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of Reliable Methods
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Working with Hazardous Chemicals

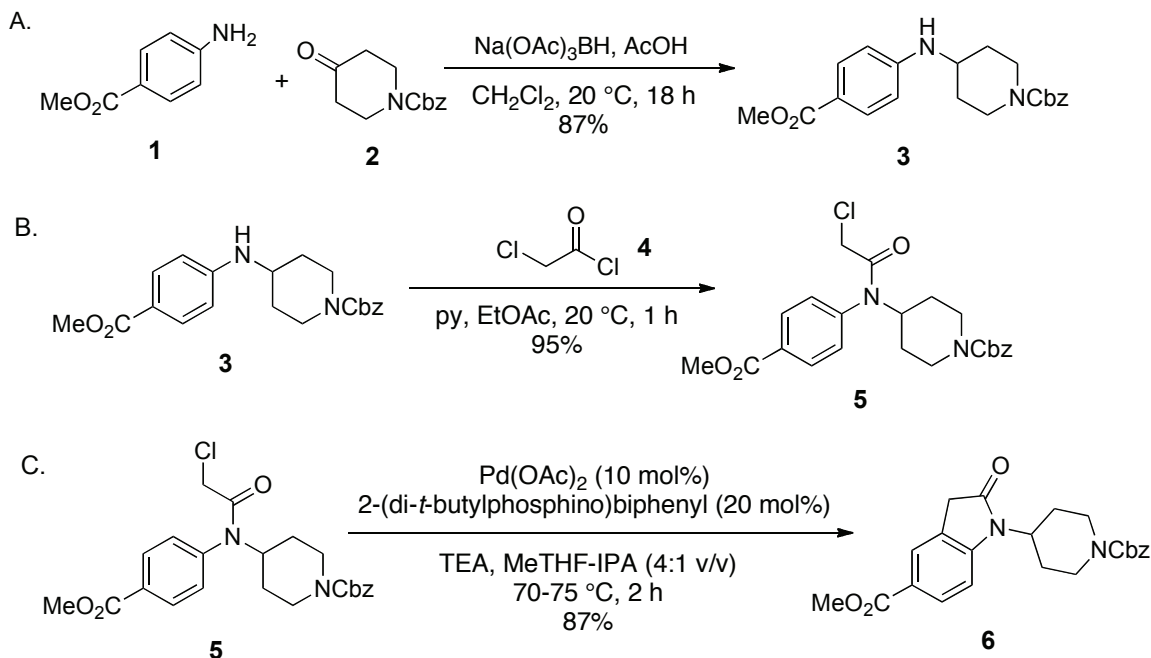
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

Oxindole Synthesis via Palladium-catalyzed C–H Functionalization



Submitted by Javier Magano,^{1*} E. Jason Kiser, Russell J. Shine, and Michael H. Chen.

Checked by David Hughes.

1. Procedure

A. *Benzyl 4-(4-(methoxycarbonyl)phenylamino)piperidine-1-carboxylate (3)*. A 1-L 3-necked round-bottomed flask equipped with a PTFE-coated magnetic stirring bar (3 x 1 cm) is fitted with a gas inlet adapter connected to a nitrogen line and a gas bubbler. The other two necks are capped with rubber septa; a thermocouple probe is inserted through one of the septa (Note 1). The flask is charged with methyl 4-aminobenzoate (**1**, 25.6 g, 169 mmol, 1 equiv), 1-benzyloxycarbonyl-4-piperidone (**2**, 47.0 g, 201 mmol, 1.2 equiv) and dichloromethane (300 mL) (Note 2). Glacial acetic acid (9.5 mL, 10.0 g, 167 mmol, 1 equiv) is added in one portion to the stirred solution using a graduated pipette. The flask is immersed in a room temperature water bath. Sodium triacetoxyborohydride (53.1 g, 250 mmol, 1.5 equiv) is added in 4 portions (12–14 g each) at 30-min intervals,

keeping the internal temperature below 27 °C (Notes 3 and 4). After 17 h at 22–23 °C (Notes 5, 6, and 7), one septum is replaced with a 125-mL dropping funnel which is charged with 2 N aq. NaOH (125 mL, 0.25 mol, 1.5 equiv). The NaOH solution is added to the flask over 5 min (Note 8), keeping the internal temperature below 30 °C. The biphasic mixture is vigorously stirred for 1 h, then the contents are transferred to a 1-L separatory funnel and the layers separated. The organic phase is washed with water (2 × 125 mL). The dichloromethane extracts are filtered through a bed of anhydrous sodium sulfate (50 g) into a tared 1-L round-bottomed flask and concentrated by rotary evaporation (bath temperature: 40 °C; 200–250 mmHg) to 130 g. Methyl *t*-butyl ether (125 mL) is added and the contents are concentrated by rotary evaporation (bath temperature: 40 °C; 100 mmHg) to 130 g. Two additional methyl *t*-butyl ether flushes are carried out (Note 9). The flask is equipped with a PTFE-coated magnetic stirring bar (3 x 1 cm) and a 500-mL addition funnel. Methyl *t*-butyl ether (250 mL) is added to the flask in one portion and the resulting clear solution is stirred at 22 °C. Crystallization initiates within 10 min. The addition funnel is charged with *n*-heptane (250 mL), which is added drop wise over 1 h. The resulting white suspension is stirred at 20–22 °C for 1 h, then vacuum-filtered through a 350-mL medium-porosity sintered-glass funnel. The solid is washed with 1:1 (vol/vol) *n*-heptane/methyl *t*-butyl ether (50 mL) and *n*-heptane (50 mL). The solid is dried in a vacuum oven (70 mmHg) at 50 °C for 24 h to afford benzyl 4-(4-(methoxycarbonyl)phenylamino)piperidine-1-carboxylate (**3**) (52.0 g, 84% yield) (Notes 10 and 11).

B. Benzyl 4-(2-chloro-N-(4-(methoxycarbonyl)phenyl)acetamido)-piperidine-1-carboxylate (5). A 1-L 3-necked round-bottomed flask equipped with a PTFE-coated magnetic stirring bar (3 x 1 cm) is fitted with a gas inlet adapter connected to a nitrogen line and a gas bubbler. The other two necks are capped with rubber septa; a thermocouple probe is inserted through one of the septa (Note 1). The flask is charged with benzyl 4-(4-(methoxycarbonyl)phenyl-amino)piperidine-1-carboxylate (**3**, 25.0 g, 68 mmol, 1 equiv), ethyl acetate (250 mL), and pyridine (8.3 mL, 103 mmol, 1.5 equiv) (Note 12). The flask is placed in an ice-water bath and cooled to an internal temperature of 3 °C. Chloroacetyl chloride (10.1 g, 89 mmol, 1.3 equiv) is added via a 12-mL syringe over 5 min, keeping the internal temperature below 10 °C. The ice-bath is removed and the orange slurry is stirred for 1.5 h at ambient temperature (Note 13). One of the septa is replaced with a 125-mL addition funnel and charged with 5% aq. KH₂PO₄

(125 mL), which is added to the reaction contents over 5 min while keeping the internal temperature below 25 °C. After stirring for 10 min (Note 14), the contents of the flask are transferred to a 1-L separatory funnel. The layers are separated and the organic layer is washed with half-saturated brine, then dried by filtration through 50 g anhydrous sodium sulfate into a 1-L round-bottomed flask. The contents are concentrated by rotary evaporation (bath temperature: 40 °C; 100 to 50 mmHg, foaming) (38 g). Methyl *t*-butyl ether (150 mL) is added to the flask and concentrated (bath temperature: 40 °C; 100 to 50 mmHg, foaming) to an orange oil (35 g). The flask is equipped with a PTFE-coated magnetic stirring bar (3 x 1 cm) and methyl *t*-butyl ether (150 mL) is added. The contents are warmed in a 50 °C water bath to dissolve the oil, then cooled to ambient temperature with stirring. Within 15 min the mixture turns turbid and a white solid begins to form (Note 15). After stirring for 4 h, the solid is filtered using a 150-mL medium porosity sintered-glass funnel and washed with methyl *t*-butyl ether (75 mL). The solid is dried in a vacuum oven (70 mmHg) at 40 °C for 2 days to afford benzyl 4-(2-chloro-*N*-(4-(methoxycarbonyl)phenyl)acetamido)-piperidine-1-carboxylate (**5**) (28.5 g, 94% yield) as an off-white solid (Note 16).

C. Methyl 1-(1-(benzyloxycarbonyl)piperidin-4-yl)-2-oxindoline-5-carboxylate (6). A 500-mL 3-necked round-bottomed flask equipped with a PTFE-coated magnetic stirring bar (3 x 1 cm) is fitted with a reflux condenser with a gas inlet adapter connected to a nitrogen line and a gas bubbler. The other two necks are capped with rubber septa; a thermocouple probe is inserted through one of the septa (Note 1). The flask is charged with benzyl 4-(2-chloro-*N*-(4-(methoxycarbonyl)phenyl)acetamido)-piperidine-1-carboxylate (**5**, 20.0 g, 44.6 mmol, 1 equiv), palladium acetate (1.01 g, 4.5 mmol, 0.1 equiv), 2-(di-*t*-butylphosphino)biphenyl (2.74 g, 9.2 mmol, 0.2 equiv), 2-methyltetrahydrofuran (130 mL), and 2-propanol (32 mL) (Note 17). The light brown suspension is sparged subsurface with nitrogen gas for 15 min (Note 18). Triethylamine (6.93 g, 68 mmol, 1.5 equiv) is added via a 12-mL syringe and the mixture is sparged for an additional 5 min. The flask is placed in an oil bath at 80 °C and heated to an internal temperature of 74–76 °C for 2 h (Note 19). The hot mixture (Note 20) is vacuum-filtered through a pad of Celite (25 g, pre-wetted with 2-MeTHF) in a 150-mL medium-porosity sintered glass funnel into a 1-L round-bottomed flask. The flask employed to carry out the reaction is rinsed with hot (75 °C) 2-MeTHF (100 mL) and used to wash the Celite pad. The filtrate is

concentrated by rotary evaporation (bath temperature: 40 °C; 40 mmHg) to give an orange-brown solid (34 g). The flask is equipped with a PTFE-coated magnetic stirring bar (3 x 1 cm) and 2-propanol (270 mL) is added. The stirred suspension is heated to a gentle reflux with a heating mantle to dissolve all solids, generating a nearly black solution. The heating mantle is turned off and the contents are allowed to cool to ambient temperature over 2 h with stirring to give thick crystallization (Note 21). The suspension is stirred for 4 h, then vacuum-filtered using a 150-mL medium-porosity sintered-glass funnel, washed with 2-propanol (2 x 30 mL, Note 22), then dried in a vacuum oven (70 mmHg) at 40 °C for 2 days to afford oxindole **6** as a gray solid (15.9 g, 87% yield) (Notes 23 and 24).

2. Notes

1. The internal temperature was monitored using a J-Kem Gemini digital thermometer with a Teflon-coated T-Type thermocouple probe (12-inch length, 1/8 inch outer diameter, temperature range -200 to +250 °C).

2. The following reagents and solvents were used as received for Step A: methyl 4-aminobenzoate (Sigma-Aldrich, 98%), 1-benzyloxycarbonyl-4-piperidone (Sigma-Aldrich, 99%), sodium triacetoxyborohydride (Sigma-Aldrich, 95%), dichloromethane (Fisher, certified ACS reagent, stabilized), glacial acetic acid (Fisher, certified ACS plus), *t*-butyl methyl ether (Sigma-Aldrich, >98.5%), and heptanes (Sigma-Aldrich, Chromasolv, >99%).

3. The first two Na(OAc)₃BH portions produced 3–5-degree exotherms.

4. The addition of Na(OAc)₃BH afforded a pale yellow/green, slightly cloudy mixture.

5. The submitters monitored the progress of the reaction after each Na(OAc)₃BH addition (5 additions) by quenching an aliquot with water after 30 min, diluting with 9/1 MeCN/water and analyzing by UPLC (Note 6). The results were (limiting reagent/product ratio): 1st portion: 42/58; second portion: 28/72; third portion: 13/87; fourth portion: 8/92. One and two h after the 5th portion had been added, the ratios were 3/97 and 2.4/97.6%, respectively. The checker monitored the reaction by ¹H NMR (CDCl₃) by quenching a reaction aliquot into dichloromethane/water, separating the layers, and concentrating the dichloromethane layer to dryness. The diagnostic resonances were δ 6.54–6.57 (m, 2H) for product **3** and 6.63–6.66

(m, 2H) for starting material **1**. Two h after the final addition of Na(OAc)₃BH, 10% unreacted **1** remained; after 16 h, the level was 3%.

6. UPLC conditions: column, ACQUITY UPLC HSS T3 1.8 μ m, 2.1 \times 50 mm; wavelength: 210 nm; column temperature: 45 $^{\circ}$ C; eluent A) water (0.05% TFA) B) MeCN; gradient: 0 min: A) 95%, B) 5%; 2.9 min: A) 0% B) 100%; 3.15 min: A) 0% B) 100%; 3.25 min: A) 95% B) 5%; 4.0 min: A) 95% B) 5%.

7. UPLC analysis by the submitters after 16 h showed 11% of benzyl 4-hydroxypiperidine-1-carboxylate (byproduct from the reduction of 1-benzyloxycarbonyl-4-piperidone; retention time: 1.35 min), 84.7% of desired product **3** (retention time: 2.08 min), and 4.4% of an unidentified byproduct (retention time: 0.88 min).

8. The flask should be kept under a nitrogen atmosphere during the quench since hydrogen gas is produced upon quenching unreacted Na(OAc)₃BH.

9. Three co-evaporations with MTBE is an efficient way to remove most of the dichloromethane and maximize the yield in the subsequent crystallization. Concentration of the dichloromethane phase to very small volumes affords a foamy oil, making further removal of dichloromethane by co-evaporation with MTBE less efficient. After the co-evaporations, ¹H NMR (CDCl₃) of the residue showed 5 mol % residual dichloromethane.

10. Amine **3** has the following physical and spectroscopic properties: Mp: 90–92 $^{\circ}$ C. ¹H NMR (400 MHz CDCl₃) δ : 1.35–1.43 (m, 2 H), 2.06 (d, J = 10.9 Hz, 2 H), 3.03 (t, J = 11.8 Hz, 2 H), 3.50–3.55 (m, 1 H), 3.85 (s, 3 H), 4.10–4.17 (m, 3 H), 5.15 (s, 2 H), 6.54–6.57 (m, 2 H), 7.31–7.38 (m, 5 H), 7.85–7.88 (m, 2 H). ¹³C NMR (100 MHz, CDCl₃) δ : 32.2, 42.9, 49.7, 51.7, 67.4, 112.0, 118.8, 128.1, 128.2, 128.7, 131.8, 136.72, 150.7, 155.4, 167.3. IR (ATR cell) cm⁻¹: 3357, 2951, 1707, 1675, 1604, 1531, 1500, 1471, 1436, 1363, 1353, 1309, 1274, 1226, 1197, 1172, 1149, 1095, 1008, 983, 951, 839, 788, 769, 750, 693. LC-MS m/z calcd for [M]⁺ (C₂₁H₂₄N₂O₄) 368.4, found, 368.7; Anal. Calcd for C₂₁H₂₄N₂O₄: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.54; H, 6.50; N, 7.57. HPLC area % purity: 97-98% (HPLC method: fused-core C-18 column, 4.6 x 100 mm, 2.7 μ m particle size; mobile phase, A = 0.1 % H₃PO₄/H₂O, B = MeCN, gradient 10-95% B in 6 min and hold at 95% B for 2 minutes, detection at 210 nm, flow 1.8 mL/min, temp 40 $^{\circ}$ C; t_R = 4.93 min).

11. A yield of 85% was obtained at half scale.

12. The following reagents and solvents were used as received for Step B: ethyl acetate (Fischer Optima, 99.9%, water level <0.002%), pyridine (Sigma-Aldrich, Reagent Plus, >99%), chloroacetyl chloride (Fluka purum \geq 99%), and *t*-butyl methyl ether (Sigma-Aldrich, >98.5%).

13. The submitters followed the reaction by UPLC as outlined in Note 6. The checker monitored the reaction by ^1H NMR as follows: A 0.1 mL reaction aliquot was quenched into 1 mL brine/1 mL EtOAc. The organic layer was separated and dried by filtering through a plug of sodium sulfate. After concentrating to dryness, the sample was dissolved in CDCl_3 . NMR analysis showed no starting material resonances at 3.85 (s, 3 H) or 6.54-6.57 (m, 2 H).

14. The reaction is quenched with phosphate buffer at pH 10 and stirred for 10 min to fully quench excess chloroacetyl chloride that will otherwise inhibit the subsequent crystallization of the product.

15. Crystallization for the first run required vigorous scratching of the flask with a glass rod. In subsequent runs, the crystallization occurred spontaneously.

16. Chloride **5** has the following physical and spectroscopic properties: Mp: 103–105 °C. ^1H NMR (400 MHz, CDCl_3) δ : 1.23–1.28 (m, 2 H), 1.84 (d, $J = 11.6$ Hz, 2 H), 2.88 (br s, 2 H), 3.68 (s, 2 H), 3.96 (s, 3 H), 4.23 (br s, 2 H), 4.74–4.80 (m, 1 H), 5.04 (br s, 2 H), 7.22 (d, $J = 8.4$, 2H), 7.28–7.35 (m, 5 H), 8.13 (d, $J = 8.7$ Hz, 2 H). ^{13}C NMR (100 MHz, CDCl_3) δ : 30.4, 42.3, 43.5, 52.7, 53.7, 67.4, 128.1, 128.2, 128.6, 130.4, 131.3, 131.4, 136.7, 141.4, 155.1, 165.7, 166.0; IR (ATR cell) cm^{-1} : 2951, 1714, 1705, 1690, 1673, 1604, 1510, 1496, 1449, 1440, 1427, 1391, 1362, 1329, 1293, 1276, 1246, 1231, 1208, 1195, 1176, 1131, 1118, 1105, 1086, 1062, 1020, 985, 968, 956, 934, 921, 870, 834, 814, 797, 788, 779, 769, 753, 715, 707, 678, 665; LC-MS m/z calcd for $[\text{M}]^+$ ($\text{C}_{23}\text{H}_{25}\text{ClN}_2\text{O}_5$) 444.4, found, 444.6; Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{ClN}_2\text{O}_5$: C, 62.09; H, 5.66; Cl, 7.97; N, 6.30. Found: C, 61.69; H, 5.39; Cl, 7.81; N, 6.17; HPLC area % purity: 98% (conditions in Note 10; $t_{\text{R}} = 4.73$ min)

17. The following reagents and solvents were used as received for Step C: palladium acetate (Strem, 98%), 2-(di-*t*-butylphosphino)biphenyl (Acros, 99%), 2-methyltetrahydrofuran (Sigma Aldrich, Reagent Plus \geq 99.5%, inhibited with 150-400 ppm BHT), 2-propanol (Sigma-Aldrich, ACS reagent >99.5%).

18. Nitrogen sparging was carried out using a 1-mL plastic syringe with a 10 cm needle with a steady stream of bubbling for 15 min. The heterogeneous mixture darkened during the sparging.

19. The submitters monitored the reaction by UPLC analysis using the conditions in Note 6. The checker monitored the reaction by ^1H NMR by diluting a 0.1 mL aliquot from the reaction mixture into 1 mL CDCl_3 and filtering through a 0.25 μM filter. At the 1 h time point, 2.5% starting material remained based on resonances integrated at δ 5.04 (br s, 2 H) and 8.13 (d, $J = 8.7$ Hz, 2 H).

20. The mixture must be filtered while still hot since the product crystallizes upon cooling.

21. Thick solids formed when the internal temperature reached 60–65 $^\circ\text{C}$. The stirring speed had to be increased for efficient mixing.

22. Care was taken to avoid cake cracking prior to the 2-propanol wash, which allowed for the efficient removal of highly colored impurities.

23. Oxindole **6** has the following physical and spectroscopic properties: Mp: 158–159 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ : 1.73–1.76 (m, 2 H), 2.29–2.39 (m, 2 H), 2.92 (br s, 2 H), 3.56 (s, 2 H), 3.93 (s, 3 H), 4.39–4.47 (m, 3 H), 5.19 (s, 2 H), 6.97 (d, $J = 8.4$ Hz, 1 H), 7.33–7.42 (m, 5 H), 7.92–7.93 (m, 1 H), 7.96–7.98 (m, 1 H). ^{13}C NMR (100 MHz, CDCl_3) δ : 28.3, 35.7, 43.9, 50.4, 52.3, 67.7, 109.3, 124.3, 124.8, 126.1, 128.3, 128.4, 128.8, 130.5, 136.8, 147.8, 155.4, 166.9, 175.1. IR (ATR cell) cm^{-1} : 2948, 1699, 1616, 1588, 1489, 1453, 1428, 1386, 1358, 1332, 1320, 1291, 1272, 1256, 1241, 1227, 1192, 1169, 1139, 1126, 1097, 1077, 1021, 986, 968, 957, 938, 902, 890, 869, 838, 802, 771, 763, 731, 696, 683, 654; LC-MS m/z calcd for $[\text{M}]^+$ ($\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5$) 408.5, found, 408.7; Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.72; H, 5.75; N, 6.77. HPLC area % purity: 98% (conditions in Note 10; $t_{\text{R}} = 4.60$ min).

24. A reaction at half scale afforded an 84% yield.

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3. Discussion

Oxindoles are an important class of compounds with ubiquitous presence in both natural products² and pharmaceuticals.³ In addition, oxindoles can be employed as immediate precursors for the preparation of indoles. Numerous methods have been reported in the literature for the synthesis of oxindoles, such as the derivatization of isatin and indoles, radical cyclizations, the cyclization of *o*-aminophenylacetic acids and α -halo or α -hydroxyacetanilides, cyanoamidation reactions, palladium-catalyzed Heck couplings, and others.⁴ Alternatively, Buchwald and co-workers have reported a palladium-catalyzed alkylation reaction via C–H functionalization⁵ and Hartwig and co-workers a palladium-catalyzed arylation reaction via amide α -arylation⁶ (Figure 1). These two technologies represent direct and unprecedented approaches to the oxindole functionality from readily accessible precursors.

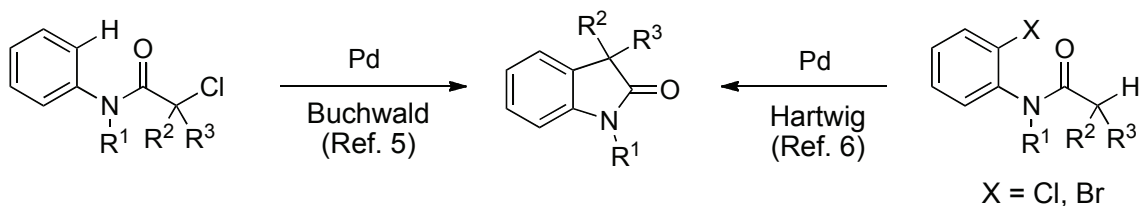


Figure 1. Buchwald's and Hartwig's palladium-catalyzed methodologies for oxindole formation

Compound **7** (Figure 2) is a serine palmitoyl transferase (SPT) enzyme inhibitor candidate for the potential treatment of heart disease. This molecule contains an oxindole functionality and was originally prepared by our Medicinal Chemistry group in nine steps from acid **8**. A key intermediate in this synthesis is oxindole **6**, which can be generated in five steps from **8**; however, this route has several disadvantages, such as the use

of unsafe reagents (NaH) and the need for several chromatographic purifications. For the preparation of large quantities of **6** (hundreds of g to several kg), we wanted to avoid those issues and also identify a shorter synthesis. We focused our attention on Buchwald's protocol since no halogenated precursor is needed to install the 5-membered oxindole ring and one precedent was found in the literature on kg-scale.⁷

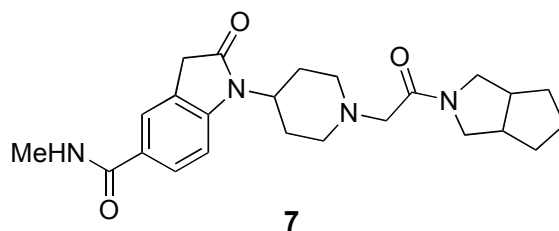
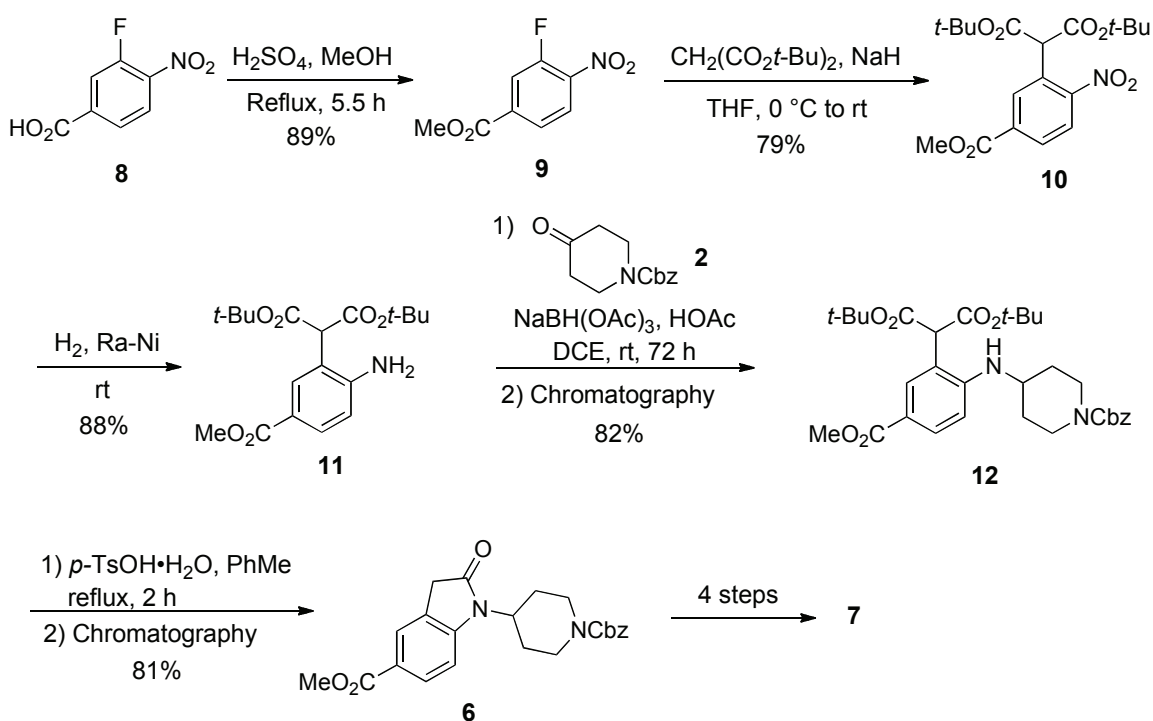


Figure 2. Structure of serine palmitoyl transferase (SPT) enzyme inhibitor **7**



Scheme 1. Medicinal Chemistry synthesis of drug candidate **7**

The new and shorter route to oxindole **6** starts with the reductive amination between methyl 4-aminobenzoate (**1**), a considerably cheaper starting material than 3-fluoro-4-nitrobenzoic acid (**8**), and 1-benzyloxycarbonyl-4-piperidone (**2**) in dichloromethane in the presence of 1 equiv of AcOH. The addition of Na(OAc)₃BH in several portions resulted in

complete conversion of **1** to secondary amine **3** and gave acceptable levels of alcohol benzyl 4-hydroxypiperidine-1-carboxylate resulting from the reduction of **2**. The crystallization of **3** from heptane/MTBE gives analytically pure material in 84% yield.

The acylation reaction between **3** and chloroacetyl chloride in anhydrous EtOAc and pyridine to afford amide **5** is fast (1 h) and clean. Pyridine gave a cleaner impurity profile compared to other bases such as triethylamine. Schotten-Baumann conditions (CH₂Cl₂ or EtOAc and aqueous K₂CO₃) were also investigated, but incomplete reaction was observed due to acid chloride hydrolysis. After an aqueous workup, amide **5** is crystallized from MTBE in 94% yield.

The cyclization step to produce oxindole **6** was first attempted under the conditions reported by Buchwald in his original publication (Pd(OAc)₂/2-(di-*t*-butylphosphino)biphenyl (1:2 ratio), triethylamine, toluene, 80 °C)⁵ but sticky solids were obtained due to the low solubility of **6** in this medium. A solvent (THF, IPA, MeCN, DMF) and base (triethylamine, *n*-Bu₃N) screen identified THF/IPA 4:1 as the optimal combination to dissolve both starting material and product in the presence of triethylamine to give complete conversion in 1 h at 74–76 °C. The Pd catalyst and ligand loadings were 10 and 20 mol%, respectively, and optimization experiments with lower loadings resulted in incomplete reactions.⁸ The reasons for the high catalyst and ligand loadings were not fully investigated and remain unclear.

In summary, a short and high yielding protocol for the preparation of oxindole **6** has been demonstrated on multi-gram scale from inexpensive and readily available starting materials. All intermediates can be isolated after crystallization in high purity and chromatographic purifications are no longer required. This chemistry has been scaled up in our laboratories to produce multi kg-quantities of **6**.⁹

1. Chemical Research & Development, Pharmaceutical Sciences, Pfizer Worldwide Research & Development, Eastern Point Road, Groton, Connecticut 06340, United States. Javier.Magano@Pfizer.com.
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 8. The Supporting Information in reference 5 (page S11) has the ratios of Pd and ligand reversed.
 9. Kiser, E. J.; Magano, J.; Shine, R. J.; Chen, M. H. *Org. Process Res. Dev.* **2012**, *16*, 255.

Appendix

Chemical Abstracts Nomenclature (Registry Number)

- Methyl 4-aminobenzoate: Benzoic acid, 4-amino-, methyl ester (619-45-4)
- 1-Benzyloxycarbonyl-4-piperidone: 1-Piperidinecarboxylic acid, 4-oxo-, phenylmethyl ester (19099-93-5)
- Benzyl 4-(4-(methoxycarbonyl)phenylamino)piperidine-1-carboxylate: 1-Piperidinecarboxylic acid, 4-[[4-(methoxycarbonyl)phenyl]amino]-, phenylmethyl ester (1037834-44-8)
- Benzyl 4-(2-chloro-N-(4-(methoxycarbonyl)phenyl)acetamido)piperidine-1-carboxylate: 1-Piperidinecarboxylic acid, 4-[(2-chloroacetyl)[4-(methoxycarbonyl)phenyl]amino]-, phenylmethyl ester (1037834-45-9)
- Methyl 1-(1-(benzyloxycarbonyl)piperidin-4-yl)-2-oxoindoline-5-carboxylate: 1H-Indole-5-carboxylic acid, 2,3-dihydro-2-oxo-1-[1-

[(phenylmethoxy)carbonyl]-4-piperidiny]-, methyl ester (1037834-34-6)

Sodium triacetoxyborohydride: Borate(1-), tris(acetato-κO)hydro-, sodium (56553-60-7)

Chloroacetyl chloride: Acetyl chloride, 2-chloro- (79-04-9)

Palladium acetate: Acetic acid, palladium(2+) salt (2:1) (3375-31-3)

2-(Di-*tert*-butylphosphino)biphenyl: Phosphine, [1,1'-biphenyl]-2-ylbis(1,1-dimethylethyl)- (224311-51-7)

Triethylamine: Ethanamine, *N,N*-diethyl- (121-44-8)

2-Methyltetrahydrofuran: Furan, tetrahydro-2-methyl- (96-47-9)



Javier Magano was born in Madrid, Spain. He received his B.S. in organic chemistry from Complutense University in Madrid in 1987 and a M.S. degree in chemistry from the University of Michigan in 1990. After working for the oil industry in Spain for three years, he obtained a M.S. degree in rubber and polymer science from the School of Plastics and Rubber at the Center for Advanced Scientific Research in Madrid. In 1995 he moved back to the United States to carry out graduate work at the University of Michigan and in 1998 he joined Pfizer Inc. to work in the early process group in Ann Arbor, MI, and currently in Groton, CT. He has also worked in the area of biologics for 1.5 years.



E. Jason Kiser was born in Chatham, Ontario (Canada) in 1971. He obtained his Bachelors of Science degree (Honors Chemistry) at the University of Windsor (Canada) in 1995. Jason went on to obtain a Master's of Science degree (Chemistry) under the direction of Dr. John M. McIntosh. Jason has over 14 years of synthesis and scale-up experience. He worked for Pfizer for over 10 years at the Ann Arbor, Michigan and Groton, Connecticut research sites as well as the Kalamazoo manufacturing site. He is currently a senior scientist in the process development group at Ash Stevens in Riverview, Michigan.



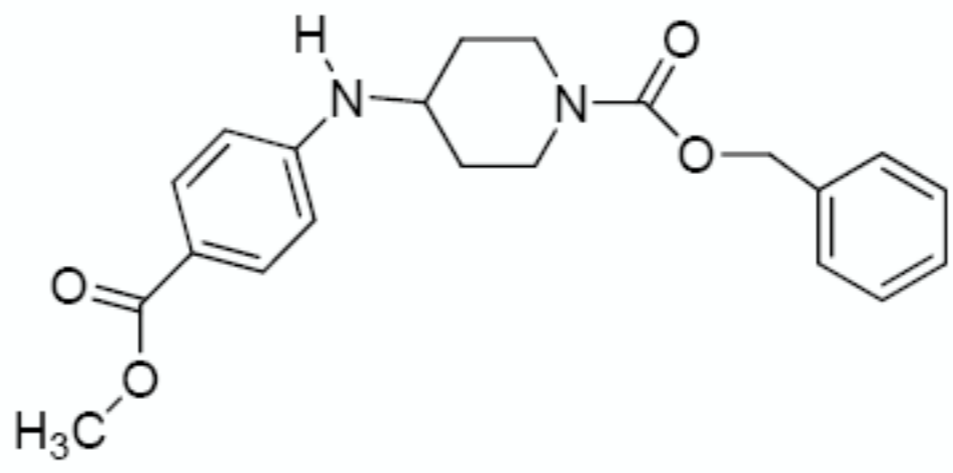
Russell J. Shine pursued his undergraduate studies at University of Pennsylvania, where he received his B.A. degree in Biology in 1981. After joining Pfizer Inc. in 1983, he joined Professor Phyllis Brown's research group at the University of Rhode Island, where he received his M.S. in Chemistry in 1991. He is currently working in the API manufacturing group within the Pharmaceutical Science Development Division of Pfizer Inc.



Michael Chen was born in Shanghai, China. He received his B.S. of chemistry from Shanghai University, and a M.S. and Ph.D. from the University of Michigan in 1988. After holding post-doctoral positions with Professor Paul Knochel at the University of Michigan and Peter Wuts and Tomi Sawyer at the Upjohn Company, Michael joined Parke-Davis Pharmaceutical Research/Pfizer where he worked until 2007 as a process chemist. He currently is the Chief Scientific Officer at MasTeam Biotech Research Institute in China.

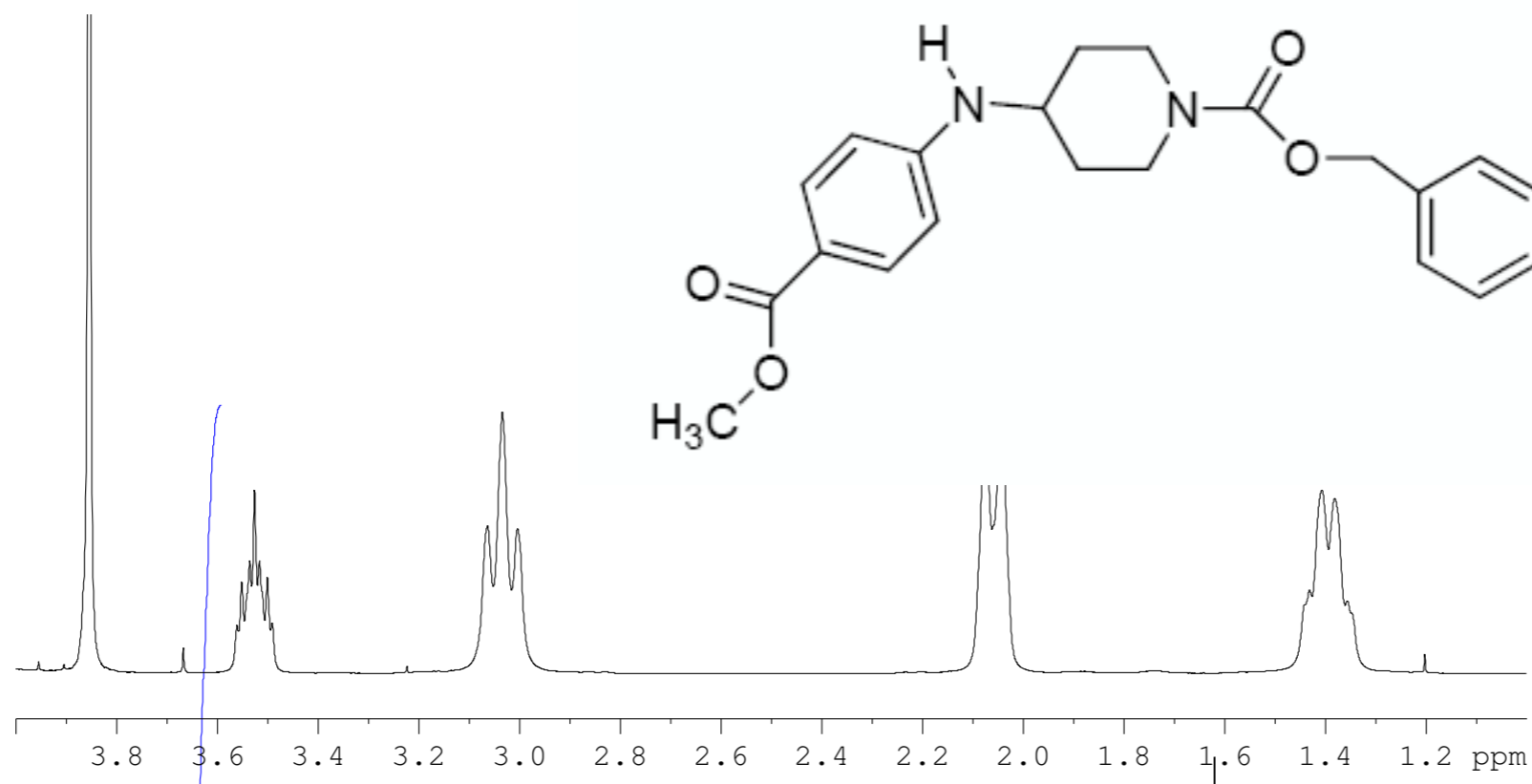
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 EXPNO 3
 PROCNO 1
 Date_ 20120730
 Time 7.15
 INSTRUM spect
 PROBHD 5 mm PABBO BB-
 PULPROG zg30
 TD 32768
 SOLVENT CDCl3
 NS 32
 DS 2
 SWH 6410.256 Hz
 FIDRES 0.195625 Hz
 AQ 2.5559540 sec
 RG 40.3
 DW 78.000 usec
 DE 6.50 usec
 TE 303.0 K
 D1 0.10000000 sec
 TD0 1

===== CHANNEL f1 =====
 NUC1 1H
 P1 10.40 usec
 PL1 0.00 dB
 SFO1 400.1324710 MHz
 SI 32768
 SF 400.1300052 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00



32077-202
 crystallized product
 nmr400c h-1
 hughesda

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity
1	7.8825	3154.0248	0.39
2	7.8761	3151.4639	3.33
3	7.8713	3149.5433	1.04
4	7.8589	3144.5817	0.99
5	7.8540	3142.6211	3.52
6	7.8476	3140.0602	0.41
7	7.3825	2953.9598	0.44
8	7.3772	2951.8391	3.32
9	7.3754	2951.1188	2.97
10	7.3658	2947.2776	10.28
11	7.3546	2942.7961	0.78
12	7.3445	2938.7548	0.96
13	7.3372	2935.8339	0.65
14	7.3345	2934.7535	0.55
15	7.3327	2934.0333	0.63
16	7.3263	2931.4725	0.32
17	7.3230	2930.1520	0.62
18	7.3171	2927.7913	0.26
19	7.3104	2925.1104	0.31
20	7.2701	2908.9852	1.00
21	6.5712	2629.3343	0.41
22	6.5648	2626.7735	3.21
23	6.5601	2624.8928	1.05
24	6.5474	2619.8112	0.95
25	6.5426	2617.8906	3.15
26	6.5363	2615.3698	0.39
27	5.1531	2061.9099	5.82
28	4.1681	1667.7819	0.47
29	4.1390	1656.1381	0.51
30	4.1014	1641.0932	0.58
31	3.8536	1541.9410	15.00
32	3.5521	1421.3018	0.26
33	3.5364	1415.0198	0.32
34	3.5266	1411.0985	0.53
35	3.5168	1407.1772	0.32
36	3.5010	1400.8551	0.27
37	3.0638	1225.9183	0.42
38	3.0343	1214.1145	0.75
39	3.0046	1202.2306	0.41
40	2.0729	829.4295	0.64
41	2.0460	818.6660	0.71
42	1.4315	572.7861	0.24
43	1.4067	562.8629	0.52
44	1.3812	552.6596	0.50
45	1.3563	542.6963	0.21



Integration values for the peaks in the spectrum:
 1.930, 4.606, 2.021, 2.000, 3.012, 2.997, 1.019, 2.019, 2.035, 2.030

9.5 9.0 8.5 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 ppm

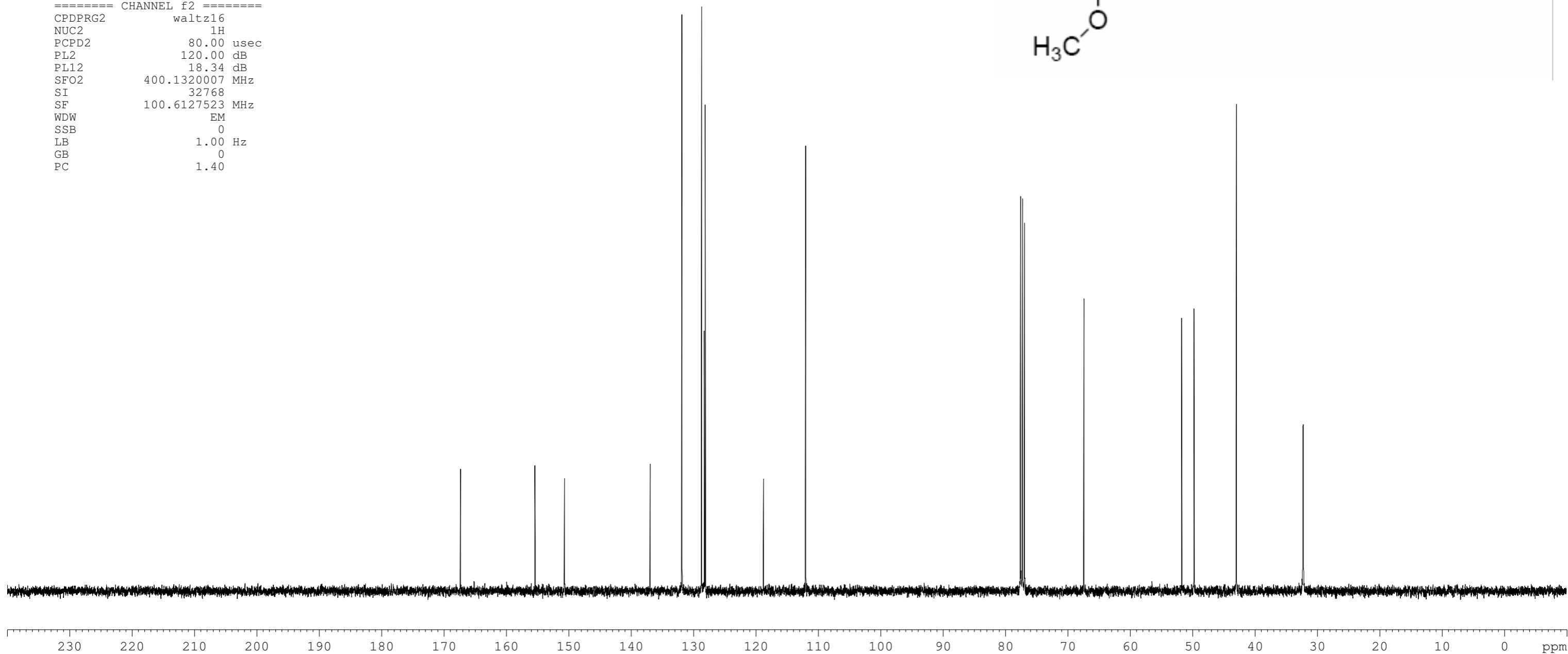
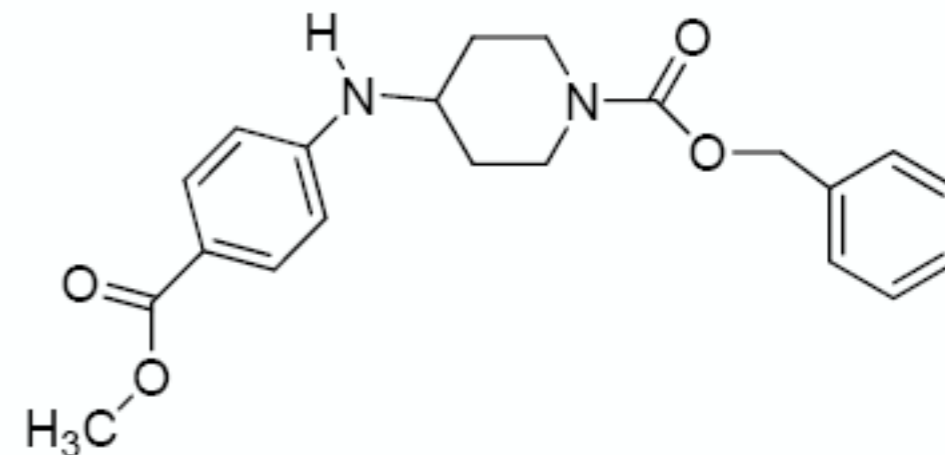
32077-202
crystallized product
nmr400c c-13
hughesda

NAME 32077-202
EXPNO 4
PROCNO 1
Date_ 20120730
Time 7.20
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 345
DS 4
SWH 26315.789 Hz
FIDRES 0.401547 Hz
AQ 1.2452340 sec
RG 8192
DW 19.000 usec
DE 6.50 usec
TE 303.0 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 40

=====
CHANNEL f1
NUC1 13C
P1 8.00 usec
PL1 4.50 dB
SFO1 100.6238364 MHz

=====
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 120.00 dB
PL12 18.34 dB
SFO2 400.1320007 MHz
SI 32768
SF 100.6127523 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

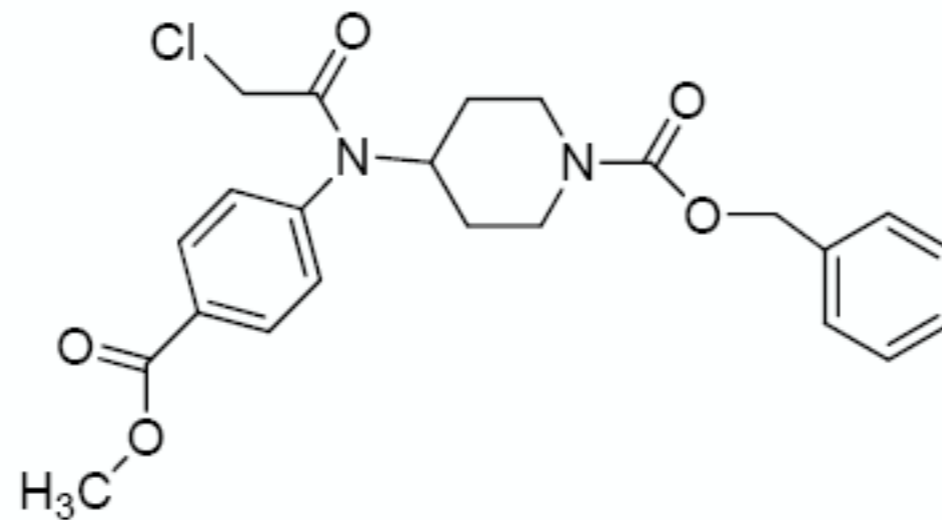
167.34 155.37 150.67 136.89 131.83 128.69 128.23 128.06 118.76 112.00 77.55 77.23 76.91 67.38 51.70 49.72 42.93 32.23



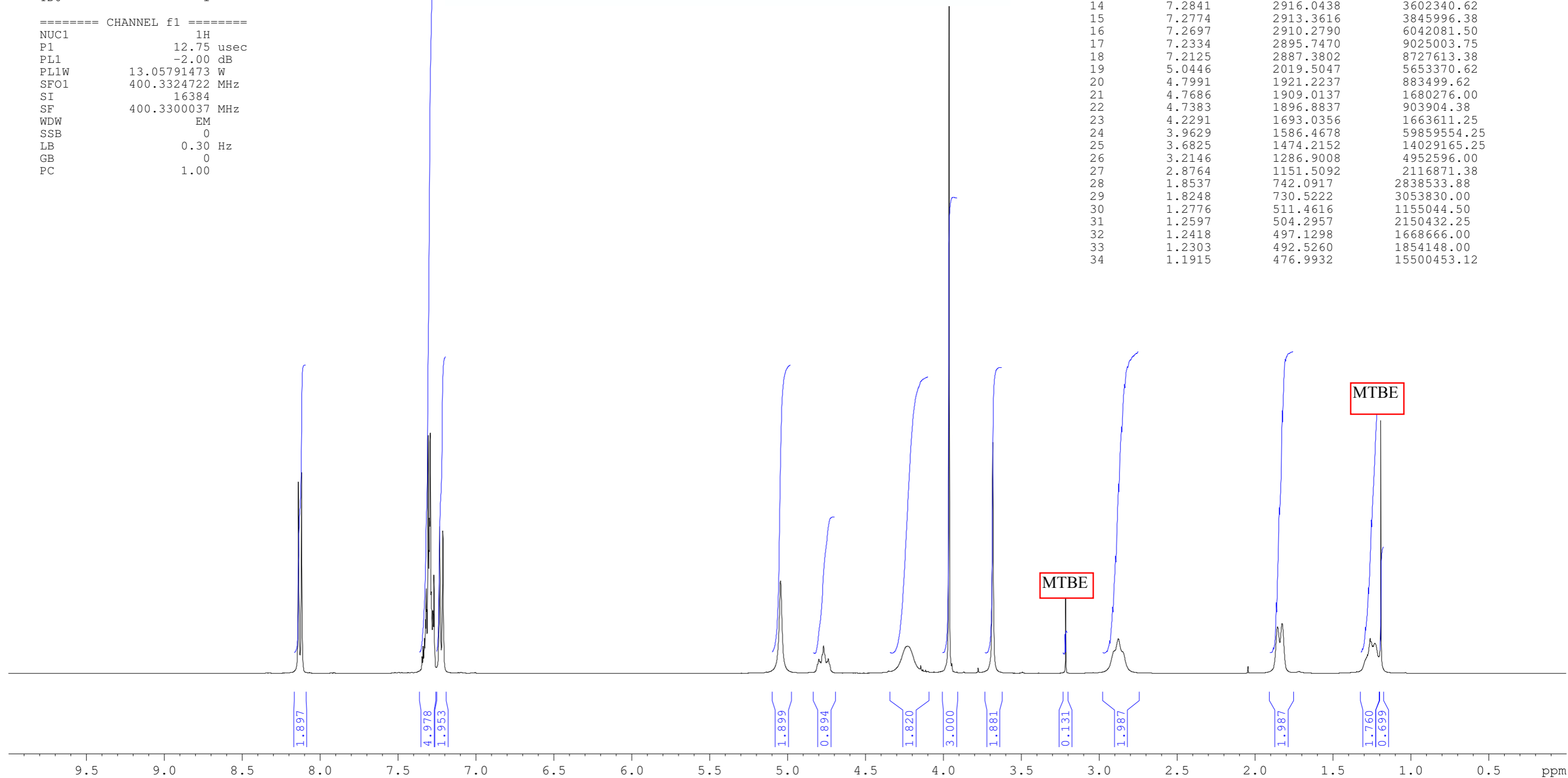
NAME 32077-204
 EXPNO 8
 PROCNO 1
 Date_ 20120813
 Time 18.12
 INSTRUM spect
 PROBHD 5 mm PABBO BB-
 PULPROG zg30
 TD 32768
 SOLVENT CDCl3
 NS 32
 DS 2
 SWH 6578.947 Hz
 FIDRES 0.200774 Hz
 AQ 2.4904180 sec
 RG 90.5
 DW 76.000 usec
 DE 6.50 usec
 TE 300.0 K
 D1 0.10000000 sec
 TD0 1

===== CHANNEL f1 =====
 NUC1 1H
 P1 12.75 usec
 PL1 -2.00 dB
 PL1W 13.05791473 W
 SFO1 400.3324722 MHz
 SI 16384
 SF 400.3300037 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

32077-204
 crystallized product
 nmr400b h-1
 hughesda



Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity [abs]
1	8.1374	3257.6454	11737674.75
2	8.1157	3248.9582	9956863.88
3	7.3460	2940.8242	1018405.25
4	7.3397	2938.3021	1666236.25
5	7.3301	2934.4590	2154468.50
6	7.3250	2932.4173	3311569.38
7	7.3193	2930.1354	4797715.12
8	7.3165	2929.0145	3799460.88
9	7.3066	2925.0512	14612752.25
10	7.3016	2923.0496	7557565.12
11	7.2992	2922.0888	8644153.62
12	7.2942	2920.0871	14173517.12
13	7.2875	2917.4049	4967737.50
14	7.2841	2916.0438	3602340.62
15	7.2774	2913.3616	3845996.38
16	7.2697	2910.2790	6042081.50
17	7.2334	2895.7470	9025003.75
18	7.2125	2887.3802	8727613.38
19	5.0446	2019.5047	5653370.62
20	4.7991	1921.2237	883499.62
21	4.7686	1909.0137	1680276.00
22	4.7383	1896.8837	903904.38
23	4.2291	1693.0356	1663611.25
24	3.9629	1586.4678	59859554.25
25	3.6825	1474.2152	14029165.25
26	3.2146	1286.9008	4952596.00
27	2.8764	1151.5092	2116871.38
28	1.8537	742.0917	2838533.88
29	1.8248	730.5222	3053830.00
30	1.2776	511.4616	1155044.50
31	1.2597	504.2957	2150432.25
32	1.2418	497.1298	1668666.00
33	1.2303	492.5260	1854148.00
34	1.1915	476.9932	15500453.12



32077-204
crystallized product
nmr400b c-13
hughesda

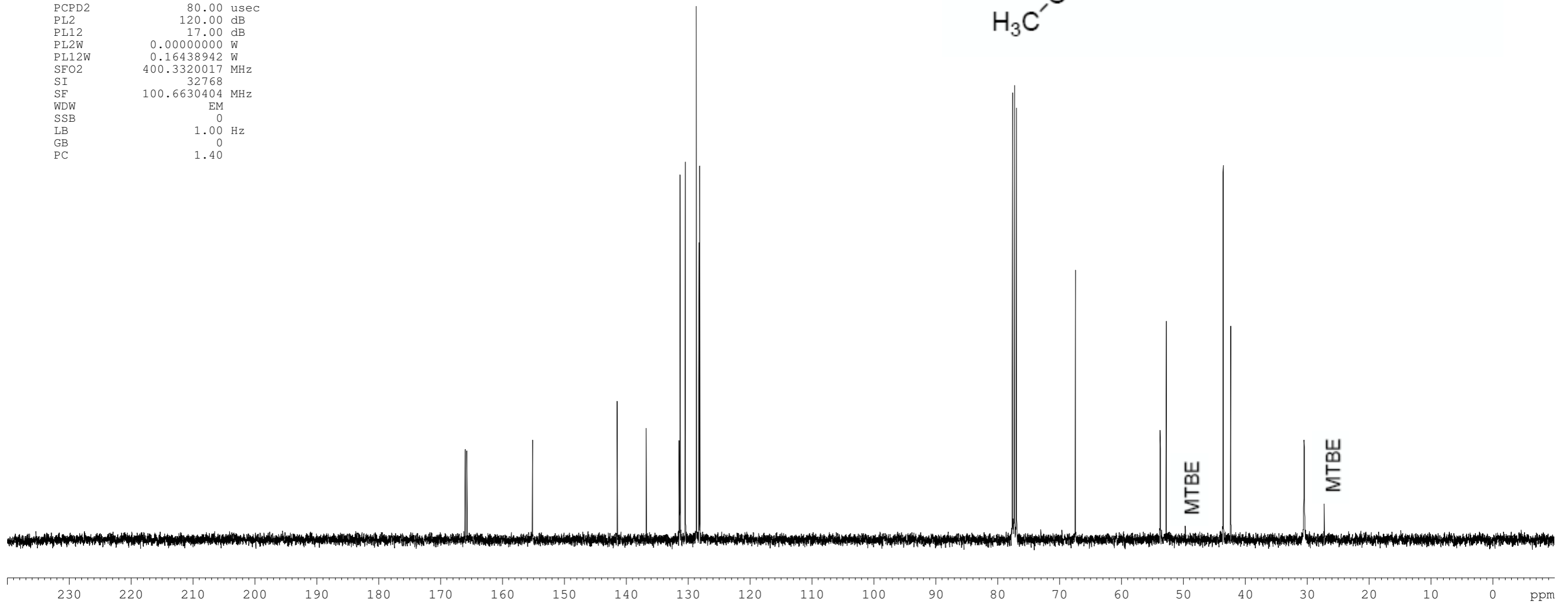
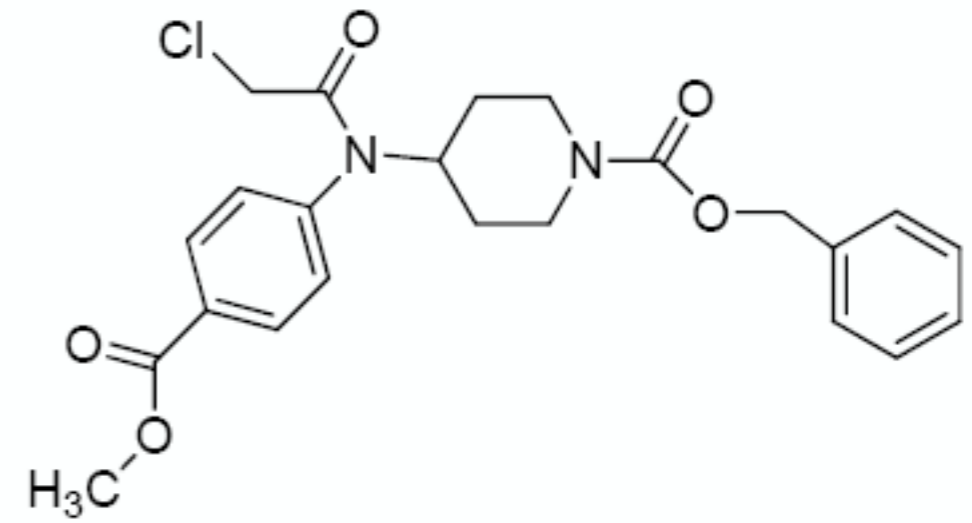
NAME 32077-204
EXPNO 9
PROCNO 1
Date_ 20120813
Time 18.19
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 472
DS 4
SWH 26315.789 Hz
FIDRES 0.401547 Hz
AQ 1.2452340 sec
RG 8192
DW 19.000 usec
DE 6.50 usec
TE 300.0 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 40

=====
CHANNEL f1
NUC1 13C
P1 3.50 usec
PL1 0.00 dB
PL1W 31.90095711 W
SFO1 100.6741319 MHz

=====
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 120.00 dB
PL12 17.00 dB
PL2W 0.00000000 W
PL12W 0.16438942 W
SFO2 400.3320017 MHz
SI 32768
SF 100.6630404 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

165.97
165.70
155.10
141.43
136.73
131.41
131.27
130.42
128.64
128.21
128.09

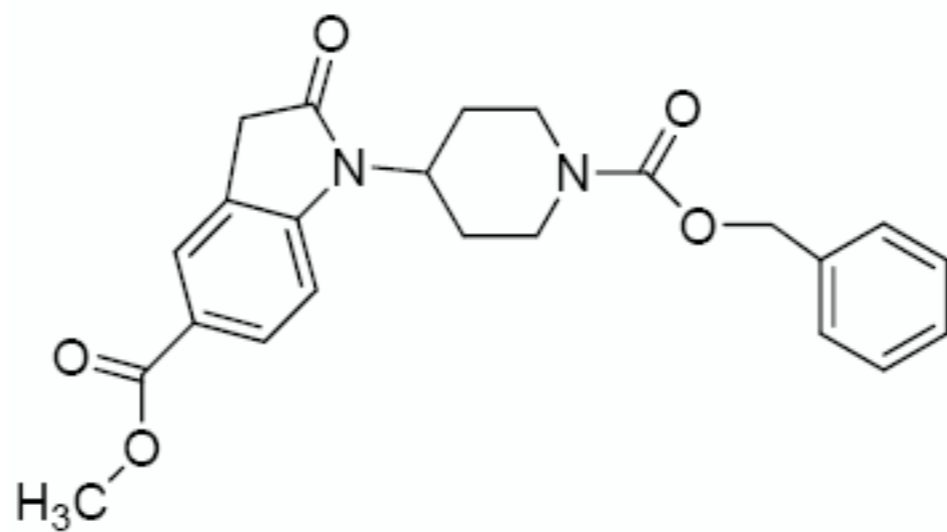
77.55
77.23
76.91
67.38
53.67
52.71
43.50
42.27
30.41
27.16



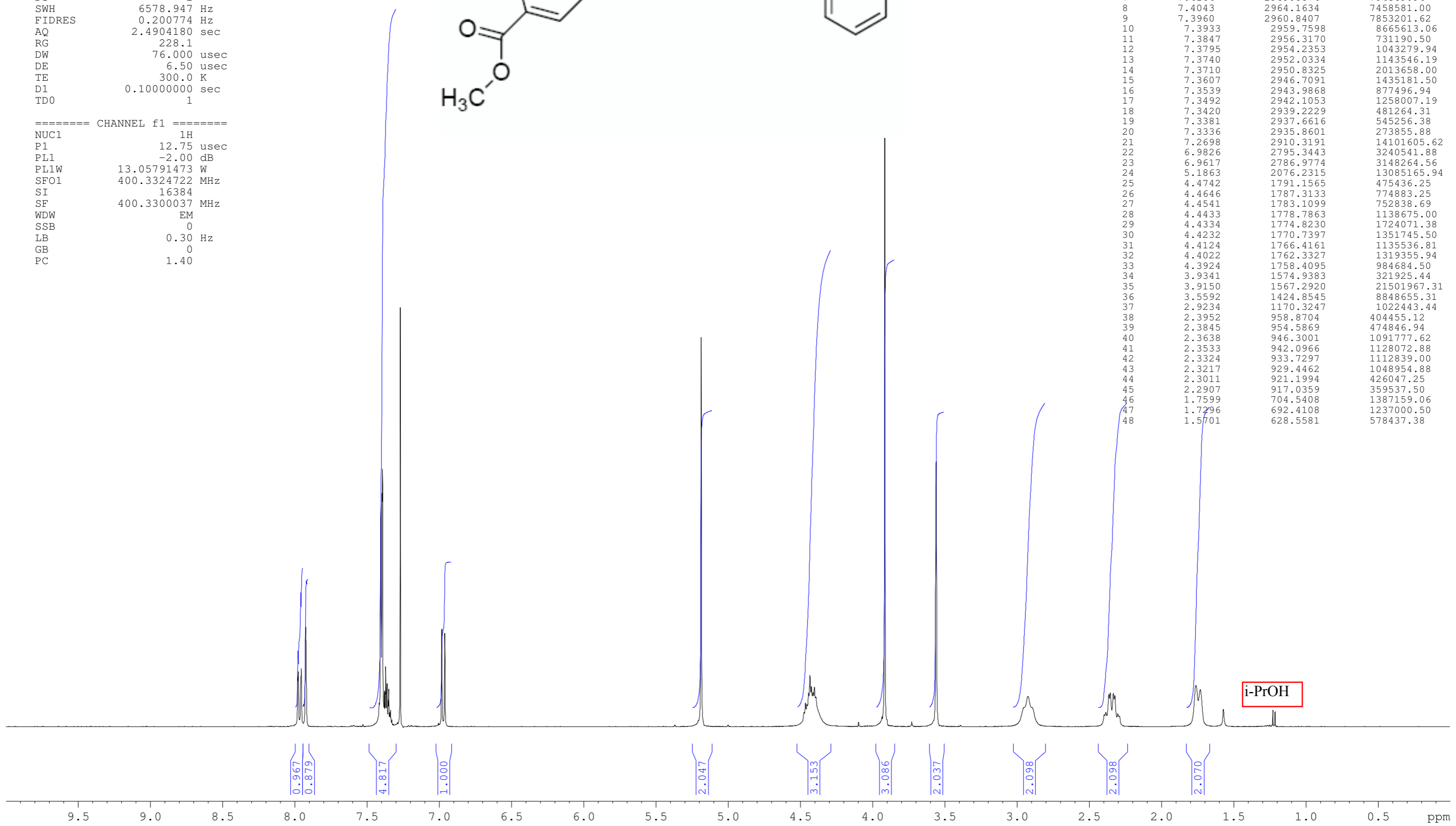
NAME 32077-206
 EXPNO 2
 PROCNO 1
 Date_ 20120826
 Time 8.12
 INSTRUM spect
 PROBHD 5 mm PABBO BB-
 PULPROG zg30
 TD 32768
 SOLVENT CDCl3
 NS 32
 DS 2
 SWH 6578.947 Hz
 FIDRES 0.200774 Hz
 AQ 2.4904180 sec
 RG 228.1
 DW 76.000 usec
 DE 6.50 usec
 TE 300.0 K
 D1 0.10000000 sec
 TD0 1

===== CHANNEL f1 =====
 NUC1 1H
 P1 12.75 usec
 PL1 -2.00 dB
 PL1W 13.05791473 W
 SFO1 400.3324722 MHz
 SI 16384
 SF 400.3300037 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.40

32077-206
 crystallized
 nmr400b h-1
 hughesda



Peak	?(F1) [ppm]	?(F1) [Hz]	Intensi
1	7.9800	3194.6334	1647449.62
2	7.9763	3193.1522	1663094.00
3	7.9589	3186.1865	1655441.56
4	7.9553	3184.7453	1771529.44
5	7.9257	3172.8955	3348556.25
6	7.9232	3171.8947	2944575.75
7	7.4164	2969.0074	794869.94
8	7.4043	2964.1634	7458581.00
9	7.3960	2960.8407	7853201.62
10	7.3933	2959.7598	8665613.06
11	7.3847	2956.3170	731190.50
12	7.3795	2954.2353	1043279.94
13	7.3740	2952.0334	1143546.19
14	7.3710	2950.8325	2013658.00
15	7.3607	2946.7091	1435181.50
16	7.3539	2943.9868	877496.94
17	7.3492	2942.1053	1258007.19
18	7.3420	2939.2229	481264.31
19	7.3381	2937.6616	545256.38
20	7.3336	2935.8601	273855.88
21	7.2698	2910.3191	14101605.62
22	6.9826	2795.3443	3240541.88
23	6.9617	2786.9774	3148264.56
24	5.1863	2076.2315	13085165.94
25	4.4742	1791.1565	475436.25
26	4.4646	1787.3133	774883.25
27	4.4541	1783.1099	752838.69
28	4.4433	1778.7863	1138675.00
29	4.4334	1774.8230	1724071.38
30	4.4232	1770.7397	1351745.50
31	4.4124	1766.4161	1135536.81
32	4.4022	1762.3327	1319355.94
33	4.3924	1758.4095	984684.50
34	3.9341	1574.9383	321925.44
35	3.9150	1567.2920	21501967.31
36	3.5592	1424.8545	8848655.31
37	2.9234	1170.3247	1022443.44
38	2.3952	958.8704	404455.12
39	2.3845	954.5869	474846.94
40	2.3638	946.3001	1091777.62
41	2.3533	942.0966	1128072.88
42	2.3324	933.7297	1112839.00
43	2.3217	929.4462	1048954.88
44	2.3011	921.1994	426047.25
45	2.2907	917.0359	359537.50
46	1.7599	704.5408	1387159.06
47	1.7296	692.4108	1237000.50
48	1.5701	628.5581	578437.38



32077-206
crystallized
nmr400b c-13
hughesda

NAME 32077-206
EXPNO 3
PROCNO 1
Date_ 20120826
Time 8.18
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 12790
DS 4
SWH 26315.789 Hz
FIDRES 0.401547 Hz
AQ 1.2452340 sec
RG 8192
DW 19.000 usec
DE 6.50 usec
TE 300.0 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 40

=====
CHANNEL f1
NUC1 13C
P1 3.50 usec
PL1 0.00 dB
PL1W 31.90095711 W
SFO1 100.6741319 MHz

=====
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 120.00 dB
PL12 17.00 dB
PL2W 0.00000000 W
PL12W 0.16438942 W
SFO2 400.3320017 MHz
SI 32768
SF 100.6630365 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

175.15 166.91 155.36 147.82 136.85 130.52 128.78 128.37 128.27 126.09 124.81 124.27 109.33 77.55 77.43 77.23 76.91 67.62 52.28 50.42 43.95 35.71 28.31

