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Electronic Supplementary Information (ESI)

Unexpected lateral-lithiation-induced alkylative ring opening of tetraydrofurans in deep eutectic solvents: synthesis of functionalised primary alcohols

Francesca C. Sassone, Filippo M. Perna, Antonio Salomone, Saverio Florio, and Vito Capriati*

Dipartimento di Farmacia-Scienze del Farmaco, Università di Bari "Aldo Moro", Consorzio C.I.N.M.P.I.S., Via E. Orabona 4, I-70125, Bari, Italy.

E-mail: vito.capriati@uniba.it

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1. General Methods

Diethyl ether (Et_2O) was freshly distilled under a nitrogen atmosphere over sodium/benzophenone ketyl. Anhydrous cyclopentyl methyl ether (CPME) was used as purchased. Alkyllithiums were of the highest commercial grade and used without further purification as hydrocarbon solutions: *s*-BuLi (1.4 M in cyclohexane), *t*-BuLi (1.7 M in pentane) and *i*-PrLi (0.7 M in pentane). These solutions were handled under a dry Argon atmosphere using standard Schlenk techniques. The deep eutectic solvent (*DES*) choline chloride (ChCl)/glycerol (Gly) (1/2 molar ratio) was prepared by gently heating under stirring at 70 °C for 5 min the corresponding individual components until a clear solution was obtained. The ^{1}H and ^{13}C NMR spectra were recorded on either Bruker spectrometers operating at 500 and 600 (^{1}H) and 125 and 150 MHz (^{13}C) or a Varian spectrometer operating at 400 (^{1}H) and 100 MHz (^{13}C), and were referenced to the residual ^{1}H and ^{13}C resonances of the solvent used ($CDCl_3$). The GC-MS spectrometry analyses were performed on a gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). The ESI-MS analyses were performed on LC/MSD trap system VL. The elemental analyses were performed by using a Carlo Erba CHNS-O EA1108-Elemental Analyzer. The infrared spectra were recorded on a Perkin-Elmer 283 spectrometer as neat samples. For flash-chromatography, Silica Gel 60, 0.04-0.063 mm particle size was used. The analytical thin layer chromatography (TLC) was carried out on pre-coated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by UV light (254 nm) or by spraying with a solution of 5 % (w/v) ammonium molybdate and 0.2 % (w/v) cerium(III) sulfate in 100 mL 17.6 % (w/v) aq. sulfuric acid and heating to 473 K for some time until the appearance of blue spots. Lithiation-electrophilic trapping reactions were performed in an acetone/dry ice bath (–78 °C) or in an ice water bath (0 °C). Tetrahydrofuran derivatives **2a**–**c** were prepared according to the reported procedure.[1] The spectroscopic data of compounds **2a** and **2b** have been reported.[1]

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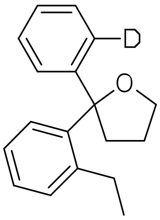
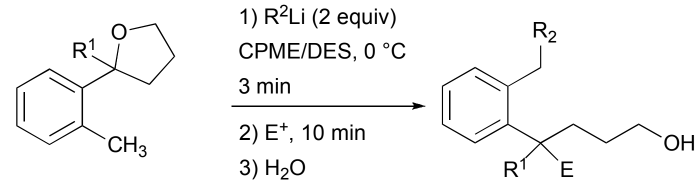
[1] V. Mallardo, R. Rizzi, F. C. Sassone, R. Mansueto, F. M. Perna, A. Salomone and V. Capriati, *Chem. Commun.* 2014, **50**, 8655.



2-(2-Deuteriophenyl)-2-(2-ethylphenyl)tetrahydrofuran (2c-D): colourless oil, 60% yield, >98% D. ^{1}H NMR (400 MHz; CDCl$_3$): δ 0.78 (t, *J* = 7.5 Hz, 3 H), 1.94−2.03 (m, 2 H), 2.43−2.50 (m, 2 H), 2.54 (t, *J* = 7.4 Hz, 2 H), 3.90−3.96 (m, 1 H), 4.09−4.15 (m, 1 H), 7.13−7.25 (m, 7 H), 7.63−7.65 (m, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 15.2, 25.8, 26.2, 39.0, 67.8, 88.5, 125.0, 125.8, 126.1, 126.5, 127.4, 127.8, 127.9, 130.4, 142.9, 143.1, 146.5, 146.6; FT-IR (film, cm^{-1}) 2960, 2871, 1731, 1464, 1050, 752, 700; ESI-MS (*m/z*): 276 [M+Na]$^+$. Anal.Calcd. for $C_{18}H_{19}DO$: C, 85.33; H, 8.35; Found: C, 85.60; H, 8.51.

2. Regioselective synthesis of functionalised alcohols 3a-H–3l-D



2a: R^1 = Ph; **2b**: R^1 = Me

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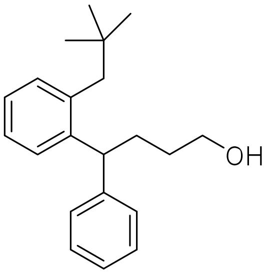
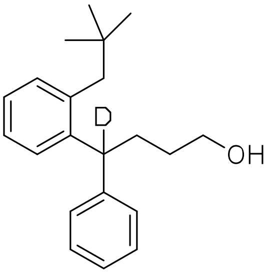
3a-H: R^1 = Ph; R^2 = *t*-Bu; E = H
3a-D: R^1 = Ph; R^2 = *t*-Bu; E = D
3b: R^1 = Ph; R^2 = *t*-Bu; E = Me
3c: R^1 = Ph; R^2 = *t*-Bu; E = Et
3d-D: R^1 = Ph; R^2 = *s*-Bu; E = D
3e: R^1 = Ph; R^2 = *s*-Bu; E = Me
3f: R^1 = Ph; R^2 = *s*-Bu; E = Et
3g-D: R^1 = Ph; R^2 = *i*-Pr; E = D
3h-D: R^1 = Me; R^2 = *s*-Bu; E = D
3i-D: R^1 = Me; R^2 = *t*-Bu; E = D
3j: R^1 = Me; R^2 = *t*-Bu; E = Me
3k: R^1 = Me; R^2 = *t*-Bu; E = CHO
3l-D: R^1 = Ph; R^2 = (3,3-dimethyl-2-butyl) ; E = D

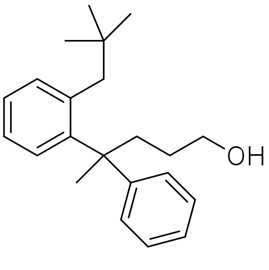
General Procedure. A CPME solution of **2** (0.5 mmol in 0.5 mL of solvent) was added to the *DES* ChCl/Gly 1/2 (molar ratio) mixture (1 g), contained in an open vessel, under vigorous stirring. After 2 min, the mixture was cooled to 0 °C. A solution of the corresponding organolithium reagent (*t*-BuLi, *s*-BuLi, or *i*-PrLi, 1.0 mmol in 1.2 ÷ 1.7 M hydrocarbon solution), handled under Argon using conventional Schlenk techniques, was then rapidly spread out over the above mixture under air. The colour of the mixture became immediately dark red. No particular problems were experienced during this addition. After 3 min, the electrophile (2.0 mmol), as pure liquid, was added all at once and the mixture was stirred for an additional 10 min at 0 °C. After this time, 5 mL of water was added and the reaction mixture was allowed to warm to room temperature, and finally extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash-chromatography (silica gel; hexane/AcOEt 8:2 ÷ 95:5) to give products **3a-H–3l-D**.



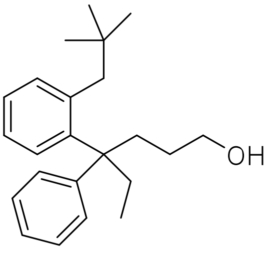
4-(2-Neopentylphenyl)-4-phenylbutan-1-ol (3a-H): colourless oil, 85% yield. ^{1}H NMR (400 MHz; CDCl$_3$): δ 0.97 (s, 9 H), 1.53−1.62 (m, 2 H), 1.94−2.14 (m, 2 H), 2.39 (d, *J* = 16.0 Hz, 1 H), 2.75 (d, *J* = 16.0 Hz, 1 H), 3.62 (t, *J* = 7.2 Hz, 2 H), 4.31 (dd, *J* = 5.2, 7.3 Hz, 1 H), 7.09−7.25 (m, 8 H), 7.33 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 30.0, 31.4, 32.7, 33.0, 44.7, 46.3, 63.0, 125.2, 125.9, 126.0, 126.8, 128.1, 128.3, 132.2, 137.7, 143.1, 144.7; FT-IR (film, cm^{-1}) 3341, 3061, 2949, 2866, 1560, 1477, 1363, 1055, 749, 700; ESI-MS (*m/z*): 319 [M+Na$^+$]. Anal. Calcd. for $C_{21}H_{28}O$: C, 85.08; H, 9.52; Found: C, 85.22; H, 9.74.



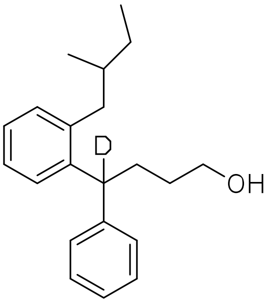
4-Deuterio-4-(2-neopentylphenyl)-4-phenylbutan-1-ol (3a-D): colourless oil, 85% yield, >98% D. ^{1}H NMR (600 MHz; CDCl$_3$): δ 0.97 (s, 9 H), 1.53−1.62 (m, 2 H), 1.94−2.14 (m, 2 H), 2.39 (d, *J* = 16.0 Hz, 1 H), 2.75 (d, *J* = 16.0 Hz, 1 H), 3.62 (t, *J* = 7.2 Hz, 2 H), 7.08−7.25 (m, 8 H), 7.34 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 30.0, 31.3, 32.7, 32.9, 44.7, 45.9, 63.0, 125.2, 125.9, 126.0, 126.8, 128.1, 128.3, 132.2, 137.7, 143.1, 144.7; FT-IR (film, cm^{-1}) 3341, 3061, 2949, 2866, 1560, 1477, 1363, 751, 700; ESI-MS (*m/z*): 320 [M+Na]$^+$. Anal. Calcd. for $C_{21}H_{27}DO$: C, 84.79; H, 9.83; Found: C, 85.13; H, 9.79.



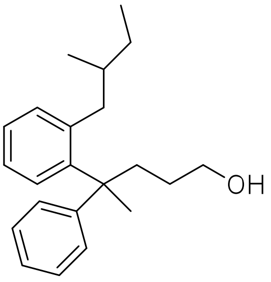
4-(2-Neopentylphenyl)-4-phenylpentan-1-ol (3b): colourless oil, 80% yield. ^{1}H NMR (500 MHz; CDCl$_3$): δ 0.69 (s, 9 H), 1.13−1.22 (m, 1 H), 1.32−1.41 (m, 1 H), 1.65 (s, 3 H), 2.10−2.16 (m, 1 H), 2.23 (d, *J* = 15.7 Hz, 1 H) 2.27 (d, *J* = 15.7 Hz, 1 H), 2.28−2.35 (m, 1 H), 3.61 (t, *J* = 6.5 Hz, 2 H), 7.13−7.28 (m, 7 H), 7.41 (d, *J* = 7.2 Hz, 1 H), 7.57 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 28.5, 29.9, 31.0, 31.9, 37.3, 43.9, 46.3, 63.5, 125.0, 125.3, 126.5, 127.5, 128.1, 130.7, 140.3, 146.1, 151.0; FT-IR (film, cm^{-1}): 3338, 3058, 2951, 2868, 1599, 1477, 1445, 1057, 755, 702; ESI-MS (*m/z*): 333 [M+Na]$^+$. Anal. Calcd. for $C_{22}H_{30}O$: C, 85.11; H, 9.74; Found: C, 85.40; H, 9.88.



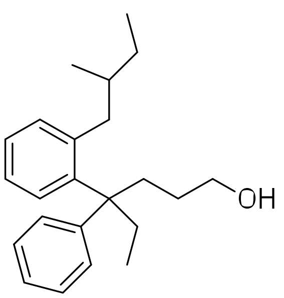
4-(2-Neopentylphenyl)-4-phenylhexan-1-ol (3c): colourless oil, 50% yield. ^{1}H NMR (400 MHz; CDCl$_3$): δ 0.56 (t, *J* = 7.3 Hz, 3 H), 0.64 (s, 9 H), 1.10−1.18 (m, 2 H), 1.52−1.60 (m, 2 H), 2.01−2.11 (m, 2 H), 2.37 (d, *J* = 13.6 Hz, 1 H), 2.73 (d, *J* = 13.6 Hz, 1 H), 3.52 (t, *J* = 6.6 Hz, 2 H), 7.06−7.20 (m, 7 H), 7.31−7.34 (m, 1 H), 7.52−7.55 (m, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 10.4, 27.7, 29.7, 30.0, 32.5, 33.0, 46.4, 63.6, 124.8, 125.3, 125.4, 126.1, 127.4, 128.1, 128.3, 130.8, 139.2, 145.7; FT-IR (film, cm^{-1}) 3392, 2952, 2869, 1477, 1464, 1050, 754, 701; ESI-MS (*m/z*): 347 $[M+Na]^+$. Anal. Calcd. for $C_{23}H_{32}O$: C, 85.13; H, 9.94; Found: C, 85.50; H, 10.11.



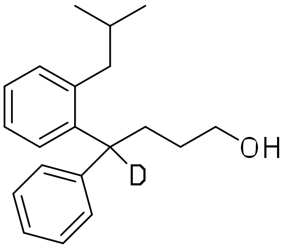
4-Deuterio-4-[2-(2-methylbutyl)phenyl]-4-phenylbutan-1-ol (3d-D): (inseparable mixture of diastereomers, dr: 1:1), colourless oil, 80% overall yield, >98% D. ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.79 (d, *J* = 7.4 Hz, 3 H), 0.84−0.88 (m, 6 H), 0.91 (t, *J* = 7.4 Hz, 3 H), 1.19−1.34 (m, 2 H), 1.45−1.52 (m, 2 H), 1.52−1.61 (m, 6 H), 1.94−2.12 (m, 4 H), 2.25 (dd, *J* = 8.7, 13.8 Hz, 1 H), 2.44 (dd, *J* = 8.1, 13.8 Hz, 1 H), 2.58 (dd, *J* = 6.2, 13.7 Hz, 1 H), 2.73 (dd, *J* = 5.9, 13.7 Hz, 1 H), 3.60−3.64 (m, 4 H), 7.06−7.33 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 11.7, 19.1, 19.2, 29.5, 29.8, 31.3_9, 31.4_2, 32.9, 33.0, 36.2, 40.1_4, 40.1_5, 45.2_8, 45.3_0,62.9_7, 62.9_8, 125.7_1, 125.7_2, 125.9, 126.0, 126.2, 127.0, 127.1, 127.9, 128.0, 128.1, 128.3, 130.7, 130.9, 139.6, 142.2, 142.3, 144.9, 145.0; FT-IR (film, cm^{-1}): 3341, 3060, 2958, 2872, 1600, 1462, 1050, 747, 700; ESI-MS (*m/z*): 320 $[M+Na]^+$. Anal.Calcd. for $C_{21}H_{27}DO$: C, 84.79; H, 9.83; Found: C, 84.82; H, 9.92.



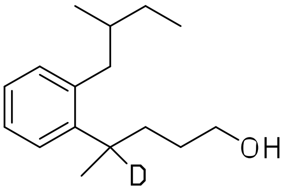
4-[2-(2-Methylbutyl)phenyl]-4-phenylpentan-1-ol (3e): (inseparable mixture of diastereomers, dr: 1:1), colourless oil, 86% overall yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.32 (d, *J* = 6.6 Hz, 3 H), 0.41 (d, *J* = 6.6 Hz, 3 H), 0.56−0.63 (m, 6 H), 0.67−0.86 (m, 4 H), 0.93−1.13 (m, 4 H), 1.36−1.43 (m, 2 H), 1.54 (s, 6 H), 1.87−2.10 (m, 6 H), 2.18−2.28 (m, 2 H), 3.49 (t, *J* = 6.6 Hz, 4 H), 7.02−7.14 (m, 16 H), 7.44−7.46 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.4, 11.5, 18.3, 18.6, 28.4, 28.5, 29.2, 29.3, 29.7, 29.9, 34.0, 34.1, 36.6, 37.0, 39.5, 39.7, 46.2, 46.3, 63.4_9, 63.5_0, 124.9, 125.0, 125.2, 125.3, 126.1, 126.3, 127.2, 127.3, 128.0, 130.1_2, 130.1_3, 140.3, 140.4, 145.8, 145.9, 150.8, 150.9; FT-IR (film, cm^{-1}) 3336, 3058, 2929, 1599, 1462, 1056, 750, 707; ESI-MS (*m/z*): 333 $[M+Na]^+$. Anal. Calcd. for $C_{22}H_{30}O$: C, 85.11; H, 9.74; Found: C, 85.02; H, 9.70.



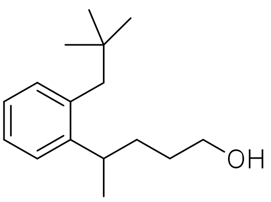
4-[2-(2-Methylbutyl)phenyl]-4-phenylhexan-1-ol (3f): (inseparable mixture of diastereomers, dr: 1:1), colourless oil, 40% overall yield. ^{1}H NMR (400 MHz; $CDCl_3$): 0.39–0.41 (m, 6 H), 0.42–0.65 (m, 12 H), 0.68–0.79 (m, 4 H), 0.99–1.23 (m, 4 H), 1.33–1.59 (m, 4 H), 1.93–2.10 (m, 6 H), 2.17–2.26 (m, 4 H), 3.50–3.53 (m, 4 H), 7.06–7.23 (m, 16 H), 7.53–7.55 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.5, 8.6, 11.4_7, 11.5_0, 18.3, 18.5, 27.8, 29.4, 29.5, 33.0, 33.1, 34.2, 34.3, 37.7, 38.0, 39.4, 39.5, 49.2_1, 49.2_4, 63.4_7, 63.5, 124.6_8, 124.7, 125.2, 125.8_8, 125.9_3, 127.3_7, 127.4_3, 127.7, 127.8, 128.0, 128.1, 128.2_8, 128.3, 130.2, 130.3, 140.5, 140.6, 149.0, 149.1; FT-IR (film, cm^{-1}) 3339, 3058, 2958, 1599, 1462, 1055, 754, 701; ESI-MS (*m/z*): 347 [M+Na]$^+$. Anal. Calcd. for $C_{23}H_{32}O$: C, 85.13; H, 9.94; Found: C, 85.43; H, 10.12.



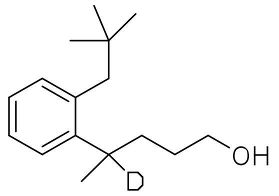
4-Deuterio-4-phenyl-4-(2-isobutylphenyl)butan-1-ol (3g-D): colourless oil, 50% yield, >98% D. ^{1}H NMR (400 MHz; CDCl$_3$): 0.85 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 1.47 (br s, 1 H), 1.51–1.58 (m, 2 H), 1.74–1.84 (m, 1 H), 2.04–2.12 (m, 1 H), 2.39 (dd, ^2J = 13.8 Hz, ^3J = 7.5 Hz, 1 H), 2.56 (dd, ^2J = 13.8 Hz, ^3J = 7.0 Hz, 1 H), 3.6 (t, J = 6.6 Hz, 2 H), 7.06-7.25 (m, 8 H), 7.29-7.31 (m, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 22.5, 22.7, 29.7, 31.3, 32.8, 42.0, 45.4 (t, $^1J_{C\text{-}D}$= 17.5 Hz), 62.9, 125.7, 125.9, 126.0, 127.0, 128.0, 128.3, 130.6, 139.6, 142.2, 144.8; FT-IR (film, cm^{-1}) 3339, 3059, 2962, 1599, 1465, 1051, 747, 699; ESI-MS (*m/z*): 306 [M+Na]$^+$. Anal. Calcd. for $C_{20}H_{25}DO$: C, 84.75; H, 9.60; Found: C, 84.90; H, 9.66.



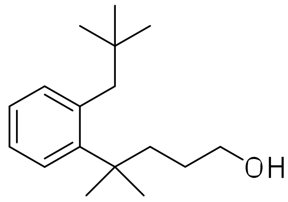
4-Deuterio-4-[2-(2-methyl-1-butyl)phenyl]pentan-1-ol (3h-D): (inseparable mixture of diastereoisomers, dr = 1:1), colourless oil, 52% overall yield, >98% D. ^{1}H NMR, (CDCl$_3$, 400 MHz), δ 0.85-0.95 (m, 12 H), 1.22 (s, 6 H), 1.41-1.44 (m, 6 H), 1.54–1.67 (m, 8 H), 2.32 (dd, ^3J = 8.5 Hz, ^2J = 13.6 Hz, 1 H), 2.43 (dd, ^3J = 8.2 Hz, ^2J = 13.6 Hz, 1 H), 2.63 (dd, ^3J = 6.4 Hz, ^2J = 13.6 Hz, 1 H), 2.74 (dd,^2J = 5.9 Hz, ^3J = 13.6 Hz, 1 H), 3.59 (t, ^3J = 6.4 Hz, 4 H), 7.08–7.09 (m, 4 H), 7.16–7.23 (m, 4 H); ^{13}C NMR (CDCl$_3$, 125 MHz), δ: 11.6, 19.0, 19.1, 22.4, 22.6, 29.4, 29.6, 31.0, 31.1, 34.2, 34.29, 34.34, 34.4, 36.5, 36.6, 40.3, 40.4, 63.1, 125.1, 125.40, 125.44, 126.2, 130.51, 130.55, 138.7, 145.4, 145.5; FT-IR (film, cm^{-1}) 3340, 3053, 2970, 1601, 1467, 1053, 750, 704; ESI-MS (*m/z*): 258 [M+Na]$^+$. Anal. Calcd. for $C_{16}H_{25}DO$: C, 81.64; H, 11.56; Found: C, 81.78; H, 11.70.



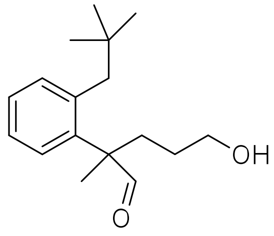
4-(2-Neopentylphenyl)pentan-1-ol (3i-H): colourless oil, 70% yield. ^{1}H NMR (400 MHz; CDCl$_3$): δ 0.94 (s, 9 H), 1.22 (d, J = 6.8 Hz, 3 H), 1.54−1.65 (m, 4 H), 2.51 (d, J = 13.5 Hz, 1 H), 2.69 (d, J = 13.5 Hz, 1 H), 3.07−3.15 (m, 1 H) 3.58 (t, J = 6.0 Hz, 2 H), 7.08−7.09 (m, 2 H), 7.16−7.26 (m, 2 H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 21.9, 29.8, 31.0, 32.6, 34.0, 34.9, 44.9, 63.3, 124.6, 125.4, 126.3, 131.8, 136.8, 146.5; FT-IR (film, cm^{-1}) 3350, 3022, 2951, 1722, 1477, 1059, 760, 712; ESI-MS (*m/z*): 257 [M+Na]$^+$. Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18; Found: C, 81.80; H, 11.01.



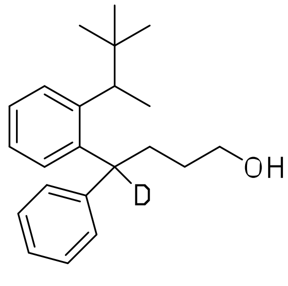
4-Deuterio-4-(2-neopentylphenyl)pentan-1-ol (3i-D): colourless oil, 70% yield. ^{1}H NMR (400 MHz; CDCl$_3$): δ 0.94 (s, 9 H), 1.21 (s, 3 H), 1.54−1.64 (m, 4 H), 2.51 (d, J = 13.5 Hz, 1 H), 2.69 (d, J = 13.5 Hz, 1 H), 3.58 (t, J = 6.0 Hz, 2 H), 7.08−7.09 (m, 2 H), 7.16−7.26 (m, 2 H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 21.8, 29.8, 31.0, 32.5, 34.0, 34.8, 44.9, 63.2, 124.6, 125.4, 126.3, 131.8, 136.8, 146.4; FT-IR (film, cm^{-1}) 3350, 3022, 2951, 1722, 1477, 1059, 760, 712; ESI-MS (*m/z*): 258 [M+Na]$^+$. Anal. Calcd. for $C_{16}H_{25}DO$: C, 81.64; H, 11.56; Found: C, 81.81; H, 11.44.



4-Methyl-4-(2-neopentylphenyl)pentan-1-ol (3j): colourless oil, 63% yield. ^{1}H NMR, (CDCl$_3$, 500 MHz), δ 0.90 (s, 6 H), 0.94 (s, 9 H), 1.53–1.62 (m, 4 H), 2.51 (d, ^2J = 13.6 Hz, 1H), 2.69 (d, ^2J = 13.6 Hz, 1H), 3.57-3.59 (m, 2 H), 7.08–7.09 (m, 2 H), 7.19–7.20 (m, 1 H), 7.22–7.24 (m, 1 H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ: 21.9, 29.8, 30.1, 32.5, 34.0, 34.9, 44.9, 63.2, 124.6, 125.4, 126.3, 131.8, 136.8, 144.0; FT-IR (film, cm^{-1}) 3335, 3021, 2950, 1636, 1477, 1056, 761, 713; ESI-MS (*m/z*): 271 [M+Na]$^+$. Anal. Calcd. for $C_{17}H_{28}O$: C, 82.20; H, 11.36; Found: C, 82.38; H, 11.55.

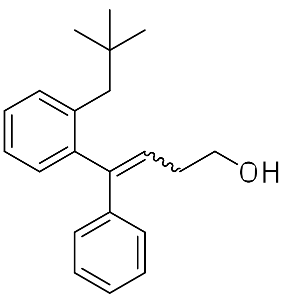


5-Hydroxy-2-methyl-2-(2-neopentylphenyl)pentanal (3k): colourless oil, 40% yield. ^{1}H NMR (400 MHz; CDCl$_3$): δ 0.88 (s, 9 H), 1.02–1.17 (m, 2 H), 1.35 (s, 3 H), 1.85–1.94 (m, 2 H), 2.38 (d, J = 15.1 Hz, 1 H), 2.46 (d, J = 15.1 Hz, 1 H), 3.88 (t, J = 6.0 Hz, 2 H), 7.13−7.18 (m, 2 H), 7.23−7.34 (m, 2 H), 9.57 (s, 1 H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 27.3, 30.9, 32.0, 32.6, 32.8, 44.0, 54.2, 63.1, 125.0, 126.2, 126.7, 126.8, 132.1, 144.3, 204.4; FT-IR (film, cm^{-1}) 3391, 2952, 1723, 1445, 1104, 760, 698; ESI-MS (*m/z*): 285 [M+Na]$^+$. Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99; Found: C, 78.05; H, 10.24.



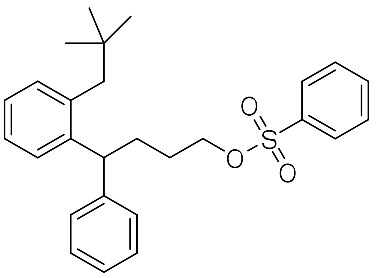
4-Deuterio-4-phenyl-4-[2-(3,3-dimethyl-2-butyl)phenyl]butan-1-ol (3l-D): (inseparable mixture of diastereomers, dr = 1:1), colourless oil, 40% yield, >98% D. ^{1}H NMR (400 MHz; CDCl$_3$): δ 0.83 (s, 9 H), 1.24 (d, J = 7.1 Hz, 3 H), 1.45-1.57 (m, 4 H), 3.09 (q, J = 7.1 Hz, 1 H), 3.61 (t, J = 6.3 Hz, 2 H), 7.04–7.21 (m, 6 H), 7.27–7.28 (m, 3 H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 17.7, 28.3, 31.3, 33.2, 34.4, 42.0, 45.4 (t, $^1J_{C\text{-}D}$ = 18.8 Hz), 62.9, 125.4, 125.5, 126.1, 127.6, 127.7, 128.3, 128.8, 142.8, 144.0, 144.1; FT-IR (film, cm^{-1}) 3350, 3023, 2950, 1599, 1476, 1049, 761, 699; ESI-MS (*m/z*): 334 [M+Na]$^+$. Anal. Calcd. for $C_{22}H_{29}DO$: C, 84.83; H, 10.03; Found: C, 85.04; H, 10.35.

3. Synthesis of 4-(2-neopentylphenyl)-4-phenylbut-3-en-1-ol (4). A CPME solution of **2** (0.5 mmol in 0.5 mL of solvent) was added to the *DES* ChCl/Gly 1/2 (molar ratio) mixture (1 g), contained in an open vessel, under vigorous stirring. After 2 min, the mixture was cooled to 0 °C. A solution of *t*-BuLi (0.59 ml of a 1.7 M solution in pentane, 1 mmol), handled under Argon using conventional Schlenk techniques, was then rapidly spread out over the above mixture under air. The colour of the mixture became immediately dark red. No particular problems were experienced during this addition. After 3 min, 2.0 mmol of the carbonyl compound (acetone, benzaldehyde or benzophenone), as pure liquid or as a solution in 1 mL of the solvent if solid, was added all at once and the mixture was stirred for an additional 10 min at 0 °C. After this time, 5 mL of water was added and the reaction mixture was allowed to warm to room temperature, and finally extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash-chromatography (silica gel; hexane/AcOEt 9/1) to afford **3a-H** (80% yield) and a mixture of isomeric alkenes **4** (20%).



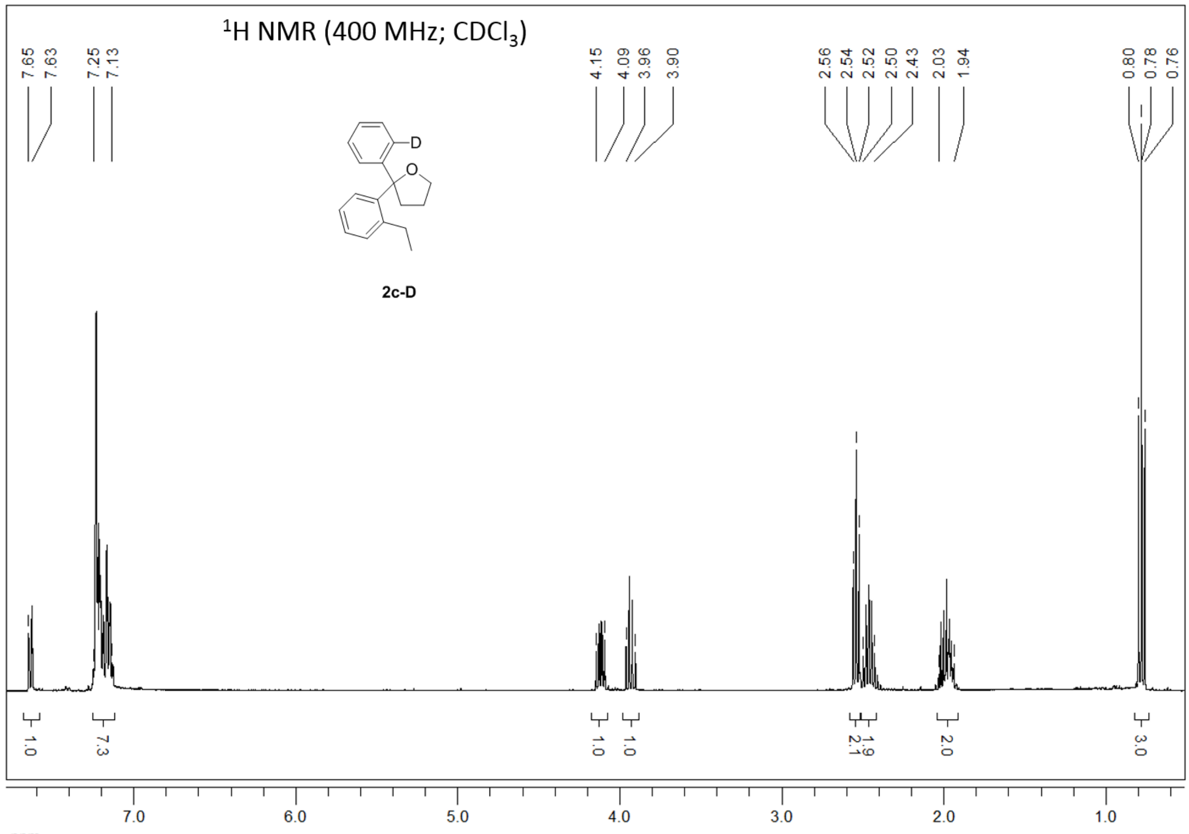
4-(2-Neopentylphenyl)-4-phenylbut-3-en-1-ol (4): (inseparable mixture of diastereomers, dr = 1:1), colourless oil, 20% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.76 (s, 9 H), 0.96 (S, 9 H), 1.94–2.12 (m, 2 H), 2.15–2.27 (m, 3 H), 2.35–2.44 (m, 2 H), 2.75 (d, ^2J = 13.7 Hz, 1 H), 3.60–3.64 (m, 2 H), 3.70–3.73 (m, 2 H), 4.29–4.33 (m, 1 H), 6.10–6.14 (m, 1 H), 7.08–7.11 (m, 2 H), 7.14–7.24 (m, 16 H), 7.32–7.34 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.9, 30.0, 32.6, 32.7, 33.0, 34.1, 46.0, 46.3, 62.5, 63.0, 125.2, 125.6, 125.9, 126.1, 126.2, 126.3, 126.7, 126.8, 126.9, 128.1, 128.2, 128.3, 131.3, 132.0, 132.2, 137.7, 139.0, 139.5, 142.4, 143.1, 144.5, 144.7; FT-IR (film, cm^{-1}) 3339, 3023, 2950, 1598, 1476, 1049, 761, 732, 698; ESI-MS (*m/z*): 317 [M+Na]$^+$. Anal. Calcd. for $C_{21}H_{26}O$: C, 85.67; H, 8.90; Found: C, 85.90; H, 9.16.

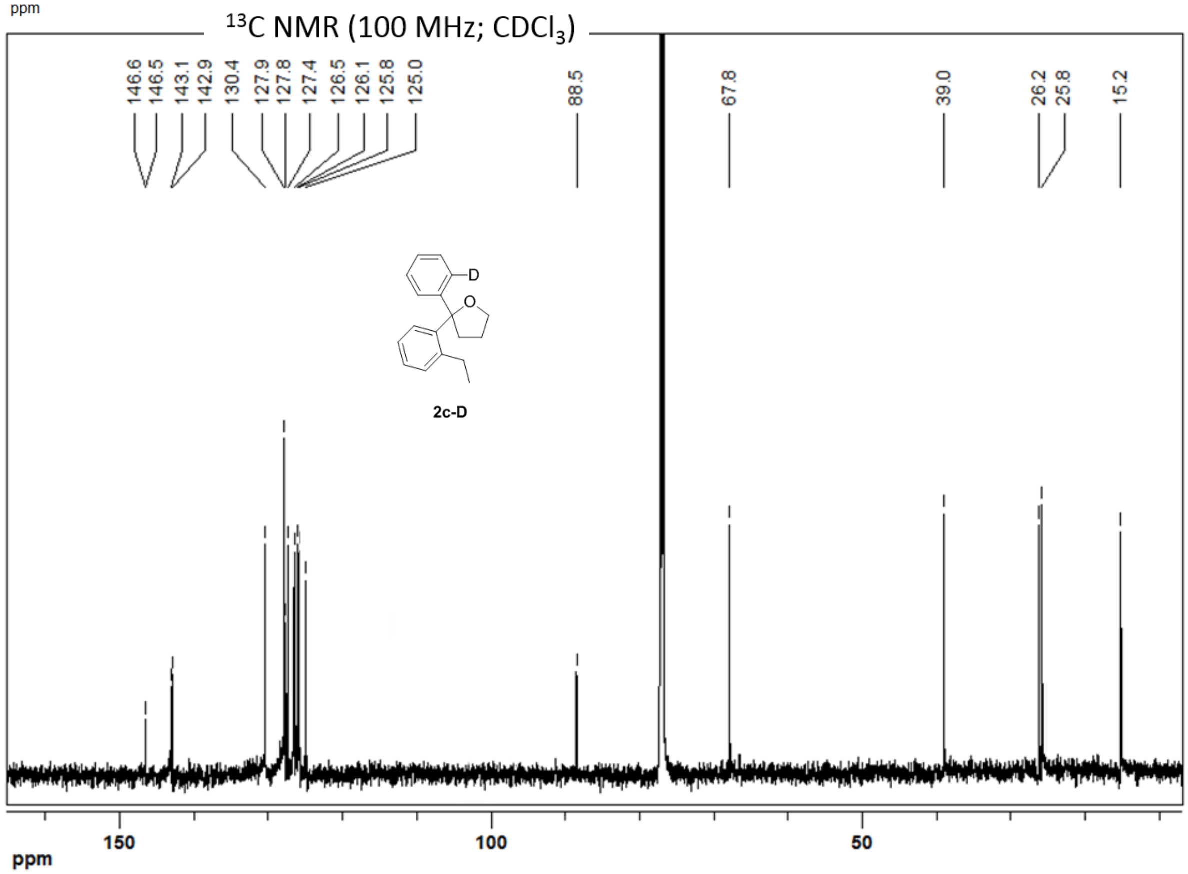
4. Synthesis of ether compounds (5a,b): A CPME solution of **2** (0.5 mmol in 0.5 mL of solvent) was added to the *DES* ChCl/Gly 1/2 (molar ratio) mixture (1 g), contained in an open vessel, under vigorous stirring. After 2 min, the mixture was cooled to 0 °C. A solution of *t*-BuLi (0.59 ml of a 1.7 M solution in pentane, 1 mmol), handled under Argon using conventional Schlenk techniques, was then rapidly spread out over the above mixture under air. The colour of the mixture became dark red. No particular problems were experienced during this addition. After 3 min, 2.0 equiv of the electrophile (as a solution in 1 mL of CPME in the case of *N*-fluorobenzenesulfonimide or as pure liquid in the case of Me_3SiCl), was added all at once and the mixture was stirred for an additional 10 min at 0 °C. After this time, 5 mL of water was added and the reaction mixture was allowed to warm to room temperature, and finally extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash-chromatography (silica gel; hexane/AcOEt 9/1). Compound **5a** could be isolated in 40% yield, whereas the *O*-silylated compound **5b** proved to be unstable on silica gel. The latter was formed with an yield of 41%, as suggested by ^1H NMR analysis of the crude reaction mixture employing an internal standard technique.



4-(2-Neopentylphenyl)-4-phenylbutyl benzenesulfonate (5a): ^1H NMR (400 MHz; $CDCl_3$): δ 0.97 (s, 9 H), 1.53−1.60 (m, 2 H), 1.82−1.98 (m, 2 H), 2.27 (d, *J* = 13.7 Hz, 1 H), 2.63 (d, *J* = 13.7 Hz, 1 H), 3.97 (t, *J* = 6.4 Hz, 2 H), 4.17 (t, *J* = 7.6 Hz, 1 H), 7.00−7.46 (m, 9 H), 7.43−7.46 (m, 2 H), 7.79−7.81 (m, 2 H), 7.53−7.58 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6, 30.0, 32.5, 32.7, 44.6, 46.0, 70.8, 125.4, 126.1, 126.6, 127.8, 128.0, 128.4, 129.2, 132.3, 133.6, 136.1, 136.2, 137.7, 142.3, 144.1; FT-IR (film, cm^{-1}) 3061, 3024, 1951, 2865, 1599, 1448, 1362, 1187, 929, 752, 700; ESI-MS (*m/z*): 459 $[M+Na]^+$. Anal. Calcd. for $C_{27}H_{32}O_3S$: C, 74.27; H, 7.39; Found: C, 74.61; H, 7.70.

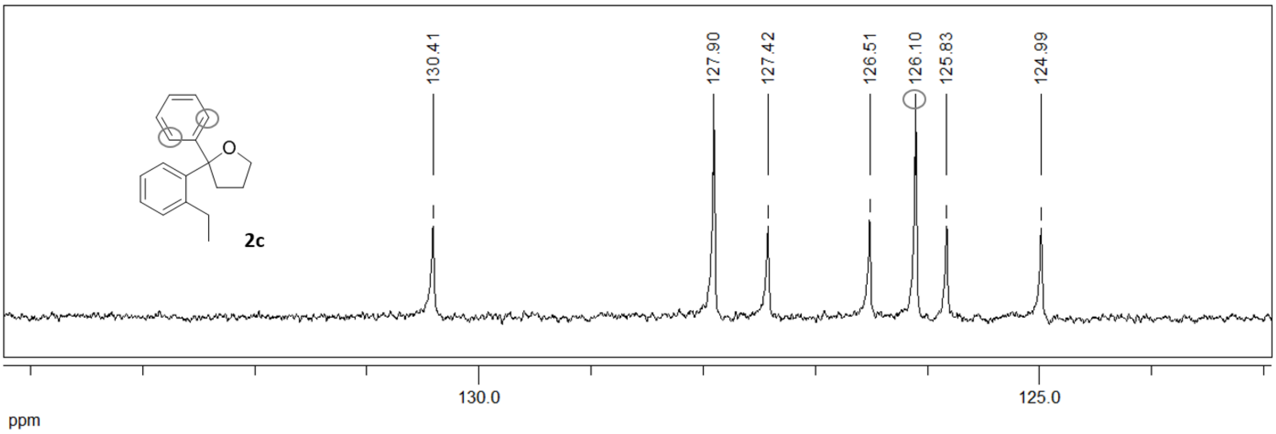
5. ^{1}H and ^{13}C NMR spectra

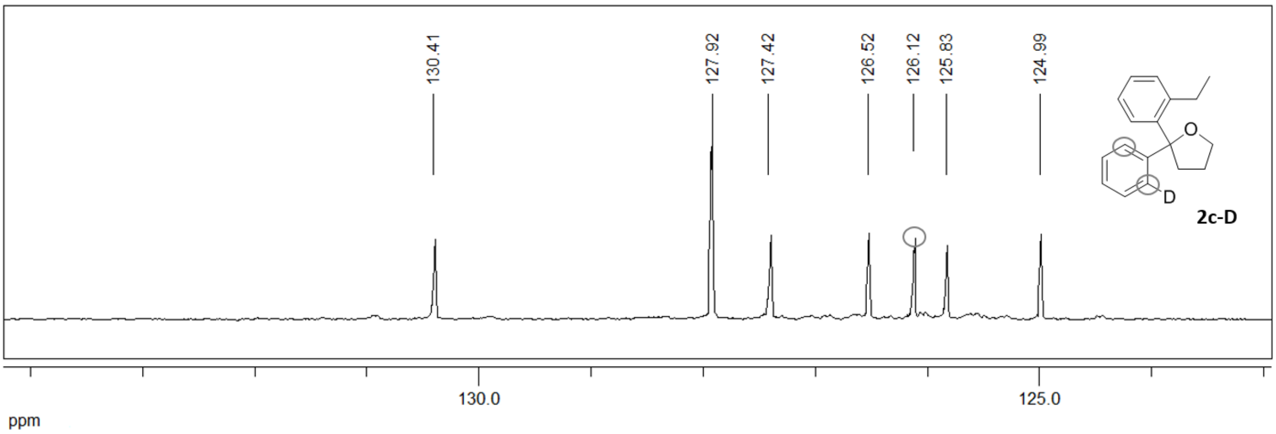


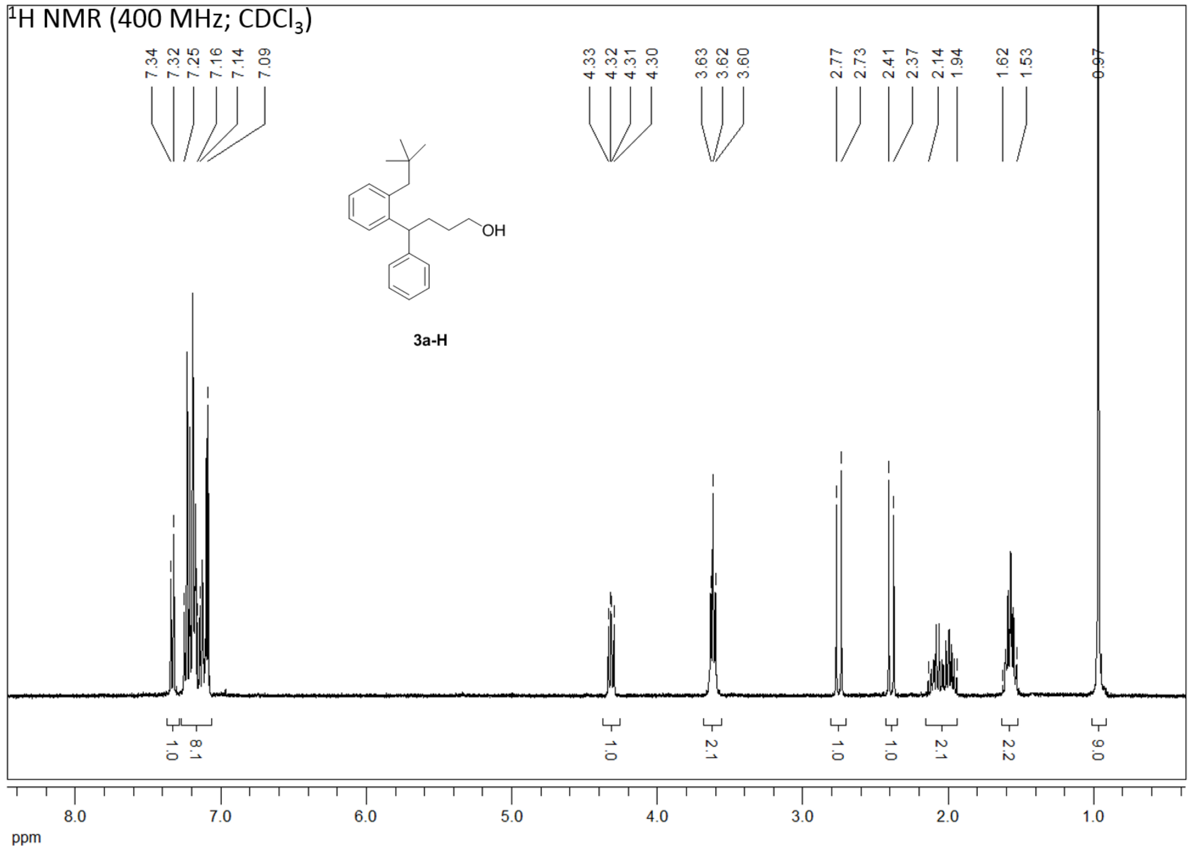


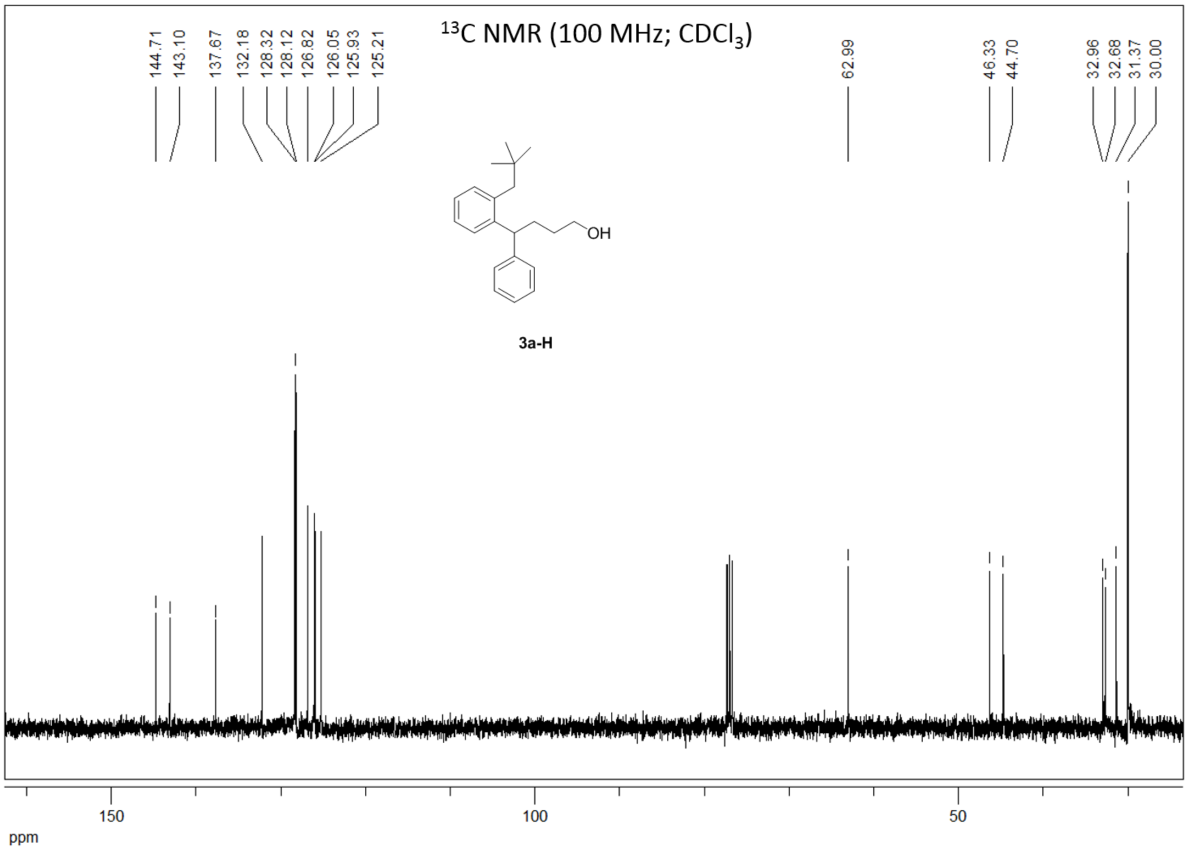
Comparison of partial ^{13}C NMR spectra of substrate **2c** and the *ortho*-deuterated **2c-D**

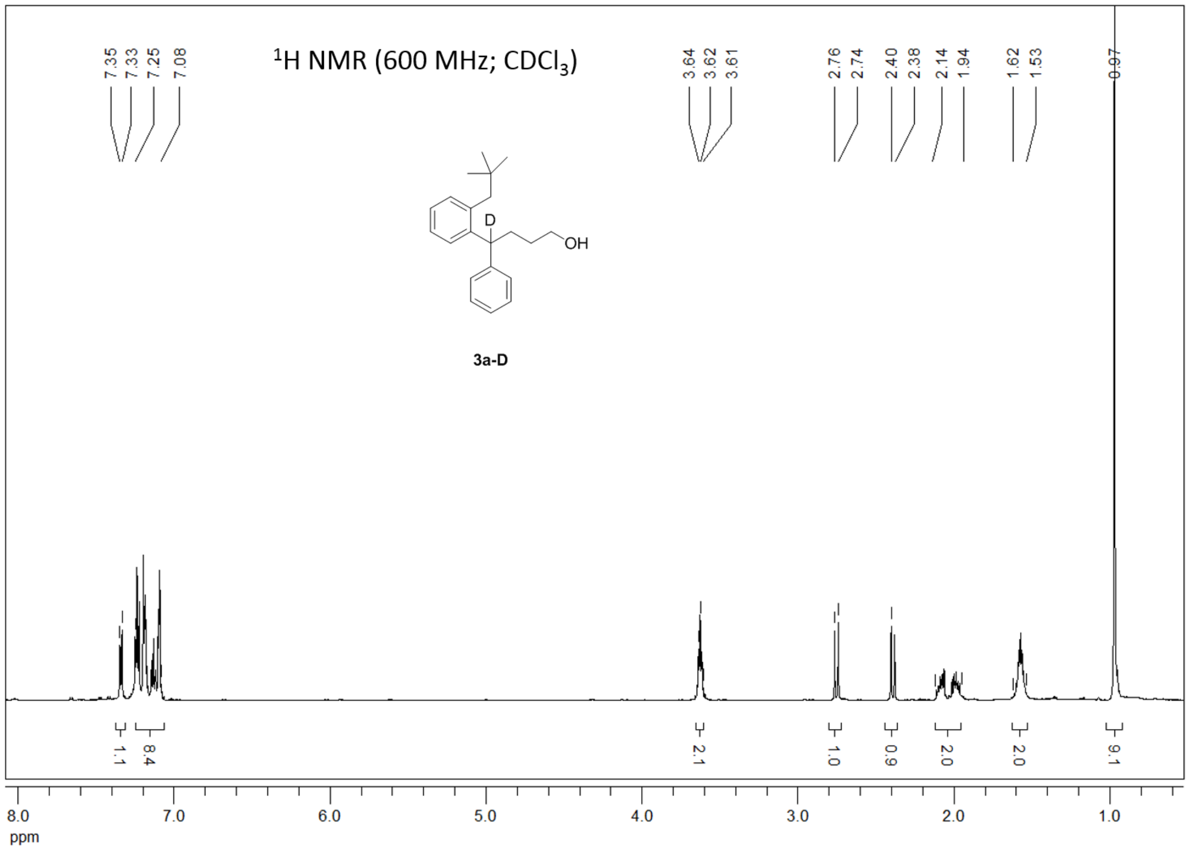
^{13}C NMR (100 MHz; CDCl$_3$)



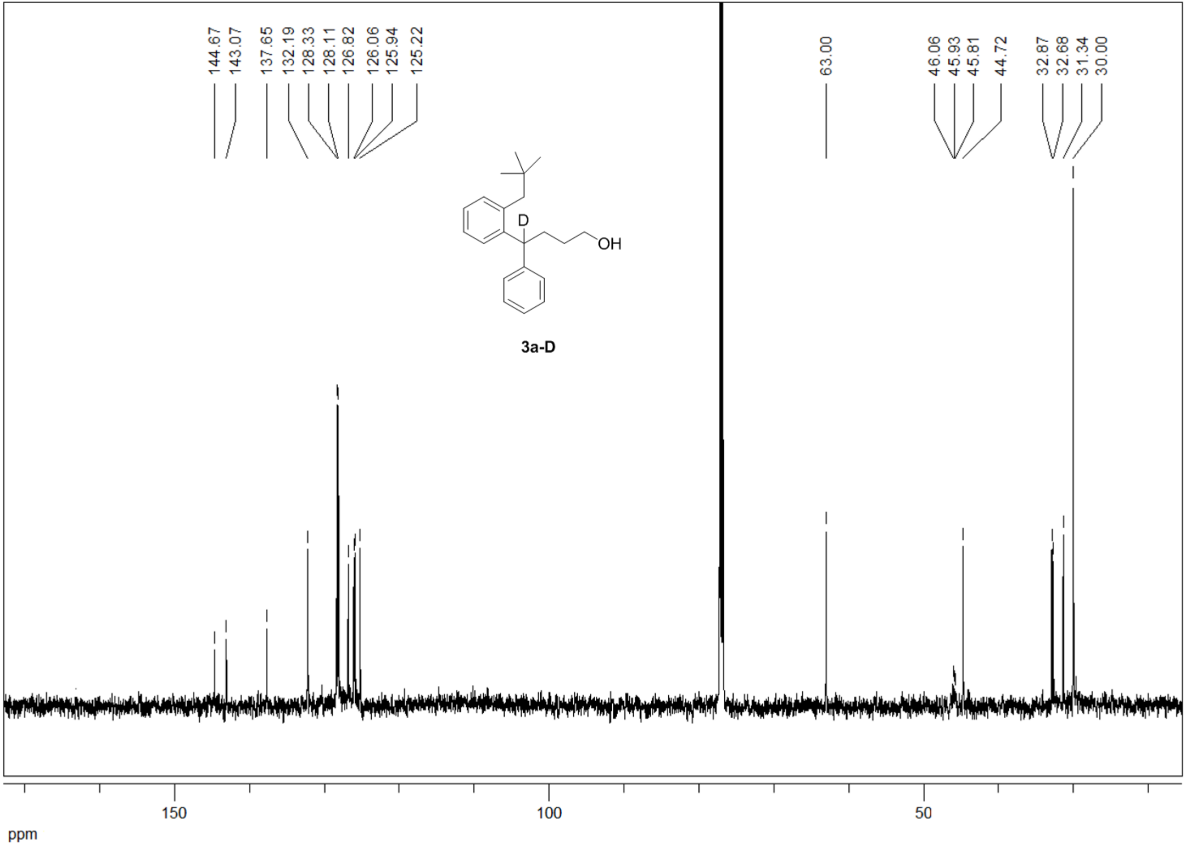


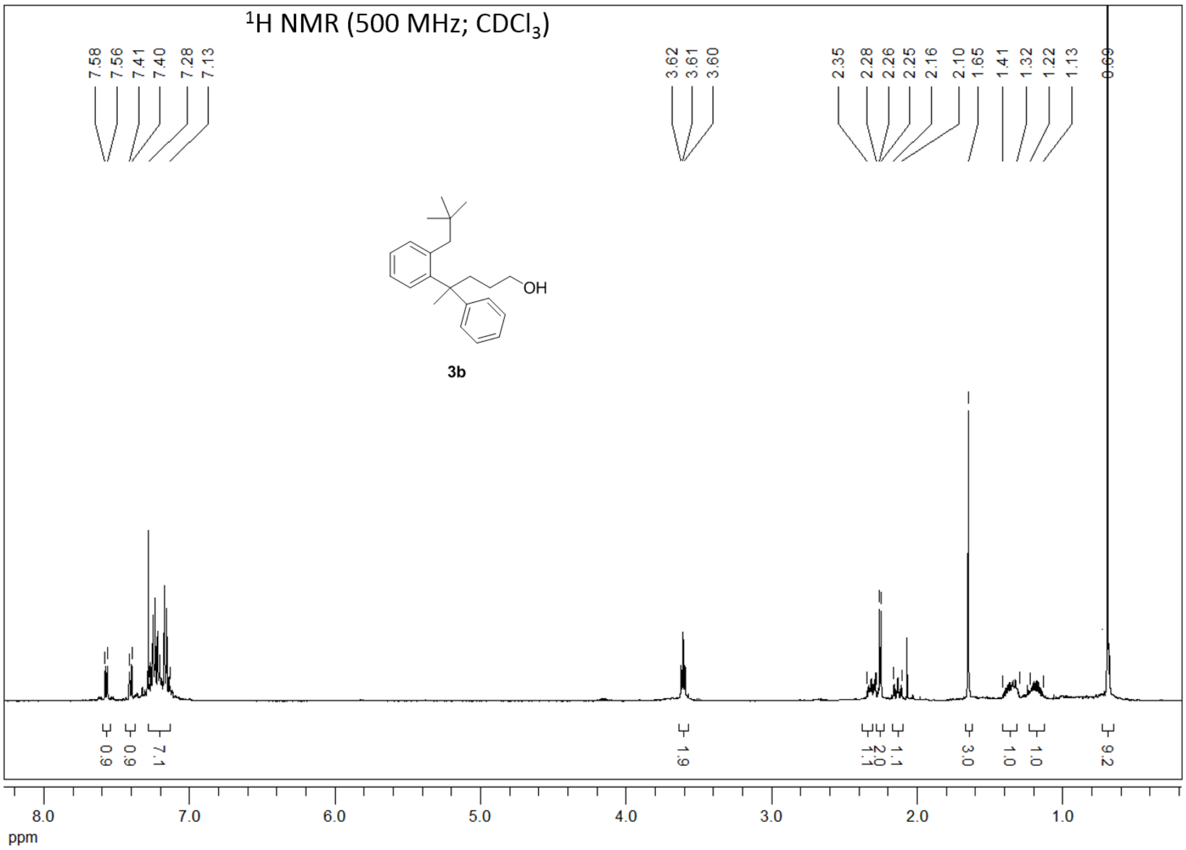

^{1}H NMR (400 MHz; CDCl$_3$)
7.34
7.32
7.25
7.16
7.14
7.09
4.33
4.32
4.31
4.30
3.63
3.62
3.60
2.77
2.73
2.41
2.37
2.14
1.94
1.62
1.53
0.97
OH
3a-H
1.0
8.1
1.0
2.1
1.0
1.0
2.1
2.2
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm


^{13}C NMR (100 MHz; CDCl$_3$)
144.71
143.10
137.67
132.18
128.32
128.12
126.82
126.05
125.93
125.21
62.99
46.33
44.70
32.96
32.68
31.37
30.00
OH
3a-H
150
100
50
ppm

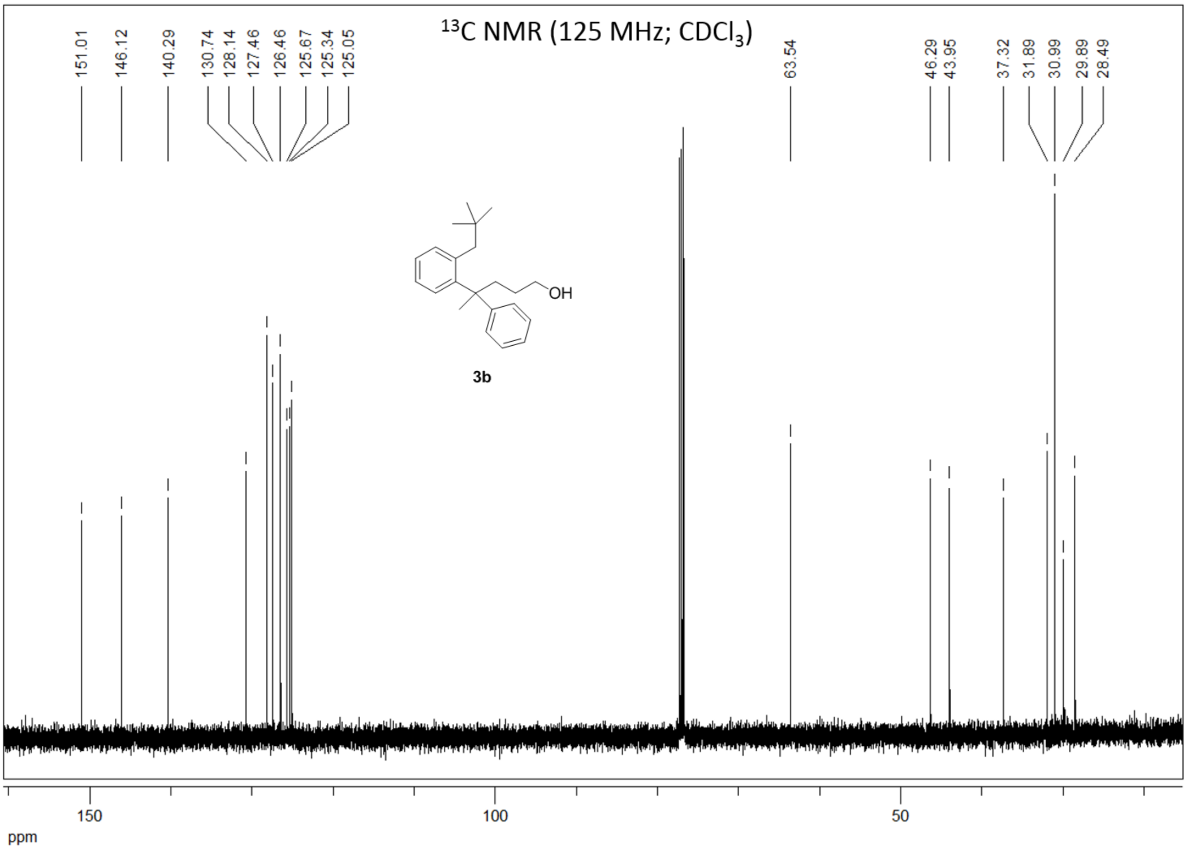


^{13}C NMR (100 MHz; CDCl$_3$)

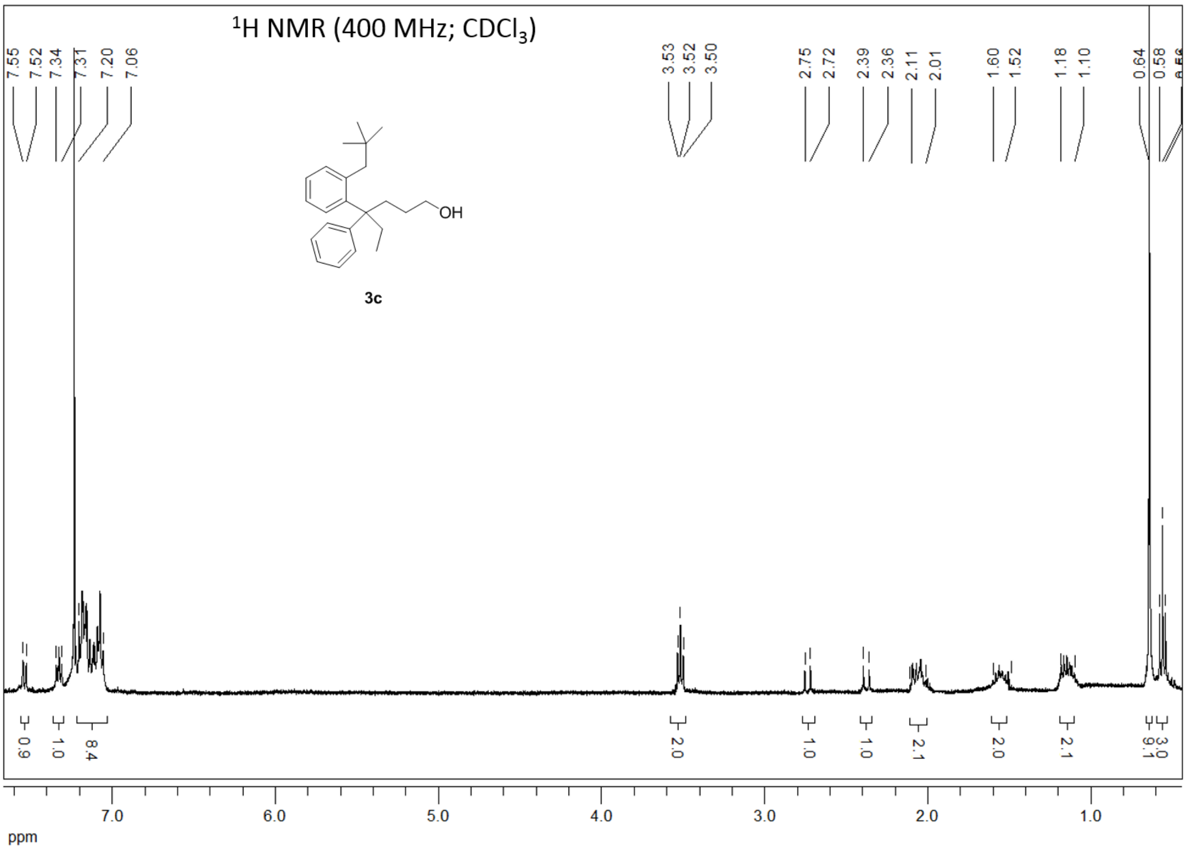




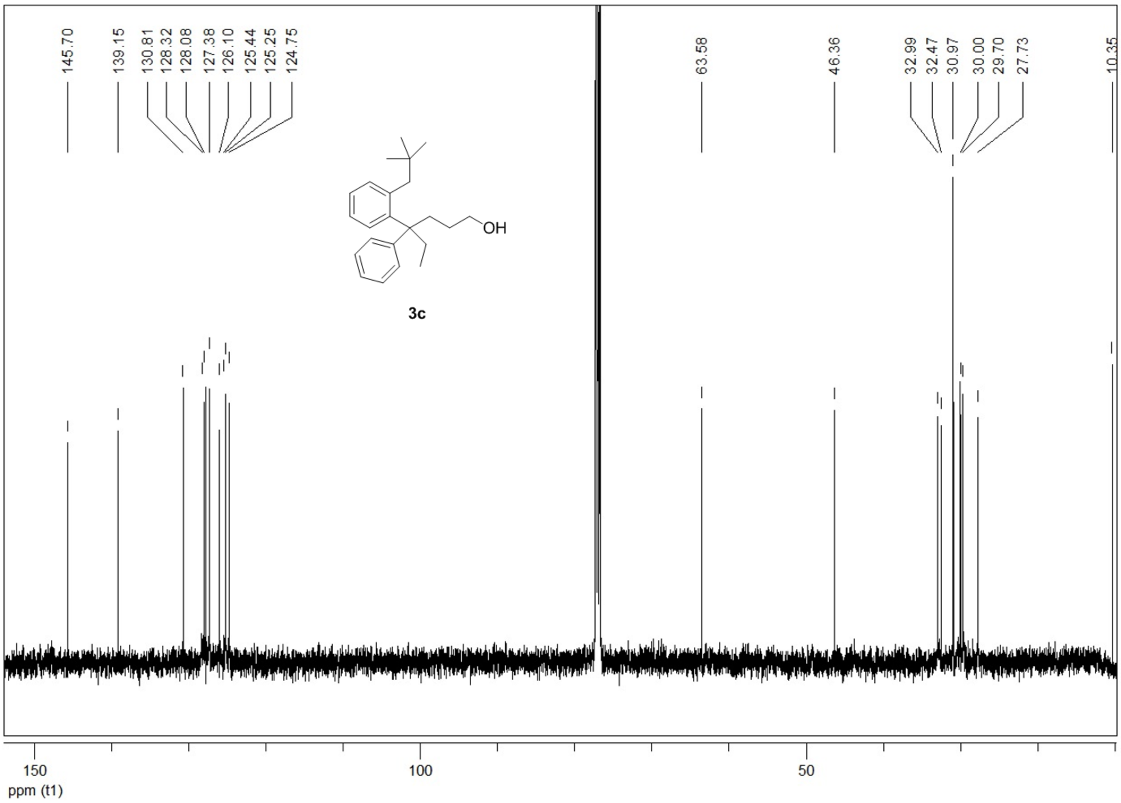
^{1}H NMR (500 MHz; $CDCl_3$)

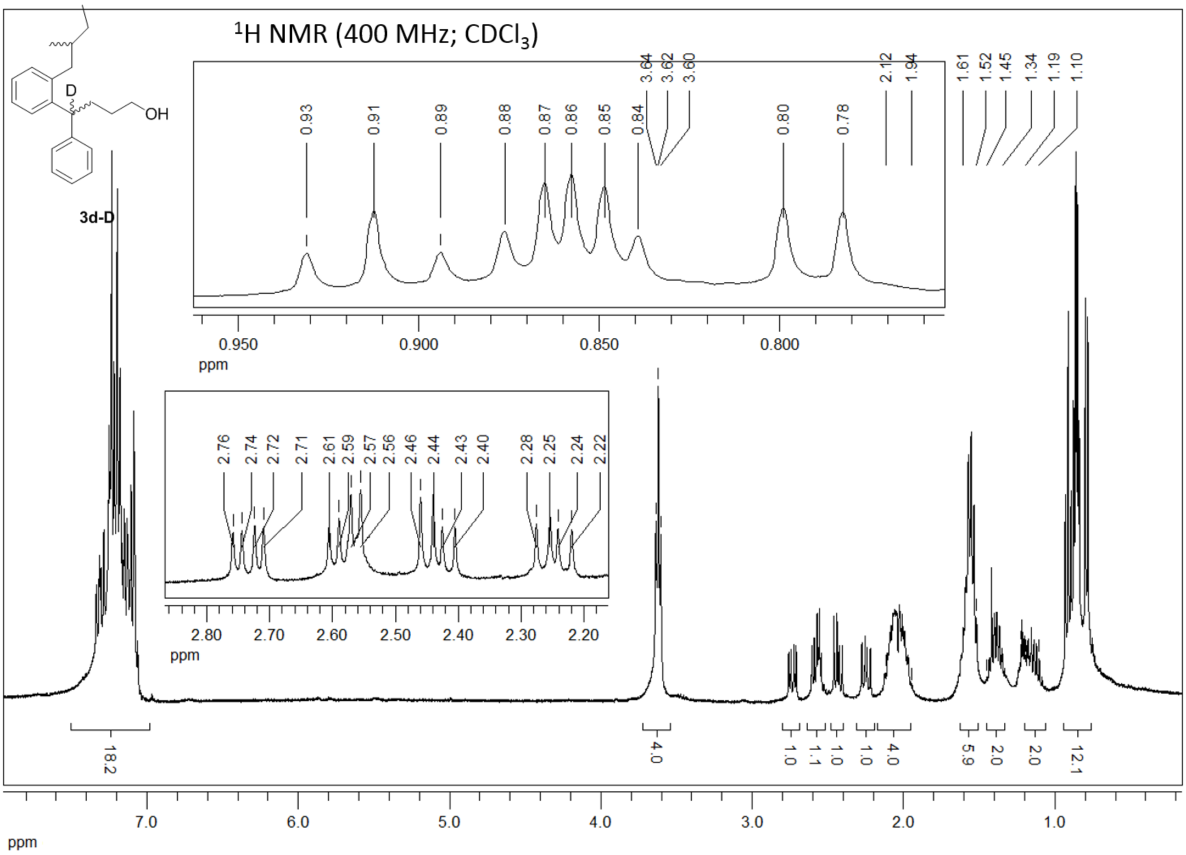


^{13}C NMR (125 MHz; $CDCl_3$)

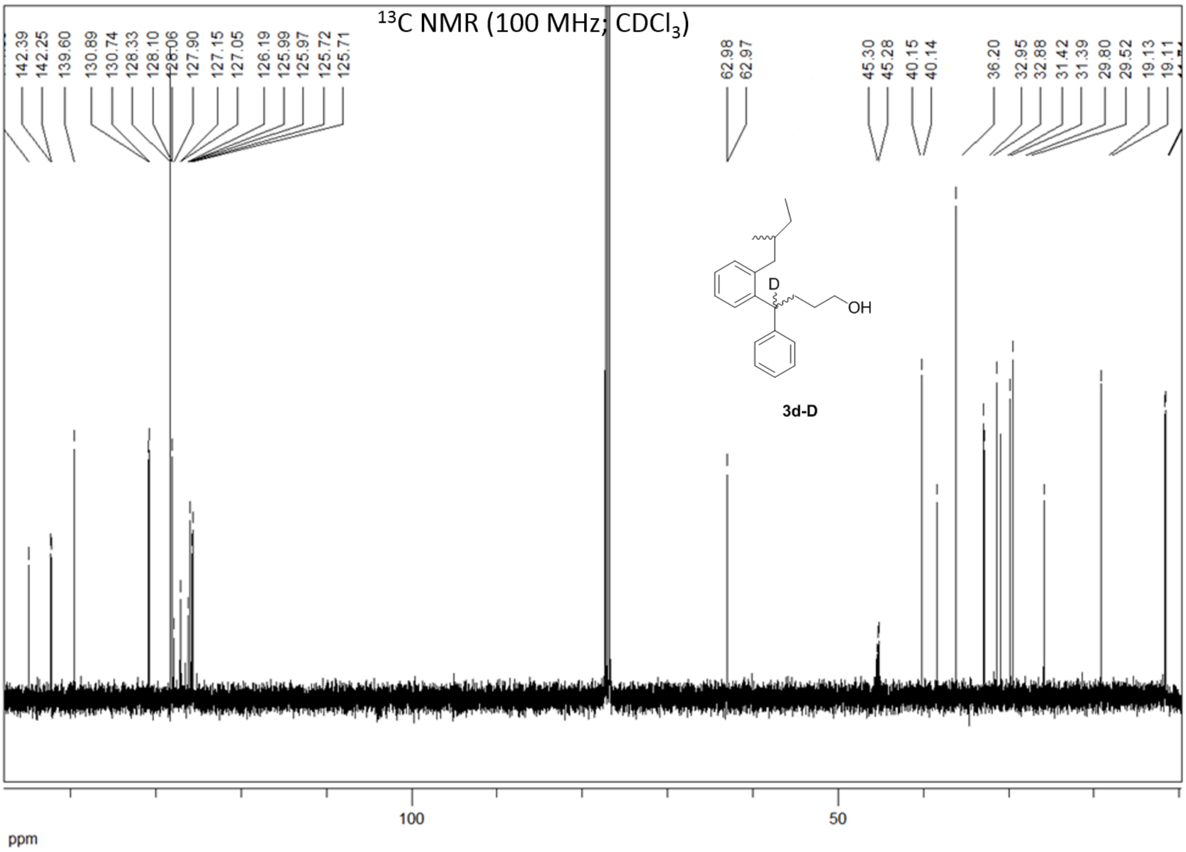


^{13}C NMR (100 MHz; CDCl$_3$)

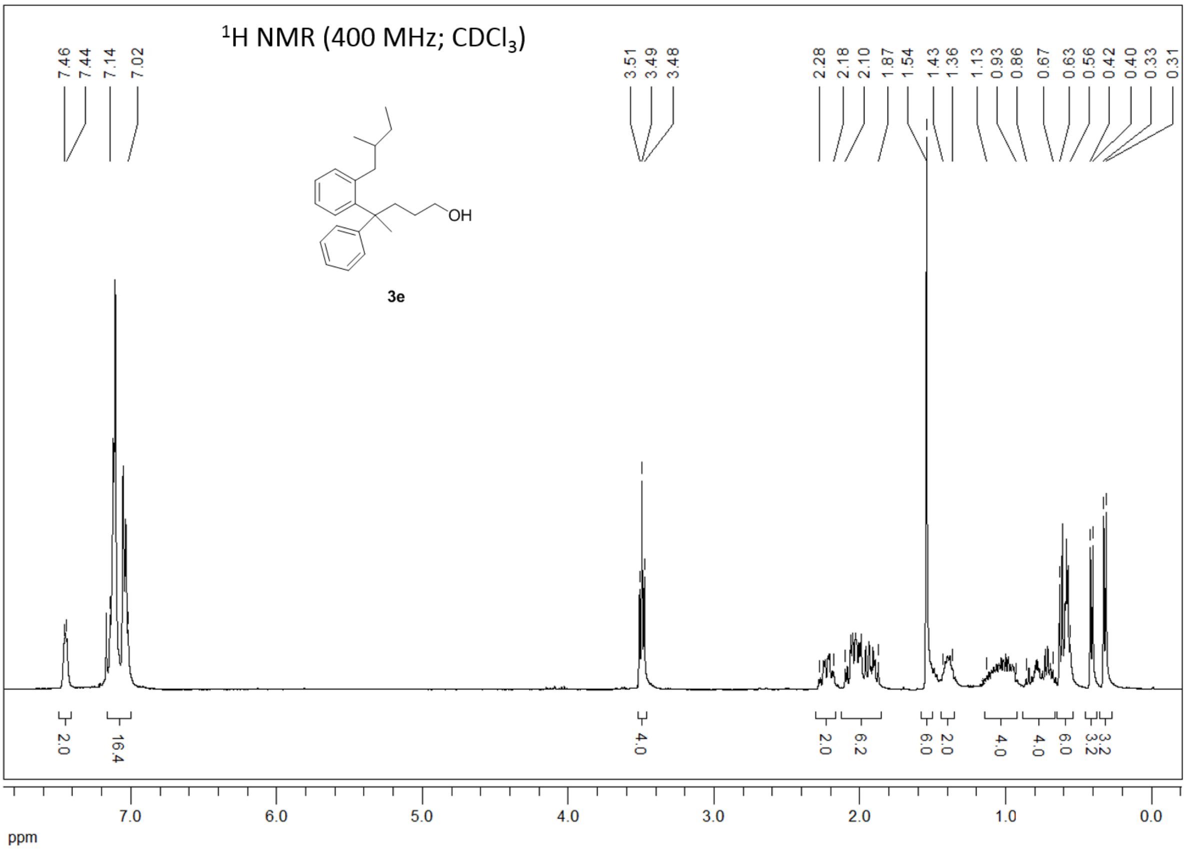


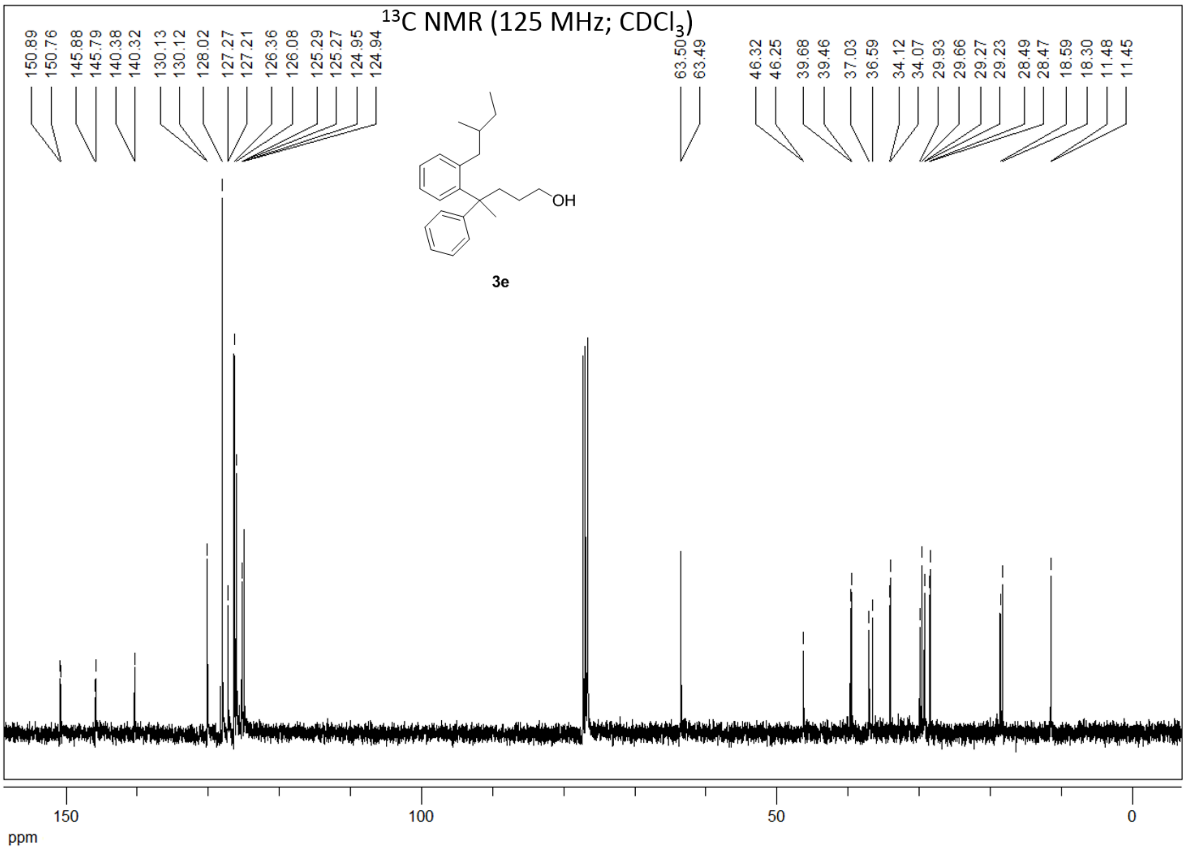


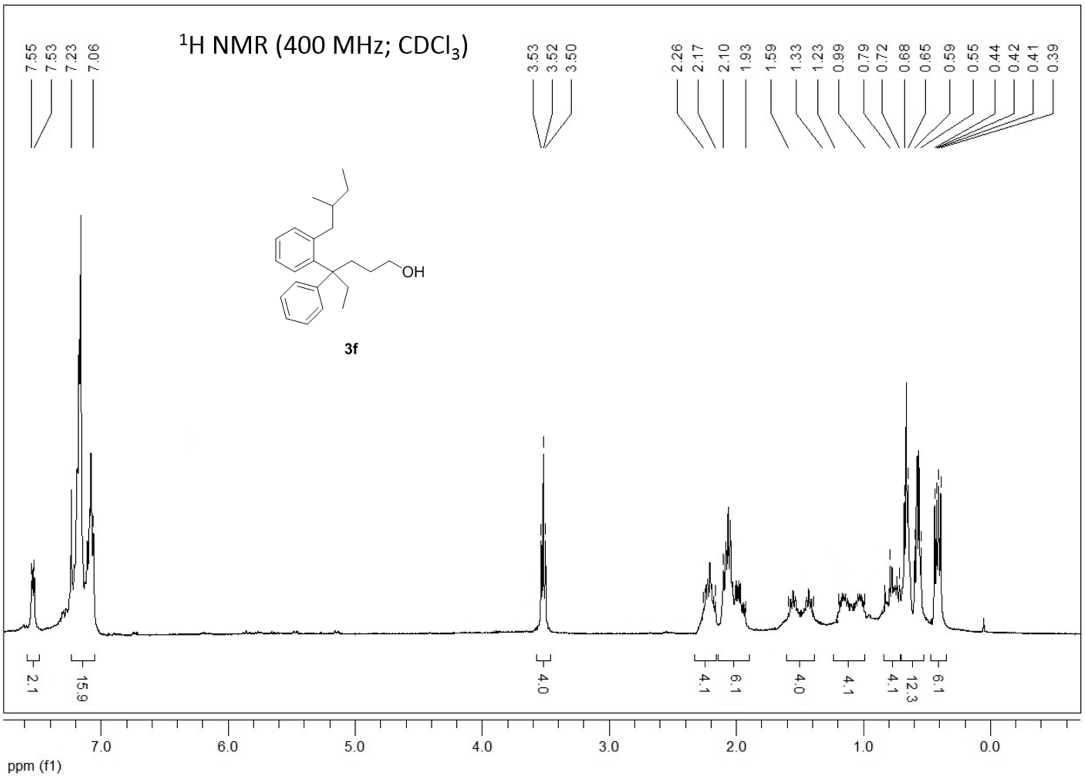
^{1}H NMR (400 MHz; CDCl$_3$)
D
OH
3d-D
0.93
0.91
0.89
0.88
0.87
0.86
0.85
0.84
3.64
3.62
3.60
0.80
0.78
2.12
1.94
1.61
1.52
1.45
1.34
1.19
1.10
0.950
0.900
0.850
0.800
ppm
2.76
2.74
2.72
2.71
2.61
2.59
2.57
2.56
2.46
2.44
2.43
2.40
2.28
2.25
2.24
2.22
2.80
2.70
2.60
2.50
2.40
2.30
2.20
ppm
18.2
4.0
1.0
1.1
1.0
1.0
4.0
5.9
2.0
2.0
12.1
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm



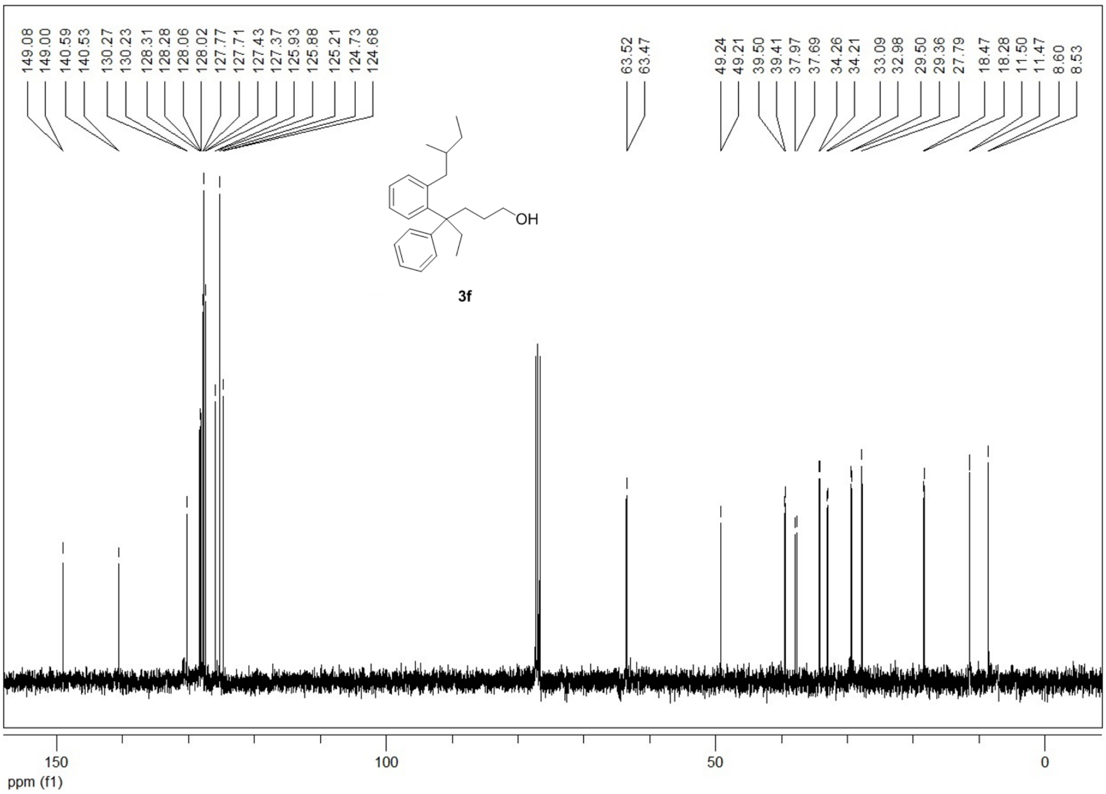
^{13}C NMR (100 MHz; CDCl$_3$)
142.39
142.25
139.60
130.89
130.74
128.33
128.10
128.06
127.90
127.15
127.05
126.19
125.99
125.97
125.72
125.71
62.98
62.97
45.30
45.28
40.15
40.14
36.20
32.95
32.88
31.42
31.39
29.80
29.52
19.13
19.11
D
OH
3d-D
100
50
ppm

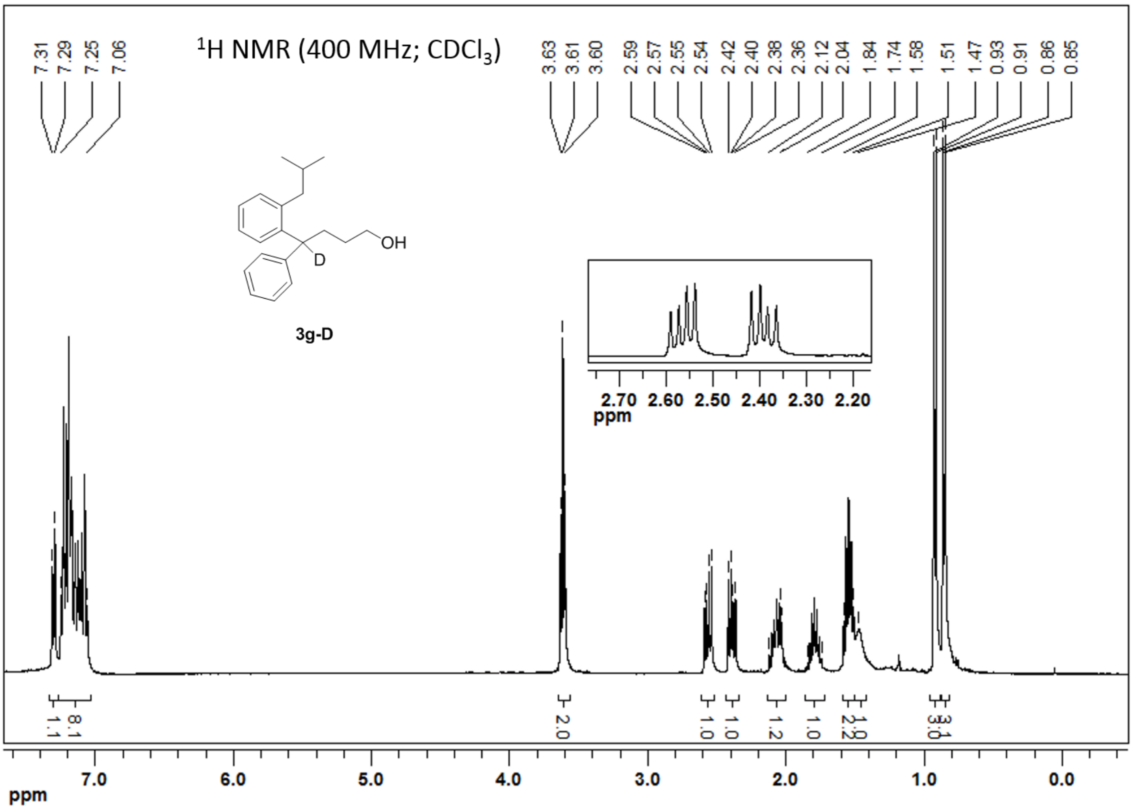

^{1}H NMR (400 MHz; CDCl$_3$)
7.46
7.44
7.14
7.02
3.51
3.49
3.48
2.28
2.18
2.10
1.87
1.54
1.43
1.36
1.13
0.93
0.86
0.67
0.63
0.56
0.42
0.40
0.33
0.31
OH
3e
2.0
16.4
4.0
2.0
6.2
6.0
2.0
4.0
4.0
6.0
3.2
3.2
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm

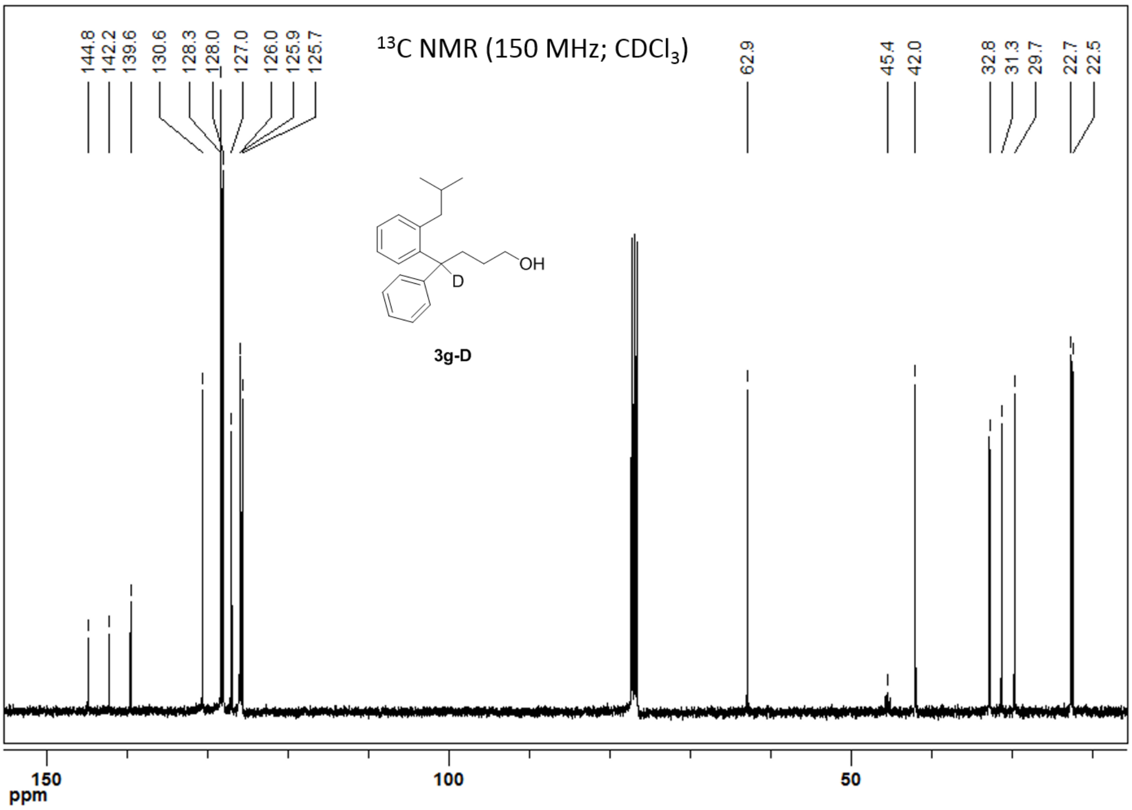

^{13}C NMR (125 MHz; CDCl$_3$)
150.89
150.76
145.88
145.79
140.38
140.32
130.13
130.12
128.02
127.27
127.21
126.36
126.08
125.29
125.27
124.95
124.94
63.50
63.49
46.32
46.25
39.68
39.46
37.03
36.59
34.12
34.07
29.93
29.66
29.27
29.23
28.49
28.47
18.59
18.30
11.48
11.45
OH
3e
150
100
50
0
ppm

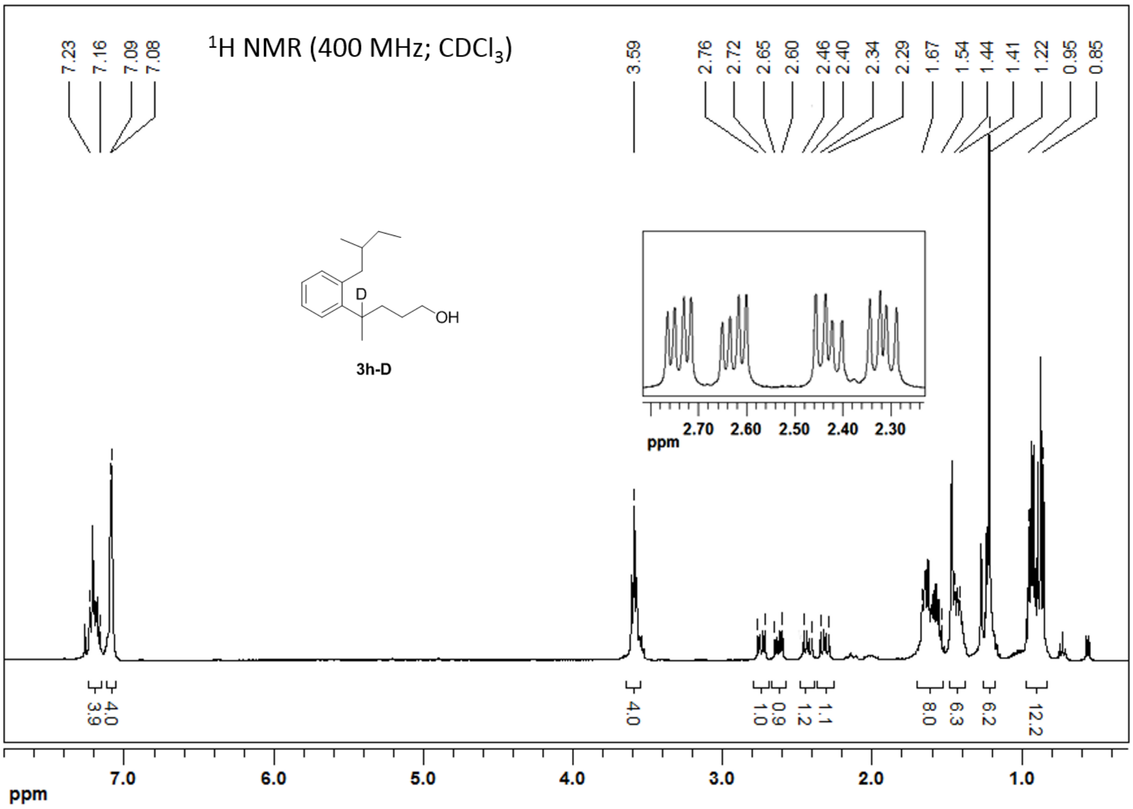


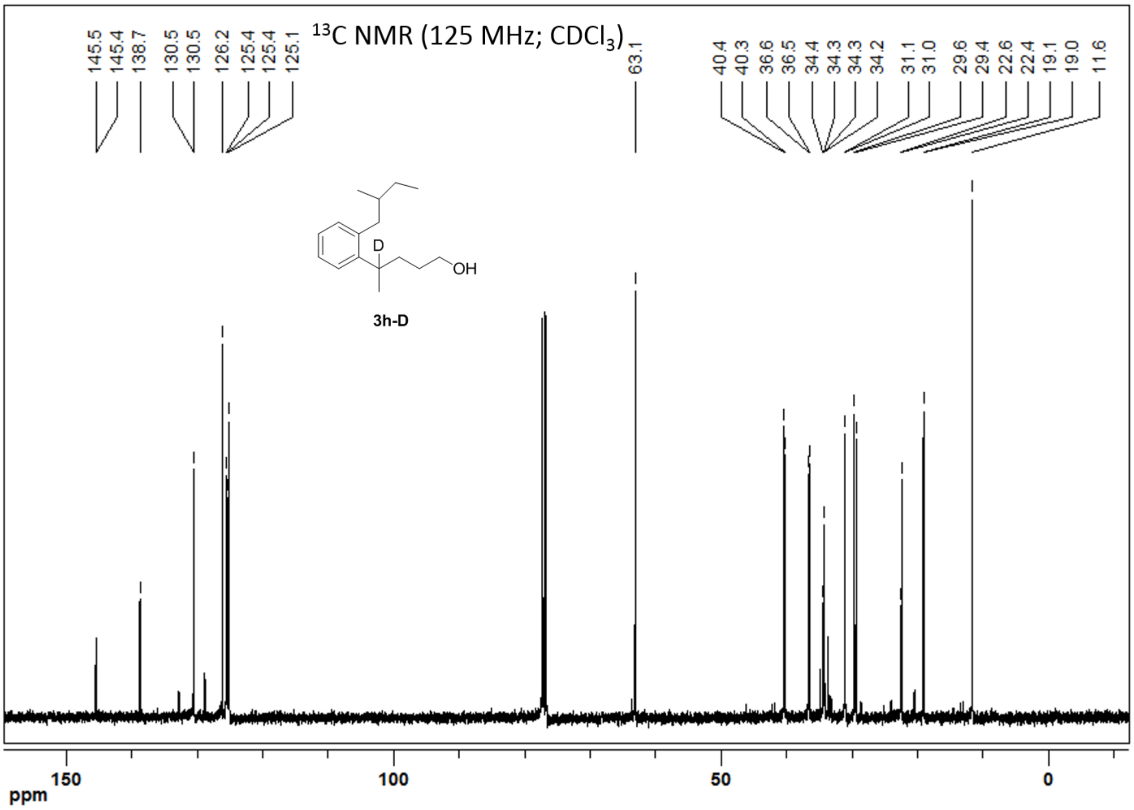
^{13}C NMR (100 MHz; CDCl$_3$)

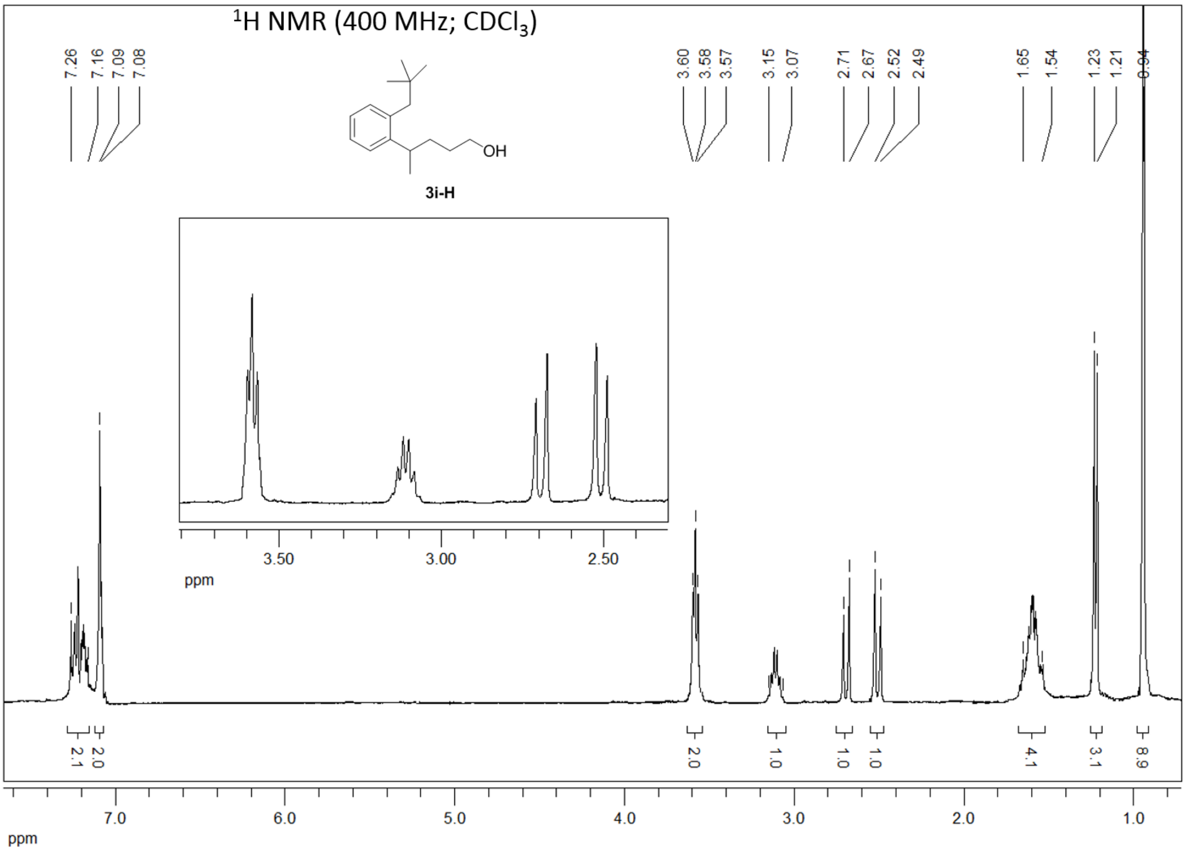



^{1}H NMR (400 MHz; CDCl$_3$)
7.31
7.29
7.25
7.06
3.63
3.61
3.60
2.59
2.57
2.55
2.54
2.42
2.40
2.38
2.36
2.12
2.04
1.84
1.74
1.58
1.51
1.47
0.93
0.91
0.86
0.85
OH
D
3g-D
2.70
2.60
2.50
2.40
2.30
2.20
ppm
1.1
8.1
2.0
1.0
1.0
1.2
1.0
2.2
1.0
3.0
3.1
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm

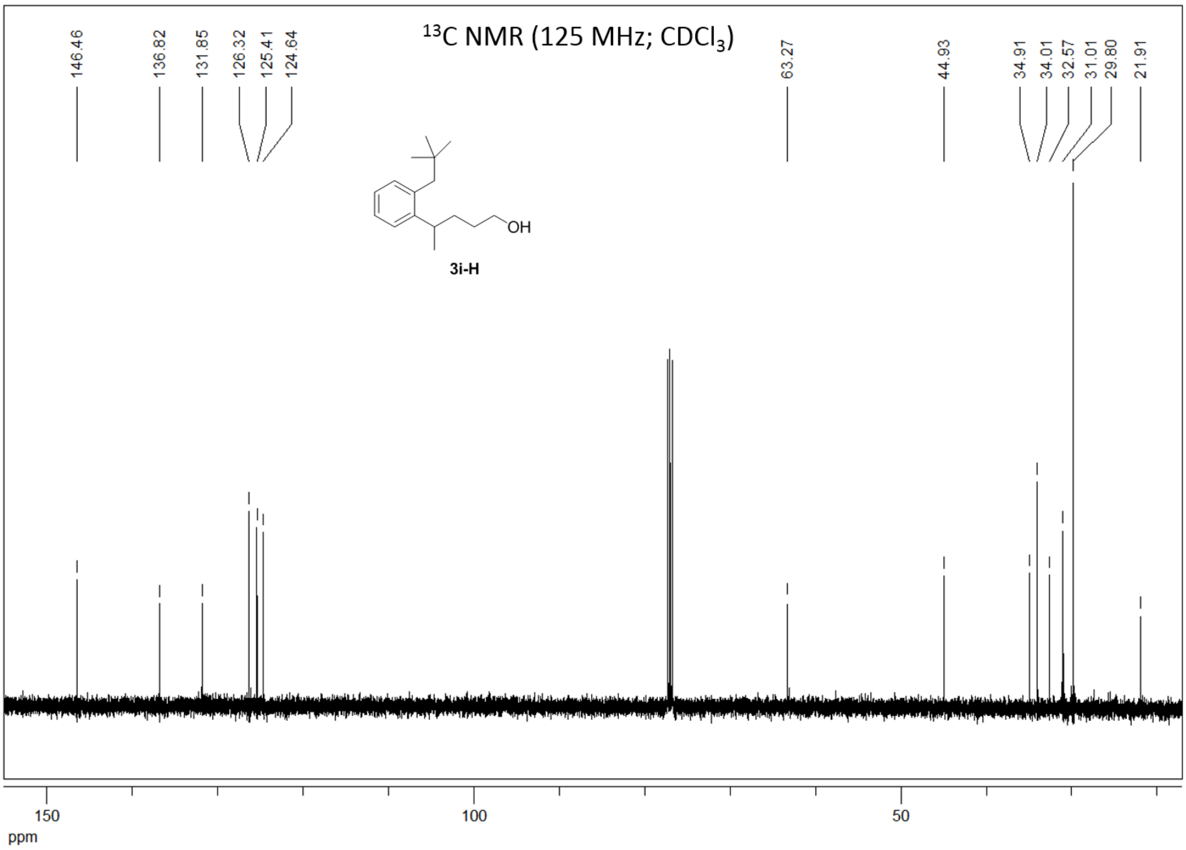

144.8
142.2
139.6
130.6
128.3
128.0
127.0
126.0
125.9
125.7
^{13}C NMR (150 MHz; CDCl$_3$)
62.9
45.4
42.0
32.8
31.3
29.7
22.7
22.5
OH
D
3g-D
150
ppm
100
50


^{1}H NMR (400 MHz; $CDCl_3$)
7.23
7.16
7.09
7.08
3.59
2.76
2.72
2.65
2.60
2.46
2.40
2.34
2.29
1.67
1.54
1.44
1.41
1.22
0.95
0.85
D
OH
3h-D
ppm
2.70
2.60
2.50
2.40
2.30
3.9
4.0
4.0
1.0
0.9
1.2
1.1
8.0
6.3
6.2
12.2
ppm
7.0
6.0
5.0
4.0
3.0
2.0
1.0

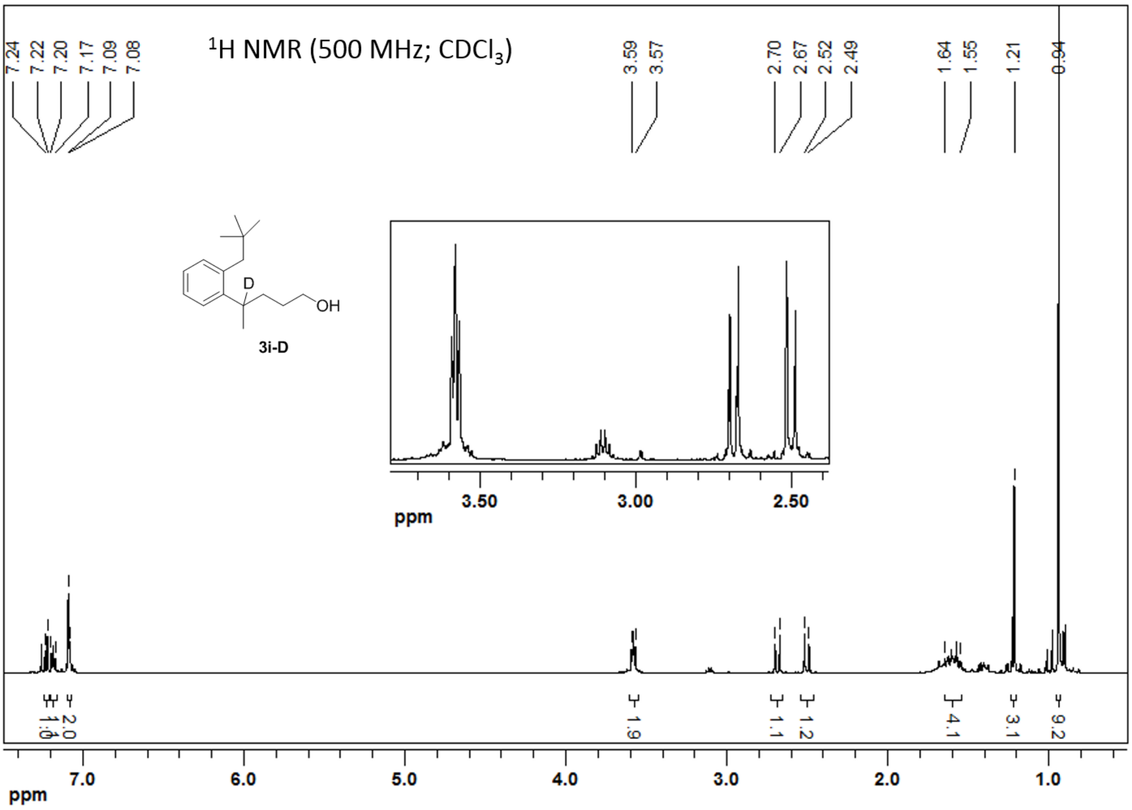

^{13}C NMR (125 MHz; $CDCl_3$)
145.5
145.4
138.7
130.5
130.5
126.2
125.4
125.4
125.1
63.1
40.4
40.3
36.6
36.5
34.4
34.3
34.3
34.2
31.1
31.0
29.6
29.4
22.6
22.4
19.1
19.0
11.6
D
OH
3h-D
ppm
150
100
50
0

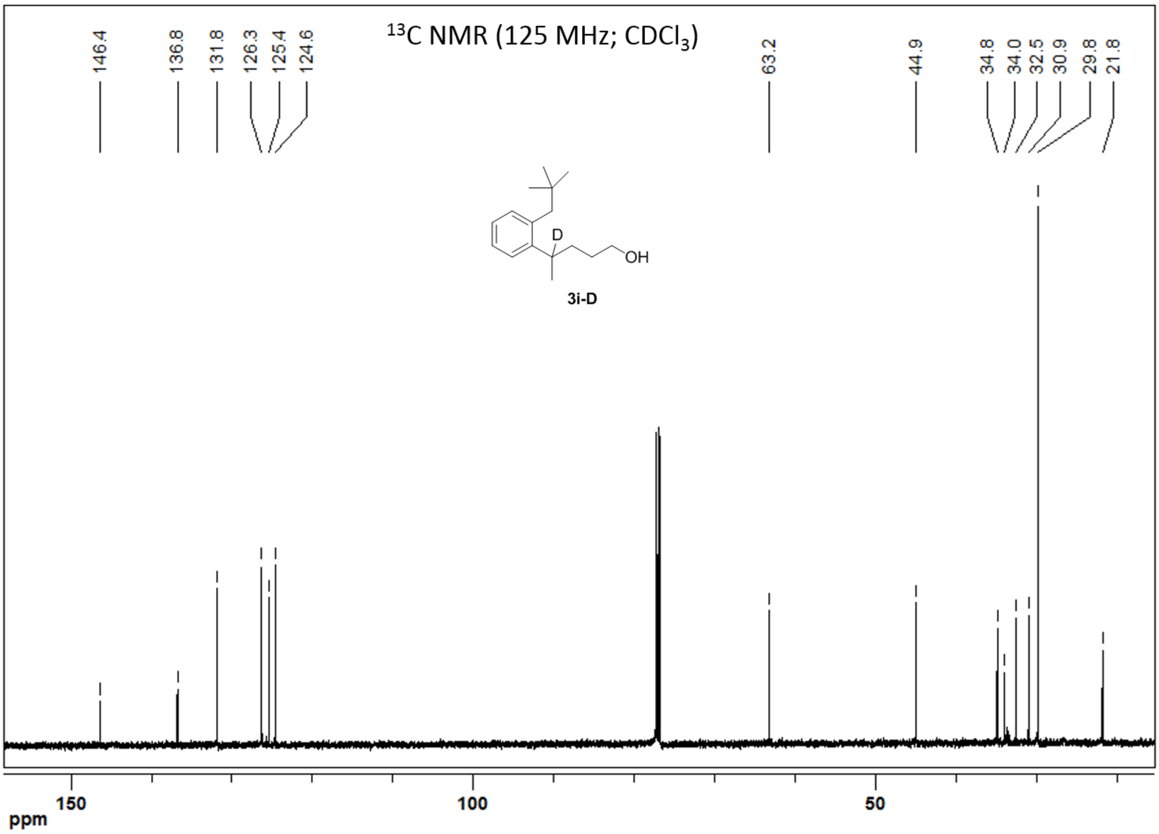


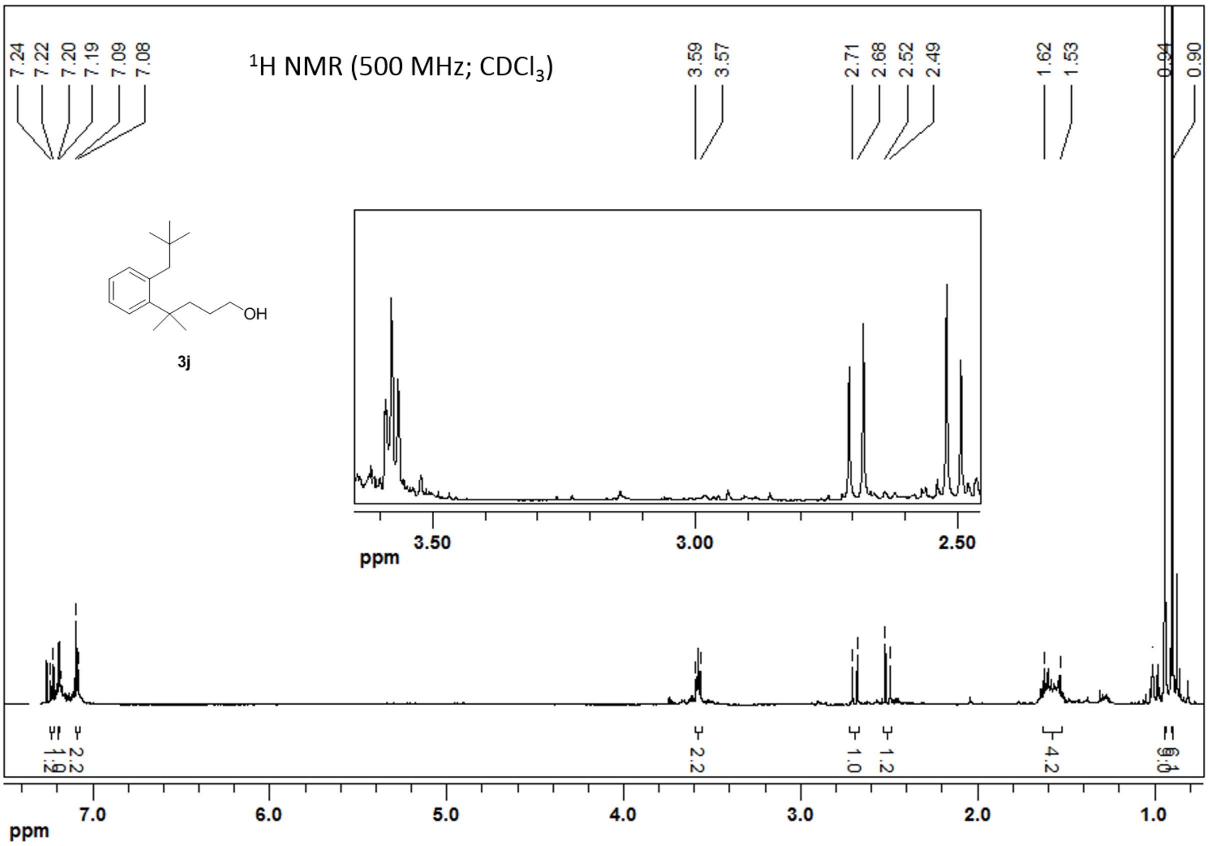
^{1}H NMR (400 MHz; CDCl$_3$)
3i-H
OH
7.26
7.16
7.09
7.08
3.60
3.58
3.57
3.15
3.07
2.71
2.67
2.52
2.49
1.65
1.54
1.23
1.21
0.94
2.1
2.0
2.0
1.0
1.0
1.0
4.1
3.1
8.9
3.50
3.00
2.50
ppm
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

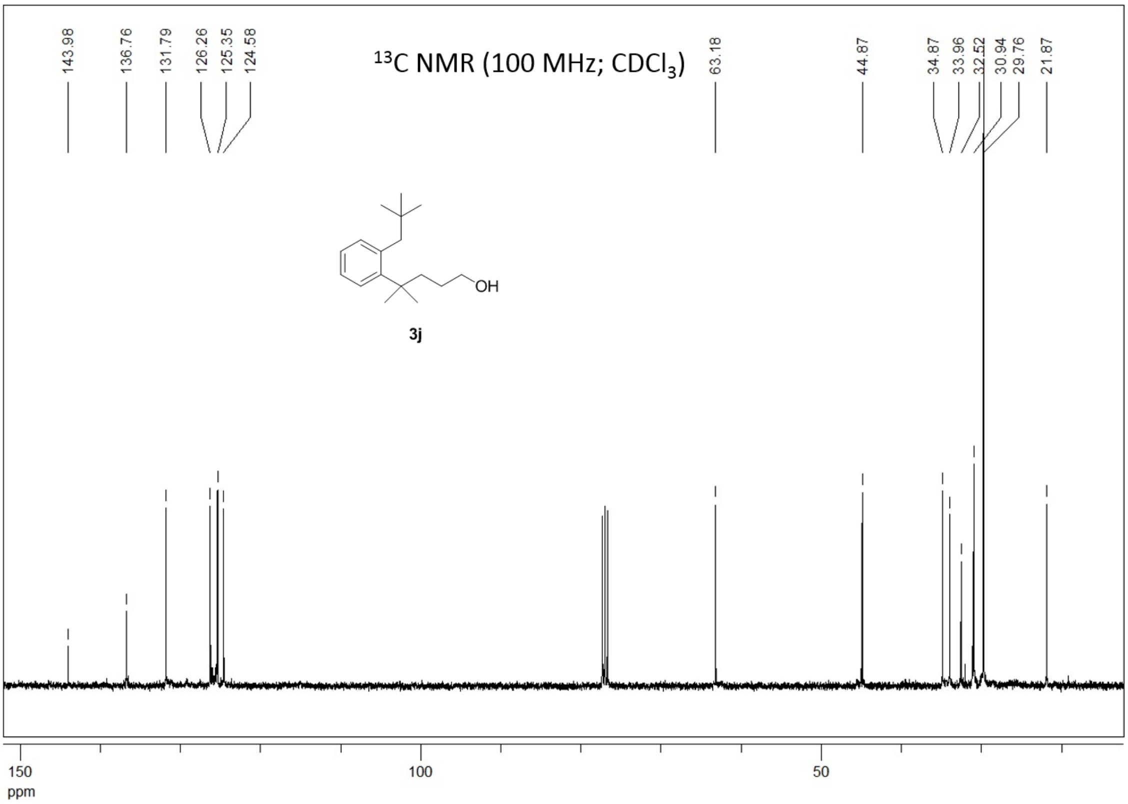


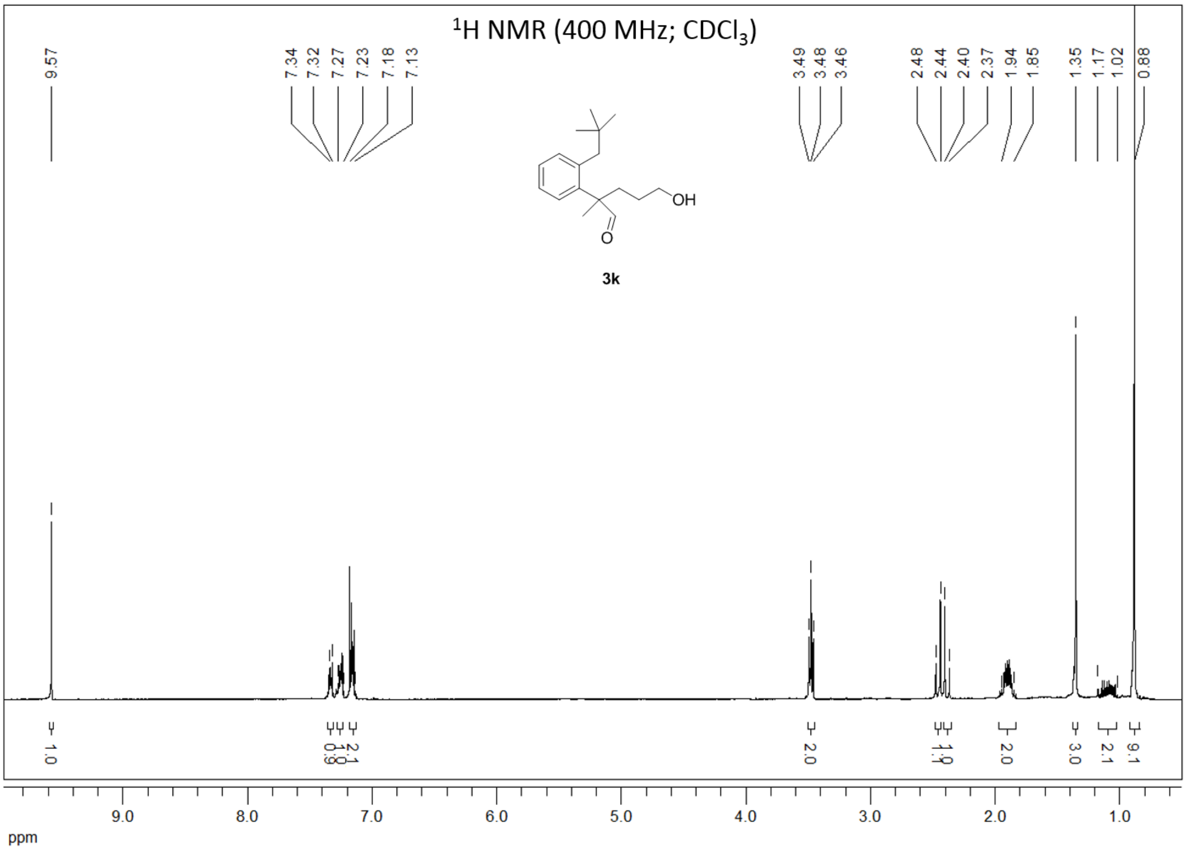
^{13}C NMR (125 MHz; CDCl$_3$)
3i-H
OH
146.46
136.82
131.85
126.32
125.41
124.64
63.27
44.93
34.91
34.01
32.57
31.01
29.80
21.91
150
100
50
ppm

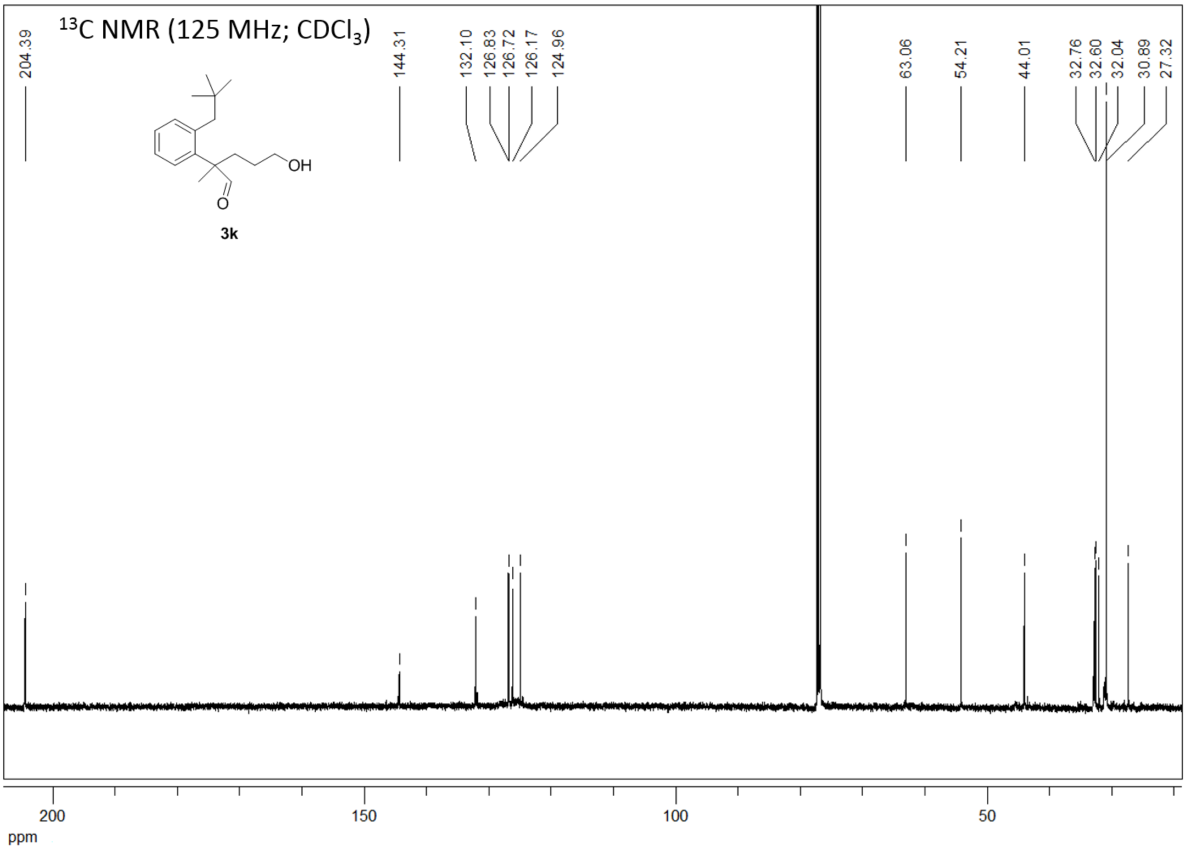

^{1}H NMR (500 MHz; CDCl$_3$)
7.24
7.22
7.20
7.17
7.09
7.08
3.59
3.57
2.70
2.67
2.52
2.49
1.64
1.55
1.21
0.94
D
OH
3i-D
3.50
3.00
2.50
ppm
1.0
2.0
1.9
1.1
1.2
4.1
3.1
9.2
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

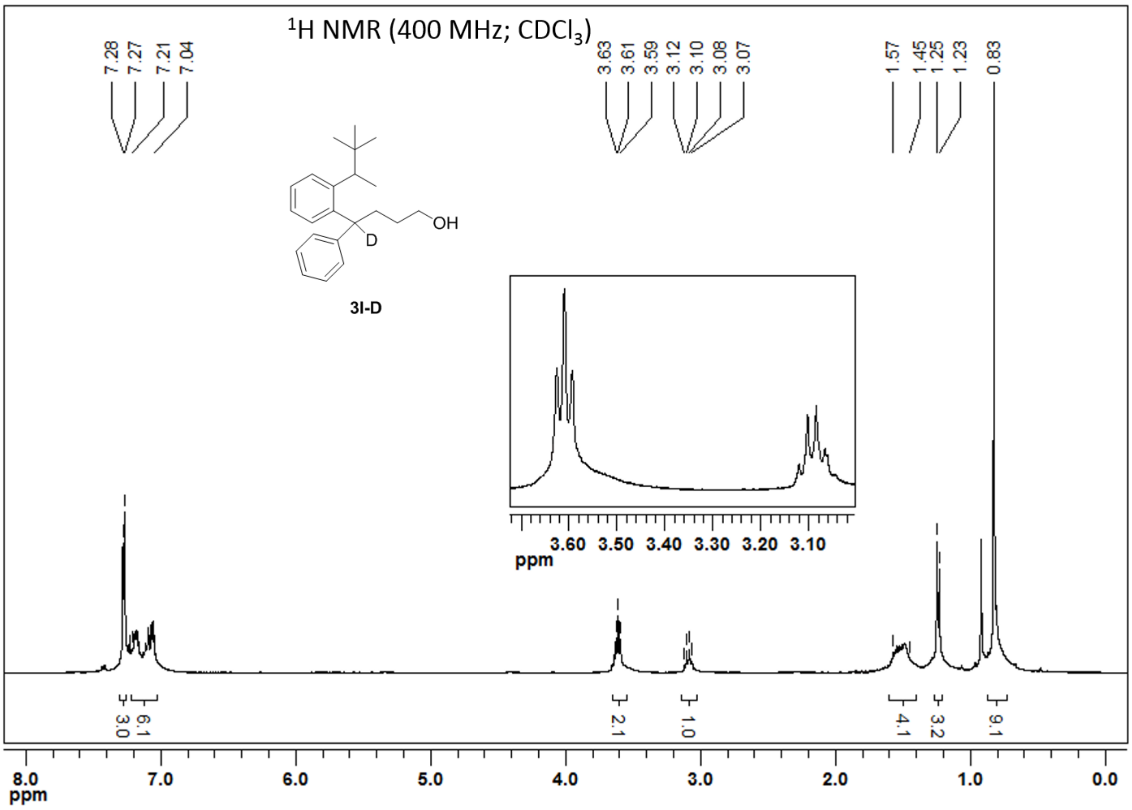

^{13}C NMR (125 MHz; CDCl$_3$)
146.4
136.8
131.8
126.3
125.4
124.6
63.2
44.9
34.8
34.0
32.5
30.9
29.8
21.8
D
OH
3i-D
150
100
50
ppm


^{1}H NMR (500 MHz; CDCl$_3$)
7.24
7.22
7.20
7.19
7.09
7.08
3.59
3.57
2.71
2.68
2.52
2.49
1.62
1.53
0.94
0.90
OH
3j
3.50
3.00
2.50
ppm
1.9
2.2
2.2
1.0
1.2
4.2
9.0
6.1
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

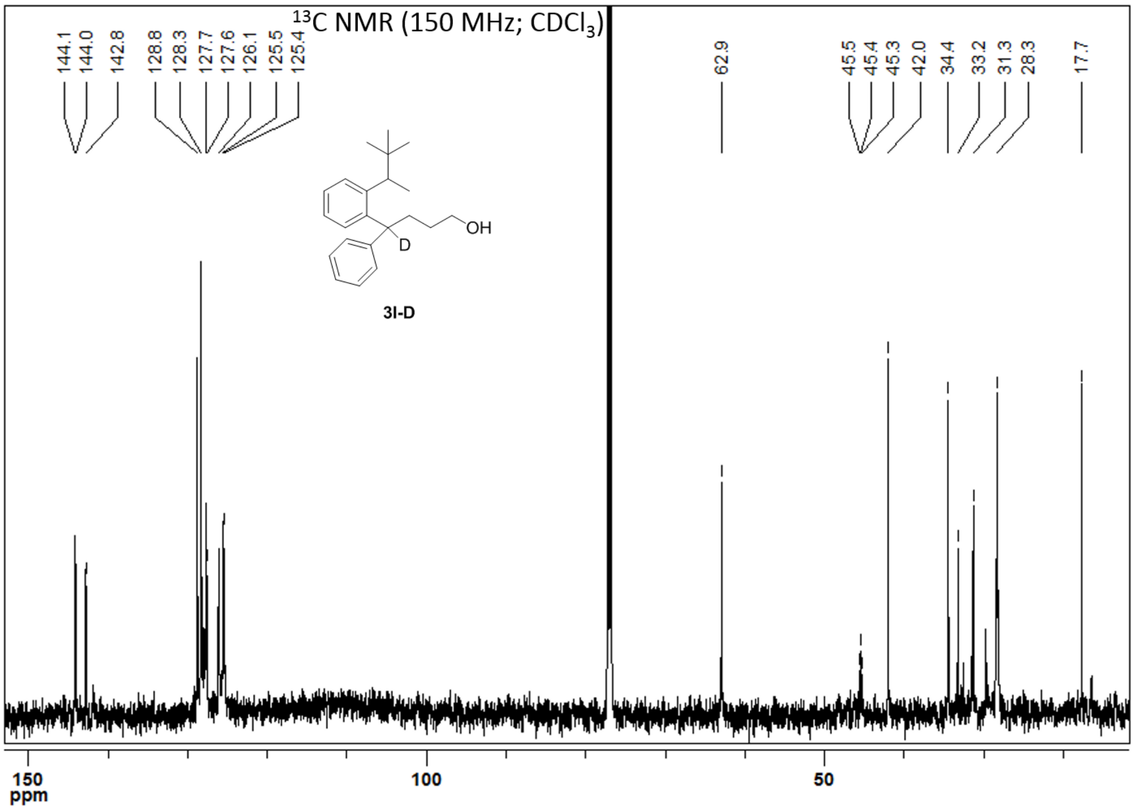

^{13}C NMR (100 MHz; CDCl$_3$)
143.98
136.76
131.79
126.26
125.35
124.58
63.18
44.87
34.87
33.96
32.52
30.94
29.76
21.87
OH
3j
150
100
50
ppm


^{1}H NMR (400 MHz; CDCl$_3$)
9.57
7.34
7.32
7.27
7.23
7.18
7.13
3.49
3.48
3.46
2.48
2.44
2.40
2.37
1.94
1.85
1.35
1.17
1.02
0.88
OH
O
3k
1.0
0.9
1.0
2.1
2.0
1.1
2.0
3.0
2.1
9.1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm


^{13}C NMR (125 MHz; CDCl$_3$)
204.39
144.31
132.10
126.83
126.72
126.17
124.96
63.06
54.21
44.01
32.76
32.60
32.04
30.89
27.32
OH
O
3k
200
150
100
50
ppm

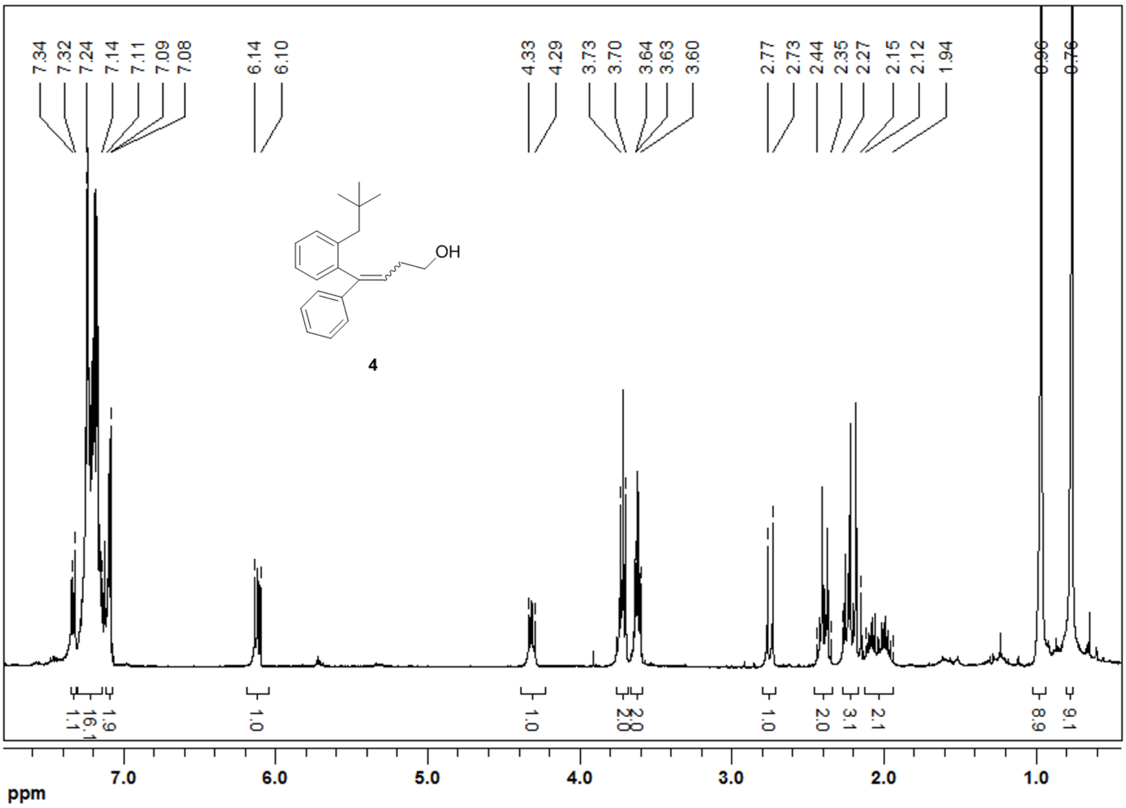


¹H NMR (400 MHz; CDCl₃)
7.28
7.27
7.21
7.04
3.63
3.61
3.59
3.12
3.10
3.08
3.07
1.57
1.45
1.25
1.23
0.83
OH
D
3l-D
3.60 3.50 3.40 3.30 3.20 3.10
ppm
3.0
6.1
2.1
1.0
4.1
3.2
9.1
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm

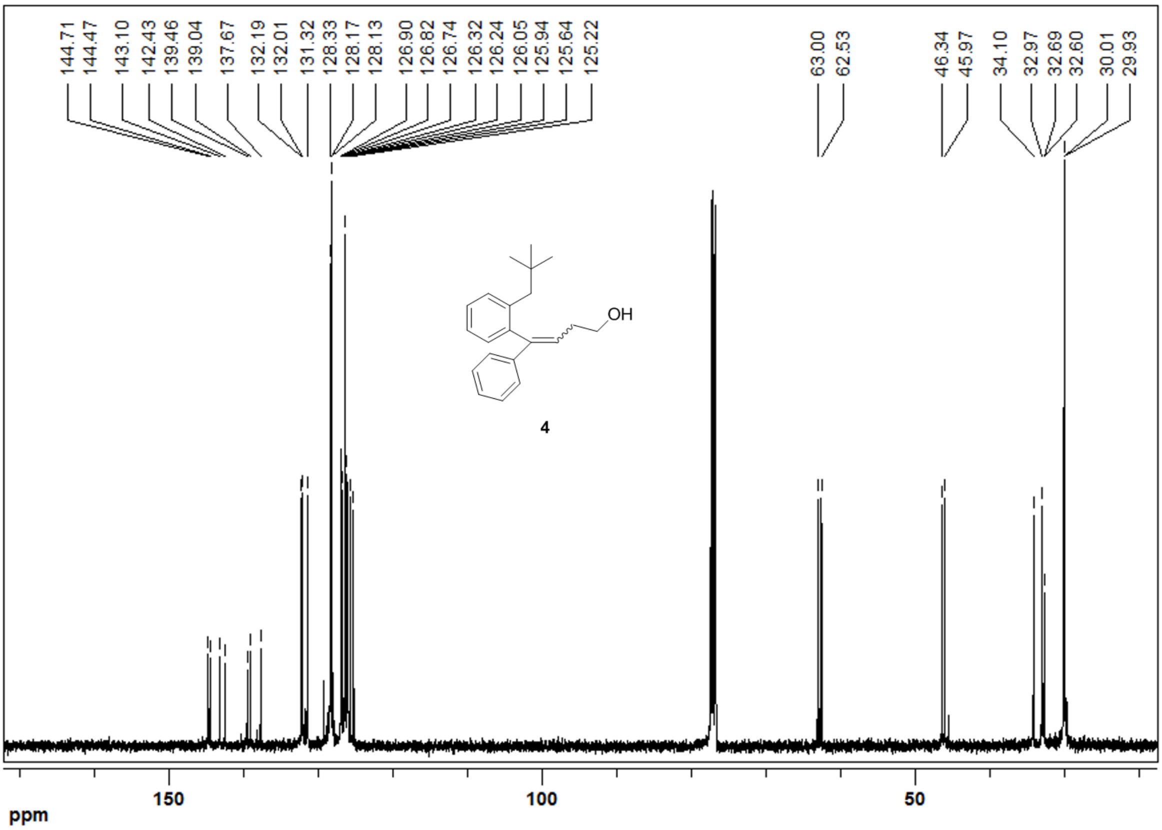


¹³C NMR (150 MHz; CDCl₃)
144.1
144.0
142.8
128.8
128.3
127.7
127.6
126.1
125.5
125.4
62.9
45.5
45.4
45.3
42.0
34.4
33.2
31.3
28.3
17.7
OH
D
3l-D
150
100
50
ppm

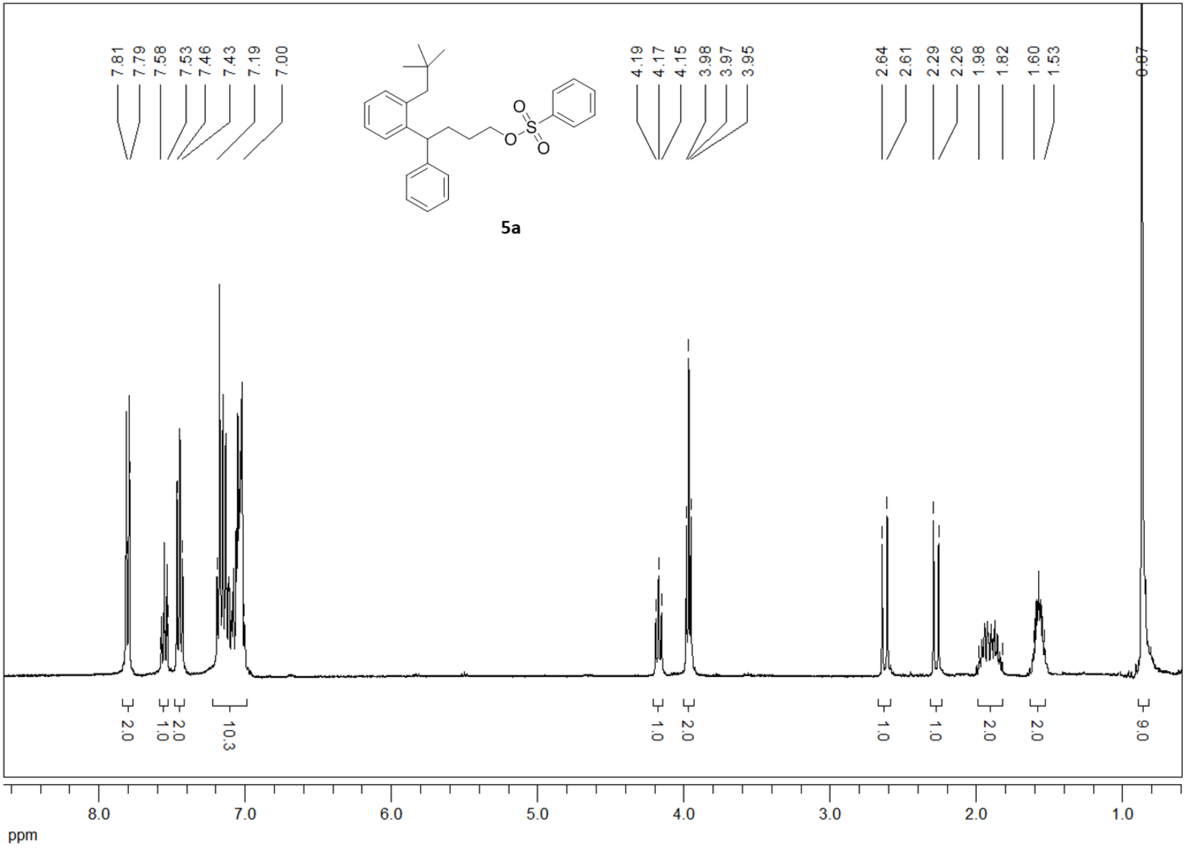
^{1}H NMR (400 MHz; $CDCl_3$)



^{13}C NMR (100 MHz; $CDCl_3$)



^{1}H NMR (400 MHz; $CDCl_3$)



^{13}C NMR (100 MHz; CDCl$_3$)