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Supplementary Materials

Direct Cross-Coupling of Alcohols with *O*-Nucleophiles Mediated by *N*-Iodosuccinimide as a Precatalyst under Mild Reaction Conditions

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Abstract: We report *N*-iodosuccinimide as the most efficient and selective precatalyst among the *N*-halosuccinimides for dehydrative *O*-alkylation reactions between various alcohols under high-substrate concentration reaction conditions. The protocol is non-metal, one-pot, selective, and easily scalable, with excellent yields; enhancing the green chemical profiles of these transformations.

Keywords: alcohols; *N*-iodosuccinimide; cross-coupling; etherification; green chemistry

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Supporting Information

Contents

1. General Information

All alcohol substrates were commercially available and were used without further purification. Reactions were carried out in 4 mL screw-capped vial. All reactions were monitored by TLC (mobile phase: dichloromethane/hexane) and visualized by UV lamp (254 nm). Column chromatography (CC) was performed using silica gel 60 (particle size: 0.063–0.200 mm). Spectroscopic methods: nuclear magnetic resonance (Varian INOVA 300 NMR instrument, ^{1}H: 303.0 MHz, ^{13}C: 76.2 MHz) using $CDCl_3$ as the solvent with $SiMe_4$ (TMS) for ^{1}H and ^{13}C as an internal reference and melting points (open capillary tube methodology; uncorrected) were used for identification and structure elucidation.

1.1. General Procedure for Etherification of Alcohols Mediated by N-Iodosuccinimide on Half mmol Scale

A mixture of benzyl alcohol (0.5 mmol), and *N*-iodosuccinimide as a precatalyst (3-10 mol%), which had been powdered in a mortar in the case of solid state reactants was transferred to a 4 mL screw-capped vial, finally added eventual liquid component alkyl alcohol (1 mmol–1 mL) and heated at 70–75 °C for 6 h–24 h. The progress of the reaction mixture was monitored by TLC. Upon completion of the reaction, the crude reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL), washed with $Na_2S_2O_3$ (6 mL), $NaHCO_3$ (6 mL) and distilled water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture obtained was analyzed by ^{1}H NMR. Finally, if necessary, the pure final products were separated by column chromatography or flash chromatography. Detailed experimental information, such as mediator loading, isolated yields, and spectroscopic and other identification data, are given below.

The isolated known compounds were identified by comparing the spectroscopic data with the literature.

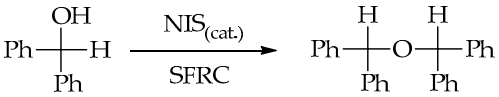
1.2. The Scale-up Procedure for the Synthesis of (Methoxymethylene)Dibenzene 4 with MeOH 3, Mediated by NIS

A mixture of diphenylmethanol 1 (10 mmol, 2.2425 g), 3 mol% NIS (67.5 mg, 0.3 mol), which had been powdered in a mortar, was transferred to a 20 mL screw-capped glass scintillation vial, finally added eventual MeOH 3 (20 mmol, (800 μl), and heated at 70–75 °C for 6 h.

The progress of the reaction mixture was followed by TLC. Upon completion of the reaction, the mixture was cooled to room temperature. Finally, the crude reaction mixture was purified by column chromatography to obtain a pure product in excellent yield colourless oil, 2.1725 g, and 90%).

The isolated known compounds were identified by comparing the spectroscopic data with the literature.

2. Optimizing the Reaction Conditions



1 **2**

Scheme S1. The conversion of diphenylmethanol 1 mediated by NIS under SFRC.

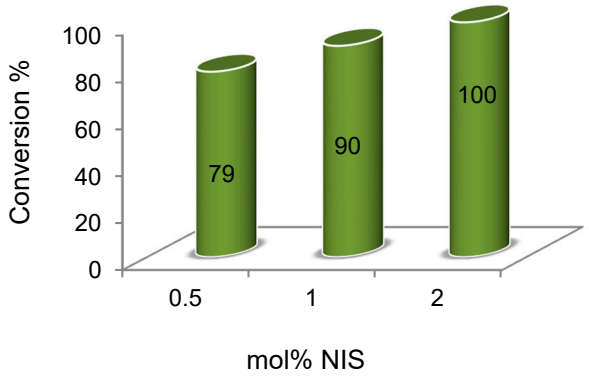
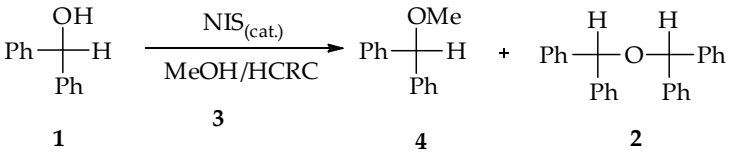


Figure S1. The effect of loading of NIS on the conversion of diphenylmethanol **1** under SFRC.



3

1 **4** **2**

Scheme S2. The conversion of diphenylmethanol 1 in the presence of MeOH 3 mediated by NIS under HCRC.

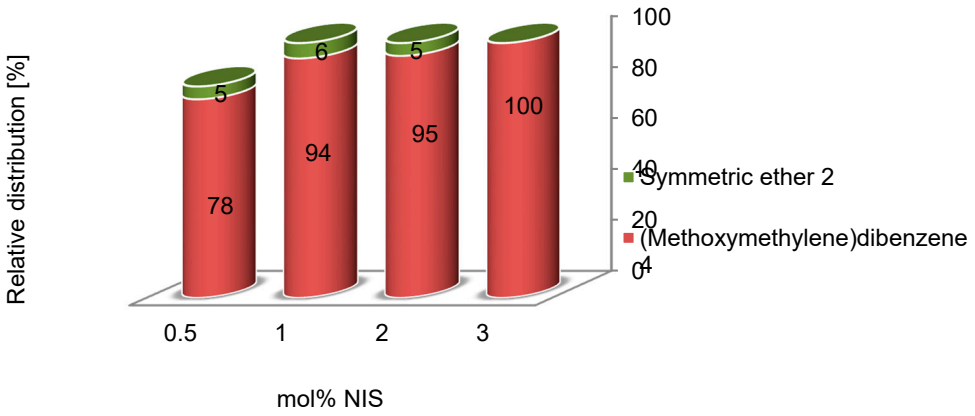
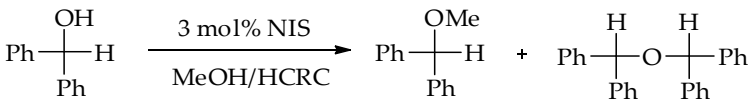


Figure S2. The effect of loading of NIS on the conversion of diphenylmethanol **1** with MeOH **3** under HCRC.



3

1 **4** **2**

Scheme S3. The conversion of diphenylmethanol 1 in the presence of MeOH 3 mediated by NIS under HCRC.

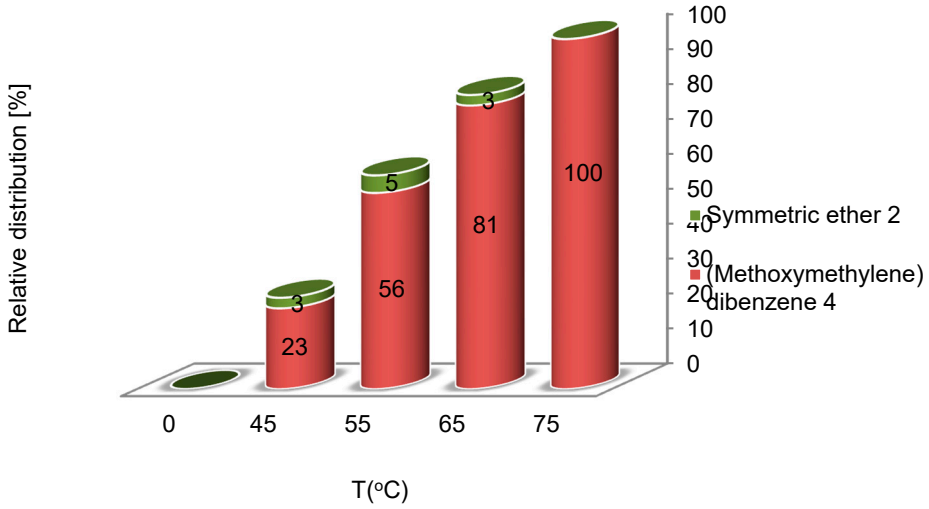


Figure S3. The catalytic effect of NIS on the conversion of diphenylmethanol **1** with MeOH **3** based on temperature, under HCRC.

3. Characterization Data of Isolated Final Products

(Methoxymethylene)Dibenzene (4) [1] (Scale-up)

$C_{14}H_{14}O$ (Mr = 198.26);

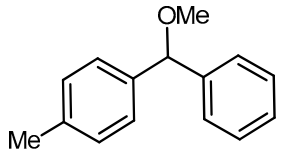
Reaction conditions:	10 mmol diphenylmethanol **1** (2.2425 g), 20 mmol MeOH **3** (800 µl), 3 mol% NIS (67.5 mg, 0.3 mol), 70–75 °C, 6 h;
Purification:	CC (SiO_2, EtOAc/Hexane 1:1);
Yield:	2.1725 g (90%), colourless oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.35–7.20 (m, 10H), 5.23 (s, 1H), 3.37 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.2, 128.5, 127.6, 127.0, 85.5, 57.1.

(±) 4,4′-(Oxybis(phenylmethylene))bis(methylbenzene) (6) [2]

$C_{28}H_{26}O$ (Mr = 378.51);

Reaction conditions:	0.5 mmol phenyl(*p*-tolyl)methanol **5** (99.1 mg), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 4.5 h – SFRC;
Purification:	Not necessary;
Yield:	94 mg (99%), colourless oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.38 – 7.21 (m, 14H), 7.11 (d, *J* = 8.2 Hz, 4H), 5.36 (s, 2H), 2.31 (s, 6H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.7, 142.6, 139.5, 139.4, 137.19, 137.15, 129.21, 129.19, 129.11, 128.46, 128.44, 127.42, 127.37, 127.36, 127.32, 127.26, 79.86, 79.85, 46.1, 21.3;

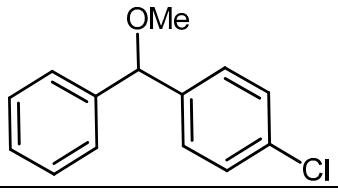
(±) 1-(Methoxy(phenyl)methyl)-4-methylbenzene (7) [3]



$C_{15}H_{16}O$ (Mr = 212.29);

Reaction conditions:	0.5 mmol phenyl(*p*-tolyl)methanol **5** (99.1 mg), 1 mmol MeOH **3** (40 µl), 3 mol% NIS (3.4 mg, 0.03 mmol), 70–75 °C, 6 h—HCRC;
Purification:	CC (SiO_2, EtOAc/Hexane 1:1);
Yield:	96 mg (90%), yellow oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.34–7.19 (m, 8H), 7.12 (d, *J* = 7.9 Hz, 2H), 5.20 (s, 1H), 3.36 (s, 3H), 2.30 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.4, 139.2, 137.2, 129.2, 128.5, 127.5, 127.02, 126.95, 85.4, 57.1, 21.2.

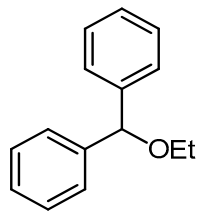
1-chloro-4-(methoxy(phenyl)methyl)benzene (9) [4]



$C_{14}H_{13}ClO$ (Mr = 232.71);

Reaction conditions:	0.5 mmol (4-chlorophenyl)(phenyl)methanol **8** (109.3 g), 1 mmol MeOH **3** (40 µl), 10 mol% NIS (11.2 mg, 0.1 mmol), 70–75 °C, 24 h;
Purification:	FC(SiO_2, EtOAc);
Yield:	115.3 mg (99%), white solid;
Mp.:	44–46 °C, (lit [4] 45-47 °C);
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.32–7.25 (m, 9H), 5.21 (s, 1H), 3.37 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 141.7, 140.8, 133.3, 131.6, 130.0, 128.7, 128.63, 128.61, 128.5, 128.3, 127.8, 127.0, 84.8, 57.1.

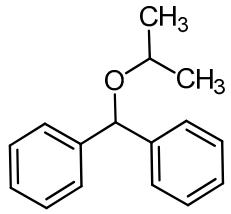
(Ethoxymethylene)dibenzene (11) [5]



$C_{15}H_{16}O$ (Mr = 212.29);

Reaction conditions:	0.5 mmol diphenylmethanol **1** (92.1 mg), 1 mmol EtOH **10** (58 µl), 3 mol% NIS (3.4 mg, 0.03 mmol), 70–75 °C, 24 h—HCRC;
Purification:	CC (SiO_2, EtOAc/Hexane 1:1);
Yield:	94 mg (89%), colourless oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.38–7.17 (m, 10H), 5.35 (s, 1H), 3.51 (q, *J* = 7.0 Hz, 2H), 1.26 (t, *J* = 7.0 Hz, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.7, 128.5, 127.4, 127.1, 83.6, 64.7, 15.5.

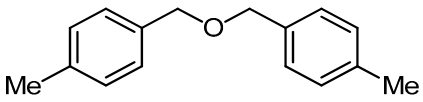
Isopropoxydiphenylmethane (13) [5]



$C_{16}H_{18}O$ (Mr = 226.31);

Reaction conditions:	0.5 mmol diphenylmethanol **1** (92.1 mg), 1mL *i*-PrOH **12**, 3 mol% NIS (3.4 mg, 0.03 mmol), 80–85 °C, 24 h, stirring 400—in solution;
Purification:	CC (SiO_2, EtOAc/Hexane 1:1);
Yield:	100 mg (88%), colourless oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.38–7.17 (m, 10H), 5.48 (s, 1H), 3.66 (hept, *J* = 6.1 Hz, 1H), 1.21 (d, *J* = 6.1 Hz, 6H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 143.1, 128.4, 127.4, 127.2, 80.6, 69.2, 22.4.

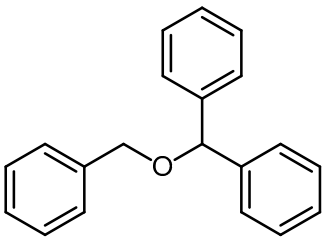
4,4′-(Oxybis(methylene))bis(methylbenzene) (23) [6]



$C_{16}H_{18}O$ (Mr = 226.31);

Reaction conditions:	0.5 mmol *p*-tolylmethanol **22** (61 mg), 3 mol% NIS (3.4 mg, 0.03 mmol), 70–75 °C, 24 h—SFRC;
Purification:	FC(SiO_2, EtOAc);
Yield:	56 mg (99%), white solid;
Mp.:	61–62 °C, (lit.[6] 62 °C);
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.24 (d, *J* = 8.0 Hz, 4H), 7.14 (d, *J* = 7.8 Hz, 4H), 4.49 (s, 4H), 2.33 (s, 6H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 137.4, 135.4, 129.2, 128.0, 71.9, 21.3.

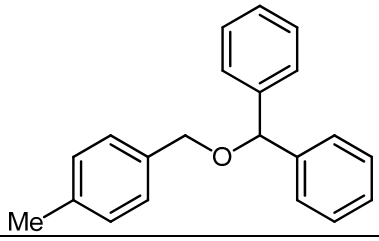
((benzyloxy)methylene)dibenzene (29) [7]



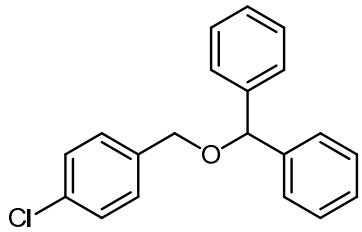
$C_{20}H_{18}O$ (Mr = 274.36);

Reaction conditions:	0.5 mmol diphenylmethanol **1** (92.1 mg), 0.65 mmol phenylmethanol **20** (58 µl), 10 mol% NIS (11.2 mg, 0.1 mmol), 70–75 °C, 24 h—HCRC;
Purification:	CC (SiO_2, Hexan/EtOAc 4:1);
Yield:	121 mg (88%), colourless oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.38–7.20 (m, 15H), 5.42 (s, 1H), 4.52 (s, 2H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.2, 138.5, 128.50, 128.46, 127.8, 127.63, 127.57, 127.2, 82.6, 70.6.

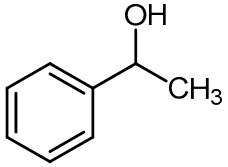
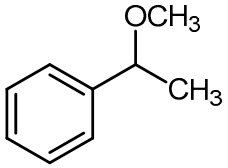
(((4-methylbenzyl)oxy)methylene)dibenzene (30) [8]

	**$C_{21}H_{20}O$ (Mr = 288.38);**
Reaction conditions:	0.5 mmol diphenylmethanol **1** (92.1 mg), 0.65 mmol *p*-tolylmethanol **22** (79.4 mg), 6 mol% NIS (6.7 mg, 0.06 mmol), 70–75 °C, 24 h—SFRC;
Purification:	CC (SiO_2, EtOAc/Hexane 1:1);
Yield:	105 mg (73%); white solid
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.38–7.12 (m, 14H), 5.42 (s, 1H), 4.49 (s, 2H), 2.34 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.3, 137.3, 135.4, 129.2, 128.5, 128.0, 127.5, 127.3, 82.3, 70.5, 21.3.

(((4-chlorobenzyl)oxy)methylene)dibenzene (31) [9]

	**$C_{20}H_{17}ClO$ (Mr = 308.80);**
Reaction conditions:	0.5 mmol diphenylmethanol **1** (92.1 mg), 0.65 mmol (4-chlorophenyl)methanol **25** (92.6 mg), 10 mol% NIS (11.2 mg, 0.1 mmol), 70–75 °C, 24 h—SFRC;
Purification:	CC (SiO_2, EtOAc/Hexane 1:1);
Yield:	139 mg (90%), white solid;
Mp.:	57–60 °C;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.37–7.23 (m, 14H), 5.40 (s, 1H), 4.47 (s, 2H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.0, 137.0, 133.4, 129.1, 128.61, 128.56, 127.7, 127.2, 82.8, 69.8.

4. Measurements of Specific Rotation

	00.159; −0.158 −0,159 −0.161 −0.160 −0.161 −0.159 −0.160 ⟶ $\bar{\alpha}$ = 160° [α] = −24°
	00.159; −0.158 −0,159 −0.161 −0.160 −0.161 −0.159 −0.160 ⟶ $\bar{\alpha}$ = 160° [α] = −24°

-00.159; −0.158 −0,159 −0.161 −0.160 −0.161 −0.159 −0.160 ⟶ $\bar{\alpha}$ = 160°
[α] = −24°

+0.106 +0103 +0.102 +0.101 +0.099 +0.103 +0.108 +0.108
[α] = +15°

(S)-(−)-1-phenylethanol $[\alpha]^{26}_{D}$ -38.1° (neat), the ether had $[\alpha]^{26}_{D}$ -114.0° (neat), $[\alpha]^{25}_{D}$ -117.3° (*c* 0.8; MeCN), and $[\alpha]^{25}_{D}$ -118.0° (*c* 7; MeCN).[10]

(R)-(+)-1-Methoxy-1-phenylethane $[\alpha]^{26}_{D}$ +125.9° (neat). [11]

References

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^{1}H NMR and ^{13}C NMR Spectra of Isolated Final Products

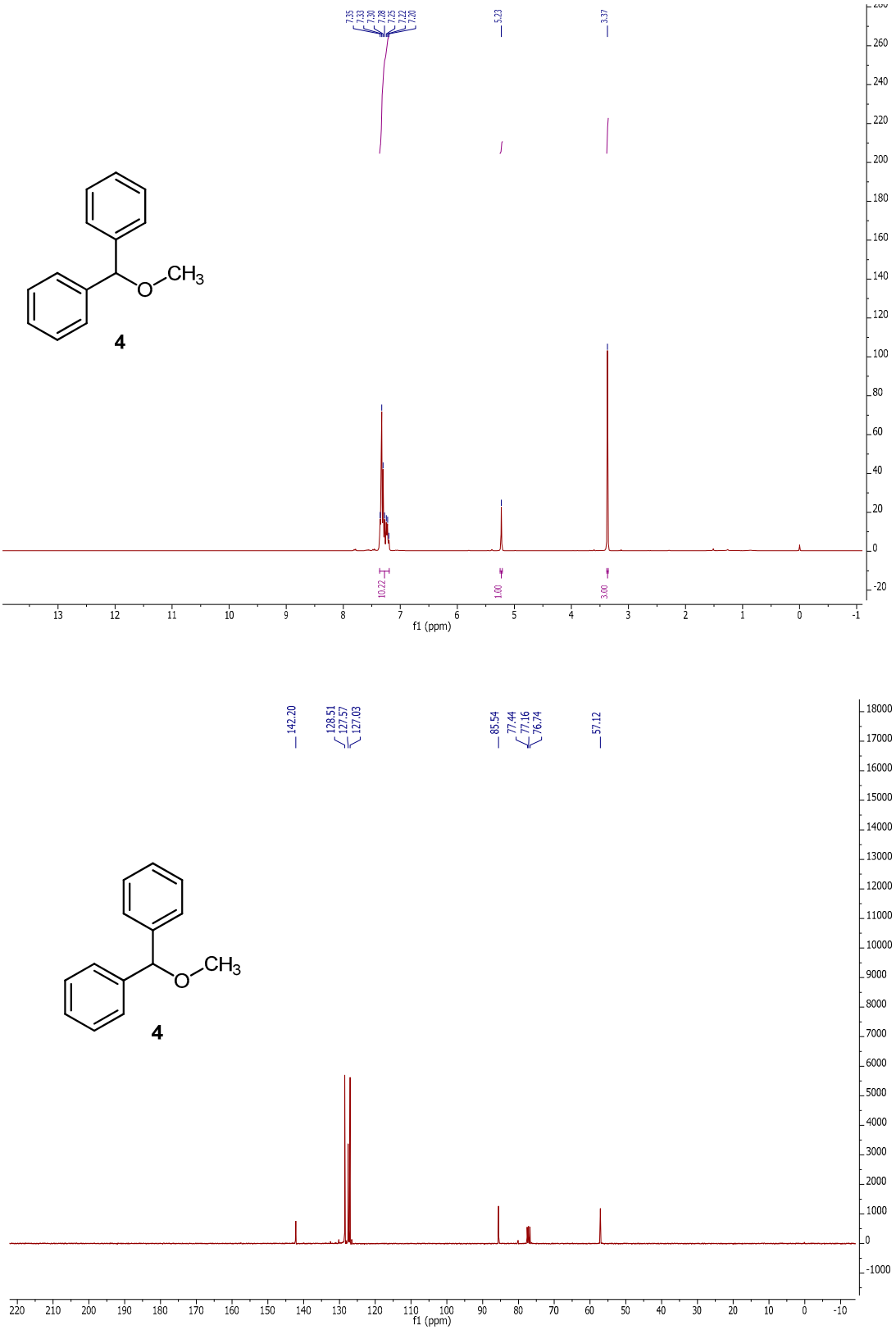

Figure S4. ^{1}H NMR and ^{13}C NMR spectra for (methoxymethylene)dibenzene **(4)**.

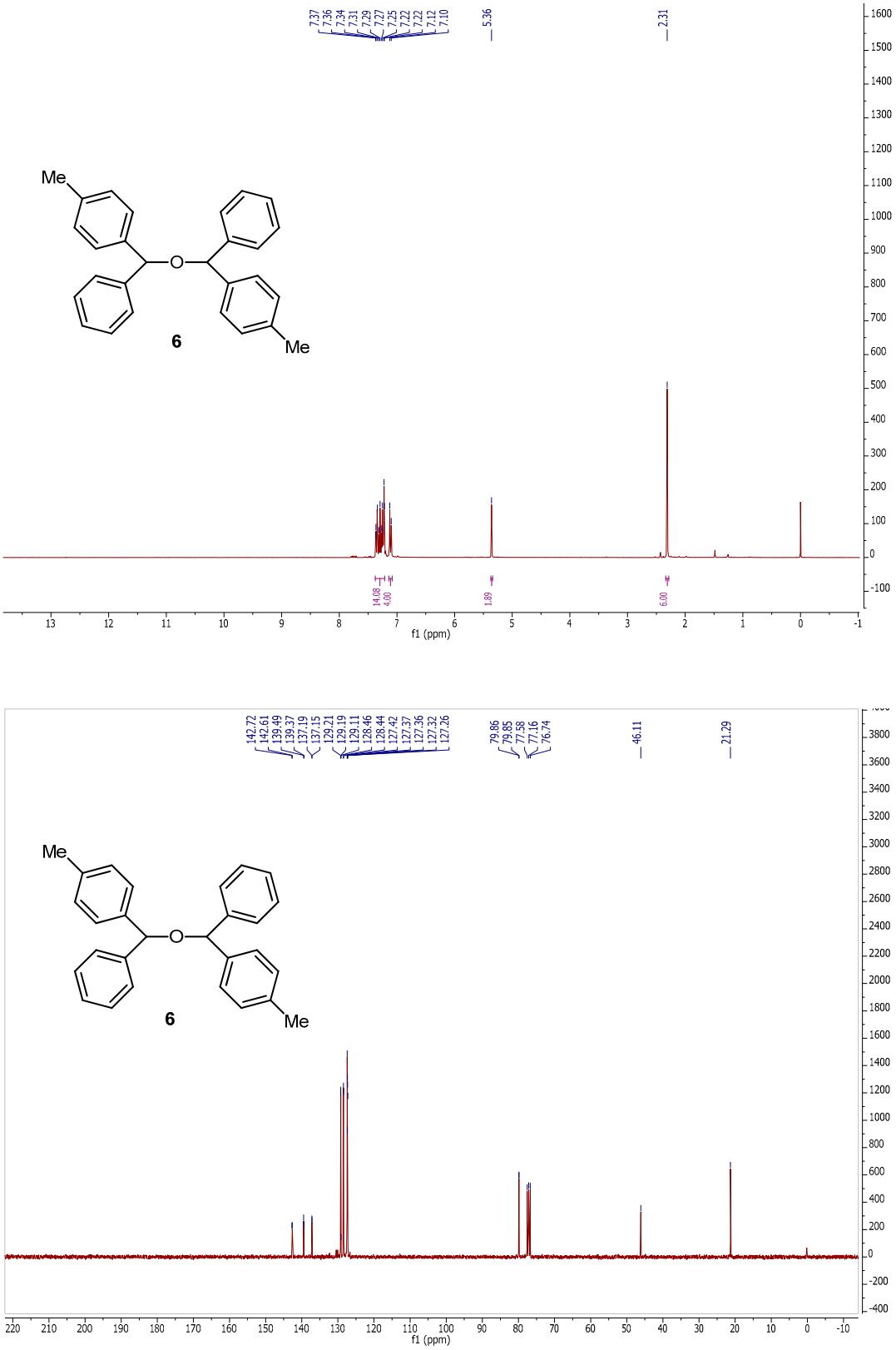

Figure S5. ^{1}H NMR and ^{13}C NMR spectra for (±) 4,4'-(oxybis(phenylmethylene))bis(methylbenzene) **(6)**.

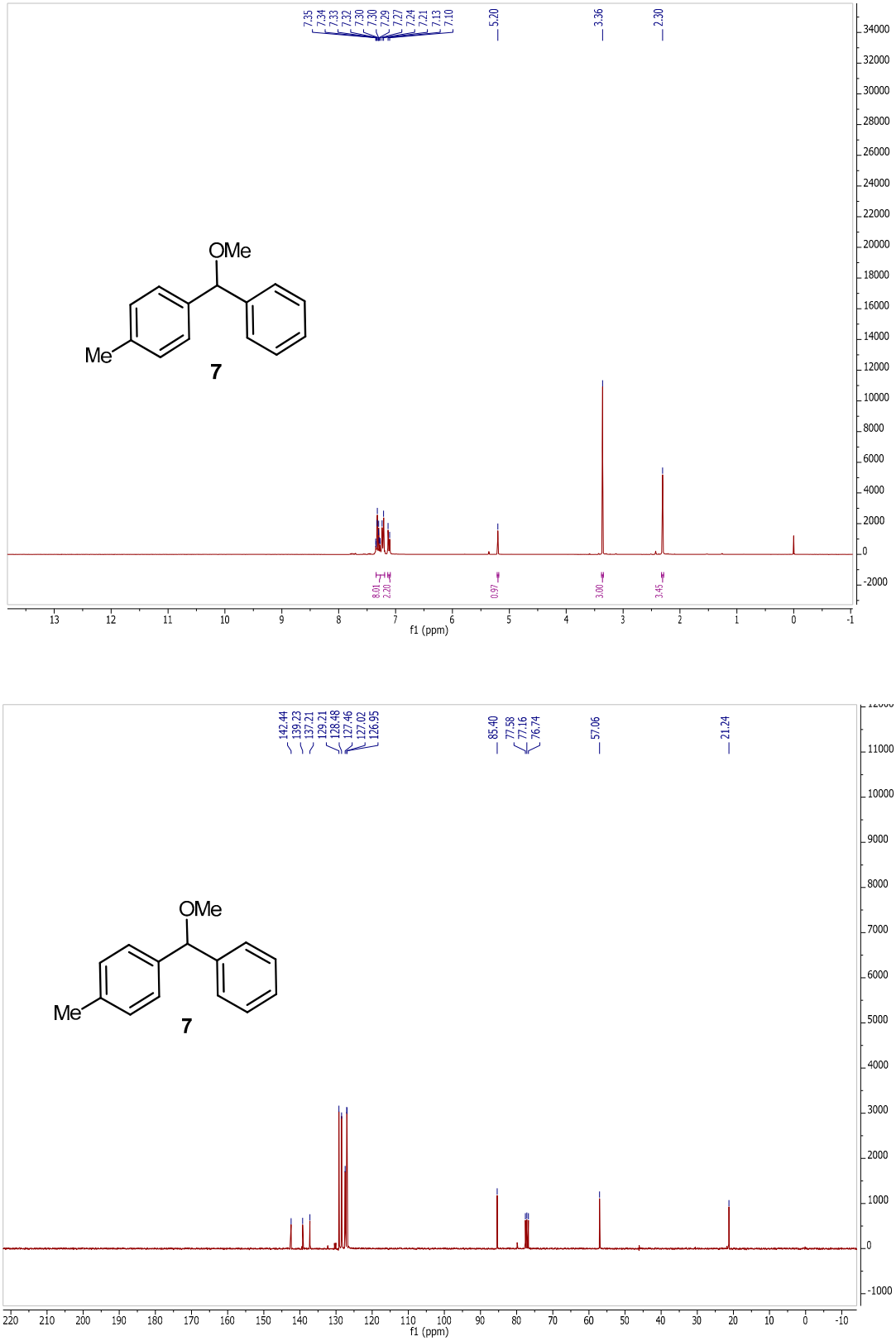

Figure S6. ^{1}H NMR and ^{13}C NMR spectra for (±) 1-(methoxy(phenyl)methyl)-4-methylbenzene **(7)**.

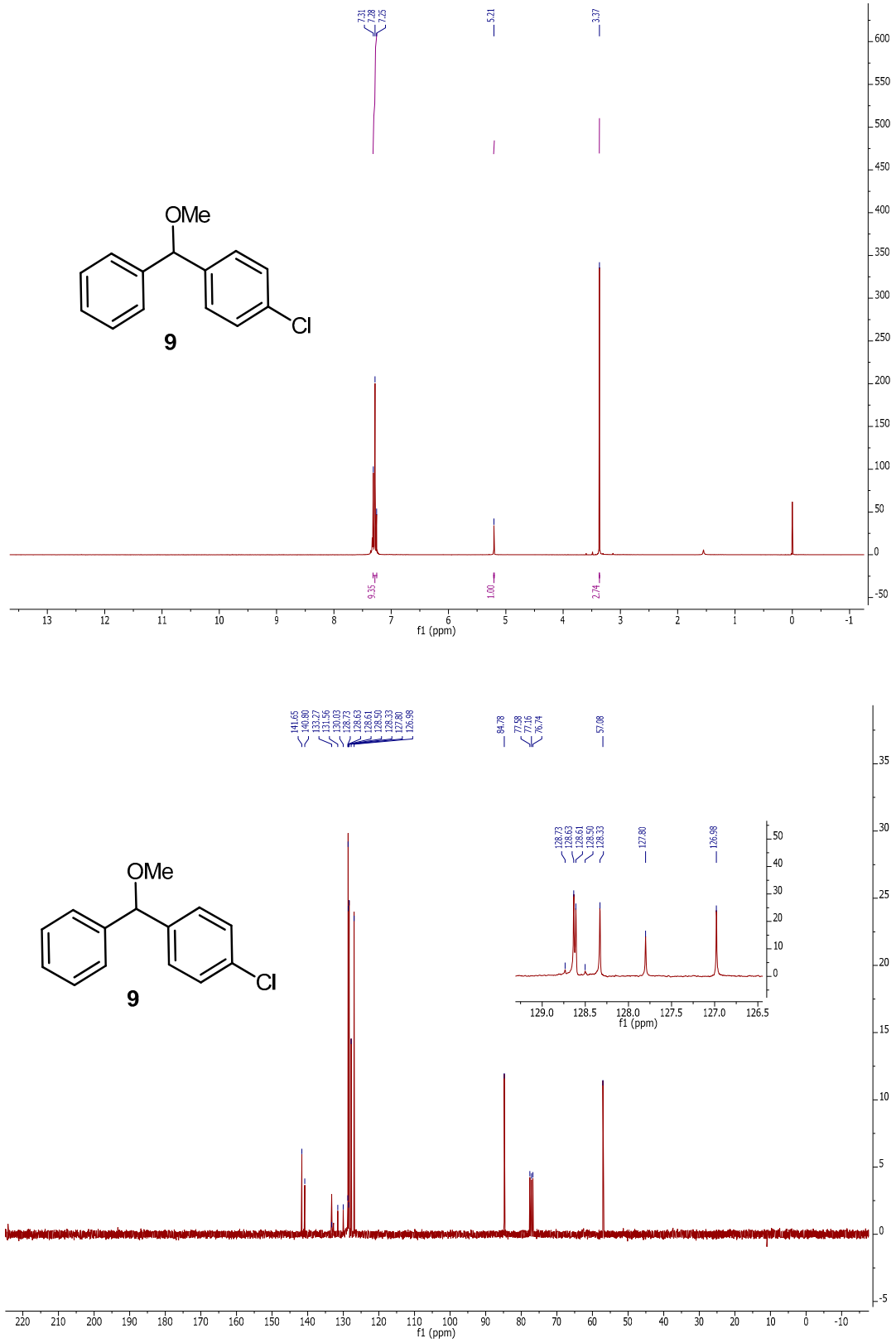

Figure S7. ^{1}H NMR and ^{13}C NMR spectra for 1-chloro-4-(methoxy(phenyl)methyl)benzene **(9)**.

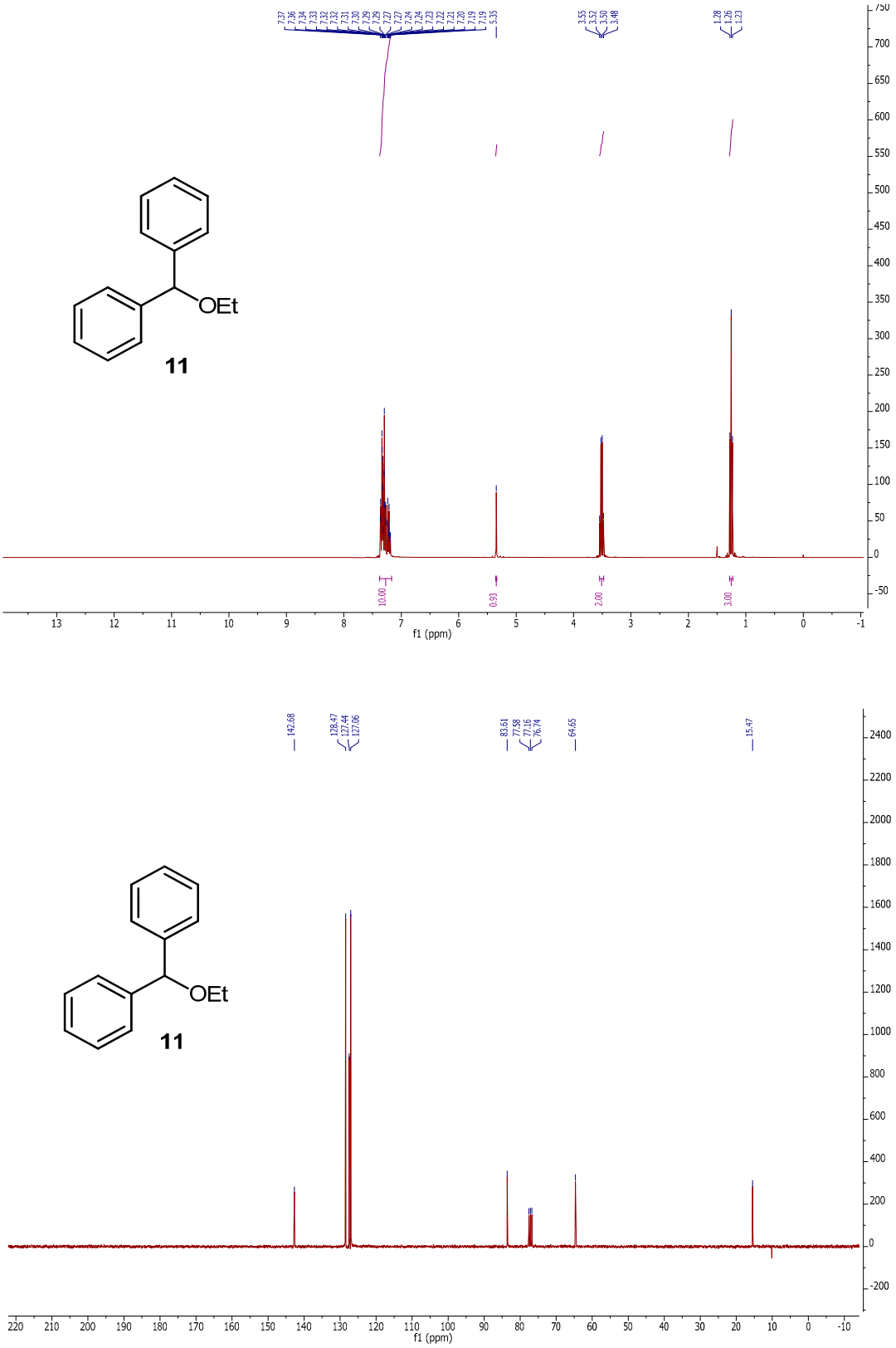

Figure S8. ^{1}H NMR and ^{13}C NMR spectra for (ethoxymethylene)dibenzene **(11)**.

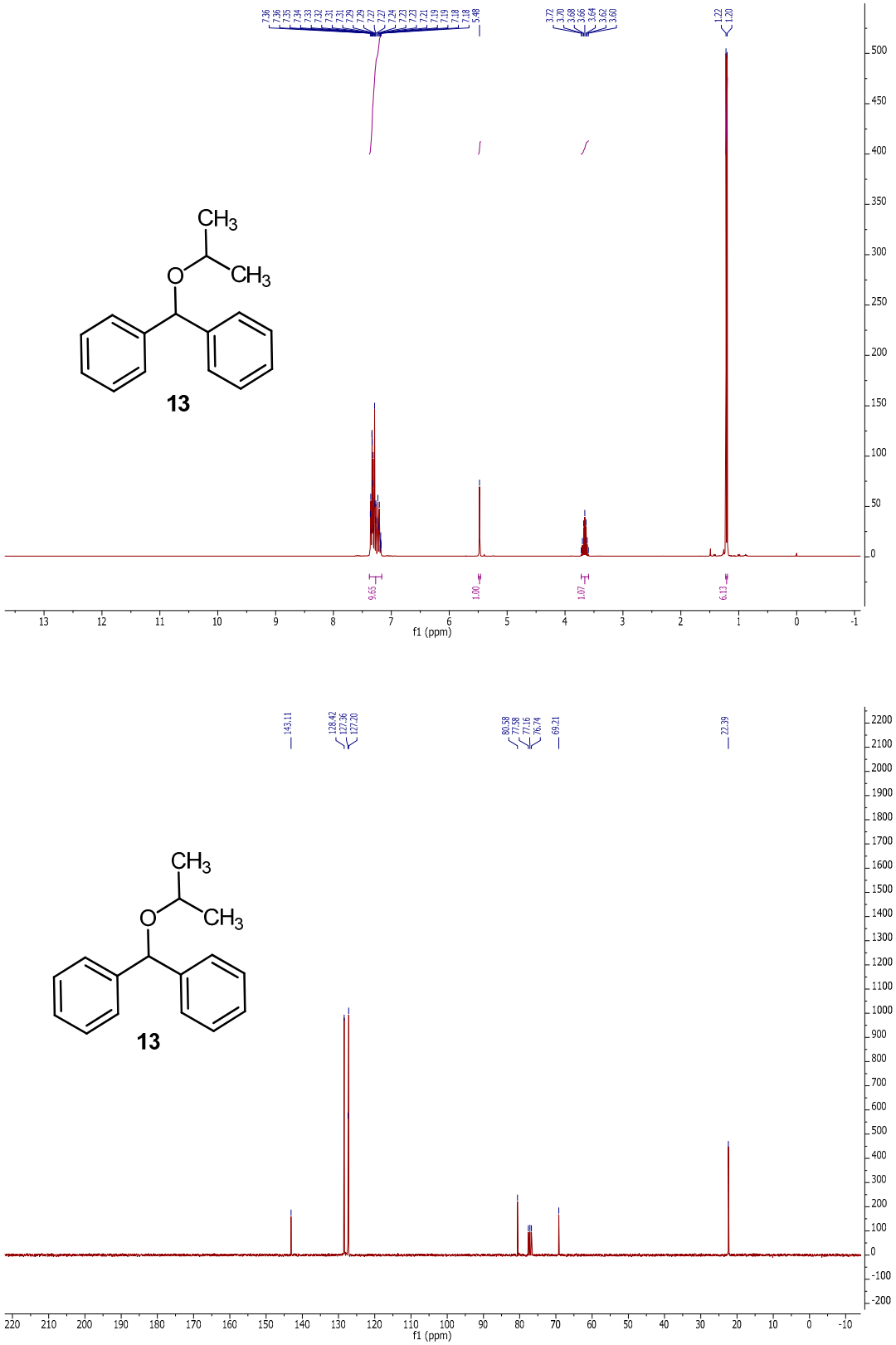

Figure S9. ^{1}H NMR and ^{13}C NMR spectra for isopropoxydiphenylmethane **(13)**.

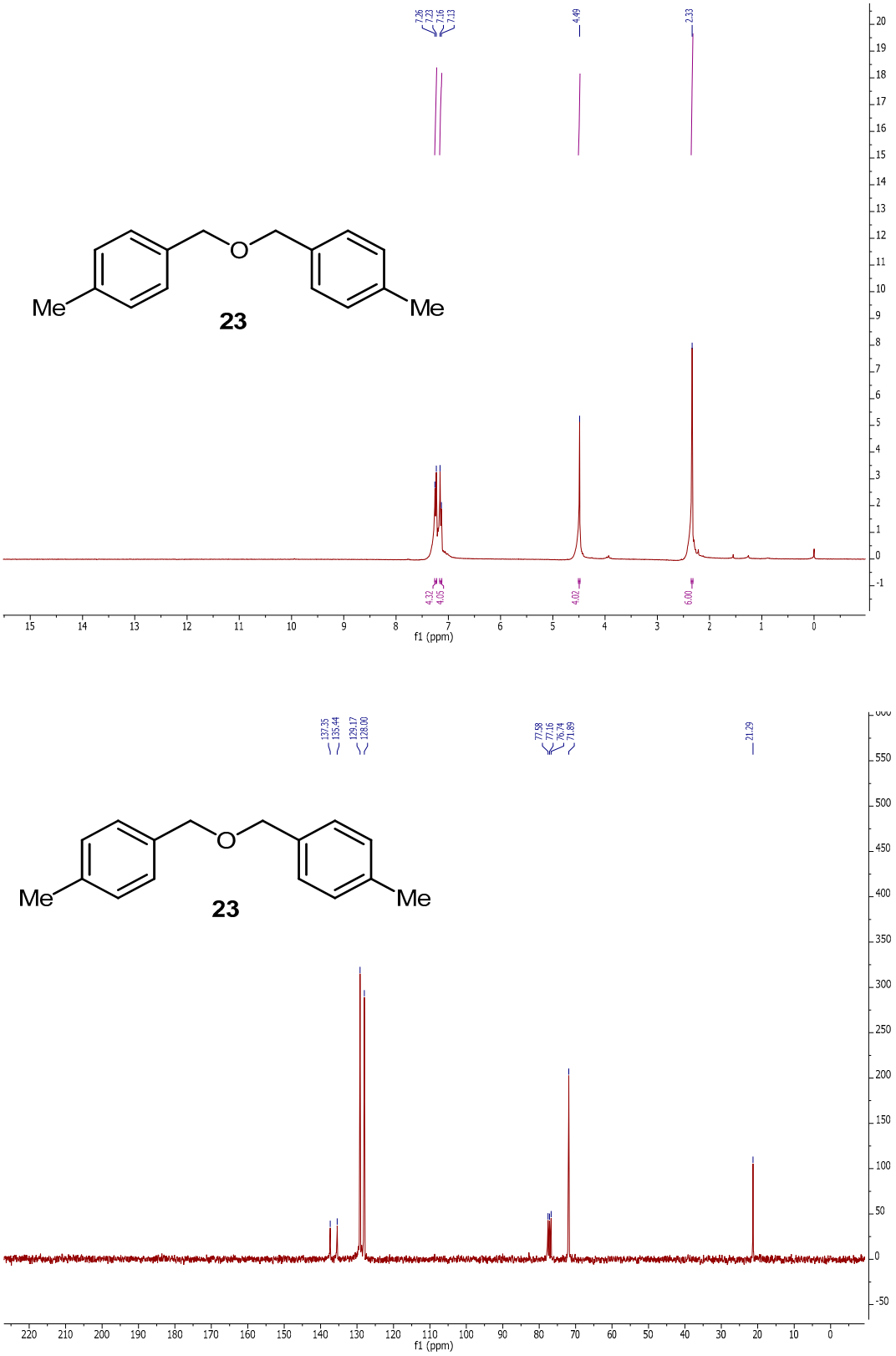

Figure S10. ^{1}H NMR and ^{13}C NMR spectra for 4,4'-(oxybis(methylene))bis(methylbenzene) **(23).**

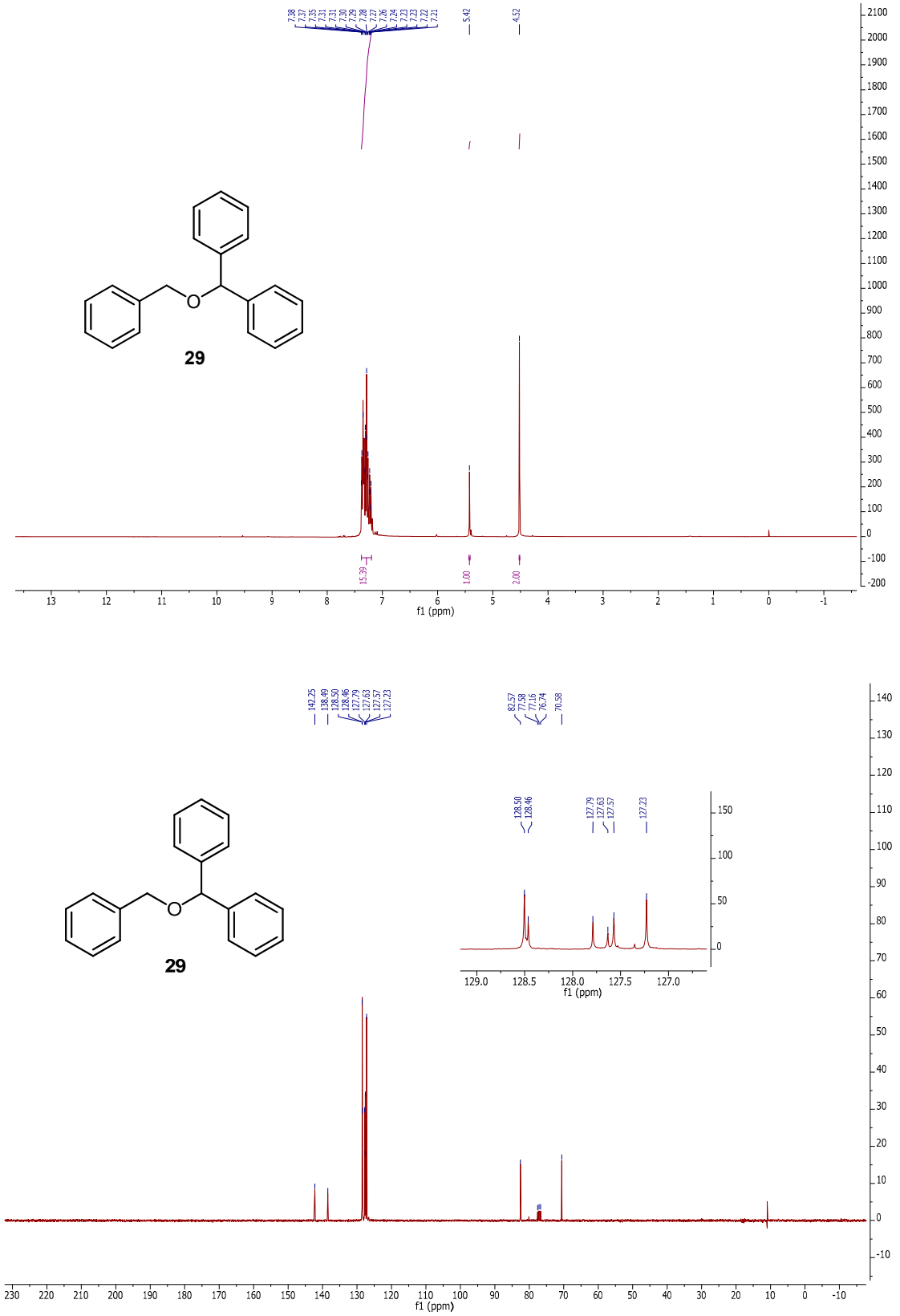

Figure S11. ^{1}H NMR and ^{13}C NMR spectra for ((benzyloxy)methylene)dibenzene **(29).**

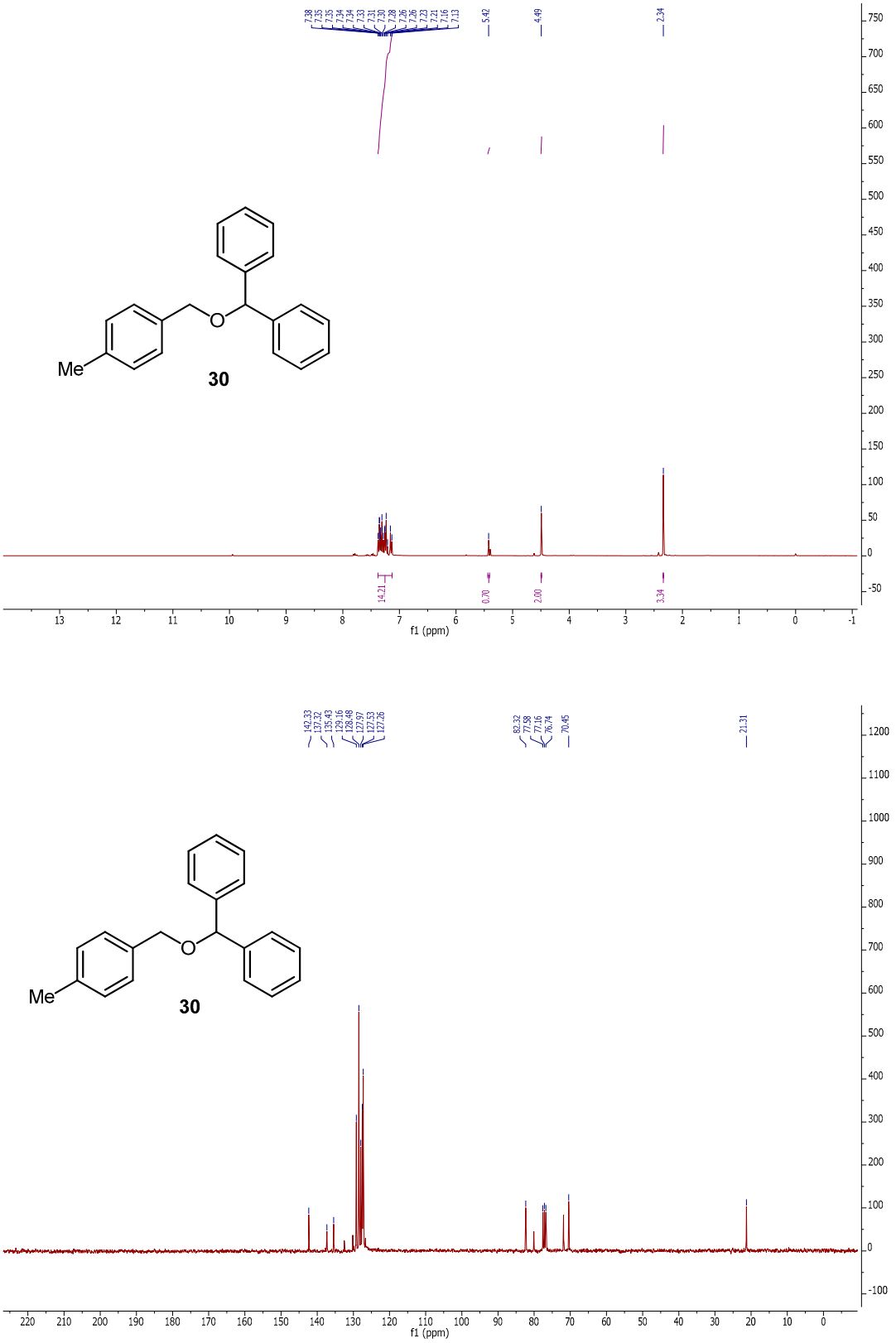

Figure S12. ^{1}H NMR and ^{13}C NMR spectra for (((4-methylbenzyl)oxy)methylene)dibenzene **(30).**

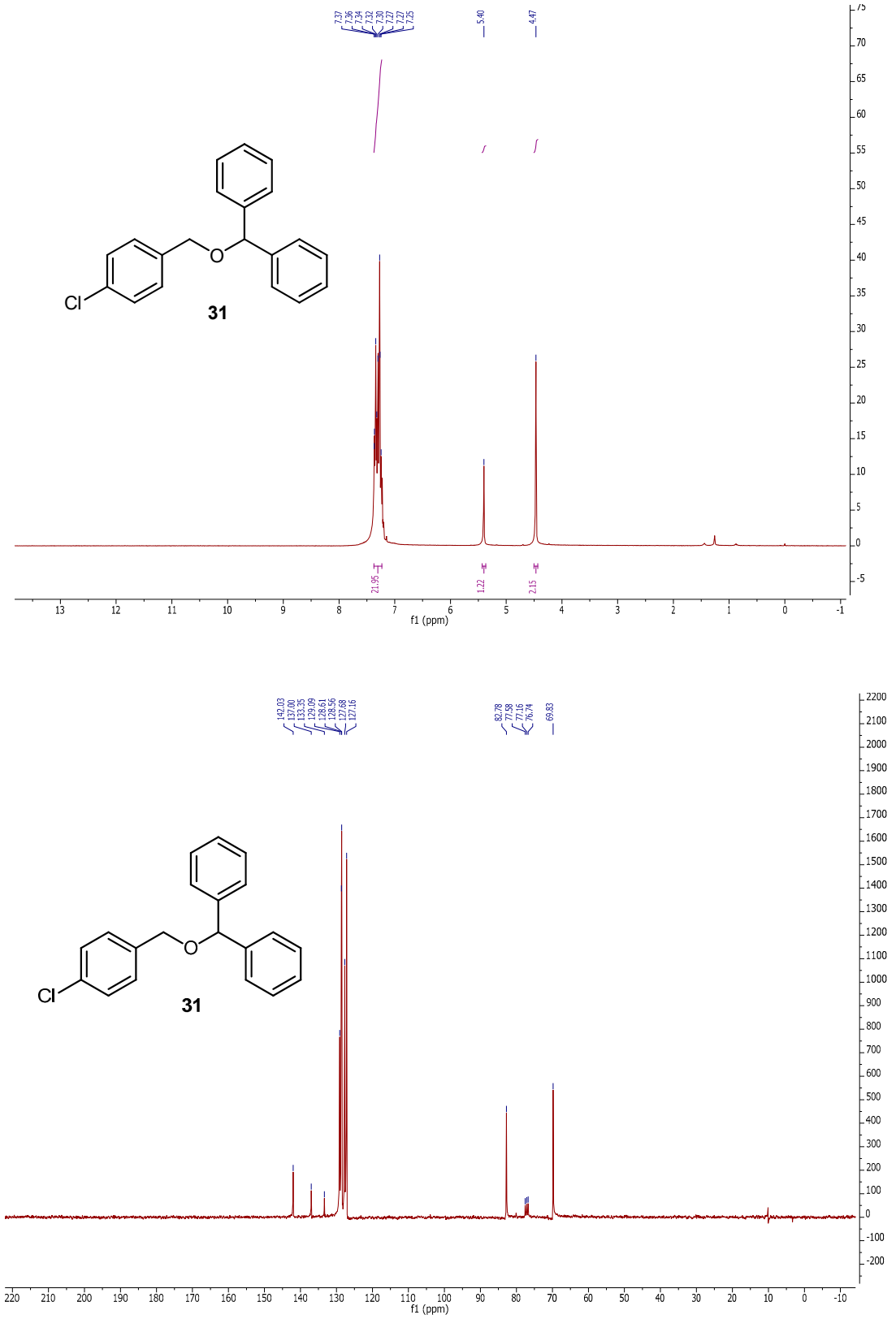

Figure S13. ^{1}H NMR and ^{13}C NMR spectra for (((4-chlorobenzyl)oxy)methylene)dibenzene **(31).**

Experimental Data Related to Thermal Analysis

Instrument: Modular system for thermal analysis - Mettler Toledo, modules: TGA/SDTA 851, DSC 822

Experimental conditions:

Temperature range: 25–200 °C

Platinum crucibles

Heating rate: 10 st/min

Atmosphere: air with flow rate 50 mL/min

Sample mass ca. 10 mg

Thermal Gravimetric (TG) analysis of the NIS

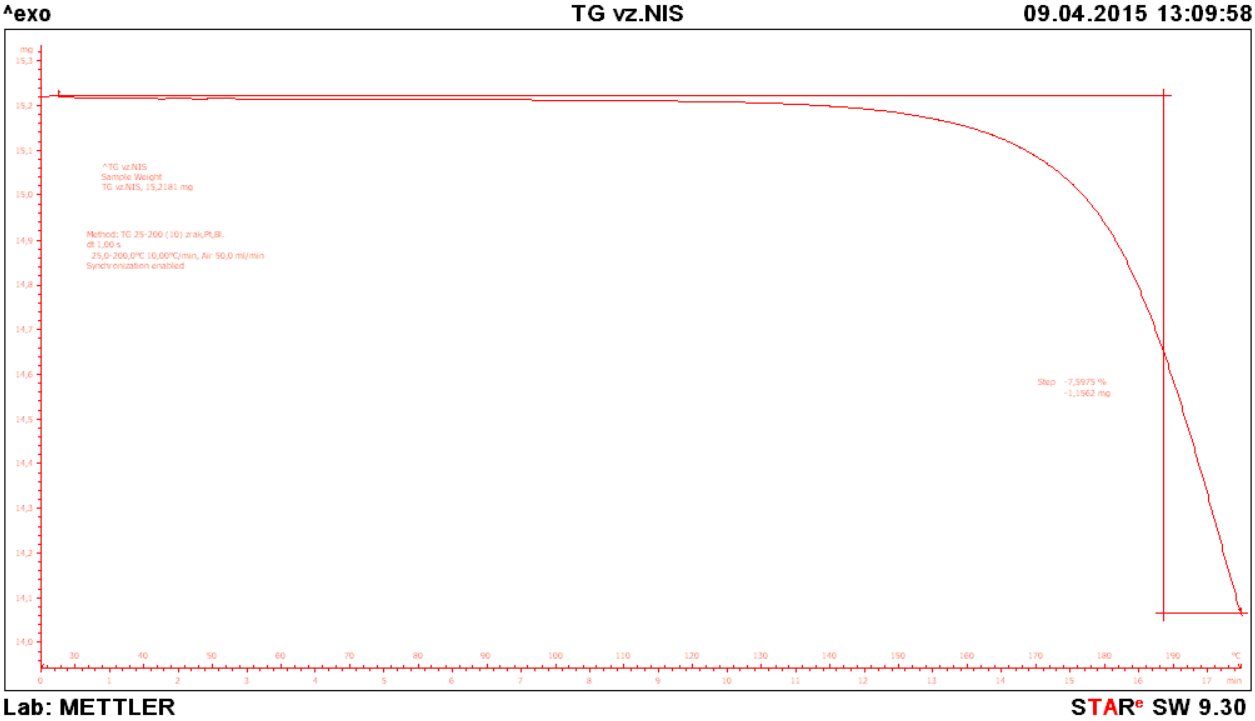

Figure S14. Thermal Gravimetric (TG) analysis of the NIS.