

Supporting Information for

Efficient and Stereocontrolled Synthesis of 1,2,4-Trioxolanes Useful for Ferrous Iron-Dependent Drug Delivery

Shaun D. Fontaine, Antonio DiPasquale, and Adam R. Renslo

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General Procedures: Reactions were magnetically stirred unless otherwise indicated. Air and/or moisture sensitive reactions were carried out under an argon atmosphere in oven-dried glassware using anhydrous solvents from commercial suppliers. Air and/or moisture sensitive reagents were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at room temperature at 20 Torr then at 0.5 Torr unless otherwise indicated. Thin phase chromatography was performed on EMD precoated glass-backed silica gel 60 F-254 0.25 mm plate.

Materials: All chemical reagents and solvents used were purchased from Sigma-Aldrich or Fisher Scientific. Anhydrous dichloromethane and tetrahydrofuran (EMD Drisolv) were used without further purification. Ketone **6**, ketone **9**, and Oxime **11** were prepared as described previously (see below).

Preparation of 6: Fontaine, S. D.; Spangler, B. S.; Gut, J.; Lauterwasser, E. M. W.; Rosenthal, P. J.; Renslo, A. R. *ChemMedChem*, **2014**, *9*, accepted.

Preparation of 9: Karmee, S. K.; van Oosten, R.; Hanefeld, U. *Tetrahedron: Asymmetry* **2011**, *22*, 1736-1739.

Preparation of 11: Vennerstrom, J. L.; Dong, Y.; Chollet, J.; Matile, H.; Padmanilayam, M.; Tang, Y.; Charman, W. N. Preparation of spiro and dispiro 1,2,4-trioxolane as antimalarials. U.S. Pat. Appl. Publ., 20040186168, 23 Sep 2004)

Instrumentation: ¹H NMR spectra were recorded on a Varian INOVA-400 400 MHz spectrometer. Chemical shifts are reported in δ units (ppm). NMR spectra were referenced relative to residual NMR solvent peaks. Coupling constants (J) are reported in hertz (Hz). Column chromatography was performed on Silicycle Sili-prep cartridges using a Biotage Isolera Four automated flash chromatography system. LC/MS and compound purity were determined using Waters Micromass ZQTM, equipped with Waters 2795 Separation Module and Waters 2996 Photodiode Array Detector. Separations were carried out with an XTerra® MS C18, 5μm, 4.6 x 50 mm column, at ambient temperature (unregulated) using a mobile phase of water-acetonitrile containing a constant 0.20 % formic acid. High resolution MS data was collected at the UCSF Mass Spectrometry Facility.

Synthetic Procedures

3'' ethenyldispiro[adamantane 2,2' [1,3,5]trioxolane 4',1'' cyclohexane] 3'' ol (8). A heat-gun dried, 25-mL, two-necked round bottom flask equipped with an argon inlet adapter, stirbar, and rubber septum was charged with CeCl₃ (110 mg, 0.446 mmol, 1.2 equiv) evacuated, heated with a heat gun, back filled with argon, and allowed to cool to rt. A solution of ketone **6**

(100 mg, 0.359 mmol, 1 equiv) in THF (5 mL) was added and the resulting mixture was stirred at rt for 1 h and then sonicated at rt for 5 min. The resulting suspension was cooled at -78 °C while a solution of vinyl magnesium bromide (0.480 mL, 0.431 mmol, 1.2 equiv) was added dropwise via syringe such that the internal temperature did not exceed -70 °C. The reaction mixture was stirred for 30 min at -78 °C. Another portion of vinylmagnesium bromide (0.480 mL, 0.431 mmol, 1.2 equiv) was added dropwise via syringe and the reaction mixture was stirred at -78 °C for 30 min. The reaction mixture was diluted with 20 mL of EtOAc, 20 mL of H₂O, and 10 mL of 10% aq KHSO₄ solution. The aqueous layer was separated and extracted with three 20-mL portions of EtOAc. The combined organic phases were washed with 20 mL of satd. aq. NaCl solution, dried over MgSO₄, filtered, and concentrated to afford a pale yellow oil. A solution of this material in 5 mL of CH₂Cl₂ was deposited onto silica gel. The resulting free flowing powder was loaded atop a 25 g column of silica gel. Gradient elution (2-20% EtOAc/hexanes) afforded two separable diastereomers of **8** (0.028 g, 25% yield and 0.034 g, 31% yield).

8 (minor diastereomer): ¹H NMR (400 MHz, CDCl₃) δ 5.88 (dd, *J*=17.2, 10.8 Hz, 1 H), 5.30 (dd, *J*=17.2, 1.5 Hz, 1 H), 5.06 (dd, *J*=10.8, 1.5 Hz, 1 H), 3.92 (s, 1 H), 1.67 - 2.08 (m, 20 H), 1.51 - 1.60 (m, 1 H), 1.41 ppm (td, *J*=13.3, 4.1 Hz, 1 H); ¹³C NMR (400MHz, CDCl₃) δ 144.3, 112.8, 112.4, 109.3, 73.1, 43.8, 36.9, 36.8, 36.4, 36.1, 35.5, 35.0, 34.94, 34.90, 33.6, 26.9, 26.6, 19.3.

8 (major diastereomer): ¹H NMR (400 MHz, CDCl₃) δ 5.90 (dd, *J* = 16.0, 11.2 Hz, 1 H), 5.31 (d, *J* = 17.0 Hz, 1 H), 5.05 (d, *J* = 10.8 Hz, 1 H), 2.70 (s, 1 H), 1.57-2.02 (m, 21 H), 1.43 (td, *J* = 13.0, 4.8 Hz, 1 H); ¹³C NMR (400 MHz, CDCl₃) δ 144.3, 112.8, 112.5, 109.3, 73.1, 43.8, 36.9, 36.8, 36.4, 36.1, 35.5, 35.0, 34.96, 34.9, 33.6, 26.9, 26.6, 19.3; LRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₈H₂₆O₄: 307.1904; found: 307.1900.

3 [(tert butyldiphenylsilyloxy)cyclohexan 1 one (10). A 100-mL recovery flask equipped with a stirbar, rubber septum, and argon inlet was charged with 3-hydroxycyclohexan-1-one (**9**) (1.96 g, 17.2 mmol, 1.0 equiv.), N,N-dimethylformamide (35 mL), and imidazole (2.34 g, 34 mmol, 2.0 equiv). The mixture was cooled at 0 °C while tert-butyl(chloro)diphenyl silane (4.69 mL, 18.0 mmol, 1.1 equiv.) was added rapidly dropwise via syringe. The reaction mixture was allowed to warm to slowly warm to rt, stir at rt for 18 h. The reaction mixture was then diluted with 100 mL of Et₂O and 15 mL H₂O and 15 mL 10% aq KSOH₄. The organic phase was

separated and washed with 3 30-mL portions of 5% aq KHSO₄ solution, washed with 30 mL of satd. aq. NaCl solution, dried over MgSO₄, filtered, and concentrated to afford a colorless oil. Purification via column chromatography on 120 g of silica gel (gradient elution with 0-40% EtOAc/hexanes) afforded 5.71 g of **10** (contaminated with 12% by weight t-BuPh₂SiOH, calculated yield ~80-85%) as a colorless oil that was used in the next step without further purification: IR (neat): 3071, 3047, 2998, 2932, 2892, 2857, 1716, 1487, 1472, 1462, 1427, 1361, 1332, 1315, 1283, 1220, 1111, 1093, 1037, 999, 938, 909, 863, 822, 786, 740, 703, 675, 612 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 7.65 - 7.70 (m, 4 H), 7.37 - 7.48 (m, 6 H), 4.21 (app. quin, *J* = 4.9 Hz, 1 H), 2.45 (d, *J* = 4.9 Hz, 2 H), 2.33 - 2.41 (m, 1 H), 2.22 - 2.31 (m, *J* = 5.3 Hz, 1 H), 2.09 - 2.21 (m, 1 H), 1.76 - 1.82 (m, 2 H), 1.60 - 1.71 (m, 1 H), 1.08 ppm (s, 9 H); ¹³C (100 MHz, CDCl₃) δ 210.1, 136.0, 135.9, 135.0 (TBDPSOH), 134.1, 133.8, 130.0, 129.9, 129.8 (TBDPSOH), 127.91 (TBDPSOH), 127.88, 127.8, 71.2, 50.6, 41.3, 33.1, 27.1, 26.8 (TBDPSOH), 20.7, 19.4; HRMS (ESI) *m/z* [2M+H]⁺ calcd for C₂₂H₂₈O₂Si: 705.3795; found: 705.3776.

Dispiro[adamantane-2,2'-[1,3,5]trioxolane-4',1''-cyclohexane]-3''-ol (13). A 200-mL recovery flask was charged with ketone **10** (3.00 g), carbon tetrachloride (130 mL), and oxime **11** (3.0 g, 17 mmol, ca. 2 equiv). The reaction mixture was cooled at 0 °C while ozone (0.6 L/min, 30% power) was bubbled through the reaction mixture for 1 h. Additional oxime (0.750 g, 4.18 mmol, ca. 0.5 equiv) was added in a single portion and ozone was bubbled through the reaction mixture for an additional 1 h. The reaction mixture was then sparged with O₂ for 5 min, sparged with argon for 5 min, and concentrated to afford intermediate **12** as colorless semi solid.

The crude **12** prepared above was cooled at 0 °C and a solution of TBAF (1.0 M in THF, 40 mL, 40 mmol, ca. 4.7 equiv) was added in a single portion. The resulting reaction mixture was stirred at rt for 3.5 h then diluted with 40 mL of EtOAc and 30 mL of H₂O. The aqueous layer was separated and extracted with four 30-mL portions of EtOAc. The combined organic phases were washed with 40 mL of satd. aq. NaHCO₃ solution, dried over MgSO₄, filtered, and concentrated to afford a yellow oil. Purification via column chromatography on 120 g of silica gel (elution with 0-50% EtOAc/Hex) afforded 1.67 g of alcohol **13** as a 90:10 mixture of diastereomers (67% over 3-steps from **9**) as a colorless semi-solid: IR (neat) 3346, 2933, 2858, 1452, 1382, 1351,

1312, 1252, 1223, 1157, 1122, 1087, 1066, 1046, 1028, 938, 926, 434 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 4.03 - 3.91 (m, 1 H), 2.57 (br. s., 1 H), 2.13 - 1.46 (m, 22 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 112.1, 109.3, 68.2, 41.9, 36.9, 36.4, 36.4, 35.2, 35.1, 34.97, 34.95, 34.0, 33.3, 27.0, 26.6, 19.3; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{24}\text{O}_4$: 281.1747; found: 281.1736

3'' methoxydispiro[adamantane 2,2' [1,3,5]trioxolane 4',1'' cyclohexane] (7). A 4-mL, scintillation vial equipped with a screw cap and stirbar was charged with alcohol **13** (0.020 g, 0.1 mmol, 1.0 equiv.), DMSO (0.5 mL), crushed/powdered KOH (0.100 g, 1.78 mmol, 25 equiv), and iodomethane (22 μL , 0.357 mmol, 5 equiv). The reaction mixture was stirred at rt for 30 min. The reaction mixture was diluted with 20 mL of EtOAc and 20 mL of H_2O . The aqueous layer was separated and extracted with three 20-mL portions of EtOAc. The combined organic phases were washed with 25 mL of satd. aq. NaCl solution, dried over MgSO_4 , filtered, and concentrated to afford a pale yellow oil. Purification via column chromatography on 12 g of silica gel (elution with 5-15% EtOAc/hexanes) afforded 0.019 g (91%) of methyl ether **7** (90:10 dr) as a colorless oil: IR (neat) 2914, 2857, 1452, 1372, 1350, 1300, 1263, 1221, 1167, 1115, 1087, 1086, 1066, 1021, 926, 478 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 3.39-3.48 (m, 1 H, minor diastereomer), 3.36 (s, 3 H, minor diastereomer), 3.35 (s, 3 H), 3.27 (tt, $J=11.2$, 4.3 Hz, 1 H), 2.30 (ddt, $J=12.8$, 4.4, 2.3 Hz, 1 H), 2.18-2.23 (ddt, $J = 12.3$, 4.1, 1.9 Hz, minor diastereomer), 1.65 - 2.08 (m, 17 H), 1.53 - 1.63 (m, 3 H), 1.40 (qt, $J = 13.4$, 3.6 Hz, 1 H), 1.06-1.16 ppm (m, 1 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 112.5, 110.5, 78.6, 56.3, 41.6, 38.04, 37.96, 37.9, 36.0, 35.95, 35.92, 35.90, 35.2, 31.7, 28.5, 28.1, 21.1; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{26}\text{O}_4$: 295.1904; found: 295.1894.

Dispiro[adamantane 2,2' [1,3,5]trioxolane 4',1'' cyclohexane] 3'' yl 4 nitrobenzoate (14). A 4-mL vial was charged with alcohol **13** (0.050 g, 0.2 mmol, 1.0 equiv.), 4-nitrobenzoic acid (0.045 g, 0.268 mmol, 1.5 equiv), 4-dimethylaminopyridine (0.011 g, 0.089 mmol, and $\text{N,N}'$ -dicyclohexylcarbodiimide (0.055 g, 0.31mmol, 1.5 equiv.), and then dichloromethane (1 mL). The reaction mixture was stirred at rt for 2 h and then diluted with 3 mL of EtOAc and filtered with the aid of ~ 10 mL EtOAc. The resulting filtrate was washed with 10 mL satd. aq. NaHCO_3 solution. The aqueous phase was separated and extracted with three 5-mL portions of

EtOAc. The combined organic phases were dried over MgSO_4 , filtered, and concentrated to afford a colorless semi-solid. The resulting residue was dissolved in 10 mL of 10% MeOH/ CH_2Cl_2 and deposited onto 5 g of silica gel. The resulting free flowing powder was loaded atop a 12 g silica gel cartridge and gradient elution (5-100% 15CV EtOAc/Hex) afforded 0.051 g (67%) of benzoate **14** (90:10 dr) as colorless powder: IR (thin film, Et_2O) 2915, 2858, 1724, 1529, 1468, 1451, 1433, 1382, 1321, 1275, 1231, 1170, 1112, 1087, 1073, 1043, 1020, 986, 874, 836, 720 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 8.25 - 8.30 (m, 2 H), 8.20 - 8.24 (m, 2 H), 5.19 (tt, $J=9.2$, 4.7 Hz, 1 H), 2.29 - 2.36 (m, 1 H), 1.52 - 2.08 ppm (m, 21 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 163.9, 150.7, 136.1, 130.9, 123.6, 112.1, 108.5, 72.3, 39.5, 36.9, 36.5, 35.0, 35.0, 34.9, 34.8, 34.2, 30.3, 27.0, 26.6, 19.8; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_7$: 430.1860; found: 430.1855.

Dispiro[adamantane-2,2'-[1,3,5]trioxolane-4',1''-cyclohexane]-3''-yl 4-nitrophenyl carbonate (15). A 50-mL heat-gun dried, two-necked, round-bottomed flask equipped with a stirbar, argon inlet adapter and rubber septum was charged with alcohol **13** (0.500 g, 1.78 mmol, 1.0 equiv), dichloromethane (7 mL), *N,N*-diisopropylethylamine (0.932 mL, 5.35 mmol, 3.0 equiv), and 4-dimethylaminopyridine (0.218 g, 1.78 mmol, 1 equiv). The mixture was cooled to 0 °C while 4-nitrophenyl chloroformate (0.719 g, 3.57 mmol, 2 equiv) was added as a solid in two portions (some gas evolution observed). The reaction mixture was stirred at 0 °C for 15 min, allowed to warm to rt over 10 min, and stirred at rt for 10 min. The reaction mixture was diluted with 30 mL of Et_2O , washed with 10 mL of 5% aq KHSO_4 solution, washed with five 10-mL portions of satd aq NaHCO_3 solution, washed with 25 mL of satd aq NaCl solution, dried over MgSO_4 , filtered, and concentrated to afford a yellow/orange semi-solid. This material was dissolved in 25 mL of CH_2Cl_2 and deposited onto 5 g of silica gel. The free flowing powder was loaded atop a 80 g silica gel cartridge. Gradient elution (0-20% EtOAc/hexanes) afforded 0.747 g (94%) of carbonate **15** (93:7 dr) as pale yellow glassy oil: IR (neat) 2915, 2859, 1765, 1615, 1594, 1526, 1493, 1452, 1348, 1259, 1215, 1168, 1114, 1140, 1087, 1067, 1045, 1020, 980, 858, 758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.26 - 8.31 (m, 2 H), 7.36 - 7.41 (m, 2 H), 4.81 - 4.90 (m, 1 H), 4.92 - 5.00 (m, 1 H, minor diastereomer), 2.40 (ddt, $J=12.9$, 4.3, 1.9 Hz, 1 H), 2.33 - 2.36 (m, 1 H, minor diastereomer), 2.07 - 2.15 (m, 1 H), 1.64 - 2.03 (m, 18 H), 1.55 ppm (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.7, 151.8, 145.5, 125.5, 121.9, 112.2, 108.5, 76.4, 39.8,

36.9, 36.6, 36.5, 35.1, 35.0, 34.9, 33.7, 30.3, 27.0, 26.6, 19.8; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{27}NO_8$: 445.1809; found 446.1789.

Dispiro[adamantane-2,2'-[1,3,5]trioxolane-4',1''-cyclohexane]-3''-yl N-(2-amino-2-methylpropyl)carbamate (16). A 20-mL scintillation vial was charged with carbonate **15** (0.300 g, 0.673 mmol, 1.0 equiv), N,N-dimethylformamide (2 mL), N,N-diisopropylethylamine (0.235 mL, 1.35 mmol, 2 equiv). 2-Methylpropane-1,2-diamine (0.105 mL, 1.01 mmol, 1.5 equiv) was added in a single portion via microliter pipettor. The reaction was stirred at rt for 1h. The reaction mixture was diluted with 30 mL of EtOAc and washed with four 15-mL portions of 1 M aq NaOH solution (until aqueous was no longer bright yellow), washed with 20 mL of satd aq NaCl, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil. Purification via column chromatography on 25 g of silica gel (75-100% EtOAc/hexanes and then 0-15% MeOH/ CH_2Cl_2) afforded 0.248 g (93%) of carbamate **16** (>95:5 dr) as a yellow foamy/sticky oil: IR (neat) 3343, 2933, 2916, 2859, 1702, 1560, 1542, 1452, 1352, 1298, 1250, 1122, 1146, 1114, 1087, 1067, 142, 1021, 1010, 929, 774 cm^{-1} ; 1H NMR (400MHz, $CDCl_3$) δ = 5.10 (br. t, J = 5.9 Hz, 1 H), 4.68 - 4.78 (m, 1 H), 3.01-3.12 (m, 2 H), 2.26 (dt, J = 13.0, 2.2 Hz, 1 H), 1.44 - 2.05 (m, 20 H), 1.21 - 1.35 (m, 1 H), 1.12 ppm (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 111.7, 109.0, 71.1, 52.4, 50.6, 40.5, 37.0, 36.5, 35.1, 35.0, 34.9, 34.0, 31.0, 28.3, 28.2, 27.1, 26.7, 20.0; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{34}N_2O_5$: 395.2540; found: 395.2526.

Crystallographic Procedures and Data

X-ray quality crystals were grown from a saturated toluene/ethanol/methanol solution followed by vapor diffusion of hexane, which was then allowed to partially evaporate at room temperature. After evaporation of 50% of the solvent volume, the sample was cooled to 3 degrees Celsius and allowed to sit for a week before crystals were harvested. A colorless plate 0.080 x 0.080 x 0.030 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 1.0°. Data collection was 99.6% complete to 67.000° in θ . A total of 44013 reflections were collected covering the indices, $-6 \leq h \leq 7$, $-15 \leq k \leq 15$, $-57 \leq l \leq 57$. 3753 reflections were found to be symmetry independent, with an R_{int} of 0.0303. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be Pbc_a (No. 61). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table S1. Crystal data and structure refinement for *trans*-14.

Empirical formula	C ₂₃ H ₂₇ N O ₇	
Formula weight	429.45	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 6.6484(4) Å	α = 90°.
	b = 12.9963(8) Å	β = 90°.
	c = 47.799(3) Å	γ = 90°.
Volume	4130.1(4) Å ³	
Z	8	
Density (calculated)	1.381 Mg/m ³	
Absorption coefficient	0.850 mm ⁻¹	
F(000)	1824	
Crystal size	0.080 x 0.080 x 0.030 mm ³	
Theta range for data collection	3.699 to 68.287°.	
Index ranges	-6 ≤ h ≤ 7, -15 ≤ k ≤ 15, -57 ≤ l ≤ 57	
Reflections collected	44013	
Independent reflections	3753 [R(int) = 0.0303]	
Completeness to theta = 67.000°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.783	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3753 / 0 / 280	
Goodness-of-fit on F ²	1.076	
Final R indices [I > 2σ(I)]	R1 = 0.0712, wR2 = 0.1864	
R indices (all data)	R1 = 0.0727, wR2 = 0.1873	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.333 and -0.383 e.Å ⁻³	

Table S2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for *trans*-**14**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
C(1)	3580(5)	7135(2)	4161(1)	31(1)
C(2)	2926(5)	6016(2)	4170(1)	37(1)
C(3)	777(5)	5934(3)	4282(1)	45(1)
C(4)	663(5)	6394(3)	4575(1)	44(1)
C(5)	2096(6)	5820(3)	4770(1)	51(1)
C(6)	4254(6)	5924(3)	4660(1)	46(1)
C(7)	4809(6)	7072(3)	4647(1)	41(1)
C(8)	3398(5)	7627(2)	4448(1)	33(1)
C(9)	1219(5)	7527(3)	4553(1)	38(1)
C(10)	4374(5)	5453(3)	4370(1)	44(1)
C(11)	5638(5)	8012(2)	3854(1)	30(1)
C(12)	7300(5)	8764(2)	3920(1)	33(1)
C(13)	7485(5)	9594(2)	3693(1)	34(1)
C(14)	7785(5)	9092(3)	3405(1)	33(1)
C(15)	6036(5)	8384(2)	3343(1)	29(1)
C(16)	5803(5)	7548(2)	3563(1)	31(1)
C(17)	6133(4)	8328(2)	2841(1)	26(1)
C(18)	6374(4)	7628(2)	2595(1)	24(1)
C(19)	6145(4)	8050(2)	2329(1)	25(1)
C(20)	6366(4)	7438(2)	2094(1)	26(1)
C(21)	6842(4)	6411(2)	2131(1)	25(1)
C(22)	7081(4)	5968(2)	2393(1)	26(1)
C(23)	6828(4)	6587(2)	2626(1)	26(1)
N(1)	7121(4)	5763(2)	1882(1)	30(1)
O(1)	2415(3)	7662(2)	3953(1)	35(1)
O(2)	3754(3)	8531(2)	3891(1)	32(1)
O(3)	5597(3)	7207(2)	4058(1)	33(1)
O(4)	6345(3)	7813(2)	3083(1)	28(1)
O(5)	5783(3)	9239(2)	2823(1)	31(1)
O(6)	8163(3)	4988(2)	1905(1)	36(1)
O(7)	6305(4)	6031(2)	1665(1)	40(1)

Table S3. Bond lengths [\AA] and angles [$^\circ$] for *trans*-14.

C(1)-O(3)	1.432(4)	C(12)-C(13)	1.535(4)
C(1)-O(1)	1.434(4)	C(12)-H(12A)	0.9900
C(1)-C(2)	1.519(4)	C(12)-H(12B)	0.9900
C(1)-C(8)	1.520(4)	C(13)-C(14)	1.534(4)
C(2)-C(3)	1.529(5)	C(13)-H(13A)	0.9900
C(2)-C(10)	1.541(5)	C(13)-H(13B)	0.9900
C(2)-H(2)	1.0000	C(14)-C(15)	1.512(4)
C(3)-C(4)	1.526(5)	C(14)-H(14A)	0.9900
C(3)-H(3A)	0.9900	C(14)-H(14B)	0.9900
C(3)-H(3B)	0.9900	C(15)-O(4)	1.464(3)
C(4)-C(9)	1.522(5)	C(15)-C(16)	1.521(4)
C(4)-C(5)	1.528(5)	C(15)-H(15)	1.0000
C(4)-H(4)	1.0000	C(16)-H(16A)	0.9900
C(5)-C(6)	1.534(5)	C(16)-H(16B)	0.9900
C(5)-H(5A)	0.9900	C(17)-O(5)	1.209(4)
C(5)-H(5B)	0.9900	C(17)-O(4)	1.343(3)
C(6)-C(10)	1.521(5)	C(17)-C(18)	1.498(4)
C(6)-C(7)	1.538(5)	C(18)-C(19)	1.392(4)
C(6)-H(6)	1.0000	C(18)-C(23)	1.394(4)
C(7)-C(8)	1.515(5)	C(19)-C(20)	1.384(4)
C(7)-H(7A)	0.9900	C(19)-H(19)	0.9500
C(7)-H(7B)	0.9900	C(20)-C(21)	1.384(4)
C(8)-C(9)	1.538(4)	C(20)-H(20)	0.9500
C(8)-H(8)	1.0000	C(21)-C(22)	1.386(4)
C(9)-H(9A)	0.9900	C(21)-N(1)	1.469(4)
C(9)-H(9B)	0.9900	C(22)-C(23)	1.386(4)
C(10)-H(10A)	0.9900	C(22)-H(22)	0.9500
C(10)-H(10B)	0.9900	C(23)-H(23)	0.9500
C(11)-O(3)	1.428(3)	N(1)-O(7)	1.224(3)
C(11)-O(2)	1.433(4)	N(1)-O(6)	1.227(3)
C(11)-C(12)	1.508(4)	O(1)-O(2)	1.468(3)
C(11)-C(16)	1.521(4)		
O(3)-C(1)-O(1)	103.6(2)	O(3)-C(1)-C(2)	109.9(3)

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O(1)-C(1)-C(2)	108.8(3)	C(6)-C(7)-H(7A)	109.7
O(3)-C(1)-C(8)	111.1(2)	C(8)-C(7)-H(7B)	109.7
O(1)-C(1)-C(8)	112.5(2)	C(6)-C(7)-H(7B)	109.7
C(2)-C(1)-C(8)	110.7(3)	H(7A)-C(7)-H(7B)	108.2
C(1)-C(2)-C(3)	110.2(3)	C(7)-C(8)-C(1)	108.4(3)
C(1)-C(2)-C(10)	107.1(3)	C(7)-C(8)-C(9)	109.9(3)
C(3)-C(2)-C(10)	109.5(3)	C(1)-C(8)-C(9)	109.5(3)
C(1)-C(2)-H(2)	110.0	C(7)-C(8)-H(8)	109.7
C(3)-C(2)-H(2)	110.0	C(1)-C(8)-H(8)	109.7
C(10)-C(2)-H(2)	110.0	C(9)-C(8)-H(8)	109.7
C(4)-C(3)-C(2)	109.9(3)	C(4)-C(9)-C(8)	109.4(3)
C(4)-C(3)-H(3A)	109.7	C(4)-C(9)-H(9A)	109.8
C(2)-C(3)-H(3A)	109.7	C(8)-C(9)-H(9A)	109.8
C(4)-C(3)-H(3B)	109.7	C(4)-C(9)-H(9B)	109.8
C(2)-C(3)-H(3B)	109.7	C(8)-C(9)-H(9B)	109.8
H(3A)-C(3)-H(3B)	108.2	H(9A)-C(9)-H(9B)	108.2
C(9)-C(4)-C(3)	107.7(3)	C(6)-C(10)-C(2)	110.0(3)
C(9)-C(4)-C(5)	111.3(3)	C(6)-C(10)-H(10A)	109.7
C(3)-C(4)-C(5)	109.8(3)	C(2)-C(10)-H(10A)	109.7
C(9)-C(4)-H(4)	109.3	C(6)-C(10)-H(10B)	109.7
C(3)-C(4)-H(4)	109.3	C(2)-C(10)-H(10B)	109.7
C(5)-C(4)-H(4)	109.3	H(10A)-C(10)-H(10B)	108.2
C(4)-C(5)-C(6)	109.3(3)	O(3)-C(11)-O(2)	104.2(2)
C(4)-C(5)-H(5A)	109.8	O(3)-C(11)-C(12)	110.4(2)
C(6)-C(5)-H(5A)	109.8	O(2)-C(11)-C(12)	108.0(2)
C(4)-C(5)-H(5B)	109.8	O(3)-C(11)-C(16)	109.5(2)
C(6)-C(5)-H(5B)	109.8	O(2)-C(11)-C(16)	111.2(2)
H(5A)-C(5)-H(5B)	108.3	C(12)-C(11)-C(16)	113.2(2)
C(10)-C(6)-C(5)	109.1(3)	C(11)-C(12)-C(13)	111.6(2)
C(10)-C(6)-C(7)	109.8(3)	C(11)-C(12)-H(12A)	109.3
C(5)-C(6)-C(7)	108.9(3)	C(13)-C(12)-H(12A)	109.3
C(10)-C(6)-H(6)	109.7	C(11)-C(12)-H(12B)	109.3
C(5)-C(6)-H(6)	109.7	C(13)-C(12)-H(12B)	109.3
C(7)-C(6)-H(6)	109.7	H(12A)-C(12)-H(12B)	108.0
C(8)-C(7)-C(6)	109.8(3)	C(14)-C(13)-C(12)	110.1(3)
C(8)-C(7)-H(7A)	109.7	C(14)-C(13)-H(13A)	109.6

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C(12)-C(13)-H(13A)	109.6	C(22)-C(21)-N(1)	118.6(3)
C(14)-C(13)-H(13B)	109.6	C(23)-C(22)-C(21)	118.2(3)
C(12)-C(13)-H(13B)	109.6	C(23)-C(22)-H(22)	120.9
H(13A)-C(13)-H(13B)	108.2	C(21)-C(22)-H(22)	120.9
C(15)-C(14)-C(13)	109.6(2)	C(22)-C(23)-C(18)	120.1(3)
C(15)-C(14)-H(14A)	109.7	C(22)-C(23)-H(23)	119.9
C(13)-C(14)-H(14A)	109.7	C(18)-C(23)-H(23)	119.9
C(15)-C(14)-H(14B)	109.7	O(7)-N(1)-O(6)	124.0(3)
C(13)-C(14)-H(14B)	109.7	O(7)-N(1)-C(21)	118.0(2)
H(14A)-C(14)-H(14B)	108.2	O(6)-N(1)-C(21)	118.0(2)
O(4)-C(15)-C(14)	111.6(2)	C(1)-O(1)-O(2)	100.4(2)
O(4)-C(15)-C(16)	103.9(2)	C(11)-O(2)-O(1)	101.1(2)
C(14)-C(15)-C(16)	112.1(2)	C(11)-O(3)-C(1)	107.5(2)
O(4)-C(15)-H(15)	109.7	C(17)-O(4)-C(15)	117.6(2)
C(14)-C(15)-H(15)	109.7		
C(16)-C(15)-H(15)	109.7		
C(15)-C(16)-C(11)	110.9(2)		
C(15)-C(16)-H(16A)	109.5		
C(11)-C(16)-H(16A)	109.5		
C(15)-C(16)-H(16B)	109.5		
C(11)-C(16)-H(16B)	109.5		
H(16A)-C(16)-H(16B)	108.0		
O(5)-C(17)-O(4)	124.9(3)		
O(5)-C(17)-C(18)	123.9(3)		
O(4)-C(17)-C(18)	111.2(2)		
C(19)-C(18)-C(23)	120.4(3)		
C(19)-C(18)-C(17)	117.8(3)		
C(23)-C(18)-C(17)	121.8(3)		
C(20)-C(19)-C(18)	120.2(3)		
C(20)-C(19)-H(19)	119.9		
C(18)-C(19)-H(19)	119.9		
C(21)-C(20)-C(19)	118.3(3)		
C(21)-C(20)-H(20)	120.9		
C(19)-C(20)-H(20)	120.9		
C(20)-C(21)-C(22)	122.9(3)		
C(20)-C(21)-N(1)	118.5(3)		

Symmetry transformations used to generate equivalent atoms:

Table S4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for *trans*-**14**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
C(1)	25(2)	34(2)	32(2)	2(1)	1(1)	0(1)
C(2)	41(2)	31(2)	39(2)	-6(1)	3(1)	-1(1)
C(3)	37(2)	37(2)	62(2)	4(2)	0(2)	-8(2)
C(4)	32(2)	43(2)	58(2)	11(2)	17(2)	5(2)
C(5)	54(2)	48(2)	51(2)	21(2)	19(2)	11(2)
C(6)	43(2)	54(2)	41(2)	18(2)	4(2)	14(2)
C(7)	44(2)	48(2)	31(2)	3(1)	-1(1)	0(2)
C(8)	36(2)	29(2)	33(2)	-1(1)	2(1)	-1(1)
C(9)	41(2)	37(2)	37(2)	3(1)	12(1)	8(2)
C(10)	40(2)	32(2)	59(2)	8(2)	13(2)	7(2)
C(11)	29(2)	36(2)	27(1)	6(1)	2(1)	-1(1)
C(12)	31(2)	37(2)	30(1)	-2(1)	-2(1)	0(1)
C(13)	35(2)	35(2)	32(2)	-3(1)	-2(1)	-7(1)
C(14)	28(2)	40(2)	32(2)	-1(1)	2(1)	-6(1)
C(15)	29(2)	33(2)	24(1)	-2(1)	2(1)	-1(1)
C(16)	32(2)	32(2)	30(2)	-1(1)	1(1)	-3(1)
C(17)	18(1)	35(2)	25(1)	4(1)	-1(1)	-5(1)
C(18)	14(1)	25(1)	32(1)	0(1)	-1(1)	0(1)
C(19)	20(1)	27(1)	28(1)	1(1)	-1(1)	-2(1)
C(20)	20(1)	29(2)	30(1)	5(1)	-1(1)	0(1)
C(21)	16(1)	33(2)	26(1)	-5(1)	1(1)	-2(1)
C(22)	18(1)	26(2)	35(1)	2(1)	1(1)	-2(1)
C(23)	17(1)	34(2)	26(1)	2(1)	0(1)	-4(1)
N(1)	25(1)	31(1)	33(1)	-2(1)	4(1)	-2(1)
O(1)	29(1)	39(1)	36(1)	5(1)	-2(1)	-1(1)
O(2)	29(1)	34(1)	35(1)	6(1)	3(1)	0(1)
O(3)	27(1)	39(1)	32(1)	5(1)	3(1)	3(1)
O(4)	31(1)	28(1)	26(1)	-1(1)	1(1)	0(1)
O(5)	33(1)	26(1)	32(1)	0(1)	0(1)	2(1)
O(6)	33(1)	38(1)	38(1)	-4(1)	7(1)	3(1)
O(7)	47(1)	43(1)	29(1)	-3(1)	-8(1)	2(1)

Table S5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for *trans*-**14**.

	x	y	z	U(eq)
H(2)	3007	5708	3979	44
H(3A)	-154	6306	4156	54
H(3B)	363	5202	4288	54
H(4)	-743	6331	4647	53
H(5A)	1716	5085	4780	61
H(5B)	2007	6112	4961	61
H(6)	5201	5558	4789	55
H(7A)	4711	7380	4835	49
H(7B)	6213	7148	4581	49
H(8)	3779	8370	4437	39
H(9A)	1085	7860	4738	46
H(9B)	296	7877	4421	46
H(10A)	4013	4715	4379	52
H(10B)	5767	5507	4298	52
H(12A)	8590	8388	3935	39
H(12B)	7027	9096	4102	39
H(13A)	6253	10022	3690	41
H(13B)	8642	10048	3735	41
H(14A)	7876	9630	3260	40
H(14B)	9055	8694	3404	40
H(15)	4767	8794	3330	34
H(16A)	6977	7080	3556	38
H(16B)	4582	7138	3523	38
H(19)	5837	8760	2309	30
H(20)	6194	7716	1912	31
H(22)	7410	5260	2412	31
H(23)	6964	6302	2808	31

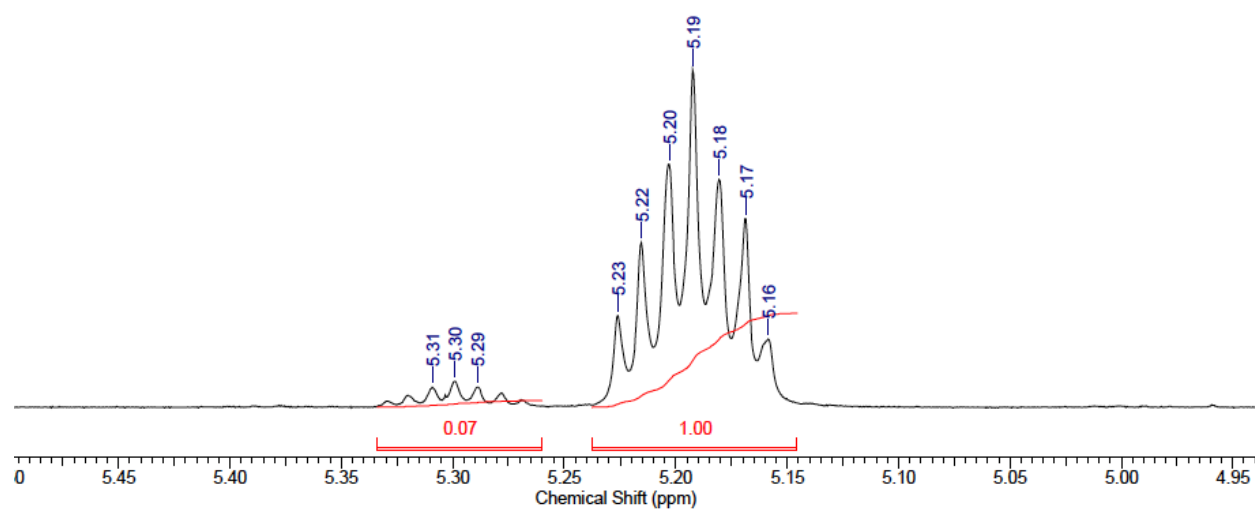
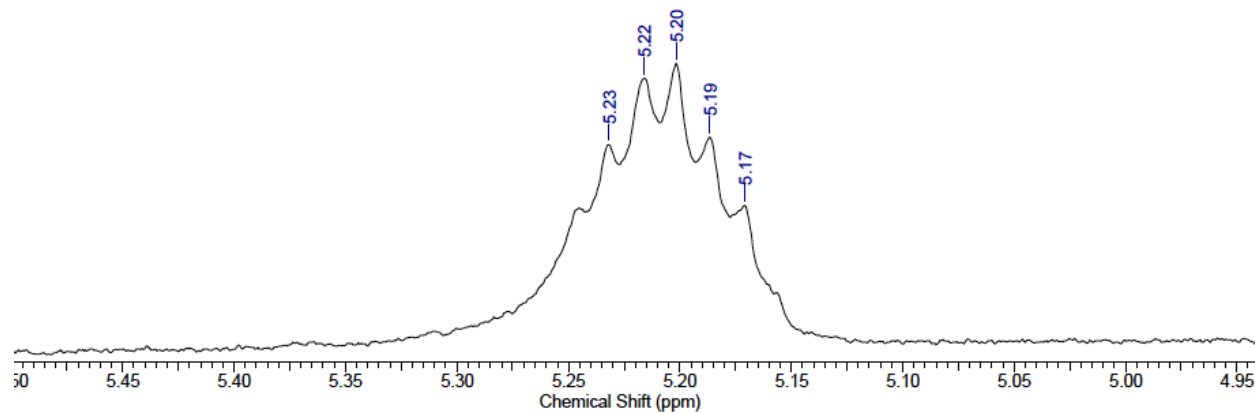
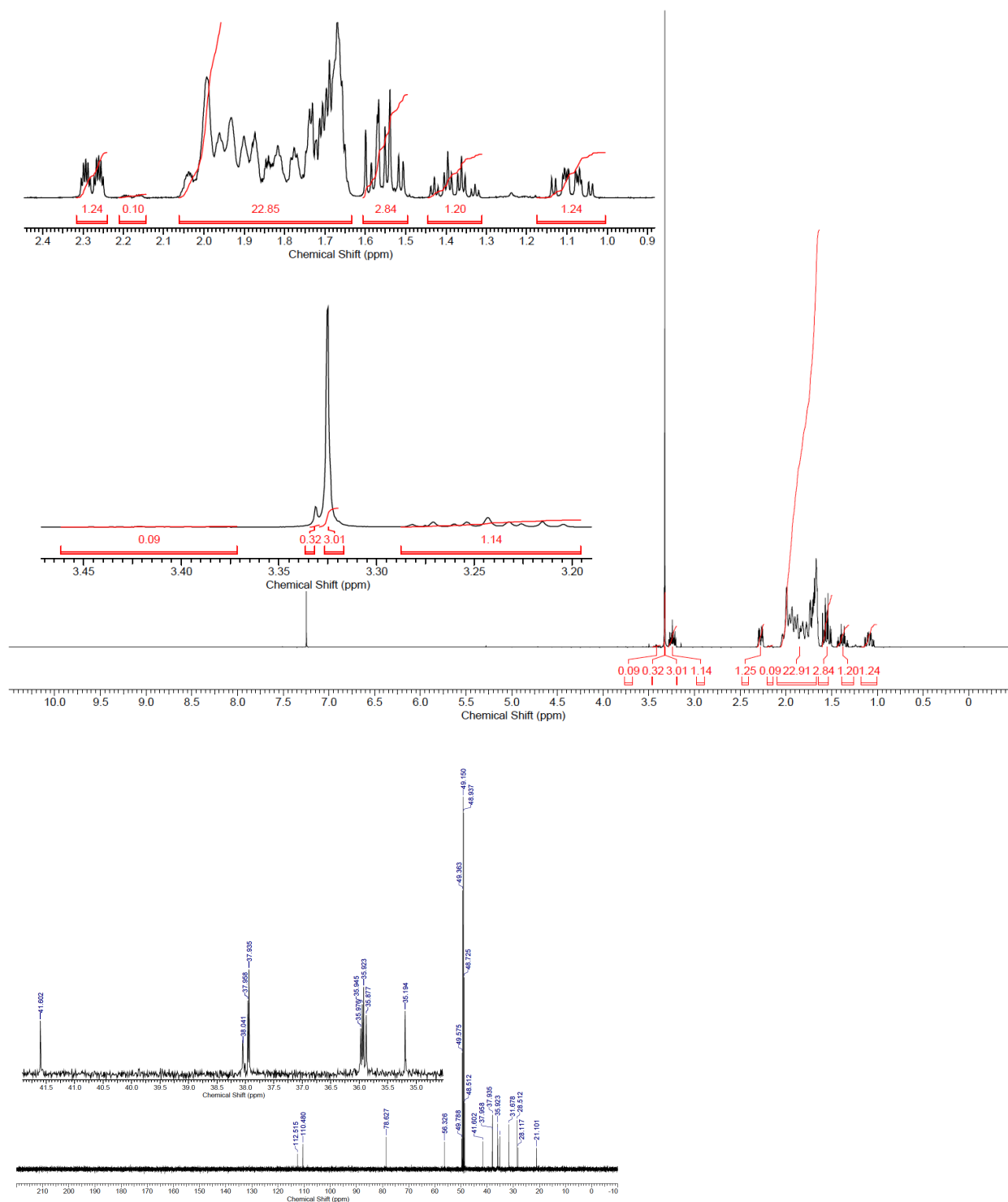


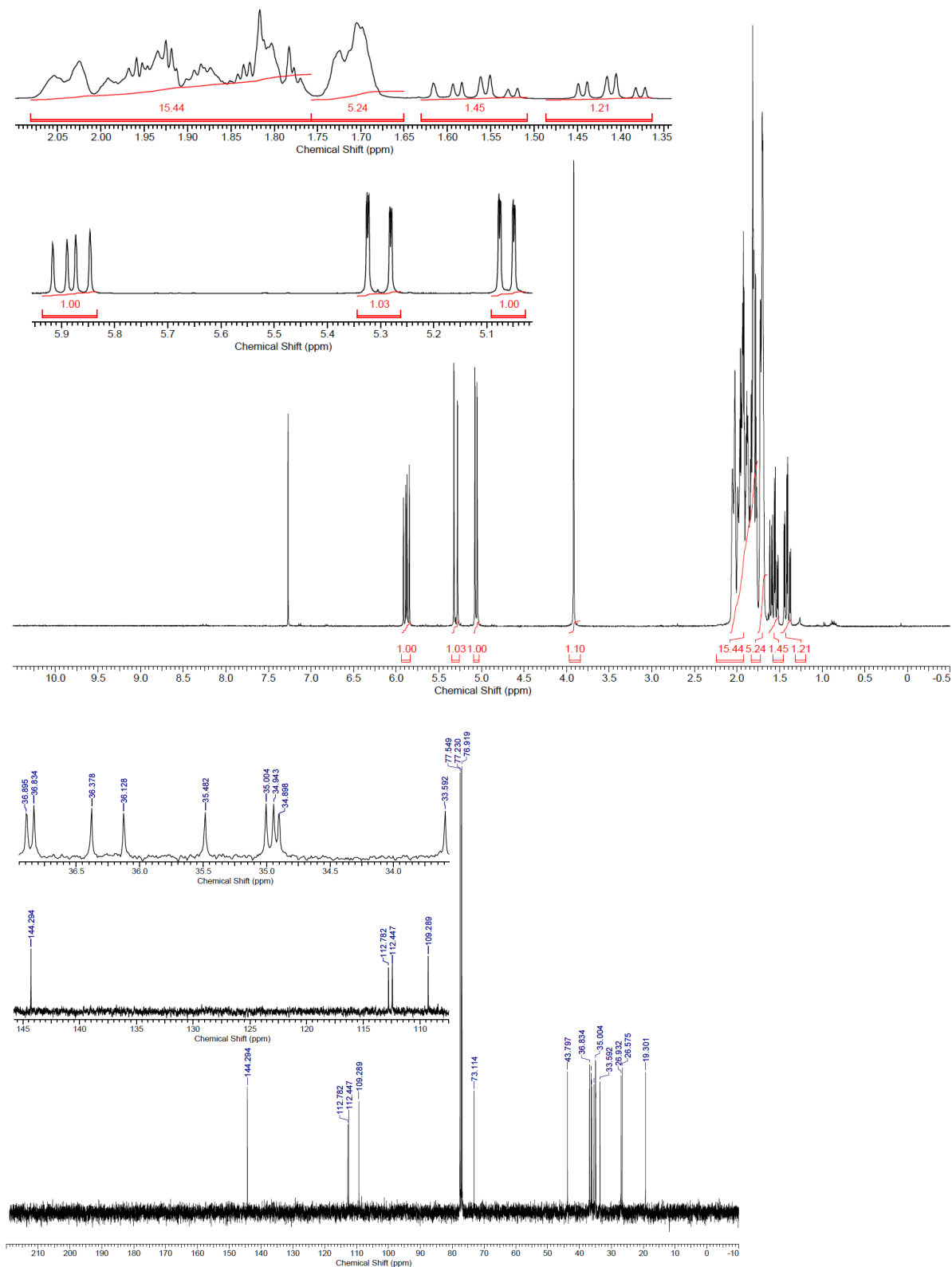
Figure S1. Diagnostic signals for the 3'' methine **H-C-OC(O)-Ar** resonance in the ^1H NMR spectra of the crystal used for X-ray data collection (top) and for the material from which the crystal was grown (bottom). This data establishes that the crystal used for X-ray data collection comprised the major diastereomer from the 90:10 mixture.

Copies of NMR spectra and LC chromatograms for new compounds

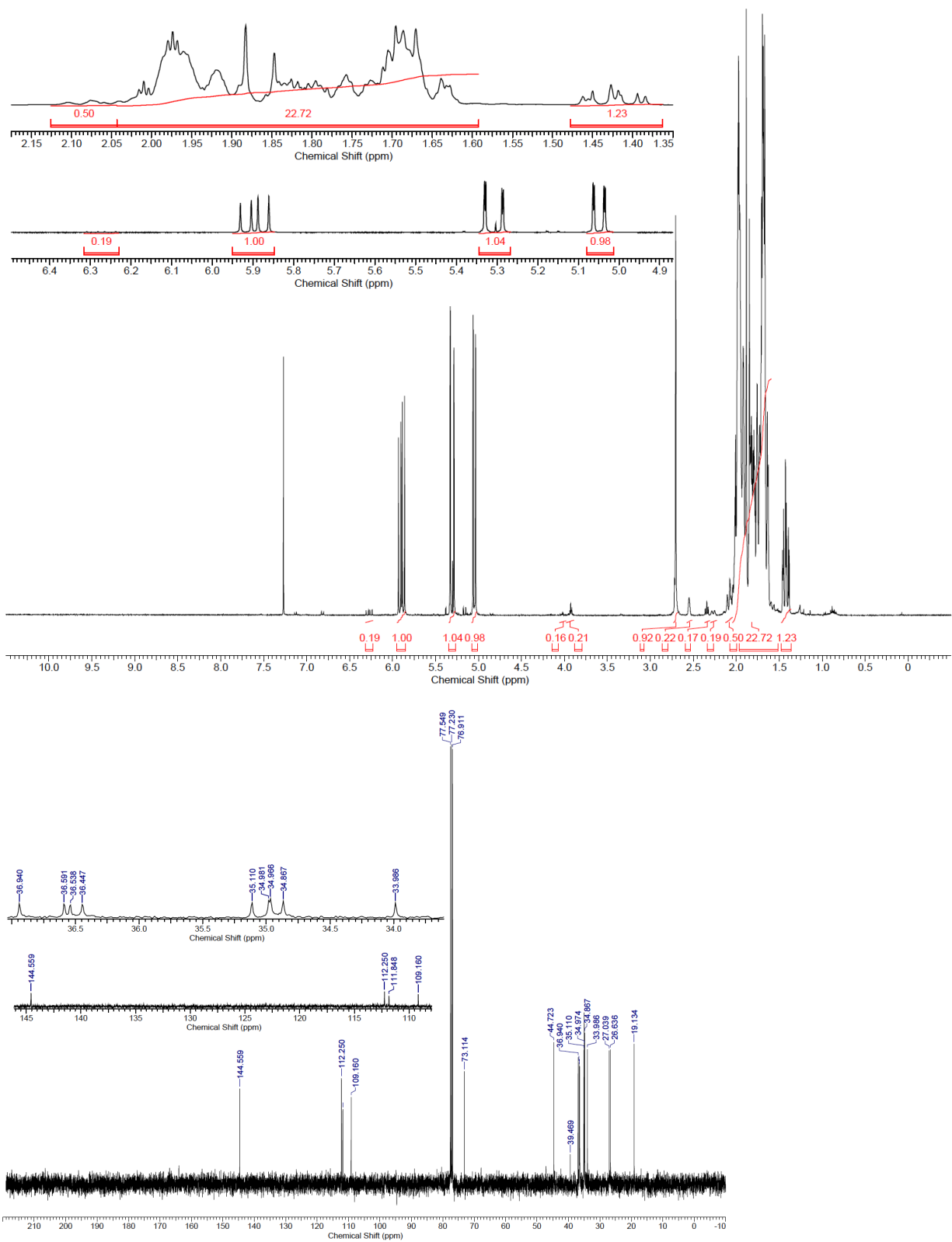
Compound 7 (90:10 dr)



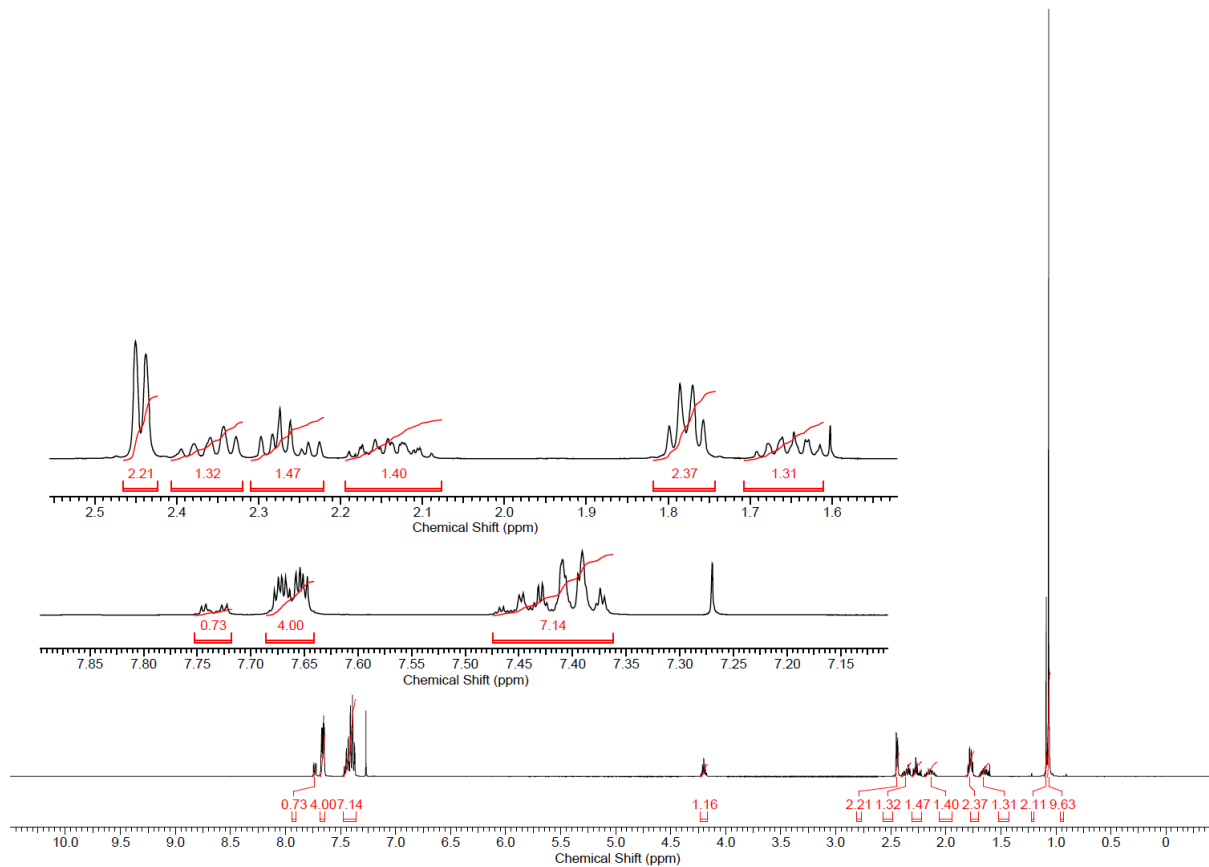
Compound 8 (minor diastereomer)

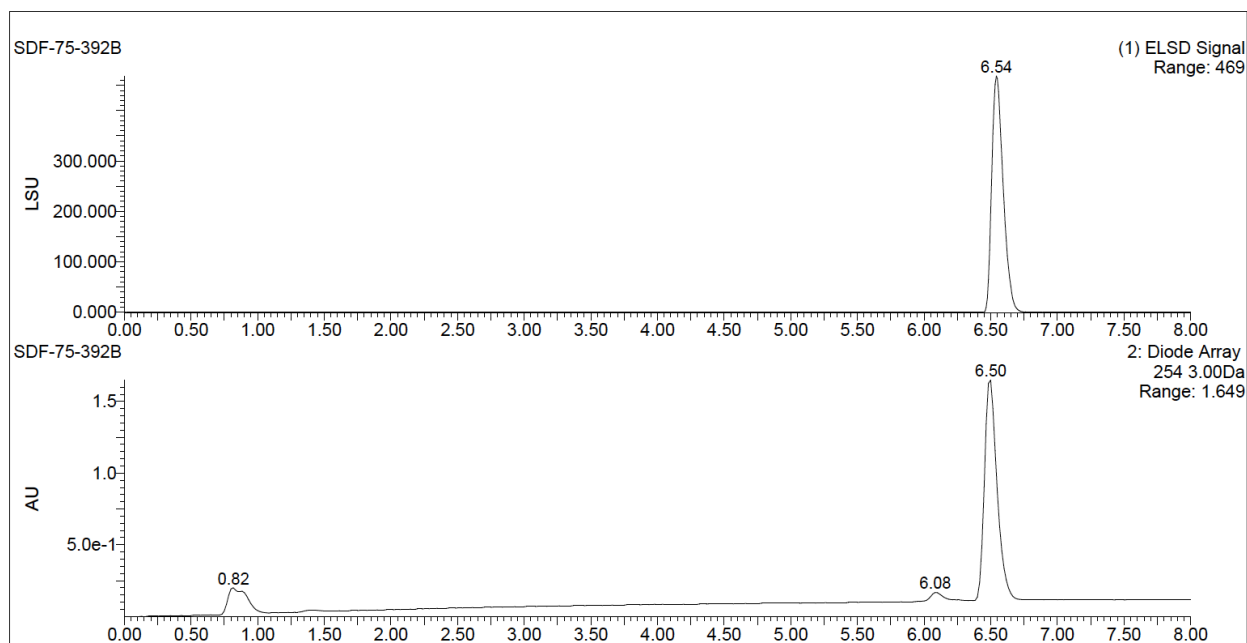
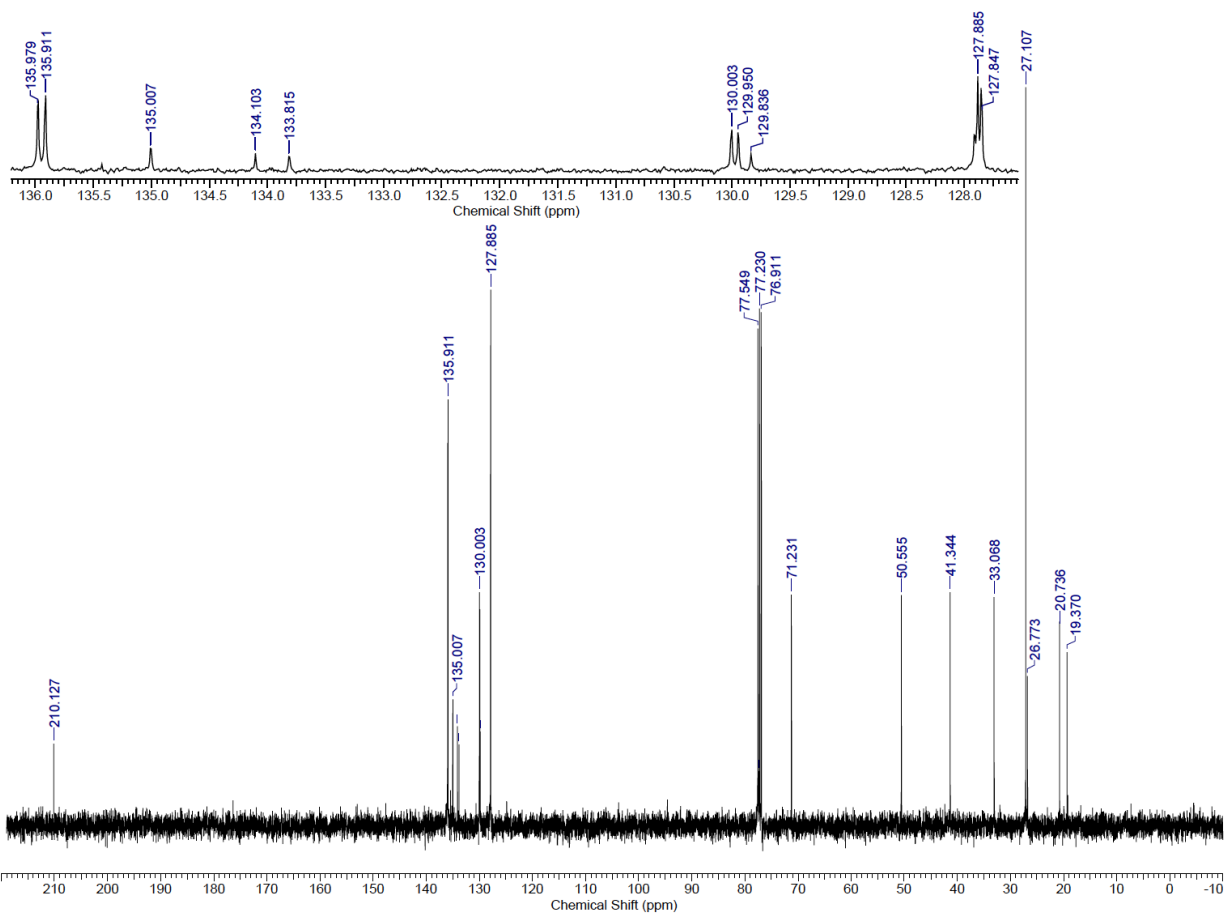


Compound 8 (major diastereomer)

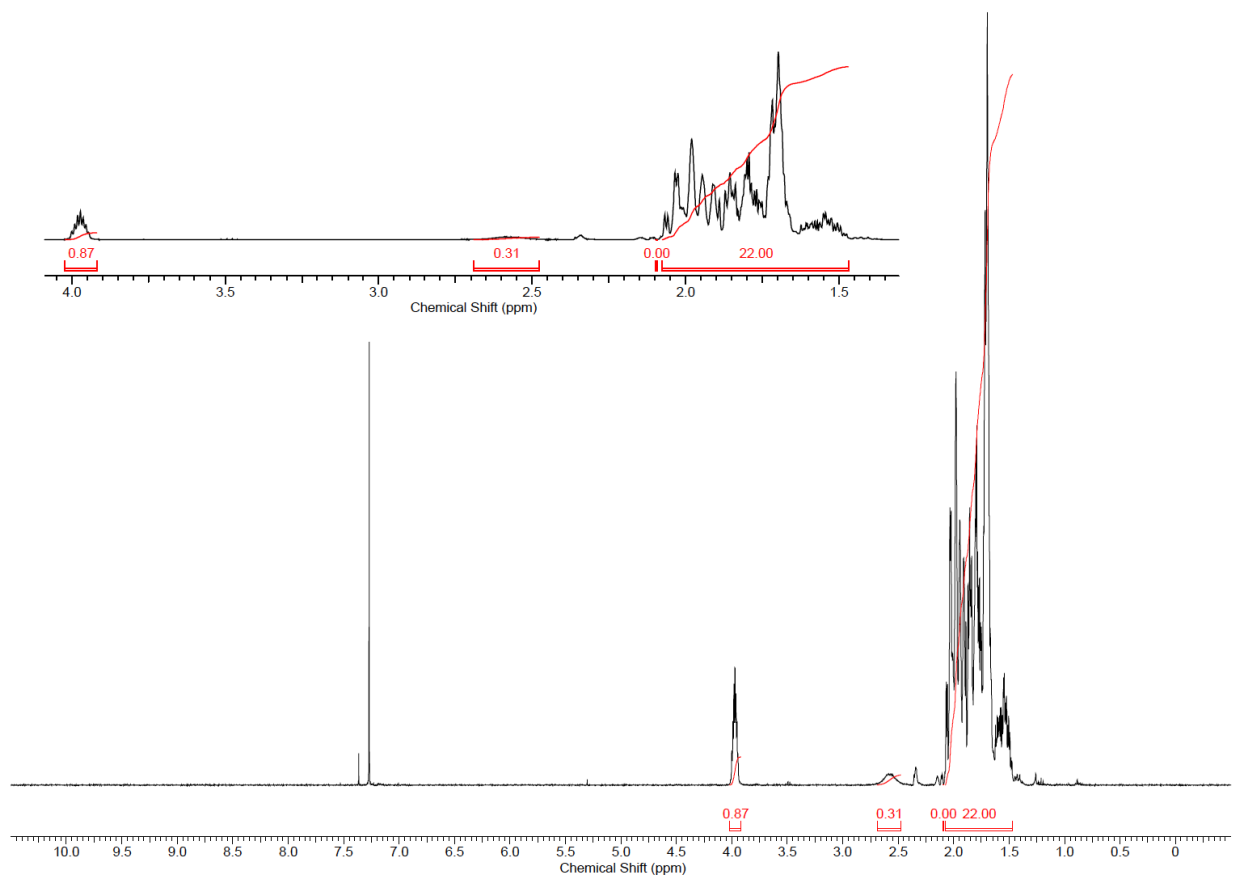


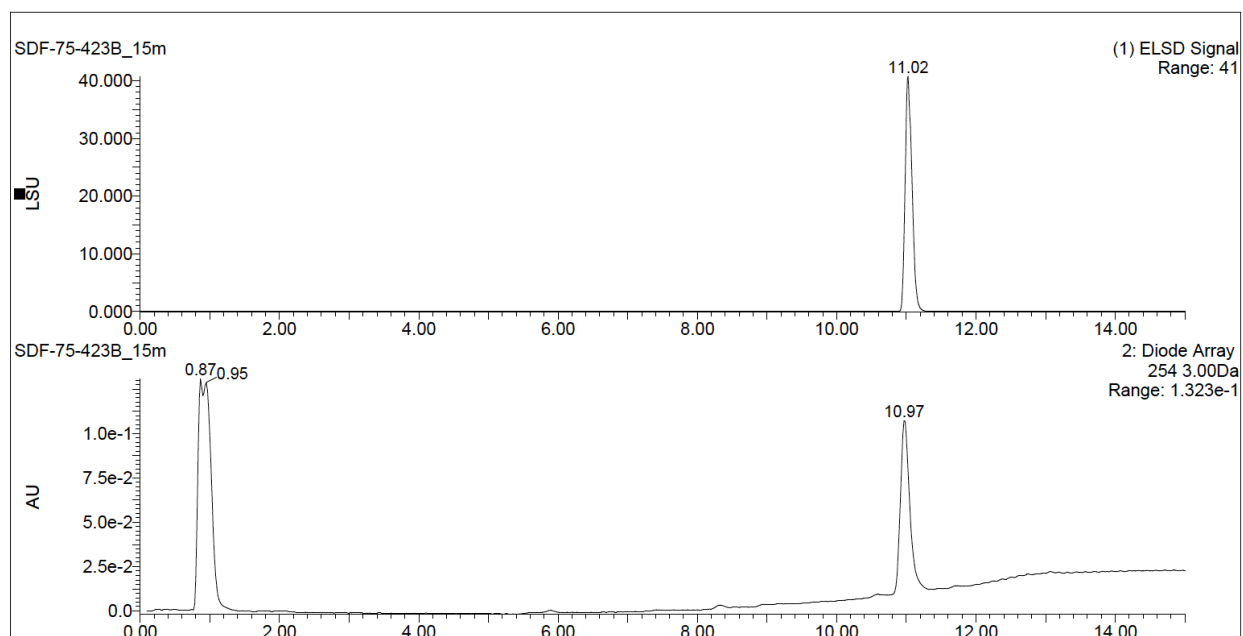
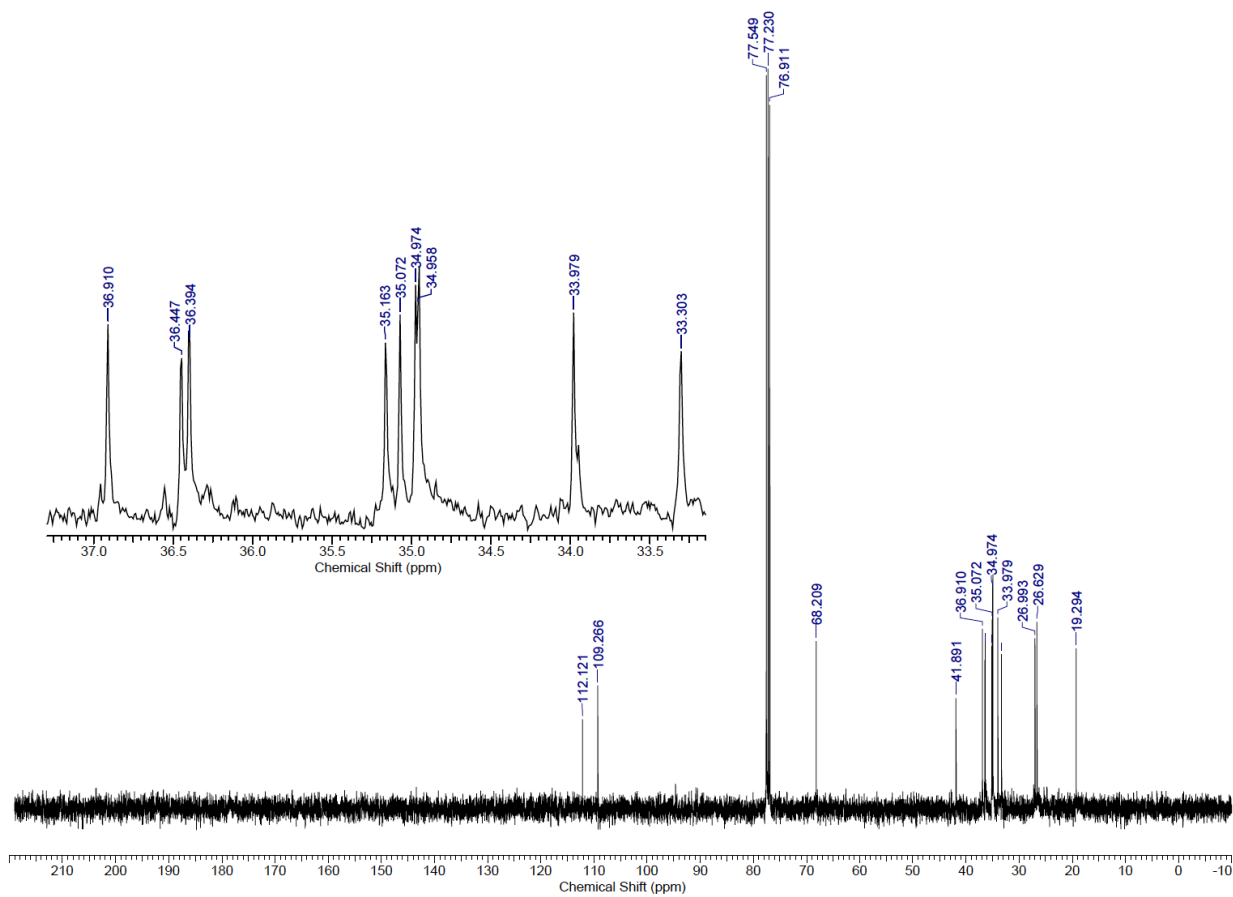
Compound 10



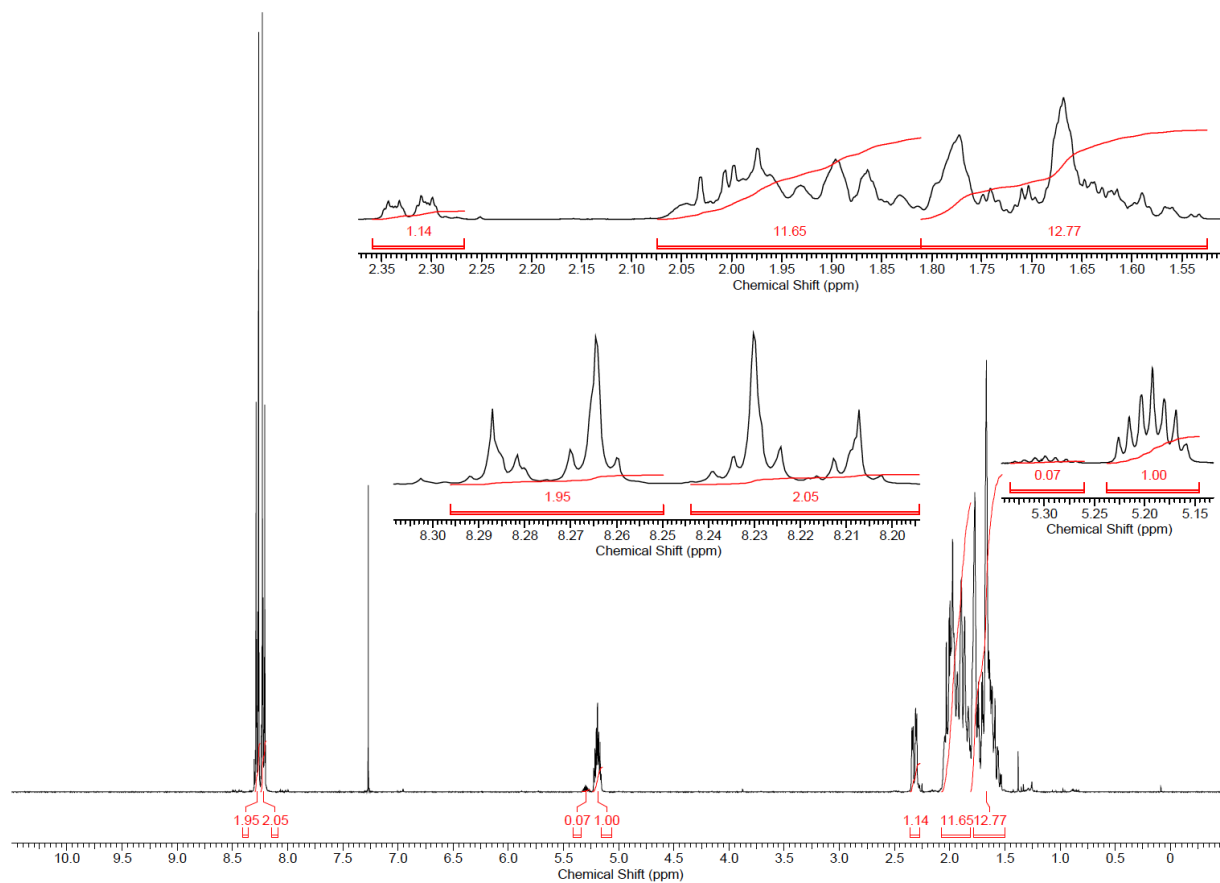


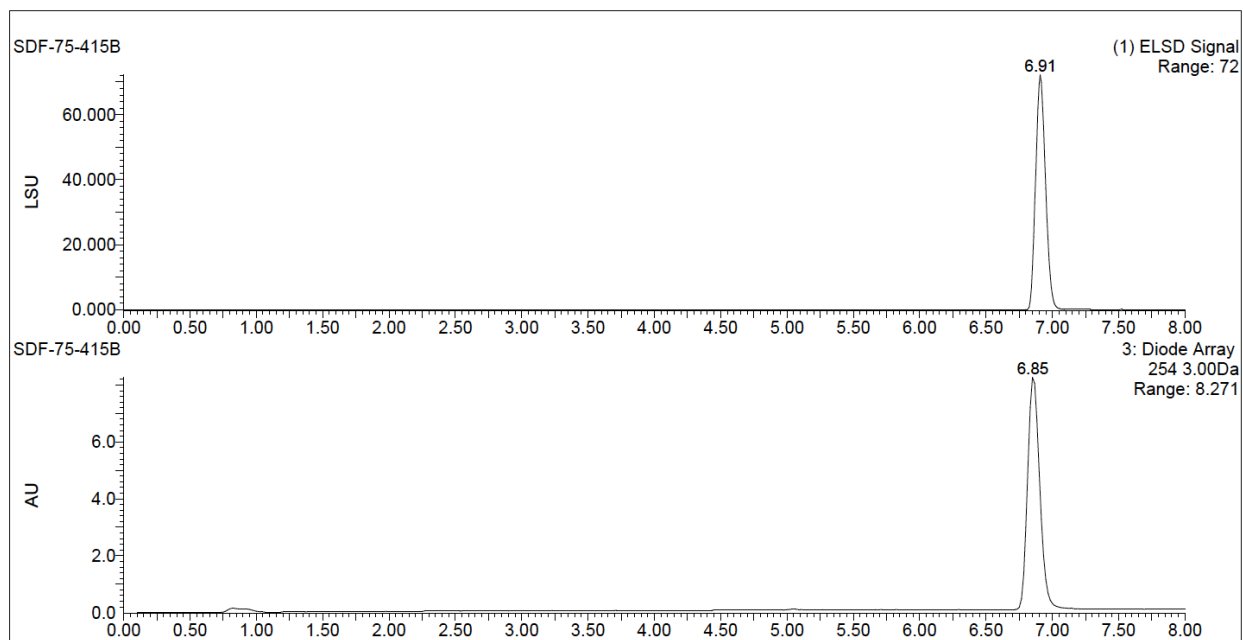
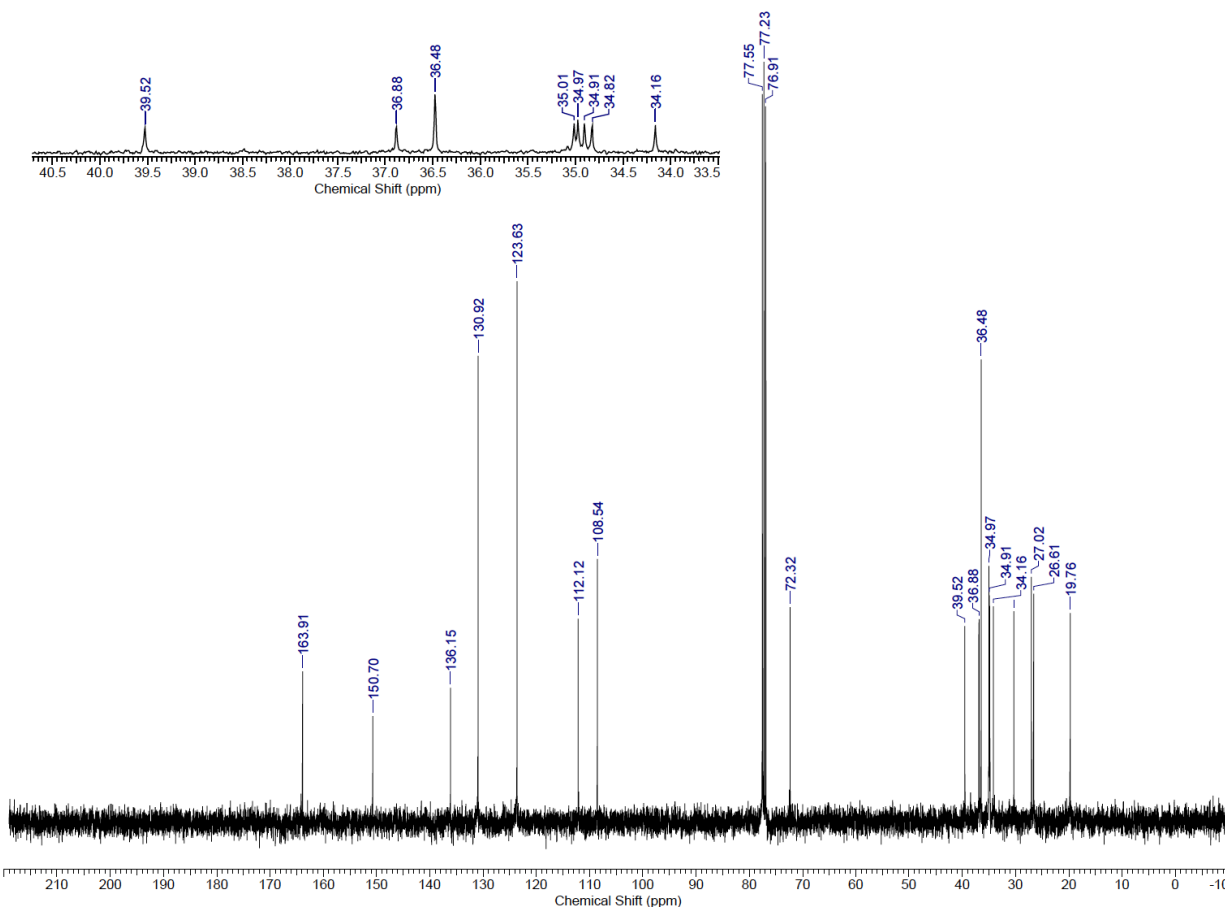
Compound 13 (90:10 dr)



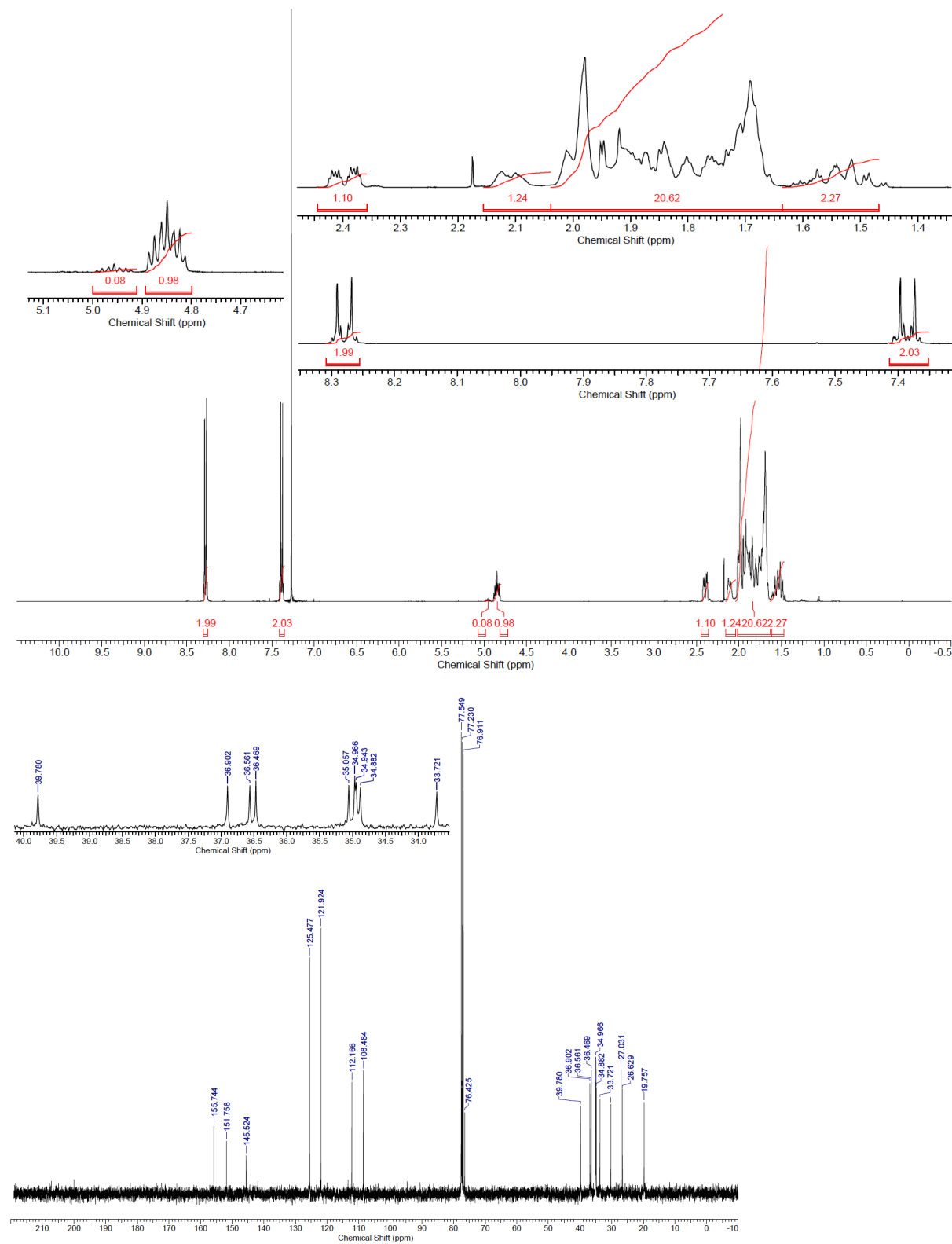


Compound 14

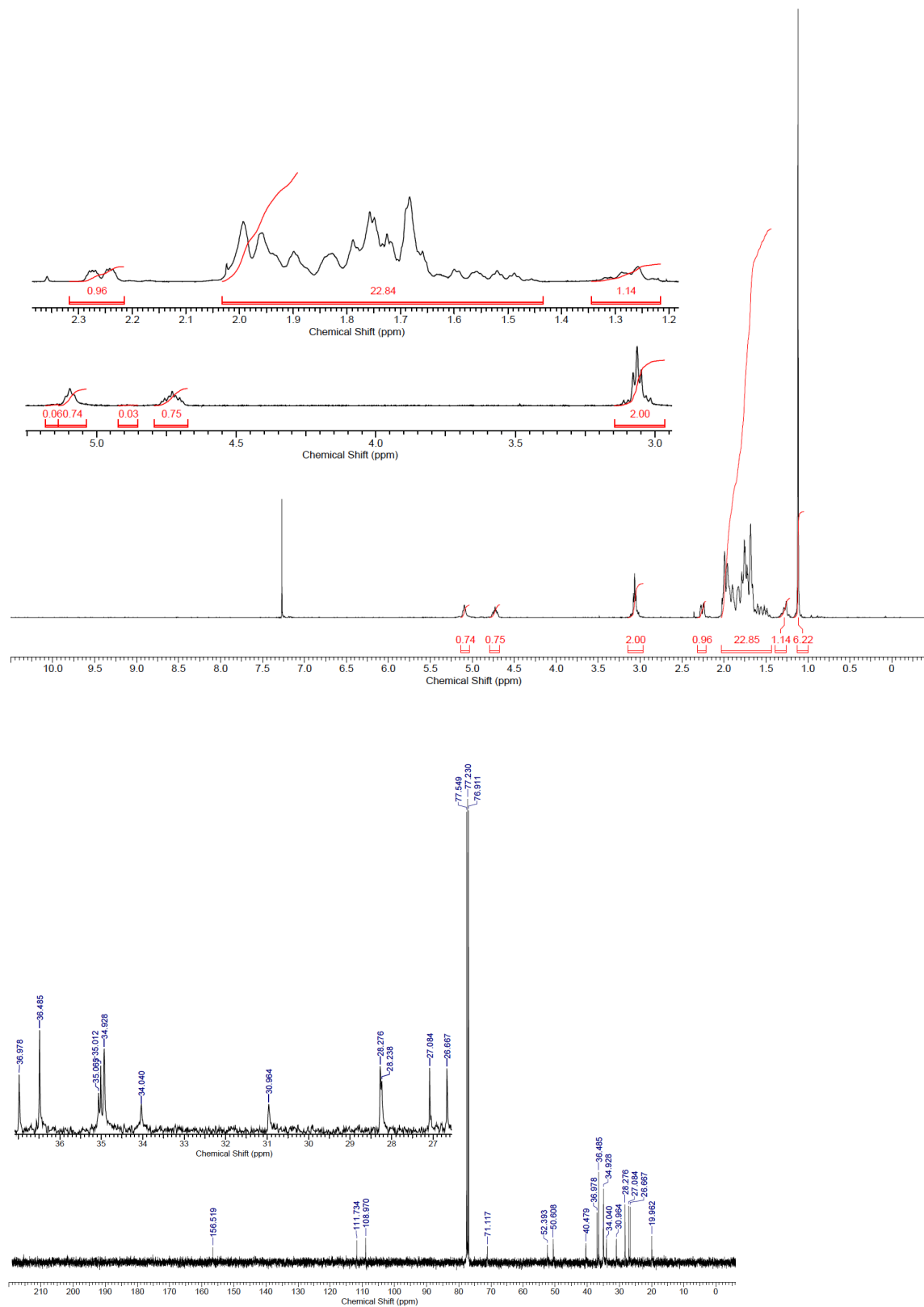




Compound 15



Compound 16 (>95:5 dr)



checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: ucsf05

Bond precision: C-C = 0.0045 A Wavelength=1.54178

Cell: a=6.6484(4) b=12.9963(8) c=47.799(3)
 alpha=90 beta=90 gamma=90

Temperature: 100 K

	Calculated	Reported
Volume	4130.1(4)	4130.1(4)
Space group	P b c a	P b c a
Hall group	-P 2ac 2ab	-P 2ac 2ab
Moiety formula	C23 H27 N O7	?
Sum formula	C23 H27 N O7	C23 H27 N O7
Mr	429.46	429.45
Dx, g cm ⁻³	1.381	1.381
Z	8	8
Mu (mm ⁻¹)	0.850	0.850
F000	1824.0	1824.0
F000'	1830.10	
h,k,lmax	8,15,57	7,15,57
Nref	3775	3753
Tmin,Tmax	0.934,0.975	0.783,0.929
Tmin'	0.934	

Correction method= MULTI-SCAN

Data completeness= 0.994 Theta(max)= 68.287

R(reflections)= 0.0712(3576) wR2(reflections)= 0.1873(3753)

S = 1.076 Npar= 280

The following ALERTS were generated. Each ALERT has the format
test-name ALERT alert-type alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

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PLAT230_ALERT_2_C Hirshfeld Test Diff for  O5  --  C17  ..          5.4 su
PLAT340_ALERT_3_C Low Bond Precision on  C-C Bonds ..... 0.0045 Ang.

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Alert level G

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PLAT083_ALERT_2_G SHELXL Second Parameter in WGHT Unusually Large.      9.75 Why ?
PLAT793_ALERT_4_G The Model has Chirality at C1 ..... S Verify
PLAT793_ALERT_4_G The Model has Chirality at C8 ..... S Verify
PLAT793_ALERT_4_G The Model has Chirality at C11 ..... R Verify
PLAT793_ALERT_4_G The Model has Chirality at C15 ..... R Verify

```

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0 ALERT level A = Most likely a serious problem - resolve or explain
0 ALERT level B = A potentially serious problem, consider carefully
2 ALERT level C = Check. Ensure it is not caused by an omission or oversight
5 ALERT level G = General information/check it is not something unexpected

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0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
2 ALERT type 2 Indicator that the structure model may be wrong or deficient
1 ALERT type 3 Indicator that the structure quality may be low
4 ALERT type 4 Improvement, methodology, query or suggestion
0 ALERT type 5 Informative message, check

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It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 20/08/2014; check.def file version of 18/08/2014

Datablock ucsf05 - ellipsoid plot

