Supporting Information

Synthesis of a new class of iminosugars based on constrained azaspirocyclic scaffolds by way of catalytic C-H amination

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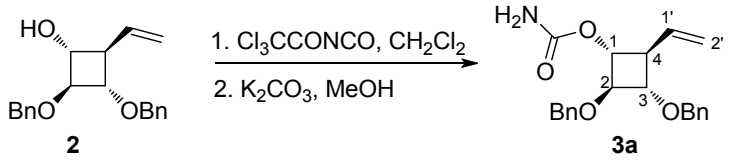
General methods

Tetrahydrofuran (THF) was dried by passage through an activated alumina column under Ar or distilled over Na/benzophenone under Ar. Dichloromethane (CH_2Cl_2) were distilled over CaH_2 under Ar. Pyridine was distilled over KOH under Ar and stored over KOH. Dried DMF was purchased from Sigma-Aldrich. All reactions were performed in standard glassware under Ar unless otherwise specified. Flash chromatographies were performed on silica gel 60 (230-400 mesh, 0.040-0.063 mm) purchased from E. Merck or using an automatic flash chromatography device. Thin Layer Chromatography (TLC) was performed on aluminum sheets coated with silica gel 60 F_{254} purchased from E. Merck. IR spectra (cm^{-1}) were recorded on a Perkin-Elmer Spectrum One spectrophotometer. NMR spectra were recorded on a 300 MHz and 400 MHz spectrometers with solvent peaks as reference.[1] Carbon multiplicities were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. The ^1H signals were assigned by 2D experiments (COSY). ESI-HRMS mass spectra were carried out on a TOF-spectrometer. Specific rotations were determined at room temperature (20 °C) in a Perkin–Elmer 241 polarimeter for sodium (λ = 589 nm).

$Rh_2(esp)_2$ (CAS : 819050-89-0), $Rh_2(OAc)_4$ (CAS :15956-28-2), $Rh_2(O_2CCF_3)_2$ (CAS : 31126-95-1) and $Rh_2(tpa)_4$ (CAS : 142214-04-8) were purchased from Sigma-Aldrich. Dowex® 1X8 (Cl^- form), 50-100 mesh, ion-exchange resin (CAS 12627-85-9) was purchased from Acros Organics.

(*1R,2R,3S,4S)*-2,3-Bis(benzyloxy)-4-vinylcyclobutyl carbamate (3a).



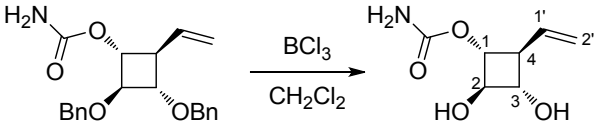
2 **3a**

Trichloroacetyl isocyanate (0.20 mL, 1.72 mmol, 1.3 equiv) was added to a solution of **2**[2] (403 mg, 1.3 mmol, 1 equiv) in CH_2Cl_2 (3.7 mL) at 0 °C. The solution was stirred at rt for 16 h and concentrated under reduced pressure. The residue was dissolved in MeOH (3.2 mL) and K_2CO_3 (18 mg, 0.13 mmol, 0.1 equiv) was added. The solution was stirred at rt for 8 h. Saturated aqueous NH_4Cl (5 mL) was added and the product was extracted with CH_2Cl_2 (3×). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:3 to 1:1) to afford carbamate **3a** (431 mg, 94%) as a white solid.

TLC R_f 0.46 (silica gel, EtOAc/petroleum ether, 1:2).
$[\alpha]_D^{20}$ +3 (c 1.0, $CHCl_3$).
m.p. 90°C.
IR (film) 3354, 1718, 1326, 1087 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$) δ 7.41 −7.20 (m, 10H, Ph), 5.95 (ddd, J = 17.3, 10.2, 7.2 Hz, 1H, H-1'), 5.19 (d, J = 17.3 Hz, 1H, H-2'a), 5.09 (d, J = 10.2 Hz, 1H, H-2'b), 4.72 −4.42 (m, 7H, 2 CH_2Ph, NH_2, H-2), 3.95 (t, J = 5.9 Hz, 1H, H-1 or H-3), 3.60 (m, 1H, H-1 or H-3), 2.48 (q, J = 7.5 Hz, 1H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0 (NCO), 137.84 (Cq-Ar), 137.82 (Cq-Ar), 136.3 (C-1'), 128.52 (2 CH-Ar), 128.50 (2 CH-Ar), 128.0 (2 CH-Ar), 127.9 (4 CH-Ar), 116.4 (C-2'), 82.6 (C-2), 77.1 (C-1 or C-3), 72.4 (C-1 or C-3), 71.62 (CH_2Ph), 71.57 (CH_2Ph), 46.3 (C-4).
HRMS (ESI) *m/z* 376.148 ([M+Na]$^+$, calcd. for $C_{21}H_{23}NO_4Na$: 376.152).

(***1R,2R,3S,4S***)**-2,3-Dihydroxy-4-vinylcyclobutyl carbamate** (**4**).

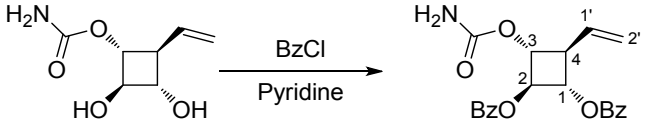


3a **4**

BCl_3 (1 M in CH_2Cl_2, 14 mL, 14 mmol, 12 equiv) was added to a solution of carbamate **3a** (411 mg, 1.16 mmol, 1 equiv) in CH_2Cl_2 (12 mL) at −60 °C. The solution was allowed to warm up slowly to rt overnight. MeOH/H_2O (20:1, 50 mL) was added and the solution was concentrated under reduced pressure. The process was repeated 1 time. The crude product was purified by flash chromatography (MeOH/CH_2Cl_2, 10:90 to 15:85) to afford diol **4** (169 mg, 84%) as a white solid.

TLC R_f 0.23 (silica gel, MeOH/CH_2Cl_2, 15:85).
[α]$_D^{20}$ −25 (c 1.0, MeOH).
m.p. 146°C.
IR (film) 3340, 1698, 1325, 1075 cm^{-1}.
^{1}H NMR (400 MHz, CD_3OD) δ 5.96 (ddd, J = 17.3, 10.4, 6.9 Hz, 1H, H-1'), 5.17 (d, J = 17.2 Hz, 1H, H-2'a), 5.06 (d, J = 10.4 Hz, 1H, H-2'b), 4.30 (m, 1H, H-1 or H-3), 3.79 (t, J = 6.3 Hz, 1H, H-2), 3.44 (m, 1H, H-1 or H-3), 2.22 (q, J = 7.5 Hz, 1H, H-4).
^{13}C NMR (100 MHz, CD_3OD) δ 159.2 (NCO), 137.7 (C-1'), 115.9 (C-2'), 79.2 (C-2), 74.4 (C-1 or C-3), 73.3 (C-1 or C-3), 48.8 (C-4).
HRMS (ESI) *m/z* 196.056 ([M+Na]$^+$, calcd. for $C_7H_{11}NO_4Na$: 196.058).

(1S,2R,3R,4S)-**3-(Carbamoyloxy)-4-vinylcyclobutane-1,2-diyl dibenzoate** (**3b**).



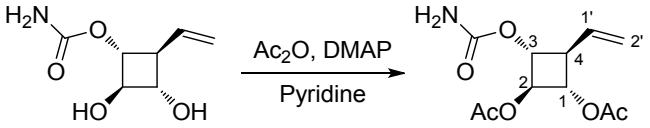
4 **3b**

BzCl (0.19 mL, 1.64 mmol, 4.6 equiv) was added to a solution of diol **4** (62 mg, 0.36 mmol, 1 equiv) in pyridine (3.6 mL) at 0 °C. The solution was stirred at 0 °C for 1 h. MeOH was added and the solution was diluted in EtOAc. The organic layer was washed with water and 1N HCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:2 to 1:1) to afford cyclobutane **3b** (118 mg, 87%) as a white solid.

TLC R_f 0.25 (silica gel, EtOAc/petroleum ether, 1:2).
[α]$_D^{20}$ +48 (c 1.0, $CHCl_3$).
m.p. 193°C.
IR (film) 3374, 1721, 1275 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.1 Hz, 4H, Ph), 7.62 – 7.53 (m, 2H, Ph), 7.49 – 7.40 (m, 4H, Ph), 6.12 (ddd, J = 17.2, 10.5, 6.5 Hz, 1H, H-1'), 5.53 (t, J = 6.3 Hz, 1H, H-2), 5.34 (dt, J = 17.2, 1.7 Hz, 1H, H-2'a), 5.23 (dt, J = 10.4, 1.2 Hz, 1H, H-2'b), 5.16 (dd, J = 7.9, 6.3 Hz, 1H, H-1 or H-3), 4.96 (dd, J = 8.1, 6.3 Hz, 1H, H-1 or H-3), 4.76 (br s, 2H, NH_2), 2.90 (q, J = 7.6 Hz, 1H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.72 (CO), 165.67 (CO), 155.4 (NCO), 134.3 (C-1'), 133.5 (2 CH-Ar), 130.1 (3 CH-Ar), 130.0 (3 CH-Ar), 129.5 (Cq-Ar), 129.4 (Cq-Ar), 128.55 (CH-Ar), 128.54 (CH-Ar), 117.5 (C-2'), 75.6 (C-2), 71.0 (C-1 or C-3), 70.6 (C-1 or C-3), 45.8 (C-4).
HRMS (ESI) *m/z* 404.109 ([M+Na]$^+$, calcd. for $C_{21}H_{19}NO_6Na$: 404.110).

***(1S,2R,3R,4S)*-3-(Carbamoyloxy)-4-vinylcyclobutane-1,2-diyl diacetate (3c).**



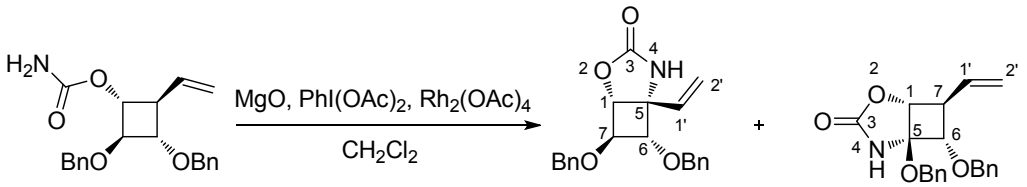
4 **3c**

Ac_2O (0.31 mL, 3.30 mmol, 6 equiv) and DMAP (136 mg, 1.11 mmol, 2 equiv) were added to a solution of diol **4** (96 mg, 0.55 mmol, 1 equiv) in pyridine (5.5 mL). The solution was stirred at rt for 17 h. Et_2O (38 mL) was added and the organic layer was washed successively with 1% aqueous HCl (22 mL), saturated aqueous $NaHCO_3$ (38 mL) and brine (38 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:2 to 1:1) to afford **3c** (115 mg, 81%) as a colorless oil.

TLC R_f 0.33 (silica gel, EtOAc/petroleum ether, 1:1).
[α]$_D^{20}$ −9 (c 1.0, $CHCl_3$).
IR (film) 3374, 1728, 1220 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (ddd, J = 17.2, 10.4, 6.7 Hz, 1H, H-1'), 5.22 (d, J = 17.2 Hz, 1H, H-2'a), 5.15 (d, J = 10.4 Hz, 1H, H-2'b), 5.09 (t, J = 6.3 Hz, 1H, H-2), 4.99 – 4.86 (br s, 2H, NH_2), 4.73 (m, 1H, H-1 or H-3), 4.68 (m, 1H, H-1 or H-3), 2.65 (q, J = 7.5 Hz, 1H, H-4), 2.06 (s, 6H, CH_3).
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.13 (CO), 170.10 (CO), 155.6 (NCO), 134.2 (C-1'), 117.3 (C-2'), 75.2 (C-2), 70.7 (C-1 or C-3), 69.9 (C-1 or C-3), 45.1 (C-4), 20.84 (CH_3), 20.80 (CH_3).
HRMS (ESI) *m/z* 280.078 ([M+Na]$^+$, calcd. for $C_{11}H_{15}NO_6Na$: 280.079).

General procedure A for C-H amination using Rh catalysts (Table 1, entry 1-6, 8-10). MgO (2.3 equiv), $PhI(OAc)_2$ (1.4 equiv) and catalyst (5mol%-30mol%) were added to a solution of carbamate **3** (1 equiv) in degassed CH_2Cl_2 or benzene. The solution was refluxed (CH_2Cl_2) or heated at 60°C (benzene). After cooling, the solution was filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography.

***(1R,5R,6S,7R)*-6,7-bis(benzyloxy)-5-vinyl-2-oxa-4-azabicyclo[3.2.0]heptan-3-one (5a)** and ***(1R,5R,6S,7S)*-5,6-Bis(benzyloxy)-7-vinyl-2-oxa-4-azabicyclo[3.2.0]heptan-3-one (6a)** (Table 1, entry 2)



3a **5a** **6a**

According to general procedure A, MgO (24 mg, 0.60 mmol, 2.3 equiv), $PhI(OAc)_2$ (115 mg, 0.36 mmol, 1.4 equiv) and $Rh_2(esp)_2$ (19 mg, 0.025 mmol, 0.1 equiv) were added to a solution of carbamate **3a** (90 mg, 0.20 mmol, 1 equiv) in degassed CH_2Cl_2 (1.8 mL). The solution was

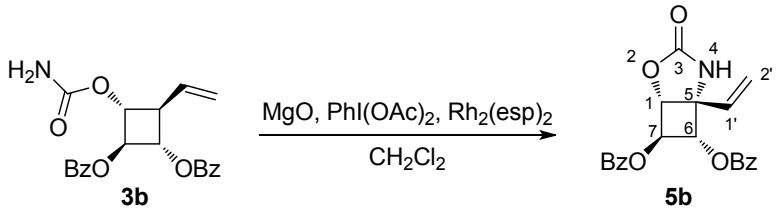
refluxed for 8.5 h. Then a second portion of $Rh_2(esp)_2$ (19 mg, 0.025 mmol, 0.1 equiv) was added and the solution was refluxed for 15.5 h. After cooling, the solution was filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:5 to 1:2) to afford compounds **6a** (50 mg, 56%) and **5a** (15 mg, 17%) as pale yellow oils.

Compound **6a**:
TLC R_f 0.48 (silica gel, EtOAc/toluene, 1:3).
[α]$_D^{20}$ −7 (c 0.6, $CHCl_3$).
IR (film) 3272, 1760 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 10H, Ph), 5.86 (m, 1H, H-1'), 5.57 (br s, 1H, NH), 5.17 (d, J = 1.0 Hz, 1H, H-2'a), 5.14 (d, J = 6.6 Hz, 1H, H-2'b), 4.63 (d, J = 11.9 Hz, 1H, CH_2Ph), 4.57 (d, J = 11.5 Hz, 1H, CH_2Ph), 4.50 (d, J = 11.9 Hz, 1H, CH_2Ph), 4.44 (d, J = 11.5 Hz, 1H, CH_2Ph), 4.30 (d, J = 4.7 Hz, 1H, H-1 or H-6), 4.02 (dd, J = 7.2, 1.0 Hz, 1H, H-1 or H-6), 2.68 (m, 1H, H-7).
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2 (NCO), 137.2 (Cq-Ar), 136.8 (Cq-Ar), 134.3 (C-1'), 128.76 (2 CH-Ar), 128.72 (2 CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 128.2 (2 CH-Ar), 127.9 (2 CH-Ar), 117.4 (C-2'), 91.1 (C-5), 81.0 (C-1 or C-6), 76.4 (C-1 or C-6), 72.5 (*C*H_2Ph), 65.9 (*C*H_2Ph), 49.0 (C-7).
HRMS (ESI) *m/z* 374.136 ([M+Na]$^+$, calcd. for $C_{21}H_{21}NO_4Na$: 374.136).

Compound **5a**:
TLC R_f 0.45 (silica gel, EtOAc/petroleum ether, 1:2).
[α]$_D^{20}$ +54 (c 1.0, $CHCl_3$).
IR (film) 3279, 1755 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 10H, Ph), 5.81 (dd, J = 17.3, 10.6 Hz, 1H, H-1'), 5.71 (br s, 1H, NH), 5.24 (d, J = 17.6 Hz, 1H, H-2'a), 5.22 (d, J = 10.6 Hz, 1H, H-2'b), 4.57 (d, J = 11.5 Hz, 1H, CH_2Ph), 4.56 (d, J = 11.9 Hz, 1H, CH_2Ph), 4.51 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.47 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.32 (d, J = 2.1 Hz, 1H, H-1 or H-6), 4.11 (dd, J = 5.3, 3.5 Hz, 1H, H-7), 3.96 (d, J = 5.5 Hz, 1H, H-1 or H-6).
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (NCO), 137.1 (Cq-Ar), 136.9 (Cq-Ar), 136.2 (C-1'), 128.74 (2 CH-Ar), 128.73 (2 CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 128.24 (2 CH-Ar), 128.21 (2 CH-Ar), 116.7 (C-2'), 84.2 (C-7), 81.3 (C-1 or C-6), 78.9 (C-1 or C-6), 72.22 (*C*H_2Ph), 72.21 (*C*H_2Ph), 62.1 (C-5).
HRMS (ESI) *m/z* 374.148 ([M+Na]$^+$, calcd. for $C_{21}H_{21}NO_4Na$: 374.136).

C-H amination of compound 3a using AgOTf (Table 1, entry 7). A mixture of bathophenanthroline (36 mg, 0.11 mmol, 0.5 equiv), AgOTf (28 mg, 0.11 mmol, 0.5 equiv) in acetonitrile (6 mL) were stirred at room temperature for 20 min. The resulting suspension was added *via* cannula to a flask containing carbamate **3a** (77 mg, 0.22 mmol, 1 equiv) and $PhI(OAc)_2$ (140 mg, 0.44 mmol, 2 equiv). The flask was sealed and the solution was heated at reflux for 8h. After cooling, the solution was filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:5 to 1:2) to afford compounds **6a** (11 mg, 14%) and **5a** (1.9 mg, 2%). Starting material **3a** (22.7 mg, 29%) was also recovered.

***(1R,5R,6S,7R)*-3-Oxo-5-vinyl-2-oxa-4-azabicyclo[3.2.0]heptane-6,7-diyl dibenzoate (5b)**. (Table 1, entry 10)

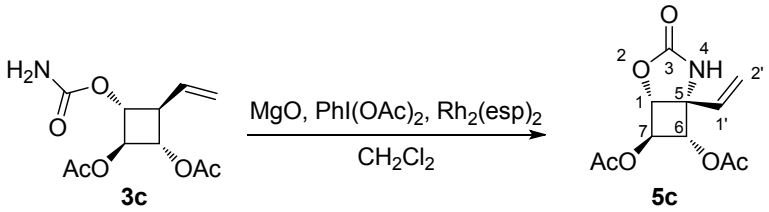


3b **5b**

According to general procedure A, MgO (26 mg, 0.65 mmol, 2.3 equiv), $PhI(OAc)_2$ (127 mg, 0.39 mmol, 1.4 equiv) and $Rh_2(esp)_2$ (32 mg, 0.04 mmol, 0.15 equiv) were added to a solution of carbamate **3b** (108 mg, 0.28 mmol, 1 equiv) in degassed CH_2Cl_2 (2 mL). The solution was refluxed for 16 h. A second portion of $Rh_2(esp)_2$ (11 mg, 0.014 mmol, 0.05 equiv) was added and the solution was refluxed for 8 h. After cooling, the solution was filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/toluene, 1:7 to 1:6) to afford compound **5b** (42 mg, 40%) as a colorless oil.

TLC R_f 0.48 (silica gel, EtOAc/toluene, 1:3).
$[\alpha]_D^{20}$ +97 (c 1.0, $CHCl_3$).
IR (film) 3321, 1762, 1722, 1248 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 – 8.04 (m, 4H, Ph), 7.65 – 7.56 (m, 2H, Ph), 7.51 – 7.43 (m, 4H, Ph), 6.20 (dd, J = 17.3, 10.7 Hz, 1H, H-1'), 5.96 – 5.90 (br s, 1H, NH), 5.54 (d, J = 17.3 Hz, 1H, H-2'a), 5.50 – 5.43 (m, 3H, H-6, H-7, H-2'b), 4.85 (dd, J = 2.8, 2.0 Hz, 1H, H-1).
^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 (CO), 165.2 (CO), 158.8 (NCO), 135.0 (C-1'), 134.0 (CH-Ar), 133.9 (CH-Ar), 130.2 (2 CH-Ar), 130.1 (2 CH-Ar), 128.82 (Cq-Ar), 128.78 (2 CH-Ar), 128.7 (2 CH-Ar), 128.6 (Cq-Ar), 118.2 (C-2'), 78.7 (C-1), 77.6 (C-6 or C-7), 75.1 (C-6 or C-7), 63.0 (C-5).
HRMS (ESI) *m/z* 402.094 ($[M+Na]^+$, calcd. for $C_{21}H_{17}NO_7Na$: 402.095).

***(1R,5R,6S,7R)*-3-Oxo-5-vinyl-2-oxa-4-azabicyclo[3.2.0]heptane-6,7-diyl diacetate (5c)** (Table 1, entry 9)

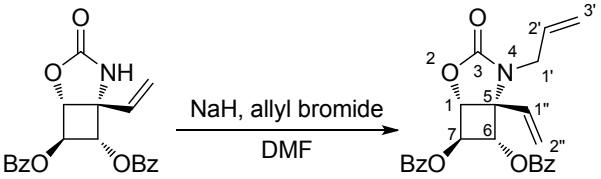


3c **5c**

According to general procedure A, MgO (24 mg, 0.59 mmol, 2.3 equiv), $PhI(OAc)_2$ (113 mg, 0.35 mmol, 1.4 equiv) and $Rh_2(esp)_2$ (9.5 mg, 0.013 mmol, 0.05 equiv) were added to a solution of carbamate **3c** (65 mg, 0.25 mmol, 1 equiv) in degassed CH_2Cl_2 (1.8 mL). The solution was refluxed for 8 h. A second portion of $Rh_2(esp)_2$ (19 mg, 0.025 mmol, 0.1 equiv) was added and the solution was refluxed for 16 h. After cooling, the solution was filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:5 to 2:1) to afford compound **5c** (20 mg, 31%) as a colorless oil.

TLC R_f 0.46 (silica gel, Et_2O/CH_2Cl_2, 1:1).
$[\alpha]_D^{20}$ +57 (c 1.0, $CHCl_3$).
IR (film) 3293, 1747, 1220 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (dd, J = 17.3, 10.6 Hz, 1H, H-1'), 5.99 (s, 1H, NH), 5.43 (d, J = 14.4 Hz, 1H, H-2'a), 5.38 (d, J = 7.6 Hz, 1H, H-2'b), 5.15 (dd, J = 5.8, 3.5 Hz, 1H, H-7), 5.08 (dd, J = 5.8, 1.7 Hz, 1H, H-6), 4.62 (dd, J = 3.5, 1.7 Hz, 1H, H-1), 2.14 (s, 3H, CH_3), 2.12 (s, 3H, CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (CO), 169.4 (CO), 158.8 (NCO), 134.9 (C-1'), 118.1 (C-2'), 78.4 (C-1), 76.9 (C-7), 74.4 (C-6), 62.6 (C-5), 20.7 (CH_3), 20.6 (CH_3).
HRMS (ESI) *m/z* 278.063 ($[M+Na]^+$, calcd. for $C_{11}H_{13}NO_6Na$: 278.064).

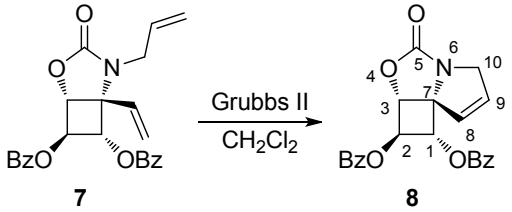
***(1R,5R,6S,7R)*-4-allyl-3-oxo-5-vinyl-2-oxa-4-azabicyclo[3.2.0]heptane-6,7-diyl dibenzoate (7).**



NaH (60%, 17 mg, 0.43 mmol, 1.05 equiv) was added to a solution of oxazolidinone **5b** (156 mg, 0.41 mmol 1 equiv) in DMF (1.6 mL) at 0 °C. The solution was stirred 30 min at 0 °C then 1 h at rt. Allyl bromide (72 µL, 0.82 mmol, 2 equiv) was added and the solution was stirred at rt for 2 h. Saturated aqueous NH_4Cl was added and the product was extracted with Et_2O (7×). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:4) to afford diene **7** (96 mg, 55%) as a colorless oil.

TLC R_f 0.30 (silica gel, EtOAc/petroleum ether, 35:65).
$[\alpha]_D^{20}$ +26 (c 1.0, $CHCl_3$).
IR (film) 1764, 1724, 1253, 1108 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.2 Hz, 2H, Ph), 8.05 (d, J = 8.9 Hz, 2H, Ph), 7.66 − 7.56 (m, 2H, Ph), 7.52 − 7.42 (m, 4H, Ph), 6.10 (dd, J = 17.4, 10.8 Hz, 1H, H-1''), 5.85 − 5.69 (m, 3H, CH-O, H-2', H-2''a), 5.57 (d, J = 10.8 Hz, 1H, H-2''b), 5.54 (dd, J = 5.9, 3.5 Hz, 1H, CH-O), 5.07 (dd, J = 17.1, 1.2 Hz, 1H, H-3'a), 4.93 (dd, J = 10.1, 1.1 Hz, 1H, H-3'b), 4.74 (dd, J = 3.4, 1.5 Hz, 1H, CH-O), 3.84 (d, J = 6.1 Hz, 2H, H-1').
^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (CO), 165.1 (CO), 157.9 (NCO), 134.0 (CH-Ar or CH-vinylic), 133.8 (CH-Ar or CH-vinylic), 133.7 (CH-Ar CH-vinylic), 132.7 (CH-Ar CH-vinylic), 130.2 (2 CH-Ar), 130.1 (2 CH-Ar), 128.8 (2 CH-Ar), 128.7 (2 CH-Ar), 120.8 (C-3' or C-2''), 118.4 (C-3' or C-2''), 77.5 (CH-O), 75.9 (CH-O), 73.8 (CH-O), 67.0 (C-5), 45.9 (C-1').
HRMS (ESI) *m/z* 442.123 ([M+Na]$^+$, calcd. for $C_{24}H_{21}NO_6Na$: 442.126).

Compound 8.

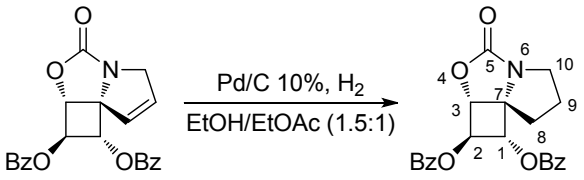


A solution of Grubbs II catalyst (5 mg, 57 µmol, 0.05 equiv) in degased CH_2Cl_2 (1 mL) was added to a solution of diene **7** (48 mg, 0.11 mmol, 1 equiv) in degased CH_2Cl_2 (3.6 mL). The solution was refluxed for 5 h. After cooling, the solution was concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 3:7 to 2:3) to afford compound **8** (40 mg, 89%) as a cream solid.

TLC R_f 0.17 (silica gel, EtOAc/petroleum ether, 1:4).
$[\alpha]_D^{20}$ +127 (c 1.0, $CHCl_3$).
m.p. 108°C.
IR (film) 1765, 1721, 1247, 1066 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.2 Hz, 2H, Ph), 8.04 (d, J = 7.2 Hz, 2H, Ph), 7.64 − 7.56 (m, 2H, Ph), 7.51 − 7.42 (m, 4H, Ph), 6.17 − 6.09 (m, 2H, H-8, H-9), 5.61(dd, J = 6.2,

1.4 Hz, 1H, CH-O), 5.47 (dd, *J* = 6.1, 3.4 Hz, 1H, CH-O), 5.15 (dd, *J* = 3.2, 1.5 Hz, 1H, CH-O), 4.47 (d, *J* = 15.9 Hz, 1H, H-10a), 3.85 (d, *J* = 16.2 Hz, 1H, H-10b).
^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (CO), 165.3 (CO), 163.4 (NCO), 133.9 (2 CH-Ar), 132.8 (C-8 or C-9), 130.11 (2 CH-Ar), 130.10 (2 CH-Ar), 128.9 (2 Cq-Ar), 128.74 (2 CH-Ar), 128.71 (2 CH-Ar), 126.8 (C-8 or C-9), 78.5 (CH-O), 77.9 (CH-O), 77.1 (C-7), 74.4 (CH-O), 55.7 (C-10).
HRMS (ESI) *m/z* 414.093 ([M+Na]$^+$, calcd. for $C_{22}H_{17}NO_6Na$: 414.095).

Compound 9.

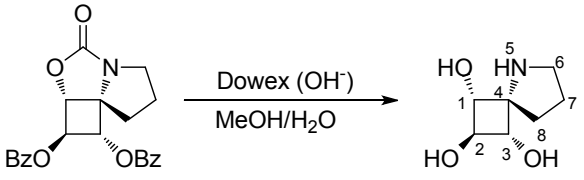


8 **9**

Pd/C 10% (10 mg) was added to a solution of **8** (78 mg, 0.199 mmol, 1 equiv) in EtOH (3 mL) and EtOAc (2 mL). The solution was placed under H_2 atmosphere and stirred at rt for 14 h. The solution was filtered through a pad of Celite and concentrated under reduced pressure to afford compound **9** (78 mg, quant.) as a white solid.

TLC R_f 0.36 (silica gel, EtOAc/cyclohexane, 3:7).
[α]$_D^{20}$ +75 (c 1.0, $CHCl_3$).
m.p. 137°C.
IR (film) 1761, 1719, 1247 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 − 8.02 (m, 4H, Ph), 7.65 − 7.55 (m, 2H, Ph), 7.51 −7.41 (m, 4H, Ph), 5.44 (dd, *J* = 5.9, 3.2 Hz, 1H, CH-O), 5.39 (dd, *J* = 5.9, 1.6 Hz, 1H, CH-O), 4.88 (dd, *J* = 3.1, 1.7 Hz, 1H, CH-O), 3.74 (ddd, *J* = 11.2, 7.8, 5.4 Hz, 1H, H-10a), 3.07 (m, 1H, H-10b), 2.47 (m, 1H, H-8a), 2.22 − 1.86 (m, 3H, H-8b, H-9).
^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (CO), 165.2 (CO), 161.6 (NCO), 133.9 (CH-Ar), 133.8 (CH-Ar), 130.09 (2 CH-Ar), 130.06 (2 CH-Ar), 129.0 (Cq-Ar), 128.9 (Cq-Ar), 128.8 (2 CH-Ar), 128.7 (2 CH-Ar), 77.3 (CH-O), 76.9 (CH-O), 76.4 (CH-O), 71.1 (C-7), 47.4 (C-10), 32.6 (C-8), 25.6 (C-9).
HRMS (ESI) *m/z* 416.114 ([M+Na]$^+$, calcd. for $C_{22}H_{19}NO_6Na$: 416.110).

***(1R,2r,3S,4r)*-5-azaspiro[3.4]octane-1,2,3-triol 10**



9 **10**

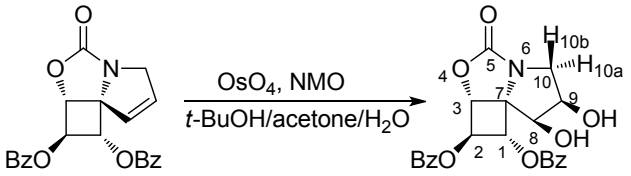
Dowex 1X8 (OH^-form) was freshly prepared from commercialy available Dowex 1X8 (Cl^- form): 4 g of Dowex 1X8 (Cl^- form) resin were washed with aqueous solution of NaOH (3N, 90 mL) then with water (45 mL) and dried under a flow of argon. The resin was washed with MeOH (55 mL) and dried for 30 min under a flow of argon.[3]
A suspension of substrate **9** (78 mg, 0.198 mmol) and Dowex 1X8 (OH^-form) (3 g) in a mixture of MeOH/H_2O (1:1, 8 mL) was stirred using a rotary evaporator for 23 h at 70 °C

under atmospheric pressure. The resin was filtrated off, washed successively with H_2O, MeOH, H_2O/MeOH (1:1), MeOH/$CHCl_3$ (1:1) and $CHCl_3$. The combined solutions were concentrated under reduced pressure to afford compound **10** (3 mg, 10 %).

Additional quantity of compound **10** was obtained as follow: 0.1 M HCl (4 x 5 mL) was added on the resulting resin and stirred 15 min. The resin was filtered and the solution was concentrated under reduced pressure. The crude product was purified by flash chromatography ($CH_3CN/H_2O/NH_4OH$, 10:1:1) to afford compound **10** (8 mg, 25%) as a white solid.

TLC R_f 0.43 (silica gel, $CH_3CN/H_2O/NH_4OH$, 5:1:1).
IR (film) 3294 cm^{-1}.
^{1}H NMR (400 MHz, D_2O) δ 3.86 (d, J = 5.6 Hz, 2H, CH-OH), 3.78 (dd, J = 7.6, 6.1 Hz, 1H, CH-OH), 3.28 (t, J = 7.2 Hz, 2H, H6), 2.09 (m, 2H, H8), 1.91 (m, 2H, H7).
^{13}C NMR (75 MHz, D_2O) δ 76.6 (CH-OH), 71.0 (CH-OH), 67.2 (C4), 46.7 (C6), 32.7 (C-7 or C-8), 22.7 (C-7 or C-8).
HRMS (ESI) *m/z* 160.098 ([M+H]$^+$, calcd. for $C_7H_{14}NO_3$: 160.097).

Compound 11.

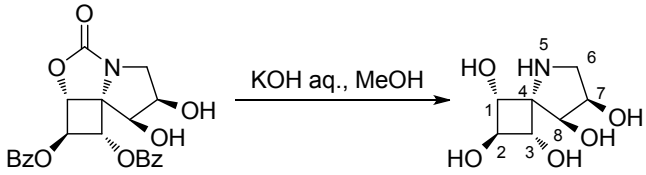


8 **11**

OsO_4 (2.5 wt.% solution in t-butanol, 110 µL, 8.58 µmol, 0.05 equiv) was added at 0 °C to a solution of **8** (65 mg, 0.166 mmol, 1 equiv) and NMO (21.6 mg, 0.184 mmol, 1.1 equiv) in acetone (300 µL) and H_2O (300 µL). The solution was allowed to warm up to rt and stirred for 4 h. The solution was concentrated under reduced pressure, taken up in 10% MeOH/CH_2Cl_2 and filtered through a pad of Celite. The Celite was further washed with 10% MeOH/CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 2:1) to afford **11** (61 mg, 86%) as a brown solid.

TLC R_f 0.31 (silica gel, EtOAc/petroleum ether, 2:1).
$[\alpha]_D^{20}$ +81 (c 0.5, $CHCl_3$).
m.p. 101°C.
IR (film) 3406, 1718, 1250 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 − 8.01 (m, 4H, Ph), 7.62 − 7.53 (m, 2H, Ph), 7.48 −7.39 (m, 4H, Ph), 5.40 (dd, J = 5.6, 3.0 Hz, 1H, H-2), 5.37 (dd, J = 5.6, 1.6 Hz, 1H, H-1), 5.08 (m, 1H, H-3), 4.84 (m, 1H, H-8), 4.38 (m, 1H, H-9), 3.87 (br s, 1H, OH), 3.73 (dd, J = 12.7, 1.9 Hz, 1H, H-10b), 3.61 (br s, 1H, OH), 3.13 (dd, J = 12.6, 3.8 Hz, 1H, H-10a).
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (CO), 165.5 (CO), 164.2 (NCO), 134.1 (CH-Ar), 133.9 (CH-Ar), 130.1 (4 CH-Ar), 128.8 (2 CH-Ar), 128.7 (2 CH-Ar), 128.5 (2 Cq-Ar), 77.0 (C-2), 75.5 (C-8), 75.2 (C-1), 74.2 (C-3), 72.4 (C-9), 72.0 (C-7), 54.5 (C-10).
HRMS (ESI) *m/z* 448.100 ([M+Na]$^+$, calcd. for $C_{22}H_{19}NO_8Na$: 448.100).

***(1R,2S,3S,4r,7R,8S)*-5-azaspiro[3.4]octane-1,2,3,7,8-pentaol 12**

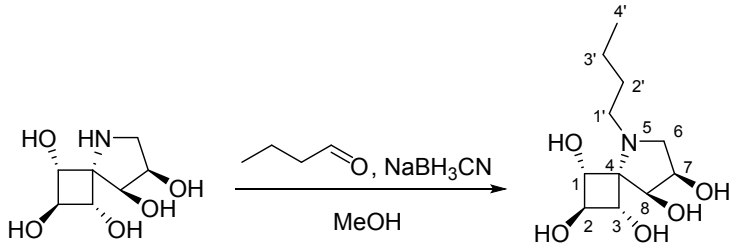


11 **12**

50% aqueous KOH (3.3 mL) was added to a solution of **11** (18.8 mg, 44.2 μmol, 1 equiv) in MeOH (0.7 mL) and the solution was stirred at rt for 16 h. The solution was cooled to 0 °C and Amberlite IR120 (H^+ form) was added until reaching pH ~ 9 – 10. Amberlite IR120 was removed by filtration and washed with MeOH and H_2O. Amberlite IR120 was put into 10% aqueous NH_3 (20 mL), the mixture was stirred and Amberlite IR120 was removed by filtration. The process was repeated 2 times. The combined filtrates were concentrated under reduced pressure and purified by flash chromatography ($CH_3CN/H_2O/NH_4OH$, 10:1:1 to 5:1:1) to afford **12** (9 mg, quant.) as a yellow oil.

TLC R_f 0.19 (silica gel, $CH_3CN/H_2O/NH_4OH$, 5:1:1).
$[\alpha]_D^{20}$ -8.8 (c 0.25, H_2O).
IR (film) 3285, 1598, 1106 cm^{-1}.
^{1}H NMR (300 MHz, D_2O) δ 4.27 (ddd, J = 5.3, 4.4, 4.1 Hz, 1H, H-7), 4.10 (d, J = 4.4 Hz, 1H, H-8), 4.01 (dd, J = 6.8, 1.5 Hz, 1H, H-1), 3.85 (t, J = 6.8 Hz, 1H, H-2), 3.80 (dd, J = 6.8, 1.5 Hz, 1H, H-3), 3.29 (dd, J = 12.2, 5.3 Hz, 1H, H-6a), 3.12 (dd, J = 12.2, 4.1 Hz, 1H, H-6b).
^{13}C NMR (75 MHz, D_2O) δ 77.2 (C-2), 74.6 (C-8), 70.1 (C-7), 69.7 (C-3), 66.8 (C-1), 66.6 (C-4), 49.8 (C-6).
HRMS (ESI) *m/z* 192.085 ($[M+H]^+$, calcd. for $C_7H_{14}NO_5$: 192.087).

***(1R,2S,3S,4r,7R,8S)*-5-butyl-5-azaspiro[3.4]octane-1,2,3,7,8-pentaol 13**



12 **13**

Sodium cyanoborohydride (6.5 mg, 98.3 μmol, 2.1 equiv) was added to a solution of **12** (9 mg, 47.1 μmol, 1 equiv) and butanal (12.5 μL, 141 μmol, 3 equiv) in MeOH (1 mL) at 0 °C. The solution was stirred at rt for 25 h and concentrated under reduced pressure. The crude product was purified by flash chromatography ($CH_3CN/H_2O/NH_4OH$, 15:1:1) to afford **13** (6.7 mg, 58%) as a brown oil.

TLC R_f 0.38 (silica gel, $CH_3CN/H_2O/NH_4OH$, 10:1:1).
$[\alpha]_D^{20}$ -27.2 (c 0.25, MeOH).
IR (film) 3306, 1080 cm^{-1}.
^{1}H NMR (300 MHz, CD_3OD) δ 4.29 (m, 1H, H-7), 4.15 – 4.11 (m, 2H, H-1 or H-3, H-2), 4.00 (d, J = 4.2 Hz, 1H, H-8), 3.81 (dd, J = 5.0, 3.0 Hz, 1H, H-1 or H-3), 3.58 (dd, J = 10.9, 6.7 Hz, 1H, H-6a), 3.48 (t, J = 8.0 Hz, 2H, H-1'), 3.19 (dd, J = 11.2, 3.0 Hz, 1H, H-6b), 1.73 – 1.56 (m, 2H, H-2'), 1.47 – 1.33 (m, 2H, H-3'), 0.98 (t, J = 7.3 Hz, 3H, H-4').
^{13}C NMR (100 MHz, CD_3OD) δ 80.9 (C-1 or C-2 or C-3), 75.5 (C-8), 72.6 (C-1 or C2 or C-3), 69.9 (C-1 or C-2 or C-3), 69.2 (C-7), 59.3 (C-6), 53.9 (C-1'), 48.1 (C-4), 29.8 (C-2'), 21.2 (C-3'), 14.1 (C-4').
HRMS (ESI) *m/z* 248.150 ($[M+H]^+$, calcd. for $C_{11}H_{22}NO_5$: 248.149).

Références

1) Gottlieb, H.E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.
2) Nocquet, P.-A.; Hazelard, D.; Gruntz, G; Compain, P. *J. Org. Chem.* **2013,** 78*,* 6751–6757.
3) B. M. Trost, A. Aponick, B. N. Stanzl, *Chem. Eur. J.* **2007**, *13,* 9547 – 9560.

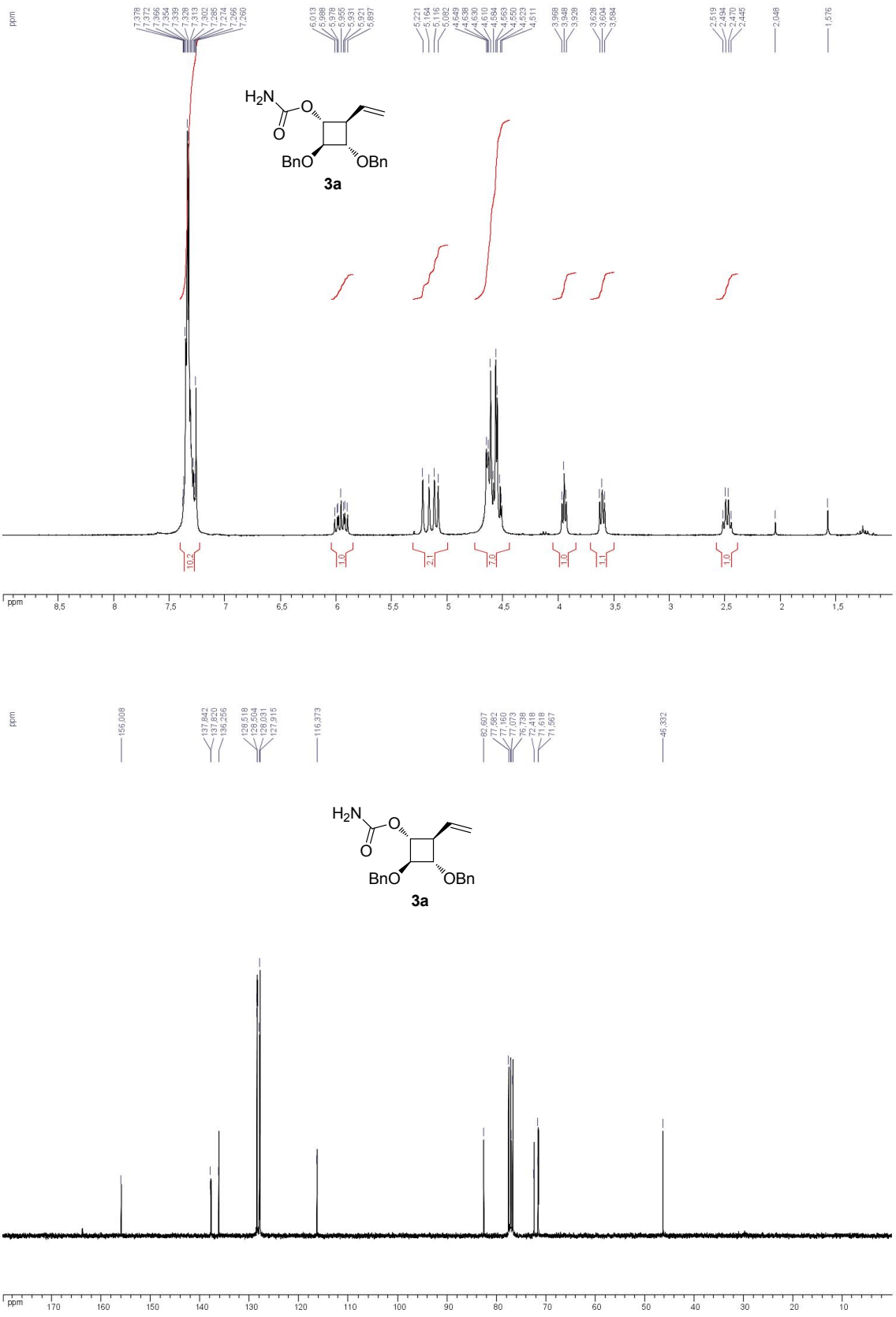


Fig 1. ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound **3a**.

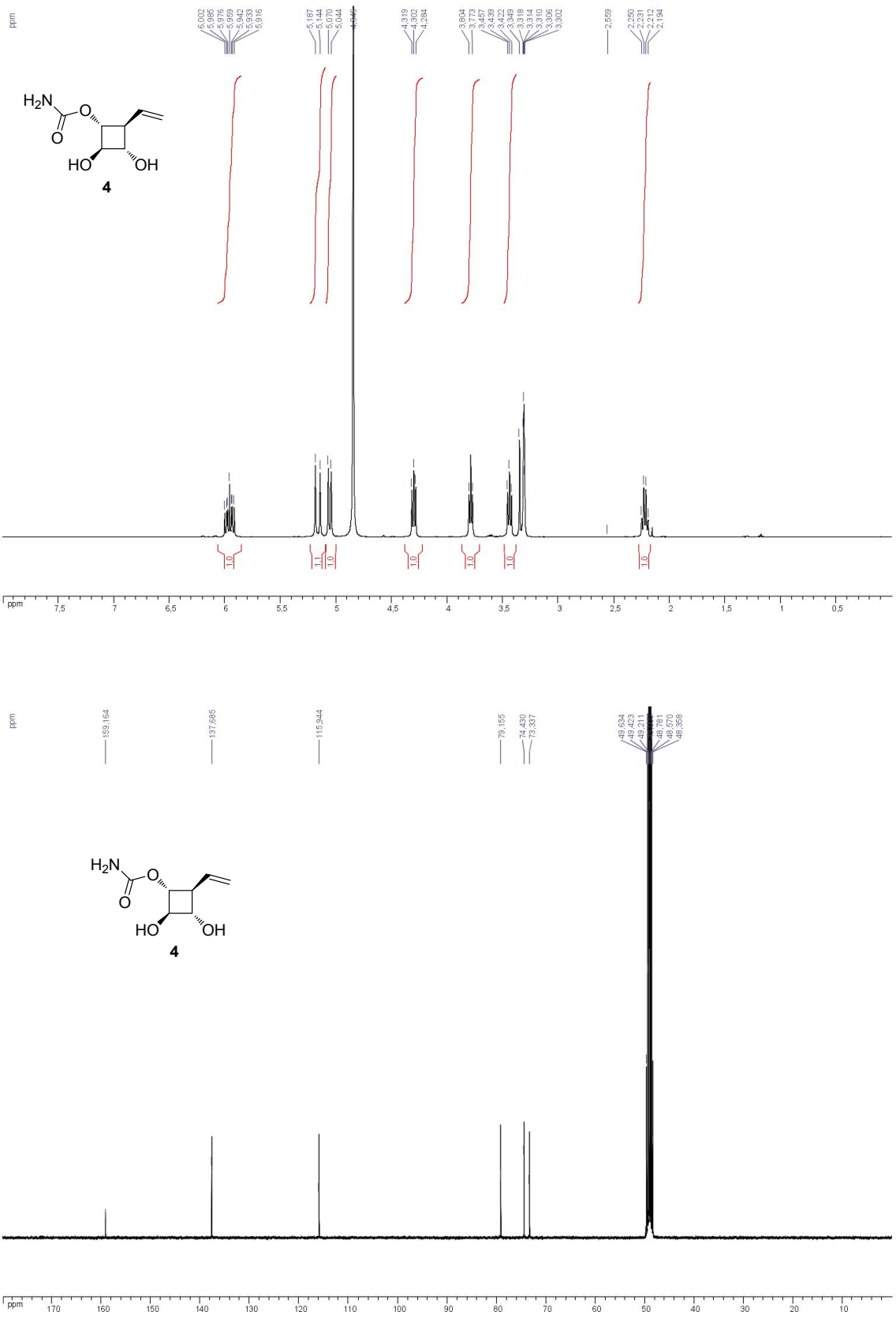


Fig 2. ^{1}H NMR (400 MHz, CD_3OD) and ^{13}C (100 MHz, CD_3OD) spectra of compound **4**.

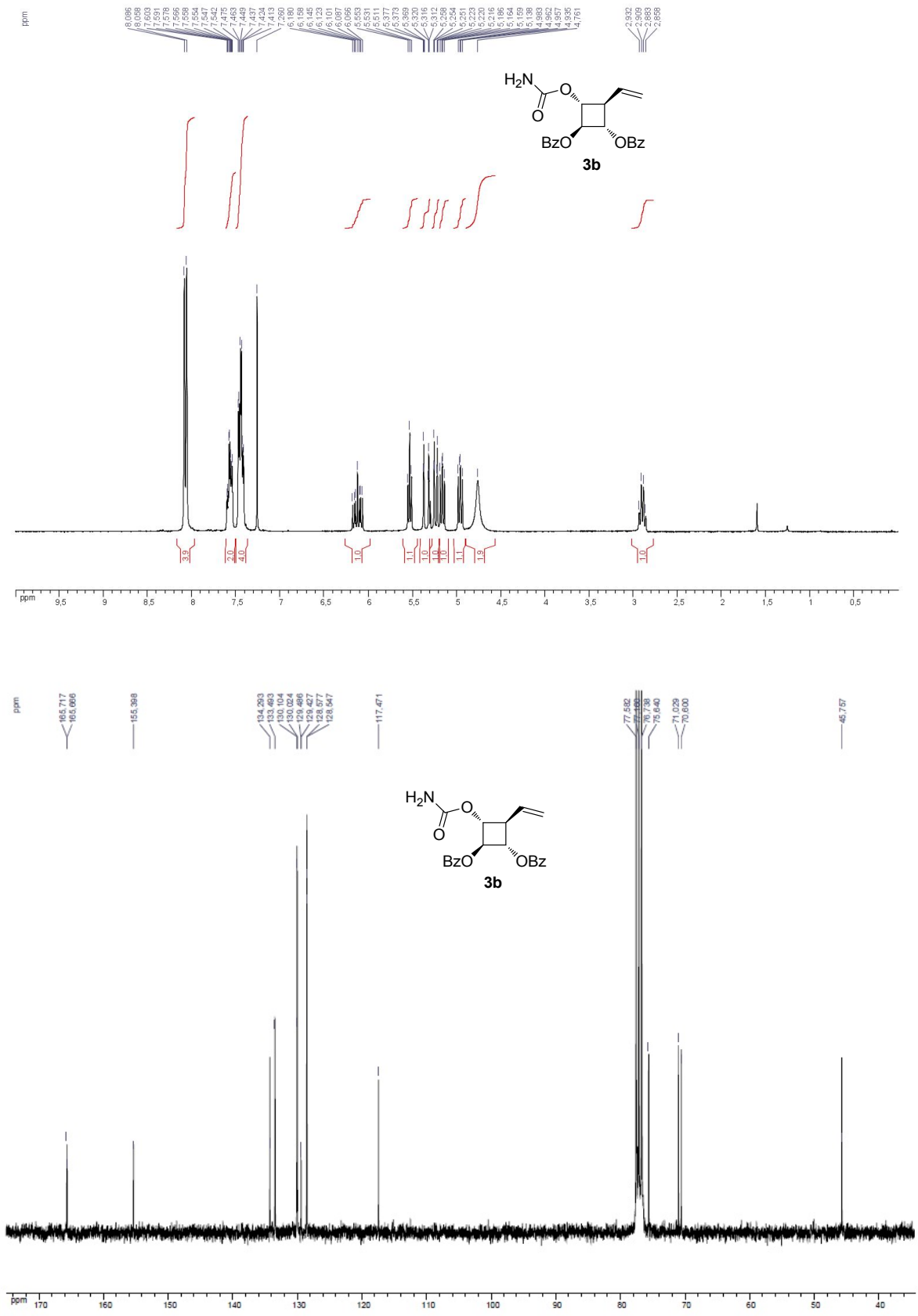


Fig 3. ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound **3b**.

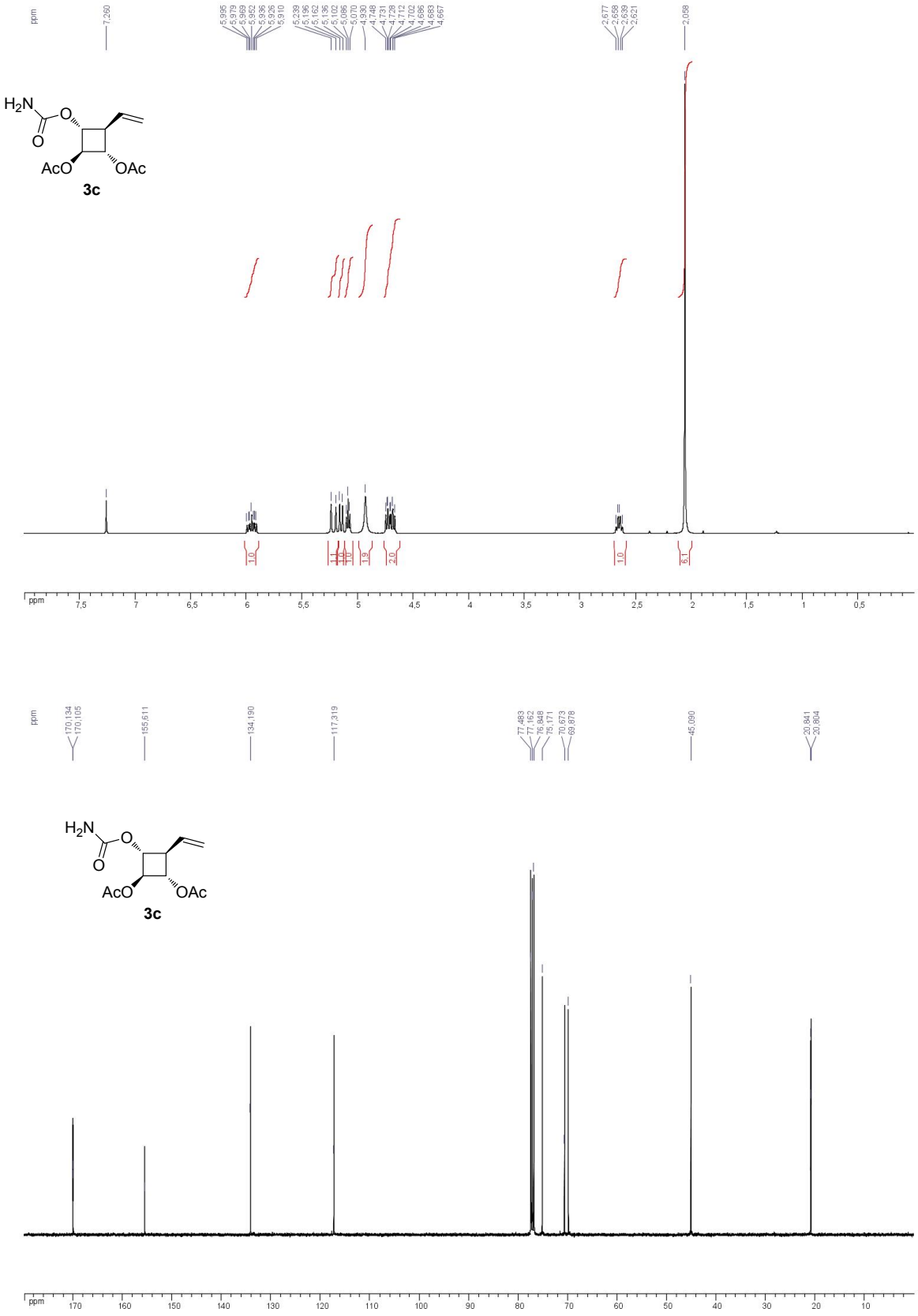


Fig 4 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of compound **3c**.

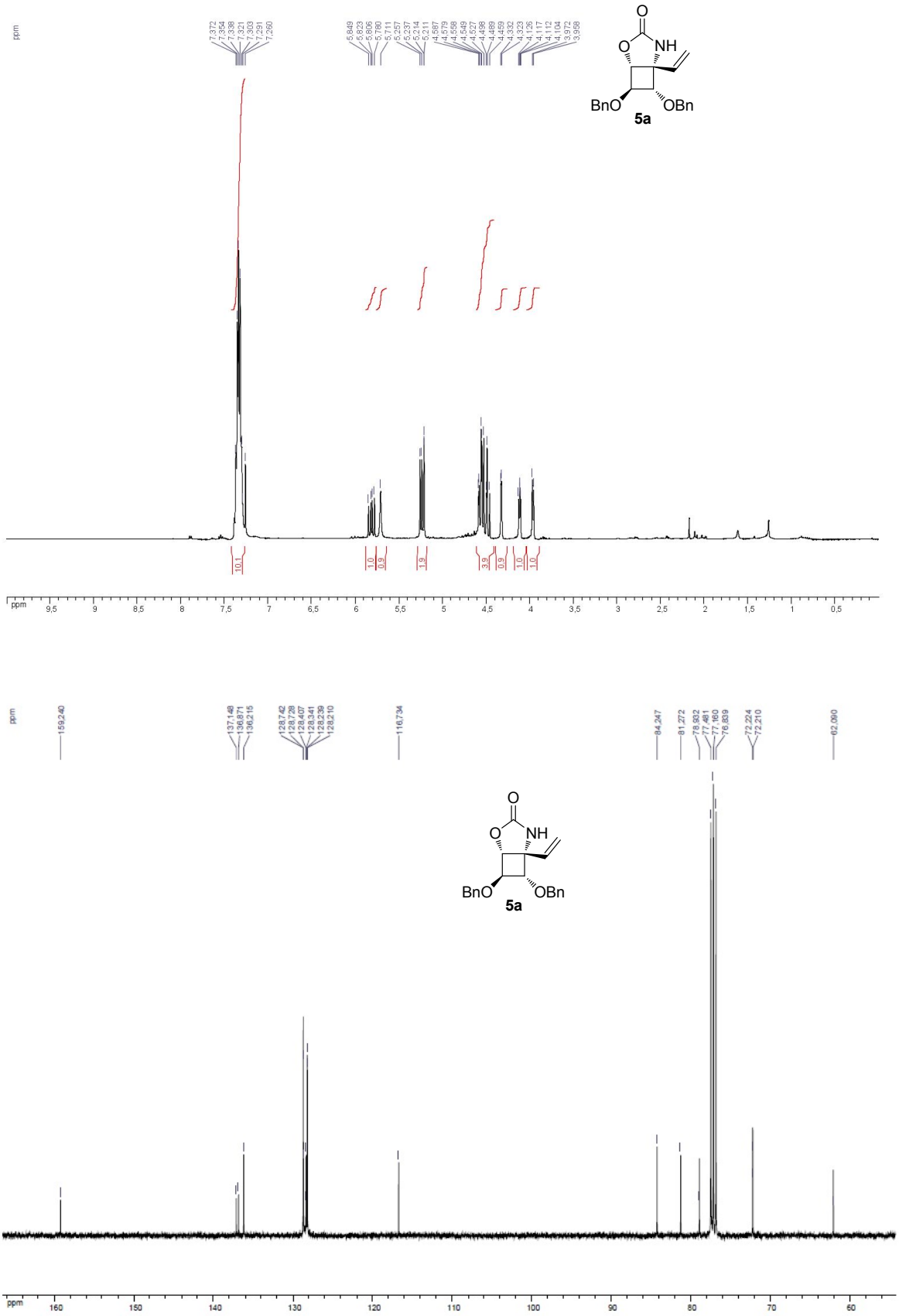


Fig 5 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of compound **5a**.

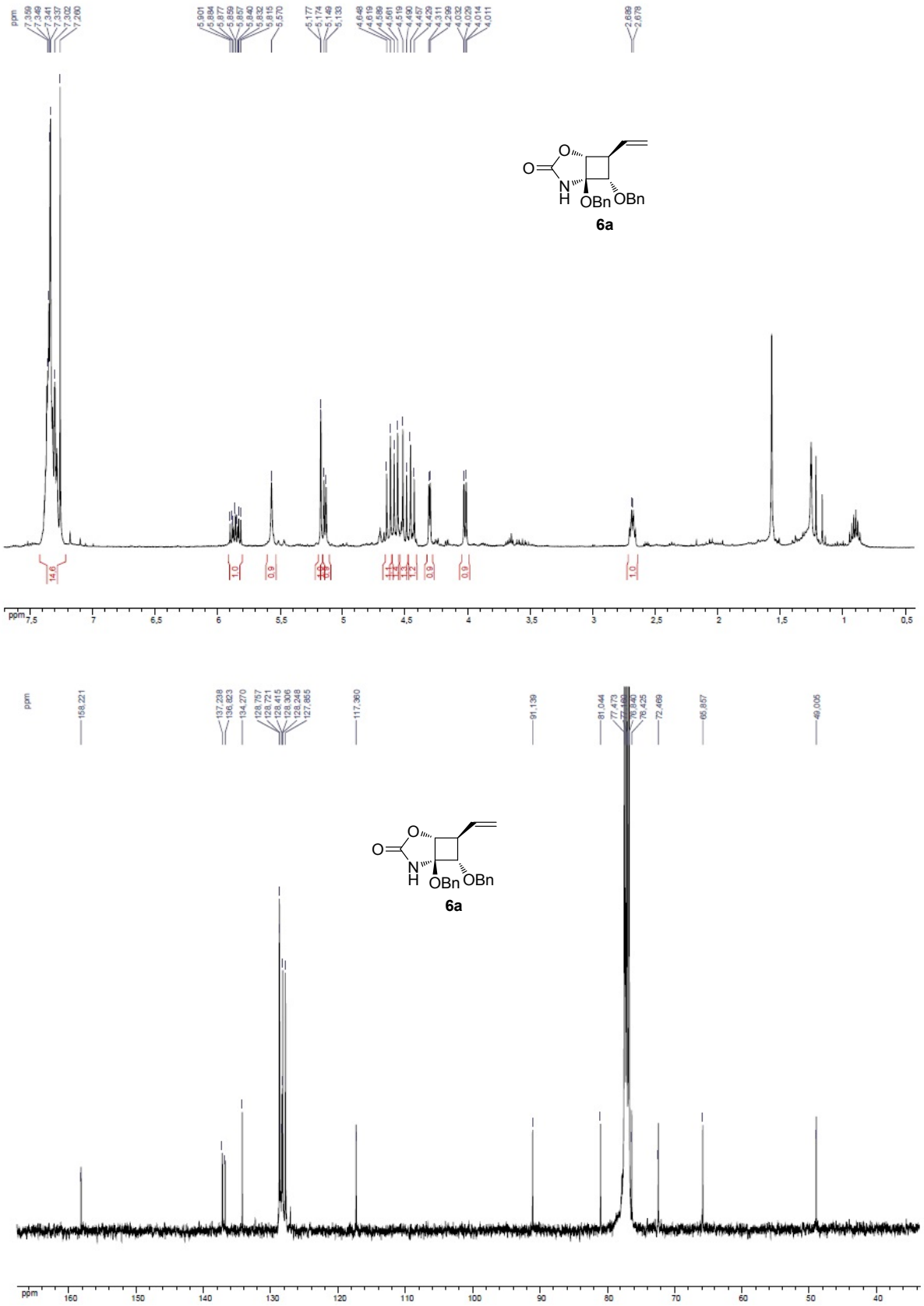


Fig 6 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of compound **6a**.

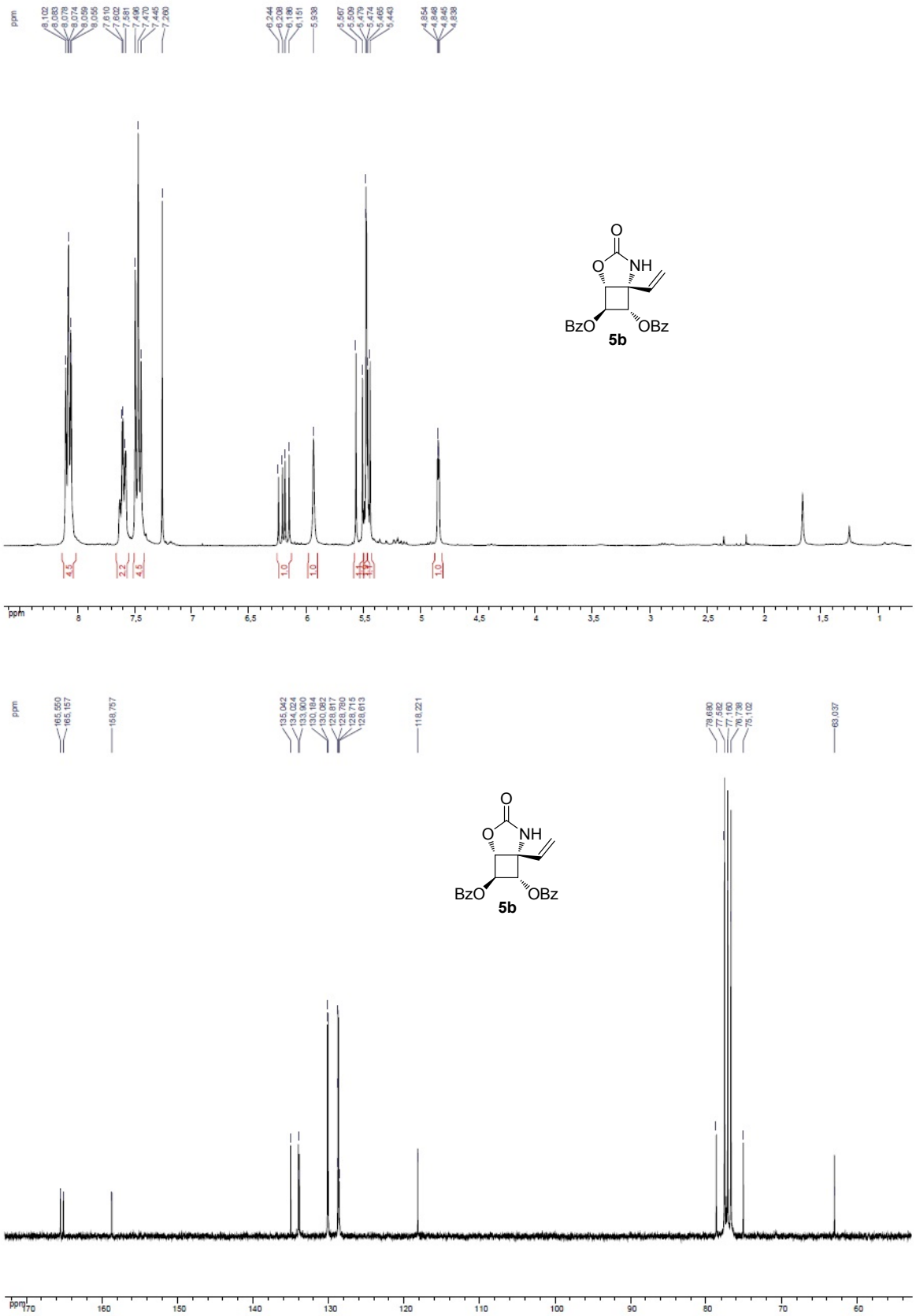


Fig 7 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound **5b**.

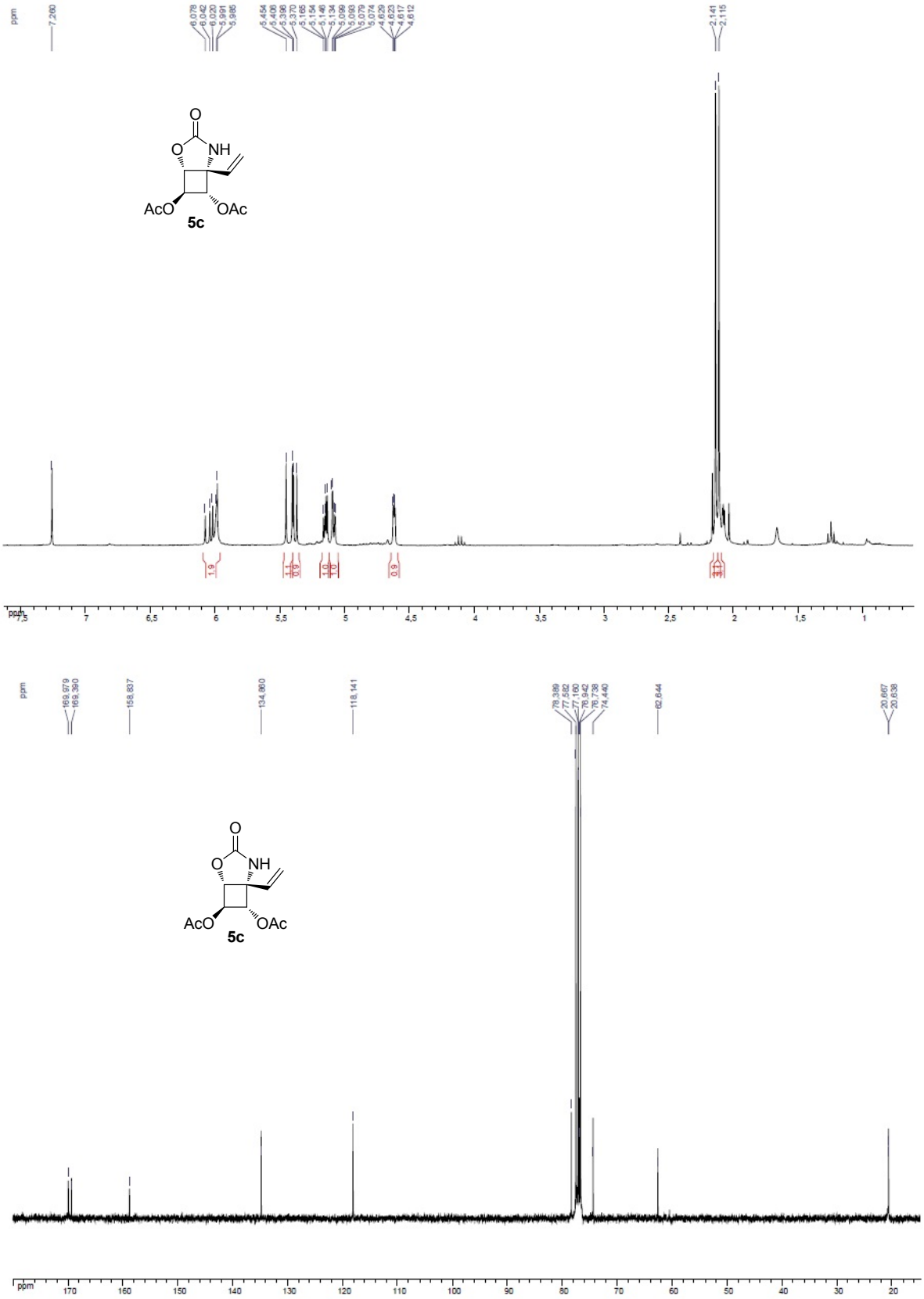


Fig 8 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound **5c**.

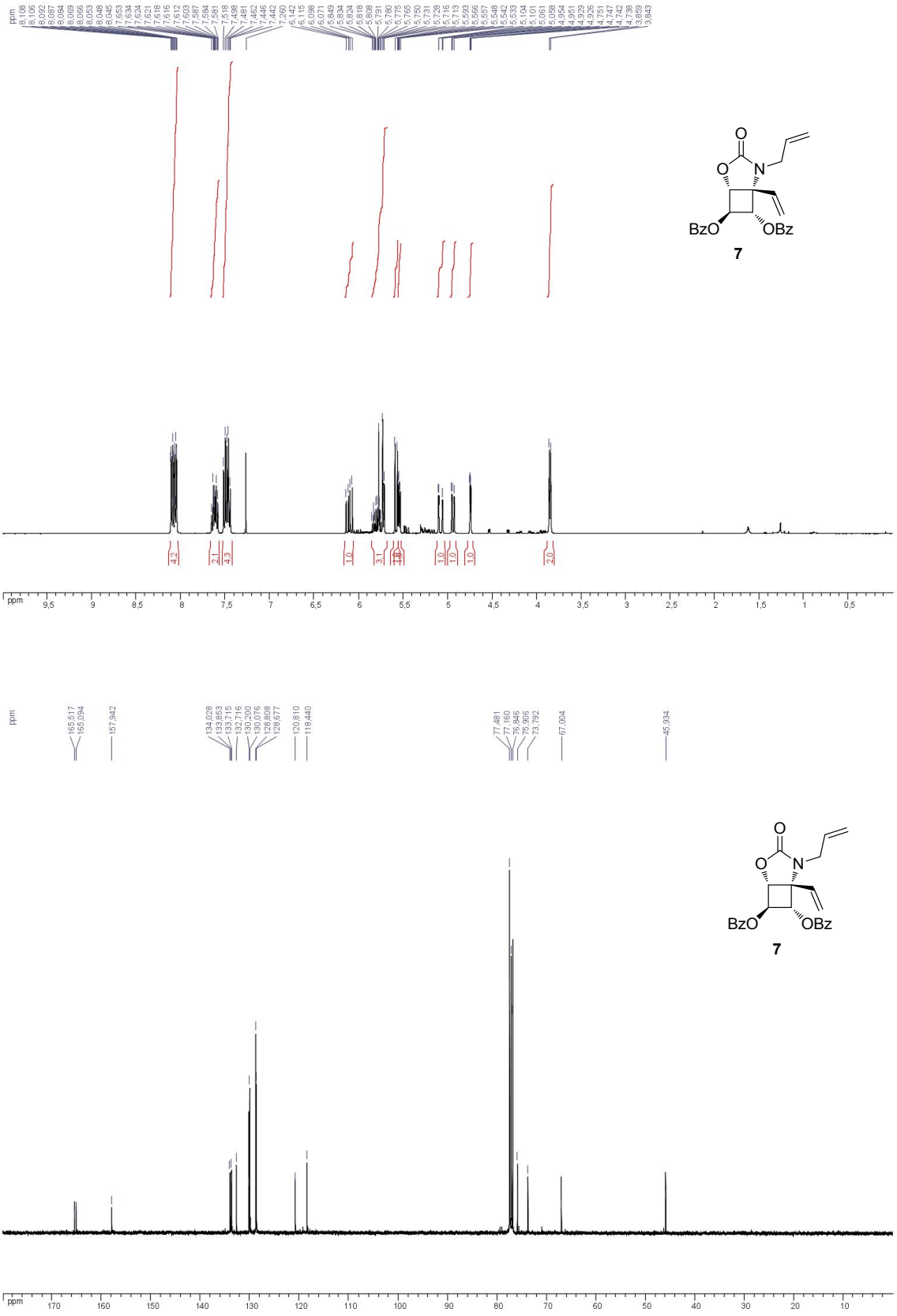


Fig 9 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of compound **5b**.

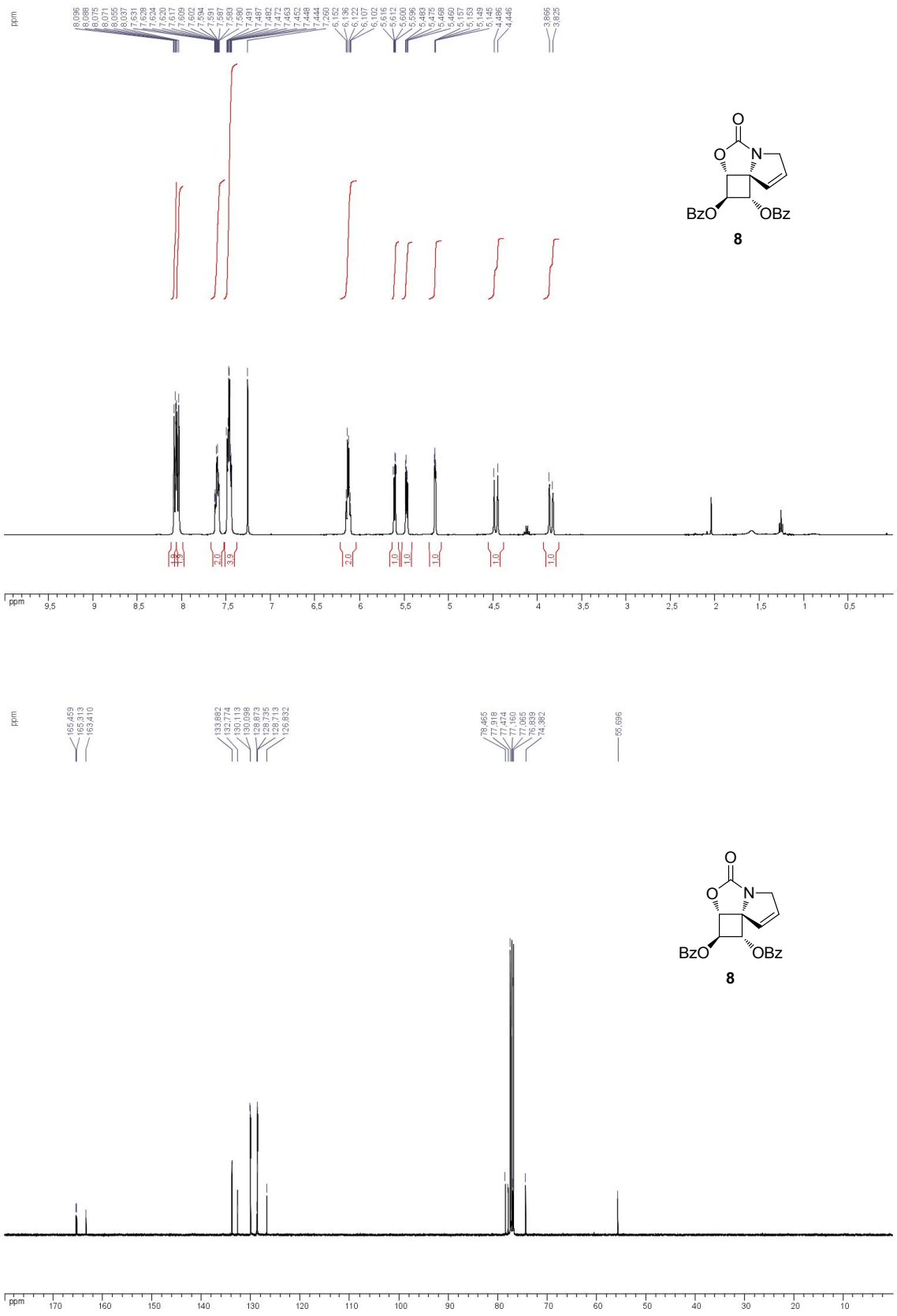


Fig 10 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of compound **8**.

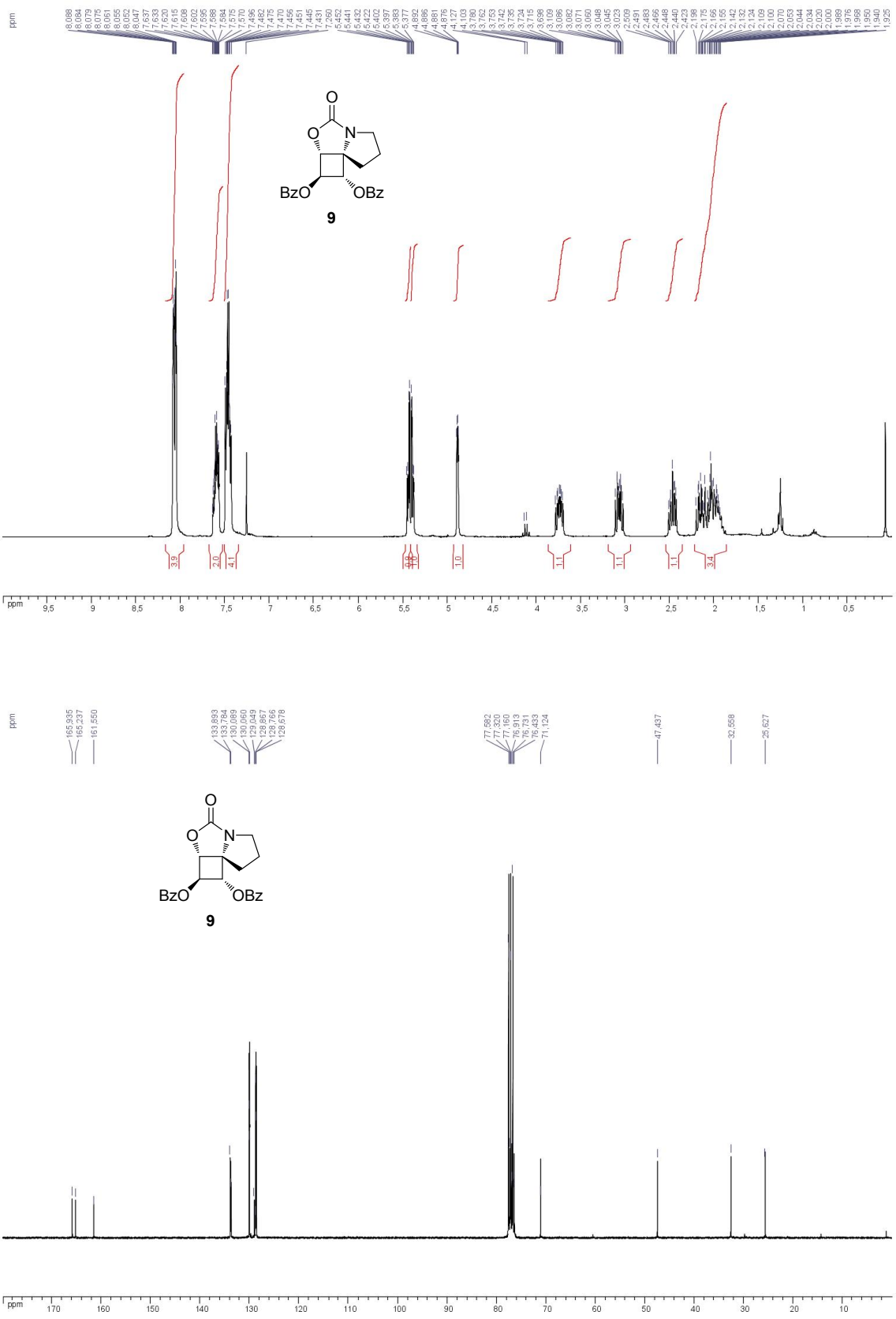


Fig 11 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75MHz, $CDCl_3$) spectra of compound **9**.

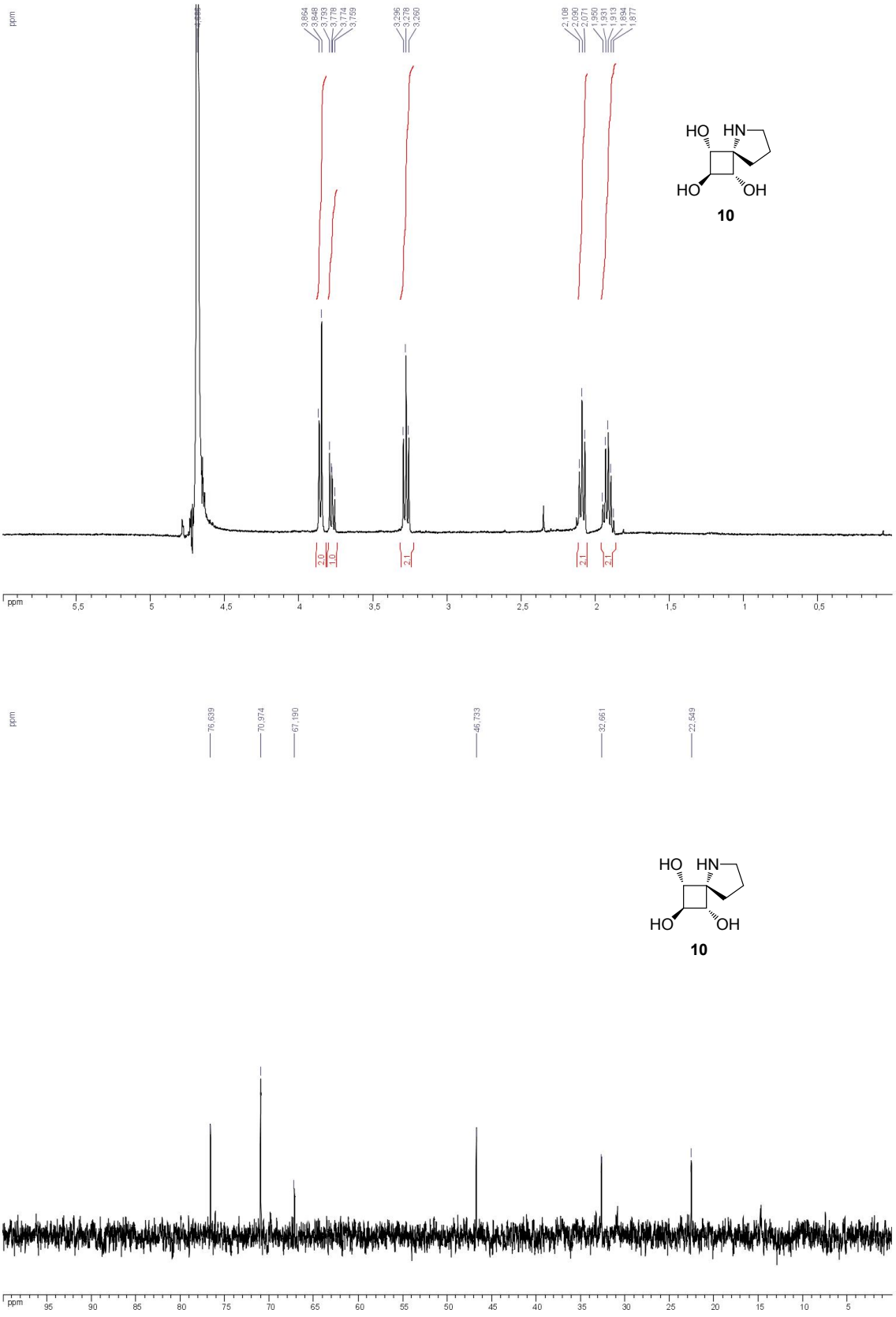


Fig 12 ^{1}H NMR (400 MHz, D_2O) and ^{13}C (100 MHz, D_2O) spectra of compound **10**.

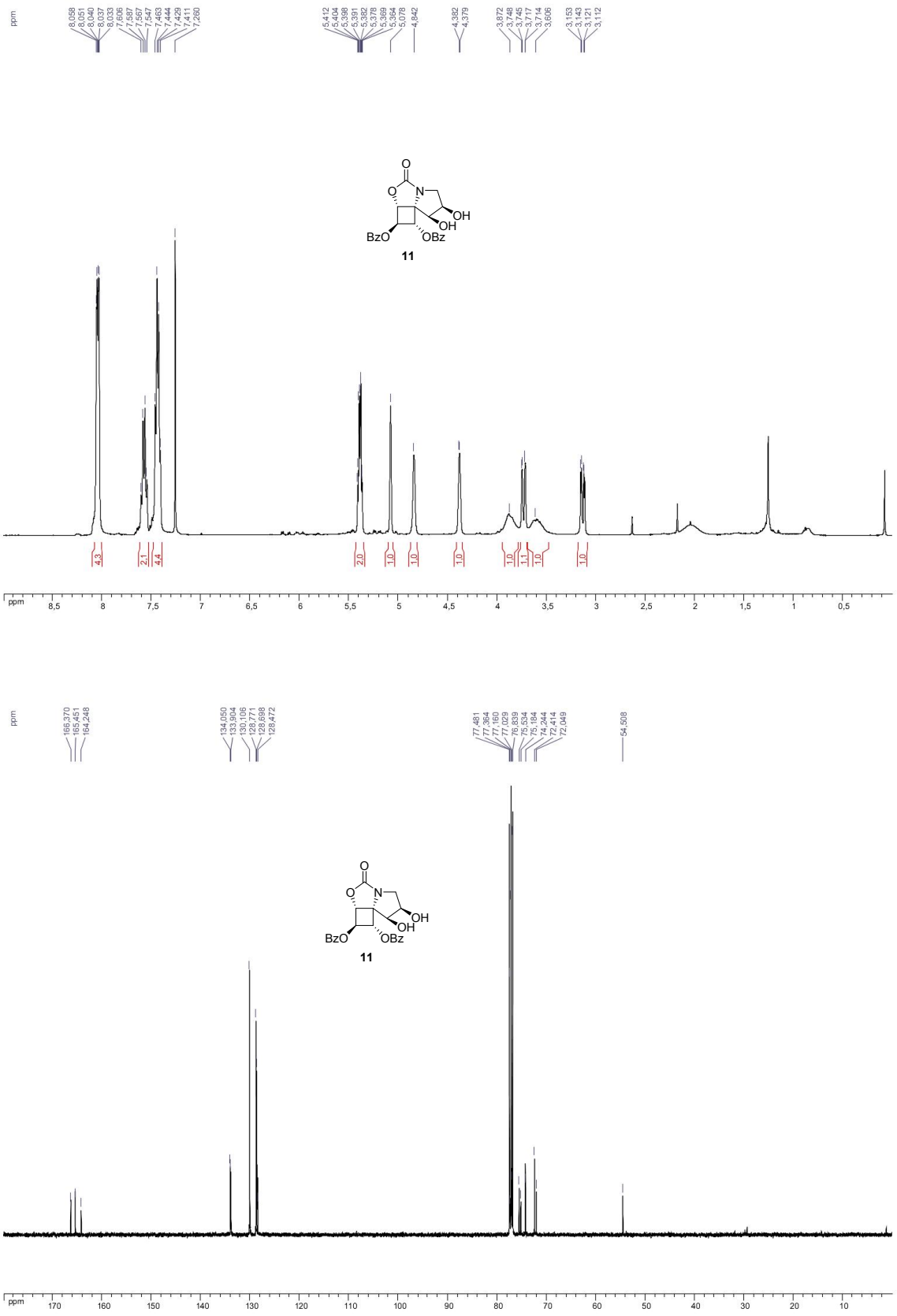


Fig 13 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of compound **11**.

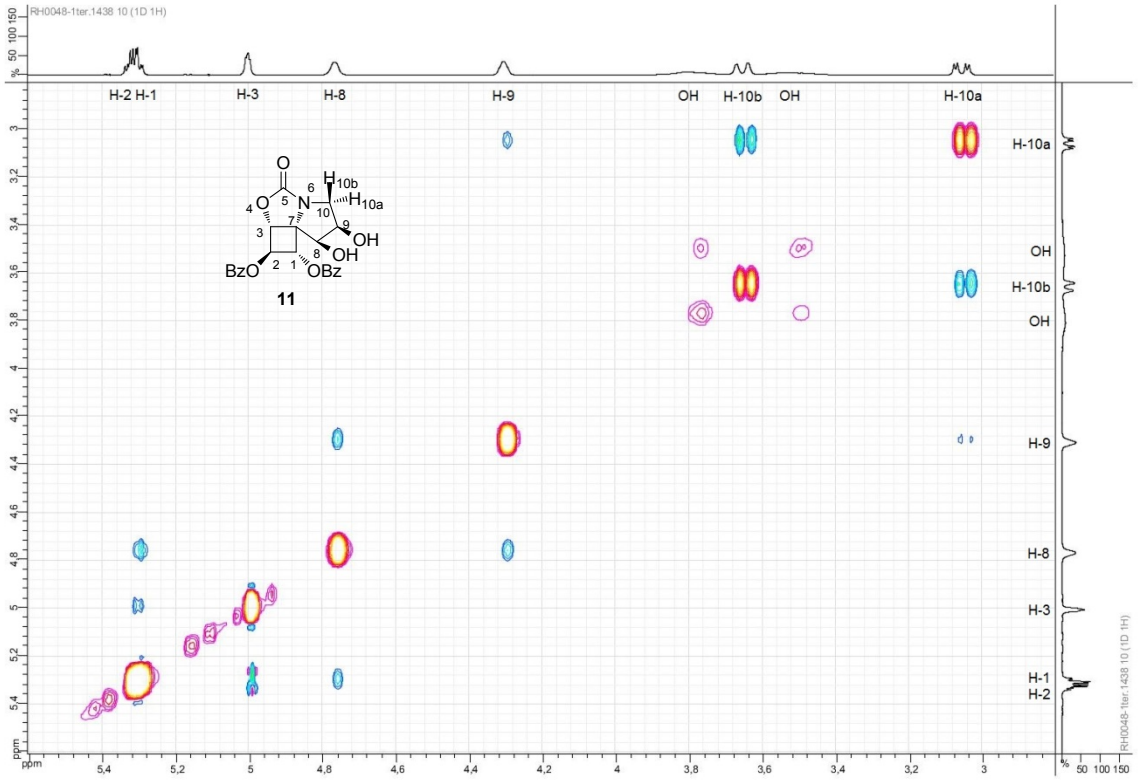


Fig 14 2D NOESY NMR spectrum of compound **11**.

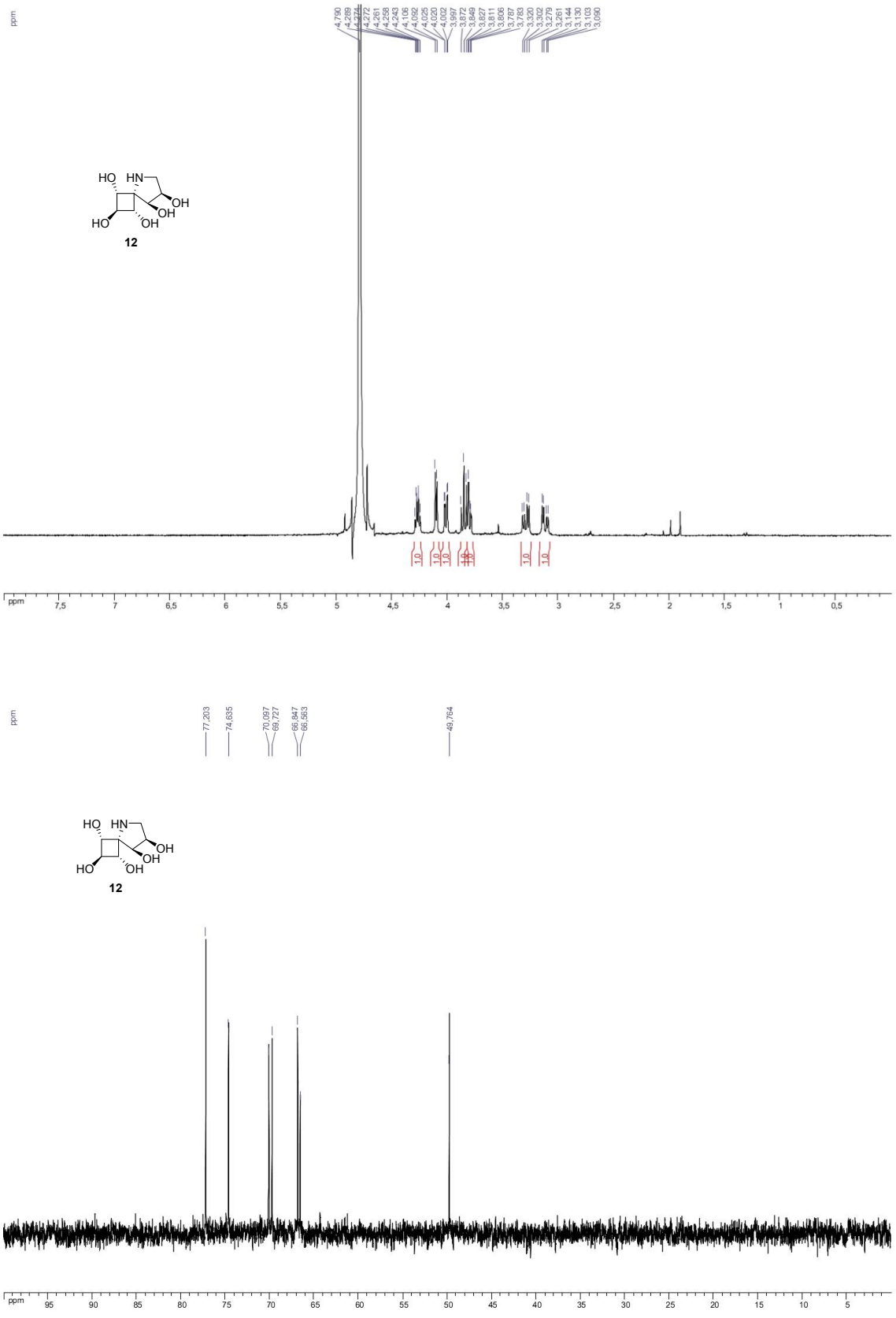


Fig 15 ^{1}H NMR (100 MHz, D_2O) and ^{13}C (75 MHz, D_2O) spectra of compound **12**.

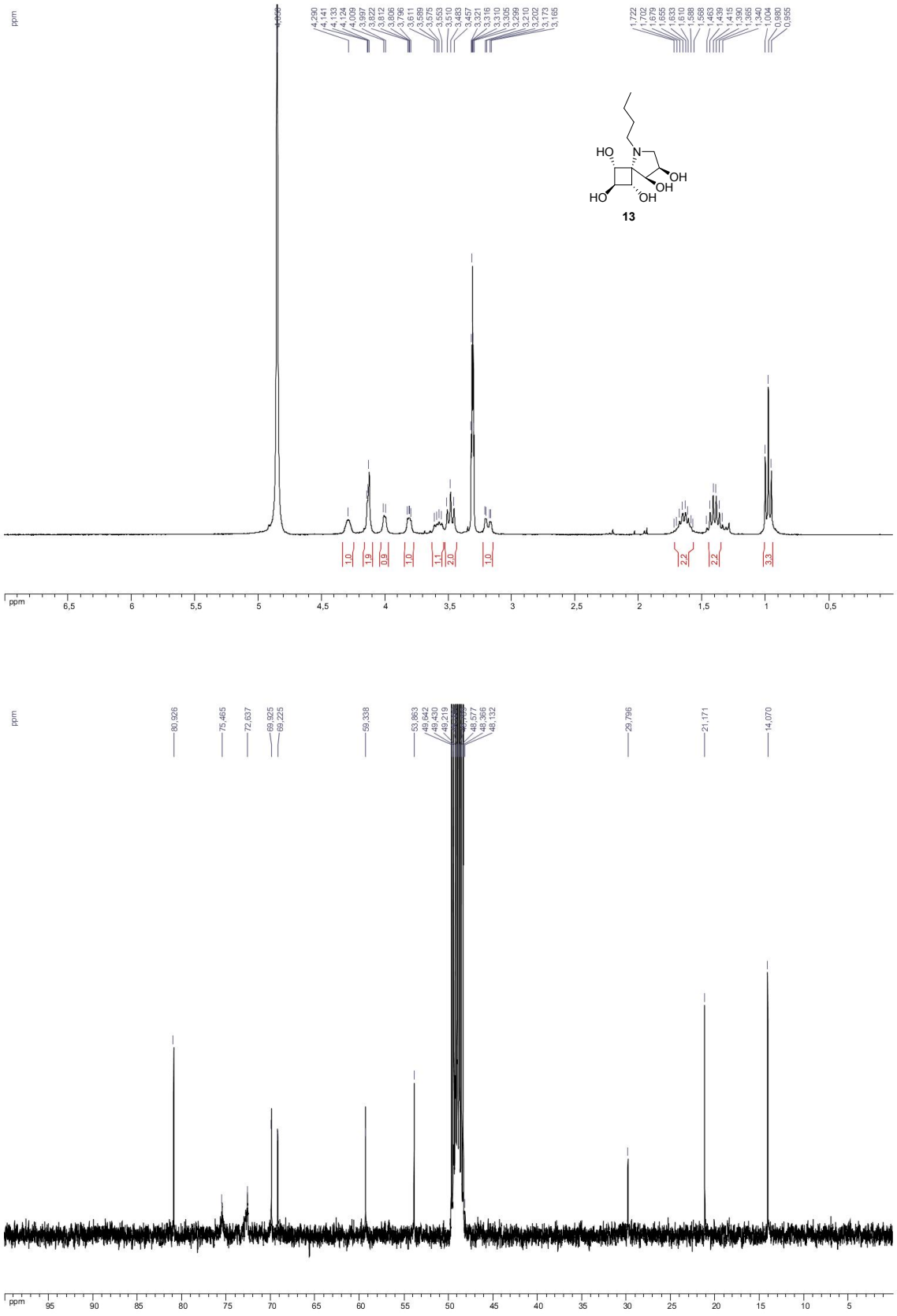


Fig 16 ^{1}H NMR (100 MHz, CD_3OD) and ^{13}C (75 MHz, CD_3OD) spectra of compound **13**.