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of Reliable Methods
for the Preparation
of Organic Compounds

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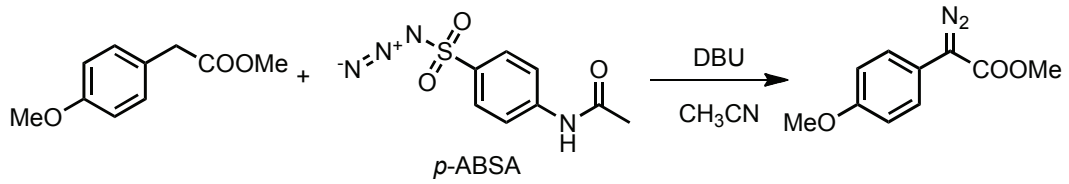
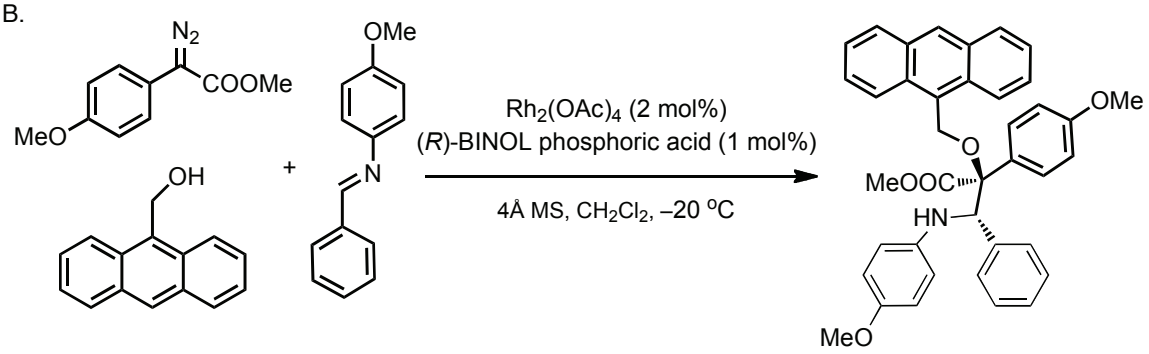
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

ENANTIOSELECTIVE THREE-COMPONENT REACTION FOR THE PREPARATION OF β-AMINO-α-HYDROXY ESTERS

A.



B.



Submitted by Jing Zhou, Xinfang Xu and Wenhao Hu.*[1]
Checked by John Frederick Briones and Huw M. L. Davies.

1. Procedure

A. Methyl 2-diazo-2-(4-methoxyphenyl) acetate. (1c) A 500-mL three-necked flask is equipped with a 100-mL dropping funnel, a rubber septum fitted with argon inlet needle and an egg-shaped 1 ¼ x 5/8 in magnetic stir bar. DBU (Note 1) (14.2 mL, 95.0 mmol, 1.50 equiv) in CH_3CN (60 mL) (Note 2) is added to the dropping funnel. The flask is charged with methyl 2-(4-methoxyphenyl) acetate (Note 3) (11.4 g, 63.3 mmol, 1.00 equiv), *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (Note 4) (18.2 g, 76.0 mmol, 1.20 equiv) and CH_3CN (120 mL). The DBU solution is added dropwise into reaction mixture. The resulting mixture is stirred over 12 h, and reaction progress is monitored by TLC analysis (Note 5). The reaction mixture is cooled with an ice bath, and saturated aqueous NH_4Cl (100 mL) (Note 6) is then added to quench the reaction. The mixture is extracted with ethyl ether (3 x 100 mL) (Note 7), and the combined organic

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layers are washed with saturated brine (150 mL) (Note 8), dried over sodium sulfate (10 g) (Note 9) and concentrated by rotary evaporation (23 °C, 40 mmHg) to afford the crude product. Column chromatography purification of the crude product over silica gel (Note 10) affords 7.9 g (60%) of methyl 2-diazo-2-(4-methoxyphenyl) acetate as an orange solid (Notes 11 and 12). The product purity is >99% by HPLC (Note 13).

B. (2S,3S)-methyl-2-(9-anthryloxymethyl)-2-(4-methoxyphenyl)-3-(4-methoxyphenylamino)-3-phenylpropanoate. (7a) To a 100-mL single-necked, round-bottomed flask equipped with an octagonal-shaped 1 x 5/16 in magnetic stir bar and a rubber septum with argon inlet, is charged in sequence with 9-anthracenemethanol (2.60 g, 12.5 mmol, 1.0 equiv) (Note 14), benzaldehyde-*p*-anisidine imine (2.64 g, 12.5 mmol, 1.0 equiv) (Note 15), $Rh_2(OAc)_4$ (110 mg, 0.25 mmol, 0.02 equiv) (Note 16), (*R*)-2,2'-(9-phenanthryl)-BINOL phosphoric acid (87.5 mg, 0.125 mmol, 0.01 equiv) (Note 17), 4 Å molecular sieves (5.0 g) (Note 18) and dry CH_2Cl_2 (50 mL) (Note 19). The suspension is stirred for 30 min at room temperature (23 °C). The reaction system is cooled to –20 °C in isopropanol bath using Neslab cooling system. Methyl 2-diazo-2-(4-methoxyphenyl) acetate (3.86 g, 18.7 mmol, 1.5 equiv) in 10 mL dry CH_2Cl_2 is then added over 1 h *via* a syringe pump. After completion of the addition, the reaction mixture is stirred for additional 2 h at –20 °C until completion of the reaction as monitored by TLC analysis (Note 20). The reaction is quenched with 2 mL of saturated aqueous sodium hydrogen carbonate solution (Note 21), and the internal temperature which was measured by a thermometer rises from –20°C to about 0 °C during the time of quenching. The molecular sieves are removed by filtration through a pad of silica gel (10 g) and the filtrate is concentrated by rotary evaporation (40 °C, 40 mmHg) to a volume of approximately 25 mL. To the residue solution is added silica gel (10 g) and the solvent is further removed by rotary evaporation (40 °C, 40 mmHg) to give a dry powder. The crude product in the powder is subjected to column chromatography over silica gel (90 g) to give 6.5 g (87%) of (2*S*, 3*S*)-methyl 2-(9-anthryloxymethyl)-2-(4-methoxyphenyl)-3-(4-methoxyphenylamino)-3-phenylpropanoate (Note 22) (Note 23). The product purity is 99% by HPLC (Note 24), and the enantiomeric purity is 94% *ee* by HPLC analysis using a chiral column (Notes 25 and 26).

2. Notes

1. DBU (98%) was purchased from Aldrich and used without further purification.

2. Acetonitrile was purchased from EMD Chemicals Inc. and used without further purification.

3. The checkers used methyl 2-(4-methoxyphenyl) acetate (>97%) that was purchased from Alfa Aesar Chemical Company, Inc. and used without further purification.

4. *p*-Acetamidobenzenesulfonyl azide was prepared from *p*-acetamidobenzenesulfonyl chloride according to the literature method.[2] *p*-Acetamidobenzenesulfonyl chloride (98+%) was purchased from Alfa Aesar Chemical Company, Inc. and sodium azide was purchased from Aldrich Chemical Company, Inc.

> Caution! The original procedure using methylene chloride as solvent should be avoided because it can produce the highly explosive material, diazidomethane, as side product.[3]

5. Thin layer chromatography was performed on Whatman precoated 60 Å silica gel plates with fluorescent indicator eluting with 9% ethyl acetate/petrol ether, visualized by a 254-nm UV lamp. The observed R_f values are 0.70 for the diazo product and 0.60 for methyl (4-methoxyphenyl) acetate.

6. NH_4Cl was purchased from Aldrich Chemical Company, Inc.

7. Ethyl ether was purchased from Aldrich Chemical Company, Inc. and used without further purification.

8. Sodium chloride was purchased from Aldrich Chemical Company, Inc.

9. Sodium sulfate was purchased from EMD Chemicals Inc.

10. Silica gel was purchased from Sorbent Technologies Company with the following specifications: porosity 60 Å, particle size 40-64 μm, surface area 450–550 m^2/g.

11. Flash column chromatography was performed on a silica gel column (5.5 cm width x 11cm length, 90 g silica gel). The product was eluted with petroleum ether, then 1500 mL of petroleum ether/ethyl acetate, 50:1. The desired product was obtained in orange fractions 7-13 (50 mL each), which were combined and concentrated by rotary evaporation (23 °C,

40 mmHg) to provide an orange solid that was dried for 3 h (25 °C, 0.1 mmHg).

12. The diazo product exhibits the following physicochemical properties: orange solid; IR (neat) 2953, 2837, 2079, 1697, 1511 cm^{-1}; mp 44–45 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.81 (s, 3 H), 3.85 (s, 3 H), 6.95 (d, J = 9.2 Hz, 2 H), 7.39 (d, J = 9.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.2, 55.5, 114.8, 117.1, 126.1, 158.3, 166.3 (C=N, signal missing); HRMS (ESI): calculated for $C_{20}H_{21}N_2O_6$ 385.1321 found 385.1392 $[2M-N_2+H]^+$; Anal. calcd. for $C_{10}H_{10}N_2O_3$ C, 58.25; H, 4.89; N, 13.59; Found C, 58.39; H, 4.90; N, 13.45.

13: Dynamax 60A column was used with 10% isopropanol in hexanes as eluent, a flow rate of 0.7 mL/min, and detection by UV (254 nm) detector. The t_R of the product is 5.83 min.

14. The checkers used 9-anthracenemethanol (97%), which was purchased from Aldrich Chemical Company, Inc. and was used without further purification.

15. Benzaldehyde-*p*-anisidine imine was prepared by condensation of benzaldehyde (>98.5%) with *p*-anisidine (99%) according to the literature method.[4] Benzaldehyde was purchased from Aldrich Chemical Company, Inc. and used without further purification. *p*-Anisidine was purchased from Alfa Aesar Chemical Company, Inc. and used without further purification.

16. $Rh_2(OAc)_4$ (98+%) was purchased from Johnson Matthey Company.

17. (*R*)-2,2'-(9-Phenanthryl)-BINOL phosphoric acid was prepared from (*R*)-BINOL (chiral purity >99%) according to the previous procedure in this volume. (*R*)-BINOL was purchased from Strem Chemicals Inc.

18. Powder 4 Å molecular sieves were purchased from Acros Organics. They were activated at 200°C in the oven before use.

19. Methylene chloride (HPLC grade) was purchased from Fischer Scientific Company and freshly distilled over calcium hydride before use.

20. Thin layer chromatography was performed on Whatman precoated 60 Å silica gel plates with fluorescent indicator eluting with 15% ethyl acetate/petrol ether and visualized by a 254-nm UV lamp. Observed R_f values are 0.30 for the desired product and 0.32 for the O-H insertion product.

21. Sodium hydrogen carbonate was purchased from Aldrich Chemical Company, Inc.

22. Column chromatography was performed using 90 g of 200-300

mesh silica gel 60 (5.5 x 11 cm), and 50-mL fractions were collected (200 mL of petroleum ether, then 500 mL of petroleum ether/CH_2Cl_2/ethyl acetate, 30:3:1, then 500 mL each of 20:2:1, 15:3:1, 15:5:1, 15:6:1, and finally 500 mL of CH_2Cl_2). The desired product was obtained in fractions 22-54, which were combined and concentrated by rotary evaporation (40 °C, 40 mmHg). The residue was then dissolved in 20 mL of CH_2Cl_2, and 20 mL of petrol ether and concentrated by rotary evaporation (40 °C, 40 mmHg) to obtain white solid. The resulting solid was dried (23 °C, 0.1 mmHg) for 5 h.

23. The product exhibits the following physicochemical properties: white solid; $[\alpha]^{20}_D$= +34.4 (c=1, EtOAc); IR(neat) 3393, 3058, 2950, 2834, 1744, 1608, 1509, 1453, 1406, 1384, 1299, 1242, 1178, 1089, 1035, 819, 735, 702 cm^{-1}; mp 141–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.65 (s, 3 H), 3.74 (s, 3 H), 3.93 (s, 3 H), 4.63 (d, *J* = 9.6 Hz, 1 H), 5.12 (d, *J* = 9.6 Hz, 1 H), 5.24 (d, *J* = 10.3 Hz, 1 H), 5.74 (d, *J* = 10.4 Hz, 1 Hz), 6.41 (d, *J* = 8.8 Hz, 2 H), 6.62 (d, *J* = 8.8 Hz, 2 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 7.15 (m, 5 H), 7.55 (m, 4 H), 7.82 (d, *J* = 9.2 Hz, 2 H), 8.07 (d, *J* = 8Hz, 2 H), 8.29 (d, *J* = 8.8 Hz, 2 H), 8.54 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 51.9, 55.4, 55.7, 60.4, 65.6, 87.7, 113.6, 114.7, 115.5, 125.2, 126.1, 127.6, 128.5, 129.0, 129.2, 129.3, 130.8, 131.2, 131.7, 138.9, 140.5, 152.2, 160.0, 172.0; HRMS(ESI): calcd for $C_{39}H_{36}NO_5$ 598.2515 found 598.2596 $[M+H]^+$; Anal. calcd. for $C_{39}H_{35}NO_5$ C, 78.37; H, 5.90; N, 2.34; Found C, 78.45; H, 5.93; N, 2.36.

24. Dynamax 60A column was used with 5% isopropanol in hexanes as eluent, a flow rate of 0.7 mL/min, and detection by UV (254 nm) detector. The t_R of the product is 6.53 min.

25. AD-H column is available from Daicel Chemical Industries, Ltd. A 30-cm column was used with 5% isopropanol in hexanes as a mobile phase, a flow rate of 0.7 mL/min, and detection by UV (254nm). The t_R of the minor isomer (2*R,*3*R*) was 27.0 min and the major (2*S,*3*S*)-isomer was 18.4 min.

26. The racemic product was prepared using the same procedure as described above. 1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate (95%, purchased from Aldrich Chemical Company, Inc.) was used instead of (*R*)-2,2'-(9-phenanthryl)-BINOL phosphoric acid.

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 catalytic asymmetric version of the three-component reaction of aryldiazoacetates, alcohols, and imines, employs a novel cooperative catalysis strategy by $Rh_2(OAc)_4$ and chiral Brønsted acid. The reaction proceeds through oxonium ylide intermediates **IIa** or **IIb**, which are generated in situ from the diazo compounds and the alcohols in the presence of $Rh_2(OAc)_4$. This intermediate can be trapped by electrophiles such as imines activated by the chiral Brønsted acid catalyst. As shown in Scheme 1, the oxonium ylide **II** and the activated iminium **III** undergo an enantioselective Mannich-type reaction via proposed transition state **IV** to generate optically active **4**.

The procedure has been employed successfully with other diazo compounds and imines (See Table 1).[5] The Brønsted acid catalyst prepared from (*S*)-BINOL has also been used to give the *(2R,3R)*-product.

Scheme 1 Proposed Reaction Mechanism of the Title Reaction

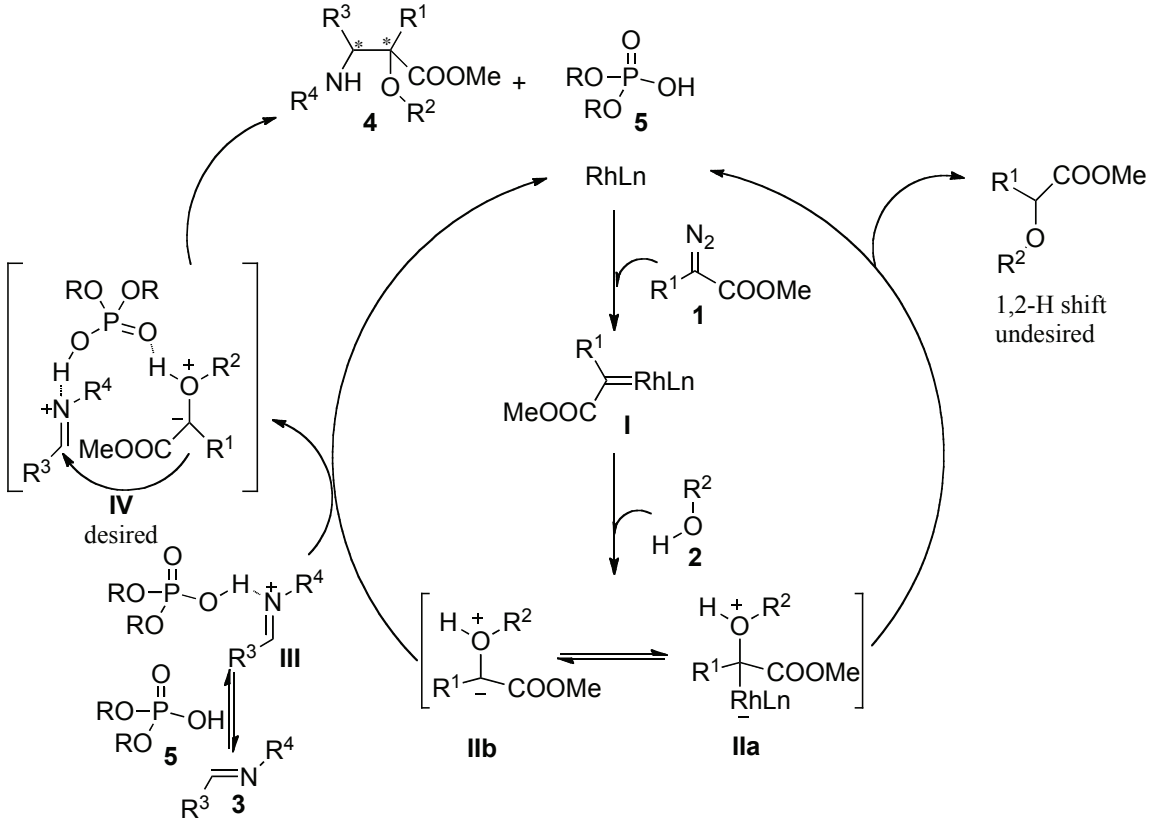
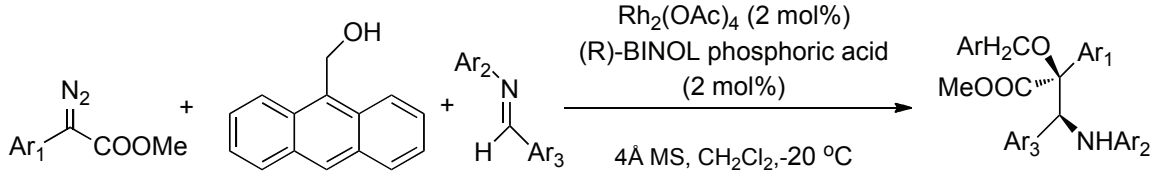


Table 1 Enantioselective Three-Component Reaction with Various Diazo Compounds and Imines



1a~1e **3**, Ar_2=Ph; **6**, Ar_2=PMP; Ar=9-anthryl **7**

entry[a]	**1**(Ar_1)	**3** or **6** (Ar_3)	**7**	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a** (Ph)	**6a** (*m*-$CH_3C_6H_4$)	**7b**	96	>99:1	90
2[e]	**1a** (Ph)	**6b** (C_6H_5)	**7c**	83	>99:1	94
3	**1a** (Ph)	**6c** (2,3-$Cl_2C_6H_3$)	**7d**	95	>99:1	93
4	**1a** (Ph)	**6d** (*o*-CH_3 C_6H_4)	**7e**	95	>99:1	93
5	**1a** (Ph)	**6e** (*p*-CH_3 C_6H_4)	**7f**	92	>99:1	98
6	**1a** (Ph)	**6f** (*o*-ClC_6H_4)	**7g**	91	>99:1	92
7	**1a** (Ph)	**3b** (*p*-BrC_6H_4)	**7h**	87	>99:1	92
8	**1a** (Ph)	**6g** (*p*-ClC_6H_4)	**7i**	83	>99:1	93
9	**1a** (Ph)	**6h** (*p*-ClC_6H_4)	**7j**	82	>99:1	94
10	**1a** (Ph)	**6i** (1-naphthyl)	**7k**	88	>99:1	95
11	**1b** (*m*-BrC_6H_4)	**3a** (C_6H_5)	**7l**	96	>99:1	84
12	**1c** (*p*-$MeOC_6H_4$)	**6h** (*p*-BrC_6H_4)	**7m**	97	>99:1	95
13	**1d** (*p*-BrC_6H_4)	**6b** (C_6H_5)	**7n**	84	>99:1	94
14	**1d** (*p*-BrC_6H_4)	**6g** (*p*-ClC_6H_4)	**7o**	95	>99:1	92
15	**1d** (*p*-BrC_6H_4)	**3a** (C_6H_5)	**7p**	84	>99:1	92
16	**1e** (*o*-BrC_6H_4)	**6h** (*p*-BrC_6H_4)	**7q**	91	>99:1	83
17[f]	**1c** (*p*-$MeOC_6H_4$)	**6b** (C_6H_5)	**7r**	81	>99:1	98

[a] Reactions performed on a 0.25 mmol scale. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [d] Determined by HPLC. [e] Reaction performed on a 2.5 mmol scale with $Rh_2(OAc)_4$ (0.5 mol%) and chiral phosphoric acid (1 mol%). [f] (*S*)-BINOL phosphoric acid is used.

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and from the MOST of China (2011CB808600).

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Benzaldehyde (100-52-7)
p-Anisidine (104-94-9)
Benzaldehyde-*p*-anisidine imine (783-08-4)
9-Anthracenemethanol (1468-95-7)
9-Anthraldehyde (642-31-9)
R-(+)-1,1'-Bi-2-naphthol, (*R*)-BINOL (18531-94-7)
(*R*)-2,2'-(9-Phenanthryl)-BINOL phosphoric acid
Dirhodium tetraacetate dehydrate (15956-28-2)
Methyl (4-methoxyphenyl)diazoacetate
4-Methoxyphenylacetic acid (101-01-8)
(2*S*, 3*S*)-Methyl-2-(9-anthryloxy-methyl)-2-(4-methoxyphenyl)-3-(4-methoxy-phenylamino)-3-phenylpropanoate; (1034152-21-0)

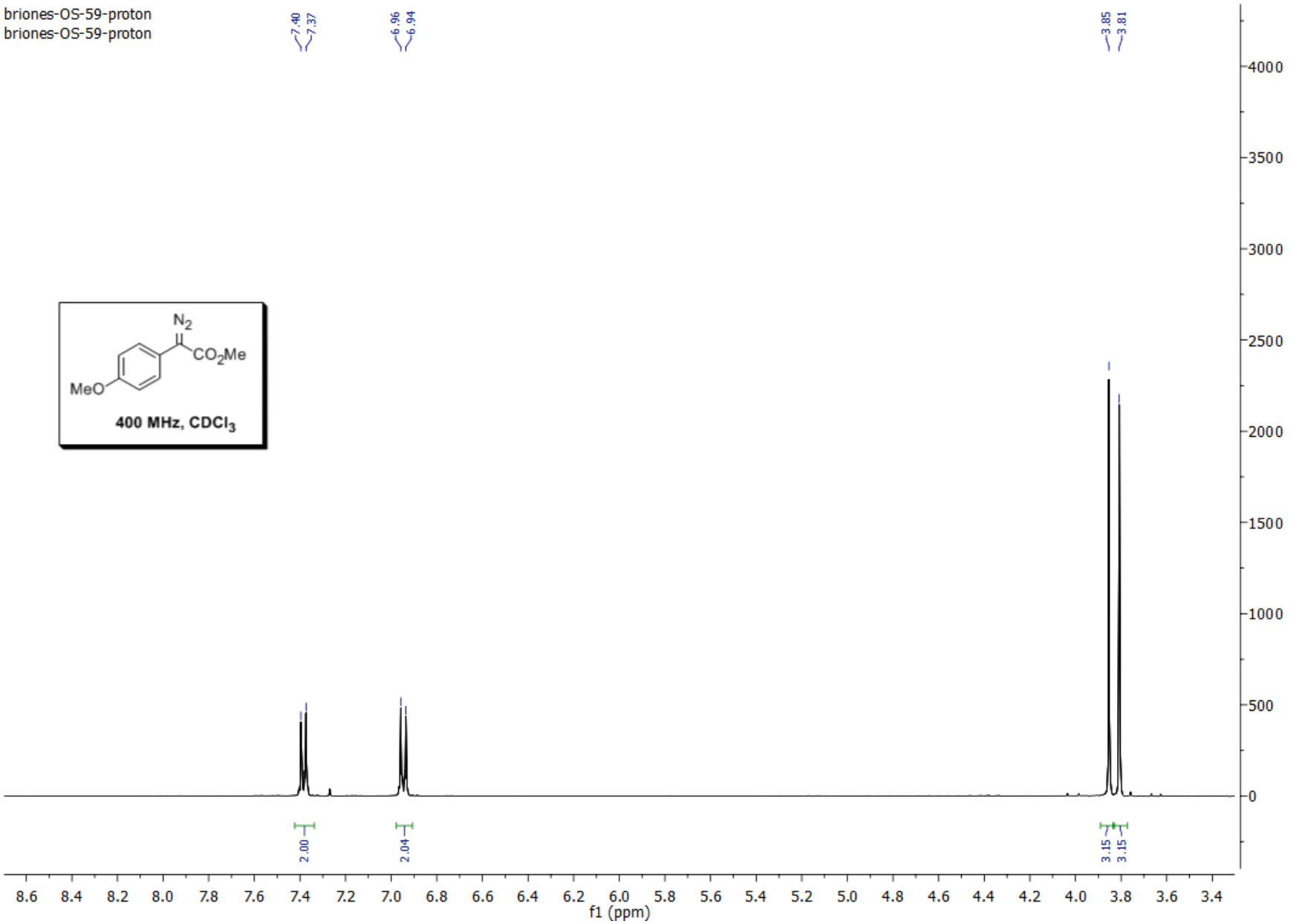
Wenhao Hu was born in 1967 in Sichuan Province, China. He received his M.S. degree in Chengdu Institute of Organic Chemistry. He obtained a Ph.D. degree from The Hong Kong Polytechnic University in 1998 under the direction of Professor Albert S. C. Chan, and was a postdoctoral fellow at University of Arizona with Professor Michael P. Doyle. He then joined GeneSoft Pharm. Inc. located in San Francisco as a Staff Scientist (2002-2003). He moved to New Jersey to join Bristol-Myers Squibb Company as a Research Investigator (2003-2006). He returned to China as a Professor in the department of chemistry at East China Normal University in 2006. His research interests include development of highly efficient synthetic methods and their application in the synthesis of biologically active compounds.

Jing Zhou was born in 1984 in Shandong Province, China. She received her bachelor's degree in Chemistry in 2007 from East China Normal University, Shanghai. She then began her graduate study in Organic Chemistry at the same university under the mentorship of Professor Wenhao Hu. She performed research on rhodium catalyzed multi-component reactions. Her current research focuses on the synthesis of immunologically active peptidyl disaccharides.

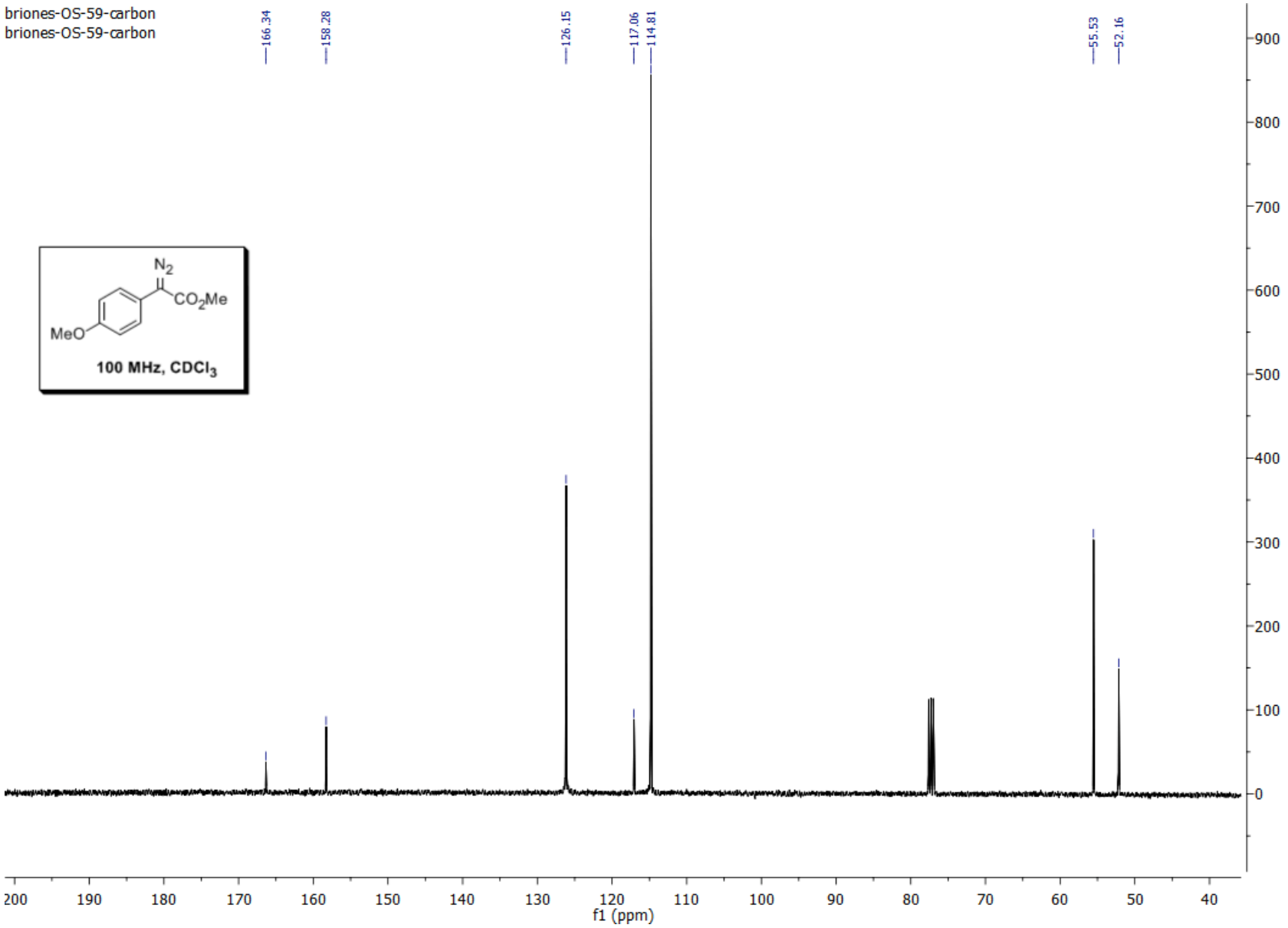
Xinfang Xu was born in 1981 in Zhejiang Province, China. He received his bachelor's degree in Chemistry from East China Normal University in 2005. He then began his graduate studies in Organic Chemistry at the same university, under the supervision of Professor Liping Yang (2005-2006) and Wenhao Hu (2006-present). His current research interest is the development of novel asymmetric multi-component reactions.

John Frederick Briones was born in 1982 in Laguna, Philippines. He earned his B.S. degree in Chemistry from the University of the Philippines, Los Banos in 2003 and later on pursued his Master's degree at the University of the Philippines, Diliman. He joined the research lab of Prof. Huw Davies in 2007 and currently his research project focuses on Rh(II)-catalyzed enantioselective transformations of alkynes.

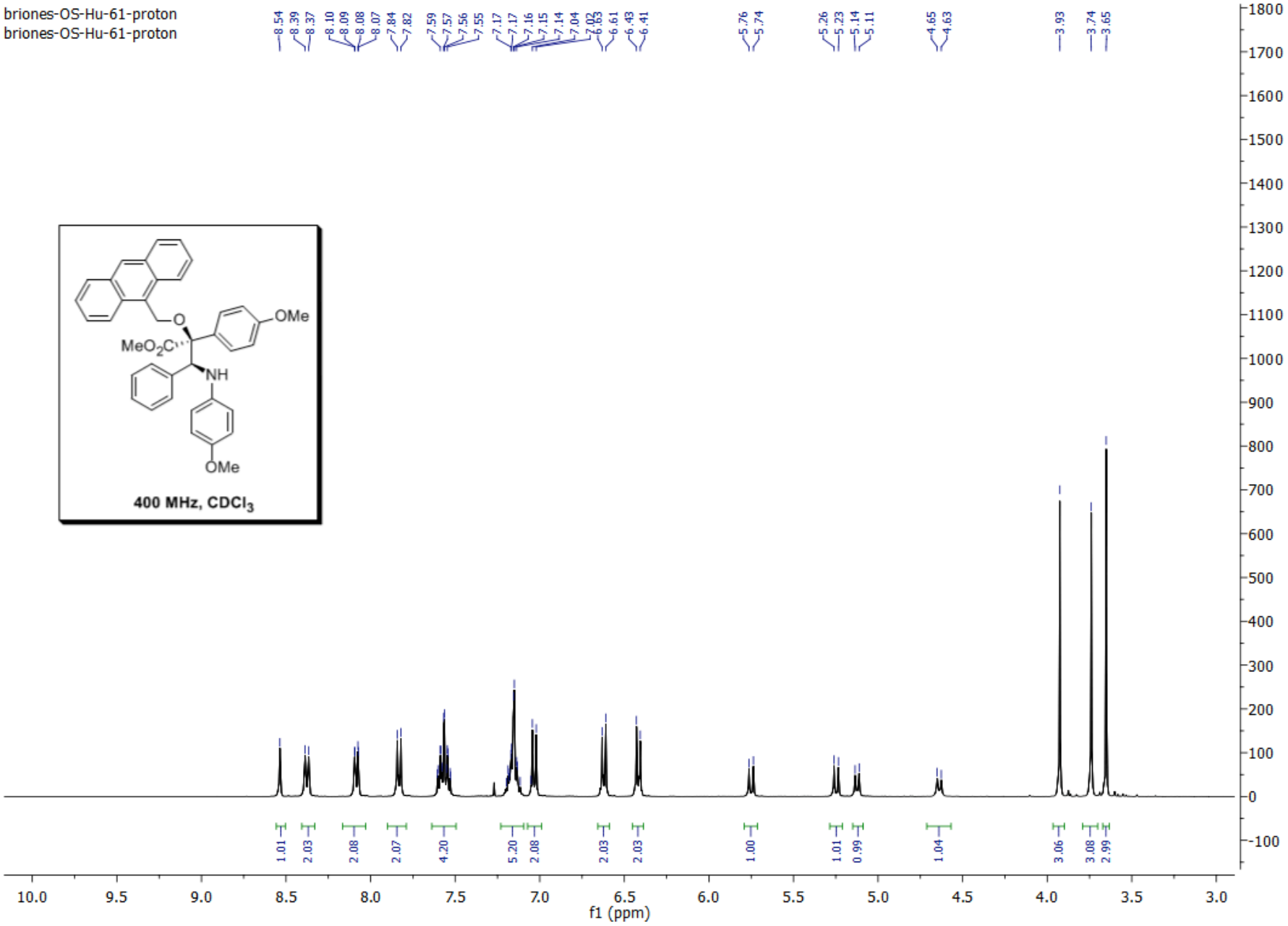
^{1}H NMR of Methyl (4-methoxyphenyl)diazoacetate



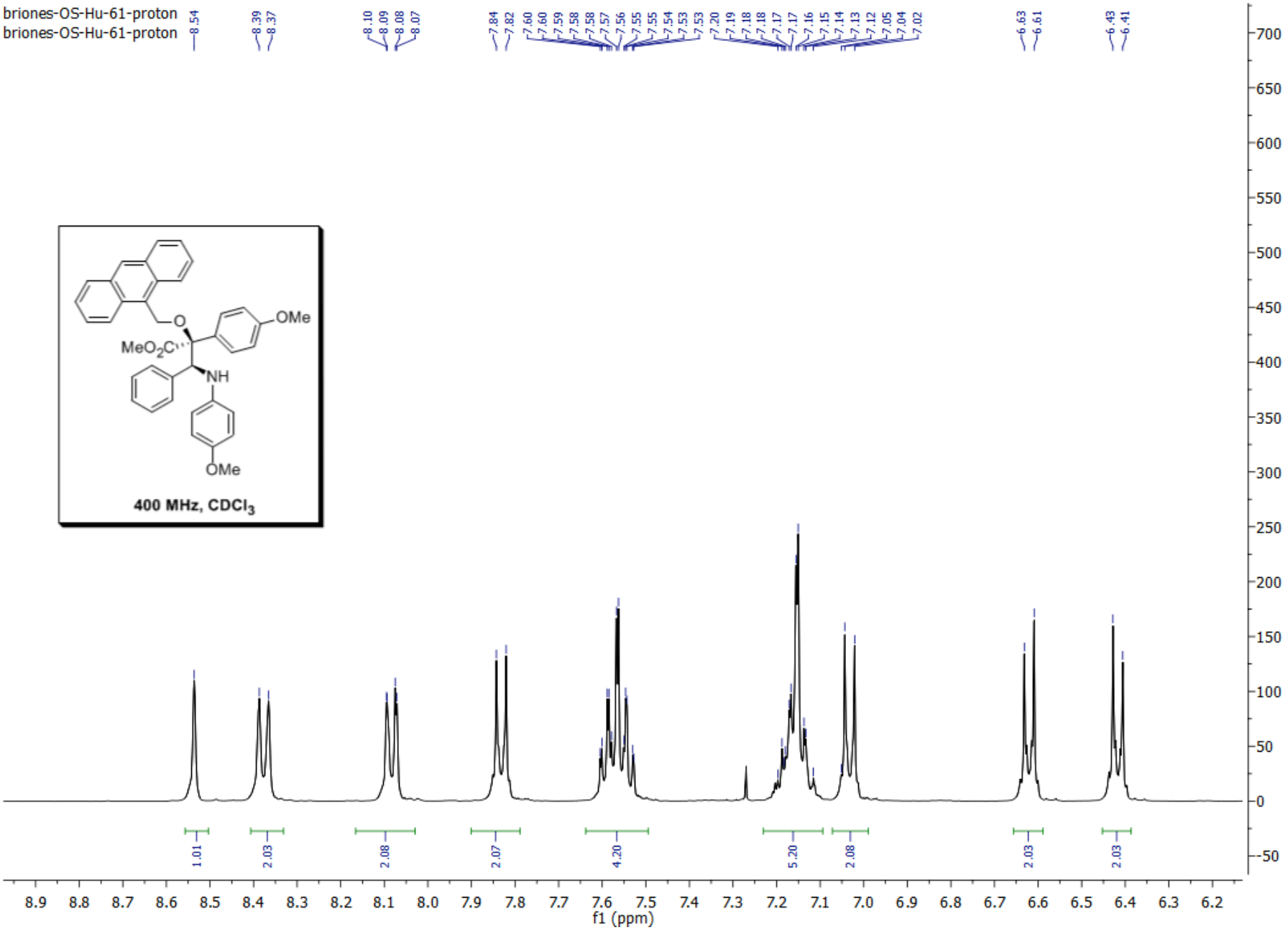
^{13}C NMR of Methyl (4-methoxyphenyl)diazoacetate



^{1}H NMR of (2*S*,3*S*)-2-(9-anthryloxymethyl)-2-(4-methoxyphenylamino)-3-propanoate



^{1}H NMR of (2*S*,3*S*)-2-(9-anthryloxymethyl)-2-(4-methoxyphenylamino)-3-propanoate



^{13}C NMR of (2*S*,3*S*)-2-(9-anthryloxymethyl)-2-(4-methoxyphenylamino)-3-propanoate