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Convenient Syntheses of *trans*-Resveratrol 3-*O* and 4′-*O*-β-D-Glucuronides and a Study of their Aqueous Stability

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Supporting information:

1. Experimental procedures and characterisations of compounds described
2. Photocopy 1H and 13C NMR spectra for compounds described.
3. Photochemical isomerisation of diesters **13** and **16**.
4. Assignment of 1H and 13C NMRs of the E/Z mixture of compound **4**

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Supporting Information

1. Experimental procedures and characterisation of compounds described, viz. 4 (E/Z), 5, 6, 8, 9, 11, 12, 13, 14, 15, 16 and **17**

General Experimental Procedures

Organic extracts were finally washed with saturated brine and dried over anhydrous Na_2SO_4 prior to rotary evaporation at <30°C. Moisture sensitive reactions were carried out in anhydrous organic solvents (purchased from Sigma-Aldrich) under a N_2 or Ar atmosphere. Reactions were monitored by analytical thin-layer chromatography using Merck Kieselgel 60 F_{254} silica plates, and were viewed under UV or by staining with $KMnO_4$ or iodine. Preparative flash column chromatography was performed on either VWR Prolabo silica gel or Sigma-Aldrich silica gel (particle size 40-63 Å). Melting points were recorded using a Bibby-Sterlin Stuart SMP3 melting point apparatus and are uncorrected. Mass spectra were obtained in either electrospray mode (ES) with a Micromass LCT or chemical ionization (CI) mode with a Micromass Trio 1000 using ammonia. Elemental analyses were performed by Mrs. Jean Ellis, University of Liverpool. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker Avance-II 400 operating at 400.20 and 100.63 or a Bruker DPX 400 instrument operating at 400.053 and 100.59 MHz, respectively; chemical shifts are reported in ppm (δ) relative to Me_4Si or DSS. Coupling constants (*J*) are reported in Hz.

3, 5, 4′-Tri-*O*-acetyl-(*E*)-resveratrol 6-The title triester was prepared from *trans*-resveratrol **3** (2 g, 8.77 mmol) using a literature procedure[17] as a white solid in essentially quantitative yield, m. p. 103-104°C, pure enough to use directly. ^{1}H NMR: δ 7.51 (J = 8.6 Hz, 2H, d, H-2′,

Comment [YE]: washed finally?

Comment [IJ]: Steve Apter? He retired more than 10 years ago

H-6′), 7.05-7.15 (5H, m, H-2, H-6, H-3′, H-5′ + 1 olef. H), 6.99 (1H, d, *J* = 16.3 Hz, olef. H), 6.85 (1H, t, *J* = 2.0 Hz, H-4) and 2.33 (s, 9H, 3xCH_3CO); ^{13}C NMR: δ 169.4, 169.0, 151.3, 150.4, 139.5, 134.5, 129.7, 127.7, 127.2, 121.9, 116.9, 114.4, 21.2 and 21.1.

3, 5, 4′-Tri-*O*-isobutyryl-(*E*)-resveratrol 15-Trans-resveratrol **3** (0.57 g, 2.5 mmol) was stirred in a mixture of CH_2Cl_2 (15 mL), Et_3N (1.05 mL) and isobutyryl chloride (0.55 mL) at 0°C. After 1 h, further Et_3N (0.2 mL) and isobutyryl chloride (0.18 mL) were added, then the mixture was allowed to warm to 20°C and stirred for 16 h. The mixture was diluted with EtOAc (50 mL) and washed with 5% aq. citric acid solution (25 mL), then with water, and evaporated to give the product which readily crystallised on trituration with Et_2O, affording **15** (1.08 g, 99%) as a white solid, m.p. 78-79°C. Found: C, 71.0; H, 6.85. $C_{26}H_{30}O_6$ requires C, 71.2; H, 6.9%; ^{1}H NMR: δ 7.51 (2H, d, H-2′, H-6′), 7.07-7.12 (5H, m, H-2, H-6, H-3′, H-5′ + 1 olef. H), 7.00 (1H, d, *J* = 16.3 Hz, olef. H), 6.82 (1H, t, *J* = 2.0 Hz, H-4),2.83 (3H, m, 3xMe_2*CH*) and 1.35 (18 H, d, 3x*Me*$_2$CH); ^{13}C NMR: δ 175.5, 175.2, 151.5, 150.6, 139.5, 134.4, 129.6, 127.6, 127.2, 121.8, 116.7, 114.3, 34.2 and 18.9 (x2).

4′, 5-Di-O-acetyl-(*E*)-resveratrol 11-A solution of 3, 5, 4′-tri-O-acetyl-(*E*)-resveratrol **6** (0.302 g, 0.85 mmol, 1.0 equiv) in 1:1 THF/MeOH (3 mL) was cooled to 0 °C. Glacial acetic acid (0.050 mL, 0.85 mmol, 1.0 equiv) was added and a white precipitate formed. 1-Methylpiperazine (0.095 mL, 0.85 mmol, 1.0 equiv) was added and the reaction was allowed to warm to room temperature with stirring over 2 hours and monitored by TLC (7% EtOAc/DCM). The starting material gradually dissolved as the reaction mixture warmed: after a further 3.5 hours at 20°C the solvent was evaporated. The resulting yellow residue was dissolved in ethyl acetate (20 mL) and washed with water (2 x 25 mL). The combined aqueous layers were washed with EtOAc (2 x 20 mL) and the combined organic layers were

evaporated to give crude product, which was purified by column chromatography (5% EtOAc/DCM) to give the title diester **11** as a white solid (0.0967 g, 36.4%). Found: *m/z* (MNa^+, ES +ve mode) 313.1070; $C_{18}H_{17}O_5$ requires 313.1071; ^{1}H NMR: δ 7.47 (2H, d, J = 8.4 Hz, H-2′, H-6′), 7.08 (2H, d, J = 8.4 Hz, H-3′ + H-5′), 7.00 (1H, d, J = 16.3 Hz,) and 6.90 (1H, d, J = 16.3 Hz, olefinic Hs), 6.81 (1H, s, H-2), 6.78 (1H, s, H-6), 6.50 (1H, d, J = 2.2 Hz, H-4), 5.72 (1H, br s, OH), 2.33 (3H, s,) and 2.32 (3H, s, 2xCH_3CO); ^{13}C NMR: δ 169.7, 169.6, 156.7, 151.8, 150.2, 139.7, 134.7, 129.0, 127.8, 127.6, 121.9, 111.9, 111.1, 108.5, 21.20 and 21.2.

4′, 5-Di-O-isobutyryl-(E)-resveratrol 16-This was obtained from **15** in a similar manner to **11** as a white solid after chromatography, ca. 40% on a 0.5 mmolar scale, m. p. 73-74°C. Found: C, 71.9; H, 6.5; m/z (MNa^+, ES +ve mode), 391.1520; $C_{22}H_{24}O_5$ requires C, 71.7; H, 6.6%; $C_{22}H_{24}O_5$.Na requires m/z, 391.1521; ^{1}H NMR: δ 7.46 (2H, d, J = 8 Hz, H-2′, H-6′), 7.08 (2H, d, J = 8.4 Hz, H-3′ + H-5′), 6.99 (1H, d, J = 16 Hz) and 6.89 (1H, d, J = 16Hz, olefinic Hs), 6.79 (1H, br s, H-2), 6.74 (1H, br s, H-6), 6.49 (1H, d, J = 1 Hz, H-4), 5.56 (1H, br s, OH), 2.84 (2H, m, 2xMe_2*CH*) and 1.35 (12H, d, J = 6.7 Hz, 2x*Me*$_2$CH); ^{13}C NMR: δ 175.9, 175.8, 156.7, 151.9, 150.4, 139.6, 134.6, 128.8, 127.7, 127.5, 121.8, 111.8, 111.0, 108.4, 34.2 and 18.9; the isopropyl signals were not split. The minor product from the above, sc. the 3,5-diester corresponding to **13**, was also isolated by chromatography, Found: m/z, 391.1518 (MNa^+); $C_{22}H_{24}O_5$.Na requires m/z, 391.1521; ^{1}H NMR ($(CD_3)_2CO$): δ 7.49 (2H, d, J = 8Hz, H-2′, H-6′), 7.21 (2H, br s, 2-H, 6-H), 7.24 (1H, d, J = 16 Hz) and 7.06 (1H, d, J = 16Hz, olefinic Hs), 6.87 (2H, d, J = 8Hz, H-3′, H-5′), 6.81 (1H, br s, 4-H), 2.85 (2H, m, 2xMe_2*CH*) and 1.30 (12H, d, J = 7 Hz, 2x*Me*$_2$CH); ^{13}C NMR ($(CD_3)_2CO$): δ 174.6, 157.7, 151.9, 140.3, 130.4, 128.5, 128.2, 123.9, 116.5, 115.5, 114.0, 33.8 and 14.7.

3, 5-Di-*O*-acetyl-(*E*)-resveratrol 13-3, 5, 4′-Tri-*O*-acetyl-(*E*)-resveratrol **6** (0.200 g, 0.56 mmol) was taken up in 1-BuOH (1 mL) and TBME (15 mL) in a round-bottomed flask. Immobilised enzyme CAL-B (0.200 g) was added and the resulting reaction mixture was stirred at 500 rpm and 45 °C for 50 min. The enzyme was then filtered off and the filtrate was concentrated to dryness under vacuum to give the crude diacetate as an off-white solid. The crude was purified by column chromatography (5% EtOAc/DCM) to give the title diester **13** as a white solid (0.130 g, 75%), m. p. 137-139°C. Found: *m/z* $(M+H)^+$ = 313.1072; $C_{18}H_{17}O_5$ requires m/z, 313.1071; ^{1}H NMR: δ 7.36 (2H, d, *J* = 8.6 Hz, H-2′, H-6′), 7.10 (2H, d, *J* = 2.1 Hz, H-2, H-6), 7.00 (1H, d, *J* = 16.2 Hz) and 6.85 (1H, d, *J* = 16.1 Hz, olefinic Hs), 6.83 – 6.78 (3H, m, H-3′, H-5′ and H-4), 5.23 (1H, br s, OH) and 2.33 (6H, s, 2xCH_3CO); ^{13}C NMR δ 169.3, 156.0, 151.3, 140.2, 130.3, 129.3, 128.2, 124.6, 116.7, 115.7, 113.8, 21.2.

Methyl 2,3,4-tri-O-acetyl-α,β-D-glucopyranuronate 8- Methyl 1,2,3,4-tetra-O-acetyl-β-D-glucopyranuronate **7** (2.496 g, 6.63 mmol, 1.0 equiv) was dissolved in anhydrous THF (50 mL). 1-Methylpiperazine (2.21 mL, 19.93 mmol, 3.0 equiv) and glacial acetic acid (1.15 mL, 19.93 mmol, 3.0 equiv) were added to the flask and the mixture was stirred overnight at 20°C. After 18 hr, TLC analysis (50% EtOAc/hexane) showed a single more polar spot. Water (75 mL) was added to the reaction mixture and the precipitate dissolved to give an orange solution. The mixture was washed with EtOAc (3 x 50 mL) and the combined organic layers were washed with aqueous citric acid (7%, 2 x 75 mL), water (75 mL), and brine (75 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness to give 2,3,4-tri-O-acetyl-D-glucuronide methyl ester **8** (4:1 α/β) as a pale yellow oil (2.076 g, 94%), sufficiently pure for immediate progression, which slowly solidified. Found: m/z, 358.0825 $(MNaH)^+$; $C_{13}H_{19}O_{10}Na$ requires m/z, 358.0876; ^{1}H NMR: δ 5.66 – 5.57 (m, 1H, H-1), 5.21 (t, *J* = 9.4 Hz, 1H, H-3), 4.94 (dd, *J* = 10.2, 3.9 Hz, 1H, H-2), 4.61 (d, *J* = 10.1 Hz, 1H, H-5),

3.77 (s, 3H, CH_3O), 3.56 (br s, 1H, OH), 2.10 (s, 3H, CH_3CO), 2.06 (s, 6H, 2xCH_3CO). ^{13}C NMR (101 MHz) δ 170.1, 170.0, 169.6, 169.5, 168.3, 95.6, 90.3, 73.0, 72.7, 71.4, 70.7, 69.5, 69.4, 69.0, 68.1, 53.0, 52.9, 20.7, 20.6, 20.5, 20.5.

Methyl 2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranuronate 9- The hemiacetal **8** (2.08 g, 6.21 mmol) and trichloroacetonitrile (5.63 mL, 56.10 mmol) were dissolved in anhydrous CH_2Cl_2 (35.0 mL). Anhydrous potassium carbonate (6.293 g, 44.88 mmol) was added and the reaction mixture was stirred at room temperature for 18.5 h, when TLC (1:1 ethyl acetate: hexane) showed complete reaction. The reaction mixture was eluted through a pad of silica with Et_2O, then 1:1 ethyl acetate: hexane. Appropriate fractions were concentrated to dryness to give a yellow oil which was dissolved in the minimum amount of EtOAc and recrystallised by addition of hexane to give the title imidate **9**[31] (1.53g, 52%), m. p. 108-110°C as colourless crystals which were stored at -18 °C. Found: *m/z* $(M+Na)^+$, 499.9890; $C_{15}H_{18}Cl_3NO_{10}Na$ requires m/z, 499.9894; ^1H NMR: *δ* 8.75 (1H, s, NH), 6.65 (1H, d, *J* = 3.6 Hz, H-1), 5.64 (1H, t, *J* = 9.9 Hz, H-4), 5.29 (1H, t, *J* = 9.9 Hz, H-3), 5.16 (1H, dd, *J* = 10.2, 3.6 Hz, H-2), 4.51 (1H, d, *J* = 10.3 Hz, H-5), 3.76 (3H, s, CH_3O), 2.06 and 2.03 (9H, 3s, 3xCH_3CO); ^{13}C NMR ($(CD_3)_2SO$): *δ* 165.0 (x2), 164.7, 162.4, 155.8, 87.9, 85.8, 65.7, 64.7, 64.3, 64.2, 48.3, 15.9, 15.7 and 15.7.

(E)-1-(3-Acetoxy-5-O-2,3,4-triacetyl-β-D-glucuronopyranosidophenyl)-2-(4′-acetoxyphenyl)ethene Methyl Ester 12-4′, 5-Di-O-acetyl-(E)-resveratrol **11** (0.101 g, 0.32 mmol) and the trichloroacetimidate **9** (0.226 g, 0.47 mmol) were dissolved in CH_2Cl_2 (3 mL) and the resulting solution was cooled to 0°C. $BF_3.OEt_2$ (0.01 mL, 0.08 mmol) was added whilst stirring. After 5 minutes, the stirring was stopped and the reaction mixture was stored

at -18 °C for 17 h. Saturated aqueous $NaHCO_{3,}$ (2.5 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were evaporated to dryness. The crude product was purified by column chromatography (10% to 20% EtOAc/toluene) to give *trans*-resveratrol penta-O-acetyl-3-β-D-glucuronide methyl ester **12** (0.106 g, 53%) as a crystalline white solid, m. p. 146-147°C. Found: C, 59.0; H, 5.1; *m/z* $(M+NH_4)^+$ = 646.2133; $C_{31}H_{32}O_{14}$ requires C, 59.2; H, 5.1%; $C_{31}H_{36}NO_{14}$ requires m/z = 646.2136. ^{1}H NMR: δ 7.51 (2H, d, J = 8.3 Hz, H-2′, H-6′), 7.11 (2H, d, J = 8.3 Hz, H-3′ + H-5′), 7.06 (d, J = 16.3 Hz, 1H, olefinic H), 7.03-6.99 (m, 2H, H-2 + H-6), 6.96 (d, J = 16.4 Hz, 1H, olefinic H), 6.67 (t, J = 2.2 Hz, 1H, H-4), 5.42 – 5.27 (3H, m, H-2′′, H-3′′ and H-4′′), 5.21 (1H, d, J = 6.9 Hz, H-1′′), 4.24 (1H, d, J = 8.9 Hz, H-5′′), 3.75 (3H, s, CH_3O), 2.33 (3H, s, Ar CH_3CO), 2.33 (3H, s, Ar CH_3CO), 2.09 (3H, s, CH_3CO), 2.07 (3H, s, CH_3CO) and 2.07 (3H, s, CH_3CO); ^{13}C NMR: δ 169.4, 169.3 (x2), 169.2, 166.9, 157.4, 151.7, 150.4, 139.7, 134.4, 129.6, 127.7, 127.4, 121.9, 114.7, 112.7, 109.9, 99.0, 72.8, 71.8, 71.1, 69.0, 53.0, 21.2, 20.7, 20.6 and 20.5.

(E)-1-(3-Isobutyryl-5-O-2,3,4-triacetyl-β-D-glucuronopyranosidophenyl)-2-(4′-isobutyrylphenyl)ethene Methyl Ester 17- This compound was prepared from diester **16** (0.214 g, 0.58 mmol) as described for compound **12** using trichloroacetimidate **9** (0.275 g, 0.57 mmol). After chromatography the title compound **17** was obtained as a white solid (0.257 g, 66%). Found: C, 61.1; H, 5.9; m/z, 707.2313 (MNa^+, ES +ve mode); $C_{35}H_{40}O_{14}$ requires C, 61.4; H, 5.84%; $C_{35}H_{40}O_{14}$.Na requires m/z 707.2316; ^{1}H NMR ($(CD_3)_2SO$): δ 7.65 (2 H, d, J = 7.8 Hz, H-2′ + H-6′), 7.34 (1 H, d, J = 16.4 Hz, olefinic H), 7.22 (1 H, d, J = 16.4 Hz, olefinic H), 7.12-7.16 (4 H, m, H-2 + H-6 + H-3′ + H-5′), 6.72 (1 H, br s, H-4), 5.80 (1 H, d, J = 8 Hz, H-1′′), 5.47 (1 H, t, J = 9.6 Hz, H-3′′), 5.07-5.15 (2 H, m, H-2′′ + H-4′′), 4.74 (1 H, d, J = 10.0 Hz, H-5′′), 3.66 (3 H, s, CH_3O), 2.84 (2 H, m, 2xMe_2CH), 2.04, 2.02

and 2.01 (9 H, 3s, 3xCH_3CO) and 1.25 (12 H, 2d, 2xMe_2CH); ^{13}C NMR: δ 175.5, 175.3, 170.1, 169.3, 169.3, 166.9, 157.4, 151.9, 150.7, 139.7, 134.3, 129.5, 127.6, 127.3, 121.9, 114.6, 112.4, 109.7, 99.0, 72.7, 71.8, 71.1, 69.0, 53.0, 34.2, 20.7, 20.6, 20.5 and 18.9.

(*E*)-1-(5-hydroxy-3-O-β-D-glucuronopyranosidophenyl)-2-(4′-hydroxyphenyl)ethene, Na salt 4-The glucuronide ester **12** (0.105 g, 0.17 mmol) was suspended in MeOH (4.0 mL) and cooled to 0 °C. A solution of sodium carbonate (0.0828 g, 0.78 mmol) in water (3.0 mL) was added over 1 minute with stirring and the reaction mixture turned from cloudy white to cloudy yellow. The resulting reaction mixture was allowed to warm to room temperature over 2 hours and THF (5.0 mL) was added to aid dissolution. After a further hour, water (1.0 mL) was added. After 10 minutes, stirring was stopped and the reaction mixture was kept in the fridge overnight. Amberlite IR-120 (H^+) resin was added with stirring until a pH of 6.0 was obtained, then the resin was filtered off and washed with water. The filtrate was evaporated to dryness then azeotroped with ethanol (3x5 mL) to give a pale beige solid, which was recrystallised from cold ethanol containing water (1 drop). The precipitate was filtered off, washed with cold ethanol, and dried *in vacuo* to give the title glucuronide **4** (0.053 g, 77%) as a beige, flaky solid. Found: *m/z* (MH^+, ES +ve mode) 427.0994; $C_{20}H_{20}O_9Na$ requires m/z, 427.1005; ^{1}H NMR (400 MHz, D_2O): δ 7.46 (2H, pd, J = 8.3 Hz, H-2′ + H-6′)[a], 7.11 (1H, ABq, J = 16.5 Hz, olefinic H)[b], 6.93 (1H, ABq, J = 16.5 Hz, olefinic H)[b], 6.81 (2H, pd, J = 8.3 Hz, H-3′ + H-5′)[a], 6.73 (1H, s, H-6)[c], 6.72 (1H, s, H-2)[c] 6.45 (1H, s, H-4), 5.12 (1H, d, J = 7.6 Hz, H-1′′), 3.92 (1H, d, J = 8.8 Hz, H-5′′), 3.70-3.56 (3 H, m, H-2′′+ H-3′′ + H-4′′). ^{13}C{^{1}H} NMR (101 MHz, D_2O)[d]: 162.9 (C-3), 161.9 (C-4'), 161.1 (C-5), 142.8 (C-1)[e], 131.9 (C-8), 131.0 (C-2',6') 130.3 (C-1')[e], 127.5 (C-7), 111.3 (C-2), 107.3 (C-6), 106.5 (C-4). ^{1}H Chemical shifts closely match the values reported by Lucas *et al.*[13] [a] pd = pseudo doublet, the ortho and meta protons of the phenol form a 2nd order spin system, apparent J(HH) given. [b]

Comment [IJ]: check

ABq = AB quartet. [c] Assignment might be reversed. [d] ^{13}C shifts taken from HSQC and HMBC spectra. [e] Assignment might be reversed. ^{13}C NMR (D_2O): δ 175.5, 158.3, 140.2, 129.2, 128.2, 127.3, 124.8, 116.9, 108.9, 104.5, 103.5, 100.2, 76.2, 75.3, 72.8 and 71.7. The corresponding diisobutyryl ester **17** gave a similar result.

(*Z*)-1-(5-hydroxy-3-O-β-D-glucuronopyranosidophenyl)-2-(4′-hydroxyphenyl)ethene, Na salt – **4** (ca. 0.005 g) was dissolved in D_2O (ca. 0.7 ml) and the solution placed in an NMR tube. After standing in the dark for ca. 2 weeks, the NMR tube containing the solution was placed on the window ledge in bright sunlight for ca. 8 h after which time the sample was transferred to the NMR spectrometer. ^1H NMR (400 MHz, D_2O): δ 7.17 (2H, pd, J = 8.7 Hz, H-2′ + H-6′) [a], 6.76 (2H, pd, J = 8.7 Hz, H-3′ + H-5′)[a], 6.62 (1H, ABq, J = 12.1 Hz, olefinic H)[b], 6.46 (1H, ABq, J = 12.1 Hz, olefinic H)[b], 6.46 (1H, s, H-2)[c], 6.40 (1H, s, H-6)[c], 6.35 (1H, s, H-4), 5.12 (1H, d, J = 7.6 Hz, H-1′′), 3.92 (1H, d, J = 8.8 Hz, H-5′′), 3.70-3.56 (3 H, m, H-2′′+ H-3′′ + H-4′′). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O)[d]: 163.3 (C-3), 160.6 (C-5), 159.7 (C-4'), 142.3 (C-1)[e], 133.4 (C-8), 133.3 (C-2',6') 131.2 (C-1')[e], 130.8 (C-7), 114.9 (C-2), 108.7 (C-6), 106.5 (C-4). [a] pd = pseudo doublet, the ortho and meta protons of the phenol form a 2nd order spin system, apparent J(HH) given. [b] ABq = AB quartet. [c] Assignment might be reversed. [d] ^{13}C shifts taken from HSQC and HMBC spectra. [e] Assignment might be reversed.

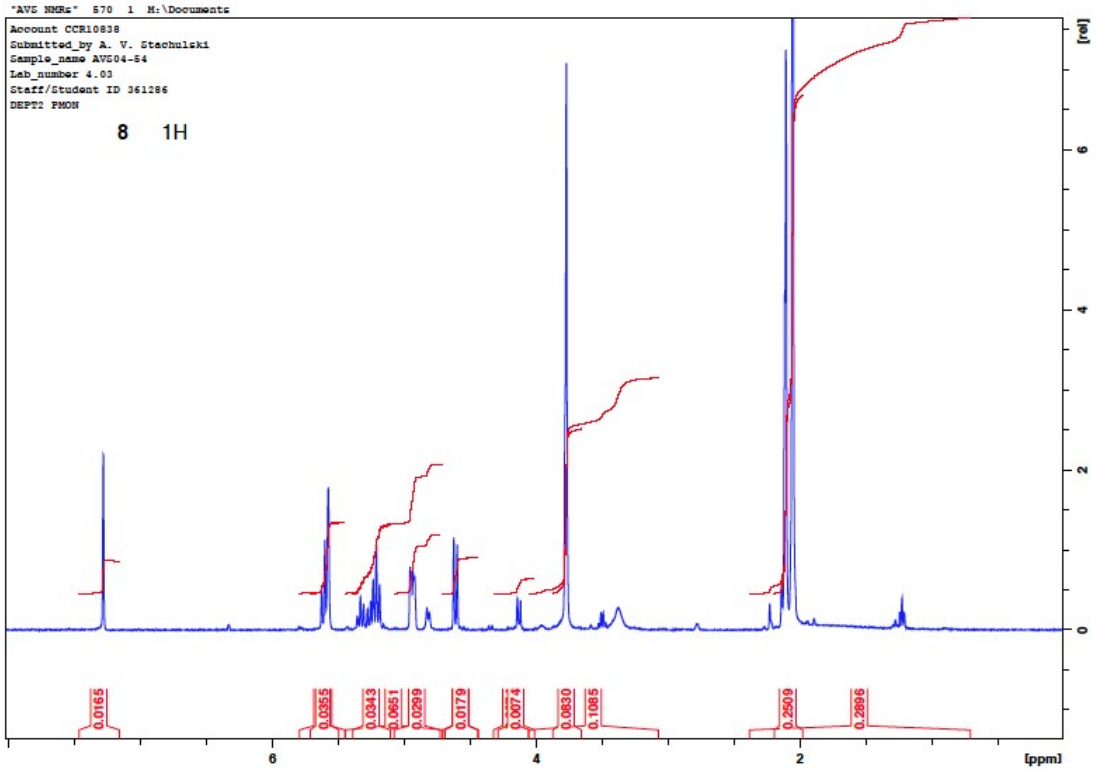
(*E*)-1-(3,5-Diacetoxyphenyl)-2-(4′-*O*-2,3,4-triacetyl-β-D-glucopyranosidophenyl)ethene Methyl Ester 14- 3, 5-Di-*O*-acetyl-(*E*)-resveratrol **13** (0.109 g, 0.35 mmol) and the trichloroacetimidate **9** (0.246 g, 0.51 mmol) were dissolved in anhydrous CH_2Cl_2 (4.0 mL) and cooled to -20 °C. $BF_3.OEt_2$ (0.012 mL, 0.10 mmol) was added and the reaction mixture was stirred for 5 minutes. After 5 minutes, stirring was stopped and the reaction mixture was

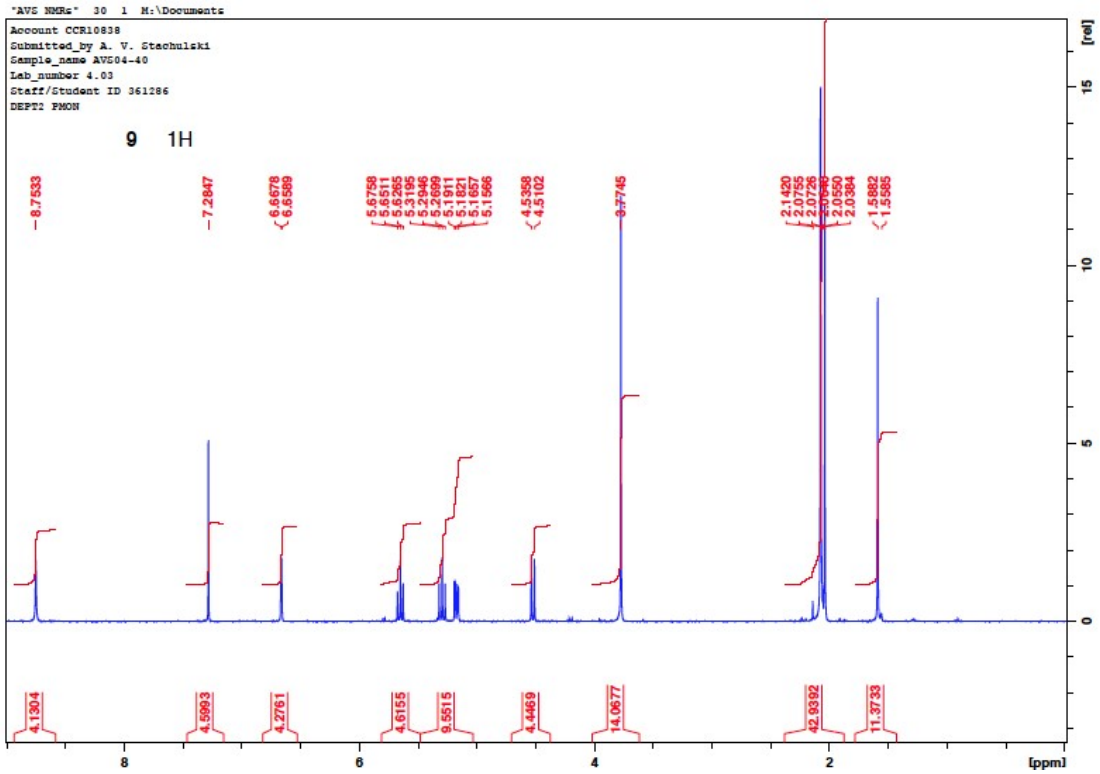
kept at -20 °C for 1.5 hours. Saturated Na_2CO_3 solution (3.0 mL) was added and the aqueous layer was washed with ethyl acetate (3 x 15 mL). The combined organic layers were evaporated to dryness under vacuum to give a yellow oil which was purified by column chromatography (20% EtOAc/toluene) to give the title compound **14** (0.122 g, 56%) as a colourless oil which solidified to a white solid, m. p. 164-165°C. Found: C, 59.2; H, 5.0; *m/z* (CI, NH_3) $(M+H)^+$ = 646.2135; $C_{31}H_{32}O_{14}$ requires C, 59.2; H, 5.1%; $C_{31}H_{36}NO_{14}$ requires m/z = 646.2136. ^{1}H NMR: δ 7.42 (2H, d, J = 8.7 Hz, H-2′, H-6′), 7.11 (2H, d, J = 2.1 Hz, 2-H + 6-H), 7.03 (1H, d, J = 16.2 Hz, olefinic H), 6.99 (2H, d, J = 8.7 Hz, H-3′ + H-5′), 6.92 (d, J = 16.2 Hz, 1H, olefinic H), 6.81 (t, J = 2.1 Hz, 1H, H-4), 5.38 – 5.27 (3H, m, H-2′′, H-3′′ and H-4′′), 5.18 (1H, d, J = 7.2 Hz, H-1′′), 4.25 – 4.19 (1H, m, H-5′′), 3.74 (3H, s, CH_3O), 2.31 (6H, s, 2xAr CH_3CO), 2.07, 2.06 and 2.05 (9H, 3s, 3xCH_3CO); ^{13}C NMR: δ 170.1, 169.3, 169.2, 169.0, 166.9, 156.5, 151.3, 139.7, 132.2, 129.7, 128.0, 126.2, 117.3, 116.8, 114.2, 99.0, 72.7, 71.8, 71.1, 69.1, 53.0, 21.1, 20.6, 20.50.

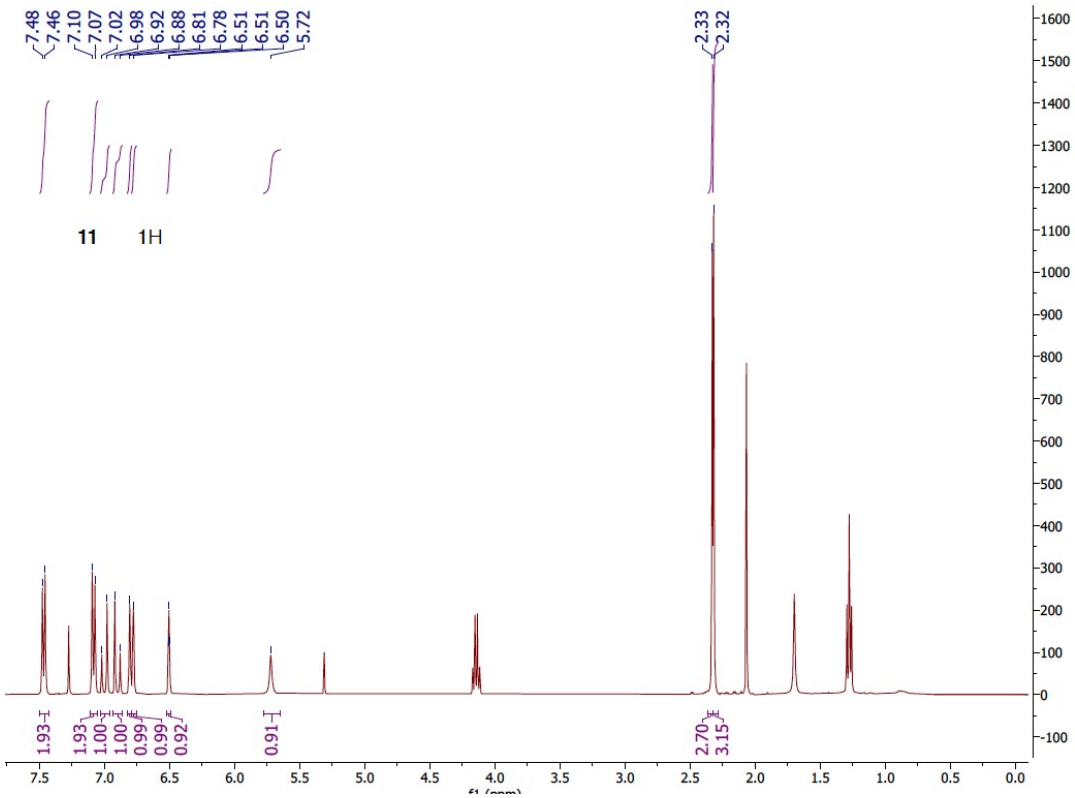
(*E*)-1-(3, 5-Dihydroxy-3-O-β-D-glucuronopyranosidophenyl)-2-(4′-hydroxyphenyl)ethane, Na salt 5-Ester **14** (0.0843 g, 0.13 mmol) was dissolved in 1:1 THF/MeOH (5.0 mL) and cooled to 0 °C. Sodium carbonate (0.0716 g, 0.68 mmol) was dissolved in water (5.0 mL) and added slowly over 3 minutes with stirring. The colourless solution gradually turned yellow and was allowed to warm to 20°C over 2 hours. After 3 h at this temperature, no starting material was present. Amberlite IR-120 (H^+) resin was added with stirring to pH 6, then the resin was filtered off and washed with water. The filtrate was evaporated and azeotroped with ethanol (3x5 mL) to give a crude pale brown solid, which was recrystallised from ethanol and 3 drops of warm water. The brown solid was filtered off and washed with cold ethanol. After drying, purified by column chromatography (5:3:1 EtOAc:^{i}PrOH: H_2O) gave a pale beige solid. Cold Et_2O was added to the solid and gently

stirred before carefully pipetting off the solvent. This was repeated once more before final drying under vacuum to give the title glucuronide **5** as a beige, flaky solid (0.0203 g, 39%). Found: *m/z* (MH^+, ES +ve mode) 427.0996; $C_{20}H_{20}O_9Na$ requires m/z, 427.1005; ^1H NMR (D_2O): δ 7.38 (2H, d, J = 8.5 Hz, H-2′ + H-6′), 7.03 (2H, d, J = 8.6 Hz, H-3′ + H-5′), 6.97 (1H, d, J = 16.4 Hz, partly obscured, alkene H), 6.81 (1H, d, J = 16.4 Hz, alkene H), 6.48 (2H, d, J = 1.9 Hz, H-2 + H-6), 6.17 (1H, d, J = 2.0 Hz, H-4), 5.00 (1H, d, J = 6.6 Hz, anomeric H), 3.80 (1 H, d, J = 8.8 Hz, 5′′-H) and 3.29 – 3.09 (3H, m, H-2′′ + H-3′′ + H-4′′); ^{13}C NMR (D_2O): δ 175.4, 157.7, 156.3, 139.8, 132.0, 128.3, 127.9, 126.9, 116.8, 100.1, 76.1, 75.3, 72.7 and 71.7.

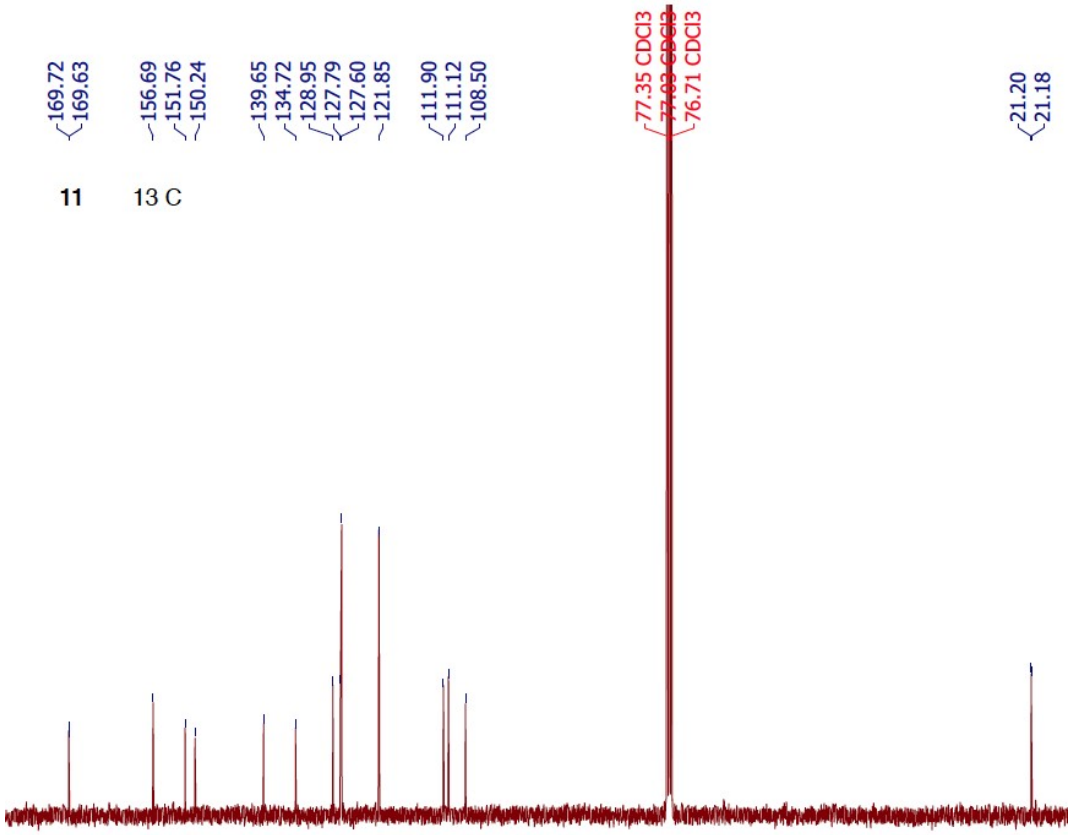
2. Photocopy 1H and 13C NMR spectra of the above

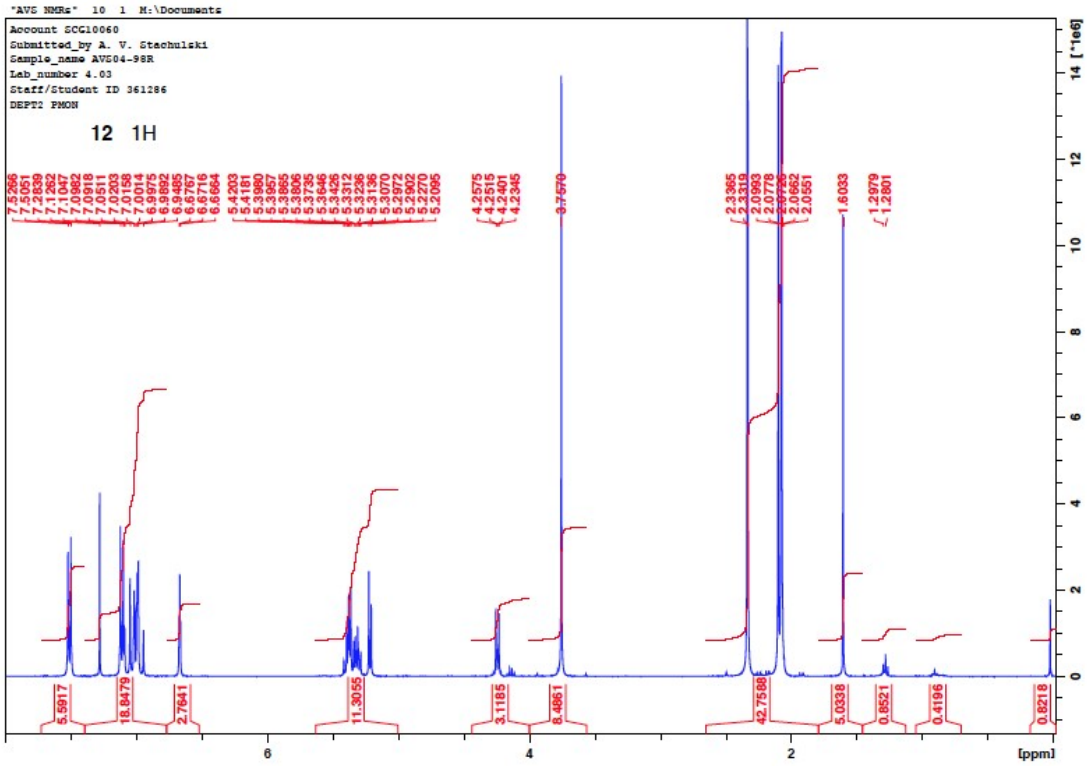






Contains some EtOAc

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Lab_number 4.03
Staff/Student ID 361286
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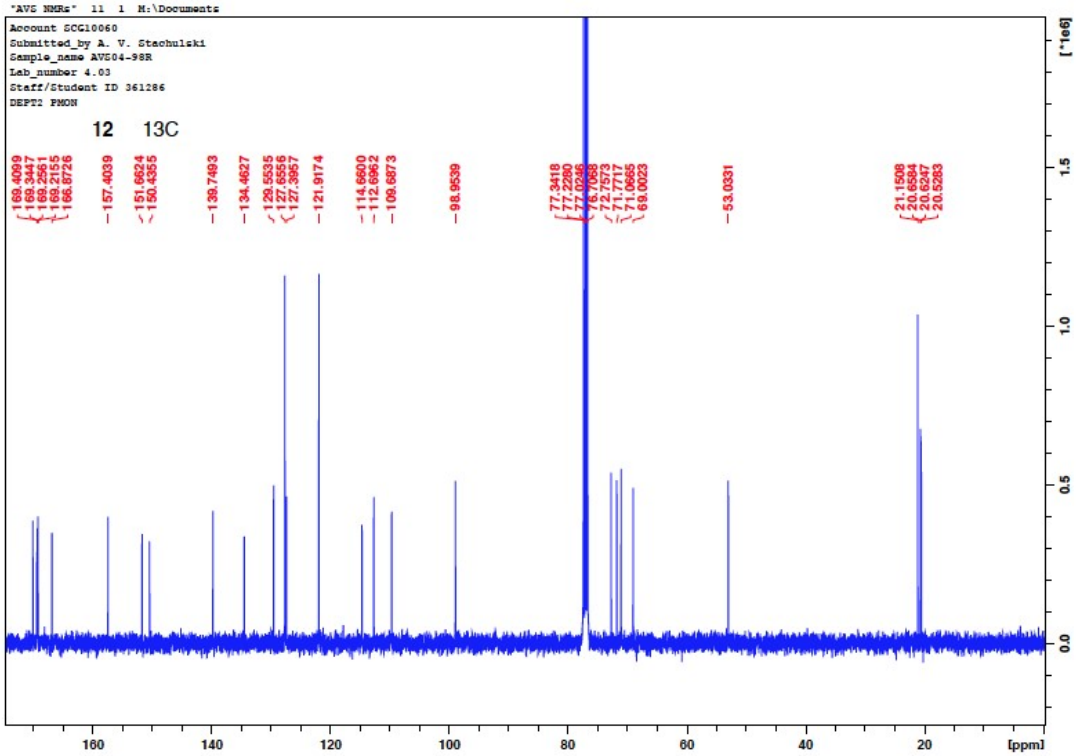
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Lab_number 4.03
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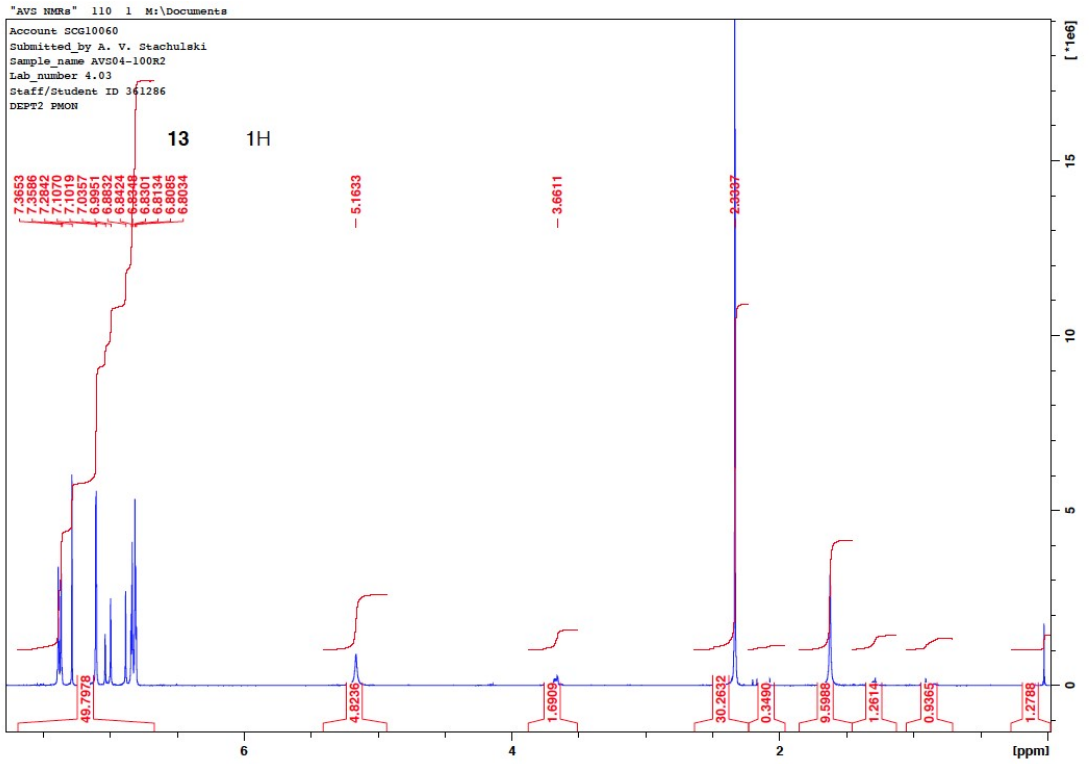
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7.0051
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6.8134
6.8085
6.8034
5.1633
3.6611
2.3337
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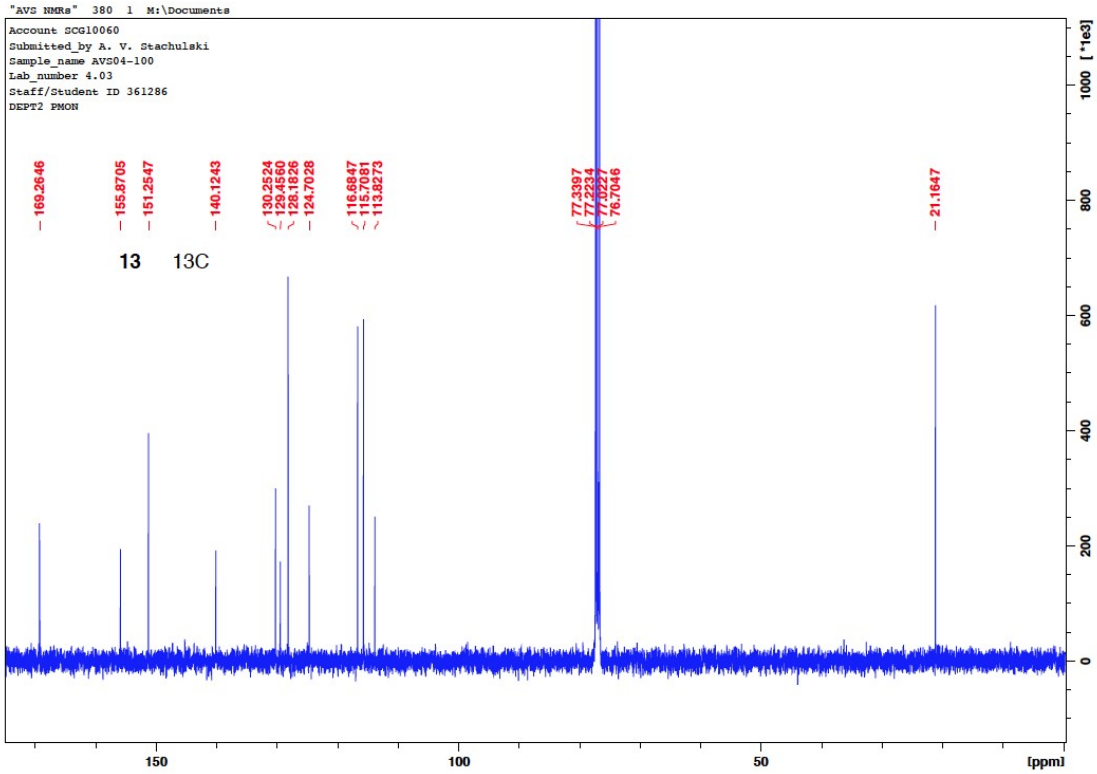
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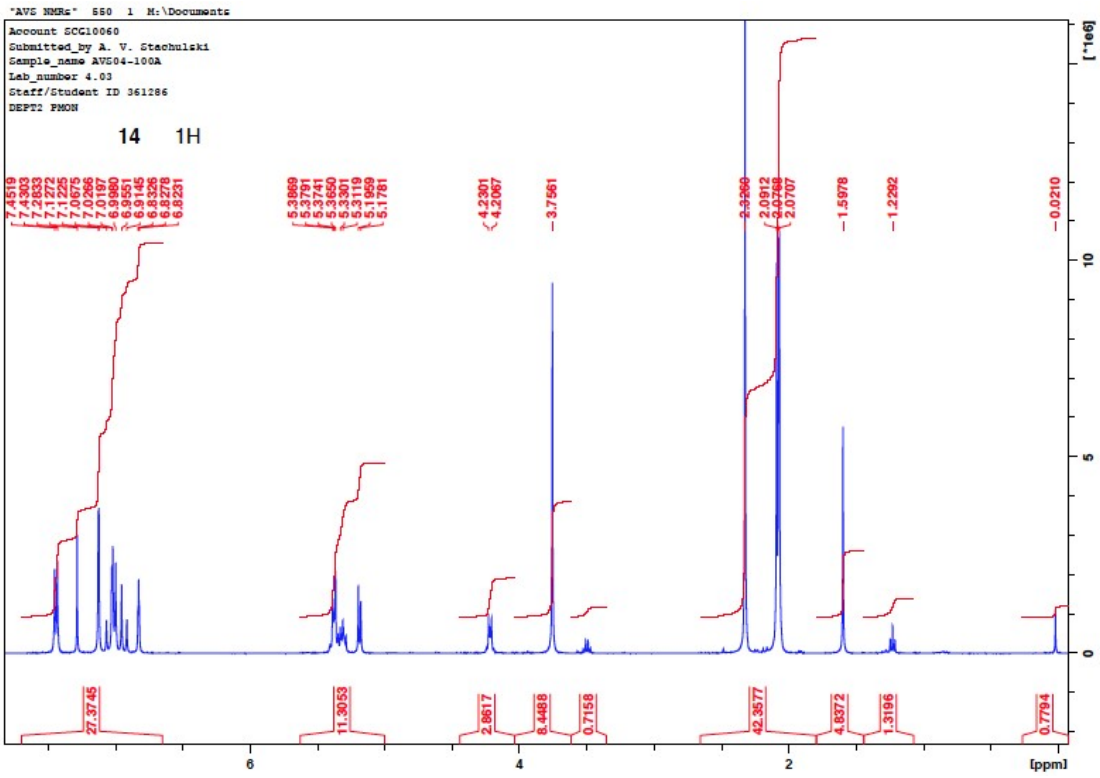
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Staff/Student ID 361286
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7.4303
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7.0266
7.0107
6.9980
6.9551
6.9145
6.8326
6.8278
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5.1989
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4.2301
4.2067
3.7561
2.3260
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2.0707
1.5978
1.2292
0.0210
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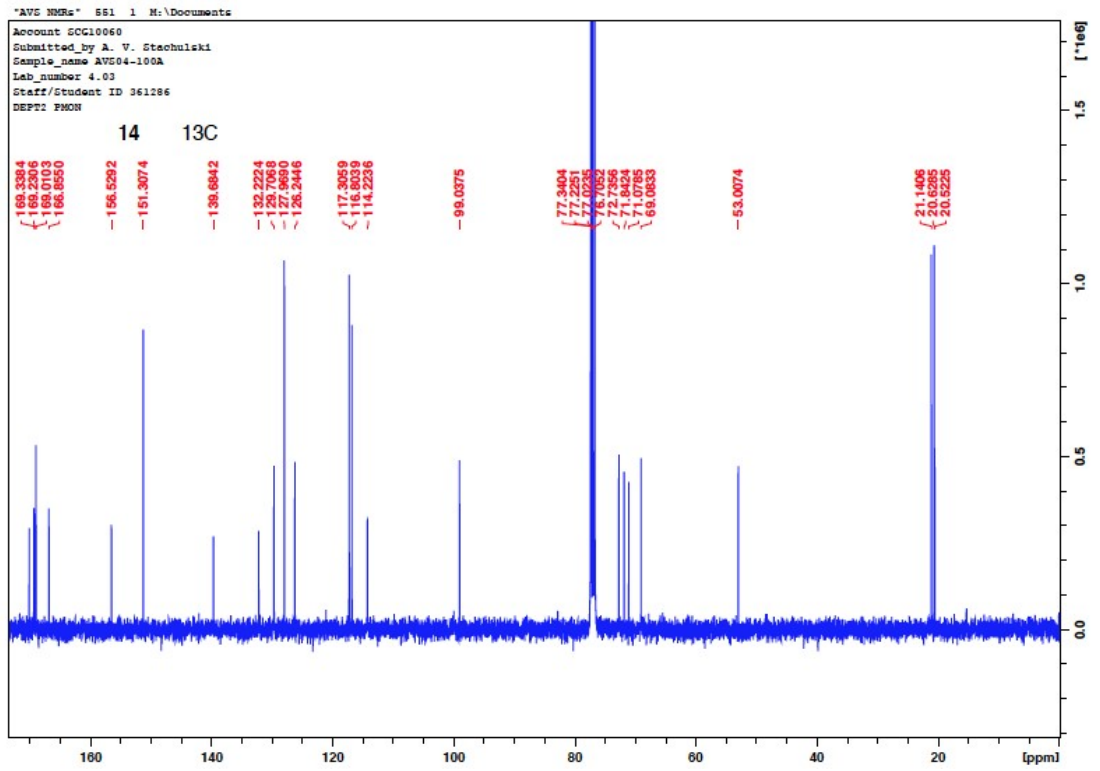
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Staff/Student ID 361286
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132.2224
129.7668
127.0980
126.2446
117.3059
116.8039
114.2236
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77.0235
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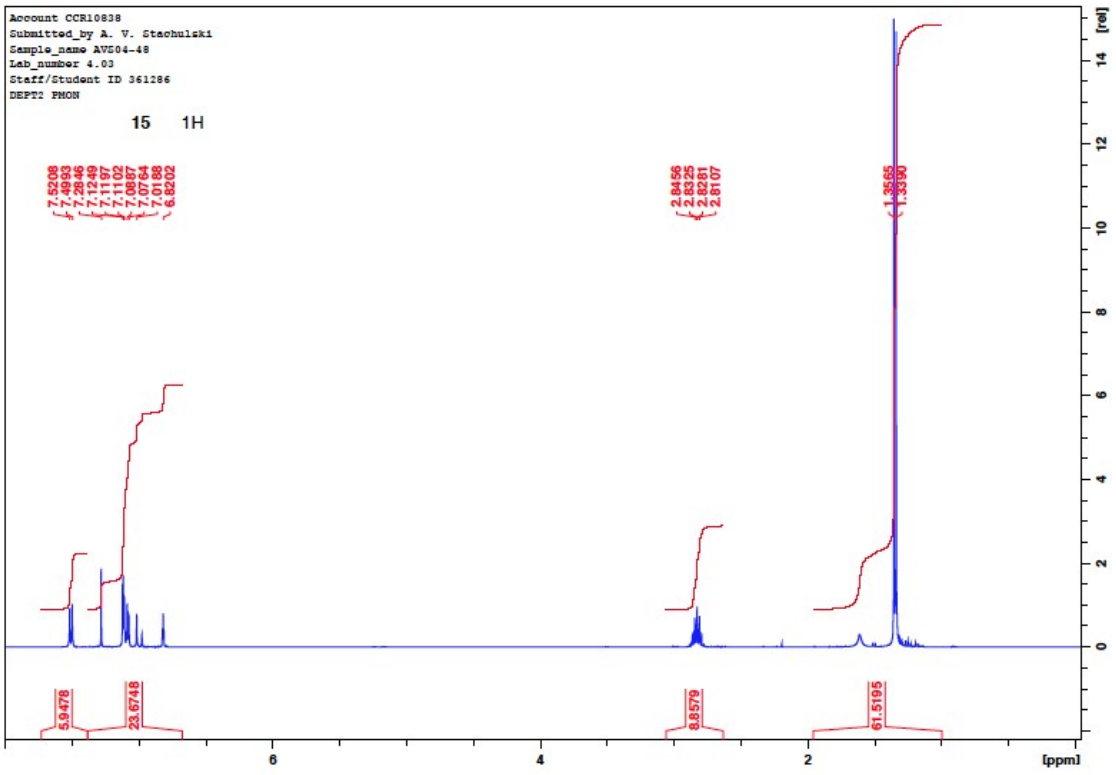
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Lab_number 4.03
Staff/Student ID 361286
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7.0188
6.8202
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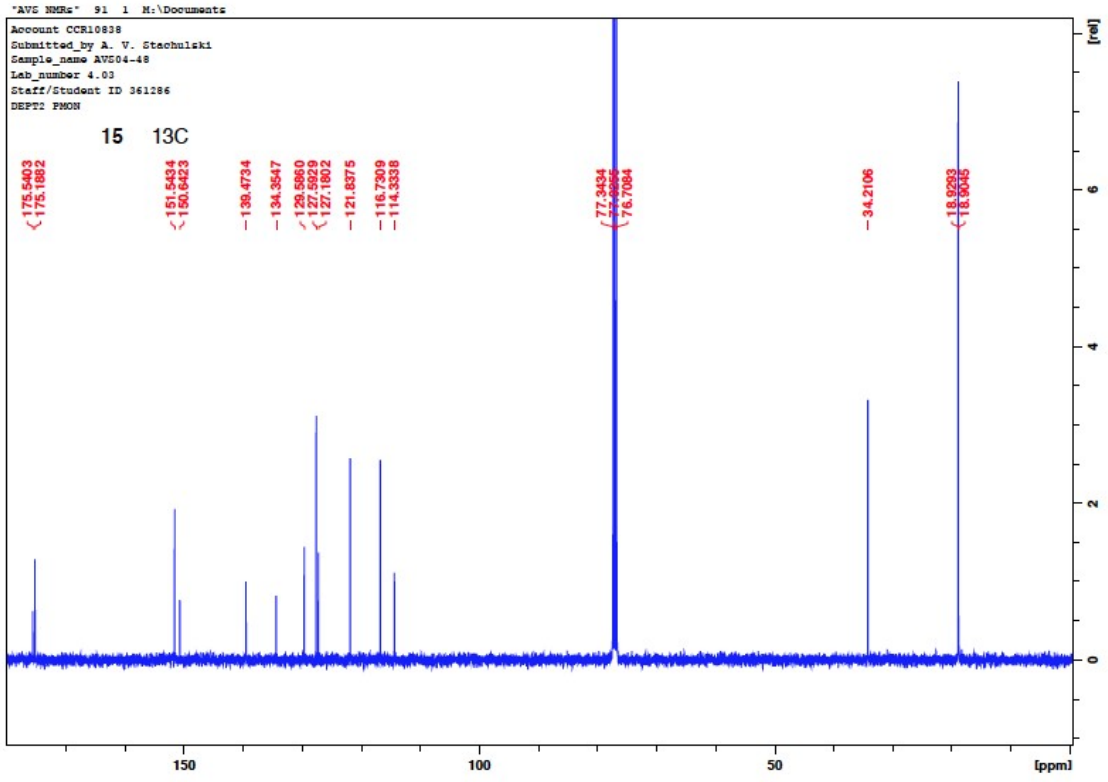
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139.4734
134.3547
129.5860
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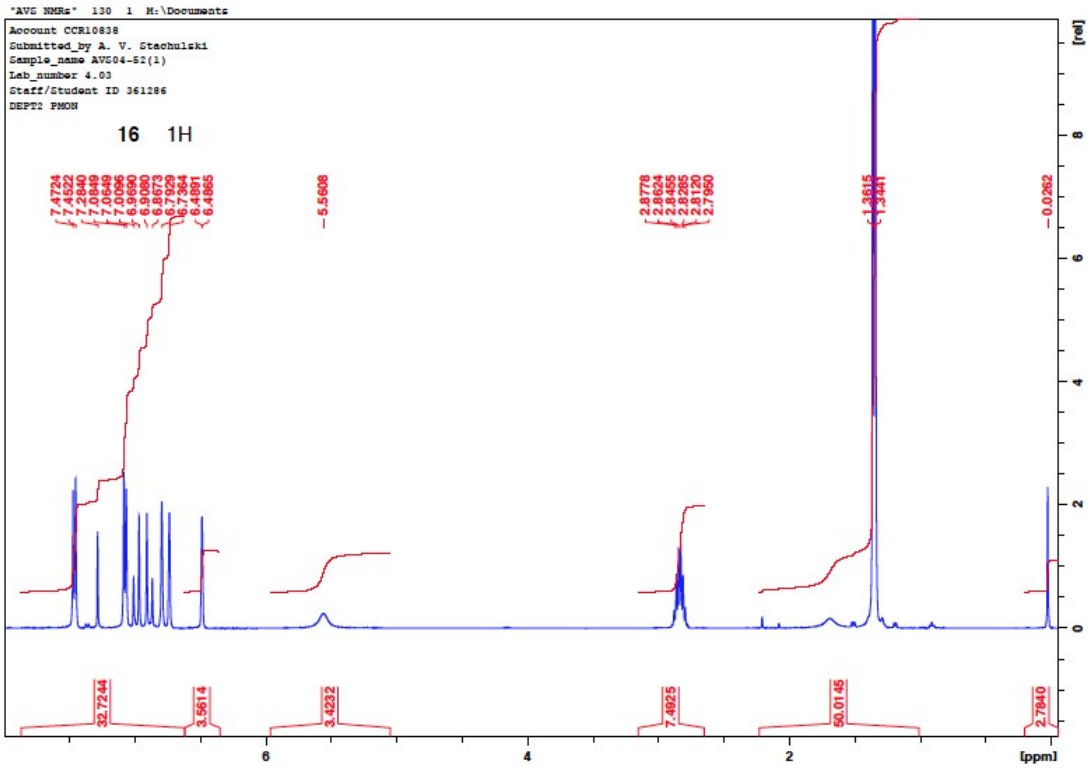
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Submitted_by A. V. Stachulski
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Staff/Student ID 361286
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7.0849
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7.0096
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6.9080
6.8673
6.7929
6.7394
6.4891
6.4865
5.5608
2.8778
2.8574
2.8455
2.8285
2.8120
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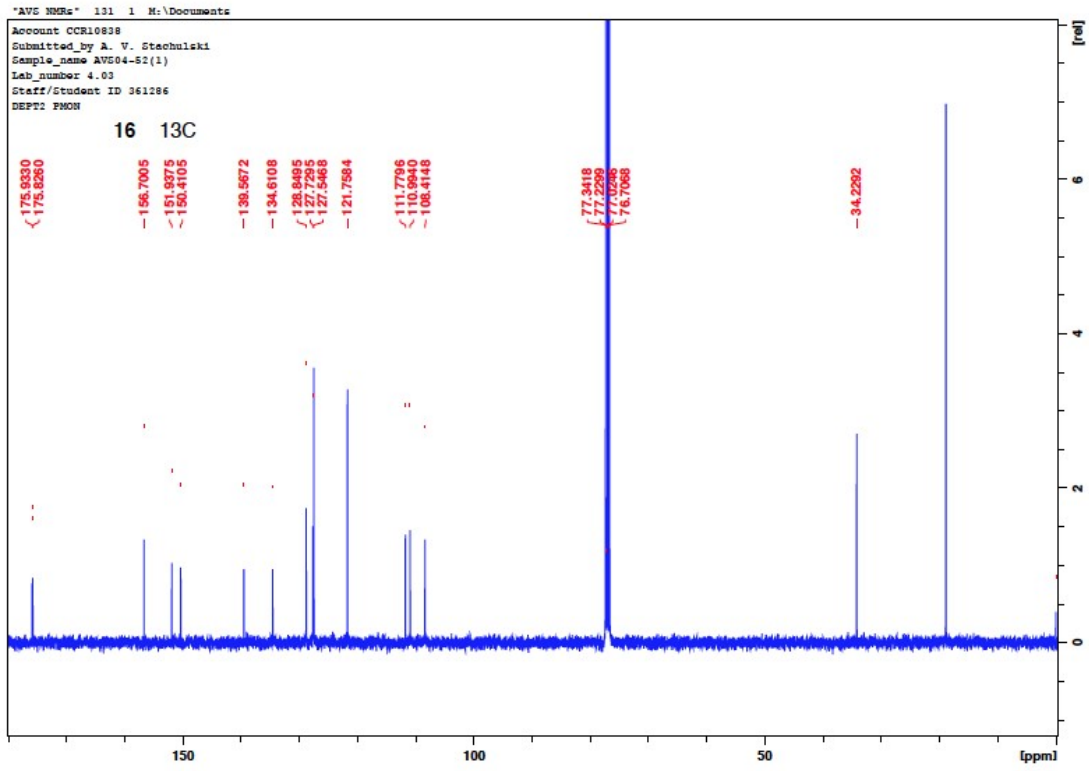
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Staff/Student ID 361286
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127.7295
127.5468
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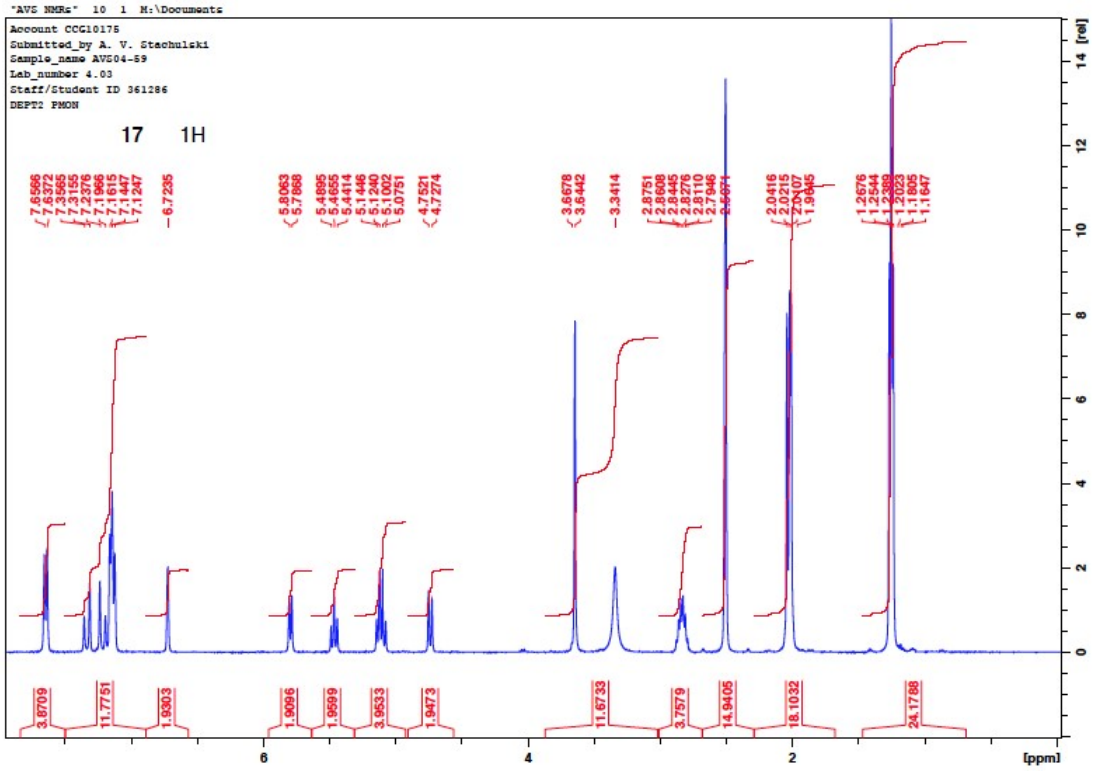
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Staff/Student ID 361286
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6.7235
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5.7668
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1.2544
1.2389
1.2023
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1.1647
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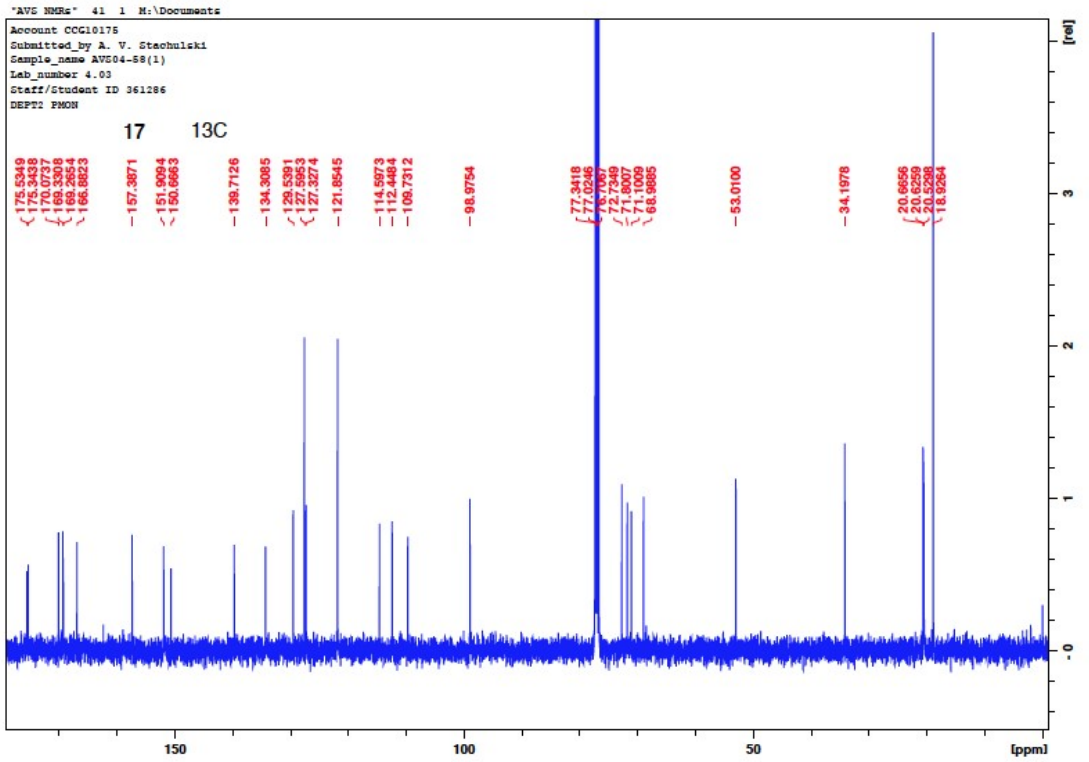
5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150.6663
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76.7067
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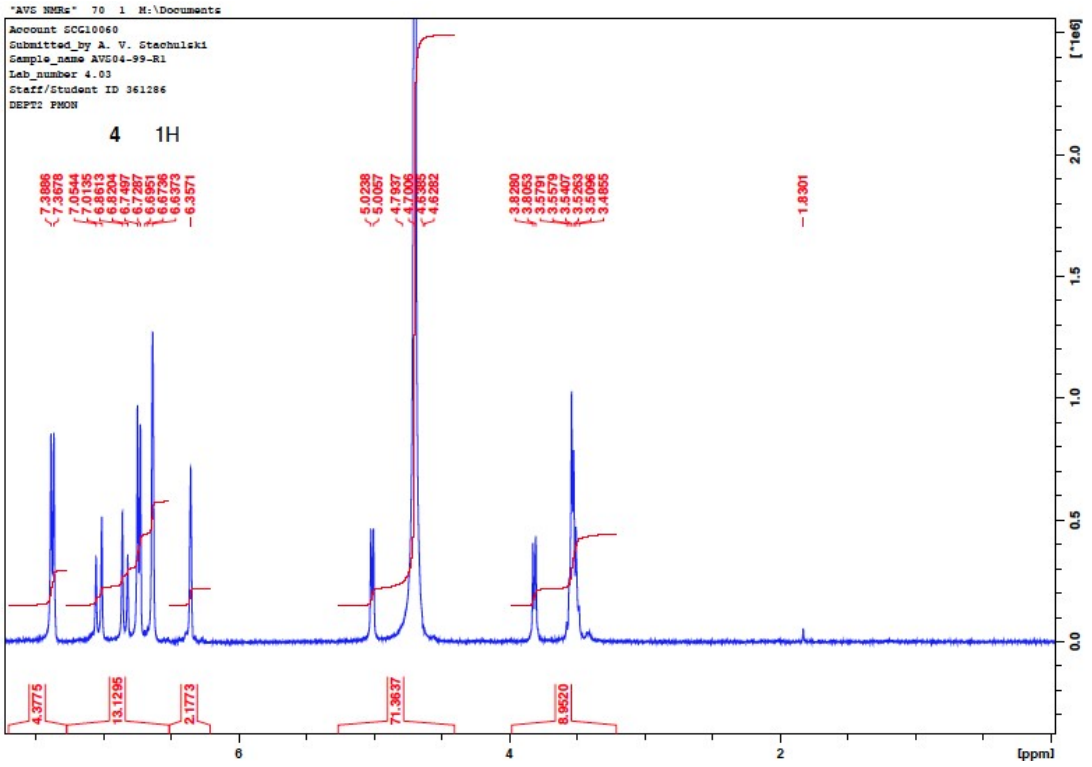
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Staff/Student ID 361286
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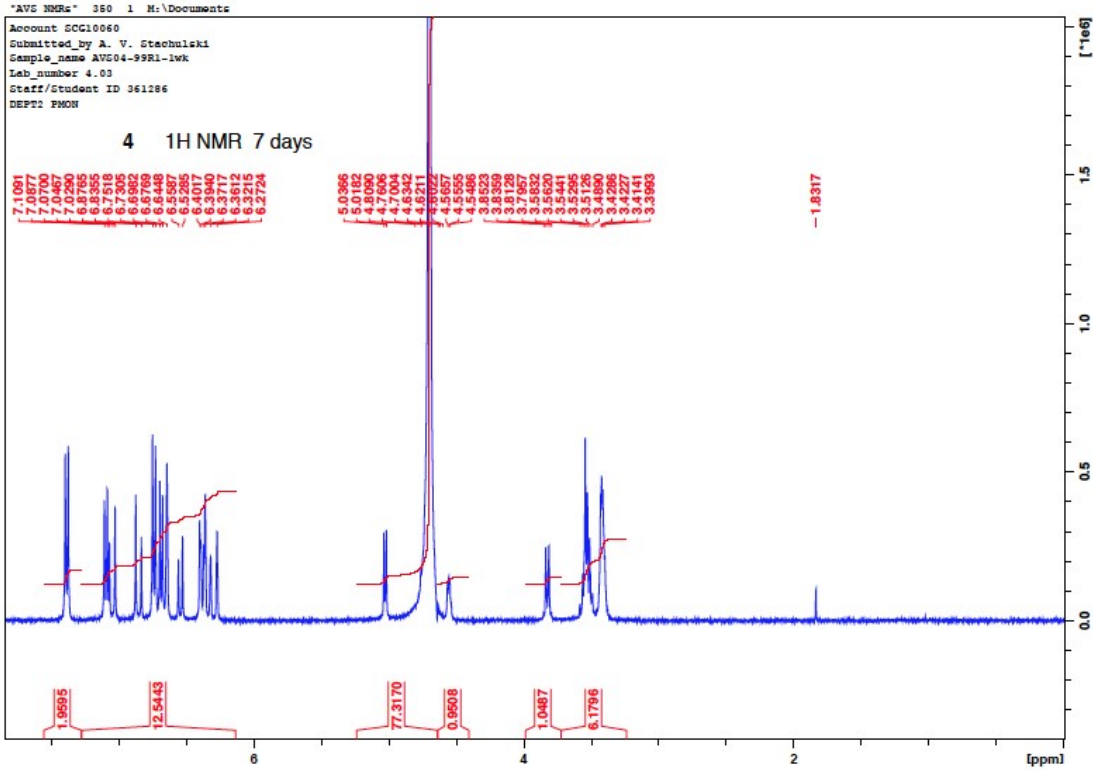
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Staff/Student ID 361286
DEPT2 PMON
4 1H NMR 7 days
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7.0877
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7.0467
7.0269
6.8765
6.8355
6.7518
6.7305
6.6982
6.6769
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3.5295
3.5126
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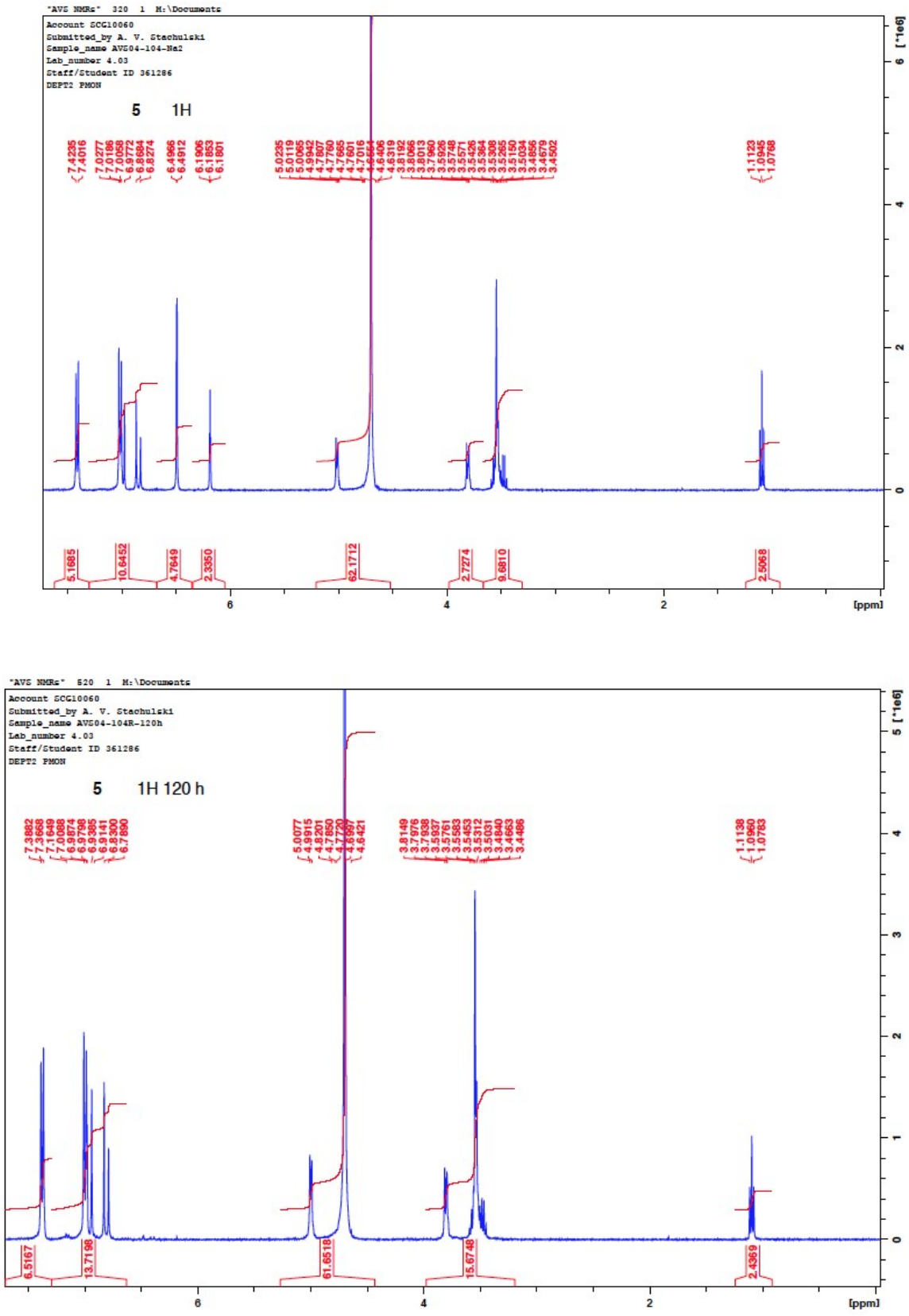
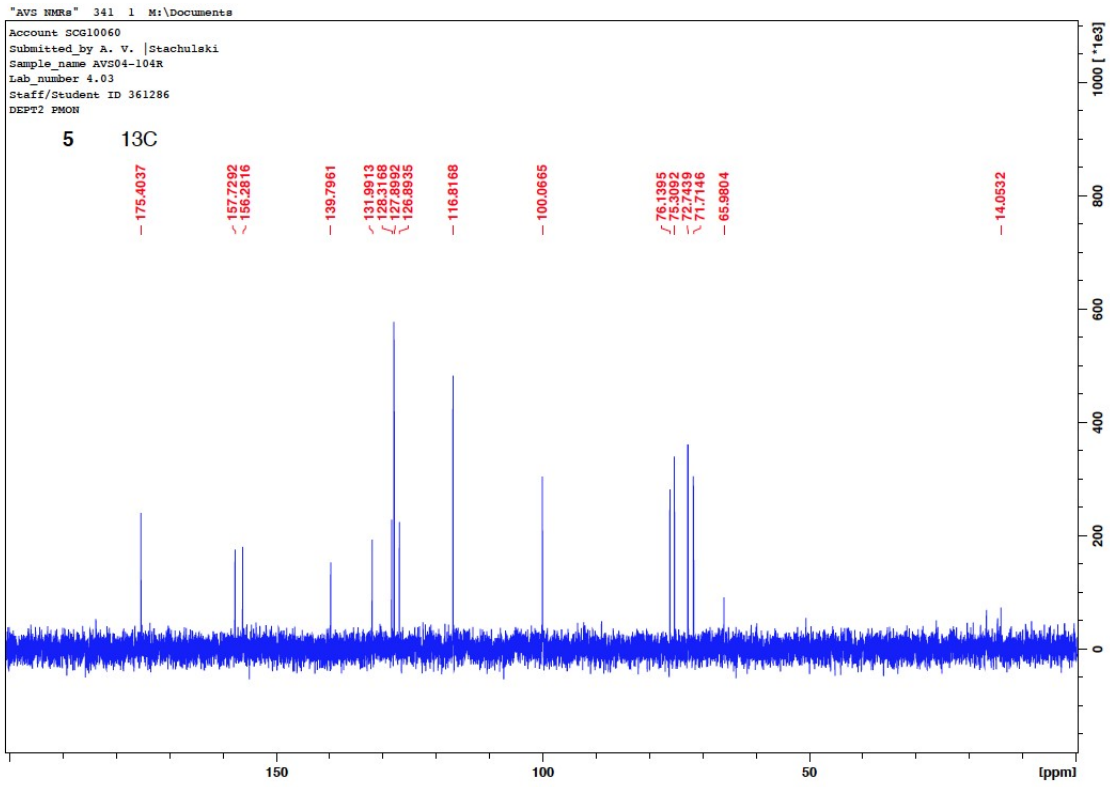


Figure 2. 1H NMR spectrum of **5.Na** after 5 days, showing H/D exchange. Contains ca. 10 mol% Et_2O.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127.8992
126.8935
116.8168
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76.1395
75.3092
72.7439
71.7146
65.9804
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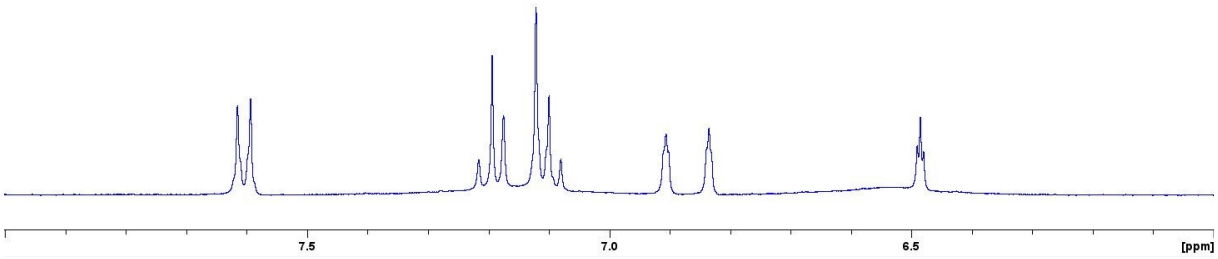
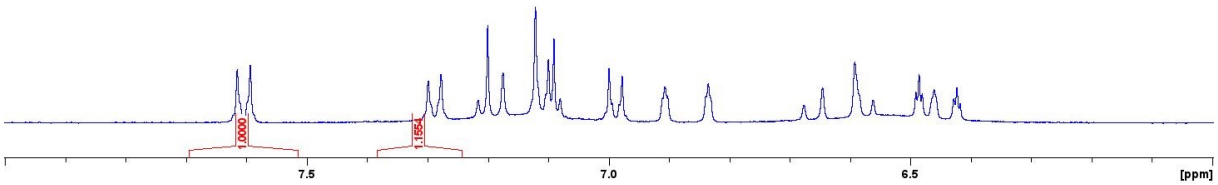
150
100
50
[ppm]

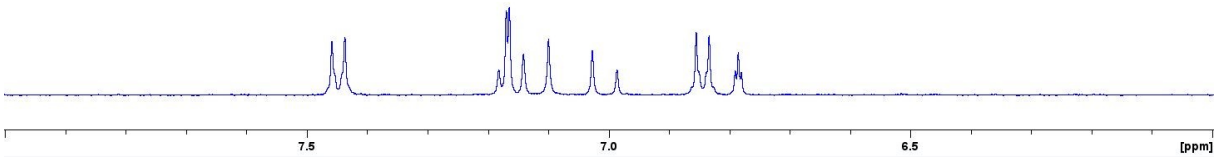
3. Photochemical isomerisation of diesters 13 and 16.



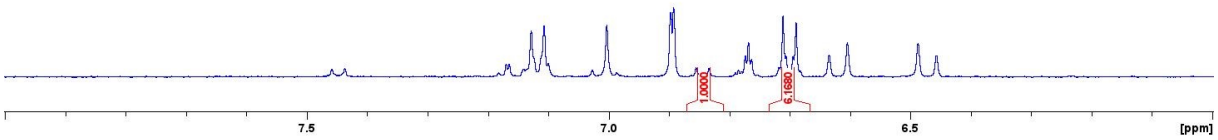
Diester **16**, t = 0 in CD_3CN



Diester **16** in CD_3CN after 12h in diffused sunlight; E:Z ~54:46



Diester **13**, t = 0 in CD_3CN



Diester **13** in CD_3CN after 12h in diffused sunlight; E:Z ~14:86

4. Assignment of 1H and 13C NMRs of the E/Z mixture of compound 4

Experimental

All spectra were recorded using a Bruker Avance-II NMR spectrometer operating at ^{1}H = 400.20 MHz equipped with an inverse ^{1}H,BB probe and Bruker GRASP II gradient accessory. Spectra were recorded in D2O at 298 K using standard Bruker pulse sequences with the exception of the nOe difference measurements which used a custom pulse sequence that combined the Bruker sequences noedif.2 and noemult to collect a pseudo 2D data set containing a series of 1D spectra in which, in turn, each multiplet was selected for irradiation and presaturation of both lines of the selected pseudo doublet occurred. Spectra are referenced to the resonances of DSS.

Photo-interconversion of trans and cis isomers

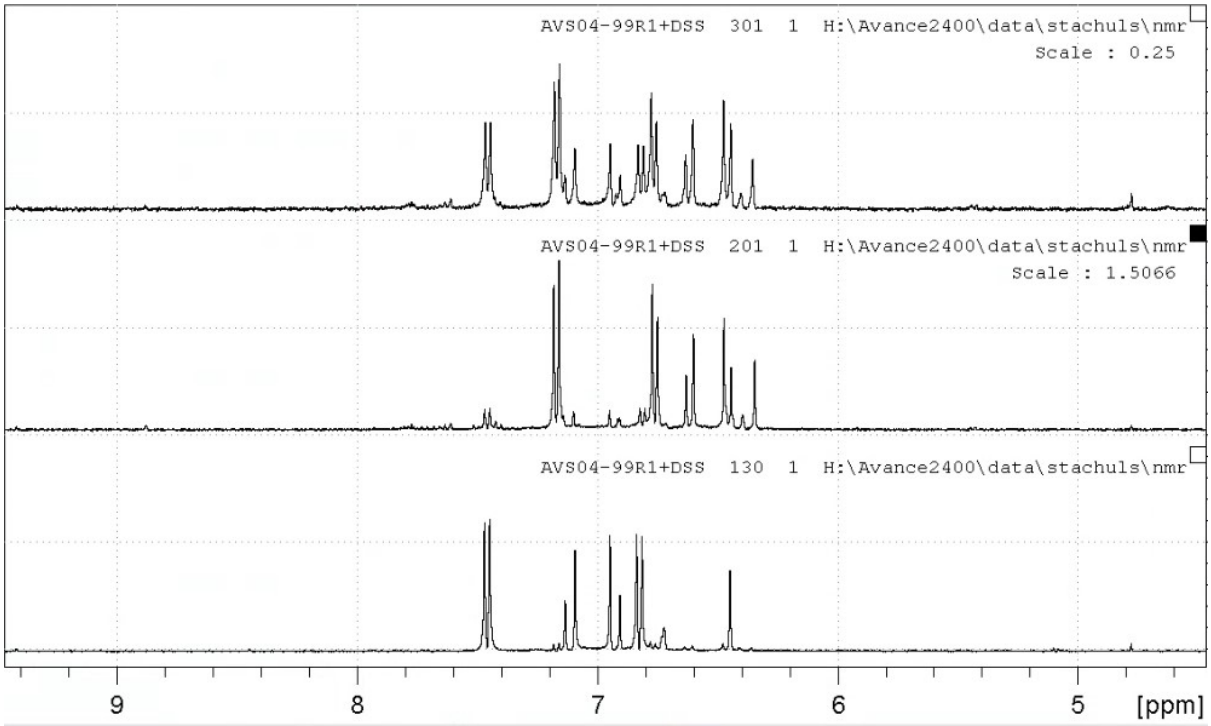
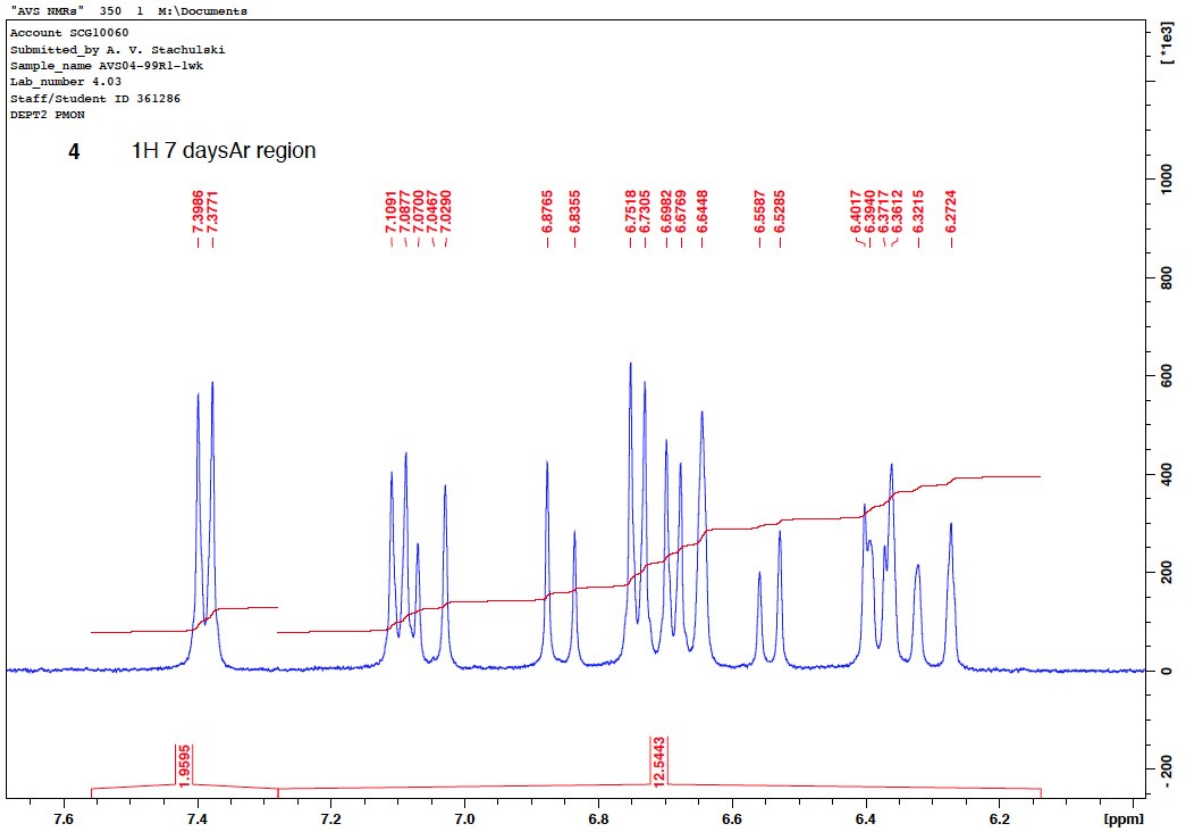


Figure 1 Interconversion of trans and cis isomers. Bottom: On extended storage in the dark. Middle: After ca 10 hours in sunlight. Top: After ca 5 days in the dark.

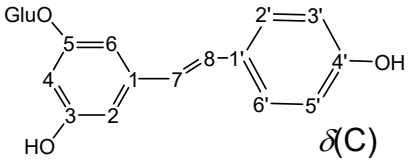


1H NMR spectrum of **4** after 7 days' standing in daylight @ 20°C, E:Z ~3:2, showing the aryl region.

Trans isomer

Table of Assignments

Trans



	δ(C)	δ(H)[a]	*J*(HH)	^{n}J(CH) correlations

	HSQC	HMBC					
4	106.5	106.5	6.45				
6[b]	107.3	107.3	6.73		7	2	
2[b]	111.3	111.3	6.72		7	2	
3',5'	119.6		6.81	*J*(10,11) 8.3			
7	127.5	127.5	6.93	*J*(7,8) 16.5	8	6/4 weak	
1'[c]	n/a	130.3			7 (*J* larger)	11 (*J* smaller)	8 weak?
2',6'	131.0	131.0	7.46	*J*(10,11) 8.3	8		
8	131.9	131.9	7.11	*J*(7,8) 16.5	10	7	
1[c]	n/a	142.8			8 (*J* larger)	7 (*J* smaller)	
5	n/a	161.1			2		
4'	n/a	161.9	-		10	11	
3	n/a	162.9			2		

[a] 10,10',11,11' and 7,8 form mutually coupled 2nd order spin systems, the apparent ^{1}H chemical shift is given. A full analysis to obtain *J*(HH) has not been attempted. [b] Assignment based on chemical shift, may be reversed. [c] Assignment based on chemical shift, may be reversed

[1]H NMR spectrum

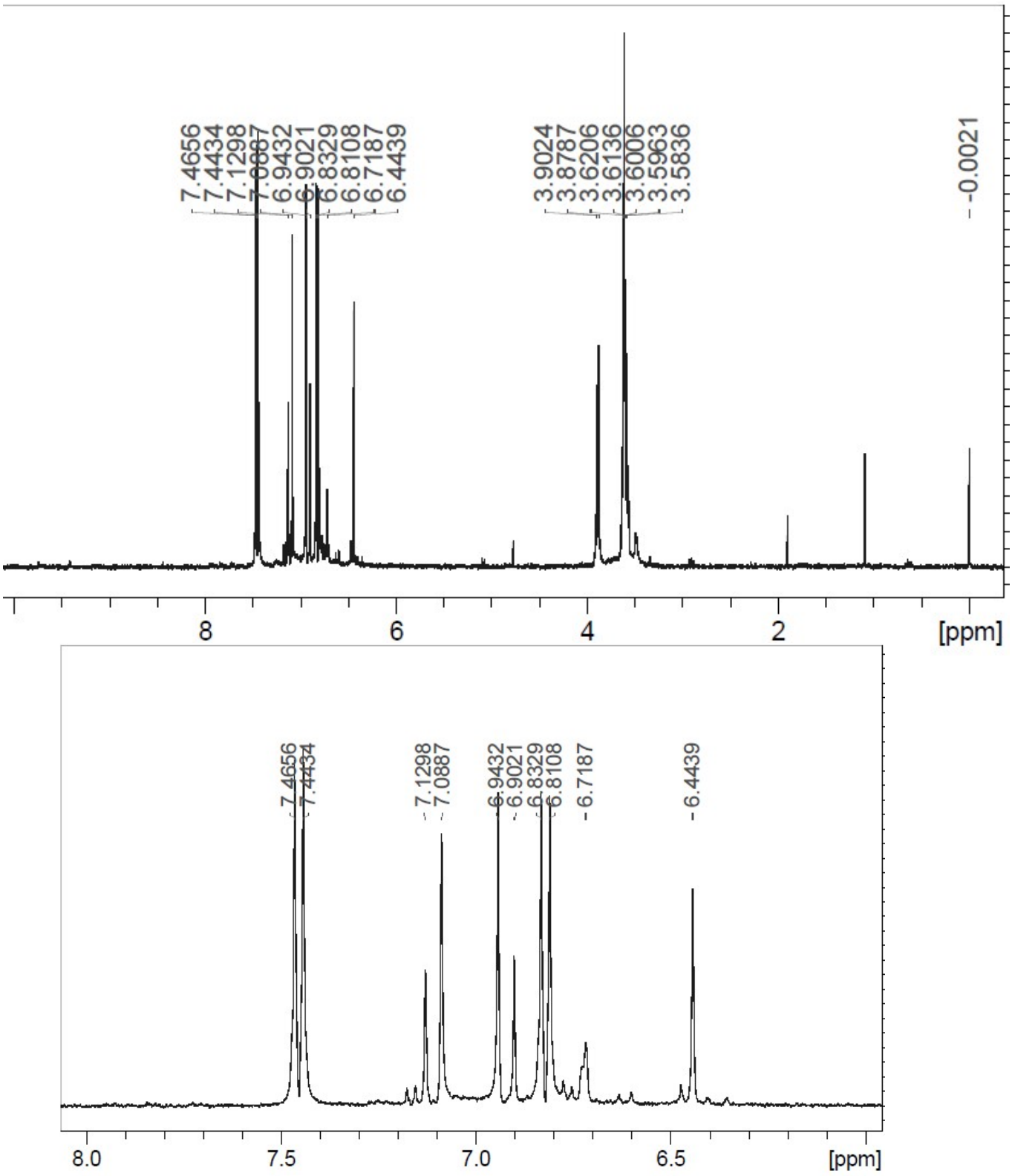
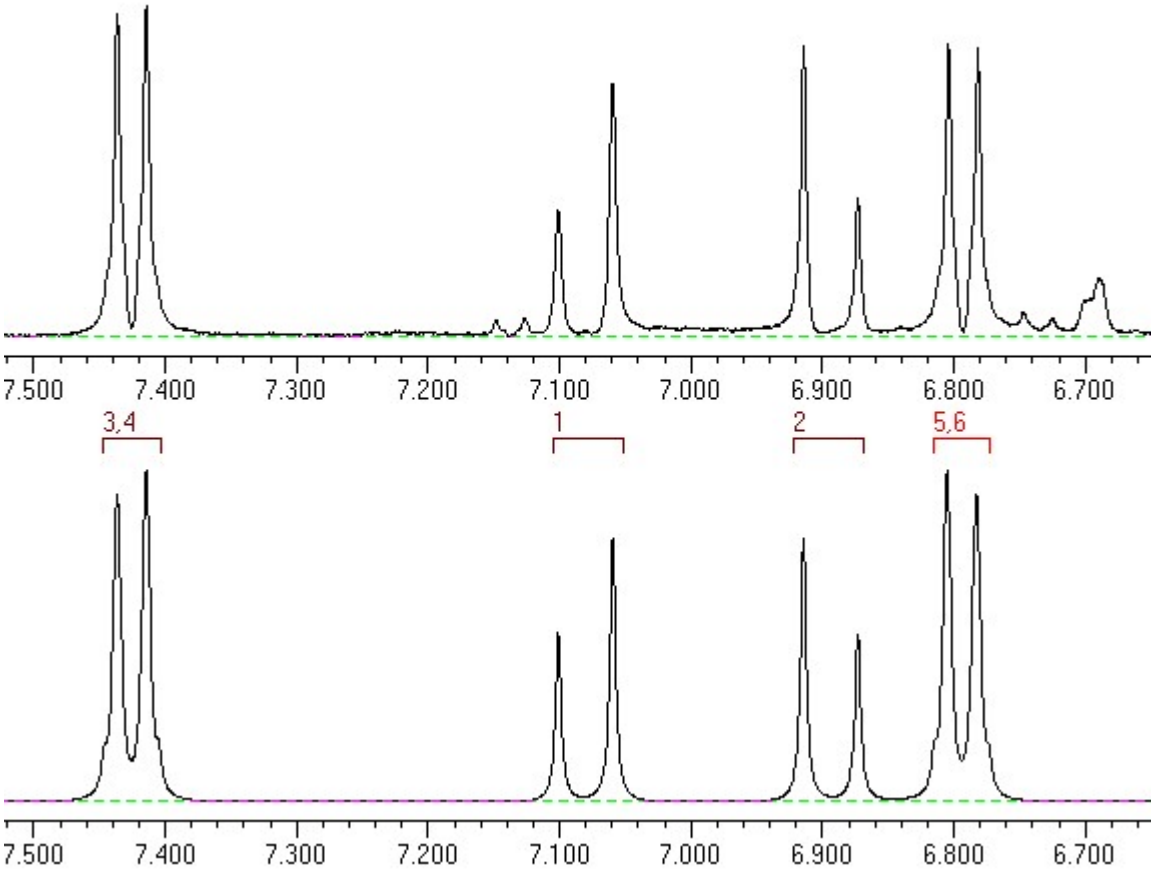


Figure 1 [1]H NMR spectrum of trans isomer. Top full spectrum; Bottom expansion of aromatic region

gNMR simulation of the AA'XX' and AB quartet of the *trans* isomer



gNMR V5.0 Molecule Description
On Tue Jun 27 17:27:51 2023
Molecule 1

#	Nucleus	n	Shift	Width	J[1]	J[2]	J[3]	J[4]	J[5]
1	1H	1	7.108	2.00					
2	1H	1	6.926	2.00	16.53				
3	1H	1	7.461	2.00	0.00	0.00			
4	1H	1	7.461	2.00	0.00	0.00	2.49		
5	1H	1	6.813	2.00	0.00	0.00	9.64	-0.91	
6	1H	1	6.813	2.00	0.00	0.00	-0.91	9.64	2.49

HSQC spectrum

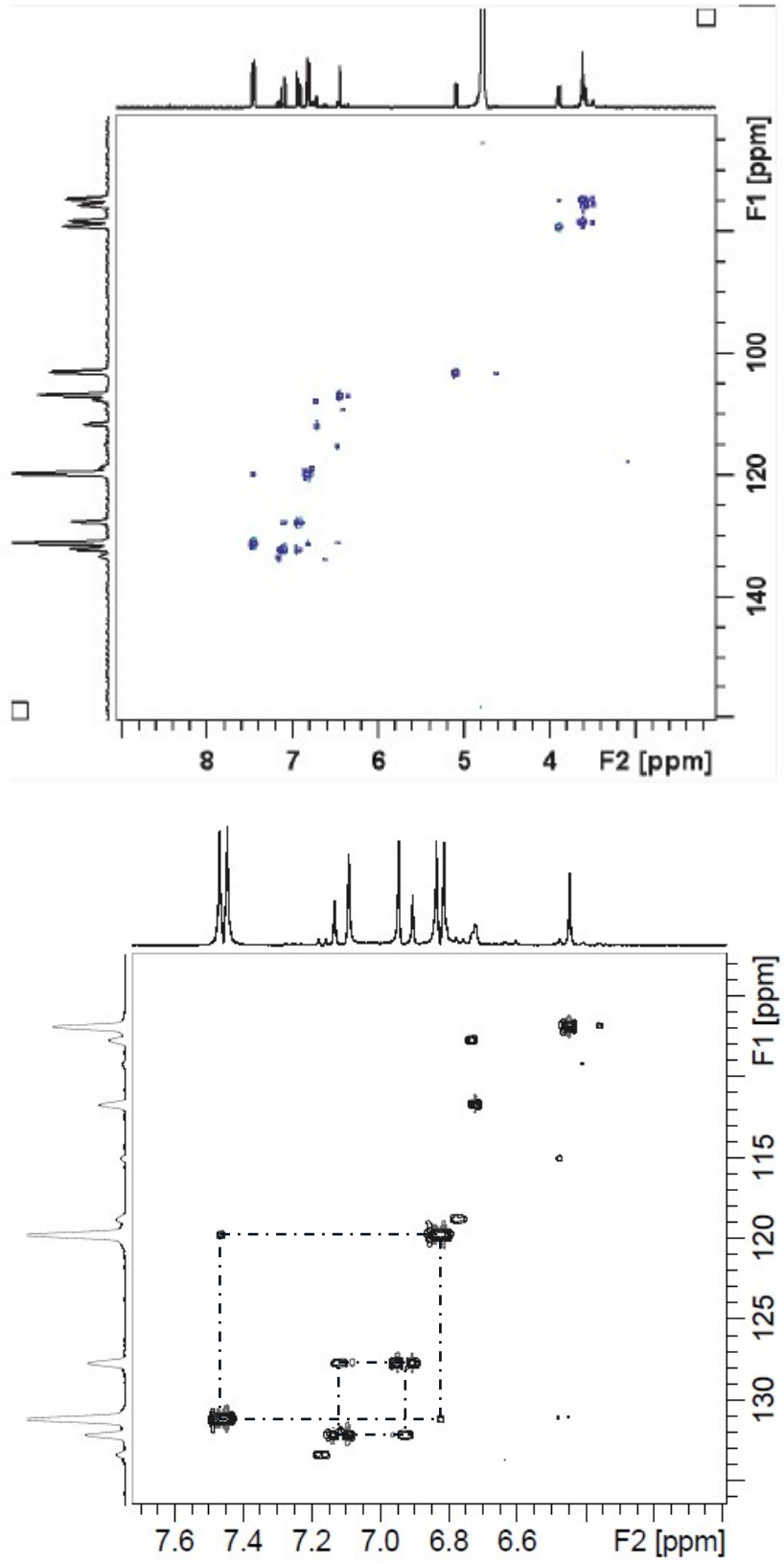


Figure 1 HSQC spectrum of the trans isomer. Top: Full spectrum; Bottom: Expansion of the aromatic region. 2nd order systems indicated by dotted lines.

HMBC spectra

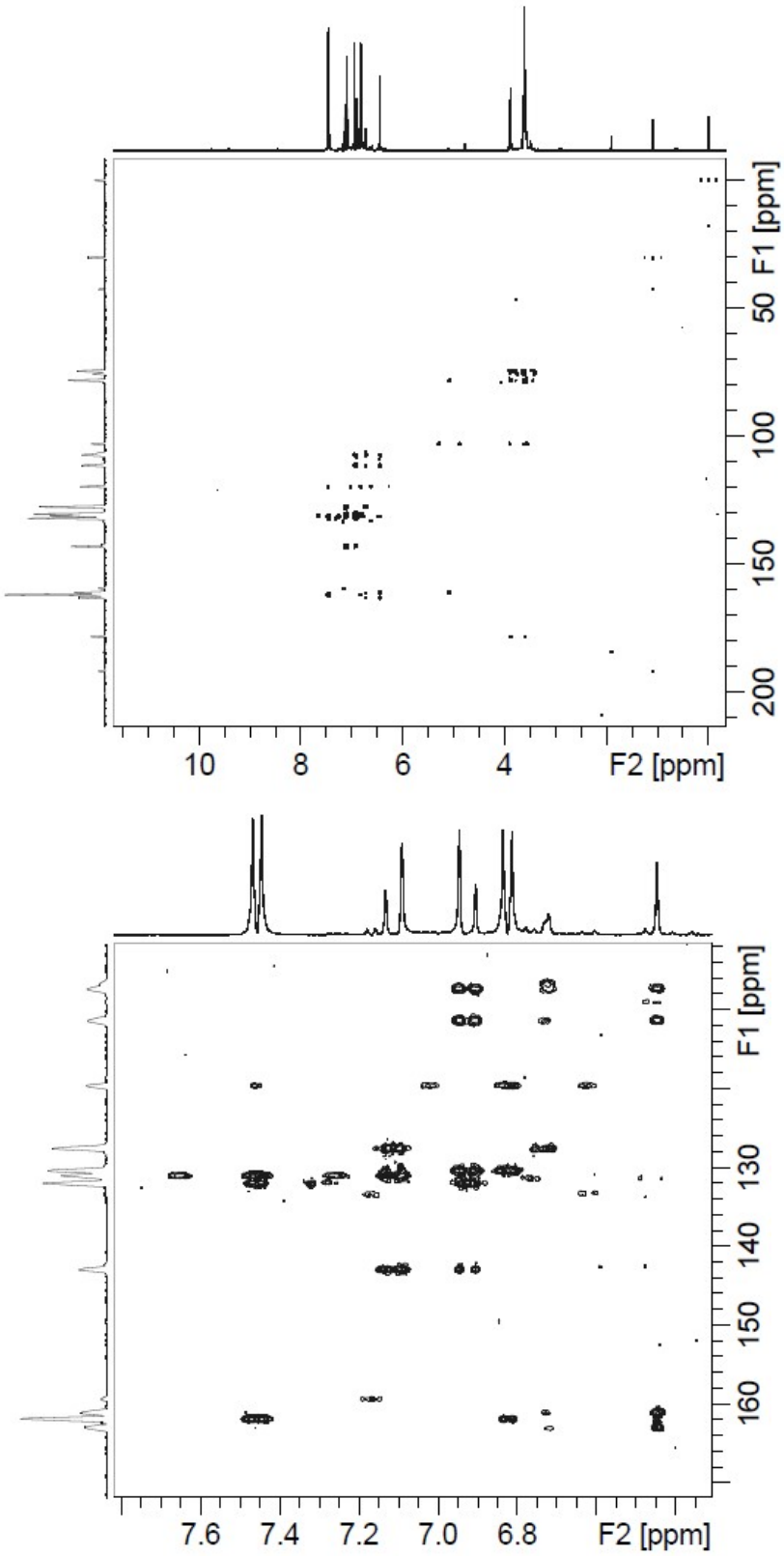


Figure 1 HMBC spectra of the trans isomer. Top: Full spectrum; Bottom: Expansion of the aromatic and quaternary region.

HSQC/HMBC Overlay

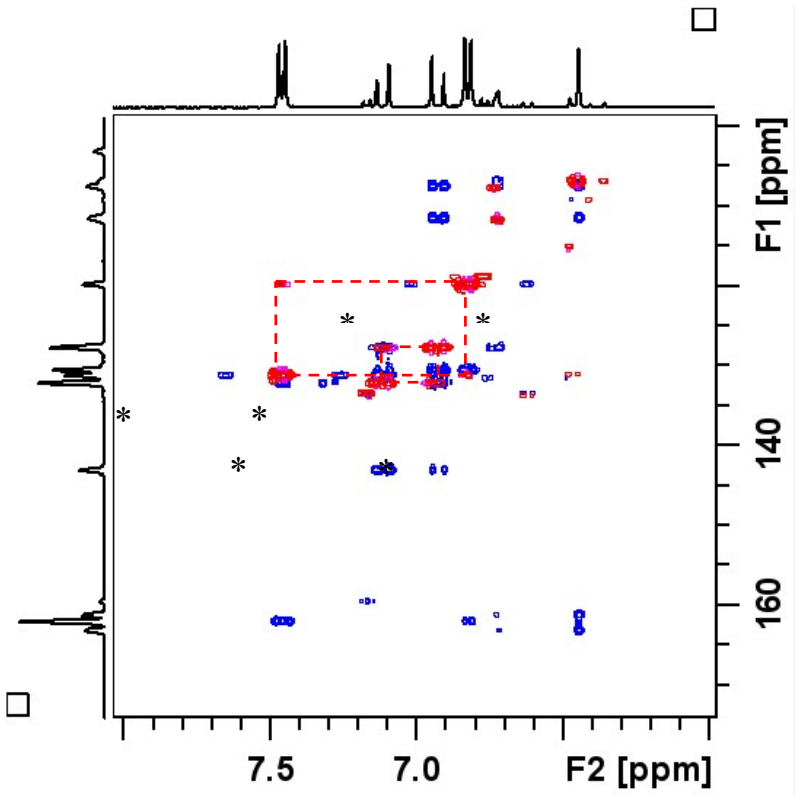
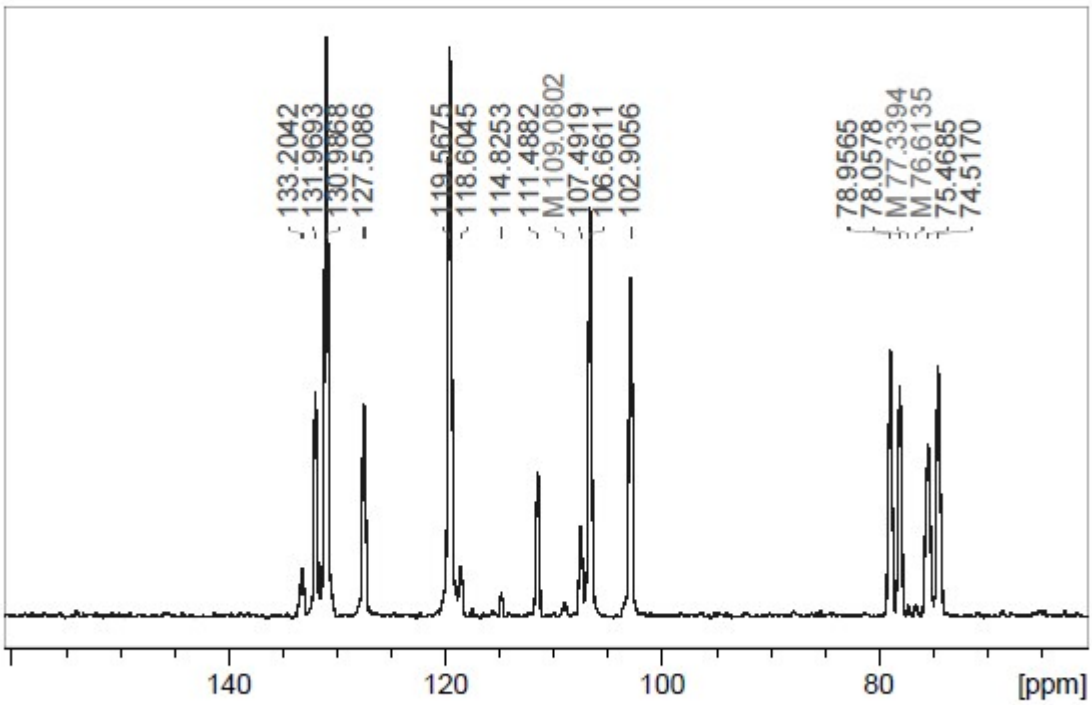
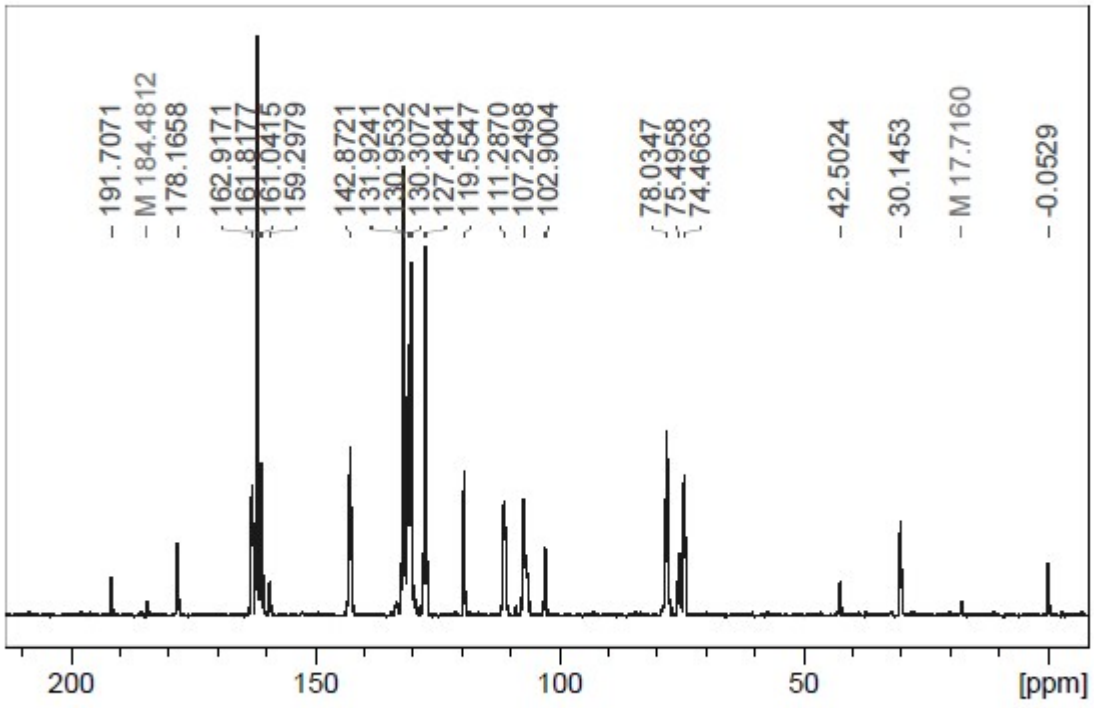


*Figure 1 Overlay of HSQC (red) and HMBC (blue) spectra, contours have been selected to reveal primarily correlations from the trans isomer. * = ^{1}J correlations, dotted boxes indicate correlations from 2nd order spin systems in the HSQC spectra*

HSQC F1 projection



HMBC F1 projection



nOes

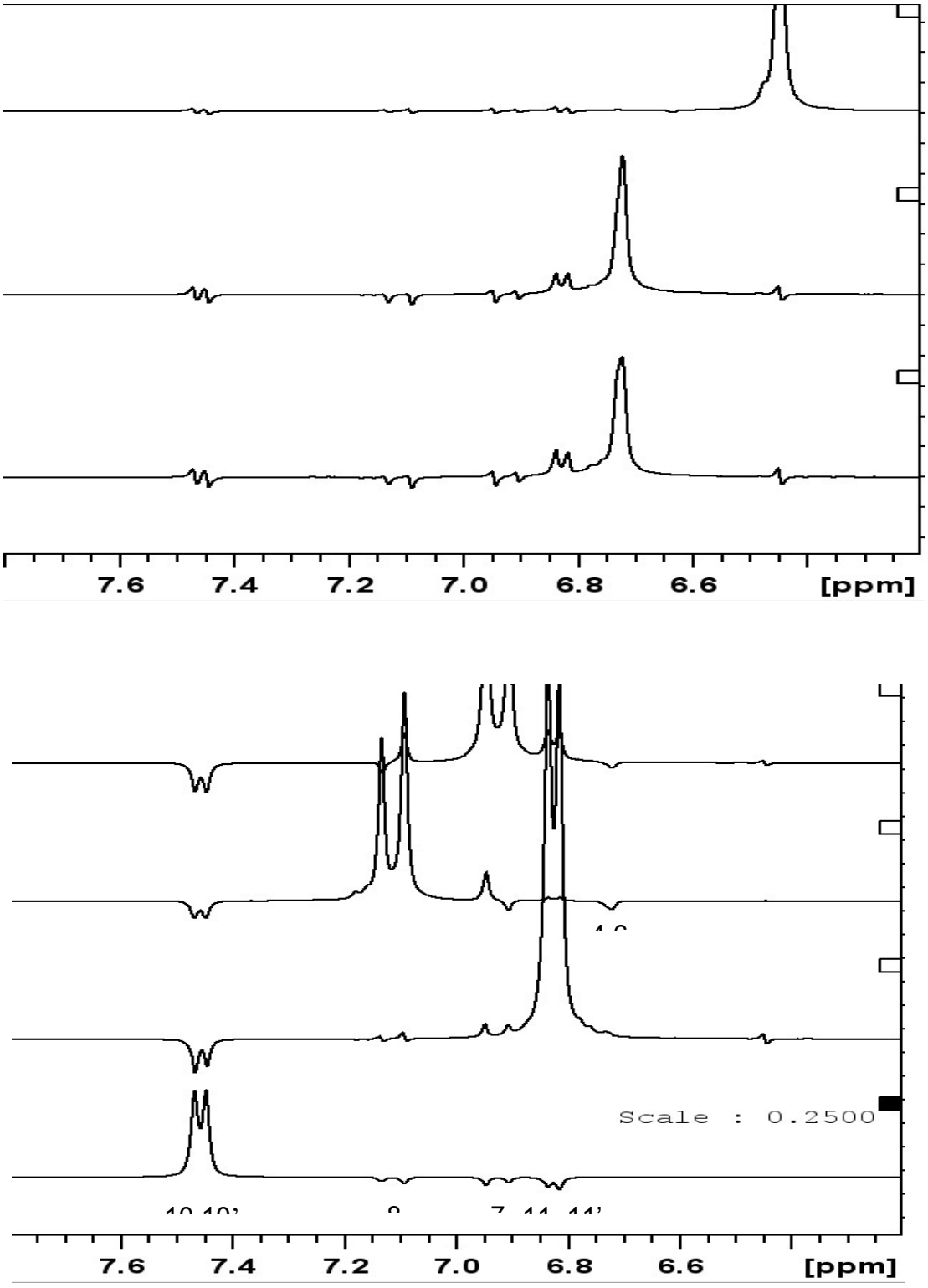
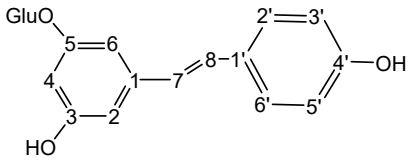


Figure 1 nOe difference spectra of the trans isomer

Table of observed nOes, *trans* isomer

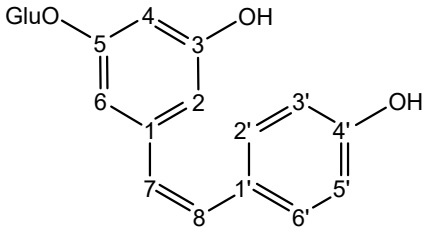


Observed nOe

Source			
H(2',6')	H1'	H8	H3',5'
H(3',5')	H10		
H(8)	H10	H2,6	
H(7)	H10	H2,6	
H(2,6)	H7	H8	
H(4)	OGlu		

Cis isomer

Table of Assignments



cis	δ(C)		δ(H)	^{n}J(HC)		nOe
	HSQC	HMBC				
4	106.5		6.35	-	-	
6[a]	108.7	108.6	6.40	7	2	6/4[a]
2[a]	114.9	114.9	6.46	7	2	4/6[a]
3',5'	118.7	118.8	6.76	10'	11'	H10
7	130.8		6.46	8		H8
1'[b]		131.2		11	7	
2',6'	133.3		7.17	8		H11, H8
8	133.5	133.3	6.62	7		H7, H10
1[b]		142.3		7	8	
4'		159.7		10	11	
5		160.6		2		
3		163.3		2		

[a] Assignment based on chemical shift, may be reversed. [b] Assignment based on chemical shift, may be reversed

^{1}H NMR spectrum

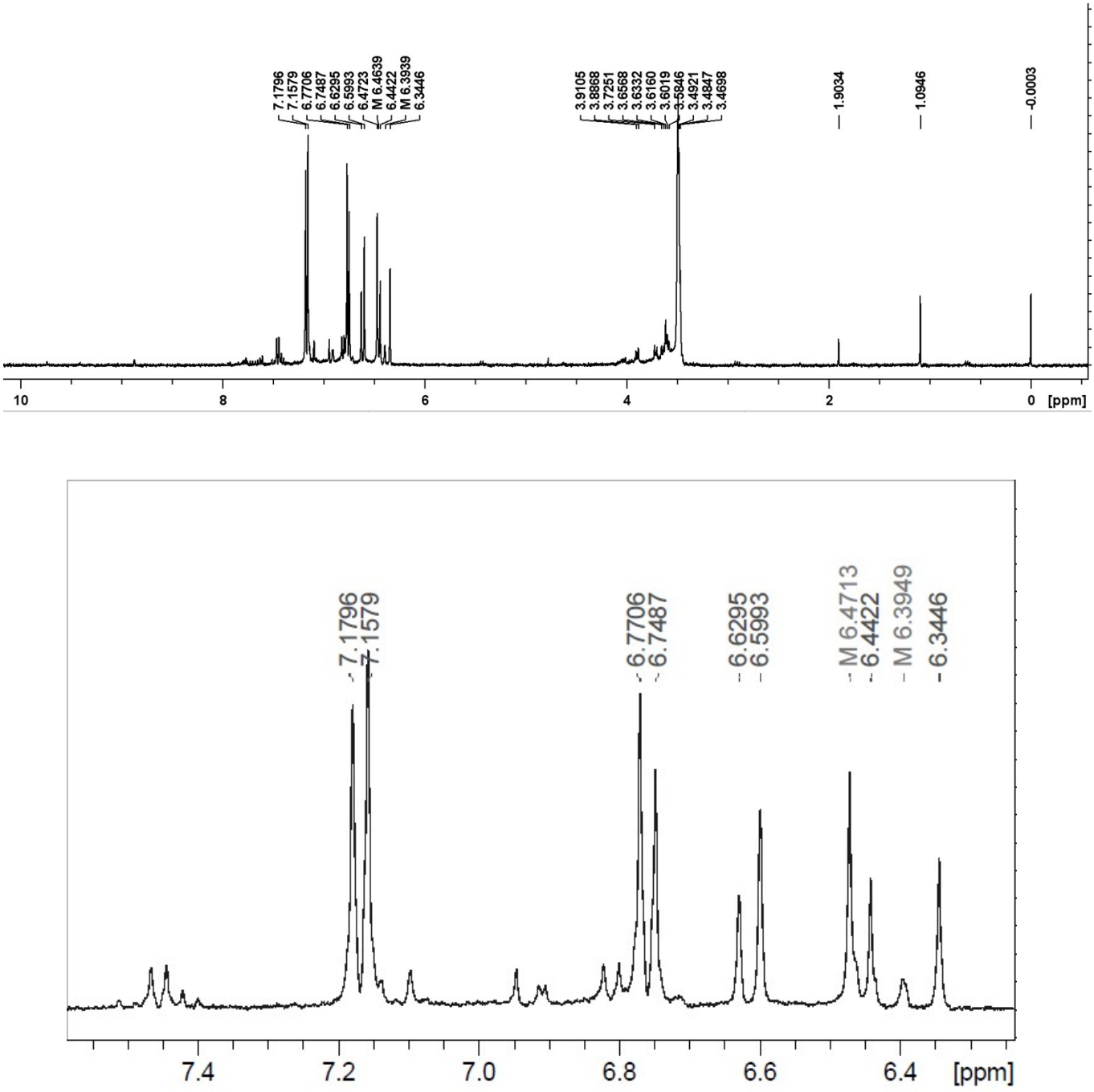
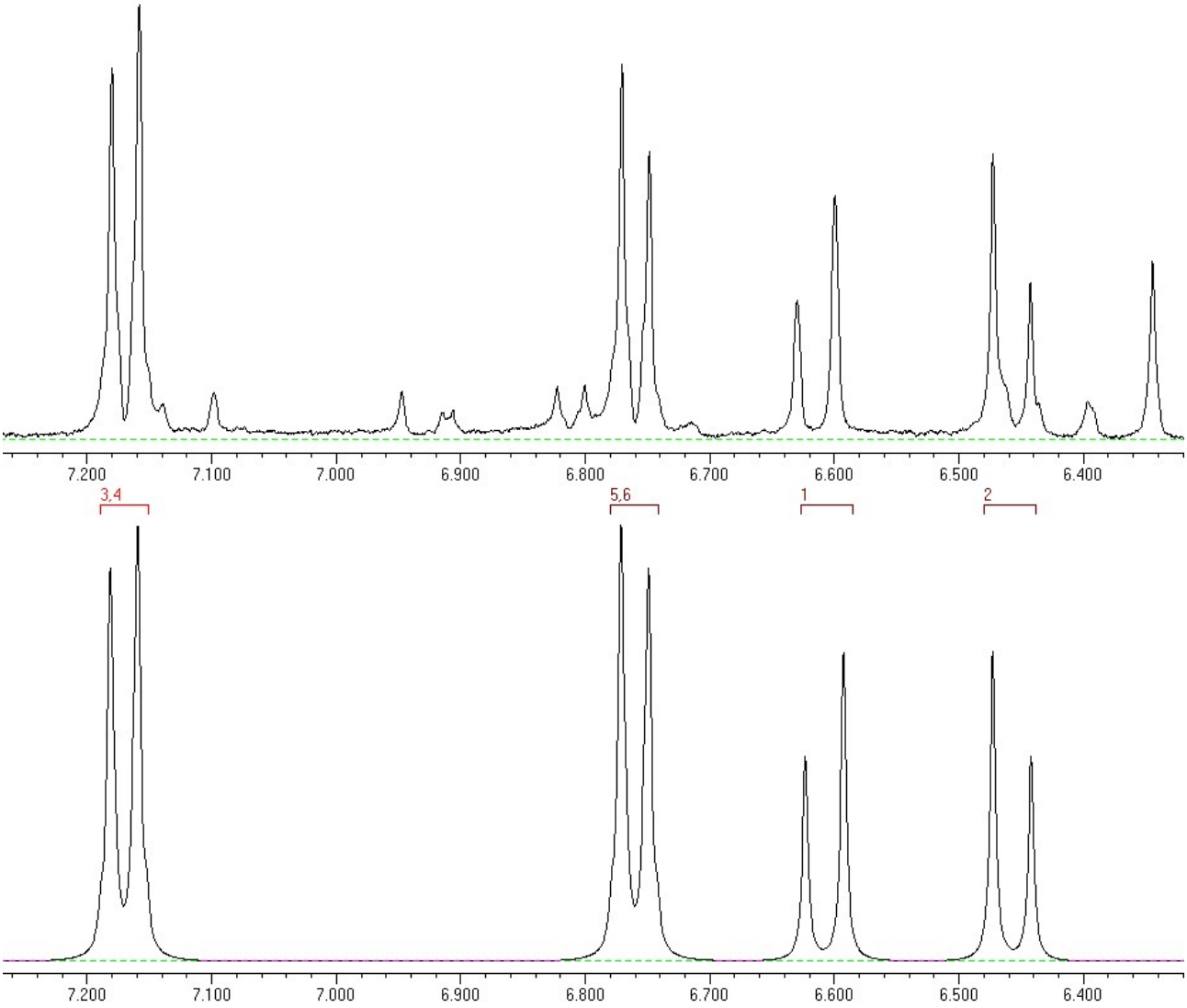


Figure 2 1H NMR spectrum of cis isomer. Top: Full spectrum; Bottom: Expansion of the aromatic region

gNMR simulation of the AA'XX' and AB resonances of the cis isomer



gNMR V5.0 Molecule Description
On Tue Jun 27 16:59:03 2023
Molecule 1

#	Nucleus	n	Shift	Width	J[1]	J[2]	J[3]	J[4]	J[5]
1	1H	1	6.616	2					
2	1H	1	6.459	2	12.31				
3	1H	1	7.170	2	0.00	0.00			
4	1H	1	7.170	2	0.00	0.00	2.16		
5	1H	1	6.760	2	0.00	0.00	9.05	-0.31	
6	1H	1	6.760	2	0.00	0.00	-0.31	9.05	2.16

COSY

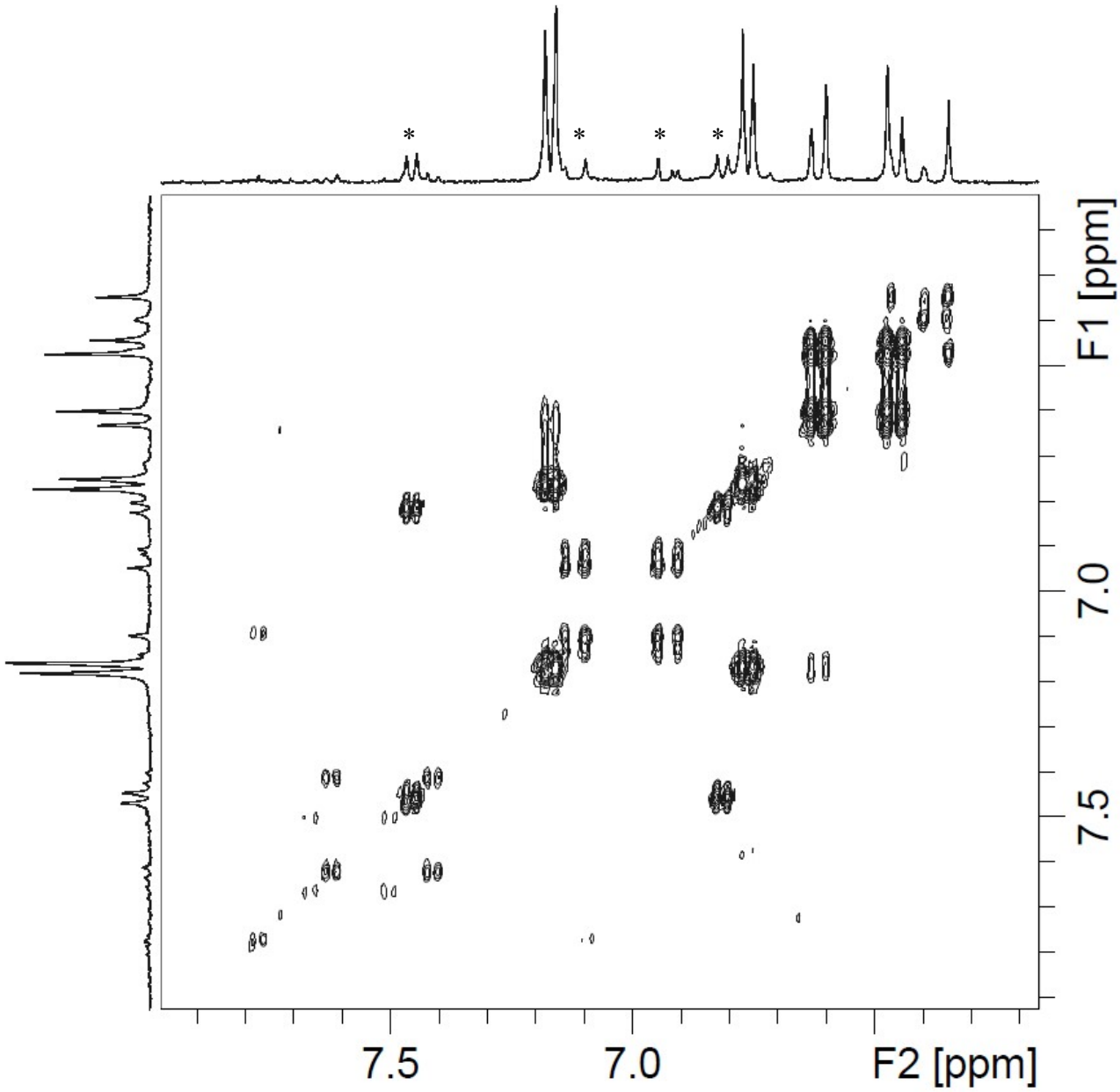


*Figure 3 COSY spectrum of cis isomer. * trans correlations*

HSQC

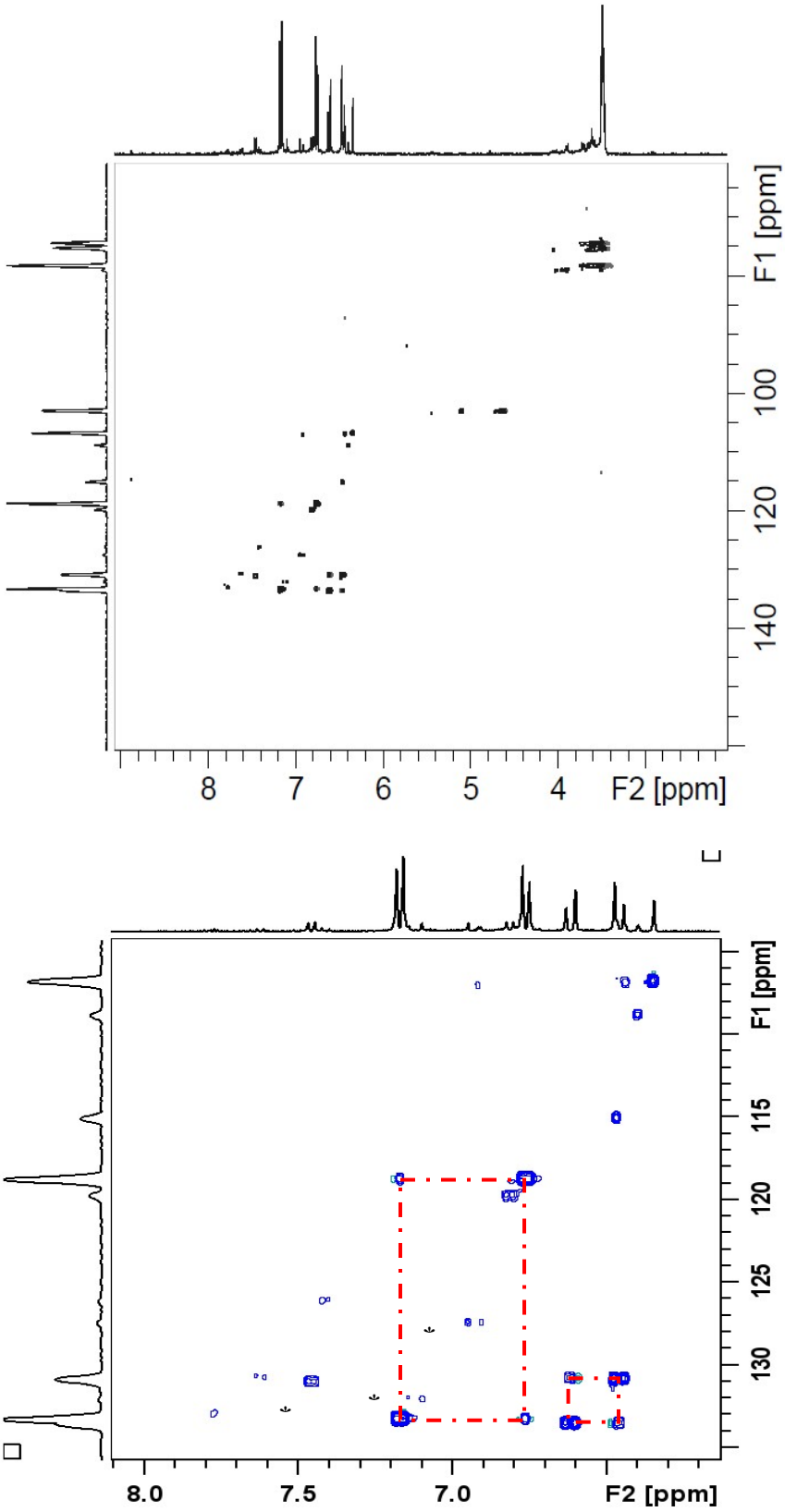


*Figure 3 HSQC spectrum of cis isomer. 2nd order systems indicated by dotted boxes * = correlations from the minor, trans isomer present. Top full spectrum. Bottom expansion of aromatic region*

HMBC

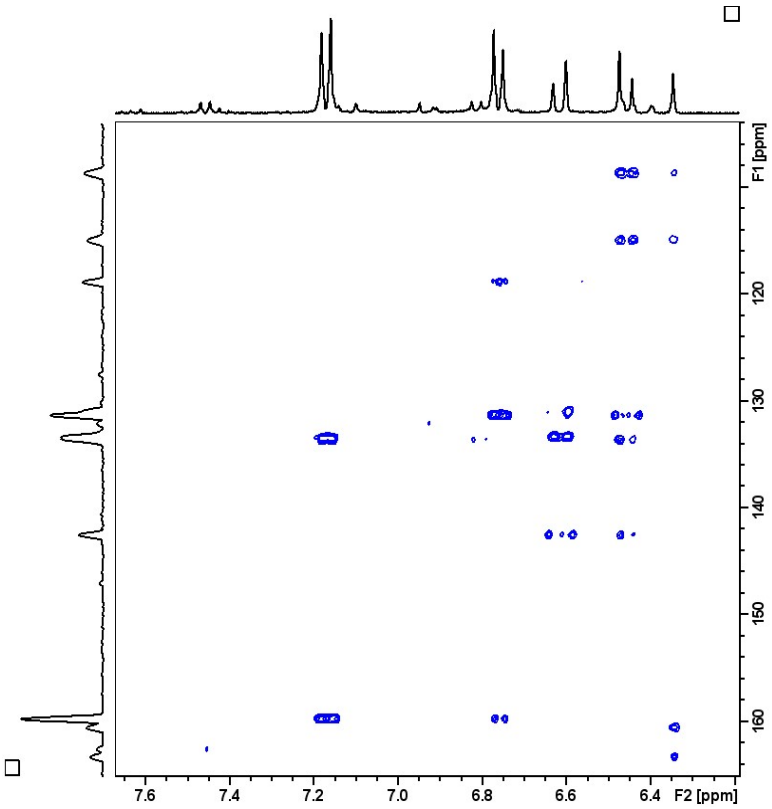


Figure 3 HMBC spectrum of cis isomer.

^{13}C projections

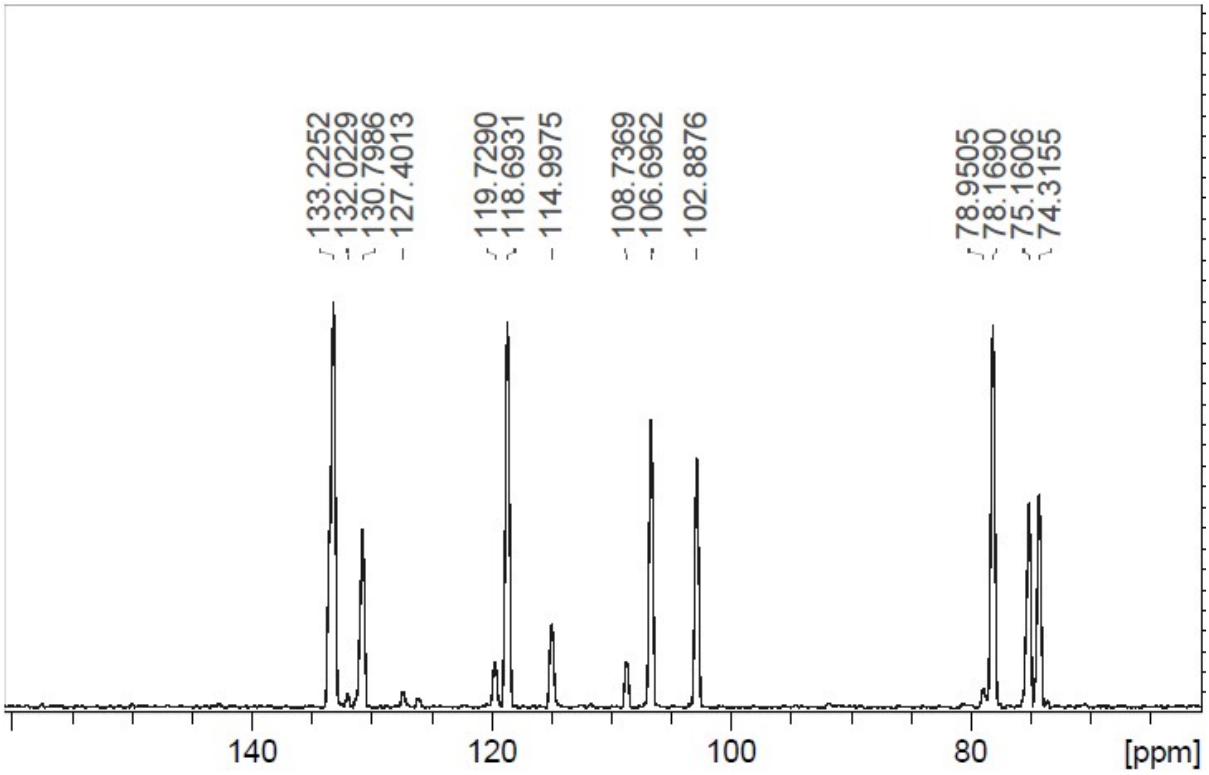


Figure 3 cis isomer HSQC F1 projection

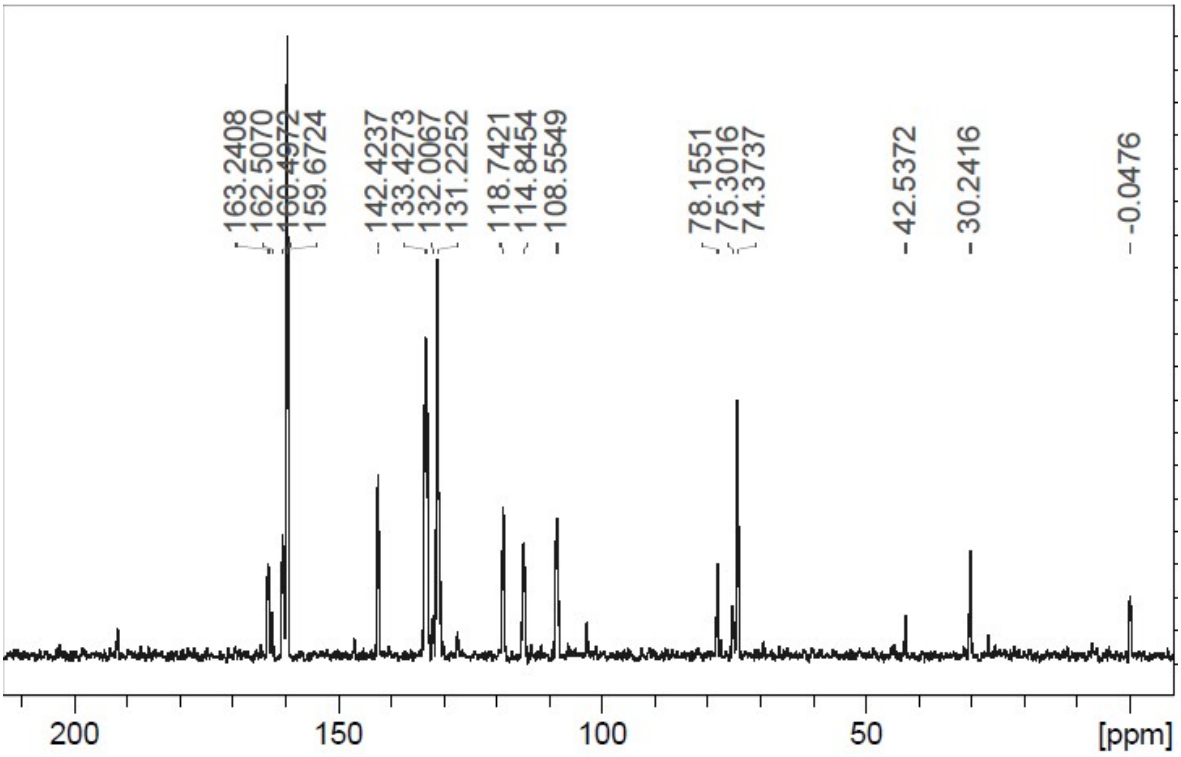


Figure 3 cis isomer HMBC F1 projection

nOes

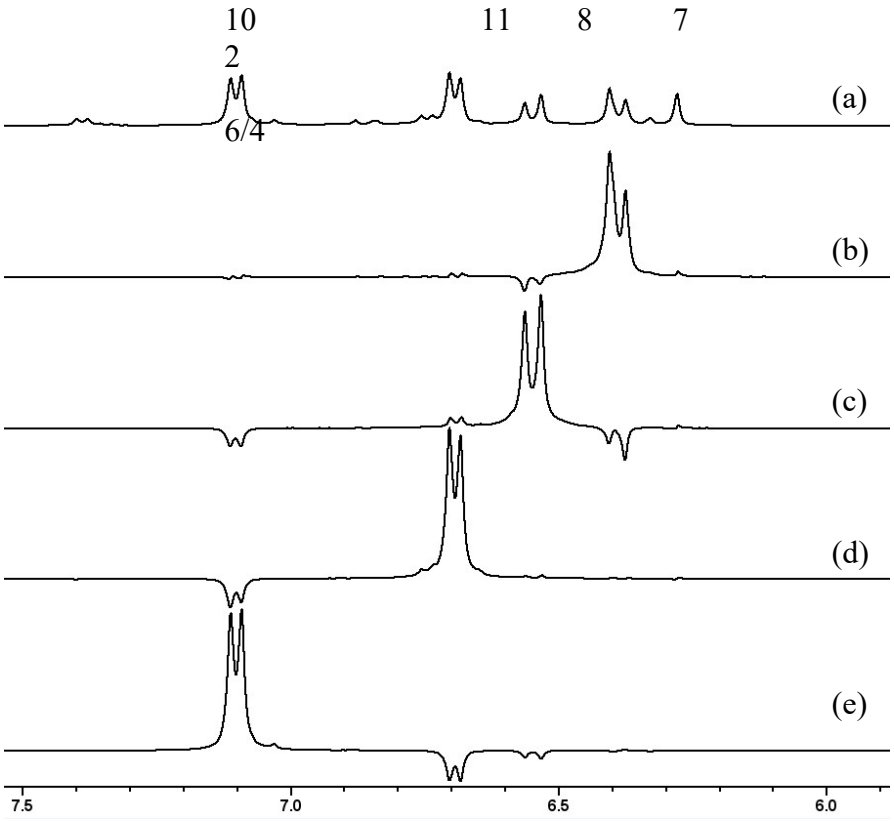
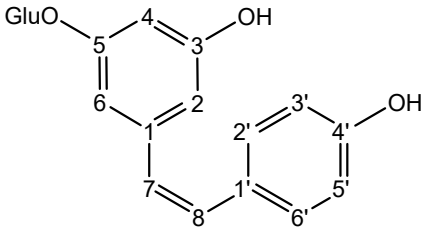


Figure 3 nOe difference spectra of cis-isomer. Strong nOes are seen between the olefinic protons 7 and 8 confirming cis arrangement. nOes from A-ring protons not detectable due to overlap of signals. (A) 1H NMR spectrum. nOe difference spectra irradiat



Source	Observed nOe	
H(2',6')	H3',5'	H8
H(3',5')	H2',6'	
H(8)	H7	H3',5'
H(7)	H8	