ELECTRONIC SUPPORTING INFORMATION

A Stereoselective Hydride Transfer Reaction With Contributions From Attractive Dispersion Force Control

D. Christopher Braddock,* Natnicha Limpaitoon, Krzysztof Oliwa, Daniel O'Reilly, Henry S. Rzepa* and Andrew J. P. White

Department of Chemistry, Imperial College London, Molecular Sciences Research Hub, White City Campus, London W12 0BZ, UK.

Email Address: c.braddock@imperial.ac.uk

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General Experimental

Reagents: Adamantanecarboxaldehyde was prepared by oxidation of adamantanemethanol.[1] All other reagents were purchased from commercial suppliers and used as received or prepared according to literature procedures.

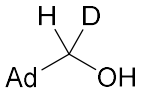
Solvents: Anhydrous tetrahydrofuran and dichloromethane were obtained from a purification column composed of activated alumina and were used directly. Diethyl ether, ethanol, ethyl acetate, methanol, and petroleum ether were used as received at HPLC grade. Petroleum ether refers to the 40 – 60 °C fraction.

Experimental techniques: Reactions involving ^{n}BuLi or acid chlorides were conducted in oven-dried glassware under an inert atmosphere of nitrogen, using dry solvents. Reaction temperatures other than room temperature were recorded as cooling bath temperatures. All volatiles and solvents were removed/concentrated *in vacuo* by rotary evaporation and/or on high vacuum. Kieselgel 60 F_{254} pre-coated aluminium-backed plates were used for analytical Thin Layer Chromatography and visualized either using UV light (254 nm) or by chemical staining with potassium permanganate. Flash column chromatography was performed using Geduran® silica gel, particle size 40-63 μm.

Characterisation: An Agilent Cary 630 FTIR spectrometer was used to obtain FT-IR spectra. ^{1}H NMR (400 MHz) spectra and ^{13}C NMR (100 MHz or 126 MHz) spectra were recorded in $CDCl_3$ or C_6D_6 at 298 K unless otherwise stated using the NMR facility at Imperial College London on either a Bruker DRX-400, Bruker AV-400, or Bruker AV-500. Chemical shifts (δ) are quoted in parts per million (ppm) and are downfield relative to tetramethylsilane ($SiMe_4$, δ = 0.00 ppm) and referenced to the residual solvent peak (δ 7.26 ppm for $CDCl_3$ and 7.16 for C_6D_6). Abbreviations used for multiplicity are as follows: s – singlet, d – doublet, t – triplet, m – multiplet. Specific rotation measurements were made using a Bellingham and Stanley ADP440+ Polarimeter, using 589 nm light, in chloroform or cyclopentane. Melting points were measured using a Stuart 20 melting point device and are uncorrected. Low resolution MS (CI and EI) and high resolution MS were recorded by the Imperial College Department of Chemistry Mass Spectrometry Service. X-Ray Crystallography studies were conducted on suitable single crystals, obtained by vapour diffusion using dichloromethane/methanol as solvent/anti-solvent, by the Imperial College Department of Chemistry X-Ray Crystallography Facility.

Experimental details and characterising data for new compounds.

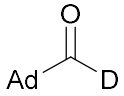
(±)-1-Adamantanemethanol-*d* [(±)-4-*d*]



(±)-**4**-*d*

To a solution of adamantanecarboxaldehyde (2.51 g, 15.0 mmol) in ethanol (70 mL) at 0 °C was added sodium borodeuteride (1.01 g, 24.0 mmol) in two portions. The solution was allowed to warm to room temperature and after 4 h additional sodium borodeuteride (0.304 g, 7.3 mmol) was added in a single portion. The reaction was allowed to stir for 16 h, quenched with water (30 mL) and aqueous HCl solution (1M, 30 mL). The resulting mixture was extracted with dichloromethane (4 x 150 mL), washed with water (2 x 300 mL), dried over magnesium sulphate, and the solvent removed *in vacuo* to yield alcohol (±)-**4**-*d* (2.40 g, 14 mmol, 94%, 96 atom % D) as a flaky white solid: R_f 0.09 (EtOAc : 40-60 petroleum ether, 1:9): m.p. 113.6 - 118.0 °C; ATIR 3400-3000, 2892, 2843, 2129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.18 (t, 1H, $^2J_{HD}$ = 1.4 Hz CDH), 2.02 - 1.95 (m, 3H, Ad-CH), 1.77 - 1.61 (m, 6H, Ad-CH_2), 1.53 – 1.48 (m, 6H, Ad-CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 73.4 (1:1:1 t, $^1J_{CD}$ = 22 Hz, CDH), 39.0 (Ad-CH_2), 37.1 (Ad-CH_2), 34.4 (Ad-C), 28.1 (Ad-CH); HRMS (CI^+) *m/z* calcd for $C_{11}H_{16}OD$ $(M - H)^+$ 166.1337 found 166.1334. D content was established by integration of CDHOH (3.18 ppm) vs CH_2OH (3.20 ppm) peaks in the ^1H NMR spectrum.

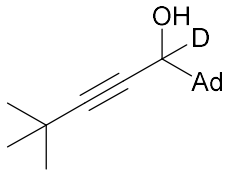
Adamantanecarboxaldehyde-*d* (2-*d*)



2-*d*

Using a modified method of Luzzio,[1] to a suspension of ground pyridinium chlorochromate (5.22 g, 24.0 mmol) and silica gel (5.26 g) in dichloromethane (30 mL) was added a solution of alcohol (±)-**4**-*d* (1.90 g, 11.0 mmol) in dichloromethane (26 mL). The mixture was stirred for 16 h, and the resulting black solution was diluted with diethyl ether (130 mL), filtered through a combined pad of silica (3 cm, top) and celite (1 cm, bottom). The resulting yellow solution was washed successively with aqueous sodium hydroxide solution (1M, 100 mL), water (200 mL) and brine (100 mL), dried over magnesium sulphate and concentrated *in vacuo* to yield aldehyde **2**-*d* (1.53 g, 9.3 mmol, 81%, 91 atom % D) as a white solid: R_f 0.45 (EtOAc : 40-60 petroleum ether, 1:9): m.p. 204.3 - 208.8 °C; ATIR 2899, 2847, 2080, 2031, 1709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 – 2.03 (m, 3H, Ad-CH), 1.82 - 1.65 (m, 12H, Ad-CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.6 (1:1:1 t, $^1J_{CD}$ = 26 Hz, CDO), 44.7 (1:1:1 t, $^2J_{CD}$ = 3.1 Hz, Ad-C), 36.5 (Ad-CH_2), 35.8 (Ad-CH_2), 27.3 (Ad-CH); HRMS (CI^+) *m/z* calcd for $C_{11}H_{16}OD$ $(M + H)^+$ 166.1337 found 166.1335. D content was established by integration of CDO (205.90, 205.64, 205.39 ppm) vs CHO (205.94 ppm) peaks in the inverse-gated ^{13}C NMR spectrum (d_1 = 150 s).

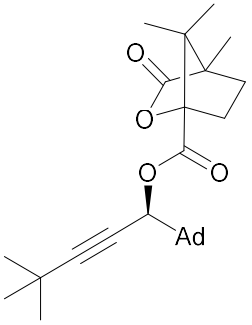
(±)-1-Adamantan-1-yl-4,4-dimethylpent-2-yn-1-*d*-1-ol [(±)-5-*d*]



(±)-**5**-*d*

Following the reported procedure of Braddock,[2] to a solution of alkyne **1** (2.0 mL, 16.0 mmol) in tetrahydrofuran (10 mL) at -78 °C was added *n*-BuLi (2.5 mL, 2.5 M, 6.3 mmol) dropwise. After 45 minutes, the mixture was allowed to warm 0 °C for 45 minutes, and subsequently recooled to -78°C and stirred for 45 minutes. Aldehyde **2**-*d* (1.13 g, 6.8 mmol) in tetrahydrofuran (10 mL) was added dropwise to the mixture, a colour change from colourless to dark red was observed, and the reaction mixture was allowed to warm to room temperature over 20 h. The reaction was quenched with saturated aqueous ammonium chloride solution (25 mL), extracted with diethyl ether (2 x 25 mL), washed with brine (3 x 60 mL), dried over magnesium sulphate, and the solvent was removed *in vacuo*. The resulting brown solid was purified by flash column chromatography (EtOAc : 40-60 petroleum ether, 1:9) to give propargyl alcohol (±)-**5**-*d* (0.342 g, 1.4 mmol, 22%, 82 atom % D) as a pale brown solid: R_f 0.28 (EtOAc : 40-60 petroleum ether, 1:9): m.p. 88.7 – 91.5 °C; ATIR 3450-3050, 2969, 2895, 2848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 – 1.97 (m, 3H, Ad-C<u>H</u>), 1.75 – 1.51 (m, 12H, Ad-C<u>H</u>$_2$), 1.23 (s, 9H, ^{t}Bu-C<u>H</u>$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 93.9 (<u>C</u>≡C), 76.3 (<u>C</u>≡C), 70.1 (1:1:1 t, $^1J_{CD}$ = 22 Hz, <u>C</u>D), 36.6 (Ad-<u>C</u>H$_2$), 36.2 (Ad-<u>C</u>), 36.0 (Ad-CH$_2$), 30.0 (^{t}Bu-<u>C</u>H$_3$), 27.2 (Ad-<u>C</u>H), 26.3 (^{t}Bu-<u>C</u>); HRMS (CI$^+$) *m/z* calcd for $C_{17}H_{24}D$ (M - OH)$^+$ 230.2014 found 230.2009. D content was established by integration of <u>C</u>DOH vs <u>C</u>HOH peaks in the inverse-gated ^{13}C NMR spectrum (d_1 = 40 s).

(*S*)-1-Adamantan-1-yl-4,4-dimethylpent-2-yn-1-yl (*1S*)-camphanoate (7)

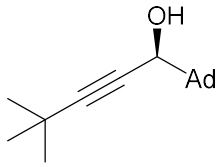


7

Following a modified procedure of Litosh,[3] to a solution of alcohol (±)-**5** (3.12 g, 13.0 mmol) and 4-dimethylaminopyridine (1.90 g, 16.0 mmol) in dichloromethane (90 mL) was added (1*S*)-(-)-camphanic chloride (3.42 g, 16.0 mmol). The mixture was stirred for 16 h, diluted with diethyl ether (200 mL) and filtered. The filtrate was washed successively with saturated aqueous sodium hydrogen carbonate solution (200 mL), water (200 mL), and brine (200 mL), dried over magnesium sulphate and the solvent was removed *in vacuo* to yield a 1:1 mixture of esters **6** and **7** (4.84 g, 11 mmol, 90%) as a white solid.

Characteristic singlets (for C≡C-C<u>H</u>OH) of equal integration were observed in the ^{1}H NMR spectrum at 5.00 and 5.02 ppm for these two diastereoisomers respectively. The mixture was recrystallised twice from boiling methanol to yield pure ester **7** (0.860 g, 2.0 mmol, 16%) as a white solid: R_f 0.19 (EtOAc : 40-60 petroleum ether, 1:9): m.p. 160.1 – 163.8 °C; $[\alpha]_D^{25}$ -45.3 (*c* 0.59, chloroform); ATIR 2987, 2922, 2892, 2848, 2244, 1782, 1755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 1H), 2.48 – 2.39 (m, 2H), 2.10 – 1.90 (m, 5H), 1.76 – 1.56 (m, 15H, Ad), 1.20 (s, 9H, ^{t}Bu), 1.11 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1, 166.5, 95.9, 91.1, 73.6, 73.5, 54.8, 54.5, 38.0, 36.9, 36.5, 30.9, 30.4, 29.2, 28.1, 27.5, 17.0, 16.6, 9.7; HRMS (CI^+) *m/z* calcd for $C_{15}H_{25}$ (M-camphanoate)$^+$ 229.1951 found 229.1950. *Crystal data for* **7**: $C_{27}H_{38}O_4$, M = 426.57, orthorhombic, $P2_12_12_1$ (no. 19), a = 10.1782(2), b = 12.5203(3), c = 19.0389(5) Å, V = 2426.21(10) Å^3, Z = 4, D_c = 1.168 g cm^{-3}, μ(Mo-Kα) = 0.077 mm^{-1}, T = 173 K, colourless blocks, Agilent Xcalibur 3 E diffractometer; 5467 independent measured reflections (R_{int} = 0.0462), F^2 refinement,[4,5] R_1(obs) = 0.0384, wR_2(all) = 0.0846, 4792 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, completeness to θ_{full}(25.2°) = 99.9%], 287 parameters. The absolute structure of **7** could not be determined by use of the Flack parameter [x = +0.3(4)] and so was set based on the known *S* stereochemistry at C6. CCDC 2151865.

(*S*)-1-Adamantan-1-yl-4,4-dimethylpent-2-yn-1-ol [(*S*)-5]



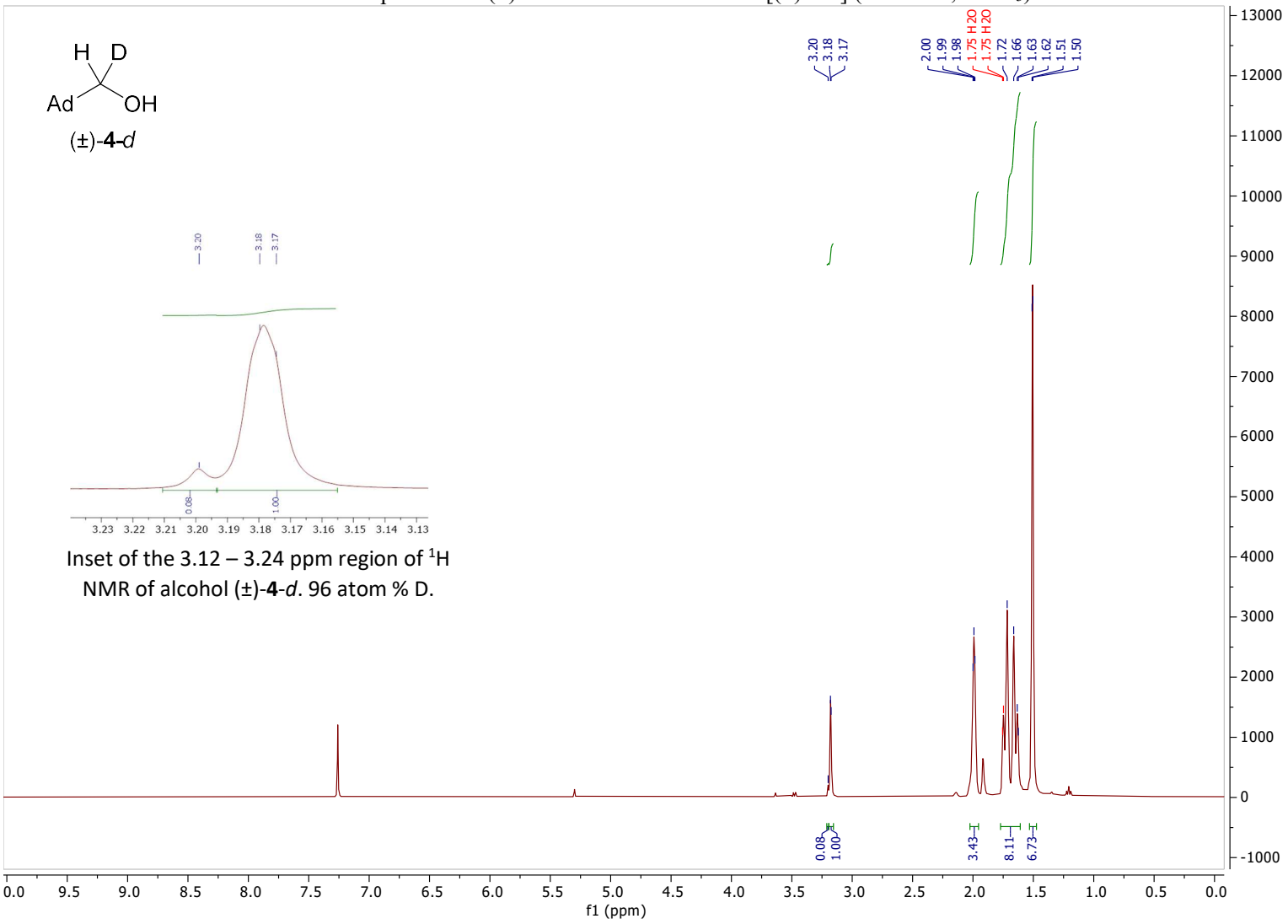
(*S*)-**5**

Following the modified procedure of Litosh,[3] a solution of ester **7** (0.860 g, 2.0 mmol) in methanol (36 mL) was heated to reflux and potassium carbonate (0.426 g, 3.1 mmol) was added. The mixture was kept at reflux for 1h and allowed to cool to room temperature, diluted with diethyl ether (65 mL), washed with water, dried over anhydrous magnesium sulphate and solvent was removed *in vacuo* to yield alcohol (*S*)-**5** (0.266 g, 1.1 mmol, 54%), as a white solid, with identical spectra to the known racemate:[1] $[\alpha]_D^{25}$ -1.62 (*c* 1.14, chloroform), containing *ca.* 15% of methyl (1*S*)-camphanoate ester.

Hydride transfer reaction of alcohol (*S*)-5 with AdCDO 2-*d* (*c.f.*, Scheme 3 in main manuscript).

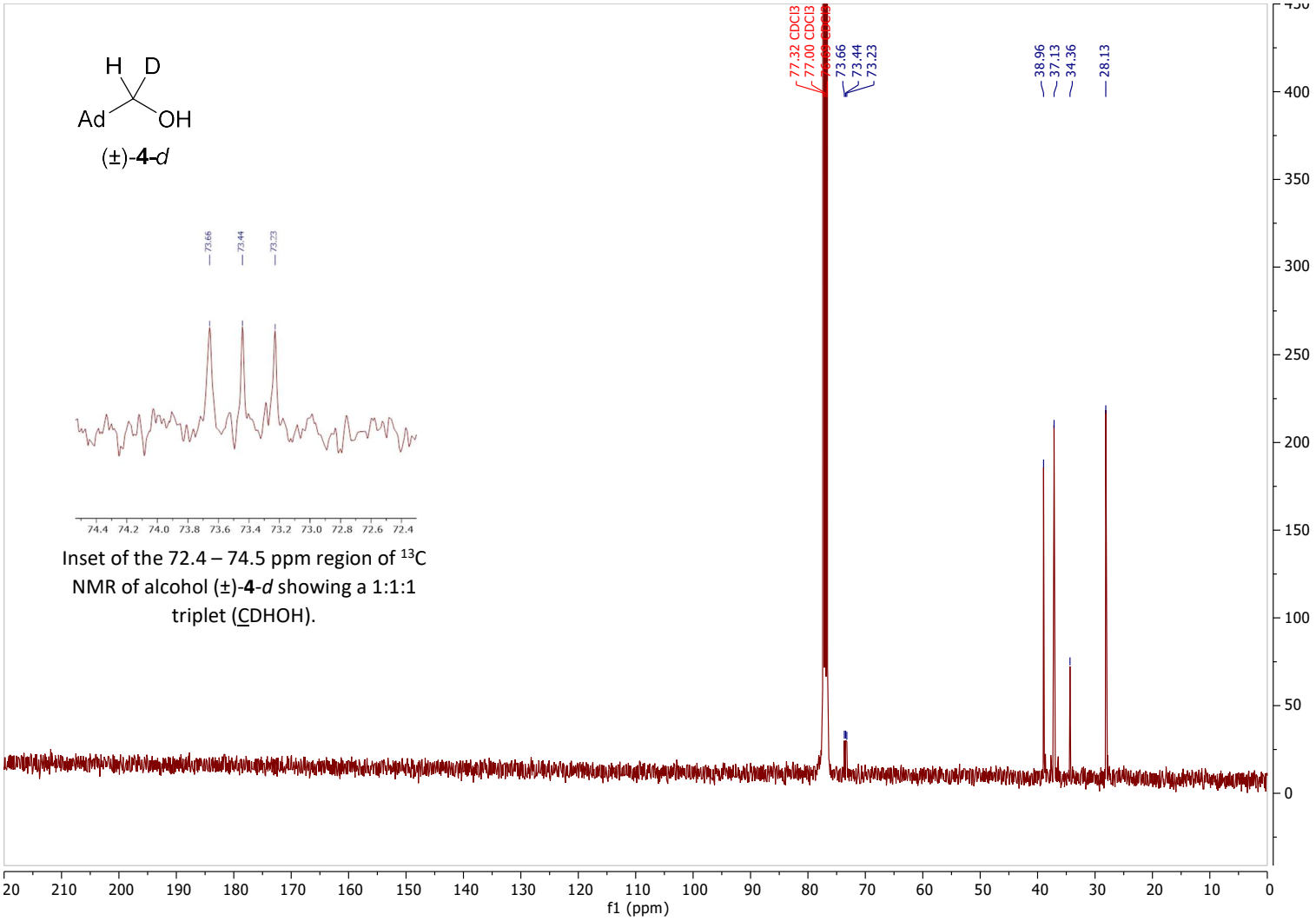
To a solution of alcohol (*S*)-**5** (0.201 g, 0.816 mmol) in THF (1 mL) at 0°C was added ^{n}BuLi (2.5 M, 0.35 mL, 0.875 mmol) and the solution was brough up to reflux. Aldehyde **2**-*d* (0.130 g, 0.78 mmol) in THF (2 mL) was added over 1.5 h and the solution was kept at reflux for a further 45 min, cooled to room temperature and quenched with saturated ammonium chloride solution (3 mL), extracted with diethyl ether (2 x 15 mL), washed with water (20 mL), brine (20 mL), dried over magnesium sulphate and the solvent was removed *in vacuo*. The crude solid purified by flash column chromatography (EtOAc : 40-60 petroleum ether, 15:85) to give alcohol **4**-*d* (55 mg, 0.33 mmol, 49%, 78 atom % D): $[\alpha]_D^{25}$ -1.39 (*c* 1.09, cyclopentane); -2.41 (*c* 1.87, chloroform) and recovered alcohol (*S*)-**5**.

^{1}H NMR spectrum of (±)-1-adamantanemethanol-*d* [(±)-**4**-*d*] (400 MHz, $CDCl_3$)



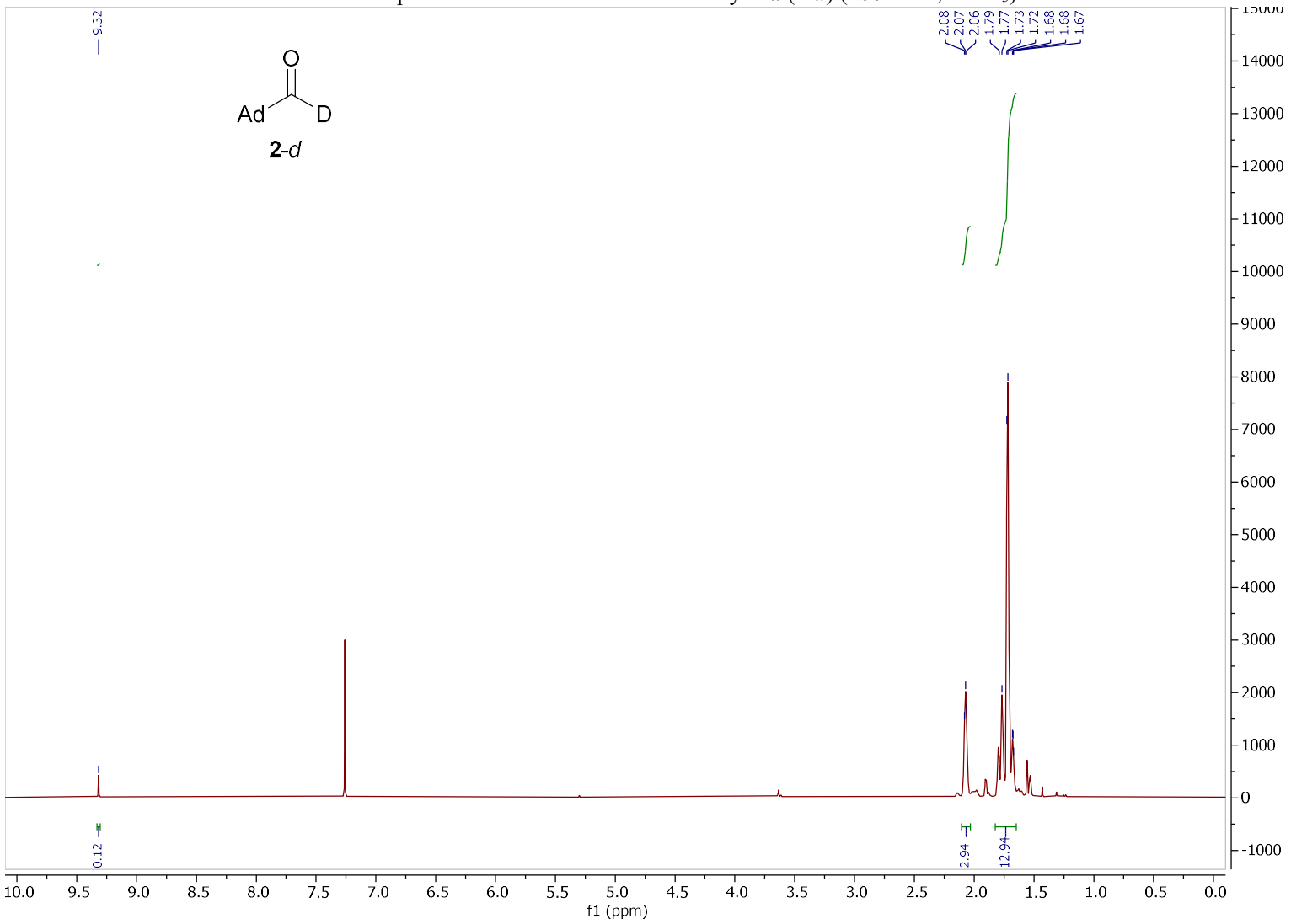
Inset of the 3.12 – 3.24 ppm region of ^{1}H NMR of alcohol (±)-**4**-*d*. 96 atom % D.

^{13}C NMR spectrum of (±)-1-adamantanemethanol-*d* [(±)-**4**-*d*] (100 MHz, $CDCl_3$)

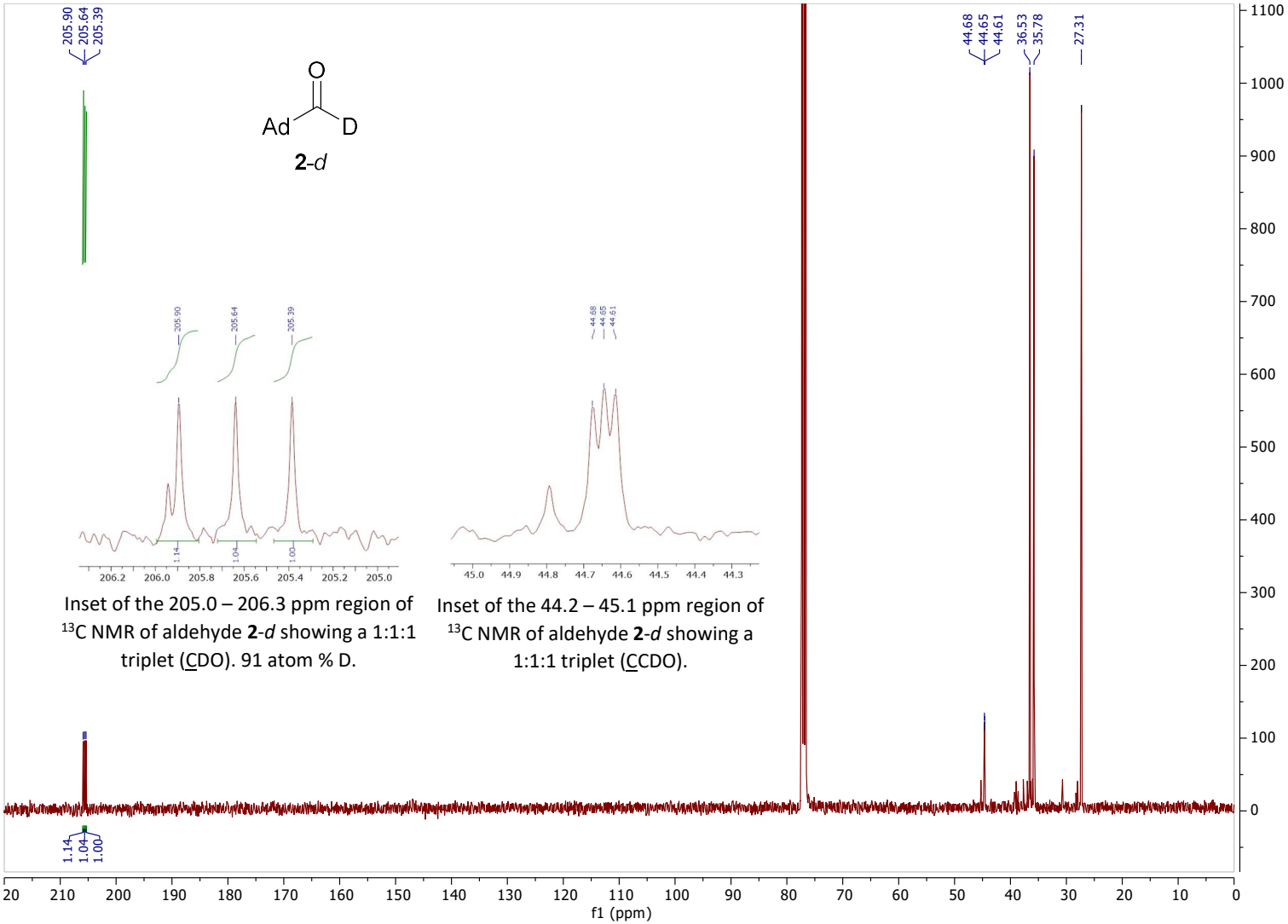


Inset of the 72.4 – 74.5 ppm region of ^{13}C NMR of alcohol (±)-**4**-*d* showing a 1:1:1 triplet (CDHOH).

^{1}H NMR spectrum of adamantanecarboxaldehyde-*d* (**2**-*d*) (400 MHz, $CDCl_3$)



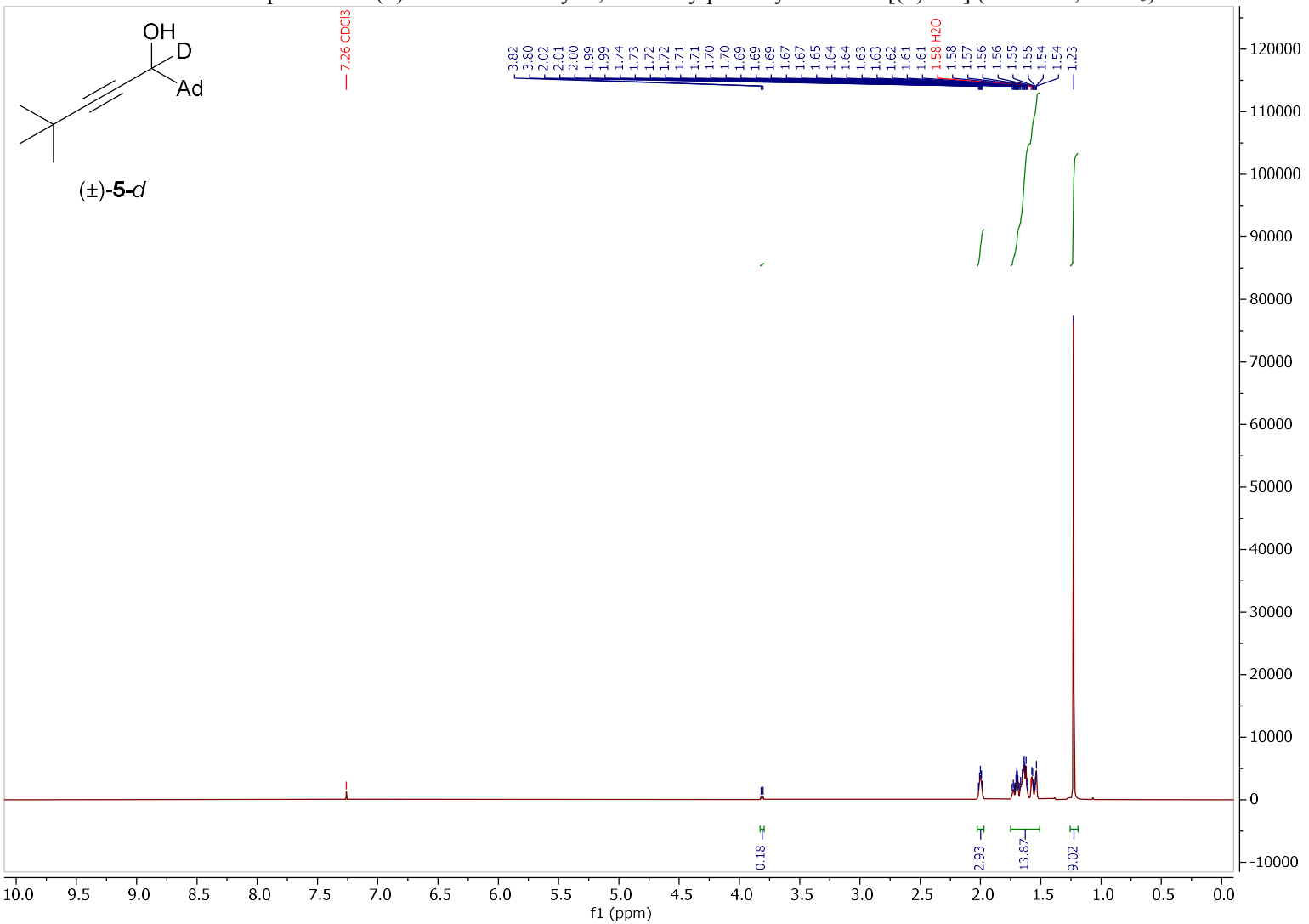
Inverse-gated ^{13}C NMR spectrum of adamantanecarboxaldehyde-*d* (**2**-*d*) (100 MHz, $CDCl_3$)



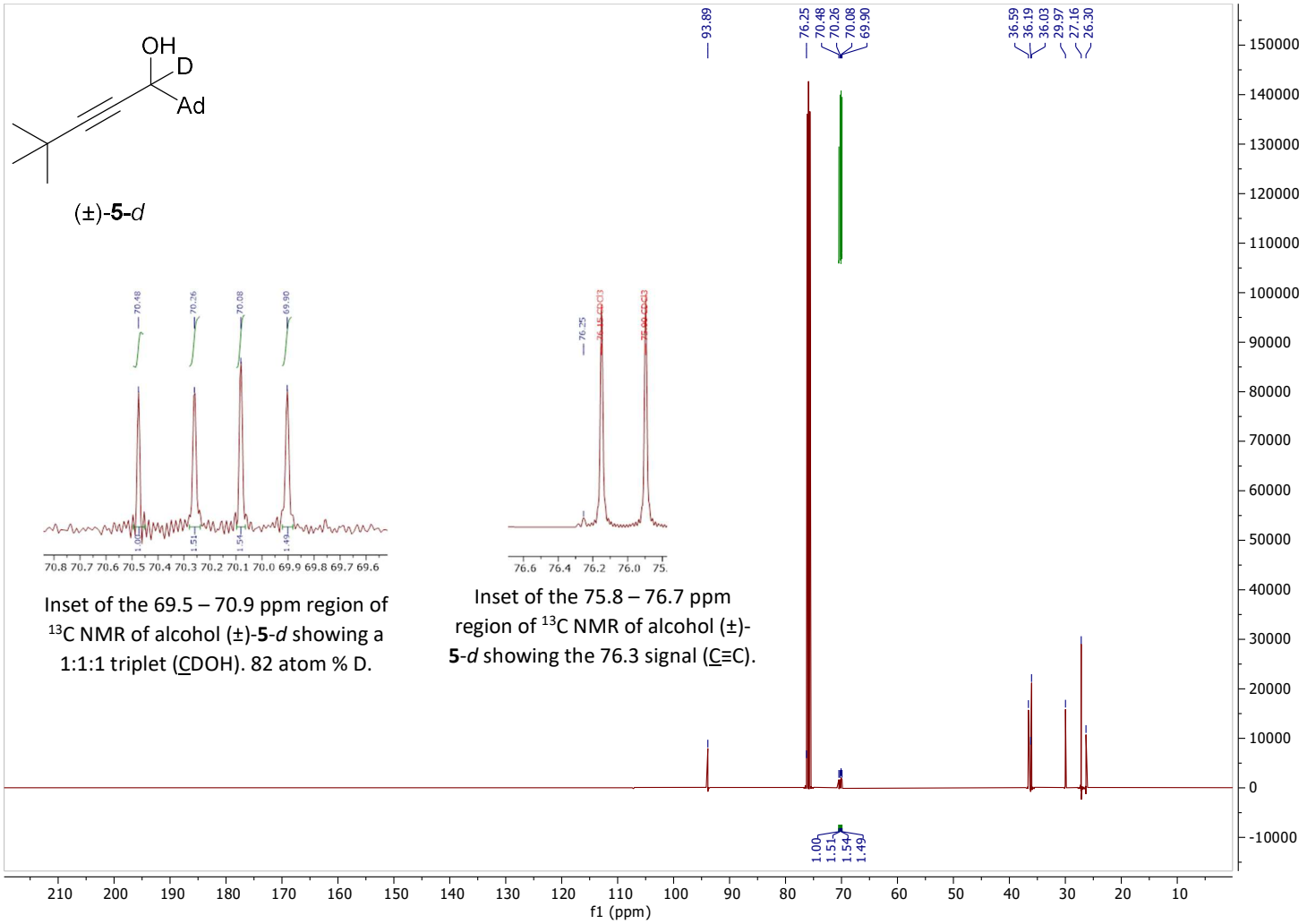
Inset of the 205.0 – 206.3 ppm region of ^{13}C NMR of aldehyde **2**-*d* showing a 1:1:1 triplet (CDO). 91 atom % D.

Inset of the 44.2 – 45.1 ppm region of ^{13}C NMR of aldehyde **2**-*d* showing a 1:1:1 triplet (CCDO).

^{1}H NMR spectrum of (±)-1-adamantan-1-yl-4,4-dimethylpent-2-yn-1-*d*-1-ol [(±)-**5**-*d*] (400 MHz, $CDCl_3$)



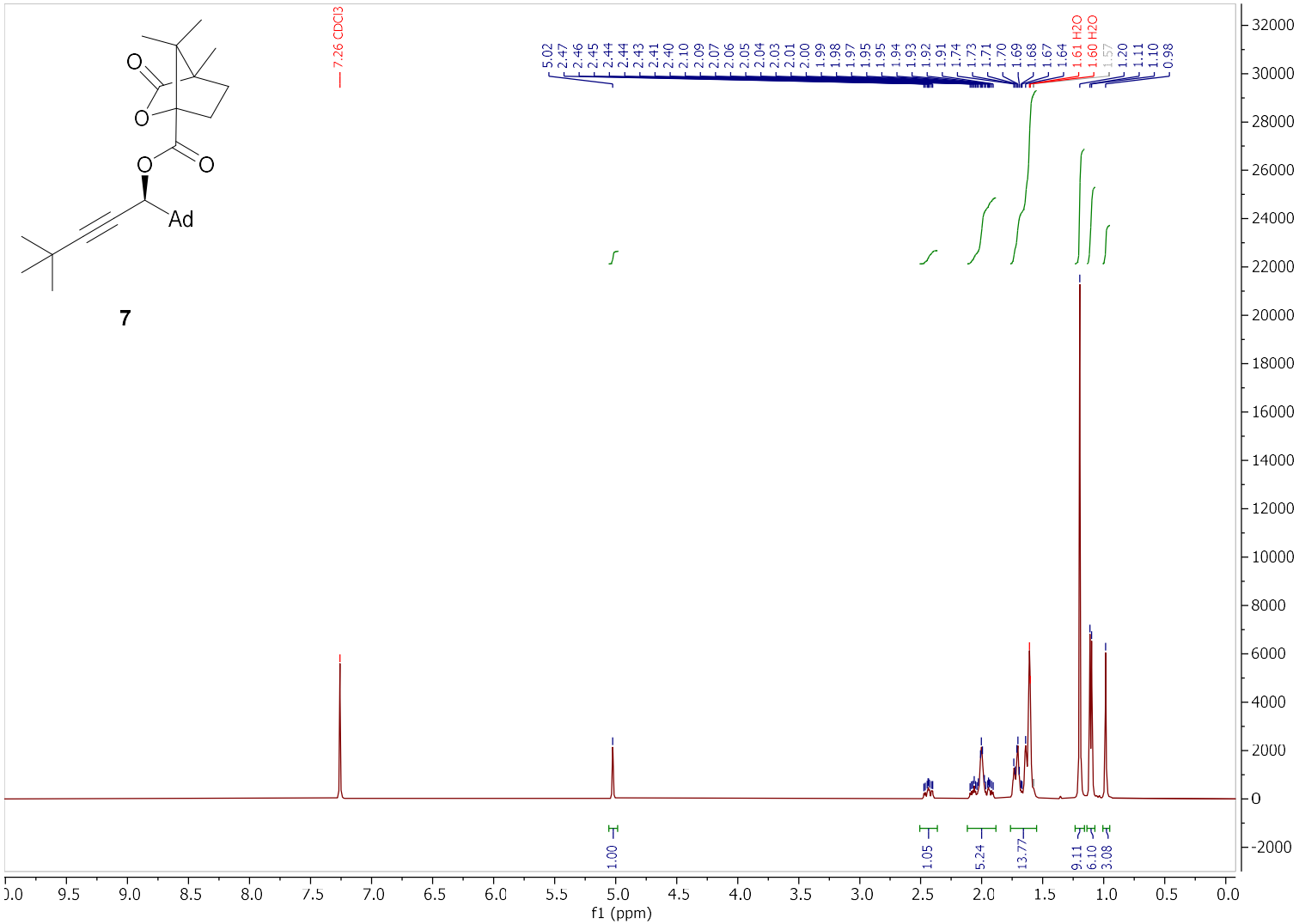
Inverse-gated ^{13}C NMR spectrum of (±)-1-adamantan-1-yl-4,4-dimethylpent-2-yn-1-*d*-1-ol [(±)-**5**-*d*] (126 MHz, $CDCl_3$)



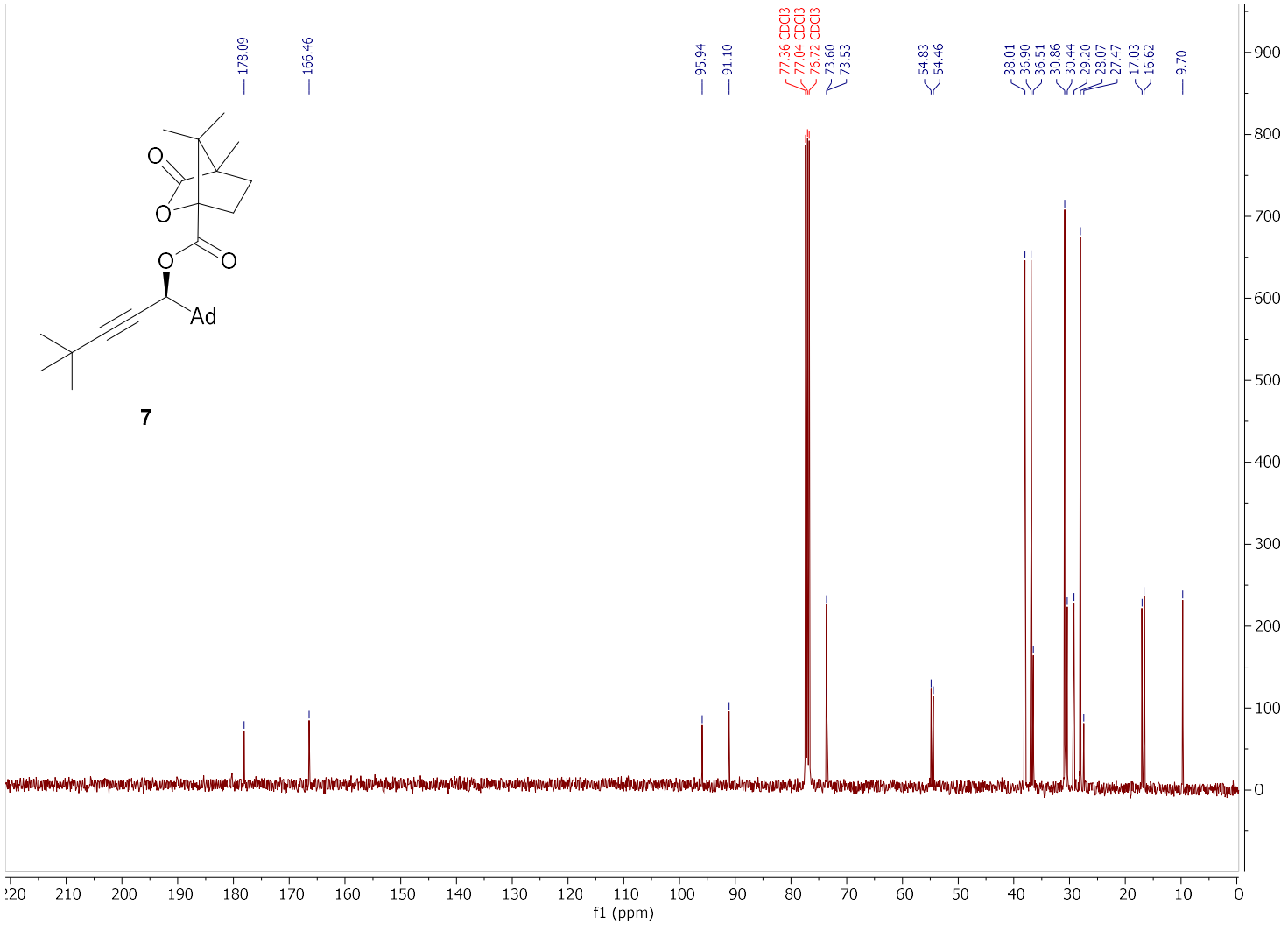
Inset of the 69.5 – 70.9 ppm region of ^{13}C NMR of alcohol (±)-**5**-*d* showing a 1:1:1 triplet (CDOH). 82 atom % D.

Inset of the 75.8 – 76.7 ppm region of ^{13}C NMR of alcohol (±)-**5**-*d* showing the 76.3 signal (C≡C).

^{1}H NMR spectrum of (*S*)-1-adamantan-1-yl-4,4- dimethylpent-2-yn-1-yl (*1S*)-camphanoate (**7**) (400 MHz, $CDCl_3$)

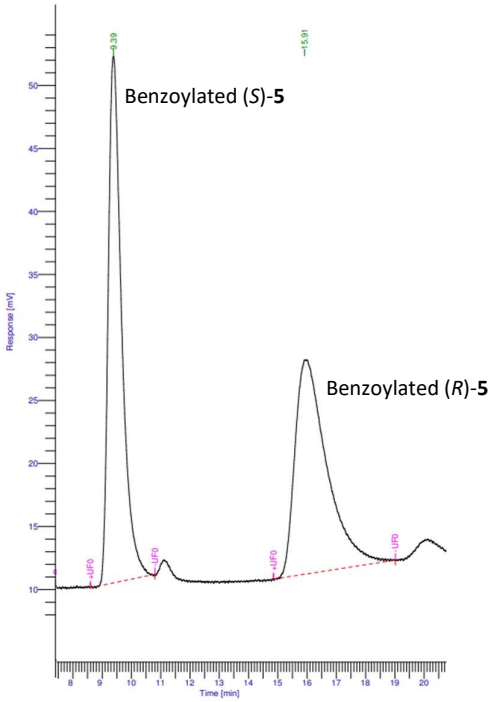


^{13}C NMR spectrum of (*S*)-1-adamantan-1-yl-4,4-dimethylpent-2-yn-1-yl (*1S*)-camphanoate (**7**) (100 MHz, $CDCl_3$)



HPLC chromatogram of benzoylated alcohol (±)-**5**

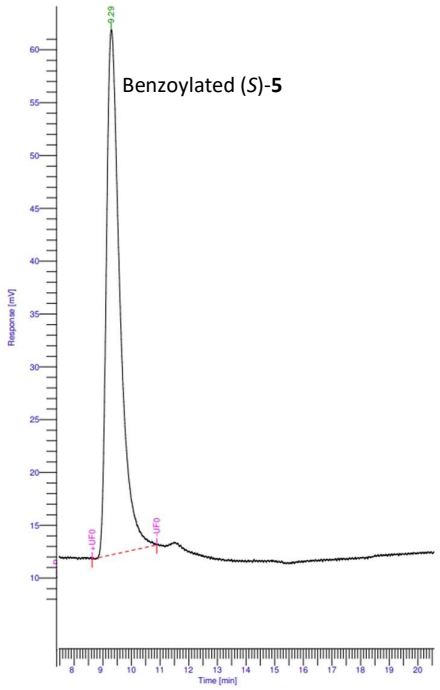
CHIRALPAK AD; 100% n-hexane; 1.0 mL/min) t_R = 9.4 min, 15.9 min – 51:49 e.r. (~0% ee)



Peak #	Time [min]	Area [µV·s]	Height [µV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
1	9.387	1385237.45	43570.26	50.82	50.82	*MM	31.7932
2	15.913	1340278.52	17733.21	49.18	49.18	*MM	75.5801
		2725515.97	61303.47	100.00	100.00		

HPLC chromatogram of benzoylated alcohol (*S*)-**5**

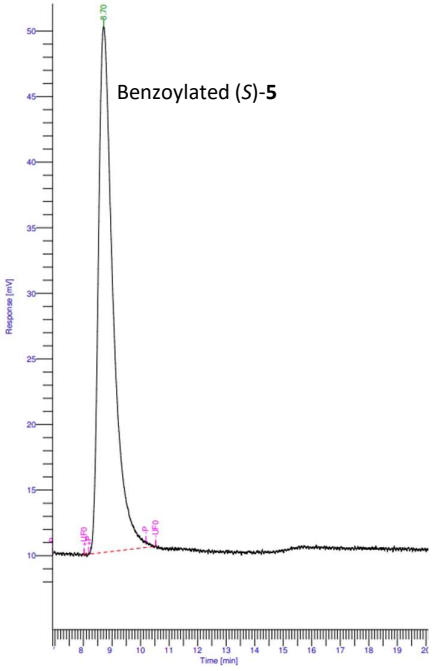
CHIRALPAK AD; 100% n-hexane; 1.0 mL/min) t_R = 9.3 min, – 100% ee



Peak #	Time [min]	Area [µV·s]	Height [µV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
1	9.291	1644991.52	49789.11	100.00	100.00	*MM	33.0392
		1644991.52	49789.11	100.00	100.00		

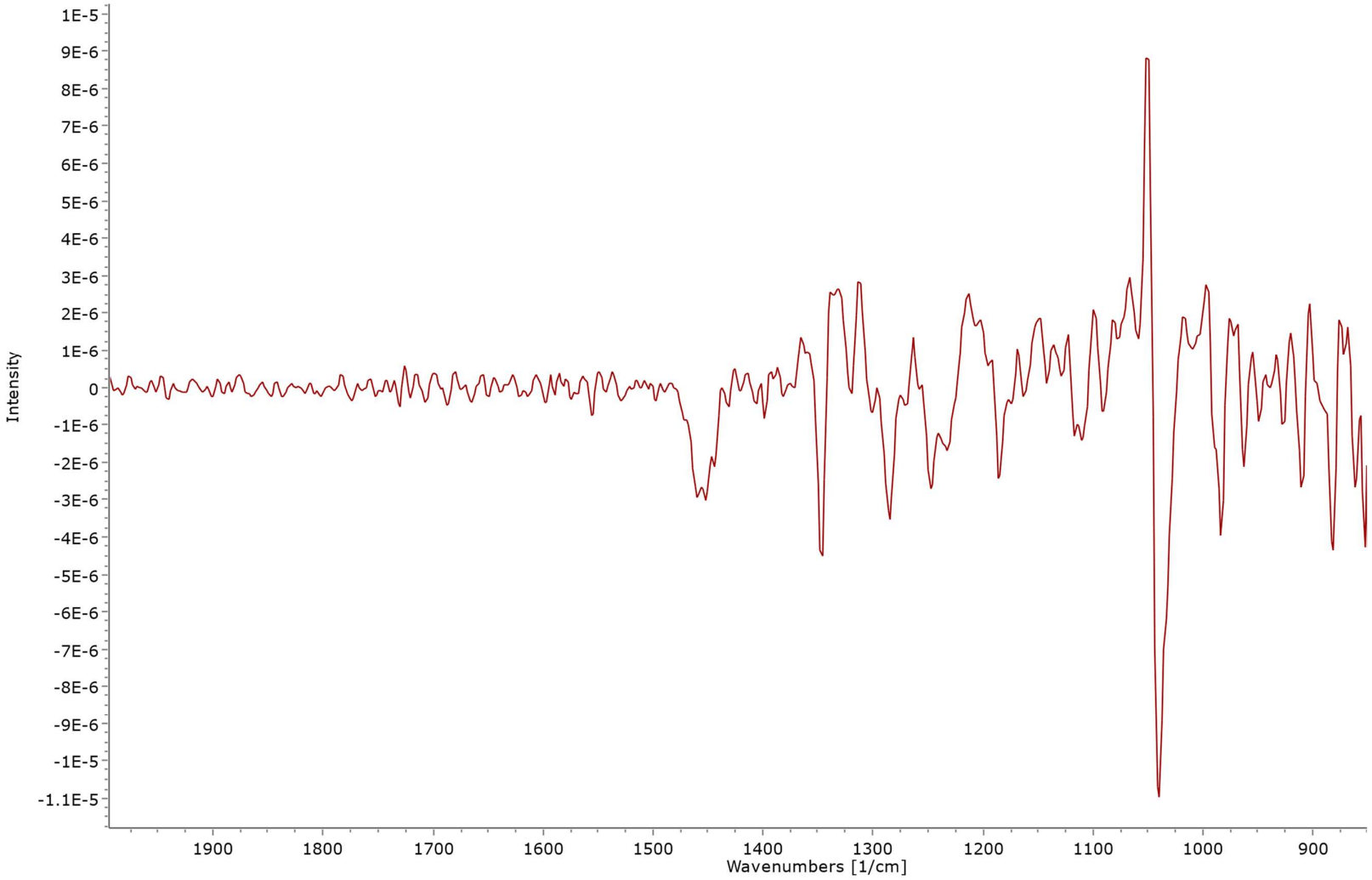
HPLC chromatogram of benzoylated recovered hydride transfer starting material (alcohol **5**)

CHIRALPAK AD; 100% n-hexane; 1.0 mL/min) t_R = 8.7 min, – 100% ee

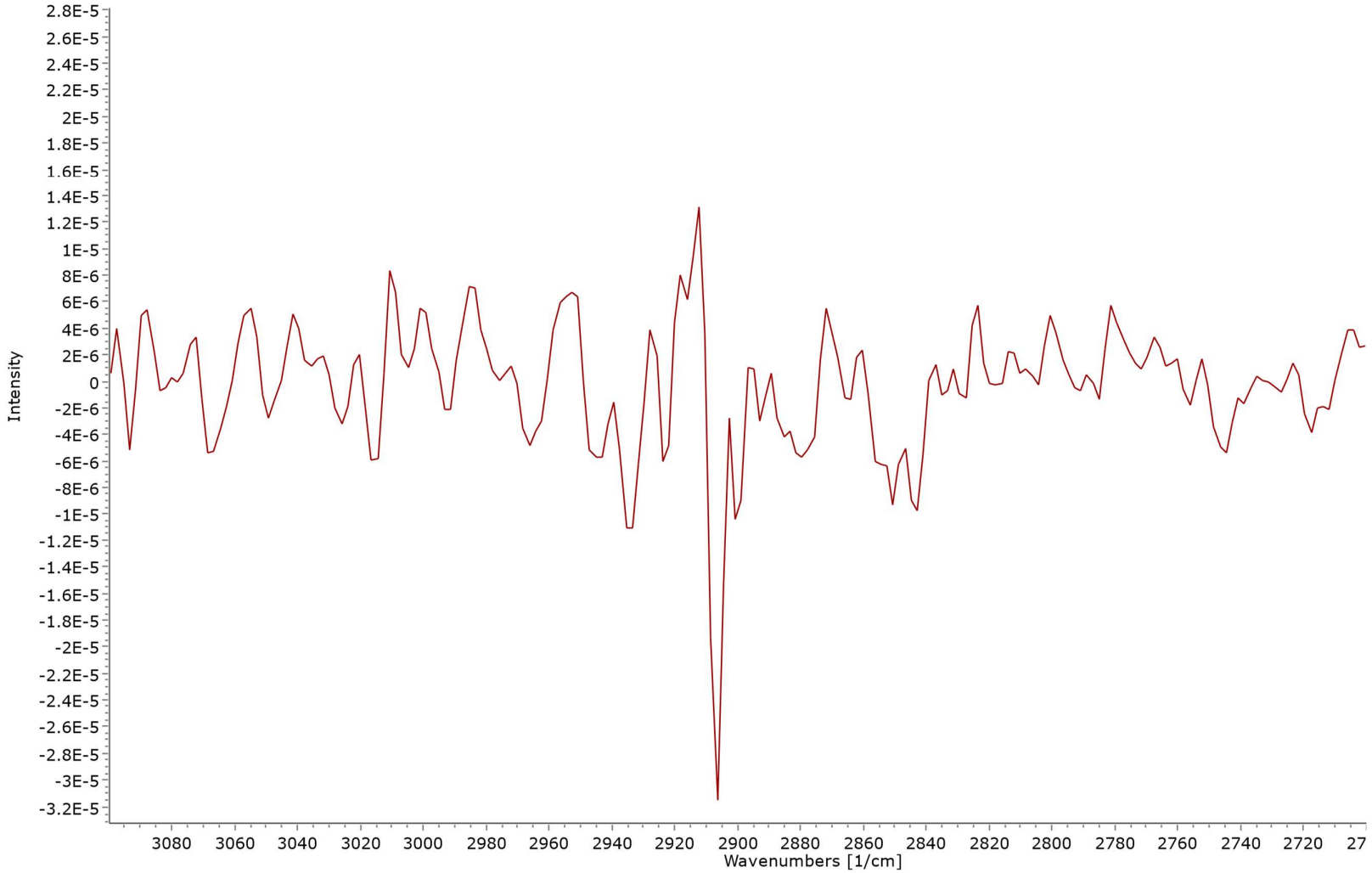


Peak #	Time [min]	Area [µV·s]	Height [µV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
1	8.705	1456502.60	40146.93	98.92	98.92	*MM	36.2793
2	15.723	15913.61	327.04	1.08	1.08	*MM	48.6591
		1472416.21	40473.97	100.00	100.00		

The fingerprint region of Vibrational Circular Dichroism (VCD) spectrum of (*R*)-**4**-*d*



The C-H region of Vibrational Circular Dichroism (VCD) spectrum of (*R*)-**4**-*d*



References

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