Supporting Information

Oxygen-Directed Intramolecular Hydroboration

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Experimental

Substrates **5b** and **5c** are commercially available, while **5a,**[1] **5d,**[2] **5e,**[3] **5f,**[2] **5g,**[4] **5h,**[5] and **5i**[6] have been reported in the literature. Alcohols **5d**, **5e**, and **5f** were prepared using methods reported by Kocienski et al.,[2] **5g** and **5h** were prepared by the method of Maryanoff et al.,[4] and **5i** was prepared using the method of Negishi et al.[7] The following diols have been reported previously: **9a**,[8] **10a**,[9] **9b**,[10] **10b**,[10] **9d**,[11] **10d**,[12] **9e**,[13] **10e**,[14] **9f**,[14] **10f**,[15] **9g**,[16] **10g**,[9] **9h**,[17] **10h**,[18] and **10i**.[19]

Preparation of borane-thioanisole complex (BH_3·SMePh, **2**)

The procedure combines features reported in prior work[20] as follows: $NaBH_4$ (4.56 g, 0.120 mol) was suspended in 60 mL of diglyme using a 250 mL rb flask fitted with an addition funnel (nitrogen atmosphere throughout). To a separate flask at 0 °C, connected to the first using a gas dispersion tube, was added thioanisole (5.08 g, 0.040 mol). Iodine (15.1 g, 0.060 mol) in 60 mL of diglyme was then added dropwise to the $NaBH_4$ suspension causing bubbling that indicated generation of diborane (B_2H_6). The gas was passed into neat thioanisole via a gas dispersion tube and any diborane that was not reacted was passed through a second outlet and quenched with acetone. Upon completion of the iodine addition, a gentle nitrogen flow was used to push any remaining diborane into the acetone-containing vessel. The BH_3·SMePh was then capped and stored at -20 °C.

The determination of molarity was performed by measuring out 0.50 mL of BH_3·SMePh into a flask with 2.0 mL of $CDCl_3$. The solution was cooled to 0 °C and an excess amount of dimethylbenzylamine (0.3-0.4 mL) was added dropwise. The mixture was stirred for 30 min and analyzed by ^{1}H NMR. The ratio between the downfield shifts of 4.0 ppm for

the complexed amine and 3.4 ppm for uncomplexed amine was used to calculate the concentration of BH_3·SMePh. Typically a range of 3-4 M was obtained.

ODHB of homoallylic alcohols; reaction of 5e with Me_2S·BH_3/TfOH.

CH_2Cl_2 (16 mL) in a 50 mL rb flask was cooled to -78 °C. Neat Me_2S·BH_3 (BMS; 300 μL, 3.03 mmol) was added followed by TfOH (270 μL, 3.04 mmol) dropwise. Each drop of TfOH initially froze on the surface, forming a white solid that dissipated after a few seconds of stirring. Gas evolution was observed. This solution was stirred for 35 min before dropwise addition of a solution of **5e** (0.214 g, 1.39 mmol) in CH_2Cl_2 (11 mL). The clear solution was stirrred at -20 °C for 10 h and was then treated slowly with a solution of 20% NaOH (4.8 mL) in MeOH (5.2 mL). The mixture was stirred 30 min at -20 ºC before being stirred vigorously at 0 °C for slow dropwise addition of 35% H_2O_2 (2.4 mL) in MeOH (2.6 mL). This mixture was warmed to rt and stirred for 10 h before transferring to a separatory funnel with 75 mL of Et_2O. Brine (10 mL) was then added, and the aqueous layer was extracted with Et_2O (3x, 75 mL). The combined organic layers were dried ($MgSO_4$), concentrated (aspirator), and purified by flash chromatography (silica gel) using 30% EtOAc in hexanes to give 0.194 g of **9e** (80%) as a 56:1 mixture with **10e** according to the NMR assay described below. All other substrates **5** reported in Table 2 were reacted under analogous conditions.

Derivatization with 2-(trifluoromethyl)benzoyl chloride for NMR assay of regioselectivity.

A sample of **9e/10e** (0.024 g, 0.136 mmol) was taken up in CH_2Cl_2 (1 mL) and cooled to 0 °C in a 10 mL rb flask. Neat 2-(trifluoromethyl)benzoyl chloride (0.1 mL, 0.68 mmol) was added dropwise to the magnetically stirred solution followed by DMAP (0.085 g,

0.69 mmol) in CH_2Cl_2 (1 mL). The clear solution was treated with Et_3N (0.08 mL, 0.57 mmol) and removed from the ice bath. The solution gradually became yellow-orange over 6h at rt. The reaction was loaded directly onto a preparatory TLC plate and was developed twice with 10% EtOAc/hexane. The UV active band with R_f of 0.25 was extracted with EtOAc. Concentration (aspirator) gave pure diaroylated product (0.069 g, 0.13 mmol) in 97% yield. Regioisomer ratios were established by comparing integrals for carefully phased, expanded ^{1}H NMR spectra as follows:

2-(trifluoromethyl)benzoate from 9a/10a: The methyl triplet (0.90 ppm) from **9a** ester was compared to the methyl doublet of **10a** ester (1.2 ppm).

2-(trifluoromethyl)benzoate from 9/10 b,c,d,e,i: The 3-CH(O) methine proton was compared to the 4-CH(O) methine proton.

2-(trifluoromethyl)benzoate from 9f/10f: The *t*-butyl singlet (0.90 ppm) from **10f** ester was compared to the ^{13}C satellite peaks of the *t*-butyl singlet (0.97 ppm by ^{1}H NMR) from **9f** ester.

Table 3. NMR data and ratios from controls using excess BH_3/THF and ODHB

precursor alcohols	ester from alcohol **9** δ C(3)H (ppm)	ester from alcohol **10** δ C(4)H (ppm)	**9 : 10** (excess BH_3)[a]	**9 : 10** (ODHB)
9a/10a	m, 5.19-5.33	m, 5.19-5.33	4.3 : 1[b]	>20 : 1
9b/10b	m, 5.23-5.31	m, 5.04-5.11	2 : 1	37 : 1
9c/10c	m, 5.23-5.31	m, 5.04-5.11	2 : 1	28 : 1
9d/10d	m, 5.29-5.35	m, 5.17-5.23	2 : 1	>20 :1
9e/10e	m, 5.42-5.49	m, 5.05-5.11	2.7 : 1	56 : 1
9f/10f	N/A	N/A	2 : 1	82 : 1
9i/10i	m, 5.34-5.41	m, 5.25-5.29	2 : 1	>20 : 1

(a) Control experiments: see procedure from **5i** to **9i/10i**, below, $THF{\cdot}BH_3$. (b) $Me_2S{\cdot}BH_3$ in THF instead of $THF{\cdot}BH_3$

Control experiments; hydroboration of 5i with $THF{\cdot}BH_3$ and characterization of 9i.

To a 0 °C solution of **5i** (0.059 g, 0.33 mmol) in THF (2 mL) was added excess $THF{\cdot}BH_3$ (1 mL, 1 mmol). The solution was stirred for 4h before treating with premixed 20% NaOH (0.8 mL) and 35% H_2O_2 (0.4 mL) dropwise. The reaction mixture was transferred to a separatory funnel containing brine and extracted with Et_2O. The organic layers were combined, dried over $MgSO_4$, and concentrated (aspirator). According to NMR assay after derivatization as described above, the crude mixture gave a 2:1 ratio of **9i**:**10i**. Purification via silica gel chromatography in 70% EtOAc in hexanes eluted pure **9i**: HRMS-ES$^+$ (*m*/*z*): $[M + Na]^+$ calcd for $C_{12}H_{18}O_2$, 217.120; found, 217.121. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.47-1.59 (m, 2H). 1.62-1.82 (m, 4H), 2.33 (br s, 1H), 2.41 (br, s, 1H). 2.64 (t, *J*= 8 Hz, 2H), 3.77-3.84 (m, 1H), 3.84-3.91 (m, 2H), 7.16-7.20 (m, 3H), 7.25-7.30 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$, δ): 27.30, 35.80, 37.35, 38.28, 61.88, 72.162, 125.79, 128.32, 128.40, 142.24. IR (neat, cm^{-1}): 3350 (br), 2950(s), 2860 (m). Regioisomer **10i** was eluted in later fractions, and was identified by comparison with literature data.[19]

ODHB of 5b in the presence of cyclohexene.

CH_2Cl_2 (60 mL) in a 250 mL rb flask was cooled to -78 °C under nitrogen. Neat BMS (1.1 mL, 11.11 mmol) was added followed by TfOH (1 mL, 11.26 mmol) dropwise. Each drop of TfOH initially froze on the surface, forming a white solid that dissipated after a few seconds of stirring. Gas evolution was observed but no temperature change was detected by internal temperature monitoring. This stirred for 30 min before addition of a solution of **5b** (0.68 mL, 5.55 mmol) and cyclohexene (3.0 mL, 29.6 mmol) in

CH_2Cl_2 (30 mL) over 45 min. The internal temperature rose 2-3 degrees during addition. The clear solution was stirrred at -20 °C for 10 h and was then treated slowly with a solution of 20% NaOH (6.0 mL) in MeOH (6.0 mL). The mixture stirred 30 min at -20 ºC and was then stirred vigorously at 0 °C for slow dropwise addition of 35% H_2O_2 (3.0 mL) in MeOH (3.0 mL). This mixture was warmed to rt, stirred for 20 h, and transferred to a separatory funnel using 75 mL of Et_2O and 8 mL of brine. The aqueous layer was extracted with Et_2O (4x, 75 mL) and the organic layers were combined, dried over $MgSO_4$, concentrated (aspirator), and purified via silica gel chromatography using 50% EtOAc in hexanes to give 0.456 g of **9b** as a >20:1 mixture with **10b**. The product was contaminated with 13% dimethylsulfone. A 62% yield of diols was calculated based on the NMR ratio of sulfone and diol signals.

Monitoring the ODHB of 5b using ^{11}B and ^{1}H NMR spectroscopy.

CD_2Cl_2 (3 mL) in a 10 mL rb flask was cooled to -78 °C. Neat BMS (60 μL, 0.61 mmol) was added followed by TfOH (55 μL, 0.62 mmol). Each drop of TfOH initially froze on the surface, forming a white solid that dissipated after a few seconds of stirring (gas evolution). This stirred for 30 min and was then treated with a solution of **5b** (0.030 g, 0.3 mmol) in CD_2Cl_2 (2 mL) dropwise. The solution was cannulated into an oven-dried, N_2-flushed, septum-capped NMR tube submersed in a -78 °C bath and ^{11}B and ^{1}H spectra were taken at -78 °C. The sample was kept in a -78 °C bath while the probe was warmed to -20 °C and ^{1}H spectra were then taken over 2.5 h – once every 5 min for the first 45 min followed by one every 15 min. The first 3 spectra contained a signal at 12.5 ppm that disappeared by the 20th min at -20 °C. Olefin signals remained, but were nearly gone after 2.5 h. Using the same sample, ^{11}B spectra were taken at 2 min, 5 min, 15 min, 45

min, 2 h, and 2.5 h after warming to -20 °C. At 5 min signals appeared at -20.6 ppm (residual BMS), -2.5 ppm (tentatively, $TfOBH_2$), 7.5 ppm (broad) and -8 ppm (broad). At 45 min all of the aforementioned signals were present but a new broad signal appeared at 34 ppm. At 2.5 h the signals at 34 and 7.5 ppm had broadened to the point of almost disappearing while the signal at -8 had sharpened slightly, appearing as a broadened triplet. The signal at -2.5 ppm dominated all ^{11}B spectra and the signal and -20.6 diminished over time.

ODHB of 5e via the lithium alkoxide.

BMS (60 μL, 0.61 mmol) was taken up in 3 mL of CH_2Cl_2 placed in a 2-neck 25 mL rb flask fitted with a cold-jacketed addition funnel containing a solution of **5e** (0.045 g, 0.29 mmol) in 2 mL of CH_2Cl_2. Both flask and funnel were cooled to -78 °C. TfOH (55 μL, 0.62 mmol) was added dropwise to the rb flask. Each drop of TfOH initially froze on the surface, forming a white solid that dissipated after a few seconds of stirring (gas evolution observed). After stirring for 30 min, *n*-BuLi (2.11M, 150 μL, 0.33 mmol) was added dropwise to the addition funnel, swirling the apparatus after addition was complete. The resulting alkoxide solution was then added dropwise into the activated borane solution at -78 °C, and the reaction was then warmed to -20 °C and stirred for 5 h before MeOH (1 mL at -20°C) was added dropwise. This stirred vigorously at 0 °C for 30 min followed by addition of premixed 20% NaOH (0.6 mL) and 35% H_2O_2 (0.3 mL) dropwise. This stirred for 12 h and was then transferred to a separatory funnel containing 1 mL of saturated K_2CO_3 solution using 20 mL Et_2O. The aqueous layer was extracted with Et_2O (4x, 20 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated (aspirator). The crude product was diaroylated as described above to give

0.097 g of the 2-(trifluoromethyl)benzoate of **9e** for NMR assay (64% over 2 steps; 63:1 mixture with the regioisomer from **10e**).

Preparation of *E*-4-cyclohexyl-1-methoxy-3-butene (13).

Sodium hydride (0.151 g, 3.77 mmol) was supended in THF (4 mL) and cooled to 0 °C in a 25 mL rb flask. A solution of **5i** (0.269 g, 1.75 mmol) in THF (2 mL) was added dropwise and the reaction was allowed to warm to rt for 1 h. The suspension was cooled to 0 °C and neat MeI (0.23 mL, 3.71 mmol) was added dropwise. The reaction and warmed to rt for 2 h, quenched with H_2O, and stirred for 15 min. The mixture was transferred to a separatory funnel with 20 mL of Et_2O and extracted with Et_2O (3x, 20 mL). The organic layers were combined, dried over $MgSO_4$, concentrated (aspirator), and purified via silica gel chromatography using 2% Et_2O in hexanes to give 0.149 g of **13** (50%). HRMS-CI$^+$ (*m/z*): $[M + H]^+$ calcd for $C_{11}H_{20}O$, 169.159; found, 169.159. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.99-1.31 (m, 5H), 1.57-1.74 (m, 5H), 1.85-1.96 (m, 1H), 2.26 (q, *J*= 6.8 Hz, 2H), 3.34 (s, 3H), 3.38 (t, *J*= 7.2 Hz, 2H) 5.23-5.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 26.04, 26.16, 33.00, 33.03, 40.65, 58.52, 72.77, 123.48, 138.57. The sample contained 12% *Z*-isomer (quartet at 2.34 ppm and singlet at 3.35 ppm by ^{1}H NMR). IR (neat, cm^{-1}): 2925(s), 2850 (m).

Control experiment hydroboration of 13; preparation of 4-cyclohexyl-3-hydroxy-1-methoxy-butane (14) and 4-cyclohexyl-4-hydroxy-1-methoxy-butane (15).

To a 0 °C solution of **13** (0.040 g, 0.26 mmol) in THF (1 mL) was added excess THF·BH_3 (1 mL, 1 mmol). The solution stirred for 2h before treating with premixed 20% NaOH (0.8 mL) and 35% H_2O_2 (0.4 mL) dropwise. The reaction mixture was transferred to a separatory funnel containing brine and extracted with Et_2O. The organic layers were

combined, dried over $MgSO_4$, and concentrated (aspirator). Crude ^1H NMR showed a 1.4:1 ratio of **14**:**15**. Silica gel chromatography with 15% EtOAc in hexanes eluted **14**; HRMS-CI$^+$ (*m*/*z*): $[M + H]^+$ calcd for $C_{11}H_{22}O_2$, 187.170; found, 187.169. ^1H NMR (400 MHz, $CDCl_3$, δ): 0.80-1.00 (m, 2H), 1.08-1.31 (m, 4H), 1.37-1.52 (m, 2H), 1.60-1.73 (m, 6H), 1.77-1.85 (m, 1H), 2.89 (br s, 1H), 3.35 (s, 3H), 3.51-3.59 (m, 1H), 3.6-3.67 (m, 1H), 3.86-3.94 (br m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 26.16, 26.31, 26.56, 32.91, 33.87, 34.06, 36.80, 45.28, 58.82, 68.60, 71.69. IR (neat, cm^{-1}): 3420 (br), 2920(s), 2850 (m). Pure **15** was eluted in later fractions; HRMS-CI$^+$ (*m*/*z*): $[M + H]^+$ calcd for $C_{11}H_{22}O_2$, 187.170; found, 187.170. ^1H NMR (400 MHz, $CDCl_3$, δ): 0.95-1.48 (m, 8H). 1.60-1.87 (m, 7H), 2.32 (br s, 1H), 3.35 (s, 4H, $-OCH_3$ + -CH-O). 3.42 (dt, *J*= 1.2, 4.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 26.19, 26.33, 26.48, 26.53, 27.95, 29.2, 31.49, 43.70, 58.56, 73.08, 75.85. IR (neat, cm^{-1}): 3420 (br), 2920(s), 2850 (m).

***In Situ* activation method for ODHB of 13.**

13 (0.10 g, 0.59 mmol) was taken up in CH_2Cl_2 (10 mL) and cooled to -78 °C in a 25 mL rb flask. Neat BMS (120 μL, 1.21 mmol) was added dropwise and the resulting solution was stirred for 30 min before being treated slowly with neat TfOH (105 μL, 1.18 mmol) dropwise. Each drop of TfOH acid initially froze on the surface, forming a white solid that dissipated after a few seconds of stirring. Gas evolution was observed. The clear solution was stirred at -20 °C for 10 h and treated slowly with a solution of 20% NaOH (0.6 mL) in MeOH (1.0 mL). The mixture stirred 10 min before being stirred vigorously at 0 °C for slow dropwise addition of 35% H_2O_2 (0.3 mL) in MeOH (0.7 mL). This mixture was warmed to rt and stirred for 10 h before transferring it to a separatory funnel containing 3 mL of brine using 30 mL of Et_2O. The aqueous layer was extracted with

Et_2O (3x, 25 mL) and the organic layers were combined, dried over $MgSO_4$, concentrated (aspirator), and purified via silica gel chromatography using 20% EtOAc in hexanes to give 0.067 g of **14** (61%) as 50:1 mixture with **15** along with 16% of recovered **13**. A trace (<1%) of demethylated alcohol (**5a**) was observed, but demethylated products **9a** or **10a** were not detected.

References for Supporting Information

1. Crombie, L.; Rainbow, L. *J. Chem. Soc. Perkin Trans 1*. **1994**, 673.

2. Kocienski, P.; Wadman, S. *J. Am. Chem. Soc*. **1989**, *111*, 2363.

3. Ryu, I.; Hirai, A.; Suzuki, H.; Sonoda, N.; Murai, S. *J. Org. Chem.* **1990**, *55*, 1409.

4. Maryanoff, B. E.; Reitz, A.B.; Duhl-Emswiler, B.A. *J. Am. Chem. Soc*. **1985**, *107*, 217.

5. Doyle, M.P.; Austin, R.E.; Bailey, A. S.; Dwyer, M.P.; Dyatkin, A. B.; Kalinin, A.V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; et al. *J. Am. Chem. Soc.* **1995**, *117*, 5763.

6. Perlman, N; Livneh, M.; Albeck, A. *Tetrahedron* **2000**, *56*, 1505.

7. Negishi, E.; Baba, S.; King, A. O. *J. Chem. Soc. Chem. Commun.*. **1976**, 17.

8. Evans, D. A., Muci, A. R.; Sturmer, R. *J. Org. Chem.* **1993**, *58*, 5307.

9. Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem*. **1984**, *49*, 2298.

10. Tanner, D. Groth, T. *Tetrahedron* **1997**, *53*, 16139.

11. Cohen, T.; Jeong, I.-H.; Mudryl, B.; Bhupathy, M.; Awad, M. M. A. *J. Org. Chem.* **1990**, *55*, 1528.

12. Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. *Org. Letters* **2007**, *9*, 1821.

13. Batey, R. A.; Smil, D. V. *Angew. Chem. Int. Ed.* **1999**, *38*, 1798.

14. Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A.; Oku, A. *J. Org. Chem*. **1992**, *57*, 1412.

15. Foubelo, F.; Saleh, S. A.; Yus, M. *J. Org. Chem*. **2000**, *65*, 3478.

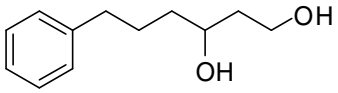
16. Klos, A. M.; Heintzelman, G. R.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 3758.

17. Fujioka, H.; Ohba, Y.; Hirose, H.; Murai, K.; Kita, Y. *Org. Lett.* **2005**, *7*, 3303.

18. Batey, R. A.; Smil, D. V. *Angew. Chem. Int. Ed.* **1999**, *38*, 1798.

19. Foubelo, F.; Saleh, S. A.; Yus, M. *J. Org. Chem.* **2000**, *65*, 3478.

20. (a) Narayana, C.; Periasamy, M. *J. Organomet. Chem*. **1987**, *323*, 145. (b) Zaidlewicz, M.; Kanth, J. V. B.; Brown, H. C. *J. Org. Chem*. **2000**, *65*, 6697.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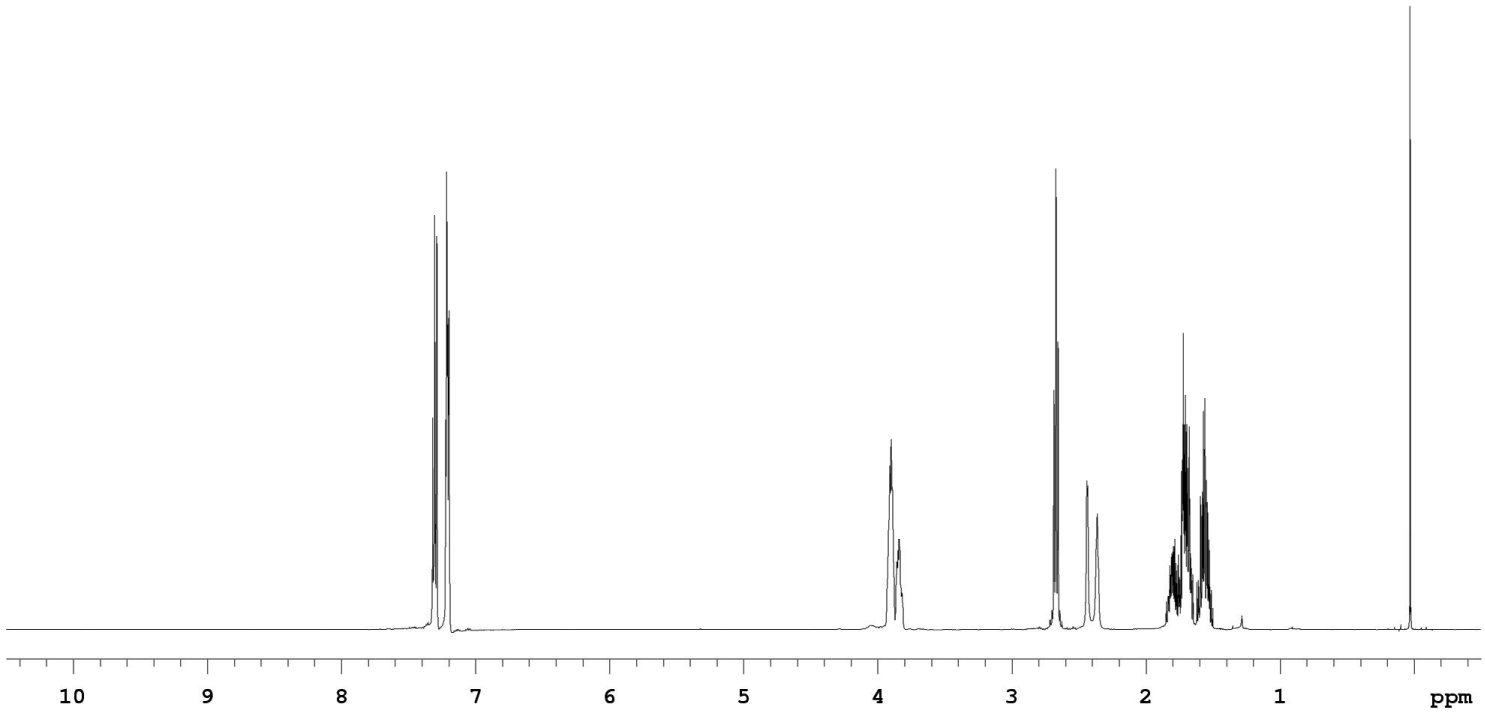
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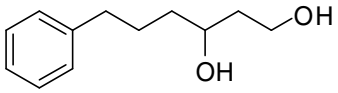
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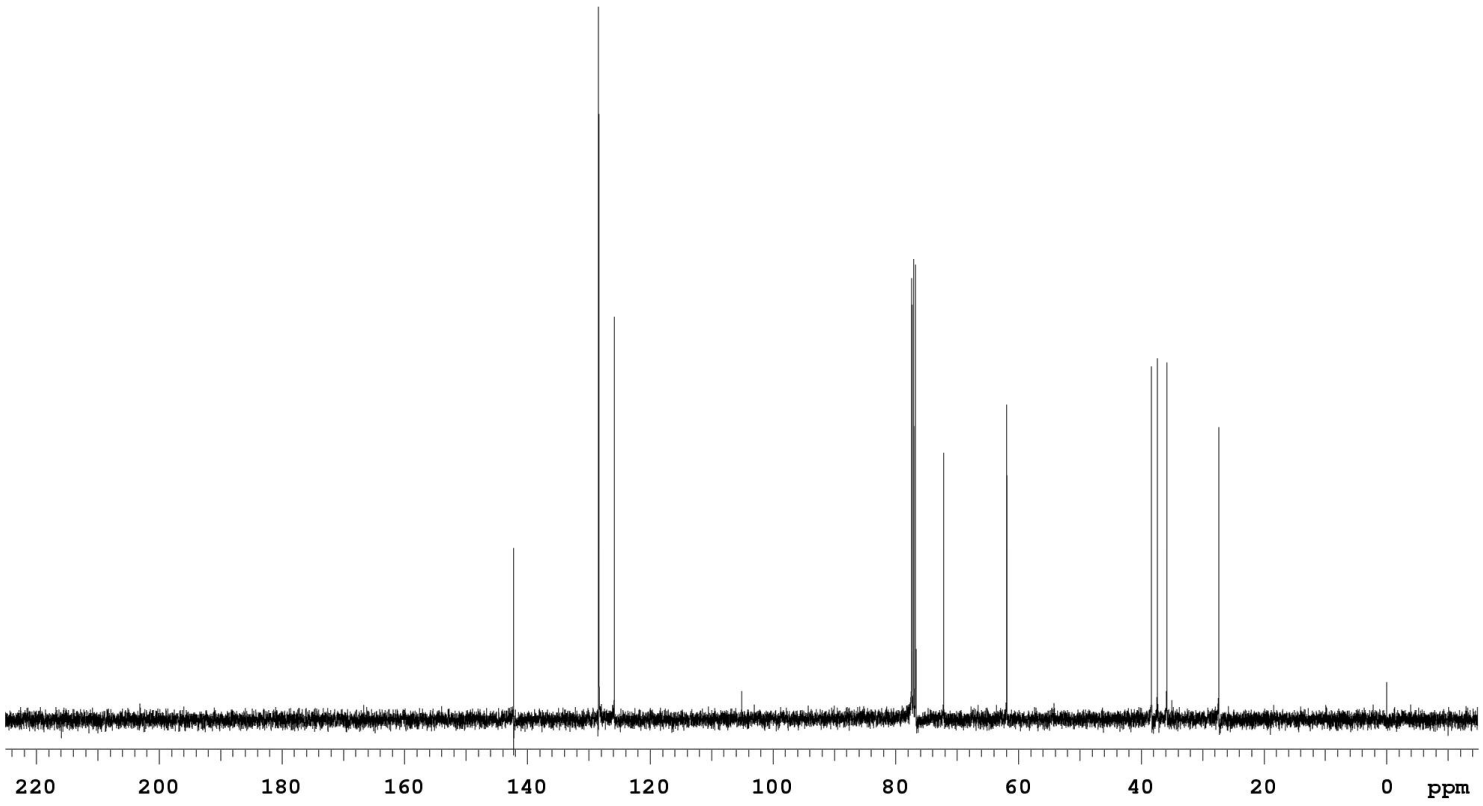
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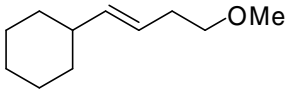
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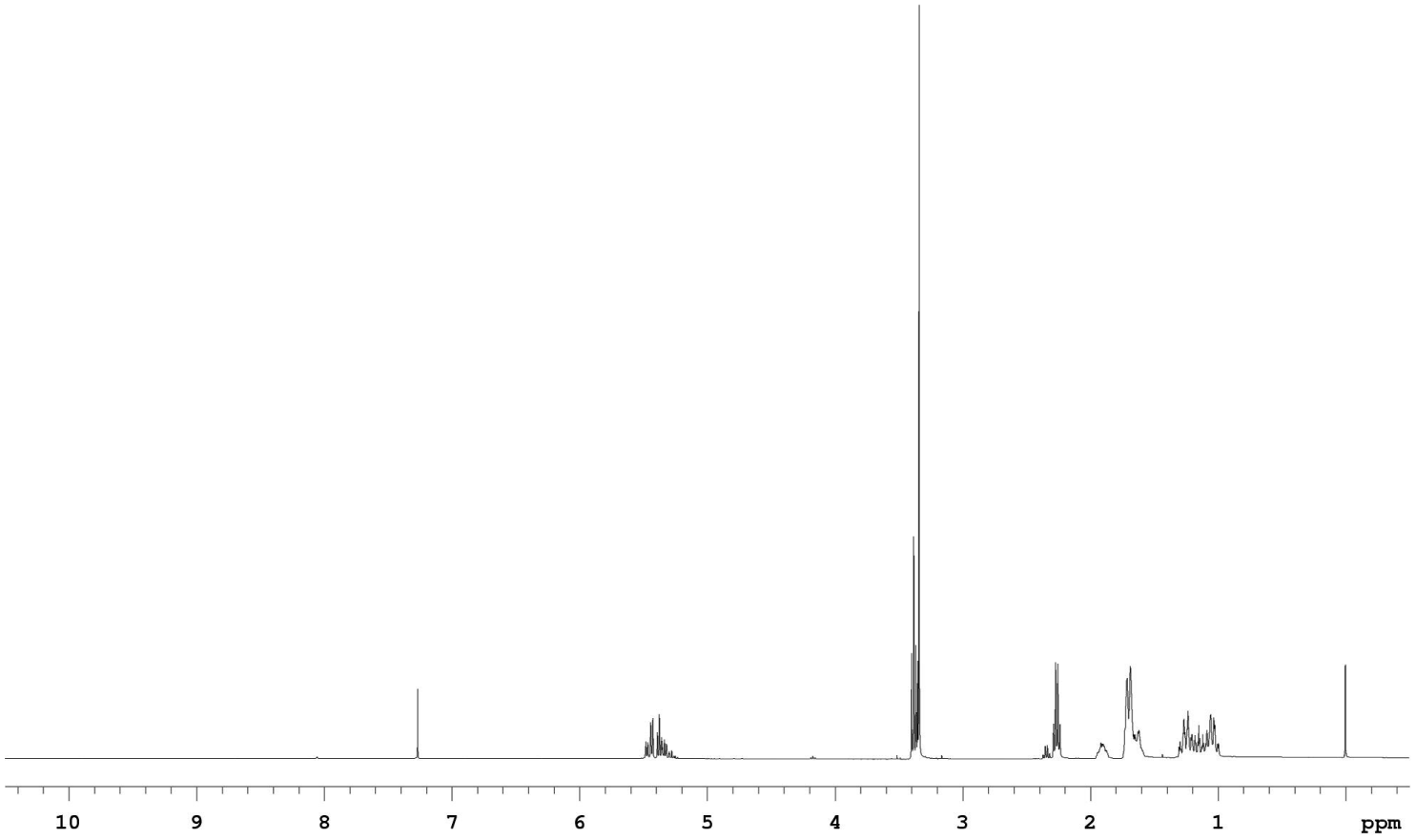
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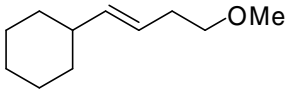
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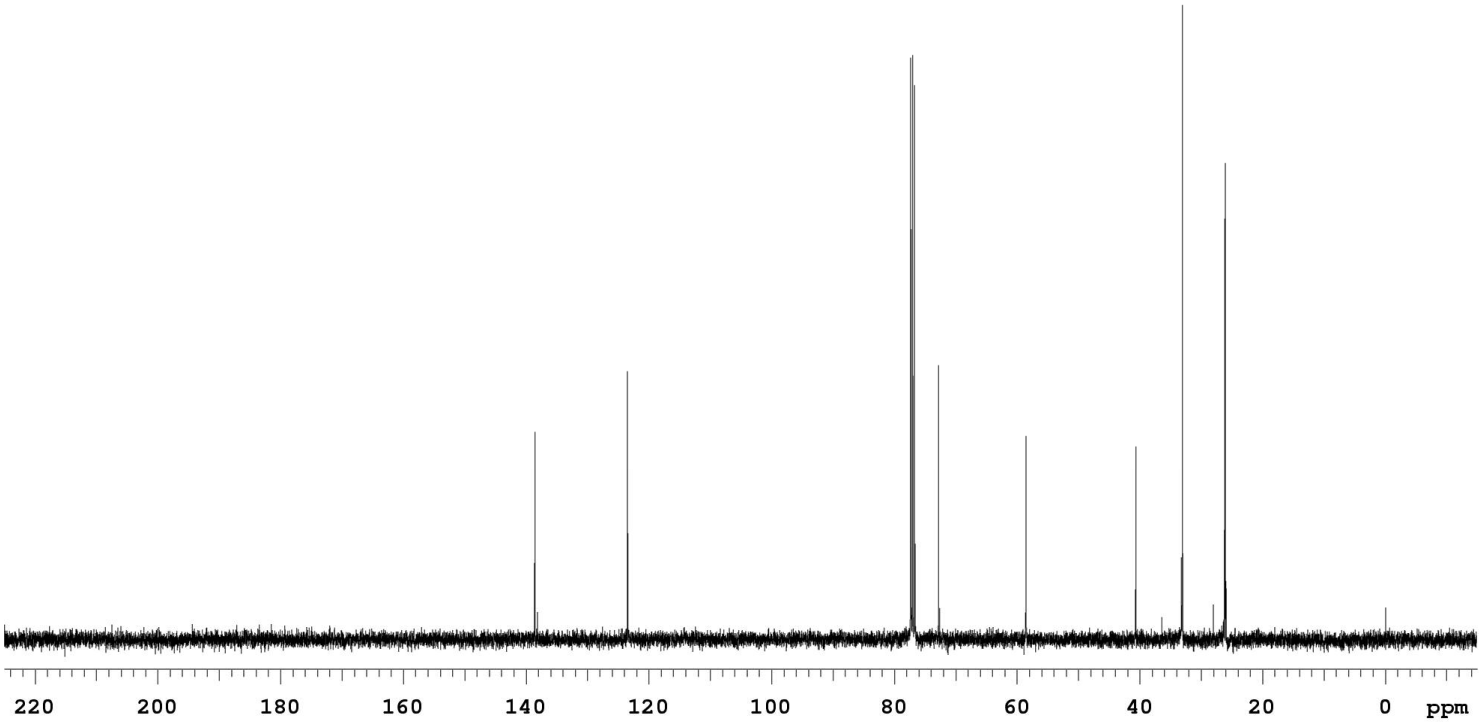
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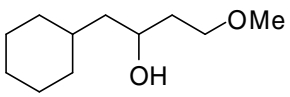
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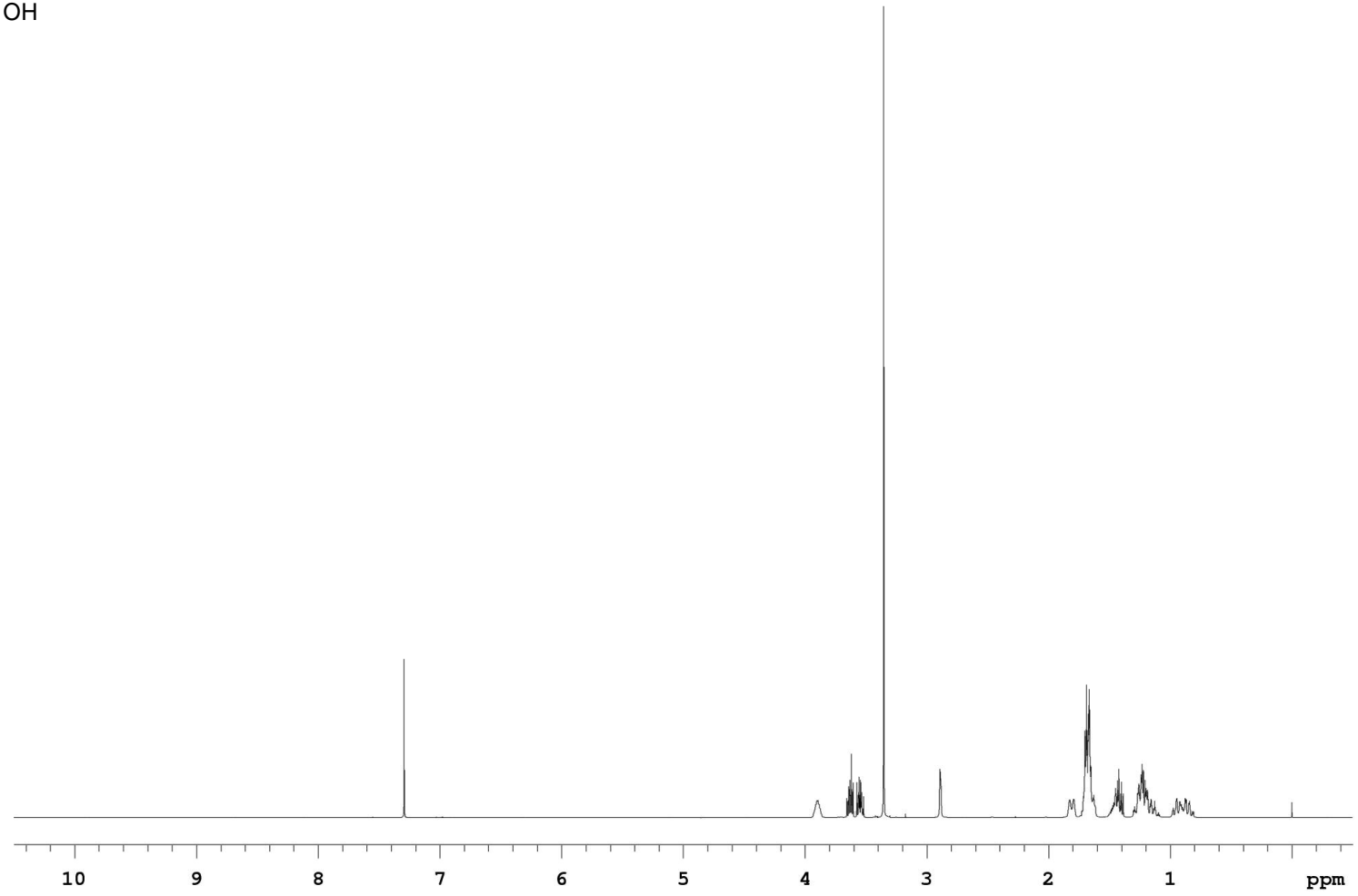
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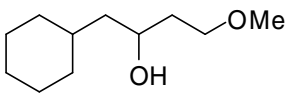
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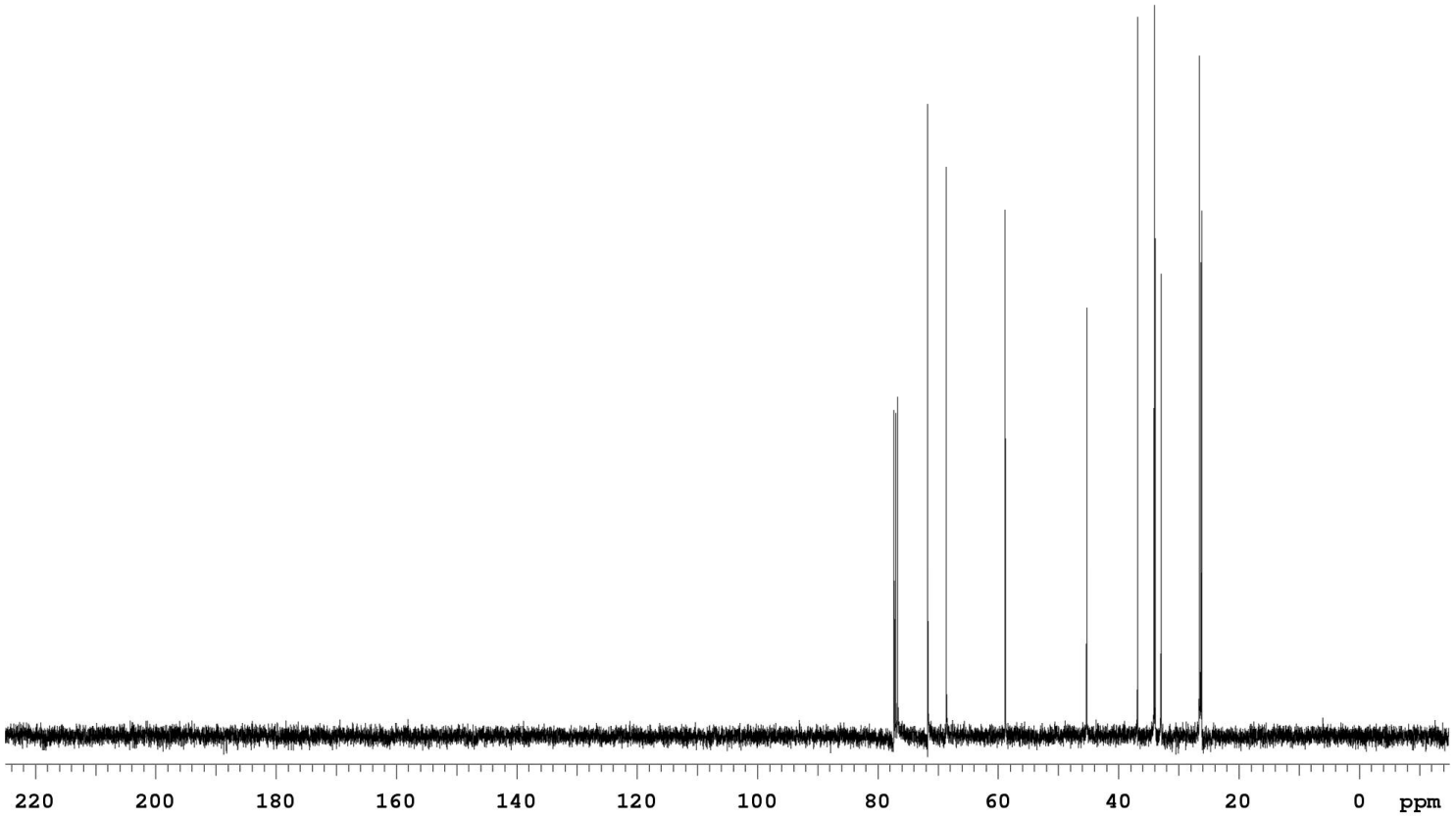
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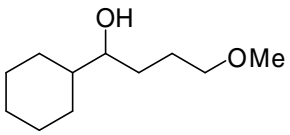
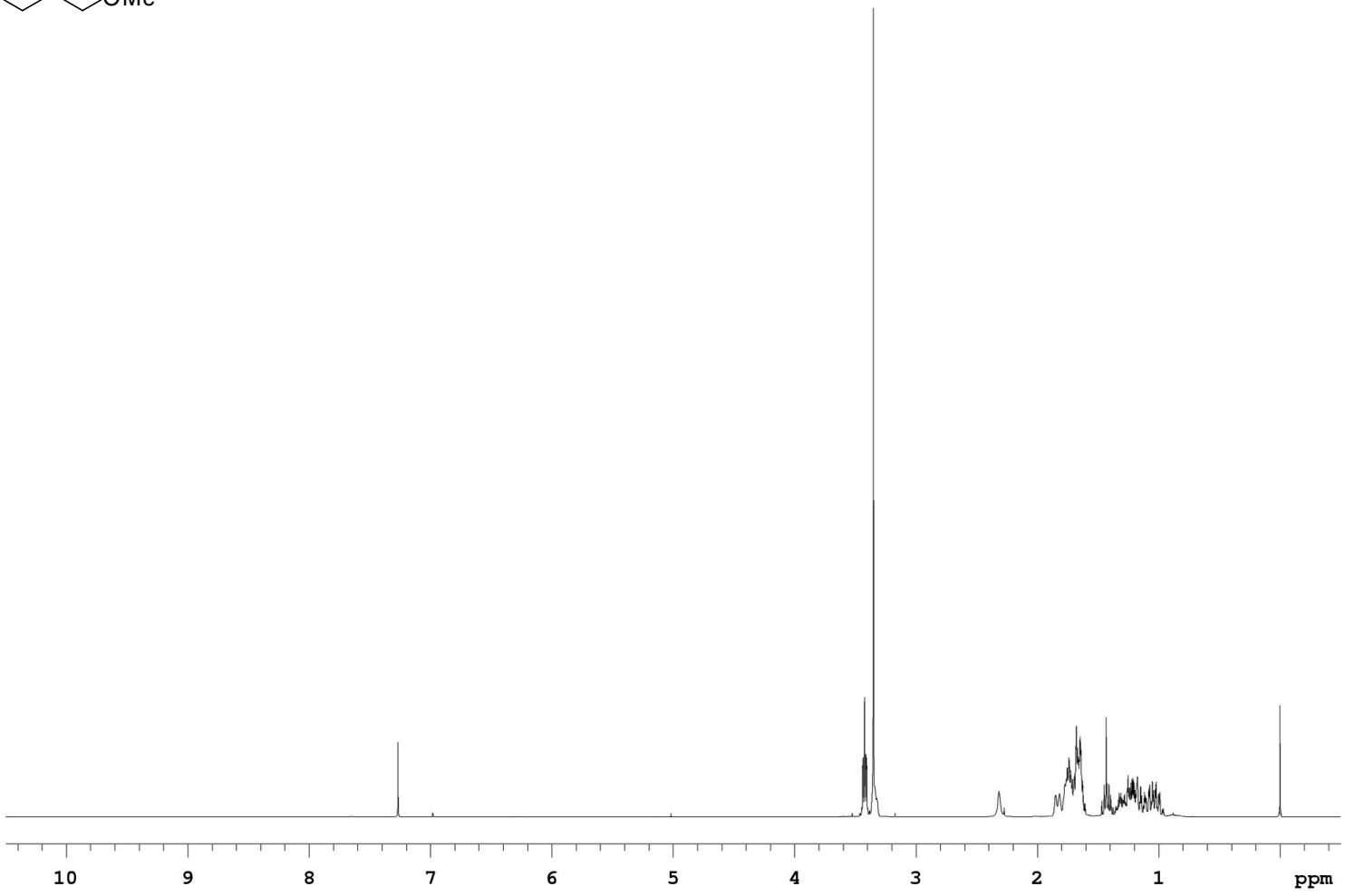
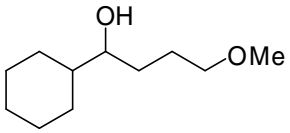
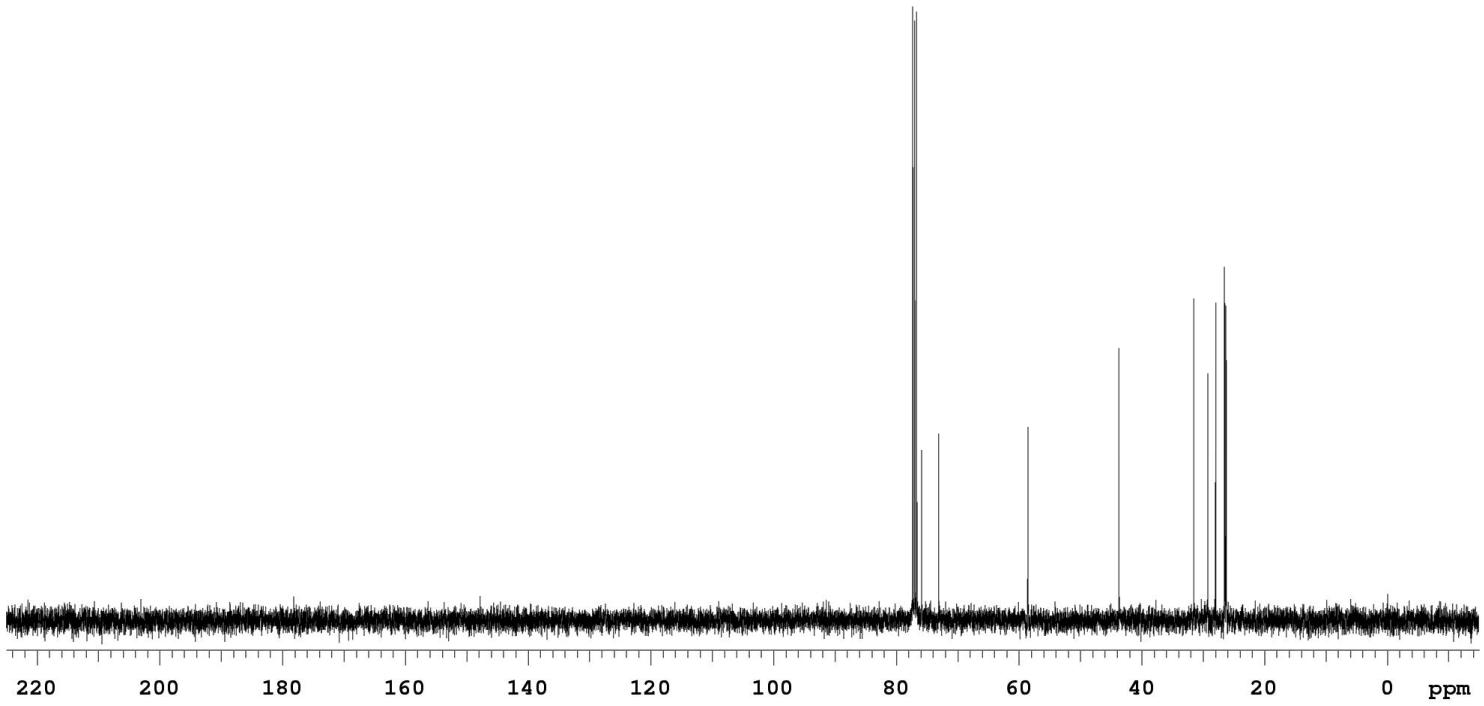

OH
OMe


10
9
8
7
6
5
4
3
2
1
ppm


OH
OMe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180
160
140
120
100
80
60
40
20
0
ppm