

A Versatile Method for the Synthesis of 3-Alkoxy carbonyl β -Lactam Derivatives

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Experimental Details

General. Diazo thioester **1**¹, imines **3a–f**², **3g–h**³, and **3i**⁴ were prepared according to published procedures. Rhodium(II) acetate, tributylstannane, AIBN, zinc powder, and glacial acetic acid were commercial reagents and were used as received. Toluene was refluxed with sodium and benzophenone, and freshly distilled prior to use. All reactions were performed under a nitrogen atmosphere. Melting points were measured on a melting point apparatus and are uncorrected. ¹H NMR (300 or 400 MHz) and ¹³C NMR (75 or 100 MHz) spectra were recorded in CDCl₃ with TMS as an internal standard. Mass spectra and HRMS data were obtained on an EI mass spectrometer. IR spectra were recorded on a FT–IR spectrometer with an OMNI sampler.

The Unsuccessful Acyl Chloride–Imine Reaction. The reaction of ethyl malonyl chloride with *N*–benzylideneaniline in the presence of triethylamine was conducted according to the well-established acyl chloride–imine method:⁵ To a solution of *N*–benzylideneaniline (86 mg, 0.48 mmol) and triethylamine (71 mg, 0.70 mmol) in 10 mL of dry toluene at ambient temperature was added a solution of ethyl malonyl chloride (100 mg, 0.66 mmol) in 5 mL of dry toluene during a period of 30 min. The resulting mixture was stirred at ambient temperature for another 1 h and was monitored by thin layer chromatography (silica gel GF₂₅₄ plate, hexanes / ethyl acetate 5:1 V/V). It was found that, although the *N*–benzylideneaniline was completely converted, no desired 3–ethoxycarbonyl β –lactam derivative (**5a** or **5b**) was found (compared with the standard sample of **5a** and **5b** prepared by our methods) and high–polar impurities were formed. This indicates that the acyl chloride–imine method cannot approach the synthetic goal towards the 3–ethoxycarbonyl β –lactam derivatives.

¹ Marino, J. P. Jr.; Osterhout, M. H.; Price, A. T.; Sheehan, S. M.; Padwa, A. *Tetrahedron Lett.* **1994**, *35*, 849–852.

² Linder, M. R.; Frey, W. U.; Podlech, J. *J. Chem. Soc., Perkin Trans. I* **2001**, 2566–2577.

³ Wenker, H. *J. Am. Chem. Soc.* **1935**, *57*, 6, 1079–1080.

⁴ Xu, J. X.; Jin S.; Xing, Q. Y. *Phosphorus, Sulfur and Silicon* **1998**, *141*, 57–70.

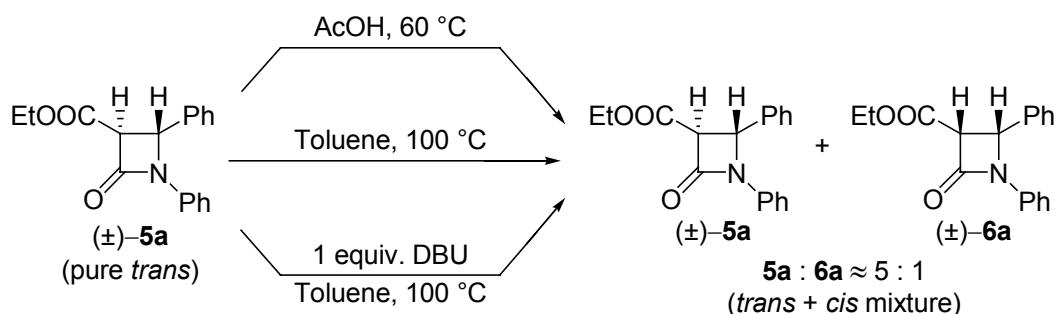
⁵ *The Organic Chemistry of β -Lactams*; Georg, G. I., Ed.; Verlag Chemie: New York, 1993.

Additional Discussion on the *trans* Selectivity of the Desulfurization Reactions

Cis-3,4-disubstituted β -lactams were generally obtained as major products in Raney Ni and $n\text{-Bu}_3\text{SnH}/\text{AIBN}$ promoted desulfurizations due to the hydrogen addition to the less hindered face of the radical intermediate.⁶ It is noteworthy that the relative configurations of the predominating 3-ethoxycarbonyl β -lactam products are thermodynamically more stable *trans* isomeric in our cases, which is quite different from those previously reported.⁶ Because of the presence of the 3-ethoxycarbonyl group in the substrates, the products possess enolizable centers. Thus, both desulfurization methods lead to the thermodynamically more stable isomers, the *trans*-3,4-disubstituted β -lactams, via a tautomeric equilibrium of the two diastereomers through their enolic intermediates under the reaction conditions.

A series of experiments were conducted (Scheme 1) to verify this proposal.

Scheme 1



Pure *trans*- β -lactam **5a** was obtained by recrystallization (from ethanol / hexanes) of the desulfurization products (**5a** + **5b**), suggesting that the tautomerization does not occur at room temperature. Then pure **5a** (13 mg each, 0.044 mmol) was solved in 1 mL of glacial acetic acid, in 1 mL of dry toluene, and in 1 mL of dry toluene plus 6 μL of DBU (1 equiv.),⁷ respectively. The first solution was maintained at 60°C , and the other two were maintained at 100°C for 2 h to simulate the desulfurization reaction conditions. After the removal of the solvent, the residue was submitted to NMR analysis. ^1H NMR results showed that pure **5a** tautomerized to a mixture of **5a** and **6a** after the above treatments, and the **5a** / **6a** ratios were about 5:1, which was very near to that of the product mixtures of desulfurization reactions (**5a** / **6a** equals to 88: 12 for $n\text{-Bu}_3\text{SnH}/\text{AIBN}$ method and 84: 16 for Zn/AcOH method). This indicates that, the *trans* selectivity of the desulfurization reactions is due to the tautomeric equilibrium of the two diastereomers under the reaction conditions, and the products (**5a** and **6a**) are thermodynamic mixture of isomers.

Another experiment was also conducted: to a solution of product mixture **5i** and **6i** (250 mg, 0.58 mmol, **5i** / **6i** = 67: 33) in 20 mL of dry benzene was added 80 μL of DBU (1 equiv.),⁶ and the solution was

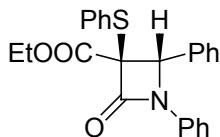
⁶ (a) Bose, A. K.; Manhas, M. S.; Chib, J. B.; Chawla, H. P. S.; Dayal, B. *J. Org. Chem.* **1974**, *39*, 2877–2884. (b) Bateson, J. H.; Quinn, A. M.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1986**, 1151–1152. (c) Palomo, C.; Cossio, F. P.; Odriozola, J. M.; Oiarbide, M.; Ontoria, J. M. *Tetrahedron Lett.* **1989**, *30*, 4577–4580. (d) Palomo, C.; Cossio, F. P.; Odriozola, J. M.; Oiarbide, M.; Ontoria, J. M. *J. Org. Chem.* **1991**, *56*, 4418–4428. (e) Bari, S. S.; Venugopalan, P.; Arora, R. *Tetrahedron Lett.* **2003**, *44*, 895–897.

⁷ The use of DBU or DBN is a method that can isomerize the 3-acetyl *cis* β -lactams to the more stable *trans* forms. See: Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575–580.

refluxed overnight. The resulting mixture was successively washed with 1 mol/L HCl, saturated NaHCO₃, and brine, and then dried over Na₂SO₄. After the evaporation of the solvent, the residue was submitted to NMR analysis, and it was found that the product ratio **5i** / **6i** maintained at 67: 33. This also suggests that the mixture of **5i** and **6i** is a thermodynamic mixture, and the observed *trans* selectivity should be attributed to the tautomeric equilibrium of the two diastereomers under the reaction conditions.

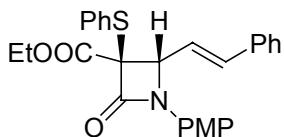
The Spectroscopic Data for the Products

Ethyl (\pm)-*trans*-2-oxo-1,4-diphenyl-3-phenylthioazetidine-3-carboxylate (4a)



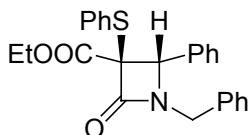
Colorless crystals, m.p. 93–94 °C. ^1H NMR (300 MHz): δ 0.78 (t, $J = 7.2$ Hz, 3H), 3.68 (q, $J = 7.2$ Hz, 2H), 5.06 (s, 1H), 7.06–7.32 (m, 13H), 7.79 (m, 2H). ^{13}C NMR (75.5 MHz): δ 13.4, 62.0, 65.0, 71.2, 117.2, 124.4, 126.9, 128.6, 128.95, 128.99, 129.1, 129.4, 132.5, 135.3, 136.7, 161.0, 164.9. MS (EI) m/z: 403 (M^+ , 4.9), 284 (86), 181 (100). IR ν (cm $^{-1}$): 1736, 1758. Calcd for $C_{24}\text{H}_{21}\text{NO}_3\text{S}$: C, 71.44; H, 5.25; N, 3.47. Found: C, 71.47; H, 5.21; N, 3.33.

Ethyl (\pm)-*trans*-1-(4-methoxyphenyl)-2-oxo-3-phenylthio-4-styrylazetidine-3-carboxylate (4b)

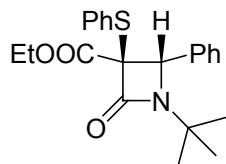


Colorless oil. ^1H NMR (300 MHz): δ 1.10 (t, $J = 7.2$ Hz, 3H), 3.74 (s, 3H), 4.14 (dq, $J = 1.8, 7.2$ Hz, 2H), 4.61 (dd, $J = 0.3, 7.5$ Hz, 1H), 6.25 (dd, $J = 7.8, 15.9$ Hz, 1H), 6.80 (m, 3H), 7.26–7.35 (m, 10H), 7.76 (m, 2H). ^{13}C NMR (75.5 MHz): δ 14.0, 55.3, 62.4, 63.8, 70.6, 114.2, 118.6, 121.6, 126.7, 128.7, 129.0, 129.1, 129.3, 130.5, 135.1, 135.2, 136.8, 156.4, 160.0, 165.5. MS (EI) m/z: 459 (M^+ , 2.3), 310 (4.2), 236 (100). IR ν (cm $^{-1}$): 1735, 1761. Calcd for $C_{27}\text{H}_{25}\text{NO}_4\text{S}$: 459.1504. Found: 459.1511.

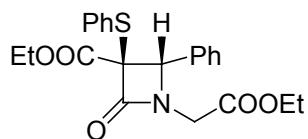
Ethyl (\pm)-*trans*-1-benzyl-2-oxo-4-phenyl-3-phenylthioazetidine-3-carboxylate (4d)



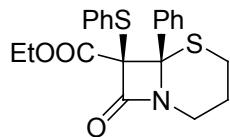
Colorless crystals, m.p. 161–162 °C. ^1H NMR (300 MHz): δ 0.80 (t, $J = 7.2$ Hz, 3H), 3.71 (q, $J = 7.2$ Hz, 2H), 3.86 (d, $J = 15.0$ Hz, 1H), 4.46 (s, 1H), 4.86 (d, $J = 15.0$ Hz, 1H), 6.77–7.75 (m, 15H). ^{13}C NMR (75.5 MHz): δ 13.4, 44.6, 61.9, 64.6, 72.6, 127.1, 127.6, 128.1, 128.5, 128.6, 128.8, 129.0, 129.1, 129.4, 132.6, 133.8, 135.8, 163.6, 165.2. MS (EI) m/z: 417 (M^+ , 1.0), 284 (100), 195 (12), 91 (82). IR ν (cm $^{-1}$): 1731, 1772. Calcd for $C_{25}\text{H}_{23}\text{NO}_3\text{S}$: 417.1399. Found: 417.1410.

Ethyl (±)-*trans*-1-*tert*-butyl-2-oxo-4-phenyl-3-phenylthioazetidine-3-carboxylate (4e)

Colorless crystals, m.p. 75–76 °C. ^1H NMR (300 MHz): δ 1.08 (t, $J = 7.2$ Hz, 3H), 1.33 (s, 9H), 4.12 (m, 2H), 5.23 (s, 1H), 7.10–7.38 (m, 10H). ^{13}C NMR (75.5 MHz): δ 13.7, 28.0, 55.3, 62.4, 62.9, 69.4, 127.8, 128.0, 128.4, 128.7, 129.0, 130.6, 133.0, 135.2, 163.2, 167.4. MS (EI) m/z: 383 (M^+ , 0.1), 284 (100), 211 (86), 135 (77). IR ν (cm $^{-1}$): 1720, 1762. Calcd for $C_{22}\text{H}_{23}\text{NO}_5\text{S}$: 383.1555. Found: 383.1558.

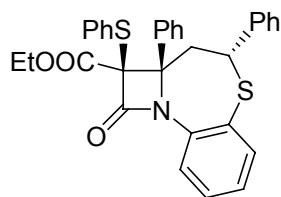
Ethyl (±)-*trans*-1-(2-ethoxy-2-oxoethyl)-2-oxo-4-phenyl-3-phenylthioazetidine-3-carboxylate (4f)

Colorless oil. ^1H NMR (300 MHz): δ 0.75 (t, $J = 7.2$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 3.56 (d, $J = 18.0$ Hz, 1H), 3.64 (q, $J = 7.2$ Hz, 2H), 4.14 (m, 2H), 4.42 (d, $J = 18.0$ Hz, 1H), 5.03 (s, 1H), 7.26–7.38 (m, 8H), 7.78 (m, 2H). ^{13}C NMR (75.5 MHz): δ 13.2, 13.8, 41.4, 61.4, 61.6, 65.62, 65.64, 72.2, 126.9, 128.5, 128.8, 128.9, 129.1, 129.6, 132.5, 134.7, 164.1, 164.9, 167.0. MS (EI) m/z: 413 (M^+ , 2.2), 284 (100), 222 (57). IR ν (cm $^{-1}$): 1742, 1781. Calcd for $C_{22}\text{H}_{23}\text{NO}_5\text{S}$: 413.1297. Found: 413.1301.

Ethyl (±)-*trans*-8-oxo-6-phenyl-7-phenylthio-5-thia-1-aza-bicyclo[4.2.0]octane-7-carboxylate (4h)

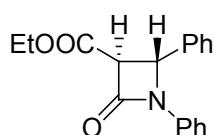
Colorless crystals, m.p. 105–106 °C. ^1H NMR (300 MHz): δ 1.13 (t, $J = 7.2$ Hz, 3H), 1.86 (m, 2H), 2.65 (m, 2H), 3.17 (m, 1H), 4.12 (m, 3H), 7.19–7.28 (m, 3H), 7.40–7.47 (m, 5H), 7.63 (m, 2H). ^{13}C NMR (75.5 MHz): δ 13.9, 23.7, 25.8, 37.9, 62.0, 70.6, 75.7, 128.1, 128.6, 129.0, 129.1, 135.5, 136.2, 163.8, 164.9. MS (EI) m/z: 399 (M^+ , 4.1), 290 (1.6), 222 (57), 150 (100). IR ν (cm $^{-1}$): 1732, 1780. Calcd for $C_{21}\text{H}_{21}\text{NO}_3\text{S}_2$: C, 63.13; H, 5.30; N, 3.51. Found: C, 63.17; H, 5.21; N, 3.40.

**Ethyl *rel*-(2*S*,2*aR*,4*R*)-1-oxo-2*a*,4-diphenyl-2-phenylthio-2,2*a*,3,4-tetrahydro-1*H*-azeto[2,1-*d*]
[1,5]benzothiazepine-2-carboxylate (4i)**



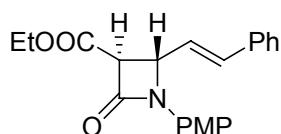
Colorless crystals, m.p. 176–177 °C. ^1H NMR (300 MHz): δ 1.08 (t, $J = 7.2$ Hz, 3H), 2.94 (dd, $J = 11.4$, 13.8 Hz, 1H), 3.25 (d, $J = 13.8$ Hz, 1H), 3.90 (d, $J = 11.4$ Hz, 1H), 4.10 (m, 2H), 7.13–7.45 (m, 16H), 7.66 (m, 2H), 8.00 (d, $J = 7.8$ Hz, 1H). ^{13}C NMR (75.5 MHz): δ 13.8, 45.2, 49.1, 62.2, 71.4, 74.0, 126.7, 126.9, 128.0, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 129.0, 129.9, 130.0, 132.1, 134.8, 135.5, 137.7, 140.5, 162.9, 166.3. MS (EI) m/z: 537 (0.9), 491 (48), 314 (42), 211 (100). IR ν (cm $^{-1}$): 1724, 1770. Calcd for C₃₂H₂₇NO₃S₂: C, 71.48; H, 5.06; N, 2.60. Found: C, 71.49; H, 5.05; N, 2.45.

Ethyl (\pm)-*trans*-2-oxo-1,4-diphenylazetidine-3-carboxylate (5a)



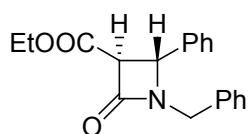
Colorless crystals, m.p. 87–89 °C. Lit.⁸ m.p. 87–89 °C The spectroscopic data is identical to the literature.⁸

Ethyl (\pm)-*trans*-1-(4-methoxyphenyl)-2-oxo-4-styrylazetidine-3-carboxylate (5b)



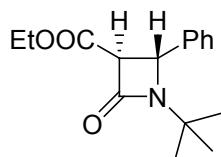
Colorless oil. ^1H NMR (300 MHz): δ 1.32 (t, $J = 7.2$ Hz, 3H), 3.75 (s, 3H), 3.96 (d, $J = 2.4$ Hz, 1H), 4.28 (q, $J = 7.2$ Hz, 2H), 4.94 (dd, $J = 2.4$, 8.4 Hz, 1H), 6.26 (dd, $J = 8.4$, 15.9 Hz, 1H), 6.86 (m, 3H), 7.26–7.41 (m, 7H). ^{13}C NMR (75.5 MHz): δ 14.1, 55.4, 56.8, 60.9, 62.0, 114.3, 118.4, 125.1, 126.6, 128.6, 128.7, 131.1, 135.2, 135.5, 156.3, 158.3, 166.4. MS (EI) m/z: 351 (M $^+$, 10), 278 (13), 236 (10), 202 (31), 149 (100), 129 (72). IR ν (cm $^{-1}$): 1728, 1758. Calcd for C₂₁H₂₁NO₄: 351.1471. Found: 351.1469.

Ethyl (\pm)-*trans*-1-benzyl-2-oxo-4-phenylazetidine-3-carboxylate (5d)

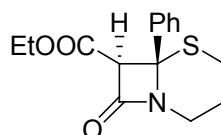


Colorless oil. Known compound. The spectroscopic data is identical to the literature.⁹

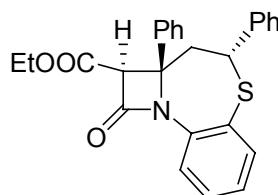
⁸ Brown, D. S.; Elliott, M. C.; Moody, J. C.; Mowlem, T. J.; Marino, J. P.; Padwa, A. *J. Org. Chem.* **1994**, 59, 2447–2455.

Ethyl (±)-*trans*-1-*tert*-butyl-2-oxo-4-phenylazetidine-3-carboxylate (5e)

Colorless oil. Known compound, but no spectroscopic data was given in the literature.¹⁰ ^1H NMR (300 MHz): δ 1.27 (s, 9H), 1.29 (t, $J = 7.2$ Hz, 3H), 3.70 (d, $J = 2.4$ Hz, 1H), 4.24 (dq, $J = 2.1, 7.2$ Hz, 2H), 4.86 (d, $J = 2.4$ Hz, 1H), 7.36–7.43 (m, 5H). ^{13}C NMR (75.5 MHz): δ 14.0, 28.0, 55.1, 56.3, 61.6, 62.4, 126.5, 128.6, 128.9, 139.1, 162.0, 167.0. MS (EI) m/z: 275 (M^+ , 3.5), 176 (98), 131 (100). IR ν (cm⁻¹): 1721, 1754. Calcd for C₁₆H₂₁NO₃: 275.1521. Found: 275.1524.

Ethyl (±)-*trans*-8-oxo-6-phenyl-5-thia-1-aza-bicyclo[4.2.0]octane-7-carboxylate (5h)

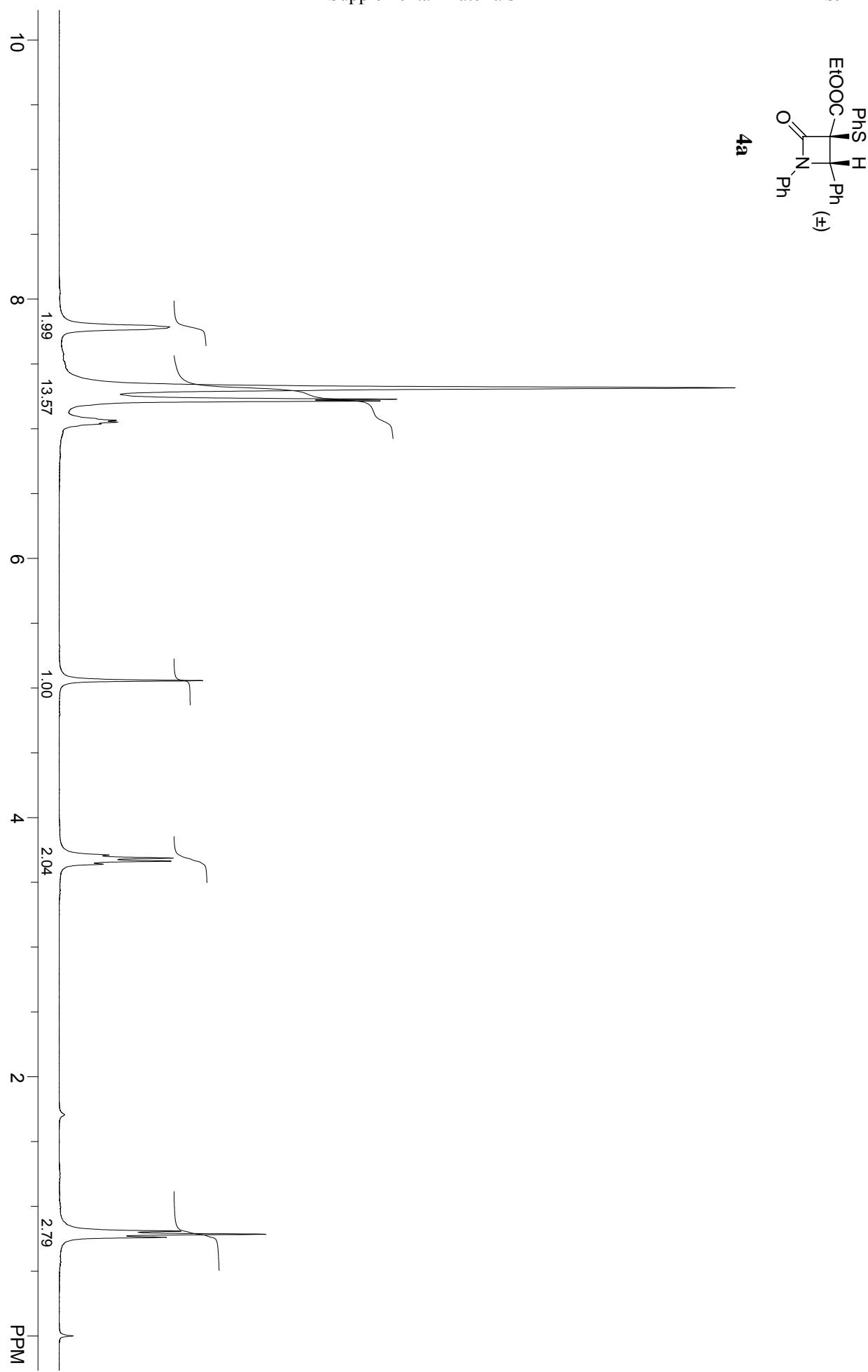
Colorless crystals, m.p. 113–115 °C. ^1H NMR (300 MHz): δ 0.82 (t, $J = 7.2$ Hz, 3H), 1.86 (m, 2H), 2.66 (m, 2H), 3.11 (m, 1H), 3.70 (q, $J = 7.2$ Hz, 2H), 4.18 (m, 1H), 4.38 (s, 1H), 7.33–7.41 (m, 3H), 7.59–7.62 (m, 2H). ^{13}C NMR (75.5 MHz): δ 13.4, 23.4, 25.7, 38.0, 61.2, 70.3, 127.7, 128.1, 128.6, 136.1, 160.9, 164.5. MS (EI) m/z: 291 (M^+ , 4.0), 218 (100), 130 (29). IR ν (cm⁻¹): 1729, 1765. Calcd for C₁₅H₁₇NO₃S: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.76; H, 5.86; N, 4.69.

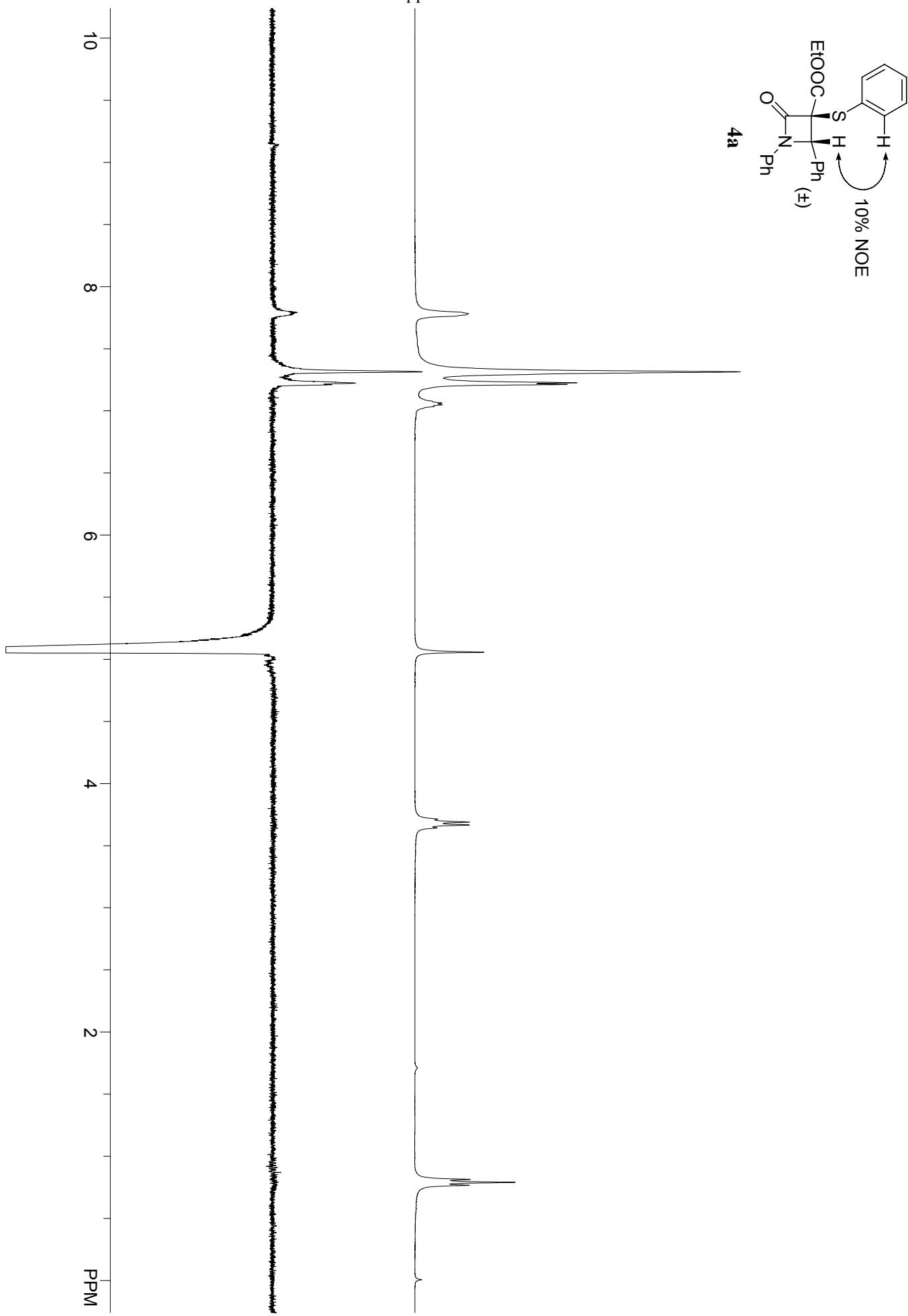
Ethyl *rel*-(2*S*,2*aS*,4*R*)-1-oxo-2*a*,4-diphenyl-2,2*a*,3,4-tetrahydro-1*H*-azeto[2,1-*d*][1,5]benzothiazepine-2-carboxylate (5i)**

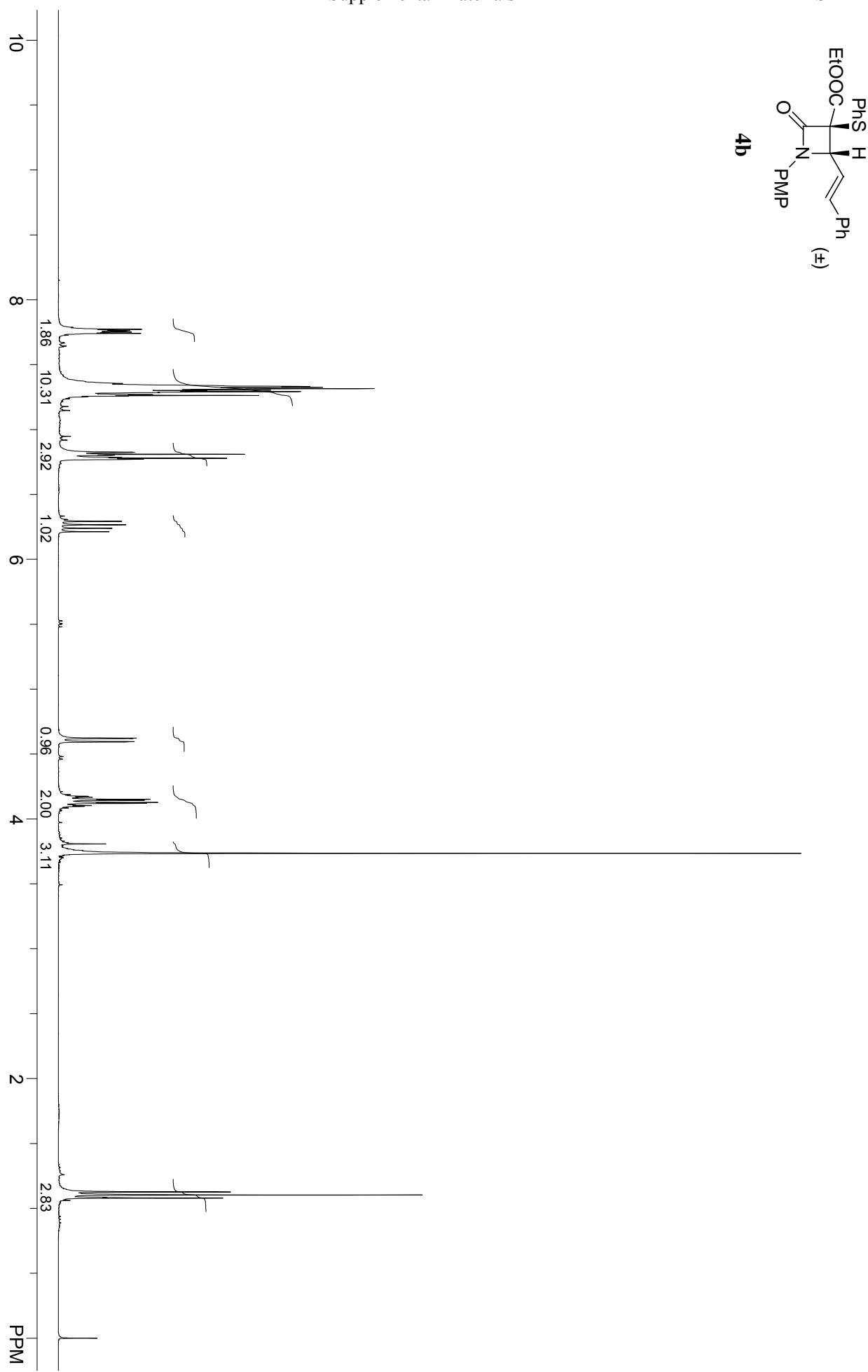
Colorless crystals, m.p. 153–155 °C. ^1H NMR (400 MHz): δ 0.84 (t, $J = 7.2$ Hz, 3H), 3.17 (dd, $J = 11.0, 14.3$ Hz, 1H), 3.68 (d, $J = 14.3$ Hz, 1H), 3.70 (q, $J = 7.2$ Hz, 2H), 3.97 (d, $J = 11.0$ Hz, 1H), 4.30 (s, 1H), 7.15–7.42 (m, 13H), 7.95 (m, 1H). ^{13}C NMR (100 MHz): δ 13.5, 46.1, 50.9, 61.2, 67.6, 76.7, 126.88, 126.91, 127.5, 128.1, 128.3, 128.4, 129.1, 130.2, 132.3, 136.0, 137.9, 140.5, 160.5, 165.3. MS (EI) m/z: 429 (56), 356 (14), 302 (26), 211 (100). IR ν (cm⁻¹): 1729, 1767. Calcd for C₂₆H₂₃NO₃S: 429.1399. Found: 429.1397.

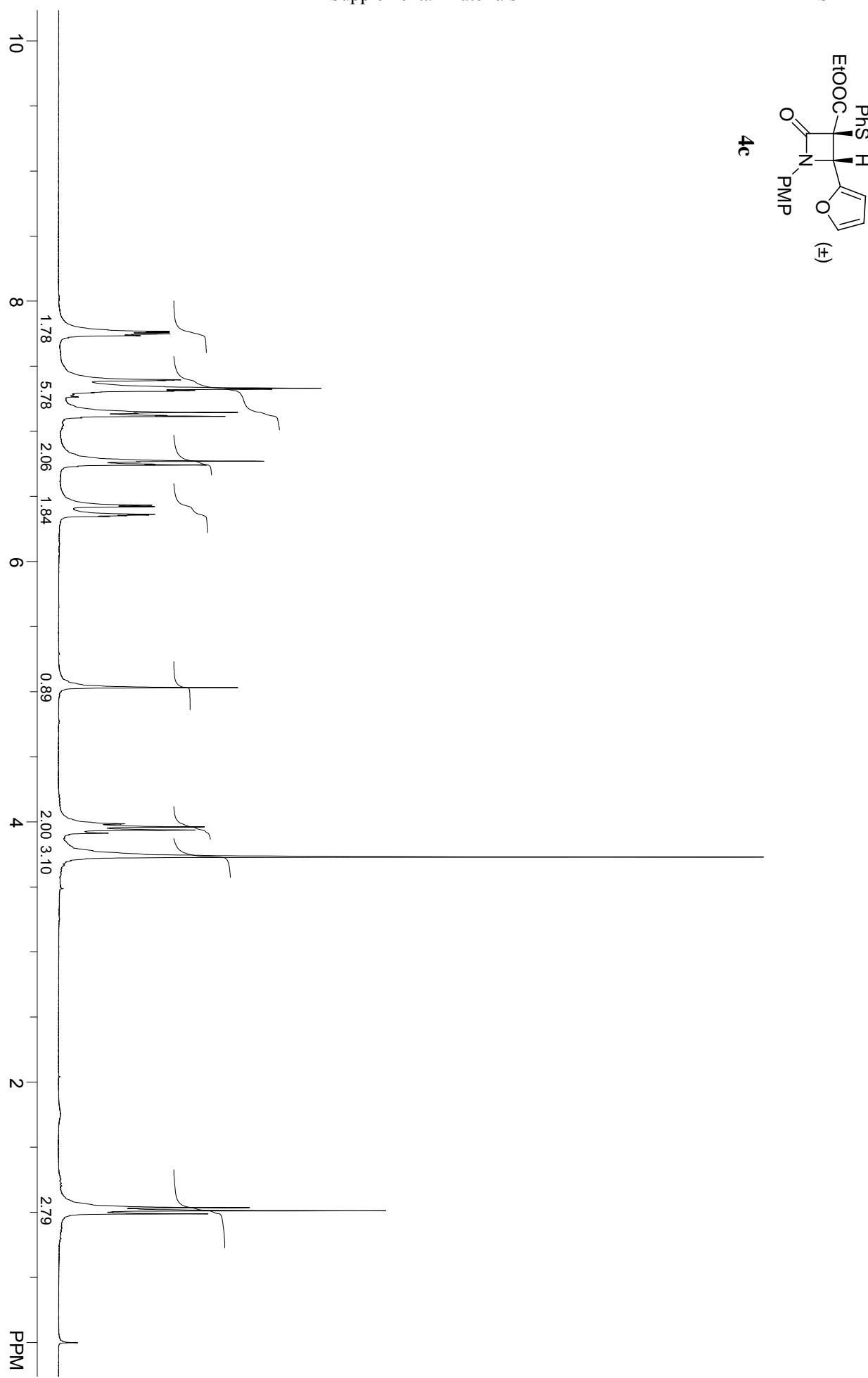
⁹ Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheehan, S. M.; Marino, J. P.; Semones, M. A.; Padwa, A.; Richards, I. C. *Tetrahedron* **1996**, *52*, 2489–2514.

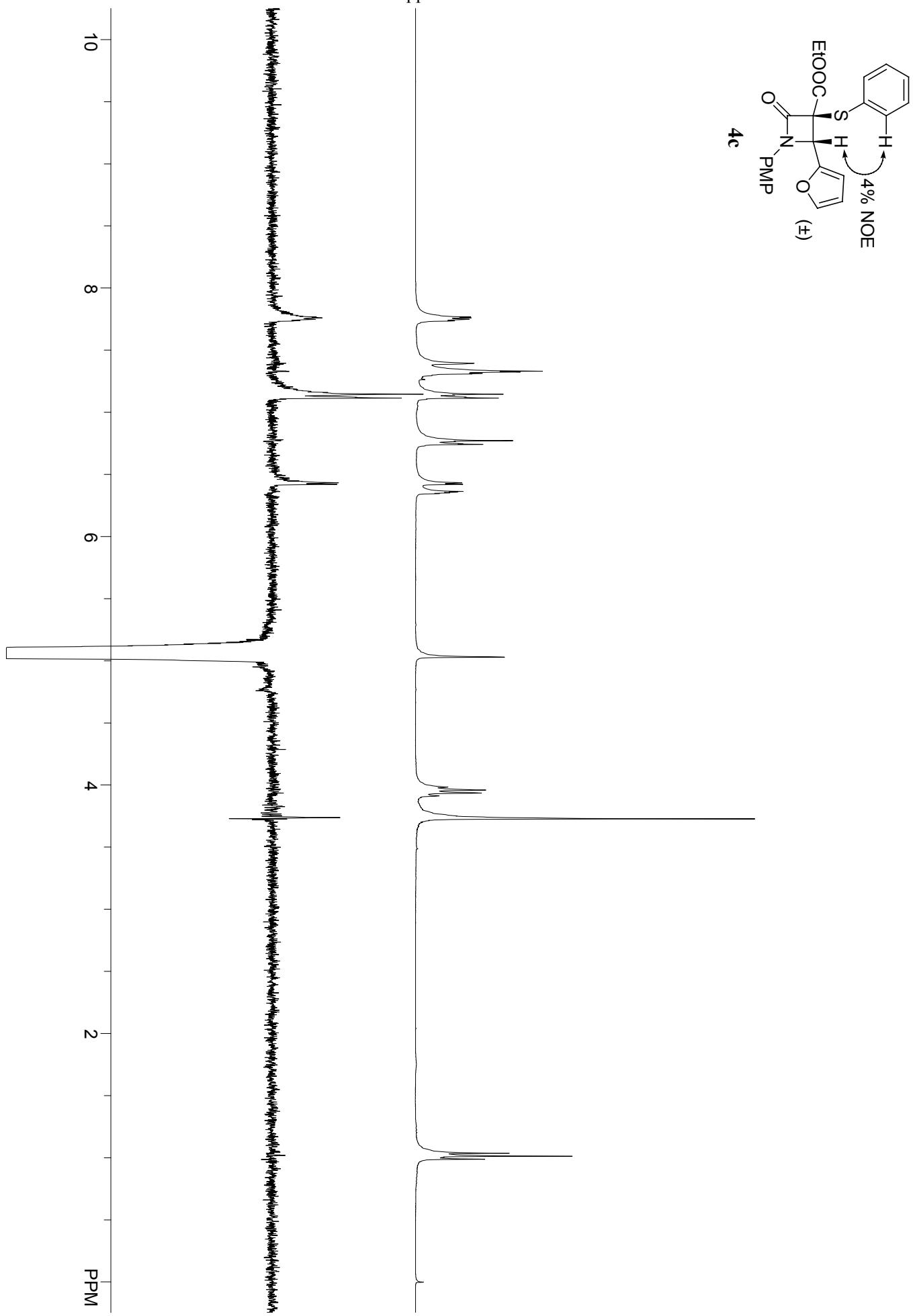
¹⁰ Choi, M. K. W.; Yu, W. Y.; Che, C. M. *Org. Lett.* **2005**, *7*, 1081–1084.

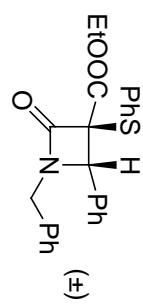




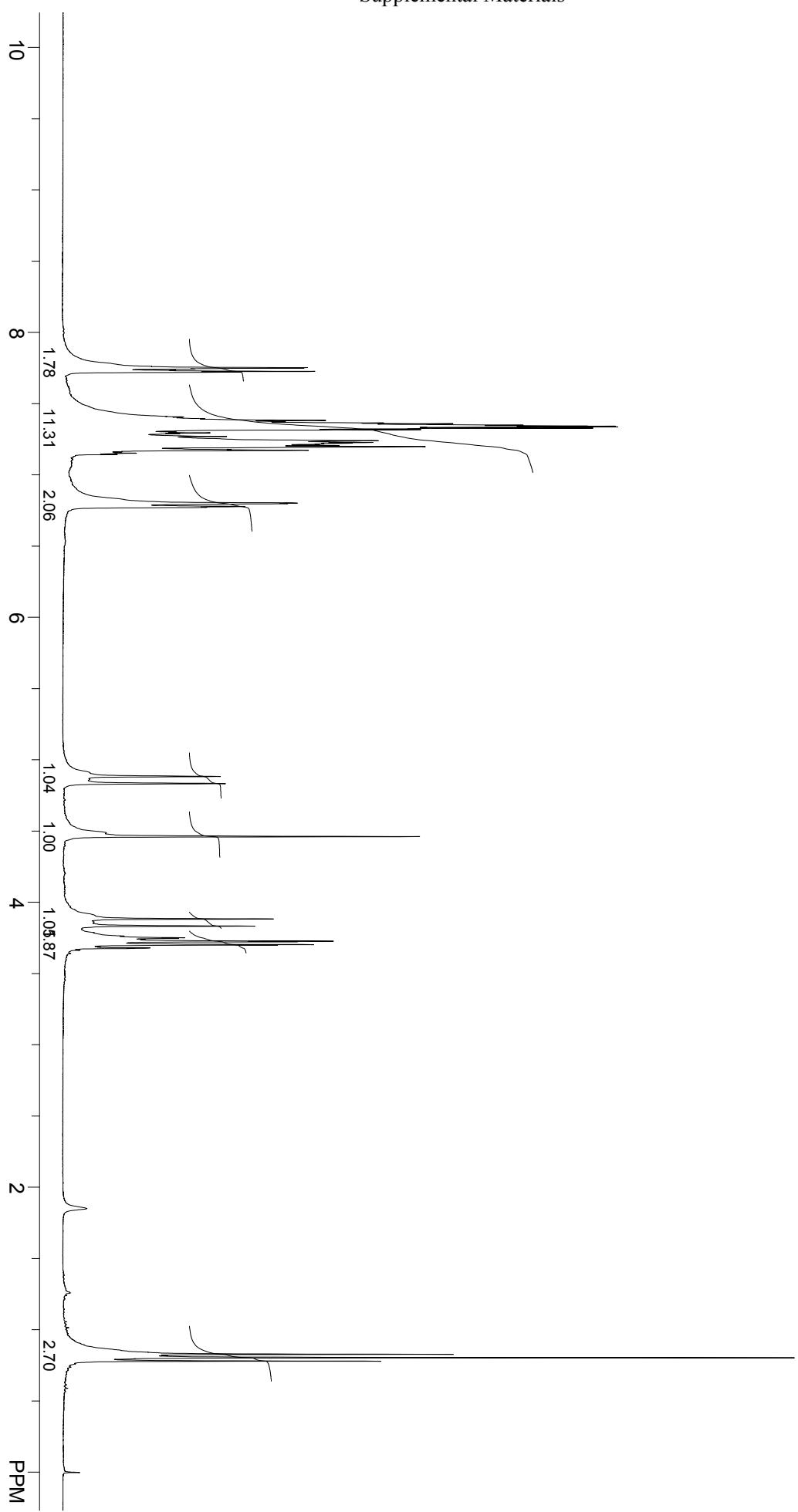


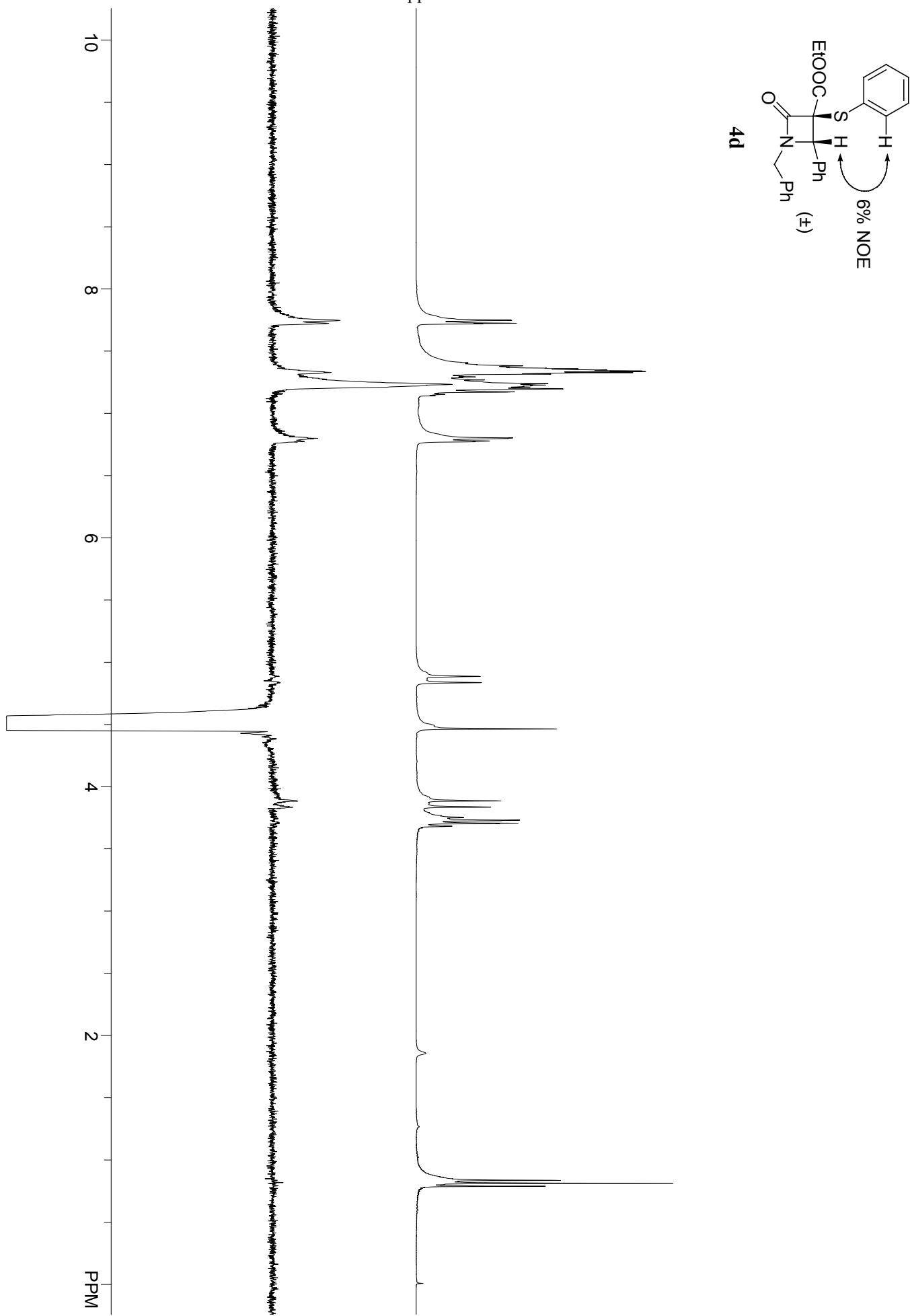


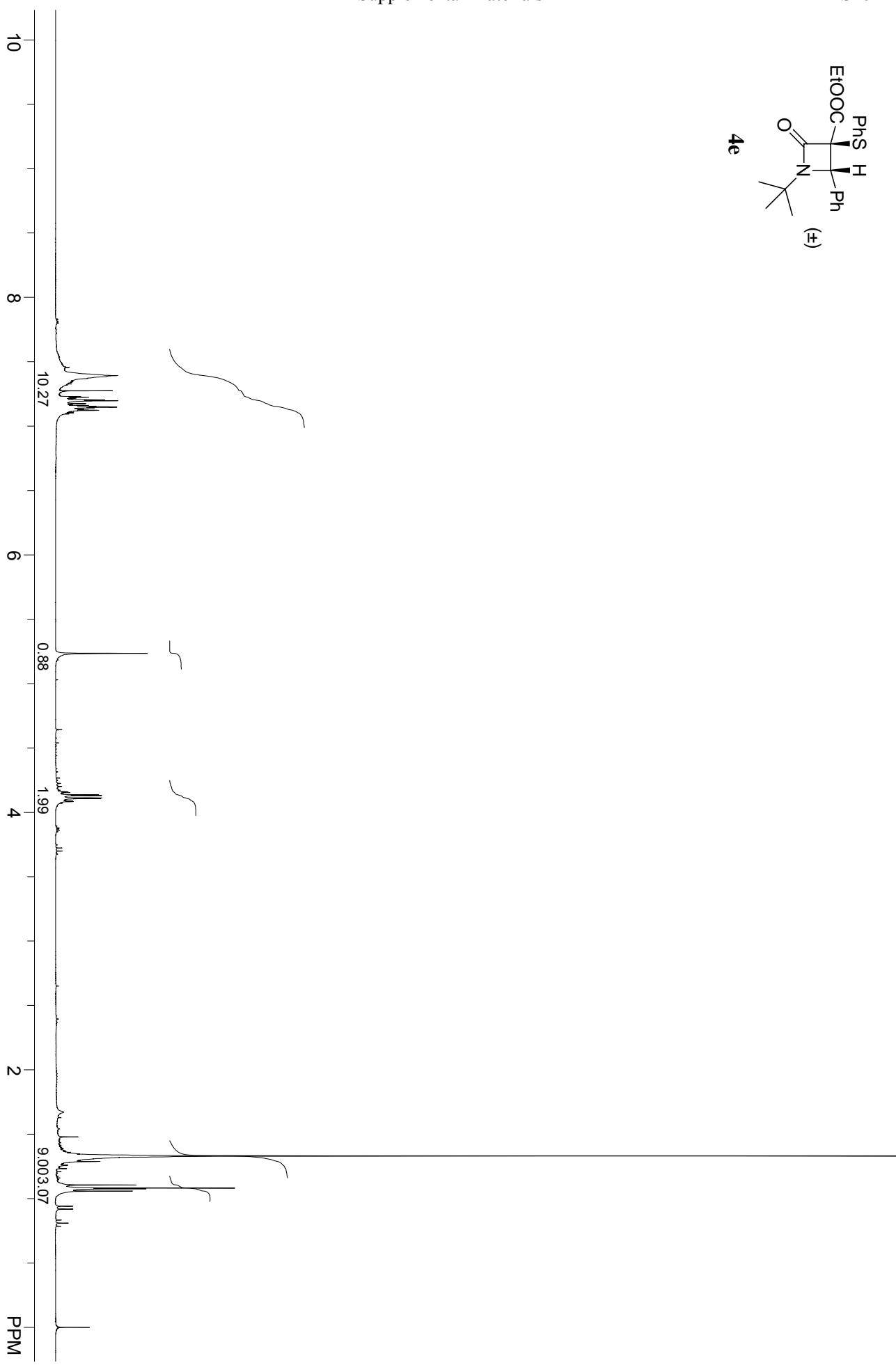


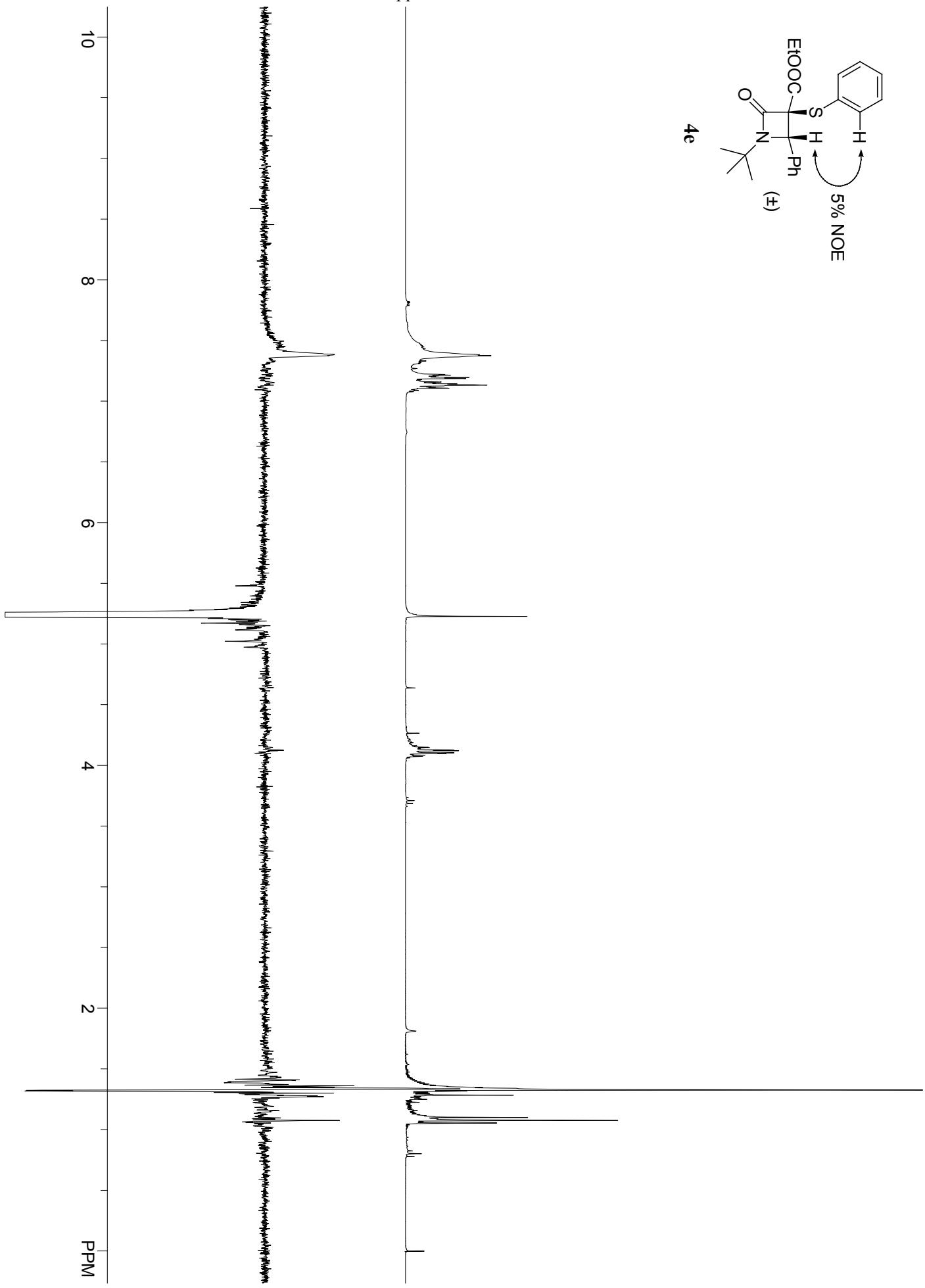


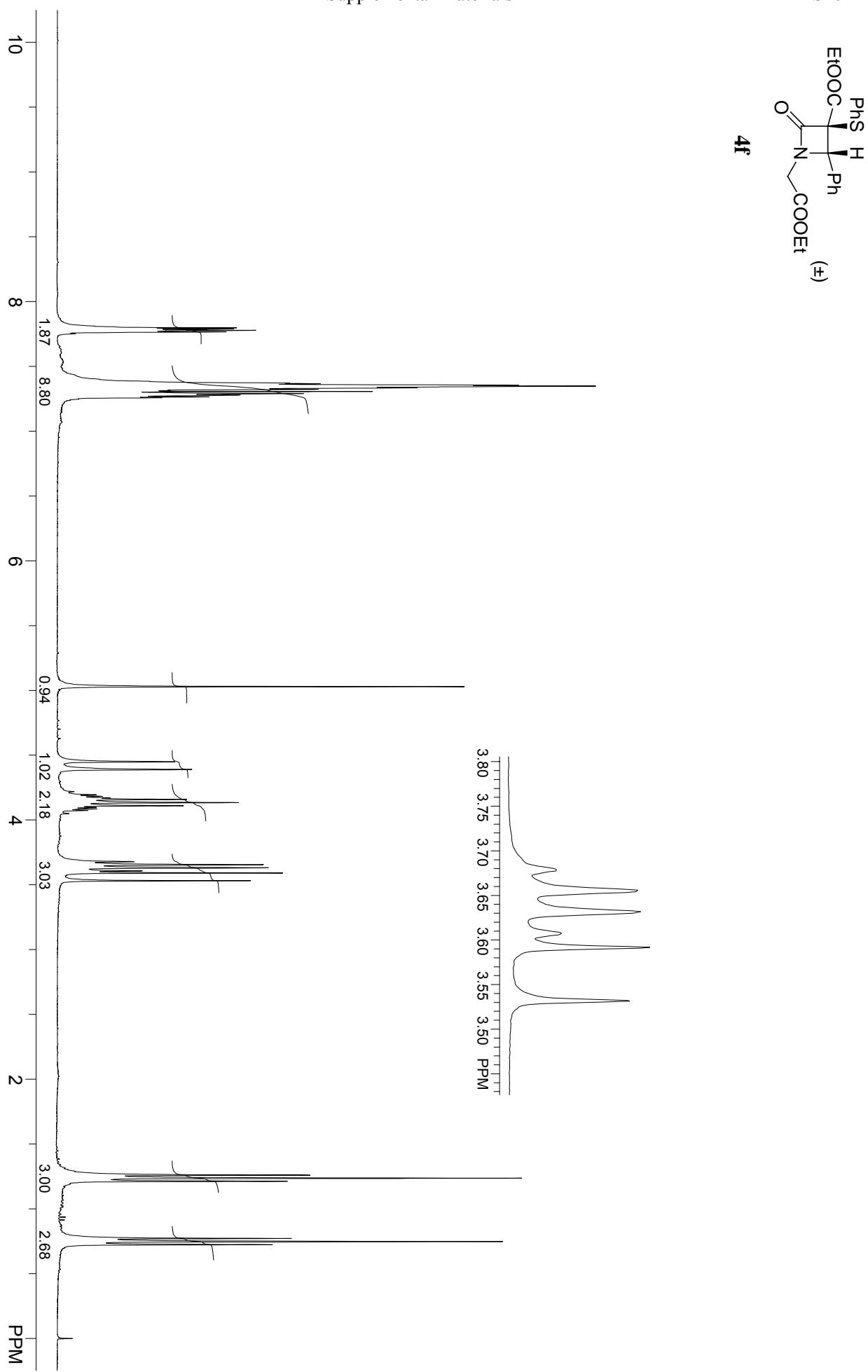
4

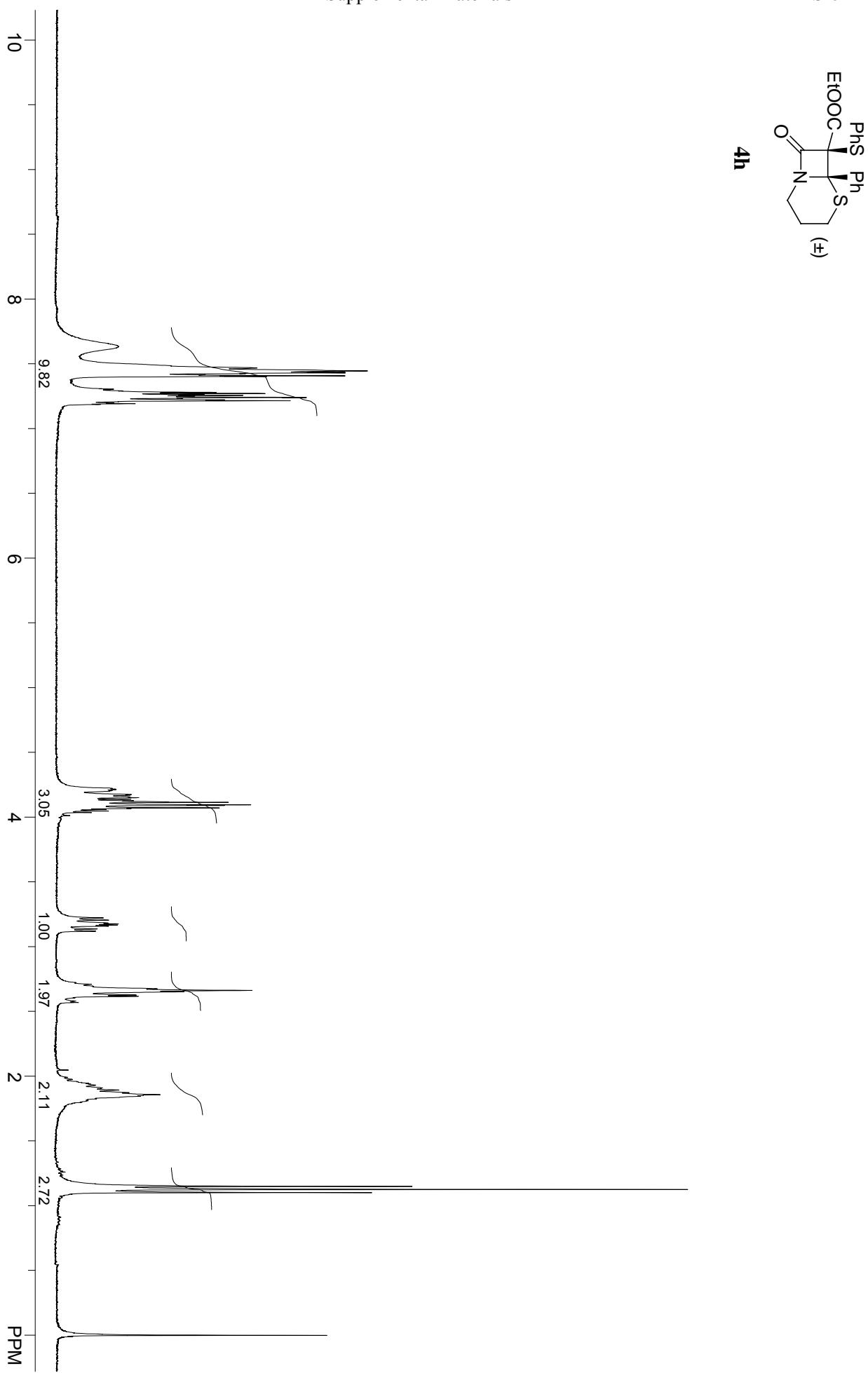


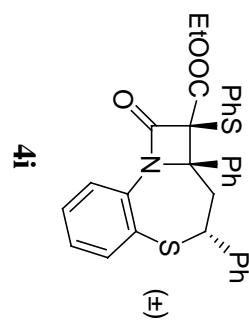
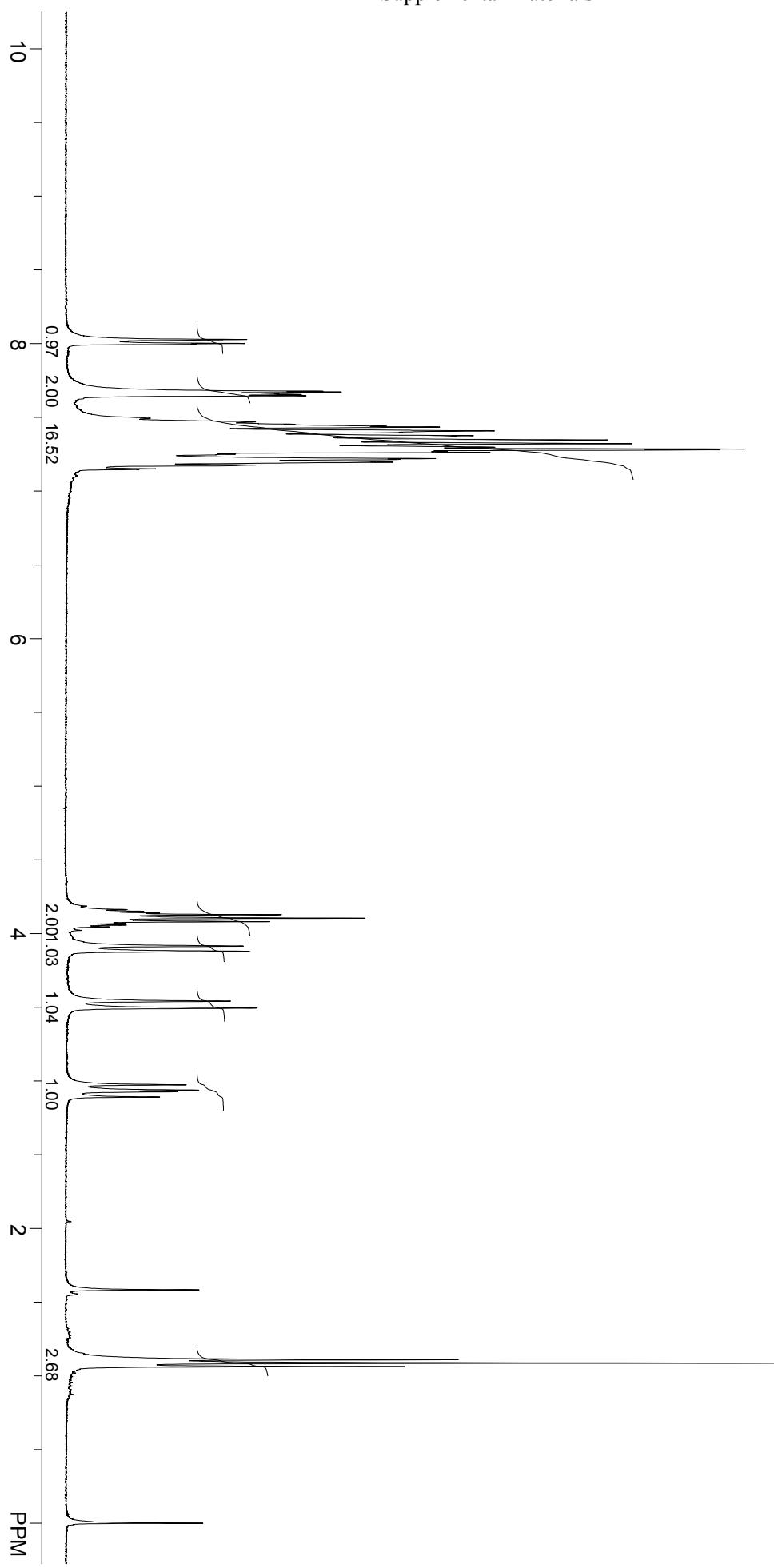


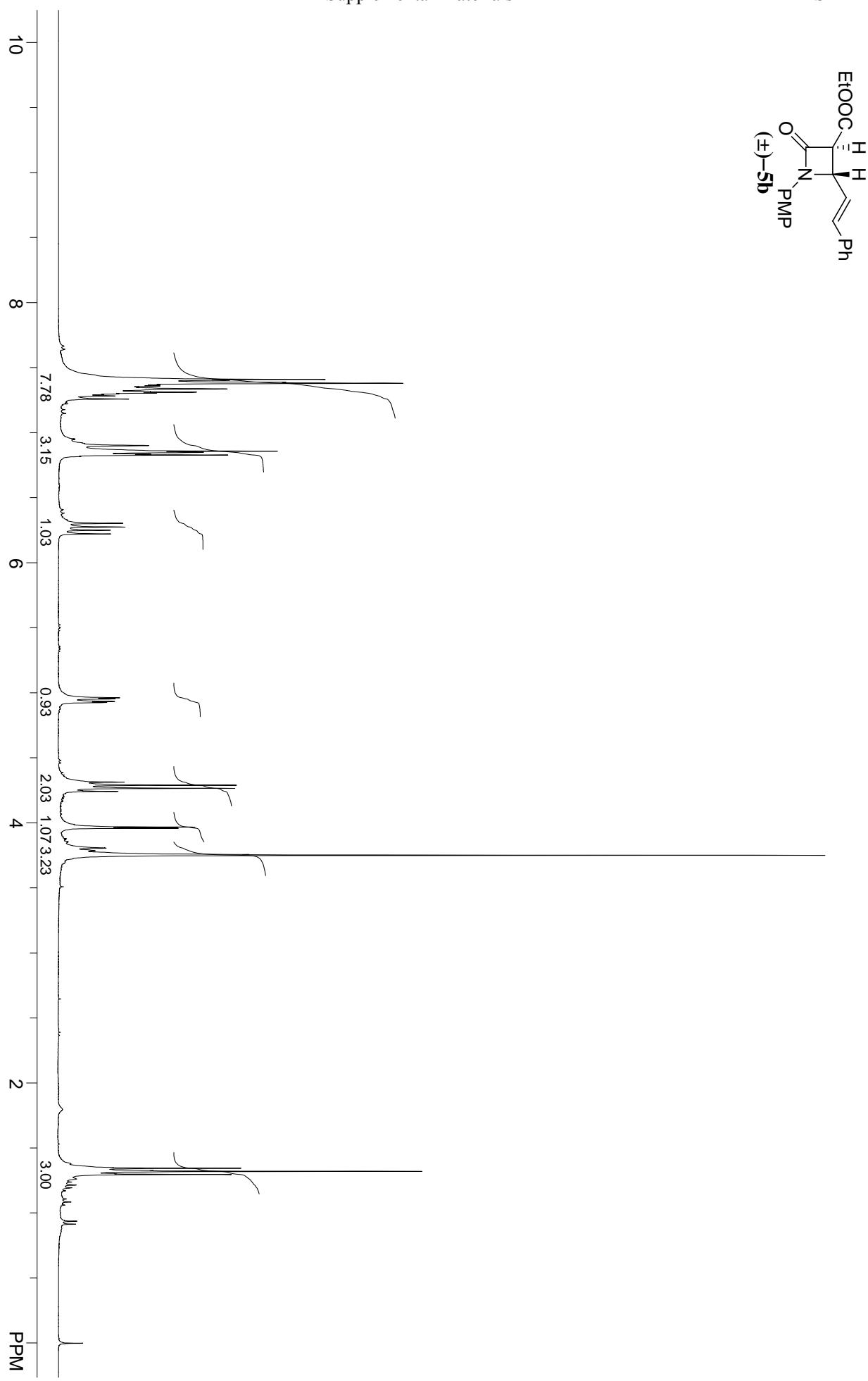


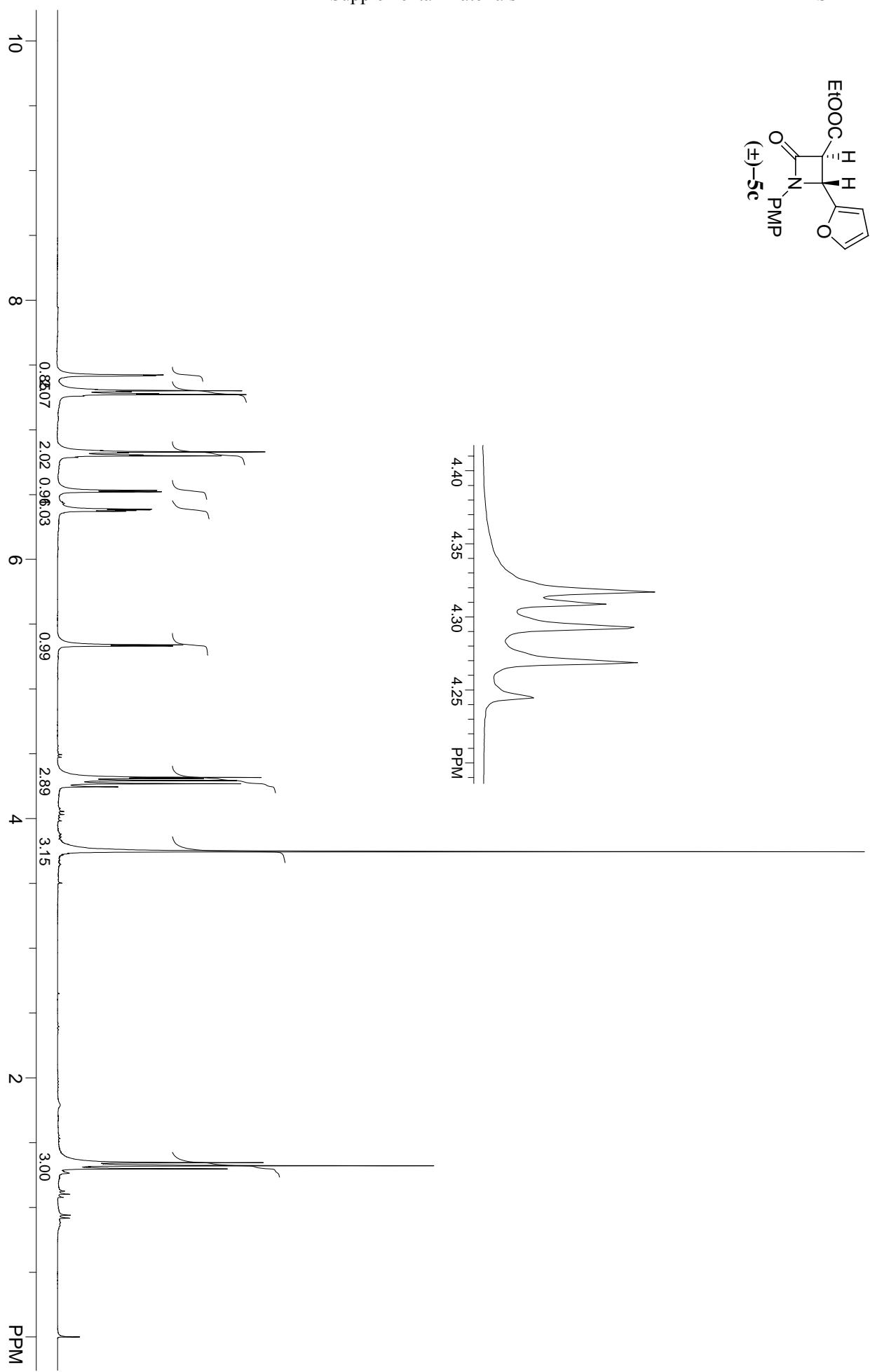


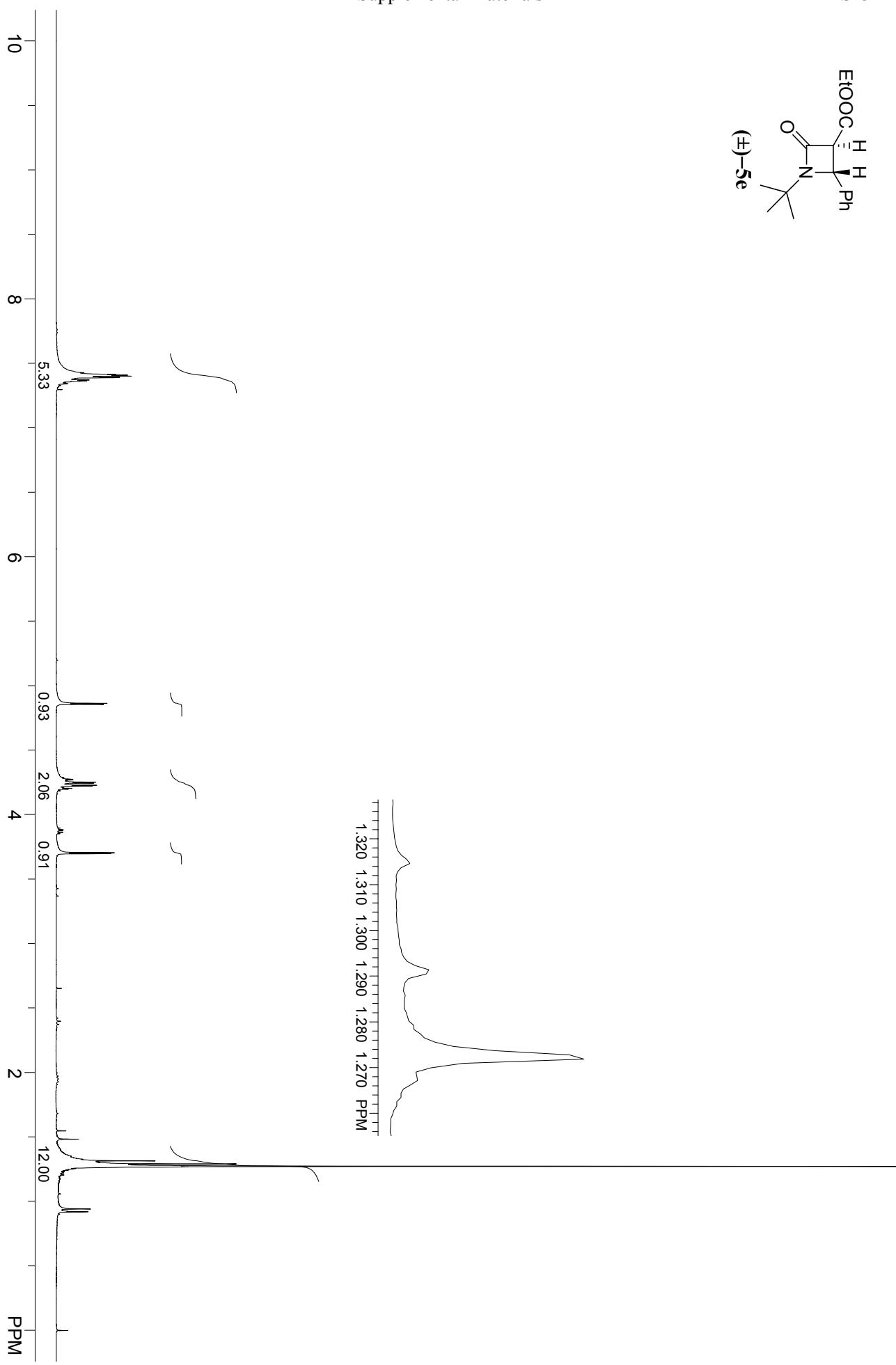


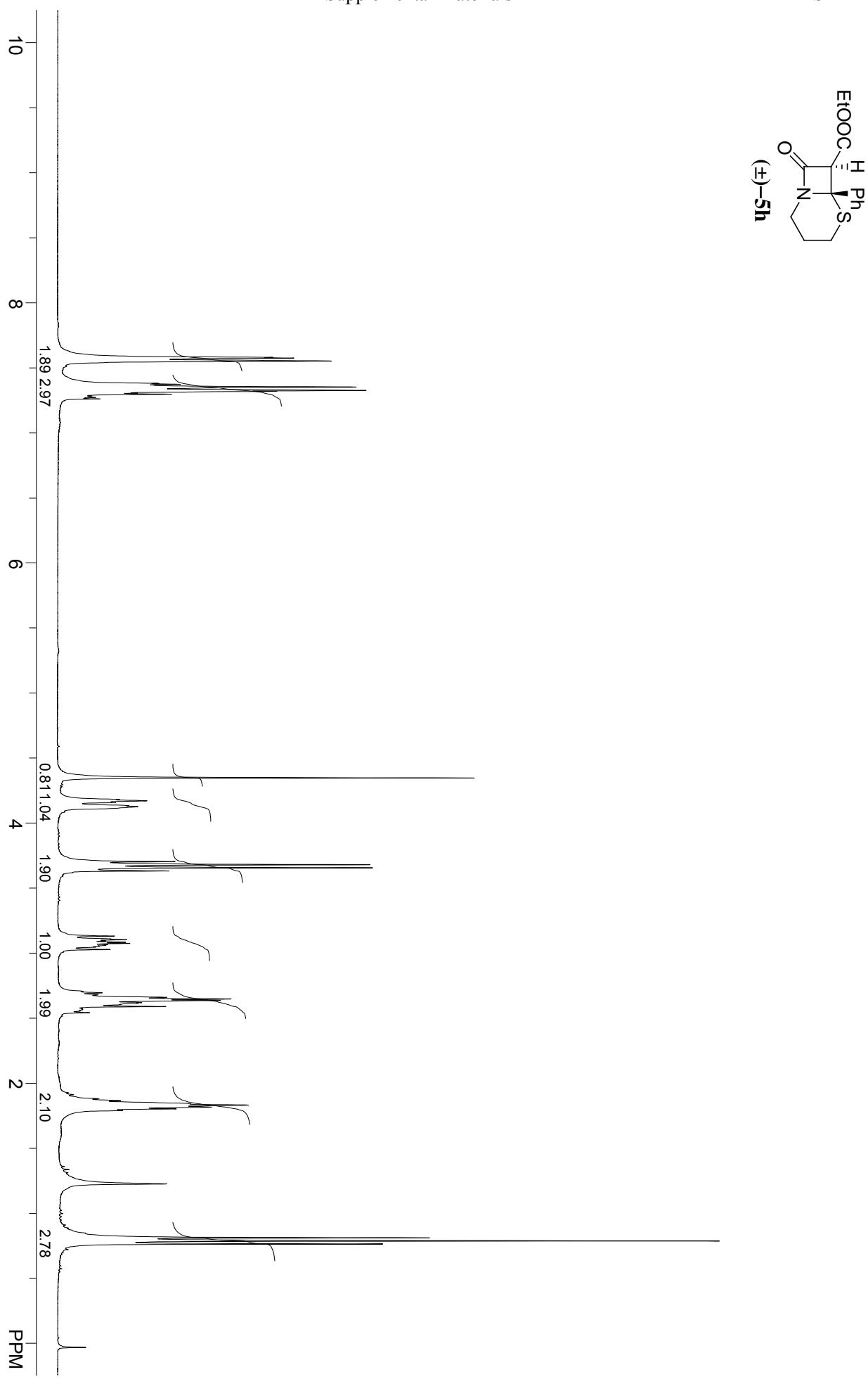


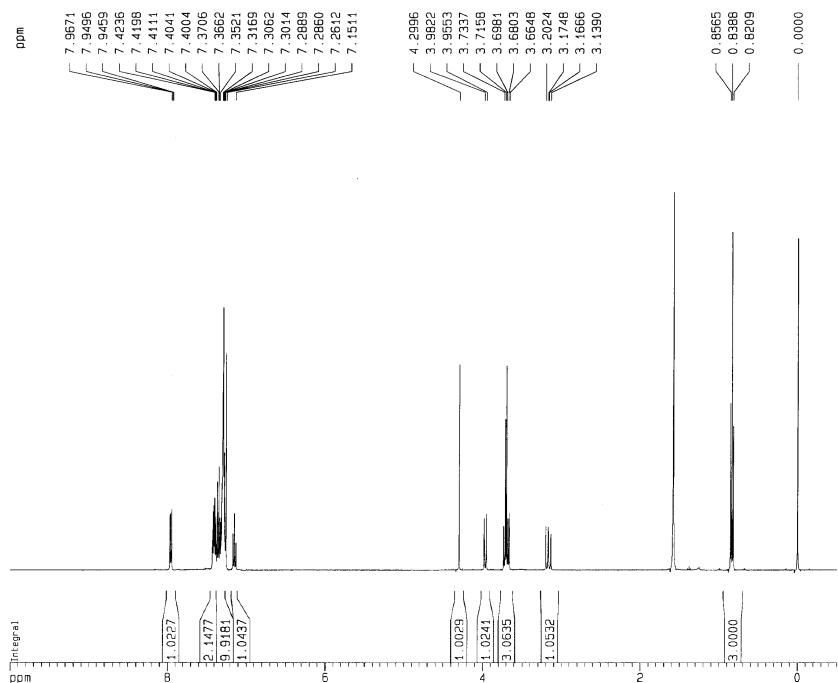
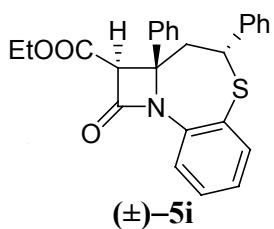




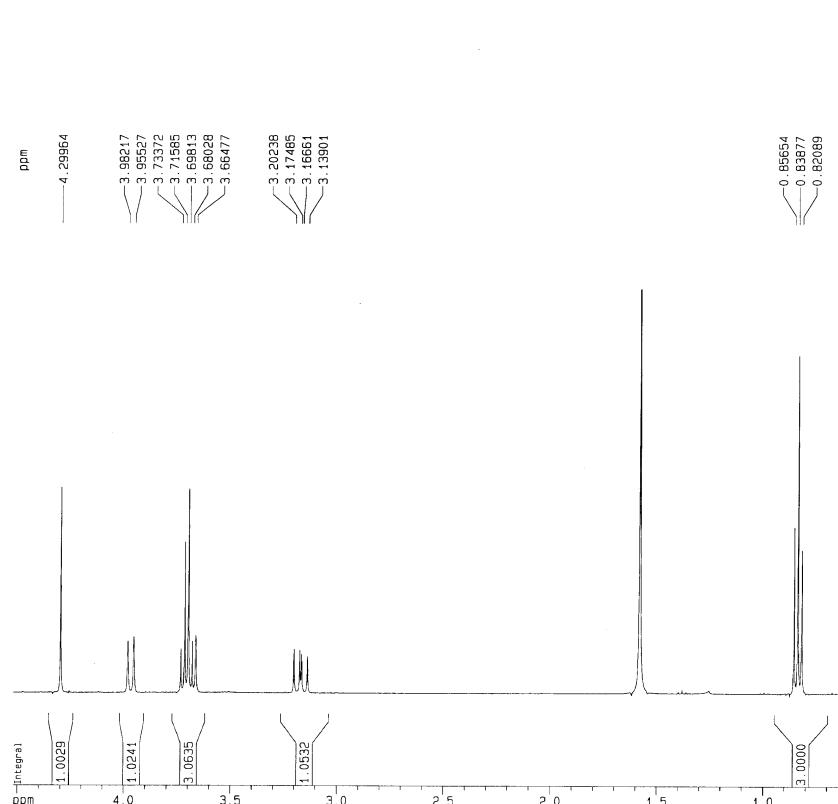








5i (partially enlarged)



Current Data Parameters
NAME h27866
EXPNO 1
PROCNO 1

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F2 ~ Acquisition Parameters
Date_      20050823
Time       9.23
INSTRUM   ARX400
PROBHD    5 mm Multinu
PULPROG  zg
TD        32768
SOLVENT   CDC13
NS         32
DS         0
SWH      6410.25 Hz
FIDRES   0.195625 Hz
AQ        2.5559540 sec
RG        1024
DW        78.000 used
DE        97.50 used
TE        300.0 K
D1        2.00000000 sec
P1        4.00 used
DE        97.50 used
SF01     400.1317965 MHz
NUCLEUS  1H

```

F2 - Processing parameters
SI 16384
SF 400.1300089 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 4.00

```

1D NMR plot parameters
CX           20.00 cm
F1P          10.000 ppm
F1           4001.30 Hz
F2P          -0.500 ppm
F2           -200.07 Hz
PPMCM        0.52500 ppm/cm
HCM          210.06825 H/cm

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Current Data Parameters
NAME h27866
EXPNO 1
PROCNO 1

F2' - Acquisition Parameters
Date_ 20050823
Time 9.23
INSTRUM ARX400
PROBHD 5 mm Multinu
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 32
DS 0
SWH 6410.256 Hz
FIDRES 0.195625 Hz
AQ 2.5559540 sec
RG 1024
DW 78.0000 usec
DE 97.50 usec
TE 300.0 K
D1 2.00000000 sec
P1 4.00 usec
DE 97.50 usec
SF01 400.1317965 MHz
NUCPIUS 1H

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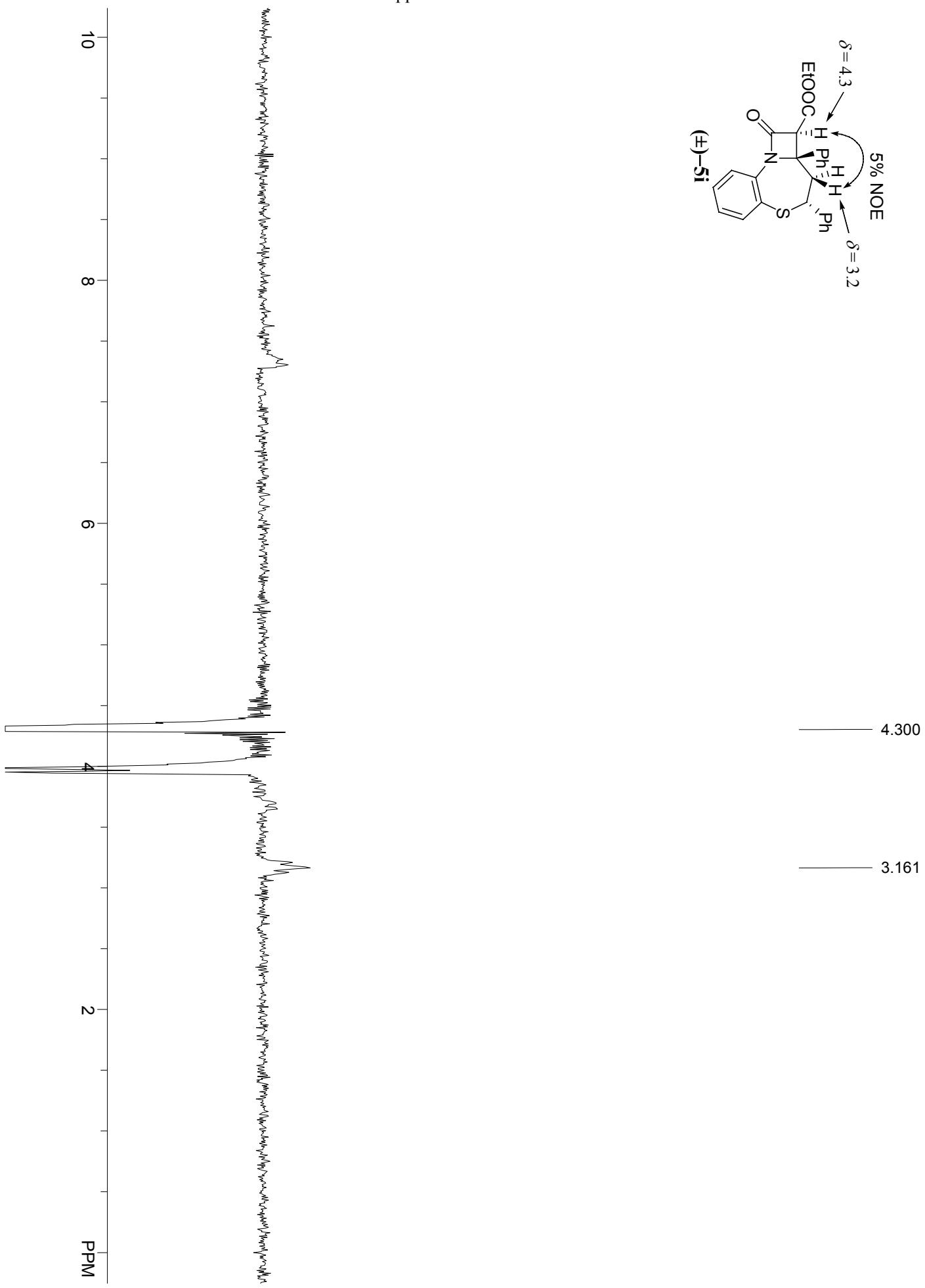
F2 - Processing parameters
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SF          400.1300089 MHz
WDW          no
SSB          0
LB           0.00 Hz
GB          0
PC          4.00

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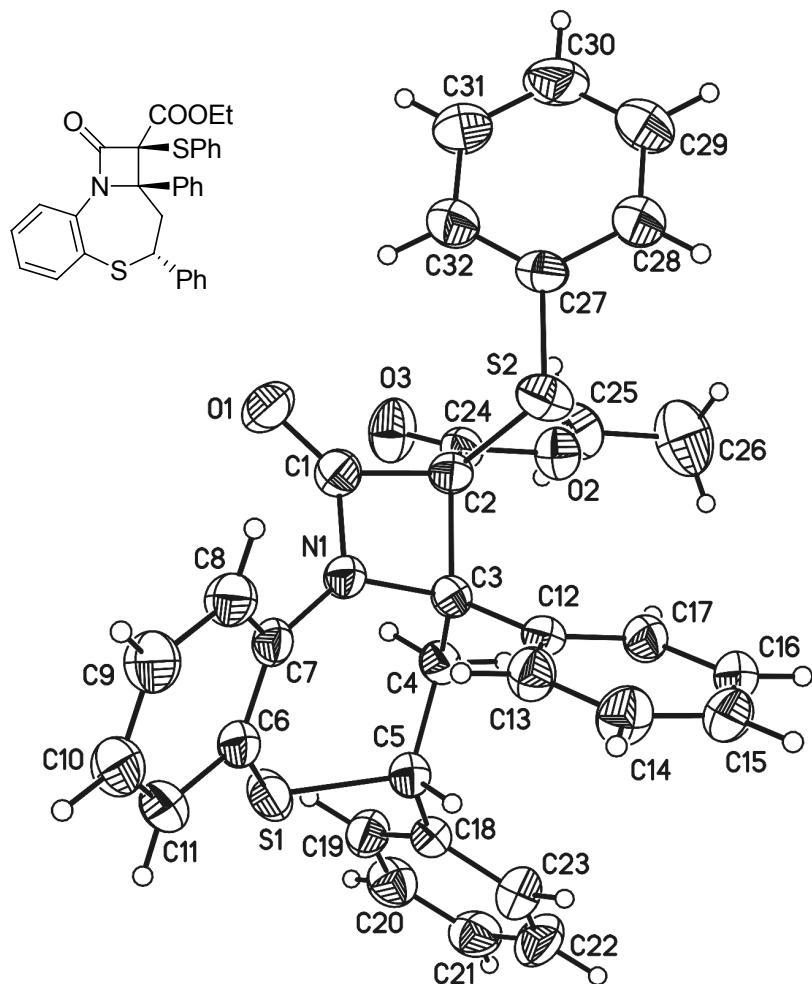
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1D NMR plot parameters
CX           20.00 cm
F1P          4.520 ppm
F1           1808.41 Hz
F2P          0.622 ppm
F2           248.94 Hz
PPMCM        0.19467 ppm/cm
HzCM        77.97360 Hz/cm

```



Crystal Structure of Polycyclic β -Lactam 4i (ORTEP Figure)



CCDC 283184 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.