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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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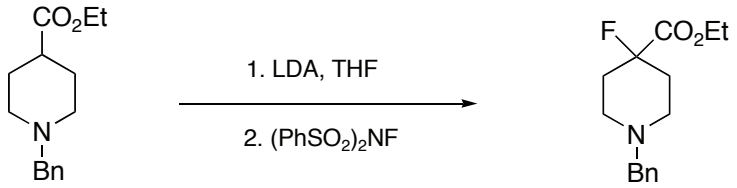
PREPARATION OF ETHYL 1-BENZYL-4-FLUOROPIPERIDINE-4-CARBOXYLATE



Submitted by Jianshe Kong,[1*] Tao Meng,[1] Pauline Ting,[1] and Jesse Wong.[1]
Checked by Chaofeng Huang and Kay M. Brummond.

1. Procedure

A flame-dried, 1-L, three-necked, round-bottomed flask is equipped with a mechanical-stirrer, a thermometer holder fitted with an internal thermometer, a rubber septum and a nitrogen inlet. The flask is charged with diisopropylamine (13.7 mL, 9.9 g, 97.8 mmol, 1.2 equiv) and THF (200 mL) via syringe. The rubber septum is replaced with a pressure-equalizing funnel equipped with a nitrogen inlet. The solution is then cooled to –78 °C with a cryocool and 2.5 M *n*-BuLi in hexanes (39 mL, 97.5 mmol, 1.2 equiv (Note 1) is added dropwise via the addition funnel over 20 min with stirring. The solution is then warmed to 0 °C by placing the flask in an ice-water bath. The addition funnel is removed and replaced by another pressure-equalizing addition funnel. The solution is continually stirred at 0 °C for 30 min and then cooled to –40 °C by placement of the flask in a cryocool.

To the above freshly prepared solution of LDA is added a solution of ethyl 1-benzylpiperidine-4-carboxylate (20.0 g, 80.9 mmol, 1.0 equiv) (Notes 2 and 3) in THF (150 mL) dropwise via the addition funnel over 30 min such that the solution is kept between –30 and –40 °C. The addition funnel is then removed and replaced with a different pressure-equalizing addition funnel. The resulting reaction mixture is continually stirred for 1 h between –10 °C and –15 °C before being cooled to –78 °C. A solution of *N*-fluorobenzenesulfonimide (NFSI) (Note 4) (26.7 g, 84.7 mmol, 1.05 equiv) in THF (150 mL) is added to the reaction via the addition funnel over 40 min while keeping the solution between –65 °C and –78 °C. After the addition, the reaction mixture is stirred for 1 h at –78 °C, then the temperature is allowed to warm to –50 °C over a 2 h period.

The reaction mixture is poured into a 2-L separatory funnel containing ice-H_2O (600 mL) and diluted with ethyl acetate (600 mL). Layers are separated and the aqueous layer is extracted with ethyl acetate (2 x 200 mL). The combined organic layers are washed with brine (200 mL), dried over $MgSO_4$ (20 g), filtered (Note 5), and concentrated by rotary evaporation (45 °C , 35 mmHg), and dried under vacuum (25 °C , 15 mmHg) to afford a deep brown oil. The crude product is purified by flash column chromatography on SiO_2 (Note 6), eluting with ethyl acetate and hexanes (0% to 15%). The fractions containing the product (TLC: $R_f = 0.39$) (Note 7) are combined and concentrated by rotary evaporation (45 °C, 20 mmHg) to yield 15.7 g (73%) of pure ethyl 1-benzyl-4-fluoropiperidine-4-carboxylate as a brown oil (Note 8).

2. Notes

1. A 2.5 M solution of *n*-butyllithium in hexanes was purchased from Aldrich Chemical Co., Inc. Diisopropylamine (99.5%) was purchased from Aldrich Chemical Co., Inc. THF (99+%) was purchased from Aldrich Chemical Co., Inc. Diethyl ether (99.9%) was purchased from Fisher Scientific. Ethyl acetate (99.5%) was purchased from EMD Chemicals. Hexanes (98.5%) was purchased from Mallinckrodt Chemicals. All of these reagents and solvent were used as received.

2. Ethyl 1-benzylpiperidine-4-carboxylate is commercially available. Both commercial material (purchased from Oakwood Inc) and freshly prepared of ethyl 1-benzylpiperidine-4-carboxylate provided similar results in the fluorination reaction. Ethyl 1-benzylpiperidine-4-carboxylate is prepared from ethyl isonipecotate and benzyl bromide (Note 3). Both ethyl isonipecotate and benzyl bromide are purchased from Aldrich Chemical Co., Inc. and used directly without further purification.

3. A 500-mL, two-necked, round-bottomed flask equipped with a magnetic-stirring bar and a pressure-equalizing addition funnel is charged with ethyl isonipecotate (21.6 g, 137 mmol, 1 equiv), K_2CO_3 (38.0 g, 275 mmol, 2 equiv) and DMF (100 mL). The solution is cooled to 0 °C (external temperature) in an ice-bath. A solution of benzyl bromide (23.5 g, 137 mmol) in DMF (100 mL) is added dropwise via the addition funnel over 20 min. The cooling bath is removed after addition, and the reaction mixture is stirred at room temperature for 14 h. The solid is filtered and washed with diethyl ether (3 x 250 mL). The combined organic layers are washed with

H_2O (4 x 150 mL), dried over $MgSO_4$ (20 g), filtered, and concentrated by rotary evaporation to afford a light-yellow oil (31.0 g, 96%), which is used directly for the fluorination reaction without further purification. The product exhibits the following physicochemical properties: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.24 (t, 3 H, *J* = 7.0 Hz), 1.75-1.80 (m, 2 H), 1.85-1.88 (m, 2 H), 2.01 (dt, 2 H, *J* = 2.0, 11.5 Hz), 2.23-2.29 (m, 1 H), 2.84 (d, 2 H, *J* = 11.5 Hz), 3.48 (s, 2 H), 4.11 (q, 2 H, *J* = 7.0 Hz), 7.24-7.31 (m, 5 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 14.3, 28.3, 41.3, 53.0, 60.3, 63.3, 127.0, 128.2, 129.1, 138.5, 175.3.

4. *N*-Fluorobenzenesulfonimide (NFSI) was purchased from Aldrich Chemical Co., Inc.

5. A 150 mL filter funnel (M) charged with 20 g Celite was used.

6. A disposable column filled with SiO_2 (330 g) provided by Teledyne Isco, Inc. was used for the purification.

7. TLC plates (UV_{254} active) were purchased from EMD Chemicals, Inc. and 15% ethyl acetate/hexanes was used as an eluent.

8. The title compound shows the following analytical and spectroscopic data: FTIR (film): 2929, 2819, 2778, 1756, 1736, 1286, 1139, 1070, 1017, 735, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.30 (t, 3 H, *J* = 7.5 Hz), 1.90–1.96 (m, 2 H), 2.14 (dtd, 2 H, *J* = 37.5 ($^3J_{HF}$), 13.0, 4.5 Hz), 2.33 (dt, 2 H, *J* = 1.5, 12.0 Hz), 2.74–2.77 (m, 2 H), 3.53 (s, 2 H), 4.23 (q, 2 H, *J* = 7.5 Hz), 7.25–7.35 (m, 5 H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ: 14.1, 32.6 (d, *J* = 21.4 Hz), 48.3, 61.6, 63.0, 92.0 (d, *J* = 186.0 Hz), 127.1, 128.3, 129.1, 138.3, 171.6 (d, *J* = 25.2 Hz); MS *m/z* (relative intensity): 265 (M^+, 75), 244 (15), 236 (30), 192 (40), 188 (70), 174 (20), 160 (10), 154 (82), 91 (100); HRMS (EI) *m/z* calcd. for $C_{15}H_{20}FNO_2$ 265.1471; found: 265.1467. Anal. calcd. for $C_{15}H_{20}FNO_2$: C, 67.90; H, 7.60; N, 5.28; F, 7.16; found: C, 68.02; H, 7.65; N, 5.27; F, 7.14.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The title compound and derivatives are important pharmaceutical building blocks.[2a-k] *N*-Boc-4-fluoropiperidine-4-carboxylate was reported recently. However, the product using the patent procedure[3] suffered from very poor purity (50%). Unreacted starting material (~50%) could not be separated by either distillation or column chromatography. The benzyl-protected 4-fluoropiperidine-4-carboxylate ester was developed as an improved version. Our synthetic procedure provides a practical, efficient method for the preparation of the title compound on larger scale, in high yield and purity.

Although other fluorinating reagents[4] are available for the synthesis of α-fluorocarbonyl-type compounds, *N*-fluorobenzenesulfonimide[5] was found to be the best with respect to reactivity, safety, and availability.

1. Merck Research Laboratories, 2015 Galloping Hill Road, K-15-2 (2800), Kenilworth, NJ 07033-1300, jianshe.kong@merck.com

2. (a) Kurose, N.; Hayashi, M.; Ogawa, T.; Masuda, K.; Kojima, E., WO 2007/058346. (b) De Lera Ruiz, M.; Aslanian, R.; Berlin, M.; Mccormick, K.; Celly, C., US 2007/066644 A1 20070322. (c) Kuang, R.; Blythin, D.; Shih, N.; Shue, H.; Chen, X.; Cao, J.; Gu, D.; Huang, Y.; Schwerdt, J.; Ting, P.; Wong, S.; Xiao, L., WO 2005/116009. (d) Zoller, G.; Petry, S.; Mueller, G.; Heuer, H.; Baringhaus, K., WO 2005/073199. (e) Inami, H.; Kawaguchi, K.; Kubota, H.; Yamasaki, S.; Matsuzawa, T.; Kaga, D.; Seki, N.; Morio, H., WO 2005/073183. (f) Alvaro, G.; Cardullo, F.; D'adamo, L.; Piga, E.; Seri, C., WO 2004/005255. (g) Ozaki, F.; Ono, M.; Kawano, K.; Norimine, Y.; Onogi, T.; Yoshinaga, T.; Kobayashi, K.; Suzuki, H.; Minami, H.; Sawada, K., WO 2003/084948. (h) Barrow, J.; Lindsley, C.; Shipe, W.; Yang, Z.; Wisnoski, D., WO 2007/002884. (i) Zeng, Q.; Aslanian, R.; Berlin, M.; Boyce, C.; Cao, J.; Kozlowski, J.; Mangiaracina, P.; McCormick, K.; Mutahi, M.; Rosenblum, S.; Shih, N.; Solomon, D.; Tom, W., WO 2003/088967. (j) Friary, R.; Kozlowski, J.; Shankar, B.; Wong, M.; Zhou, G.; Lavey, B.; Shih, N.; Tong, L.; Chen, L.; Shu, Y., WO 2003/042174. (k) Aslanian, R.; Shih, N.; Ting, P.; Berlin, M.; Rosenblum, S.; McCormick, K.; Tom, W.; Boyce, C.; Mangiaracina, P.; Mutahi, M.; Piwinski, J., WO 2002/032893.

3. Aslanian, R.; Berlin, M.; Mangiaracina, P.; McCormick, K.; Mutahi, M.; Rosenblum, S., WO 2004/000831.
4. (a) Sankar Lal, G.; Pez, G.; Syvret, R. *Chem. Rev.* **1996**, *5*, 1737-1756. (b) Taylor, S.; Kotoris, C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431-12477.
5. Differding, E.; Ofner, H. *Synlett* **1991**, 187-189.

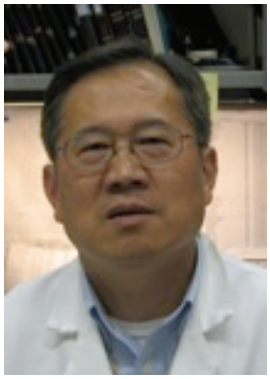
Appendix
Chemical Abstracts Nomenclature (Registry Number)

Diisopropylamine (108-18-9)
n-Butyllithium (109-72-8)
Ethyl isonipecotate (1126-09-6)
Benzyl bromide (100-39-0)
Ethyl 1-benzylpiperidine-4-carboxylate (24228-40-8)
N-Fluorobenzenesulfonimide (133745-75-2)

Jianshe Kong received his B.S. from Nankai University and Ph.D. from Oviedo University of Spain in 1993 under the direction of the Professor José Barluenga. After doing postdoctoral studies with Professors Jeff Aubé and Robert Hanzlik at University of Kansas and Professor Robert Coleman at The Ohio State University, he joined Schering-Plough Research Institute in 1998. He is currently working in the Discovery Synthetic Group as a Senior Principal Scientist of Merck Research Laboratories at Kenilworth.

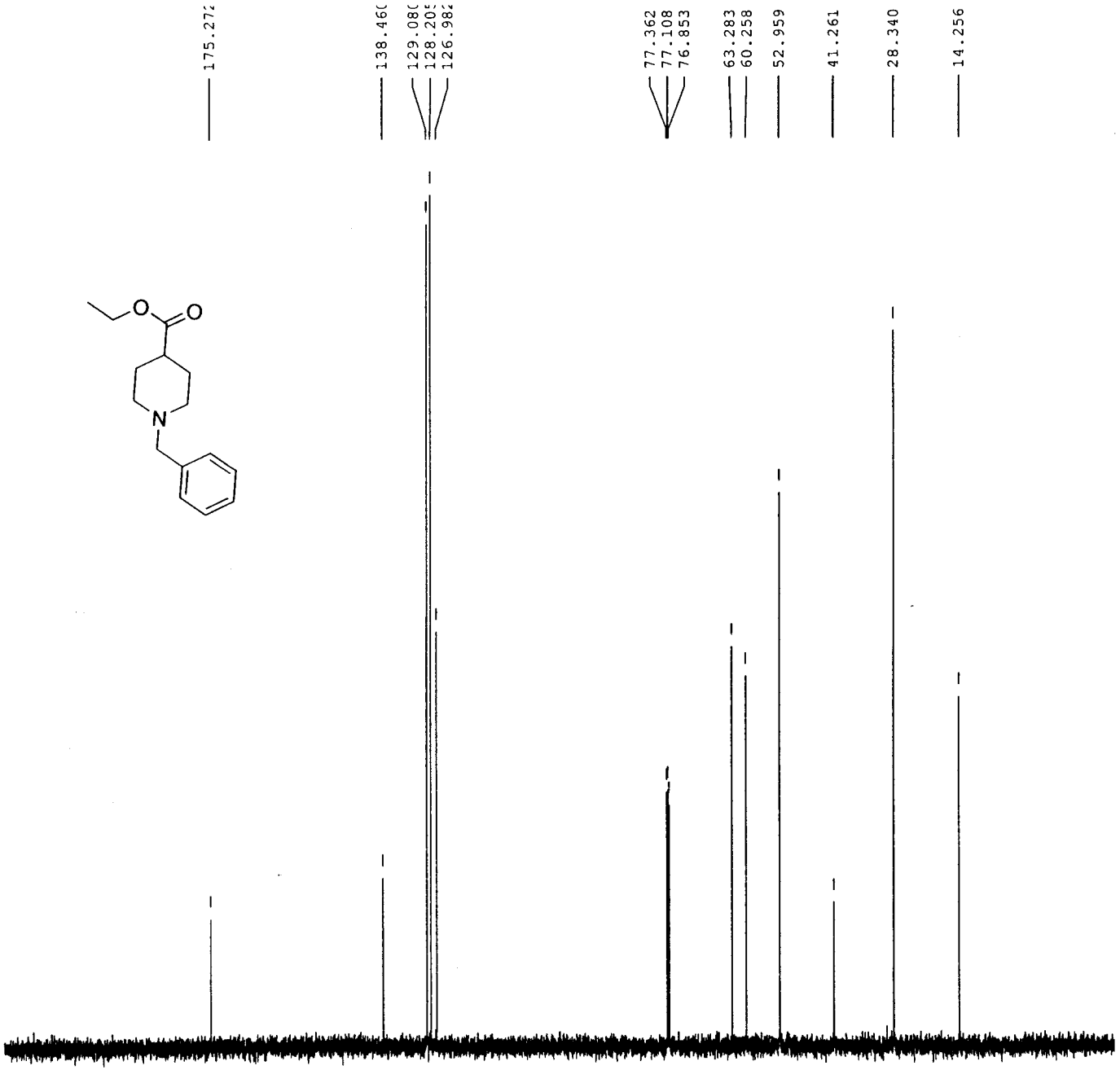
Tao Meng went to Middle Tennessee State University in 1998 and studied organic chemistry under the guidance of Dr. Norma K. Dunlap. He received the Master of Science degree in Organic Chemistry in 2000. After graduation, he joined the Discovery Synthetic Group in Schering-Plough Research Institute at Kenilworth, which now is Merck Research Laboratories.

Pauline Ting received her bachelor's degree in chemistry from the University of Illinois at Champaign-Urbana and her Ph.D. degree in organic chemistry from the University of California at Berkeley with Professor Paul Bartlett. She is currently a Director in the Merck Research Laboratories at Kenilworth, New Jsersey.



Jesse K. Wong received his B.S. and M.S. at Rutgers University. He joined Schering Plough Research Institute in 1980, which now is Merck Research Laboratories, as a medicinal chemist. Four years later he received his Ph.D. with Professor Hugh W. Thompson at Rutgers while working at Schering. In 1993 he was appointed to lead the Discovery Synthetic Group where he developed many new techniques in large scale synthesis. He has 21 patents and 27 publications.

Chaofeng Huang was born in 1978 in China. After completing his Ph.D. under the supervision of Prof. Michael Harmata at the University of Missouri-Columbia, he works as a post-doctoral fellow in the group of Prof. Kay Brummond at the University of Pittsburgh. Currently, his research efforts are focused on extending the synthetic utility of the rhodium(I)-catalyzed cyclocarbonylation reaction to a class of highly oxygenated sesquiterpene lactones.



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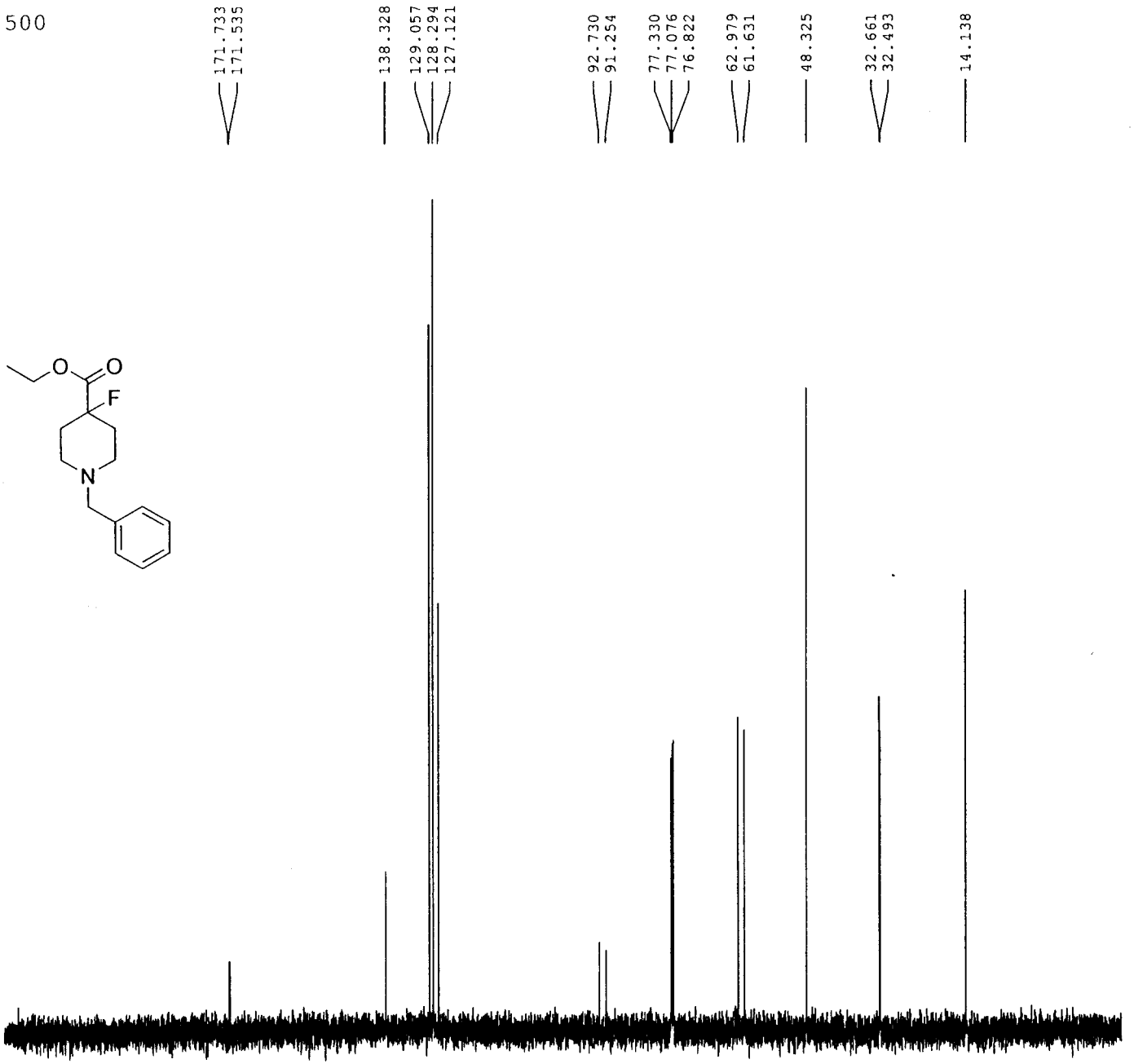

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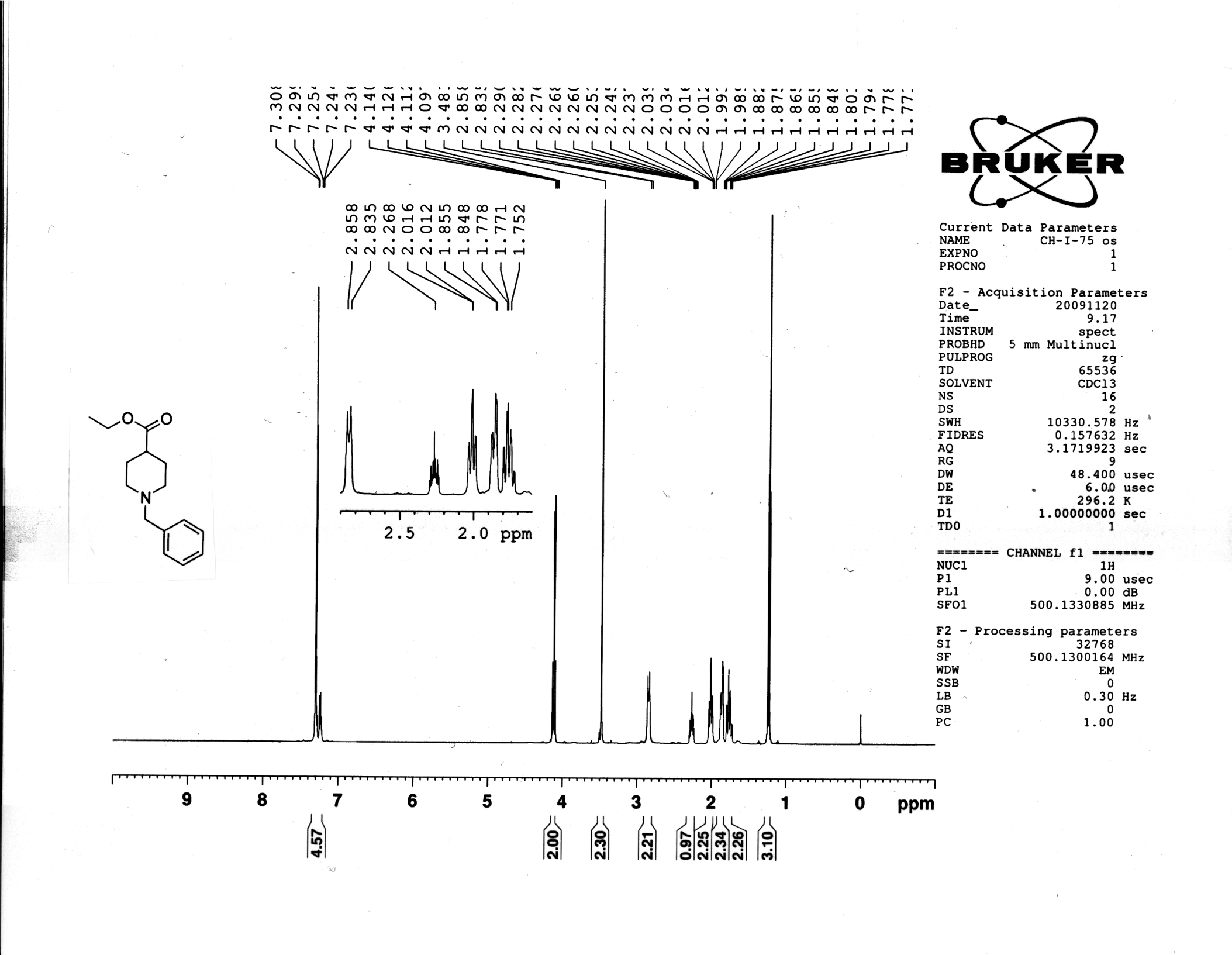

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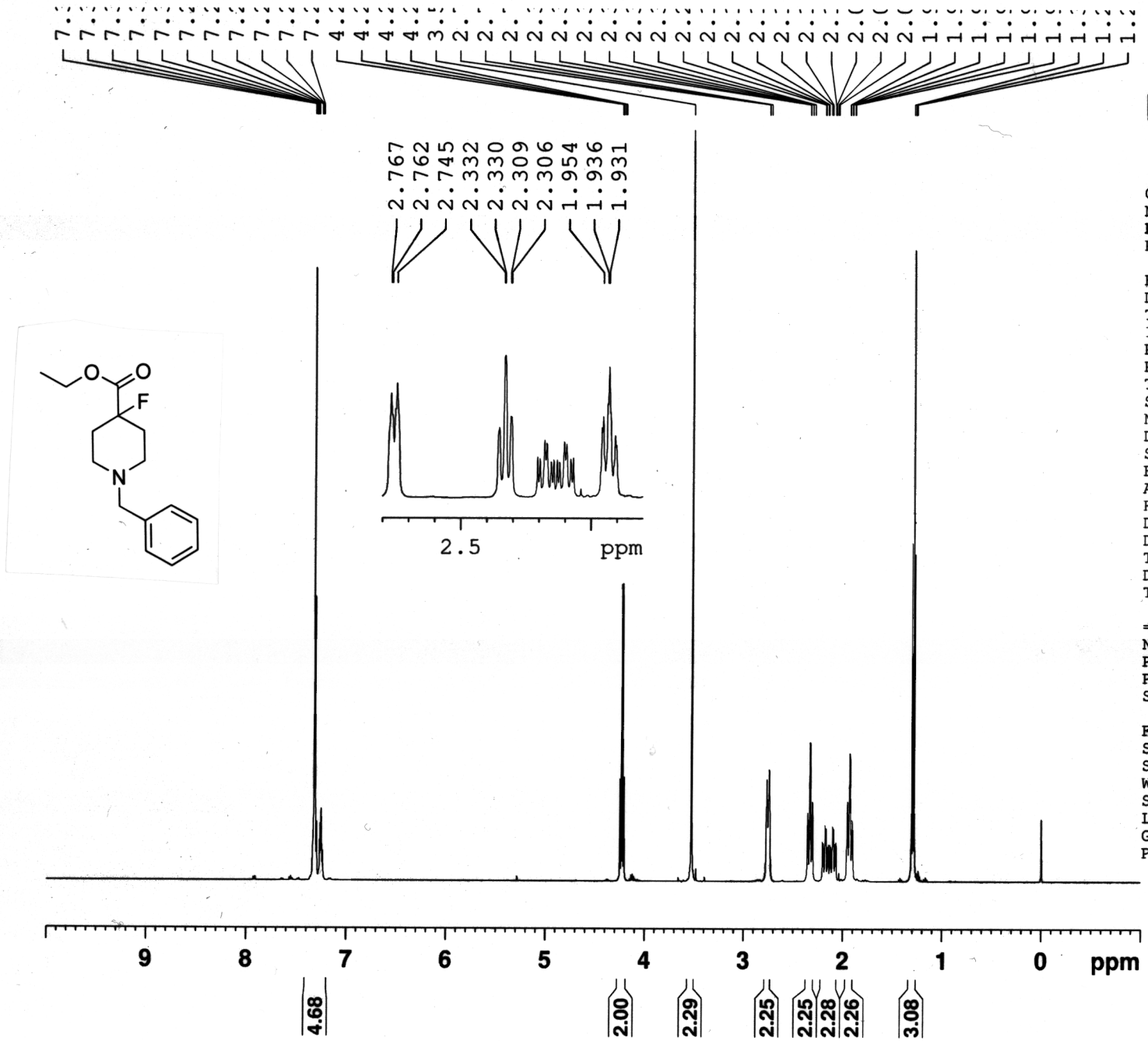

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