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Sodium Dispersion-Mediated Reductive Dimerization of Benzylic Halides For Symmetrical Bibenzyls: Column-Free Applications to Natural Products

Bubwoong Kang [a,*,1], Tatsuro Imamura [a,1], Tetsuya Satoh[b]

[a] *Department of Applied Chemistry in Bioscience, Graduate School of Agricultural Science, Kobe University, 1-1 Rokkodai, Nada, Kobe 657-8501, Japan*

[b] *Department of Chemistry, Graduate School of Science, Osaka Metropolitan University, 3–3–138, Sugimoto, Sumiyoshi-ku, Osaka 558–8585, Japan*

[*] Corresponding author.
E-mail address: kangb@pegasus.kobe-u.ac.jp (B. Kang).

[1] These authors contributed equally: Bubwoong Kang, Tatsuro Imamura.

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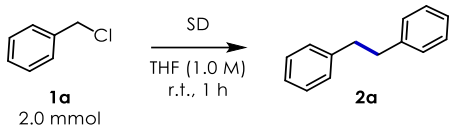
1. General experimental details

For reactions that required heating, a heat block and an oil bath were used as the heat source. Column chromatography was performed on Silica Gel 60 N (spherical, neutral), 100–210 μm (purchased from Kanto Chemical Company, Incorporated). Reactions and chromatography fractions were analyzed by Thin-Layer Chromatography (TLC) on TLC plates purchased from FUJIFILM Wako Pure Chemical Corporation (Product name: Silicagel 70 F254 TLC Plate-Wako) with visualization by ultraviolet light (UV) irradiation at 254 nm, and *p*-anisaldehyde (contains acetic acid, and sulfuric acid) ethanol, or phosphomolybdic acid ethanol solution for staining. Preparative TLC was performed on TLC plates purchased from the same supplier with 1 mm layer thickness and 20 cm^2 area (Product name: Silicagel 70 F254 PLC Plate-Wako) with visualization by UV irradiation at 254 nm. Melting points (Mp) were determined on YANACO micro melting point apparatus. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECZ-400S instrument at 400 and 101 MHz, respectively. Chemical shifts (δ) and coupling constants (*J*) are presented in ppm (relative to internal standards), and Hz, respectively. For internal standard on ^{1}H NMR spectroscopy, Me_4Si (δ 0.00) was used. Quantitative ^{1}H NMR (qNMR) was performed with 20 seconds of relaxation delay using triphenylmethane (Ph_3CH) as internal standard. For internal standard on ^{13}C NMR spectroscopy, $CDCl_3$ (δ 77.00) was used. ^{13}C NMR spectra were recorded with ^{1}H NMR decoupling. To distinguish mono- (CH_3), di- (CH_2), tri- (CH), and tetra-substituted (C) carbon atoms, distortionless enhancement by polarization transfer (DEPT) spectra were obtained by variation of selection angle (90° and 135°) parameters (DEPT90, and DEPT135). High-resolution mass spectrometry (HRMS) data were obtained using an LTQ Orbitrap XL instrument (Thermo Fisher Scientific Inc.) with an atmospheric pressure chemical ionization ion source in positive ion mode. When HRMS data for protonated molecule ions ($[M+H]^+$) could not be acquired, MS samples were directly infused into the instrument to obtain HRMS data for radical cation analyte ions (M^+). Fourier transform (FT)-IR spectra were recorded with a ThermoFisher Nicolet iS5 instrument with an iD5 attenuated total reflection (ATR) attachment and are reported in terms of frequency absorption.

2. Materials

Sodium dispersion (SD) with its product name of SD Super Fine™ (sodium 25wt% dispersion in mineral oil) was purchased from Tokyo Chemical Industry Co., Ltd. (Product Number: D5792). The average size of SD particles is approximately 10 μm (for more information on SD, see the following link of the manufacturer, Kobelko Eco-Solutions Co., Ltd.: https://www.kobelco-eco.co.jp/english/sodium_dispertion/). SD was transferred into a heat gun-dried 50-mL syringe vial purchased from Maruem Corp., Osaka, Japan (Product Code: CV-7) and the vial was filled with argon gas and stored at lower than −20 °C. When using SD, the vial was vigorously shaken in order to uniformely disperse SD. SD was taken and used from the vial by syringe with its inside positively pressurized with argon-filled balloon. After using SD, parafilm was partially melted by heat gun to fill the resulting holes on the Teflon/silicone rubber septum of the syringe vial. Even though SD was taken from each vial many times, it was confirmed that the activity of SD was maintained after six months in our hands. Dry solvents and all other substrates were also purchased from chemical companies and were used as received.

3. Table S1. Reductive dimerization of chloride **1a** by SD[a]



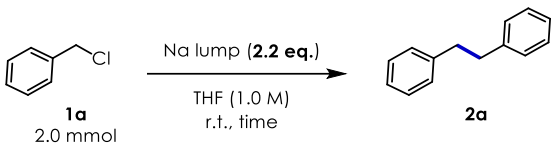
entry	SD	yield[b]	
		recovered **1a**	**2a**
1	1.3 eq.	11%	77%
2	1.5 eq.	0%	100%
3	2.2 eq.	0%	100%
4[c]	2.2 eq.	65%	5%

(a) Benzyl chloride **1a** (232 µL, 2.00 mmol, 1.00 eq.), SD (266–450 µL, 2.6–4.4 mmol, 1.3–2.2 eq.), dry tetrahydrofuran (THF) (2.00 mL), room temperature (r.t.), 1 h.

(b) Yields were determined by qNMR.

(c) Solvent was not used.

4. Table S2. Reductive dimerization of chloride **1a** by Na lump[a]



entry	time (h)	**2a** yield[b]
1	1	0%
2	3	2%
3	5	44%
4	24	80%

(a) Benzyl chloride **1a** (232 µL, 2.00 mmol, 1.00 eq.), Na lump (0.10 g, 4.4 mmol, 2.2 eq.), dry THF (2.00 mL), r.t., 1–24 h.

(b) Yields were determined by qNMR.

5. Typical procedure for reductive dimerization of benzylic halides **1a**–**1t** (**Scheme 1**)

To a stirring solution of benzylic halides **1** (2.00 mmol, 1.00 eq.) in dry THF (2.00 mL, 1.00 M) was dropwisely added SD (450 µL, 4.4 mmol, 2.2 eq.) under an argon atmosphere at r.t.. After stirring for 1 h, the reaction was quenched with H_2O (10 mL), evaporated to remove THF, and extracted with $CHCl_3$ (10 mL×3). The combined $CHCl_3$ extract was washed with brine (30 mL), dried over Na_2SO_4, and evaporated. The resulting crude product was purified by silica gel (SiO_2 10 g) column chromatography, and/or PTLC using hexane/EtOAc to give bibenzyls **2a**–**2t**. Even though the weight of each crude product was relatively high (typically around 0.5 g), the entire amount was successfully applied to a TLC plate for PTLC, resulting in a purified product. Modified protocols were shown in each compound section.

6. Synthesis and characterization of compounds

The analytical data for the known and new compounds including natural products are as follows. The NMR data for the known compounds **2a** [S1], **2b** [S2], **2c** [S3], **2d** [S4], **2e** [S5], **2f** [S6], **2g** [S5], **2j** [S7], **2k** [S7], **2l** [S8], **2m** [S9], **2n** [S5], **2o** [S5], **2p** [S10], **2q** [S11], **2r** [S12], **2t** [S13] and **2t'**[S14] were in good agreement with the literature values.

6.1. Synthetic protocols and characterization of bibenzyls 2a–2t

Bibenzyl (2a) [S1]

The "**5. Typical procedure**" with benzyl chloride **1a** (239 µL, 2.00 mmol, 1.00 eq.), or **1a-Br** (232µL, 2.00 mmol, 1.00 eq.), and silica gel column chromatography using hexane gave the title compound as a white solid. Yield: from **1a** 180 mg (99%), from **1a-Br** 177 mg (97%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.25 (m, 4H), 7.24–7.14 (m, 6H), 2.92 (s, 4H).

4,4′-Dimethylbibenzyl (2b) [S2]

The "**5. Typical procedure**" with 4-methylbenzyl chloride **1b** (263 µL, 2.00 mmol, 1.00 eq.), and PTLC using hexane gave the title compound as a white solid. Yield: 186 mg (88%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (s, 8H), 2.86 (s, 4H), 2.32 (s, 6H).

2,2′-Dimethylbibenzyl (2c) [S3]

The "**5. Typical procedure**" with 2-methylbenzyl chloride **1c** (260 µL, 2.00 mmol, 1.00 eq.), and silica gel column chromatography using hexane gave the title compound as a white solid. Yield: 180 mg (99%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.08 (m, 8H), 2.85 (s, 4H), 2.32 (s, 6H).

4,4′-Dimethoxybibenzyl (2d) [S4]

The "**5. Typical procedure**" with 4-methoxybenzyl chloride **1d** (272 µL, 2.00 mmol, 1.00 eq.), and PTLC using hexane/EtOAc (7/1) gave the title compound as a pale yellow solid: 240 mg, (99%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11–7.05 (m, 4H), 6.85–6.79 (m, 4H), 3.79 (s, 6H), 2.82 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.7 (C), 133.9 (C), 129.3 (CH), 113.6 (CH), 55.2 (CH_3), 37.2 (CH_2); IR: 3030, 3010, 2963, 2931, 2915, 2852, 2836, 1898, 1610, 1582, 1508, 1463, 1455, 1440, 1418, 1317, 1303, 1266, 1242, 1215, 1181, 1175, 1143, 1094, 1030 cm^{-1}; Mp: 127–129 °C; HRMS: M^+, found 242.1300. $C_{16}H_{18}O_2^+$ requires 242.1301.

3,3′-Dimethoxybibenzyl (2e) [S5]

The "**5. Typical procedure**" with 3-methoxybenzyl chloride **1e** (282 µL, 2.00 mmol, 1.00 eq.), and silica gel column chromatography using hexane/EtOAc (9/1) gave the title compound as a

colorless oil. Yield: 233 mg (96%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (dd, *J* = 11.7, 4.2 Hz, 2H), 6.81–6.71 (m, 6H), 3.78 (s, 6H), 2.89 (s, 4H).

3,3′,4,4′-Tetramethoxybibenzyl (2f) [S6]

The "**5. Typical procedure**" with veratryl chloride **1f** (373 mg, 2.00 mmol, 1.00 eq.), and a less amount of SD (245 µL, 2.4 mmol, 1.2 eq.), PTLC using hexane/EtOAc (4/1) gave the title compound as a white solid. Yield: 197 mg, (65%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, *J* = 8.1 Hz, 2H), 6.71 (dd, *J* = 8.1, 1.9 Hz, 2H), 6.66 (d, *J* = 1.9 Hz, 2H), 3.86 (s, 6H), 3.84 (s, 6H), 2.85 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.6 (C), 147.1 (C), 134.3 (C), 120.3 (CH), 111.8 (CH), 111.0 (CH), 55.9 (CH_3), 55.7(CH_3), 37.7 (CH_2); IR: 2998, 2964, 2937, 2853, 2838, 1589, 1514, 1453, 1464, 1418, 1338, 1255, 1234, 1189, 1151, 1027 cm^{-1}; Mp:104–106 °C; HRMS: $[M+H]^+$, found 303.1593. $C_{18}H_{23}O_4^+$ requires 303.1591.

Brittonin A (2g) [S5]

To a stirring solution of 3,4,5-trimethoxybenzyl chloride 1g (108 mg, 0.500 mmol, 1.00 eq.) in dry THF (10 mL, 1.00 M) was dropwisely added SD (61 µL, 0.6 mmol, 1.2 eq.) at r.t. After stirring for 1 h, the reaction was quenched with H_2O (20 mL). The yield of the title compound was determined by qNMR of the resulting crude product to be 64%. An analytically pure sample of the title compound was obtained by PTLC from a small portion of this crude product. Yield: 64%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 (s, 4H), 3.83 (s, 18H), 2.85 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.0 (C), 137.3 (C), 136.1 (C), 105.4 (CH), 60.9 (CH_3), 56.0 (CH_3), 38.4 (CH_2); IR: 3008, 2947, 2923, 2860, 2843, 2822, 1588, 1506, 1456, 1421, 1332, 1261, 1244, 1232, 1196, 1187, 1113, 1059, 1039, 1005 cm^{-1}; Mp: 137–140 °C; HRMS: $[M+H]^+$, found 363.1809. $C_{20}H_{27}O_6^+$ requires 363.1802.

In addition to **2g**, 3,3′,5,5′-tetramethoxybibenzyl (**2l**) was also detected as a side product. Yield: 20%; see compound **2l** section for characterization.

2,2′-Diphenoxybibenzyl (2h)

The "**5. Typical procedure**" with 2-phenoxybenzyl bromide **1h** (376 µL, 2.00 mmol, 1.00 eq.), and silica gel column chromatography using hexane, followed by PTLC using hexane gave the title compound as a white solid. Yield: 213.8 mg (58%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.24 (m, 6H), 7.19–7.11 (m, 4H), 7.07–6.98 (m, 4H), 6.89–6.82 (m, 6H), 2.93 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9 (s), 154.5 (s), 133.4 (s), 130.8 (s), 129.6 (s), 127.3 (s), 123.7 (s), 122.4 (s), 119.4 (s), 117.7 (s), 30.9 (s); IR: 3061, 3037, 2934, 2360, 2338, 1580, 1484, 1452, 1233 cm^{-1}; Mp: 106 °C; HRMS: M^+, found 366.1618. $C_{26}H_{22}O_2^+$ requires 366.1614.

In addition to **2h**, 2-phenoxybibenzyl (**2h'**) was also obtained as a colorless oil. Yield: 43.9 mg (16%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.28 (m, 2H), 7.25–7.21 (m, 3H), 7.20–7.11 (m, 4H), 7.09–7.02 (m, 2H), 6.96–6.88 (m, 3H), 2.98–2.85 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9 (C), 154.4 (C), 141.9 (C), 133.3 (C), 130.7 (CH), 129.7 (CH), 128.5 (CH), 128.2 (CH), 127.4 (CH), 125.8 (CH), 123.8 (CH), 122.5 (CH), 119.6 (CH), 117.7 (CH), 36.5 (CH_2), 32.5 (CH_2); IR: 3061, 3026, 2925, 2859, 1580, 1485, 1452, 1233 cm^{-1}; HRMS: $[M+H]^+$, found 275.1431. $C_{20}H_{19}O^+$ requires 275.1430.

Column-free protocol for 2h

The "**5. Typical procedure**" with 2-phenoxybenzyl bromide **1h** (338 µL, 1.80 mmol, 1.00 eq.), and a less amount of SD (220 µL, 2.2 mmol, 1.2 eq.), and recrystallization from hexane (2 mL) gave **2h** as a white solid. Yield: 176.9 mg (54%).

4,4′-Diphenylthiobibenzyl (2i)

The "**5. Typical procedure**" with 4-(phenylthio)benzyl bromide **1i** (405 µL, 2.00 mmol, 1.00 eq.), and PTLC using hexane gave the title compound as a white solid. Yield: 136 mg, (34%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.26 (m, 12H), 7.21 (ddt, J = 7.0, 4.4, 3.7 Hz, 2H), 7.11 (d, J = 8.2 Hz, 4H), 2.90 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.8 (C), 136.6 (C), 132.3 (C), 131.9 (CH), 130.1 (CH), 129.4 (CH), 129.1 (CH), 126.6 (CH), 37.2 (CH_2); IR: 3052, 3018, 2919, 2853, 1580, 1493, 1478, 1439, 1403, 1080, 1016 cm^{-1}; Mp: 96 °C; HRMS: $[M+H]^+$, found 399.1235. $C_{26}H_{23}S_2^+$ requires 399.1236.

4,4′-Di-*tert*-butylbibenzyl (2j) [S7]

The "**5. Typical procedure**" with 4-*tert*-butylbenzyl bromide **1j** (368 µL, 2.00 mmol, 1.00 eq.) and PTLC using hexane gave the title compound as a white solid. Yield: 235 mg (80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.31 (m, 4H), 7.21–7.16 (m, 4H), 2.89 (s, 4H), 1.32 (s, 18H).

3,3′-Dimethylbibenzyl (2k) [S7]

The "**5. Typical procedure**" with 3-methylbenzyl bromide **1k** (270 µL, 2.00 mmol, 1.00 eq.), and silica gel (SiO_2 20 g) column chromatography using hexane gave the title compound as a colorless oil. Yield: 193 mg (92%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20–7.15 (m, 2H), 7.06–6.96 (m, 6H), 2.86 (s, 4H), 2.33 (s, 6H).

3,3′,5,5′-Tetramethoxybibenzyl (2l) [S8]

The "**5. Typical procedure**" with 3,5-dimethoxybenzyl bromide **1l** (462 mg, 2.00 mmol, 1.00 eq.), and PTLC using hexane/EtOAc (5/1) gave the title compound as a yellow solid. Yield: 299 mg

(99%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.36 (d, J = 2.3 Hz, 4H), 6.32 (t, J = 2.3 Hz, 2H), 3.77 (s, 12H), 2.85 (s ,4H).

4,4′-Dicyanobibenzyl (2m) [S9]

The "**5. Typical procedure**" with 4-cyanobenzyl bromide **1m** (392 mg, 2.00 mmol, 1.00 eq.), and hexane wash gave the title compound as an orange solid. Yield: 230 mg (99%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.0 Hz, 4H), 7.22 (d, J = 8.0 Hz, 4H), 3.00 (s, 4H).

4,4′-Trifluoromethylbibenzyl (2n) [S5]

The "**5. Typical procedure**" with 4-trifluoromethyl bromide **1n** (478 mg, 2.00 mmol, 1.00 eq.) give the crude product of the title compound as an inseparable mixture with **1n** and unidentified side products. The yield of the title compound was determined by qNMR. Yield: 25%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 8.0 Hz, 4H), 7.25 (d, J = 8.0 Hz, 4H), 2.99 (s, 4H).

4,4′-Difluorobibenzyl (2o) [S5]

The "**5. Typical procedure**" with 4-fluorobenzyl chloride **1o** (246 µL, 2.00 mmol, 1.00 eq.), and a less amount of SD (225 µL, 2.2 mmol, 1.1 eq.), and silica gel (SiO_2 8 g) column chromatography using hexane gave the title compound as a white solid. Yield: 86.7 mg (40%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (dd, J = 8.5, 5.5 Hz, 4H), 6.94 (t, J = 8.5 Hz, 4H), 2.85 (s, 4H).

2,3-Diphenylbutane (2p) [S10]

The "**5. Typical procedure**" with 1-phenylethyl chloride **2p** (264 µL, 2.00 mmol, 1.00 eq.), and silica gel column chromatography using hexane gave the title compound as a white solid. Yield: 175 mg (83%, *dl*:*meso* = 1:1.1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.27 (m, 4H, *meso* isomer), 7.24–7.19 (m, 6H, *meso* isomer), 7.18–7.13 (m, 4H, *dl* isomer), 7.11–7.05 (m, 2H, *dl* isomer), 7.03–6.98 (m, 4H, *dl* isomer), 2.99–2.89 (m, 2H, *dl* isomer), 2.85–2.75 (m, J = 9.8, 7.0 Hz, 2H, *meso* isomer), 1.31–1.25 (m, 6H, *dl* isomer), 1.05–0.98 (m, 6H, *meso* isomer).

1,1,2,2-Tetraphenylethane (2q) [S11]

The "**5. Typical procedure**" with benzhydryl chloride **2q** (356 µL, 2.00 mmol, 1.00 eq.), and hexane wash gave the title compound as a white solid. Yield: 187 mg (56%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, J = 7.4 Hz, 8H), 7.10 (t, J = 7.4 Hz, 8H), 7.01 (t, J = 7.4Hz, 4H), 4.77 (s, 2H).

9,9′-Bifluorene (2r) [S12]

The "**5. Typical procedure**" with 9-fluorenyl bromide **1r** (490 mg, 2.00 mmol, 1.00 eq.), SD (204 µL, 2.0 mmol, 1.0 eq.), an ice-water bath when adding SD, and recrystallization from

hexane/EtOAc (1/5) gave the title compound as a white solid. Yield: 356 mg (54%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 7.5 Hz, 4H), 7.28 (t, J = 7.5 Hz, 4H), 7.09 (t, J = 7.5 Hz, 4H), 6.96 (d, J = 7.5 Hz, 4H), 4.85 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.6 (C), 141.5 (C), 127.3 (CH), 126.7 (CH), 124.1 (CH), 119.6 (CH), 49.8 (CH).

1,2-Bis-(4-methoxyphenyl)-1,1,2,2-tetraphenylethane (2s)

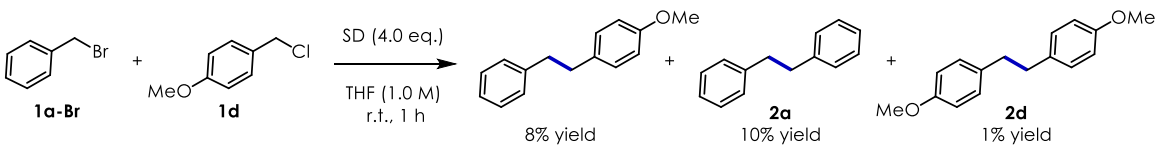
The "**5. Typical procedure**" with 4-methoxytrityl chloride **1s** (618 mg, 2.00 mmol, 1.00 eq.), SD (204 µL, 2.0 mmol, 1.0 eq.), an ice-water bath when adding SD, and silica gel column chromatography using hexane/EtOAc (20/1), followed by PTLC using hexane/EtOAc (20/1) gave the title compound as a yellow oil. Yield: 330 mg (65%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.12 (m, 20H), 7.10–7.05 (m, 4H), 6.76–6.71 (m, 4H), 3.78 (s, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.6 (C), 147.0 (C), 139.2 (C), 129.2 (CH), 127.82 (CH),127.80 (CH),127.1 (CH), 113.1(CH), 81.7 (C), 55.2 (CH_3); IR: 3057, 3033, 3002, 2953, 2930, 2835, 1607, 1581, 1509, 1491, 1463, 1446, 1414, 1300, 1251, 1220, 1180, 1152, 1116, 1081, 1034 cm^{-1}; Mp: 151–153 °C; HRMS: M^+, found 546.2569. $C_{40}H_{34}O_2^+$ requires 546.2559.

[2.2]Orthocyclophane (2t) [S13]

The "**5. Typical procedure**" with 1,2-bis(bromomethyl)benzene **1t** (528 mg, 2.00 mmol, 1.00 eq.), and a larger amount of SD (900 µL, 8.8 mmol, 4.4 eq.), and PTLC using hexane/EtOAc (12/1) gave the title compound as a white solid. Yield: 4.2 mg (2%); ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.06–6.94 (m, 8H), 3.07 (s, 8H).

In addition to **2t**, 5,6,11,12,17,18-hexahydrotribenzo[a,e,i]cyclododecene (**2t'**) [S14] was also obtained as a white solid. Yield: 22 mg (7%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.31 (m, 6H), 7.27–7.22 (m, 6H), 3.05 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1 (C), 130.5 (CH), 126.7 (CH), 37.3 (CH_2).

6.2.



Scheme S1. Attempted synthesis of an unsymmetrical bibenzyl: To a stirring solution of benzylic bromide **1a-Br** (1.00 mmol, 1.00 eq.) and **1d** (1.00 mmol, 1.00 eq.) in dry THF (2.00 mL, 1.00 M) was dropwisely added SD (409 µL, 4.0 mmol, 2.0 eq.) under argon at r.t.. After stirring for 1 h, the reaction was quenched with H_2O (10 mL), and the yields of 4-methoxybibenzyl, **2a**, and **2d** were determined by qNMR to be 8%, 10%, and 1%, respectively.

6.3. Application to column-free natural products (Scheme 2)

Column-free synthetic protocol for 4,4′-dimethoxybibenzyl (2d) [S4]

To a stirring solution of 4-methoxybenzyl chloride **1d** (1.36 mL, 10.0 mmol, 1.00 eq.) in dry THF (10.0 mL, 1.00 M) was dropwisely added SD (2.23 mL, 22 mmol, 2.2 eq.) at r.t.. After stirring for 1 h, the reaction was quenched with H_2O (20 mL) in an ice-water bath, evaporated to remove THF, and extracted with $CHCl_3$ (20 mL×3). The combined $CHCl_3$ extract was washed with brine (60 mL), dried over Na_2SO_4, and evaporated. The resulting crude product was washed with hexane, and then acetonitrile to give the title compound as a pale yellow solid. Yield: 891 mg (74%)

Column-free synthetic protocol for 3,3′,4,4′-tetramethoxybibenzyl (2f) [S6]

To a stirring solution of veratryl chloride **1f** (1.87 g, 10.0 mmol, 1.00 eq.) in dry THF (10 mL, 1.00 M) was dropwisely added SD (1.23 mL, 12 mmol, 1.2 eq.) at r.t.. After stirring for 1 h, the reaction was quenched with H_2O (20 mL) with the reaction flask in an ice-water bath, evaporated to remove THF, and extracted with $CHCl_3$ (20 mL×3). The combined organic $CHCl_3$ extract was washed with brine (60 mL), dried over Na_2SO_4, and evaporated. The resulting crude product was purified by recrystallization from hexane/EtOAc (3/1) gave the title compound as a white solid. Yield: 832 mg (55%)

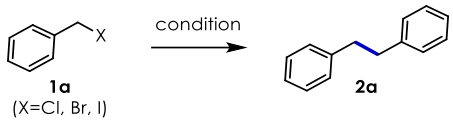
Column-free synthetic protocol for brittonin A (2g) [S5]

To a stirring solution of 3,4,5-trimethoxybenzyl chloride **1g** (2.16 g, 10.0 mmol, 1.00 eq.) in dry THF (10.0 mL, 1.00 M) was dropwisely added SD (1.26 mL, 12 mmol, 1.2 eq.) with the reaction flask in an ice-water bath. After removing the flask from the bath, the reaction mixture was stirred for 1 h. The reaction mixture was quenched with H_2O (20 mL) in an ice-water bath, evaporated to remove THF, and extracted with $CHCl_3$ (20 mL×3). The combined $CHCl_3$ extract was washed with brine (60 mL), dried over Na_2SO_4, and evaporated. The resulting residue was dissolved in acetonitrile (12 mL), and the resulting solution was washed with hexane (6 mL) to remove SD-derived mineral oil, and evaporated. The resulting solid was recrystallized from hot EtOH (7 mL) to give the title compound as a white solid. Yield: 1.02 g (56%)

6.4. Decagram-scale reaction with 2-methyltetrahydrofuran (Scheme 3)

To a stirring solution of **1a-Br** (7.65 mL, 64.0 mmol, 1.00 eq.) in dry 2-methyltetrahydrofuran (64.0 mL, 1.00 M) was dropwisely added SD (14.4 mL, 141 mmol, 2.2 eq.) with the reaction flask in an ice-water bath. After removing the flask from the bath, the reaction mixture was stirred for 1 h. The reaction mixture was quenched with H_2O (40 mL) in an ice-water bath, evaporated to remove THF, and extracted with $CHCl_3$ (40 mL×3). The combined $CHCl_3$ extract was washed with brine (120 mL), dried over Na_2SO_4, and evaporated. The resulting crude product was purified by silica gel (SiO_2 200 g) column chromatography using hexane to give **2a** as a white solid. Yield: 5.50 g (94%)

7. Table S3. Green metrics comparison of the present and reported methods



entry	**1a**	condition	yield	origin	green metrics [S15]		
					RME[a]	AE[b]	MI[c]
1	**1a**	SD	99%	this work	72	71	13
2	**1a**	Na lump	0%	**Table S1**, entry 1	0	0	N/A[d]
3	**1a-I**[e]	In	89%	ref. S16	37	42	27[f]
4	**1a**	Li	76%	ref. S17	55	71	61[f]
5	**1a-Br**	Rieke Cu	97%	ref. S18	52	54	41[f]
6	**1a**	Ti cat.	90%	ref. S19	65	71	27[f]
7	**1a-Br**	Rh cat.	quant	ref. S20	54	54	58[f]
8	**1a-Br**	Ir cat.	96%	ref. S21	51	54	52[f]
9	**1a-Br**	Ni cat.	85%	ref. S22	45	54	37[f]

(a) RME (reaction mass efficiency) = {molecular weight (M.W.) of product / M.W. of reactant **A** + M.W. of reactant **B** × molar ratio **B**/**A**} × yield (%) = (M.W. of **2a** / 2 × M.W. of **1a**) × yield (%)

(b) AE (atom economy) = (M.W. of product / sum of M.W. of reactants) × yield (%) = (M.W. of **2a** / 2 × M.W. of **1a**) × yield (%)

(c) MI (mass intensity) = total mass used in a process or process step (kg) / mass of product (kg)

(d) Not applicable

(e) Benzyl iodide (**1a-I**)

(f) Each MI was calculated based on the reported protocols in the references S16−22.

8. References for Supporting Material

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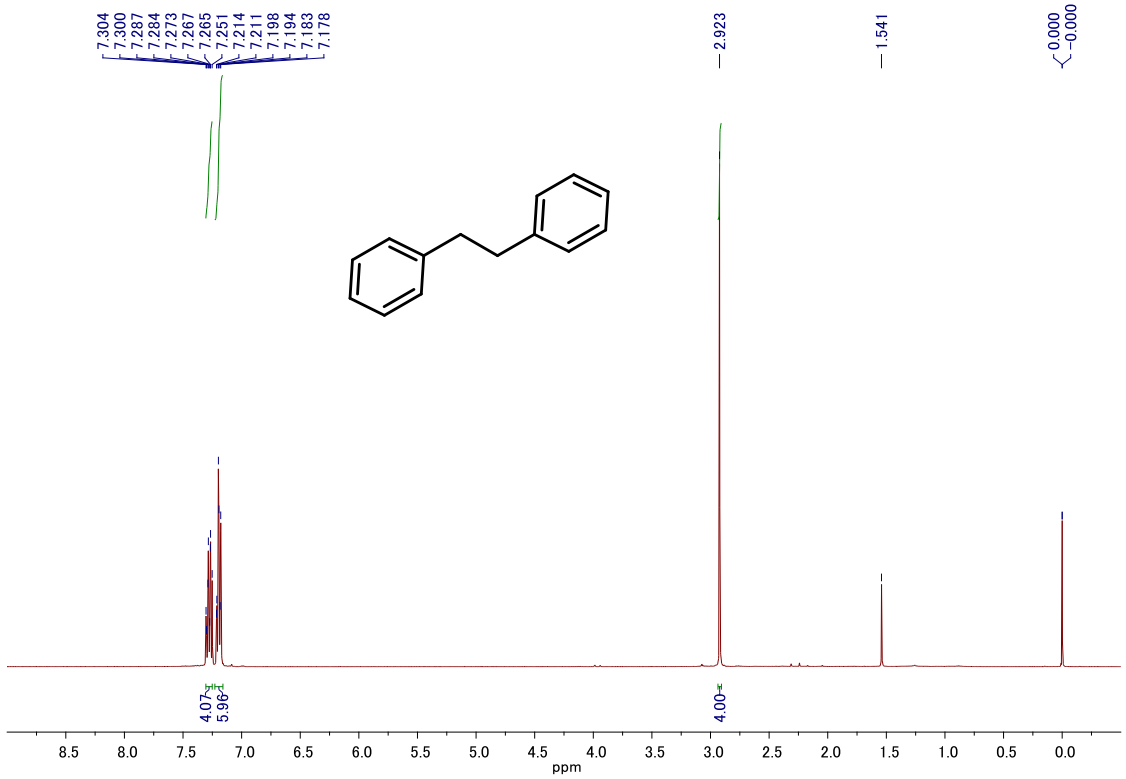
^{1}H NMR (400 MHz, $CDCl_3$) of 2a



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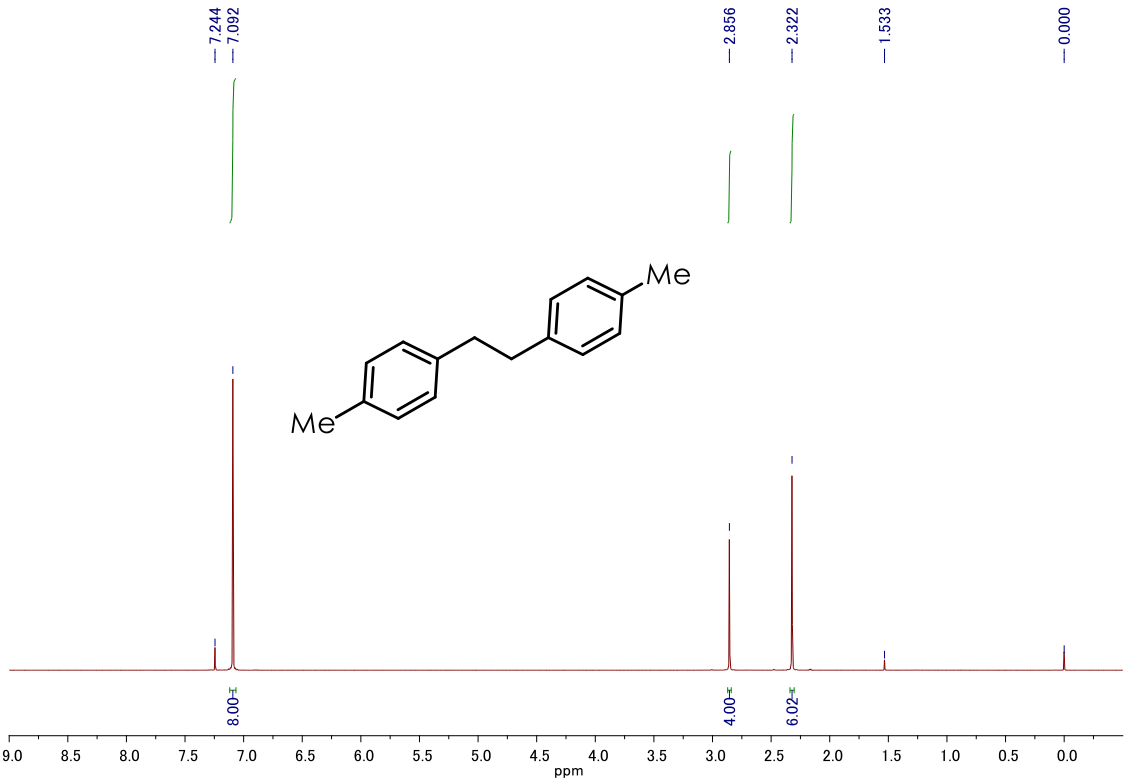

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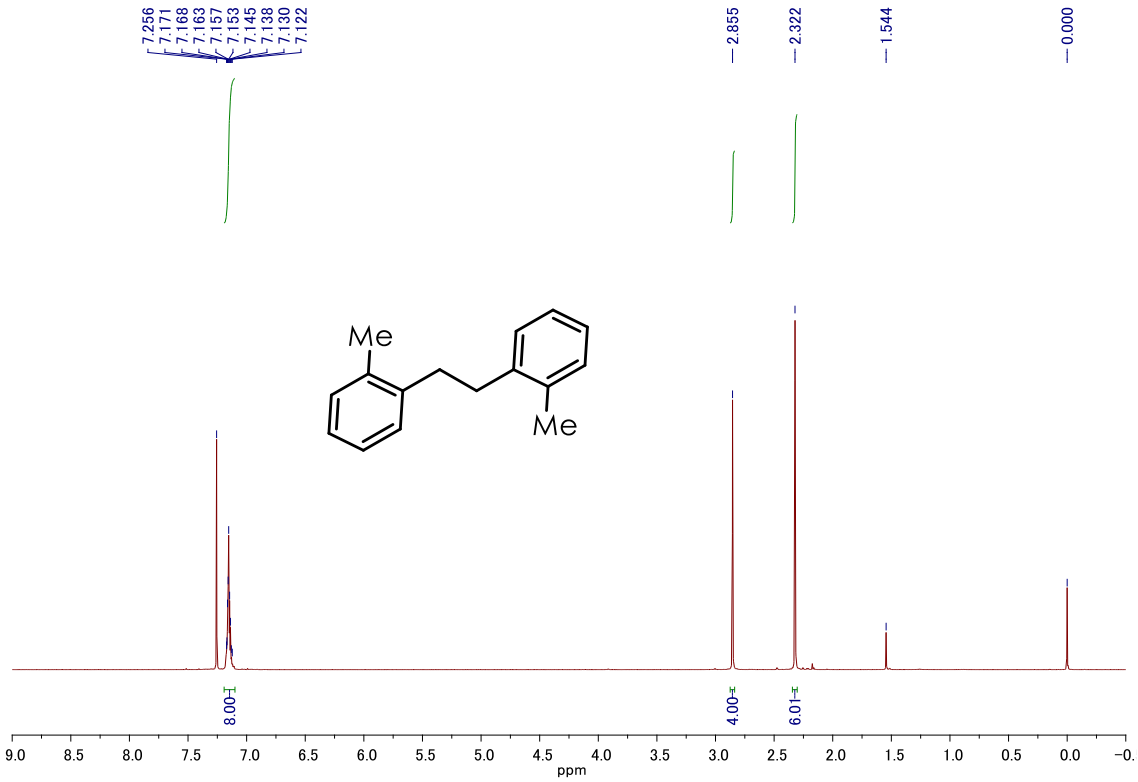

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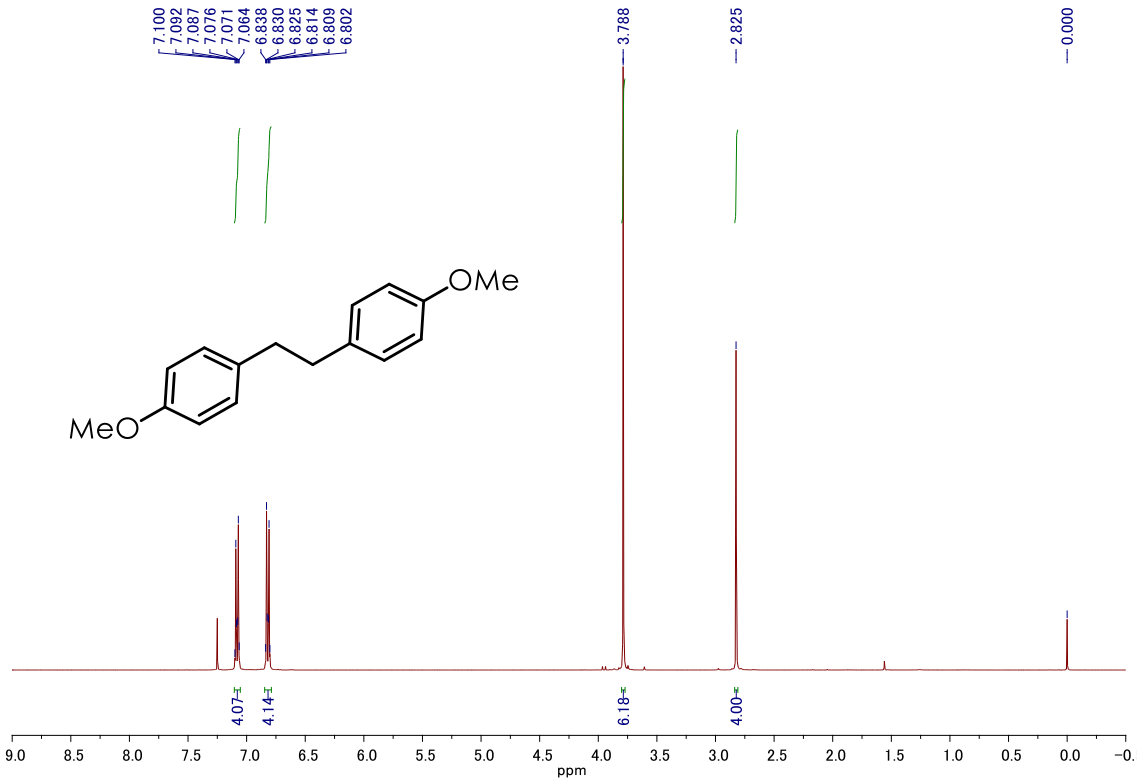

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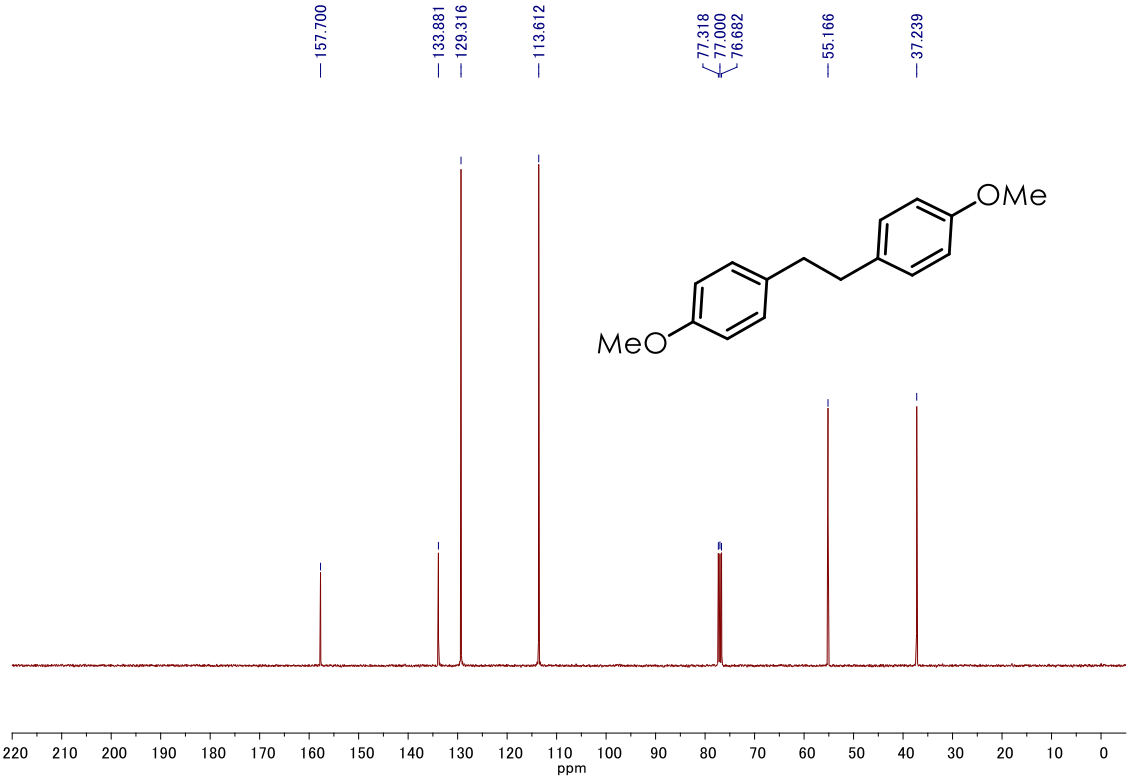

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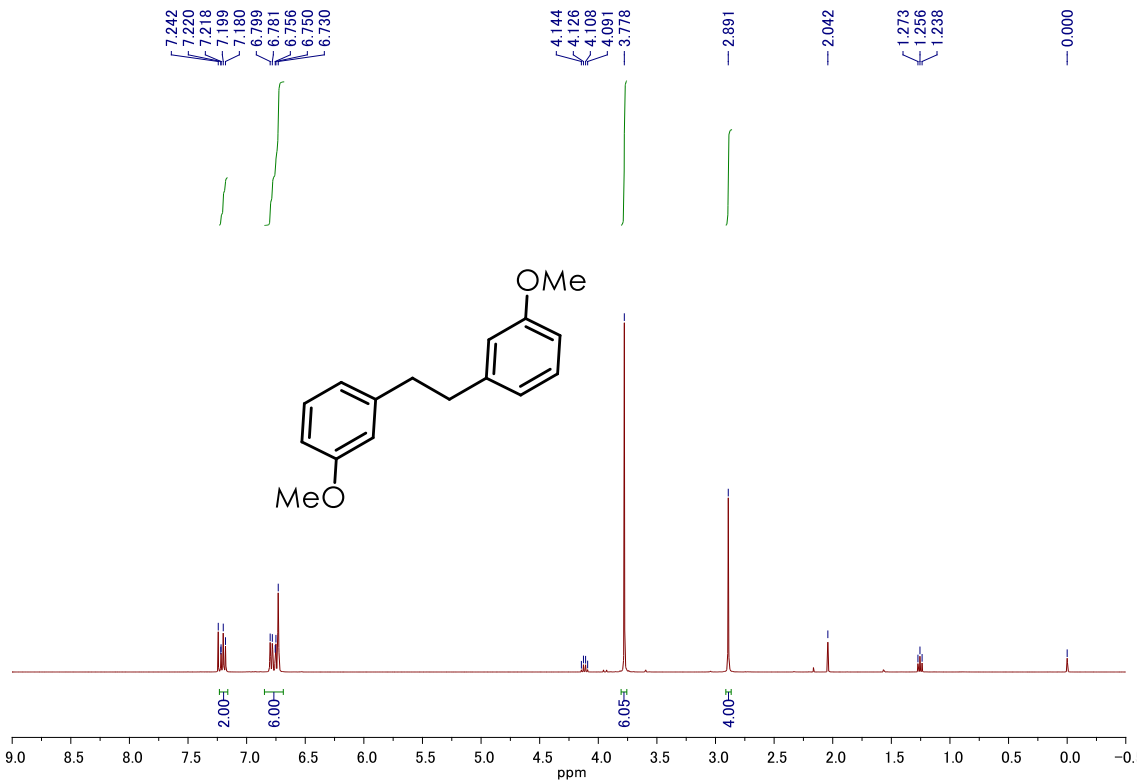

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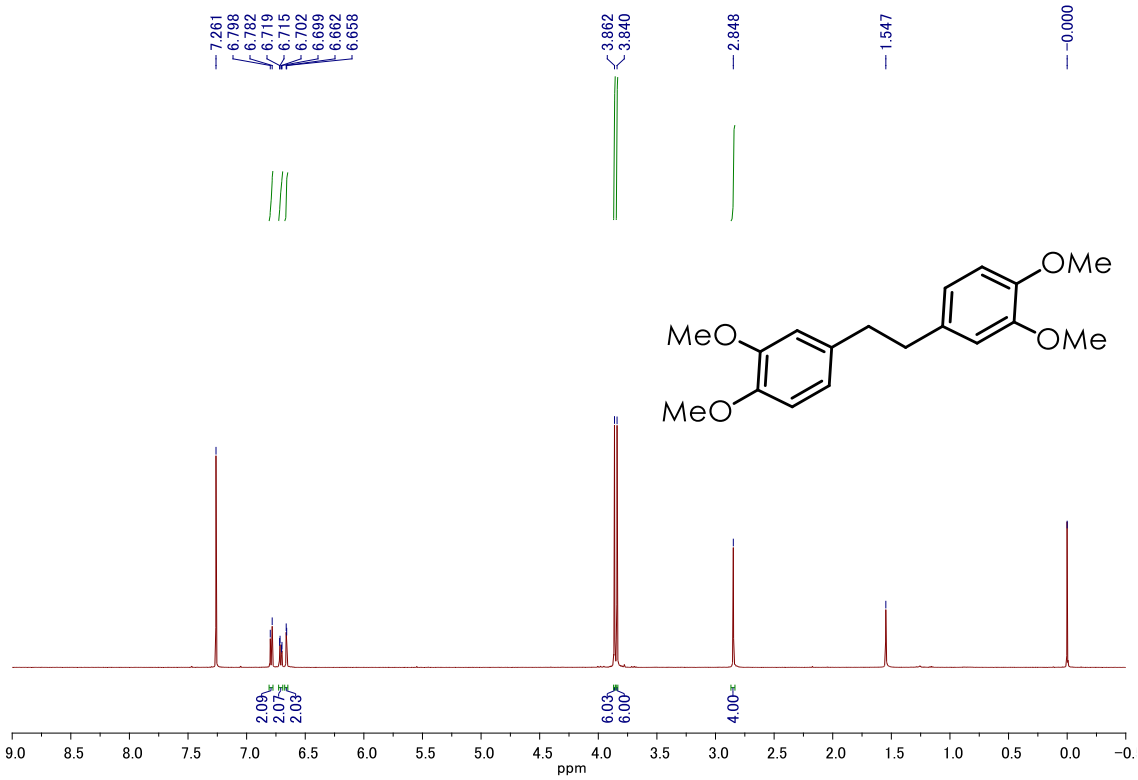

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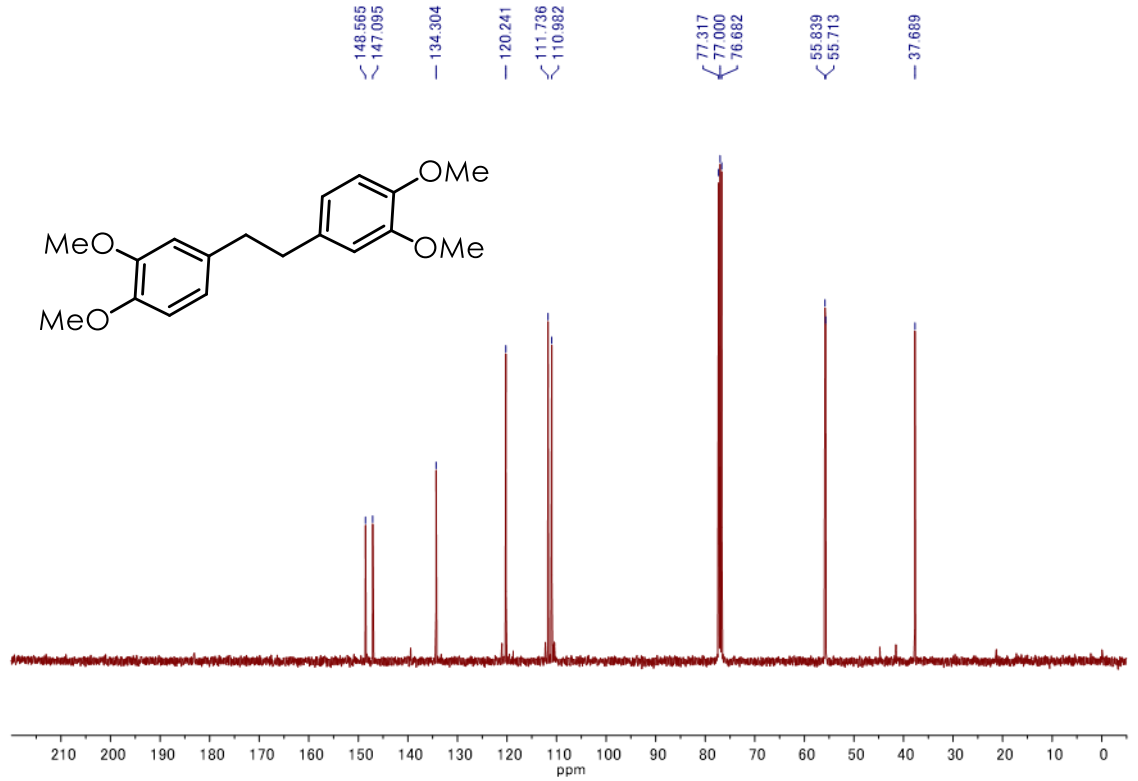

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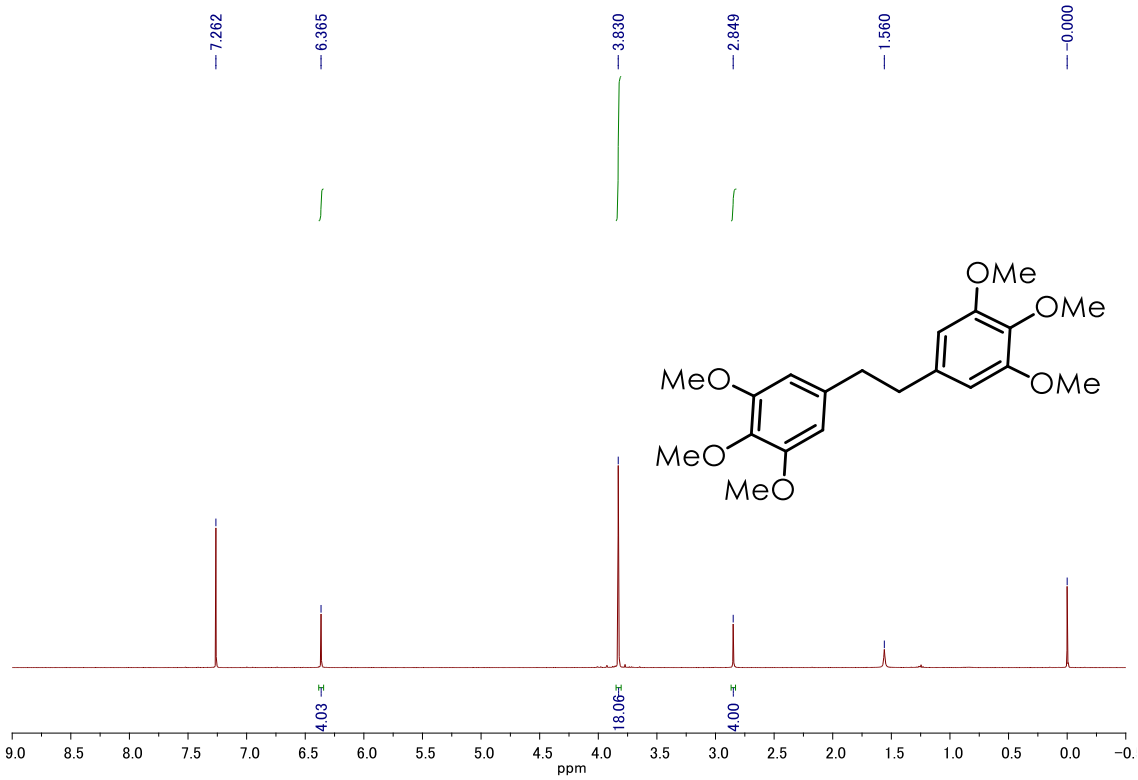

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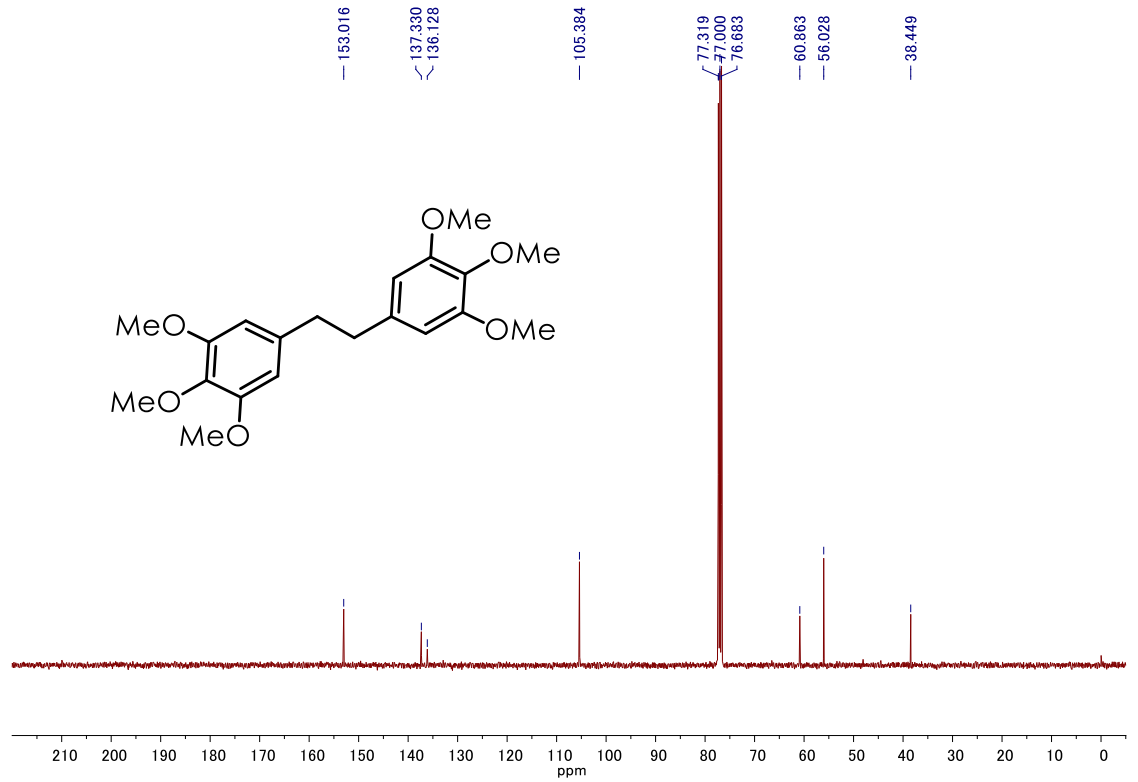

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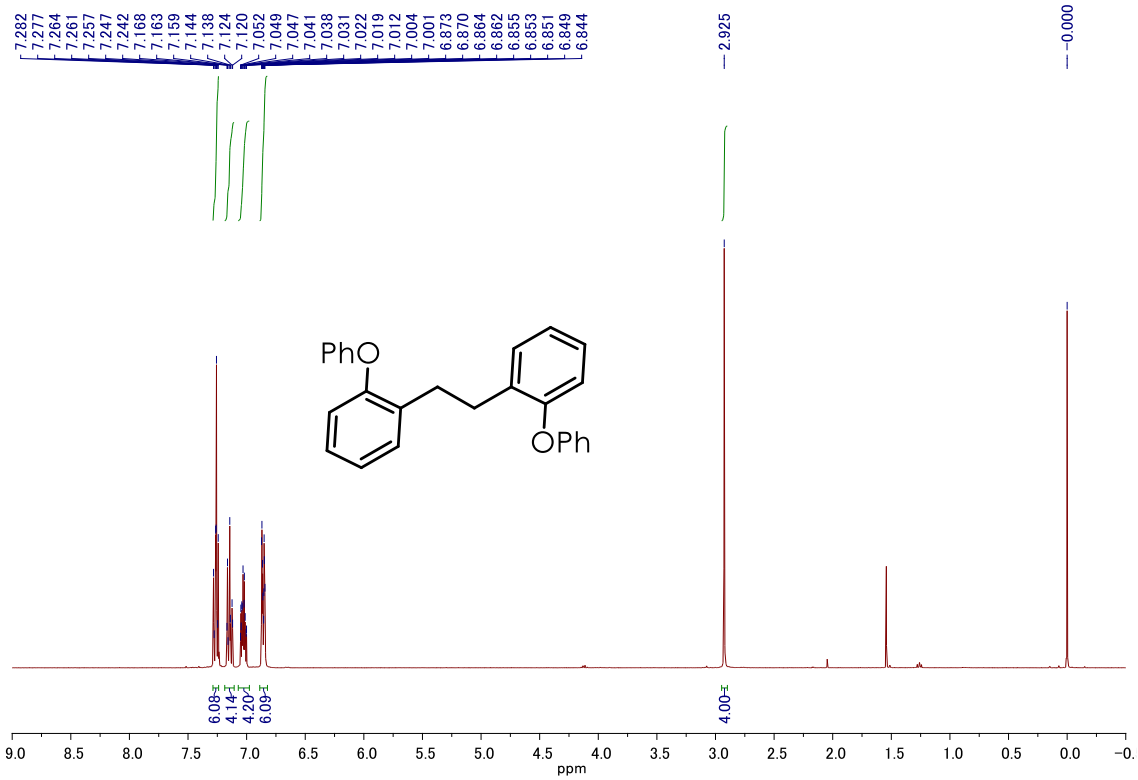

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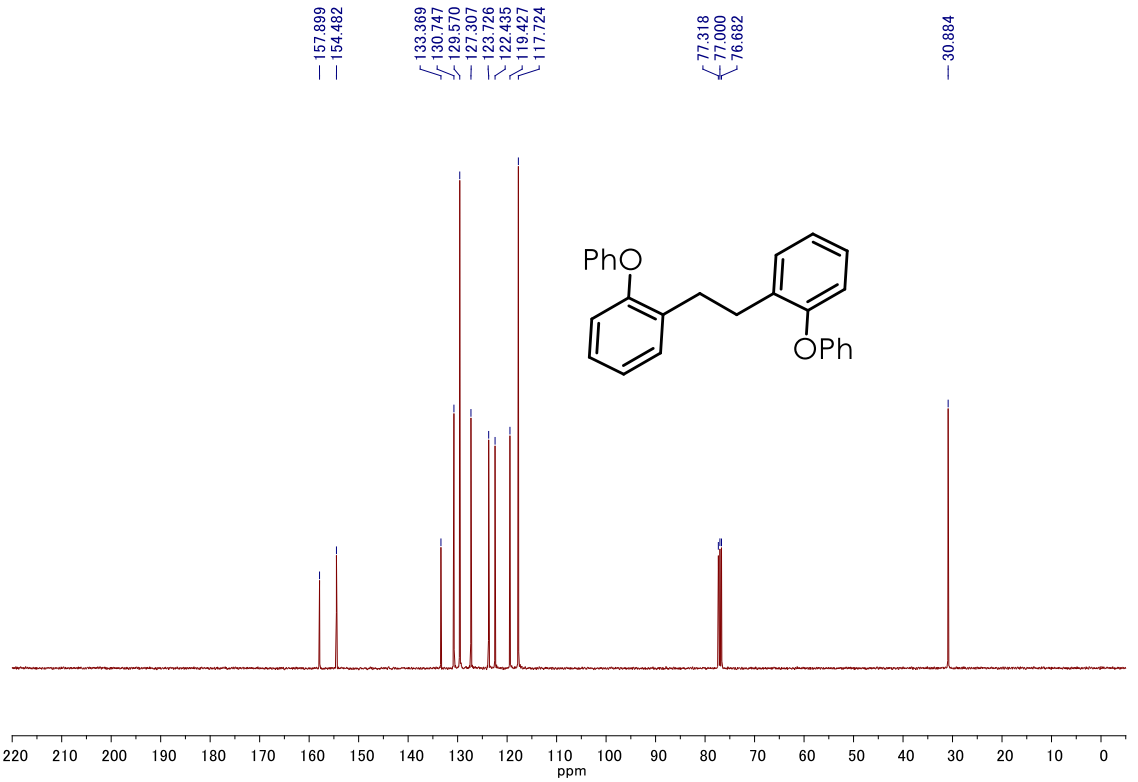

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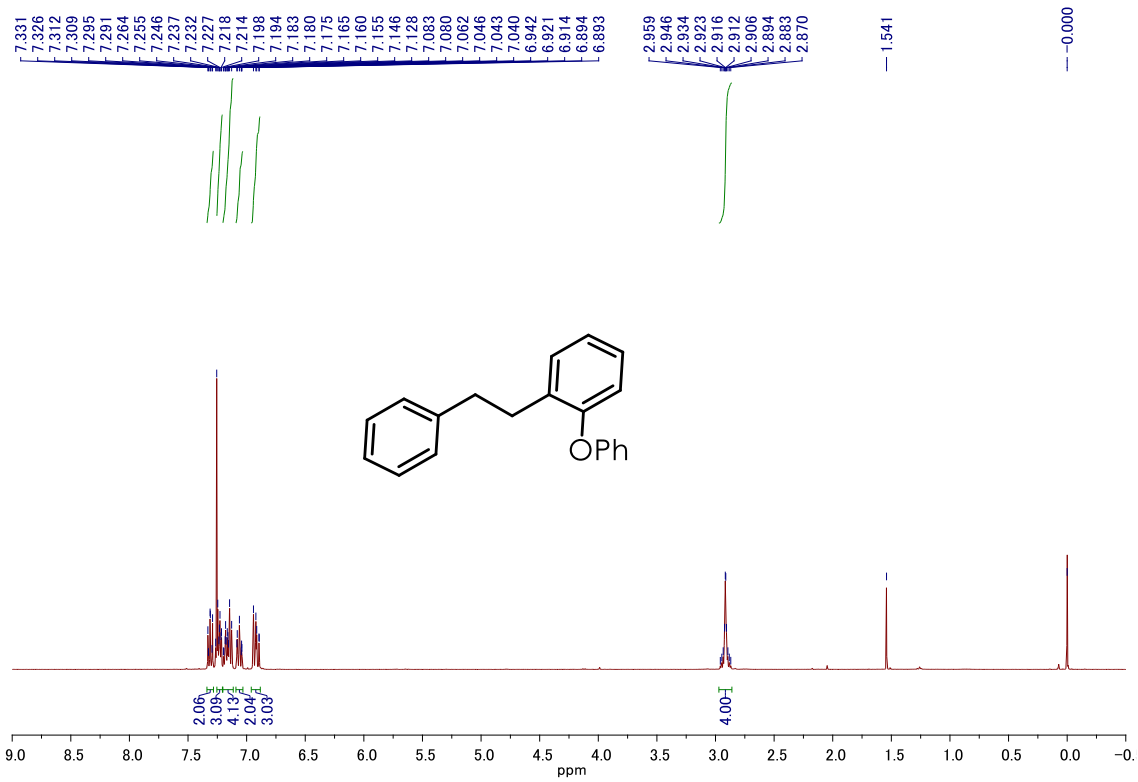

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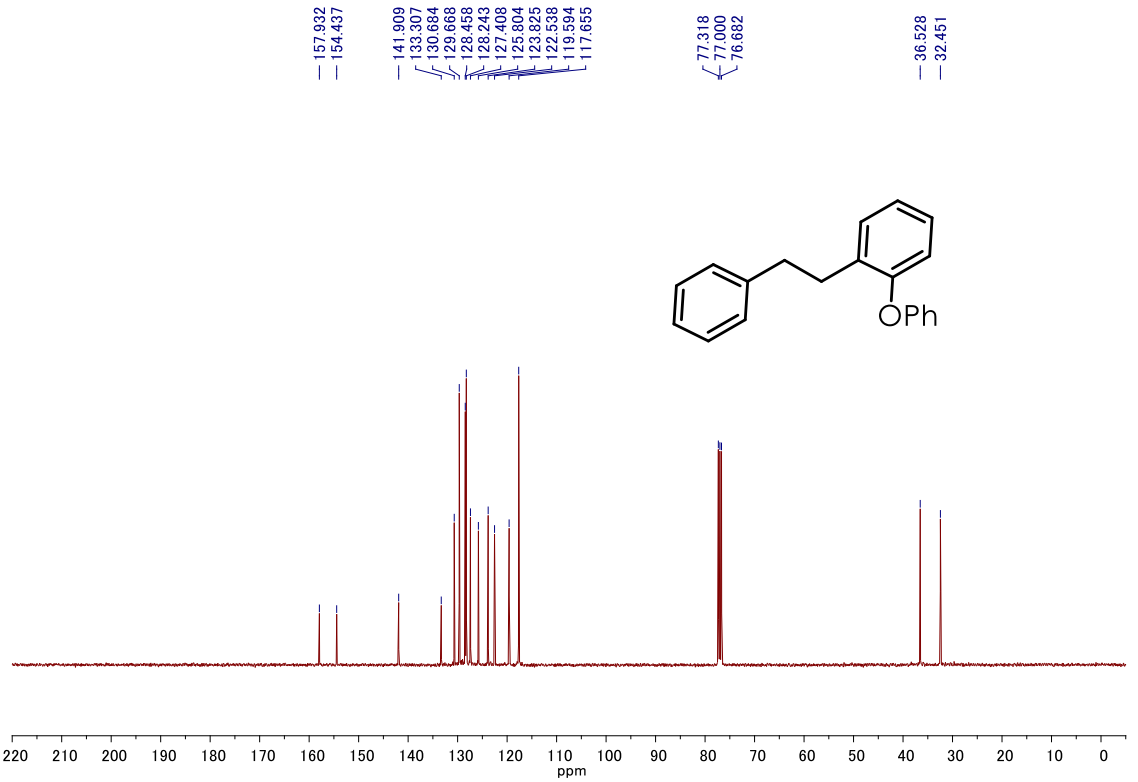

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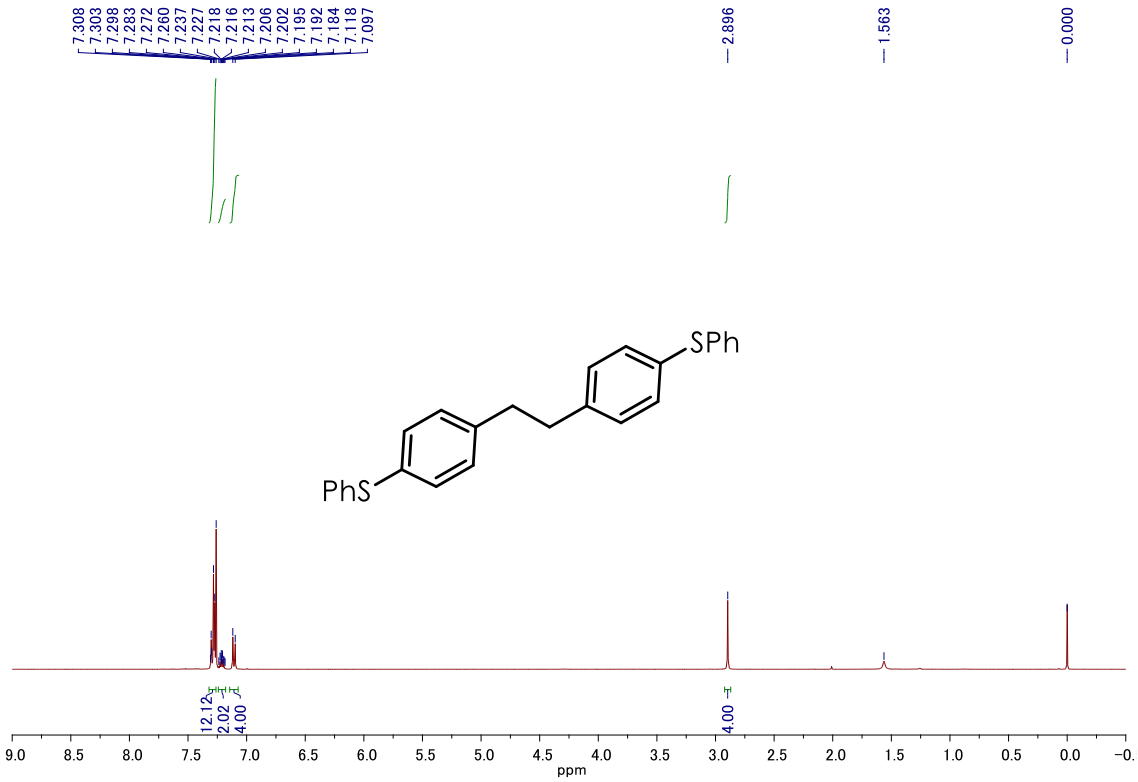

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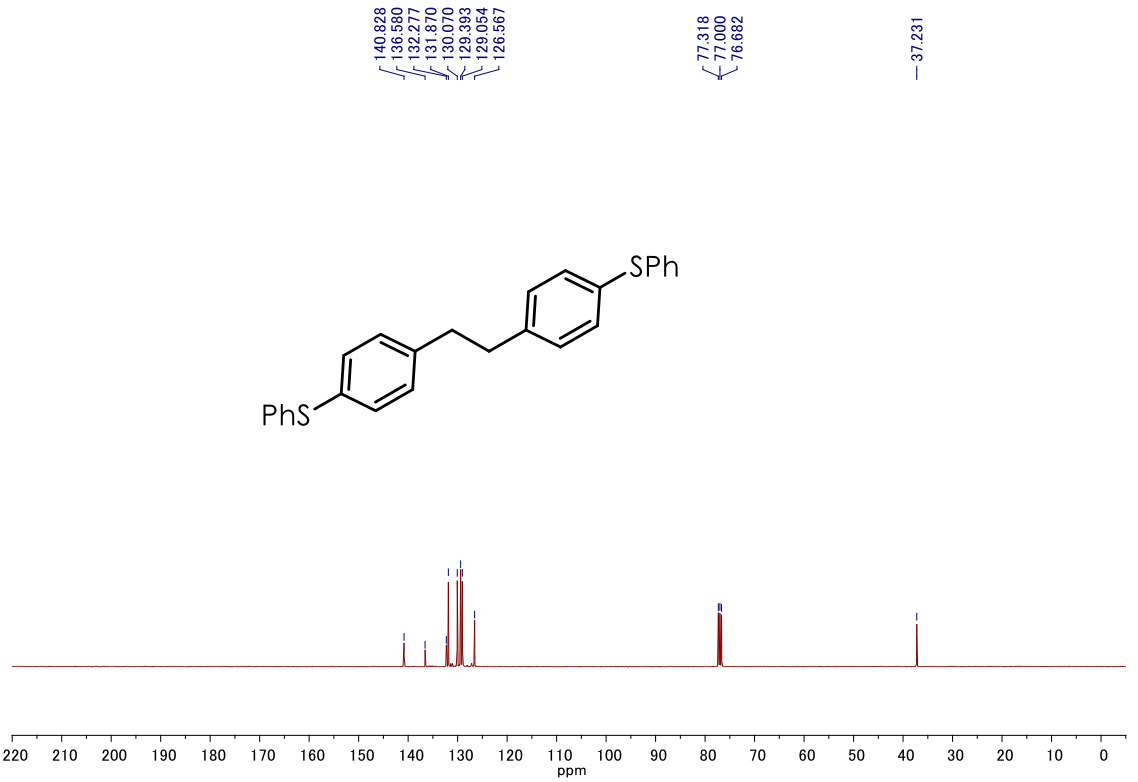

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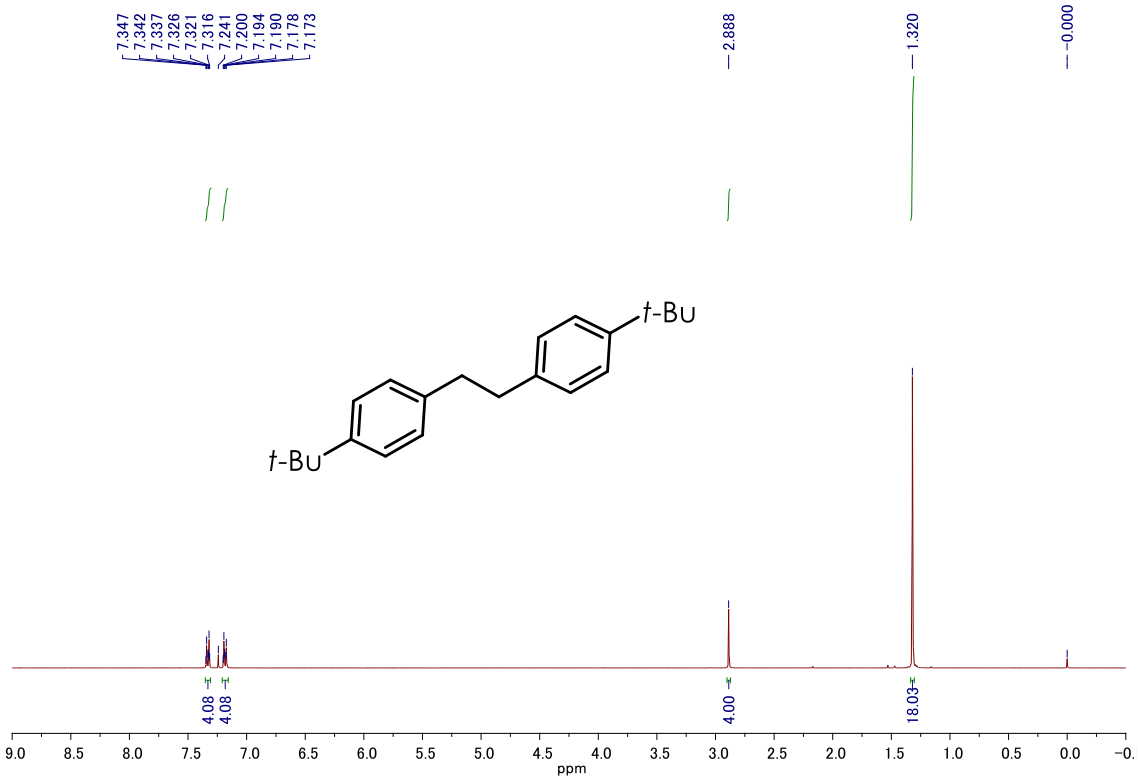

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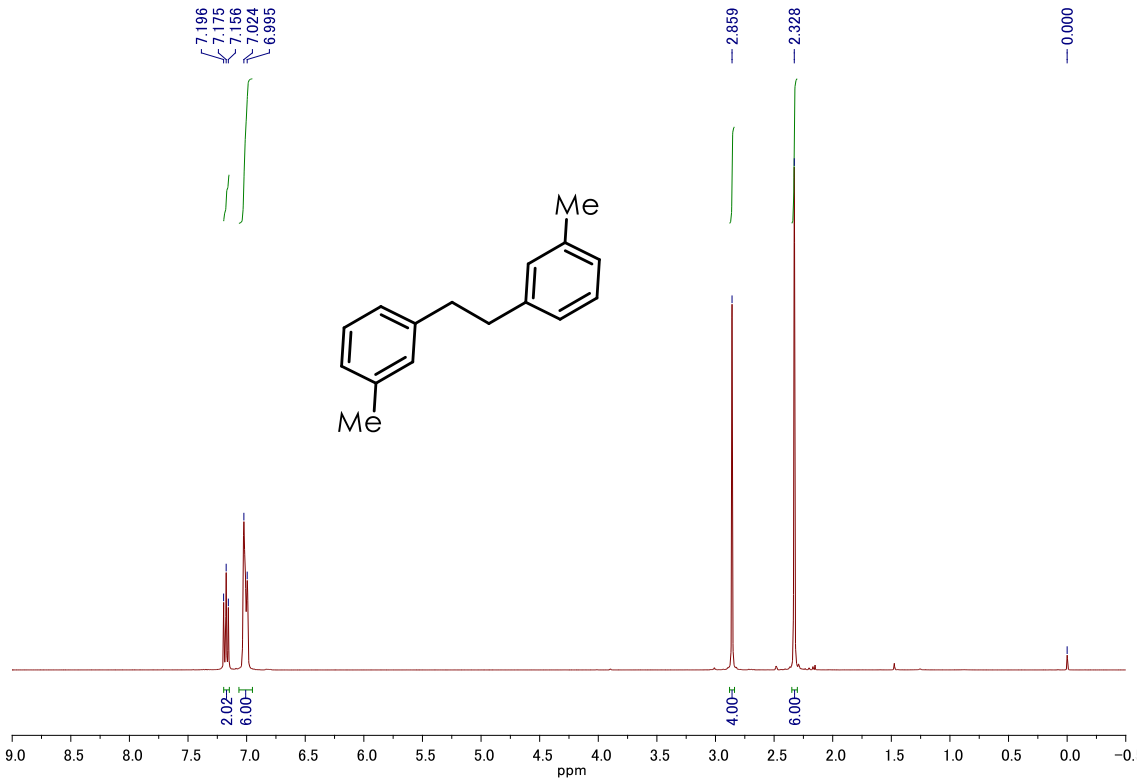

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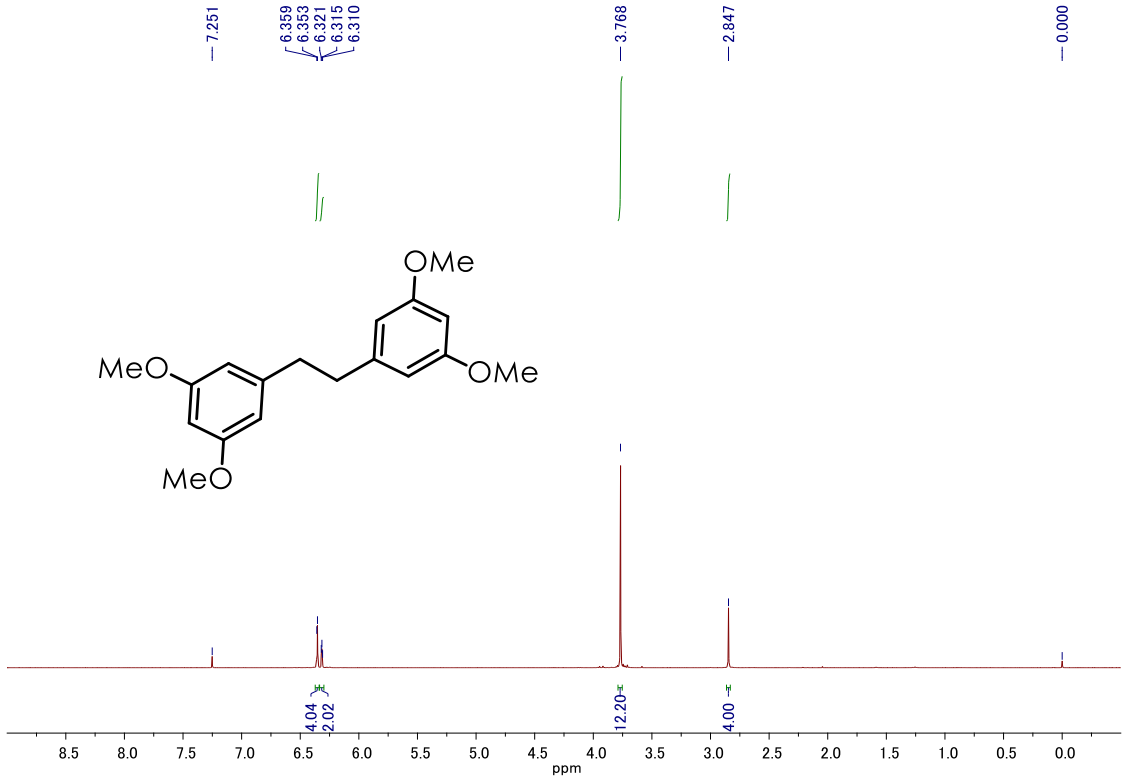

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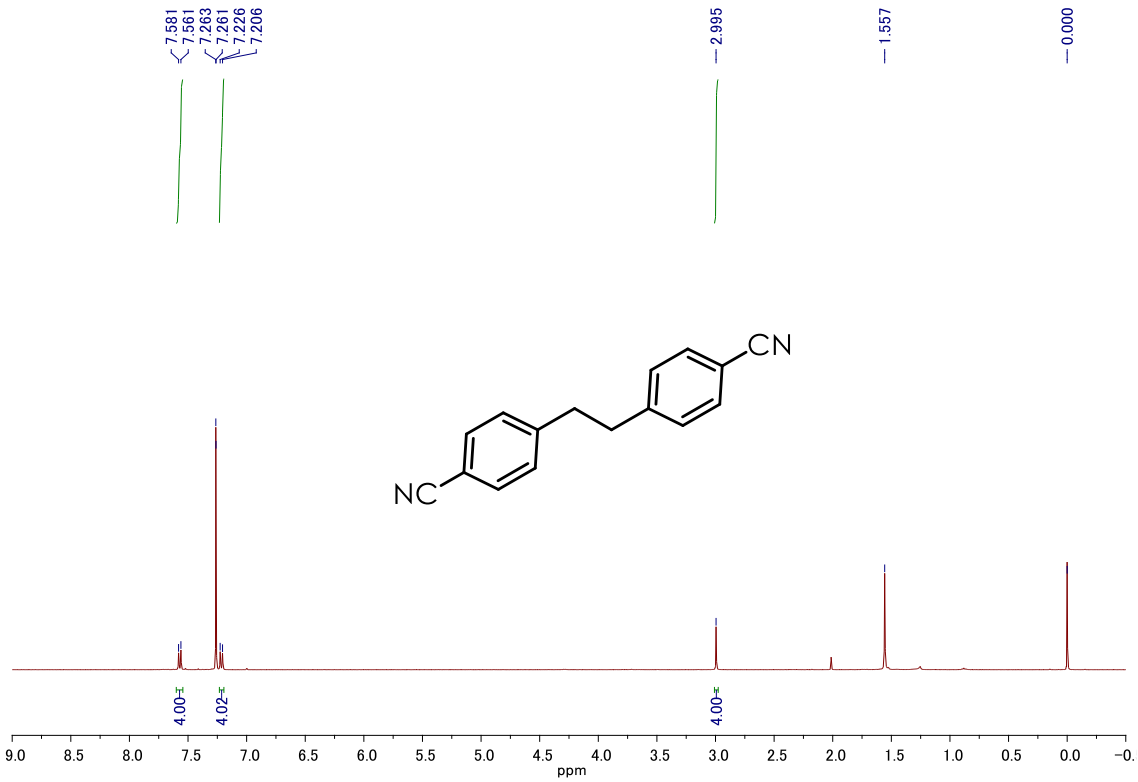

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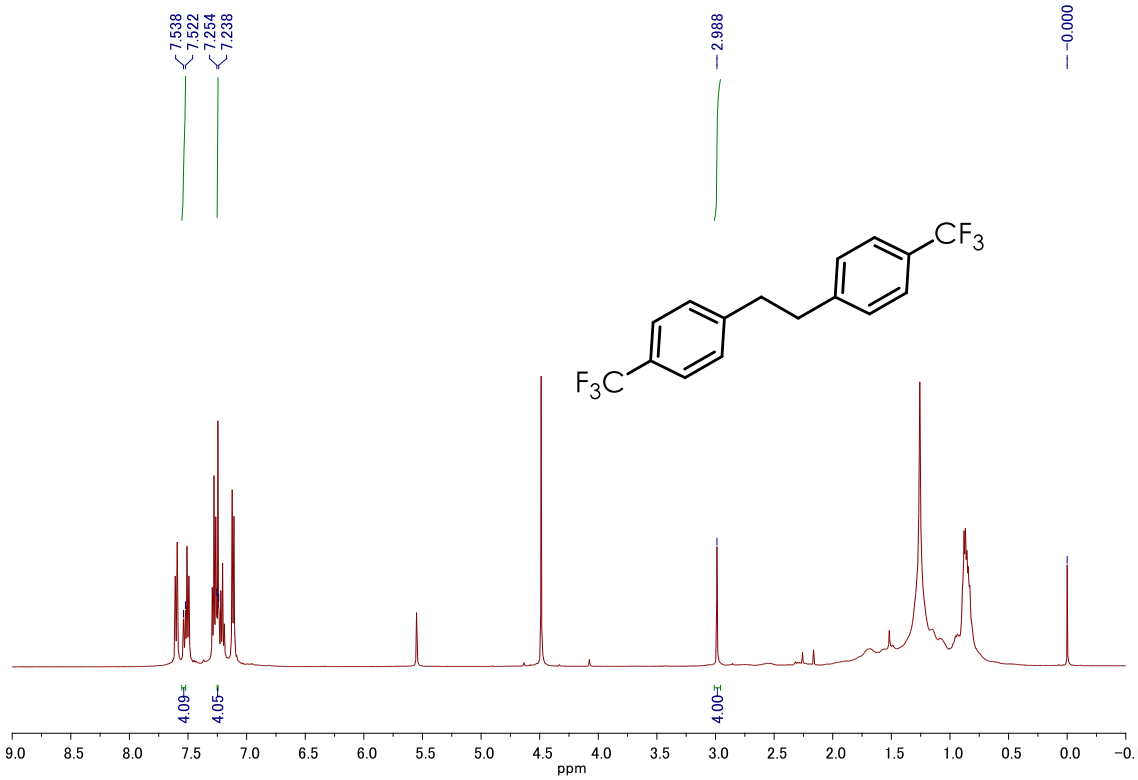

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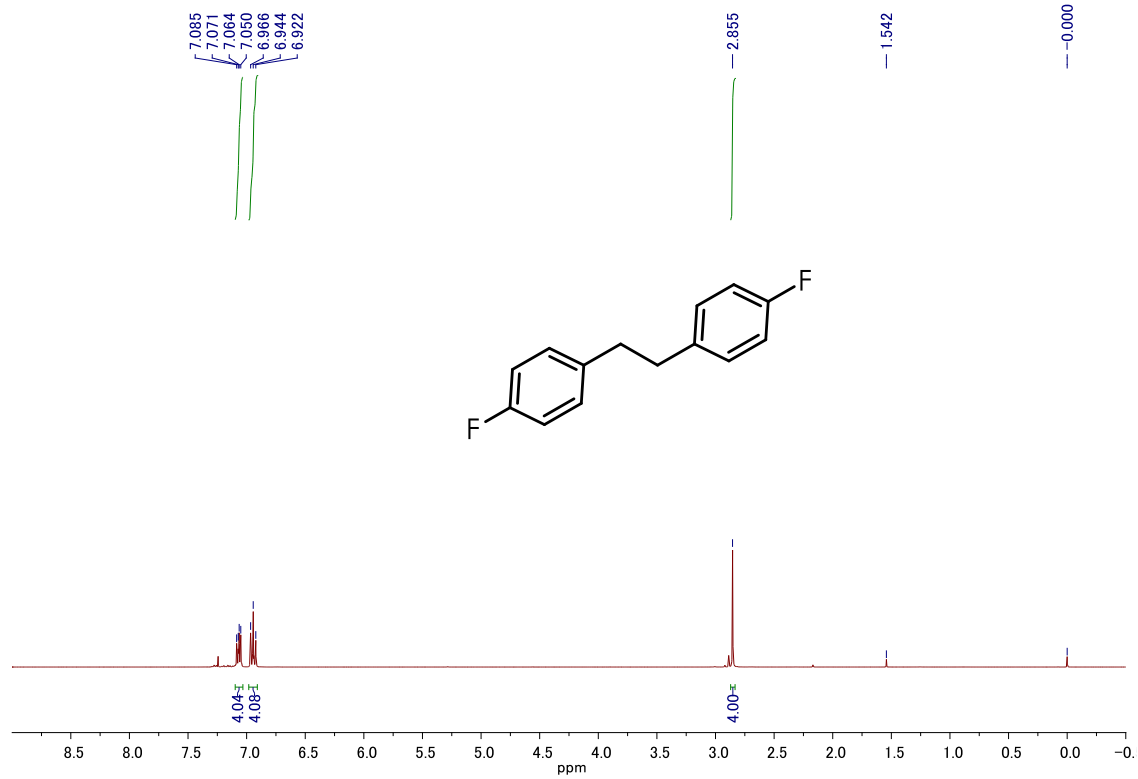

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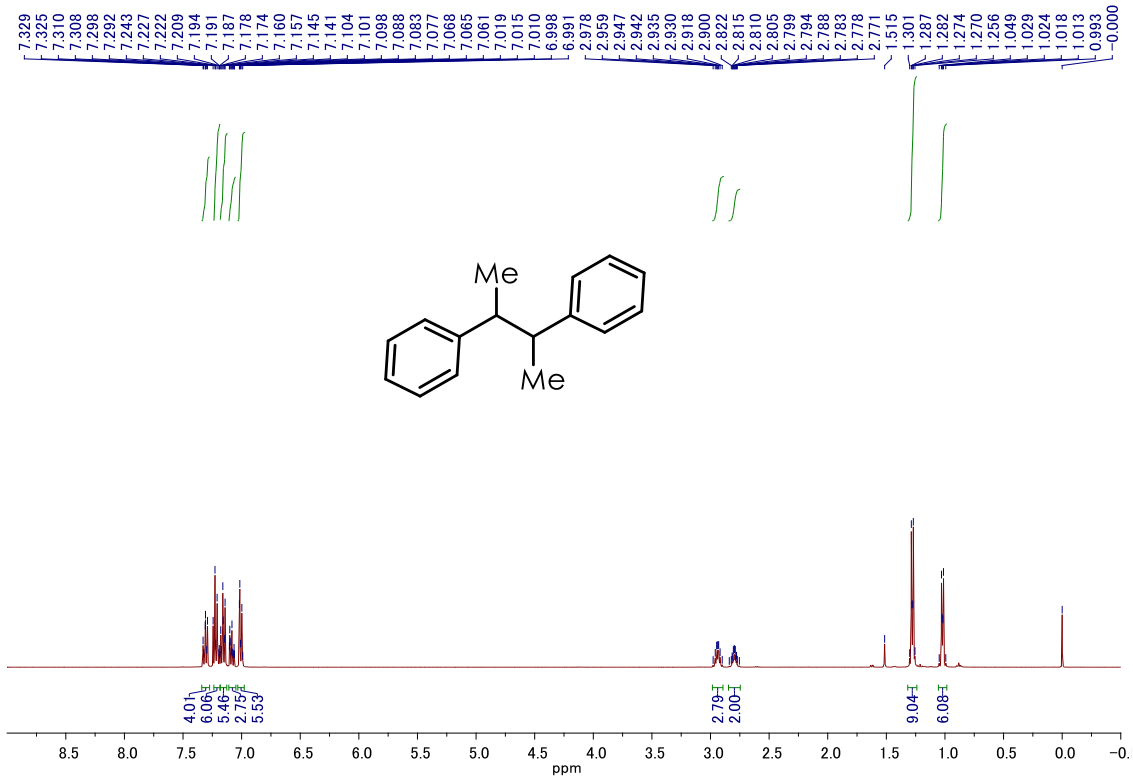

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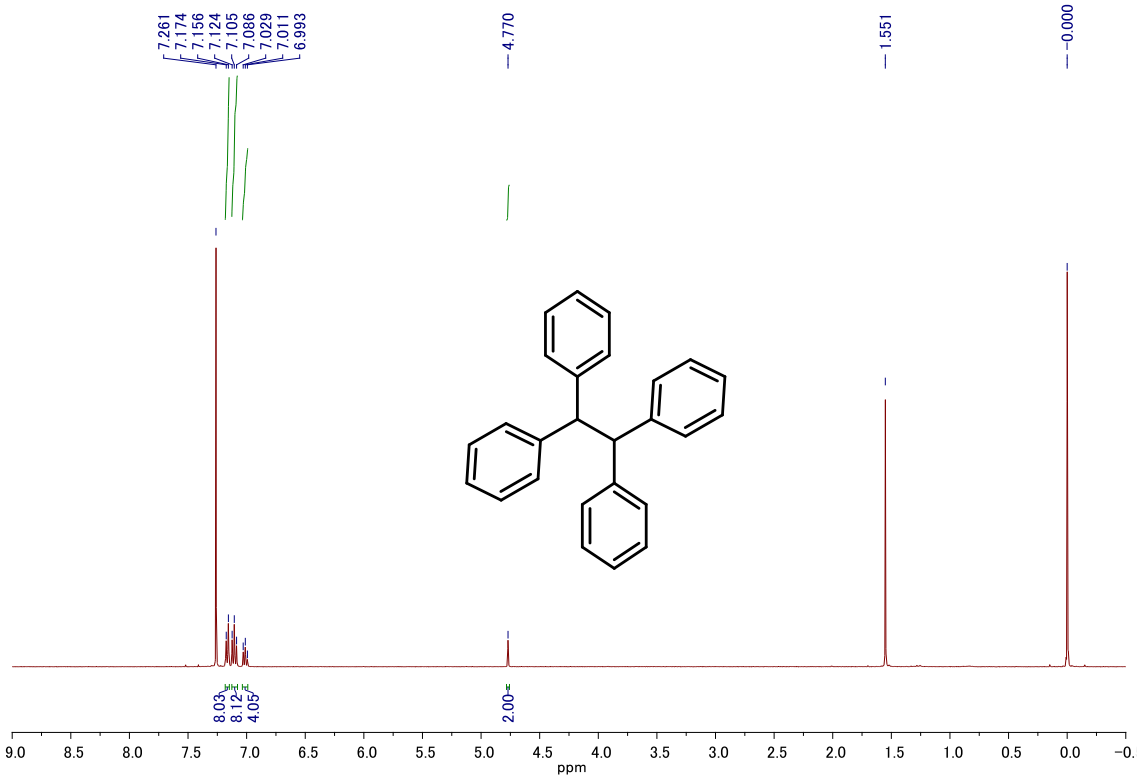

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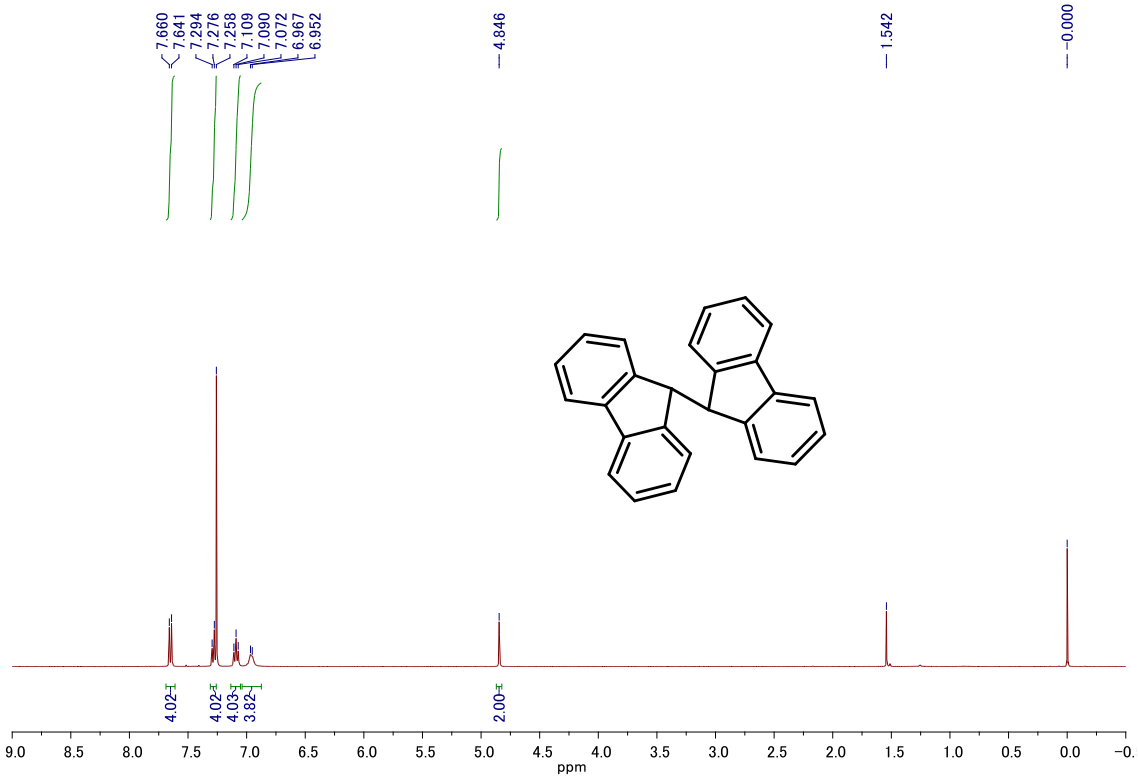

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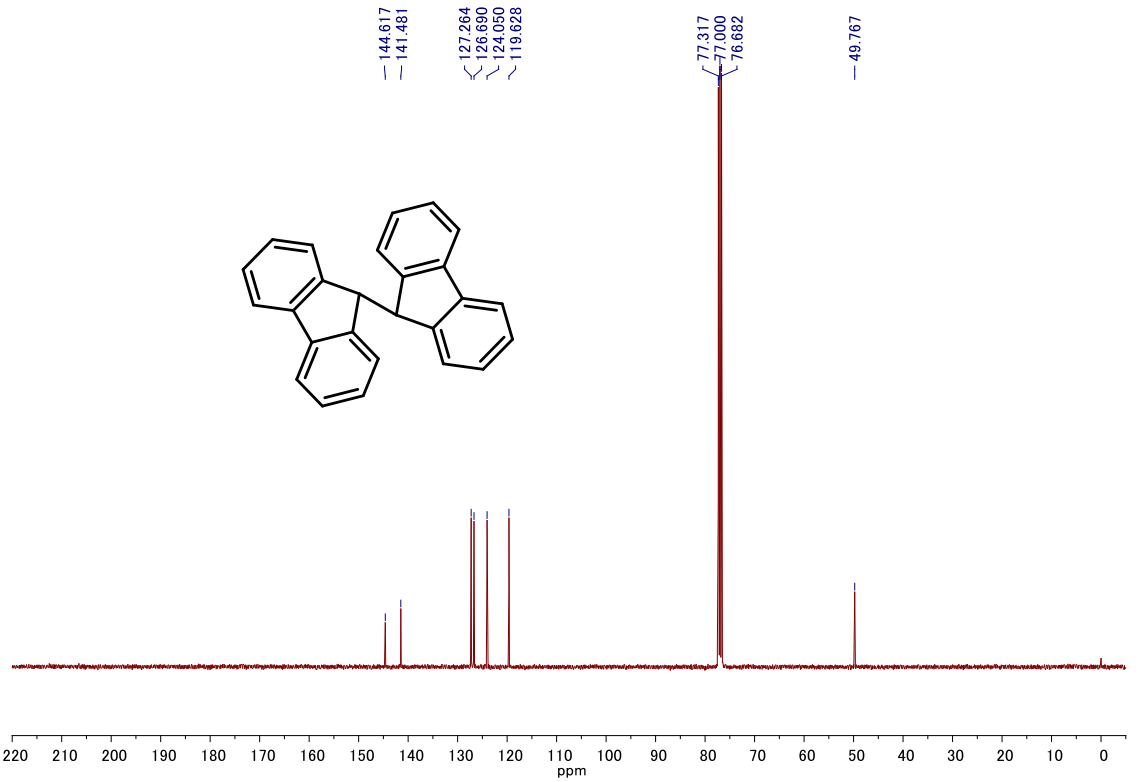

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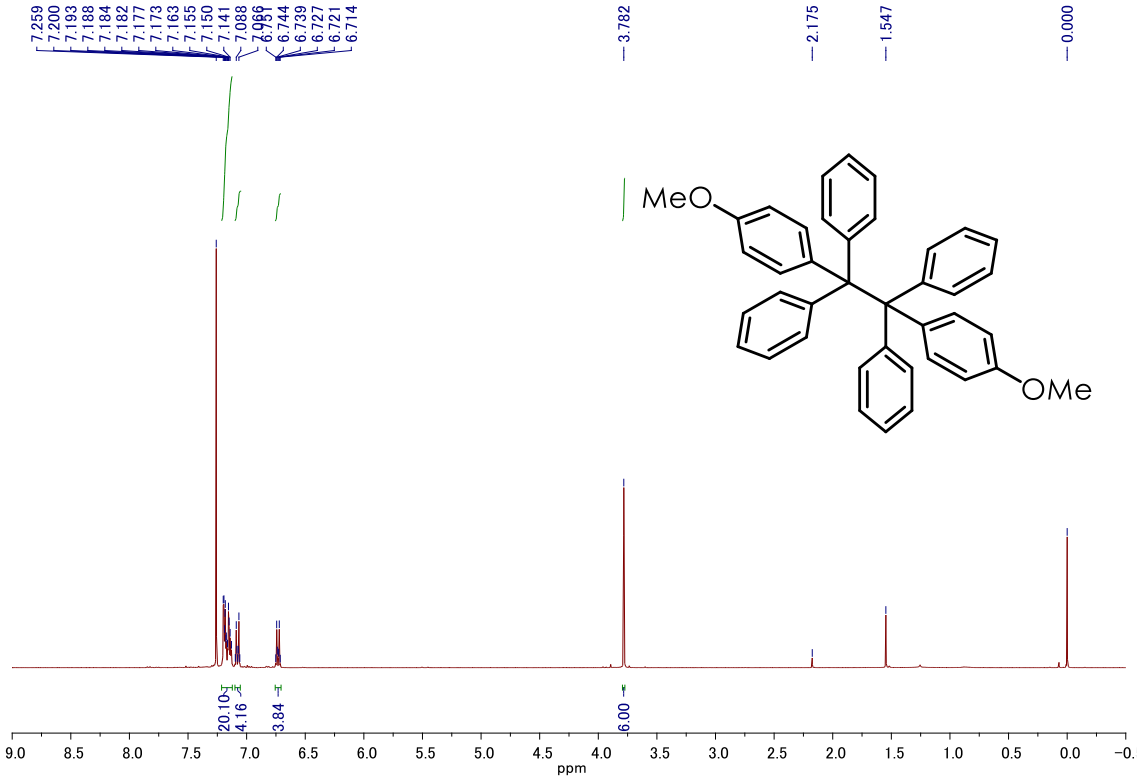

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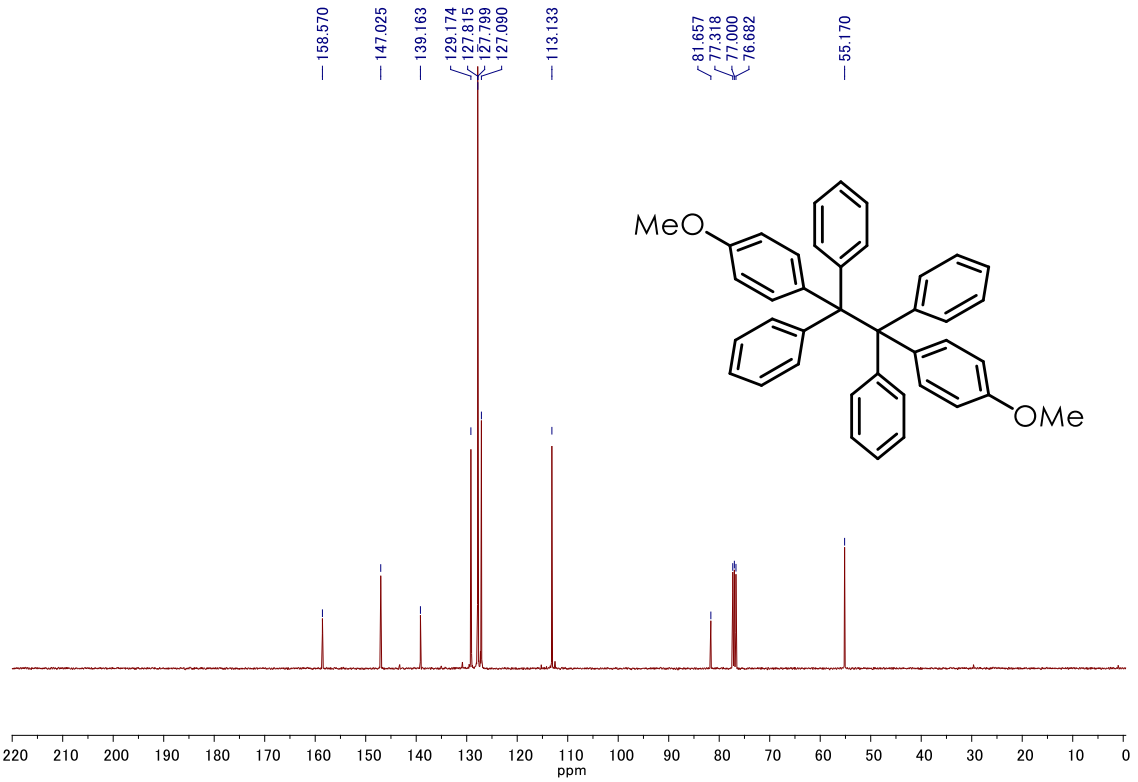
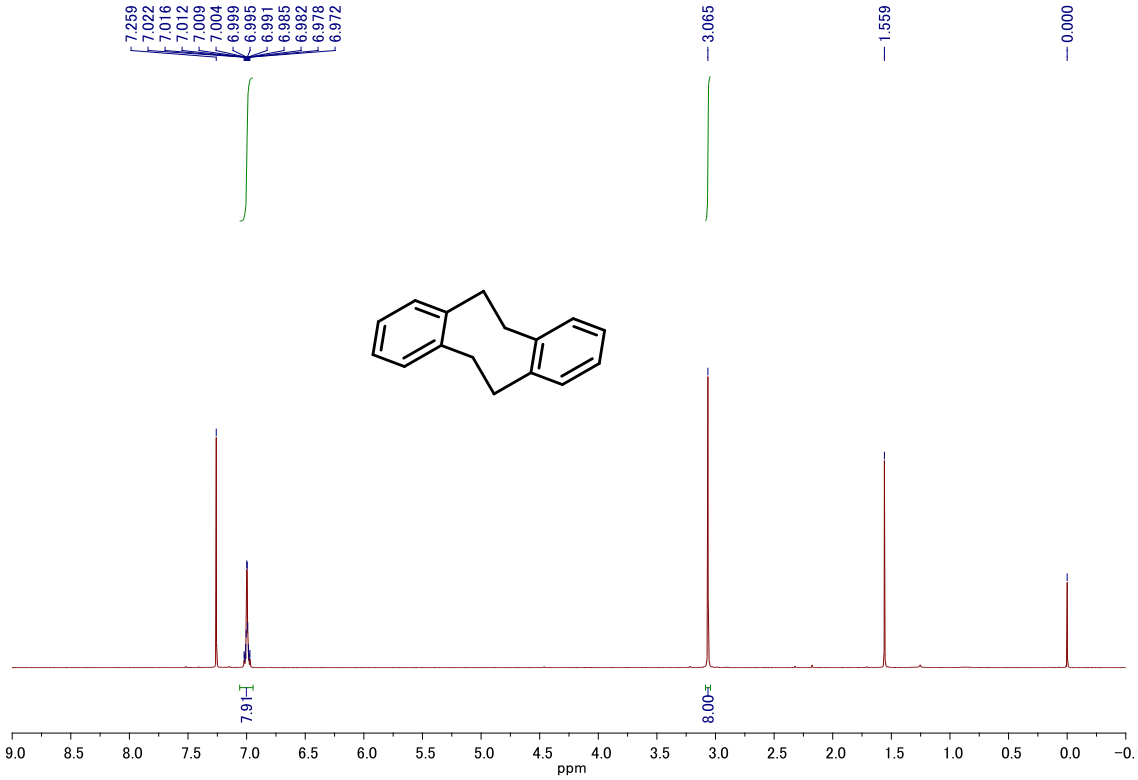


^{1}H NMR (400 MHz, $CDCl_3$) of 2t



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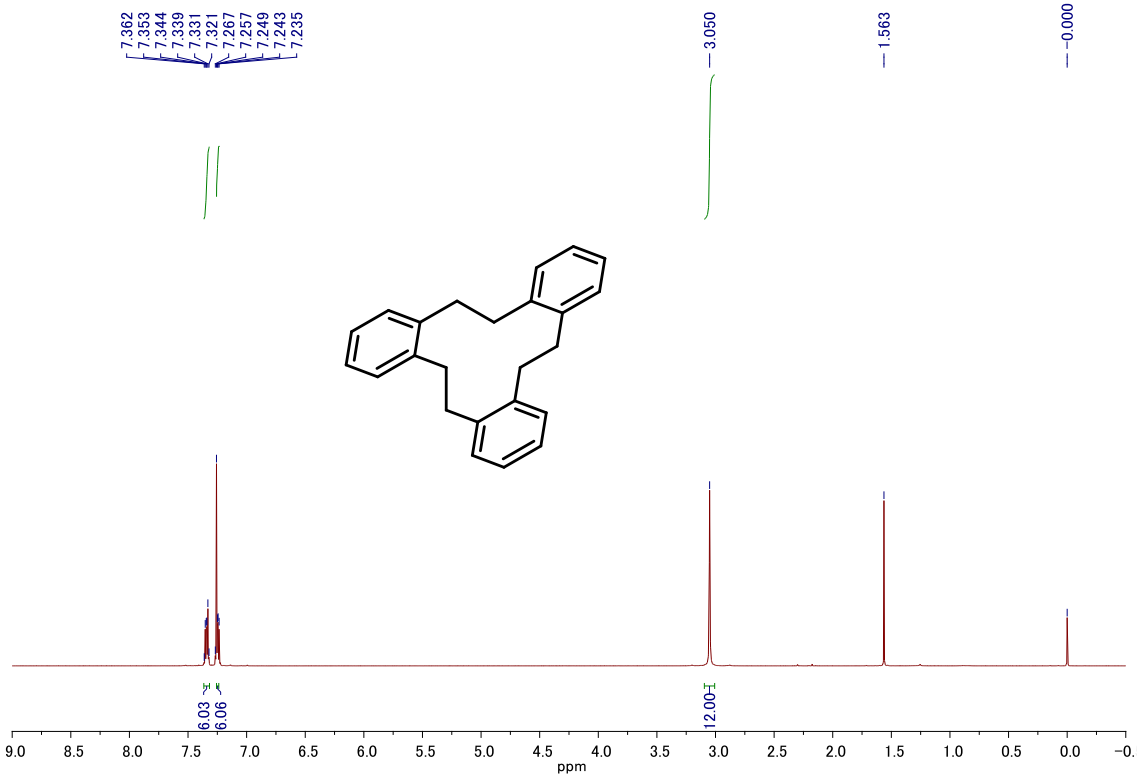

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