

Supporting Information for:

Hydroxymethyl-Branched Polyhydroxylated Indolizidines: Novel Selective α -Glucosidase Inhibitors

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1- General experimental methods

All reactions were performed under a positive pressure of dry argon in dried glassware equipped with a magnetic stir bar. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Solvents and liquid reagents were added through a syringe. THF and ether were distilled over sodium in presence of benzophenone prior to use. Toluene was distilled over sodium. Dichloromethane, acetonitrile, pyridine, triethylamine and TMEDA were distilled over CaH_2 .

Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel plates (Merck, Kieselgel 60 F₂₅₄). TLC spots were viewed under ultraviolet light and by heating the plate after treatment with 1% triphenyl tetrazolium chloride (TTC) in ethanol or 3% solution of potassium permanganate in 10% aqueous potassium hydroxide (w/v). Product purification by flash column chromatography was performed using Macherey-Nagel Silica Gel 60 (0.04-0.063 mm or 0.015-0.04 mm).

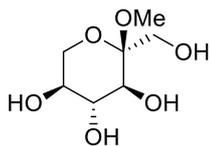
Optical rotations were measured on a Perkin Elmer 341 polarimeter. Infrared spectra were obtained from neat compounds, on a Nicolet 'Magna 550' spectrometer using an ATR (Attenuated Total Reflexion) module. The data are reported in reciprocal centimeters (cm^{-1}). ^1H -NMR and ^{13}C -NMR spectra were recorded on either a Brücker Advance 300 (^1H : 300 MHz, ^{13}C : 75 MHz), Advance 400 (^1H : 400 MHz, ^{13}C : 100 MHz) or Advance 500 (^1H : 500 MHz, ^{13}C : 125 MHz) spectrometers. Chemical shifts (δ) for ^1H spectra are values from tetramethylsilane in CDCl_3 (δ 0.00 ppm), toluene- d^8 (δ 2.08 ppm) or CD_3OD (δ 3.31 ppm). Chemical shifts for ^{13}C spectra are values from CDCl_3 (δ 77.16 ppm), toluene- d^8 (δ 20.43 ppm) or CD_3OD (δ 49.00 ppm). ^1H -NMR spectra are reported as follows: chemical shift (ppm), multiplicity (br: broad; s: singlet; d: doublet; dd: doublet of doublet; t: triplet; dt: doublet of triplet; q: quadruplet; m: multiplet), coupling constants (Hz) and integration. Proton and carbon assignments were established using COSY, HSQC, HMBC and ^{13}C mult experiments. High resolution mass spectra (HRMS) were recorded on a MALDI-TOF mass spectrometer. Elemental analyses were performed at the Service d'Analyse Elementaire du Département de Chimie Moléculaire, Grenoble.

In this supporting information the numbering displayed on the structures relates to NMR assignments, not to the IUPAC name of described compounds.

2- Preparation and characterization of new compounds

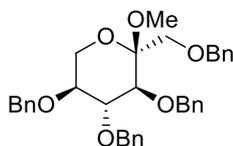
2a- Preparation of 1,3,4,5-tetra-*O*-benzyl sorbose (3)¹

Methyl α -L-sorbopyranoside



Acetyl chloride (4.5 mL, 63.3 mmol) was slowly introduced in MeOH (300 mL) at 0 °C then L-sorbose (15 g, 83.3 mmol) was added. MeOH (200 mL) was added and the mixture was stirred at room temperature during 4 days. The mixture was neutralized with Ag₂CO₃, decolourized with charcoal then concentrated under vacuum. The solid residue was washed with THF to remove impurities and afford methyl α -L-sorbopyranoside (13 g, 81%) as a beige solid that exhibited spectroscopic data identical to those reported in the literature.¹

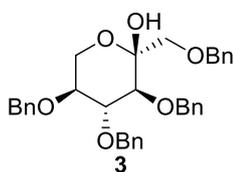
Methyl 1,3,4,5-tetra-*O*-benzyl- α -L-sorbopyranoside



Sodium hydride (9.31 g of a 60% suspension in oil, 243.8 mmol) was washed three times with pentane (50 mL), then 35 mL of THF was added. A solution of methyl α -L-sorbopyranoside (6 g, 30.4 mmol) in DMF (100 mL) was added to the suspension of NaH at 0 °C. The suspension was stirred for 1 h at room temperature, then tetrabutylammonium iodide (562 mg, 1.47 mmol) and benzyl bromide (29 mL, 243.8 mmol) were added at 0 °C. The mixture was stirred 15 h at room temperature. After addition of methanol (50 mL) and water (50 mL), the mixture was concentrated under vacuum. Brine was added (300 mL) and the aqueous phase was extracted three times with ether (300 mL). The organic layers were dried over MgSO₄ then concentrated to give a residue which upon column chromatography over silica gel (pentane / AcOEt, 9:1 to 1:1), afforded methyl 1,3,4,5-tetra-*O*-benzyl- α -L-sorbopyranoside (16.43 g, 96%) as a sticky oil, that exhibited spectroscopic data identical to those reported in the literature.¹

¹ Helleur, R.; Rao, V. S.; Perlin, A. S. *Carbohydr. Res.* **1981**, *89*, 83–90.

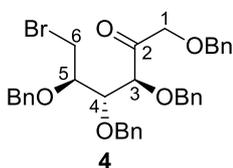
1,3,4,5-tetra-*O*-benzyl- α -L-sorbose (3)



Methyl 1,3,4,5-tetra-*O*-benzyl- α -L-sorbose (16 g, 28.9 mmol) was dissolved in AcOH (75% in water, 320 mL). The solution was stirred during 2.5 h at 110 °C. The mixture was concentrated under vacuum then coevaporated four times with cyclohexane (100 mL) then four times with toluene (100 mL) to give a crude syrup which, upon column chromatography over silica gel (pentane / AcOEt, 9:1 to 1:1) afforded **3** (14.6 g, 93%) as beige powder, that exhibited spectroscopic data identical to those reported in the literature.¹

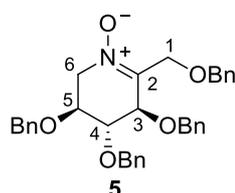
2b- Preparation of nitrone **5** from **3**

(3*S*,4*S*,5*R*)-1,3,4,5-tetrakis(benzyloxy)-6-bromohexan-2-one (**4**)



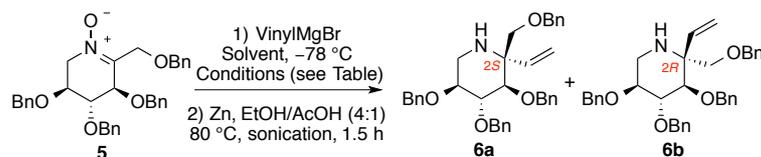
To a solution of 1,3,4,5-tetra-*O*-benzyl sorbose **3** (5.40 g, 10 mmol) in dry THF (90 mL) were added dry pyridine (1.613 mL, 20 mmol) and Ph₃P.Br₂ (7.590 g, 18 mmol). The mixture was stirred 3 h at reflux until the completion of the reaction (monitoring by TLC) then quenched with Na₂S₂O₃ saturated solution. The aqueous phase was extracted three times with ethyl acetate and the organic phases were washed with brine, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (pentane / AcOEt) to afford compound **4** (5.3 g, 87%) as a colorless oil.

$[\alpha]_D^{20} = -20.9$ (*c* 0.18, CHCl₃); **IR** ν 3088 (w), 3063 (w), 3030 (w), 2867 (m), 1731 (s), 1497 (m), 1454 (m), 1209 (w), 1071 (m), 1027 (m); **¹H-NMR (400 MHz, CDCl₃)** δ 3.29 (dd, *J* = 6.0 and 10.5 Hz, 1H, ⁶CH₂), 3.52 (dd, *J* = 6.0 and 10.5 Hz, 1H, ⁶CH₂), 3.89 (q, *J* = 6.0 Hz, 1H, ⁵CH), 4.03 (dd, *J* = 4.5 and 6.0 Hz, 1H, ⁴CH), 4.13 (d, *J* = 17.5 Hz, 1H, ¹CH₂), 4.20 (d, *J* = 17.5 Hz, 1H, ¹CH₂), 4.22 (d, *J* = 4.5 Hz, 1H, ³CH), 4.39 (s, 2H, ^{Bn}CH₂), 4.42 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 4.51-4.60 (m, 4H, ^{Bn}CH₂), 4.63 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 7.18-7.36 (m, 20H, ^{Ar}CH); **¹³C-NMR (100 MHz, CDCl₃)** δ 31.5 (⁶CH₂), 73.4 (^{Bn}CH₂), 73.6 (^{Bn}CH₂), 73.7 (^{Bn}CH₂), 74.4 (¹CH₂), 74.7 (^{Bn}CH₂), 78.8 (⁵CH), 79.6 (⁴CH), 81.2 (³CH), 128.0-128.7 (^{Ar}CH), 136.9, 137.4, 137.4 and 137.7 (^{Ar}Cq), 206.7 (²Cq); **HRMS (ESI)** Calcd for C₃₄H₃₅BrNaO₅: *m/z* = 625.1560 [M+Na]⁺; Found *m/z* = 625.1556.

(3*R*,4*R*,5*S*)-3,4,5-tris(benzyloxy)-2-((benzyloxy)methyl)-3,4,5,6-tetrahydropyridine 1-oxide (5)

To a solution of compound **4** (6.97 g, 11.5 mmol), in dry THF (150 mL), were added NH₂OH.HCl (4 g, 57.6 mmol) and dry Et₃N (7.52 mL, 57.6 mmol). The mixture was stirred at room temperature during 4 days. Then water was added and the aqueous phase was extracted three times with AcOEt. The organic phases were washed with brine, dried over MgSO₄, and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (pentane / AcOEt) to give compound **5** (5.03 g, 81%) as a colorless oil.

$[\alpha]_D^{20} = -53.1$ (*c* 1.00, CHCl₃); **IR** ν 3412 (br), 3054 (m), 3024 (m), 2859 (m), 1606 (m), 1489 (m), 1450 (s), 1237 (m), 1068 (s); **¹H-NMR (400 MHz, CDCl₃)** δ 3.79-3.88 (m, 2H, ⁴CH, ⁵CH), 3.96 (dd, *J* = 5.5 and 15.0 Hz, 1H, ⁶CH₂), 4.00 (dd, *J* = 4.5 and 15.0 Hz, 1H, ⁶CH₂), 4.40-4.67 (m, 10H, ¹CH₂, ³CH, ^{Bn}CH₂), 4.82 (d, *J* = 15.5 Hz, 1H, ^{Bn}CH₂), 7.18-7.36 (m, 20H, ^{Ar}CH); **¹³C-NMR (100 MHz, CDCl₃)** δ 60.3 (⁶CH₂), 66.0 (¹CH₂), 73.6 (³CH, ⁴CH), 76.2 (⁴CH), 71.9 (^{Bn}CH₂), 72.9 (^{Bn}CH₂), 73.5 (^{Bn}CH₂), 73.8 (^{Bn}CH₂), 127.9-128.6 (^{Ar}CH), 137.4, 137.5, 137.7 and 137.8 (^{Ar}Cq), 144.1 (²Cq); **HRMS (ESI)** Calcd for C₃₄H₃₆NO₅: *m/z* = 538.2588; [M+H]⁺; Found *m/z* = 538.2588.

2c- Vinylation of nitron 5**Table S1. Screening of conditions for the diastereoselective vinylation of nitron 5**

entry	solvent	equiv. vinylMgBr ^a	additive ^b (equiv)	yield ^c	d.r. ^d 6a/6b
1	THF	1.2	–	89%	66:33
2	Toluene	1.2	–	83%	48:52
3	Ether	1.2	–	80%	55:45
4	CH ₂ Cl ₂	1.2	–	91%	85:15
5	CH ₂ Cl ₂	1.2	MgBr ₂ •OEt ₂ (1.2) ^e	82%	75:25
6	CH ₂ Cl ₂	1.2 + 1	Et ₂ AlCl (1.2) ^e	82%	76:24
7	CH ₂ Cl ₂	1.2	TMSOTf (1.1) ^e	87%	12:88
8	CH ₂ Cl ₂	1.2	Zn(OTf) ₂ (1.2) ^e	88%	19:81
9	CH ₂ Cl ₂	1.2 + 2.4	ZnCl ₂ (1.2) ^e	97%	10:90
10	CH ₂ Cl ₂	1.2 + 2.4	ZnCl ₂ (1.2) ^f	86%	<2:98

^a Solution 0.7 M in THF. ^b – means no additive. ^c Combined yield in piperidines **6a** and **6b** after two steps and purification by chromatography. ^d Measured by integration of NMR signals on the crude mixture of piperidines. ^e The additive was premixed with the nitron in CH₂Cl₂ at –78 °C during 5 min before addition of vinylMgBr. ^f ZnCl₂ was premixed with vinylMgBr at r.t. during 15 min before cooling to –78 °C, followed by addition of the nitron in solution in CH₂Cl₂.

- **Method for obtention of 6a as the major product (conditions A)**

Nitrone **5** (1.328 g, 2.473 mmol) was placed in a Schlenk tube to be coevaporated three times with toluene, then it was dissolved in dry DCM (20 mL) and cooled to -78 °C. Vinylmagnesium bromide (0.54 M in THF, 5.5 mL, 2.968 mmol) was added at the same temperature. After 40 min, the reaction was completed (from TLC). A saturated aqueous solution of NH_4Cl was added, and the temperature was allowed to rise to room temperature. The aqueous phase was extracted three times with DCM, and the organic layers were washed with brine, dried over MgSO_4 , and concentrated under vacuum to yield 1.440 g of a mixture of two diastereoisomeric hydroxylamines (85:15 ratio determined from the next step), that were used in the next step without purification.

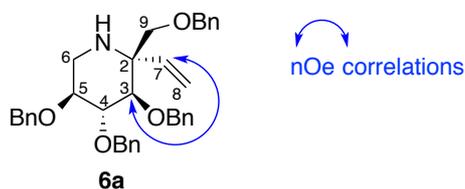
To a solution of these hydroxylamines in a 4 / 1 mixture of ethanol / acetic acid (95 mL) was added zinc dust (3.2 g, 49.4 mmol). The solution was placed in an ultra-sound bath at 80 °C for 1.5 h. The mixture was then treated with a solution of 10% NaOH and the aqueous layer was extracted three times with DCM. The organic layers were washed with brine, dried over MgSO_4 , and then concentrated under reduced pressure. Amines **6a** and **6b** (**6a:6b** = 85:15 from NMR analysis of their crude mixture) were partially separated by column chromatography on silica gel (pentane / AcOEt 9:1, 4:1, then 1:1) to afford pure amine **6a** (906 mg), pure amine **6b** (149 mg) and a mixture of amines **6a** and **6b** (184 mg) as colorless oils. The overall yield for the two steps was 91%.

- **Method for obtention of 6b as the major product (conditions B)**

Vinylmagnesium bromide (0.63 M solution in THF, 3.12 mL, 1.966 mmol) and ZnCl_2 (1 M solution in THF, 2 mL, 1.970 mmol) were mixed in a dry Schlenk tube during 15 min at room temperature, then cooled at -78 °C. A solution of nitrone **5** (883 mg, 1.638 mmol, prealably dried by three coevaporations with toluene) in dry DCM (16.4 mL) was then added drop-wise, at -78 °C, to the organometallic solution. After 1.5 h, nitrone **5** being unconsumed (from TLC analysis), an excess of vinylmagnesium bromide was introduced in the reaction mixture (6.24 mL, 3.932 mmol). After completion of the reaction (1 h from TLC analysis), a saturated aqueous solution of NH_4Cl was added and the temperature was allowed to rise to room temperature. The aqueous phase was extracted three times with DCM, the organic phases were washed with brine, dried over MgSO_4 , and concentrated under vacuum to yield 996 mg of hydroxylamine (only one diastereomer detected from NMR analysis, d.r. estimated <2:98) that was used in the next reaction without purification.

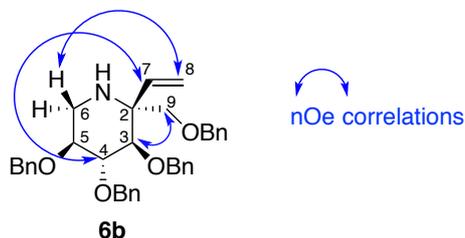
To a solution of this hydroxylamine in a 4 / 1 mixture of ethanol / acetic acid (44 mL) was added zinc dust (2.136 g, 32.742 mmol). The solution was placed in an ultra-sound bath at 80 °C for 1.5 h. The mixture was then treated with a solution of 10% NaOH and the aqueous layer was extracted three times with DCM. The organic layers were washed with brine, dried over MgSO_4 , and then concentrated under reduced pressure. Amine **6b** (774 mg, 86%) was isolated pure from chromatography on silica gel (pentane / AcOEt 9:1 to 1:1) as a colorless oil.

(2*S*,3*R*,4*R*,5*S*)-3,4,5-tris(benzyloxy)-2-(benzyloxymethyl)-2-ethenylpiperidine (6a)



$[\alpha]_D^{20} = -16$ (*c* 1.32, CHCl₃) ; **IR** ν 3348 (w), 3087 (m), 3063 (m), 3030 (m), 2909 (m), 2864 (m), 1496 (m), 1453 (m) ; **¹H-NMR (400 MHz, CDCl₃)** δ 2.29 (br s, 1H, NH), 2.68 (dd, *J* = 10.5 and 11.5 Hz, 1H, ⁶CH₂), 3.13 (dd, *J* = 5.5 and 11.5 Hz, 1H, ⁶CH₂), 3.37 (d, *J* = 9.0 Hz, 1H, ³CH), 3.57-3.71 (m, 3H, ⁴CH, ⁵CH, ⁹CH₂), 3.91 (d, *J* = 10.0 Hz, 1H, ⁹CH₂), 4.48-4.81 (m, 7H, ^{Bn}CH₂), 4.89 (d, *J* = 11.0 Hz, 1H, ^{Bn}CH₂), 5.17 (dd, *J* = 1.0 and 11.0 Hz, 1H, ⁸CH₂), 5.35 (dd, *J* = 1.0 and 17.5 Hz, 1H, ⁸CH₂), 6.02 (dd, *J* = 11.0 and 17.5 Hz, 1H, ⁷CH), 7.20-7.37 (m, 20H, ^{Ar}CH) ; **¹³C-NMR (100 MHz, CDCl₃)** δ 43.4 (⁶CH₂), 61.7 (²C_q), 67.2 (⁹CH₂), 72.8, 73.7, 75.7, 76.1 (^{Bn}CH₂), 80.4 (⁵CH), 84.1 (⁴CH), 85.8 (³CH), 114.9 (⁸CH₂), 127.6-128.5 (^{Ar}CH), 138.4, 138.6, 138.8 and 139.0 (^{Ar}C_q), 142.3 (⁷CH) ; **Anal. Calcd for C₃₆H₃₉NO₄**: C, 78.66; H, 7.16; N, 2.55. Found: C, 78.53; H, 7.20; N, 2.62 ; **HRMS (ESI)** Calcd for C₃₆H₄₀NO₄: *m/z* = 550.2952 [M+H]⁺; Found *m/z* = 550.2943.

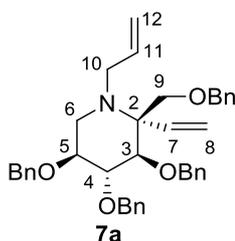
(2*R*,3*R*,4*R*,5*S*)-3,4,5-tris(benzyloxy)-2-(benzyloxymethyl)-2-ethenylpiperidine (6b)



$[\alpha]_D^{20} = +9$ (*c* 0.99, CHCl₃) ; **IR** ν 3336 (w), 3087 (m), 3063 (m), 3029 (m), 2908 (m), 2861 (m), 1605 (w), 1496 (m), 1453 (m) ; **¹H-NMR (400 MHz, CDCl₃)** δ 1.80 (br s, 1H, NH), 2.72 (dd, *J* = 11.0 and 13.5 Hz, 1H, ⁶CH₂), 2.98 (dd, *J* = 5.5 and 13.5 Hz, 1H, ⁶CH₂), 3.07 (d, *J* = 9.0 Hz, 1H, ⁹CH₂), 3.40-3.48 (m, 1H, ⁵CH), 3.57-3.63 (m, 2H, ⁴CH, ⁹CH₂), 3.73 (d, *J* = 10.0 Hz, 1H, ³CH), 4.36 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 4.44 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 4.51-4.94 (m, 6H, ^{Bn}CH₂), 5.33 (dd, *J* = 2.0 and 11.0 Hz, 1H, ⁸CH₂), 5.49 (dd, *J* = 2.0 and 17.5 Hz, 1H, ⁸CH₂), 6.00 (dd, *J* = 11.0 and 17.5 Hz, 1H, ⁷CH), 7.20-7.35 (m, 20H, ^{Ar}CH) ; **¹³C-NMR (100 MHz, CDCl₃)** δ 43.6 (⁶CH₂), 62.9 (²C_q), 73.0 (^{Bn}CH₂), 73.4 (^{Bn}CH₂), 74.1 (⁹CH₂), 75.5 (^{Bn}CH₂), 75.8 (^{Bn}CH₂), 81.2 (³CH), 82.2 (⁵CH), 84.7 (⁴CH), 118.1 (⁸CH₂), 127.5-128.5 (^{Ar}CH), 134.9 (⁷CH), 138.0, 138.8, 139.1 and 139.3 (^{Ar}C_q) ; **Anal. Calcd for C₃₆H₃₉NO₄**: C, 78.66; H, 7.16; N, 2.55. Found: C, 78.33; H, 7.51; N, 2.88; **HRMS (ESI)** Calcd for C₃₆H₄₀NO₄: *m/z* = 550.2952 [M+H]⁺; Found *m/z* = 550.2947.

2d- *N*-allylation of piperidines **6a** and **6b**

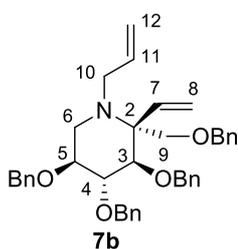
(2*S*,3*R*,4*R*,5*S*)-1-allyl-3,4,5-tris(benzyloxy)-2-((benzyloxy)methyl)-2-vinylpiperidine (**7a**)



To a solution of amine **6a** (906 mg, 1.648 mmol) in dry CH₃CN (80 mL) was added potassium carbonate (387 mg, 2.802 mmol), allyl bromide (0.230 mL, 2.637 mmol) and a catalytic amount of potassium iodide. The mixture was stirred during 6.5 h at 82 °C, then a saturated solution of sodium hydrogenocarbonate was added, the aqueous layer was extracted three times with DCM, the organic layers were dried over MgSO₄ and the solvents were evaporated under reduced pressure. Purification by chromatography on silica gel (pentane / AcOEt) afforded the *N*-allyl piperidine **7a** (800 mg, 82%) as a yellow oil.

$[\alpha]_D^{20} = -31$ (*c* 1.05, CHCl₃) ; **IR** ν 3087 (m), 3063 (m), 3029 (m), 2863 (m), 1640 (w), 1605 (w), 1497 (m), 1453 (m) ; **¹H-NMR** (400 MHz, CDCl₃) δ 2.73 (t, *J* = 11.0 Hz, 1H, ⁶CH₂), 2.88 (dd, *J* = 7.5 and 15.5 Hz, 1H, ¹⁰CH₂), 3.09 (dd, *J* = 5.5 and 11.5 Hz, 1H, ⁶CH₂), 3.34 (d, *J* = 9.5 Hz, 1H, ³CH), 3.55-3.66 (m, 2H, ⁵CH, ¹⁰CH₂), 3.83 (d, *J* = 10.0 Hz, 1H, ⁹CH₂), 3.90 (t, *J* = 9.5 Hz, 1H, ⁴CH), 4.11 (d, *J* = 10.0 Hz, 1H, ⁹CH₂), 4.53 (s, 2H, ^{Bn}CH₂), 4.59 (d, *J* = 11.0 Hz, 1H, ^{Bn}CH₂), 4.64 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 4.69 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 4.76 (d, *J* = 11.0 Hz, 1H, ^{Bn}CH₂), 4.79 (d, *J* = 11.0 Hz, 1H, ^{Bn}CH₂), 4.87 (d, *J* = 11.0 Hz, 1H, ^{Bn}CH₂), 5.03 (br d, *J* = 10.0 Hz, 1H, ¹²CH₂), 5.14 (dd, *J* = 1.0 and 17.0 Hz, 1H, ¹²CH₂), 5.20-5.30 (m, 2H, ⁸CH₂), 5.65-5.77 (m, 2H, ⁷CH and ¹¹CH), 7.17-7.38 (m, 20H, ^{Ar}CH) ; **¹³C-NMR** (100 MHz, CDCl₃) δ 49.1 (⁶CH₂), 54.0 (¹⁰CH₂), 66.2 (²Cq), 68.1 (⁹CH₂), 72.8, 73.7, 75.5 and 76.2 (^{Bn}CH₂), 79.8 (⁵CH), 83.8 (⁴CH), 86.0 (³CH), 115.4 (¹²CH₂), 116.8 (⁸CH₂), 127.4-128.5 (^{Ar}CH), 137.8 (¹¹CH), 138.7, 138.9, 139.2 and 139.3 (^{Ar}C_q), 142.1 (⁷CH) ; **HRMS (ESI)** Calcd for C₃₉H₄₄NO₄: *m/z* = 590.3265 [M+H⁺]; Found *m/z* = 590.3268.

(2*R*,3*R*,4*R*,5*S*)-1-allyl-3,4,5-tris(benzyloxy)-2-((benzyloxy)methyl)-2-vinylpiperidine (**7b**)



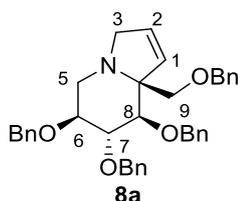
To a solution of amine **6b** (278 mg, 0.506 mmol) in dry CH₃CN (25 mL) was added potassium carbonate (125 mg, 0.906 mmol), allyl bromide (0.070 mL, 0.809 mmol) and a catalytic amount of

potassium iodide. The mixture was stirred during 4 h at 82 °C, then a saturated solution of sodium hydrogenocarbonate was added, the aqueous layer was extracted three times with DCM, the organic layers were dried over MgSO₄ and the solvents were evaporated under reduced pressure. Purification by chromatography on silica gel (pentane / AcOEt) afforded the *N*-allyl piperidines **7b** (241 mg, 81%) as a yellow oil.

$[\alpha]_D^{20} = +4$ (c 0.81, CHCl₃) ; **IR** ν 3087 (w), 3063 (m), 3029 (m), 2905 (m), 2859 (m), 1640 (w), 1605 (w), 1585 (w), 1496 (m), 1453 (m) ; **¹H-NMR (400 MHz, CDCl₃)** δ 2.50 (dd, $J = 10.0$ and 12.0 Hz, 1H, ⁶CH₂), 2.96 (dd, $J = 7.5$ and 14.0 Hz, 1H, ¹⁰CH₂), 3.04 (dd, $J = 5.0$ and 12.0 Hz, 1H, ⁶CH₂), 3.39-3.46 (m, 2H, ⁹CH₂, ¹⁰CH₂), 3.61-3.75 (m, 3H, ⁴CH, ⁵CH, ⁹CH₂), 3.87 (d, $J = 9.5$ Hz, 1H, ³CH), 4.38 (d, $J = 12.0$ Hz, 1H, ^{Bn}CH₂), 4.46-4.56 (m, 2H, ^{Bn}CH₂), 4.62 (d, $J = 11.5$ Hz, 1H, ^{Bn}CH₂), 4.67 (d, $J = 11.5$ Hz, 1H, ^{Bn}CH₂), 4.77 (d, $J = 11.0$ Hz, 1H, ^{Bn}CH₂), 4.88 (d, $J = 11.0$ Hz, 1H, ^{Bn}CH₂), 4.91 (d, $J = 11.0$ Hz, 1H, ^{Bn}CH₂), 5.07 (br d, $J = 10.0$ Hz, 1H, ¹²CH₂), 5.12 (dd, $J = 1.5$ and 17.0 Hz, 1H, ¹²CH₂), 5.28 (dd, $J = 1.5$ and 6.5 Hz, 1H, ⁸CH₂), 5.32 (dd, $J = 1.5$ and 13.0 Hz, 1H, ⁸CH₂), 5.77-5.87 (m, 1H, ¹¹CH₂), 5.91 (dd, $J = 11.5$ and 18.0 Hz, 1H, ⁷CH), 7.16-7.19 (m, 2H, ^{Ar}CH), 7.20-7.33 (m, 18H, ^{Ar}CH); **¹³C-NMR (100 MHz, CDCl₃)** δ 48.8 (⁶CH₂), 52.4 (¹⁰CH₂), 66.0 (²Cq), 69.3 (⁹CH₂), 72.8, 73.3, 75.3 and 75.5 (^{Bn}CH₂), 79.2 (⁵CH), 80.5 (³CH), 84.5 (⁴CH), 116.6 (¹²CH₂), 118.7 (⁸CH₂), 127.9-128.4 (^{Ar}CH), 134.3 (⁷CH), 137.0 (¹¹CH), 138.0, 138.8, 139.3 and 139.4 (^{Ar}Cq) ; **HRMS (ESI)** Calcd for C₃₉H₄₄NO₄: $m/z = 590.3265$ [M+H⁺]; Found $m/z = 590.3268$.

2e- Ring closing metathesis of *N*-allylvinylpiperidines **7a** and **7b**

(6*S*,7*R*,8*R*,8*aS*)-6,7,8-tris(benzyloxy)-8*a*-[(benzyloxy)methyl]-3,5,6,7,8,8*a*-hexahydroindolizine (**8a**)

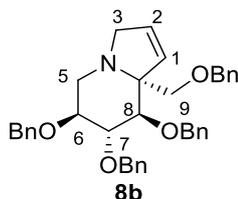


To a solution of piperidine **7a** (96 mg, 0.163 mmol) in dry and degazed (30 min of argon bubbling) DCM (8.2 mL), second generation Grubbs catalyst (7.4 mg, 0.009 mmol) was added and the reaction was heated during 3 h at 40 °C. After cooling, the reaction mixture was filtered on a plug of silica gel (rinsed with Et₂O), then the solvents were removed in vacuo. The crude oil was purified by flash chromatography on silica gel (pentane / AcOEt) to afford **8a** (82 mg, 85%) as a colorless oil.

$[\alpha]_D^{20} = +29.3$ (c 0.68, CHCl₃) ; **IR** ν 3063 (w), 3029 (w), 2861 (m), 1496 (w), 1453 (m), 1362 (w), 1072 (s) ; **¹H-NMR (400 MHz, CDCl₃)** δ 3.10-3.16 (m, 2H, ⁵CH₂), 3.44 (d, $J = 9.5$ Hz, 1H, ⁸CH), 3.64 (d, $J = 9.5$ Hz, 1H, ⁹CH₂), 3.66-3.73 (m, 2H, ³CH₂, ⁶CH), 3.81-3.87 (m, 2H, ³CH₂, ⁷CH), 3.90 (d, $J = 9.5$ Hz, 1H, ⁹CH₂), 4.54 (d, $J = 11.5$ Hz, 1H, ^{Bn}CH₂), 4.59 (s, 2H, ^{Bn}CH₂), 4.67 (d, $J = 11.5$ Hz, 1H,

^{Bn}CH₂), 4.73 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 4.77 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 4.81 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 4.85 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 5.75 (br d, *J* = 6.0 Hz, 1H, ²CH), 5.80 (br d, *J* = 6.0 Hz, 1H, ¹CH), 7.18-7.40 (m, 20H, ^{Ar}CH) ; ¹³C-NMR (100 MHz, CDCl₃) δ 47.8 (⁵CH₂), 58.7 (³CH₂), 70.7 (⁹CH₂), 72.8 (^{8a}Cq), 73.0, 73.6, 75.6 and 75.7 (^{Bn}CH₂), 77.4 (⁶CH), 83.4 (⁷CH), 85.2 (⁸CH), 127.4-128.5 (¹CH, ^{Ar}CH), 134.8 (²CH), 138.8, 138.9, 139.1 and 139.2 (^{Ar}Cq) ; HRMS (ESI) Calcd for C₃₇H₄₀NO₄: *m/z* = 562.2952 [M+H]⁺; Found *m/z* = 562.2947.

(6*S*,7*R*,8*R*,8*aR*)-6,7,8-tris(benzyloxy)-8a-[(benzyloxy)methyl]-3,5,7,8,8a-hexahydroindolizine (8b)

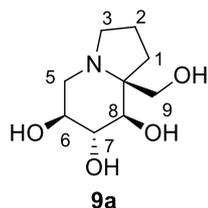


To a solution of piperidine **7b** (74 mg, 0.125 mmol) in dry and degazed (30 min of argon bubbling) DCM (6.3 mL), second generation Grubbs catalyst (5.3 mg, 0.006 mmol) was added, and the reaction was heated during 3 h at 40 °C. After cooling, the reaction mixture was filtered on a plug of silica gel (rinsed with Et₂O), then the solvents were removed in vacuo. The crude oil was purified by flash chromatography on silica gel (pentane / AcOEt) to afford **8b** (65 mg, 93%) as a colorless oil.

[α]_D²⁰ = +20.7 (*c* 0.69, CHCl₃) ; IR ν 3062 (w), 3029 (w), 2922 (w), 2854 (m), 1698 (w), 1496 (w), 1453 (m), 1067 (m) ; ¹H-NMR (400 MHz, CDCl₃) δ 3.00 (dd, *J* = 5.0 and 13.5 Hz, 1H, ⁵CH₂), 3.24 (dd, *J* = 5.0 and 13.5 Hz, 1H, ⁵CH₂), 3.35 (d, *J* = 9.0 Hz, 1H, ⁹CH₂), 3.47 (d, *J* = 9.0 Hz, 1H, ⁹CH₂), 3.76 (dd, *J* = 6.5 and 7.5 Hz, 1H, ⁷CH), 3.85 (q, *J* = 5.0 Hz, 1H, ⁶CH), 3.91 (dt, *J* = 2.0 and 15.0 Hz, 1H, ³CH₂), 3.97-4.03 (m, 2H, ³CH₂, ⁸CH), 4.32 (d, *J* = 12.0 Hz, 1H, ^{Bn}CH₂), 4.41 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 4.52 (d, *J* = 12.0 Hz, 1H, ^{Bn}CH₂), 4.58 (d, *J* = 12.0 Hz, 1H, ^{Bn}CH₂), 4.64-4.68 (m, 2H, ^{Bn}CH₂), 4.71 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 4.76 (d, *J* = 11.5 Hz, 1H, ^{Bn}CH₂), 5.75 (br d, *J* = 6.0 Hz, 1H, ¹CH), 5.89 (br d, *J* = 6.0 Hz, 1H, ²CH), 7.19-7.36 (m, 20H, ^{Ar}CH) ; ¹³C-NMR (100 MHz, CDCl₃) δ 49.8 (⁵CH₂), 62.5 (³CH₂), 71.8 (^{Bn}CH₂), 73.3 (^{Bn}CH₂), 73.7 (^{Bn}CH₂), 74.3 (^{Bn}CH₂), 75.3 (^{8a}Cq), 75.5 (⁹CH₂), 78.8 (⁸CH), 83.5 (⁶CH, ⁷CH), 127.5-127.9 and 128.3-128.5 (^{Ar}CH), 129.0 (²CH), 129.9 (¹CH), 138.7, 138.7, 138.9 and 139.0 (^{Ar}Cq) ; HRMS (ESI) Calcd for C₃₇H₄₀NO₄: *m/z* = 562.2952 [M+H]⁺; Found *m/z* = 562.2954.

2f- Hydrogenolysis of 1,2-unsaturated indolizidines **8a** and **8b**

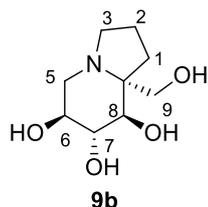
(6*S*, 7*R*, 8*R*, 8*aS*)-8*a*-(hydroxymethyl)-octahydroindolizine-6,7,8-triol (**9a**)



To a solution of **8a** (19 mg, 0.033 mmol) in dry MeOH (0.6 mL), was added 20% Pd(OH)₂/C (8 mg, 0.011 mmol) and HCl (2 M in Et₂O, 0.025 mL, 0.050 mmol). The suspension was stirred overnight under hydrogen (5 bars) then filtered over Celite. The Celite was rinsed with MeOH and the filtrate was concentrated under vacuum. The residue was purified through a column of DOWEX 50W-X8 ion exchange resin (H⁺ form), eluting with water and aqueous ammonia (1 N). Evaporation afforded **9a** (5.4 mg, 80%) as a beige solid.

$[\alpha]_D^{20} = +21.7$ (*c* 0.66, MeOH); IR ν 3362 (s), 2923 (m), 2853 (m), 1035 (m); ¹H-NMR (500 MHz, CD₃OD) δ 1.79-1.93 (m, 2H, ²CH₂), 1.95-2.01 (m, 2H, ¹CH₂), 2.76 (dd, *J* = 11.0 and 13.5 Hz, 1H, ⁵CH₂), 3.02 (dd, *J* = 5.0 and 13.5 Hz, 1H, ⁵CH₂), 3.06-3.14 (m, 2H, ³CH₂), 3.42 (d, *J* = 9.5 Hz, 1H, ⁸CH), 3.52 (t, *J* = 9.5 Hz, 1H, ⁷CH), 3.66-3.74 (m, 3H, ⁶CH, ⁹CH₂); ¹³C-NMR (125 MHz, CD₃OD) δ 22.1 (²CH₂), 33.2 (¹CH₂), 49.8 (⁵CH₂), 52.8 (³CH₂), 60.8 (⁹CH₂), 68.4 (^{8a}Cq), 68.8 (⁶CH), 75.3 (⁸CH), 77.1 (⁷CH); HRMS (ESI) Calcd for C₉H₁₈NO₄: *m/z* = 204.1230 [M+H]⁺; Found *m/z* = 204.1228.

(6*S*, 7*R*, 8*R*, 8*aR*)-8*a*-(hydroxymethyl)-octahydroindolizine-6,7,8-triol (**9b**)



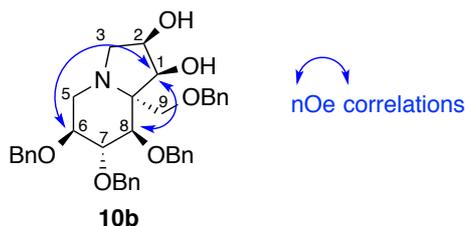
To a solution of **8b** (50 mg, 0.089 mmol) in dry MeOH (1.4 mL), was added 20% Pd(OH)₂/C (17.9 mg, 0.025 mmol) and HCl (2 M in Et₂O, 0.066 mL, 0.133 mmol). The suspension was stirred overnight under hydrogen (5 bars) then filtered over Celite. The Celite was rinsed with MeOH and the filtrate was concentrated under vacuum. The residue was purified through a column of DOWEX 50W-X8 ion exchange resin (H⁺ form), eluting with water and aqueous ammonia (1 N). Evaporation afforded **9b** (16 mg, 89%) as a beige solid.

$[\alpha]_D^{20} = +27.9$ (*c* 0.41, MeOH); IR ν 3330 (s), 2924 (m), 1652 (w), 1031 (m); ¹H-NMR (500 MHz, CD₃OD) δ 1.46-1.53 (m, 1H, ¹CH₂), 1.67-1.76 (m, 1H, ²CH₂), 1.88-1.96 (m, 1H, ¹CH₂), 1.98-2.08 (m, 1H, ²CH₂), 2.46 (t, *J* = 11.0 Hz, 1H, ⁵CH₂), 2.80-2.89 (m, 2H, ³CH₂, ⁵CH₂), 3.09-3.18 (m, 1H, ³CH₂), 3.33-3.41 (m, 2H, ⁷CH, ⁹CH₂), 3.43-3.49 (m, 1H, ⁶CH), 3.53 (d, *J* = 11.5 Hz, 1H, ⁹CH₂), 3.76 (d, *J* = 9.5 Hz, 1H, ⁸CH); ¹³C-NMR (125 MHz, CD₃OD) δ 21.0 (²CH₂), 26.1 (¹CH₂), 53.8 (³CH₂), 55.9

(⁵CH₂), 63.6 (⁹CH₂), 71.0 (⁶CH), 73.0 (⁸CH), 73.2 (^{8a}Cq), 76.5 (⁷CH) ; **HRMS (ESI)** Calcd for C₉H₁₈NO₄: *m/z* = 204.1236 [M+H]⁺; Found *m/z* = 204.1234.

2g- Dihydroxylation of compound **8b**

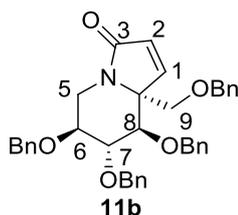
(1S,2R,6S,7R,8R,8aS)-6,7,8-tris(benzyloxy)-8a-[(benzyloxy)methyl]-octahydroindolizine-1,2-diol (10b)



Compound **8b** (50 mg, 0.089 mmol) was dissolved in dry DCM (0.9 mL). Then, TMEDA (0.051 mL, 0.338 mmoles) was added and the mixture was cooled to -78 °C. Subsequently, OsO₄ was added (2.5% in *t*BuOH, 1.90 g, 0.187 mmoles), the temperature was allowed to rise until -20 °C and the mixture was stirred 3 h at this temperature. After this time, ethylenediamine (0.070 mL, 1.048 mmoles) was added and the mixture was stirred at room temperature during 16 h. The reaction was then quenched by NaHSO₃ saturated solution (overnight). The aqueous layer was extracted three times with AcOEt. The organic layers were washed with brine, dried over MgSO₄ and the solvents were evaporated under reduced pressure. The crude oil was purified by flash column chromatography on silica gel (DCM / MeOH) to afford **10b** (33 mg, 62%) yields as a colorless oil.

[α]_D²⁰ = +14.3 (*c* 0.82, CHCl₃) ; **IR** ν 3404 (br), 3087 (w), 3062 (w), 3029 (w), 2922 (m), 2857 (m), 1496 (w), 1453 (m), 1364 (w), 1063 (s) ; **¹H-NMR (500 MHz, toluene-d₈)** δ 2.74 (dd, *J* = 9.0 and 11.0 Hz, 1H, ⁵CH₂), 2.81 (dd, *J* = 4.0 and 10.0 Hz, 1H, ³CH₂), 3.00 (dd, *J* = 4.0 and 11.0 Hz, ⁵CH₂), 3.15 (d, *J* = 10.0 Hz, 1H, ³CH₂), 3.23 (d, *J* = 8.5 Hz, 1H, ¹OH), 3.52-3.57 (m, 2H, ⁷CH, ⁹CH₂), 3.59 (d, *J* = 9.5 Hz, 1H, ⁹CH₂), 3.75 (d, *J* = 9.5 Hz, 1H, ²OH), 3.77-3.83 (m, 2H, ⁶CH, ⁸CH), 4.01-4.07 (m, 1H, ²CH), 4.16 (d, *J* = 12.0 Hz, 1H, ^{Bn}CH₂), 4.21 (d, *J* = 12.0 Hz, 1H, ^{Bn}CH₂), 4.35 (d, *J* = 12.0 Hz, 1H, ^{Bn}CH₂), 4.41-4.48 (m, 3H, ^{Bn}CH₂), 4.51 (d, *J* = 12.0 Hz, 1H, ^{Bn}CH₂), 4.67 (dd, *J* = 5.0 and 8.0 Hz, 1H, ¹CH), 7.02-7.27 (m, 20H, ^{Ar}CH) ; **¹³C-NMR (125 MHz, toluene-d₈)** δ 49.5 (⁵CH₂), 60.1 (³CH₂), 67.2 (^{8a}Cq), 71.5 (²CH), 71.6 (^{Bn}CH₂), 71.9 (⁹CH₂), 72.4 (^{Bn}CH₂), 73.1 (^{Bn}CH₂), 73.8 (^{Bn}CH₂), 75.1 (¹CH), 79.7 (⁷CH), 81.1 (⁶CH), 82.2 (⁸CH), 125.4-129.2 (^{Ar}CH), 137.9, 138.6, 139.1 and 139.3 (^{Ar}Cq) ; **HRMS (ESI)** Calcd for C₃₇H₄₂NO₆: *m/z* = 596.3007 [M+H]⁺; Found *m/z* = 596.3002.

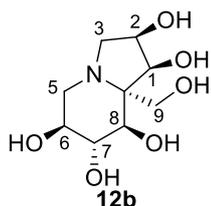
(6*R*,7*R*,8*S*,8*aR*)-6,7,8-tris(benzyloxy)-8a-((benzyloxy)methyl)-6,7,8,8a-tetrahydroindolizin-3-one
(11b)



IR ν 3086 (w), 3062 (w), 3029 (w), 2921 (m), 2860 (m), 1689 (s), 1604 (w), 1496 (m), 1453 (m), 1092 (s); **¹H-NMR (400 MHz, CDCl₃)** δ 3.13 (dd, $J = 3.0$ and 14.5 Hz, 1H, ⁵CH₂), 3.22 (d, $J = 9.0$ Hz, 1H, ⁹CH₂), 3.57-3.79 (m, 2H, ⁶CH, ⁸CH), 3.94 (d, $J = 9.0$ Hz, 1H, ⁹CH₂), 4.17 (d, $J = 3.5$ Hz, 1H, ⁷CH), 4.33-4.48 (m, 7H, ⁵CH₂, ^{Bn}CH₂), 4.54 (d, $J = 12.0$ Hz, 1H, ^{Bn}CH₂), 4.71 (d, $J = 12.0$ Hz, 1H, ^{Bn}CH₂), 6.16 (d, $J = 6.0$ Hz, 1H, ¹CH), 7.09-7.74 (m, 21H, ²CH, ^{Ar}CH); **¹³C-NMR (100 MHz, CDCl₃)** δ 36.8 (⁵CH₂), 53.4 (^{8a}Cq), 69.4 (^{Bn}CH₂), 70.7 (^{Bn}CH₂), 71.7 (⁹CH₂), 72.7 (^{Bn}CH₂), 73.5 (^{Bn}CH₂), 74.3 (⁶CH), 74.5 (⁸CH), 75.7 (⁷CH), 126.6 (¹CH), 127.4 (²CH), 127.7-128.5 (^{Ar}CH), 137.7, 137.8, 137.9 and 138.2 (^{Ar}Cq), 171.4 (³Cq); **HRMS (ESI)** Calcd for C₃₇H₃₈NO₅: $m/z = 576.2745$ [M+H]⁺; Found $m/z = 576.2744$.

2h- Hydrogenolysis of dihydroxylated product 10b

(1*S*,2*R*,6*S*,7*R*,8*R*,8*aS*)-8a-(hydroxymethyl)-octahydroindolizine-1,2,6,7,8-pentaol (12b)



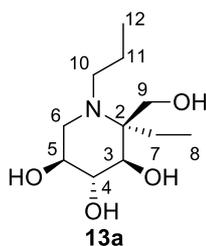
To a solution of diol **10b** (30.4 mg, 0.055 mmol) in MeOH (0.9 mL), was added 20% Pd(OH)₂/C (9 mg, 0.013 mmol) and HCl (2 M in Et₂O, 0.110 mL, 0.22 mmol). The suspension was stirred during 47 h under 1 atmosphere of hydrogen, then filtered over Celite when the reaction is over (monitoring by TLC). The Celite was rinsed with MeOH and the filtrate was concentrated under vacuum. The residue was purified through a column of DOWEX 50W-X8 ion exchange resin (H⁺ form), eluting with water and aqueous ammonia (1 N). Evaporation afforded **12b** (10.9 mg, 91% yield) as a beige solid.

$[\alpha]_D^{20} = +28.7$ (c 0.54, MeOH); **IR** ν 3385 (s), 2927 (w), 2852 (w), 1646 (w), 1436 (w), 1035 (w); **¹H-NMR (500 MHz, CD₃OD)** δ 2.65 (dd, $J = 6.0$ and 12.5 Hz, 1H, ⁵CH₂), 3.02 (dd, $J = 2.5$ and 11.5 Hz, 1H, ³CH₂), 3.10 (dd, $J = 3.5$ and 12.5 Hz, 1H, ⁵CH₂), 3.21 (dd, $J = 5.0$ and 11.5 Hz, 1H, ³CH₂), 3.59-3.64 (m, 3H, ⁶CH, ⁷CH, ⁸CH), 3.66 (d, $J = 11.5$ Hz, 1H, ⁹CH₂), 3.72 (d, $J = 11.5$ Hz, 1H, ⁹CH₂), 4.20-4.24 (m, 1H, ²CH), 4.55 (d, $J = 7.0$ Hz, 1H, ¹CH); **¹³C-NMR (125 MHz, CD₃OD)** δ 53.9 (⁵CH₂),

60.4 (³CH₂), 61.5 (⁹CH₂), 69.7 (^{8a}Cq), 70.5 (²CH), 73.0 (⁶ or ⁷ or ⁸CH), 73.1 (⁶ or ⁷ or ⁸CH), 74.0 (¹CH), 76.4 (⁶ or ⁷ or ⁸CH); **HRMS (ESI)** Calcd for C₉H₁₈NO₆: *m/z* = 236.1129 [M+H]⁺; Found *m/z* = 236.1126.

2i- Synthesis of piperidines 13a and 13b

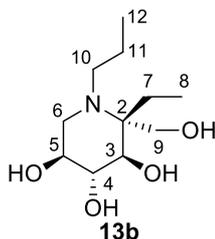
(2*S*,3*R*,4*R*,5*S*)-2-ethyl-2-(hydroxymethyl)-1-propylpiperidine-3,4,5-triol (13a)



2-Nitrobenzenesulfonyl chloride (87 mg, 0.393 mmol) was added to a solution of **7a** (32 mg, 0.054 mmol) in dry CH₃CN (0.25 mL). The resulting solution was cooled to 0 °C and hydrazine monohydrate (0.038 mL, 0.783 mmol) was added dropwise. The temperature was allowed to rise to room temperature and the mixture was stirred 28 h. Water was added, the aqueous phase was extracted three times with DCM, then the organic layers were washed with brine, dried over MgSO₄, and concentrated under vacuum. Purification by flash column chromatography (pentane / AcOEt) afforded a mixture of two compounds (26.7 mg, 83%, 1:1 mixture) resulting from the monohydrogenation of allyl group and the dihydrogenation of allyl and vinyl groups. This mixture of two products was dissolved in MeOH (0.8 mL), 20% Pd(OH)₂/C (8.4 mg, 0.012 mmol) and HCl (2 M in Et₂O, 0.054 mL, 0.108 mmol) were added, and the suspension was stirred under 1 atmosphere of hydrogen during 40 h. The mixture was filtered over Celite, the Celite was rinsed with MeOH and the filtrate was concentrated under vacuum. The residue was purified through a column of DOWEX 50W-X8 ion exchange resin (H⁺ form), eluting with water and aqueous ammonia (1 N). Evaporation afforded **13a** (7.5 mg, 60%) as a beige solid.

[α]_D²⁰ = -57.5 (*c* 0.36, MeOH); **IR** ν 3304 (s), 2958 (s), 2932 (s), 2872 (m), 2831 (m), 1473 (w), 1376 (w), 1157 (w), 1097 (w), 1040 (w), 1006 (m); **¹H-NMR (500 MHz, CD₃OD)** δ 0.86 (t, *J* = 7.5 Hz, 3H, ⁸CH₃), 0.88 (t, *J* = 7.5 Hz, 3H, ¹²CH₃), 1.37-1.46 (m, 1H, ¹¹CH₂), 1.52-1.62 (m, 1H, ¹¹CH₂), 1.68-1.78 (m, 1H, ⁷CH₂), 1.81-1.90 (m, 1H, ⁷CH₂), 2.23-2.34 (m, 1H, ¹⁰CH₂), 2.55-2.64 (m, 1H, ⁶CH₂), 2.74-2.83 (m, 1H, ¹⁰CH₂), 2.94-3.00 (m, 1H, ⁶CH₂), 3.34 (d, *J* = 9.5 Hz, 1H, ³CH), 3.37-3.44 (m, 1H, ⁵CH), 3.57 (t, *J* = 9.0 Hz, 1H, ⁴CH), 3.76-3.83 (m, 2H, ⁹CH₂); **¹³C-NMR (125 MHz, CD₃OD)** δ 6.5 (⁸CH₃), 11.9 (¹²CH₃), 23.1 (¹¹CH₂), 23.6 (⁷CH₂), 51.8 (¹⁰CH₂), 52.2 (⁶CH₂), 62.1 (⁹CH₂), 71.9 (⁵CH), 74.5 (³CH), 76.7 (⁴CH); **HRMS (ESI)** Calcd for C₁₁H₂₄NO₄: *m/z* = 234.1700 [M+H]⁺; Found *m/z* = 234.1698.

(2*R*,3*R*,4*R*,5*S*)-2-ethyl-2-(hydroxymethyl)-1-propylpiperidine-3,4,5-triol (13b)



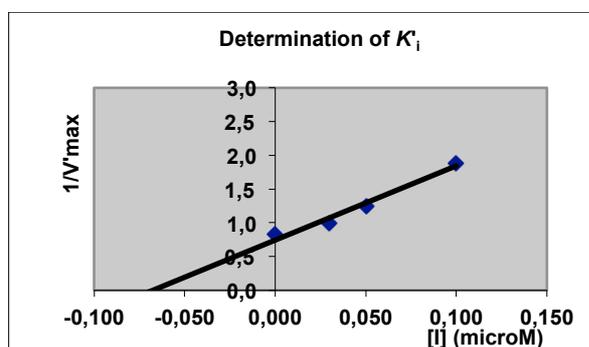
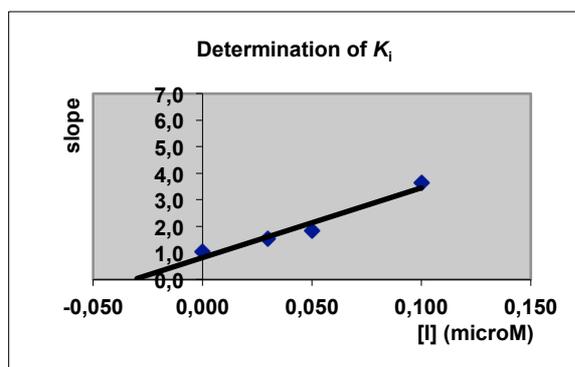
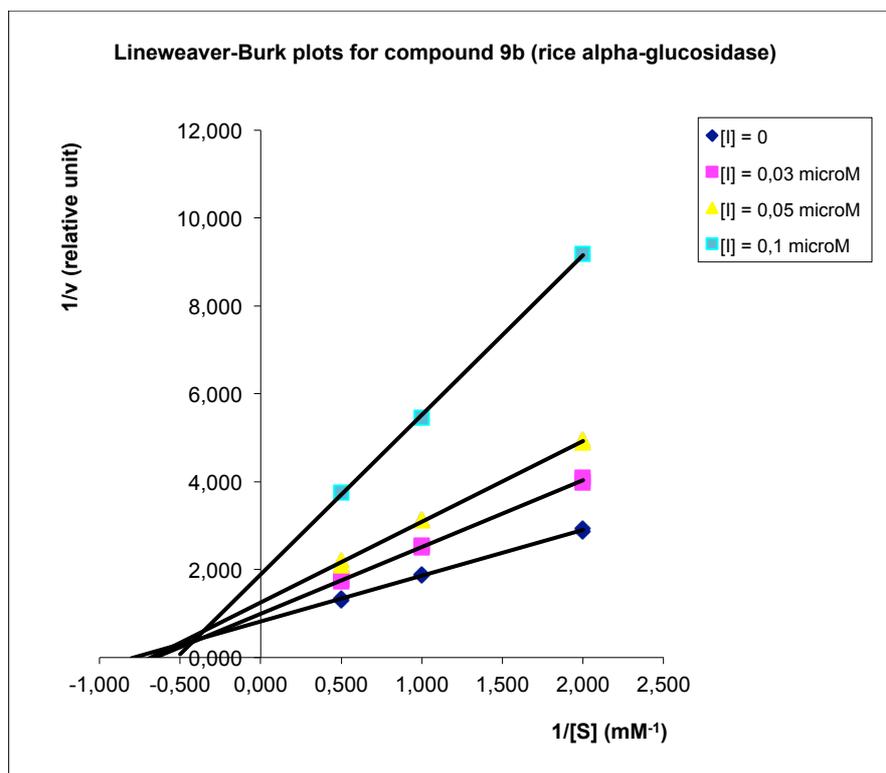
2-Nitrobenzenesulfonyl chloride (186 mg, 0.840 mmoles), was added to a solution of **7b** (62 mg, 0.105 mmol) in dry CH₃CN (0.5 mL). The resulting solution was cooled to 0 °C and hydrazine monohydrate (0.080 mL, 1.680 mmol) was added dropwise. The temperature was allowed to rise to room temperature and the mixture was stirred 28 h. Water was added, the aqueous phase was extracted three times with DCM, then the organic layers were washed with brine, dried over MgSO₄, and concentrated under vacuum. Purification by flash column chromatography (pentane / AcOEt) afforded a mixture of two compounds (58 mg, 94%, 3:7 mixture) resulting from the monohydrogenation of allyl group and the dihydrogenation of allyl and vinyl groups. This mixture of two products was dissolved in MeOH (1.5 mL), 20% Pd(OH)₂/C (16.8 mg, 0.119 mmol) and HCl (2 M in Et₂O, 0.200 mL, 0.400 mmol) were added, and the suspension was stirred under 1 atmosphere of hydrogen during 48 h. The mixture was filtered over Celite, the Celite was rinsed with MeOH and the filtrate was concentrated under vacuum. The residue was purified through a column of DOWEX 50W-X8 ion exchange resin (H⁺ form), eluting with water and aqueous ammonia (1 N). Evaporation afforded **13b** (11.9 mg, 49%) as a beige solid.

$[\alpha]_D^{20} = -40.7$ (*c* 0.60, MeOH) ; **IR** ν 3363 (s), 2962 (m), 2932 (m), 2874 (m), 2826 (w), 1653 (w), 1464 (w), 1379 (w), 1097 (w), 1048 (w), 1016 (w) ; **¹H-NMR (500 MHz, CD₃OD)** δ 0.90 (t, *J* = 7.5 Hz, 3H, ¹²CH₃), 0.96 (t, *J* = 7.5 Hz, 3H, ⁸CH₃), 1.39-1.50 (m, 1H, ¹¹CH₂), 1.51-1.60 (m, 1H, ¹¹CH₂), 1.61-1.75 (m, 2H, ⁷CH₂), 2.26-2.34 (m, 1H, ¹⁰CH₂), 2.42-2.51 (m, 1H, ⁶CH₂), 2.76-2.85 (m, 1H, ¹⁰CH₂), 2.93-3.00 (m, 1H, ⁶CH₂), 3.40-3.52 (m, 3H, ³CH, ⁴CH, ⁵CH), 3.65 (d, *J* = 11.0 Hz, 1H, ⁹CH₂), 3.79 (d, *J* = 11.0 Hz, 1H, ⁹CH₂) ; **¹³C-NMR (125 MHz, CD₃OD)** δ 9.6 (⁸CH₃), 11.9 (¹²CH₃), 19.2 (⁷CH₂), 23.2 (¹¹CH₂), 52.0 (⁶CH₂), 52.2 (¹⁰CH₂), 62.5 (⁹CH₂), 71.5 (⁵CH), 74.9 (³CH), 76.4 (⁴CH) ; **HRMS (ESI)** Calcd for C₁₁H₂₄NO₄: *m/z* = 234.1700 [M+H]⁺; Found *m/z* = 234.1696.

3- Glycosidase inhibitory activities: standard assay

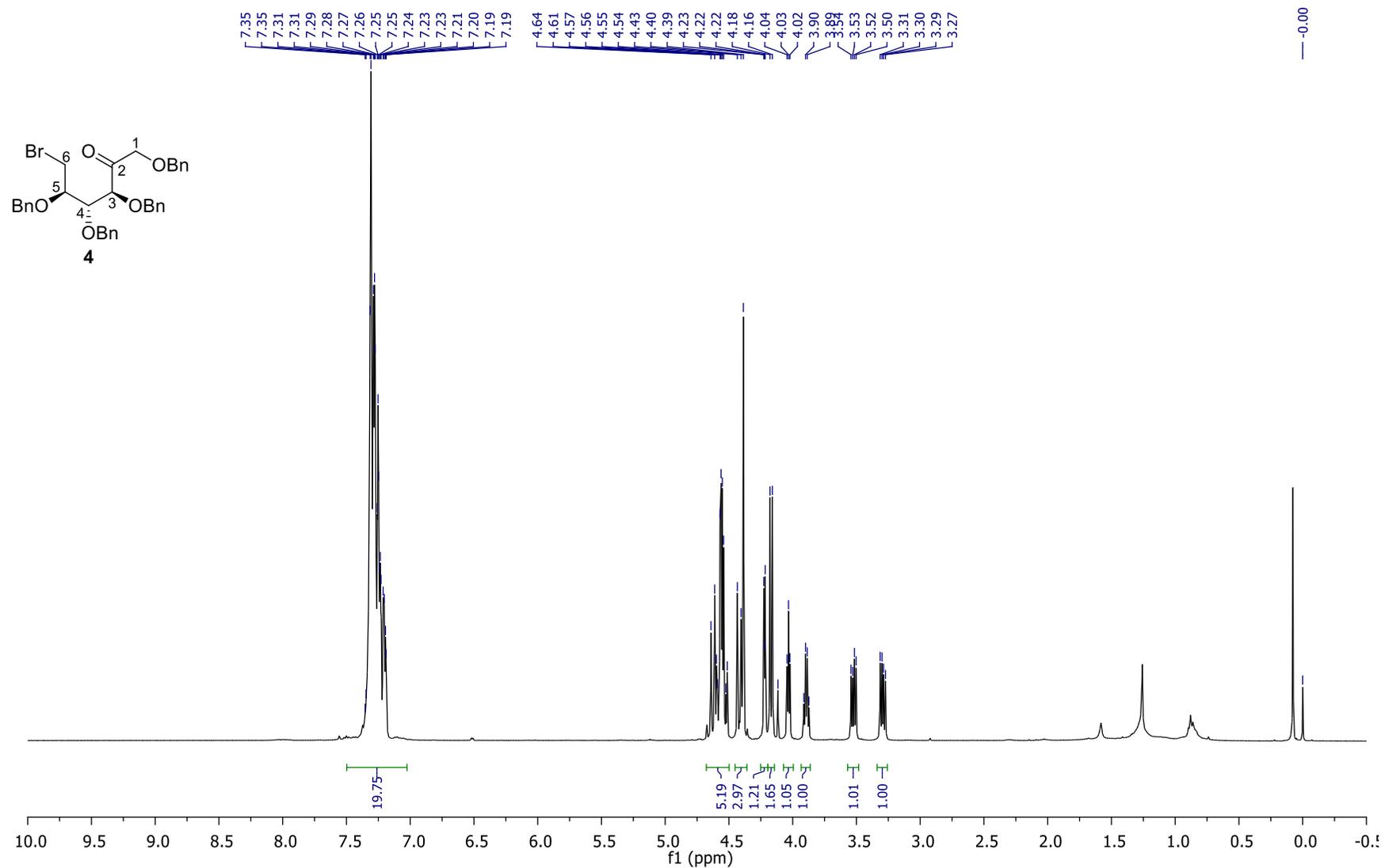
α -Glucosidase (from rice and from *Saccharomyces cerevisiae*), β -glucosidase (from almond), β -galactosidase (from *Aspergillus oryzae*), α -mannosidase (from Jack bean), β -mannosidase (from *Helix pomatia*), hesperidinase (α -rhamnosidase from *Aspergillus niger*) and the *p*-nitrophenyl glycosides used for the bioassays were purchased from Sigma Chemical Co. The Nitrophenol experimental procedure was used for the measurement of glycosidase activity with some modifications. In a typical experiment, the glycosidase (0.013 U/mL) was pre-incubated at 33 °C for 5 min in the presence of the inhibitor in 50 mM acetate buffer (pH 5.65). The reaction was started by addition of the appropriate *p*-nitrophenyl glycoside substrate (2 mM) to a final volume of 250 μ l. The reaction was stopped after 15 min by addition of 400 μ l of 0.4 M Na₂CO₃. The released *p*-nitrophenolate was quantified by UV spectrophotometry at 410 nm. In a first series of experiments, the compounds were tested at 1 mM and the results are expressed as % inhibition vs control. In case of complete inactivation (inhibition >96%), the IC₅₀ value was determined after assaying decreasing concentrations of inhibitor and exploiting the results by regression analysis of 1/v against [I] (Dixon plot).

4- Determination of kinetic parameters for inhibitor 9b

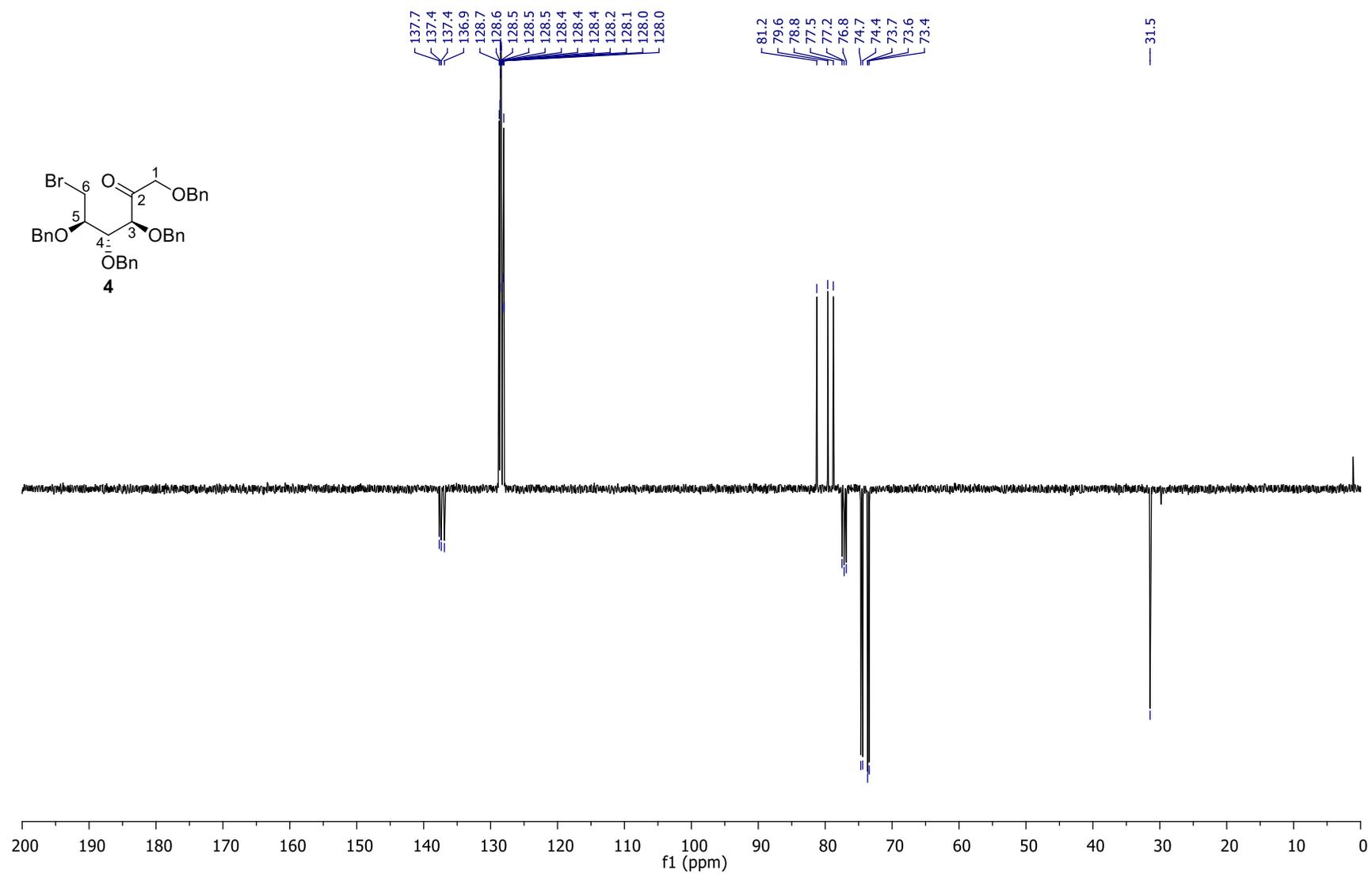


5- Copies of NMR spectra

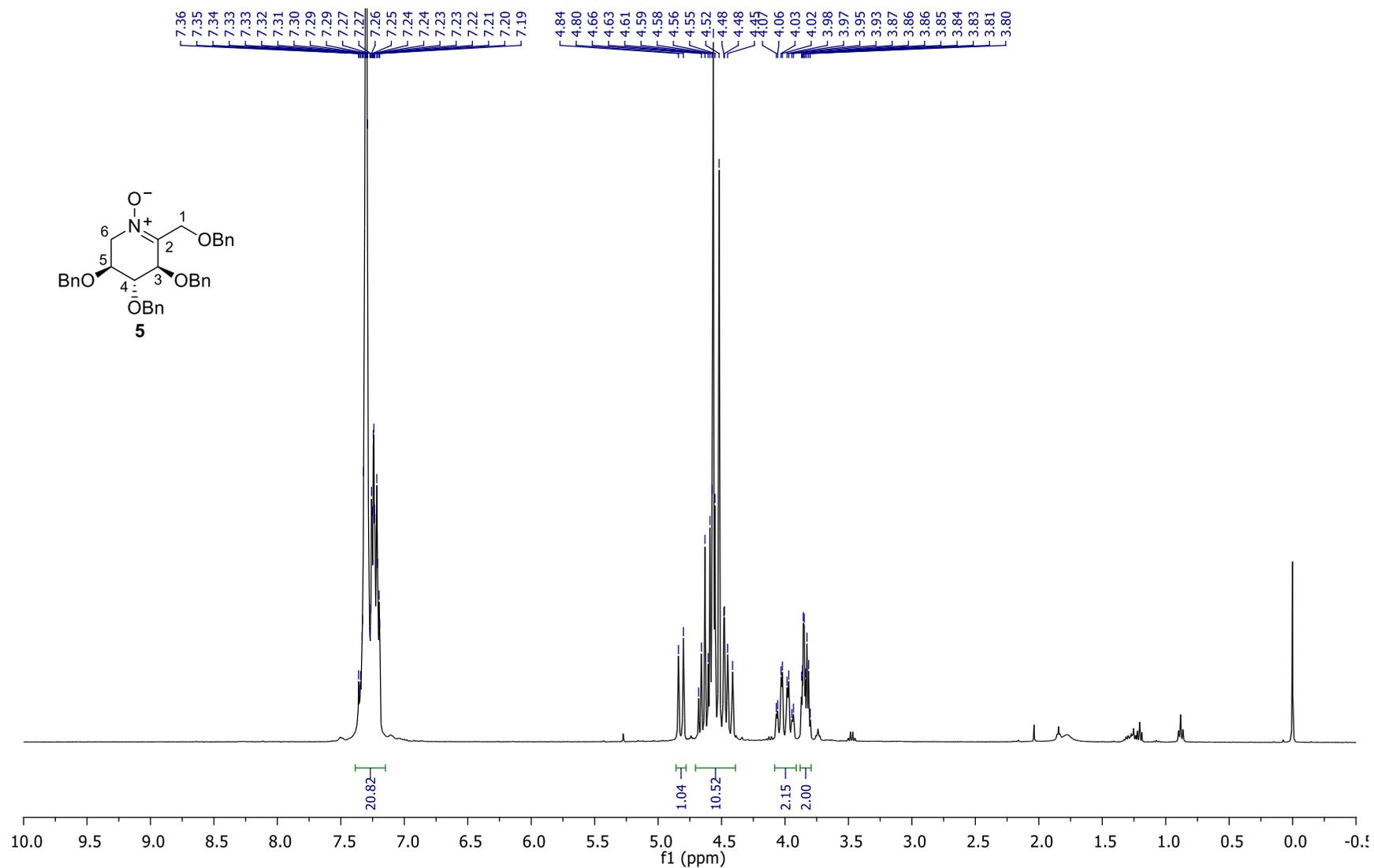
¹H NMR (CDCl₃, 400 MHz)



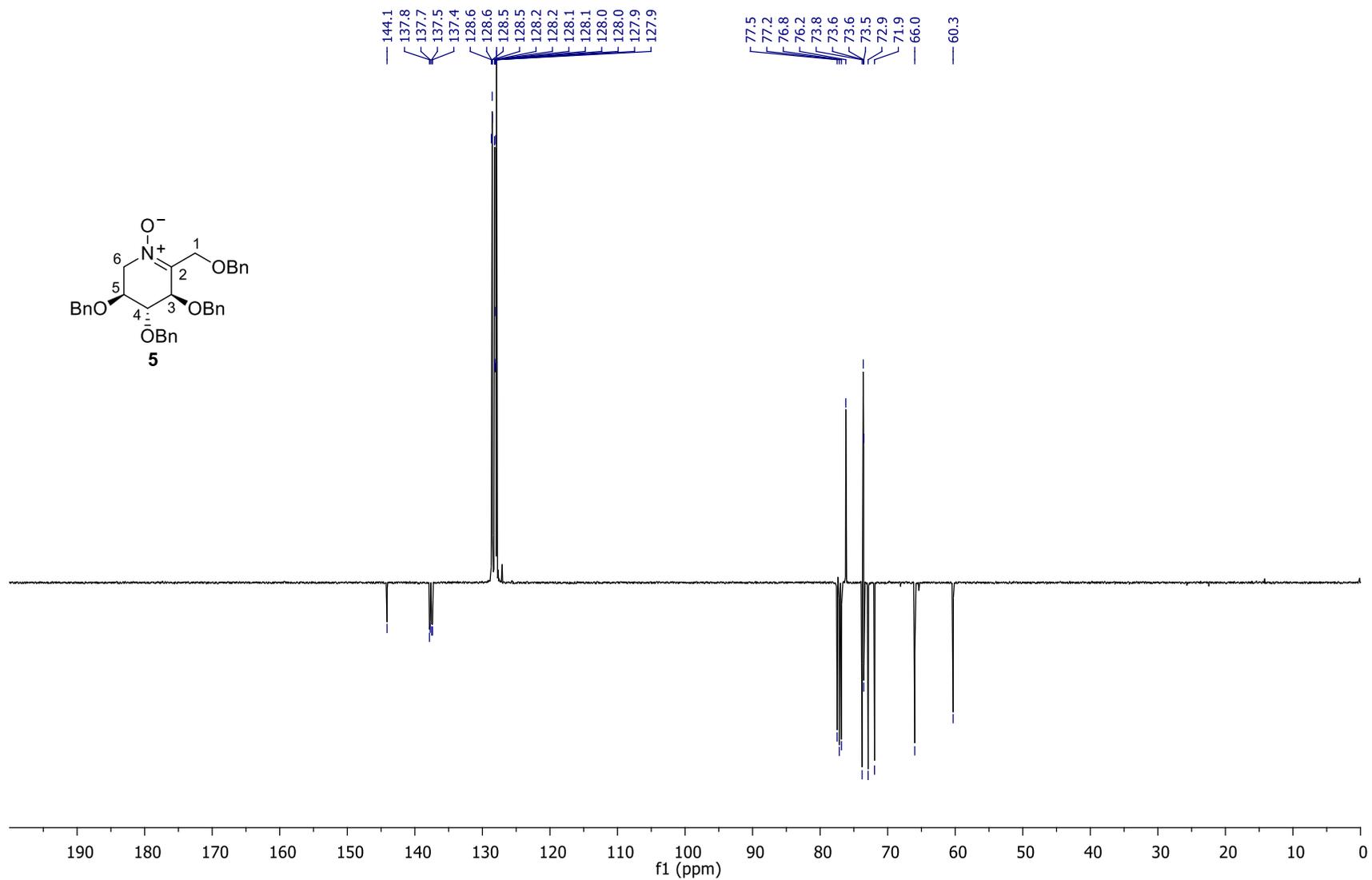
^{13}C NMR (CDCl_3 , 100 MHz)



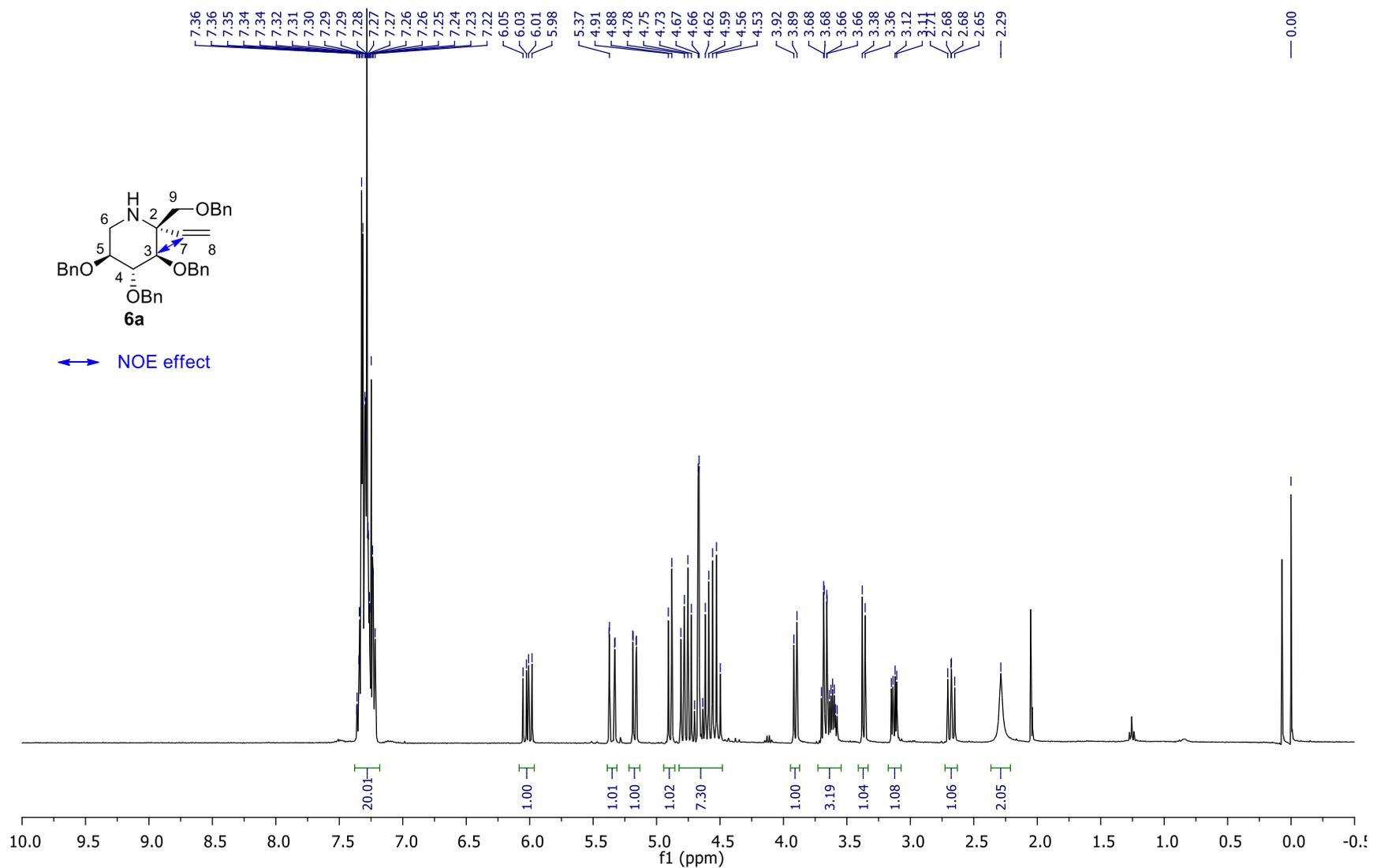
^1H NMR (CDCl_3 , 400 MHz)



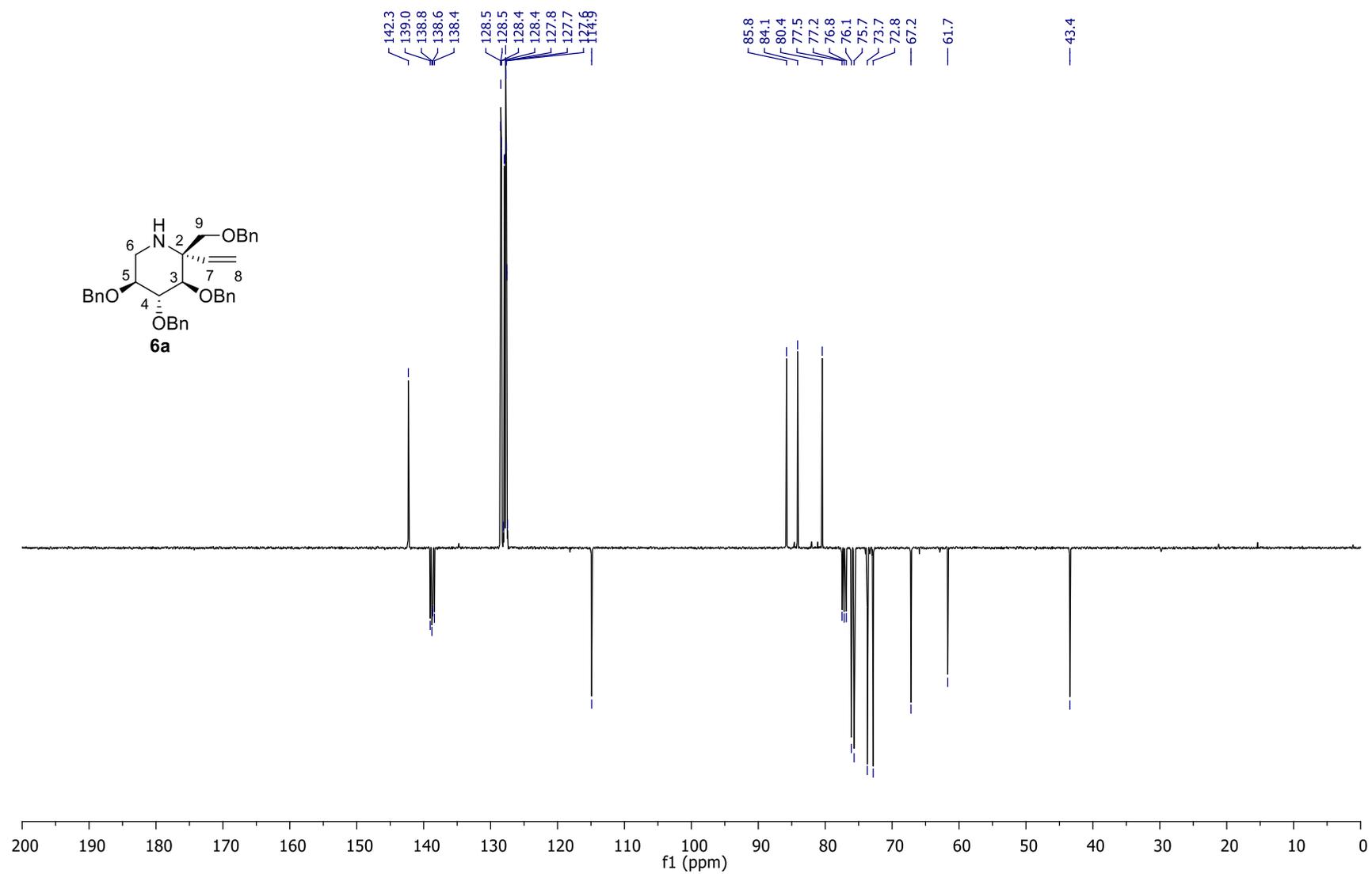
^{13}C NMR (CDCl_3 , 100 MHz)



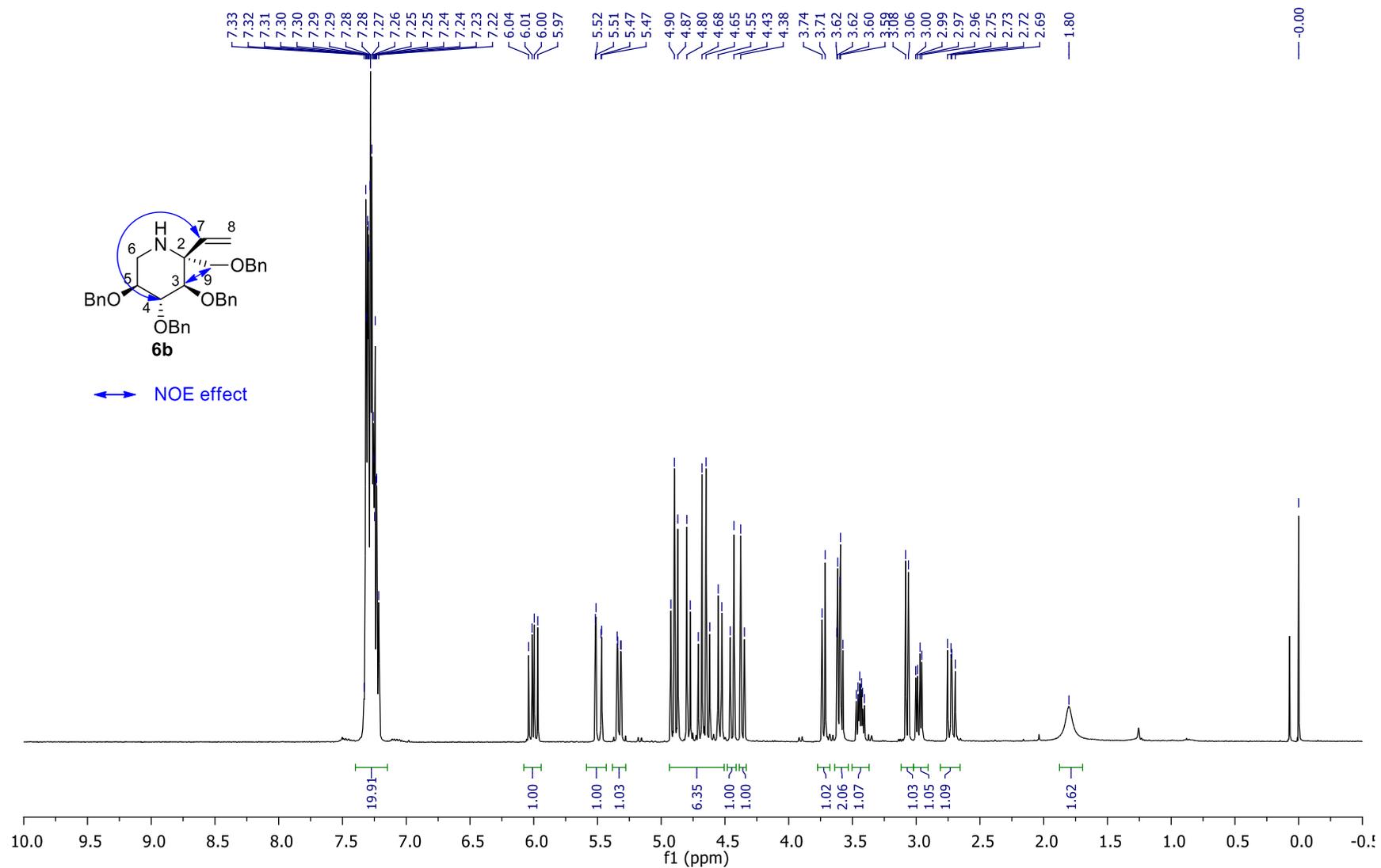
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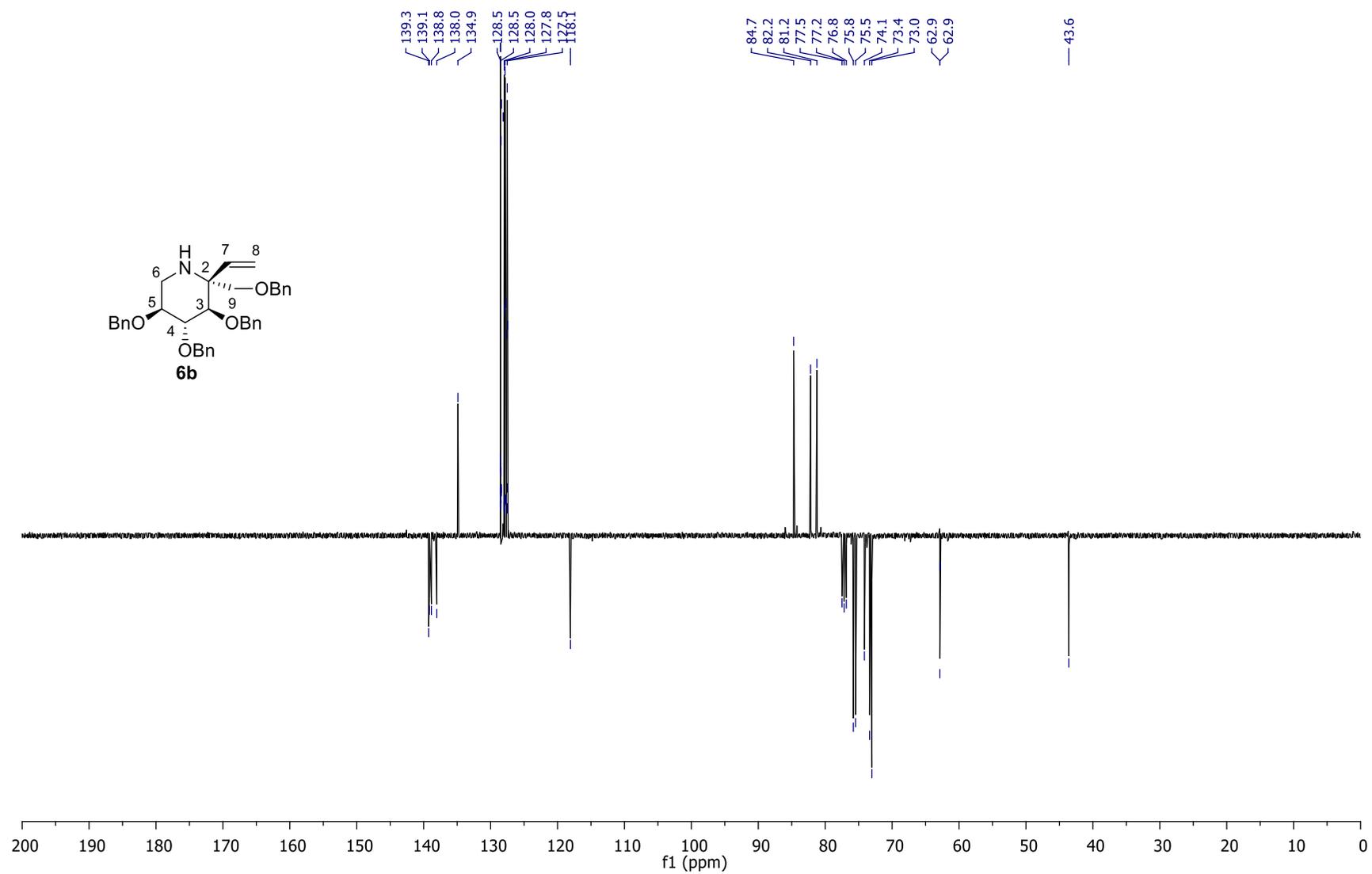
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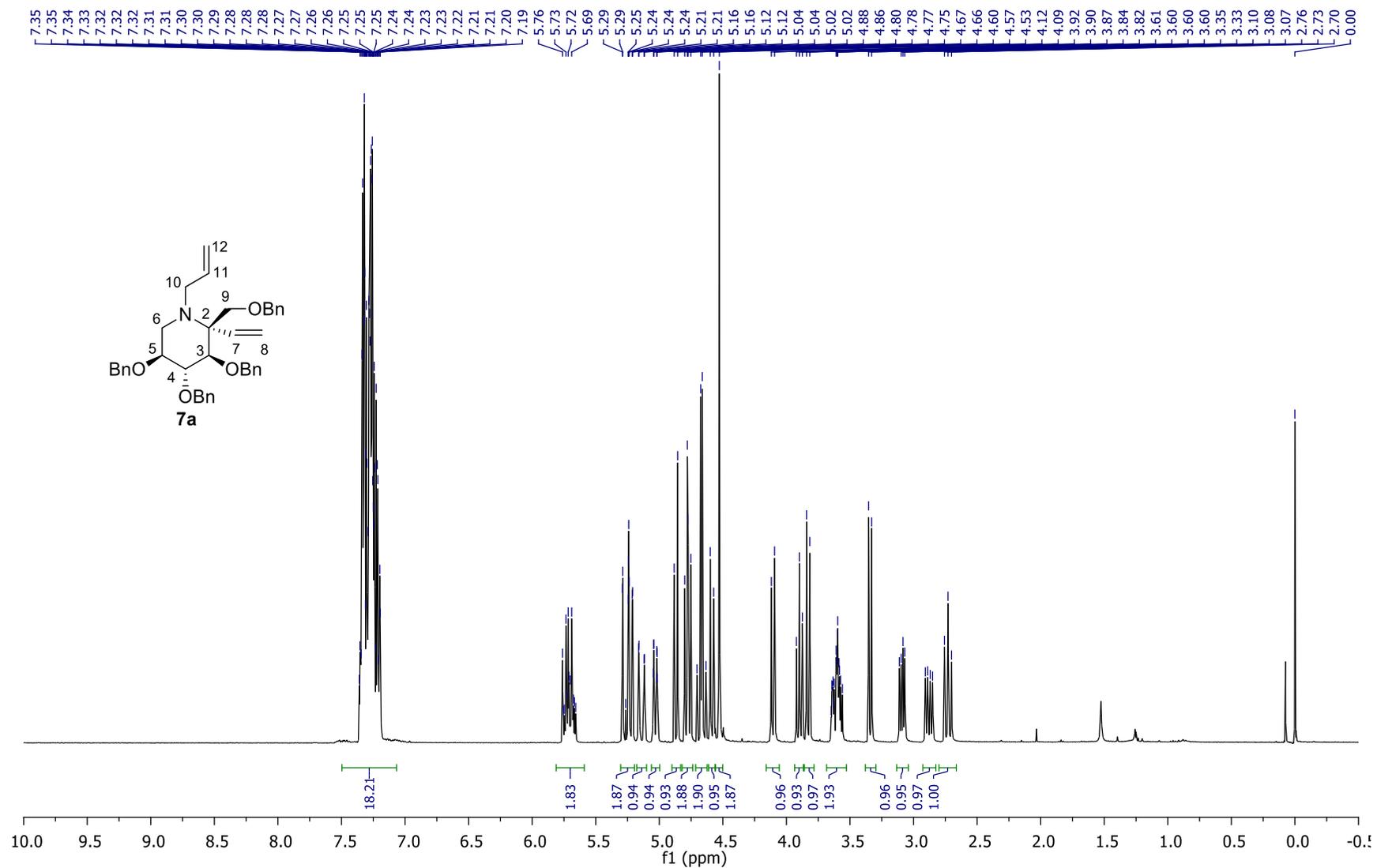
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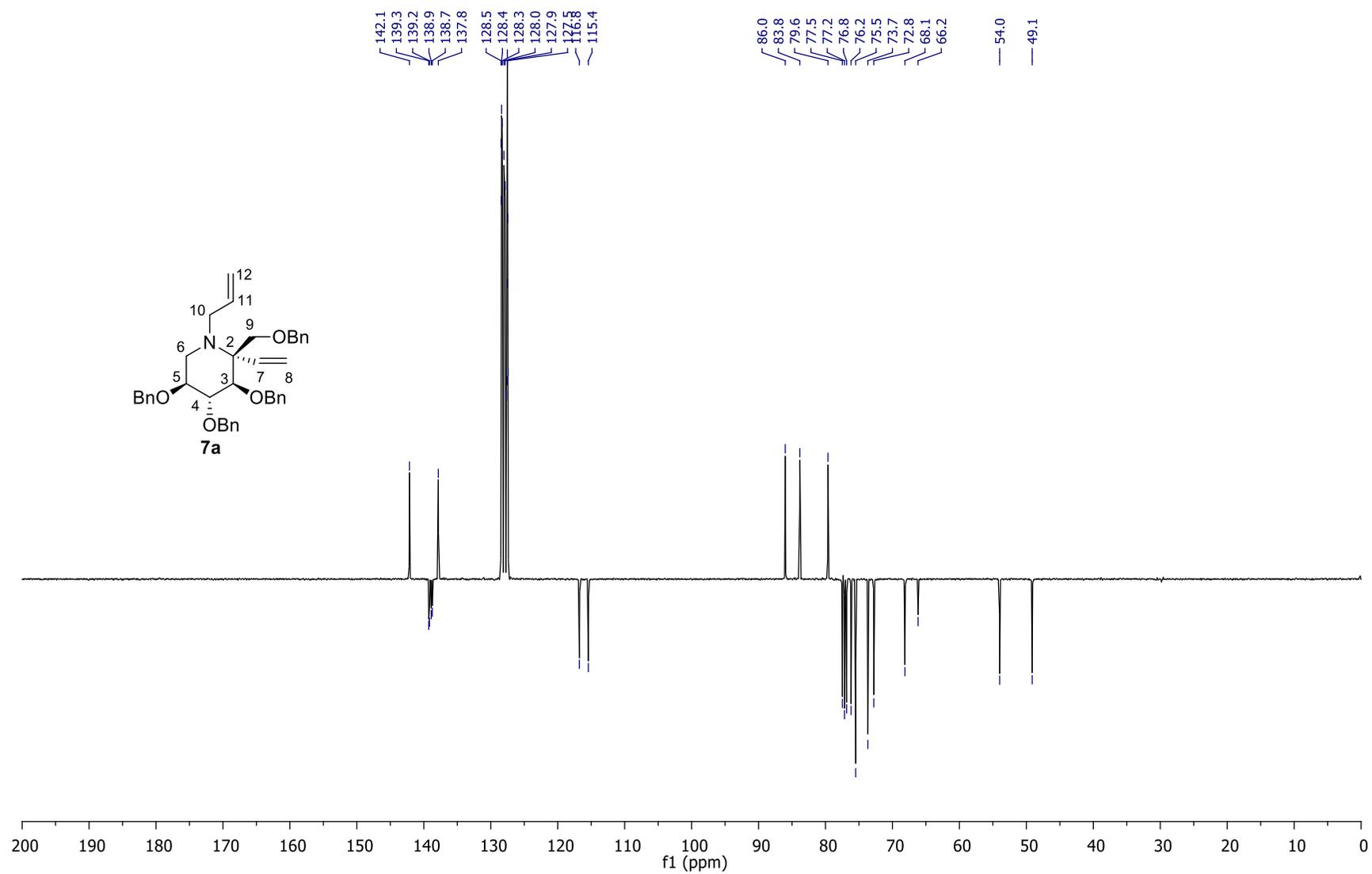
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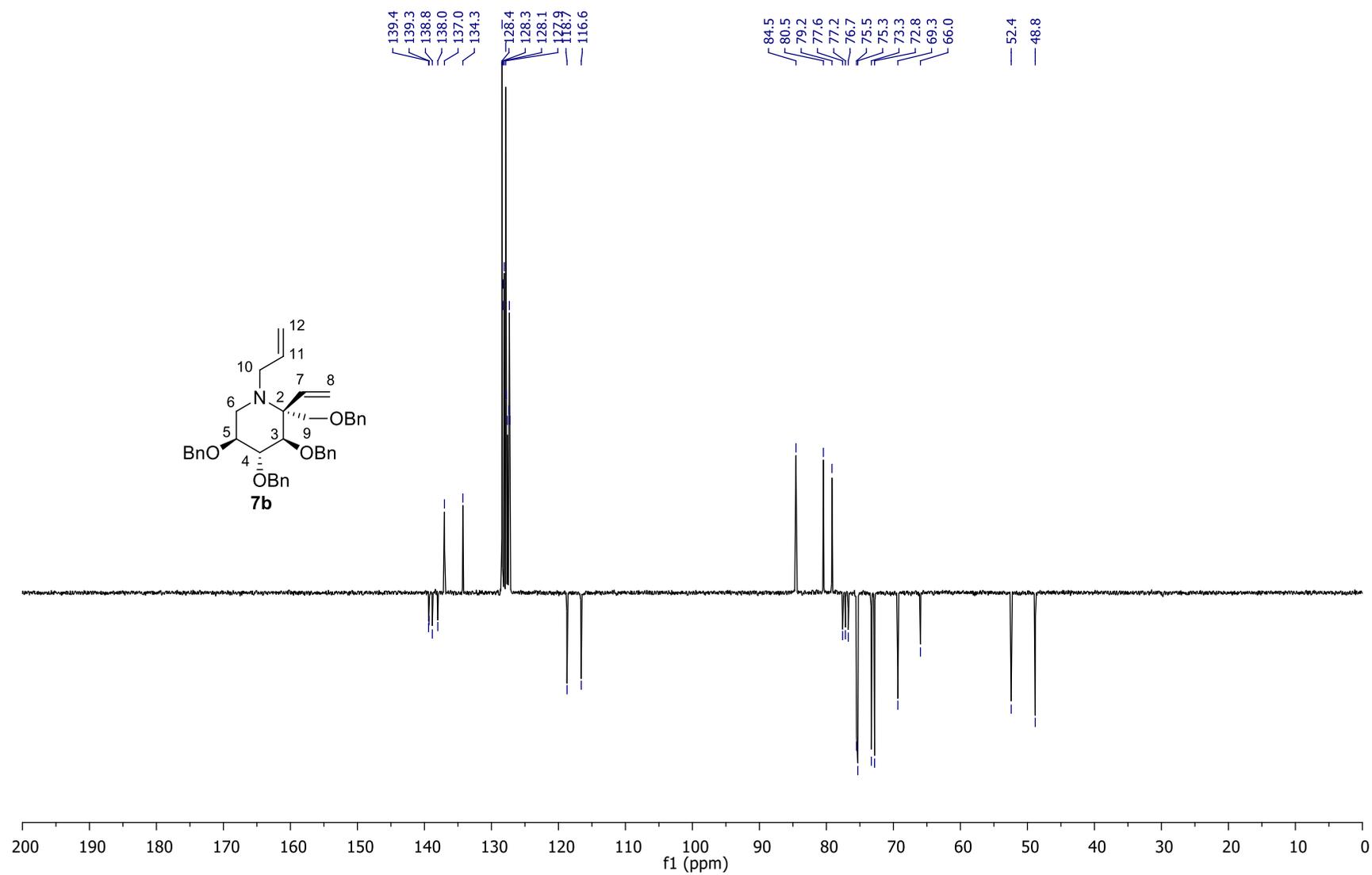
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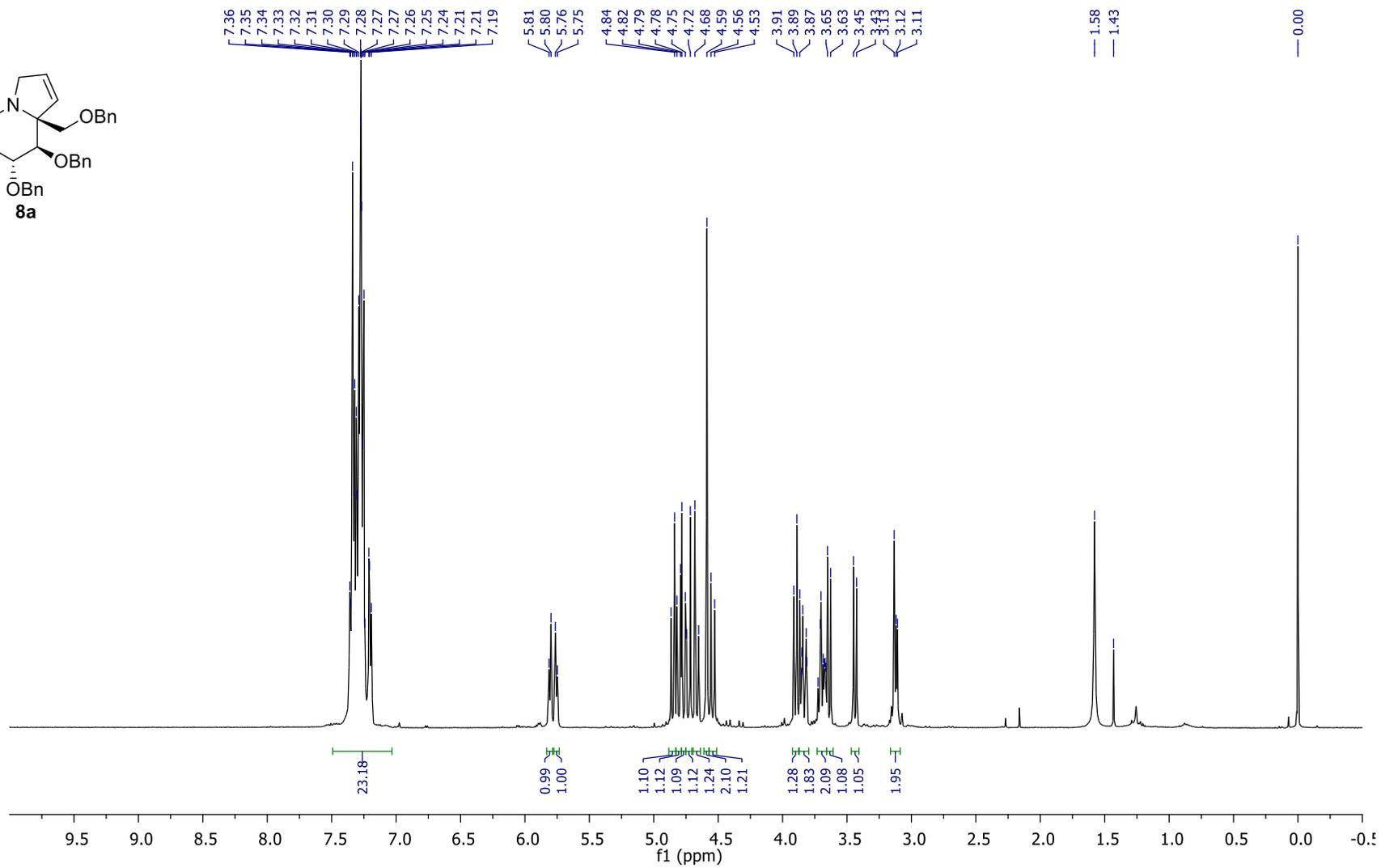
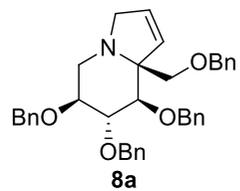
^{13}C NMR (CDCl_3 , 100 MHz)



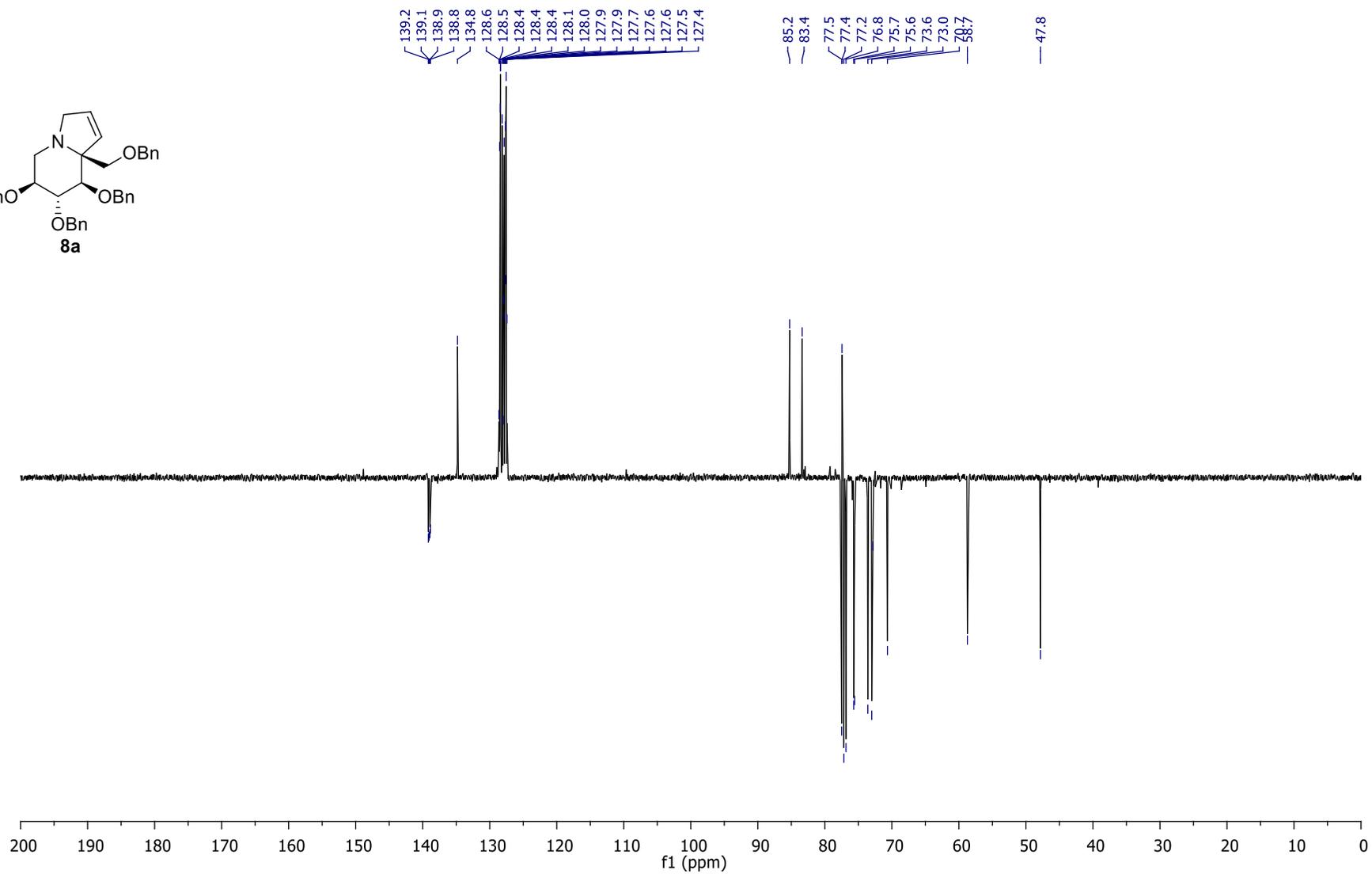
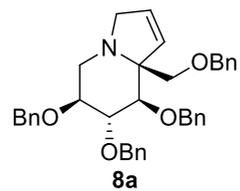
^{13}C NMR (CDCl_3 , 100 MHz)



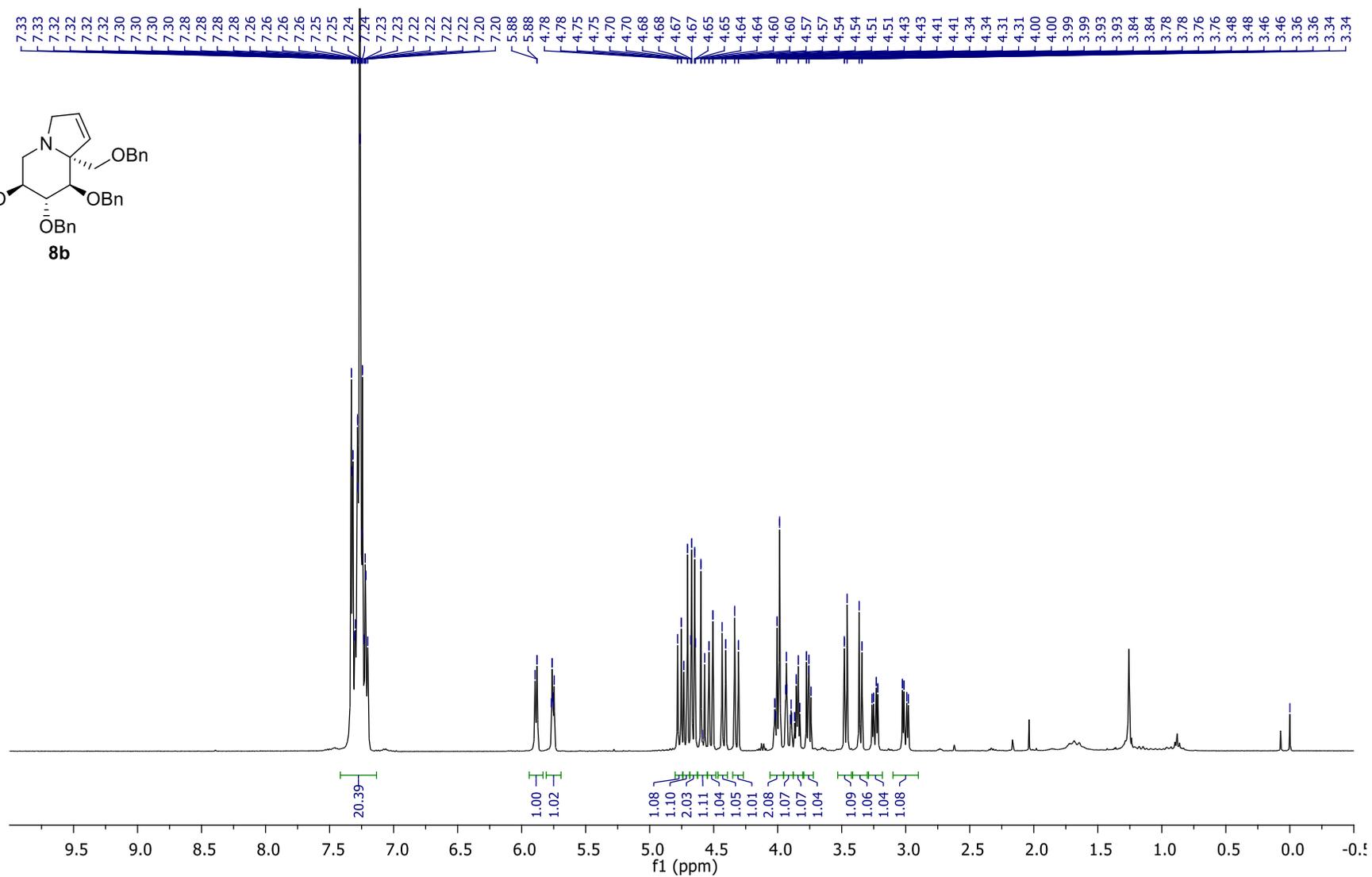
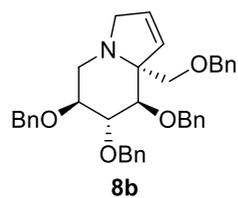
¹H NMR (CDCl₃, 400 MHz)



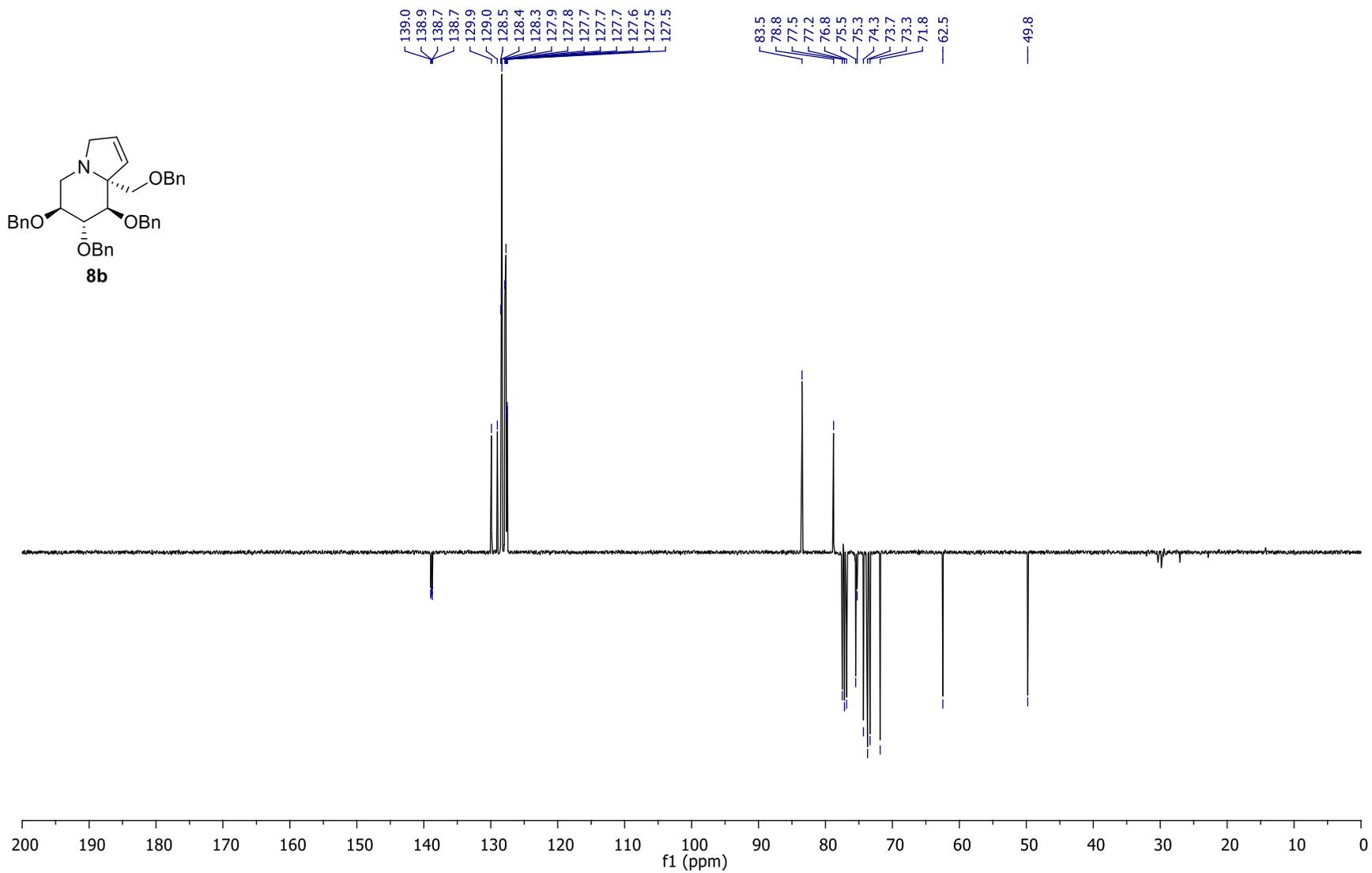
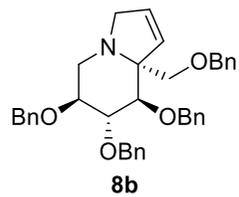
^{13}C NMR (CDCl_3 , 100 MHz)



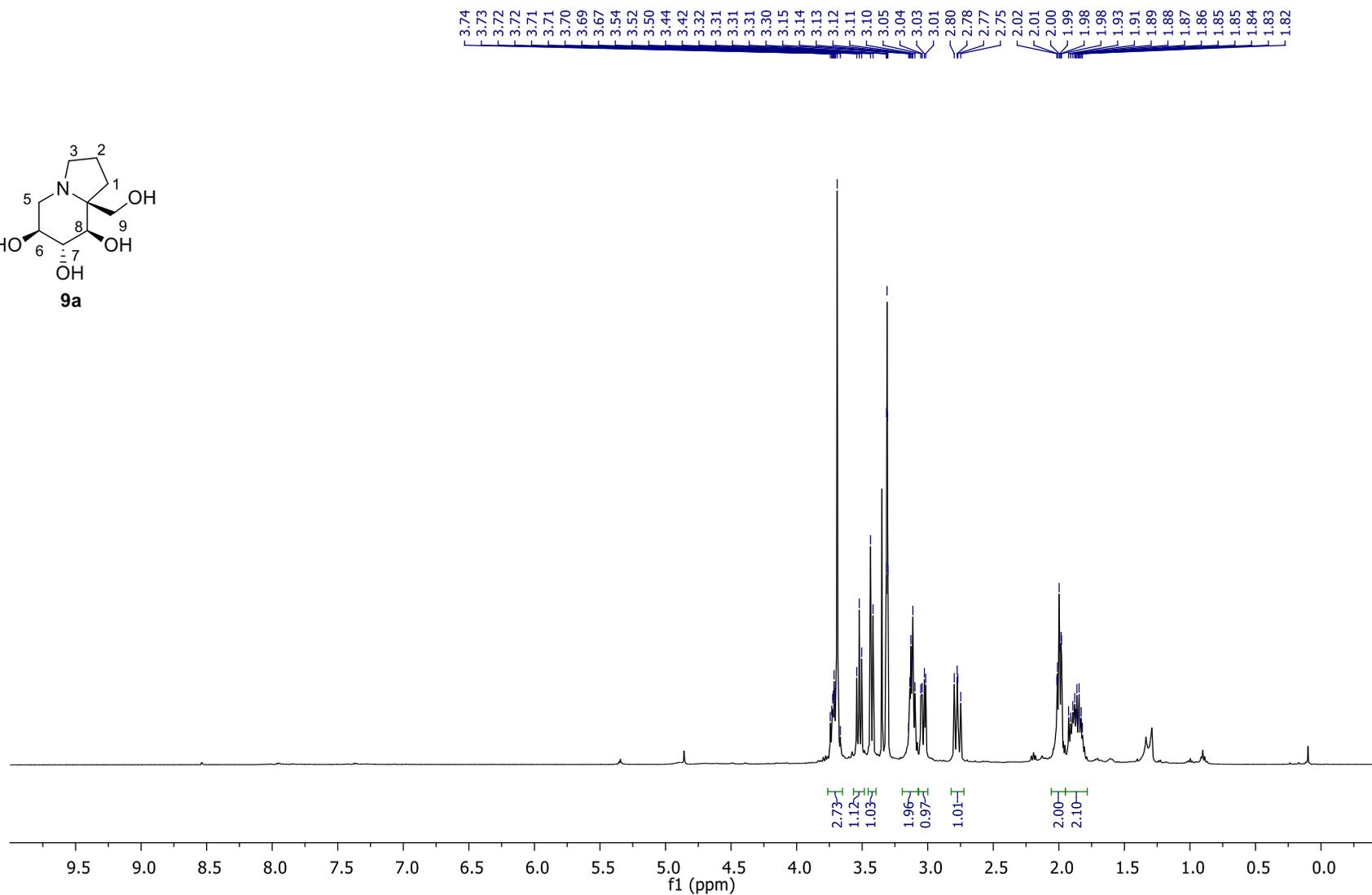
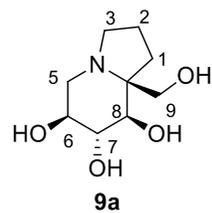
¹H NMR (CDCl₃, 400 MHz)



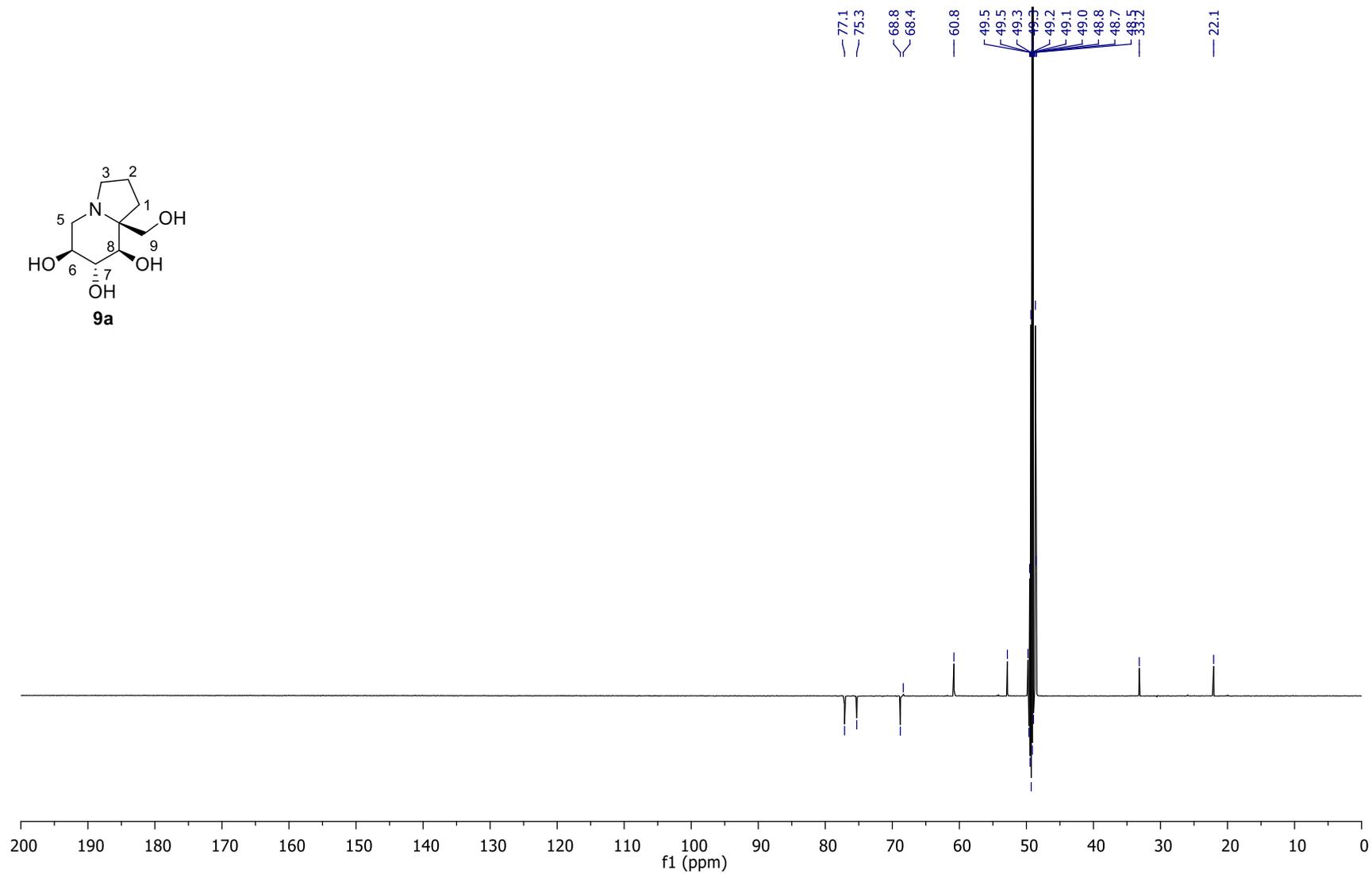
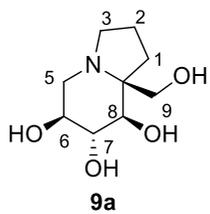
^{13}C NMR (CDCl_3 , 100 MHz)



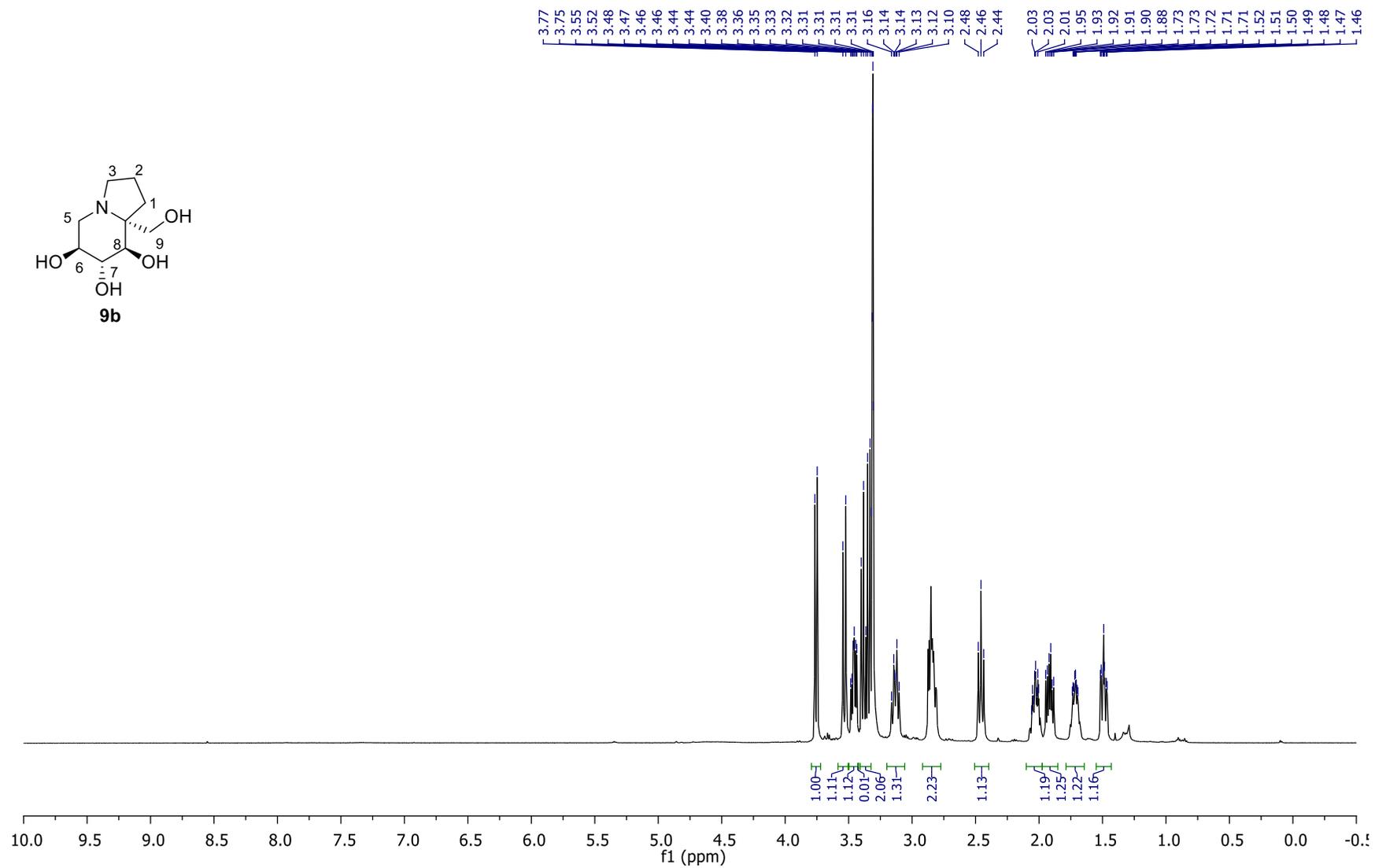
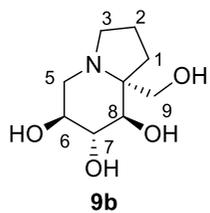
^1H NMR (CD_3OD , 500 MHz)



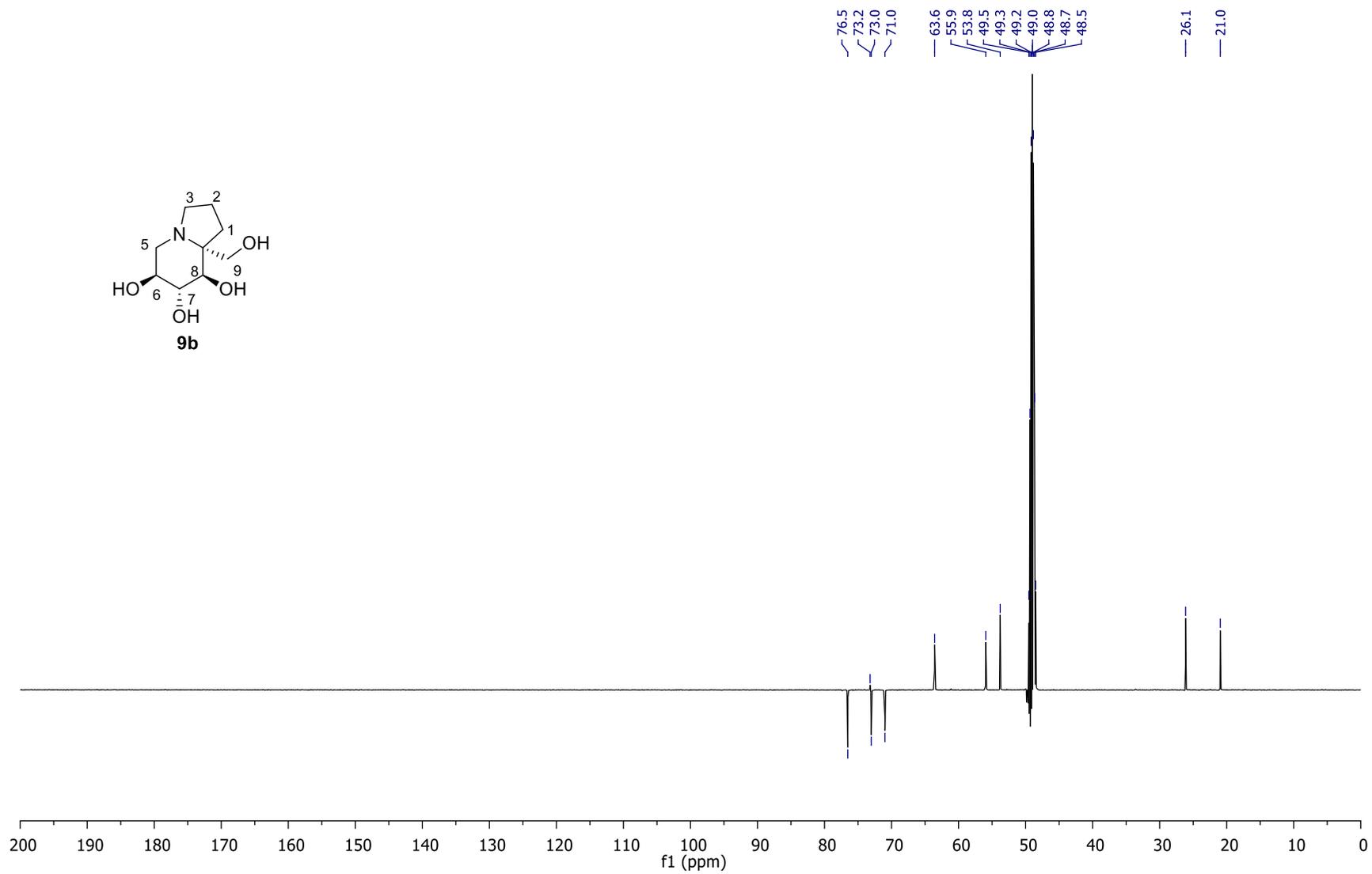
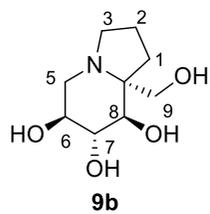
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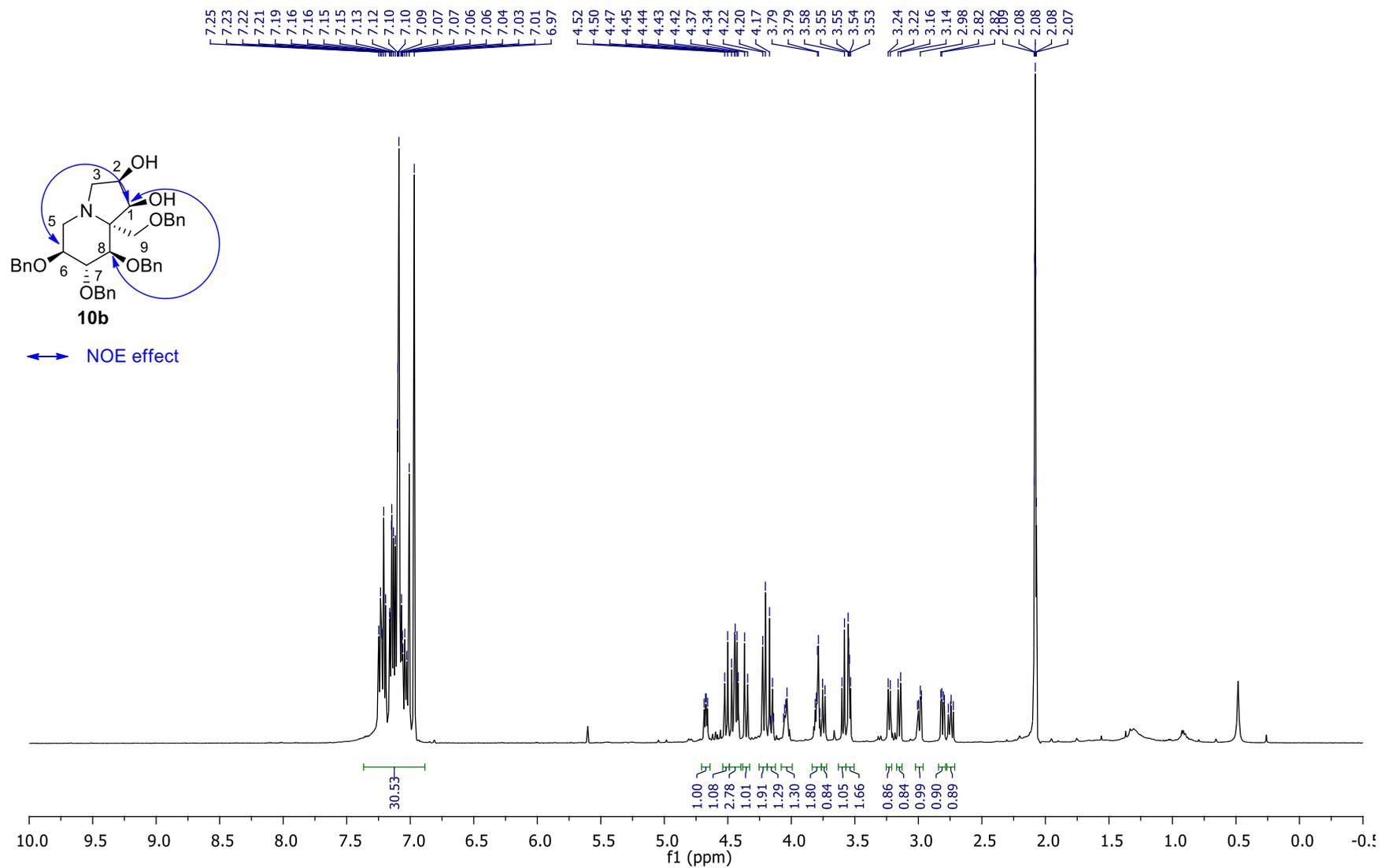
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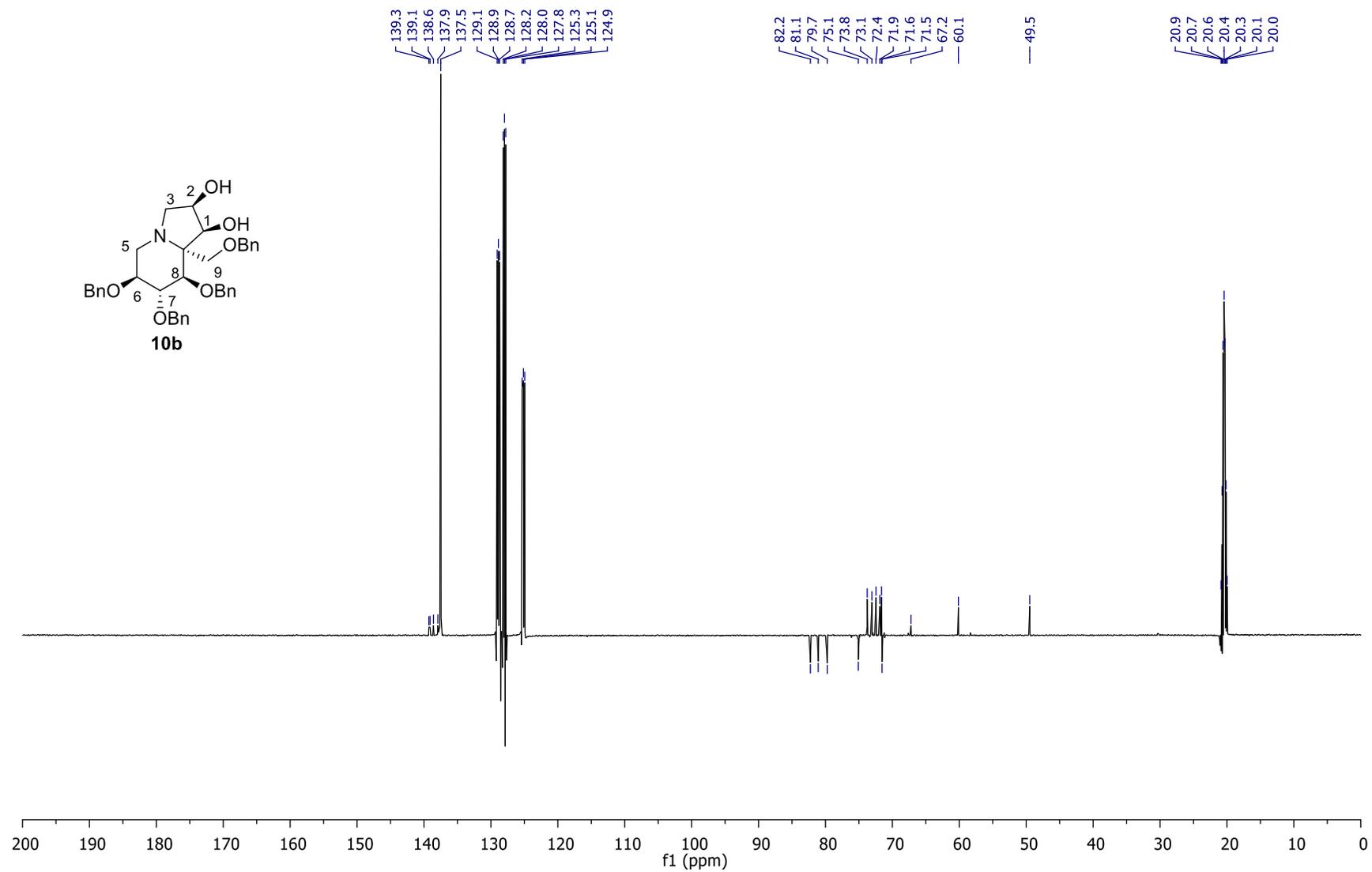
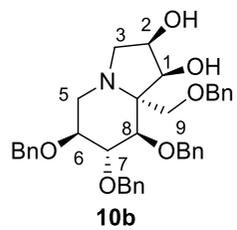
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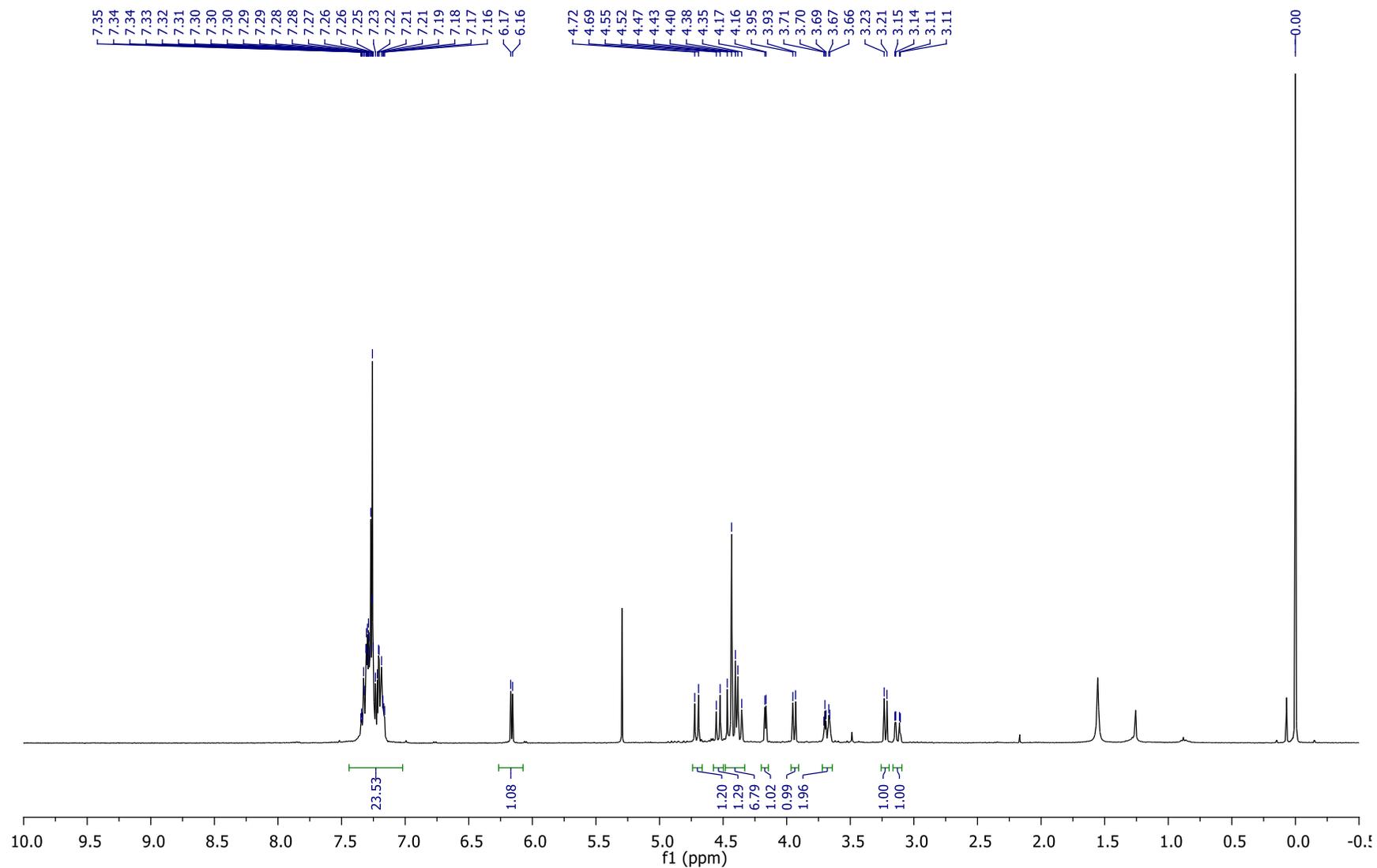
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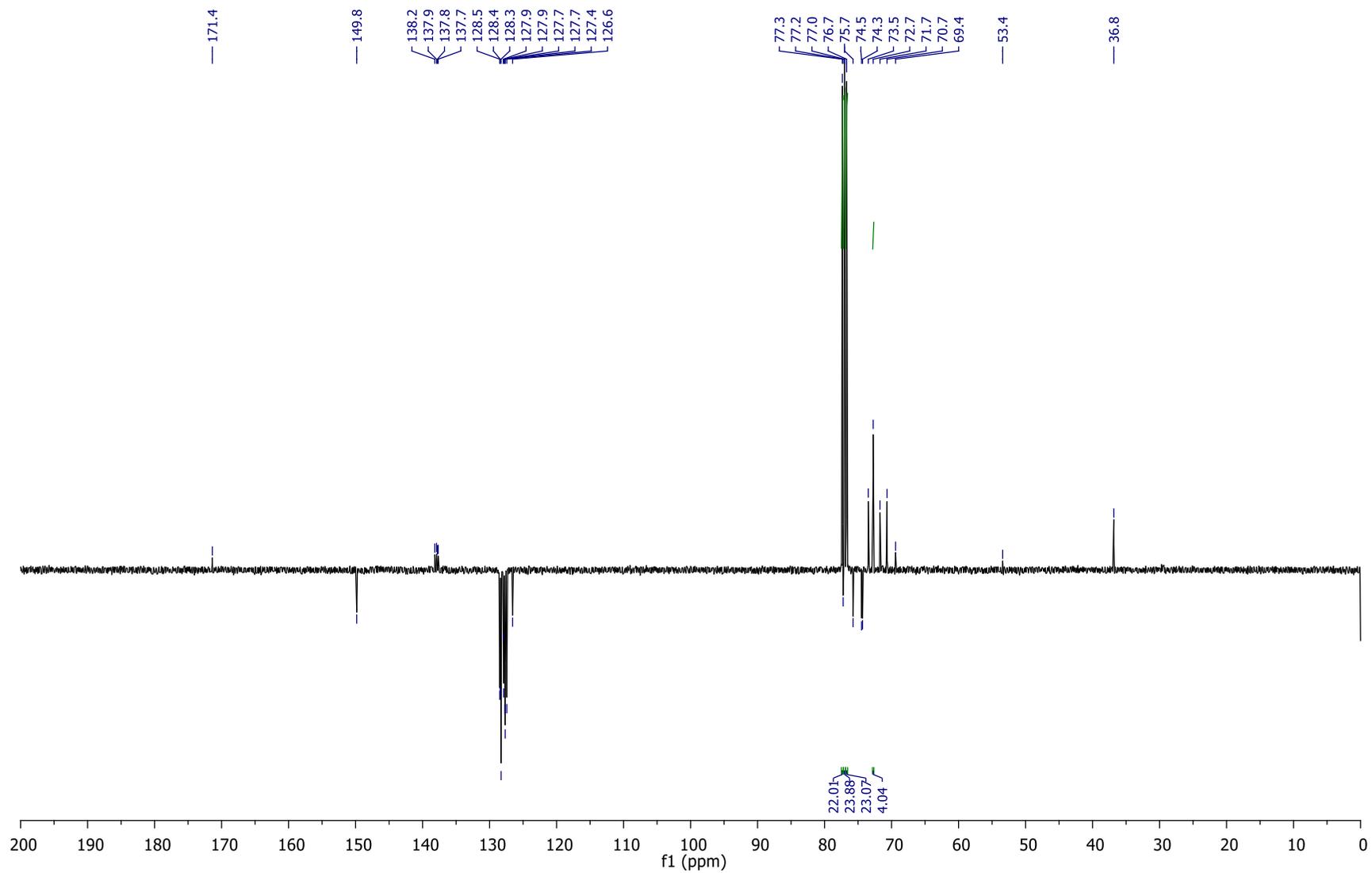
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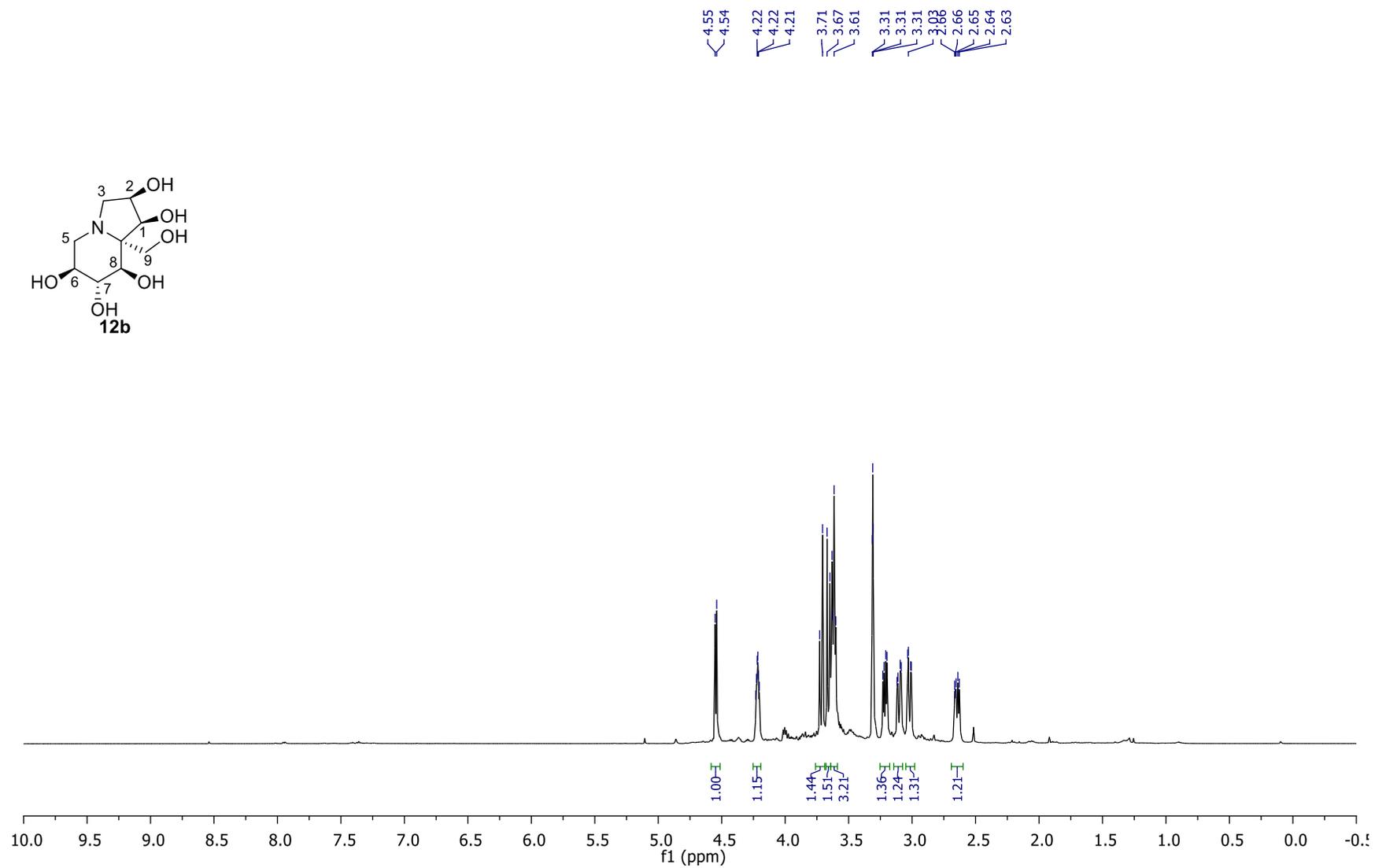
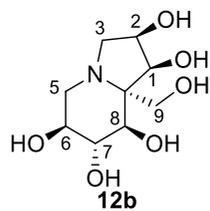
¹H NMR (CDCl₃, 400 MHz)



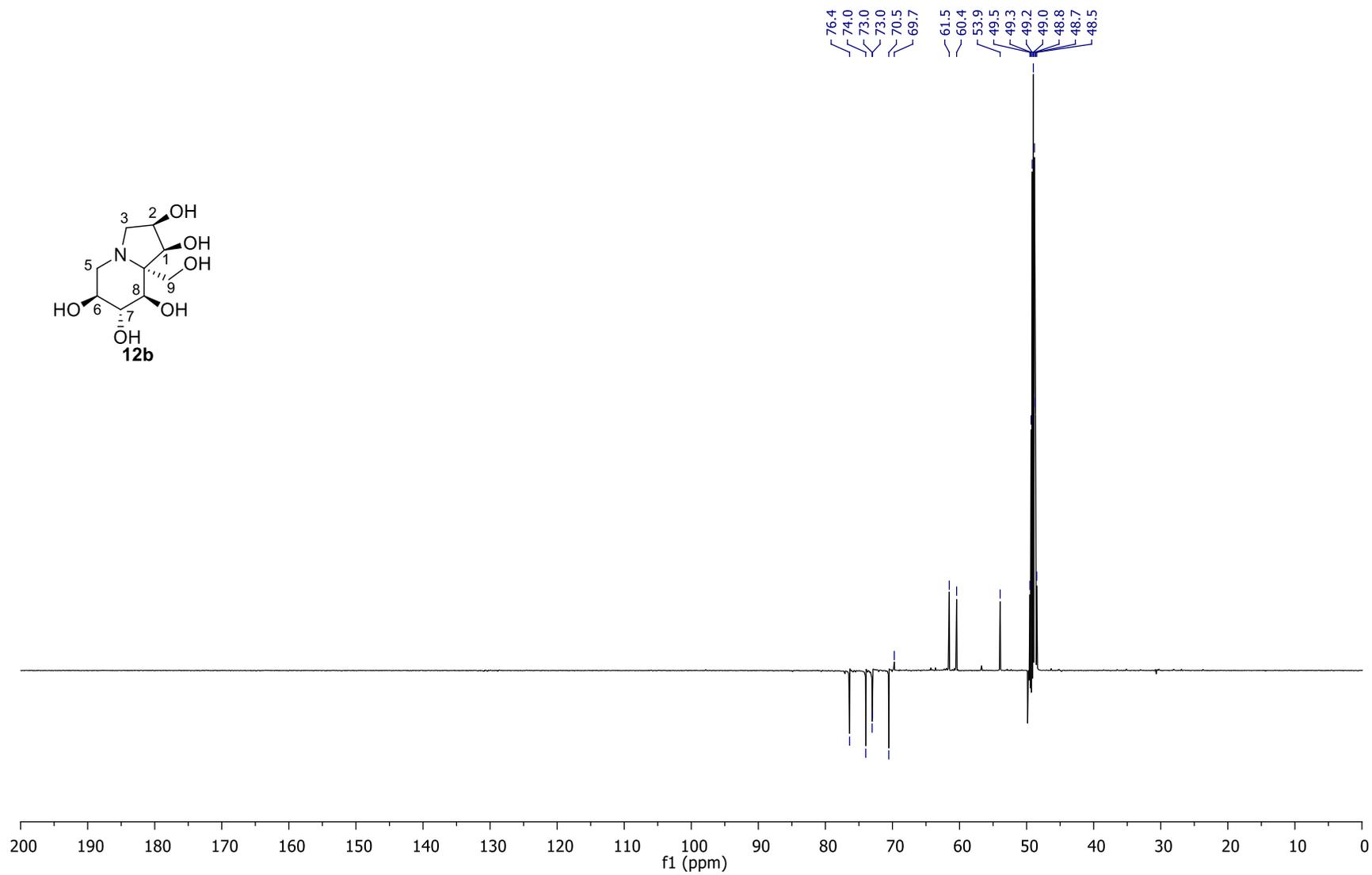
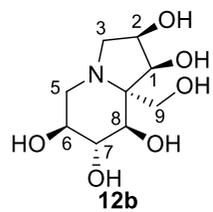
^{13}C NMR (CDCl_3 , 100 MHz)



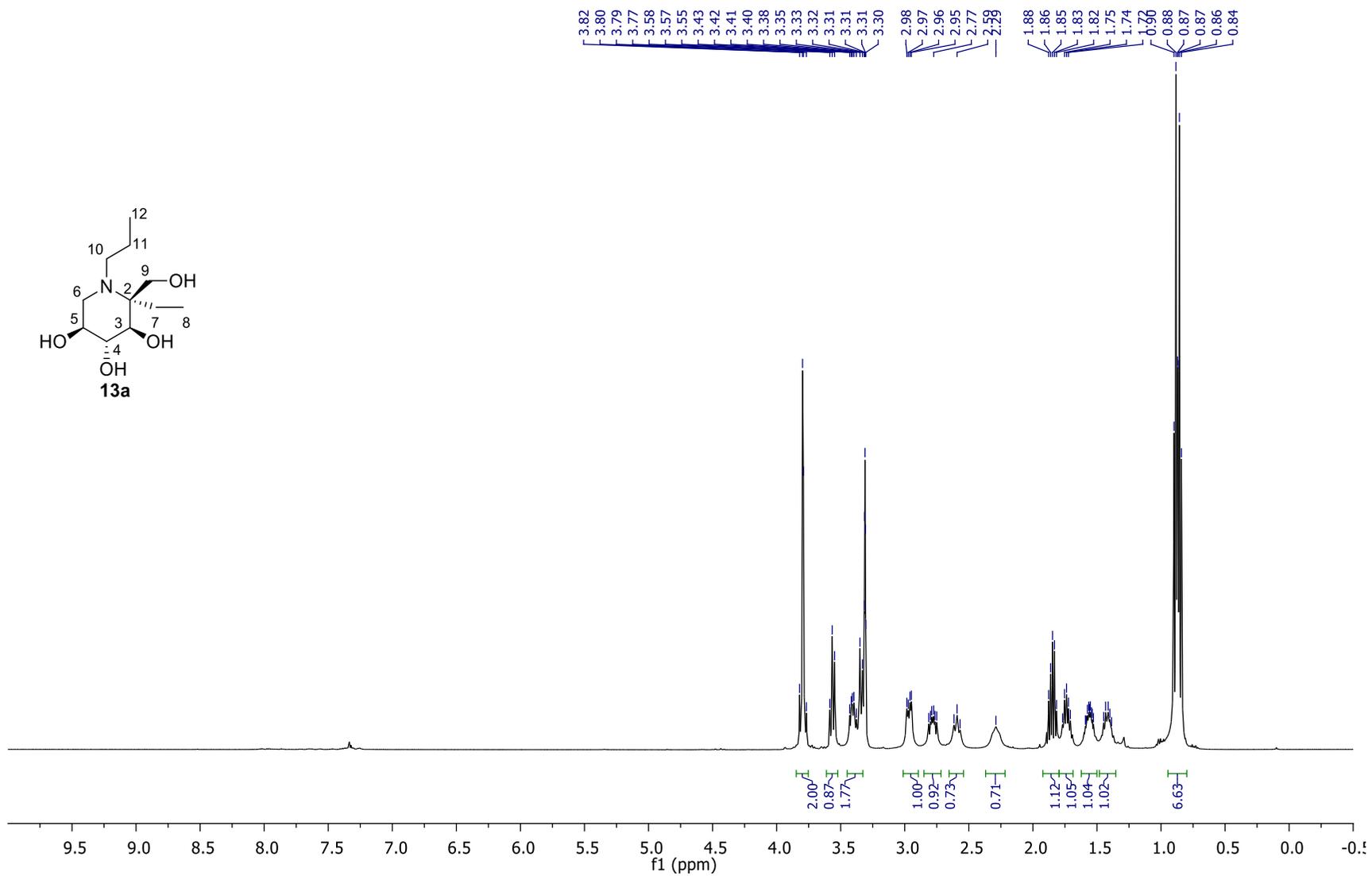
^1H NMR (CD_3OD , 500 MHz)



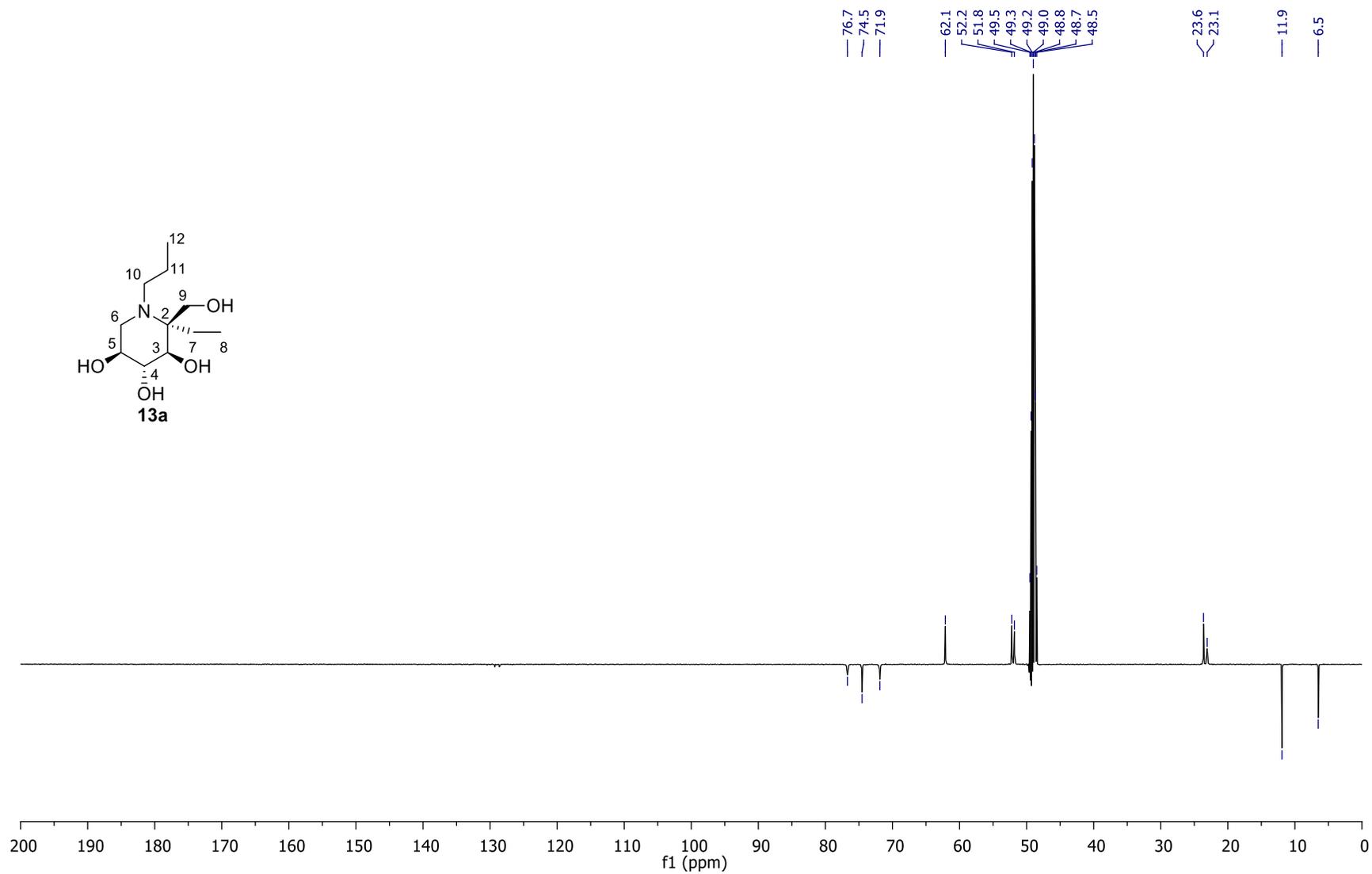
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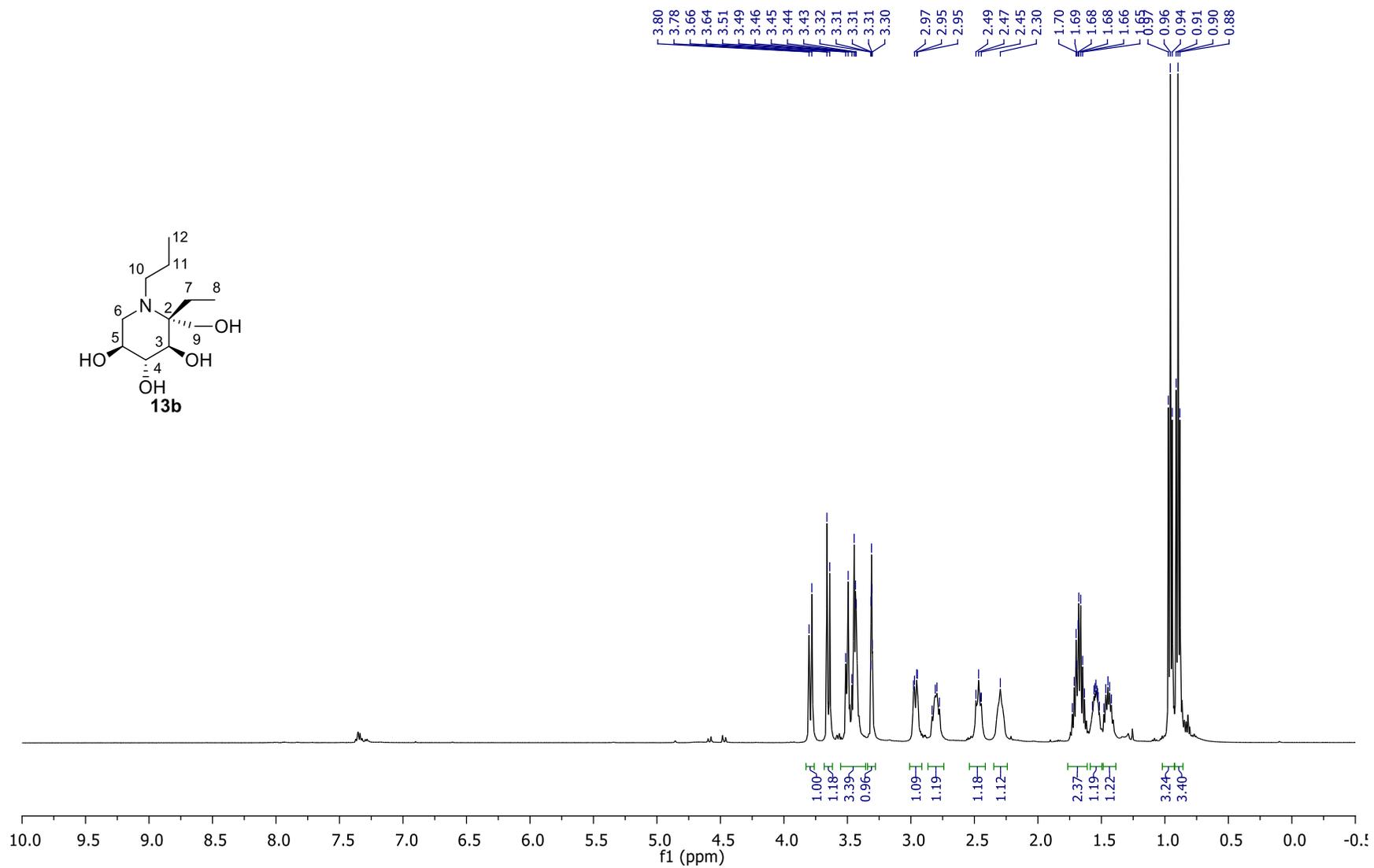
^1H NMR (CD_3OD , 500 MHz)



^{13}C NMR (CD_3OD , 125 MHz)



^1H NMR (CD_3OD , 500 MHz)



^{13}C NMR (CD_3OD , 125 MHz)

