Electronic Supplementary Information

Synthesis and NMR investigation of styrene glycopolymers containing D-galactose units functionalized with (4-hydroxybutoxy)benzylamine residues

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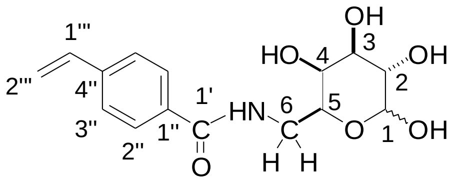
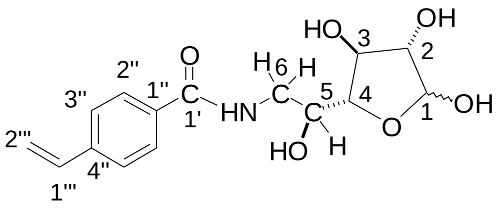
Numbering of the carbons of 1αβ*p*, 1αβ*f*, 9αβ*p*, 9αβ*f*, 13αβ*p*, and 13αβ*f* for NMR assignments



1αβ*p*



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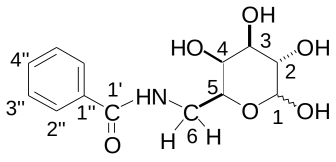
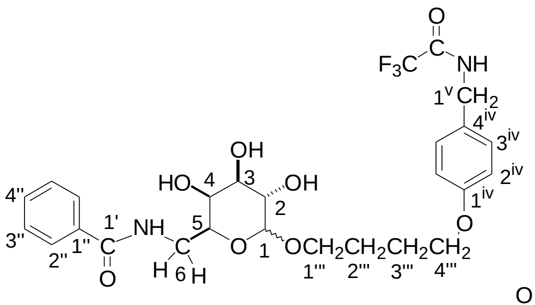
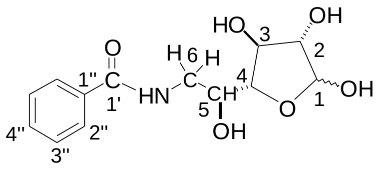


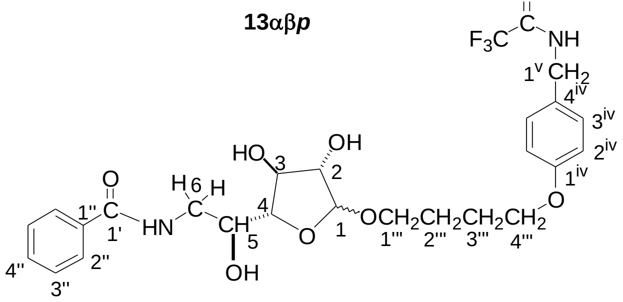
9αβ*p*



13αβ*p*

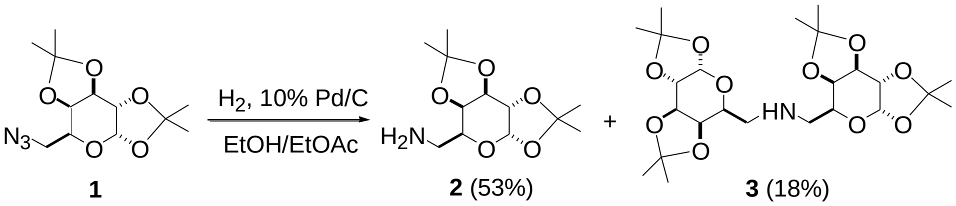


9αβ*f*



13αβ*f*

Catalytic hydrogenation of 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (1)



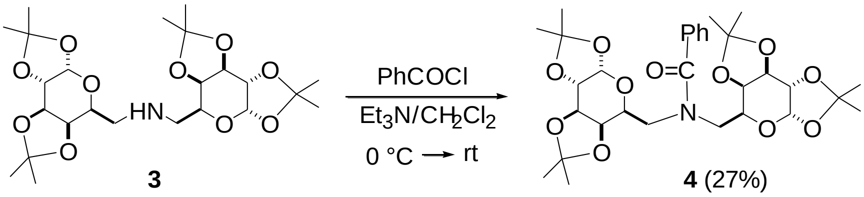
1 **2** (53%) **3** (18%)

Scheme 1

A solution of azide **1** (2.30 g, 8.1 mmol) in absolute EtOH (12.5 mL) and EtOAc (17 mL) was treated with H_2 (3.4 atm) at rt for 4 h under magnetic stirring in presence of 10% Pd/C (0.6401 g) in a flanged cylindrical glass autoclave (140 mL) equipped with valves and manometer.

The catalyst was removed by filtration and washed with THF (5x10 mL). Filtrate and washings were combined and concentrated at reduced pressure to afford a pale yellow oil which was subjected to FC. The mixture $CHCl_3$/MeOH = 96/4 allowed the eluition of the secondary amine **3** (0.73 g, 1.5 mmol, 19%). FTIR (film, cm^{-1}): 3326 (NH). ^{1}H-NMR ($CDCl_3$, δ ppm): 1.32 (s, 6H); 1.33 (s, 6H); 1.44 (s, 6H); 1.54 (s, 6H); 2.86 (m, 4H); 3.82 (m, 2H); 4.21 (dd, 2H, J_1 = 1.9 Hz, J_2 = 8.0 Hz); 4.30 (dd, 2H, J_1 = 2.3 Hz, J_2 = 5.1 Hz); 4.59 (dd, 2H, J_1 = 2.3 Hz, J_2 = 7.9 Hz); 5.53 (d, 2H, J=5.0 Hz). ^{13}C-NMR: 24.64, 25.16, 26.21, 26.34, 49.55, 66.98, 70.84, 71.06, 72.06, 96.58, 108.61, 109.30. The mixture $CHCl_3$/MeOH = 20/80 allowed the eluition of **2** (1.10 g, 4.2 mmol, 53%) as colorless oil with the same spectroscopic data of the amine obtained from $LiAlH_4$.

N,*N*-Bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyl)benzamide (4)

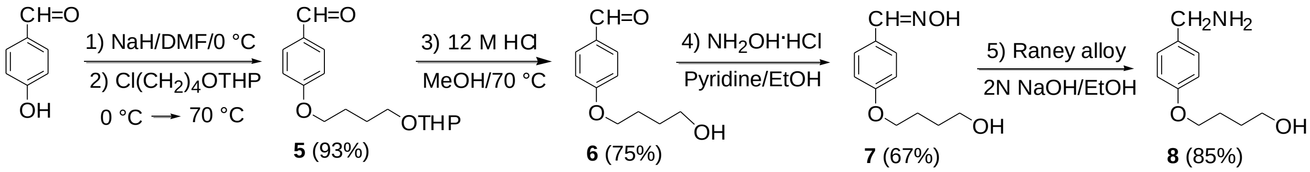


3 **4** (27%)

Scheme 2

A solution of **3** (1.35 g, 2.7 mmol) and Et_3N (2.09 g, 20.7 mmol) in CH_2Cl_2 (13 mL) was cooled to 0 °C, added with benzoyl chloride (0.7267 g, 5.2 mmol), left under magnetic stirring for 3 h at rt, hydrolyzed with H_2O (10 mL, pH = 7-8) and extracted with CH_2Cl_2 (3x15 mL). The extracts were dried ($MgSO_4$) and concentrated at reduced pressure to afford crude **4** which was purified by FC using a mixture petroleum ether/acetone = 7/3 as eluent followed by crystallization in the form of a white solid from diisopropyl ether (0.4438 g, 0.73 mmol, 27%). Mp 127-132°C. Purity 98% by HPLC. $[\alpha]_D = -45.2$ (*c* 1.08, $CHCl_3$, 22 °C). FTIR (KBr, cm^{-1}): 1625 (C=O, amide). ^{1}H-NMR ($CDCl_3$, δ ppm): 1.19 (s, 3H); 1.25 (s, 3H); 1.32 (s, 6H); 1.36 (s, 3H); 1.46 (s, 3H); 1.49 (s, 3H); 1.53 (s, 3H); 3.50-3.74 (m, 3H); 3.87-3.95 (m, 3H); 4.27-4.35 (m, 4H); 4.57 (dd, 2H, *J* = 6.6 Hz); 5.50 (dd, 2H, *J* = 4.5 Hz); 7.24-7.41 (m, 5H). ^{13}C-NMR: 24.57, 24.66, 24.90, 25.17, 25.71, 25.99, 26.10 (2C), 46.62, 50.61, 66.08, 66.39, 70.36, 70.69, 70.79, 71.07 (2C), 71.82, 96.30, 96.45, 108.58, 108.92, 109.38 (2C), 126.95, 128.17, 128.97, 137.17, 172.78. Found: C, 61.3; H, 7.5; N 2.2. $C_{31}H_{43}NO_{11}$ requires C, 61.5; H, 7.2; N 2.3.

Alternative synthesis of 4-(4-hydroxybutoxy)benzylamine (8)



Scheme 3

4-[4-(2-Tetrahydropyranyloxybutoxy)]benzaldehyde (5)

NaH (60% suspension in white oil, 2.50 g, 62.5 mmol) was washed with dry pentane (3x4mL), suspended in dry DMF (24 mL), treated under N_2 with a solution of 4-hydroxybenzaldehyde (6.90 g, 56.5 mmol) in dry DMF (24 mL) and stirred at rt for 60 min. The mixture was then cooled to 0 °C, treated with a solution of 2-(4-chlorobutoxy]tetrahydropyran[1] (10.80 g, 56.0 mmol) in dry DMF (11.5 mL) and stirred at 70 °C for 31 h. The mixture was hydrolyzed with 10% KOH (20 mL, pH = 14), extracted with Et_2O (3x50 mL), then with CH_2Cl_2 (3x50 mL) and the extracts were combined and dried ($MgSO_4$). The removal of the solvent at reduced pressure afforded **5** as an oil which was purified by filtration through a short silica gel column (h = 100 mm, ϕ = 20 mm) using a mixture of petroleum ether/EtOAc = 1/1 as eluent (200 mL) (14.59 g, 52.4 mmol, 93%). Purity 98% by HPLC. FTIR (KBr, cm^{-1}): 2943, 2872 (THP); 1691 cm^{-1} (C=O, aldehyde). ^{1}H-NMR ($CDCl_3$): δ 1.75 (m, 10H), 3.49 (m, 2H), 3.85 (m, 2H), 4.09 (t, 2H, *J* = 6.3 Hz), 4.60 (t, 1H, *J* = 2.7 Hz), 6.98-7.02 (m, 2H), 7.80-7.85 (m, 2H), 9.87 (s, 1H). ^{13}C-NMR: δ 19.68, 25.47, 26.10, 26.25, 30.76, 62.41, 66.99, 68.15, 98.94, 114.76, 129.81, 131.97, 164.18, 190.76. Found: C, 69.3; H, 8.05. $C_{16}H_{22}O_4$ requires C, 69.0; H, 8.0.

4-(4-Hydroxybutoxy)benzaldehyde[2] (6)

A solution of **5** (8.49 g, 30.5 mmol) in MeOH (20 mL) was treated with a solution of 12 N HCl (5.8 mL) in H_2O (11.5 mL) at 70 °C for 50 h then the mixture was added with 10 % NaOH (100 mL, pH=14) and extracted with CH_2Cl_2 (5x50 mL). The extracts were dried ($MgSO_4$), concentrated at reduced pressure and filtered through a short silica gel column (h = 120 mm; ϕ = 20 mm) using a mixture of petroleum ether/EtOAc = 1/1 as eluent (250 mL) to afford **6** as an orange oil[2] (4.46 g, 23.0 mmol, 75%). Purity 99% by HPLC. FTIR (KBr, cm^{-1}): 3419 (OH); 1688 (C=O). ^{1}H-NMR ($CDCl_3$): δ 1.83 (m, 4H), 2.75 (s, 1OH), 3.72 (t, 2H, *J* = 6.3 Hz), 4.07 (t, 2H, *J* = 6.3 Hz), 6.95-6.99 (m, 2H), 7.00-7.83 (m, 2H), 9.84 (s, 1H). ^{13}C-NMR: δ 25.59, 29.09, 62.05, 68.18, 114.77, 129.68, 132.03, 164.17, 191.05. GC/MS (CI, m/z): 195 (M^++1, 100%), 177 (M^+ +1 - H_2O, 50%). Found: C, 68.0; H, 7.5. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3.

4-(4-Hydroxybutoxy)benzaldoxime (7)

A solution of **6** (4.46 g, 23.0 mmol) in 95% EtOH (34.2 mL) was treated with a solution of $NH_2OH\cdot HCl$ (4.19 g, 60.3 mmol) in dry pyridine (9.2 mL) at rt for 45 h, hydrolyzed with H_2O (35 ml) and extracted with EtOAc (4x35 mL). The extracts were dried ($MgSO_4$), concentrated at reduced pressure and passed through a short silica gel column (h = 150 mm; ϕ = 20 mm) using a mixture of petroleum ether/acetone = 1/1 as eluent (250 mL) to afford **7** as a waxy solid which turned to crystalline by treatment with diisopropyl ether (3.21 g, 15.3 mmol, 67%). Mp 103-105 °C. Purity 99% by HPLC. FTIR (KBr, cm^{-1}): 3179 (OH); 1476 (C=N). ^{1}H-NMR (DMSO-d_6): δ 1.65 (m, 4H), 3.45 (t, 2H, J = 6.4 Hz), 3.99 (t, 2H, J = 6.4 Hz), 4.44 (bs, 1OH), 6.93-6.96 (m, 2H), 7.31-7.52 (m, 2H), 8.06 (s, 1OH), 10.96 (s, 1H). ^{13}C-NMR: δ 27.27, 30.83, 62.27, 69.38, 116.54, 127.34, 129.71, 149.54, 161.43. Found: C, 63.4; H, 7.5; N, 6.8. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2; N, 6.7.

4-(4-Hydroxybutoxy)benzylamine (8)

A mixture of oxime **7** (6.96 g, 33.3 mmol), absolute EtOH (130 mL) and 2 N NaOH (130 mL) was treated with Ni-Al Raney alloy (9.05 g) at rt under stirring for 2 h, then Ni-Al Raney alloy was removed by filtration and washed with EtOH. Filtrate and washings were combined, concentrated at reduced pressure, taken with THF and washed with satd NaCl solution. The extracts were dried ($MgSO_4$), concentrated at reduced pressure to give crude **8** (4.91 g, 25.1 mmol, 76%) as an oil which turned to a waxy solid by treatment with petroleum ether. **8** showed spectral data coincident with those of 4-(4-hydroxybutoxy)benzylamine synthesized as reported in the main paper.

Synthesis of ethyl 4-(4-cyanophenoxy)butanoate (9)

A 60% oil dispersion of NaH (1.88 g, 47.1 mmol) was washed two times with dry pentane, suspended in dry DMF (37 mL), cooled to 0 °C and treated under N_2 with a solution of 4-cyanophenol (5.10 g, 42.2 mmol) in dry DMF (15 mL). The suspension was left to reach rt, stirred for 1 h, cooled to 0 °C, added with ethyl 4-bromobutanoate (8.60 g, 44.0 mmol) and left under stirring overnight. The suspension was hydrolyzed with water (25 ml, pH = 8-9), extracted with Et_2O (3x30 mL) and dried ($MgSO_4$). The removal of the solvent at reduced pressure afforded **9** as a solid which was crystallized from hexane: (9.19 g, 94%). Mp 60-62 °C. Purity 99% by HPLC. FTIR

(KBr, cm^{-1}): 2219 (CN), 1732 (C=O, ester). ^{1}H-NMR ($CDCl_3$, δ ppm): 1.26 (t, 3H, *J* = 7.1 Hz); 2.09-2.18 (m, 2H); 2.52 (t, 2H, *J* = 7.3 Hz); 4.07 (t, 2H, *J* = 6.2 Hz); 4.15 (q, 2H, *J* = 7.2 Hz); 6.96-7.60 (m, 4H). ^{13}C-NMR: 14.23, 24.36, 30.56, 60.57, 67.17, 104.04, 115.21, 119.20, 134.01, 162.14, 172.92. Found: C, 71.6; H, 7.3; N 6.2. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N 6.45.

Table 1. Typical homopolymerization data of **1** at 60 °C.

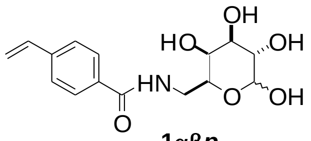
Run	Monomer g (mmol)	AIBN mg (%)	Solvent Ml	Time H	Polymer g (%)
1	***1αβpf*** 1.21 (3.91)	12.1 (1.0)	DMSO 20	24	***P1αβpf*** 0.554 (45.8)
2	***1αβpf*** 1.50 (4.85)	15.4 (1.0)	DMSO 26	72	***P1αβpf*** 1.10 (73.3)

AIBN = Azo*bis*(2-methylpropionitrile); *p* = pyranose form; *f* = furanose form.

References

1. Jian Guan, D. E. Kyle, L. Gerena, Quang Zhang, W. K. Milhous, A-J. Lin, *J. Med. Chem.*, 2002, **45**, 2741-2748.

2. S. Peterli, D. Hubmann,; U. Séquin, H. Mett, P. Traxler, *Helv. Chim. Acta*, 1994, **77**, 59-69.



1αβ*p*

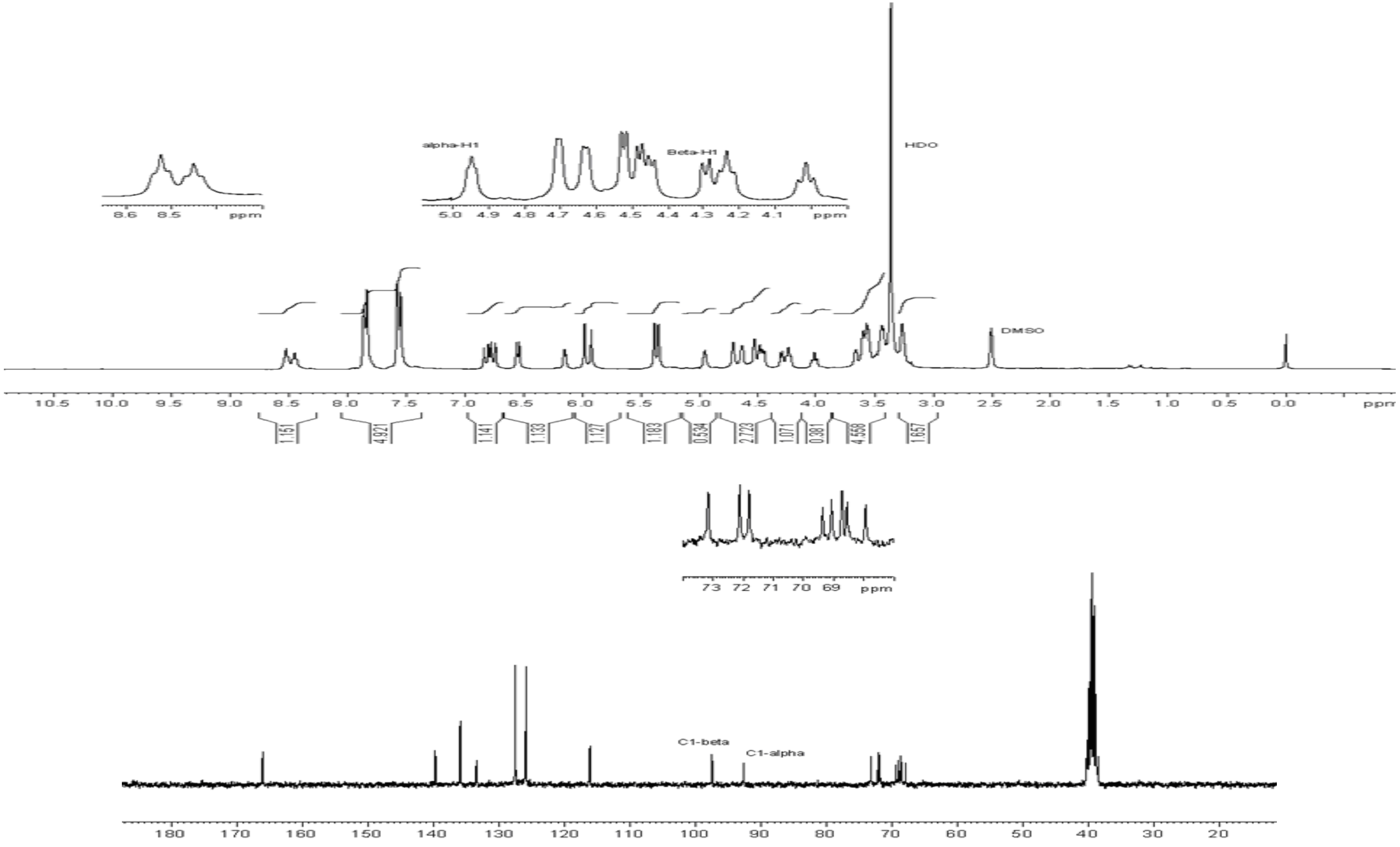
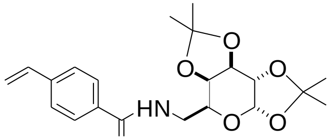


Figure S1. ^{1}H and ^{13}C NMR spectra of **1αβ*p*** in DMSO-*d6*



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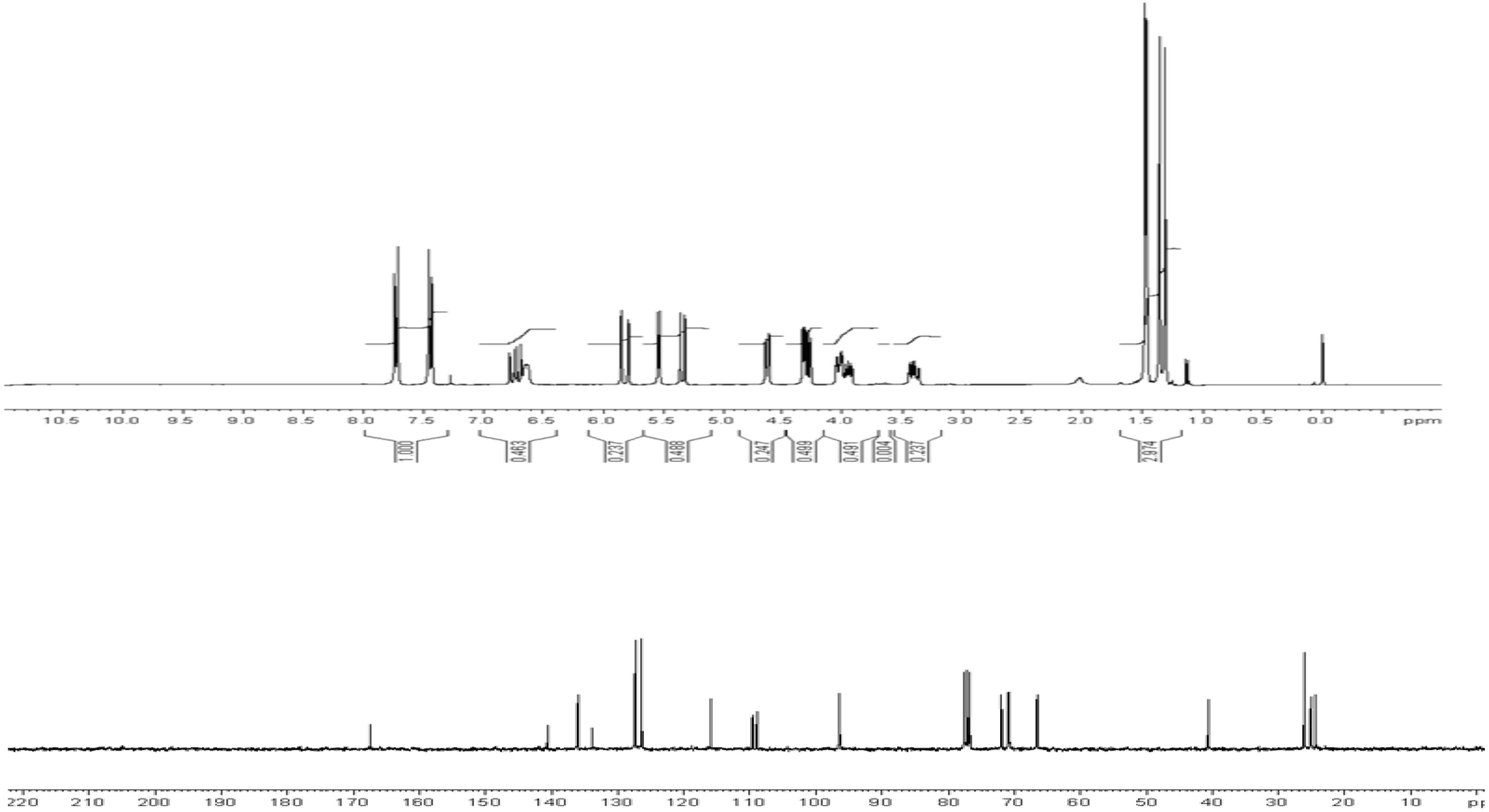
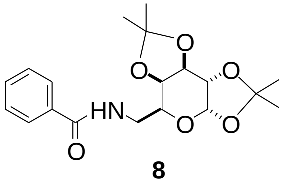


Figure S2. ^{1}H and ^{13}C NMR spectra of **7** in $CDCl_3$



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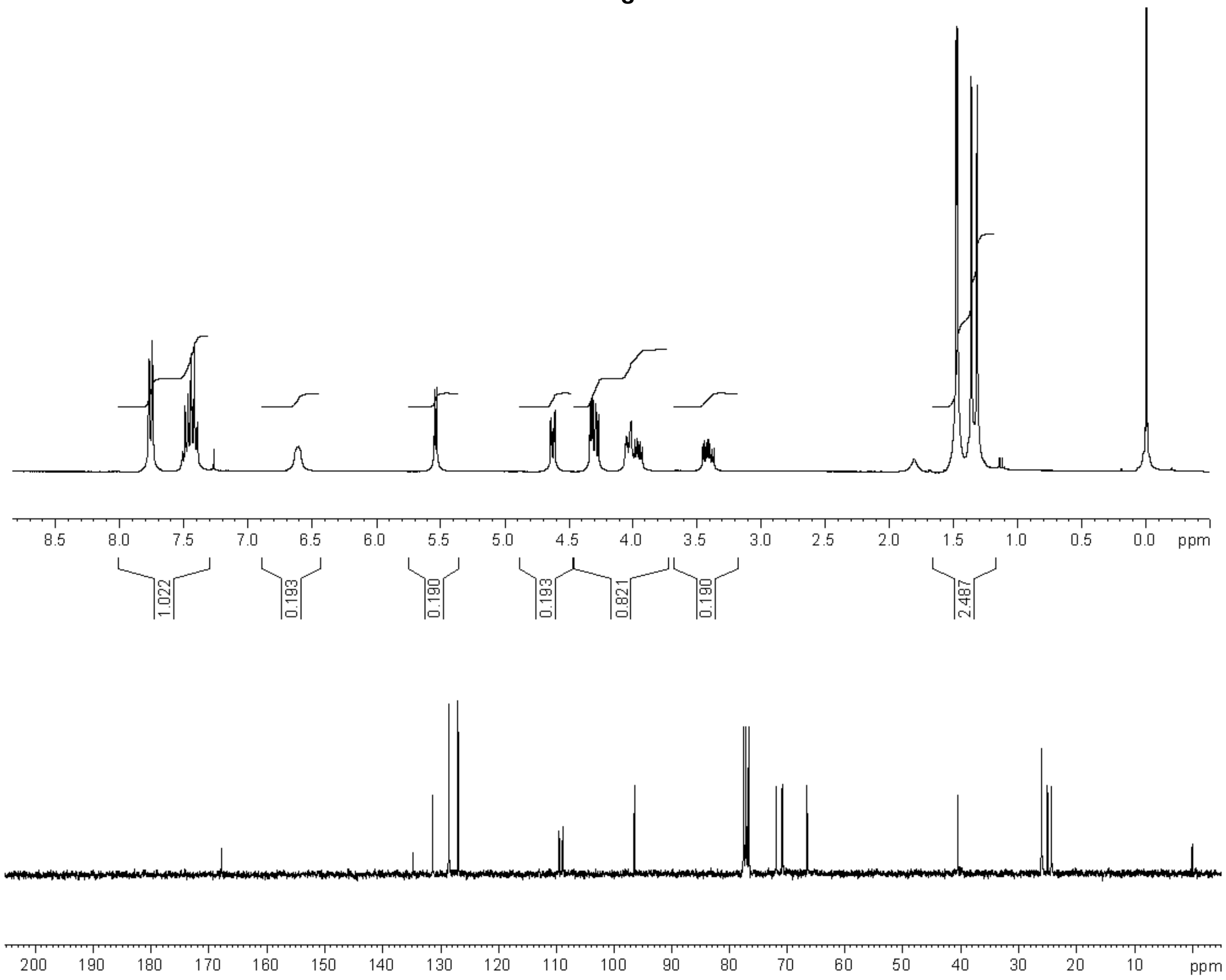
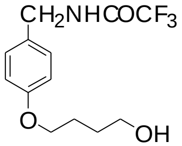


Figure S3. ^{1}H and ^{13}C NMR spectra of **8** in $CDCl_3$.



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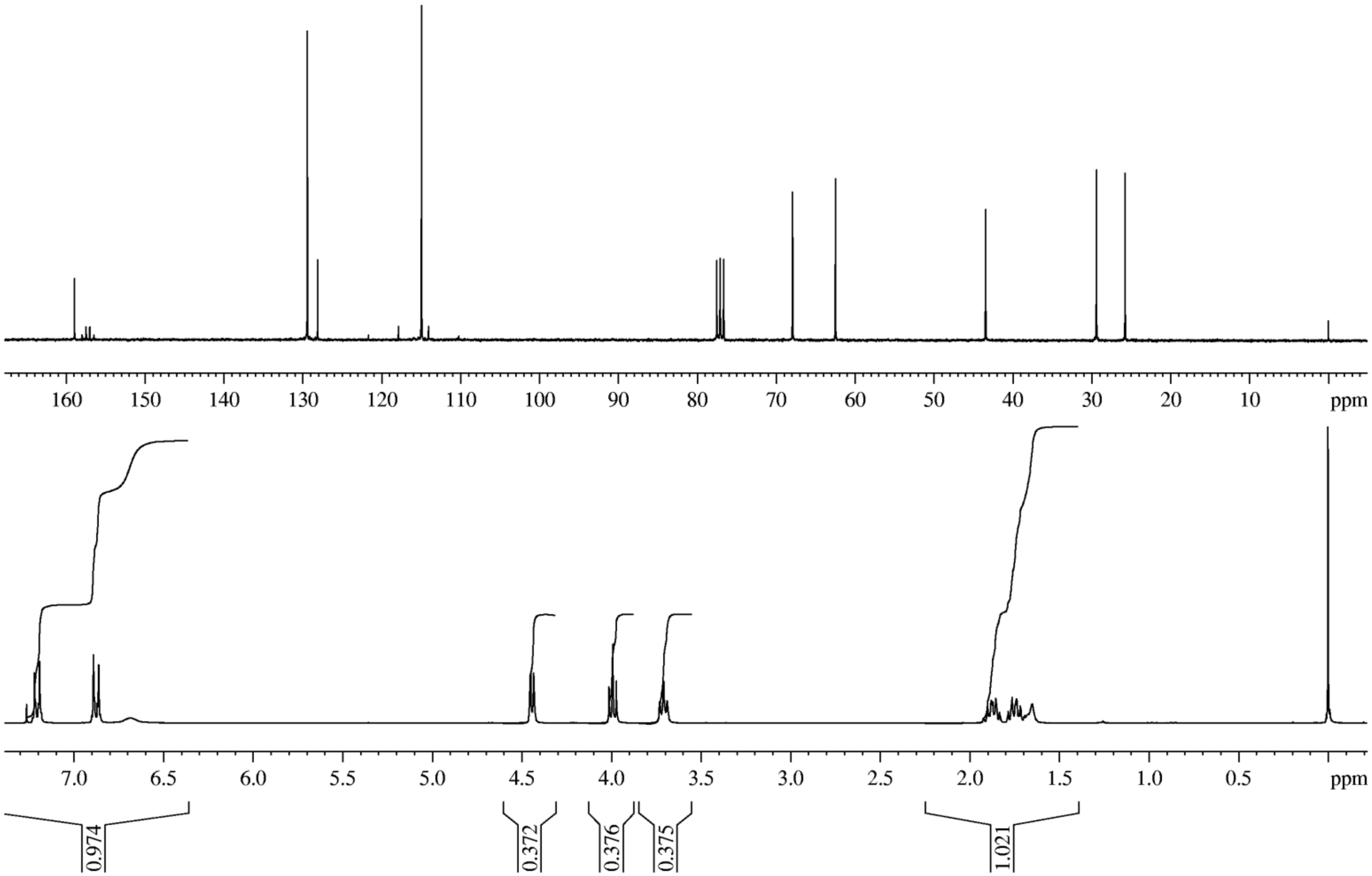
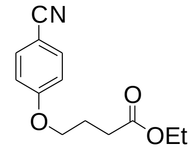


Figure S4. ^{1}H and ^{13}C NMR spectra of **10** in $CDCl_3$.



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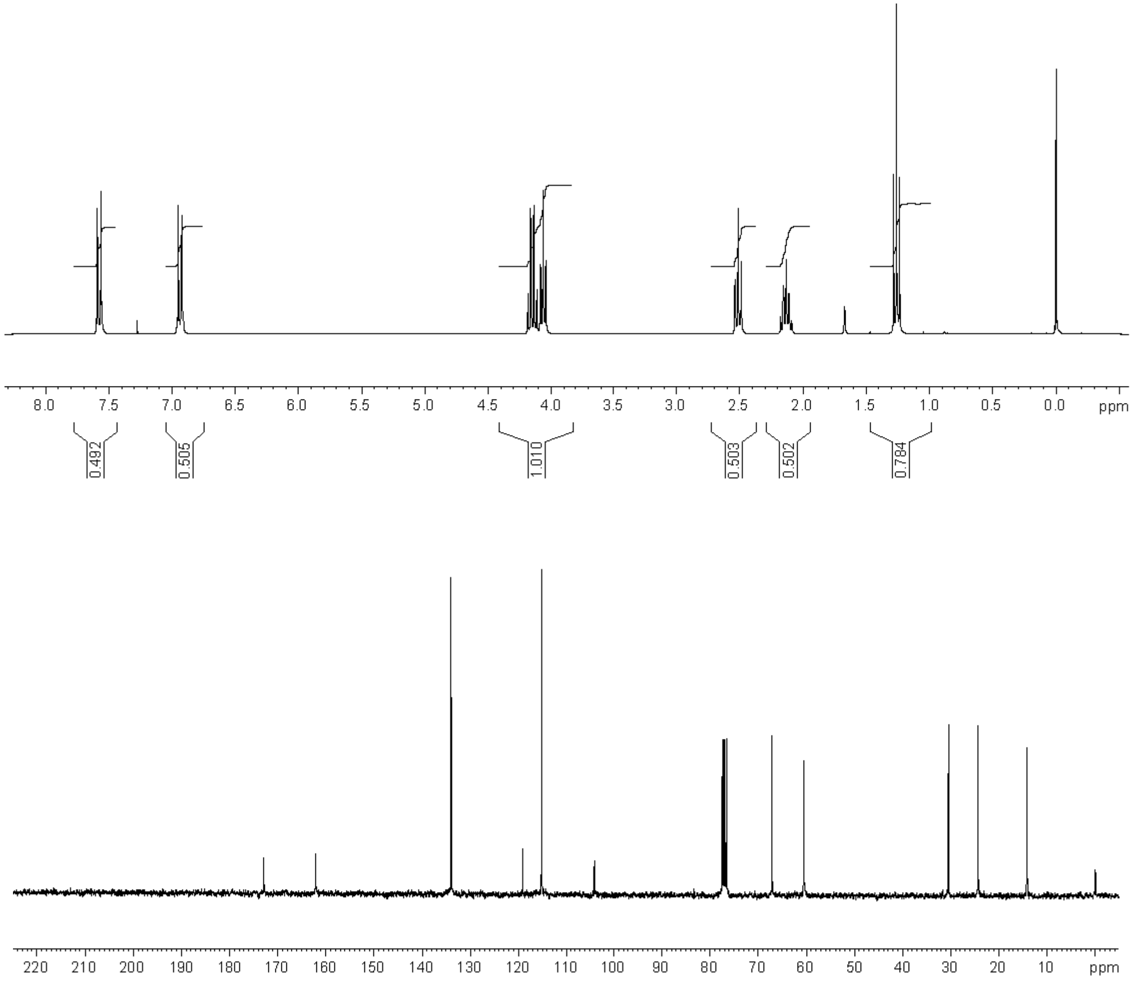
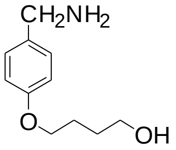


Figure S5. ^{1}H and ^{13}C NMR spectra of **11** in $CDCl_3$.



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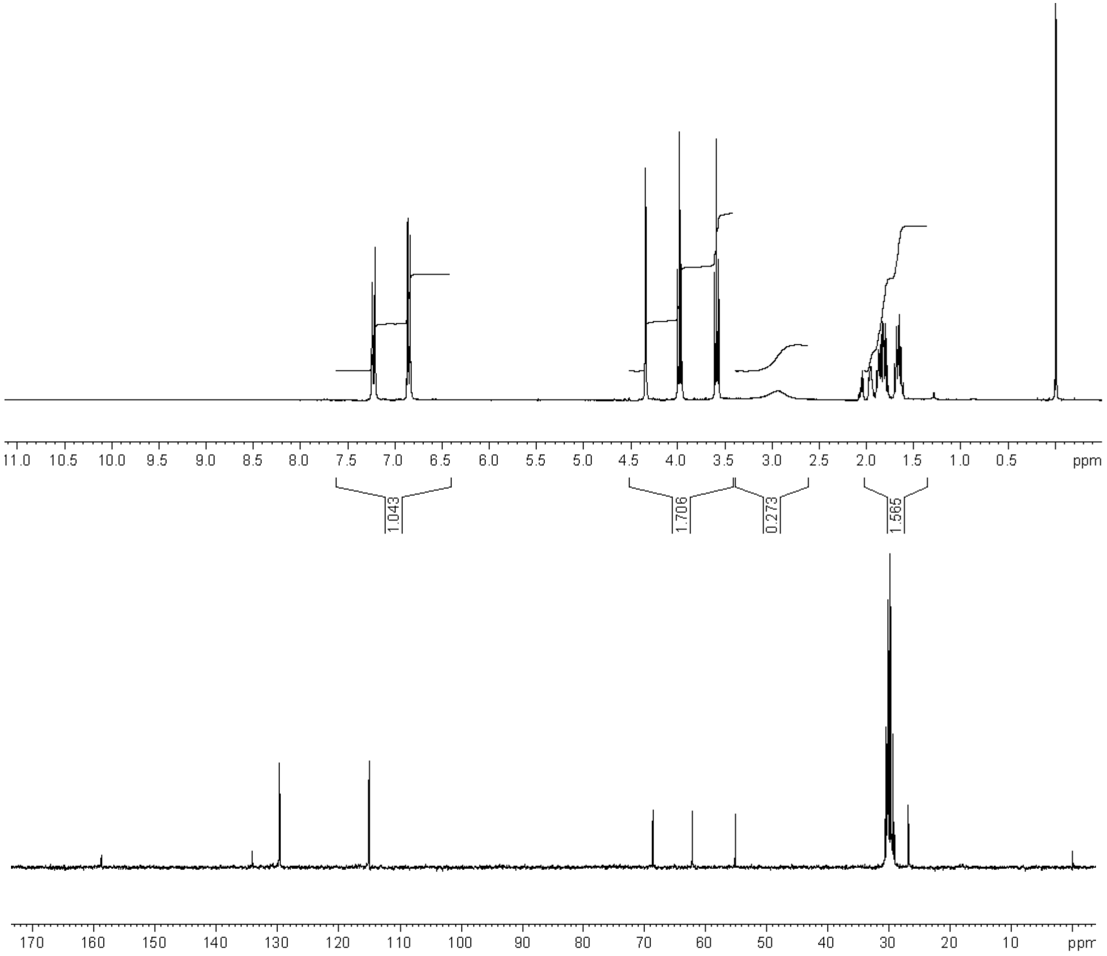


Figure S6. ^{1}H and ^{13}C NMR spectra of **12** in acetone-*d6*.

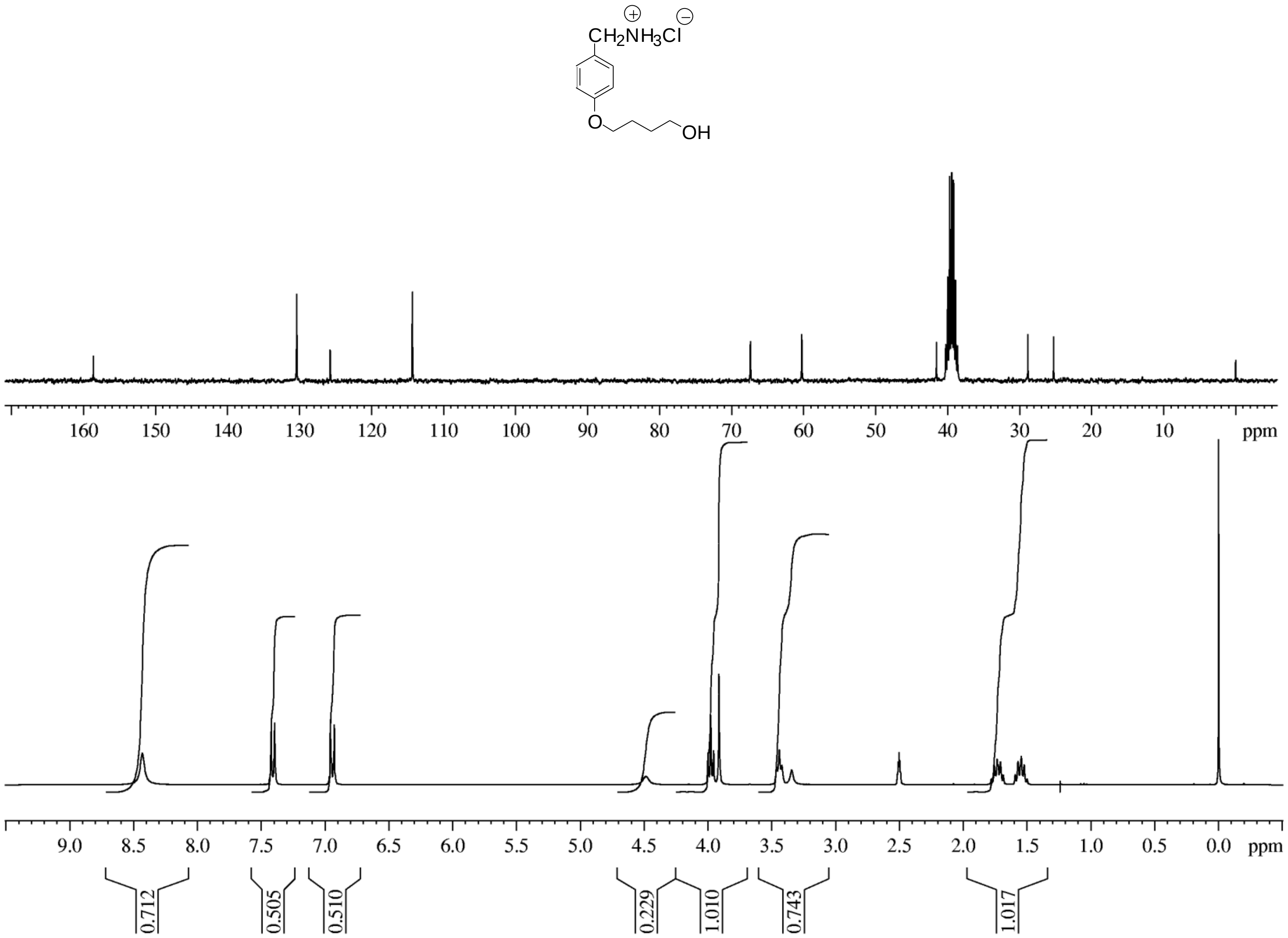
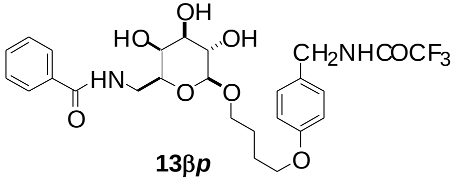


Figure S7. ^{1}H and ^{13}C NMR spectra of hydrochloride of **12** in DMSO-*d6*.



13βp

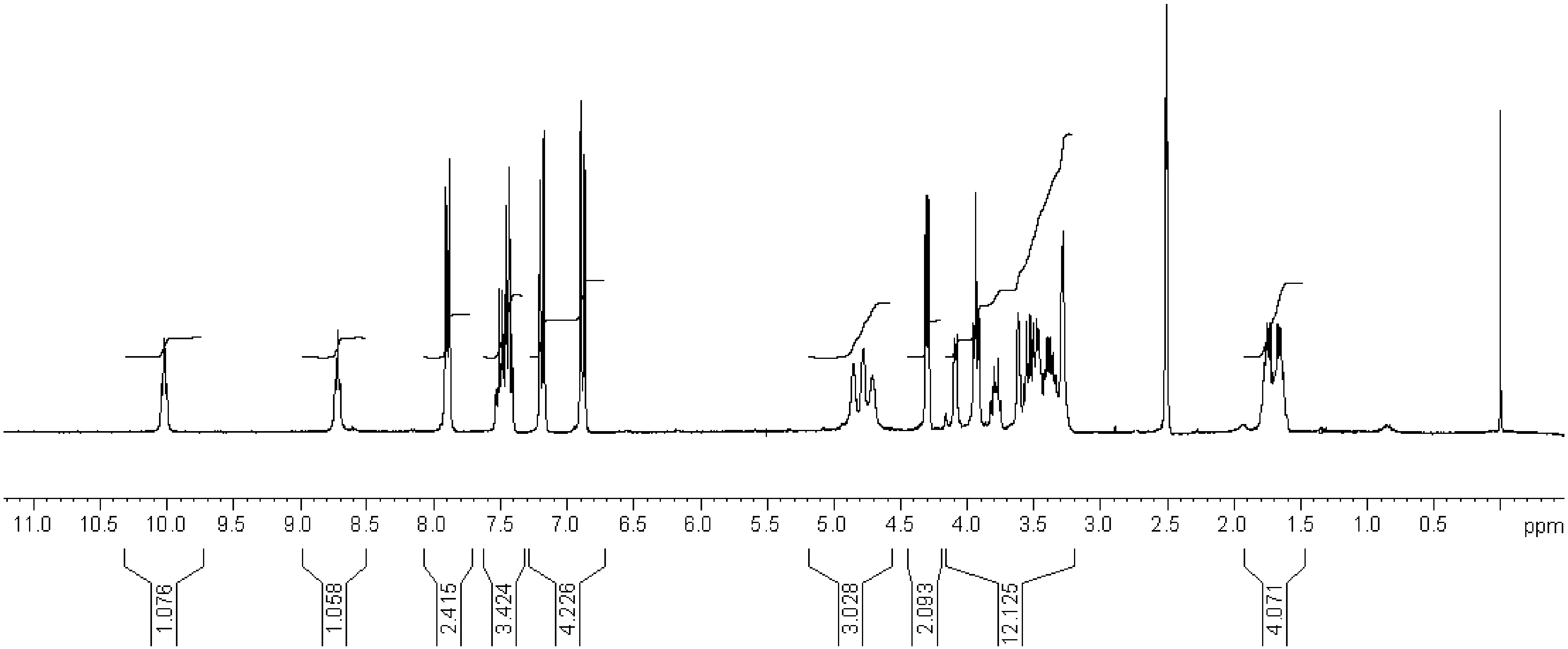


Figure S8. ^{1}H NMR spectrum of **13β*p*** in DMSO-*d6*.

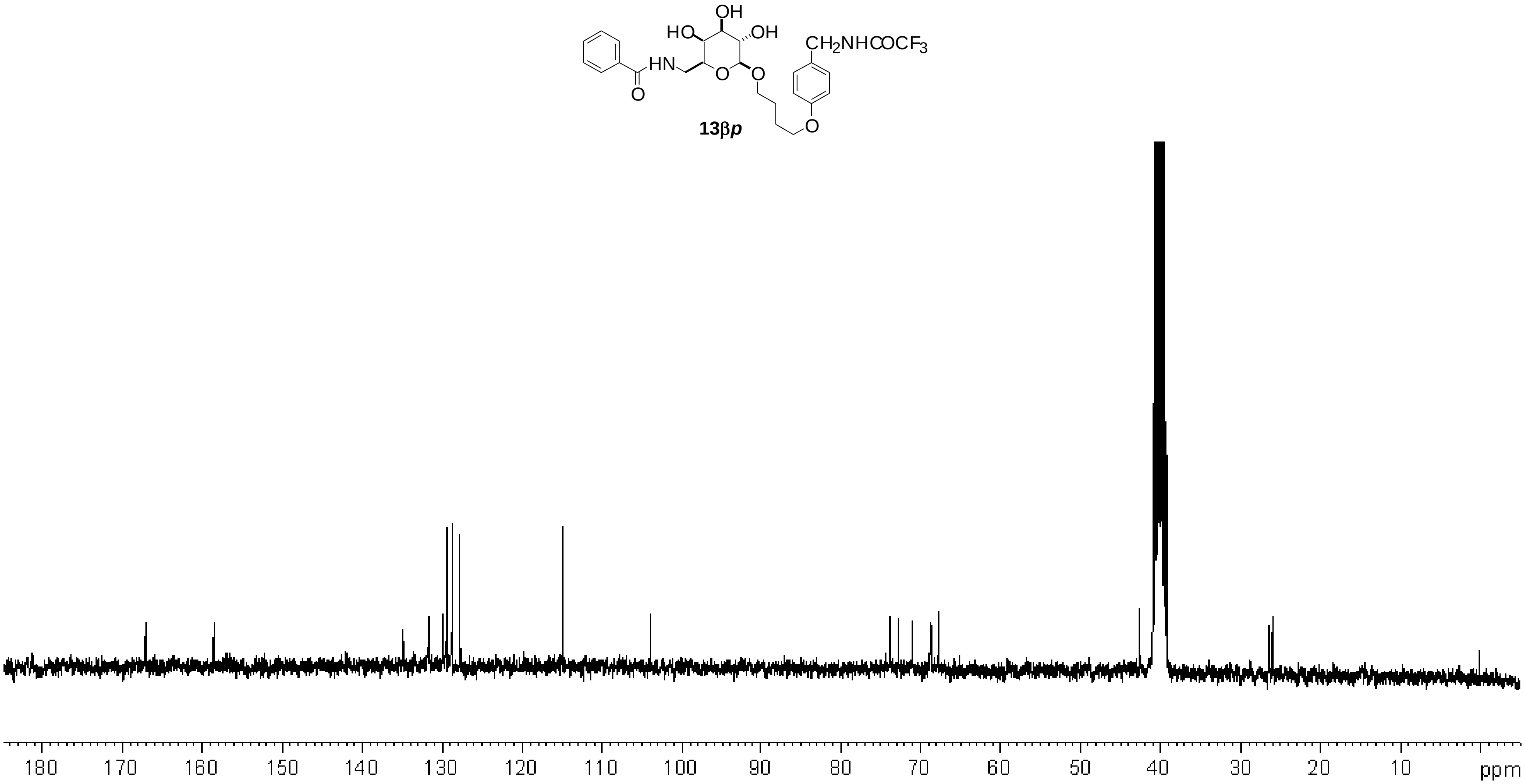
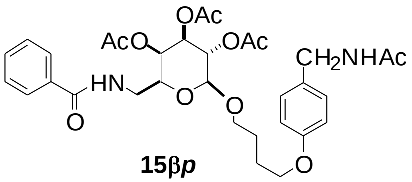


Figure S9. ^{13}C NMR spectrum of **13β*p*** in DMSO-*d6*.



15β*p*

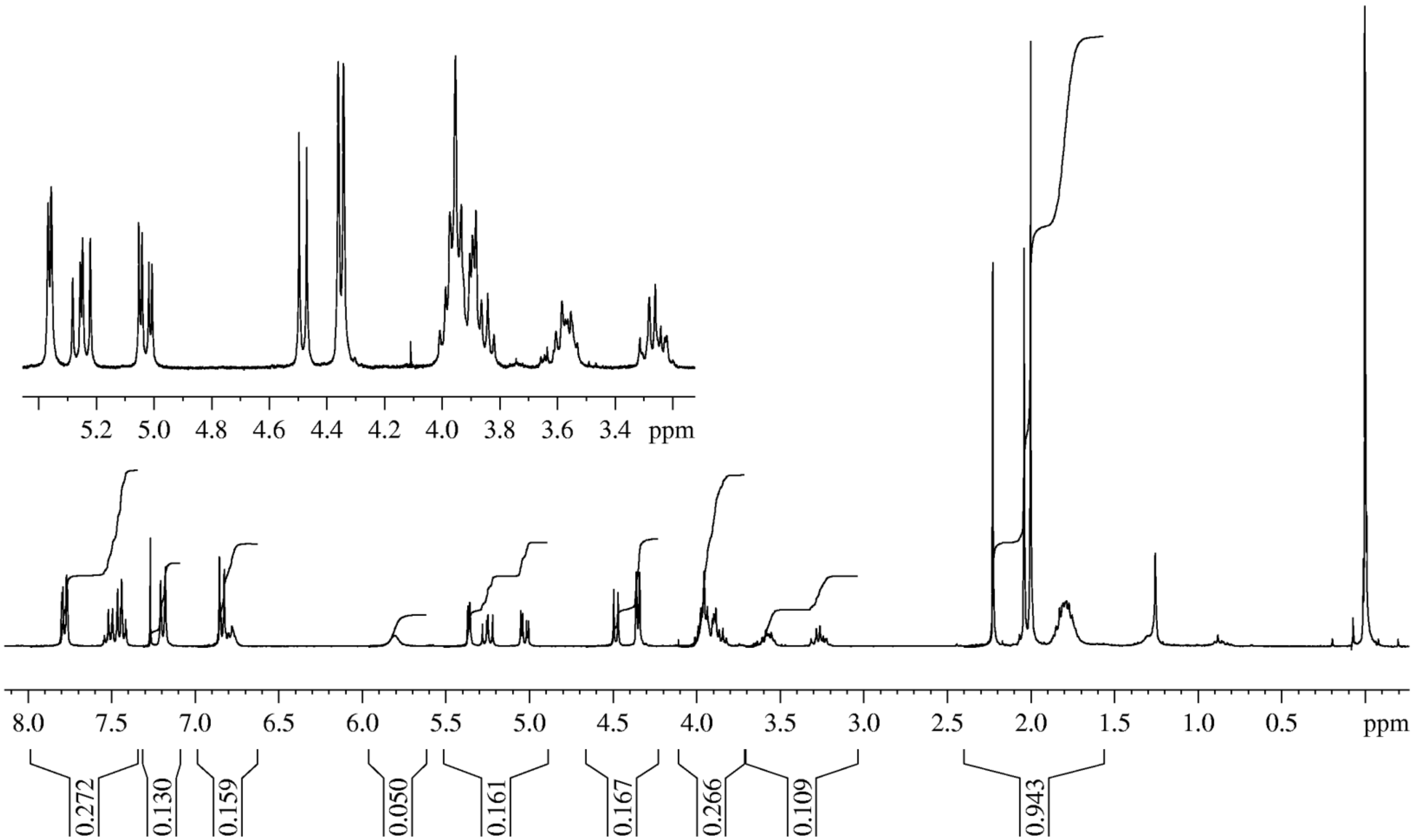
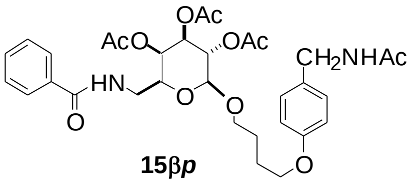


Figure S10. ^{1}H NMR spectrum of **15β*p*** in $CDCl_3$.



15β*p*

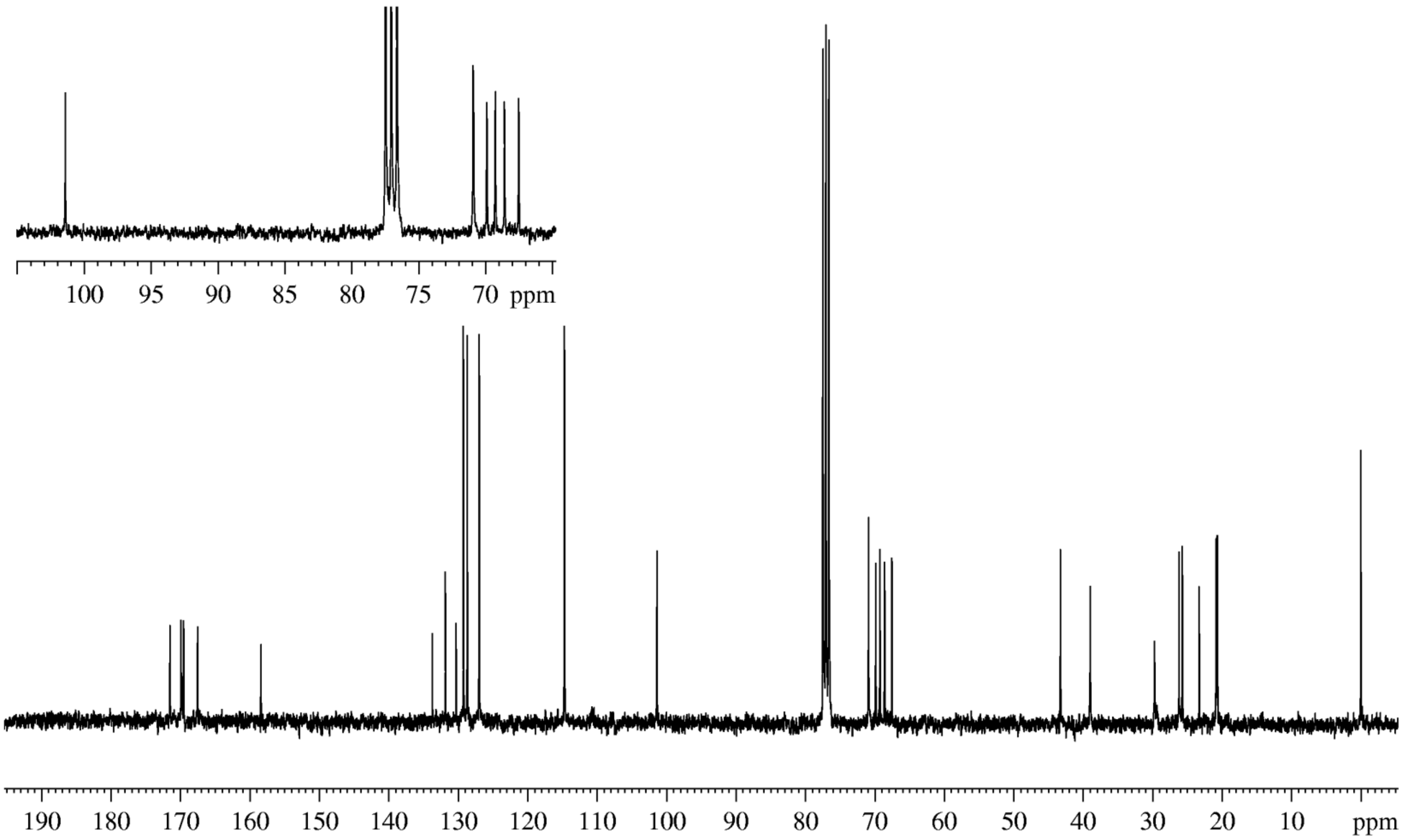


Figure S11. ^{13}C NMR spectrum of **15β*p*** in $CDCl_3$.