Organic Syntheses

Trichloroboron-promoted Deprotection of Phenolic Benzyl Ether Using Pentamethylbenzene as a Non Lewis-Basic Cation Scavenger

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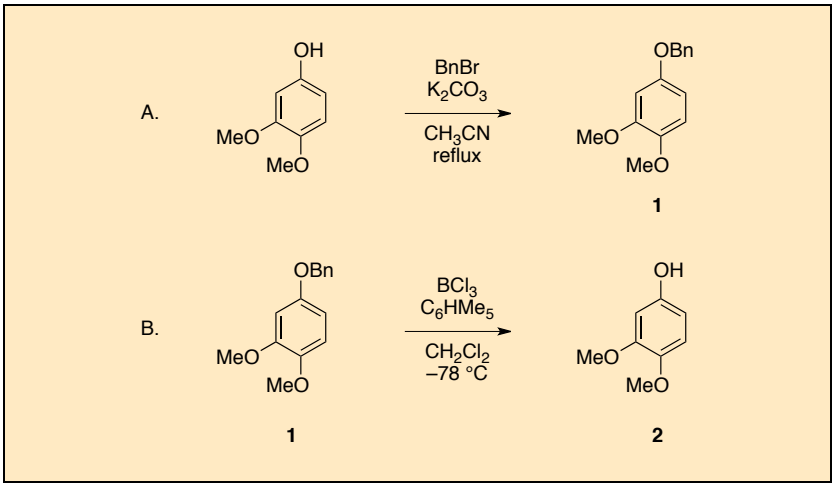
Checked by Brandon Nelson, Nicholas Garcia, and Mohammad Movassaghi



Procedure

A. *4-Benzyloxy-1,2-dimethoxybenzene (**1**).* A 500-mL one-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar (3.5 x 1.0 cm), with an argon gas inlet is charged with 3,4-dimethoxyphenol (8.32 g, 54.0 mmol) (Note 1), potassium carbonate (8.29 g, 60.0 mmol, 1.11 equiv) (Note 2), and is fitted with a reflux condenser with an argon gas inlet. MeCN (95 mL) (Note 3) is added to the reaction flask. After stirring for

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10 min at ambient temperature, benzyl bromide (6.54 mL, 55.0 mmol, 1.02 equiv) (Note 4) is added. The reflux condenser is washed with MeCN (5 mL) and the resulting mixture is stirred for 20 min. Then, the reaction mixture is heated to reflux for 2 h (Note 5). The mixture is cooled to ambient temperature, and filtered through a 2 cm pad of Celite; the transfer is completed by washing the reaction flask with EtOAc (2 x 25 mL). The filtrate is concentrated on a rotary evaporator under reduced pressure (30 °C, 8 mmHg) and dried in vacuo (2.5 mmHg) to afford 13.95 g of a crude benzyl ether as an orange solid, which is purified by silica gel column chromatography (elution: 15% EtOAc in hexanes) (Note 6) to provide 4-benzyloxy-1,2-dimethoxybenzene (**1**) as colorless crystals (11.90 g, 90%) (Notes 7, 8, and 9).

B. *3,4-Dimethoxyphenol* (**2**). A 1-L oven-dried three-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar (3.5 x 1.0 cm), a rubber septum, a glass stopper, and an argon gas inlet is charged with 4-benzyloxy-1,2-dimethoxybenzene (**1**) (7.33 g, 30.0 mmol), pentamethylbenzene (13.34 g, 90.0 mmol, 3.0 equiv) (Note 10), and anhydrous CH_2Cl_2 (150 mL) (Note 11) (**Figure 1**). After the reaction mixture

Figure 1. Apparatus assembly for Step B

is cooled to –78 °C (bath temperature), 1 M boron trichloride in CH_2Cl_2 (60.0 mL, 60.0 mmol, 2.0 equiv) (Note 12) is added to the flask dropwise over 5 min at –78 °C. After stirring for 45 min at –78 °C, the mixture is quenched by syringe addition of chloroform/methanol (10/1, 60.0 mL) (Note 13) at –78 °C and is warmed to ambient temperature. The solution is concentrated on a rotary evaporator under reduced pressure (30 °C, 8 mmHg), and dried *in vacuo* (2.5 mmHg) to afford 24.58 g of a crude phenol as a pale yellow solid, which is purified by silica gel column chromatography (elution: 30% EtOAc, 5% toluene, 65% hexanes) (Notes 14 and 15). The fraction containing the product are collected and concentrated on a rotary evaporator under reduced pressure to yield 3,4-dimethoxyphenol (**2**) as pale yellow crystals (4.22 g, 91.2%) (Notes 16 and 17).

Notes

1. 3,4-Dimethoxyphenol (96%) was purchased from Tokyo Chemical Industry Co., Ltd. and used as received without further purification.
2. Potassium carbonate (99%, powdered, ~325 mesh) was purchased from Sigma-Aldrich Co. and used as received without further purification.
3. Acetonitrile (>99.5%) was purchased from Wako Pure Chemical Industries, Ltd. and used as received without further purification.
4. Benzyl bromide (>98%) was purchased from Wako Pure Chemical Industries, Ltd. and used as received without further purification.
5. The reaction typically requires 2 h to complete and is monitored by TLC analysis on Merck silica gel 60 F_{254} plates eluting with EtOAc/hexanes (1:1). The R_f values of the phenol and benzyl ether are 0.33 and 0.65, respectively (visualized with 254 nm UV lamp and stained with an ethanol solution of *p*-anisaldehyde. After dipping the TLC plate to the solution, the chromatogram is stained by heating.
6. The crude material is dissolved in eluent (20 mL) and CH_2Cl_2 (5 mL) and is charged onto a column (diameter = 10 cm, height = 20 cm) of 400-gram silica gel. The column was eluted with 15% EtOAc/hexanes and 75-mL fractions were collected. Fraction 19-29 were combined and concentrated on a rotary evaporator under reduced pressure.
7. When the reaction was performed on half-scale, the isolated yield was 5.70 g (86%).

8. If crystallization is desired after chromatography, the residue is dissolved in hot EtOAc/hexanes, 1:3 (40 mL) using an oil bath (bath temperature: 95 ℃). The solution is then cooled at 0 ℃ in an ice bath for 30 min. The colorless crystals are collected by filtration (78~86%).
9. The compound (purified by chromatography) exhibits the following physicochemical properties: R_f = 0.65 (hexanes/EtOAc = 1:1); Merck silica gel 60 F_{254} plates (visualized with 254 nm UV lamp and stained with an ethanol solution of *p*-anisaldehyde. After dipping the TLC plate to the solution, the chromatogram is stained by heating); mp 48–48.5 °C (EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}): 2936, 1596, 1509, 1450, 1280, 1227, 1196, 1159, 1137, 731; ^1H NMR (500 MHz, $CDCl_3$) δ: 3.84 (s, 3H), 3.85 (s, 3H), 5.02 (s, 2H), 6.48 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.61 (d, *J* = 2.8 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 7.33 (app-t, *J* = 7.2 Hz, 1H), 7.40 (app-t, *J* = 7.4 Hz, 2H), 7.44 (app-d, *J* = 6.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 56.5, 57.1, 71.3, 101.9, 104.7, 112.4, 128.3, 128.7, 129.3, 137.8, 144.3, 150.5, 154.1. [M + H] calcd. for $C_{15}H_{16}O_{3:}$: 245.1172, Found: 245.1163. Anal. calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.51; H, 6.59.
10. Pentamethylbenzene (>99%) was purchased from Tokyo Chemical Industry Co., Ltd. and used as received without further purification.
11. CH_2Cl_2 (>99.5% anhydrous, water content: <0.001%) was purchased from Kanto Chemical Co., Inc. and used as received without further purification.
12. Boron trichloride 1.0 M in CH_2Cl_2 was purchased from Sigma-Aldrich Co. and used as received without further purification.
13. The reaction typically requires 30 min to consume all the 3,4-dimethoxyphenol-1-benzyl ether and is monitored by TLC analysis on Merck silica gel 60 F_{254} plates eluting with EtOAc/hexanes (1:1). The R_f values of the starting material, the undesired 2-benzyl-4,5-dimethoxyphenol, the desired 3,4-dimethoxyphenol are 0.65, 0.40, and 0.33, respectively (visualized with 254 nm UV lamp and stained with an solution of *p*-anisaldehyde. After dipping the TLC plate to the solution, the chromatogram is stained by heating).
14. Integration of the ^1H NMR spectra of the crude material indicated that the molar ratio of desired phenol: benzylpentamethylbenzene: pentamethylbenzene = 1:1.07: 2.20. The crude material is dissolved in eluent (15 mL) and then charged onto a column (diameter = 8 cm, height = 35 cm) of 400-gram silica gel. The column is eluted with 30% EtOAc, 5% toluene, 65% hexanes and 100-mL fractions are collected. Fractions 1-16 contain pentamethylbenzene and

benzylpentamethylbenzene. Fractions 36-42 and 45-60 are combined and concentrated on a rotary evaporator under reduced pressure to provide undesired 2-benzyl-4,5-dimethoxyphenol and desired 3,4-dimethoxyphenol, respectively. Benzylpentamethylbenzene: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.17 (s, 3H x 2), 2.25 (s, 3H x 2), 2.27 (s, 3H), 4.11 (s, 2H), 7.04 (d, *J* = 7.2 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.21-7.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.83, 16.85, 16.9, 36.1, 125.6, 127.9, 128.3, 132.5, 132.8, 133.1, 133.8, 140.62.

15. Undesired 2-benzyl-4,5-dimethoxyphenol is obtained as a colorless oil (595 mg, 8%). Its physicochemical properties are as follows: R_f = 0.40 (EtOAc/hexanes = 1:1); Merck silica gel 60 F_{254} plates (visualized with 254-nm UV lamp and stained with an ethanol solution of $Ce_2(SO_4)_3$ and phosphomolybdic acid (Ce-PMA). After dipping the TLC plate to the Ce-PMA solution, the chromatogram is stained by heating); IR (neat, cm^{-1}): 3442, 2935, 1617, 1521, 1451, 1414, 1204, 1109, 998, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.80 (s, 3H), 3.83 (s, 3H), 3.93 (s, 2H), 4.34 (s, 1H), 6.45 (s, 1H), 6.66 (s, 1H), 7.17–7.24 (m, 3H), 7.26–7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.8, 55.8, 56.6, 101.3, 114.6, 117.8, 126.2, 128.4, 128.5, 140.1, 142.9, 147.8, 148.3; HRMS (ESI). $[M + Na]^+$ calcd. for $C_{15}H_{16}NaO_3$: 267.0992. Found: 267.0988; Anal. calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 72.99; H, 6.65. (The yields and data were provided by the submitters. This byproduct was not characterized by the checkers).
16. When the reaction was performed on half-scale, the isolated yield was 2.09 g (90%).
17. Desired 3,4-dimethoxyphenol is obtained as pale yellow crystals (4.22 g, 91.2%). The compound exhibits the following physicochemical properties: R_f = 0.33 (EtOAc/hexanes = 1:1); Merck silica gel 60 F_{254} plates (visualized with 254-nm UV lamp and stained with an solution of *p*-anisaldehyde. After dipping the TLC plate in the solution, the plate is stained by heating); mp 75.5–76.5 °C (hexanes/EtOAc); IR (neat, cm^{-1}): 3418, 2937, 2835, 1604, 1507, 1455, 1434, 1219, 1194, 1154, 1022, 950, 764; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.77 (s, 3H), 3.80 (s, 3H), 6.35 (dd, *J* = 8.6, 2.8 Hz), 6.46 (d, *J* = 2.8 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.5, 57.5, 101.4, 106.7, 113.2, 143.6, 150.5, 151.0; [M + H] calcd. for $C_8H_{10}O_3$: 155.0703 Found: 155.0707. Anal. calcd. for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.42; H, 6.51.

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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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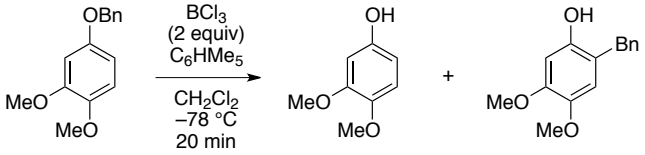
Discussion

The benzyl group is one of the most useful protective groups for a phenolic hydroxy group since phenol benzyl ethers are easily synthesized and tolerate various reaction conditions.[2] Deprotection of a benzyl group is generally performed by palladium-catalyzed hydrogenolysis or acidic treatment. However, these methods are inapplicable for a substrate having an olefinic/acetylenic moiety and acid-labile functional groups. During our

synthetic studies on yatakemycin having electron-rich aromatic rings and a thiol ester, we determined that a combination of BCl_3 and pentamethylbenzene (C_6HMe_5) facilitated smooth debenzylation even at −78 °C[3] by modifying Yoshino's conditions using TFA and C_6HMe_5.[4] Pentamethylbenzene is a non-Lewis-basic cation scavenger and does not reduce Lewis acidity of BCl_3 by coordination, unlike general cation scavengers such as PhSMe or Me_2S that have lone electron pairs as a Lewis base.[5] In addition, benzylpentamethylbenzene[4,6] has low polarity, thus easily separated with the desired phenol by column chromatography (see Note 14).

Table 1. Effect of Pentamethylbenzene to Suppress Undesired Migration of Benzyl Group



1 **2** **3**

entry	C_6HMe_5 (equiv)	**2** (%)[a]	**3** (%)[a]
1	0	56	43
2	2	81	11
3	3	84	8
4	5	85	8

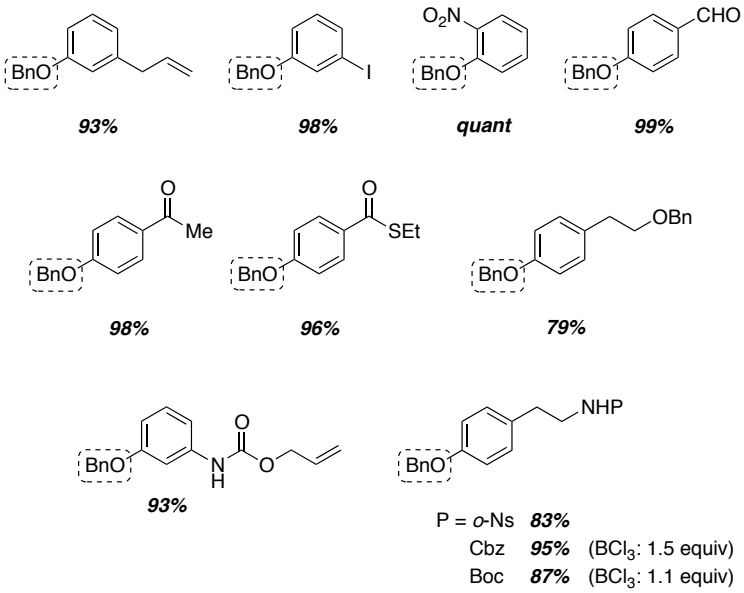
[a] Isolated yields.

The effectiveness of C_6HMe_5 was examined through a control experiment using 4-benzyloxy-1,2-dimethoxybenzene (**1**) as a substrate (Table 1). Thus, in the absence of pentamethylbenzene, a substantial amount of the undesired product **3** was obtained via electrophilic *C*-benzylation (entry 1). After an extensive optimization of C_6HMe_5 equivalents, we determined that three C_6HMe_5 equivalents were sufficient to suppress the formation of an undesired product.

The deprotection conditions were applicable to a series of phenol benzyl ethers (Table 2). Allyl, iodo, nitro, formyl, acetyl, and thiol ester groups remained intact in this reaction. Selective removal of the benzyl group was

also accomplished in the presence of aliphatic benzyl ether, Alloc carbamate, *o*-Ns amide, Cbz carbamate, and Boc carbamate to provide the corresponding phenols in good to excellent yields.[5] In addition, the less polar benzylpentamethylbenzene as a co-product was easily removed by column chromatography.

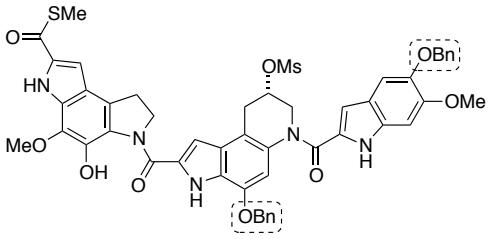
Table 2. Debenzylation of Various Aryl Benzyl Ethers



Debenzylation is used in the synthesis of natural products and highly functionalized complex molecules (Table 3). In the total synthesis of yatakemycin, we performed the removal of the two benzyl groups with the labile thiol ester intact.[3] At the later stage in the synthesis of haplophytine, we performed the deprotection of a Cbz carbamate in the presence of α,β-unsaturated imine.[7] Nicolaou and Chen also employed the conditions to a similar substrate and successfully removed both benzyl and Cbz groups.[8] Erhardt performed the deprotection of the two benzyl groups in the final step of the total synthesis of (±)-vestitol and bolusanthin III.[9] They also provided a comment on this step that conventional conditions such as pentamethylbenzene/trifluoroacetic acid[4] and boron tribromide proved to

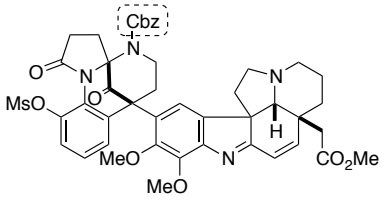
be very harsh, resulting in decomposition of the starting material. Vogel performed a selective deprotection of a benzyl group in the synthesis of polypropionates.[10] Interestingly, they successfully discriminated two benzyl groups according to their electron densities; the more electron-rich benzyl group was removed faster than the other benzyl group bearing the CF_3 group. In addition, *exo*-methylene and enol benzoate remained unreacted after the reaction. Kobayashi and co-workers applied the conditions to remove aliphatic benzyl ethers by replacing BCl_3 with BBr_3.[11] Acid-labile and easily reduced triene remained intact under the conditions to provide the corresponding pentaol in 59% yield.

Table 3. Application of the Mild Deprotection Conditions



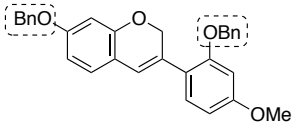
83%

Fukuyama and Tokuyama *et al.*[3]



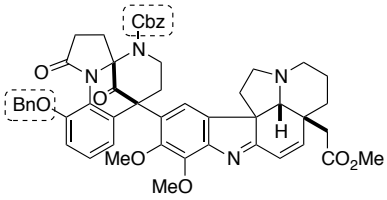
67%

Tokuyama and Fukuyama *et al.*[6]



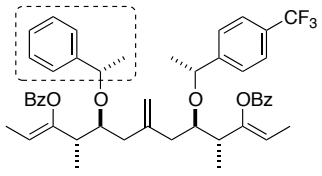
61%

Erhardt *et al.*[8]



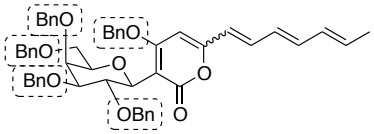
58%

Nicolaou and Chen *et al.*[7]



76%

Vogel *et al.*[9]



59% (BBr_3 was used instead of BCl_3)

Kobayashi *et al.*[10]

References

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

3,4-Dimethoxyphenol: Phenol, 3,4-dimethoxy-; (2033-89-8)
Benzyl bromide: Benzene, (bromomethyl)-; (100-39-0)
Potassium carbonate: Carbonic acid, potassium salt (1:2); (584-08-7)
Acetonitrile: Acetonitrile; (75-05-8)
Trichloroborane: Borane, trichloro-; (10294-34-5)
Pentamethylbenzene: Benzene, 1,2,3,4,5-pentamethyl-; (700-12-9)
Dichloromethane: Methane, dichloro-; (75-09-2)

Shun Okaya was born in Shizuoka in 1990. He received his B.S. in 2013 from the Faculty of Pharmaceutical Sciences, Tohoku University, where he carried out undergraduate research in the laboratories of Professor Hidetoshi Tokuyama. In the same year, he then began his graduate studies at the Graduate School of Pharmaceutical Sciences, Tohoku University under the supervision of Professor Hidetoshi Tokuyama. His research focuses on the total synthesis of epidithiodiketopiperazine natural products.
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Keiichiro Okuyama received his B.S. in 2006 from Tohoku Pharmaceutical University, where he carried out undergraduate research under the supervision of Professor Tadashi Kato. He then moved to the laboratories of Professor Hidetoshi Tokuyama, Tohoku University and started his Ph.D. research on synthetic studies toward Haouamine B. In 2011, he received his Ph.D. from Tohoku University under the direction of Professor Hidetoshi Tokuyama. He is currently working for Astellas Pharma Inc. as a drug discovery researcher.

Kentaro Okano was born in Tokyo in 1979. He received his B.S. in 2003 from Kyoto University under the supervision of Professor Tamejiro Hiyama. He then moved to the laboratories of Professor Tohru Fukuyama at the University of Tokyo. In 2007, he joined the faculty at Tohoku University, where he is currently an assistant professor in Professor Hidetoshi Tokuyama's group. In 2014, he visited Professor Amir Hoveyda's laboratories at Boston College as a visiting researcher. His current research interest is natural product synthesis based on the development of new synthetic methodologies.
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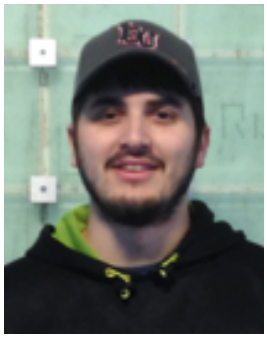
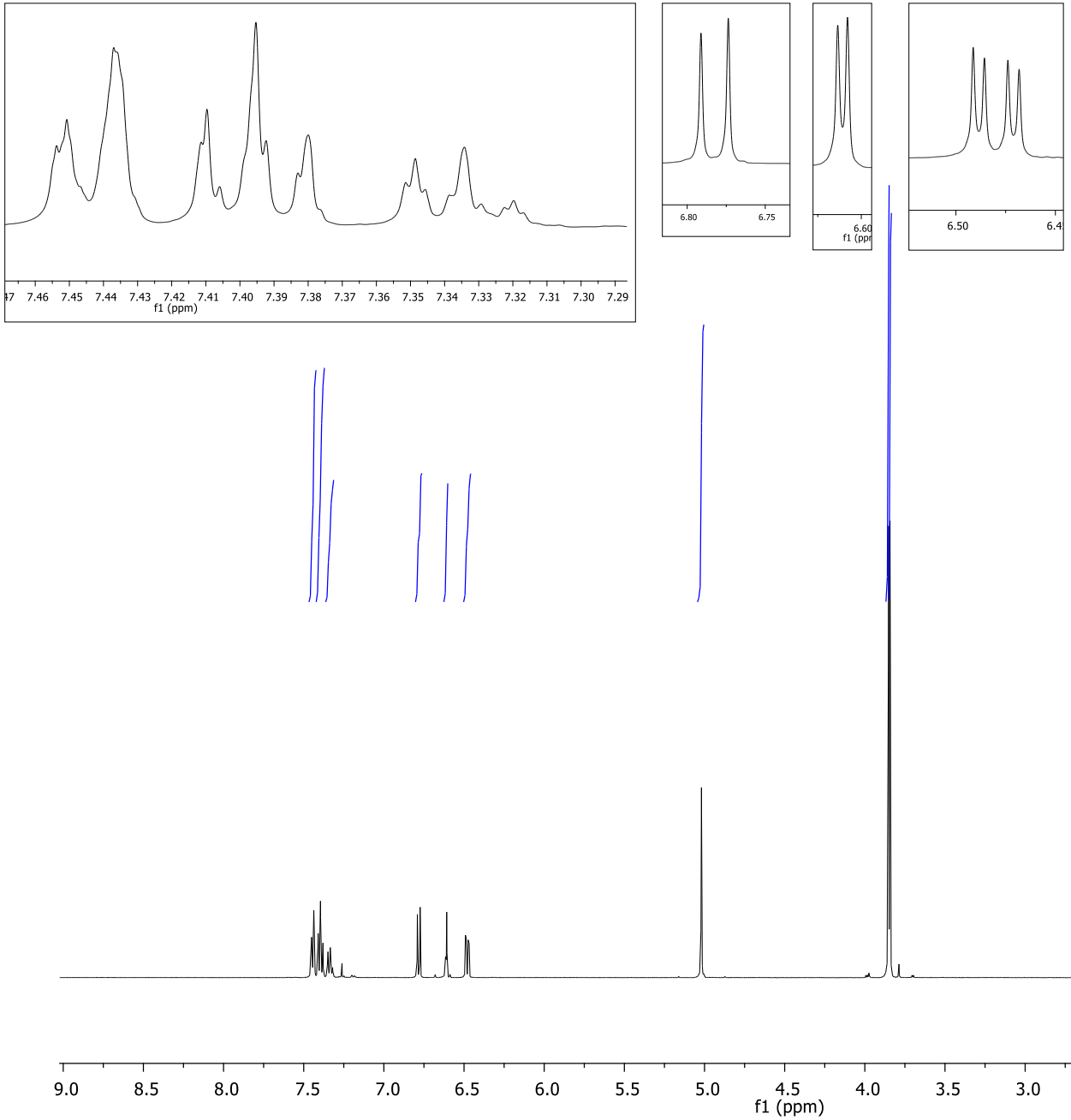
Hidetoshi Tokuyama was born in Yokohama in 1967. He received his Ph.D. in 1994 from Tokyo Institute of Technology under the direction of Professor Ei-ichi Nakamura. He spent one year (1994-1995) at the University of Pennsylvania as a postdoc with Professor Amos B. Smith, III. He joined the group of Professor Tohru Fukuyama at the University of Tokyo in 1995 and was appointed Associate Professor in 2003. In 2006, he was move to Tohoku University, where he is currently Professor of Pharmaceutical Sciences His research interest is on the development of synthetic methodologies and total synthesis of natural products.



Brandon Nelson was born in Streamwood, Illinois in 1991. He received his B.S. in 2013 from Illinois State University where he carried out research in the labs of Professor Hitchcock and Professor McLauchlan. He then moved to the Massachusetts Institute of Technology to pursue his Ph.D. focused on complex natural products total synthesis under the advisement of Professor Movassaghi.

Nicholas Garcia was born in Oklahoma City, Oklahoma in 1994. In 2013, he began working towards his B.S. in Chemistry at the Massachusetts Institute of Technology. In 2015, he joined the laboratories of Professor Mohammad Movassaghi, where he is currently carrying out undergraduate research focused on alkaloid total synthesis.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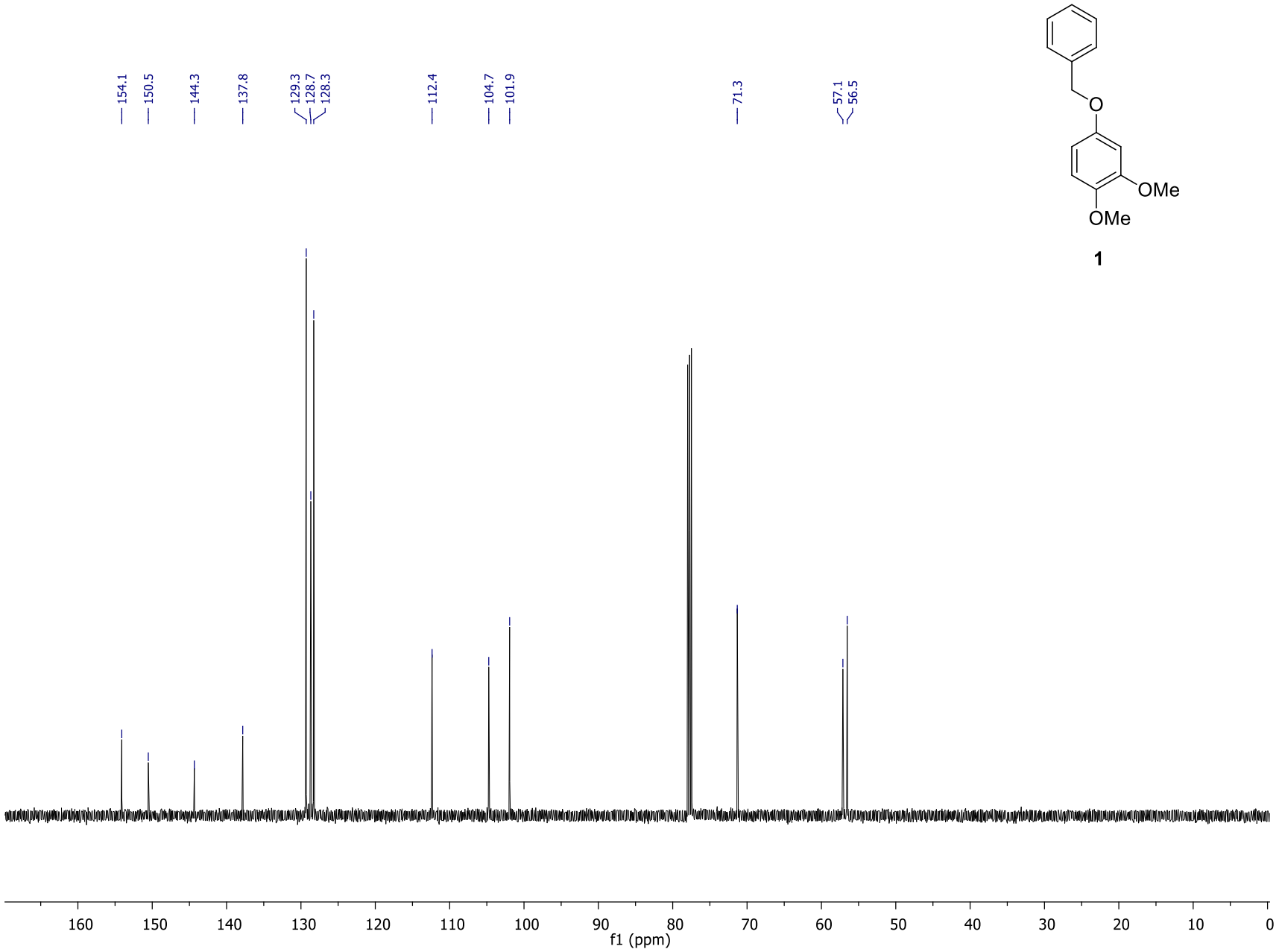
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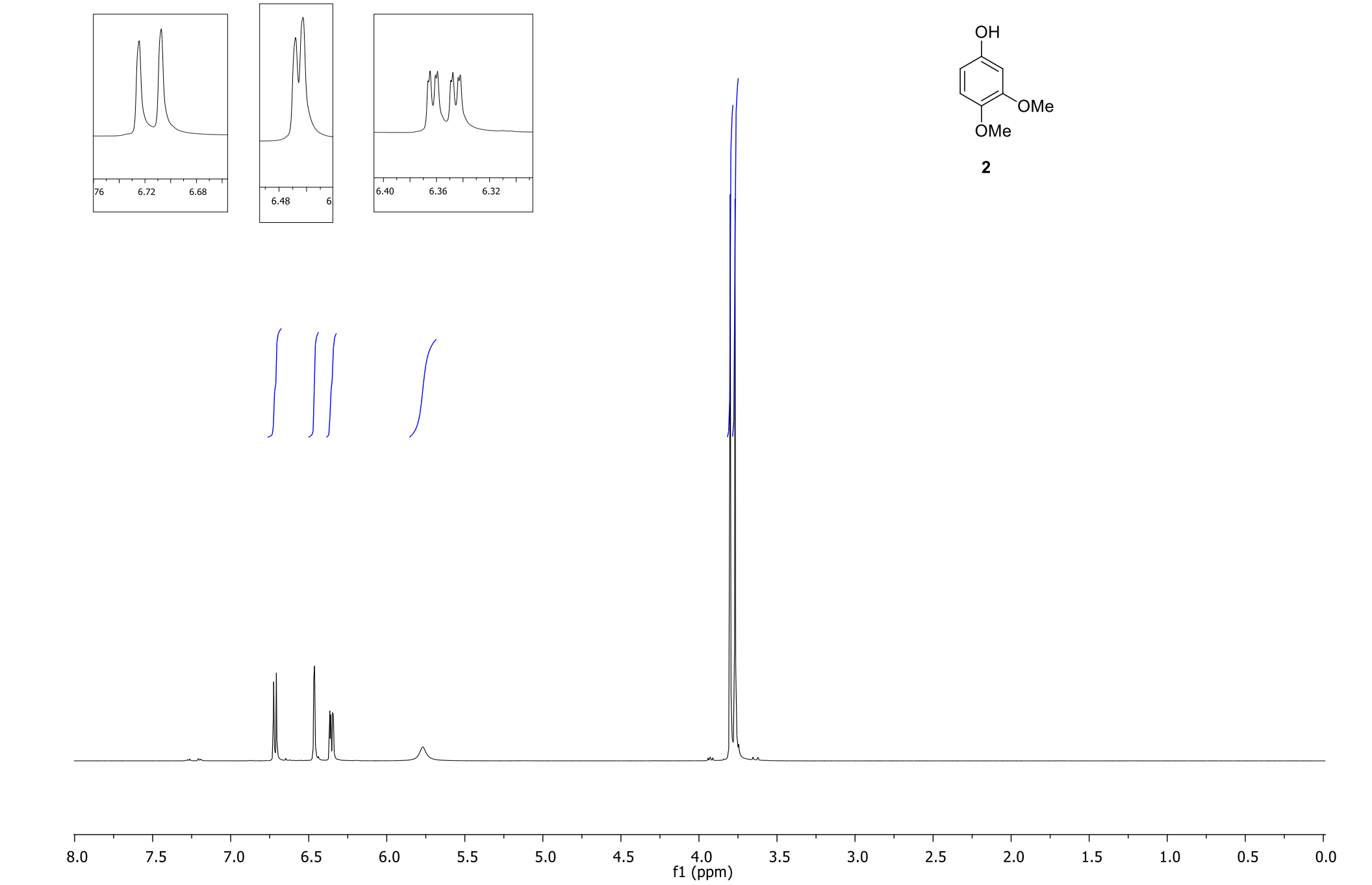
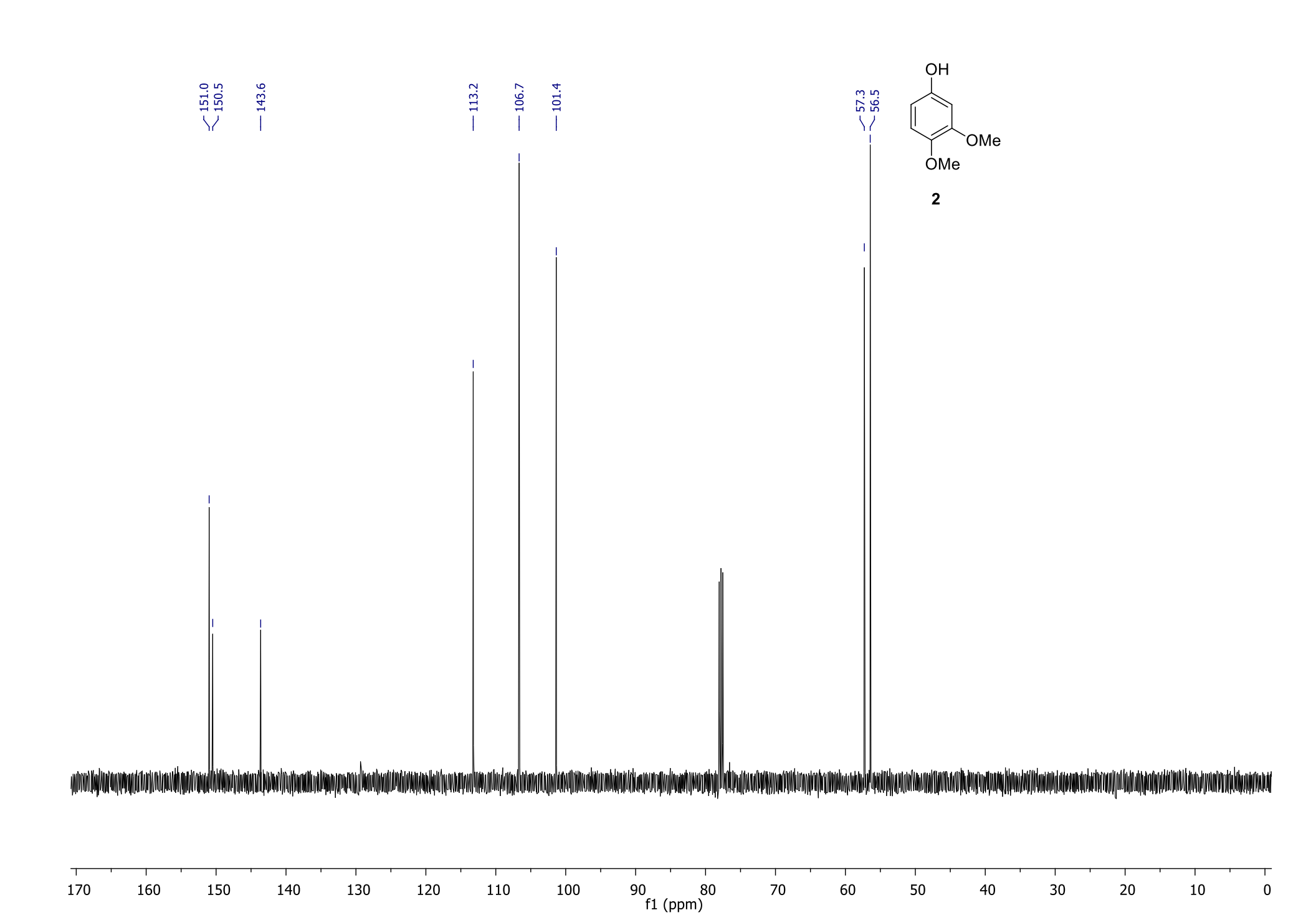
f1 (ppm)

1


6.76
6.72
6.68
6.48
6.40
6.36
6.32
OH
OMe
OMe
2
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


151.0
150.5
143.6
113.2
106.7
101.4
57.3
56.5
OH
OMe
OMe
2
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)