10.1071/CH15342_AC

Australian Journal of Chemistry 2015, 68(11), 1657-1661

Supplementary Material

A Facile Preparation of α-Aryl Carboxylic Acid via One-Flow Arndt-Eistert Synthesis

Shinichiro Fuse,[A,B,C] *Yuma Otake*,[A] *Yuto Mifune*,[A] *and Hiroshi Tanaka*[A]

[A]Department of Applied Chemistry, Tokyo Institute of Technology, 2-12-1, Ookayama, Meguro-ku, Tokyo 152-8552, Japan.
[B]Current address: Chemical Resources Laboratory, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8503, Japan.
[C]Corresponding author. Email: sfuse@res.titech.ac.jp

Table of Contents

General techniques

NMR spectra were recorded on JEOL Model EX-270 (270 MHz for ^{1}H, 67.5 MHz for ^{13}C) or JEOL Model ECP-400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) instrument in the indicated solvent. Chemical shifts were reported in units of parts per million (ppm) relative to the signal (0.00 ppm) for internal tetramethylsilane for solutions in $CDCl_3$ (7.26 ppm for ^{1}H, 77.0 ppm for ^{13}C) or DMSO-d_6 (2.50 ppm for ^{1}H, 39.5 ppm for ^{13}C). Multiplicities were reported by using the following abbreviations: s; singlet, d; doublet, t; triplet, m; multiplet, br; broad, *J*; coupling constants in Hertz (Hz). IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer or a JASCO Corporation FT/IR-4100 FT-IR Spectrometer. Only the strongest and/or structurally important peaks were reported as the IR data given in cm^{-1}. HRMS (ESI-TOF) were measured with a Waters LCT Premier^{TM} XE.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light, visualized by 5% ethanolic *p*-anisaldehyde solution or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Silica Gel 60 N, purchased from Kanto Chemical Co., Inc. and Chromatorex NH, purchased from Fuji Silysia Chemical Ltd. Automated column chromatography was performed using a Purif-α® (Shoko Scientific Co., Ltd.) with Purif-Pack (SI 30 μm). $TMSCHN_2$ was purchased from Sigma-Aldrich as a 2 M solution in Et_2O. MeCN and THF were dried by a Glass Contour Solvent dispensing system (Nikko Hansen & Co., Ltd.). 1,4-Dioxane was dried by distillation from sodium benzophenone ketyl. Isopropylamine was distilled from CaH_2. DIEA was distilled from ninhydrine and KOH. Benzoic acid derivatives used for micro-flow reactions were azeotropically dried twice with distilled 1,4-dioxane. Solvents used for photochemical reactions were degassed three times by sonication under vacuum.

Micro-flow reactor setup

Stainless steel T-shape mixers were purchased from Sanko Seiki Co. Ltd. (inner diameter: 0.25 and 0.5 mm). Teflon® tubes were purchased from Senshu Scientific Co., Ltd. (inner diameter: 0.8 mm). PEEK fittings, PEEK unions (inner diameter: 0.8 mm) and back pressure regulator (40 psi) were purchased from GL Science Inc. Solutions were introduced to a micro-flow system with syringe pumps (KDS Model 200, KDS Model 100, and Harvard Pump 11) equipped gastight syringes (SGE 10 mL). The gastight syringes and the Teflon® tubes were connected with joints purchased from Techno Applications Co. Ltd. A 6 W UV lamp (wavelength: 254 nm) was purchased from AS ONE Corporation. A fluorinated ethylene propylene copolymer (FEP) tube

was purchased from Flon Industry Co., Ltd. (inner diameter: 1.0 mm). *In-situ* IR analysis was performed using Mettler-Toledo React IR^{TM} 15 DS Micro Flow Cell (Silicon sensor).

The employed micro-flow system was shown in Figure S-1. The gastight syringes and the T-shape mixers **M1**, **M2** (inner diameter: 0.25 mm) and **M3** (inner diameter: 0.5 mm) were connected with the Teflon® tubes. Reaction tubes **R1**, **R2** (Teflon® tube) and **M1** were immersed in water bath. Cooling tubes **C1** and **C2** (Teflon® tube) were immersed in ice bath. A Photochemical reaction tube **P** (FEP tube) was tightly wrapped around the UV lamp. The back pressure regulator (BPR) was installed in the outlet of the micro-flow system.

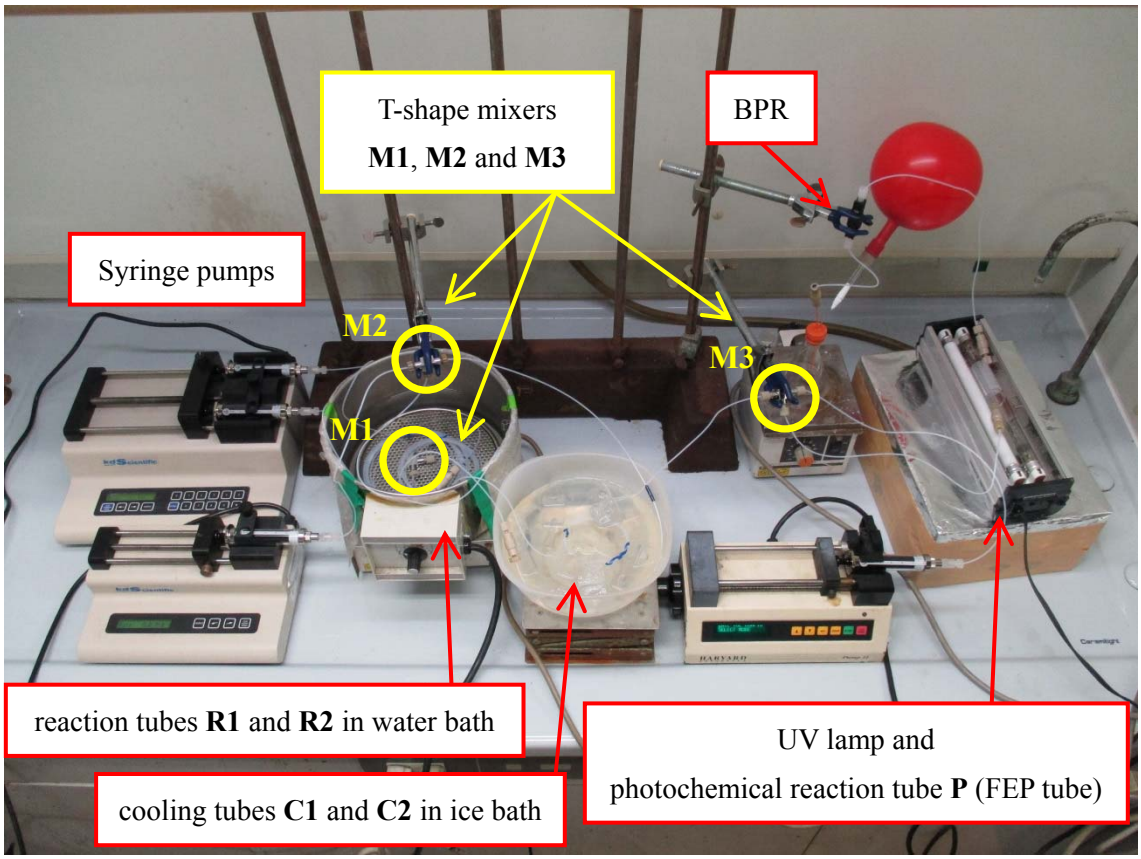
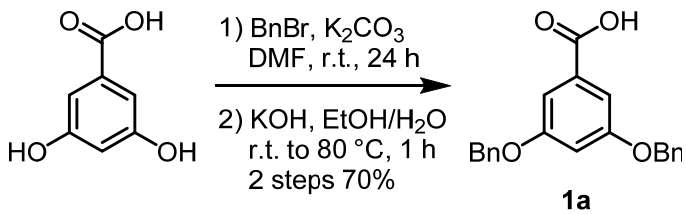


Figure S-1

3,5-Bis(benzyloxy)benzoic acid (1a)



1a

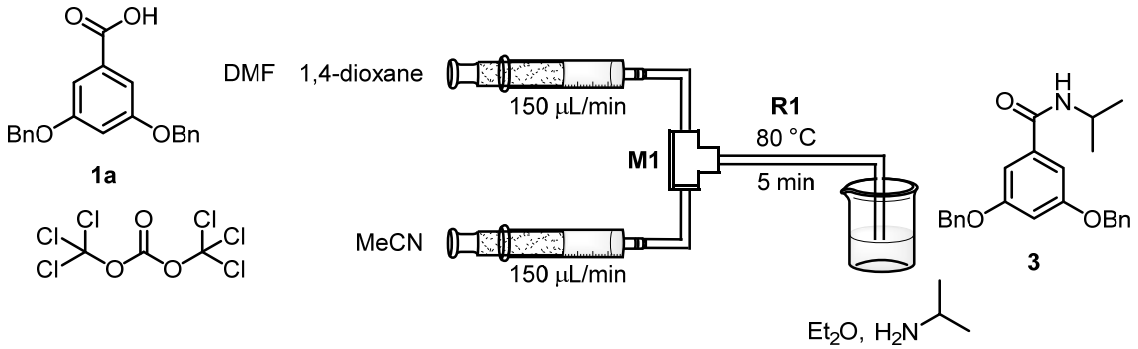
To a suspension of 3,5-dihydroxybenzoic acid (10.0 g, 64.9 mmol, 1.00 equiv.) and potassium

carbonate (53.8 g, 389 mmol, 6.00 equiv.) in DMF (130 mL), benzyl bromide (23.5 mL, 198 mmol, 3.05 equiv.) was added at room temperature under argon atmosphere. After being stirred at the same temperature for 24 h, the reaction mixture was filtered through a pad of Celite® and acidified with 1 M HCl at 0 °C. The aqueous layer was extracted twice with Et_2O. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of crude ester in EtOH (65.0 mL) and H_2O (65.0 mL), potassium hydroxide (36.4 g, 649 mmol, 10.0 equiv.) was added at 0 °C. After being stirred at 80 °C for 1 h, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was diluted with EtOAc and acidified with 6 M HCl at 0 °C. The aqueous layer was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was recrystallized from hexane/EtOAc to give 3,5-bis(benzyloxy)benzoic acid (**1a**)[1] (15.2 g, 45.4 mmol, 2 steps 70%) as a white solid.

^{1}H NMR (270 MHz, DMSO-d_6): δ 13.1 (brs, 1H), 7.48-7.25 (m, 12H), 6.95 (s, 1H), 5.14 (s, 4H); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 167.0, 159.5, 136.8, 133.0, 128.5, 127.9, 127.7, 108.2, 106.6, 69.6; HRMS (ESI-TOF): calcd for $[C_{21}H_{18}O_4+H]^+$ 335.1283, found 335.1246.

Typical procedure for acid chloride formation with triphosgene in micro-flow reactor and amidation with isopropylamine

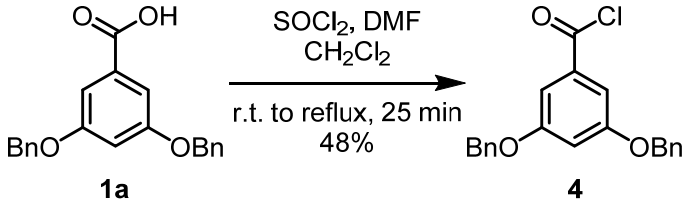


A solution of 3,5-bis(benzyloxy)benzoic acid (**1a**) (133 mM, 1.00 equiv.) and DMF (13.3 mM, 0.100 equiv.) in 1,4-dioxane (flow rate: 150 μL/min) and a solution of triphosgene (66.7 mM, 0.500 equiv.) in MeCN (flow rate: 150 μL/min) were introduced to **M1** at 80 °C with the syringe pumps. The resultant mixture was passed through **R1** (length: 2.98 m, volume: 1.50 mL, reaction time: 5 min) at the same temperature. After being eluted for *ca.* 8 min to reach a steady state, the resultant mixture was poured into a solution of isopropylamine (114 μL, 1.33 mmol, 5.00 equiv.) in Et_2O (5.00 mL) for 13 min 19 s at room temperature. The reaction mixture was acidified with 1 M HCl at 0 °C and the aqueous layer was extracted three times with Et_2O. The combined organic layer was washed with 1 M NaOH and brine, dried over Na_2SO_4, filtered and concentrated *in*

vacuo. The residue was purified by column chromatography on silica gel and a small amount of amine silica gel added to the top of the column with chloroform : methanol = 99 : 1 to give *amide **3*** (84.2 mg, 0.224 mmol, 84%) as a white solid.

mp: 173-174 °C; IR (neat): 3289, 2970, 1630, 1594, 1536, 1359, 1170, 734, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.30 (m, 10H), 6.98 (d, *J* = 2.2 Hz, 2H), 6.71 (t, *J* = 2.2 Hz, 1H), 5.91 (brd, *J* = 7.3 Hz, 1H), 5.04 (s, 4H), 4.24 (m, 1H), 1.23 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 160.1, 137.4, 136.6, 128.7, 128.2, 127.7, 106.2, 104.9, 70.4, 42.0, 22.9; HRMS (ESI-TOF): calcd for $[C_{24}H_{25}NO_3+H]^+$ 376.1913, found 376.1909.

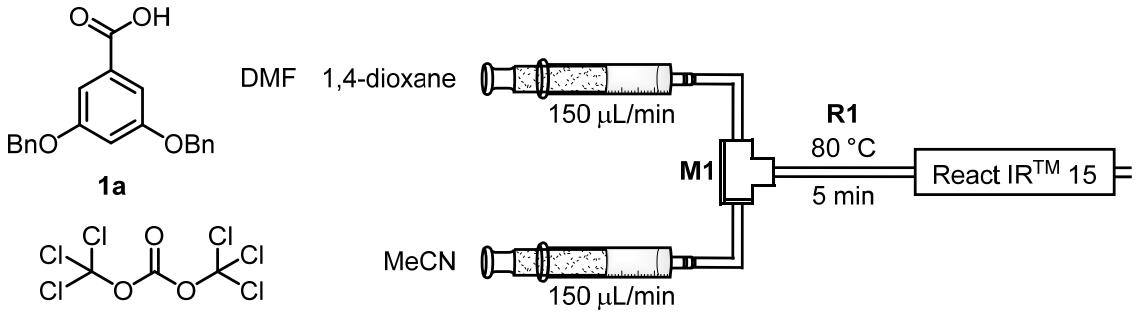
3,5-Bis(benzyloxy)benzoyl chloride 4



To a solution of 3,5-bis(benzyloxy)benzoic acid (**1a**) (350 mg, 1.05 mmol, 1.00 equiv.) in CH_2Cl_2 (5.15 mL), thionyl chloride (638 μL, 8.80 mmol, 8.38 equiv.) and one drop of DMF were added at room temperature under argon atmosphere. After being stirred at the reflux temperature for 25 min, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was recrystallized from hexane/CH_2Cl_2 to give 3,5-bis(benzyloxy)benzoyl chloride (**4**)[2] (178 mg, 0.504 mmol, 48%) as a white solid.

mp: 72-73 °C; IR (KBr): 3092, 3037, 2873, 1764, 1751, 1601, 1592, 1443, 1356, 1295, 1170, 763, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.29 (m, 12H), 6.90 (t, *J* = 2.4 Hz, 1H), 5.07 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 160.1, 136.1, 135.1, 128.9, 128.5, 127.8, 110.4, 109.6, 70.7.

Procedure for *in-situ* IR analysis



A solution of 3,5-bis(benzyloxy)benzoic acid (**1a**) (133 mM, 1.00 equiv.) and DMF (13.3 mM, 0.100 equiv.) in 1,4-dioxane (flow rate: 150 μL/min) and a solution of triphosgene (66.7 mM,

0.500 equiv.) in MeCN (flow rate: 150 μL/min) were introduced to **M1** at 80 °C with the syringe pumps. The resultant mixture was passed through **R1** (length: 2.98 m, volume: 1.50 mL, reaction time: 5 min) at the same temperature. After being eluted for *ca.* 8 min to reach a steady state, the resultant mixture was analyzed by Mettler-Toledo React IR^{TM} 15 DS Micro Flow Cell. The IR spectra of the resultant mixture and 3,5-bis(benzyloxy)benzoyl chloride (**4**) in 1,4-dioxane/MeCN were shown in Figure S-2.

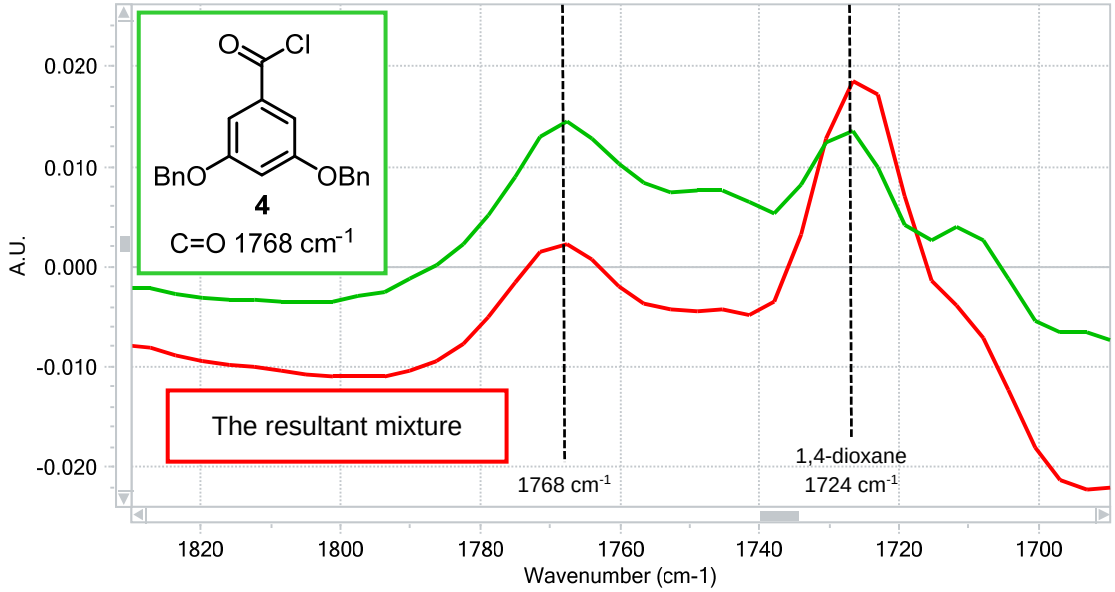
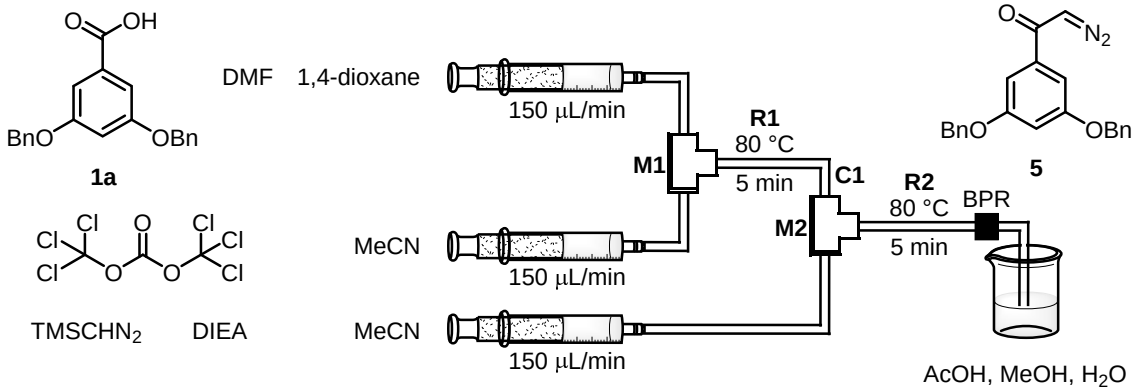


Figure S-2

Typical procedure for one-flow synthesis of α-diazo ketone 5

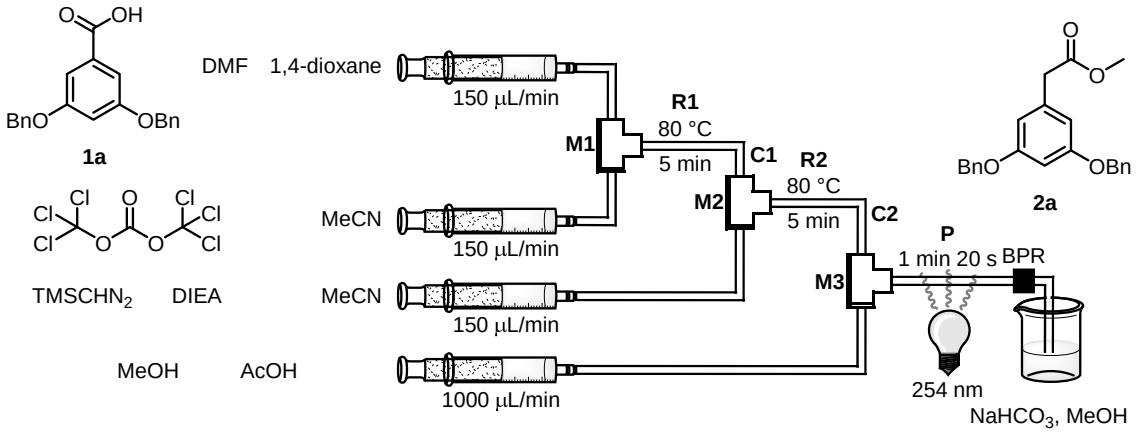


A solution of 3,5-bis(benzyloxy)benzoic acid (**1a**) (133 mM, 1.00 equiv.) and DMF (13.3 mM, 0.100 equiv.) in 1,4-dioxane (flow rate: 150 μL/min) and a solution of triphosgene (66.7 mM, 0.500 equiv.) in MeCN (flow rate: 150 μL/min) were introduced to **M1** at 80 °C with the syringe pumps. The resultant mixture was passed through **R1** (length: 2.98 m, volume: 1.50 mL, reaction

time: 5 min) at the same temperature, and **C1** (length: 0.597 m, volume: 0.300 mL, residence time: 1 min) at 0 °C. After being eluted for *ca.* 7 min, the resultant mixture and a solution of $TMSCHN_2$ (400 mM, 3.00 equiv.) and DIEA (533 mM, 4.00 equiv.) in MeCN (flow rate: 150 μL/min) were introduced to **M2** at room temperature with the syringe pumps. The resultant mixture was passed through **R2** (length: 4.48 m, volume: 2.25 mL, reaction time: 5 min) at 80 °C. After being eluted for *ca.* 9 min to reach a steady state, the resultant mixture was poured into a solution of AcOH (0.240 mL, 4.20 mmol, 15.0 equiv.) in MeOH (5.00 mL) and water (10.0 mL) for 13 min 59 s at room temperature. The aqueous layer was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with hexane : EtOAc = 85 : 15 to give α-diazo ketone **5**[1] (62.8 mg, 0.175 mmol, 63%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.30 (m, 10H), 6.98 (d, J = 2.2 Hz, 2H), 6.77 (t, J = 2.2 Hz, 1H), 5.78 (s, 1H), 5.04 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.0, 160.1, 138.8, 136.5, 128.7, 128.3, 127.7, 106.4, 105.9, 70.4, 54.5; HRMS (ESI-TOF): calcd for $[C_{22}H_{18}N_2O_3+H]^+$ 359.1396, found 359.1397.

Typical procedure for one-flow synthesis of α-aryl ester 2a

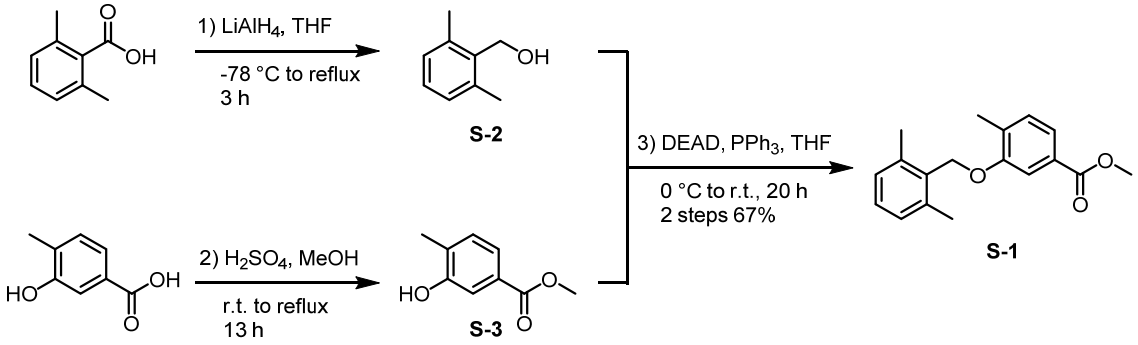


A solution of 3,5-bis(benzyloxy)benzoic acid (**1a**) (133 mM, 1.00 equiv.) and DMF (13.3 mM, 0.100 equiv.) in 1,4-dioxane (flow rate: 150 μL/min) and a solution of triphosgene (66.7 mM, 0.500 equiv.) in MeCN (flow rate: 150 μL/min) were introduced to **M1** at 80 °C with the syringe pumps. The resultant mixture was passed through **R1** (length: 2.98 m, volume: 1.50 mL, reaction time: 5 min) at the same temperature, and **C1** (length: 0.597 m, volume: 0.300 mL, residence time: 1 min) at 0 °C. After being eluted for *ca.* 7 min, the resultant mixture and a solution of $TMSCHN_2$ (400 mM, 3.00 equiv.) and DIEA (533 mM, 4.00 equiv.) in MeCN (flow rate: 150 μL/min) were introduced to **M2** at room temperature with the syringe pumps. The resultant mixture was passed through **R2** (length: 4.48 m, volume: 2.25 mL, reaction time: 5 min) at 80 °C,

and **C2** (length: 0.895 m, volume; 0.450 mL, residence time; 1 min) at 0 °C. After being eluted for *ca.* 9 min, the resultant mixture and a solution of AcOH (667 mM, 15.0 equiv.) in MeOH (flow rate: 1000 μL/min) were introduced to **M3** at room temperature with the syringe pumps. The resultant mixture was passed through **P** (FEP tube, length: 2.46 m, volume: 1.93 mL, reaction time: 1 min 20 s) at room temperature. After being eluted for *ca.* 3 min to reach a steady state, the resultant mixture was poured into a suspension of excess $NaHCO_3$ (4.50 g) in MeOH (10.0 mL) for 6 min 54 s at 0 °C. Then, $NaBH_4$ (302 mg, 8.12 mmol, 58.0 equiv.) was added to the resultant suspension at the same temperature. After being stirred at room temperature for 2 h, the reaction mixture was acidified with 1 M HCl at 0 °C and the aqueous layer was extracted three times with Et_2O. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by Purif-α® (size: 20) with a linear gradient: 0-5 min hexane : EtOAc = 97 : 3, 5- min hexane : EtOAc = 97 : 3 to give α-aryl ester **2a**[3] (16.6 mg, 0.0458 mmol, 33%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.30 (m, 10H), 6.54 (s, 3H), 5.02 (s, 4H), 3.68 (s, 3H), 3.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 160.2, 137.0, 136.2, 128.7, 128.1, 127.7, 108.6, 101.0, 70.2, 52.2, 41.6; HRMS (ESI-TOF): calcd for $[C_{23}H_{22}O_4+H]^+$ 363.1596, found 363.1564.

Methyl 3-{(2,6-dimethylbenzyl)oxy}-4-methylbenzoate (S-1)



To a solution of lithium aluminum hydride (1.52 g, 40.0 mmol, 2.00 equiv.) in THF (40.0 mL), a solution of 2,6-dimethylbenzoic acid (3.00 g, 20.0 mmol, 1.00 equiv.) in THF (40.0 mL) was added dropwise at -78 °C under argon atmosphere. After being stirred at reflux temperature for 3 h, the reaction mixture was cooled to room temperature and saturated aqueous potassium sodium tartrate was added dropwise at 0 °C. After being stirred for 30 min, the reaction mixture was filtered through a pad of Celite®, and the aqueous layer was extracted twice with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue of the 2,6-dimethylbenzyl alcohol (**S-2**) was used for the next reaction without further purification.

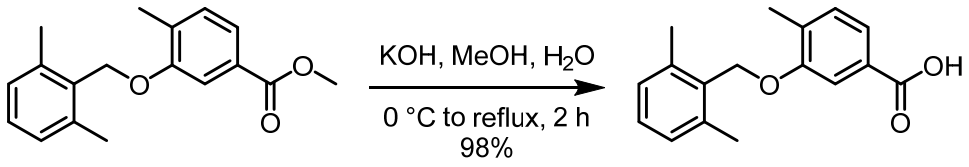
To a solution of 3-hydroxy-4-methylbenzoic acid (3.04 g, 20.0 mmol, 1.00 equiv.) in MeOH

(80.0 mL), 18 M H_2SO_4 (2.40 mL, 45.0 mmol, 2.25 equiv.) was added at room temperature. After being stirred at reflux temperature for 13 h, the reaction mixture was cooled to room temperature and poured into water at 0 °C. The aqueous layer was extracted three times with Et_2O. The combined organic layer was washed with H_2O, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue of the methyl 3-hydroxy-4-methylbenzoate (**S-3**) was used for the next reaction without further purification.

To a solution of crude 2,6-dimethylbenzyl alcohol (**S-2**), crude methyl 3-hydroxy-4-methylbenzoate (**S-3**) and triphenylphosphine (5.48 g, 20.9 mmol, 1.05 equiv.) in THF (76.0 mL), diethyl azodicarboxylate (2.2 M solution in toluene, 9.50 mL, 20.9 mmol, 1.05 equiv.) was added dropwise at 0 °C under argon atmosphere. After being stirred at room temperature for 20 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with hexane : EtOAc = 85 : 15 and further purified by recrystallization from hexane/EtOAc to give *methyl 3-{(2,6-dimethylbenzyl)oxy}-4-methylbenzoate (**S-1**)* (3.82 g, 13.4 mmol, 2 steps 67%) as a white solid.

mp: 110-111 °C; IR (neat): 2950, 1717, 1585, 1505, 1435, 1236, 1011, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 1.5 Hz, 1H), 7.59 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.21-7.06 (m, 4H), 5.09 (s, 2H), 3.92 (s, 3H), 2.39 (s, 6H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 157.3, 138.3, 133.1, 133.0, 130.6, 129.0, 128.6, 128.4, 122.2, 111.6, 65.1, 52.1, 19.7, 16.7; HRMS (ESI-TOF): calcd for $[C_{18}H_{20}O_3+H]^+$ 285.1491, found 285.1457.

3-{(2,6-Dimethylbenzyl)oxy}-4-methylbenzoic acid (1b)



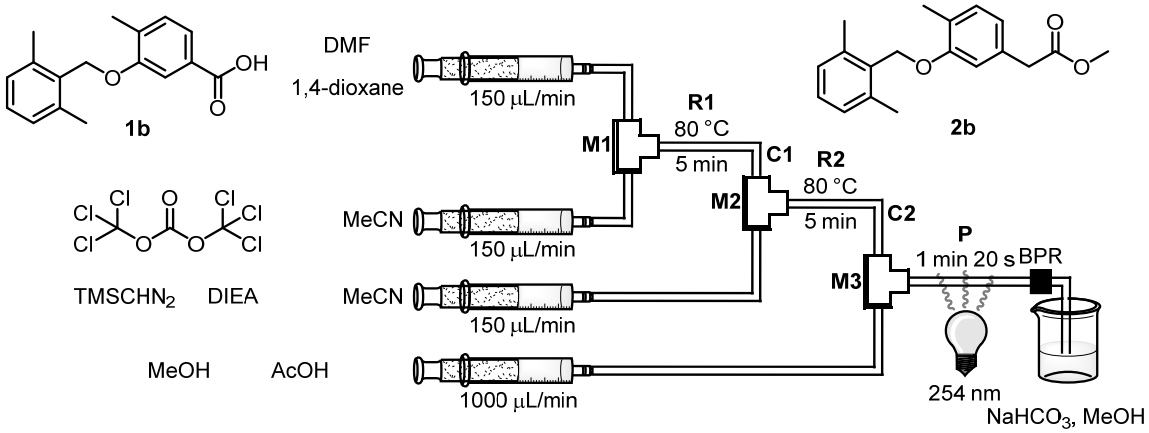
S-1 **1b**

To a suspension of methyl 3-{(2,6-dimethylbenzyl)oxy}-4-methylbenzoate (**S-1**) (3.89 g, 13.7 mmol, 1.00 equiv.) in MeOH (55.0 mL) and H_2O (55.0 mL), potassium hydroxide (7.68 g, 137 mmol, 10.0 equiv.) was added at 0 °C. After being stirred at reflux temperature for 2 h, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was diluted with EtOAc and acidified with 6 M HCl at 0 °C. The aqueous layer was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was recrystallized from toluene to give *3-{(2,6-dimethylbenzyl)oxy}-4-methylbenzoic acid (**1b**)* (3.62 g, 13.4 mmol, 98%) as a white solid.

mp: 205-206 °C; IR (neat): 2854, 2654, 1683, 1611, 1585, 1428, 1296, 1277, 1242, 1010 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 12.9 (s, 1H), 7.67 (d, *J* = 1.0 Hz, 1H), 7.50 (dd, *J* = 1.5, 7.3

Hz, 1H), 7.28-7.07 (m, 4H), 5.11 (s, 2H), 2.35 (s, 6H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, 156.8, 137.9, 132.9, 131.6, 130.5, 129.8, 128.3, 128.1, 121.8, 111.8, 64.7, 19.1, 16.2; HRMS (ESI-TOF): calcd for $[C_{17}H_{18}O_3+H]^+$ 271.1334, found 271.1344.

Methyl 2-[3-{(2,6-dimethylbenzyl)oxy}-4-methylphenyl]acetate 2b

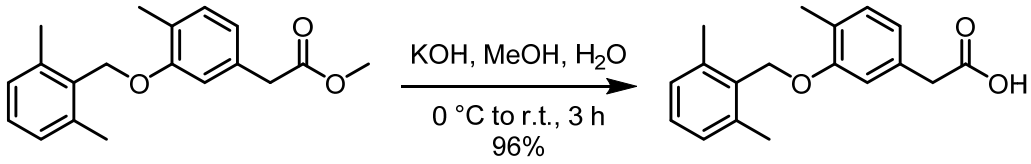


A solution of 3-{(2,6-dimethylbenzyl)oxy}-4-methylbenzoic acid (**1b**) (133 mM, 1.00 equiv.) and DMF (13.3 mM, 0.100 equiv.) in 1,4-dioxane (flow rate: 150 μL/min) and a solution of triphosgene (66.7 mM, 0.500 equiv.) in MeCN (flow rate: 150 μL/min) were introduced to **M1** at 80 °C with the syringe pumps. The resultant mixture was passed through **R1** (length: 2.98 m, volume: 1.50 mL, reaction time: 5 min) at the same temperature, and **C1** (length: 0.597 m, volume: 0.300 mL, residence time: 1 min) at 0 °C. After being eluted for *ca.* 7 min, the resultant mixture and a solution of $TMSCHN_2$ (400 mM, 3.00 equiv.) and DIEA (533 mM, 4.00 equiv.) in MeCN (flow rate: 150 μL/min) were introduced to **M2** at room temperature with the syringe pumps. The resultant mixture was passed through **R2** (length: 4.48 m, volume: 2.25 mL, reaction time: 5 min) at 80 °C, and **C2** (length: 0.895 m, volume; 0.450 mL, residence time; 1 min) at 0 °C. After being eluted for *ca.* 9 min, the resultant mixture and a solution of AcOH (667 mM, 15.0 equiv.) in MeOH (flow rate: 1000 μL/min) were introduced to **M3** at room temperature with the syringe pumps. The resultant mixture was passed through **P** (FEP tube, length: 2.46 m, volume: 1.93 mL, reaction time: 1 min 20 s) at room temperature. After being eluted for *ca.* 3 min to reach a steady state, the resultant mixture was poured into a suspension of excess $NaHCO_3$ (4.50 g) in MeOH (10.0 mL) for 6 min 54 s at 0 °C. Then, $NaBH_4$ (302 mg, 8.12 mmol, 58.0 equiv.) was added to the resultant suspension at the same temperature. After being stirred at room temperature for 2 h, the reaction mixture was acidified with 1 M HCl at 0 °C and the aqueous layer was extracted three times with Et_2O. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by Purif-α® (size: 20) with a linear gradient: 0-5 min hexane : EtOAc = 97 : 3, 5- min hexane :

EtOAc = 97 : 3 to give *methyl 2-[3-{(2,6-dimethylbenzyl)oxy}-4-methylphenyl]acetate (**2b**)* (9.40 mg, 0.0315 mmol, 23%) as a colorless oil.

IR (neat): 3475, 2951, 1738, 1612, 1587, 1509, 1418, 1254, 1130, 1012, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.19-7.07 (m, 4H), 6.95 (d, *J* = 1.0 Hz, 1H), 6.81 (dd, *J* = 1.5, 7.8 Hz, 1H), 5.02 (s, 2H), 3.72 (s, 3H), 3.64 (s, 2H), 2.40 (s, 6H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 157.6, 138.4, 133.3, 132.7, 130.9, 128.5, 128.4, 126.3, 121.4, 112.3, 65.0, 52.2, 41.4, 19.8, 16.2; HRMS (ESI-TOF): calcd for $[C_{19}H_{22}O_3+H]^+$ 299.1647, found 299.1625.

2-[3-{(2,6-Dimethylbenzyl)oxy}-4-methylphenyl]acetic acid 6



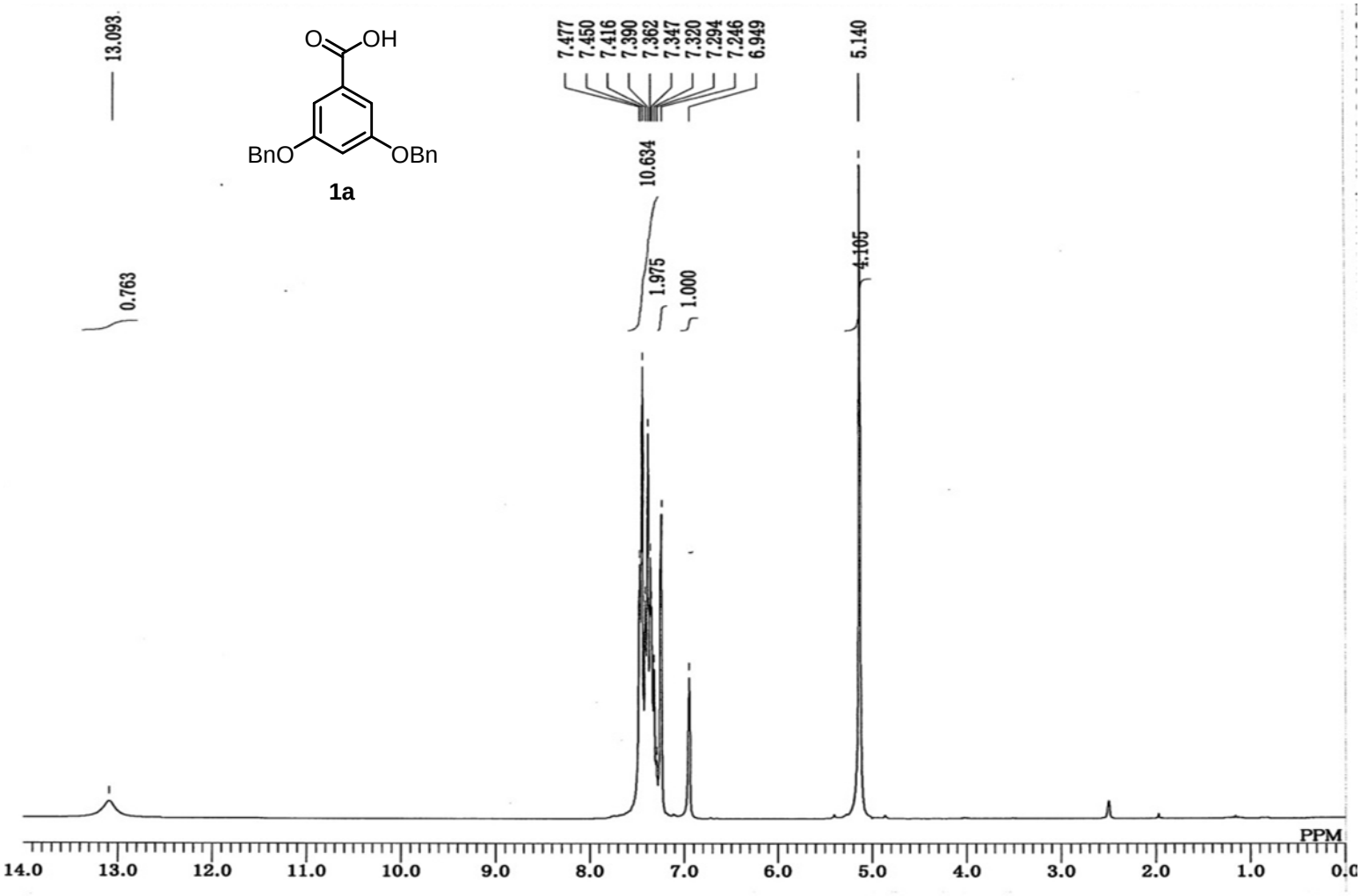
2b **6**

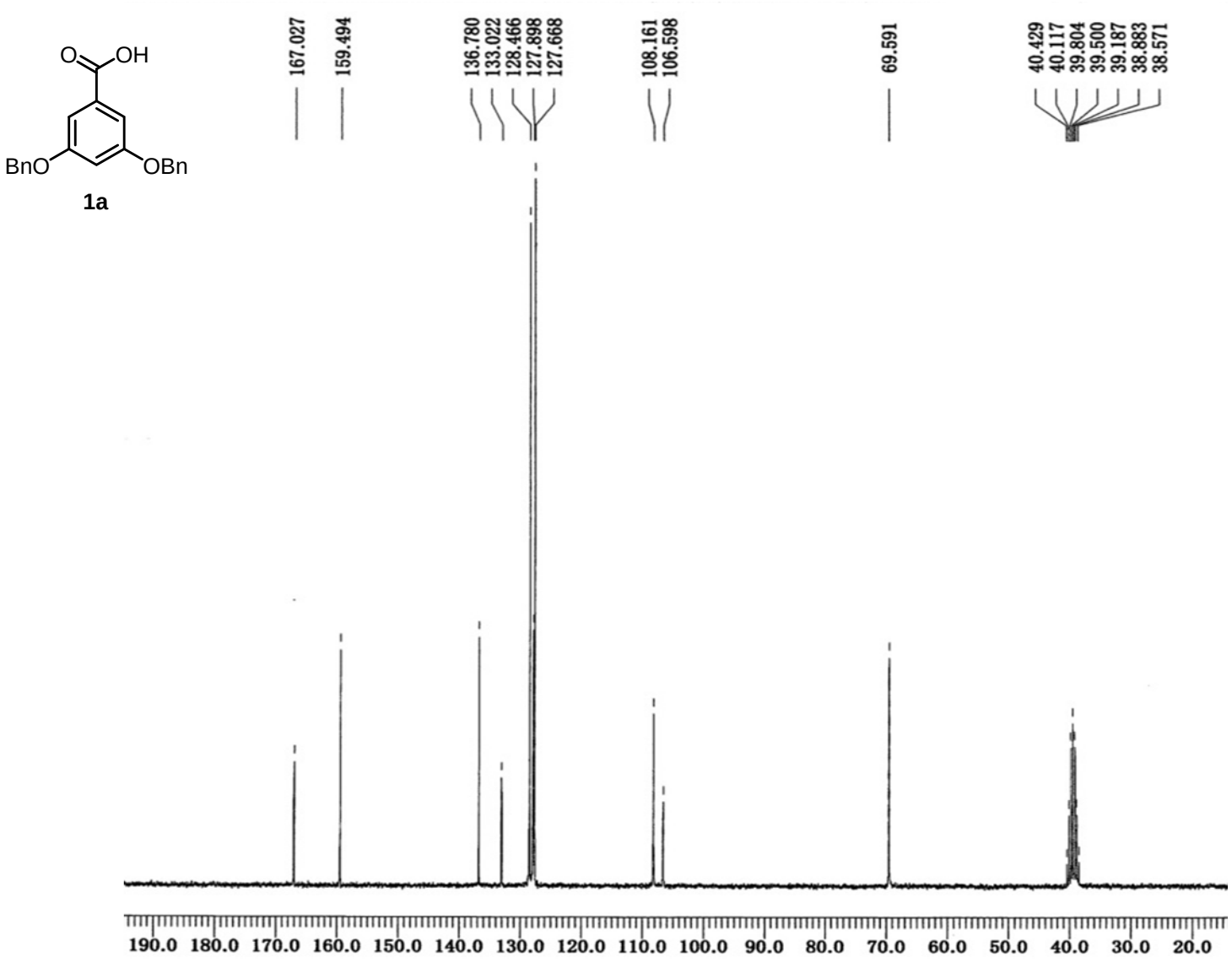
To a suspension of methyl 2-[3-{(2,6-dimethylbenzyl)oxy}-4-methylphenyl]acetate (**2b**) (5.80 mg, 0.0194 mmol, 1.00 equiv.) in MeOH (1.00 mL) and H_2O (1.00 mL), potassium hydroxide (15.5 mg, 0.276 mmol, 14.2 equiv.) was added at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was acidified with 1 M HCl at 0 °C and the aqueous layer was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform to give *2-[3-{(2,6-dimethylbenzyl)oxy}-4-methylphenyl]acetic acid (**6**)* (5.30 mg, 0.0186 mmol, 96%) as a white solid.

mp: 113-114 °C; IR (neat): 3026, 2924, 1709, 1613, 1587, 1509, 1418, 1253, 1130, 1013, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.19-7.07 (m, 4H), 6.94 (d, *J* = 1.5 Hz, 1H), 6.82 (dd, *J* = 1.5, 7.8 Hz, 1H), 5.02 (s, 2H), 3.66 (s, 2H), 2.39 (s, 6H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 157.6, 138.4, 133.2, 132.0, 130.9, 128.5, 128.4, 126.6, 121.5, 112.4, 65.0, 41.2, 19.8, 16.2; HRMS (ESI-TOF): calcd for $[C_{18}H_{20}O_3+H]^+$ 285.1491, found 285.1486.

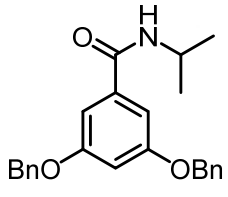
NMR spectra

3,5-Bis(benzyloxy)benzoic acid (**1a**)

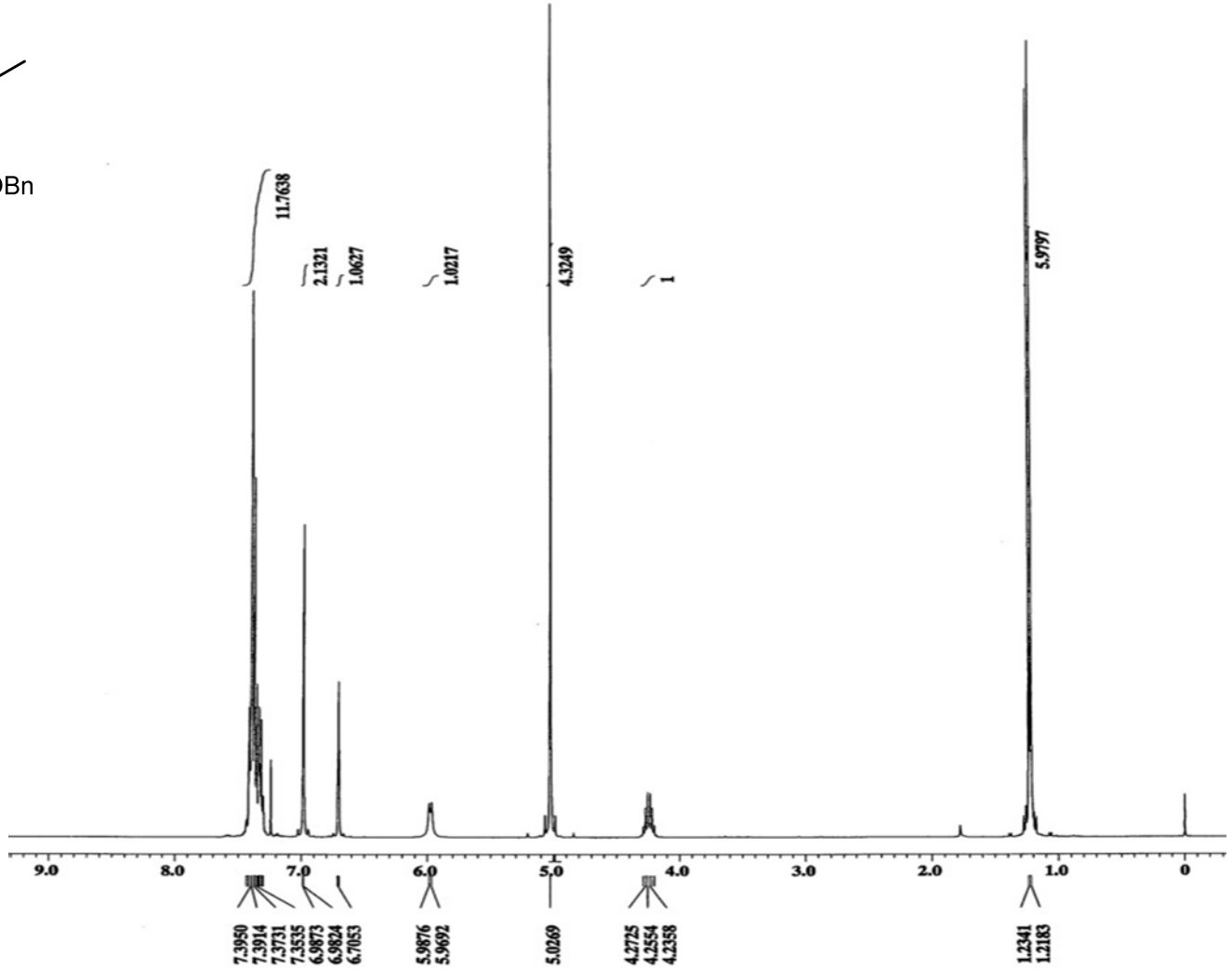


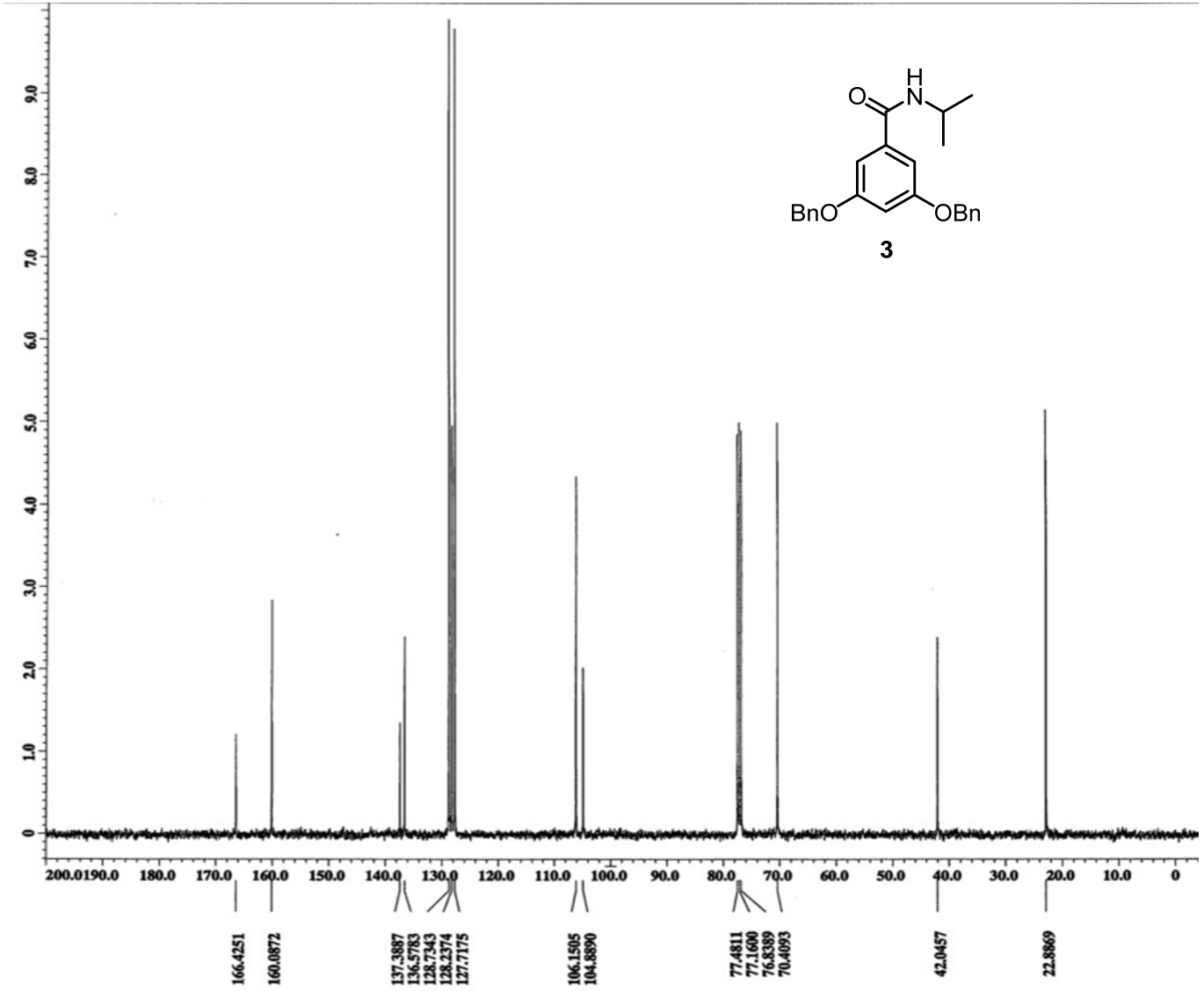

O
OH
BnO
OBn
1a
167.027
159.494
136.780
133.022
128.466
127.898
127.668
108.161
106.598
69.591
40.429
40.117
39.804
39.500
39.187
38.883
38.571
190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0

Amide **3**

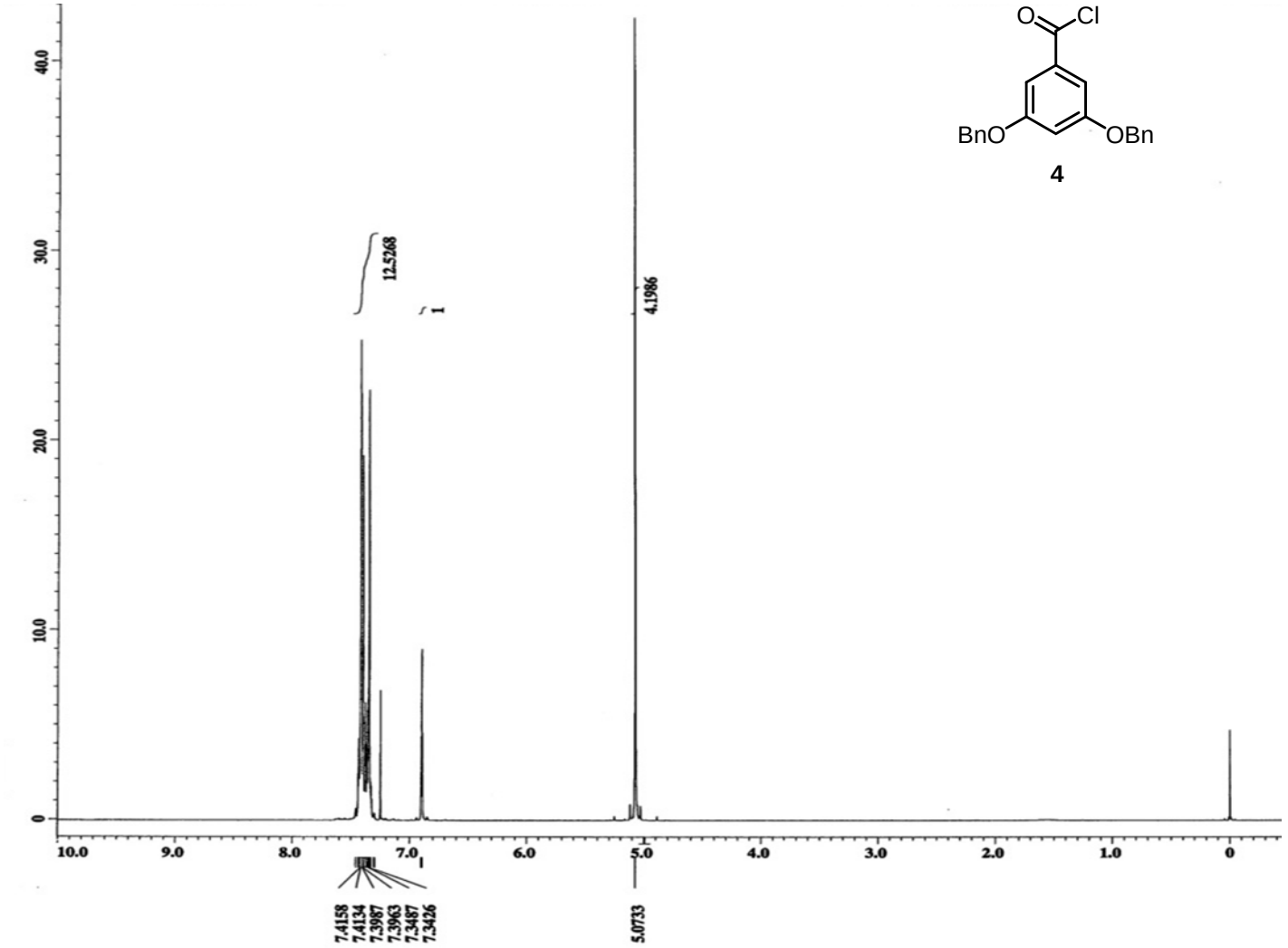

H
N
O
BnO
OBn

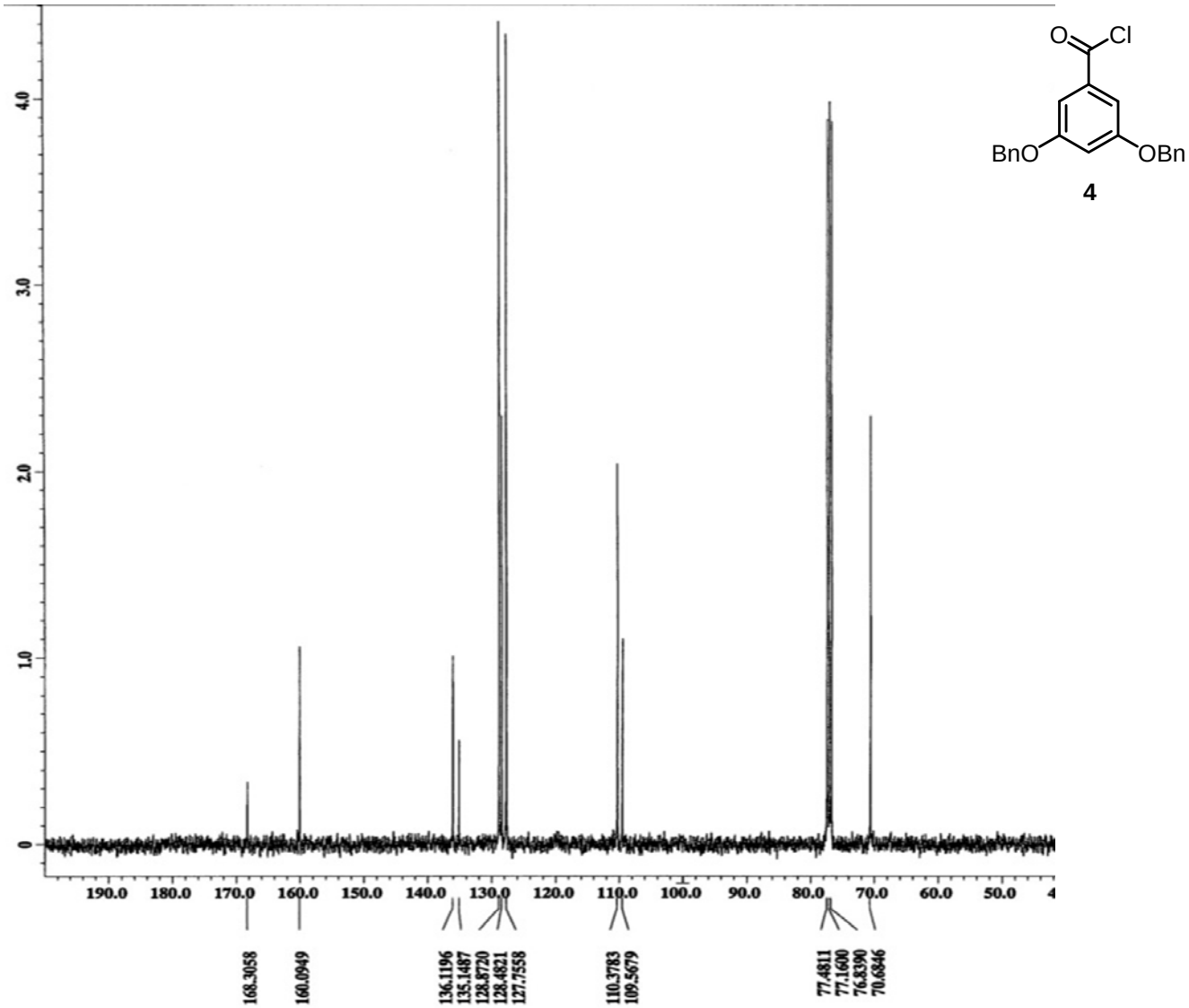
3


11.7638
2.1321
1.0627
1.0217
4.3249
1
5.9797
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.3950
7.3914
7.3731
7.3535
6.9873
6.9824
6.7053
5.9876
5.9692
5.0269
4.2725
4.2554
4.2358
1.2341
1.2183

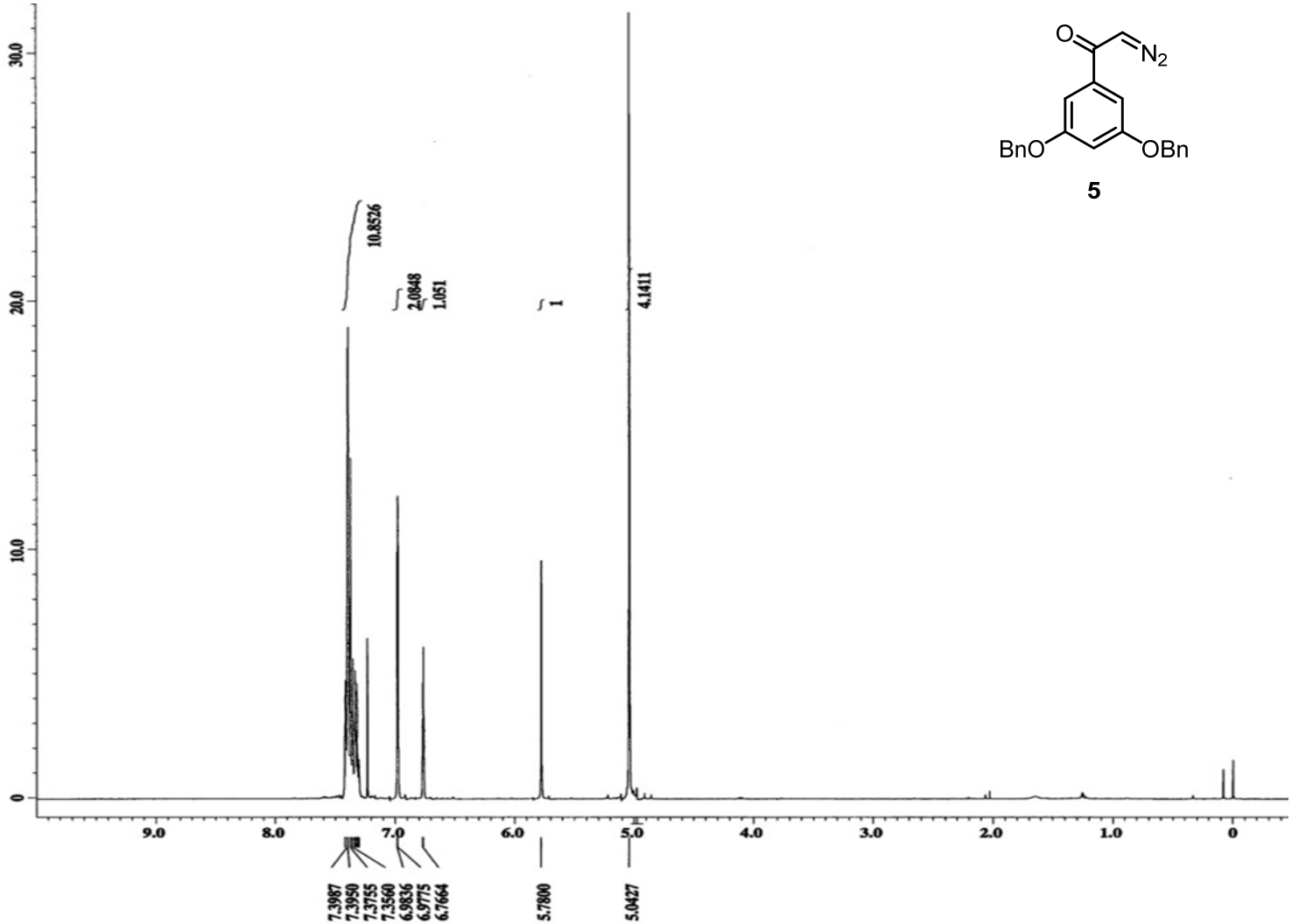

O
H
N
BnO
OBn
3
166.4251
160.0872
137.3887
136.5783
128.7343
128.2374
127.7175
106.1505
104.8890
77.4811
77.1600
76.8389
70.4093
42.0457
22.8869

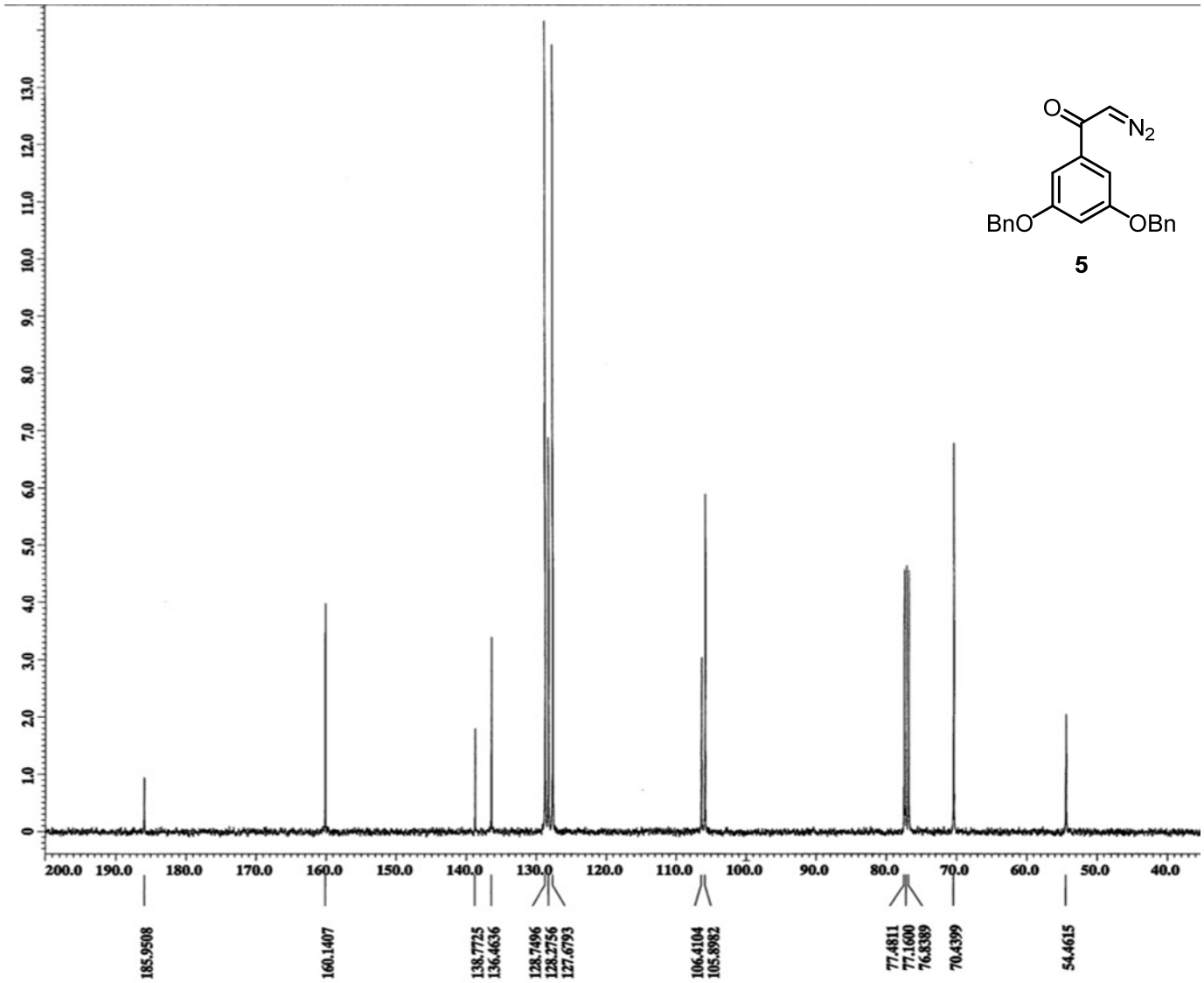
3,5-Bis(benzyloxy)benzoyl chloride (**4**)



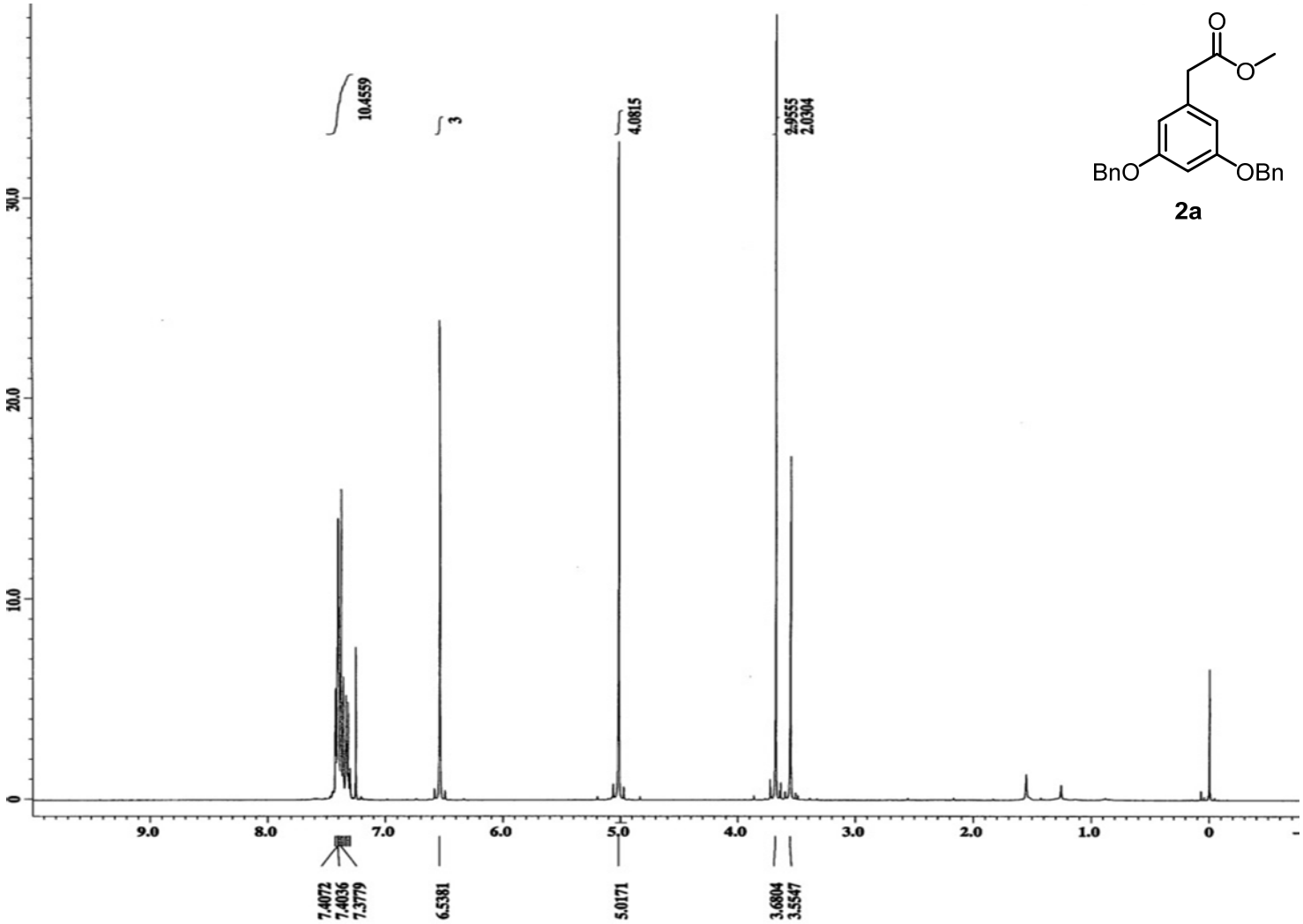

O
Cl
BnO
OBn
4
4.0
3.0
2.0
1.0
0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
168.3058
160.0949
136.1196
135.1487
128.8720
128.4821
127.7558
110.3783
109.5679
77.4811
77.1600
76.8390
70.6846

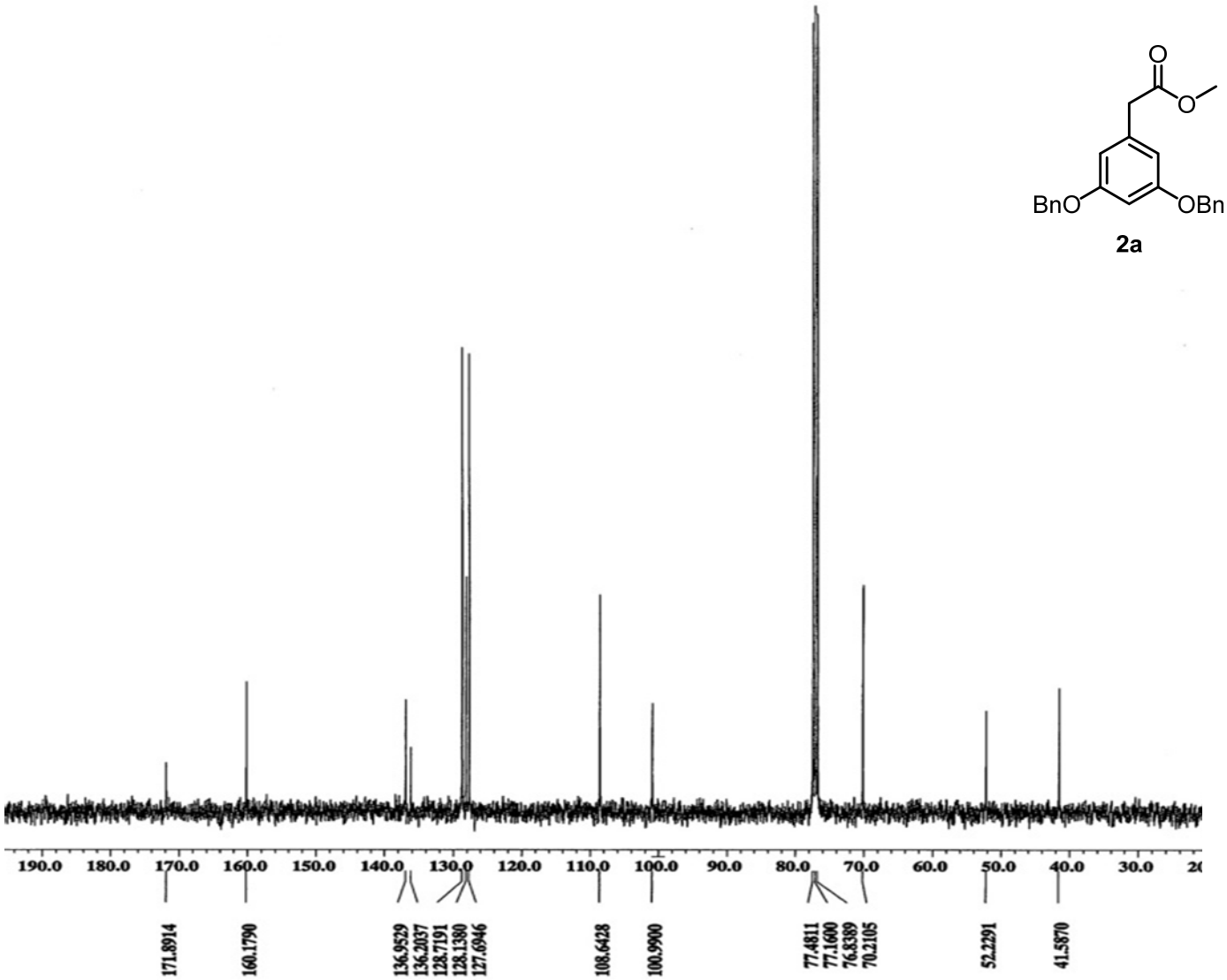
α-Diazo ketone **5**



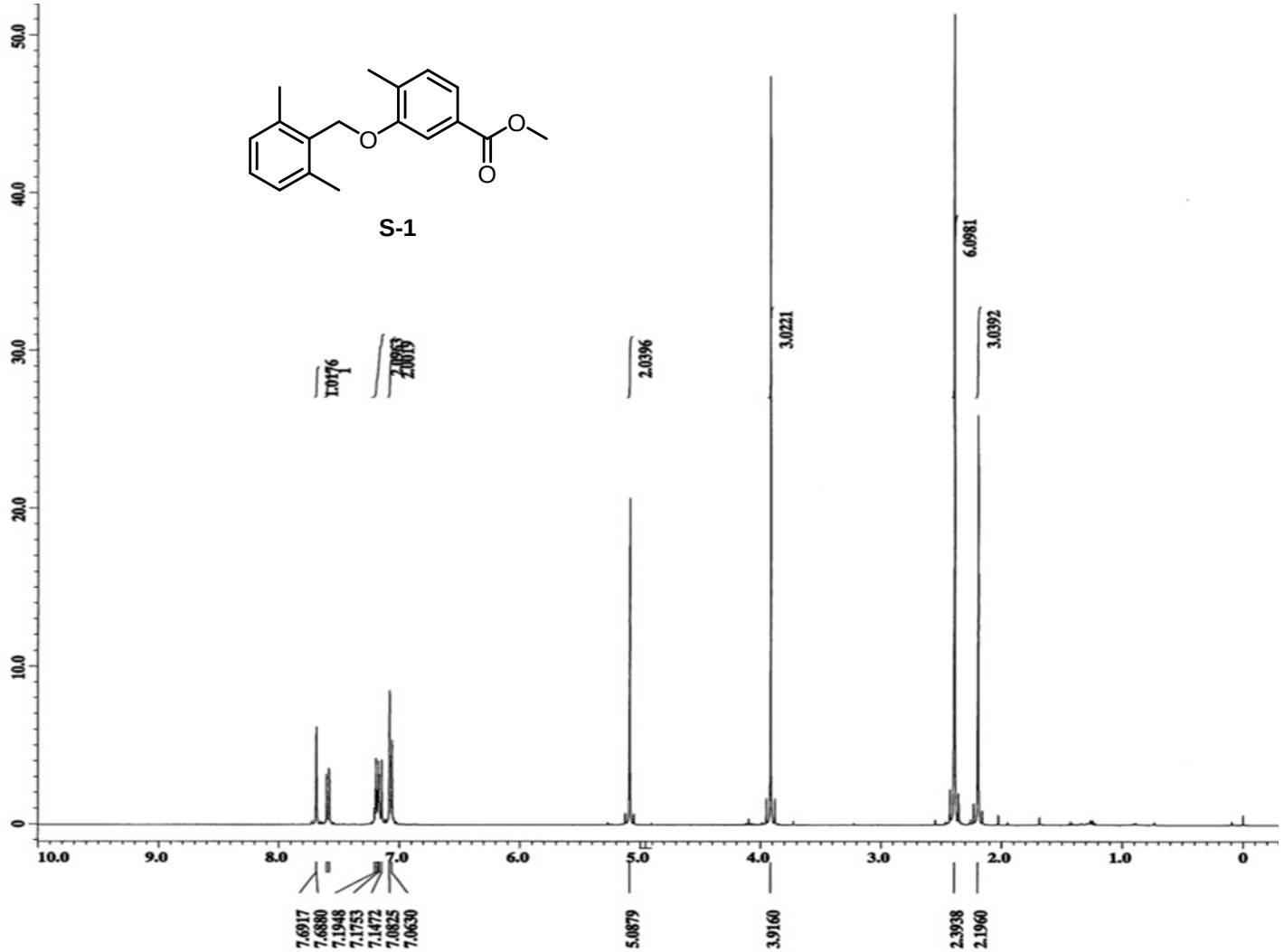

O
N2
BnO
OBn
5
185.9508
160.1407
138.7725
136.4636
128.7496
128.2756
127.6793
106.4104
105.8982
77.4811
77.1600
76.8389
70.4399
54.4615

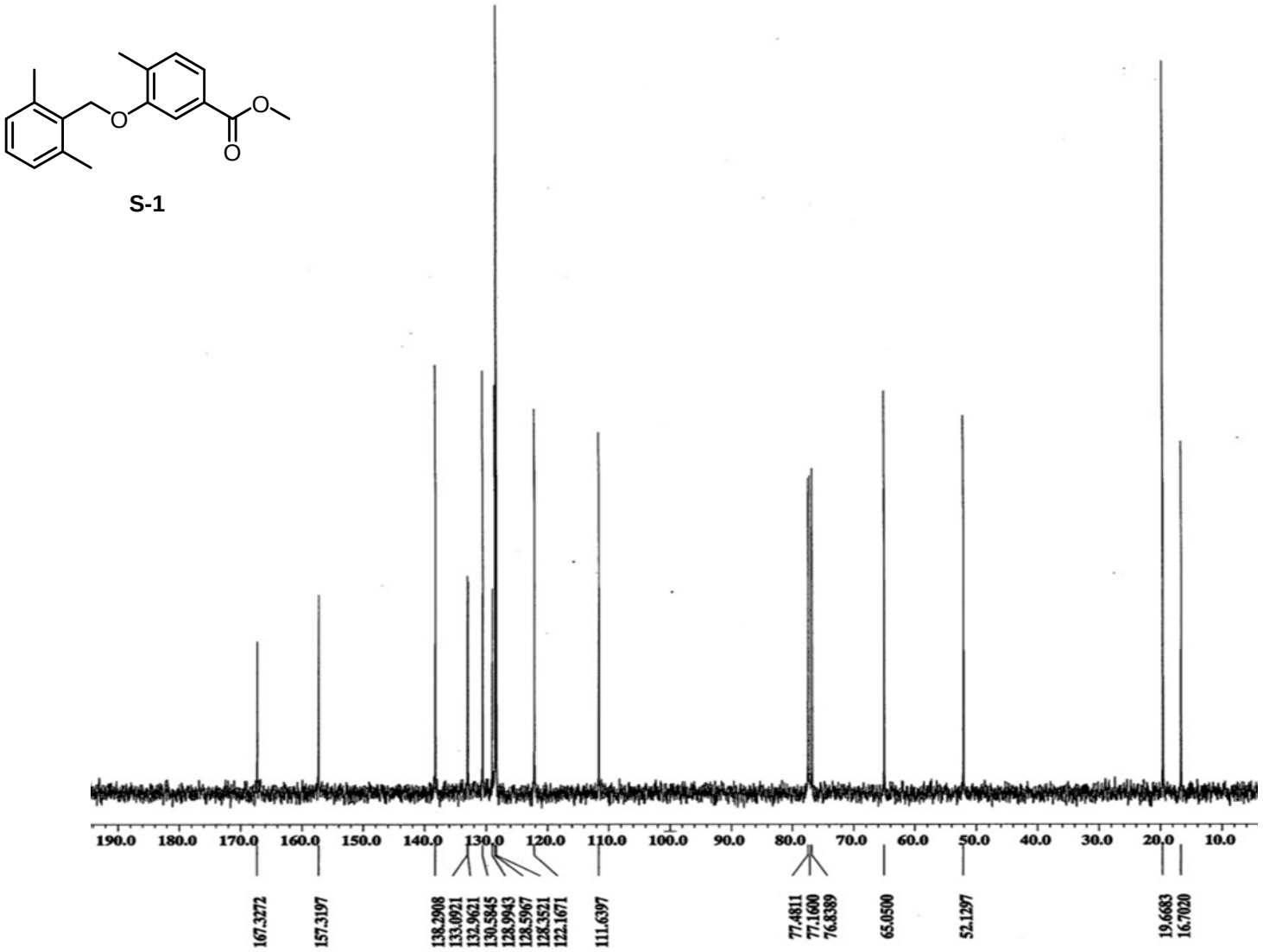
α-Aryl ester **2a**




O
O
BnO
OBn
2a
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
171.8914
160.1790
136.9529
136.2037
128.7191
128.1380
127.6946
108.6428
100.9900
77.4811
77.1600
76.8389
70.2105
52.2291
41.5870

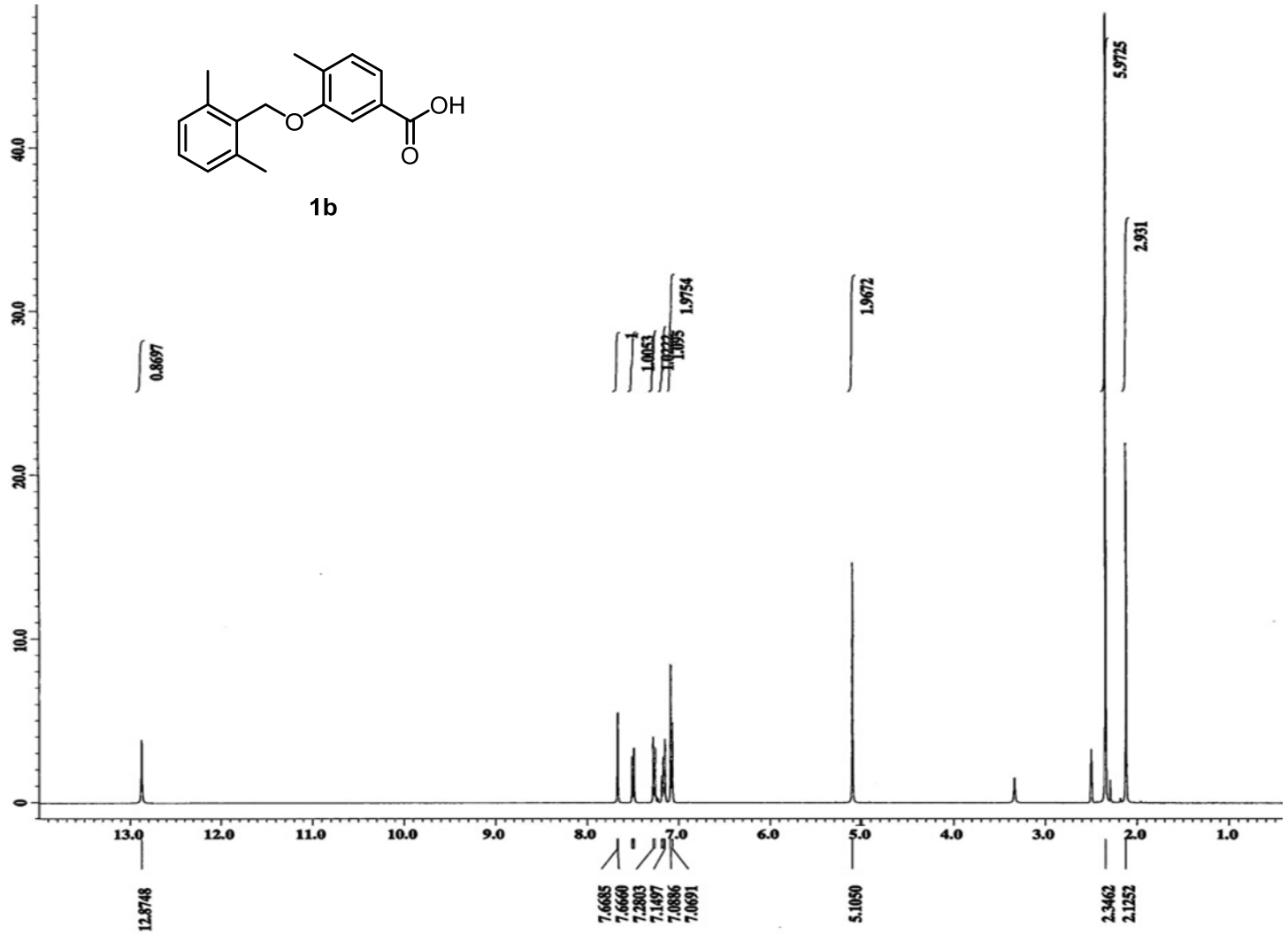
Methyl 3-{(2,6-dimethylbenzyl)oxy}-4-methylbenzoate (**S-1**)

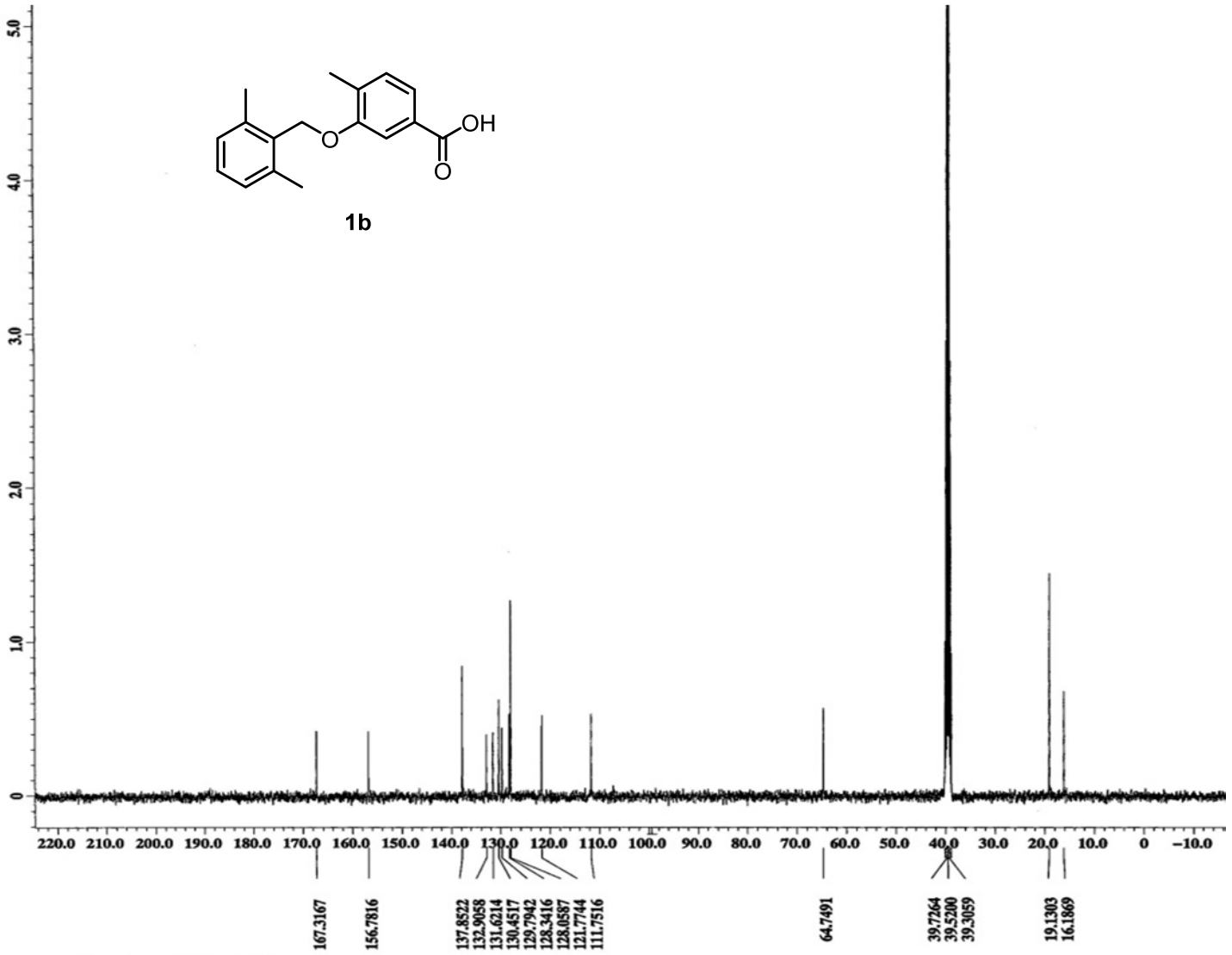



O
O
O
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
167.3272
157.3197
138.2908
133.0921
132.9621
130.5845
128.9943
128.5967
128.3521
122.1671
111.6397
77.4811
77.1600
76.8389
65.0500
52.1297
19.6683
16.7020

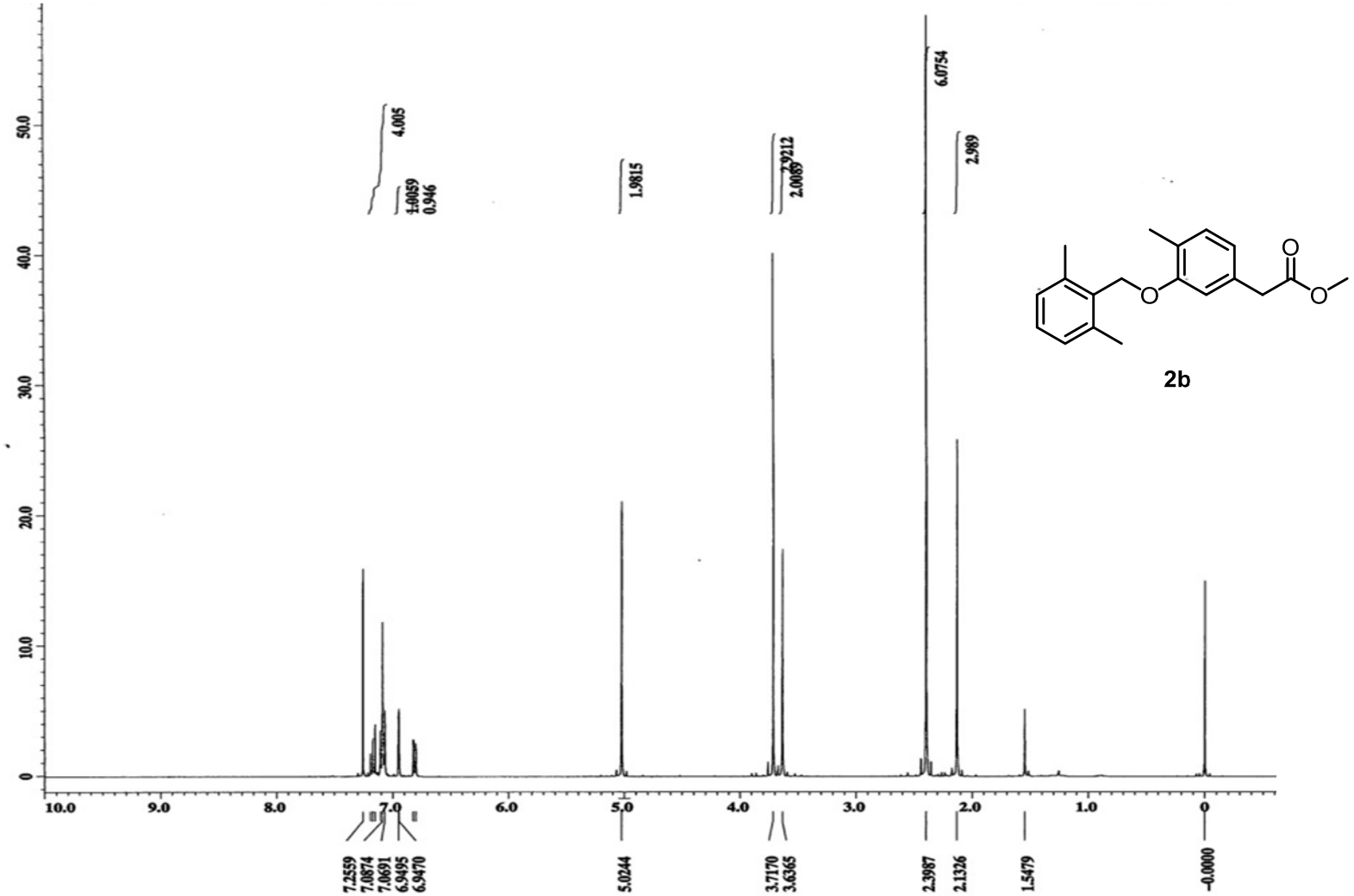
S-1

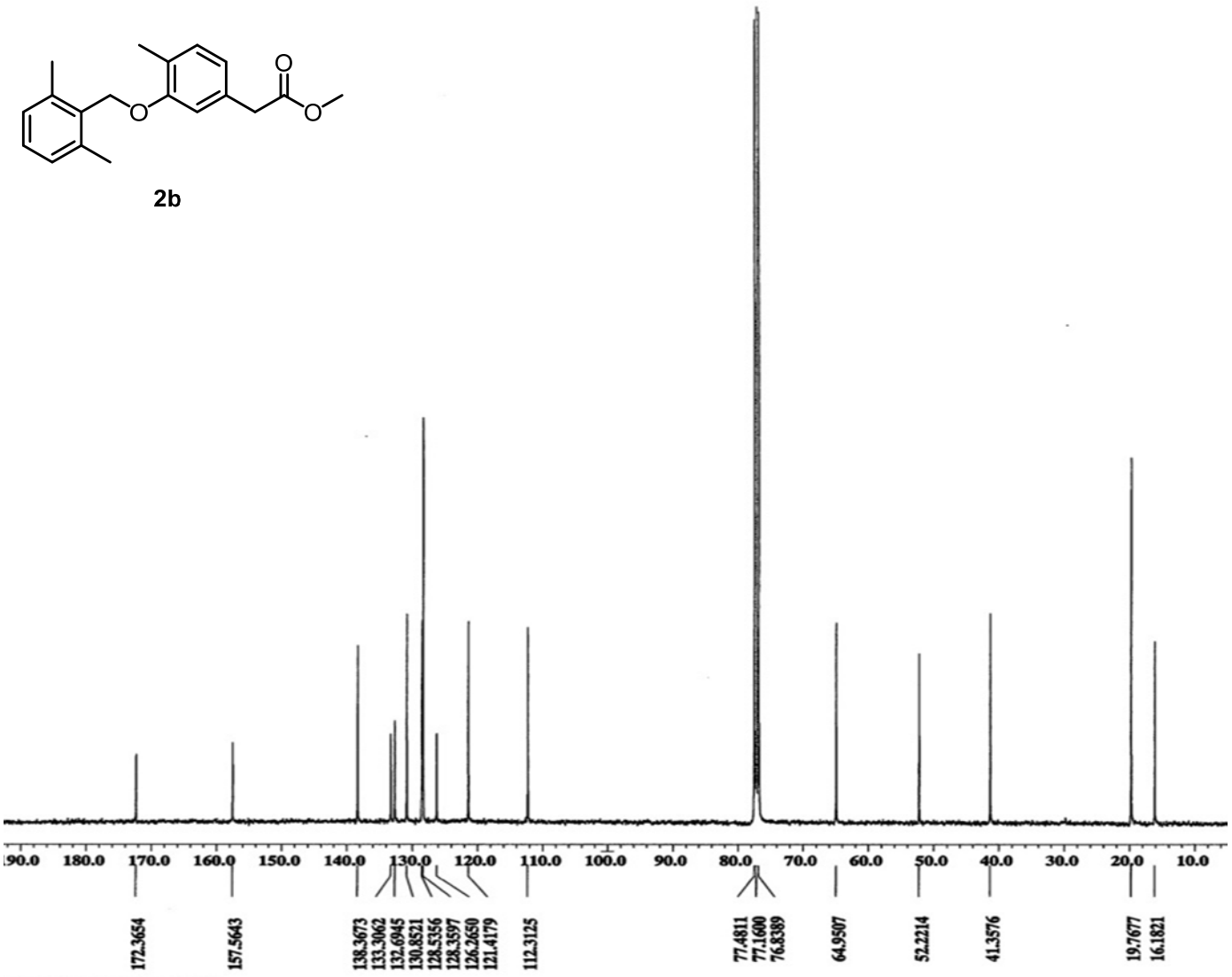
3-{(2,6-Dimethylbenzyl)oxy}-4-methylbenzoic acid (**1b**)



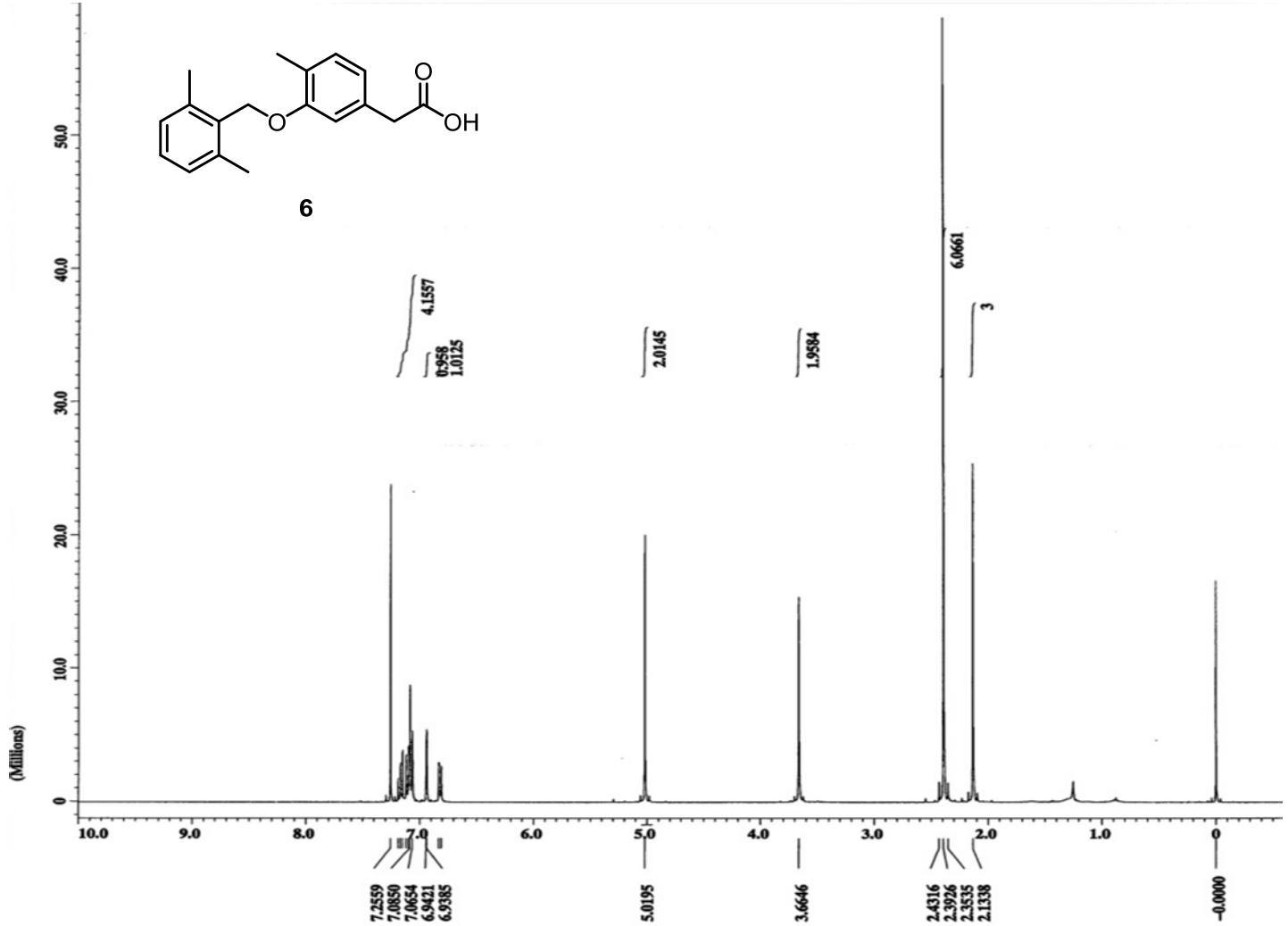

OH
O
O
1b
5.0
4.0
3.0
2.0
1.0
0
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 −10.0
167.3167
156.7816
137.8522
132.9058
131.6214
130.4517
129.7942
128.3416
128.0587
121.7744
111.7516
64.7491
39.7264
39.5200
39.3059
19.1303
16.1869

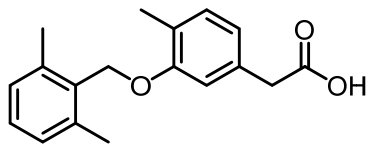
Methyl 2-[3-{(2,6-dimethylbenzyl)oxy}-4-methylphenyl]acetate (**2b**)




O
O
O
2b
90.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
172.3654
157.5643
138.3673
133.3062
132.6945
130.8521
128.5356
128.3597
126.2650
121.4179
112.3125
77.4811
77.1600
76.8389
64.9507
52.2214
41.3576
19.7677
16.1821

2-[3-{(2,6-Dimethylbenzyl)oxy}-4-methylphenyl]acetic acid (**6**)




O
O
OH

6

190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
177.9311
157.5949
138.3673
133.2374
131.9836
130.9285
128.5432
128.3597
126.5708
121.5402
112.3966
77.4811
77.1600
76.8389
64.9507
41.2277
19.7600
16.1897

References

[1] Y. Mifune, S. Fuse, H. Tanaka, *J. Flow Chem.* **2014**, *4*, 172.

[2] D. M. Haddleton, H. S. Sahota, P. C. Taylor, S. G. Yeates, *J. Chem. Soc., Perkin Trans. 1* **1996**, 649.

[3] S. Elzner, D. Schmidt, D. Schollmeyer, G. Erkel, T. Anke, H. Kleinert, U. Förstermann, H. Kunz, *ChemMedChem* **2008**, *3*, 924.