

Dehalogenation of *Functionalized* Alkyl Halides in Water at Room Temperature

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Experimental

General Information

Unless otherwise noted, all reactions were performed under an atmosphere of argon. All commercially available reagents were used without further purification. A 2 wt % TPGS-750-M/H₂O solution was prepared by dissolving 4 g TPGS-750-M in 196 g water (HPLC grade), followed by degassing with argon. TPGS-750-M was made as previously described.¹ TPGS-750-M is also available commercially.² Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F₂₅₄ plates (Merck, 0.25 mm thick). The developed chromatogram was analyzed by UV lamp (254 nm). For non-UV active compounds were visualized by aqueous potassium permanganate (KMnO₄), vanillin, or ninhydrin stain developed by heat with a heat gun. Flash chromatography was performed in glass columns using Silica Flash[®] P60 (SiliCycle, 40-63 μm). GC-MS data was recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). As capillary column a HP-5MS cross-linked 5% phenylmethylpolysiloxanediphenyl column (30 m x 0.250 mm, 0.25 micron, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min. Retention times (t_R) refer to the following temperature program: 50 °C for 5 min; heating rate 20°C/min; 300 °C for 20 min; injection temperature 250 °C; detection temperature 280 °C. ¹H and ¹³C NMR were recorded at 22 °C on a Varian UNITY INOVA 400 MHz, 500 MHz, or 600 MHz. Chemical shifts in ¹H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.26 or 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sex = sextet, sep = septet, oct = octet, m = multiplet, br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ¹³C NMR spectra are reported in ppm from the central peak of CDCl₃ (77.23 ppm) on the δ scale. Chiral HPLC data was collected using a Shimadzu SPD-m20a Prominence diode array detector. Chiral GC analysis was performed using a Restek RT-*beta*DEXcst column (30 m x 0.250 mm, 0.25 micron). Retention times (t_R) are from compound dependent temperature programs; split-inlet at 200 °C at 11.60 psi (H₂, constant pressure) with 20:1 split, FID 290 °C. High resolution mass analyses were obtained using an APE Sciex QStar Pulsar quadrupole/TOF instrument (API) for ESI, or a GCT Premier TOF MS (Waters Corp) for FI.

- 1) Lipshutz, B. H.; Ghorai, S.; Abela, A. R.; Moser, R.; Nishikata, T.; Duplais, C.; and Krasovskiy, A. J. *Org. Chem.* **2011**, *76*, 4379.
- 2) TPGS-750-M: Aldrich catalog numbers 733857 and 763918.

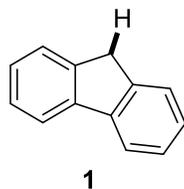
General Experimental

1. Inside a dry box, a flame-dried 5 mL round bottom flask or 5 mL microwave vial equipped with a stir bar, fitted with a rubber septum and cooled under argon atmosphere was sequentially charged with Zn (4 equiv). Outside the dry box, under a positive flow of argon were added *via* syringe the 2 wt % TPGS-750-M/H₂O solution (0.5 mL, 0.5 M). While stirring vigorously, TMEDA (2 equiv) was added via syringe followed by the alkyl halide (0.25 mmol). The mixture was vigorously stirred at rt until completion (monitored by TLC and/or GC-MS). The mixture was diluted with EtOAc and filtered through a pad of silica gel. The solvent was removed via rotary evaporation. The crude was purified by column chromatography (eluent: EtOAc/hexanes).

2. Inside a dry box, a flame-dried 5 mL round bottom flask or 5 mL microwave vial equipped with a stir bar, fitted with a rubber septum and cooled under an argon atmosphere was sequentially charged with Zn (1.1 to 2 equiv) and NH₄Cl (0.5 to 2 equiv) Outside the dry box, under a positive flow of argon was added *via* syringe the 2 wt % TPGS-750-M/H₂O solution (0.5 mL, 0.5 M). While stirring vigorously, the alkyl halide (0.25 mmol) was added. The mixture was vigorously stirred at rt until completion (monitored by TLC and/or GC-MS). The mixture was diluted with EtOAc and filtered through a pad of silica gel. The solvent was removed via rotary evaporation. The crude material was purified by column chromatography (eluent: EtOAc/hexanes).

Substrate Scope

Synthesis of 9H-fluorene from 9-bromo-9H-fluorene



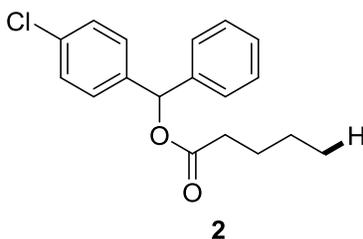
Following the general procedure **1** above (0.25 mmol, 0.5 M, reaction time: 3.5 h), the desired product **1** was obtained as a white solid (39 mg, 95% yield). The ¹H NMR spectrum matched that previously reported.

Following the general procedure **2** above (0.5 mmol, 0.5 M, 1.5 equiv Zn, 0.5 equiv NH₄Cl, reaction time: 16 h), the desired product was obtained as a white solid (83 mg, 99% yield). The ¹H NMR spectrum matched that previously reported.

$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.80 (d, $J = 7.8$ Hz, 2H), 7.56 (d, $J = 7.8$ Hz, 2H), 7.39 (t, $J = 7.2$ Hz, 2H), 7.31 (dt, $J = 0.6$ Hz, 7.8 Hz, 2H), 3.92 (s, 2H).

Ref: Clive, D. L. J.; Sunasae, R.; *Org. Lett.* **2007**, *9*, 2677-2680.

Synthesis of (4-chlorophenyl)(phenyl)methyl pentanoate from (4-chlorophenyl)(phenyl)methyl 5-bromopentanoate



Following general procedure **1 above** (0.25 mmol, 0.5 M, reaction time: 19 h), the desired product **2** was obtained as a colorless oil (72 mg, 96% yield).

TLC: 10% EtOAc/hexanes

Purification (eluent): 2, 4, 6% EtOAc/hexanes

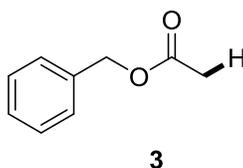
$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.33-7.7.23 (m, 9H), 6.82 (s, 1H), 2.39 (t, $J = 7.8$ Hz, 2H), 1.62 (p, $J = 7.8$ Hz, 2H), 1.31 (sex, $J = 7.2$ Hz, 2H), 0.88 (t, $J = 7.2$ Hz, 3H).

$^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 172.9, 140.0, 139.1, 133.9, 128.9, 128.8, 128.7, 128.2, 127.2, 76.1, 34.4, 27.1, 22.4, 13.9.

IR (neat): 3033, 2959, 2932, 2873, 1737, 1491, 1240, 1160, 1088, 753, 717, 551 cm^{-1} .

HRMS-FI (m/z) [M] $^+$ calculated for $\text{C}_{18}\text{H}_{19}\text{ClO}_2$ 302.1074, found 302.1088.

Synthesis of benzyl acetate from benzyl 2-bromoacetate

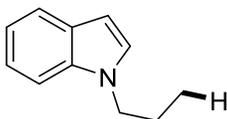


Following general procedure **1 above** (0.25 mmol, 0.5 M, reaction time: 4 h), the desired product **3** was obtained as a colorless oil (30 mg, 81% yield). The product is volatile. The $^1\text{H NMR}$ spectrum matched that of a commercial bottle obtained from Sigma-Aldrich®.

Following general procedure **2** (0.50 mmol, 0.5 M, Zn (1.1 equiv) NH₄Cl (0.5 equiv), reaction time: 12 h), the desired product **3** was obtained as a colorless oil (64 mg, 85% yield). The product is volatile. The ¹H NMR spectrum matched that of a commercial bottle obtained from Sigma-Aldrich®.

¹H NMR (600 MHz, CDCl₃): δ 7.39-7.36 (m, 3H), 7.33-7.30 (m, 1H), 5.12 (s, 2H), 2.12 (s, 3H).

Synthesis of 1-propyl-1H-indole from 1-(3-bromopropyl)-1H-indole



4

Following general procedure **1** above (0.25 mmol, 0.5 M, reaction time: 16 h), the desired product **4** was obtained as a colorless oil (58 mg, 90% yield). The ¹H NMR spectrum matched that previously reported.

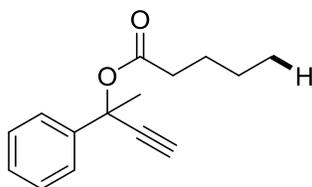
TLC: 5% EtOAc/hexanes

Purification (eluent): 5% EtOAc/hexanes

¹H NMR (600 MHz, CDCl₃): δ 7.67-7.65 (m, 1H), 7.38-7.34 (m, 1H), 7.23 (dt, *J* = 0.6, 7.8 Hz, 1H), 7.15-7.11 (m, 2H), 6.53 (dd (asymmetric), *J* = 2.4, 19.8 Hz, 1H), 4.11 (t, *J* = 7.2 Hz, 2H), 1.90 (sex, *J* = 7.2 Hz, 2H), 0.96 (t, *J* = 7.2 Hz, 2H).

Ref: Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050-8057.

Synthesis of 2-phenylbut-3-yn-2-yl pentanoate from 2-phenylbut-3-yn-2-yl 5-bromopentanoate



5

Following general procedure **1** above (0.25 mmol, 0.5 M, reaction time: 15 h), the desired product **5** was obtained as a colorless oil (54 mg, 95% yield).

TLC: 10% EtOAc/hexanes

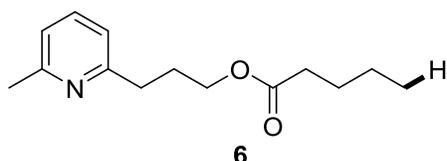
Purification (eluent): 2, 4, 6% EtOAc/hexanes

¹H NMR (600 MHz, CDCl₃): δ 7.59 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 2.81 (s, 1H), 2.38 (m, 2H), 1.91 (s, 3H), 1.62 (p, *J* = 7.8 Hz, 2H), 1.35 (s, *J* = 7.8 Hz, 2H), 0.92 (t, *J* = 7.2 Hz, 3H).
¹³C NMR (150 MHz, CDCl₃): δ 171.8, 142.7, 128.7, 128.2, 125.2, 83.5, 75.8, 75.5, 34.9, 32.4, 27.2, 22.6, 14.1.

IR (neat): 3284, 2959, 2934, 2873, 1746, 1236, 1155, 1057, 762, 697 cm⁻¹.

HRMS-FI (*m/z*) [M]⁺ calculated for C₁₅H₁₈O₂ 230.1307, found 230.1302.

Synthesis of 3-(6-methylpyridin-2-yl)propyl pentanoate from 3-(6-methylpyridin-2-yl)propyl 5-bromopentanoate



Following general procedure **1** above (0.25 mmol, 0.5 M, reaction time: 9 h), the desired product **6** was obtained as a colorless/yellow oil (54 mg, 93% yield). The compound was not purified by column chromatography as the crude ¹H NMR looked reasonably clean.

TLC: 10% EtOAc/hexanes

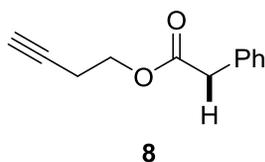
¹H NMR (600 MHz, CDCl₃): δ 7.49 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.8, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 4.12 (t, *J* = 6.6 Hz, 2H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.07 (p, *J* = 6.6 Hz, 2H), 1.61 (p, *J* = 7.8 Hz, 2H), 1.36 (sex, *J* = 7.2 Hz, 2H), 0.93 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 174.1, 160.5, 158.1, 136.9, 120.9, 119.8, 63.9, 34.9, 34.3, 29.0, 27.3, 24.7, 22.5, 13.9.

IR (neat): 3064, 2958, 2873, 1732, 1592, 1456, 1255, 1172, 1095, 988, 791 cm⁻¹.

HRMS-ESI (*m/z*) [M + Na]⁺ calculated for C₁₄H₂₁NO₂Na 258.1470, found 258.1474.

Synthesis of But-3-yn-1-yl 2-phenylacetate from But-3-yn-1-yl 2-chloro-2-phenylacetate



Following general procedure **1** above (0.5 mmol, 0.5 M, reaction time: 6 h), the desired product **11** was obtained as a colorless oil (81.8 mg, 87% yield). The ¹H NMR spectrum matched that previously reported.

Following general procedure **2** above (0.5 mmol, 0.5 M, Zn (1.1 equiv), NH₄Cl (0.5 equiv), reaction time: 12 h), the desired product **11** was obtained as a colorless oil (97.5 mg, 98% yield). The ¹H NMR spectrum matched that previously reported.

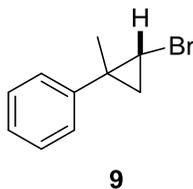
TLC: 5% EtOAc/hexanes, R_f = 0.23

Purification (eluent): 5% EtOAc/hexanes

¹H NMR (500 MHz, CDCl₃): δ 7.36-7.28 (m, 4H), 4.22 (t, *J* = 7.0 Hz, 2H), 3.66 (s, 3H), 2.54 (dt, *J* = 3.0, 7.0 Hz, 2H), 1.99 (t, *J* = 3.0 Hz, 1H).

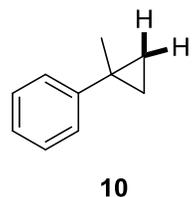
Ref: Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756-8757.

Synthesis of (2-bromo-1-methylcyclopropyl)benzene from (2,2-dibromo-1-methylcyclopropyl)benzene



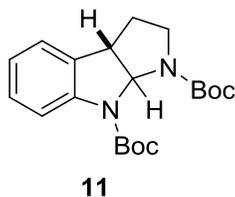
Following general procedure **1** above (0.25 mmol, 0.5 M, reaction time: 21 h). The crude mixture was analyzed by GCMS to determine conversion. The ratio of mono-dehalogenation product **9** to di-dehalogenation was determined to be 87:13, respectively, by GC-MS integration. The product was too volatile to isolate.

Synthesis of (1-Methylcyclopropyl)benzene from (2,2-Dibromo-1-methylcyclopropyl)benzene



Following general procedure **1 above** (0.25 mmol, 0.5 M, Zn(nano-sized), reaction time: 24 h) the crude mixture was analyzed by GCMS to determine conversion. The ratio of di-dehalogenation product **10** to mono-dehalogenation was determined to be 88:12, respectively, by GCMS integration. The product was too volatile to isolate.

Synthesis of di-*t*-butyl (3*aS*)-2,3,3*a*,8*a*-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate from di-*t*-butyl (3*aR*)-3*a*-bromo-2,3,3*a*,8*a*-tetrahydropyrrolo [2,3-*b*]indole-1,8-dicarboxylate



Following general procedure **1** above (0.1 mmol, Zn (4 equiv +4 equiv), 0.5 M, reaction time: 24 h), the desired product was obtained as a colorless oil (34 mg, 94% yield). Zn was added in two portions to achieve full conversion: once at t = 0 min and again at t = 6 h. The ^1H NMR spectrum matched that previously reported.

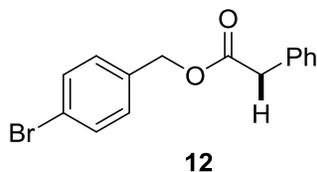
TLC: 20% EtOAc/hexanes, R_f = 0.23

Purification (eluent): 7% EtOAc/hexanes

^1H NMR (600 MHz, CDCl_3): δ 7.62 (br. s, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 7.00 (t, J = 7.3 Hz, 1H), 6.44 (br. d, J = 6.6 Hz, 1H), 3.99 (t, J = 7.8 Hz, 1H), 3.81 (dd, J = 7.8, 11.4 Hz, 1H), 2.83 (dt, J = 4.8, 11.4 Hz, 1H), 2.14-2.01 (m, 2H), 1.58 (s, 9H), 1.50 (s, 9H).

Ref: Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756-8757.

Synthesis of 4-bromobenzyl 2-phenylacetate from 4-bromobenzyl 2-chloro-2-phenylacetate



Following general procedure **1** above (0.25 mmol, 0.5 M, reaction time: 6 h), the desired product **13** was obtained as a colorless oil (75.4 mg, 99% yield). The ^1H NMR spectrum matched that previously reported.

Following general procedure **2** (0.25 mmol, 0.5 M, Zn (1.1 equiv), NH_4Cl (0.5 equiv), reaction time: 16 h), the desired product **13** was obtained as a colorless oil (74.0 mg, 97% yield). The ^1H NMR spectrum matched that previously reported.

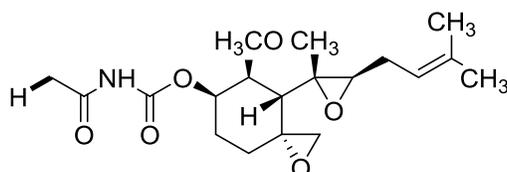
TLC: 5% EtOAc/hexanes, R_f = 0.22

Purification (eluent): 5% EtOAc/hexanes

^1H NMR (500 MHz, CDCl_3): δ 7.49-7.43 (dt, $J = 2.0, 8.3$ Hz, 2H), 7.35-7.26 (m, 5H), 7.19-7.14 (dt, $J = 2.0, 8.3$ Hz, 2H), 5.07 (s, 2H), 3.67 (s, 1H).

Ref: Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756-8757.

Synthesis of (3R,4S,5S,6R)-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-5-(oxo- λ^6 -methyl)-1-oxaspiro[2.5]octan-6-yl acetylcarbamate from TNP-470



14

Following general procedure **2** above (0.02 mmol, 0.01 M, Zn (2 equiv), NH_4Cl (1 equiv) reaction time: 16 h), the desired product **14** was obtained as a colorless oil (6.2 mg, 85% yield). The compound was not purified by column chromatography as the crude ^1H NMR looked reasonably clean.

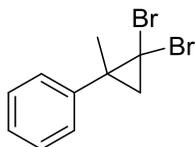
^1H NMR (600 MHz, CDCl_3): δ 7.44 (br. d, $J = 7.2$ Hz, 1H), 5.58 (s, 1H), 5.21 (t, $J = 7.2$ Hz, 1H), 3.70-3.65 (m, 1H), 3.48 (s, 3H), 3.02-2.98 (m, 1H), 2.59-2.55 (m, 1H), 2.41 (s, 3H), 2.39-2.36 (m, 1H), 2.28-2.16 (m, 2H), 2.07-2.02 (m, 3H), 1.96-1.89 (m, 2H), 1.75 (s, 3H), 1.67 (s, 3H), 1.44 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 171.5, 151.5, 135.2, 118.6, 79.3, 69.0, 61.2, 58.5, 57.1, 51.1, 48.5, 30.5, 29.9, 29.4, 27.5, 25.9, 25.8, 24.2, 18.2, 14.0.

HRMS-ESI (m/z) [$M + \text{Na}$] $^+$ calculated for $\text{C}_{19}\text{H}_{29}\text{NO}_6\text{Na}$ 390.1893, found 390.1886.

Synthesis of Starting Materials

Synthesis of (2,2-Dibromo-1-methylcyclopropyl)benzene



An oven-dried 10 mL round bottom flask with a septum and Teflon stir bar was charged with (α -methyl styrene (260 μL , 2 mmol, 1 equiv, den. 0.91 g/mL) and KO-*t*-Bu (235 mg, 2.1 mmol, 1.05 equiv). Next, *t*-BuOH (5 mL) was added and stirred for several min. The mixture was cooled to 0 $^\circ\text{C}$ with an ice-bath. Slowly, via syringe, bromoform (183 mL, 2.1 mmol, 1.05 equiv, den. 2.889 g/mL) was added. The ice-

bath was then removed and the resulting solution was allowed to stir overnight. Afterwards, H₂O was added to the flask and extracted with hexanes in a separatory funnel. The crude mixture was purified by column chromatography to afford a colorless oil (285 mg, 49% yield). The conversion was roughly 50% by ¹H NMR.

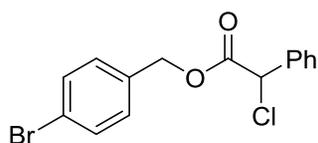
TLC: hexanes, R_f = 0.65

Purification (eluent): hexanes

¹H NMR (400 MHz, CDCl₃): δ 7.39-7.35 (m, 2H), 7.33-7.28 (m, 3H), 2.18 (d, J = 7.6 Hz, 1H), 1.79 (d, J = 7.6 Hz, 1H), 1.73 (s, 3H).

Ref: Clavier, H.; Jeune, K. L.; Riggi, I. D.; Tanaglia, A.; Buono, G. *Org. Lett.* **2011**, *13*, 308-311.

Synthesis of 4-bromobenzyl 2-chloro-2-phenylacetate



An oven-dried 25 mL round bottom flask with a septum and Teflon stir bar was charged with (4-bromophenyl)methanol (0.375 g, 2.0 mmol, 1.0 equiv) and dissolved in CH₂Cl₂ (20 mL). NEt₃ (0.28 mL, 2.2 mmol, 1.1 equiv) was added dropwise to the flask while stirring. Subsequent addition of 2-chloro-2-phenylacetyl chloride (0.32 mL, 2.0 mmol, 1.0 equiv) was added dropwise. The resulting solution was stirred, and monitored by TLC for 3 h. The reaction mixture was transferred with 100 mL Et₂O into a separatory funnel containing 100 mL H₂O. The layers were separated and the aqueous phase was extracted twice with Et₂O (100 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated via rotary evaporation. The crude material was purified by column chromatography, using the indicated solvent system, to afford the desired product (0.57 g, 84% yield) as white solid.

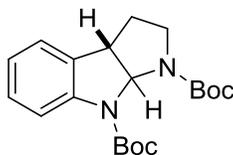
TLC: 5% EtOAc/hexanes, R_f = 0.22

Purification (eluent): 5% EtOAc/hexanes

¹H NMR (500 MHz, CDCl₃): δ 7.48-7.33 (m, 7H), 7.11 (d, J = 8.3 Hz, 2H), 5.37 (s, 1H), 5.12 (dt, J = 3.9, 12.7 Hz, 2H).

Ref: Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756-8757.

Synthesis of di-*t*-butyl (3*aR*)-3*a*-bromo-2,3,3*a*,8*a*-tetrahydropyrrolo [2,3-*b*]indole-1,8-dicarboxylate



An oven-dried 100 mL round bottom flask with a septum and Teflon stir bar was charged bis-Boc-protected typtamine (0.999 g, 2.77 mmol) and dissolved in DCM (25 mL). Subsequently, NBS (0.498 g, 2.77 mmol) and PPTS (0.697 g, 2.77 mmol) were added to the reaction mixture. The solution was stirred at rt for 6 h. Afterwards, the mixture was diluted with DCM (~20 mL), transferred to a separatory funnel, and washed with NH₄Cl (sat. aq., ~40 mL). The product was extracted twice with DCM (~20 mL, each), collected, and dried over anhydrous MgSO₄. The solvent was removed via rotary evaporation and purified by column chromatography affording a white solid/foam (605 mg, 50% yield).

Note: This compound is light sensitive! It was immediately placed in the freezer and wrapped in foil.

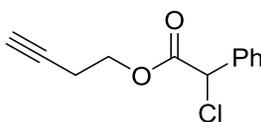
TLC: 20% EtOAc/hexanes, R_f = 0.22

Purification (eluent): 2, 4, 6, 8, 10% EtOAc/hexanes

¹H NMR (500 MHz, CDCl₃): δ 7.59 (br. s, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.29 (dt, *J* = 1.5, 9 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.44 (s, 1H), 3.74 (dd, *J* = 2.5, 10 Hz, 1H), 2.84-2.70 (m, 3H), 1.59 (s, 9H), 1.49 (s, 9H).

Ref: Espejo, V. R.; Rainier, J. D. *J. Am. Chem. Soc.* **2008**, *130*, 12894-12895.

Synthesis of but-3-yn-1-yl 2-chloro-2-phenylacetate



An oven-dried 25 mL round bottom flask with a septum and Teflon stir bar was charged with but-3-yn-1-ol (0.23 mL, 3.0 mmol, 1.0 equiv) and dissolved in CH₂Cl₂ (30 mL). NEt₃ (0.42 mL, 3.3 mmol, 1.1 equiv) was added dropwise to the flask while stirring. Subsequent addition of 2-chloro-2-phenylacetyl chloride (0.47 mL, 3.0 mmol, 1.0 equiv) was added dropwise. The resulting solution was stirred, and monitored by TLC for 4 h. The reaction mixture was transferred with 150 mL Et₂O into a separatory funnel containing 150 mL H₂O. The layers were separated and the aqueous phase was extracted twice with Et₂O (150 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated via rotary evaporation. The crude material was purified by column chromatography, using the indicated solvent system, to afford the desired product (0.54 g, 81% yield) as white solid.

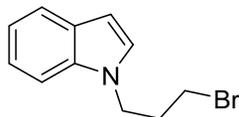
TLC: 5% EtOAc/hexanes, R_f = 0.21

Purification (eluent): 5% EtOAc/hexanes

¹H NMR (500 MHz, CDCl₃): δ 7.53-7.34 (m, 5H), 5.38 (s, 1H), 4.27 (m, 2H), 2.53 (dt, *J* = 2.7, 6.8 Hz, 2H), 1.96 (t, *J* = 2.7 Hz, 1H).

Ref: Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756-8757.

Synthesis of 1-(3-Bromopropyl)-1H-indole



To a flame-dried 100 mL round bottom flask under Ar, equipped with a stir bar 1,3-dibromopropane was added (2.03 mL, 4.04 g, 20 mmol, 3 equiv, density: 1.989 g/mL) and dissolved in DMF (33 mL). 1H-Indole (0.78 g, 6.6 mmol, 1.0 equiv) and *ground* KOH (0.38 g, 6.6 mmol, 1.0 equiv) was added to the flask. The reaction mixture was stirred for 48 h. Water (75 mL) was added to the mixture. The product was extracted three times with Et₂O (50 mL, each). The combined organics were washed again with H₂O, dried with brine, and then over anhydrous MgSO₄. The solvent was evaporated via rotary evaporation. The crude material was purified by column chromatography to afford a slightly yellow oil (650 mg, 40% yield). The yield of 75% by Hassner and Dehaen was never achieved. The material was roughly 80% pure by GCMS integration. The impurity was unknown and couldn't be removed by standard purification techniques.

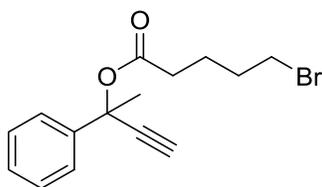
TLC: 10% EtOAc/hexanes

Purification (eluent): first, hexanes flush, then 2 to 10% EtOAc/hexanes

¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.28 (m, 1H), 7.19 (m, 2H), 6.57 (d, *J* = 3.0 Hz, 1), 4.37 (t, *J* = 6.2 Hz, 2H), 3.34 (t, *J* = 6.2 Hz, 2H), 2.38 (m, 2H).

Ref: Dehaen, W.; Hassner, A. *J. Org. Chem.* **1991**, *56*, 896-900.

Synthesis of 2-phenylbut-3-yn-2-yl 5-bromopentanoate



To a flame-dried 100 mL round bottom flask under Ar, equipped with a stir bar, EDCI (600 mg, 3 mmol, 2 equiv), DMAP (91 mg, 0.75 mmol, 0.5 equiv), and 2-phenylbut-3-yn-2-ol (219 mg, 1.5 mmol, 1 equiv) was added. The round bottom flask was purged with argon, and dissolved in DCM (20 mL). The reaction mixture was cooled to 0 °C with an ice-bath. 5-Bromopentanoic acid (353 mg, 1.95 mmol, 1.3 equiv) was added to the reaction mixture as a solution in DCM (5 mL). Subsequently Et₃N (0.32 mL, 2.25 mmol, 1.5 equiv, den. 0.72 g/mL) was added to the flask. The reaction mixture was allowed to warm to rt overnight while stirring. The solution was diluted with DCM, transferred to a separatory funnel, and

washed with 1 M HCl (40 mL, twice), brine, and dried over anhydrous MgSO₄. The organic solvent was removed via rotary evaporation and the residual material purified by column chromatography. A colorless oil was afforded (230 mg, 75% yield).

TLC: 10% EtOAc/hexanes, R_f = 0.5

Purification (eluent): 2, 4, 6% EtOAc/hexanes

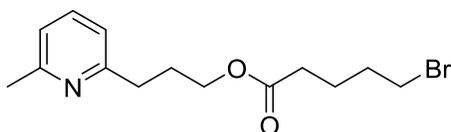
¹H NMR (600 MHz, CDCl₃): δ 7.58 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 3.40 (t, *J* = 6.6 Hz, 2H), 2.83 (s, 1H), 2.39 (oct, *J* = 6.0 Hz, 2H), 1.91 (s, 3H), 1.90-1.87 (m, 2H), 1.79 (sex, *J* = 6.6 Hz, 2H).

¹³C NMR (150 MHz, CDCl₃): δ 170.9, 142.2, 128.6, 128.2, 125.0, 83.1, 75.9, 75.6, 33.9, 33.2, 32.2, 32.1, 23.5.

IR (neat): 3286, 3067, 2935, 1744, 1448, 1057, 763, 698, 559 cm⁻¹.

HRMS-FI (*m/z*) [M]⁺ calculated for C₁₅H₁₇BrO₂ 308.0412, found 308.0423.

Synthesis of 3-(6-methylpyridin-2-yl)propyl 5-bromopentanoate



To a flame-dried 100 mL round bottom flask under Ar, equipped with a stir bar, EDCI (600 mg, 3 mmol, 2 equiv), DMAP (91 mg, 0.75 mmol, 0.5 equiv), and 3-(6-methylpyridin-2-yl)propan-1-ol (218 μL, 1.5 mmol, 1 equiv, den. 1.04 g/mL) were added. The round bottom flask was purged with argon, and dissolved in DCM (20 mL). The reaction mixture was cooled to 0 °C with an ice-bath. 5-Bromopentanoic acid (353 mg, 1.95 mmol, 1.3 equiv) was added to the reaction mixture as a solution in DCM (5 mL). Subsequently Et₃N (0.32 mL, 2.25 mmol, 1.5 equiv, den. 0.72 g/mL) was added to the flask. The reaction mixture was allowed to warm to rt overnight while stirring. The solution was diluted with DCM, transferred to a separatory funnel, and washed with 1 M HCl (40 mL, twice), brine, and dried over anhydrous MgSO₄. The organic solvent was removed via rotary evaporation and the residual material purified by column chromatography. A colorless oil was afforded (371 mg, 79% yield).

TLC: 25% EtOAc/hexanes, R_f = 0.2

Purification (eluent): 10, 20, 30% EtOAc/hexanes

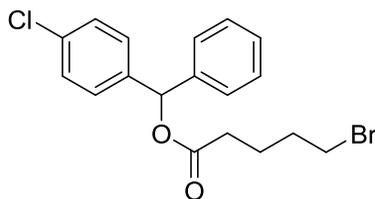
¹H NMR (600 MHz, CDCl₃): δ 7.50 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 4.14 (t, *J* = 6.6 Hz, 2H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.54 (s, 3H), 2.35 (t, *J* = 7.2 Hz, 2H), 2.08 (p, *J* = 6.6 Hz, 2H), 1.91 (p, *J* = 7.2 Hz, 2H), 1.79 (p, *J* = 7.8 Hz, 2H).

¹³C NMR (150 MHz, CDCl₃): δ 173.4, 160.4, 158.1, 136.9, 121.0, 119.8, 64.2, 34.9, 33.5, 33.2, 32.2, 24.7, 23.7.

IR (neat): 3283, 2961, 1727, 1594, 1519, 1255, 905, 725, 648 cm⁻¹.

HRMS-ESI (*m/z*) [M + Na]⁺ calculated for C₁₄H₂₀NO₂BrNa 336.0575, found 336.0591.

Synthesis of (4-chlorophenyl)(phenyl)methyl 5-bromopentanoate



To a flame-dried 100 mL round bottom flask under Ar, equipped with a stir bar, EDCI (600 mg, 3 mmol, 2 equiv), DMAP (91 mg, 0.75 mmol, 0.5 equiv), and (4-chlorophenyl)(phenyl)methanol (328 mg, 1.5 mmol, 1 equiv) were added. The round bottom flask was purged with argon, and dissolved in DCM (20 mL). The reaction mixture was cooled to 0 °C with an ice-bath. 5-Bromopentanoic acid (353 mg, 1.95 mmol, 1.3 equiv) was added to the reaction mixture as a solution in DCM (5 mL). Subsequently Et₃N (0.32 mL, 2.25 mmol, 1.5 equiv, den. 0.72 g/mL) was added to the flask. The reaction mixture was allowed to warm to rt overnight while stirring. The solution was diluted with DCM, transferred to a separatory funnel, and washed with 1 M HCl (40 mL, twice), brine, and dried over anhydrous MgSO₄. The organic solvent was removed via rotary evaporation and the residual material purified by column chromatography. A colorless oil was afforded (232 mg, 40% yield).

TLC: 10% EtOAc/hexanes, R_f = 0.5

Purification (eluent): 2, 5, 10% EtOAc/hexanes

¹H NMR (600 MHz, CDCl₃): δ 7.78-7.68 (m, 10H), 3.81 (t, *J* = 6.6 Hz, 2H), 2.88 (t, *J* = 7.8 Hz, 2H), 2.32-2.21 (m, 4H).

¹³C NMR (150 MHz, CDCl₃): δ 172.2, 139.8, 138.9, 134.0, 128.9, 128.8, 128.7, 128.3, 127.2, 76.4, 33.7, 33.1, 32.0, 23.6.

IR (neat): 3032, 2939, 1734, 1490, 1247, 1128, 1089, 801, 698, 551 cm⁻¹.

HRMS-FI (*m/z*) [M]⁺ calculated for C₁₈H₁₈BrClO₂ 380.0179, found 380.0192.

E Factor Determination and Recycle Study

Inside a dry box, a 5 mL microwave vial equipped with a stir bar, fitted with a rubber septum and cooled under an argon atmosphere was charged with Zn (4 equiv). Outside the dry box, under a positive flow of argon, was added *via* syringe the 2 wt % TPGS-750-M/H₂O solution (1.0 mL, 1.0 M). While stirring vigorously, TMEDA (2 equiv) was added via syringe followed by but-3-yn-1-yl 2-chloro-2-phenylacetate (1.0 mmol). The reaction was allowed to stir until complete. The product was extracted with EtOAc: 250 μ L + 250 μ L. To ease separation a centrifuge can be used. The organic solvent was evaporated via rotary evaporation. The crude product was purified by silica gel column chromatography (eluent: gradient from 1 to 10% EtOAc/hexanes) to provide the desired compound as a colorless oil (170 mg, 90% yield).

Re-use of surfactant solution:

Additional Zn (2 equiv) was added to the flask. Next NH₄Cl (0.5 equiv) and 4-bromobenzyl 2-chloro-2-phenylacetate (1.0 mmol) were added to the flask. The reaction was allowed to stir at rt for 7 h. The product was extracted with EtOAc: 350 μ L + 350 μ L. The organic solvent was evaporated via rotary evaporation. The crude product was purified by silica gel column chromatography (eluent: gradient from 1 to 10% EtOAc/hexanes) to provide the desired compound as a colorless oil (262 mg, 86% yield).

E Factor calculations:

Note: Density of each liquid at 25 °C; ethyl acetate = 0.897 g/mL; water = 1.00 g/mL, TMEDA = 0.775 g/mL, diethyl ether = 0.7131 g/mL, dimethylformamide = 0.944 g/mL.

Water NOT included as waste

Solvents:	first-cycle	second-cycle
<i>first-cycle</i>		
500 μ L EtOAc (449 mg)	$\frac{0.449 \text{ g waste}}{0.170 \text{ g product}} = 2.6 \text{ E Factor}$	$\frac{0.628 \text{ g waste}}{0.262 \text{ g product}} = 2.4 \text{ E Factor}$
<i>second-cycle</i>		
700 μ L EtOAc (628 mg)		

Water included as waste

Solvents:	first-cycle	second-cycle
1 mL H ₂ O (1 g)		
<i>first-cycle</i>	$\frac{1.449 \text{ g waste}}{0.170 \text{ g product}} = 8.5 \text{ E Factor}$	$\frac{1.628 \text{ g waste}}{0.262 \text{ g product}} = 6.4 \text{ E Factor}$
500 μ L EtOAc (449 mg)		
<i>second-cycle</i>		
700 μ L EtOAc (628 mg)		

Water NOT included as waste + reagents

Solvents:

first-cycle

500 μ L EtOAc (449 mg)

4 equiv Zn (260 mg)

2 equiv TMEDA (233 mg)

second-cycle

700 μ L EtOAc (628 mg)

2 equiv Zn (130 mg)

0.5 equiv NH_4Cl (27 mg)

$$\begin{array}{l} \text{first-cycle} \\ \frac{0.942 \text{ g waste}}{0.170 \text{ g product}} = 5.5 \text{ E Factor} \end{array}$$

$$\begin{array}{l} \text{second-cycle} \\ \frac{0.785 \text{ g waste}}{0.262 \text{ g product}} = 3.0 \text{ E Factor} \end{array}$$

Water included as waste + reagents

Solvents:

1 mL H_2O (1 g)

first-cycle

500 μ L EtOAc (449 mg)

4 equiv Zn (260 mg)

2 equiv TMEDA (233 mg)

second-cycle

700 μ L EtOAc (628 mg)

2 equiv Zn (130 mg)

0.5 equiv NH_4Cl (27 mg)

$$\begin{array}{l} \text{first-cycle} \\ \frac{1.942 \text{ g waste}}{0.170 \text{ g product}} = 11.4 \text{ E Factor} \end{array}$$

$$\begin{array}{l} \text{second-cycle} \\ \frac{1.785 \text{ g waste}}{0.262 \text{ g product}} = 6.8 \text{ E Factor} \end{array}$$

The Editorial Board of *Green Chemistry* insisted that we include calculations of E Factors with the “state-of-the-art” for comparison purposes, which is Ru-catalyzed photoredox methodology (see below) previously published (*J. Am. Chem. Soc.* **2009**, *131*, 8756). We realize that the contributing authors to this earlier work did not attempt to minimize their use of organic solvents, and therefore, these numbers below do not reflect the true E Factors that could potentially be achieved if the authors were to re-examine their procedures and the amounts of solvent used.

We also acknowledge that our calculated E Factors are not directly translatable to industrial scale level of reactions; rather, they are meant as a rough indication for researchers who are considering this methodology in hopes of achieving ‘greener’ transformations. Our E Factor calculations only take solvent into consideration, and while this parameter is well known to account for >85% of the organic waste created, is only meant to demonstrate that we can achieve numbers that far lower than those typically achieved in industrial labs, as previously documented (*Angew. Chem., Int. Ed.* **2013**, *52*, 10952). This is why a direct academic lab to academic lab comparison was avoided in the original manuscript submitted.

Solvents:

1 mL DMF (944 mg)

125 mL Et_2O (89.1 g)

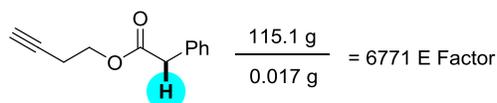
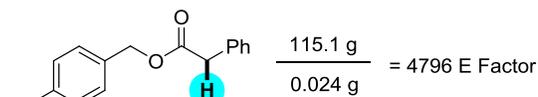
25 g H_2O (25 g)

Reagents:

2.5 mol % Ru cat. (1.9 mg)

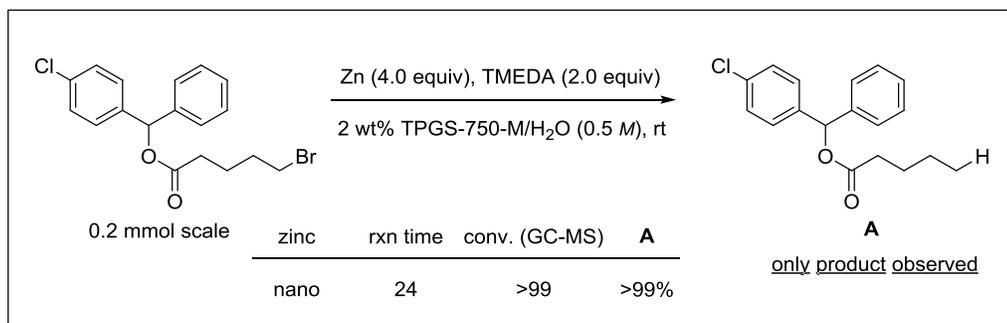
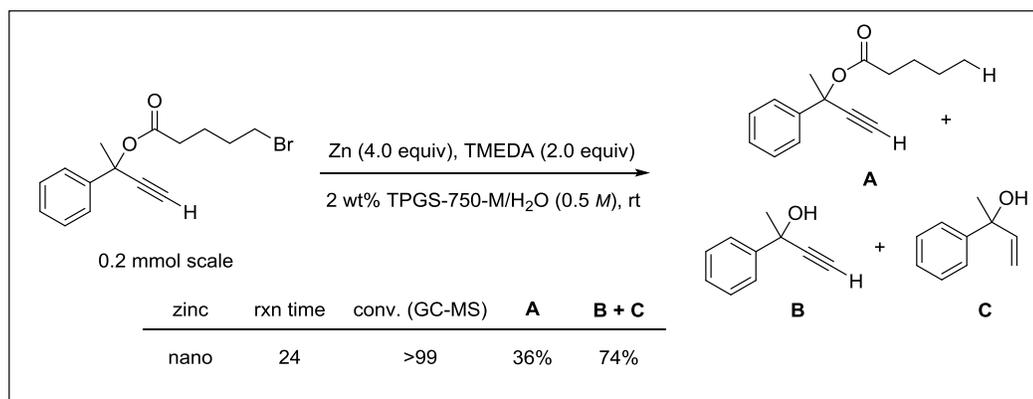
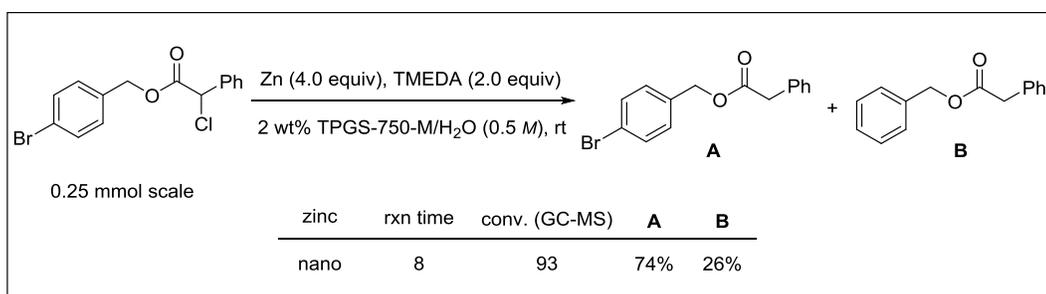
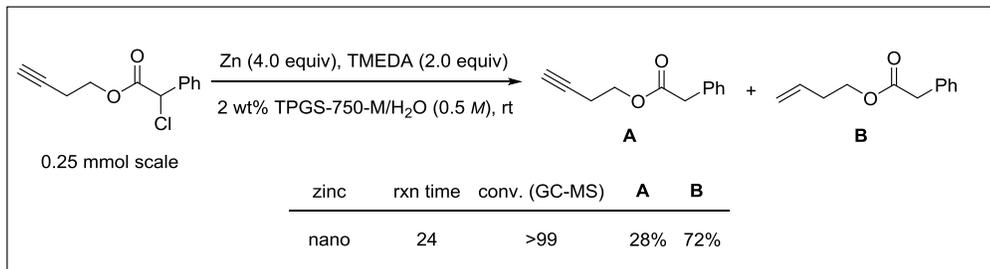
Hantzsch Ester (28 mg)

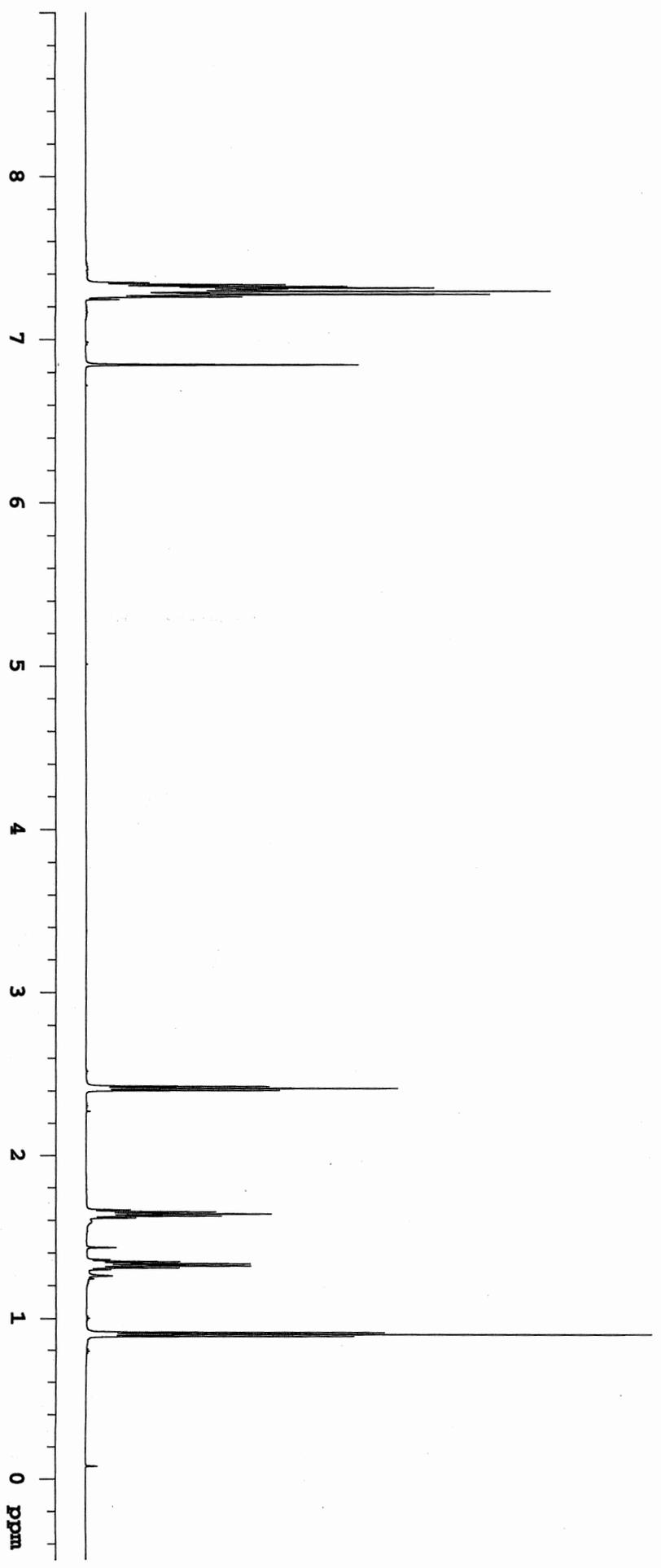
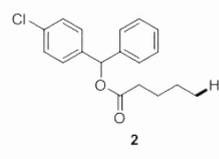
DIPEA (25 mg)

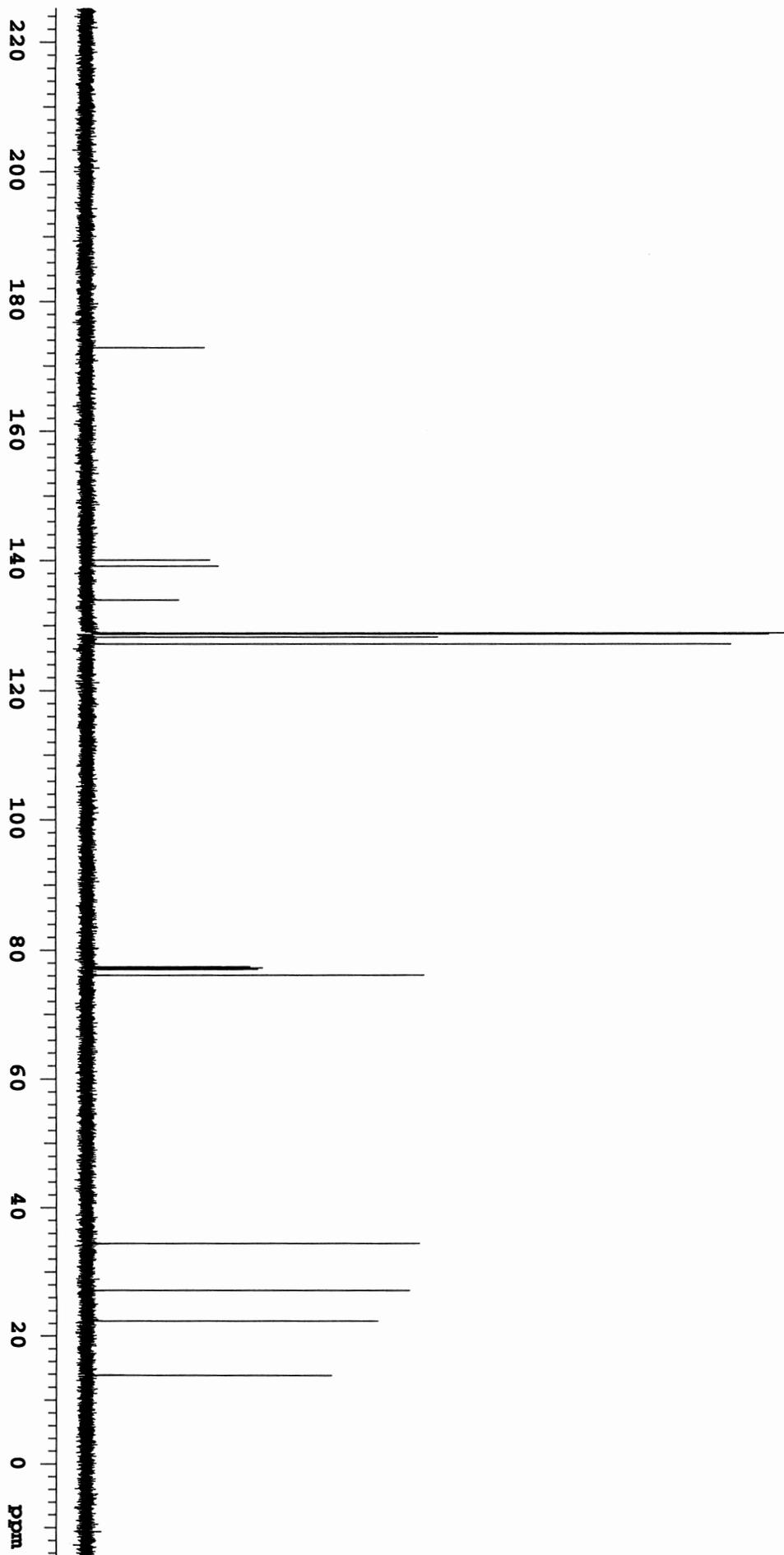
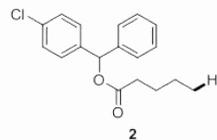


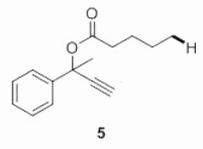
Conditions: $\text{Ru}(\text{bipy})_3\text{Cl}_2$, Hantzsch Ester, DIPEA, $h\nu$, DMF, rt

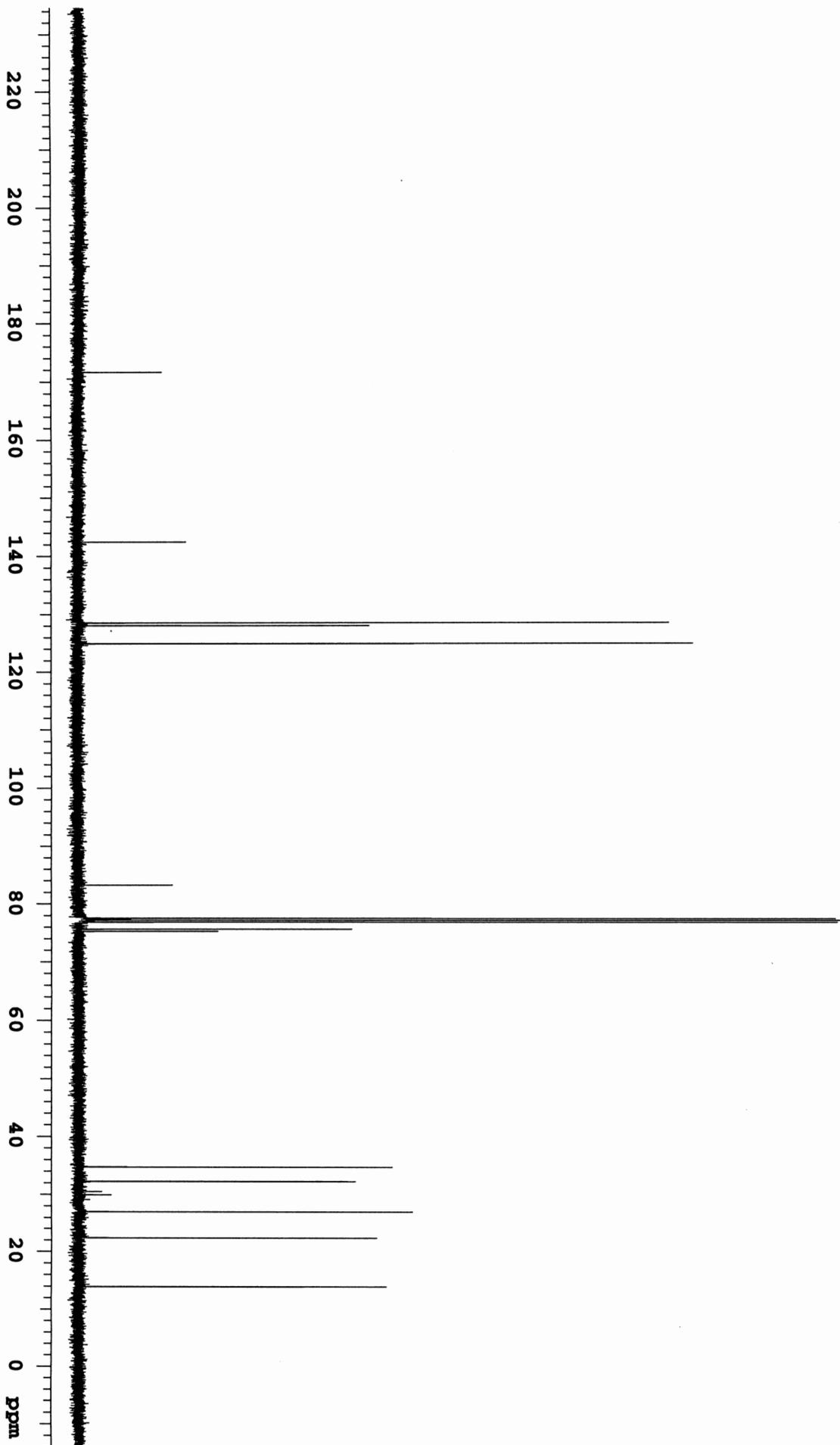
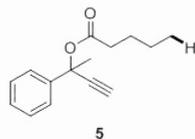
Additional Experiments with Nanoparticle Zinc

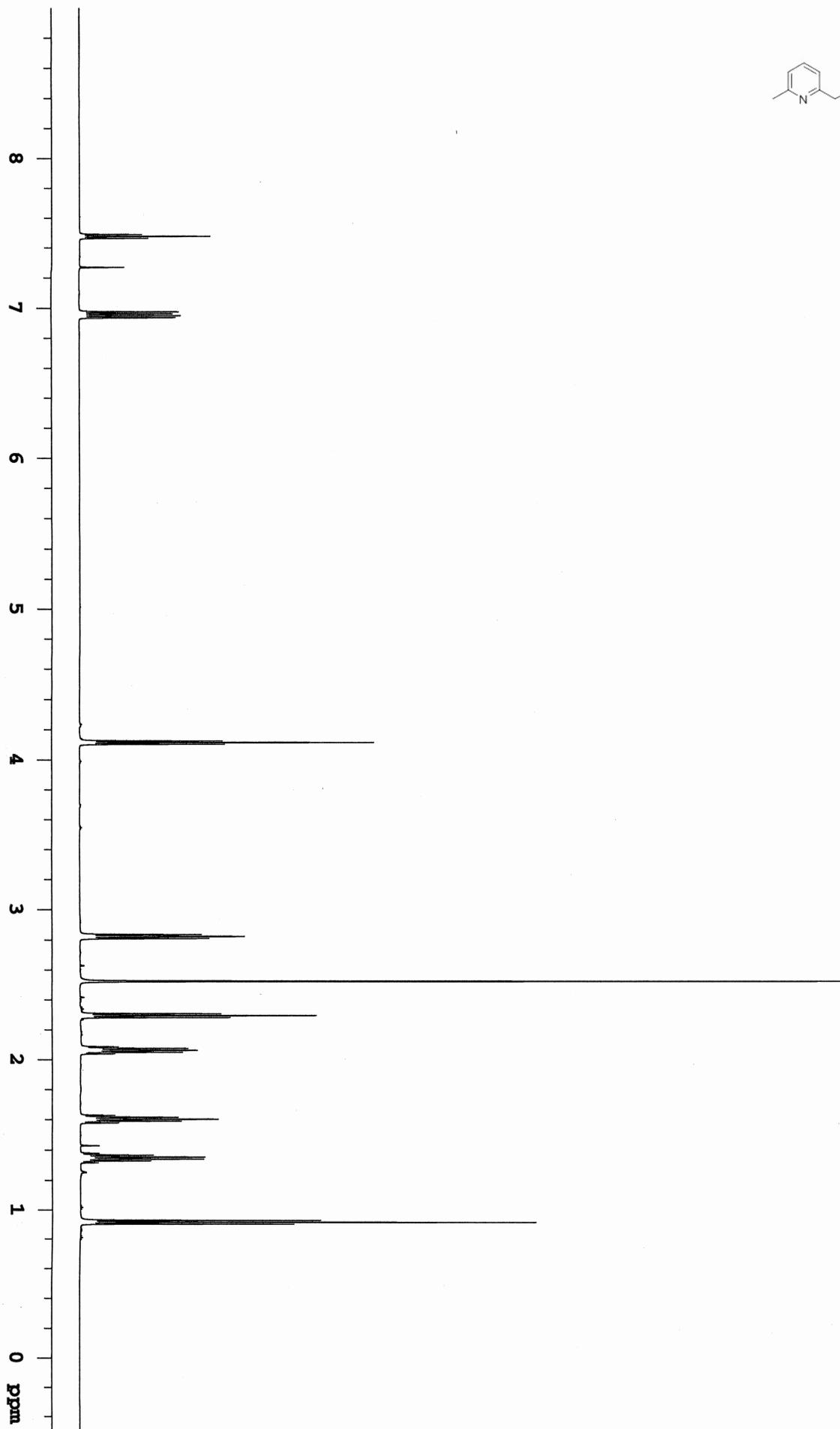
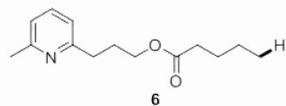


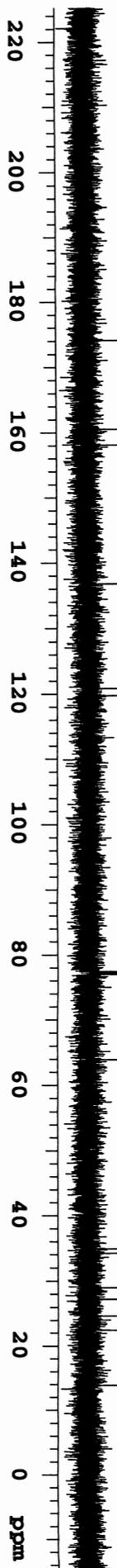
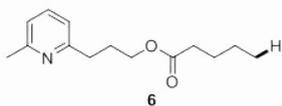




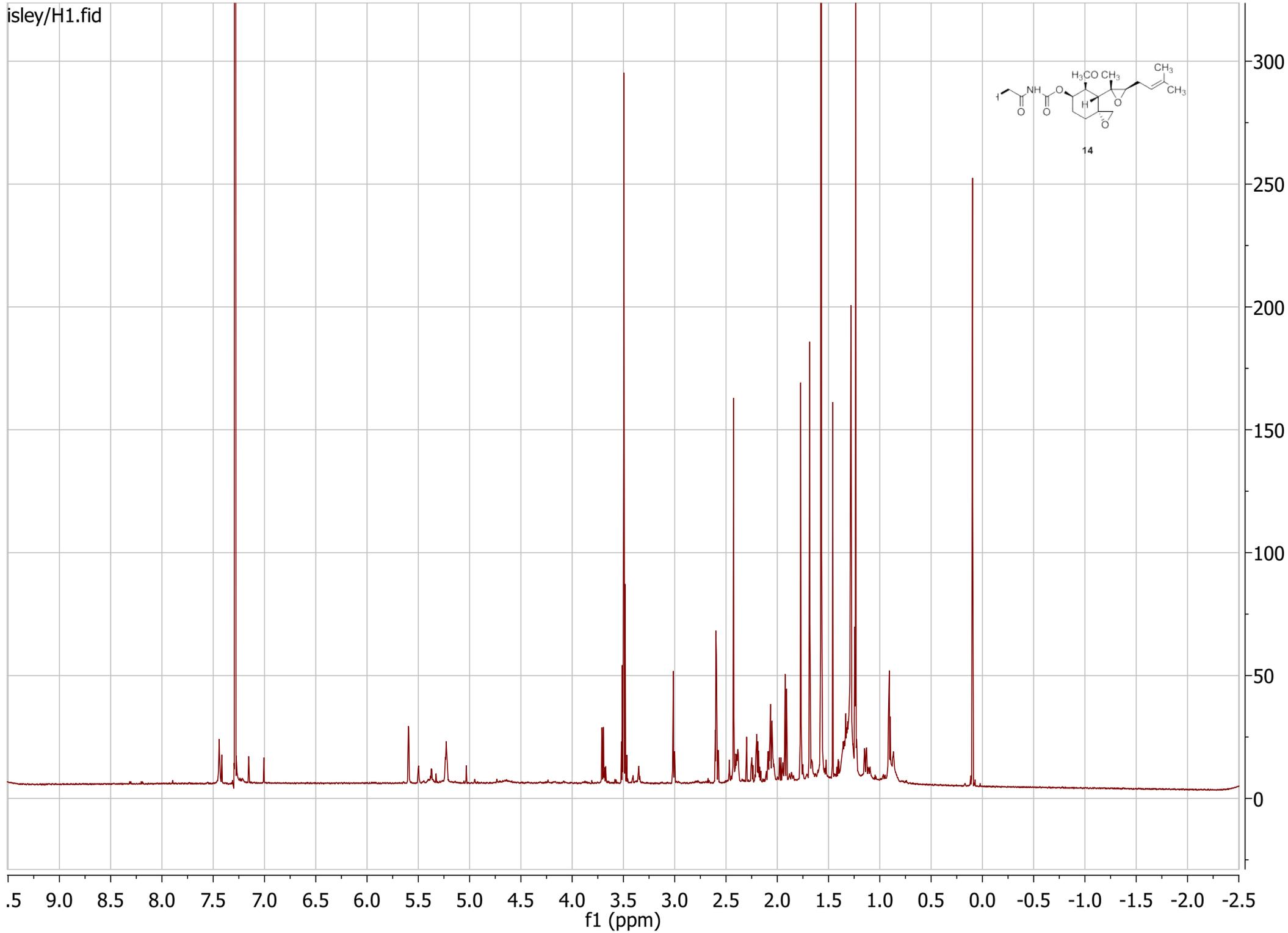


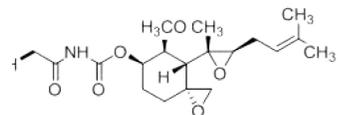






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