Selective Functionalization of the 1,6-Anhydro Moiety and of the Double Bond of Levoglucosenone

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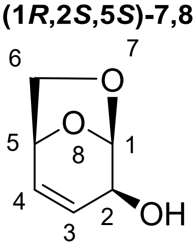
SUPPORTING INFORMATION

Summary:

Experimental procedures

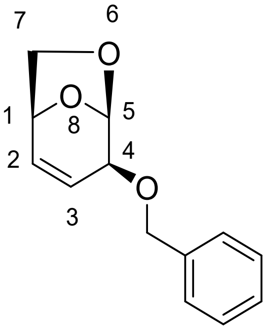
General methods
NMR spectra were taken at the indicated temperature in $CDCl_3$ at 400 MHz (^1H), and 100 MHz (^{13}C), using, as internal standard, TMS (^1H NMR: 0.000 ppm) or the central peak of $CDCl_3$ (^{13}C: 77.02 ppm). Chemical shifts are reported in ppm (δ scale). Peak assignments were made with the aid of COSY and HSQC experiments. In ABX system proton A is the one upfield. HRMS: samples were analysed with a Synapt G2 QToF mass spectrometer. MS signals were acquired from 50 to 1200 m/z in ESI positive ionization mode. TLC analyses were carried out on silica gel plates and viewed at UV (254 nm) and/or developed with Hanessian stain (dipping into a solution of $(NH_4)_4MoO_4\cdot 4\ H_2O$ (21 g) and $Ce(SO_4)_2\cdot 4\ H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming). R_f were measured after an elution of 7-9 cm. Column chromatographies were done with the "flash" methodology using 220-400 mesh silica. Petroleum ether (40-60 °C) is abbreviated as PE. In extractive work-up, aqueous solutions were always reextracted three times with the appropriate organic solvent. Organic extracts were always dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions using dry solvents were carried out under a nitrogen atmosphere.

(1*R*,2*S*,5*S*)-7,8-dioxabicyclo[3,2,1]oct-3ene-2-ol 2



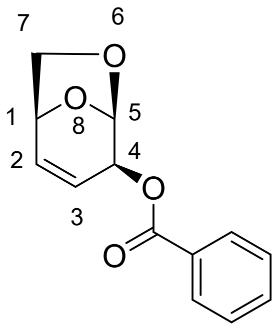
A solution of Levoglucosenone **1** (1.00 g, 7.93 mmol) in MeOH (6 mL) is cooled to 0 °C, and treated with $CeCl_3\bullet 7\ H_2O$ (1.48 g, 3.97 mmol). $NaBH_4$ (120 mg, 3.17 mmol) is then added in 2 portions. After 1 h, further $NaBH_4$ (120 mg, 3.17 mmol) is added. After stirring for other 1.5 h at 0 °C, the reaction is complete by TLC. Citric acid (1.52 g, 7.93 mmol) and ethyl acetate (30 mL) are added. The mixture is stirred at rt for 1h, and then filtered through a celite cake, washing 2 times with AcOEt/MeOH 9:1 and then 2 times with THF/MeOH 9:1. Silica 40-60 mesh (5 g) is added and the suspension evaporated to dryness. The resulting powder is introduced in a chromatography column packed and eluted with PE / AcOEt 6:4 + 1% MeOH. Nearly diastereomeric pure **2** (d.r. 98:2) is obtained (830 mg) along with some mixed fractions containing **2** and the 2*R* epimer (87 mg, d.r. = 58:42). Overall yield: 90%. The overall d.r., determined by ^1H NMR on a sample of the crude product, was 94:6.
R_f of **2**: 0.42 (PE/AcOEt 6:4). R_f of the epimer : 0.35 (PE/AcOEt 6:4).
Compound **2** solidifies upon evaporation to give a white solid, which has some tendency to sublimate if attached to high vacuum pump. M.p.: 65-66 ° C. $[\alpha]_D$ −32.3 (c 1, $CHCl_3$).[1] Note: since the 2S epimer has a very high negative rotation,[2] this value is quite variable from batch to batch, depending on the d.r. Even traces of the other epimer can increase the absolute value of $[\alpha]_D$ The spectroscopic data are coincident to those reported in the literature.[1, 3]

(1*S*,4*S*,5*R*)-4-Benzyloxy-6,8-dioxabicyclo[3,2,1]oct-2-ene 3



A solution of alcohol **2** (1.69 g, 13.2 mmol) in dry DMSO (44 mL) is rapidly cooled for few minutes in a cold water bath (avoiding to solidify DMSO) and treated with NaH (60% in mineral oil) (773 mg, 19.4 mmol). After 10 min, the cooling bath is removed and benzyl bromide (2.09 mL, 17.6 mmol) is added. After 2 h, the mixture is cooled again, diluted with water (20 mL), and vigorously stirred for 10 min. The mixture is poured into saturated aqueous NH_4Cl and extracted with Et_2O. The organic phases are washed with brine, dried and evaporated to dryness. Chromatography (PE / AcOEt 80:20) afforded pure **3** as an yellowish oil (1.988 g, 69%). R_f: 0.34 (PE/AcOEt 8:2). R_f of the 4*R* epimer is 0.44. Therefore, it is also possible to prepare this benzyl ether starting from the diastereomeric mixture of **2** and separate the two isomers at this stage. $[\alpha]_D$ -13.3 (c 1, $CHCl_3$).
^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.25 (m, 5H, aromatics), 6.10 (ddd, *J*= 9.9, 4.2, 1.4, 1 H, *H*-2), 5.71 (dd, *J*= 9.9, 2.2, 1 H, *H*-3), 5.56 (t, *J*= 2.3, 1 H, *H*-5), 4.69, 4.67 (AB system, *J*= 12.2, 2H, C*H*$_2$Ph), 4.63 (t, *J*= 4.2, 1 H, *H*-1), 4.30-4.26 (m, 1H, *H*-4), 3.98 (d, *J*= 6.5, 1H, *H*-7), 3.78 (ddd, *J*= 6.5, 4.1, 1.0, 1H, *H*-7). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0 (quat.), 130.9 (*C*-2), 128.4 (*C* ortho or meta), 128.0 (*C* ortho or meta), 127.9 (*C* para), 126.5 (*C*-3), 100.2 (*C*-5), 75.7 (*C*-4), 71.49 (*C*-7), 71.47 (*C*-1), 71.2 (*C*H$_2$Bn).
^1H spectrum and the other spectroscopic and polarimetric values were in agreement to what reported (^{13}C spectrum was not reported).[4]

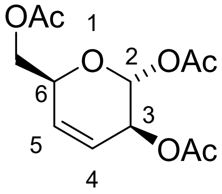
(1*S*,4*S*,5*R*)-4-Benzoyloxy-6,8-dioxabicyclo[3,2,1]oct-2-ene 4



A solution of alcohol **2** (627 mg, 4.89 mmol) in dry CH_2Cl_2 (1.0 mL) was treated with 4-dimethylaminopyridine (9.6 mg,79 µmol), triethylamine (181 µL, 1.30 mmol), and finally with benzoic anhydride (226 mg, 1.00 mmol). After 3 h at rt the reaction is complete and is quenched with saturated aqueous $NaHCO_3$ (10 mL). Extraction with AcOEt, washing with brine, evaporation and chromatography (PE / AcOEt 8:2) afforded pure **4** as a white solid. R_f: 0.38 (PE/AcOEt 80:20). $[\alpha]_D$ +26.7 (c 1, $CHCl_3$). M.p. 117-120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.7, 2 H, *H* ortho to C=O), 7.57 (t, *J*= 7.4, 1 H, *H* para to C=O), 7.44 (t, *J*= 7.7, 2 H, *H* meta to C=O), 6.26 (dd, *J*= 9.3, 4.2, 1 H, *H*-2), 5.80-5.73 (m, 3 H, *H*-3 + *H*-5 + *H*-4), 4.74 (t, *J*= 4.2, 1 H, *H*-1), 4.03 (d, *J*= 6.6, 1H, *H*-7), 3.84 (dd, *J*= 6.0, 4.3, 1H, *H*-7). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (*C*=O), 133.3 (*C* para to C=O), 132.6 (*C*-2), 129.9 (*C* ortho to C=O), 129.7 (quat.), 128.4 (*C* meta to C=O), 124.9 (*C*-3), 99.3 (*C*-5), 72.1 (*C*-4), 71.5, 71.4 (*C*-1, *C*-7). ^{1}H spectrum and the other spectroscopic and polarimetric values were in agreement to what was reported (^{13}C spectrum was not reported).[4]

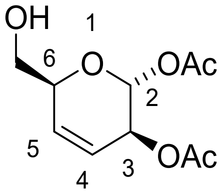
(2*R*,3*S*,6*S*)-6-(Acetoxymethyl)-2,3-diacetoxy-3,6-dihydro-2*H*-pyran 10



10

A solution of alcohol **2** (1.961 g, 15.3 mmol) in Ac_2O (20 mL) is cooled to 0 °C, and treated with 85% phosphoric acid (1.0 mL, 14.6 mmol). After 5 min the cooling bath is removed and the yellow solution stirred at rt for 2 h. Then the solution is poured into saturated aqueous Na_2CO_3 (the amount necessary to adjust the pH to 9. Estraction with AcOEt, evaporation, and chromatography (PE / AcOEt 7:3 to 6:4) afforded diastereomerically enriched **10** (d.r. = 95:5) as an oil (3.59 g, 86%). R_f: 0.44 (PE/AcOEt 6:4). The minor diastereomer at *C*-2 is slower running (R_f: 0.39). The d.r. was determined by ^{1}H NMR of the crude and was = 91:9. The overall yield of the two diastereomers was calculated as 94%. $[\alpha]_D$ +125.8 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.18 (s, 1H, *H*-2), 6.03 (s, 2H, *H*-4 and *H*-5), 4.92 (s, 1 H, *H*-3), 4.53-4.47 (m, 1H, *H*-6), 4.28-4.14 (m, 2 H, C*H*$_2$O), 2.08 (s, 9H, C*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.1, 168.9 (*C*=O), 130.6, 121.9 (*C*-4 and *C*-5), 90.8 (*C*-2), 67.8 (*C*-6), 65.0 (*C*H$_2$O), 64.2 (*C*-3), 20.94, 20.89, 20.8 (*C*H$_3$C=O). **HRMS** (ESI+): calcd. for $C_{12}H_{17}O_7$ $[M+H]^+$ 273.0974, found 273.0977.

(2*R*,3*S*,6*S*)-2,3-Diacetoxy-6-(hydroxymethyl)-3,6-dihydro-2*H*-pyran 16



16

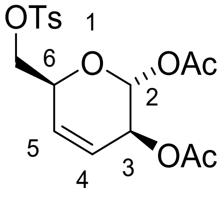
0.25 M TRIS buffer was prepared by dissolving 3.035 g of *tris*(hydroxymethyl)aminomethane in 100 mL of water. Then it was adjusted to pH = 7.5 by addition of 1 M HCl.

Triacetate **10** (1.452 g, 5.33 mmol) was dissolved in THF (10 mL), and diluted with 70 mL (17.5 mmol) of this TRIS buffer. Then Amano PS-IM lipase (286 mg) was added and the mixture stirred for 18h at rt. Then it was diluted with 1 M citric acid solution in water (50 mL), and extracted with AcOEt. Evaporation and chromatography (PE/AcOEt from 60:40 to 50:50) afforded pure **16** as an oil (1.065 g, 87%). R_f: 0.29 (PE/AcOEt 50:50). $[\alpha]_D$ +175.1 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.17 (s, 1H, *H*-2), 6.08-5.99 (m, 2H, *H*-4 and *H*-5), 5.00-4.97 (m, 1 H, *H*-3), 4.43-4.37 (m, 1H, *H*-6), 3.81 (ddd, *J*= 11.8, 6.3, 3.5, 1H, C*H*HO), 3.70 (dt, *J*= 11.8, 6.0, 1H, C*H*HO),

2.11, 2.10 (2s, 2 x 3H, C*H*$_3$), 2.08 (t, *J*= 6.4, 1 H, O*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 169.1 (*C*=O), 131.4, 121.6 (*C*-4 and *C*-5), 90.7 (*C*-2), 67.8 (*C*-6), 64.5 (*C*-3), 64.0 (*C*H$_2$O), 20.85, 20.78 (*C*H$_3$C=O). **HRMS** (ESI+): calcd. for $C_{10}H_{15}O_6$ $[M+H]^+$ 231.08686, found 231.08697.

(2*R*,3*S*,6*S*)-2,3-Diacetoxy-6-(tosyloxymethyl)-3,6-dihydro-2*H*-pyran 18



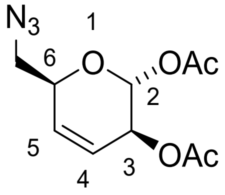
18

A solution of alcohol **10** (1.00 g, 4.34 mmol) in dry CH_2Cl_2 (13 mL) was treated with Et_3N (1.82 mL, 13.03 mmol), 4-dimethylaminopyridine (DMAP) (105.3 mg, 869 µmol), and finally with *p*-toluenesulfonyl chloride (1.242 g, 6.52 mmol). The solution was stirred overnoght at rt, and then poured into a saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. After evaporation, the crude was chromatographed (PE/AcOEt from 6:4 to 1:1) to give pure **18** as a white solidi

(1.491 g, 89%). R*f*: 0.65 (PE / AcOEt 1:1). A very pure sample was obtained by trituration from Et_2O-pentane. M.p.: 105.8-106.4 °C. $[\alpha]_D$ +96.6 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J*= 8.2, 2 H, *H* meta to CH_3), 7.35 (d, *J*= 8.2, 2 H, *H* ortho to CH_3), 6.10 (s, 1H, *H*-2), 6.08-5.99 (m, 2H, *H*-4 and *H*-5), 4.91-4.87 (m, 1 H, *H*-3), 4.51-4.46 (m, 1H, *H*-6), 4.14 (dd, *J*= 10.3, 5.5, 1H, C*H*$_2$O), 4.08 (dd, *J*= 10.3, 5.4, 1H, C*H*$_2$O), 2.46 (s, 3H, C*H*$_3$ of Ts), 2.08 (s, 6H, C*H*$_3$CO). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 168.8 (*C*=O), 145.1, 132.6 (quat.), 129.9 (*C* ortho to CH_3), 129.8, 122.3 (*C*-4 and *C*-5), 128.1 (*C* meta to CH_3), 90.6 (*C*-2), 69.9 (*C*H$_2$O), 67.1 (*C*-6), 64.0 (*C*-3), 21.7 (*C*H$_3$ of tosyl), 20.9, 20.8, (*C*H$_3$C=O). **HRMS (ESI+)**: calcd. for $C_{17}H_{20}O_8S$ $[M+H]^+$ 385.09571, found 385.0962.

(2*R*,3*S*,6*S*)-6-(Azidomethyl)-2,3-diacetoxy-3,6-dihydro-2*H*-pyran 19



19

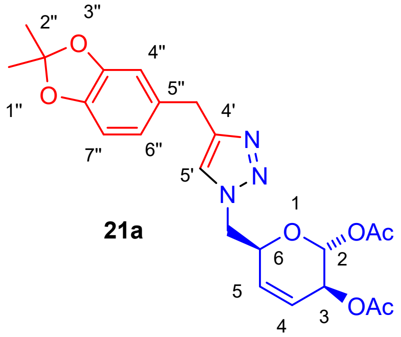
A solution of tosylate **18** (1.200 g, 4.16 mmol) in dry DMF (12 mL) was treated with NaN_3 (288.8 mg, 4.44 mmol) and stirred overnight at 60 °C. In some cases the reaction was complete, but in others (probably depending on the quality of NaN_3), the reaction was not yet complete (by TLC). Thus, further 0.3 mmol of NaN_3 were added and the solution stirred for other 4 h until completion. Work-up was made by pouring into a 1:1 mixture of saturated aqueous NH_4Cl and H_2O. Extraction with Et_2O, evaporation and chromatography (PE/AcOEt from 75:25 to 6:4) gave pure **19** as an oil (1.008 g, 95%). R*f*: 0.53 (PE / AcOEt 6:4). $[\alpha]_D$ +229.5 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.20 (s, 1H, *H*-2), 6.12-5.93 (m, 2H, *H*-4 and *H*-5), 4.95 (ddd, *J*=4.7, 2.1, 1.2, 1 H, *H*-3), 4.49-4.44 (m, 1H, *H*-6), 3.53 (dd, *J*= 13.0, 4.2, 1H, C*H*$_2$N), 4.08 (dd, *J*= 13.0, 5.2, 1H, C*H*$_2$N), 2.114, 2.109 (2s, 2 x 3H, C*H*$_3$CO). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 168.9 (*C*=O), 131.2, 122.1 (*C*-4 and *C*-5), 90.8 (*C*-2), 69.0 (*C*-6), 64.0 (*C*-3), 53.3 (*C*H$_2$N), 20.9, 20.8, (*C*H$_3$C=O). **HRMS (ESI+)**: calcd. for $C_{10}H_{14}N_3O_5$ $[M+H]^+$ 256.09335, found 256.0929.

Typical procedure for the synthesis of triazoles 21 (Procedure A)

Azide **19** (54.4 mg, 213 µmol) and alkyne **20a** (44.1 mg, 234 µmol, 1.1 equiv.)(prepared as already described by us.[5]) were dissolved under nitrogen in 500 µL of *tert*-butanol + 500 µL of H_2O, and treated with a 1 M aqueous solution of sodium ascorbate (21 µL, 21 µmol, 0.1 equiv.) and finally with $CuSO_4{\bullet}5\ H_2O$ (1.0 mg, 4.0 µMol), 0.02 equiv). The solution was stirred for 4 h at rt, and then, since it was not complete by TLC, the same amount of copper sulfate and sodium ascorbate was added. After 1 h more, the reaction was complete. The mixture was diluted with water and extracted with AcOEt. After drying, evaporation, and chromatography (PE/AcOEt from 6:4 to 0:10), pure **21a** was obtained as an oil (61.1 mg, 65%).

(2*R*,3*S*,6*S*)-2,3-Diacetoxy-6-[(4-((2,2-dimethylbenzo[d][1,3]dioxol-5-yl)methyl)-1*H*-1,2,3-triazolyl)methyl]-3,6-dihydro-2*H*-pyran 21a

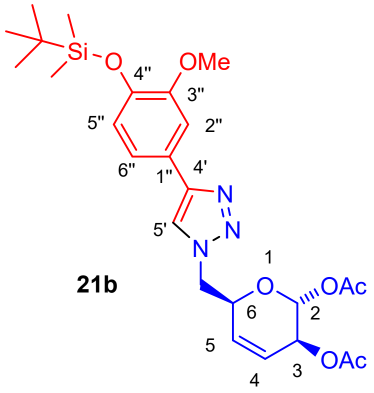


21a

R*f*: 0.**13** (PE / AcOEt **7:3**). $[\alpha]_D$ +76.1 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 1 H, *H*-5'), 6.67-6.61 (m, 3H, *H*-4", *H*-6", *H*-7"), 6.13 (s, 1H, *H*-2), 6.06 (dd, 1H, *J*= 10.5, 1.6, *H*-5), 5.96 (dddd, 1H, *J*= 10.5, 5.0, 2.1, 1.2, *H*-4), 4.90 (ddq, 1H, *J*=4.3, 2.2, 0.6, *H*-3), 4.65 (td, 1H, *J*= 4.6, 2.3, *H*-6), 4.55 (d, 2H, *J*=4.8, C*H*$_2$N), 3.98, 3.96 (AB syst., 2 H, *J*= 16.0, C*H*$_2$Ar), 2.09 (s, 3H, C*H*$_3$C=O), 2.01 (s, 3H, C*H*$_3$C=O), 1.65 (s, 6H, (C*H*$_3$)$_2$C). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 168.9 (*C*=O), 147.63, 147.56, 145.97 (*C*-3a", *C*-7a", *C*-4'), 132.0 (*C*-5"), 130.0 (*C*-5), 122.6 (*C*-4), 123.0 (*C*-5'), 120.8 (*C*-6"), 117.8 (*C*-2"), 108.9, 108.0 (*C*-4", *C*-7"), 90.6 (*C*-2), 68.2 (*C*-6), 63.8 (*C*-3), 52.7 (*C*H$_2$N), 31.8 (*C*H$_2$Ar), 25.8 (CH$_3$*C*CH$_3$), 20.8, 20.7 (*C*H$_3$C=O). HRMS (ESI+): calcd. for $C_{22}H_{26}N_3O_7^+$ $[M+H]^+$ 444.1765, found 444.1779.

(2*R*,3*S*,6*S*)-2,3-Diacetoxy-6-[4-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl)-1*H*-1,2,3-triazolyl)methyl]-3,6-dihydro-2*H*-pyran 21b



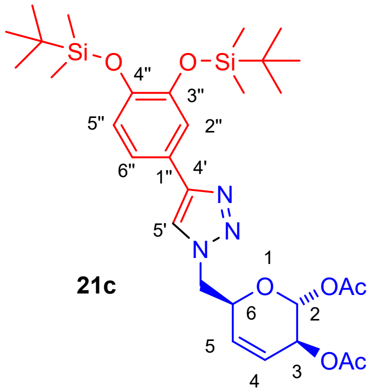
21b

It was prepared following the general procedure, starting from 138.0 mg of azide **19** (541 μmol) and 170.3 mg (649 μMol, 1.2 equiv.) of alkyne **20b**, prepared as previously described by us.[5] Time: 3 h + 2 h after second addition of catalysts. Chromatography (PE/AcOEt from 50:50 to 30:70) gave pure **21b** as a white foam (185 mg, 66%). R_f: 0.31 (PE / AcOEt 50:50). $[\alpha]_D$ +96.0 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1 H, *H*-5'), 7.38 (dd, 1H, *J*= 8.3, 2.1, *H*-6"), 7.35 (d, 1H, *J*= 2.1, *H*-2"), 6.88 (d, 1H, *J*= 8.3, *H*-5"), 6.18 (s, 1H, *H*-2), 6.09 (dd, 1H, *J*= 10.5, 1.3, *H*-5), 5.95 (ddt, 1H, *J*= 10.4, 3.0, 1.3, *H*-4), 4.87 (dt, 1H, *J*=5.2, 1.2, *H*-3), 4.74-4.66 (m, 2H, *H*-6 and C*H*HN), 4.61 (dd, 1H, *J*= 15.6, 4.7, CH*H*N), 3.83 (s, 3H, CH_3O), 2.11 (s, 3H, CH_3C=O), 1.83 (s, 3H, CH_3C=O), 1.02 (s, 9H, $(CH_3)_3C$), 0.18, 0.17 (2 s, 2H, $(CH_3)_2Si$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 169.1 (*C*=O), 151.0, 147.5, 145.3 (*C*-3", *C*-4", *C*-4'), 129.9 (*C*-5), 123.7 (*C*-1"), 122.7 (*C*-4), 120.7 (*C*-5'), 119.1, 118.4 (*C*-5", *C*-6"), 112.1 (*C*-2"), 90.6 (*C*-2), 68.5 (*C*-6), 63.6 (*C*-3), 55.4 (CH_3O), 52.6 (CH_2N), 25.7 ($C(CH_3)_3$), 20.8, 20.6 (CH_3C=O), 18.5 ($C(CH_3)_3$), -4.62, -4.65 ($((CH)_3)_2Si$. HRMS (ESI+): calcd. for $C_{25}H_{36}N_3O_7Si^+$ $[M+H]^+$ 518.2317, found 518.2302.

(2*R*,3*S*,6*S*)-2,3-Diacetoxy-6-[4-(3,4-*bis*((*tert*-butyldimethylsilyl)oxy)phenyl)-1*H*-1,2,3-triazolyl)methyl]-3,6-dihydro-2*H*-pyran 21c



21c

It was prepared following the general procedure, starting from 80.0 mg of azide **19** (313 μmol) and 136.0 mg (375 μMol, 1.2 equiv.) of alkyne **20c**, prepared as previously described by us.[5] Time: 2 h + 1 h after second addition of catalysts. Chromatography (PE/AcOEt from 70:30 to 30:70) gave pure **21c** as a white solid (175 mg, 90%). M.p.: 116,4-120,9 °C. R_f: 0.40 (PE / AcOEt 70:30). $[\alpha]_D$ +10.4 (c 1, $CHCl_3$).

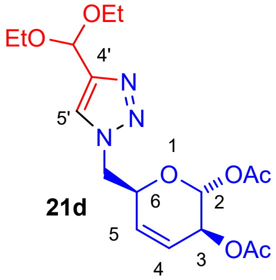
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1 H, *H*-5'), 7.37 (d, 1H, *J*= 2.1, *H*-2"), 7.23 (dd, 1H, *J*= 8.2, 2.2, *H*-6"), 6.86 (d, 1H, *J*= 8.2, *H*-5"), 6.17 (s, 1H, *H*-2), 6.09 (dd, 1H, *J*= 10.5, 1.4, *H*-5), 5.95 (ddt, 1H, *J*= 9.1, 3.8, 1.5, *H*-4), 4.86 (dt, 1H, *J*=4.8, 1.2, *H*-3), 4.73-4.56 (m, 3H, *H*-6 and CH_2N), 2.11 (s, 3H, CH_3C=O), 1.81 (s, 3H, CH_3C=O), 1.01 (s, 9H, $(CH_3)_3C$), 0.98 (s, 9H, $(CH_3)_3C$), 0.234 (s, 3 H), 0.228(s, 3 H), 0.21 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 169.1 (*C*=O), 147.5, 147.3, 147.1 (*C*-3", *C*-4", *C*-4'), 129.9 (*C*-5), 124.3 (*C*-1"), 122.7 (*C*-4), 121.4 (*C*-5"), 120.7 (*C*-5'), 118.9 (*C*-6"), 118.6 (*C*-2"), 90.6 (*C*-2), 68.5 (*C*-6), 63.6 (*C*-3), 52.6 (CH_2N), 25.9 ($C(CH_3)_3$), 20.8, 20.6 (CH_3C=O), 18.53, 18.45 ($C(CH_3)_3$), -4.1 ($((CH)_3)_2Si$. HRMS (ESI+): calcd. for $C_{30}H_{48}N_3O_7Si_2^+$ $[M+H]^+$ 618.3025, found 618.3067.

Typical procedure for the synthesis of triazoles 21 (Procedure B)

A solution of azide **19** (105.1 mg, 412 μmol) in *t*-BuOH (1.5 mL) and H_2O (1.5 mL) was treated with 3,3-diethoxy-1-propyne (63 mg, 494 μmol), sodium ascorbate (36 mg, 182 μmol) and $CuSO_4$ pentahydrate (18 mg, 72 μmol). The mixture was stirred in a closed vessel at room temperature for 4 h. At this point it was complete by TLC. The mixture was diluted with saturated aqueous NH_4Cl, and extracted with AcOEt. After evaporation and chromatography **(**PE/AcOEt 5:5 to 1:9) pure **21d** was obtained as a white solid (143 mg) (91%).

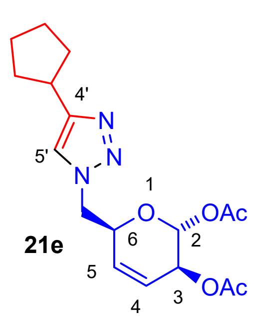
(2*R*,3*S*,6*S*)-2,3-Diacetoxy-6-[4-(1,1-diethoxymethyl)-1*H*-1,2,3-triazolyl)methyl]-3,6-dihydro-2*H*-pyran 21d



21d

R_f: 0.27 (PE / AcOEt 50:50). M.p.: 93.4 °C. $[\alpha]_D$ +112.3 (c 2,5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1 H, *H*-5'), 6.17 (s, 1H, *H*-2), 6.06 (dd, 1H, *J*= 10.5, 1.5, *H*-5), 5.96 (dddd, 1H, *J*= 10.6, 5.2, 2.0, 1.2, *H*-4), 5.72 (s, 1 H, C*H*(OEt)$_2$), 4.91-4.87 (m, 1H, *H*-3), 4.71-4.61 (m, 2H, *H*-6, C*H*HN), 4.58 (dd, 1H, *J*= 14.1, 3.7, CH*H*N), 3.75-3.55 (m, 4H, C*H*$_2$CH$_3$), 2.10 (s, 3H, C*H*$_3$C=O), 2.08 (s, 3H, C*H*$_3$C=O), 1.234 (t, 3H, *J*= 7.0, C*H*$_3$CH$_2$), 1.231 (t, 3H, *J*= 7.0, C*H*$_3$CH$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 168.8 (*C*=O), 147.0 (*C*-4'), 129.9 (*C*-5), 123.6 (*C*-5'), 122.7 (*C*-4), 96.7 (*C*(OEt)$_2$), 90.6 (*C*-2), 68.1 (*C*-6), 63.6 (*C*-3), 61.41, 61.35 (*C*H$_2$CH$_3$), 52.7 (*C*H$_2$N), 20.74, 20.70 (*C*H$_3$C=O), 15.11, 15.09 (CH$_2$*C*H$_3$). HRMS (ESI+): calcd. for $C_{17}H_{26}N_3O_7^+$ $[M+H]^+$ 384.1765, found 384.1788.

(2*R*,3*S*,6*S*)-2,3-Diacetoxy-6-[4-cyclopentyl-1*H*-1,2,3-triazolyl)methyl]-3,6-dihydro-2*H*-pyran 21e



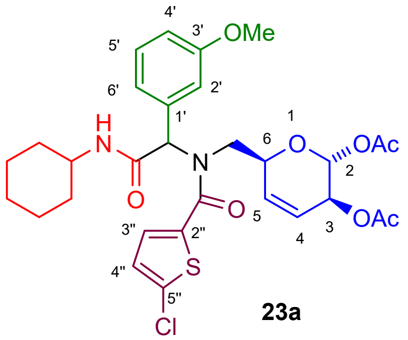
21e

It was prepared following the general procedure B, starting from 100.0 mg of azide **19** (392 μmol) and 50.0 μL (431 μMol, 1.1 equiv.) of commercially available alkyne **20e**. Time: 4 h. Chromatography (PE/AcOEt from 60:40 to 0:10) gave pure **21e** as a foam (127 mg, 93%). R_f: 0.15 (PE / AcOEt 50:50). $[\alpha]_D$ + 127.6 (c 1, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, 1 H, *J*= 0.8, *H*-5'), 6.16 (s, 1H, *H*-2), 6.06 (dd, 1H, *J*= 10.5, 1.5, *H*-5), 5.95 (dddd, 1H, *J*= 10.5, 4.9, 2.1, 1.3, *H*-4), 4.91 (dtd, 1H, *J*=4.0, 1.4, 0.7, *H*-3), 4,65 (tq, 1H, *J*= 4.0, 1.8, *H*-6), 4.58, 4.55 (AB part of an ABX syst., J_{AB}= 11.8, J_{AX}= 2.7, J_{BX}= 2.2, C*H*$_2$N), 3.18 (mc, 1H, C*H* cyclopentyl), 2.10 (s, 3H, C*H*$_3$C=O), 2.06 (s, 3H, C*H*$_3$C=O), 2.14-2.05 (m, 2H, C*H*$_2$ cyclopentyl), 1.79-1.63 (m, 6H, C*H*$_2$ cyclopentyl).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 168.9 (*C*=O), 152.7 (*C*-4'), 130.1 (*C*-5), 122.6 (*C*-4), 121.2 (*C*-5'), 90.7 (*C*-2), 68.3 (*C*-6), 63.9 (*C*-3), 52.6 (*C*H$_2$N), 36.7 (*C*H *cy*Pent), 33.22, 33.16, 25.1 (x 2) (*C*H$_2$ *cy*Pent), 20.8 (x 2) (*C*H$_3$C=O). HRMS (ESI+): calcd. for $C_{17}H_{24}N_3O_5^+$ $[M+H]^+$ 350.1710, found 350.1701.

Typical procedure for the Ugi reaction on azide 19 (METHOD A). (2*R*,3*S*,6*S*)-2,3-Diacetoxy-6-((*N*-(2-(cyclohexylamino)-1-(3-methoxyphenyl)-2-oxoethyl)-(5-chlorothiophene-2-carboxyamido)methyl)-3,6-dihydro-2*H*-pyran 23a



23a

A solution of azide **19** (100 mg, 392 μmol), is dissolved in dry CH_2Cl_2 (1.6 mL), and treated, in this order, with 3-methoxybenzaldehyde (58.7 mg, 431 μmol) and triphenylphosphine (144 mg, 549 μmol). After stirring for 2 h at rt, the solvent was evaporated to dryness. The residue was taken up with dry MeOH (1.6 mL) and treated with 5-chlorothiophene-2-carboxylic acid (76.4 mg, 470 μmol) and cyclohexyl isocyanide (73 μL, 588 μmol). The solution was stirred at rt for 48 h. Then it was diluted with AcOEt and washed with a saturated aqueous $NaHCO_3$ solution. After evaporation, the crude product was chromatographed with petroleum ether / ACOEt 60:40 to afford a mixture of diastereomers A (faster running) and B (slower running) only slightly separated (115 mg, 48%). A:B ratio was determined by NMR of the crude product, by integration of signals at 6.19 and 6.10 ppm and resulted: A:B = 44:56. R_f: 0.54 (A), 0.49 (PE / AcOEt 60:40). The two diastereomers could be separated using CH_2Cl_2 / Et_2O / AcOEt 20:2:1 R_f: 0.80 (A), 0.55 (B).

Diastereomer A

$[\alpha]_D$ + 51.9 (c 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.22 (m, 2H, *H*-5', *H*-3''), 6.90 (d, 1H, *J*= 4.0, *H*-4''), 6.85 (dd, 1H, *J*= 8.2, 2.2, *H*-4'), 6.78 (broad d, 1H, *J*=7.4, *H*-6'), 6.74 (broad s, 1H, *H*-2'), 6.19 (s, 1H, *H*-2), 5.95-5.81 (m, 3H, *H*-5, *H*-4, C*H*N), 4.93-4.87 (m, 1H, *H*-3), 4.75 (very broad signal, 1H, *H*-6), 4.05-3.92 (m, 1H, C*H*NH), 3.86-3.78 (m, 1H, C*H*HN), 3.78 (s, 3H, OC*H*$_3$), 3.48 (A) (broad d, 1H, *J*= 13.5, CH*H*N), 2.95 (broad s, 1H, N*H*), 2.10, 2.04 (2s, 2x3H, C*H*$_3$CO), 1.95-1.05 (m, 10H, cyclohexyl).

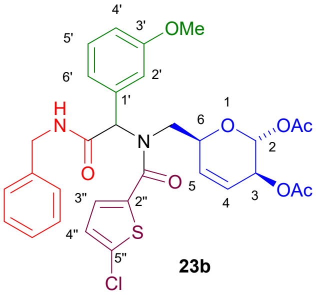
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8 (A), 168.7 (A), 167.7 (A), 166.6 (broad) (*C*=O), 159.9 (*C*-3'), 136.4, 136.0 (x2) (*C*-2'', *C*-5'', *C*-1'), 131.6 (*C*-5), 130.0, 129.9 (*C*-5' and *C*-3''), 126.9 (*C*-4''). 121.5 (*C*-6'), 120.9 (*C*-4), 115.3, 113.7 (*C*-2' and *C*-4'), 90.2 (*C*-2), 67.7 (very broad) (*C*HN), 65.9 (*C*-6), 64.5 (*C*-3),

55.3 (O*C*H$_3$), 50.5 (A) (*C*H$_2$N), 48.7 (*C*HNH), 33.3, 32.8, 25.5, 25.3, 25.2 (*C*H$_2$ cyclohexyl), 20.8 (x2) (*C*H$_3$CO). HRMS (ESI+): calcd. for $C_{30}H_{36}ClN_2O_8S^+$ [M+H]$^+$ 619.1875, found 619.1890.

Diastereomer B

[α]$_D$ + 20.6 (c 1, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.40-7.22 (m, 2H, *H*-5', *H*-3''), 6.97 (broad d, 1H, *J*=8.0, *H*-6' or *H*-4'), 6.94 (broad s, 1H, *H*-2'), 6.88 (dd, 1H, *J*=8.1, 2.1, *H*-6' or *H*-4'), 6.83 (d, 1H, *J*= 4.0, *H*-4''), 6.41 (d, 1H, *J*= 8.0, N*H*), 6.10 (s, 1H, *H*-2), 6.02 (d, 1H, *J*= 10.7, *H*-5), 5.95-5.87 (m, 1H, *H*-4), 5.62 (s, 1H, C*H*N), 4.88 (d, 1H, *J*=4.8, *H*-3), 4.49-4.41 (m, 1H, *H*-6), 3.89-3.74 (m, 2H, C*H*NH, C*H*HN), 3.79 (B) (s, 3H, OC*H$_3$*), 3.60 (dd, 1H, *J*= 15.0, 4.7, CH*H*N), 2.08, 2.03 (2s, 2x3H, C*H$_3$*CO), 1.95-1.05 (m, 10H, cyclohexyl).^{13}C NMR (101 MHz, CDCl$_3$) δ 169.9, 168.7, 167.8, 165.2 (*C*=O), 159.9 (*C*-3'), 136.3, 136.1, 135.1 (*C*-2'', *C*-5'', *C*-1'), 131.7 (*C*-5), 129.9, 129.8 (*C*-5' and *C*-3''), 126.1 (*C*-4''), 121.2 (B) (*C*-6'), 120.8 (*C*-4), 114.6, 114.1 (*C*-2' and *C*-4'), 90.4 (*C*-2), 67.3 (*C*-6) 66.4 (broad) (*C*HN), 64.3 (*C*-3), 55.3 (O*C*H$_3$), 51.3 (broad) (*C*H$_2$N), 48.7 (*C*HNH), 32.7 (x2), 25.4, 24.7 (x2) (*C*H$_2$ cyclohexyl), 20.9, 20.8 (*C*H$_3$CO). HRMS (ESI+): calcd. for $C_{30}H_{36}ClN_2O_8S^+$ [M+H]$^+$ 619.1875, found 619.1899.

(2*R*,3*S*,6*S*)-2,3-Diacetoxy-6-((*N*-(2-(benzylamino)-1-(3-methoxyphenyl)-2-oxoethyl)-(5-chlorothiophene-2-carboxyamido)methyl)-3,6-dihydro-2*H*-pyran 23b



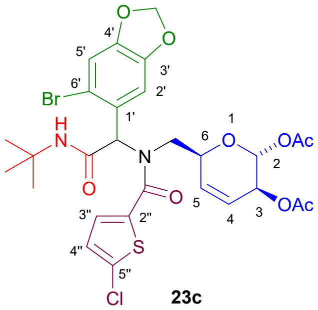
23b

It was prepared following the typical procedure A, starting from 127 mg of azide **19**. Overall yield: 171 mg (55 %). By chromatography it was possible to separate the two isomers. R$_f$: 0.44 (A), 0.38 (B) (PE / AcOEt 60:40). A:B ratio (from weight after chromatography): 40:60.

Major diastereomer (B, slower running). [α]$_D$ +52.0 (c 1, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35-7.20 (m, 7H, *H*-5', *H*-3'', *H* of benzyl), 7.05-6.91 (m, 3H, *H*-6', *H*-2', N*H*), 6.87 (dd, 1H, *J*=8.2, 2.3, *H*-4'), 6.78 (d, 1H, *J*=4.0, *H*-4''), 6.04 (s, 1H, *H*-2), 5.99 (d, 1H, *J*=10.2, *H*-5), 5.97-5.86 (m, 1H, *H*-4), 5.67 (s, 1H, C*H*N), 4.88 (d, 1H, *J*=4.5, *H*-3), 4.54 (dd, 1H, *J*=14.9, 6.2, C*H*HPh), 4.53-4.45 (m, 1H, *H*-6), 4.44 (dd, 1H, *J*=14.9, 5.6, C*H*HPh), 3.88-3.72 (m, 1H, C*H*HN), 3.76 (s, 3H, OC*H$_3$*), 3.66 (dd, 1H, *J*=14.9, 4.3, C*H*HN), 2.06, 2.01 (2s, 2x3H, C*H$_3$*CO). ^{13}C NMR (101 MHz, CDCl$_3$) δ 169.9, 168.8, 168.7, 165.0 (*C*=O), 159.9 (*C*-3'), 138.1 (quat. benzyl), 136.1, 135.7, 135.3 (*C*-2'', *C*-5'', *C*-1'), 131.4 (*C*-5), 130.0, 129.9 (*C*-3'' and *C*-5'), 128.6, 127.7 (*C* meta and ortho of benzyl), 127.3 (*C* para of benzyl), 126.2 (*C*-4''), 121.3 (*C*-6'), 120.9 (*C*-4), 114.7, 114.1 (*C*-2' and *C*-4'), 90.4 (*C*-2), 67.2 (*C*-6), 66.5 (broad)(*C*HN), 64.1 (*C*-3), 55.2 (*C*H$_3$O), 51.6 (*C*H$_2$N), 43.6 (Ph*C*H$_2$), 20.8, 20.7 (*C*H$_3$CO). HRMS (ESI+): calcd. for $C_{31}H_{32}ClN_2O_8S^+$ [M+H]$^+$ 627.1562, found 627.1556.

Minor diastereomer (**A,** faster running**)**. [α]$_D$ +58.2 (c 1, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.45-7.17 (m, 7H, *H*-5', *H*-3'', *H* of benzyl), 6.88-6.83 (m, 2H, *H*-4'', *H*-4'), 6.81-6.75 (m, 1H, *H*-6'), 6.72 (broad s, 1H, *H*-2'), 5.96 (s, 1H, C*H*N), 4.86-4.82 (m, 1H, *H*-3), 4.82-4.72 (very broad m, 1H, C*H*HPh), 4.88-4.47 (very broad signal, *H*-6), 3.76-3.70 (m, 1H, C*H*HN), 3.72 (s, 3H, OC*H$_3$*), 3.66-3.54 (broad d, 1H, C*H*HN), 2.04, 2.03 (2s, 2x3H, C*H$_3$*CO).^{13}C NMR (101 MHz, CDCl$_3$) δ 169.8, 169.2, 169.0, 166.2 (*C*=O), 159.9 (*C*-3'), 138.5 (quat. benzyl), 136.1 (x2), 136.0 (*C*-2'', *C*-5'', *C*-1'), 131.3 (*C*-5), 130.03, 129.96 (*C*-3'' and *C* para of benzyl), 128.6, 128.1 (*C* meta and ortho of benzyl), 127.3 (*C*-4''), 127.0 (*C*-5'), 121.6 (*C*-6'), 121.1 (*C*-4), 114.9, 114.2 (*C*-2' and *C*-4'), 90.6 (*C*-2), 67.9 (very broad) (*C*HN), 66.3 (*C*-6), 64.1 (*C*-3), 55.2 (*C*H$_3$O), 50.4 (*C*H$_2$N), 43.6 (Ph*C*H$_2$), 20.9, 20.7 (*C*H$_3$CO). HRMS (ESI+): calcd. for $C_{31}H_{32}ClN_2O_8S^+$ [M+H]$^+$ 627.1562, found 627.1549.

(2*R*,3*S*,6*S*)-2,3-Diacetoxy-6((*N*-(2-(*tert*-butylamino)-1-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-2-oxoethyl)-(5-chlorothiophene-2-carboxyamido)methyl)-3,6-dihydro-2*H*-pyran 23c

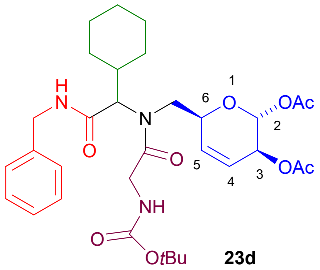


23c

It was prepared following the typical procedure A, starting from 152 mg of azide **19**. After chromatography (CH$_2$Cl$_2$ / Et$_2$O / AcOEt 20:2:1), we obtained 116 mg of nearly pure diastereomer **A** (d.r. = 95:5) (faster running) plus 105 mg of enriched diastereomer **B** (d.r. = 92:8). Overall yield: 221 mg (54%). The calculated diastereomeric ratio was 53:47 (**A** major). R$_f$: 0.76 (A), 0.71 (B) (CH$_2$Cl$_2$ / Et$_2$O / AcOEt 20:2:1).

Major diastereomer (A, faster running). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.21 (broad s, 1H, *H*-3''), 7.01 (s, 1H, *H*-5'), 6.89 (d, 1H, *J*=3.9, *H*-4''), 6.75 (broad s, 1H, *H*-2'), 6.17 (s, 1H, *H*-2), 6.05 (d, 1H, *J*=1.2, OC*H*HO), 6.00 (d, 1H, *J*=1.2, OC*H*HO), 5.94 (s, 2H, *H*-4 and *H*-5), 5.77 (s, 1H, C*H*N), 5.04 (very broad m, 1H, *H*-6), 4.92 (s, 1H, *H*-3), 3.67 (very broad signal, 1H, C*H*HN), 2.70 (very broad signal, 1H, C*H*HN), 2.12, 2.05 (2s, 2x 3H, C*H$_3$*CO), 1.51 (s, 9H, (C*H$_3$*)$_3$C). ^{13}C NMR (101 MHz, CDCl$_3$) δ 169.81, 168.78, 168.6, 167.2 (very broad) (*C*=O), 148.7, 147.5 (*C*-3', *C*-4'), 136.8, 135.9 (broad), 127.7 (*C*-2", *C*-5", *C*-1'), 131.8 (*C*-5), 129.2 (*C*-3"), 126.6 (*C*-4"), 120.9 (*C*-4), 117.3 (*C*-6'), 113.1 (*C*-5'), 110.8 (*C*-2'), 102.2 (OCH_2O), 90.2 (*C*-2), 68.7 (very broad) (*C*HN), 65.6 (broad) (*C*-6), 64.5 (*C*-3), 52.0 ($C(CH_3)_3$, 49.9 (broad) (CH_2N), 28.5 ($C(CH_3)_3$), 20.8, 20.7 (CH_3CO). HRMS (ESI+): calcd. for $C_{28}H_{31}BrClN_2O_9S^+$ $[M+H]^+$ 685.0617, found 685.0609.

Minor diastereomer (B, slower running). ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (broad s, 1H, *H*-3"), 7.07 (broad s, 1H, *H*-2'), 7.01 (s, 1H, *H*-5'), 6.83 (d, 1H, *J*= 4.0, *H*-4"), 6.07 (d, 1H, *J*=1.2, OC*H*HO), 6.04 (d, 1H, *J*=1.2, OC*H*HO), 6.15-5.83 (m, 3H, *H*-4, *H*-5, *H*-2), 5.73 (s, 1H, C*H*N), 4.84 (d, 1H, *J*=4.8, *H*-3), 4.24 (broad s, 1H, *H*-6), 3.85-3.46 (broad m, 2H, CH_2N), 2.07, 2.04 (2s, 2x 3H, CH_3CO), 1.38 (s, 9H, $(CH_3)_3C$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 168.6, 167.7, 165.2 (slightly broad) (*C*=O), 148.9, 147.9 (*C*-3', *C*-4'), 136.3, 134.9, 127.0 (*C*-2", *C*-5", *C*-1'), 132.3 (very broad) (*C*-5), 129.1 (broad) (*C*-3"), 126.0 (*C*-4"), 120.4 (broad) (*C*-4), 117.3 (broad) (*C*-6'), 113.0 (*C*-5'), 110.8 (*C*-2'), 102.4 (OCH_2O), 90.4 (*C*-2), 67.8 (broad) (*C*HN), 66.3 (broad) (*C*-6), 64.2 (*C*-3), 51.9 ($C(CH_3)_3$, 50.8 (broad) (CH_2N), 28.5 ($C(CH_3)_3$), 20.9, 20.8 (CH_3CO). HRMS (ESI+): calcd. for $C_{28}H_{31}BrClN_2O_9S^+$ $[M+H]^+$ 685.0617, found 685.0611.



23d

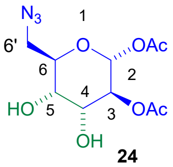
(2*R*,3*S*,6*S*)-2,3-Diacetoxy-6-((*N*-(2-(benzylamino)-1-(cyclohexyl)-2-oxoethyl)-(2-*tert*butoxycarbonylaminoacetamido)methyl)-3,6-dihydro-2*H*-pyran 23d

It was prepared following a different procedure. A solution of azide **19** (100 mg, 392 µmol), was dissolved in dry CH_2Cl_2 (1.6 mL), and treated with triphenylphosphine (144 mg, 549 µmol). After stirring overnight at rt, freshly activated powder 3 Å molecular sieves (20 mg), and cyclohexanecarboxaldehyde (57 µL, 470 µmol) was added and the mixture further stirred for 4 h. After filtration of molecular sieves, the solvent was evaporated to dryness. The residue was taken up with dry MeOH (1.6 mL) and treated with Boc-glycine (82.3 mg, 470 µmol) and benzyl isocyanide (72 µL, 588 µmol). The solution was stirred at rt for 48 h. Then it was diluted with AcOEt and washed with a saturated aqueous $NaHCO_3$ solution. After evaporation, the crude product was chromatographed with petroleum ether / ACOEt 60:40 to give 61 mg of nearly pure diastereomer **A** (faster running) plus 60 mg of mixed fractions enriched in diastereomer **B** (slower running)(d.r. = 89:11), and 11 mg of pure diastereomer **B**. Overall yield: 132 mg (55%). The calculated diastereomeric ratio was 51:49 (**A** major). R_f: 0.23 (A), 0.21 (B) (ETP/AcOEt 60:40).

Major diastereomer (A, faster running). White solid. M.p.: 70.4-72.6 °C. $[\alpha]_D$ +136.8 (c 1, $CHCl_3$).
^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.20 (m, 5H, benzyl C*H*), 7.00 (broad s, 1H, N*H*), 6.12 (s, 1H, *H*-2), 6.09-5.82 (m, 2H, *H*-4, *H*-5), 5.38 (slightly broad s, 1H,N*H*), 4.92 (slightly broad s, 1H, *H*-3), 4.75-4.62 (m, 1H, *H*-6), 4.54 (dd, 1H, *J*= 14.8, 6.8, C*H*HPh), 4.45-4.22 (broad m, 1H, C*H*N), 4.25-4.10 (m, 2H, CH_2NHBoc), 4.06 (dd, 1H, *J*= 17.3, 5.4, C*H*HPh), 3.48 (dd, 1H, *J*= 15.5, 10.4, C*H*HN), 3.38 (dd, 1H, *J*= 15.5, 3.5, C*H*HN), 2.30-2.02 (m, 1H, C*H* cycloexyl), 2.14, 2.07 (2s, 2x3H, CH_3CO), 1.87-1.47 (m, 4H, CH_2 cyclohexyl), 1.44 (s, 9H, $(CH_3)_3C$), 1.43-1.04 (m, 4H, CH_2 cyclohexyl), 1.01-0.73 (m, 2H, CH_2 cyclohexyl). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 170.5, 170.2, 168.9, 155.7 (*C*=O), 138.2 (quat. of benzyl), 131.3 (*C*-5), 128.7, 127.6 (C*H* ortho and meta of benzyl), 127.5 (C*H* para of benzyl), 121.6 (*C*-4), 90.2 (*C*-2), 79.2 ($C(CH_3)_3$), 66.5 (*C*-6), 64.2 (*C*-3), 48.4 (very broad) (CH_2N), 43.3 (CH_2Ph), 42.9 (CH_2NHBoc), 34.7 (broad) (*C*H cyclohexyl), 30.3, 29.3, 26.4, 25.7 (x2) (CH_2 cyclohexyl), 28.4 ($C(CH_3)_3$), 20.9 (x2) (CH_3C=O). **Note**: the peak of *C*HN is not visble because it is very broad. It probably falls under the peak at 64.2. HRMS (ESI+): calcd. for $C_{32}H_{46}N_2O_9^+$ $[M+H]^+$ 616.3229, found 616.3238.

Minor diastereomer (B, slower running). Oil. $[\alpha]_D$ +86.0 (c 1, $CHCl_3$).
^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (very broad s, N*H*), 7.36-7.18 (m, 5H, benzyl C*H*), 6.12 (s, 1H, *H*-2), 6.08-5.94 (m, 1H, *H*-4), 5.91 (d, 1H, *J*=10.4, *H*-5), 5.36 (slightly broad s, 1H,N*H*), 4.92 (slightly broad d, 1H, *J*=4.0, *H*-3), 4.74-4.58 (m, 1H, *H*-6), 4.49 (dd, 1H, *J*= 14.9, 6.2, C*H*HPh), 4.27 (dd, 1H, *J*= 14.9, 4.6, C*H*HPh), 4.20-3.98 (m, 2H, CH_2NHBoc), 3.75 (broad m, C*H*N), 3.60-3.26 (m, 2H, CH_2N), 2.43-2.26 (m, 1H, C*H* cyclohexyl), 2.14, 2.12 (2s, 2x3H, CH_3CO), 1.83-1.60 (m, 4H, CH_2 cyclohexyl), 1.44 (s, 9H, $(CH_3)_3C$), 1.32-1.07 (m, 4H, CH_2 cyclohexyl), 0.99-0.78 (m, 2H, CH_2 cyclohexyl). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 170.4 (x2), 168.9, 155.6 (*C*=O), 138.3 (quat. of benzyl), 130.7 (*C*-5), 128.6, 127.5 (C*H* ortho and meta of benzyl), 127.3 (C*H* para of benzyl), 122.0 (*C*-4), 90.2 (*C*-2), 79.6 ($C(CH_3)_3$), 66.1 (*C*-6), 64.2 (*C*-3), 43.2 (CH_2Ph), 43.0 (CH_2NHBoc), 36.6 (*C*H cyclohexyl), 30.4, 29.5, 26.2, 25.6 (x2) (CH_2 cyclohexyl), 28.3 ($C(CH_3)_3$), 20.8 (x2) (CH_3C=O). **Note**: the peaks of *C*HN and of CH_2N are not visible because most likely they are very broad. HRMS (ESI+): calcd. for $C_{32}H_{46}N_2O_9^+$ $[M+H]^+$ 616.3229, found 616.3242.

(2*R*,3*S*,4*R*,5*S*,6*R*)-6-(Azidomethyl)-2,3-diacetoxy-4,5-dihydroxy-tetrahydropyran 24



24

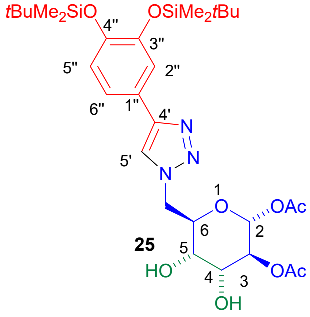
A solution of azide **19** (100.0 mg, 392 µmol) in acetone (1.5 mL) and H_2O (0.5 mL) was treated with *N*-methylmorpholine *N*-oxide monohydrate (NMO) (105 mg, 777 µmol) and with a 2.5% w/w solution of OsO_4 in *tert*-butanol (76.8 mM) (120 µL, 9.2 µmol). The solution was stirred for 18h at rt. Addition of 10% $NaHSO_3$ solution, extraction with AcOEt, washing with brine, evaporation and chromatography (PE/AcOEt 4:6) gave diastereomerically pure (d.r. > 99:1) **24** as an oil (114 mg) (82%). Examination of the NMR spectrum of crude and of the first eluted fractions showed two impurities (both faster running) that may be stereoisomers of the main product. We call here them B and C (B faster running, C slower running; both are faster running compared to the main diastereosmer A (**24**=). B gives a doublet at 6.22 (*H*-2, *J*=2.0). C gives a doublet at 6.14 (*H*-2, *J*= 1.6). They are well separated from the singlet of major diast. A (*H*-2, 6.00 ppm). From the crude, the ratio A:B:C seems = 91.1 : 3.6 : 5.3. Other typical signals of B and C are: 5.15 (**C**, dd, 1 H, *J*= 4.2, 1.5, *H*-3), 5.01 (**B**, t, 1 H *J*= 3.2, *H*-3). We were not able to determine the structures of **B** and **C**, but we suppose that **C** is the *talo* isomer, whereas **B** is a *trans* isomer caused by a not completely stereospecific osmylation. In this hypothesis the relative diastereoselectivity *altro* / *talo* is = 95:5.

Only the major diastereomer was fully characterized.

R_f: 0.25 (PE / AcOEt 4:6). $[\alpha]_D$ +81.9 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.00 (s, 1H, *H*-2), 5.00 (dd, 1H, *J*= 3.3, 1.3, *H*-3), 4.10 (ddd, 1H, *J*= 9.7, 5.7, 2.7, *H*-6), 4.04 (broad q, 1H, *J*= 3.2, *H*-4), 3.84 (td, 1H, *J*= 9.4, 3.5, *H*-5), 3.63, 3.52 (AB part of an ABX syst., 2H, J_{AB} = 13.4, J_{AX}=5.7, J_{BX}= 2.3, *H*-6'), 3.29 (d, 1H, *J*= 5.0, O*H* at C-4), 2.89 (d, 1H, *J*= 8.8, O*H* at C-5), 2.153, 2.146(2s, 2 x 3H, CH_3CO). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 168.9 (*C*=O), 90.8 (*C*-2), 70.3 (*C*-3), 69.1 (*C*-6), 67.5 (*C*-4), 64.9 (*C*-5), 51.3 (*C*-6'), 20.9, 20.8, (CH_3C=O). **HRMS (ESI+)**: calcd. for $C_{10}H_{16}N_3O_7$ $[M+H]^+$ 290.09828, found 290.09802.

(2*R*,3*S*,4*R*,5*S*,6*R*)-2,3-Diacetoxy-6-[4-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl)-1*H*-1,2,3-triazolyl)methyl]-4.5-dihydroxy-3,6-dihydro-2*H*-pyran 25



It was prepared from alkyne **20c** (45.0 mg, 125 µmol) and diastereomerically pure azide **24** (30.0 mg, 104 µmol) following the general **procedure A** for click chemistry (with two subsequent additions of catalyst). Chromatography (PE/AcOEt from 3:7 to 0:10) gave pure **25** as a solid (47.7 mg, 71%).

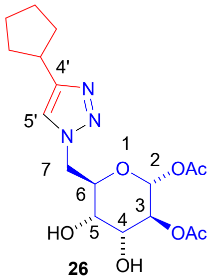
The same compound was also obtained starting from triazole **21c** (50 mg, 80.9 µmol) following the above described procedure for the synthesis of **24**, 43 mg of product were obtained (81%).

D.r., determined on the crude product, was 98:2. In particular it is possible to integrate the signals of *H*-2 at 5.96 (singlet, major) and at 6.11 (doublet, *J*= 1.2 Hz., minor). Anyway, the major diastereomer can be obtained in pure form by chromatography.

Solid. M.p.: 70,6-76,6 °C. R_f: 0.21 (PE / AcOEt 4:6). $[\alpha]_D$ +10.4 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1 H, *H*-5'), 7.34 (d, 1H, *J*= 2.2, *H*-2''), 7.24 (dd, 1H, *J*= 8.2, 2.2, *H*-6''), 6.88 (d, 1H, *J*= 8.2, *H*-5''), 5.96 (s, 1H, *H*-2), 5.03 (dd, 1H, *J*= 3.2, 1.1, *H*-3), 4.81, 4.69 (AB part of an ABX syst., 2H, J_{AB}= 14.7, J_{AX}= 5.8, J_{BX}= 1.8, CH_2N), 4.36 (ddd, 1H, *J*= 10.0, 5.6, 2.0, *H*-6), 4.06 (slightly broad s, 1 H, *H*-4), 3.75 (broad s, 1H, O*H*), 3.52 /broad d, 1 H, *J*= 7.2, *H*-5), 3.42 (broad s, 1H, O*H*), 2.05 (s, 3H, CH_3C=O), 2.02 (s, 3H, CH_3C=O), 1.01 (s, 9H, (CH_3)$_3$C), 0.99 (s, 9H, (CH_3)$_3$C), 0.24 (s, 6 H, CH_3Si), 0.22 (s, 6 H, CH_3Si). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 169.0 (*C*=O), 147.8, 147.4, 147.3 (*C*-3'', *C*-4'', *C*-4'), 123.8 (*C*-1''), 121.4 (*C*-5''), 121.0 (*C*-5'), 119.0 (*C*-6''), 118.6 (*C*-2''), 90.7 (*C*-2), 70.3 (*C*-3), 68.6 (*C*-6), 67.9 (*C*-4) 64.8 (*C*-5), 51.0 (CH_2N), 25.9 (C(CH_3)$_3$), 20.9, 20.7 (CH_3C=O), 18.5, 18.4 (*C*(CH_3)$_3$), -4.05, -4.07 (x2), -4.09 ((*C*H)$_3$)$_2$Si. HRMS (ESI+): calcd. for $C_{30}H_{50}N_3O_9Si_2^+$ $[M+H]^+$ 652.30801, found 652.30796.

(2*R*,3*S*,4*R*,5*S*,6*R*)-2,3-Diacetoxy-6-[(4-cyclopentyl-1*H*-1,2,3-triazolyl)methyl]-4.5-dihydroxy-3,6-dihydro-2*H*-pyran 26



26

A solution of diastereomerically pure azide **24** (104.2 mg, 360 μmol) in *t*-BuOH (1.5 mL) and H_2O (1.5 mL) was treated with cyclopentylacetylene (50 μL, 431 μmol), sodium ascorbate (36 mg, 182 μmol) and $CuSO_4$ pentahydrate (18 mg, 72 μmol). The mixture was stirred ina closed vessel at room temperature for 4 h. At this point it was complete by TLC. The mixture was diluted with saturated aqueous NH_4Cl, and extracted with AcOEt. After evaporation and chromatography **(**PE/AcOEt 3:7 to 0:10) pure **26** was obtained as an oil (95 mg) (72%).

The same compound was also obtained from triazole **21e**. A solution of triazole **21e** (127 mg, 363 μmol) in acetone (1.6 mL) and H_2O (0.4 mL) was treated with *N*-methylmorpholine *N*-oxide monohydrate (NMO) (97 mg, 718 mol) and with a 2.5% (w/w)(76.8 mM) solution of OsO_4 in *tert*-butanol (142 μL, 10.9 μmol, 0.03 equiv.). The solution was stirred for 48 h at rt, Addition of 10% $NaHSO_3$ solution, extraction with AcOEt, washing with brine, evaporation and chromatography (PE/AcOEt 3:7 to 0:10) gave nearly pure **26** (containing some diastereomer) as an oil (113 mg) (81%). D.r., determined on the crude product, was 93:7. In particular it is possible to integrate the signals of *H*-2 at 5.92 (singlet, major) and at 6.21 (doublet, *J*= 1.6 Hz., minor). The two diastereomers were not separated by chromatography.

R_f: 0.13 (PE / AcOEt 3:7). $[\alpha]_D$ +39.3 (c 1.2, $CHCl_3$).

Only the signals of major diastereomer are here reported.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (s, 1 H, *H*-5'), 5.93 (s, 1H, *H*-2), 5.02 (dd, 1H, *J*= 3.2, 1.1, *H*-3), 4.77 (dd, 1 H, *J*= 14.5, 2.1, *H*-7), 4.58 (dd, 1 H, *J*= 14.5, 6.3, *H*-7), 4.50-4.19 (very broad signal, 2 H, O*H*),

4.32 (ddd, 1H, *J*= 10.0, 6.3, 1.9 *H*-6), 4.05 (t, 1 H, *J*= 3.1, *H*-4), 3.49 (dd, 1 H, *J*= 10.1, 3.4, *H*-5), 3.16 (quint., 1 H, *J*= 8.0, C*H* cyclopentyl), 2.06 (s, 3H, CH_3C=O), 2.05 (s, 3H, CH_3C=O), 2.12-2.03 (m, 2 H, CH_2 cyclopentyl), 1.80-1.56 (m, 6 H, CH_2 cyclohexyl).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 169.1 (*C*=O), 152.7 (*C*-4'), 121.7 (*C*-5''), 90.6 (*C*-2), 70.5 (*C*-3), 68.7 (*C*-6), 67.6 (*C*-4) 64.7 (*C*-5), 50.9 (*C*H_2N), 36.6 (*C*H cyclopentyl), 33.2, 33.1, 25.0 (x 2) (*C*H_2 cyclopentyl), 20.9, 20.7 (*C*H_3C=O). HRMS (ESI+): calcd. for $C_{17}H_{26}N_3O_7^+$ $[M+H]^+$ 384.1765, found 384.1767.

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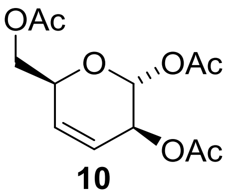
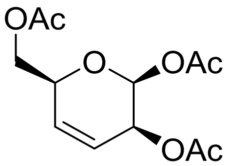
Determination of the relative configuration of triacetate 10

The conformational equilibria of the two possible isomers **10** and *iso*-**10** were examined, also with the aid of Chem3D program, using MOPAC (AM1).

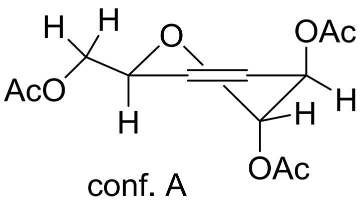


10



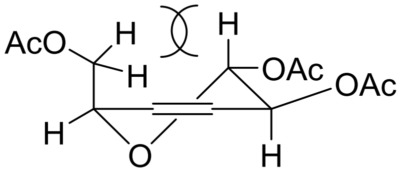
***iso*-10**

Both isomers may exist in two alternative *half-chair* conformations.
For *trans-trans* isomer **10**, the preferred conformation is expected to be Conf. A, whereas for the *cis-cis*-isomer it should be again A. For conformations A of **10** and both conformations of *iso*-**10,** a small coupling constant between *H*-1 and *H*-2 is predicted (diedral angles 103° for conf. A of **10** and 41° and 40° respectively for conformations A and B of *iso*-**10**). *H*-1 in **10** appears as a singlet at 6.18 ppm, and this very low J seems to be more consistent with conf. A of **10**. However, the main proof comes from the NOESY experiment, which shows a weak nOe between *H*-1 and *H*-6, and this is clearly possible only in conformation B of **10**.

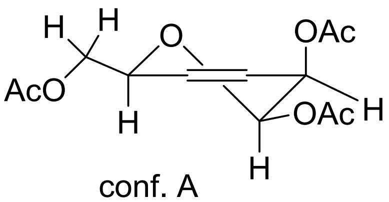


conf. A
(most likely)

10

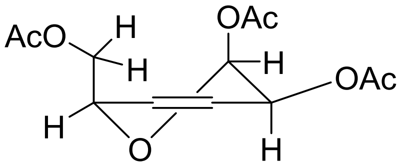


conf. B
(less likely)



conf. A
(most likely)

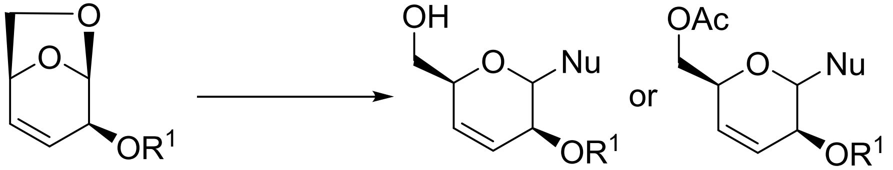
iso-**10**



conf. B
(less likely)

Attempts to convert compounds 3,4 into open adducts 6 or 7, and optimization of the synthesis of 8, 9, and 10

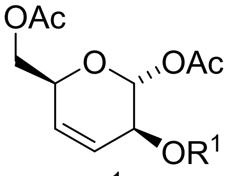
Here we report a Table with some selected results of the attempts made to carry out the following reaction.



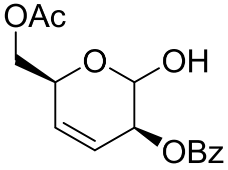
2 R^1 = H
3 R^1 = Bn
4 R^1 = Bz
5 R^1 = Ac

6

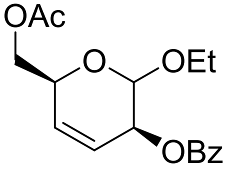
7



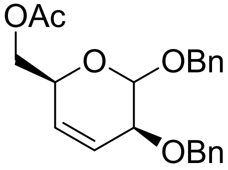
8 R^1 = Bn
9 R^1 = Bz
10 R^1 = Ac



S1



S2



S3

Entry	Substrate	Nucleophile	Promoter 1	Promoter 2	Solvent	Time - Temp.	Product	Yield	d.r.
1	**4**	*t*BuNC (1.2 eq.)	$Zn(OAc)_2$ (1.2 eq.)	-	THF	2 days rt	no reaction	-	
2	**2**	*t*BuNC (1.2 eq.)	$Zn(OAc)_2$ (1.2 eq.)	-	THF	2 days rt	no reaction	-	
3	**4**	*t*BuNC (1.2 eq.)	$ZnCl_2$ (0.5eq.)	-	THF	3 days rt	no reaction	-	
4	**4**	*t*BuNC	$ZnCl_2$	AcOH	THF	2 days	no reaction	-	

		(1.2 eq.)	(0.5eq.)	(1.2 eq.)		50 °C			
5	**4**	*t*BuNC (1.2 eq.)	$ZnCl_2$ (0.5eq.)	AcOH (2.5eq.)	Toluene	2 days 90 °C	no reaction	-	
6	**4**	*t*BuNC (1.2 eq.)	$ZnCl_2$ (0.5eq.)	Ac_2O (1.5eq.)	Toluene	2 days 90 °C	no reaction	-	
7	**4**	*t*BuNC (1.5 eq.)	TMS-OTf (0.5eq.)	Ac_2O (1.5eq.)	Toluene	1 day rt	**9**	67%	91:9
8	**4**	*t*BuNC (1.5 eq.)	TMS-OTf (0.5eq.)		Toluene	1 day rt	no reaction	-	
9	**4**	2,6-MeC_6H_3NC	TMS-OTf (0.5eq.)	Ac_2O (1.5eq.)	Toluene	1 day rt	**9**	50%	91:9
10	**4**		TMS-OTf (0.5eq.)	Ac_2O (1.5eq.)	Toluene	1 day rt	**9**	50%	91:9
11	**4**	2,6-MeC_6H_3NC	TMS-OTf (0.5eq.)	AcONa (1.5eq.)	Toluene	1 day rt	no reaction	-	
12	**4**	*t*BuNC (1.5 eq.)	TMS-OTf (0.5eq.)	AcCl	Toluene	1 day rt	**S1**	5%	
13	**4**	*t*BuNC (1.5 eq.)	TMS-OTf (0.5eq.)	$(CF_3CO)_2O$	Toluene	1 day rt	no reaction	-	
14	**4**	-	TMS-OTf (0.5eq.)	AcOEt	Toluene	1 day rt	**S2**	10%	
15	**4**	-	TMS-OTf (0.5eq.)	*p*NO_2-C_6H_4OAc	Toluene	1 day rt	no reaction	-	
16	**4**	-	TMS-OTf (0.5eq.)	Ac_2O (1.5eq.)	MeCN	1 day rt	**9**	40%	91:9
17	**4**	-	TMS-OTf (0.5eq.)	Ac_2O (1.5eq.)	$MeNO_2$	1 day rt	**9**	43%	91:9
18	**4**	-	TMS-OTf (0.5eq.)	Ac_2O (1.5eq.)	Toluene / MeCN 8:1	1 day rt	**9**	60%	91:9
19	**4**		TMS-OTf (2 µmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	30 min 0 °C	**9**	75%	87:13
20	**4**	-	85% H_3PO_4 (0.7 mmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	30 min 0 °C to rt	**9**	88%	91:9
21	**3**	*t*BuNC (1.5 eq.)	TMS-OTf (0.5eq.)	Ac_2O (1.5eq.)	Toluene	1 day rt	**8**	63%	92:8
22	**3**	-	TMS-OTf	Ac_2O	Toluene	1 day	**8** + **10**	13%	92:8

			(0.5eq.)	(1.5eq.)		rt	**(59 : 41) + S3**	(**S3**), 33% (**8**), 20% (**10**)	(**10**)
23	**3**	-	85% H_3PO_4 (0.7 mmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	60 min 0 °C to rt	**8**	71%	92:8
24	**3**	-	98% H_2SO_4 (0.1 mmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	30 min 0 °C	**only 10**	62%	86:14
25	**3**	-	$ZnCl_2$ (0.5 mmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	30 min 0 °C	**8** + **10** **(73 : 27)**	n.d.	93:7
26	**3**	-	BF_3●Et_2O (0.5 mmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	30 min 0 °C	**only 10**	65%	92:8
27	**3**	-	BF_3●Et_2O (0.5 mmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	30 min 0 °C	**8** + **10** **(73 : 27)**	n.d.	93:7
28	**5**		TMS-OTf (2 μmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	30 min 0 °C	**10**	78%	87:13
29	**5**		85% H_3PO_4 (0.7 mmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	60 min 0 °C to rt	**10**	95%	91:9
30	**5**		Sc(OTf)$_3$ (52 μmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	30 min 0 °C	**10**	88%	91:9
31	**5**		$FeCl_3$ (0.27 mmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	30 min 0 °C	**10**	81%	91:9
32	**5**		$ZnCl_2$ (0.5 mmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	30 min 0 °C	**10**	71%	91:9
33	**2**		85% H_3PO_4 (0.7 mmol/mL)	Ac_2O (1.2 mL/mmol of substrate)	no	60 min 0 °C to rt	**10**	92%	91:9

Discussion of results. Entries 1-6 show that zinc based promoters are not able to induce opening of the bicyclic system, at least in presence of an isocyanide. However, using excess of Ac_2O and with no isocyanide in the reaction mixture, opening can take place (entries 25 and 32). Probably the isocyanide complexes with the Lewis acid making it less efficient.

Entries 7-19, 21-22, and and 28 show that TMS-OTf is able to promote ring opening. However, in the absence of the co-promoter (Ac_2O) non reaction occurs (entry 8). In the presence of Ac_2O reaction occurs, but the entering nucleophile is not the isocyanide (entries 7-13) (as expected) but the acetate anion. This is somehow surprising, because in normal Passerini reactions (also in the presence of catalysts, the isocyanide seems to be a better nucleophile than the carboxylate anion. However, the result of entry 11 shows that the acetate anion itself is not able to promote the reaction, in the absence of the anhydride.

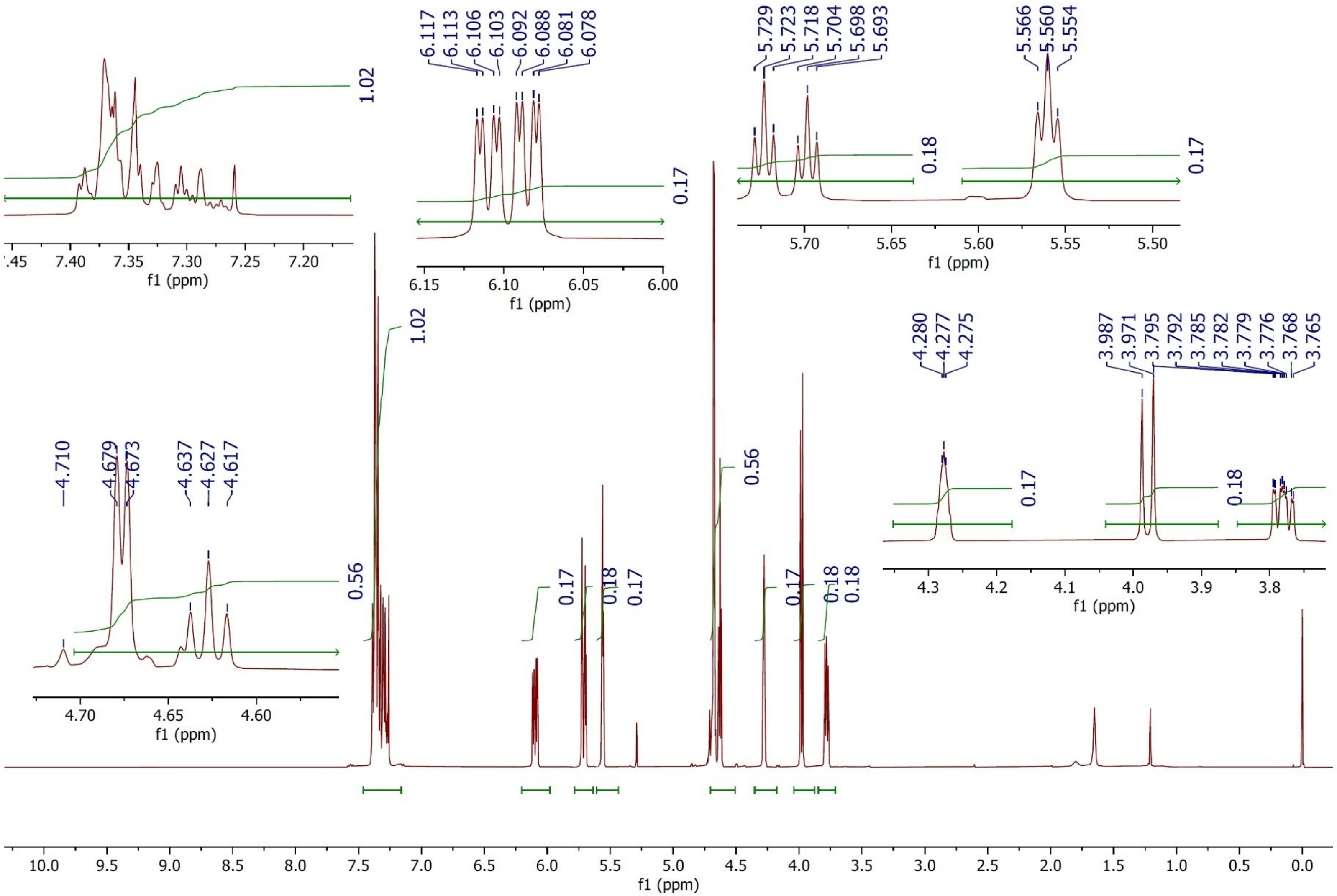
Also acetyl chloride (entry 12) is by far less efficient than Ac_2O in promoting the reaction, and no entrance of acetoxy group at carbon 1 is observed. This fact somehow points in favour of a concerted mechanism C (see Scheme 2 of main paper). The use of esters (entries 14 and 15) gave only poor results. Different solvents were also tested on benzoyl compound **4**, leading to some difference in yield, but no difference in diastereoselectivity, which remained high.

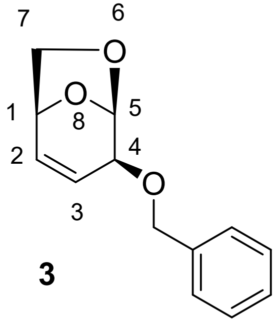
Using the benzyl protected derivative (**3**), the benzyl group proved to be labile under some conditions, affording **10** and/or **S3** plus benzyl acetate. The comparison of entries 21 and 22 is interesting. Although the isocyanide never entered in the isolated products, the presence of isocyanide is beneficial to avoid loss of benzyl cation, probably by attenuating the strength of TMS-OTf.

The only promoters that afforded good yields for diacetate **8** starting from benzyl derivative **3** are TMSOTf (but only in the presence of isocyanide)(entry 21) or phosphoric acid. (entry 23). In the other cases substantial loss of benzyl group was observed, with formation of **10**, and of benzyl acetate.

The best conditions to get **9** or **10** (also in view of green chemistry) involve the use of phosphoric acid in neat Ac_2O (entries 29, 33). Obviously, the best synthesis of **10** starts directly from **2** with no use of protecting groups (entry 33).

Copies of ^{1}H and ^{13}C N.M.R. spectra





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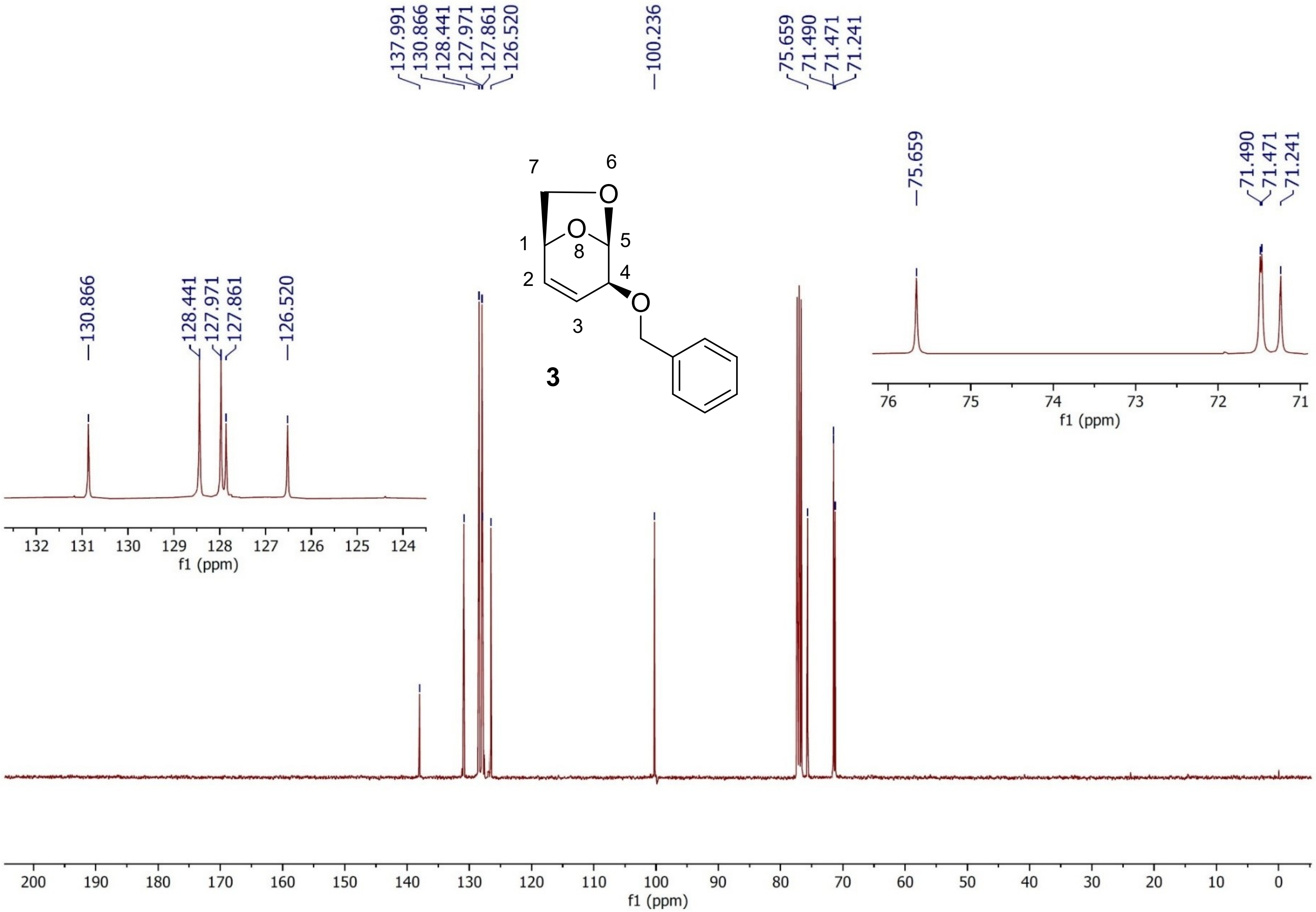
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O
1
O
8
5
4
2
O
3
3
130.866
128.441
127.971
127.861
126.520
132 131 130 129 128 127 126 125 124
f1 (ppm)
75.659
71.490
71.471
71.241
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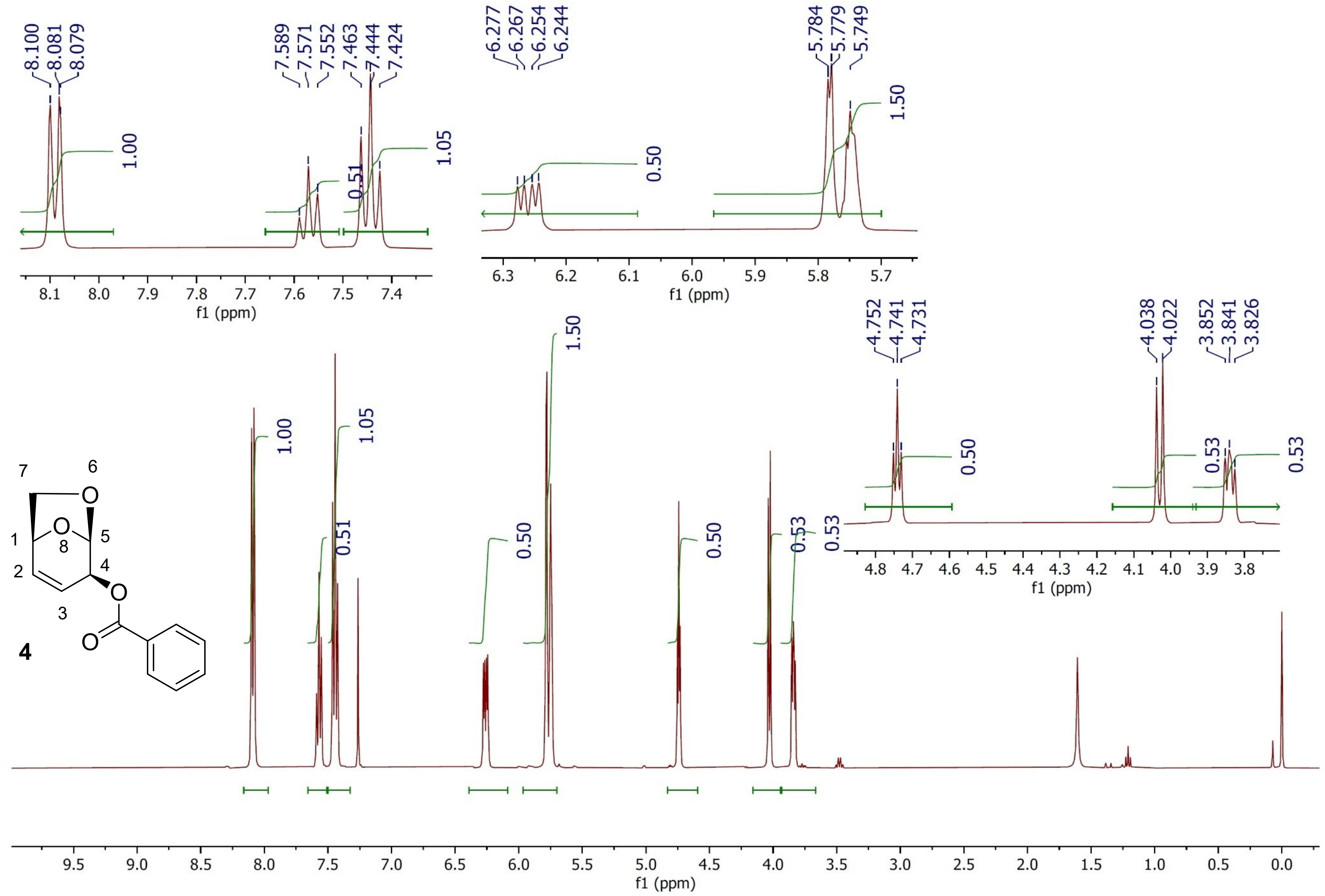
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

-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7.9
7.8
7.7
7.6
7.5
7.4
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6.244
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6.2
6.1
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5.9
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5.7
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4.741
4.731
4.038
4.022
3.852
3.841
3.826
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0.53
0.53
4.8
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
f1 (ppm)
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6
1
8
5
2
4
3
O
O
O
O
4
1.00
1.05
0.51
0.50
1.50
0.50
0.53
0.53
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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2.5
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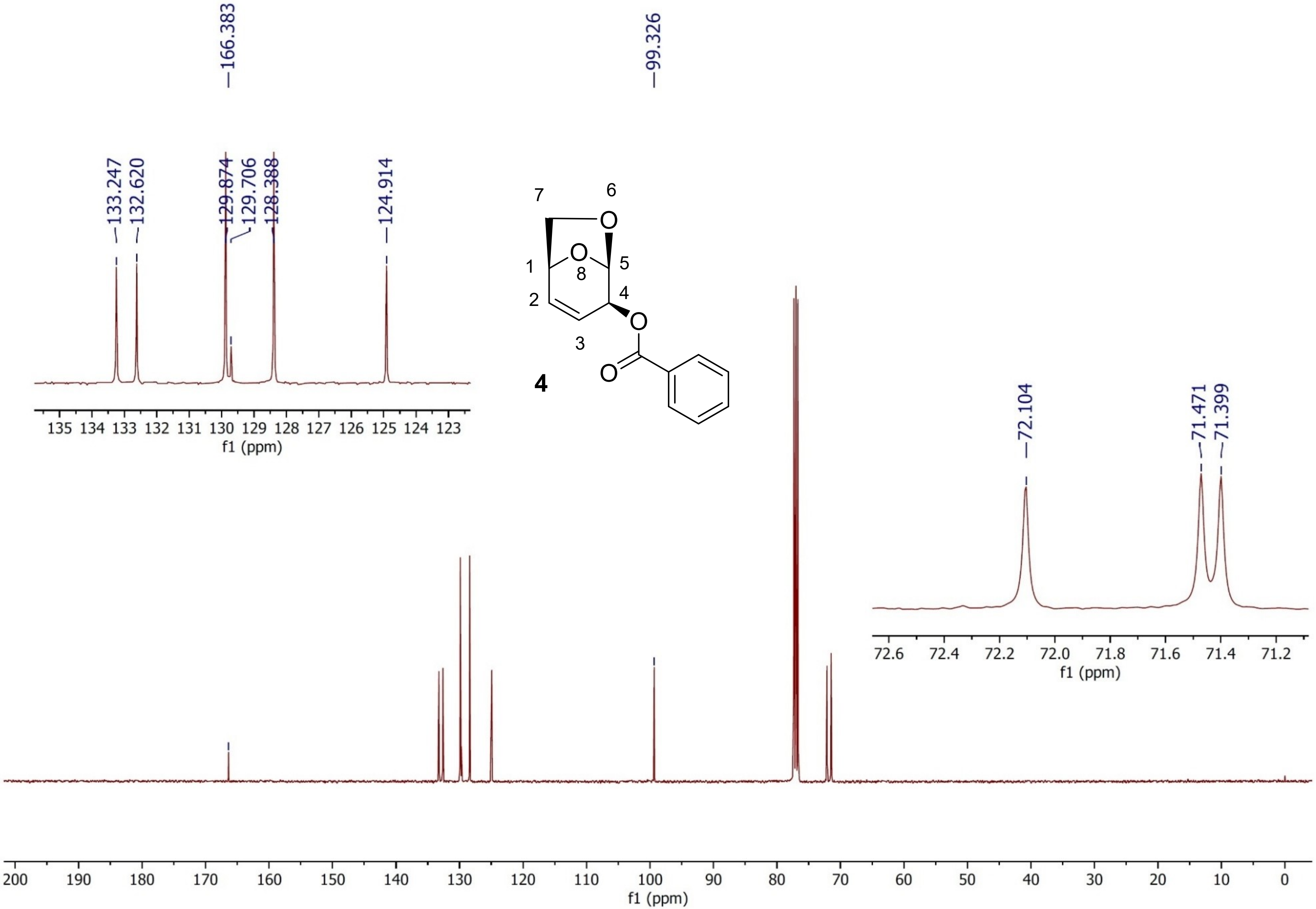
0.0
f1 (ppm)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6
O
1
O
8
5
2
4
O
3
O
4
72.104
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71.399
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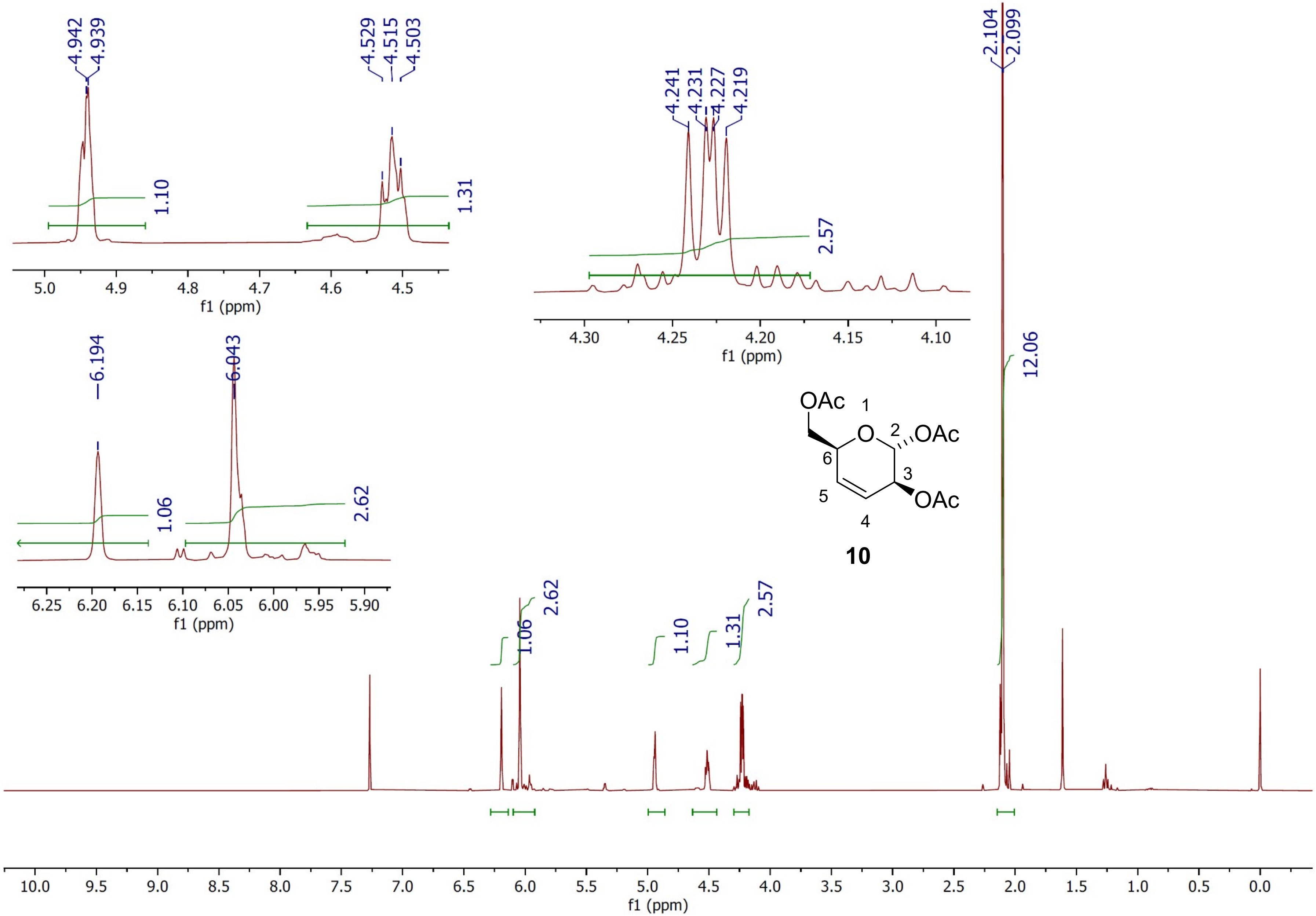
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4.231
4.227
4.219
2.57
4.30 4.25 4.20 4.15 4.10
f1 (ppm)
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2.099
12.06
6.194
6.043
1.06
2.62
6.25 6.20 6.15 6.10 6.05 6.00 5.95 5.90
f1 (ppm)
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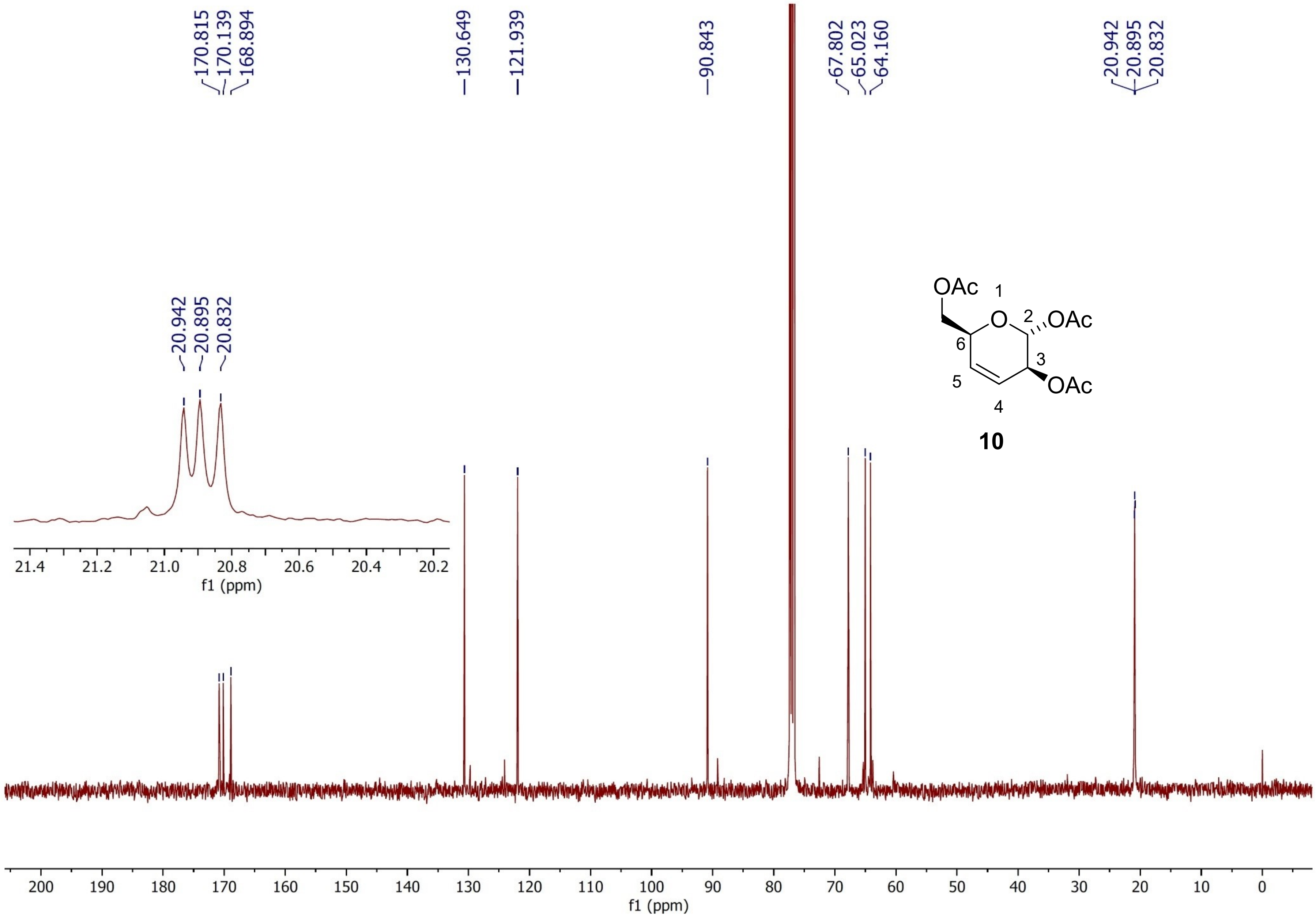
1
2
OAc
O
6
3
5
OAc
4
1.06
2.62
1.10
1.31
2.57
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

10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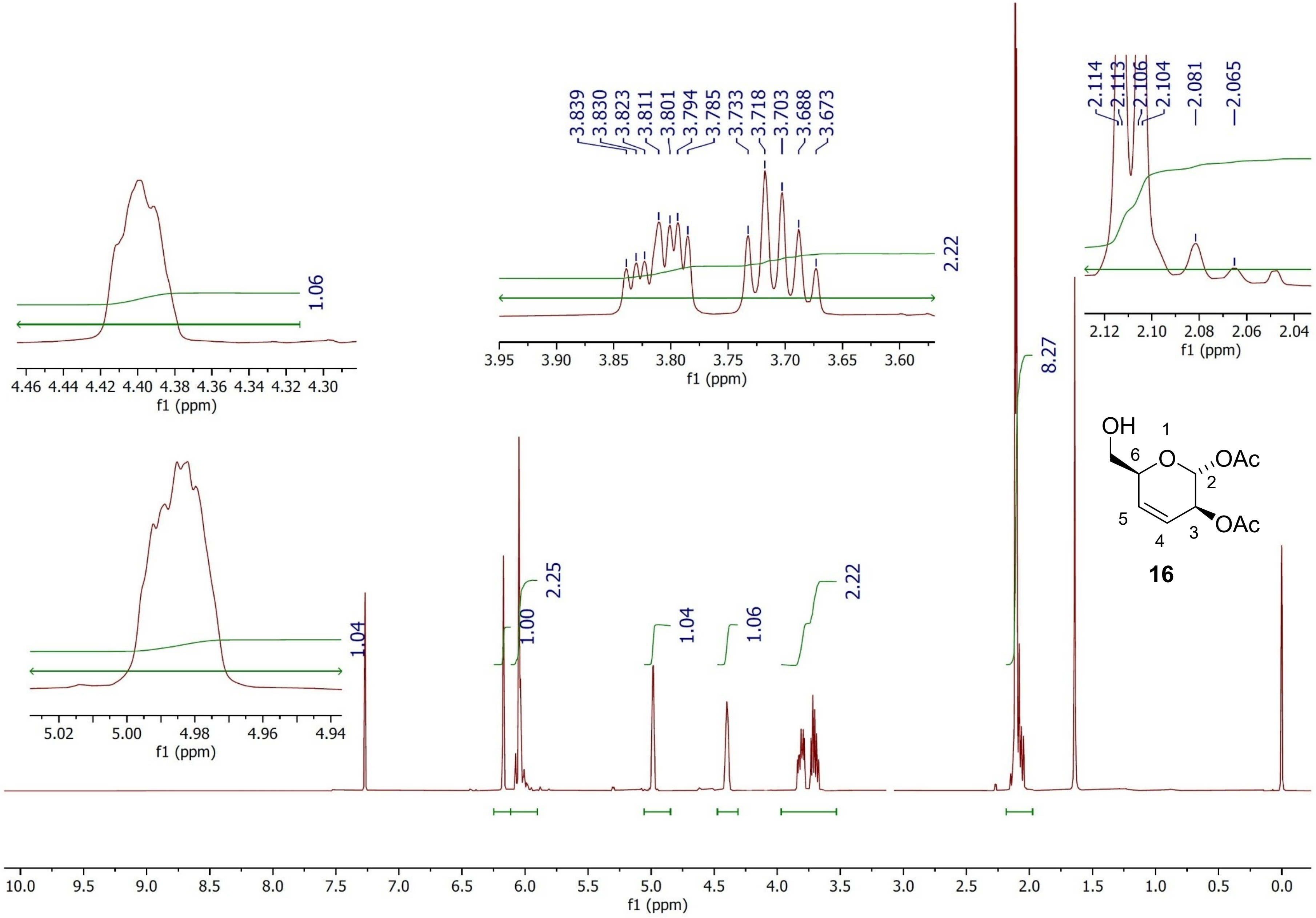
20.832
OAc
1
2
OAc
O
6
3
5
OAc
4
20.942
20.895
20.832
21.4
21.2
21.0
20.8
20.6
20.4
20.2
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

10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3.673
2.22
3.95 3.90 3.85 3.80 3.75 3.70 3.65 3.60
f1 (ppm)
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2.113
2.106
2.104
2.081
2.065
2.12 2.10 2.08 2.06 2.04
f1 (ppm)
1.06
4.46 4.44 4.42 4.40 4.38 4.36 4.34 4.32 4.30
f1 (ppm)
5.02 5.00 4.98 4.96 4.94
f1 (ppm)
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1.00
2.25
1.04
1.06
2.22
8.27
OH
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6
O
OAc
2
5
4
3
OAc
16
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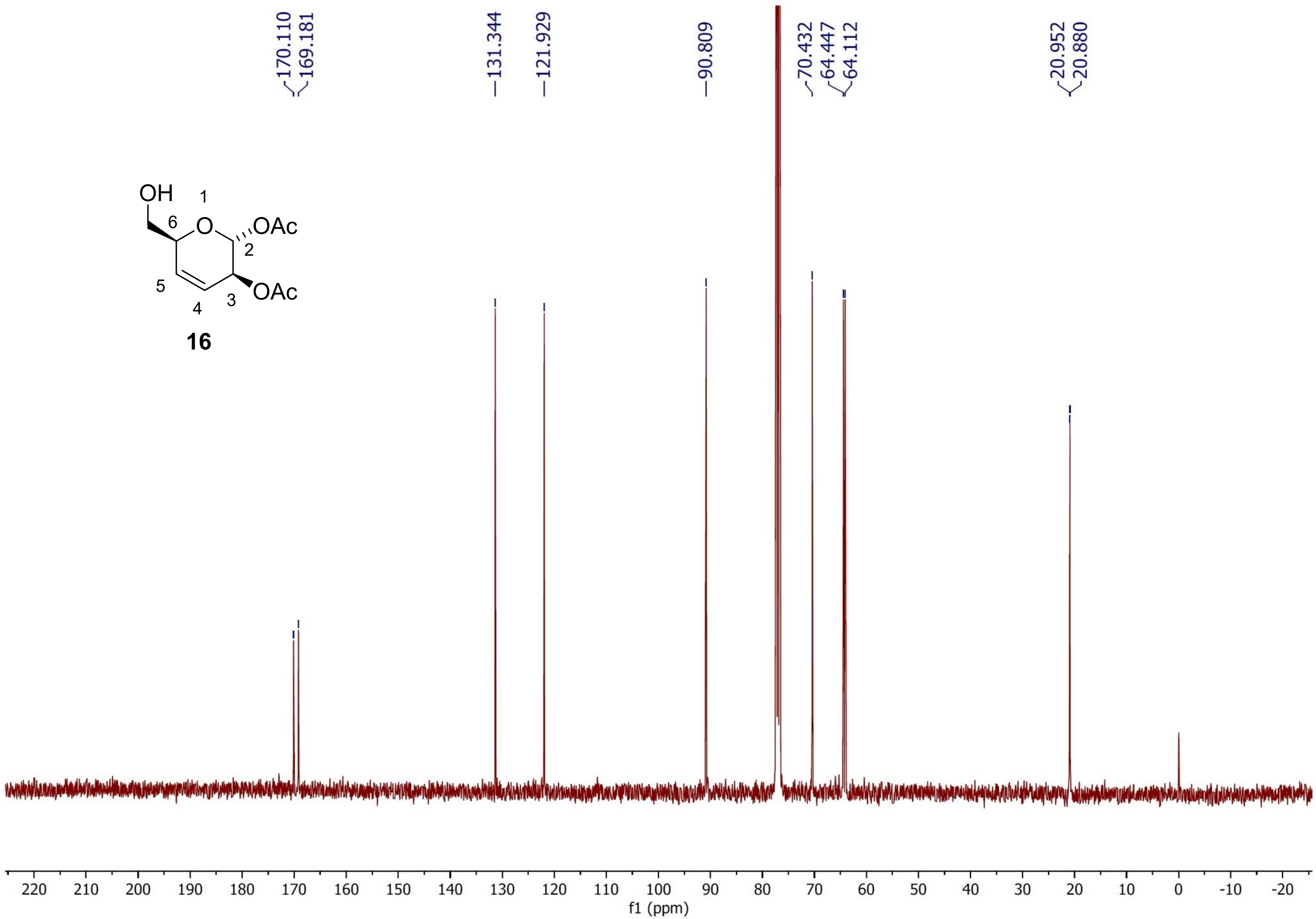
f1 (ppm)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O
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2
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OAc
3
4
220
210
200
190
180
170
160
150
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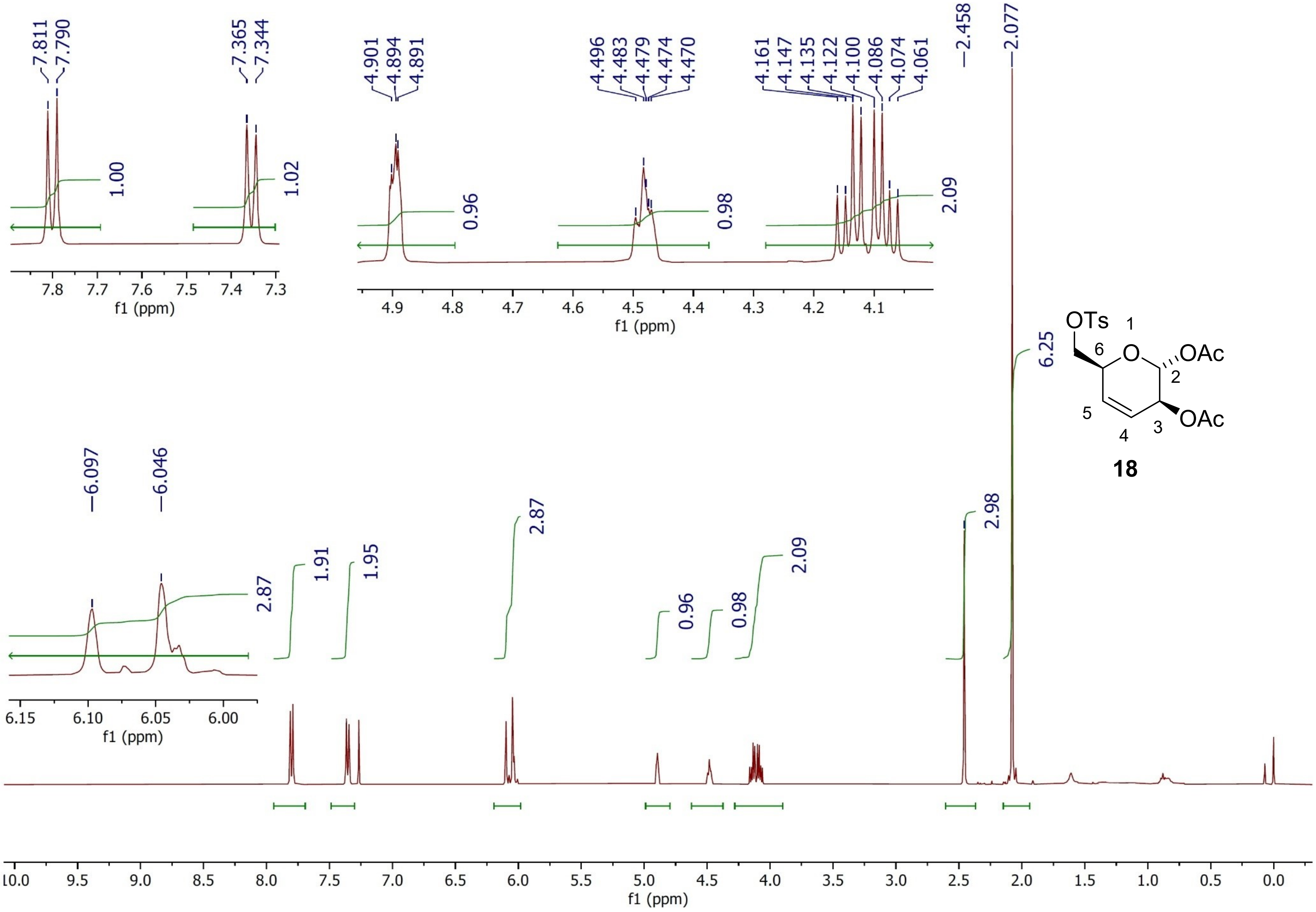
-20
f1 (ppm)

16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4.479
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4.161
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4.135
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4.100
4.086
4.074
4.061
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2.09
4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1
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6.25
OTs
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6
O
OAc
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5
4
3
OAc
18
6.097
6.046
2.87
6.15 6.10 6.05 6.00
f1 (ppm)
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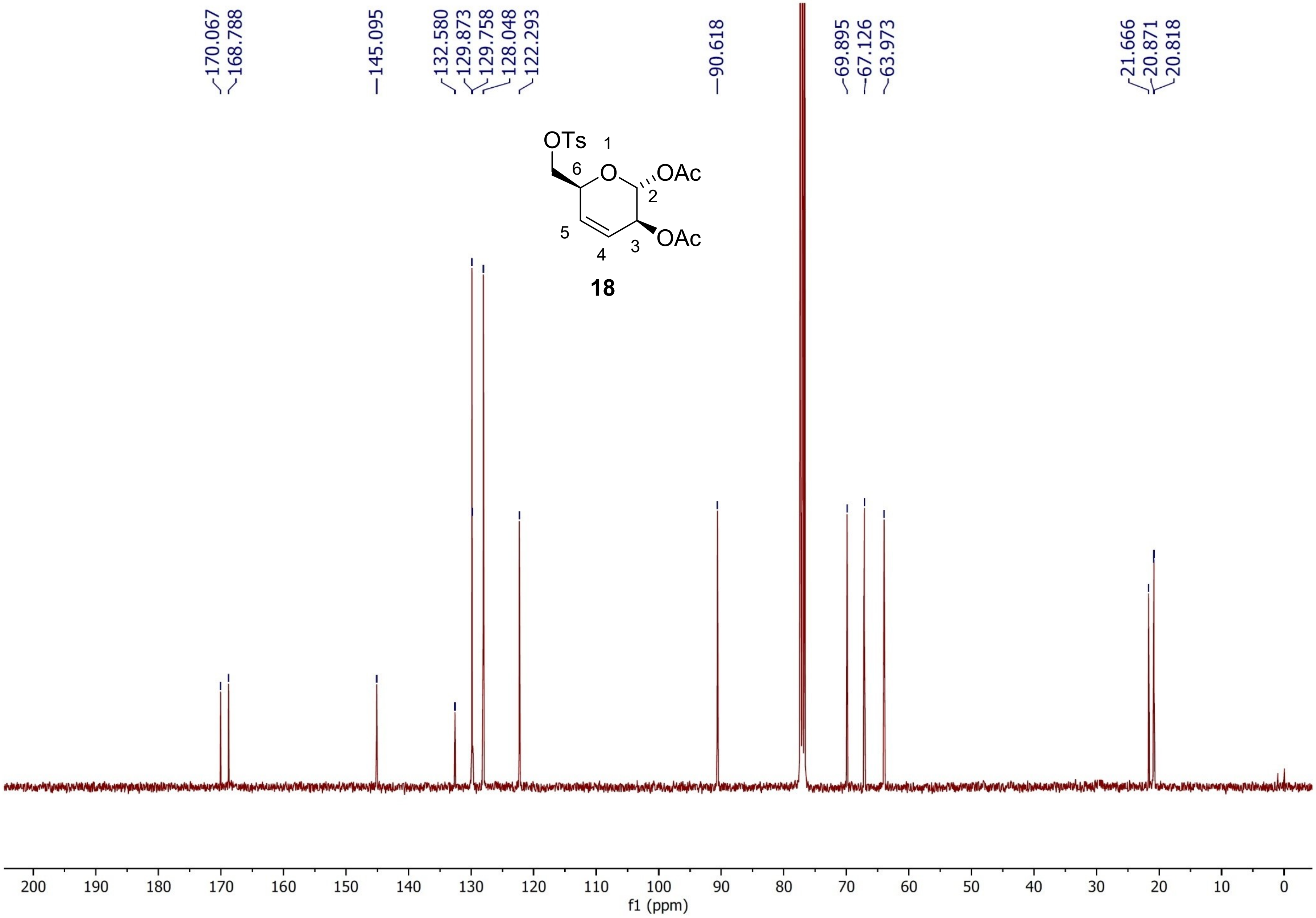
1.95
2.87
0.96
0.98
2.09
2.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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20.871
20.818
OTs
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O
OAc
2
5
4
3
OAc
18
200
190
180
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70
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50
40
30
20
10
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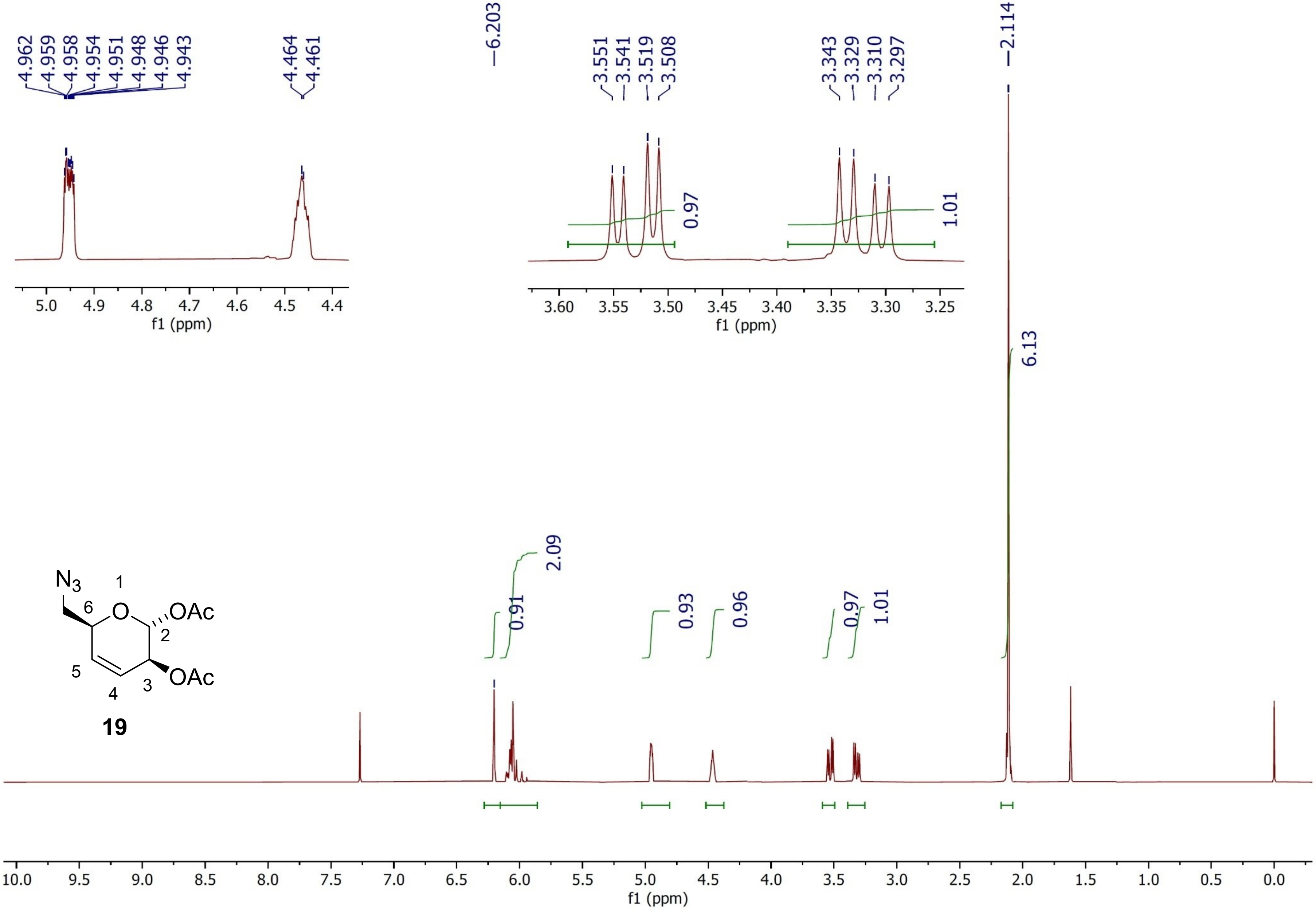
f1 (ppm)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3.508
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3.297
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4.6
4.5
4.4
f1 (ppm)
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3.45
3.40
3.35
3.30
3.25
f1 (ppm)
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0.96
0.97
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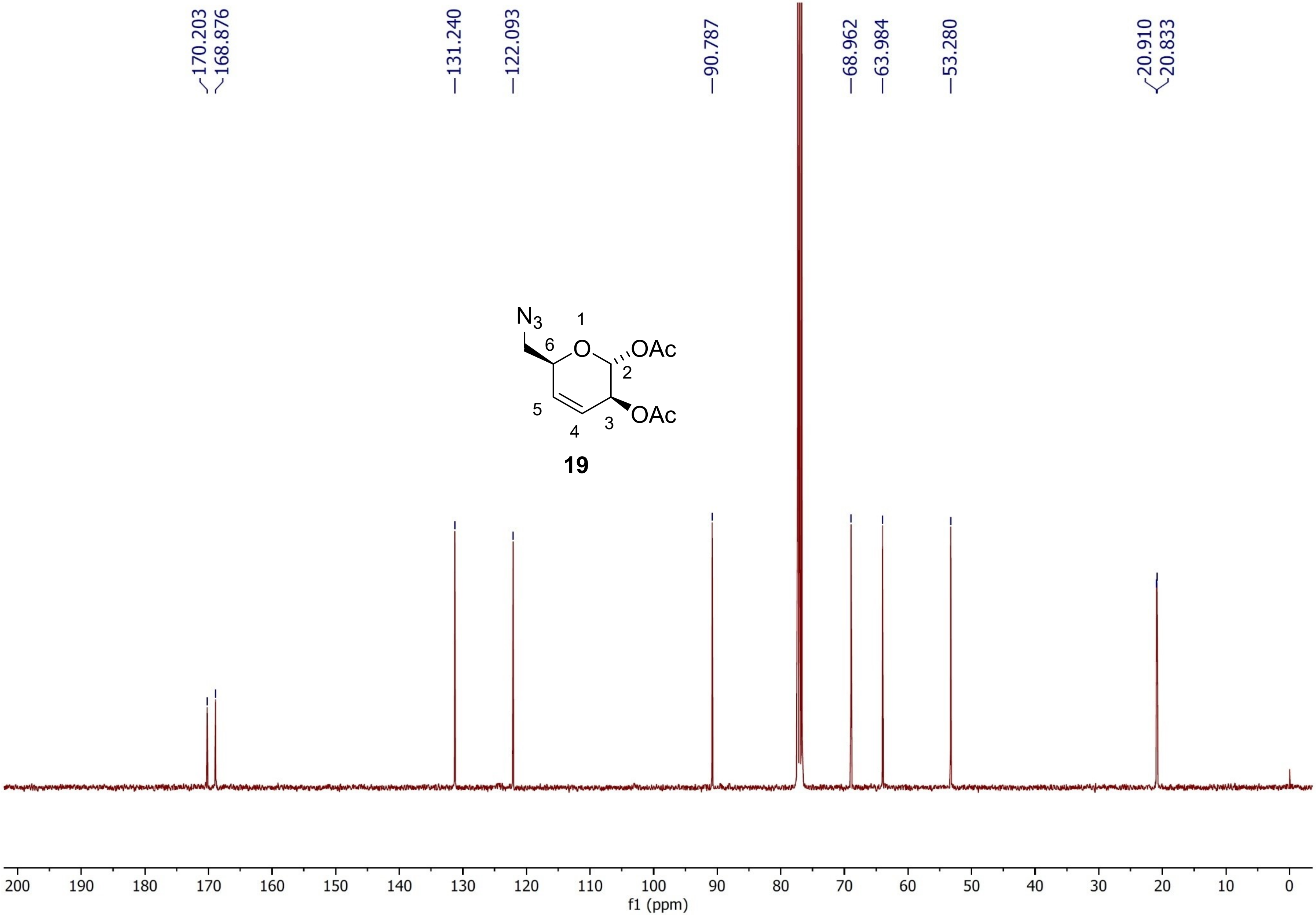
f1 (ppm)

19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O
OAc
2
5
OAc
4
3
19
200
190
180
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30
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10
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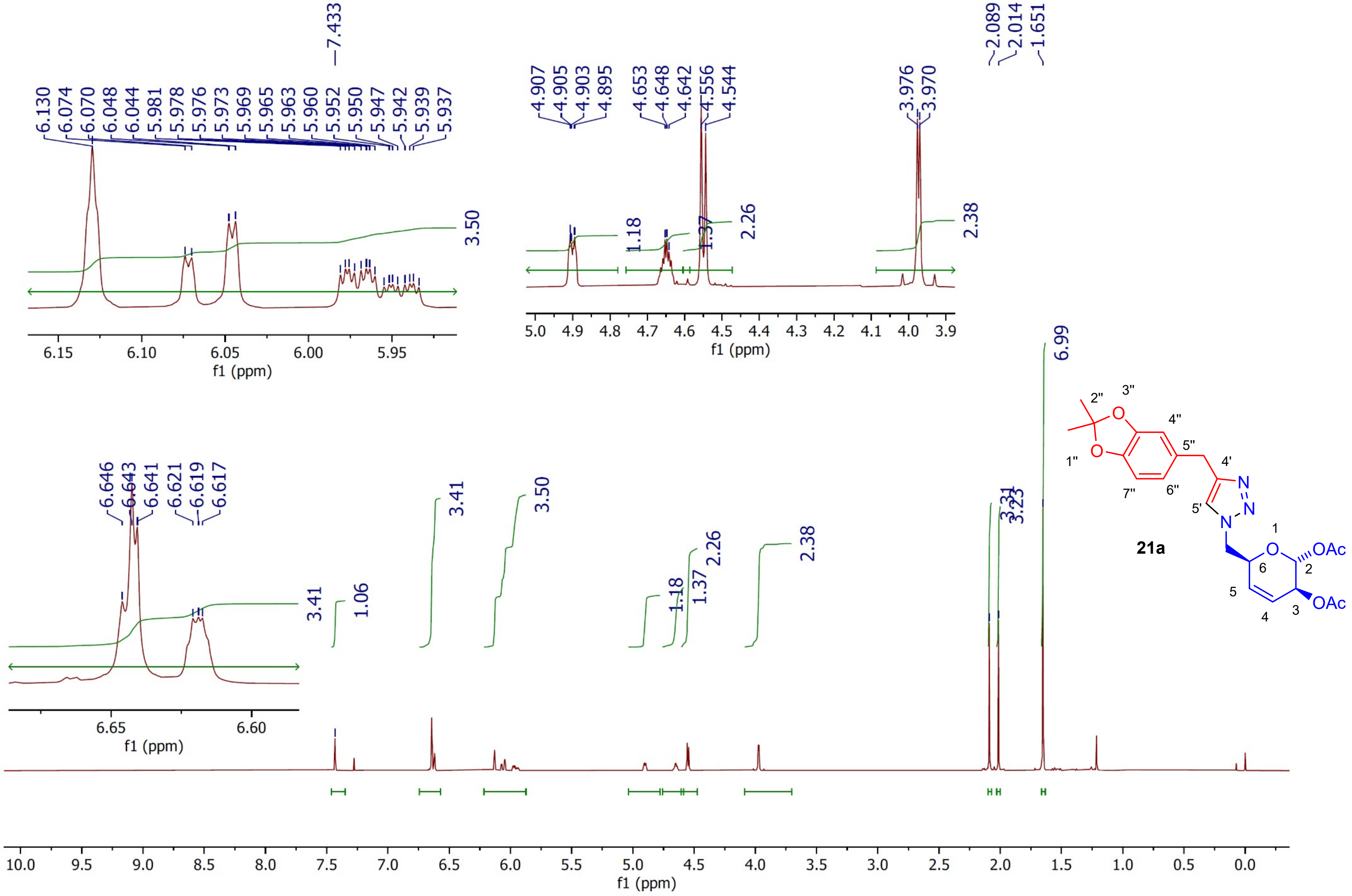
f1 (ppm)



21a

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5.965
5.963
5.960
5.952
5.950
5.947
5.942
5.939
5.937
3.50
6.15
6.10
6.05
6.00
5.95
f1 (ppm)
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4.905
4.903
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4.648
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4.544
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3.970
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4.4
4.3
4.2
4.1
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f1 (ppm)
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6.99
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6.619
6.617
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6.65
6.60
f1 (ppm)
3.41
1.06
3.41
3.50
1.18
1.37
2.26
2.38
3.31
3.23
2''
3''
4''
5''
4'
1''
7''
6''
5'
1
2
3
4
5
6
O
N
OAc
10.0
9.5
9.0
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6.5
6.0
5.5
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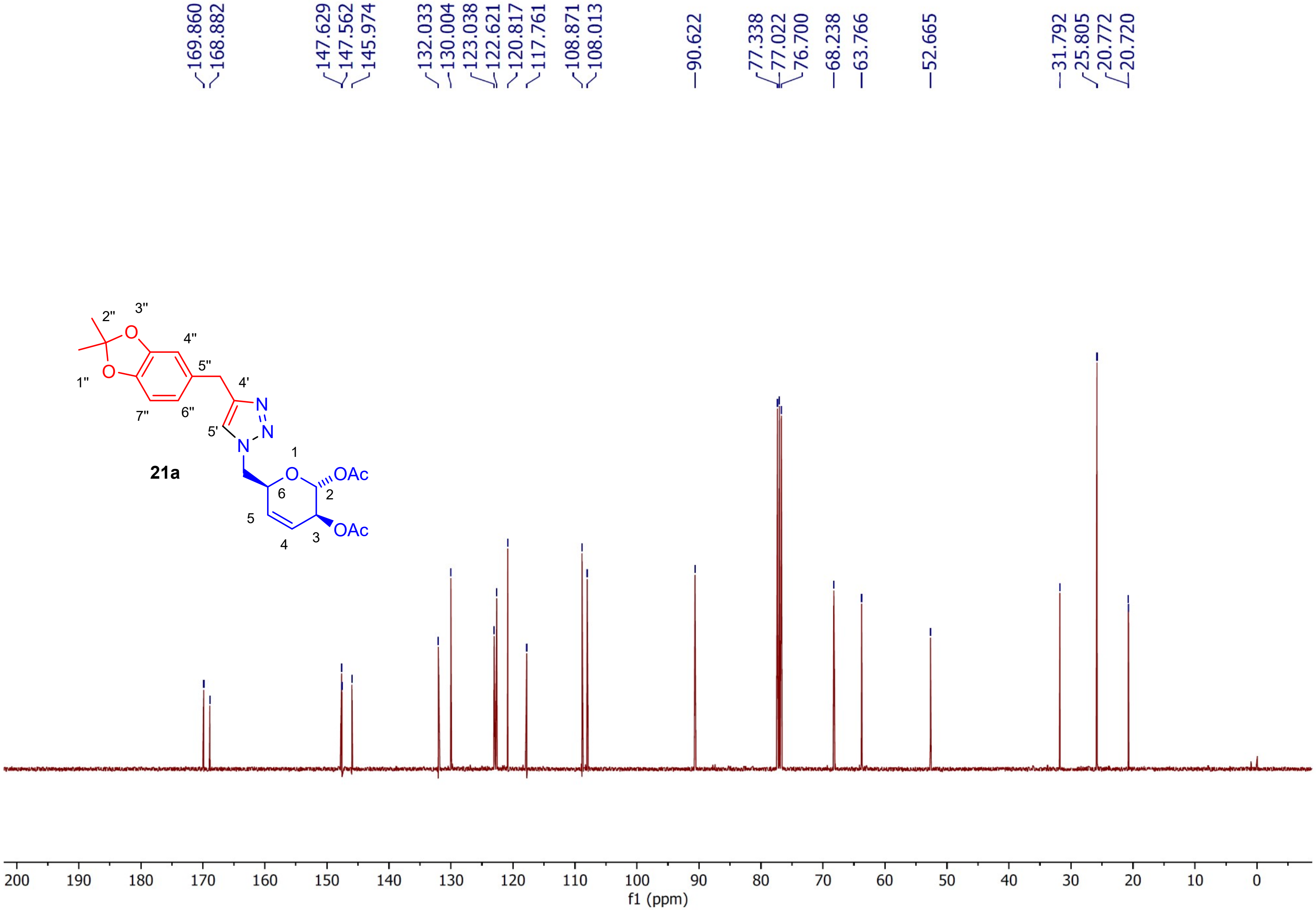
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77.022
76.700
68.238
63.766
52.665
31.792
25.805
20.772
20.720
21a
1"
2"
3"
4"
5"
6"
7"
4'
5'
1
2
3
4
5
6
O
N
OAc
200
190
180
170
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20
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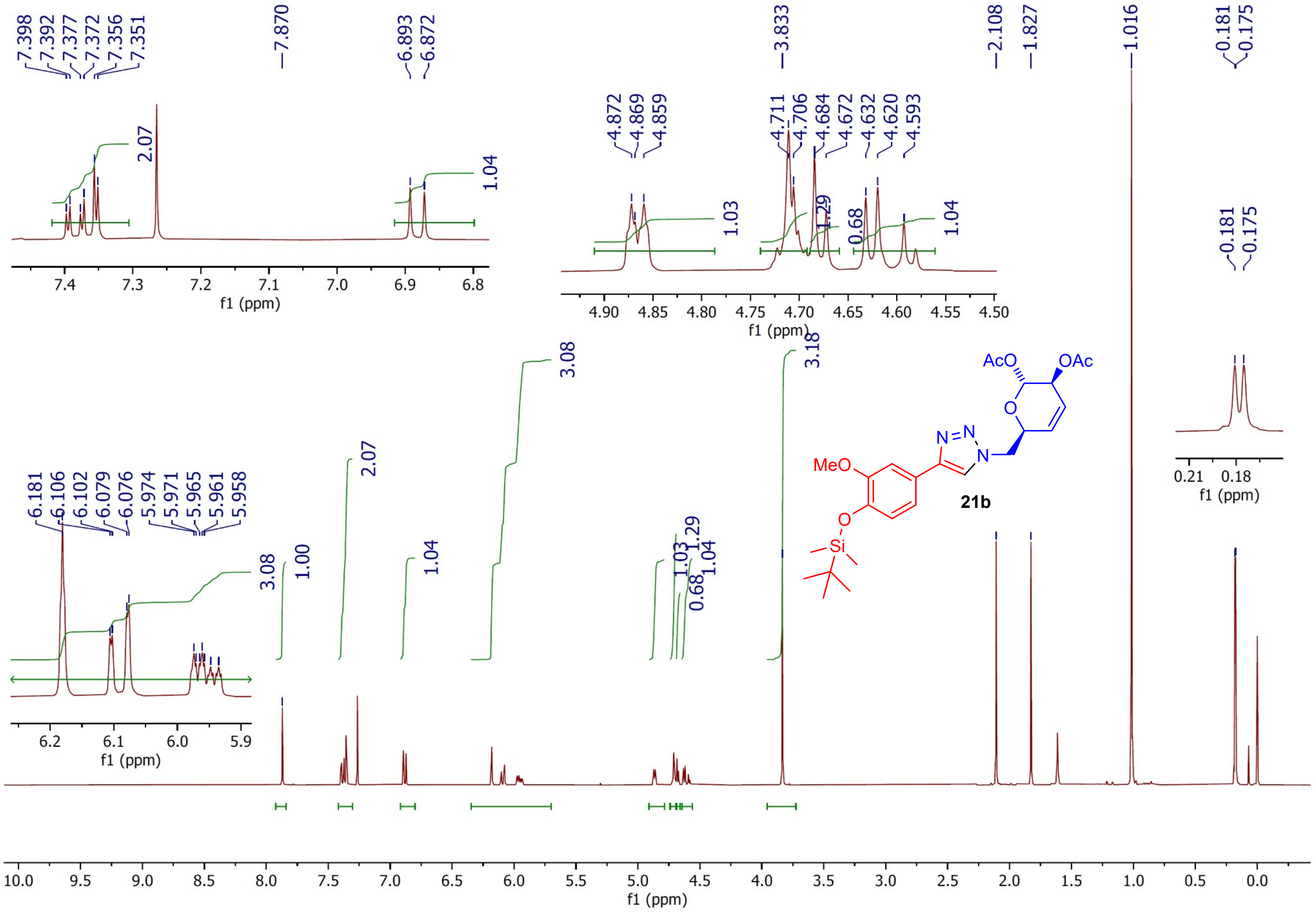
f1 (ppm)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6.893
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1.016
0.181
0.175
2.07
1.04
7.4
7.3
7.2
7.1
7.0
6.9
6.8
f1 (ppm)
4.872
4.869
4.859
4.711
4.706
4.684
4.672
4.632
4.620
4.593
1.03
1.29
0.68
1.04
4.90
4.85
4.80
4.75
4.70
4.65
4.60
4.55
4.50
f1 (ppm)
0.181
0.175
0.21
0.18
f1 (ppm)
6.181
6.106
6.102
6.079
6.076
5.974
5.971
5.965
5.961
5.958
6.2
6.1
6.0
5.9
f1 (ppm)
3.08
1.00
2.07
1.04
3.08
1.03
1.29
0.68
1.04
3.18
AcO
OAc
O
N=N
N
MeO
O
Si
10.0
9.5
9.0
8.5
8.0
7.5
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6.5
6.0
5.5
5.0
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3.0
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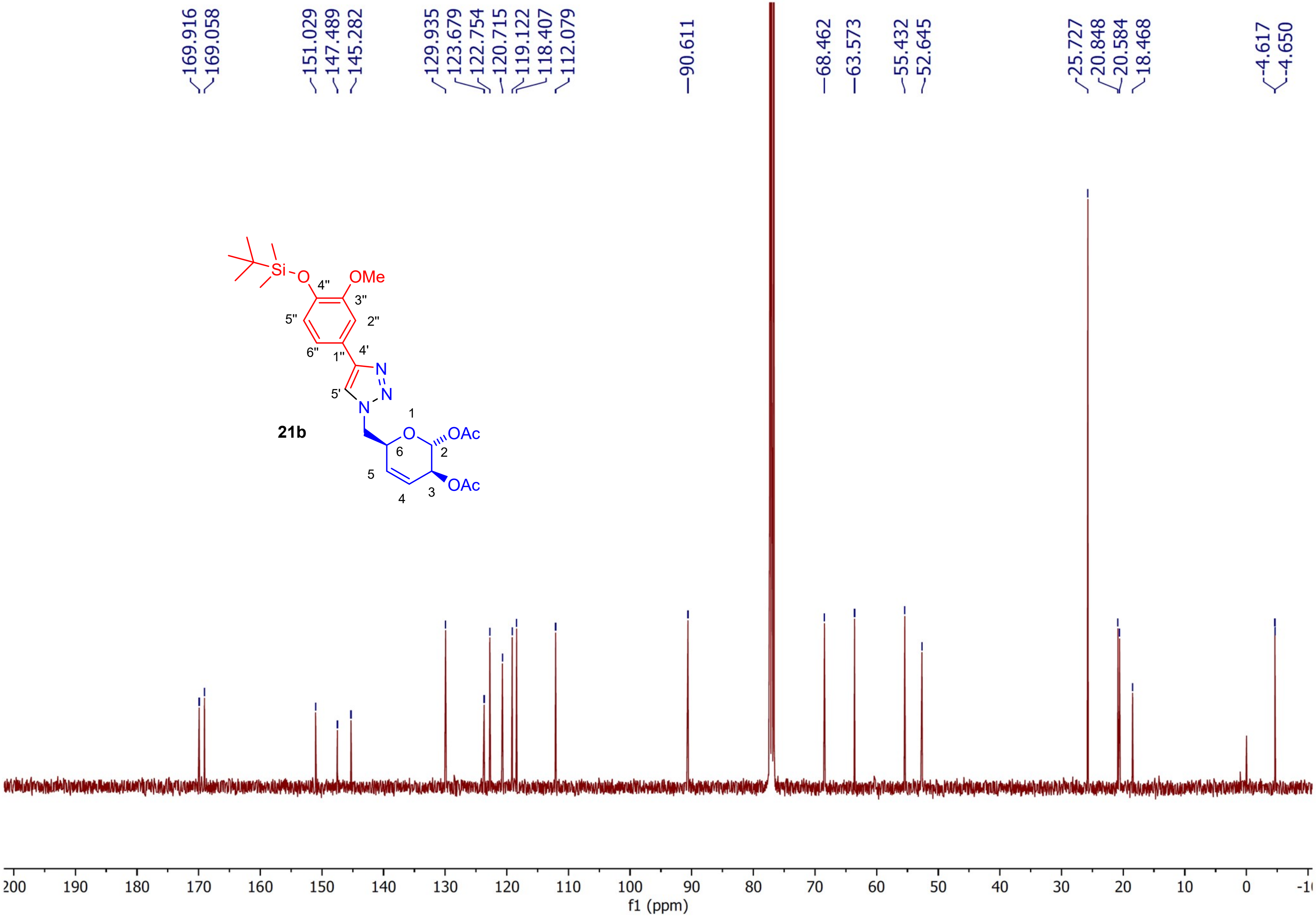
1.0
0.5
0.0
f1 (ppm)

21b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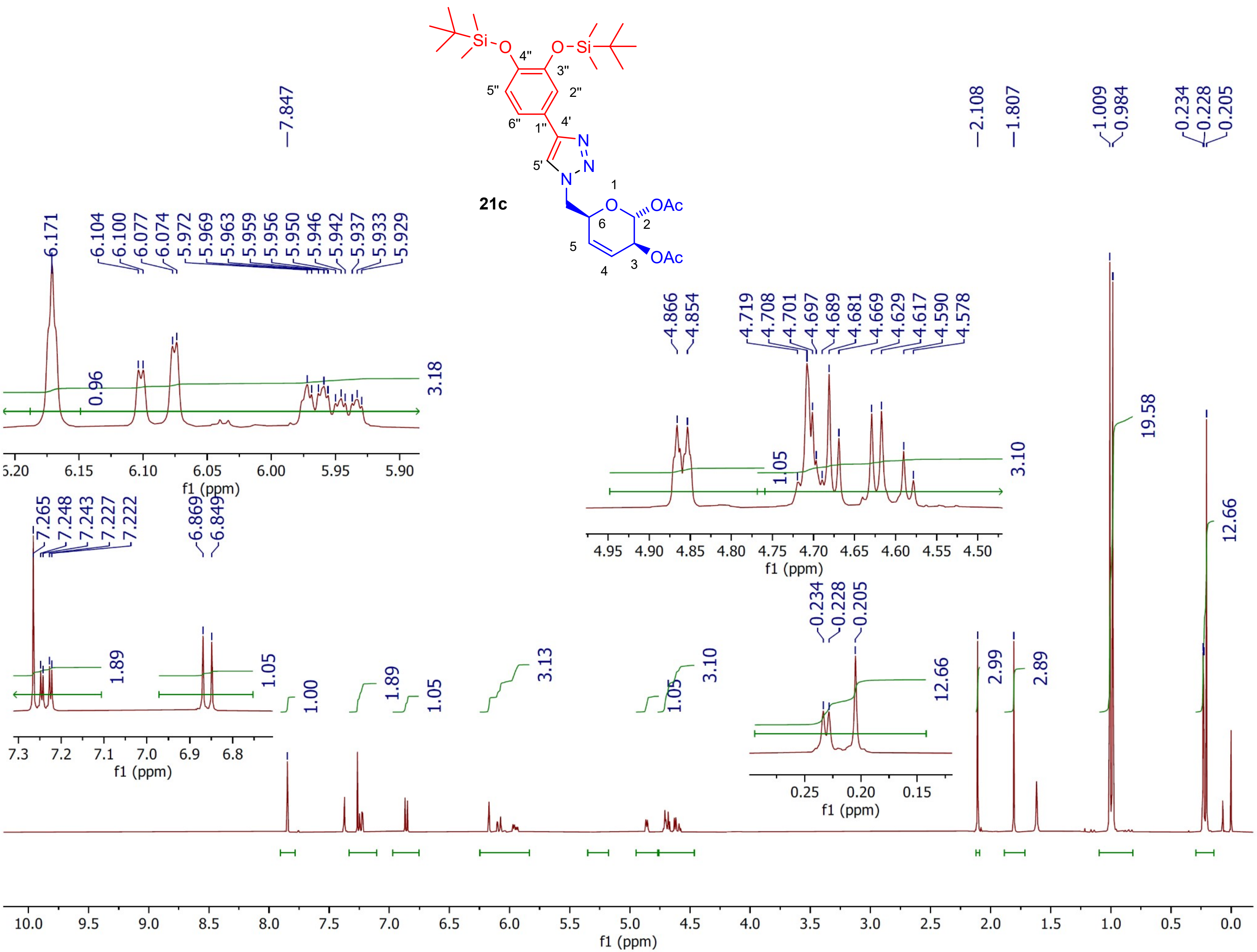
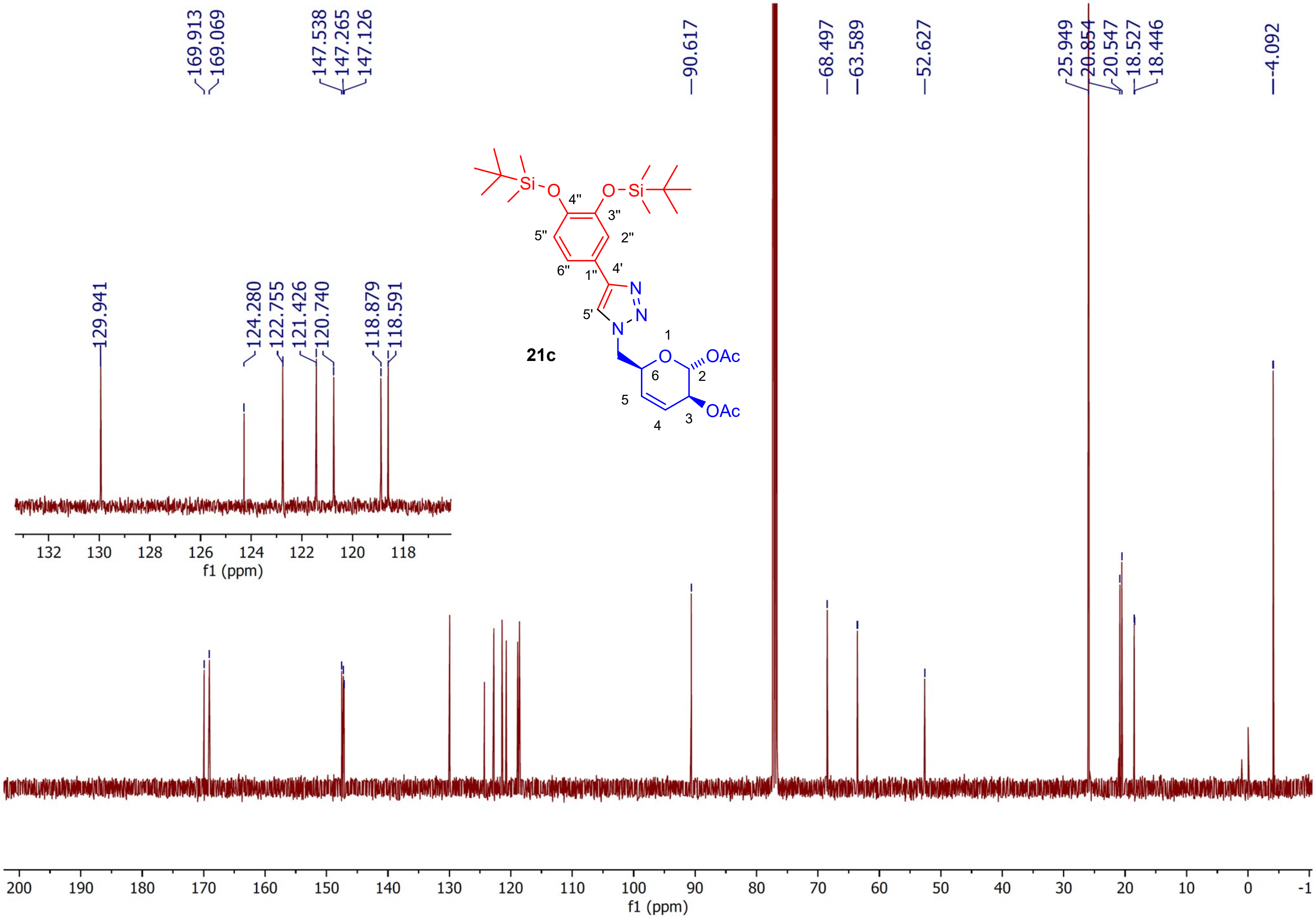
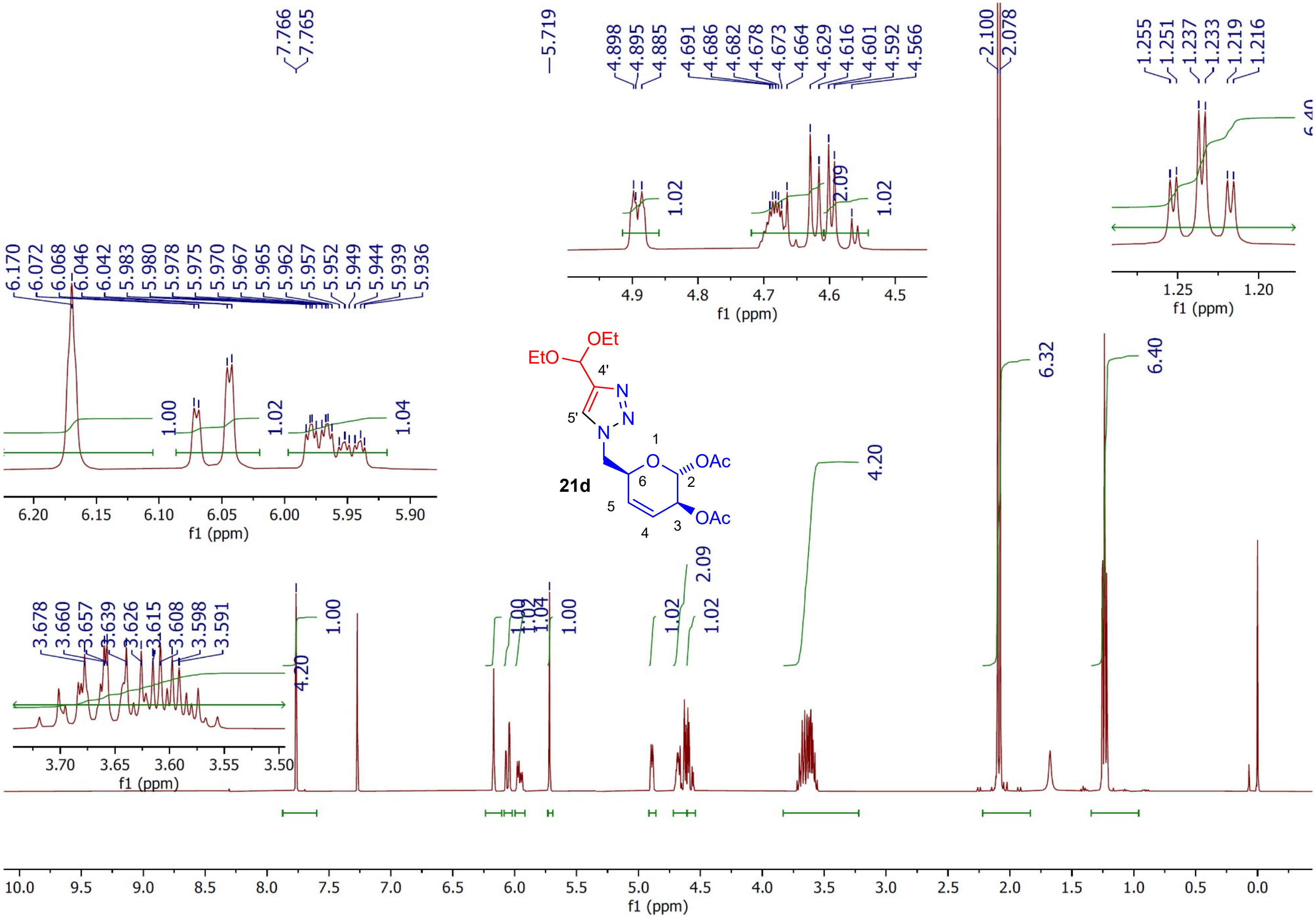
63.573
55.432
52.645
25.727
20.848
20.584
18.468
-4.617
-4.650
21b
OMe
4"
3"
2"
5"
6"
1"
4'
5'
N
N
N
Si
O
1
2
3
4
5
6
OAc
OAc
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)


21c
4"
3"
2"
5"
6"
1"
4'
5'
1
2
3
4
5
6
O
Si
N
OAc
7.847
6.171
6.104
6.100
6.077
6.074
5.972
5.969
5.963
5.959
5.956
5.950
5.946
5.942
5.937
5.933
5.929
0.96
3.18
4.866
4.854
4.719
4.708
4.701
4.697
4.689
4.681
4.669
4.629
4.617
4.590
4.578
1.05
3.10
7.265
7.248
7.243
7.227
7.222
6.869
6.849
1.89
1.05
0.234
0.228
0.205
12.66
2.108
1.807
1.009
0.984
19.58
1.00
1.89
1.05
3.13
1.05
3.10
2.99
2.89
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

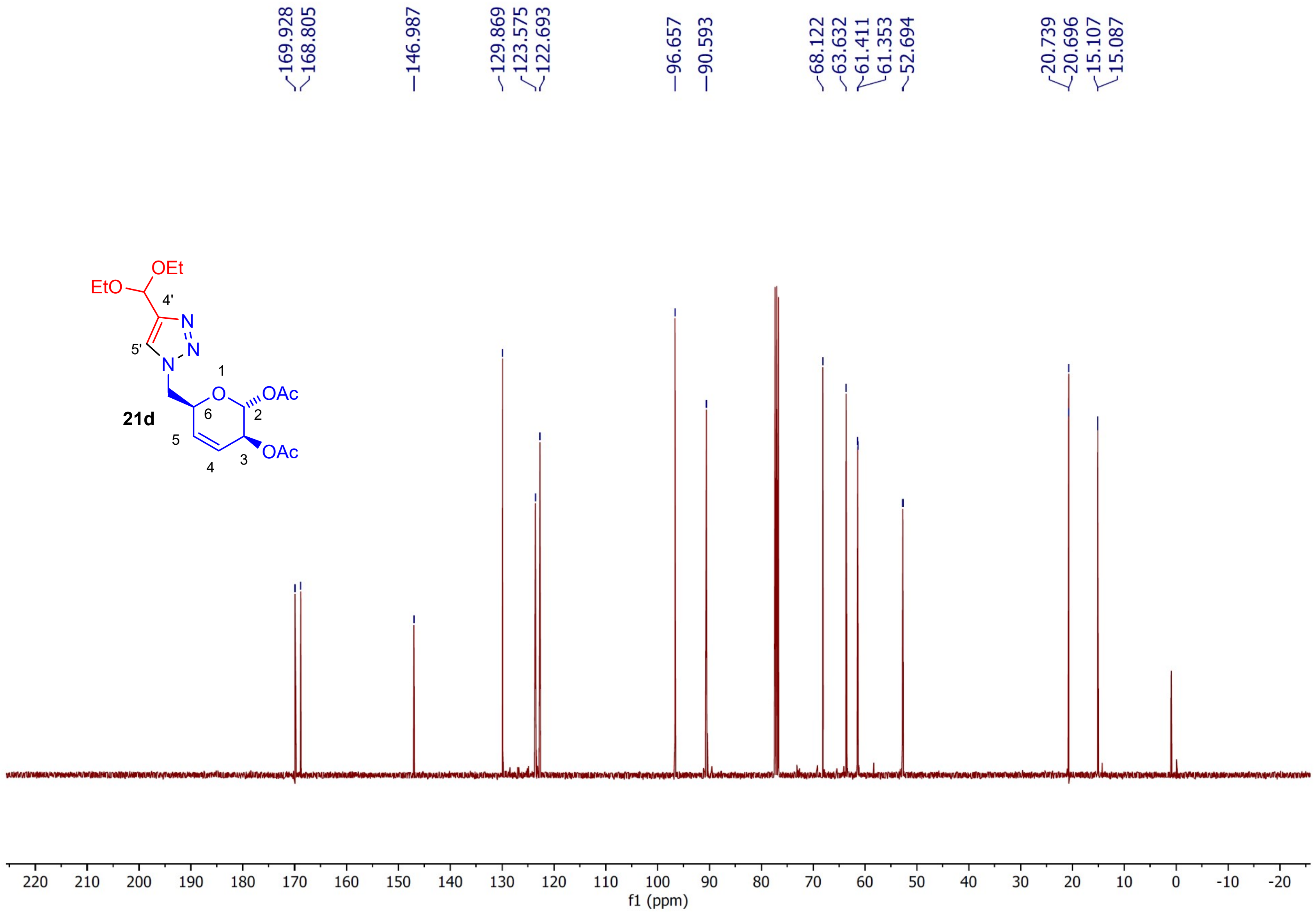

169.913
169.069
147.538
147.265
147.126
90.617
68.497
63.589
52.627
25.949
20.854
20.547
18.527
18.446
-4.092
129.941
124.280
122.755
121.426
120.740
118.879
118.591
132
130
128
126
124
122
120
118
f1 (ppm)
Si
O
O
Si
4"
3"
5"
2"
6"
1"
4'
N
N
N
5'
1
O
OAc
6
2
5
OAc
4
3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

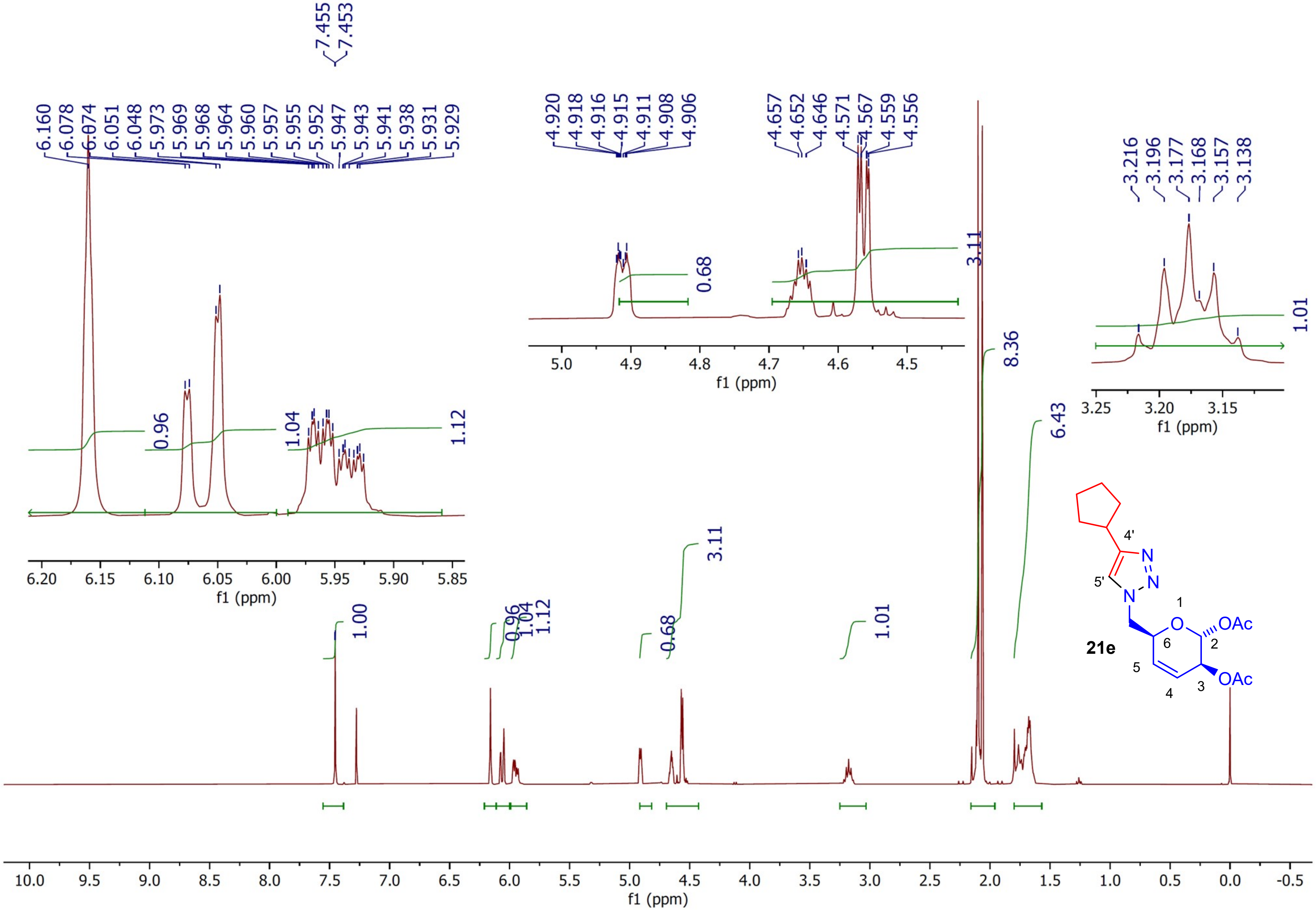
21c

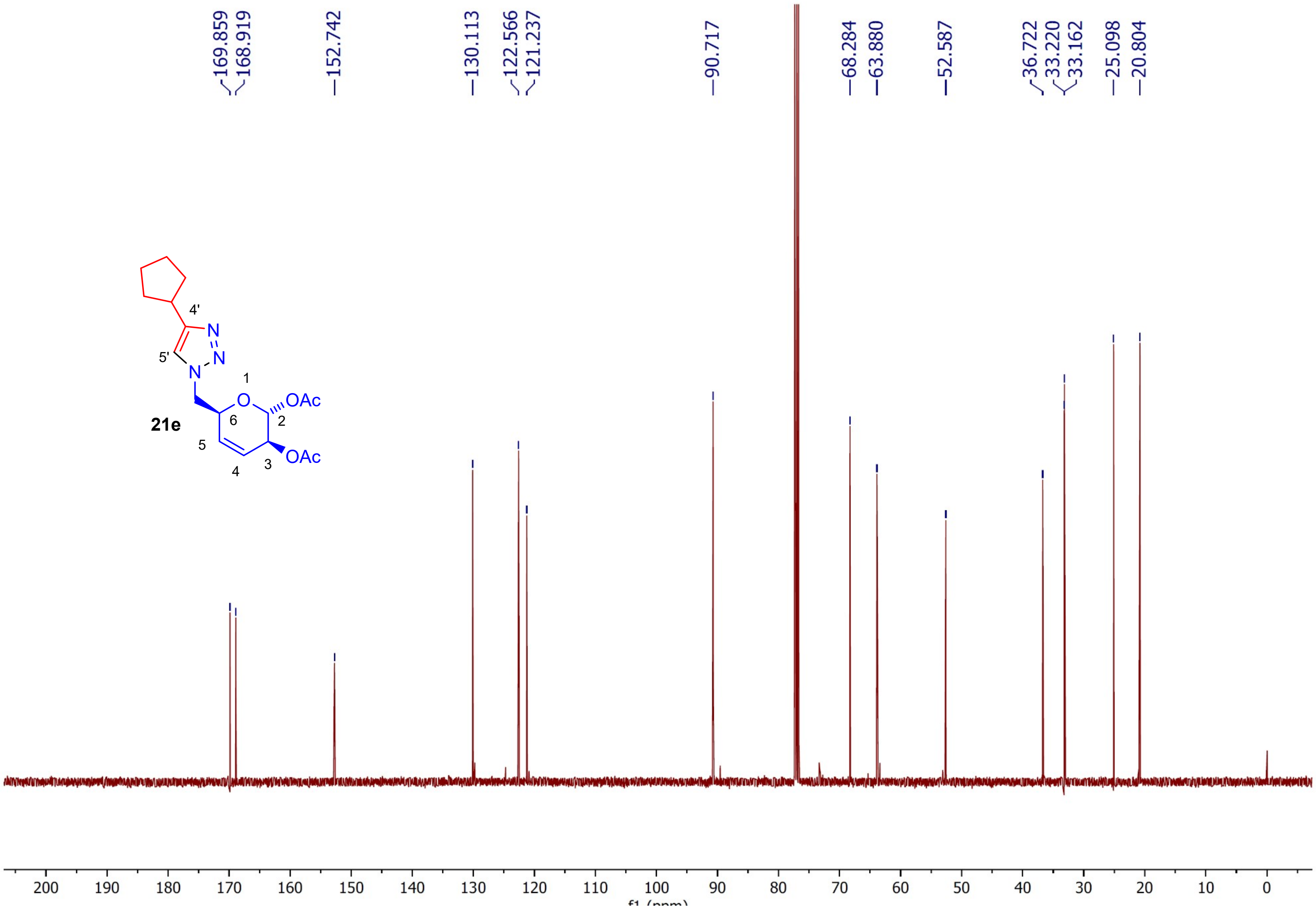


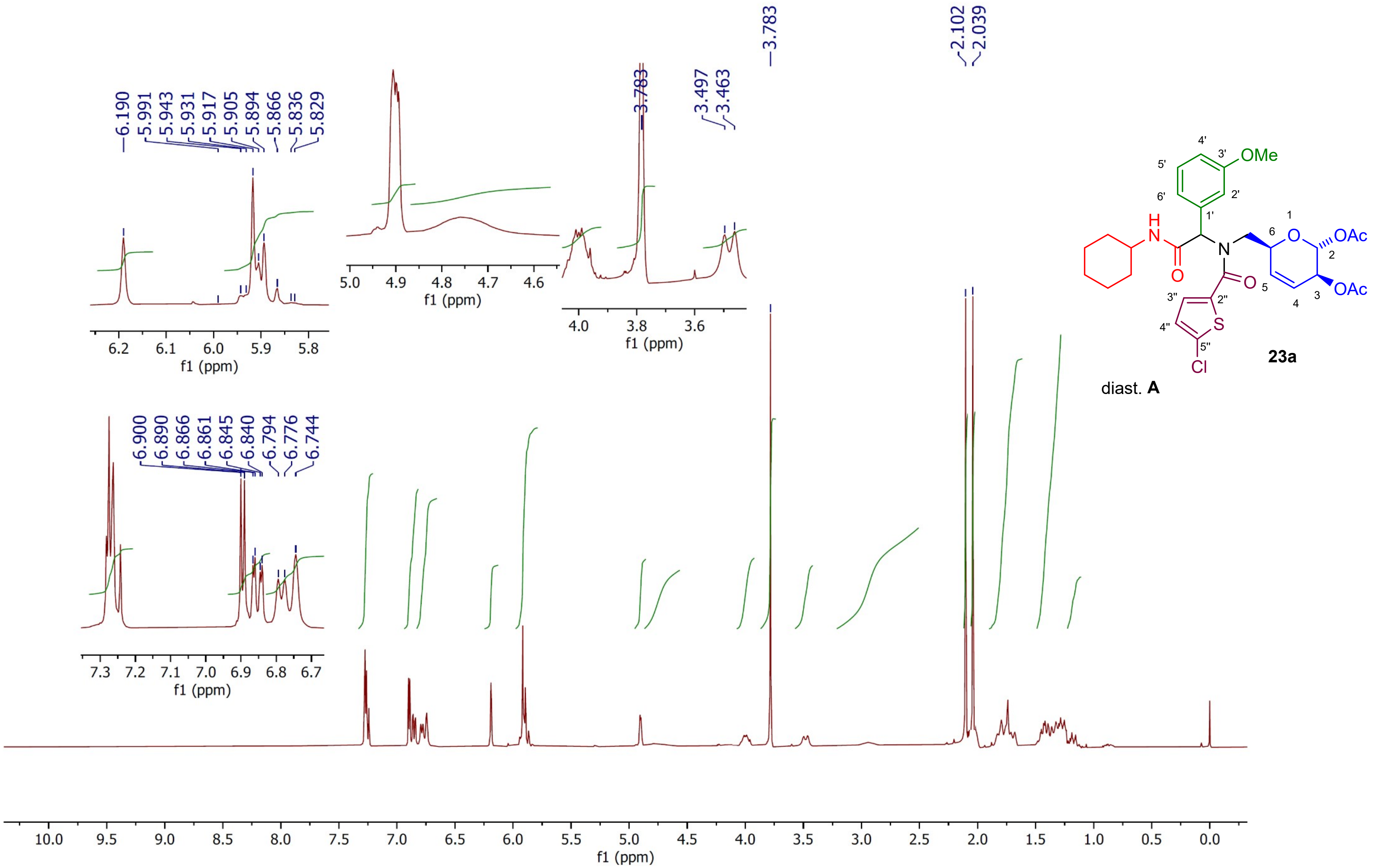
21d

7.766
7.765
5.719
4.898
4.895
4.885
4.691
4.686
4.682
4.678
4.673
4.664
4.629
4.616
4.601
4.592
4.566
2.100
2.078
1.255
1.251
1.237
1.233
1.219
1.216
6.170
6.072
6.068
6.046
6.042
5.983
5.980
5.978
5.975
5.970
5.967
5.965
5.962
5.957
5.952
5.949
5.944
5.939
5.936
3.678
3.660
3.657
3.639
3.626
3.615
3.608
3.598
3.591
1.00
1.02
1.04
2.09
4.20
6.32
6.40
1.00
1.02
1.02
f1 (ppm)
EtO
OEt
4'
5'
N
N
N
1
O
OAc
2
6
5
4
3
OAc
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


169.928
168.805
146.987
129.869
123.575
122.693
96.657
90.593
68.122
63.632
61.411
61.353
52.694
20.739
20.696
15.107
15.087
EtO
OEt
4'
N
N
5'
N
1
O
OAc
6
2
21d
5
3
OAc
4
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

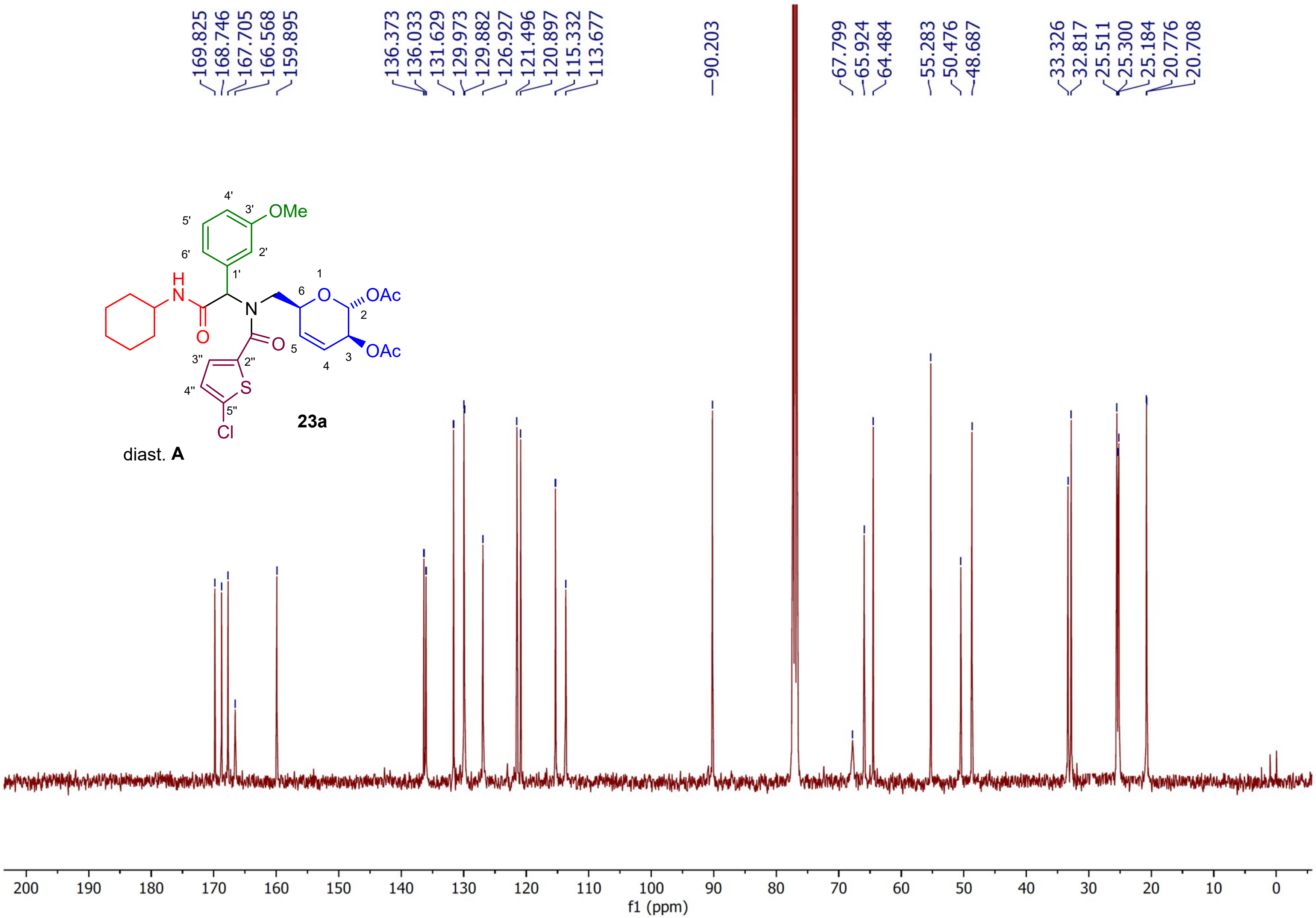

7.455
7.453
6.160
6.078
6.074
6.051
6.048
5.973
5.969
5.968
5.964
5.960
5.957
5.955
5.952
5.947
5.943
5.941
5.938
5.931
5.929
0.96
1.04
1.12
6.20 6.15 6.10 6.05 6.00 5.95 5.90 5.85
f1 (ppm)
4.920
4.918
4.916
4.915
4.911
4.908
4.906
4.657
4.652
4.646
4.571
4.567
4.559
4.556
0.68
3.11
5.0 4.9 4.8 4.7 4.6 4.5
f1 (ppm)
3.216
3.196
3.177
3.168
3.157
3.138
1.01
3.25 3.20 3.15
f1 (ppm)
1.00
0.96
1.04
1.12
0.68
3.11
1.01
3.11
8.36
6.43
4'
5'
N
N
N
1
O
OAc
6
2
5
4
3
OAc
21e
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


169.859
168.919
152.742
130.113
122.566
121.237
90.717
68.284
63.880
52.587
36.722
33.220
33.162
25.098
20.804
4'
5'
N
N
N
1
O
OAc
6
2
5
4
3
OAc
21e
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


6.190
5.991
5.943
5.931
5.917
5.905
5.894
5.866
5.836
5.829
6.2
6.1
6.0
5.9
5.8
f1 (ppm)
5.0
4.9
4.8
4.7
4.6
f1 (ppm)
3.783
3.497
3.463
4.0
3.8
3.6
f1 (ppm)
3.783
2.102
2.039
6.900
6.890
6.866
6.861
6.845
6.840
6.794
6.776
6.744
7.3
7.2
7.1
7.0
6.9
6.8
6.7
f1 (ppm)
4'
3'
OMe
5'
6'
2'
1'
H
N
O
N
1
6
O
2
OAc
5
4
3
OAc
O
3"
2"
S
4"
5"
Cl
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

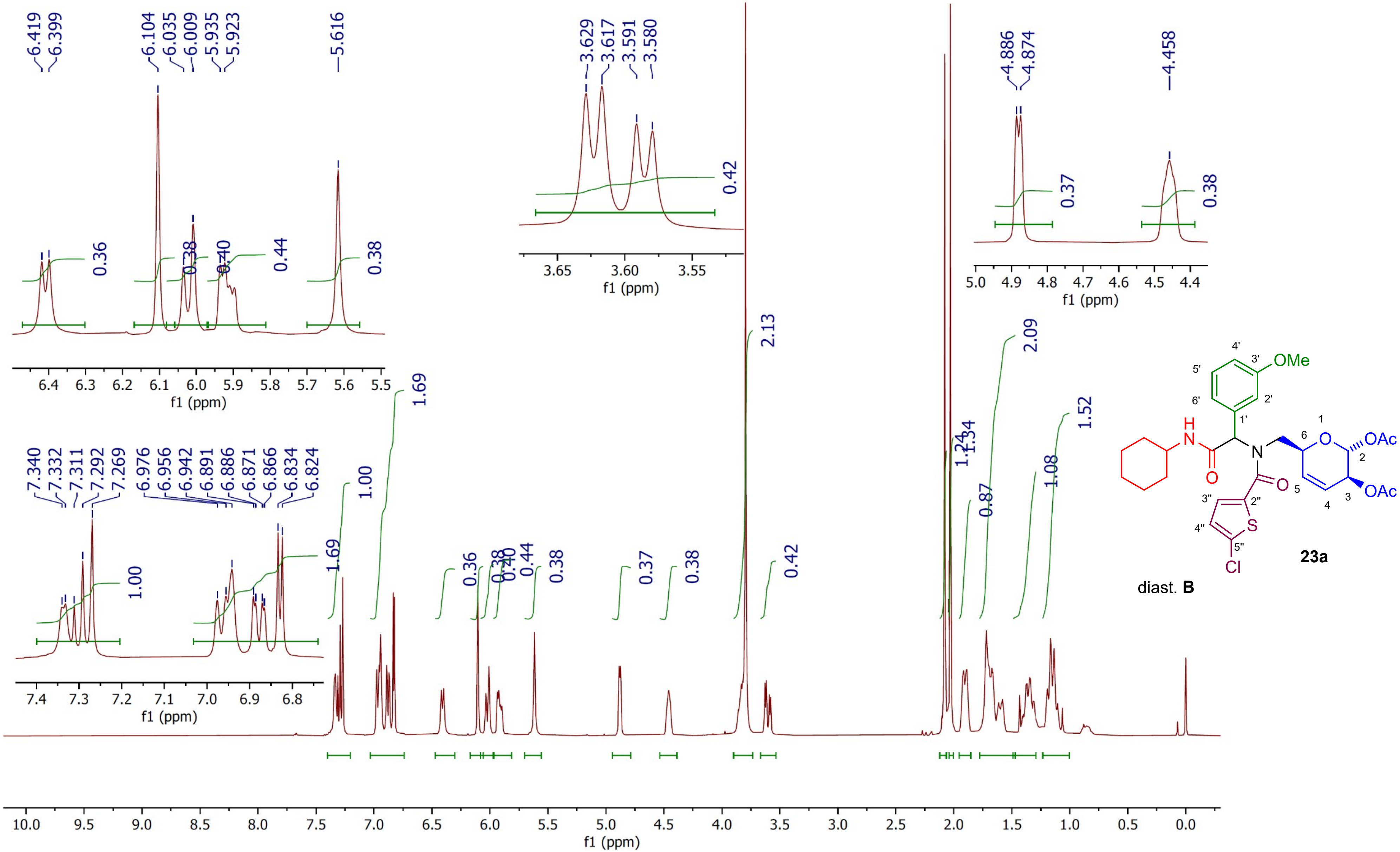
23a

diast. **A**


169.825
168.746
167.705
166.568
159.895
136.373
136.033
131.629
129.973
129.882
126.927
121.496
120.897
115.332
113.677
90.203
67.799
65.924
64.484
55.283
50.476
48.687
33.326
32.817
25.511
25.300
25.184
20.776
20.708
4'
3'
OMe
5'
6'
2'
1'
H
N
O
N
1
6
O
OAc
2
O
5
4
3
OAc
3''
2''
4''
S
5''
Cl
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

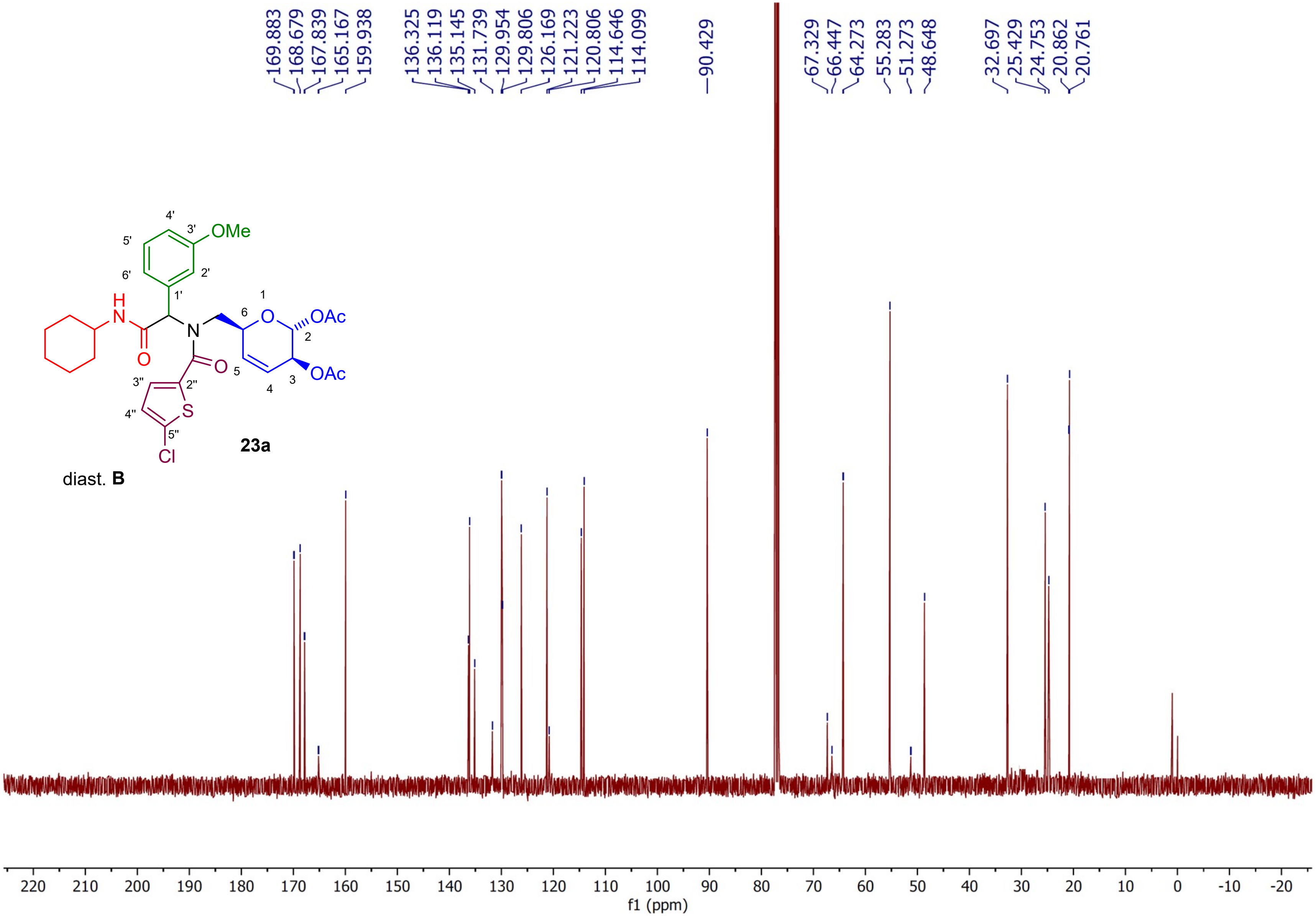
23a

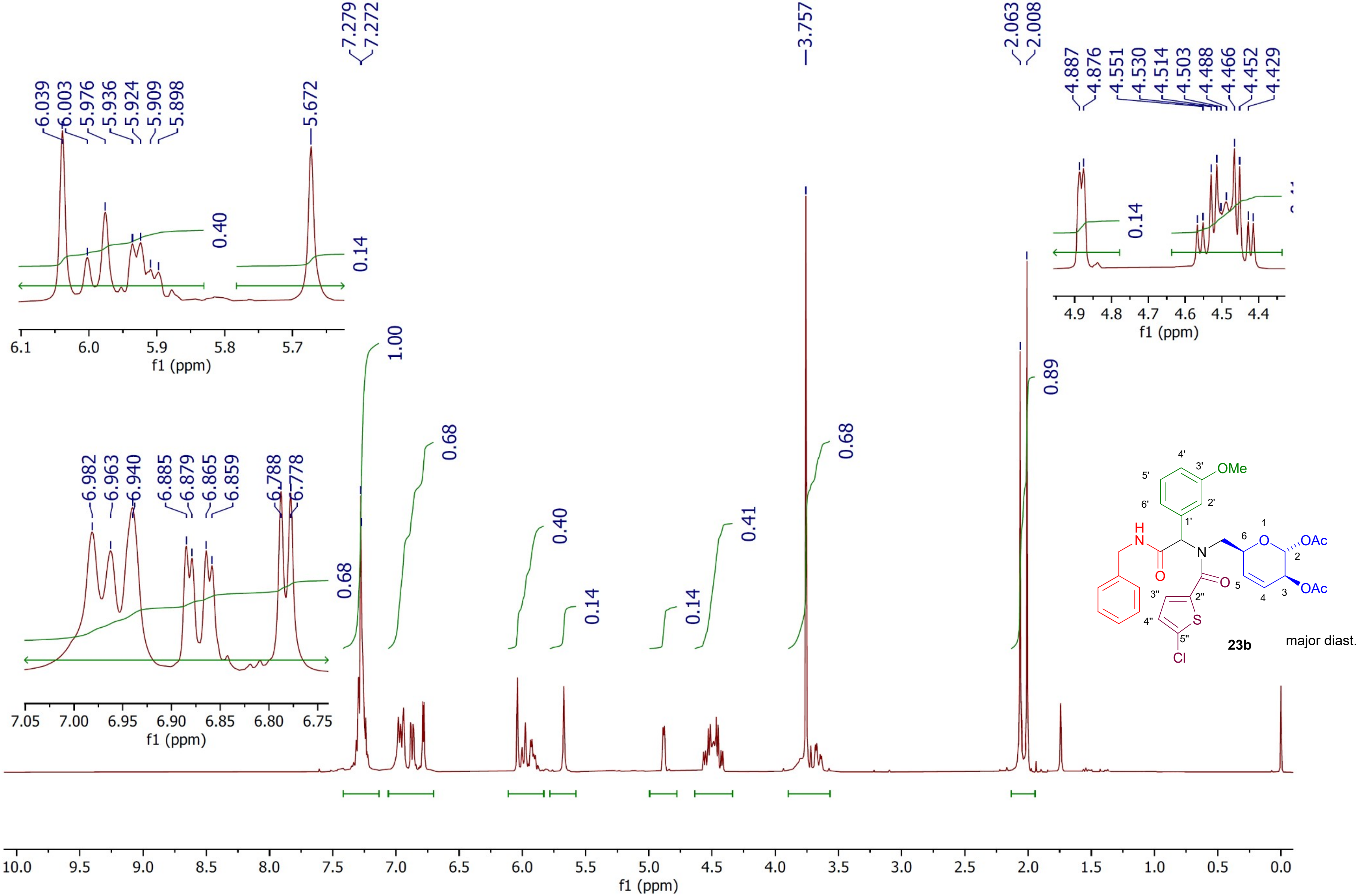
diast. **A**


6.419
6.399
6.104
6.035
6.009
5.935
5.923
5.616
0.36
0.38
0.40
0.44
0.38
6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5
f1 (ppm)
3.629
3.617
3.591
3.580
0.42
3.65 3.60 3.55
f1 (ppm)
4.886
4.874
4.458
0.37
0.38
5.0 4.9 4.8 4.7 4.6 4.5 4.4
f1 (ppm)
7.340
7.332
7.311
7.292
7.269
6.976
6.956
6.942
6.891
6.886
6.871
6.866
6.834
6.824
1.00
1.69
7.4 7.3 7.2 7.1 7.0 6.9 6.8
f1 (ppm)
1.69
1.00
1.69
0.36
0.38
0.40
0.44
0.38
0.37
0.38
2.13
0.42
1.24
1.34
0.87
2.09
1.08
1.52
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
4'
3'
OMe
5'
2'
6'
1'
H
N
O
N
1
6
O
OAc
2
O
5
4
3
OAc
3''
2''
4''
S
5''
Cl

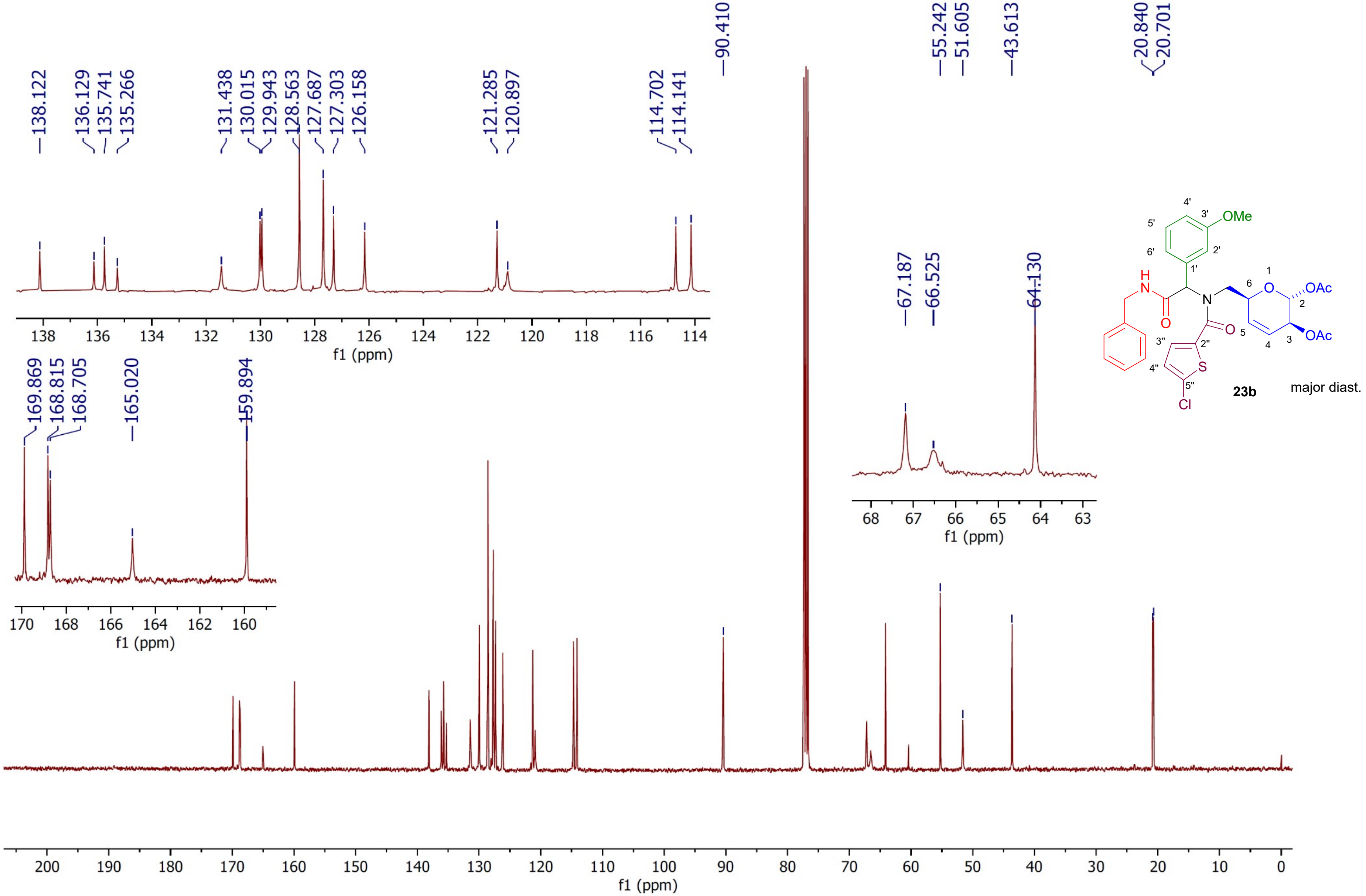
23a

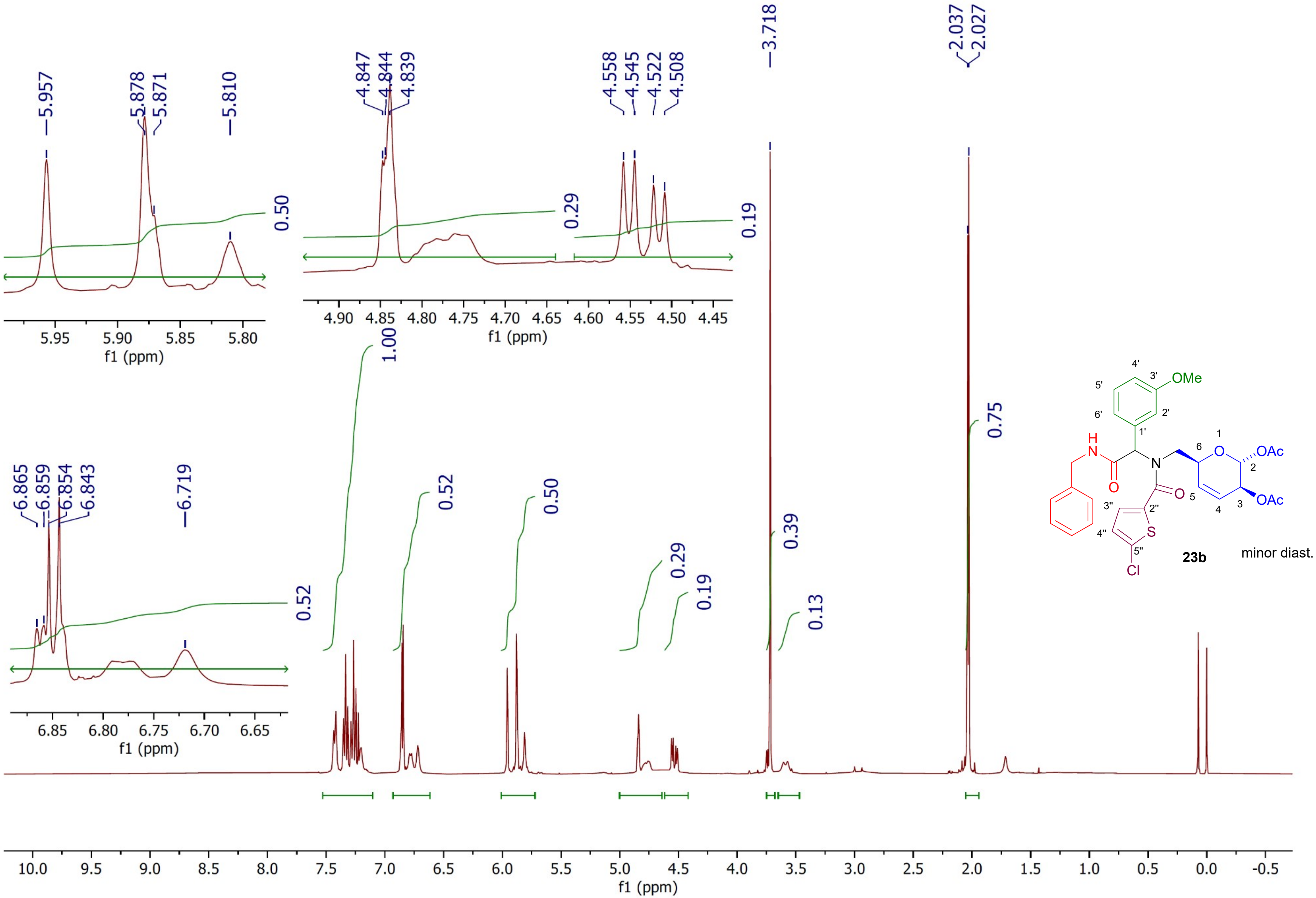
diast. **B**


169.883
168.679
167.839
165.167
159.938
136.325
136.119
135.145
131.739
129.954
129.806
126.169
121.223
120.806
114.646
114.099
90.429
67.329
66.447
64.273
55.283
51.273
48.648
32.697
25.429
24.753
20.862
20.761
4'
3'
OMe
5'
6'
2'
H
N
1'
1
6
O
OAc
2
N
O
O
5
3
OAc
4
3"
2"
S
4"
5"
Cl
23a
diast. B
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

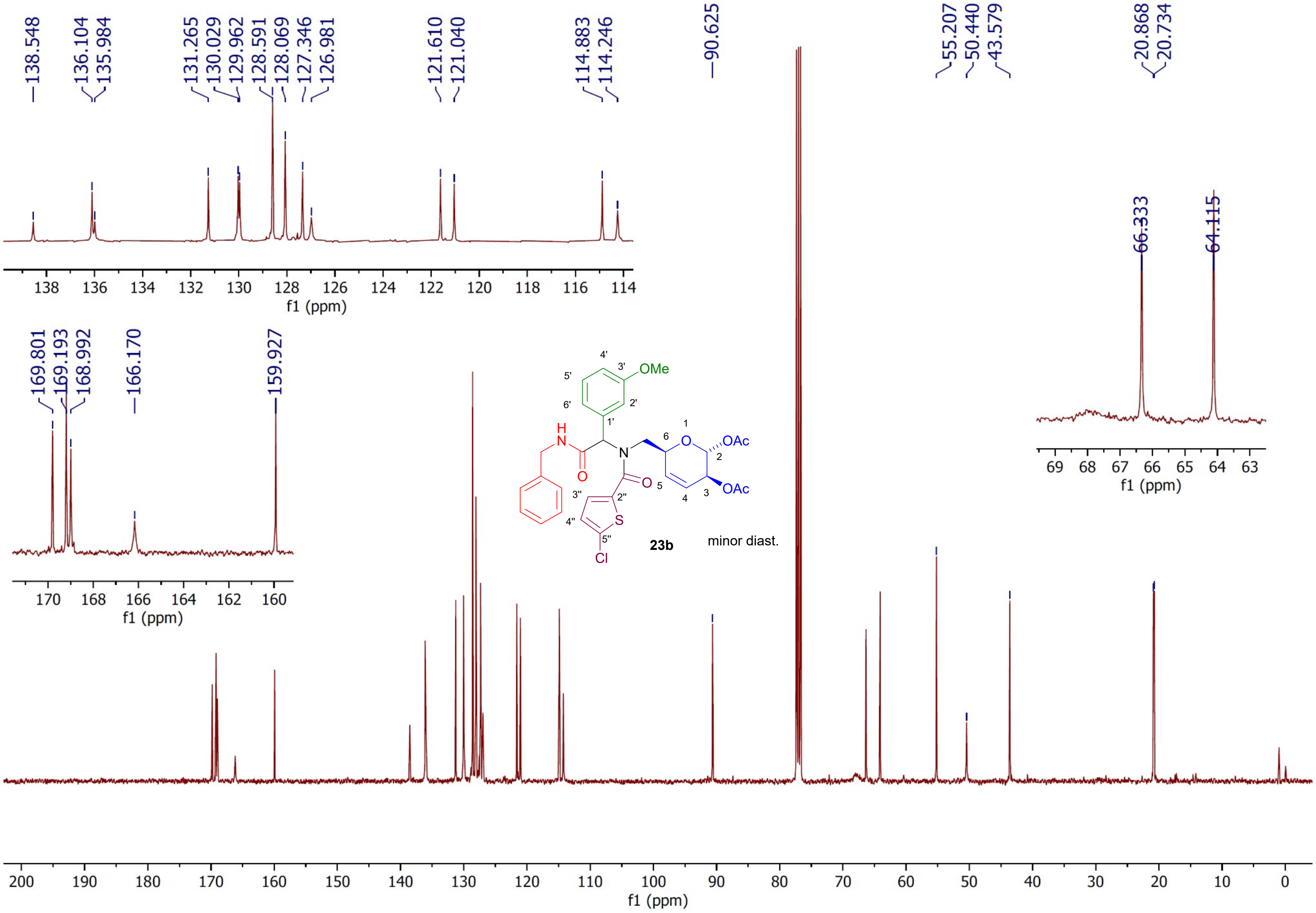


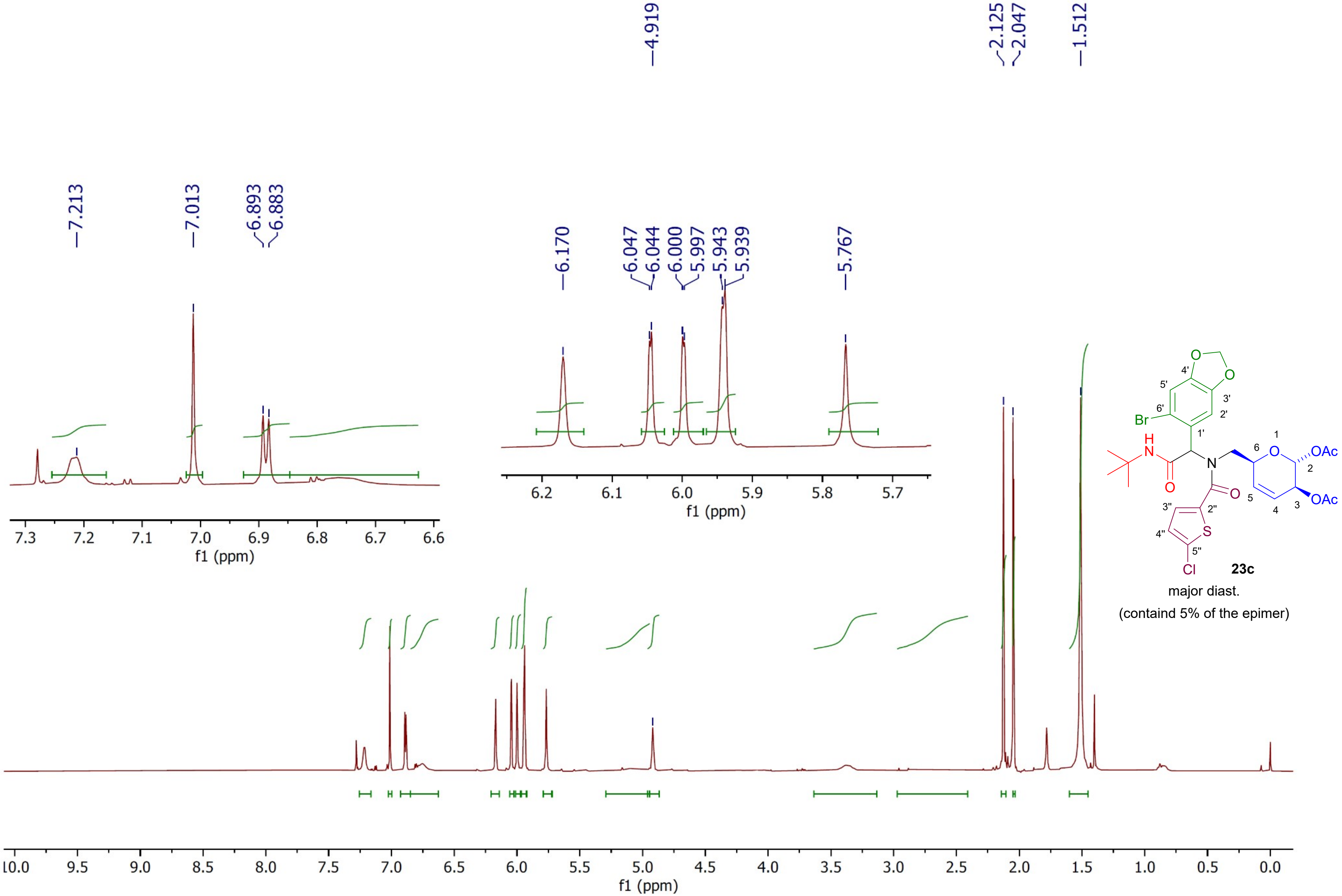
23b major diast.


138.122
136.129
135.741
135.266
131.438
130.015
129.943
128.563
127.687
127.303
126.158
121.285
120.897
114.702
114.141
90.410
55.242
51.605
43.613
20.840
20.701
67.187
66.525
64.130
169.869
168.815
168.705
165.020
159.894
138
136
134
132
130
128
126
124
122
120
118
116
114
f1 (ppm)
170
168
166
164
162
160
f1 (ppm)
68
67
66
65
64
63
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
4'
3'
OMe
5'
6'
2'
1'
H
N
O
N
6
O
1
OAc
2
O
5
4
3
OAc
3''
2''
4''
S
5''
Cl
23b
major diast.



5.957
5.878
5.871
5.810
0.50
5.95 5.90 5.85 5.80
f1 (ppm)
4.847
4.844
4.839
0.29
4.558
4.545
4.522
4.508
0.19
4.90 4.85 4.80 4.75 4.70 4.65 4.60 4.55 4.50 4.45
f1 (ppm)
3.718
2.037
2.027
6.865
6.859
6.854
6.843
6.719
0.52
6.85 6.80 6.75 6.70 6.65
f1 (ppm)
1.00
0.52
0.50
0.29
0.19
0.39
0.13
0.75
OMe
4'
3'
5'
6'
2'
1'
H
N
O
N
6
O
1
2
OAc
OAc
3
4
5
O
3''
2''
4''
S
5''
Cl
23b
minor diast.
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

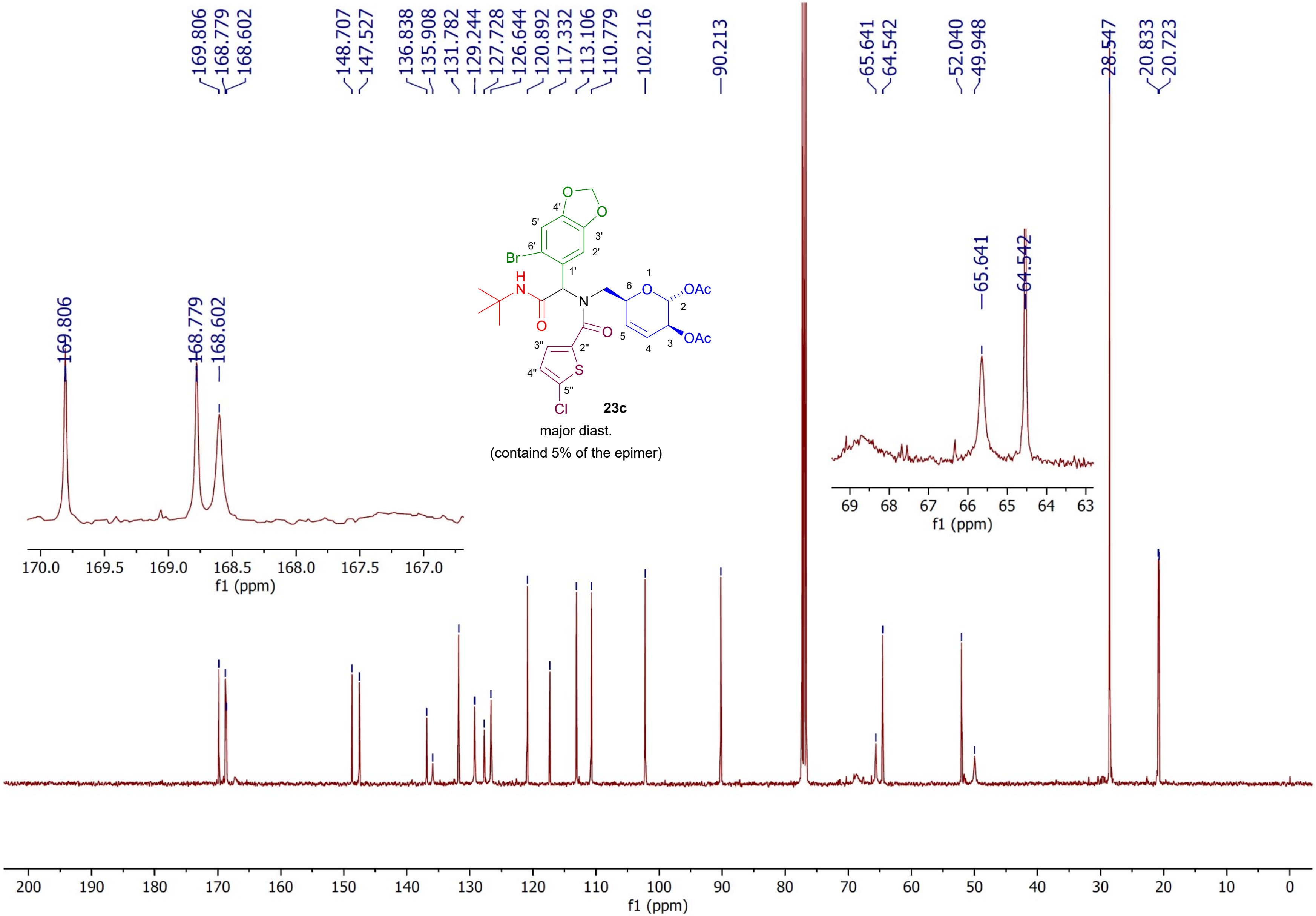

138.548
136.104
135.984
131.265
130.029
129.962
128.591
128.069
127.346
126.981
121.610
121.040
114.883
114.246
90.625
55.207
50.440
43.579
20.868
20.734
66.333
64.115
169.801
169.193
168.992
166.170
159.927
138 136 134 132 130 128 126 124 122 120 118 116 114
f1 (ppm)
170 168 166 164 162 160
f1 (ppm)
69 68 67 66 65 64 63
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
4'
3'
OMe
5'
6'
2'
1'
H
N
O
N
1
6
O
2
OAc
O
5
4
3
OAc
3''
2''
S
4''
5''
Cl
23b
minor diast.



23c

major diast.

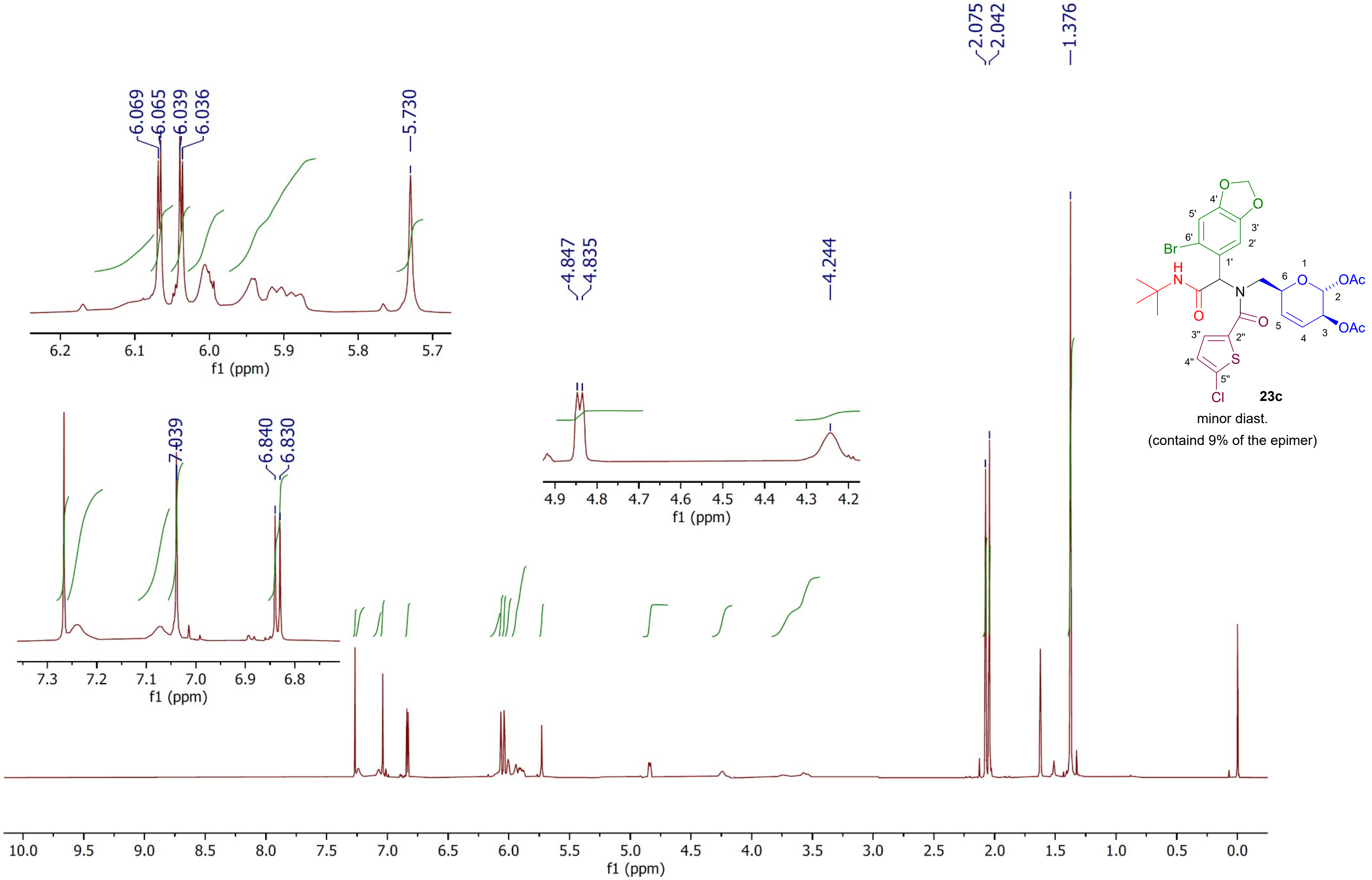
(containd 5% of the epimer)



23c

major diast.

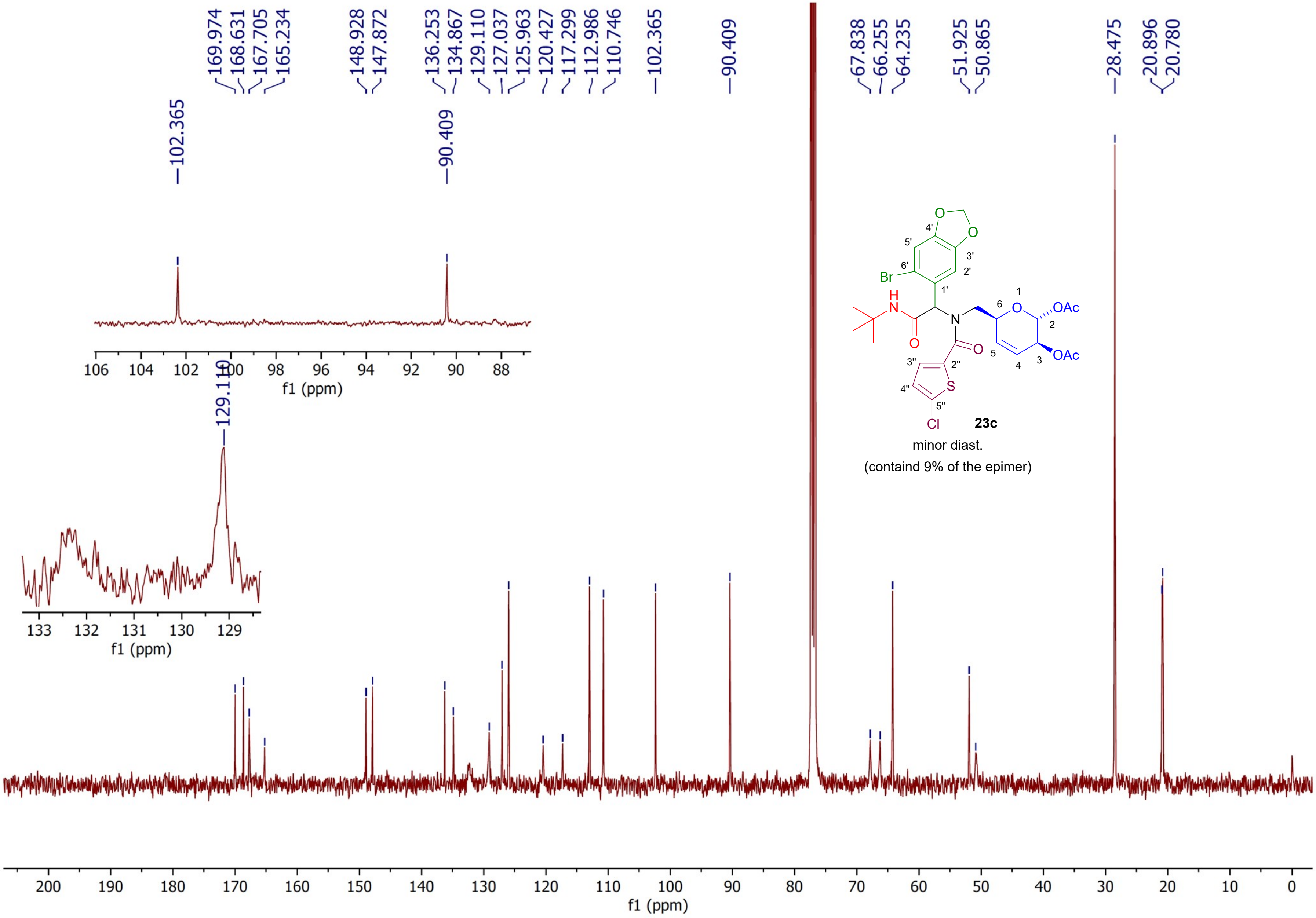
(containd 5% of the epimer)

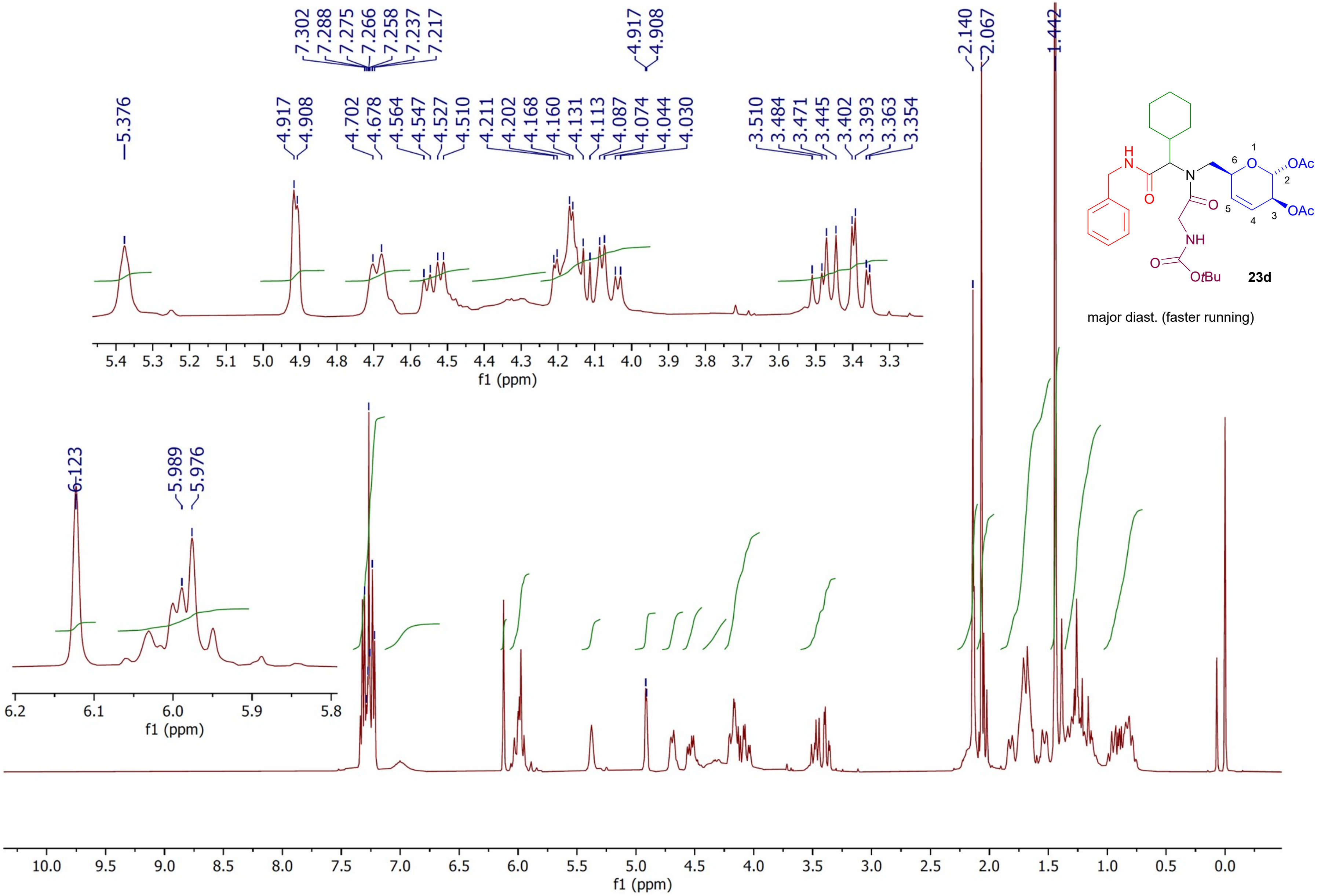


23c

minor diast.

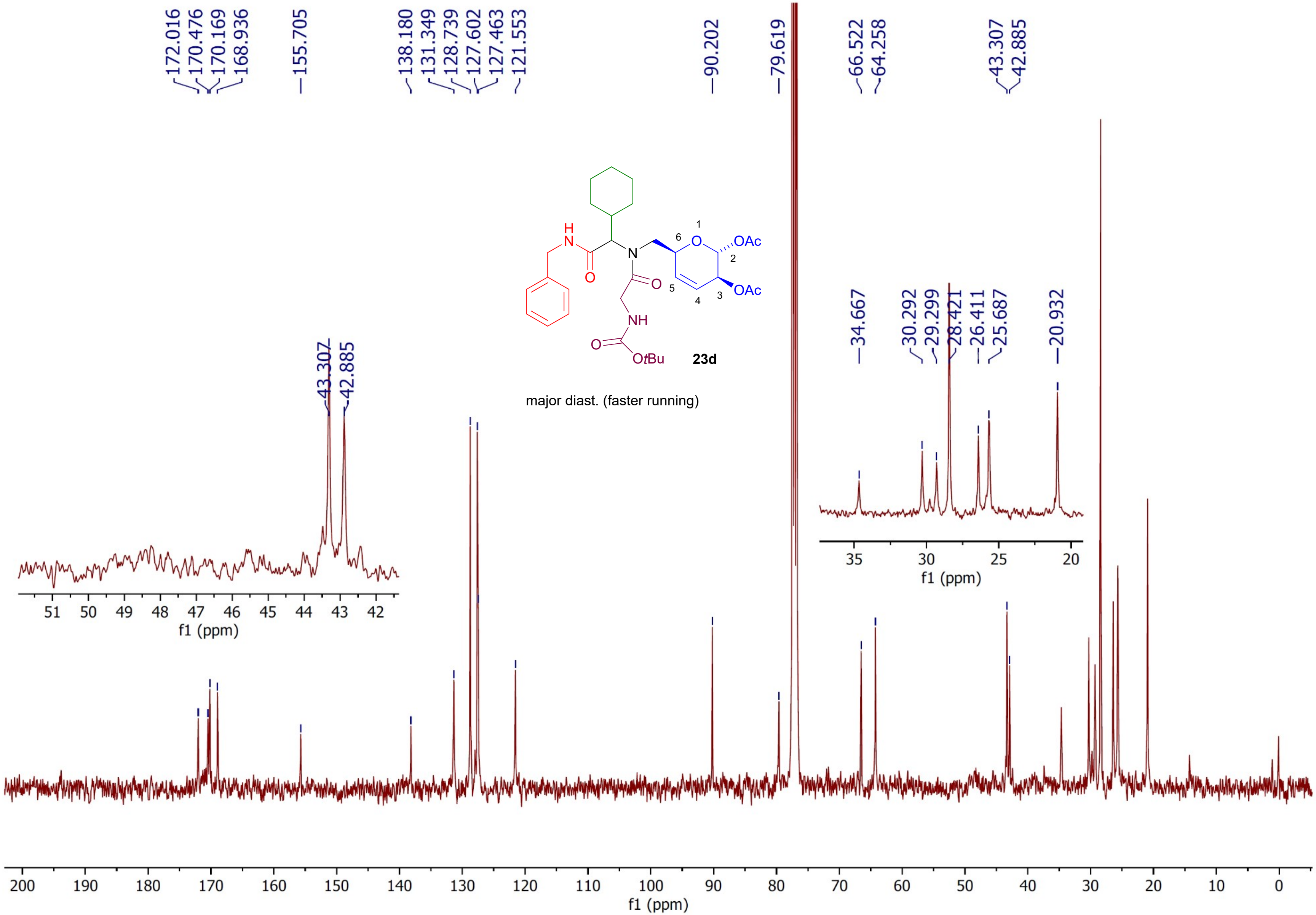
(containd 9% of the epimer)


169.974
168.631
167.705
165.234
148.928
147.872
136.253
134.867
129.110
127.037
125.963
120.427
117.299
112.986
110.746
102.365
90.409
67.838
66.255
64.235
51.925
50.865
28.475
20.896
20.780
102.365
90.409
106
104
102
100
98
96
94
92
90
88
f1 (ppm)
129.110
133
132
131
130
129
f1 (ppm)
O
O
4'
5'
3'
6'
2'
Br
1'
H
N
O
N
6
O
1
OAc
2
O
5
4
3
OAc
3''
2''
4''
S
5''
Cl
23c
minor diast.
(containd 9% of the epimer)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

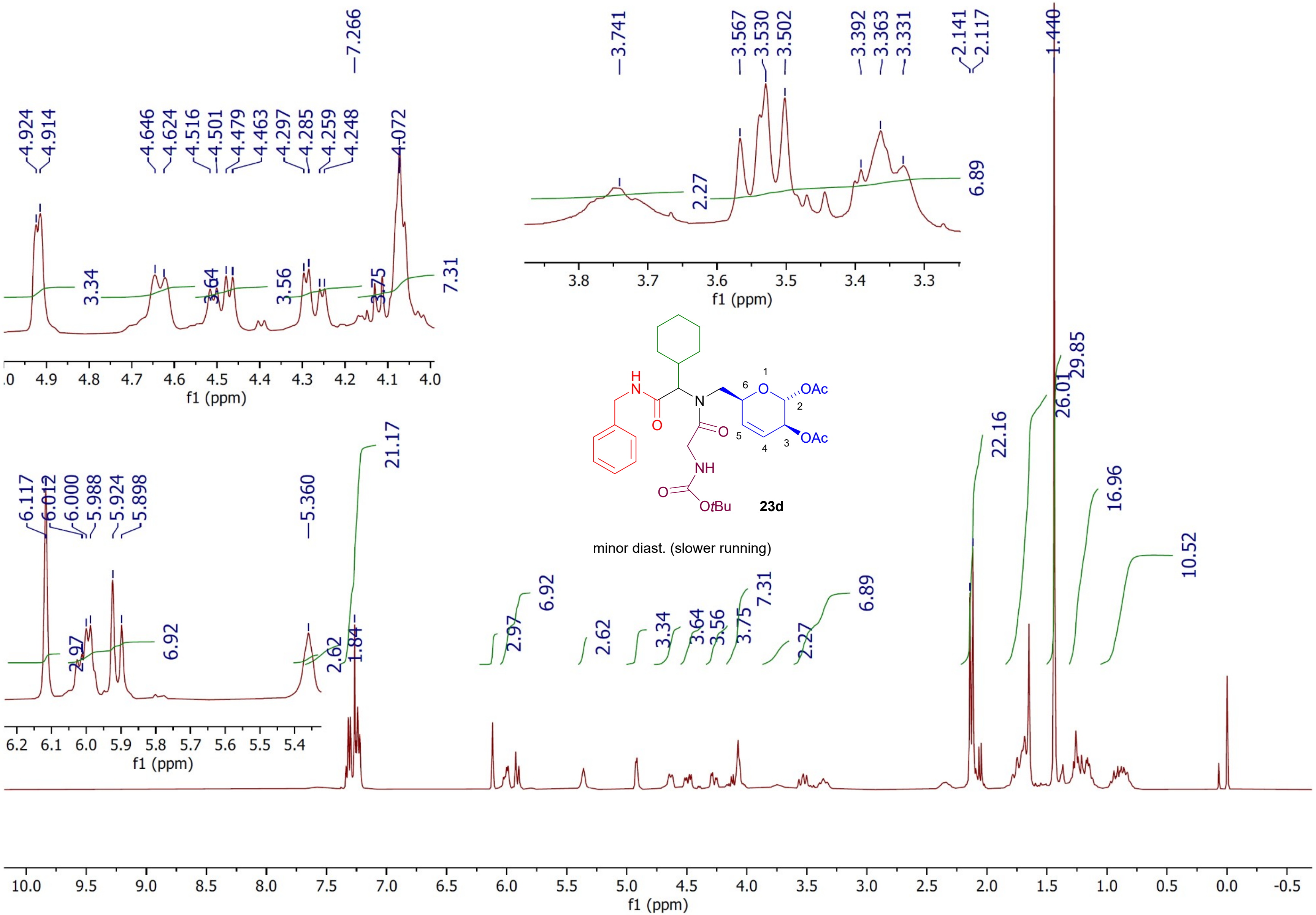


23d

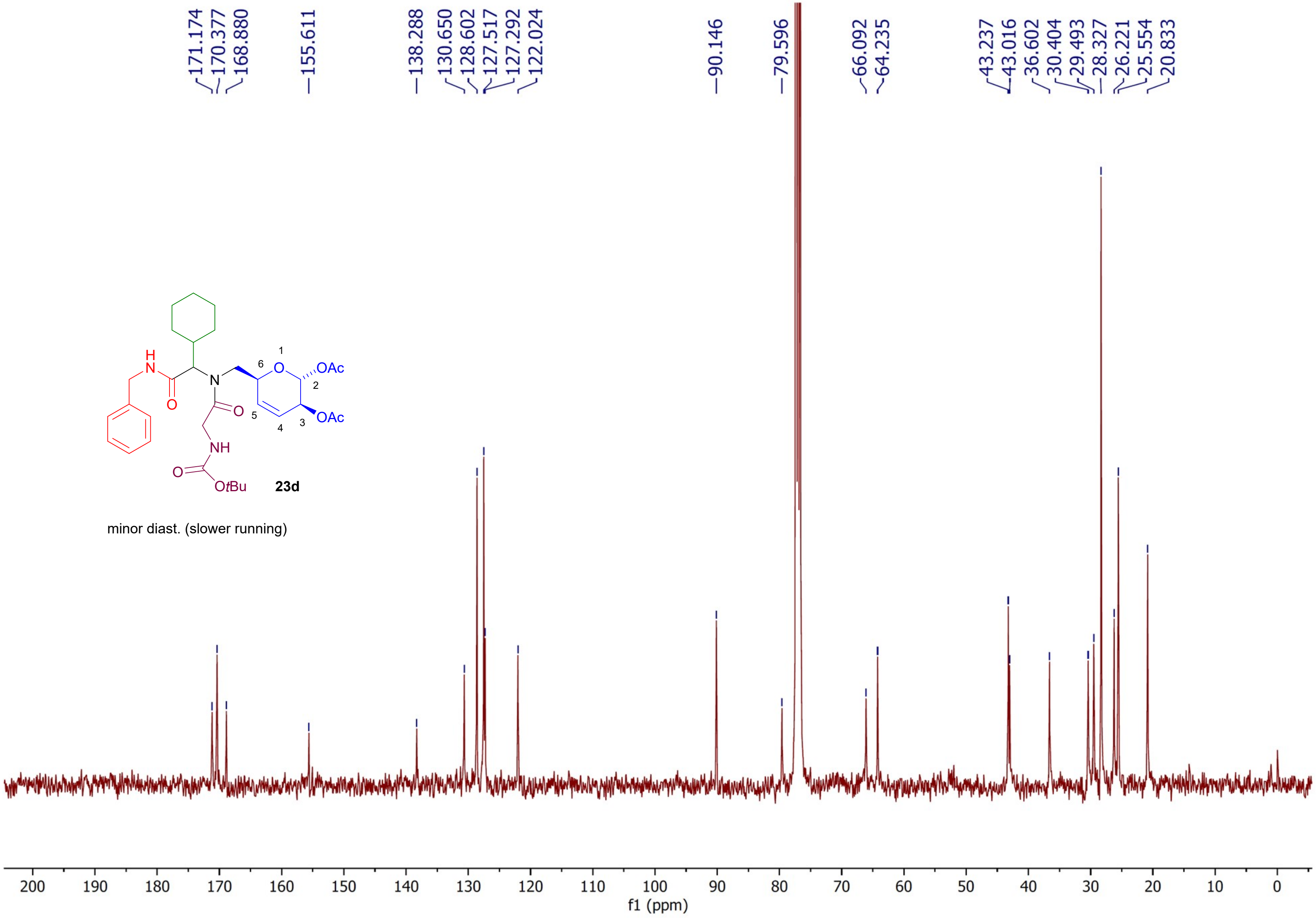
major diast. (faster running)


172.016
170.476
170.169
168.936
155.705
138.180
131.349
128.739
127.602
127.463
121.553
90.202
79.619
66.522
64.258
43.307
42.885
34.667
30.292
29.299
28.421
26.411
25.687
20.932
1
2
3
4
5
6
H
N
O
N
O
NH
O
O*t*Bu
OAc
OAc
major diast. (faster running)
51
50
49
48
47
46
45
44
43
42
f1 (ppm)
35
30
25
20
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

23d

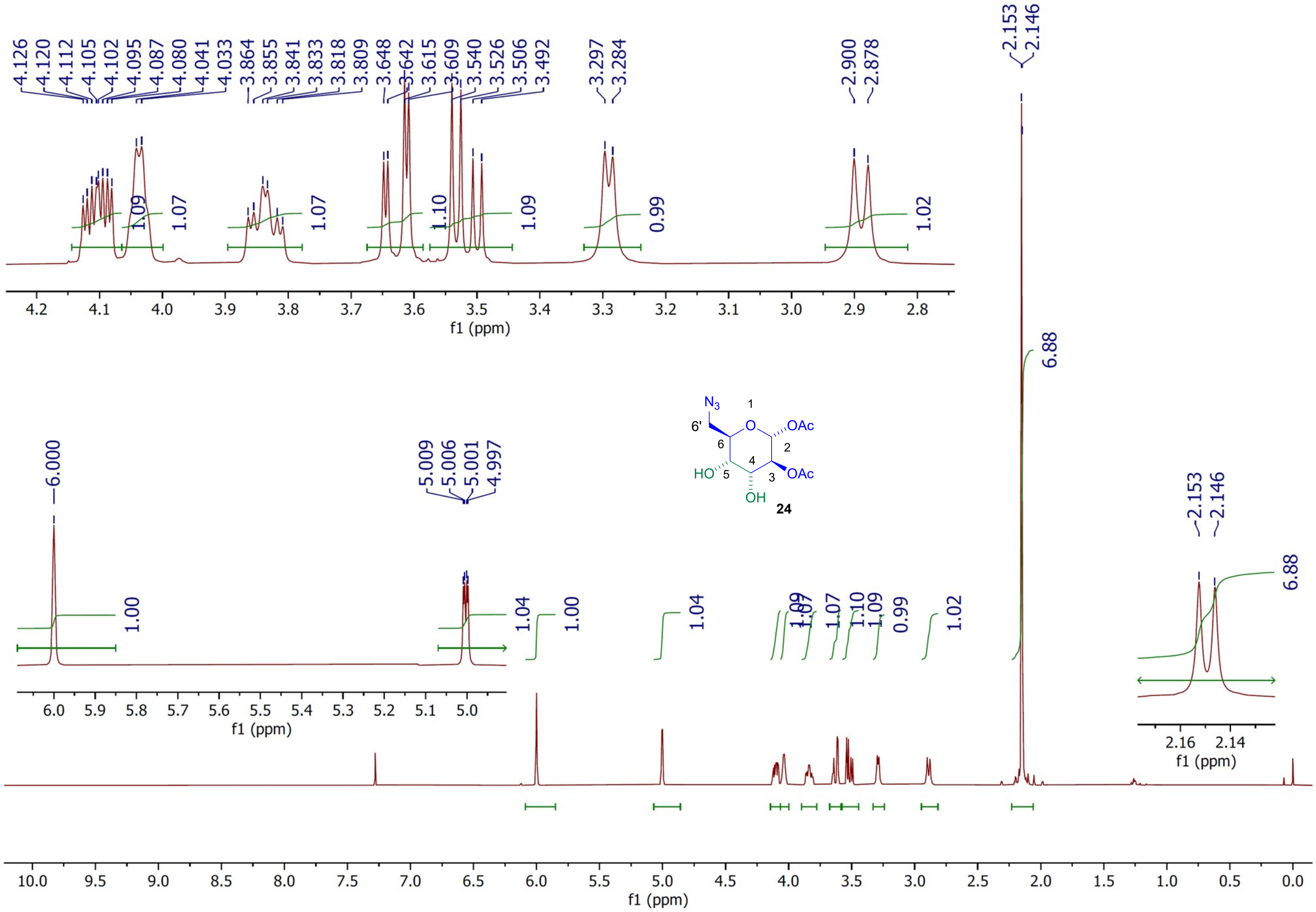


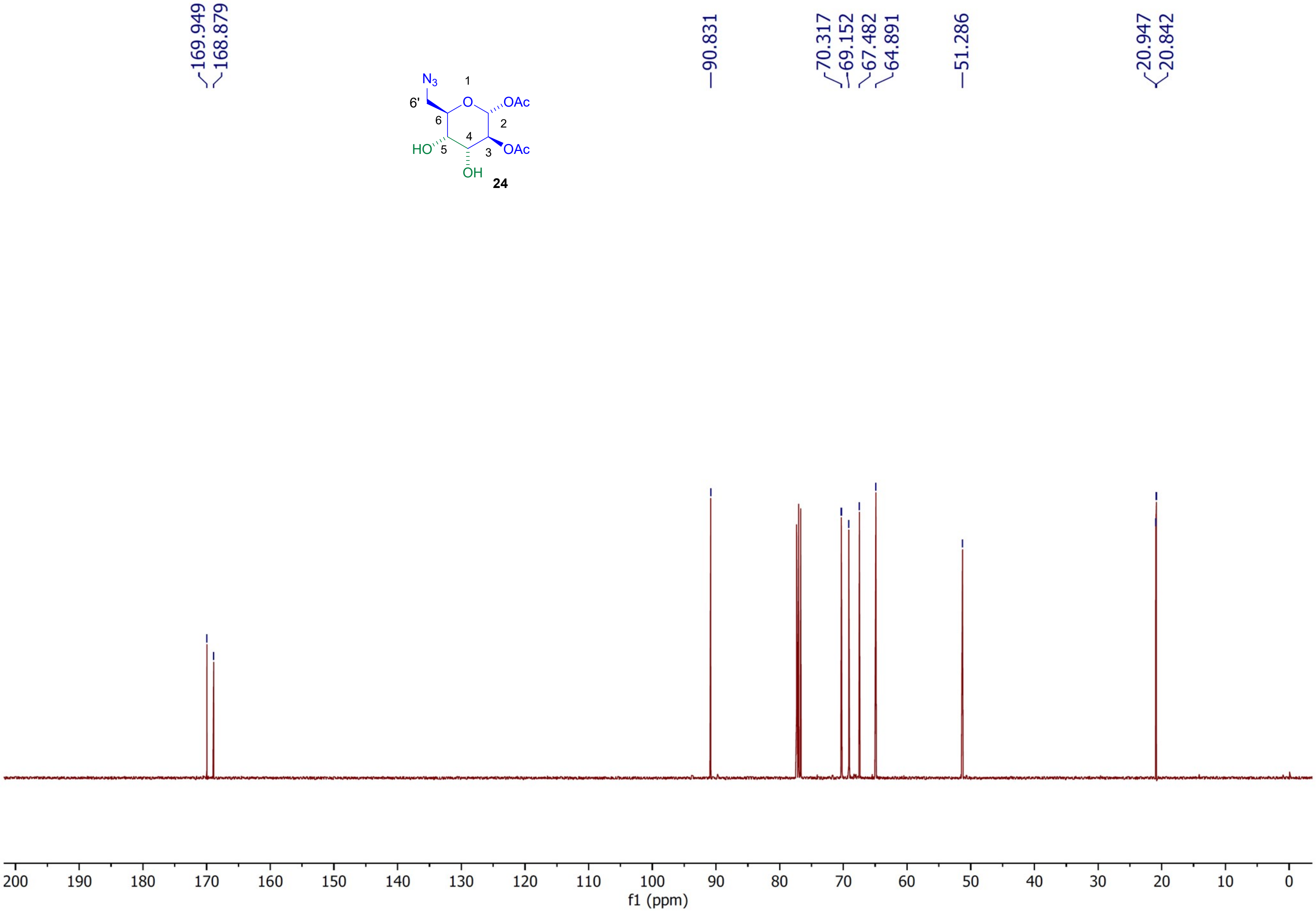
-7.266
4.924
4.914
4.646
4.624
4.516
4.501
4.479
4.463
4.297
4.285
4.259
4.248
4.072
3.34
3.64
3.56
3.75
7.31
4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0
f1 (ppm)
-3.741
3.567
3.530
3.502
3.392
3.363
3.331
2.141
2.117
1.440
2.27
6.89
3.8 3.7 3.6 3.5 3.4 3.3
f1 (ppm)
6.117
6.012
6.000
5.988
5.924
5.898
-5.360
2.97
6.92
2.62
1.84
21.17
6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4
f1 (ppm)
H
N
O
N
O
1
2
3
4
5
6
OAc
OAc
NH
O
OtBu
23d
minor diast. (slower running)
2.97
6.92
2.62
3.34
3.64
3.56
3.75
7.31
2.27
6.89
22.16
26.01
29.85
16.96
10.52
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



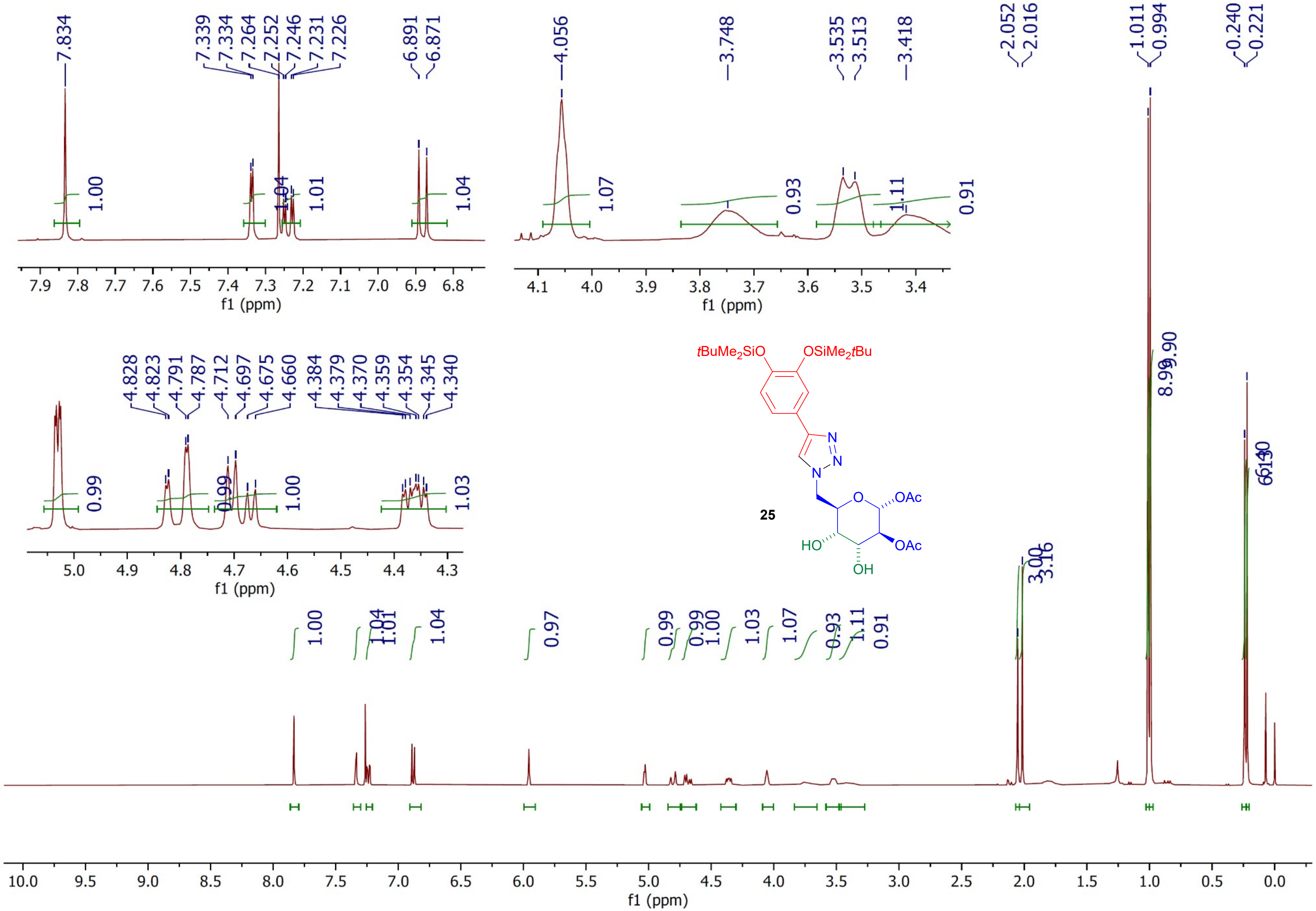
23d

minor diast. (slower running)

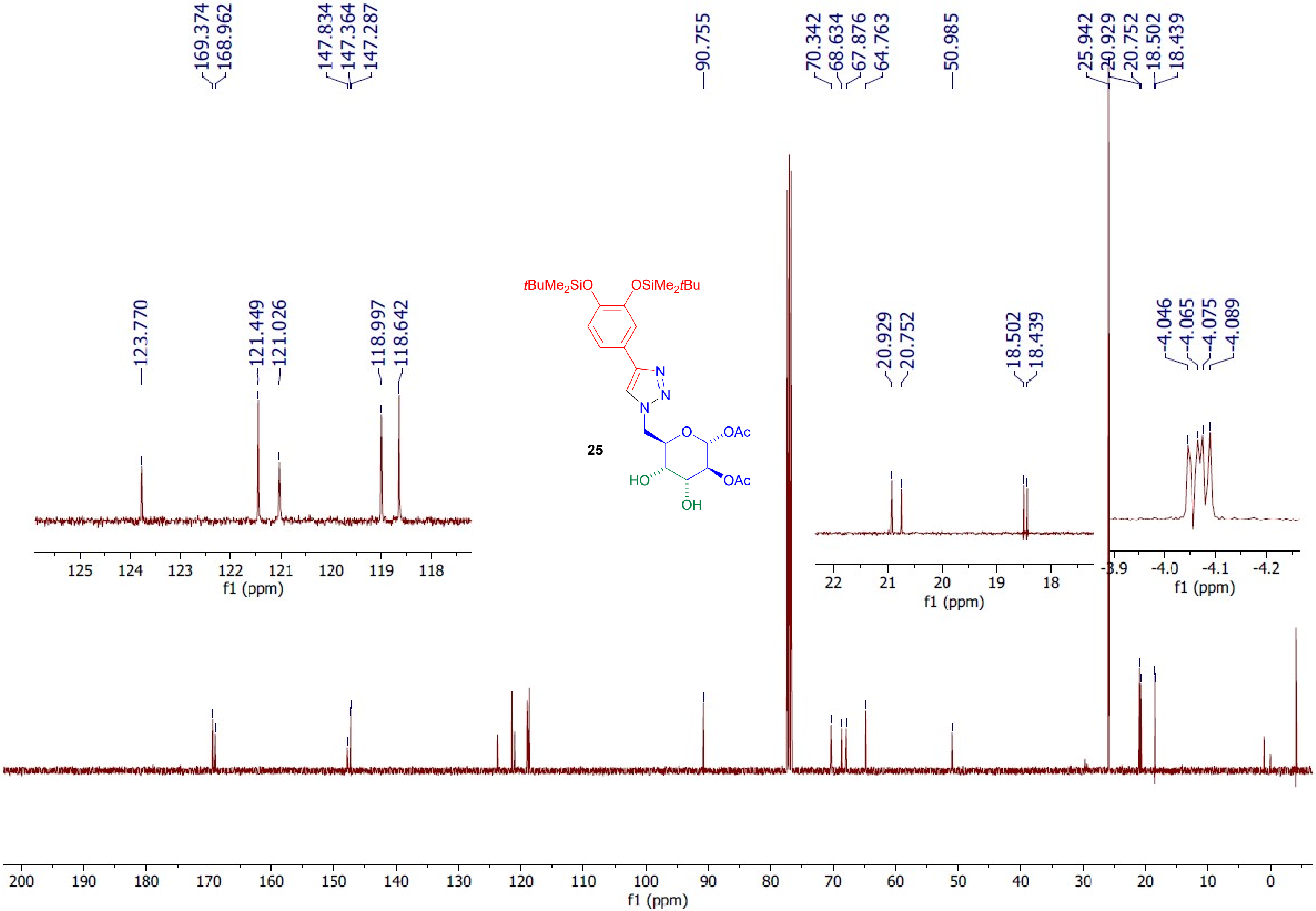

4.126
4.120
4.112
4.105
4.102
4.095
4.087
4.080
4.041
4.033
3.864
3.855
3.841
3.833
3.818
3.809
3.648
3.642
3.615
3.609
3.540
3.526
3.506
3.492
3.297
3.284
2.900
2.878
2.153
2.146
1.09
1.07
1.07
1.10
1.09
0.99
1.02
6.88
6.000
5.009
5.006
5.001
4.997
1.00
1.04
1.00
1.04
1.09
1.07
1.07
1.10
1.09
0.99
1.02
f1 (ppm)
N3
1
6'
O
OAc
6
2
4
HO
5
3
OAc
OH
24


169.949
168.879
90.831
70.317
69.152
67.482
64.891
51.286
20.947
20.842
N3
1
6'
O
OAc
6
2
HO
5
4
3
OAc
OH
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

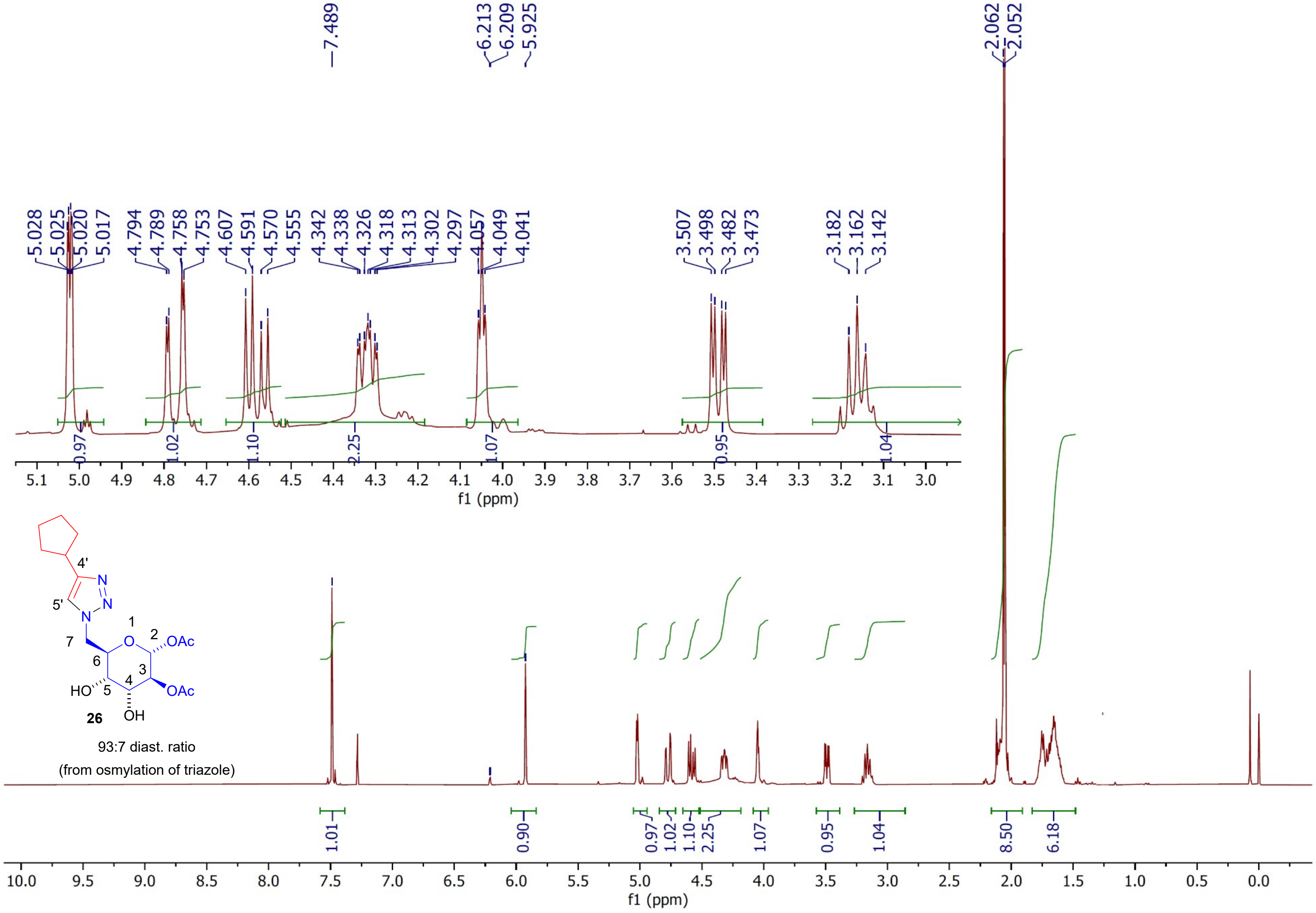
24


7.834
7.339
7.334
7.264
7.252
7.246
7.231
7.226
6.891
6.871
1.00
1.04
1.01
1.04
4.056
3.748
3.535
3.513
3.418
1.07
0.93
1.11
0.91
2.052
2.016
1.011
0.994
0.240
0.221
4.828
4.823
4.791
4.787
4.712
4.697
4.675
4.660
4.384
4.379
4.370
4.359
4.354
4.345
4.340
0.99
0.99
1.00
1.03
8.99
9.90
6.40
6.13
3.00
3.16
0.97
tBuMe2SiO
OSiMe2tBu
N
N
N
O
OAc
OAc
HO
OH
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

25


169.374
168.962
147.834
147.364
147.287
90.755
70.342
68.634
67.876
64.763
50.985
25.942
20.929
20.752
18.502
18.439
123.770
121.449
121.026
118.997
118.642
125
124
123
122
121
120
119
118
f1 (ppm)
tBuMe2SiO
OSiMe2tBu
N
N
N
O
OAc
OAc
HO
OH
20.929
20.752
18.502
18.439
22
21
20
19
18
f1 (ppm)
-4.046
-4.065
-4.075
-4.089
-3.9
-4.0
-4.1
-4.2
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

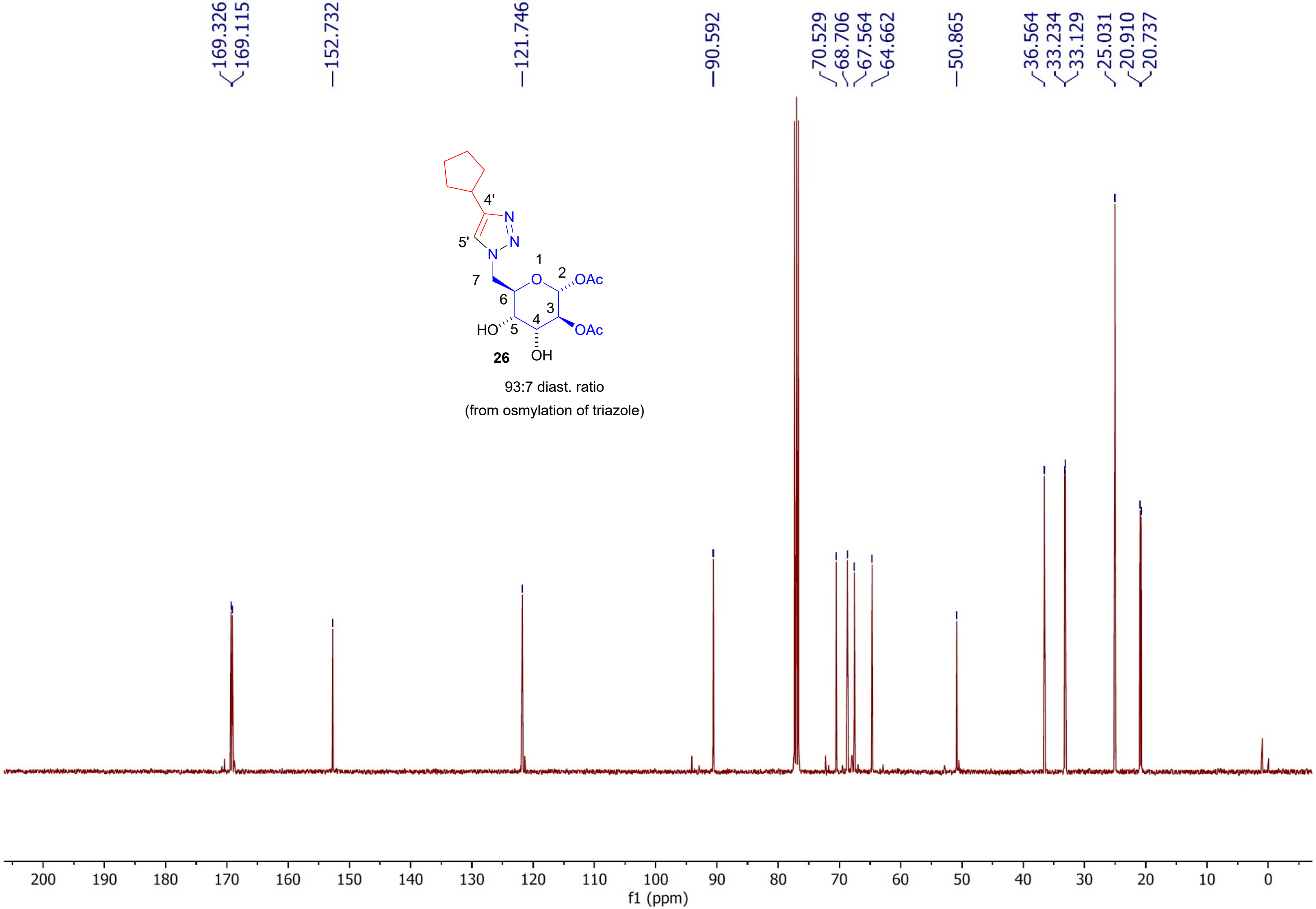
25



26

93:7 diast. ratio

(from osmylation of triazole)


169.326
169.115
152.732
121.746
90.592
70.529
68.706
67.564
64.662
50.865
36.564
33.234
33.129
25.031
20.910
20.737
4'
5'
N
N
N
1
2
7
6
3
4
5
O
OAc
OAc
HO
OH
26
93:7 diast. ratio
(from osmylation of triazole)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)