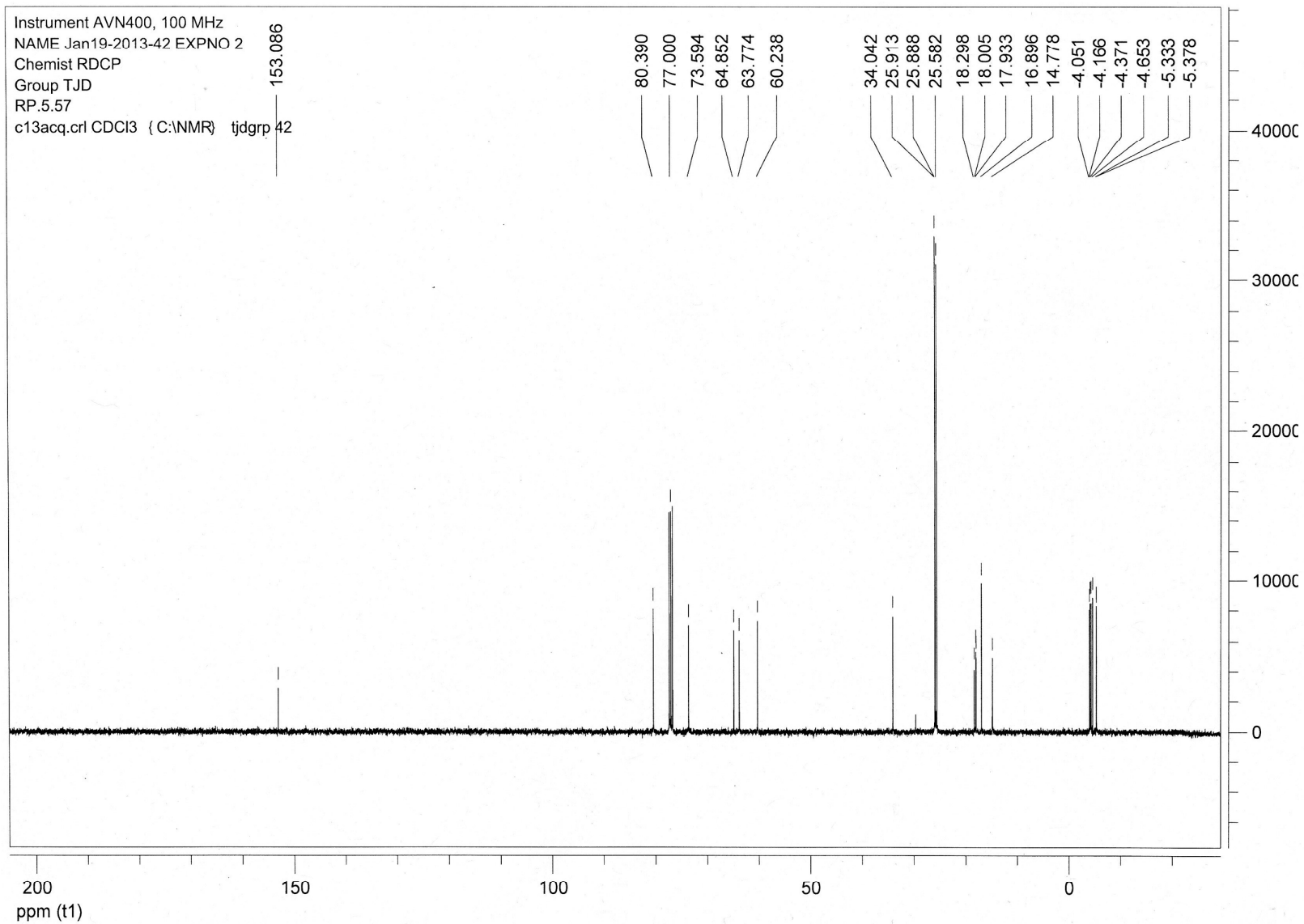
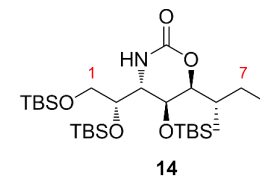


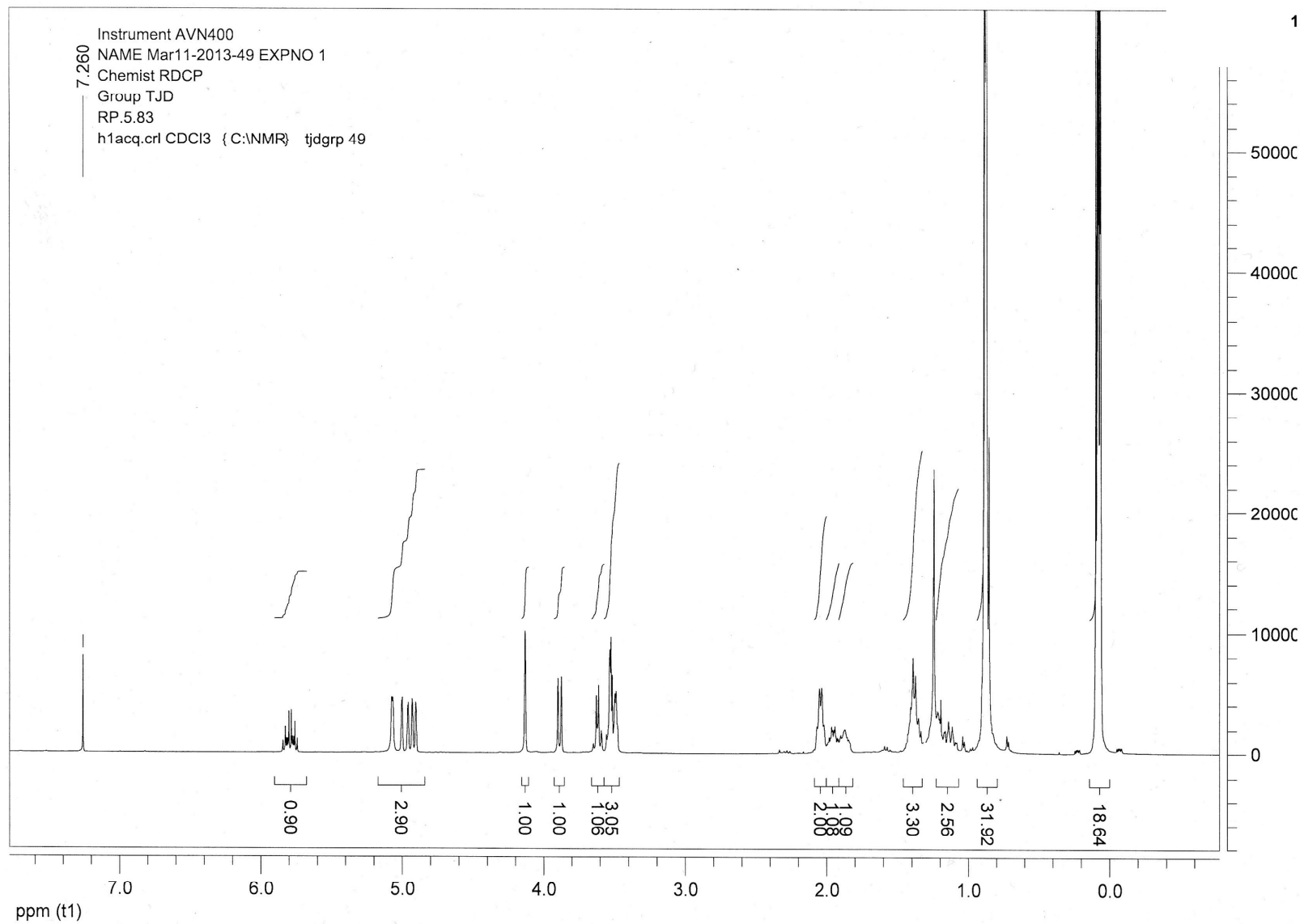
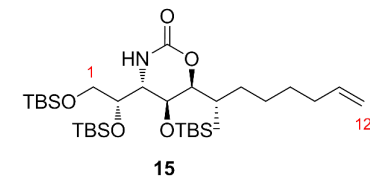


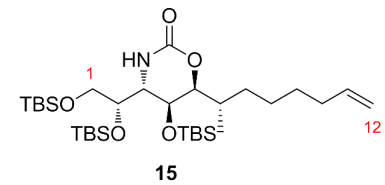


Instrument AVN400
NAME Jan19-2013-42 EXPNO 1
Chemist RDCP
Group TJD
RP.5.57
h1acq.crl CDCl3 {C:\NMR} tjdgrp 42

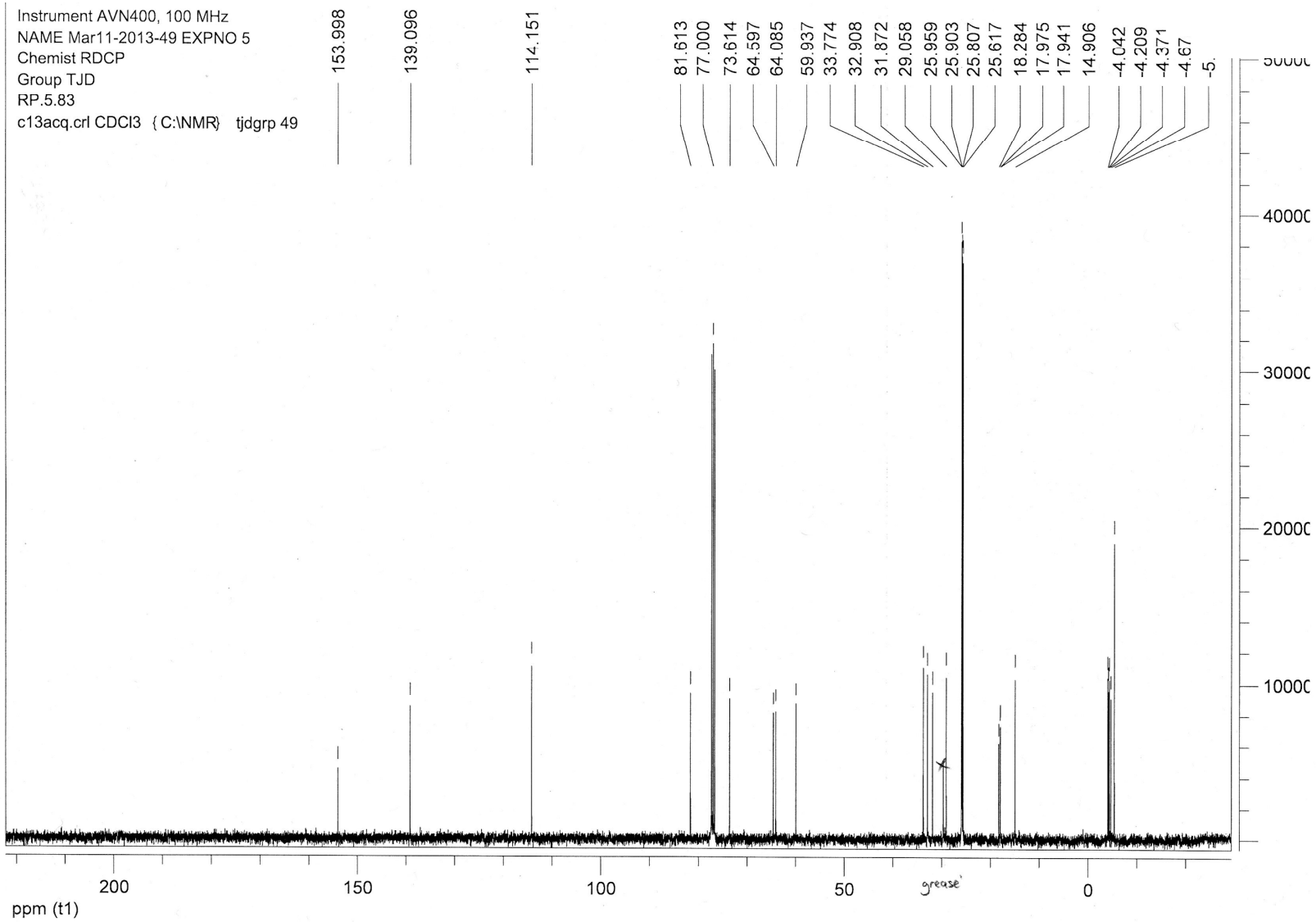


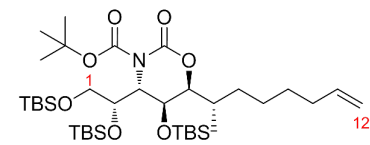




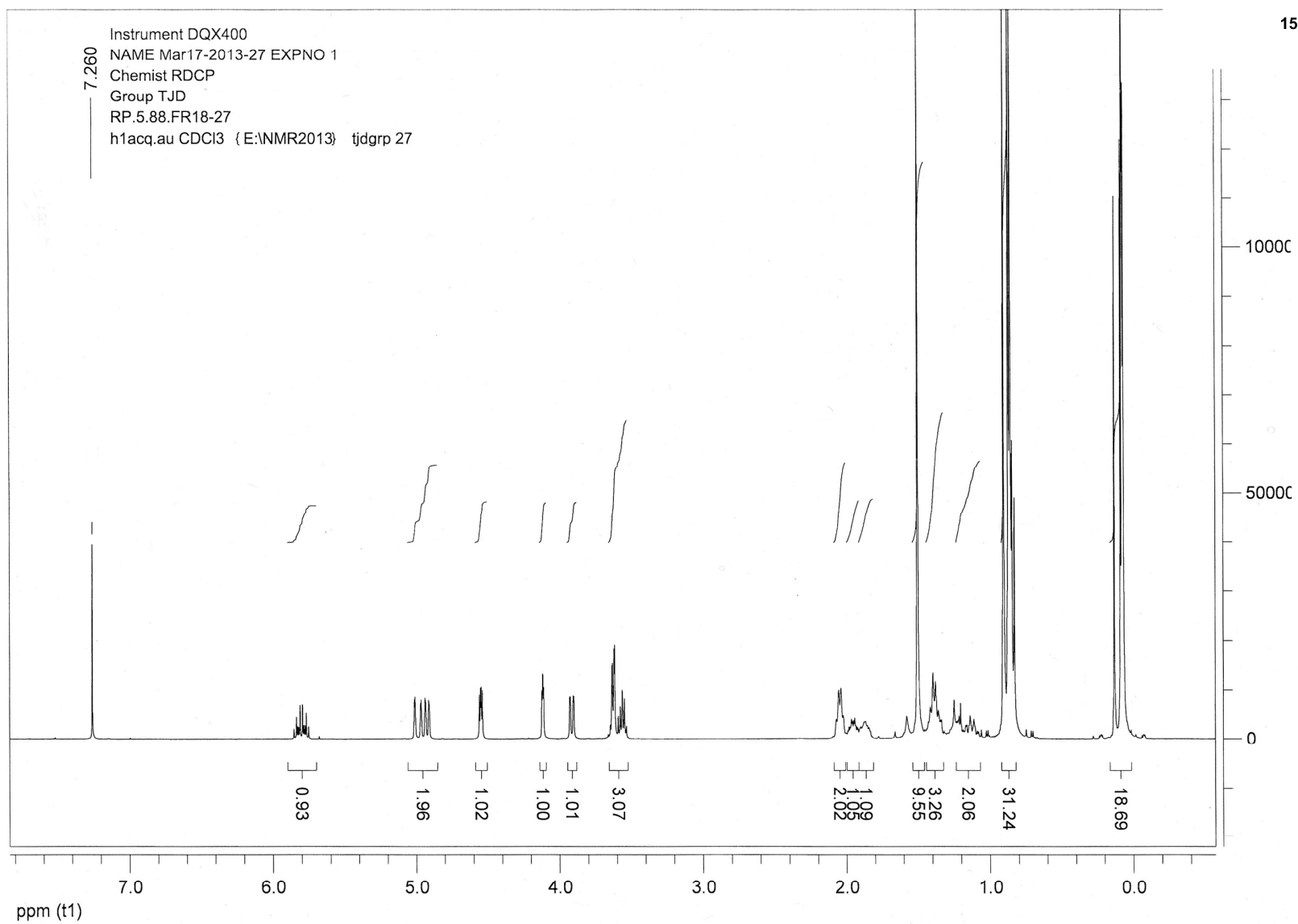


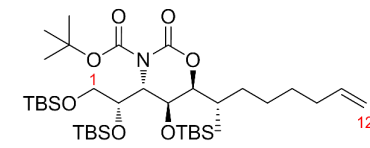
Instrument AVN400, 100 MHz
 NAME Mar11-2013-49 EXPNO 5
 Chemist RDCP
 Group TJD
 RP.5.83
 c13acq.crl CDCl3 {C:\NMR} tjdgrp 49





15a





15a

