Organic Syntheses

Enantioselective Synthesis of α-Bromonitroalkanes for Umpolung Amide Synthesis: Preparation of *tert*-Butyl ((1*R*)-1-(4-(benzyloxy)phenyl)-2-bromo-2-nitroethyl)carbamate

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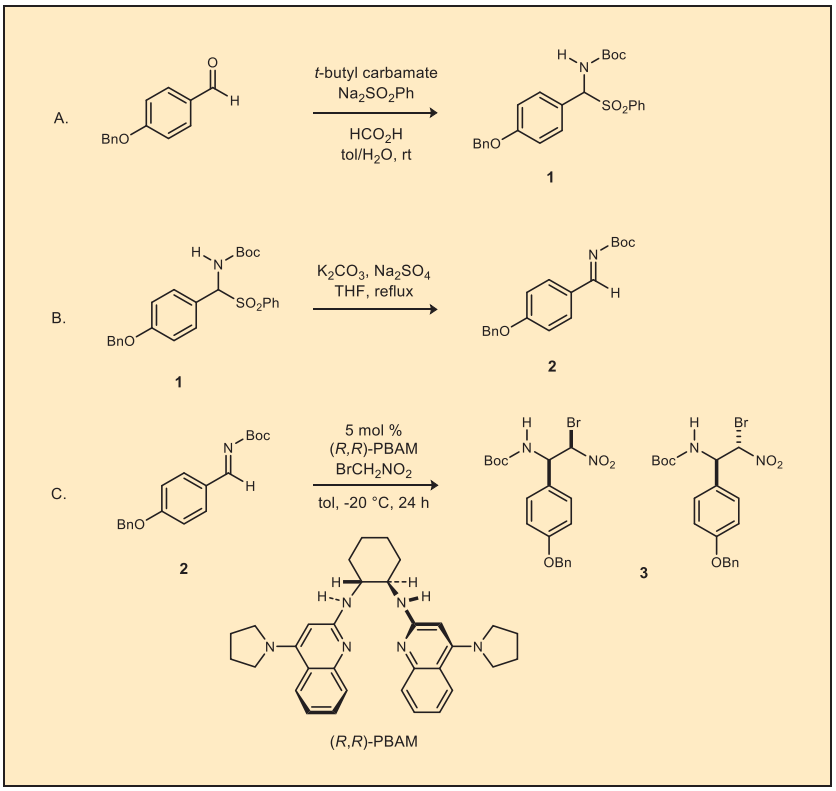
Checked by Fabian Konrad, Estíbaliz Merino and Cristina Nevado



Procedure

Caution! Bromonitromethane is a strong oxidizing agent with properties similar to nitromethane. Keep away from heat and avoid mixing with combustible materials.

A. *tert-Butyl ((4-(benzyloxy)phenyl)(phenylsulfonyl)methyl)carbamate* (***1***). A 500-mL round-bottomed flask (29/32 neck) is equipped with a teflon-coated, egg-shaped stir bar (30 x 16 mm). The flask is charged with 4-benzyloxybenzaldehyde (10.0 g, 47.1 mmol, 1.2 equiv) and *tert*-butyl carbamate (4.60 g, 39.3 mmol, 1.0 equiv) (Note 1), then toluene (157 mL) (Note 2) is added, and the mixture is stirred until homogeneity is achieved. Benzenesulfinic acid sodium salt dihydrate (12.9 g, 64.4 mmol, 1.6 equiv) (Note 3) is introduced and then water (33 mL) is slowly added until the salt is completely dissolved. The flask is fitted with a rubber septum and an argon inlet needle. Formic acid (2.84 mL, 75.3 mmol, 2.0 equiv) (Note 4) is added, and the reaction is stirred for one week at room temperature (Note 5) Figure 1). The suspension is filtered through a Büchner funnel (7 cm diameter), fitted with filter paper. The reaction flask is rinsed with ether (2 x 100 mL and 1 x 50 mL) (Note 6) and the solid is soaked with the rinsates (2 x 100 mL and 1 x 50 mL) at room temperature for 30 min (Note 7). The suspension is stirred with a spatula every 5 min. Reduced pressure is used to facilitate the filtering process. The resulting crude product is

Figure 1. Initial appearance of Step A, appearance after 44 h, and appearance after 1 week.

transferred to a 500 mL Erlenmeyer flask. Residual solid is washed from the filter with dichloromethane (50 mL) (Note 8). Additional dichloromethane (200 mL) is added, and the flask is stirred until the crude product is fully dissolved. The resulting solution is dried over $MgSO_4$ (17.0 g) (Note 9), then filtered through a 350-mL fritted filter funnel into a pre-weighed 500-mL round-bottomed flask. The flask and the filter were rinsed with additional dichloromethane (2 x 50 mL). The dichloromethane solution is concentrated by rotary evaporation (40 °C, 23 mmHg) and further dried under vacuum (1-2 mmHg) for at least 10 h to leave 9.45–9.98 g of a white solid (Notes 7 and 10). The solid is used in step B without further purification.

B. *(E)-tert-Butyl 4-(benzyloxy)benzylidenecarbamate (**2**).* A 500-mL round-bottomed flask (29/32 neck) is equipped with a teflon-coated, egg-shaped stir bar (30 x 16 mm) (Note 11), charged with K_2CO_3 (18.2 g, 131.7 mmol, 6.0 equiv) and Na_2SO_4 (22.5 g, 158.3 mmol, 7.2 equiv) (Note 12). Sulfone (**1**) (9.97 g, 22.0 mmol) (Note 7) and THF (235 mL) (Note 13) were added. A condenser is attached to the reaction vessel, and the system is placed under an argon atmosphere. The reaction vessel is placed in an oil bath (85 °C), and heated to reflux for 3 h. The resulting mixture is cooled to room temperature (25 °C) and filtered through Celite® (1 inch layer) (Note 14) using a 350-mL fritted-filter funnel, washed with diethyl ether (2 x 100 mL) (Note 6) and additional diethyl ether (2 x 50 mL) is used to rinse residual material from the reaction vessel. The clear, colorless solution is collected in a pre-weighed 500-mL round-bottomed flask and concentrated by rotary evaporation (40 °C, 23 mmHg). The resulting product is further dried under vacuum (1-2 mmHg) to afford a white solid (6.80–6.94 g) (Note 15), which is used in step C without further purification (Note 16).

C. *tert-Butyl ((1R)-1-(4-(benzyloxy)phenyl)-2-bromo-2-nitroethyl)carbamate (**3**).* A 250-mL round-bottomed flask (29/32 neck) equipped with a teflon-coated, egg-shaped stir bar (30 x 16 mm) (Note 17), a rubber septum, and an argon inlet needle is charged with imine (**2**) (6.80 g, 21.9 mmol), toluene (120 mL) (Note 18), and (1*R*,2*R*)-N^1,N^2-bis[4-(1-pyrrolidinyl)-2-quinolinyl]-1,2-cyclohexanediamine, ((*R*,*R*)-PBAM) (0.54 g, 1.10 mmol, 0.05 equiv) (Note 19). The reaction vessel is placed under argon atmosphere and the solution is cooled to –20 °C (Note 20) followed by the addition of bromonitromethane (1.81 mL, 26.1 mmol, 1.2 equiv) (Note 21). The reaction mixture is stirred at –20 °C for 24 h and the resulting yellow-orange solution (Figure 2) is concentrated using rotary evaporation (40 °C, 23 mmHg).

The product is redissolved in 50 mL of hot ethyl acetate (Note 22), filtered through a silica plug (Note 23), and washed with additional hot

ethyl acetate (3 x 100 mL) into a 1000-mL receiving flask. The resulting clear, light yellow solution is concentrated by rotary evaporation (40 °C, 23 mmHg) and is dried under vacuum (1-2 mmHg) for 1 h. The resulting white solid is then transferred to a 50-mL Erlenmeyer flask and redissolved

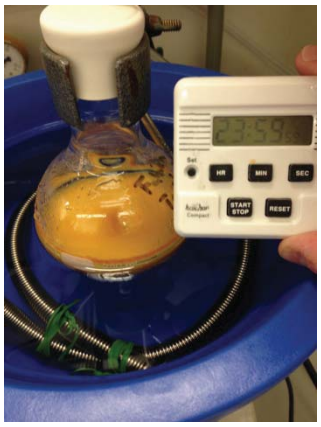


Figure 2. Appearance of Step C after 24 h.

in hot ethyl acetate (ca. 30 mL). The solution is allowed to slowly cool to room temperature before it is placed in an ice-water bath. After 1 h the resulting crystals were vacuum filtered through a Büchner funnel (5 cm diameter). The crystallized product is washed with ice-cold ethyl acetate on the filter. The mother liquor and crystal washings were concentrated and subjected to the same recrystallization procedure twice to obtain additional product. The solid is transferred to a 100-mL round-bottomed flask and dried under vacuum (1-2 mmHg) to leave the product **3** as a 1.2:1 mixture of diastereoisomers (6.26–7.52 g, 34–40% overall yield) (Notes 25).

Notes

1. 4-Benzyloxyaldehyde (98%) was purchased from Alfa Aesar and *tert*-butyl carbamate (98%) was purchased from Sigma-Aldrich.
2. Toluene (99.9%) was purchased from Fisher Scientific Company and used as received.

3. Benzenesulfinic acid sodium salt dihydrate (97%) was purchased from Alfa Aesar. Benzene acid sodium salt anhydrous (Sigma Aldrich, 123579) also can be used with similar results.
4. Formic acid (≥95%) was purchased from Sigma-Aldrich.
5. A clear, pale yellow mixture was observed after addition of all reagents, and the product started to precipitate as a white solid after 1-2 h. By the second day, a thick white slurry of the product was formed.
6. Ethyl ether (99.9%) was purchased from Fisher Scientific Company and used as received.
7. The checkers observed more residual aldehyde (11-22%) than the submitters (<3%) by ^{1}H-NMR of the crude reaction mixture. The submitters note that the suflone is insoluble in ether, allowing fresh ether to be used to thoroughly soak and wash the solid during the filtration process.
8. Dichloromethane (99.9%) was purchased from Fisher Scientific Company and used as received.
9. Magnesium sulfate was purchased from Fisher Scientific Company and used as received.
10. Data of product **1**: R_f = 0.46 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (s, 9H), 5.09 (s, 2H), 5.74 (d, *J* = 10.6 Hz, 1H), 5.88 (d, *J* = 10.0 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.31–7.43 (m, 7H), 7.52 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 28.0, 70.1, 73.5, 81.2, 115.2, 122.0, 124.9, 127.4, 128.1, 128.6, 129.0, 129.4, 130.2, 133.8, 136.5, 137.0, 153.5, 160.0.
11. The apparatus with the salts was flame dried under reduced pressure (1-2 mmHg) and was allowed to cool to room temperature.
12. Potassium carbonate and sodium sulfate were purchased from Sigma-Aldrich and used as received.
13. Tetrahydrofuran (THF) was dried by passage through a column of activated alumina as described by Grubbs.[2]
14. Celite was purchased from Sigma-Aldrich and used as received.
15. The imine product was stored in a –78 °C freezer. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.59 (s, 9H), 5.13 (s, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 7.33–7.37 (m, 1H), 7.40–7.42 (m, 4H), 7.89 (d, *J* = 8.8 Hz, 2H), 8.89 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 27.9, 70.2, 81.9, 115.2, 127.1, 127.5, 128.2, 128.7, 132.5, 136.0, 162.8, 163.3, 169.6; IR (CH_2Cl_2): 1698, 1507, 1496, 1455, 1366, 1236, 1162, 1016, 881, 830, 735, 696 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$ 312.1594, found 312.1598.

16. The material was used as a reactant to prepare **3** and contained 3-16% of 4-benzyloxybenzaldehyde.
17. The flask was flame dried under reduced pressure (1-2 mmHg) and was allowed to cool to room temperature.
18. Toluene was dried by passage through a column of activated alumina as described by Grubbs.[2]
19. (*R*,*R*)-PBAM was prepared according to a published procedure.[4]
20. The reaction was cooled using a cryostat (at –20 °C) with an isopropanol bath.
21. Bromonitromethane (90%, tech.) was purchased from Sigma-Aldrich and used as received.
22. Ethyl acetate (99.9%) was purchased from Fisher Scientific Company and used as received.
23. A 350-mL fritted-glass funnel was packed with Celite® (1 inch layer) and silica gel (50 g).
24. A sample of racemic **3** can be prepared by stirring the imine and bromonitromethane in toluene with DMAP (10 mol%) for 10 min at room temperature, followed by its filtration through silica gel.
25. The enantiomeric excess of the major and minor diastereomers was determined to be 97% and 95% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1 mL/min, $t_r(d_1e_1$, major) = 15.6 min, $t_r(d_1e_2$, minor) = 19.33 min, $t_r(d_2e_2$, minor) = 20.4 min), $t_r(d_2e_1$, major) = 26.1 min. R_f = 0.38 (20% EtOAc/hexanes); mp = 149–151 °C; R_f = 0.38 (20% EtOAc/hexanes); IR (film) 3359, 1687, 1561, 1509, 1352, 1251, 1162, 1039, 1027, 834, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ: 1.45 (s, 9H), 1.46 (s, 9H), 5.05 (s, 2H), 5.06 (s, 2H), 5.38 (d, *J* = 9.2 Hz, 1H), 5.42 (br s, 1H), 5.57 (dd, *J* = 8.9 and 4.3 Hz, 1H), 5.68 (br s, 1H), 6.27 (d, *J* = 2.5 Hz, 1H), 6.31 (d, *J* = 4.1 Hz, 1H), 6.96 (m, 2H), 6.99 (m, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.31–7.45 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 28.1, 28.2, 57.6, 57.8, 70.1 (2C), 81.0, 81.1, 82.0 (2C), 85.1, 115.2, 115.3, 126.8 (2C), 127.4 (2C), 128.1 (2C), 128.2 (2C), 128.3 (2C), 128.7 (2C), 136.5 (2C), 154.4, 154.7, 159.2, 159.3; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}BrN_2NaO_5$ $[M+Na]^+$ 473.0683, found 473.0685; Anal. calcd. for $C_{20}H_{23}BrN_2O_5$: C, 53.23; H, 5.14; N, 6.21; found: C, 53.04; H, 5.17; N, 6.13.

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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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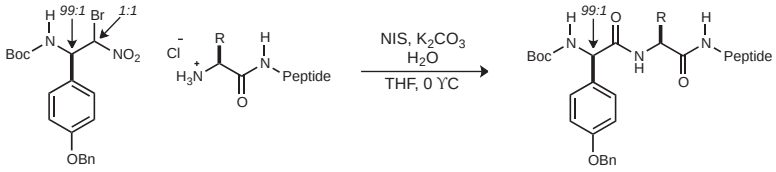
Discussion

The amide bond might be considered a treasured functional group within organic synthesis, owing to its natural abundance among small molecules and peptidic biomolecules, its utility within the process of drug development, and the existence of an array of methods and reagents to prepare amides. The role of synthetic peptides and peptidomimetics among marketed pharmaceuticals continues to increase, with over 50 approved as

medicines.[4] This has resulted in substantial pressure to improve amide bond-forming methods, particularly those reliant on 'coupling reagents' used for carboxylic acid-amine condensations.[5] This has accelerated innovation in amide bond synthesis, leading to a range of new methods.[6]

We discovered that α-bromo nitroalkanes could engage amines in amide bond formation with the assistance of *N*-iodosuccinimide.[7] Evidence collected during the initial study, and conistent with subsequent mechanistic studies, suggested that the key carbon-nitrogen bond-forming step involved a nucleophilic nitronate carbon and an electrophilic iodamine nitrogen.[8] This inversion of polarity relative to all other known amide bond-forming reactions led to our description of this reaction as Umpolung Amide Synthesis (UmAS).[9]



Scheme 1. Use of an Umpolung Amide Synthesis reaction (UmAS) to homologate with a *para*-hydroxyl phenyl glycine residue (Hpg) using 3.

This preparation highlights the utility of bis(amidine)-based organocatalysis in enantioselective α-amino amide synthesis. Oxygenated aryl glycines are observed in a range of interesting peptidic natural products, including the vancomycin class of antibiotics. *para*-Hydroxy phenyl glycine (Hpg) is a key component of cephadroxil and feglymycin,[10] and in vancomycin where it is crosslinked and/or halogenated.[11] Use of the Sharpless aminohydroxylation reaction remains a prevailing approach to Hpg based on enantioselective catalysis, targeting the protected α-amino acid for the homologation step.[12] The preparation described above provides gram-scale access to α-bromo nitroalkanes **3** which converge during UmAS to achieve homologation with (protected) D-Hpg. The coupling of aryl glycines using conventional dehydrating agents and a carboxylic acid donor is subject to competitive epimerization of the α-stereocenter.[13] Preservation of this stereochemical integrity is a key advantage of UmAS due to its

unique mechanism which avoids an electrophilic active ester and acidic α-C–H bond.

This practical three-step protocol is straightforward, is characterized by a good overall yield, and does not require any chromatographic purification steps. In the first two steps the corresponding aldehyde was converted into an imine via an α-amido sulfone intermediate by a similar procedure previously described.[3] The final enantioselective organocatalytic aza-Henry step with bromonitromethane was conducted in the presence of 5 mol % of PBAM catalyst.[4] Filtration of the reaction through a plug of silica gel alleviates the need for chromatography and simplifies the isolation of the product. The α-bromonitroalkanes **3** are obtained with high ee (95-97%) and good overall yield for use directly in an UmAS coupling.

References

1. Department of Chemistry and Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, Tennessee 37235, USA; Fax: 615-343-6361, E-mail: jeffrey.n.johnston@vanderbilt.edu. This work was financially supported by the National Institutes of Health, General Medical Sciences (GM 063557 & GM 084333).
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

4-(Phenylmethoxy)-benzaldehyde; (4397-53-9)
Benzenesulfinic acid sodium salt dihydrate; (25932-11-0)
Carbamic acid, 1,1-dimethylethyl ester, *tert*-butyl carbamate; (4248-19-5)
Formic acid; (64-18-6)
Sulfuric acid sodium salt (1:2), Sodium sulfate; (7757-82-6)
Carbonic acid, potassium salt (1:2), Potassium carbonate; (584-08-7)
Bromonitromethane; (563-70-2)
((*R*,*R*)-PBAM): (1*R*,2*R*)-N^1,N^2-bis[4-(1-pyrrolidinyl)-2-quinolinyl]- 1,2-cyclohexanediamine; (1214287-91-8)

Victoria Lim, a native of Spring Hill, TN, received her B.S. degree in both chemistry and mathematics from Belmont University in 2015. She was an undergraduate researcher in the Johnston laboratory, and matriculated at the University of California, Irvine, in 2015 to pursue research in computational chemistry.

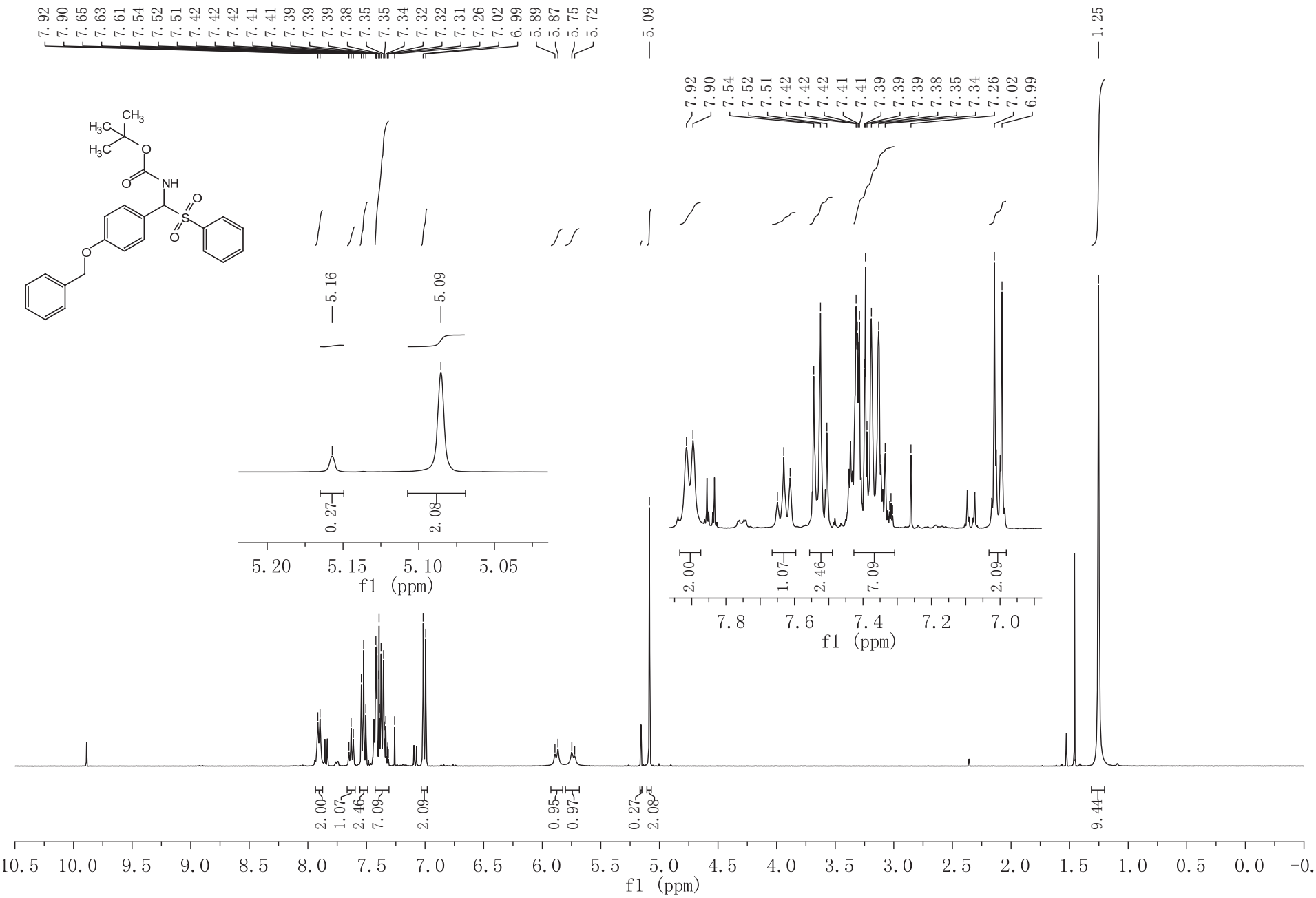
Sergey Tsukanov completed his Master's Degree from Moscow State Academy of Fine Chemical Technology in 2007. Then he received his Ph.D. in Organic Chemistry under the guidance of Prof. Daniel L. Comins at North Carolina State University where he studied the total synthesis of complex alkaloids. In 2012 he started his postdoctoral training at Vanderbilt University focusing on synthesis of the peptidic natural product feglymycin using Umpolung Amide Synthesis and enantioselective aza-Henry chemistry. He received a Lilly Innovation Fellowship Award in 2013 and led a collaborative project to develop a continuous flow paradigm appropriate for nitroalkane synthesis and enantioselective organocatalysis.

Amanda Stephens (née Doody) completed her B.S. Chemistry degree in 2008 at Wofford College. She was an NSF-REU fellow at Columbia University in Summer 2007, where she worked with Prof. Gerard Parkin. Amanda completed her Ph.D. in Organic Chemistry at Vanderbilt Universtiy in 2014 under the mentorship of Prof. Jeffrey N. Johnston, where she focused on the applications of Brønsted acid-catalyzed additions of azides and diazo-ylides to electrophiles, and Umpolung Amide Synthesis to the synthesis of alkaloid and peptidic natural products. Amanda is currently an Academic Professional at the Georgia Institute of Technology, where she coordinates and teaches the organic and inorganic synthesis laboratories for the School of Chemistry & Biochemistry.

Jeffrey N. Johnston completed his B.S. Chemistry degree at Xavier University in 1992, and a Ph.D. in organic chemistry at The Ohio State University in 1997 with Prof. Leo A. Paquette. He then worked as an NIH postdoctoral fellow with Prof. David A. Evans at Harvard University. He began his independent career at Indiana University, where he was promoted to Professor of Chemistry in 2005. In 2006, his research program moved to Vanderbilt University. His group has developed a range of new reactions and reagents that are used to streamline the chemical synthesis of complex small molecules. The integration of new enantioselective Brønsted acid-catalyzed reactions with target-oriented synthesis is an ongoing investigational theme.

Fabian Konrad completed his education as a laboratory technician at the Organic Chemistry Institute of the University of Zürich in 2009. He worked in Virometix AG and Merck before joining Prof. Cristina Nevado´s group at the University of Zürich (2013-2015).

Estíbaliz Merino obtained her PhD degree from the Autónoma University (Madrid-Spain). After a postdoctoral stay with Prof. Magnus Rueping at Goethe University Frankfurt and RWTH-Aachen University in Germany, she worked with Prof. Avelino Corma at Instituto de Tecnología Química-CSIC (Valencia) and Prof. Félix Sánchez at Instituto de Química Orgánica General-CSIC (Madrid) in Spain. At present, she works as research associate in Prof. Cristina Nevado´s group at the University of Zürich. She is interested in the synthesis of natural products using catalytic tools and in the development of new materials with application in heterogeneous catalysis.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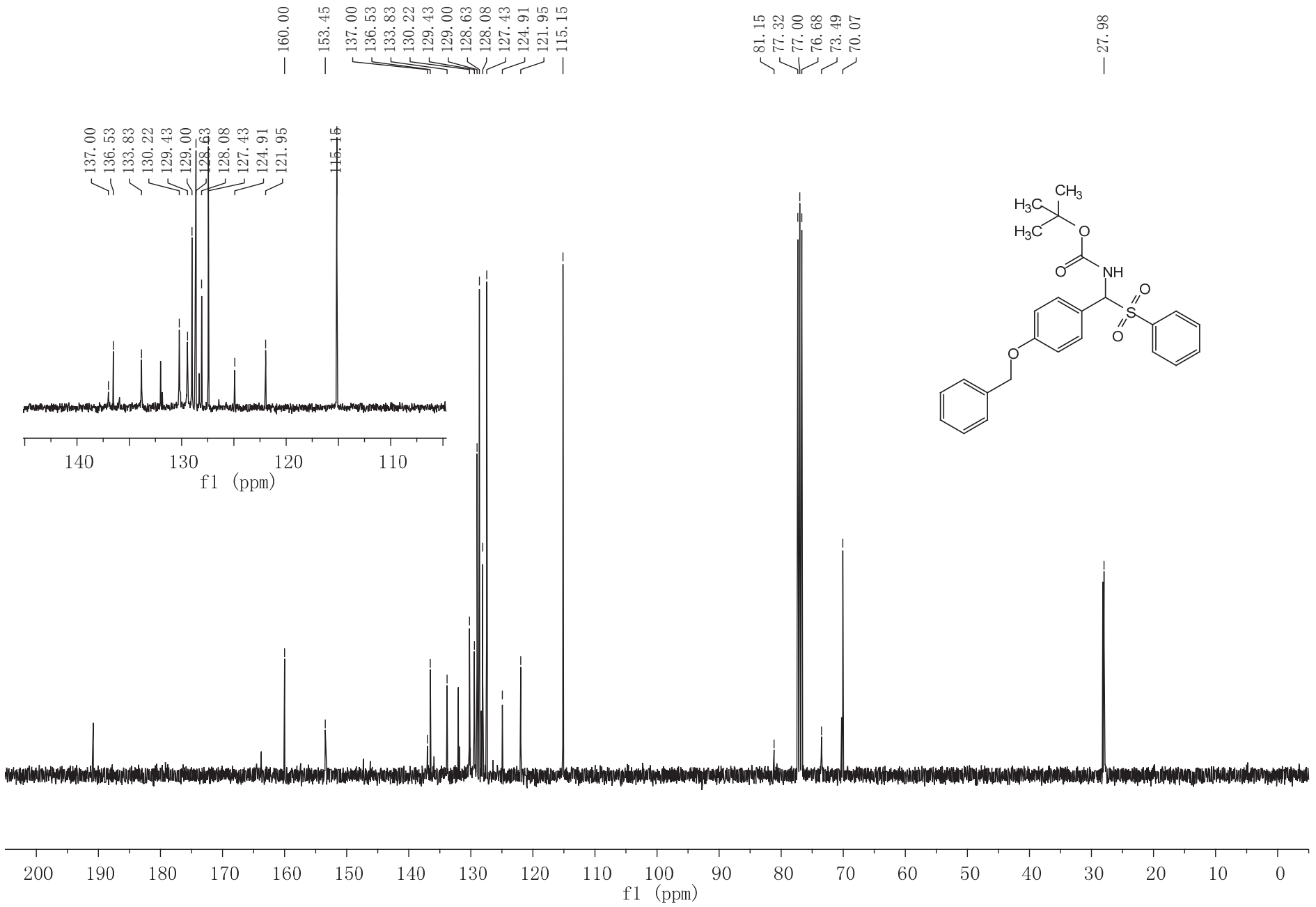
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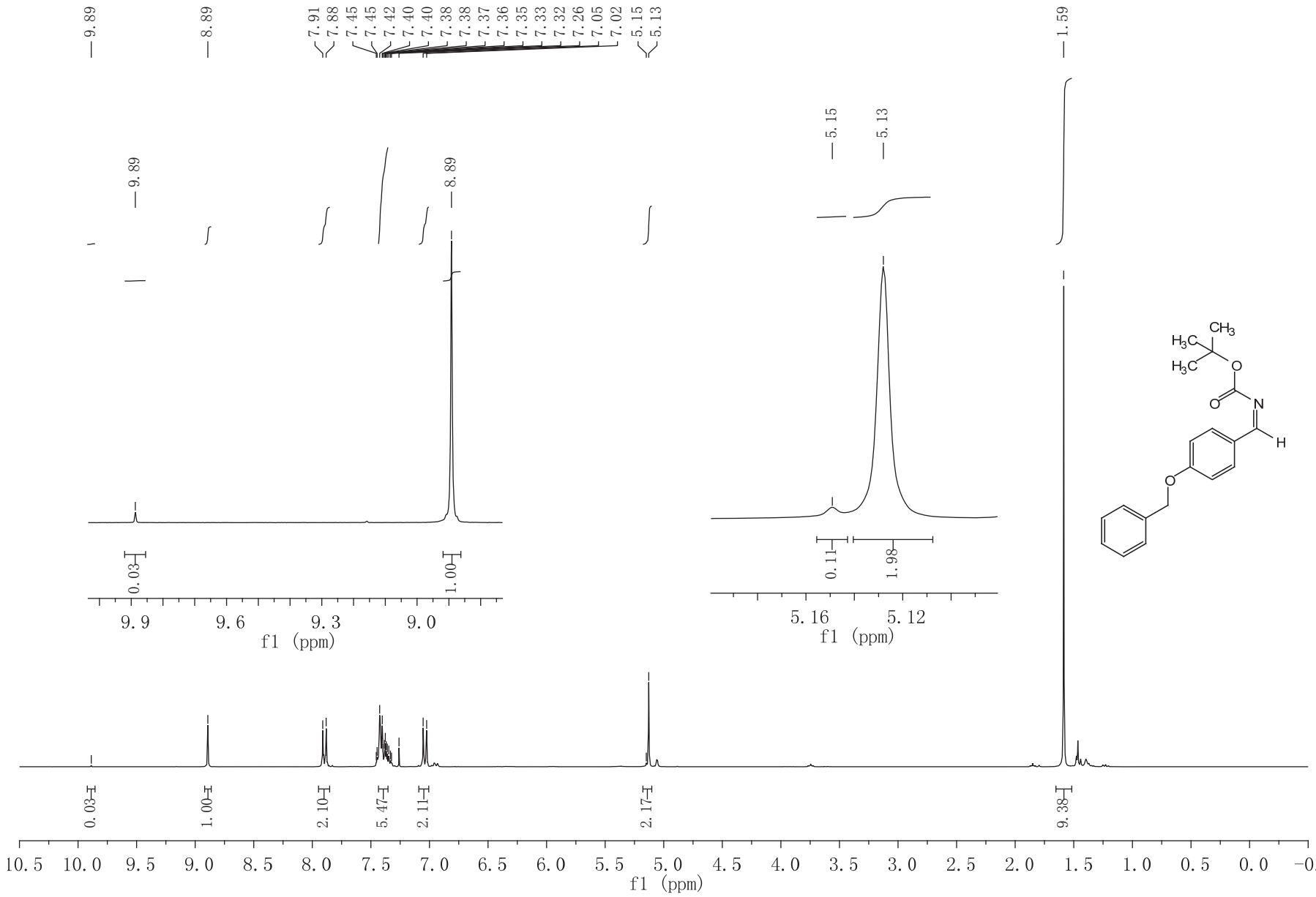
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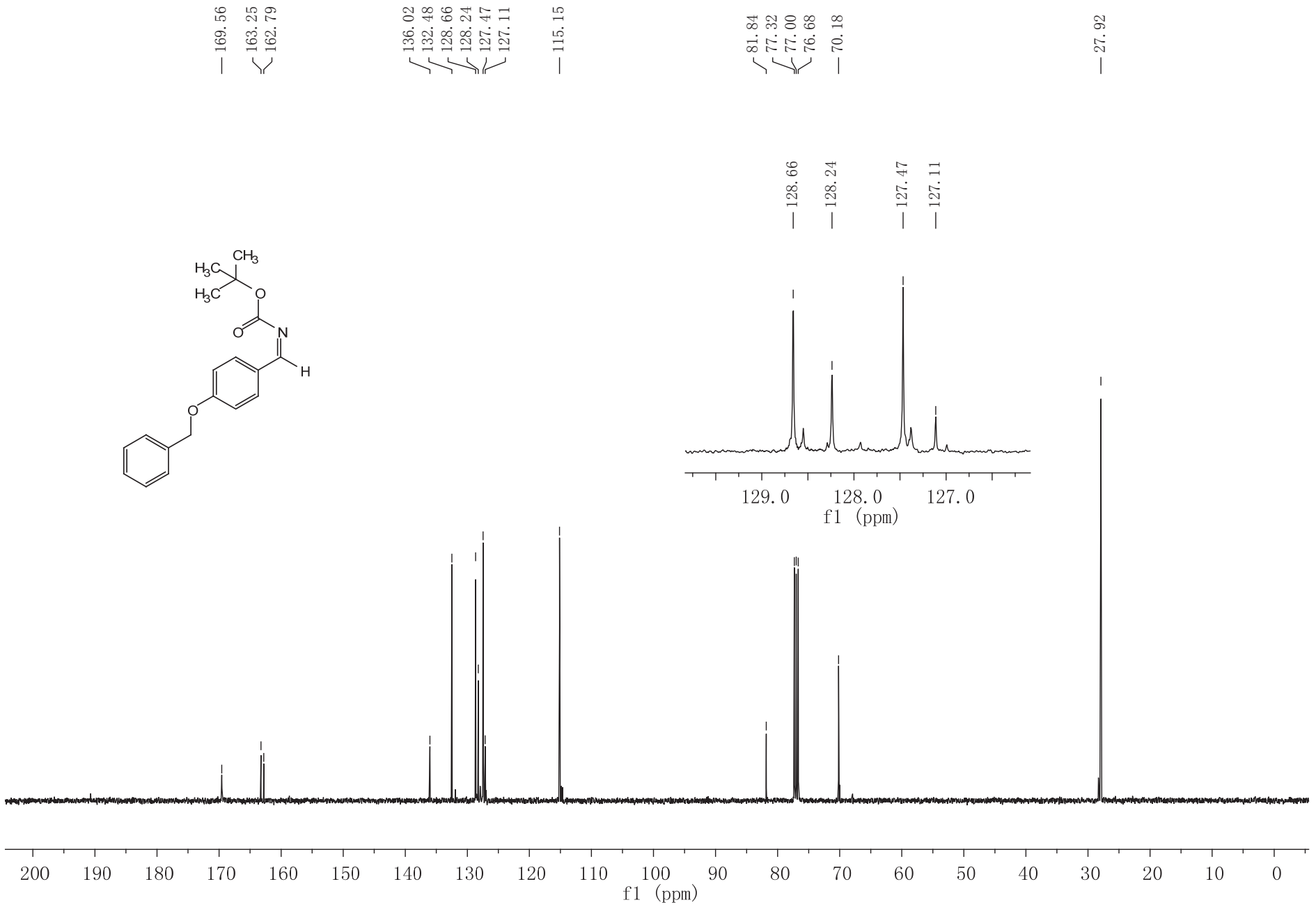
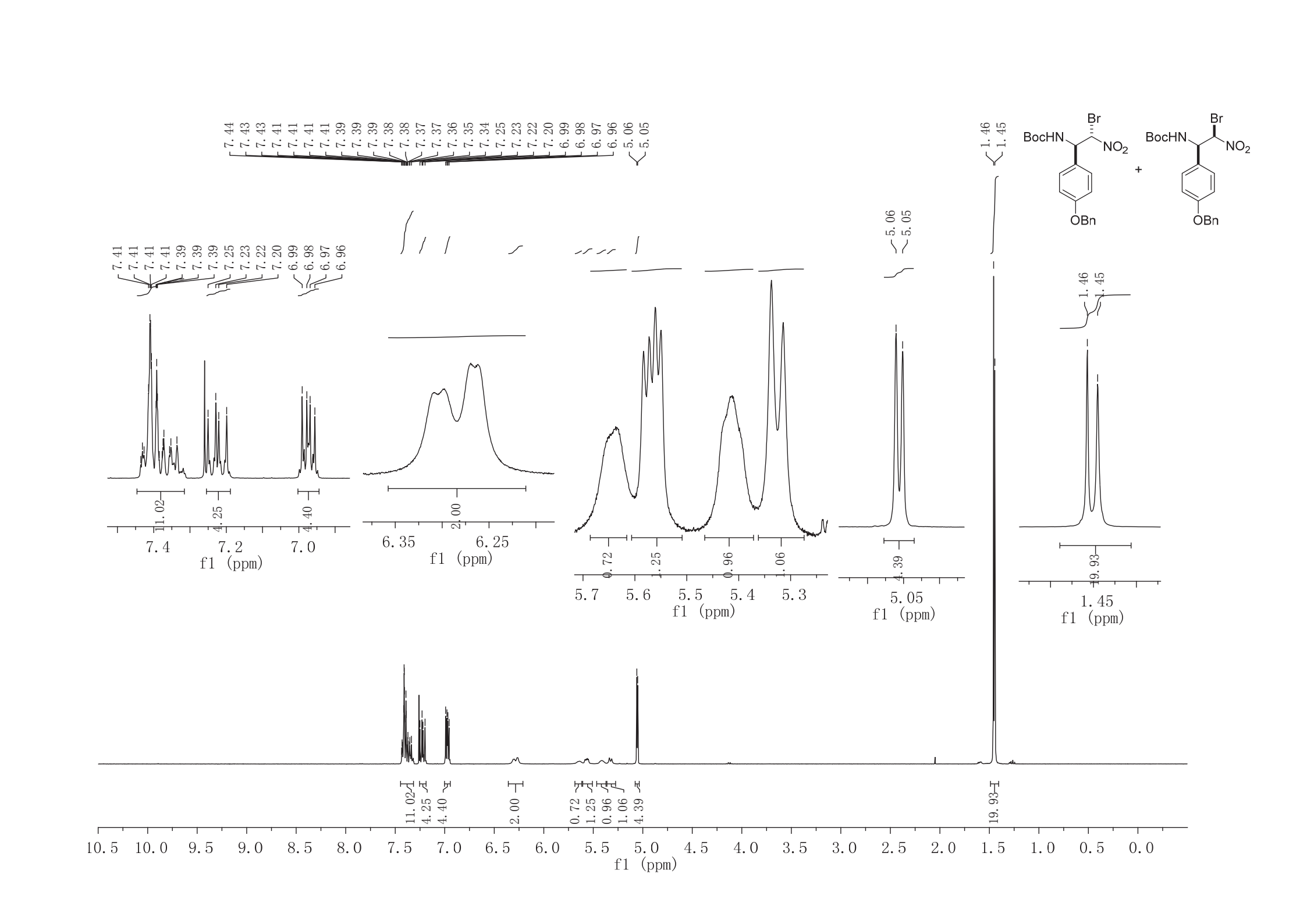
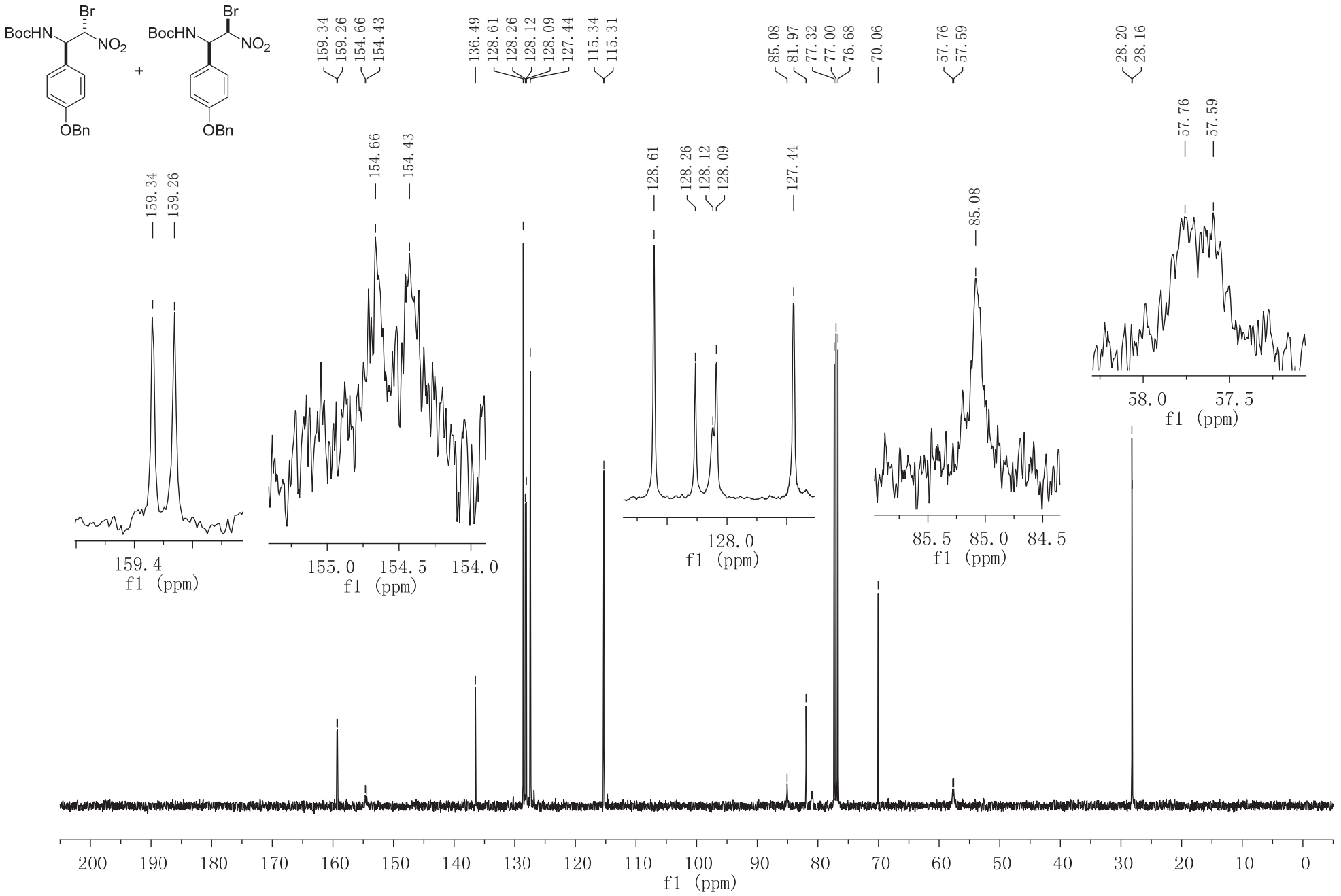
CH3
H3C
H3C
O
O
N
H
O


169.56
163.25
162.79
136.02
132.48
128.66
128.24
127.47
127.11
115.15
81.84
77.32
77.00
76.68
70.18
27.92
128.66
128.24
127.47
127.11
129.0
128.0
127.0
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.44 7.43 7.43 7.41 7.41 7.41 7.41 7.39 7.39 7.39 7.38 7.38 7.37 7.37 7.36 7.35 7.34 7.25 7.23 7.22 7.20 6.99 6.98 6.97 6.96 5.06 5.05
1.46 1.45
BocHN Br NO2 OBn
+
BocHN Br NO2 OBn
11.02 4.25 4.40 2.00 0.72 1.25 0.96 1.06 4.39 19.93
f1 (ppm)


Br
BocHN
NO2
OBn
+
159.34
159.26
154.66
154.43
136.49
128.61
128.26
128.12
128.09
127.44
115.34
115.31
85.08
81.97
77.32
77.00
76.68
70.06
57.76
57.59
28.20
28.16
159.4
f1 (ppm)
155.0
154.5
154.0
128.0
85.5
85.0
84.5
58.0
57.5
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0