



SEP 12, 2023

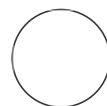
## Synthetic Procedure of Dimethyl 2-methoxy-4,4'-biphenyldicarboxylate

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**protocols.io**  
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**MANUSCRIPT CITATION:**

Zhi-Ming Su, Jack Twilton, Caroline B. Hoyt, Fei Wang, Lisa Stanley, Heather B. Mayes, Kai Kang, Daniel J. Weix, Gregg T. Beckham, and Shannon S. Stahl. (2023). Ni- and Ni/Pd-Catalyzed Reductive Coupling of Lignin-Derived Aromatics to Access Biobased Plasticizers. ACS Cent. Sci. DOI <https://doi.org/10.1021/acscentsci.2c01324>

### ABSTRACT

Lignin represents the largest source of biomass-derived aromatic chemicals and is an ideal supplement or alternative to petroleum-based feedstocks. In connection with efforts focused on oxidative lignin depolymerization, it is recognized that some of the most common products, 4-hydroxybenzoic acid (**H**), vanillic acid (**G**), and syringic acid (**S**), could serve as precursors to biaryl dicarboxylates. The parent analogue, biphenyl-4,4'-dicarboxylic acid (BPDA), has been the focus of commercial interest as a monomer for polyesters and as the core structure for nonphthalate plasticizers for poly(vinyl chloride) (PVC). Reductive coupling of phenol derivatives represents a different route to BPDA derivatives that accesses a single product regioisomer. The biomass-derived **H** compound provides a means to access the same BPDA analogue currently sourced from petroleum, while the **G** and **S** compounds that have methoxy substituents will afford BPDA derivatives that could have favorable properties (e.g., as a PVC plasticizer). The following protocol describes the synthetic procedure of three biaryl dicarboxylates: dimethyl 2-methoxy-4,4' biphenyldicarboxylate (**H-G**), dimethyl 2,2'-dimethoxy-4,4'-biphenyldicarboxylate (**G-G**), and biphenyl dimethyl dicarboxylate (**H-H**).

### MATERIALS

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**Protocol status:** Working  
We use this protocol and it's working

**Created:** Sep 12, 2023

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**PROTOCOL integer ID:** 87697

**Keywords:** biaryl dicarboxylates, Ni catalyst, NMR spectroscopy, dimers, plasticizer, biobased



Methyl paraben Merck MilliporeSigma (Sigma-Aldrich) Catalog #H5501

Step

1.1



Methyl vanillate Merck MilliporeSigma (Sigma-Aldrich) Catalog #138126

Step

1.1



Dimethylaminopyridine Merck MilliporeSigma (Sigma-Aldrich) Catalog #107700

Step 1.1



Triethylamine Merck MilliporeSigma (Sigma-Aldrich) Catalog #471283

Step

1.1



Dichloromethane anhydrous Merck MilliporeSigma (Sigma-Aldrich) Catalog #270997

Step 1.1



p-Toluenesulfonyl chloride TCI Chemicals Catalog #T0272

Step 1.1



Sodium Sulfate Merck MilliporeSigma (Sigma-Aldrich) Catalog #238597

Steps 1.1 and 1.3



Nickel (II) bromide trihydrate Merck MilliporeSigma (Sigma-Aldrich) Catalog #72243

Step 1.2



Ethanol 200 proof Fisher Scientific Catalog # BP28184

Step 1.2



22-bipyridine Merck MilliporeSigma (Sigma-Aldrich) Catalog #D216305

Step

1.2



Dimethylformamide anhydrous Merck MilliporeSigma (Sigma-Aldrich) Catalog #227056

Step 1.3



Manganese powder Merck MilliporeSigma (Sigma-Aldrich) Catalog #463728

Step 1.3



Trifluoroacetic acid Merck MilliporeSigma (Sigma-Aldrich) Catalog #T6508

Step 1.3



Hydrochloric acid Merck MilliporeSigma (Sigma-Aldrich) Catalog #258148

Step 1.3

Diethyl ether Merck MilliporeSigma (Sigma-Aldrich) Catalog #676845

Step

1.3

Silica gel Supelco Catalog #60737 Steps 2.1 and 2.2

Hexane mixture of isomers Merck MilliporeSigma (Sigma-Aldrich) Catalog #178918

Steps 2.1 and 2.2

Ethyl acetate Fisher Scientific Catalog #E145 Steps 2.1 and 2.2

Chloroform-D Cambridge Isotope Laboratories, Inc. Catalog #DLM-7-100

Steps 3.1, 3.2, 3.3, and 3.4

## SAFETY WARNINGS

Almost all chemicals used for this procedure are hazardous. Read the Safety Data Sheet (SDS) for all chemicals and follow all applicable chemical handling and waste disposal procedures.

## BEFORE START INSTRUCTIONS

All glassware is dried in an oven set to 105°C then cooled in a desiccator prior to use.

## Synthetic Procedure

1

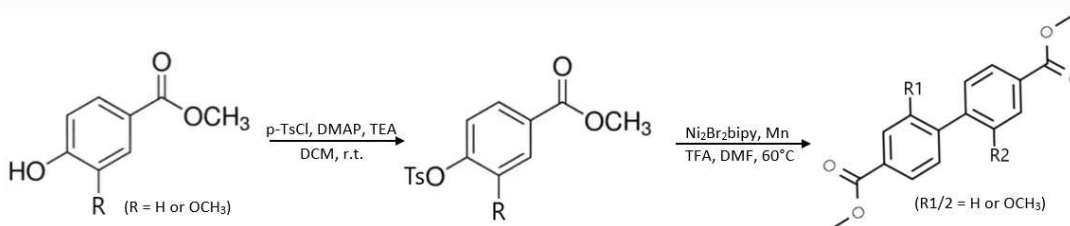


Figure 1. Two-step reaction scheme for the synthesis of dimethyl 2-methoxy-4,4'-biphenyldicarboxylate, dimethyl 2,2'-dimethoxy-4,4'-biphenyldicarboxylate, and biphenyl dimethyl dicarboxylate.

### 1.1 Synthesis of Methyl 4-(tosyloxy)benzoate and Methyl 3-methoxy-4-(tosyloxy)benzoate.

Methyl paraben ( 6.6194 g , 0.0435 mol), dimethylaminopyridine ( 0.5315 g , 0.00435

mol), and triethylamine ( 8.805 g, 0.0870 mol) were charged into a round-bottom flask. 60 mL of anhydrous dichloromethane (DCM) was added to the reaction which was allowed to stir until all material dissolved. p-Toluenesulfonyl chloride ( 9.9531 g, 0.0522 mol) was added in three parts to the mixture over two minutes. The reaction was allowed to proceed under a protective atmosphere of inert gas at room temperature for 4-5 hours.<sup>1,2</sup> After which, the reaction was added to a separatory funnel filled with deionized (D.I.) water ( 80 mL) and DCM ( 80 mL). The reaction was extracted three times with DCM ( 60 mL x3). The organic layers were combined, dried over sodium sulfate, and filtered. Solvent was removed by rotary evaporation *in vacuo*. The crude product was purified via flash chromatography to get methyl 4-(tosyloxy)benzoate (5.6911, 83.5%).

Methyl vanillate ( 8.000 g, 0.439 mol), dimethylaminopyridine ( 0.5365 g, 0.00439 mol), and triethylamine ( 8.8875 g, 0.0878 mol) were charged into a round-bottom flask. 65 mL of anhydrous DCM was added to the reaction which was allowed to stir until all material dissolved. p-Toluenesulfonyl chloride ( 10.0464 g, 0.0527 mol) was added in three parts to the mixture over two minutes.<sup>1,2</sup> The reaction was allowed to proceed under a protective atmosphere of inert gas at room temperature for 4-5 hours. After which, the reaction was added to a separatory funnel filled with D.I. water ( 80 mL) and DCM ( 80 mL). The reaction was extracted three times with DMC ( 60 mL x3). The organic layers were combined, dried over sodium sulfate, and filtered. Solvent was removed by rotary evaporation *in vacuo*. The crude product was purified via flash chromatography to yield methyl 3-methoxy-4-(tosyloxy)benzoate (13.9814g, 93.6%).

[1]

#### CITATION

George W. Kabalka, Manju Varma, Rajender S. Varma, Prem C. Srivastava and Furn F. Knapp (1986).  
Tosylation of Alcohols. J. Org. Chem..

LINK

<https://doi.org/10.1021/jo00362a044>




[2]

## CITATION

Hongli Jia, Qi Li, Aruohan Bayaguud, Shan She, Yichao Huang, Kun Chen & Yongge Wei (2017). Tosylation of alcohols: an effective strategy for the functional group transformation of organic derivatives of polyoxometalates. *Nature Scientific Reports*.

LINK

[10.1038/s41598-017-12633-8](https://doi.org/10.1038/s41598-017-12633-8)

- 1.2 Synthesis of Nickel Bromide Bipyridine (NiBr<sub>2</sub>bipy) catalysis.** Nickel (II) bromide trihydrate (  10.902 g, 40 mmol) was added to a round-bottom flask and dissolved in absolute ethanol (  150 mL ). 2,2'-bipyridine (  6.2476 g, 40 mmol) was added to the reaction once all of the nickel (II) bromide trihydrate had dissolved. The reaction was allowed to stir at room temperature for 24 hours during which the desired product precipitates from solution [See Note 1].<sup>3</sup> The solution was filtered to collect the product which was then dried in a vacuum dessicator to yield a light green nickel bromide bipyridine solid (10.311g, 68.8%).

## Note

Note 1. During the 24 hours, the solution should go from a purple-brown to a dark green before eventually lightening to a yellow-green with a light green precipitate.





[3]









## CITATION

Muriel Durandetti, Jacques Maddaluno (2014). Nickel Bromide Bipyridine. *Encyclopedia of Reagents for Organic Synthesis*.

LINK

[10.1002/047084289X.rn01736](https://doi.org/10.1002/047084289X.rn01736)

- 1.3 Synthesis of biaryl dimer(s).** Methyl 3-methoxy-4-(tosyloxy)benzoate (  2.4156 g, 0.00718 mol) was charged into a round-bottom flask and dissolved in  17 mL anhydrous dimethylformamide (DMF). A protective atmosphere was provided and the reaction was heated to 60°C. Manganese (Mn) powder (  1.1471 g, 0.209 mol) was added to the reaction, then the NiBr<sub>2</sub>bipy catalyst (  0.3912 g, 0.001 mol), followed quickly by

trifluoroacetic acid (  40  $\mu$ L ). Methyl 4-(tosyloxy)benzoate (  1.000 g , 0.00326 mol) in  3 mL anhydrous DMF was added slowly to the reaction mixture.<sup>4</sup> The reaction proceeded at 60°C for 1 hour before it was acidified with 1M hydrochloric acid (  20 mL ). Diethyl ether (  50 mL ) was added slowly to the reaction mixture which was then extracted three times with diethyl ether (  50 mL x3). The organic layers were washed twice with D.I. water (  50 mL ) and once with brine (  50 mL ) [See Note 2]. It was then dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified via flash chromatography to yield dimethyl 2-methoxy-4,4'-biphenyldicarboxylate (H-G dimer, 0.5506g, 58.5%), dimethyl-2,2'-dimethoxy-4,4'-biphenyldicarboxylate (G-G dimer, 0.2586g, 21.8%), and biphenyl dimethyl dicarboxylate (H-H dimer, 0.0462g, 9.4%).

#### Note

Note 2. Preparation of saturated brine solution: Fill a container partially with D.I. water. Add a spatula full of sodium chloride (NaCl) and stir until dissolved. Repeat until excess NaCl begins to settle onto the bottom of the container.

[4]

#### CITATION

Jacques Maddaluno, Muriel Durandetti (2015). Dimerization of Aryl Sulfonates by in situ Generated Nickel(0). Synlett.

LINK

[10.1055/s-0035-1560712](https://doi.org/10.1055/s-0035-1560712)

## Purification

- 2 Flash chromatography was performed using a Teledyne Isco Combiflash® NextGen 300+. Collected fractions were determined using a UV detector with wavelengths set at 254 and 280 nm. Samples were prepared by dissolving the crude material in the smallest amount of compatible solvent. Silica gel (mesh size 70-230) was then added to adsorb the material. Excess solvent was vacuum evaporated and the sample was loaded into a RediSep® R<sub>f</sub> 25 g sample cartridge (catalog # 69-3873-240).
- 2.1 Methyl 4-(tosyloxy)benzoate was purified via flash chromatography. Column used was a RediSep® Silver 80 g silica gel flash column (catalog # 69-2203-380). Solvent system was

hexane (Solvent A) and ethyl acetate (Solvent B). Methyl 4-(tosyloxy)benzoate was purified from impurities using a ratio of 45% ethyl acetate:55% hexane.

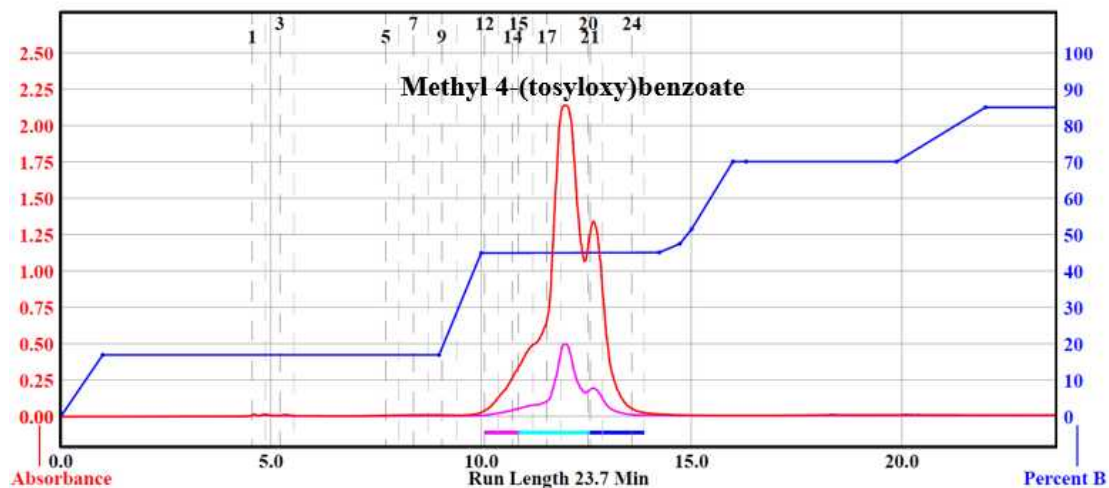


Figure 2. Run program from Combiflash® NextGen 300+ of methyl 4-(tosyloxy)benzoate separation.

Methyl 4-(tosyloxy)benzoate was purified via flash chromatography. Column used was a RediSep® Silver 80 g silica gel flash column (catalog # 69-2203-380). Solvent system was hexane (Solvent A) and ethyl acetate (Solvent B). Methyl 4-(tosyloxy)benzoate was purified from impurities using a ratio of 45% ethyl acetate:55% hexane.

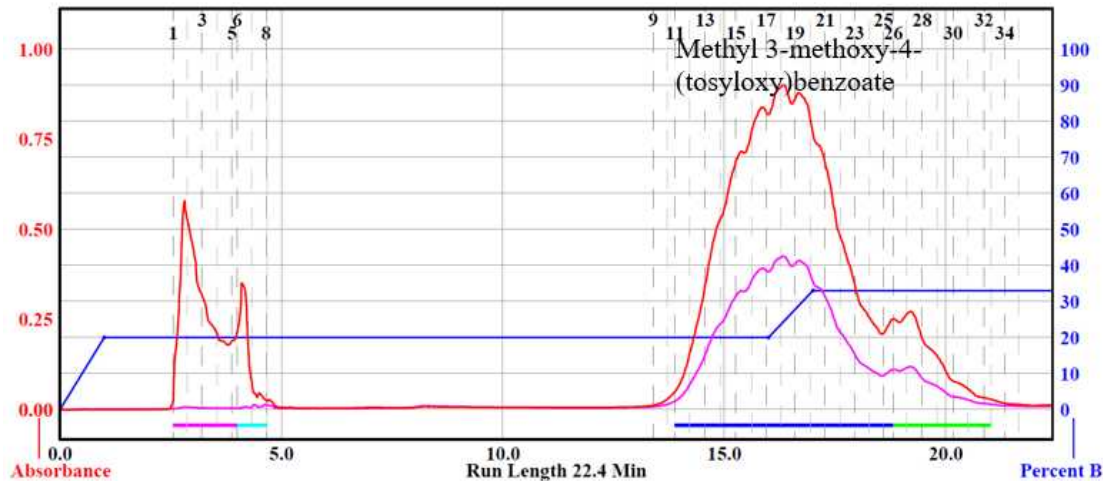


Figure 3. Run program from Combiflash® NextGen 300+ of methyl 3-methoxy-4-(tosyloxy)benzoate separation.

**2.2** Biaryl dimers (H-G, G-G, and H-H) were purified via flash chromatography. Column used was a RediSep® Silver 40 g silica gel flash column (catalog # 69-2203-340). Solvent system was



hexane (Solvent A) and ethyl acetate (Solvent B). The three dimers were purified using a ratio of 10% ethyl acetate to 90% hexane.

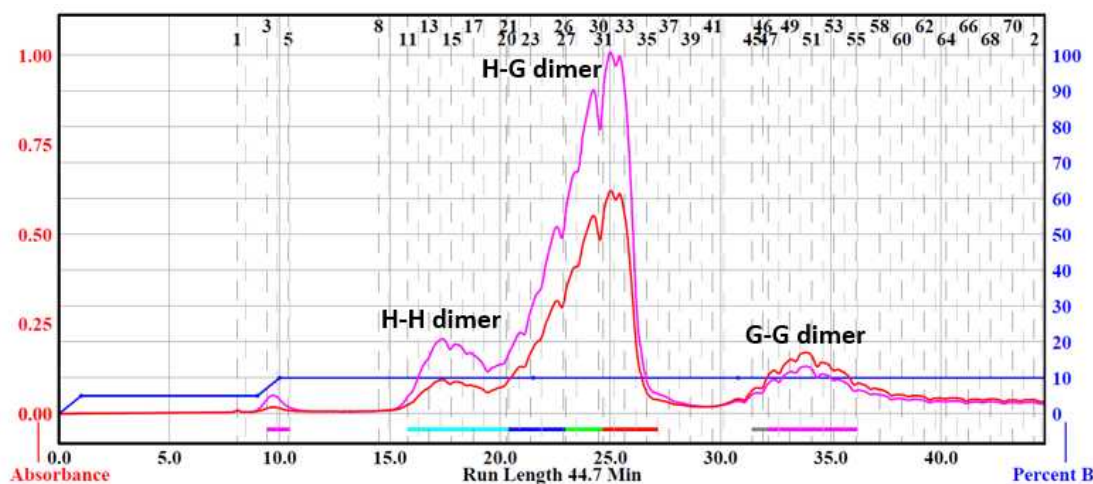


Figure 4. Run program from Combiflash® NextGen 300+ of biaryl dimer separation.

## Nuclear Magnetic Resonance (NMR) Spectroscopy

- 3 Nuclear magnetic resonance (NMR) spectra are acquired in a suitable deuterated NMR solvent at 25°C on a Bruker AVANCE 400 MHz spectrometer equipped with a 5 mm BBO probe. Chemical shifts ( $\delta$ ) are reported in ppm.  $^1\text{H}$ -NMR spectra are recorded with a relaxation delay of 1.0 s and an acquisition time of 4.09 s. The acquisition parameters for  $^{13}\text{C}$ -NMR include a 90° pulse width, a relaxation delay of 1.0 s, and an acquisition time of 1.36 s. Tetramethylsilane is used as a reference.

### 3.1 Methyl 4-(tosyloxy)benzoate (H-OTs)

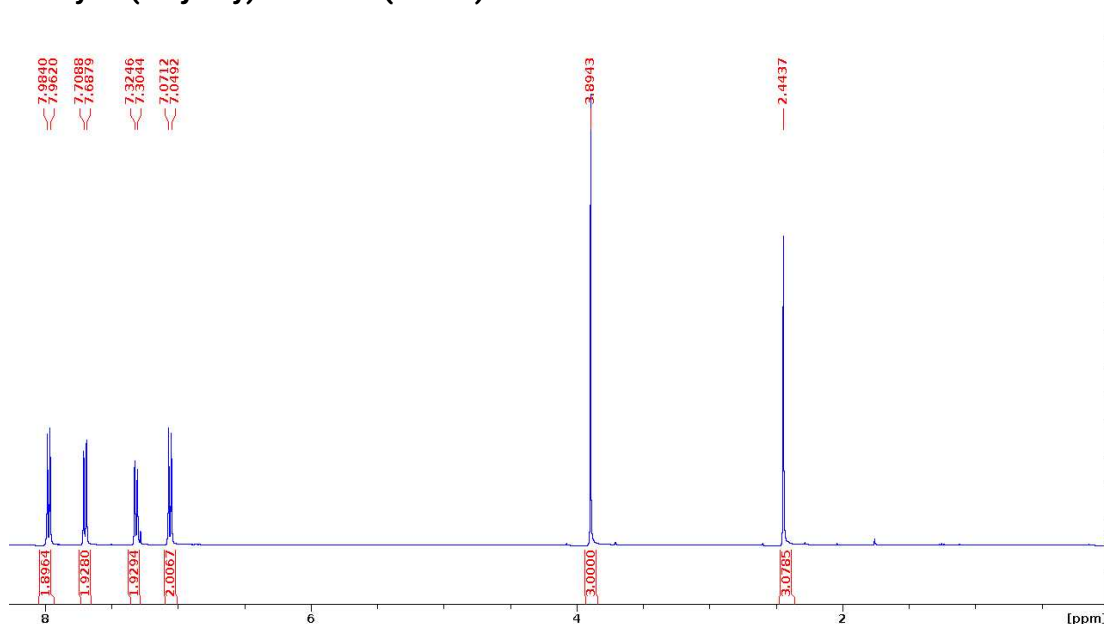




Figure 5.  $^1\text{H}$  NMR spectrum of methyl 4-(tosyloxy)benzoate.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (d,  $J=8.8$  Hz, 2H), 7.71 (d,  $J=8.4$  Hz, 2H), 7.32 (d,  $J=8.1$  Hz, 2H), 7.07 (d,  $J=8.8$  Hz, 2H), 3.89 (s, 3H), 2.44 (s, 3H).

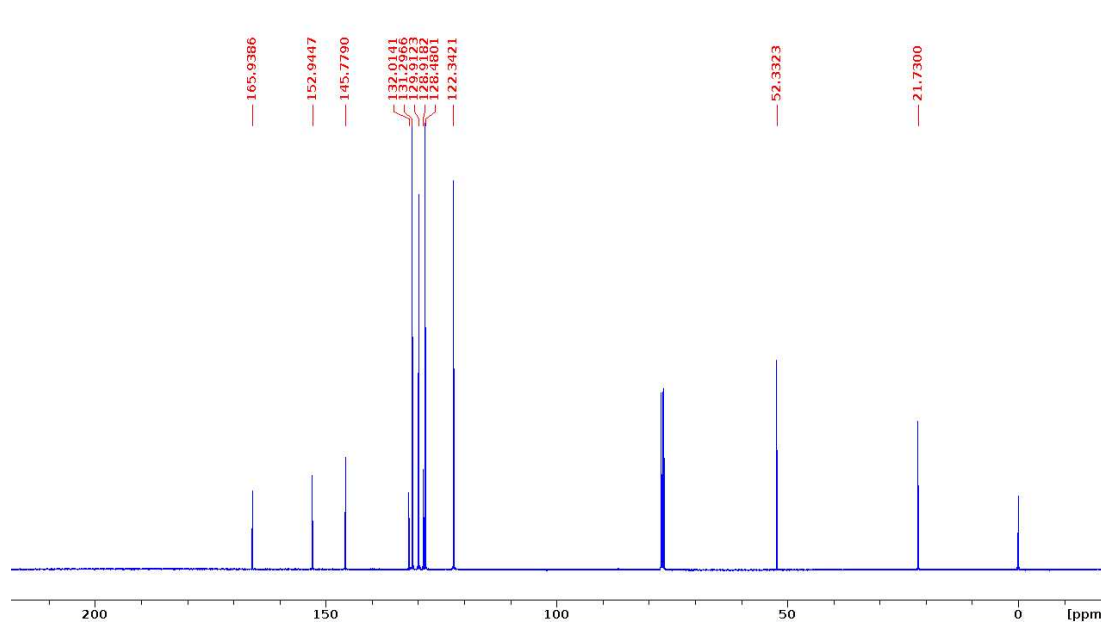


Figure 6.  $^{13}\text{C}$  NMR spectrum of methyl 4-(tosyloxy)benzoate.

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  165.9, 152.9, 145.8, 132.0, 131.3, 129.9, 128.9, 128.4, 122.3, 52.3, 21.7.

### Methyl 3-methoxy-4-(tosyloxy)benzoate (G-OTs)

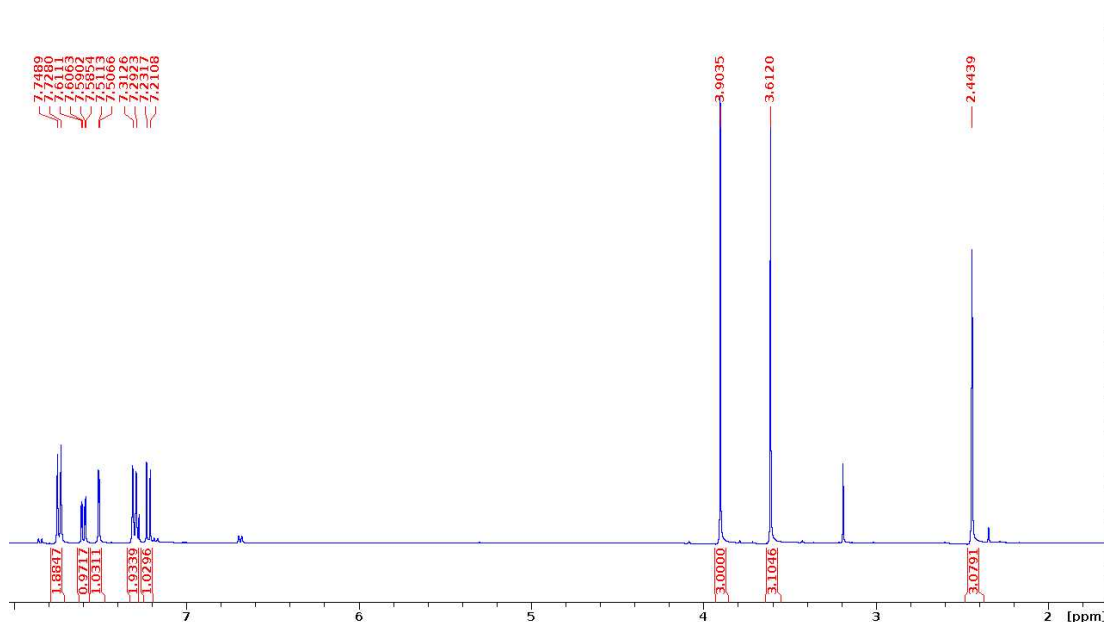


Figure 7. <sup>1</sup>H NMR spectrum of methyl 3-methoxy-4-(tosyloxy)benzoate.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.75 (d, J=8.4 Hz, 2H), 7.61 (dd, J=6.4, 1.9 Hz, 1H), 7.51 (d, J=1.9 Hz, 1H), 7.31 (d, J=8.1 Hz, 2H), 7.23 (d, J=8.4 Hz, 2H), 3.90 (s, 3H), 3.61 (s, 3H), 2.44 (s, 3H).

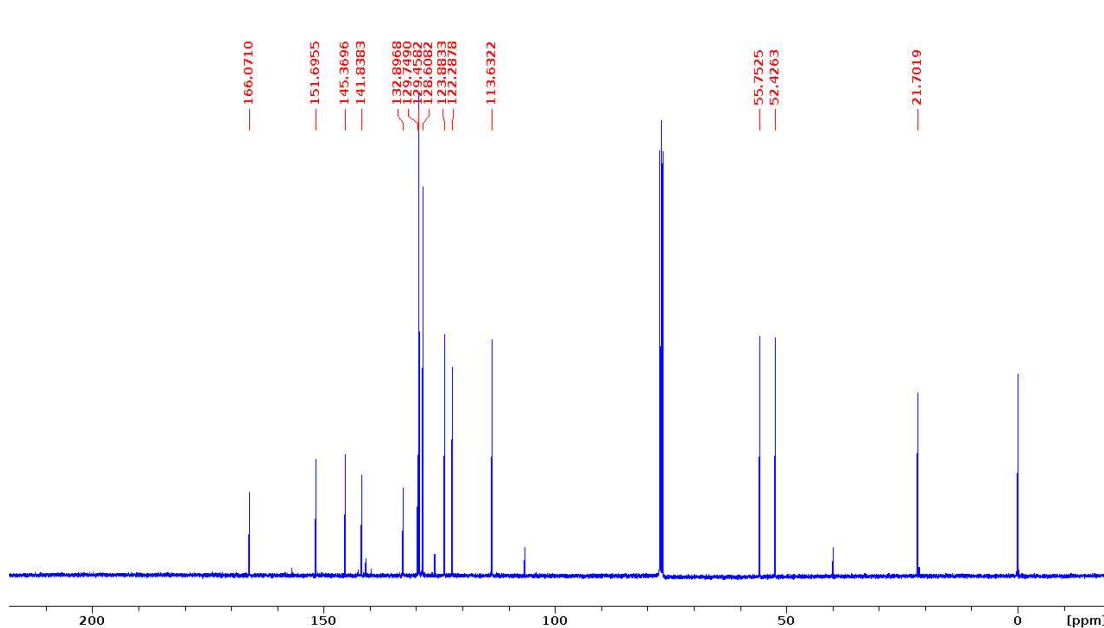


Figure 8. <sup>13</sup>C NMR spectrum of methyl 3-methoxy-4-(tosyloxy)benzoate.

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.1, 151.7, 145.4, 141.8, 132.9, 129.7, 129.5, 128.6, 123.9,

122.3, 113.6, 55.8, 52.4, 21.7.

### 3.2 Dimethyl 2-methoxy-4,4'-biphenyldicarboxylate (H-G dimer)

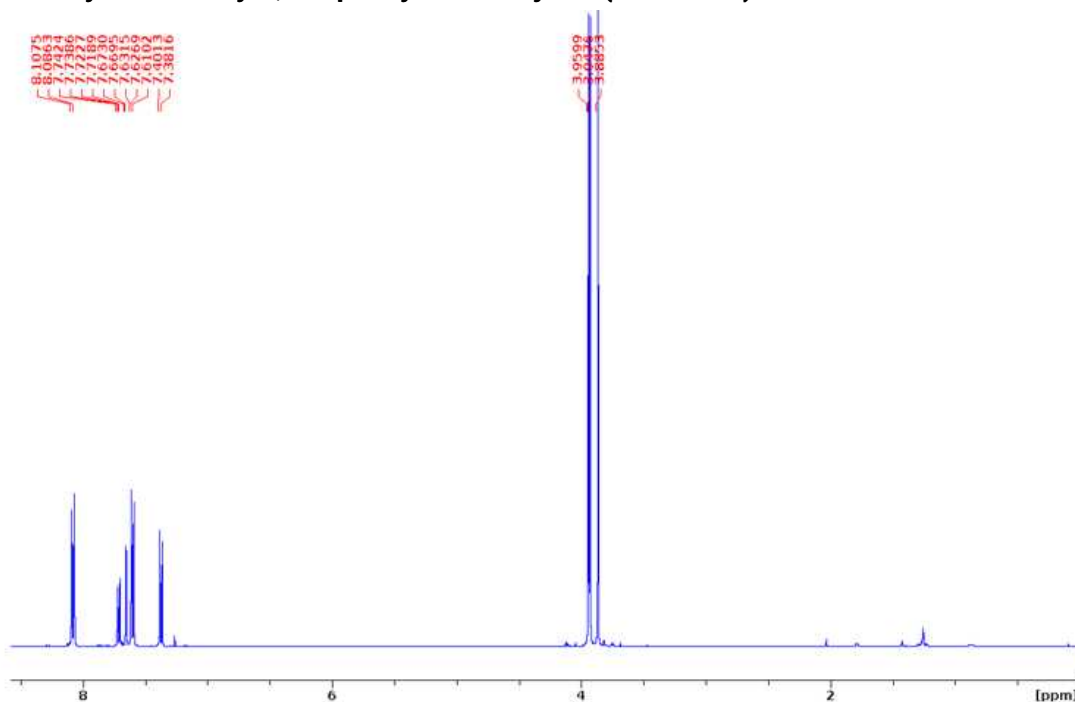


Figure 9.  $^1\text{H}$  NMR spectrum of dimethyl 2-methoxy-4,4'-biphenyldicarboxylate.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.11-8.09 (m, 2H), 7.74 (dd,  $J$ = 6.3, 1.5 Hz, 1H), 7.67 (d,  $J$ = 1.4 Hz, 1H), 7.63–7.61 (m, 2H), 7.40 (d,  $J$ = 7.9 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H).

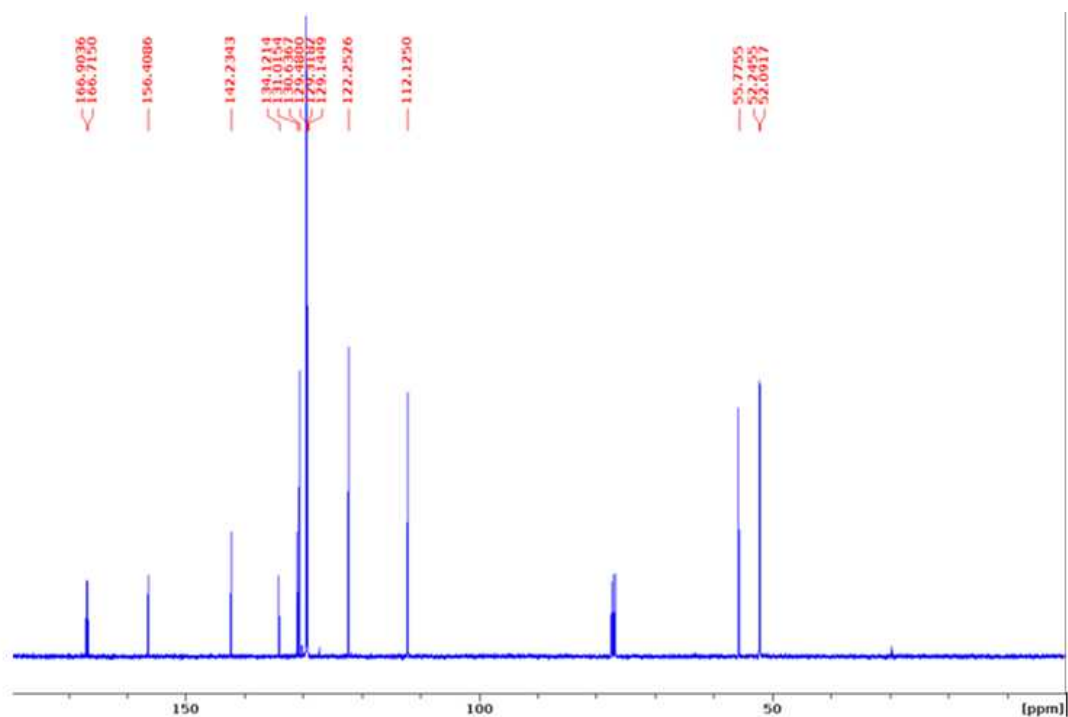


Figure 10.  $^{13}\text{C}$  NMR spectrum of dimethyl 2-methoxy-4,4'-biphenyldicarboxylate.

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.9, 166.7, 156.4, 142.2, 134.1, 131.0, 130.6, 129.5, 129.3, 129.1, 122.3, 112.1, 55.8, 52.3, 52.1.

### 3.3 Dimethyl 2,2'-dimethoxy-4,4'-biphenyldicarboxylate (G-G dimer)

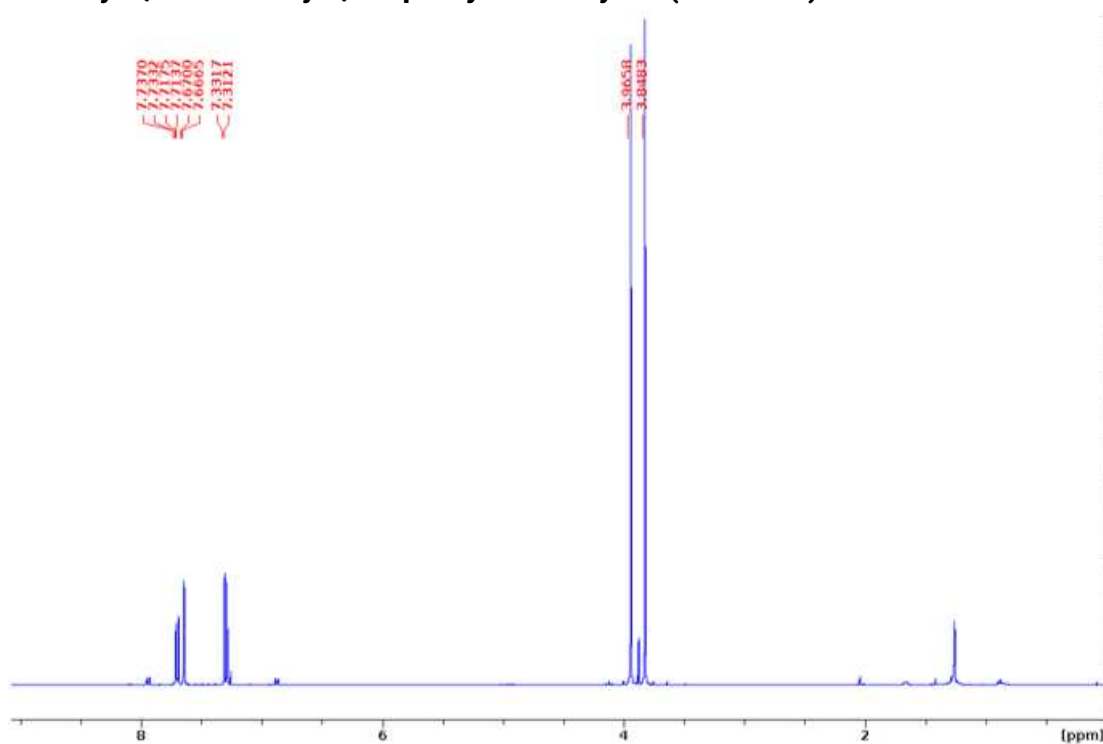


Figure 11.  $^1\text{H}$  NMR spectrum of dimethyl 2,2'-dimethoxy-4,4'-biphenyldicarboxylate.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.74 (dd,  $J$  = 6.3, 1.5 Hz, 2H), 7.67 (d,  $J$  = 1.4 Hz, 2H), 7.33 (d,  $J$  = 7.8 Hz, 2H), 3.87 (s, 6H), 3.85 (s, 6H).

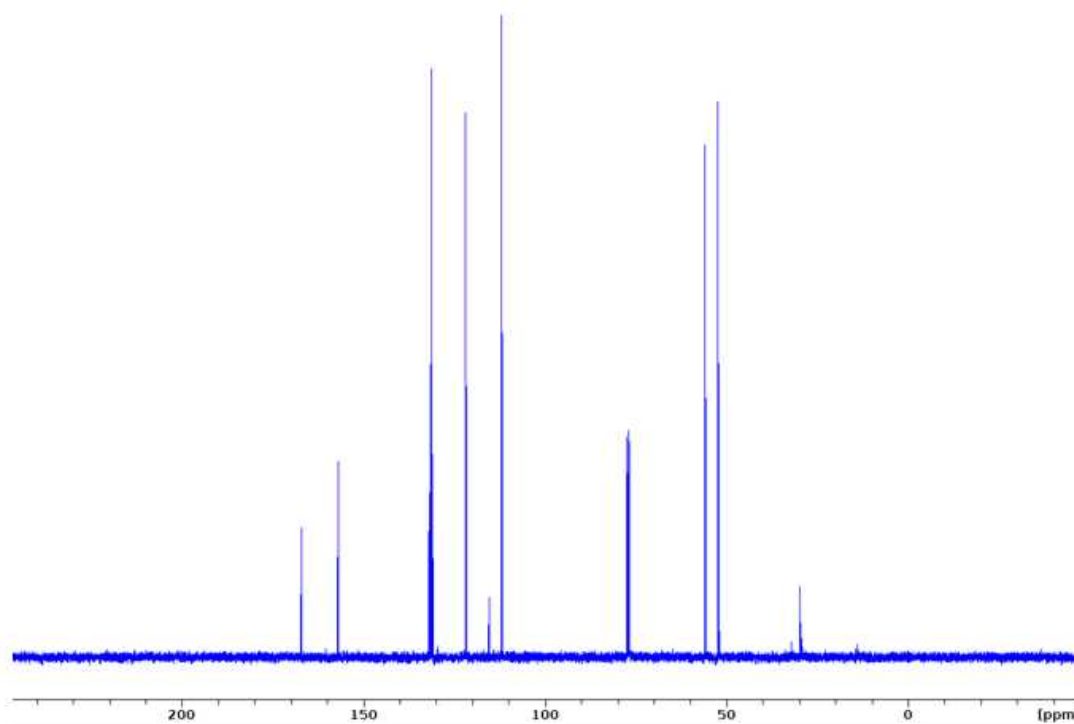


Figure 12.  $^{13}\text{C}$  NMR spectrum of dimethyl 2,2'-dimethoxy-4,4'-biphenyldicarboxylate.

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.9, 156.9, 131.8, 131.1, 130.9, 121.8, 111.9, 55.4, 52.2.

### 3.4 Biphenyl dimethyl dicarboxylate (H-H dimer)

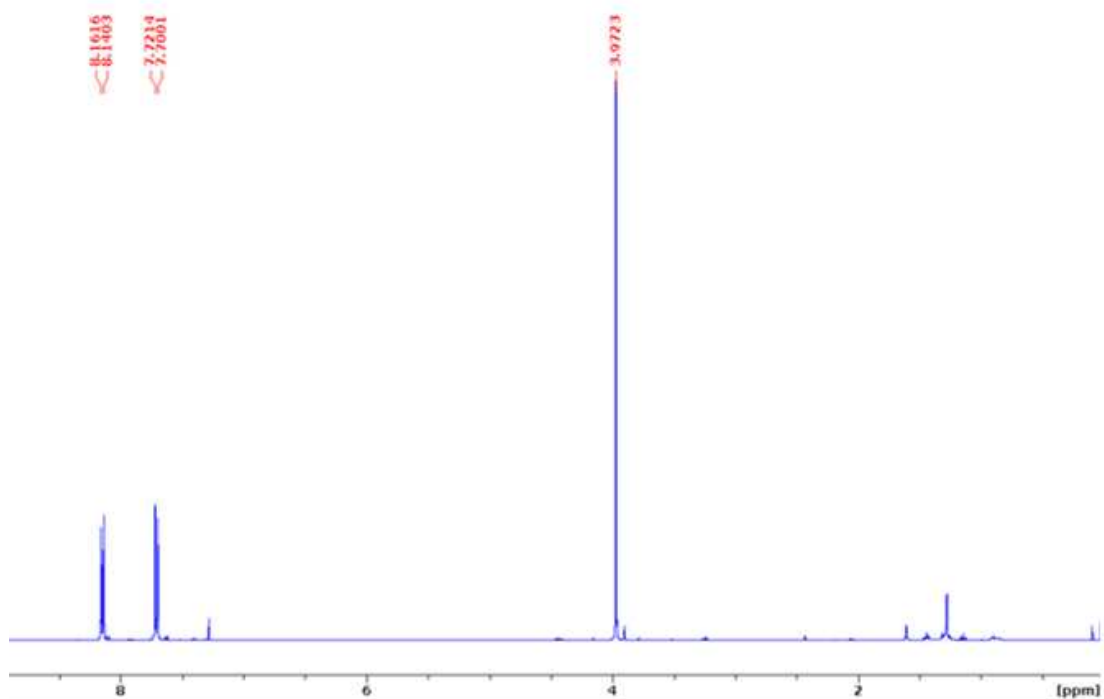


Figure 13.  $^1\text{H}$  NMR spectrum of biphenyl dimethyl dicarboxylate.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.16 (d,  $J$  = 8.5 Hz, 4H), 7.72 (d,  $J$  = 8.5 Hz, 4H), 3.97 (s, 6H).

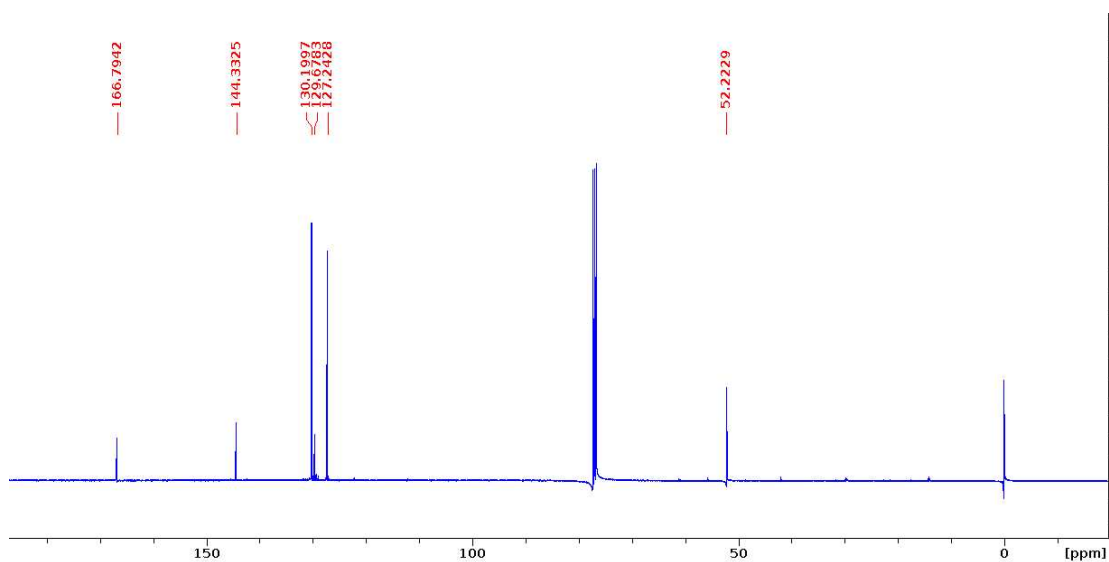


Figure 14.  $^{13}\text{C}$  NMR spectrum of biphenyl dimethyl dicarboxylate.

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.8, 144.3, 130.2, 129.7, 127.2, 55.2.

