

Supporting Information for

Selective Isomerization-Hydroformylation Sequence: a Strategy to Valuable α -Methyl-Branched Aldehydes from Terminal Olefins

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Materials and Methods

General information and instrumentation

Unless stated otherwise, all reactions were carried out under an argon atmosphere using standard Schlenk techniques. The experiments carried out in the glove box were performed under the atmosphere of nitrogen. THF, pentane, hexane and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen; CH_2Cl_2 , isopropanol and methanol were distilled from CaH_2 under nitrogen; toluene was distilled from sodium under nitrogen and triethylamine was distilled from KOH pellets under nitrogen. CD_2Cl_2 and DIPEA were dried over molecular sieves (3 \AA) and degassed by at least 3 freeze-pump-thaw cycles.

NMR spectra were measured on a Bruker AMX 400 (400.1MHz, 100.6MHz and 162.0 for ^1H , ^{13}C and ^{31}P respectively). The GC analysis was conducted on a Simadzu 17A GC with a supelco SPBTM-1 fused silica capillary column (length 30 m, diameter 0.32 mm, film thickness 2.0 μm for experiments with pentenoic acid isomers, and on a HP-Agilent GC-MS with a Restek RTX \circledcirc -5 amine(crossbond \circledcirc 5% diphenyl/95% dimethylpolysiloxane) column (length 30 m, diameter 0.25 mm, film thickness 0.25 μm for all other experiments. The GC methods are reported in the description of the experiments for which they were relevant.

If not stated otherwise, syngas refers to a 1 : 1 mixture of H_2 and CO , and the pressure refers to a sum pressure of both.

Materials

All reagents and solvents were purchased from commercial suppliers and used without further purification. Ligand **L1** was prepared via literature procedure.¹

Catalysis studies

General procedure for the isomerization experiments with Pd-PPh₃ catalyst

In a flame-dried Schlenk flask, Silver triflate, PPh₃ ligand and allylpalladium(II) chloride dimer were mixed in dry DCM in a 1:1:0.5 ratio in the indicate mol% (in respect to a substrate). The substrate was subsequently added (1.0 M) and the reaction mixture was left stirring at room temperature for the required reaction time. Subsequently, triethylamine was added to each reaction vessel to prevent any further reaction. In experiments with allyl ether as an activating additive (1 or 0.5 equivalent in respect to the catalyst) was added 20 minutes prior to the substrate addition. For GC analysis, 20 μ l samples were methylated with methyl iodide according to the general method for preparation of GC samples. The GC analysis was performed. In case of internal alkenes, the significant preference of the trans geometric isomer formation was observed (over the formation of the cis isomer). GC method for pentenoic acid isomers: 70°C for 1 min, then 7°Cmin⁻¹ to 250°C, then 250°C for 5 min. Retention times (verified with commercial compounds): 6.28 min for 4-pentenoic acid methyl ester; 6.78 min for (trans)-3-pentenoic acid methyl ester and 6.89 min for (cis)-3-pentenoic acid methyl ester. GC-MS method for hexenoic acid isomers: 55°C for 10 min, then 50°Cmin⁻¹ to 300°C, then 300°C for 2 min. Retention times (verified with commercial compounds): 4.31 min for 5-hexenoic acid methyl ester; 4.76 min and 5.00 for (cis/trans)-4-hexenoic acid methyl ester; and 5.11 min (trans)-3-hexenoic acid methyl ester. GC-MS method for heptenoic acid isomers: 65°C for 10 min, then 50°Cmin⁻¹ to 300°C, then 300°C for 2 min. Retention time: 5.93 min for 6-heptenoic acid methyl ester (verified with a commercial sample); 6.43 min for (trans)-5-heptenoic acid methyl ester and 6.64 min for (cis)-5-heptenoic acid methyl ester (verified with a commercial sample); and 6.10 min for (cis/trans)-4-heptenoic acid (the next upcoming isomer); 6.56 min for (trans)-3-heptenoic acid methyl ester and 8.55 min for (cis)-3-heptenoic acid methyl ester (verified with a commercial sample).

General procedure for preparation of GC samples

The specified amount of a reaction mixture sample was added to dimethylformamide (0.3 ml) saturated with KHCO₃ in a reaction tube under air. Methyl iodide (50 μ l) was added and the mixture was stirred for ~ 1 hour. Then ethyl acetate (1 ml) and distilled water (1 ml) were added. The mixture was shaken, followed by separation of the layers. Next, the ethyl acetate layer was dried over MgSO₄, filtered over a syringe HPLC filter, and transferred to a GC vial, followed by the GC analysis.

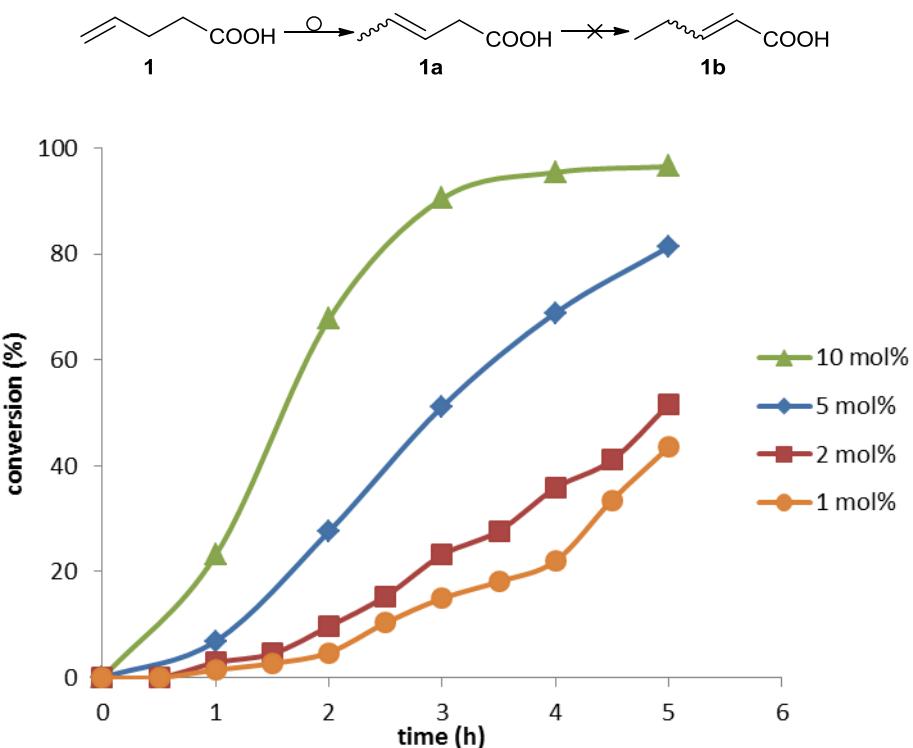


Figure S1 Isomerization of 4-pentenoic acid (**1**) by the Pd-PPh₃ catalyst followed in time – the influence of the catalyst loading on the reaction rate. Reaction conditions: 1,0 M 4-pentenoic acid in DCM with *in situ* formed catalyst consisting of n/2 mol% of (allyl)Pd(II)chloride dimer, n mol% of triphenylphosphine and n mol% of silver triflate. Relative concentrations of isomers analyzed with GC/MS.

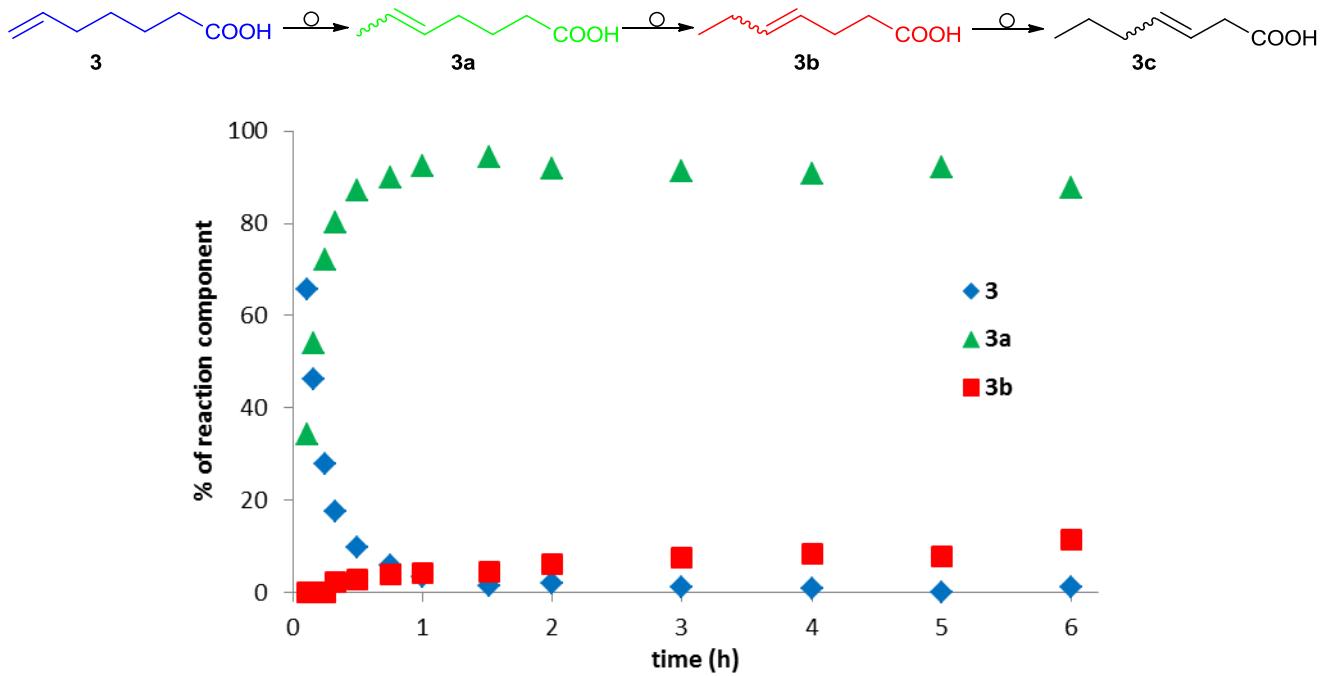


Figure S2 Isomerization of 6-heptenoic acid (**3**) followed in time. Reaction conditions: 1,0 M 6-heptenoic acid in DCM with *in situ* formed catalyst consisting of 5 mol% (allyl)Pd(II)chloride dimer, 10 mol% triphenylphosphine and 10 mol% silver triflate. Relative concentrations of isomers analyzed with GC/MS. No formation of 3-heptenoic acid (**3c**) was observed.

General procedure for the sequential isomerization-hydroformylation

In a flame-dried Schlenk flask, allylpalladium(II) chloride dimer (9.020 mg, 0.025 mmol), triphenylphosphine (12.936 mg, 0.049 mmol) and silver triflate (13.5 mg, 0.053 mmol) were dissolved in 10 ml DCM and stirred for 3 h at room temperature in the glove box. Next, the isomerization catalyst stock solution was transferred to flame-dried GC vials equipped with magnetic stirring bars (1 ml of the solution to each one), followed by the substrate addition to obtain the 1.0 M solution of a substrate in each vial (ranging from 4-pentenoic acid to 8-nonenoic acid). The isomerization reaction mixtures were left stirring at room temperature in the glove box for 24 hours. Next, in an another flame-dried Schlenk flask, 11 ml stock solution of Rh(acac)(CO)₂ (7.11 mg), ligand **L1** (39.4 mg) and triethylamine (364 μ l)² in DCM was prepared. From each isomerization reaction mixture, 200 μ l sample was transferred to a new flame-dried GC vial equipped with a magnetic stirring bar, followed by addition of 800 μ l aliquot of the Rh-**L1** stock solution. Each vial was then capped with a septum cap, which was then punctured with a needle (25G x 5/8"), which was left piercing through the cap throughout the catalysis. The vials were put in a stainless steel autoclave, which was then sealed and flushed three times with 20 bar syngas, and then pressurized with 10 bar of syngas. The autoclave was then put in an oil bath at 50°C, and the vials were left stirring for 72 h. Next, the autoclave was cooled down and vented to 1 bar. From each GC vial, 100 μ l aliquots of the reaction mixture was taken for the NMR analysis (see the Appendix). The analysis was performed according to the previously developed methodology, and the results were compared with those for the analogues reaction mixtures.³ Analyses of characteristic signals in the aliphatic and aldehyde regions were in agreement. The results are reported in Table 1 in the main text. For pivotal examples, that is for substrates **1-2**, the aldehyde products were isolated using the previously developed isolation protocol (a column chromatography on SiO₂ using a hexane : diethyl ether : acetic acid mixture (200 : 100 :1) as an eluent – ref. S3a). These samples of pure products (or a mixture of the major aldehyde with minor isomeric products for substrate **2**) were analyzed and compared with the actual aldehyde samples (the previously obtained aldehydes via direct hydroformylation of internal alkenes (ref. S3a). This gave essentially the same data (see Figure S8-S9), confirming the structure of the major products.

For more details concerning the hydroformylation of the terminal and internal alkenes with a carboxylic group, see the previous studies (ref. S3).

Appendix

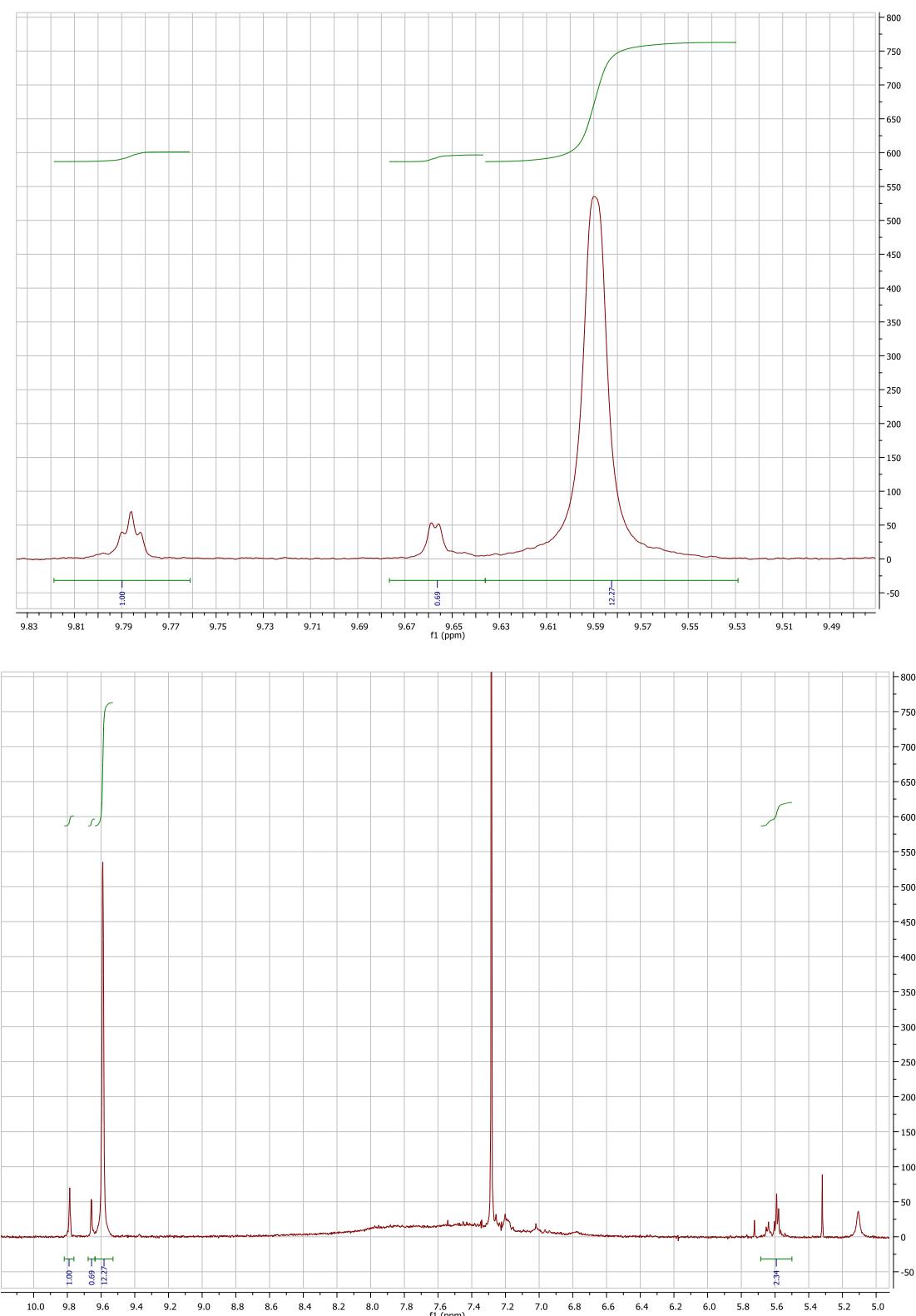


Figure S3 ^1H NMR spectrum of the reaction mixture for sequential isomerisation-hydroformylation of 4-pentenoic acid in CDCl_3 : aldehyde (above), and aldehyde + alkene region (below) - 400 MHz. Assignment of the integrated peaks downfield to upfield: linear aldehyde, other branched aldehyde, α -branched aldehyde, remaining internal alkenoic acid isomers.

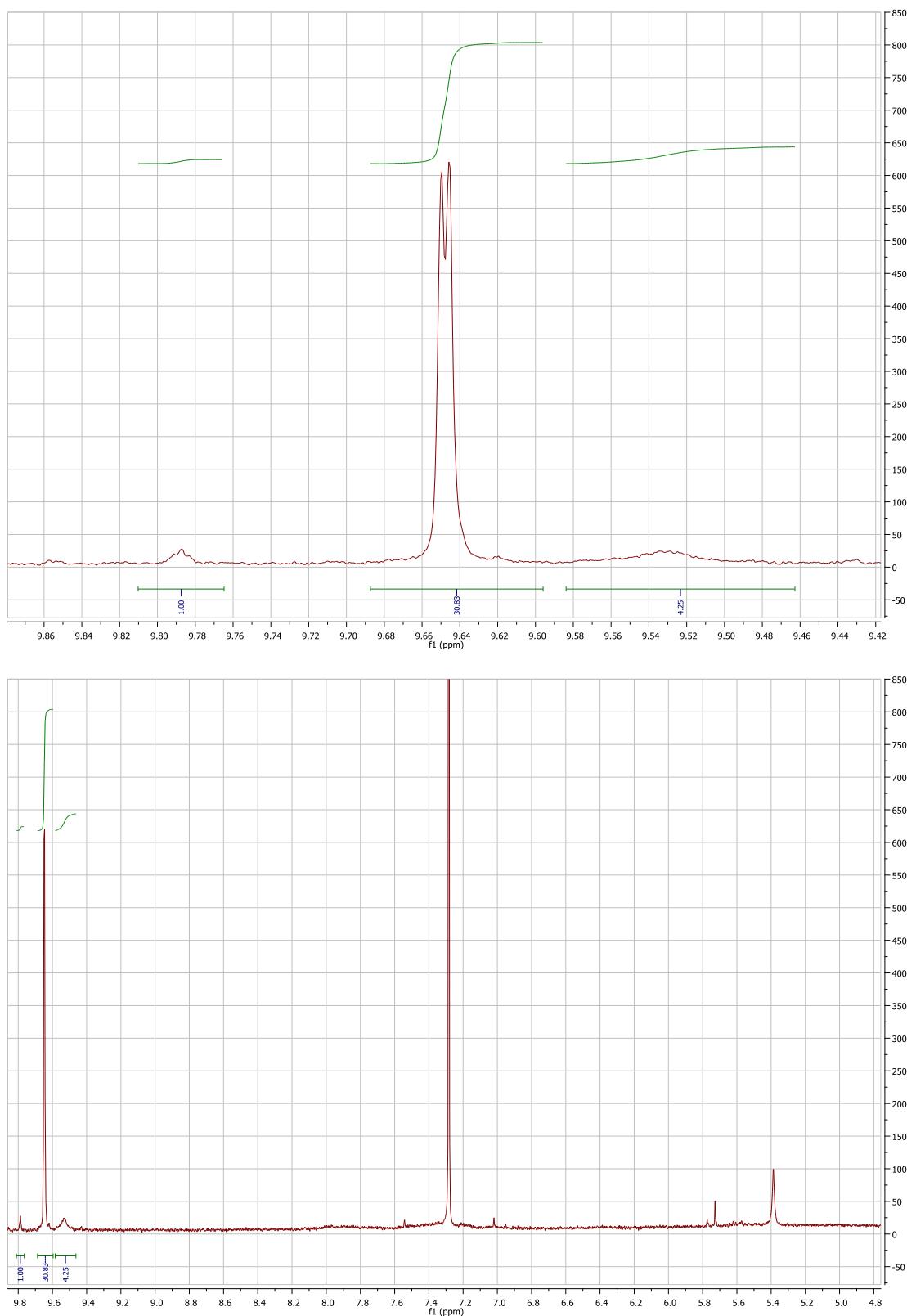


Figure S4 ^1H NMR spectrum of the reaction mixture for sequential isomerisation-hydroformylation of 5-hexenoic acid in CDCl_3 : aldehyde (above), and aldehyde + alkene region (below) - 400 MHz. Assignment of the integrated peaks downfield to upfield: linear aldehyde, α -branched aldehyde, other branched aldehydes, (no remaining internal alkenoic acid isomers).

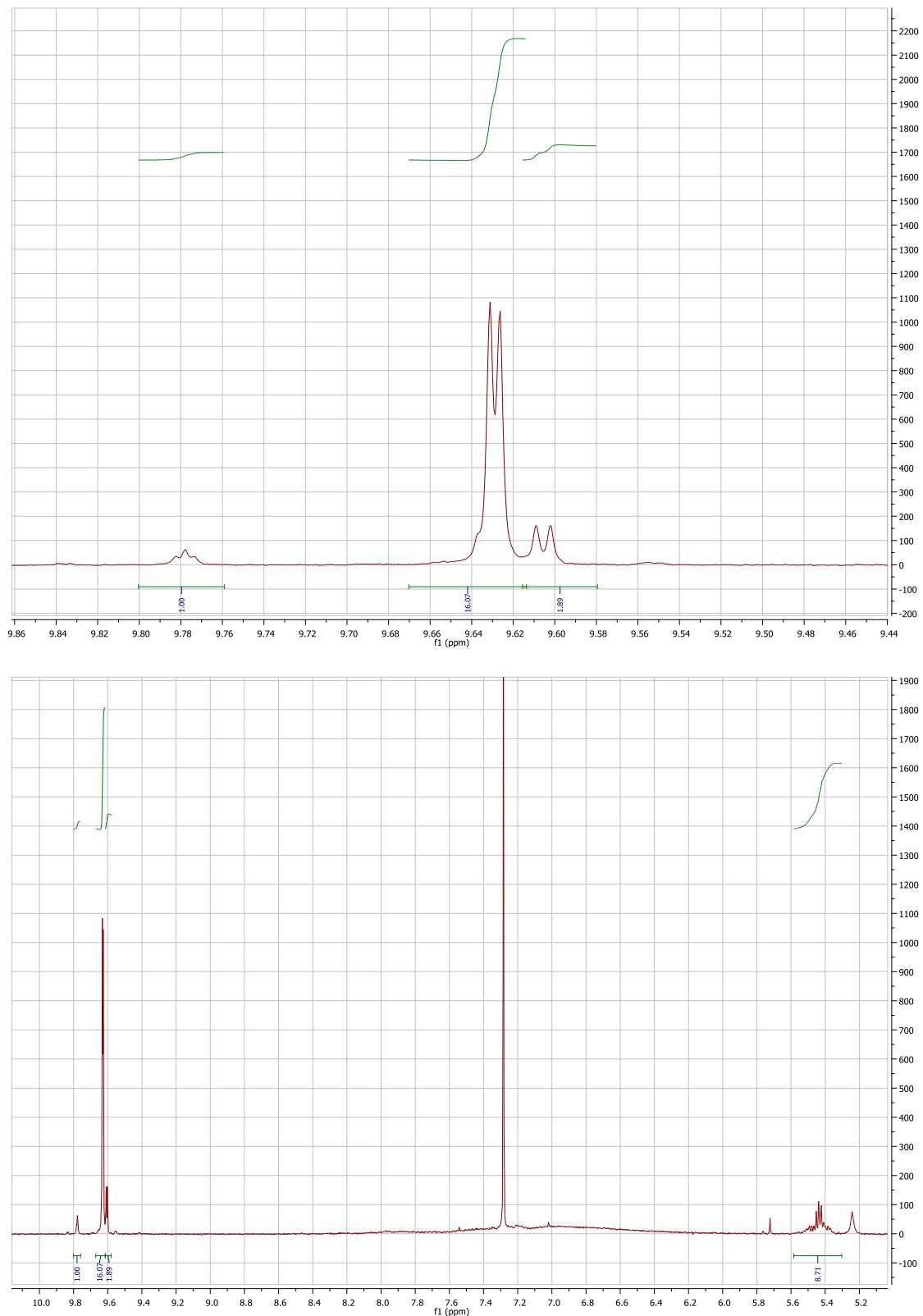


Figure S5 ¹H NMR spectrum of the reaction mixture for sequential isomerisation-hydroformylation of 6-heptenoic acid in CDCl₃: aldehyde (above), and aldehyde + alkene region (below) - 400 MHz. Assignment of the integrated peaks downfield to upfield: linear aldehyde, α -branched aldehyde, other branched aldehydes and remaining internal alkenoic acid isomers.

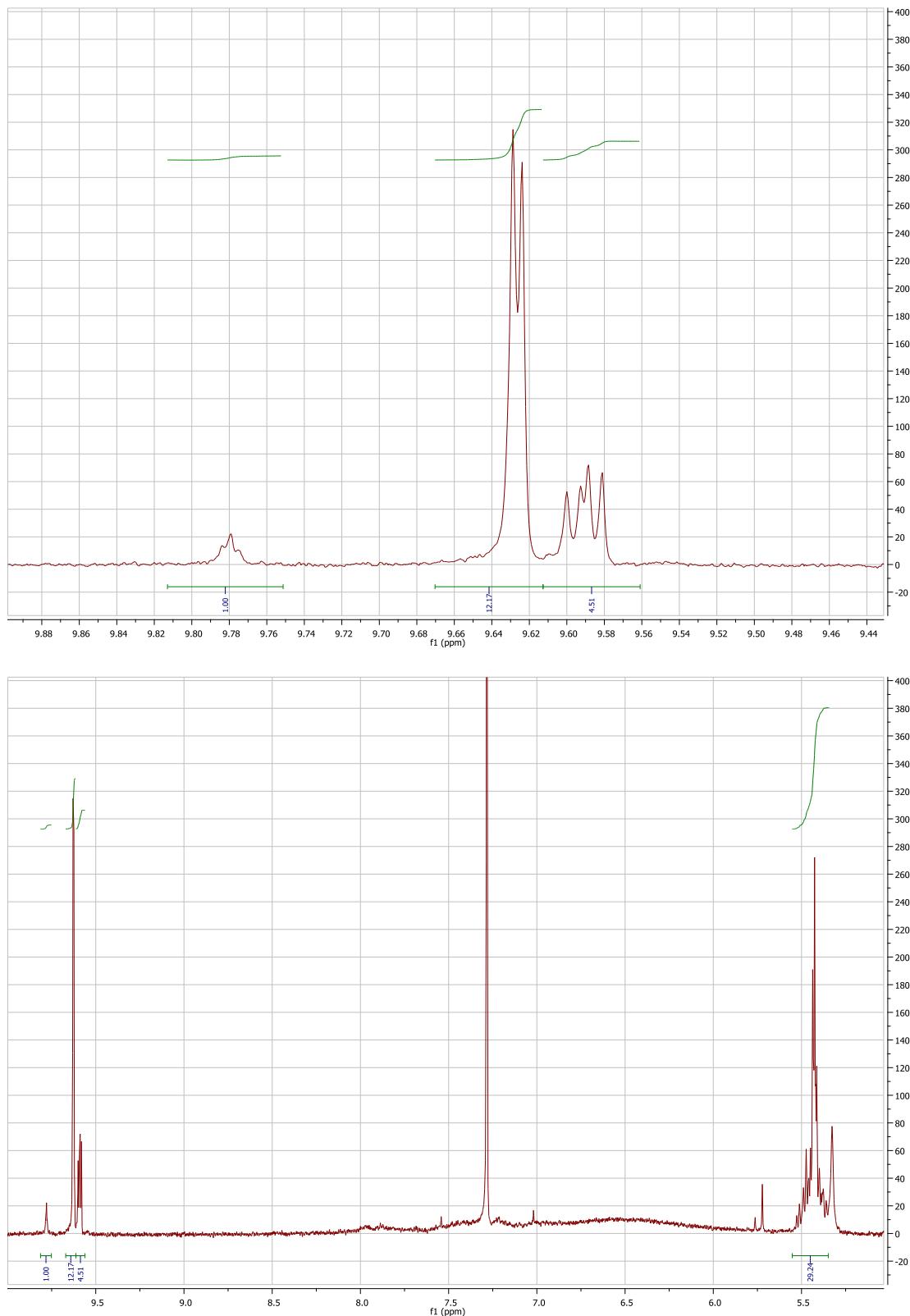


Figure S6 ^1H NMR spectrum of the reaction mixture for sequential isomerisation-hydroformylation of 7-octenoic acid in CDCl_3 : aldehyde (above), and aldehyde + alkene region (below) - 400 MHz. Assignment of the integrated peaks downfield to upfield: linear aldehyde, α -branched aldehyde, other branched aldehydes and remaining internal alkenoic acid isomers.

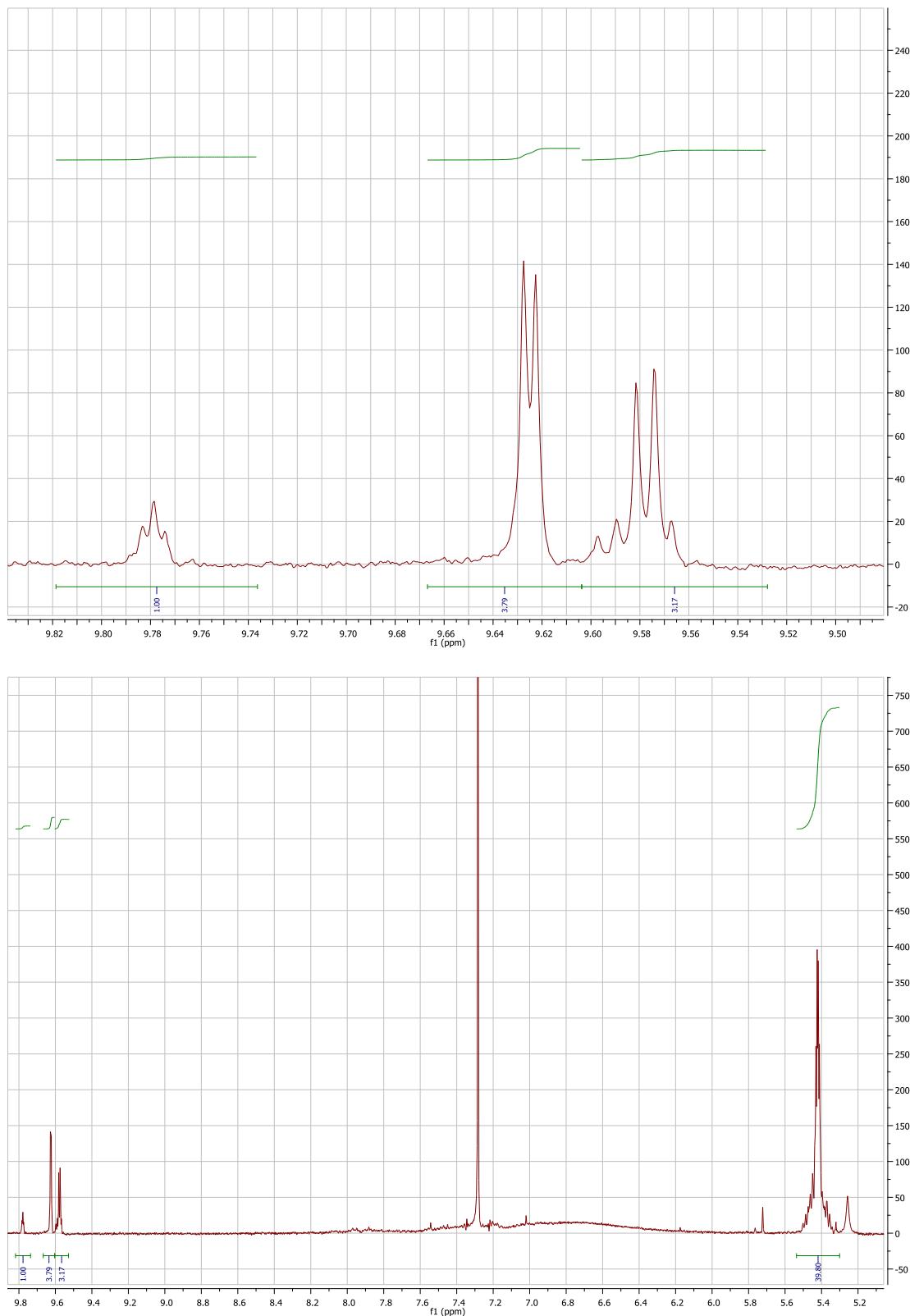


Figure S7 ^1H NMR spectrum of the reaction mixture for sequential isomerisation-hydroformylation of 8-nonenoic acid in CDCl_3 : aldehyde (above), and aldehyde + alkene region (below) - 400 MHz. Assignment of the integrated peaks downfield to upfield: linear aldehyde, α -branched aldehyde, other branched aldehydes and remaining internal alkenoic acid isomers.

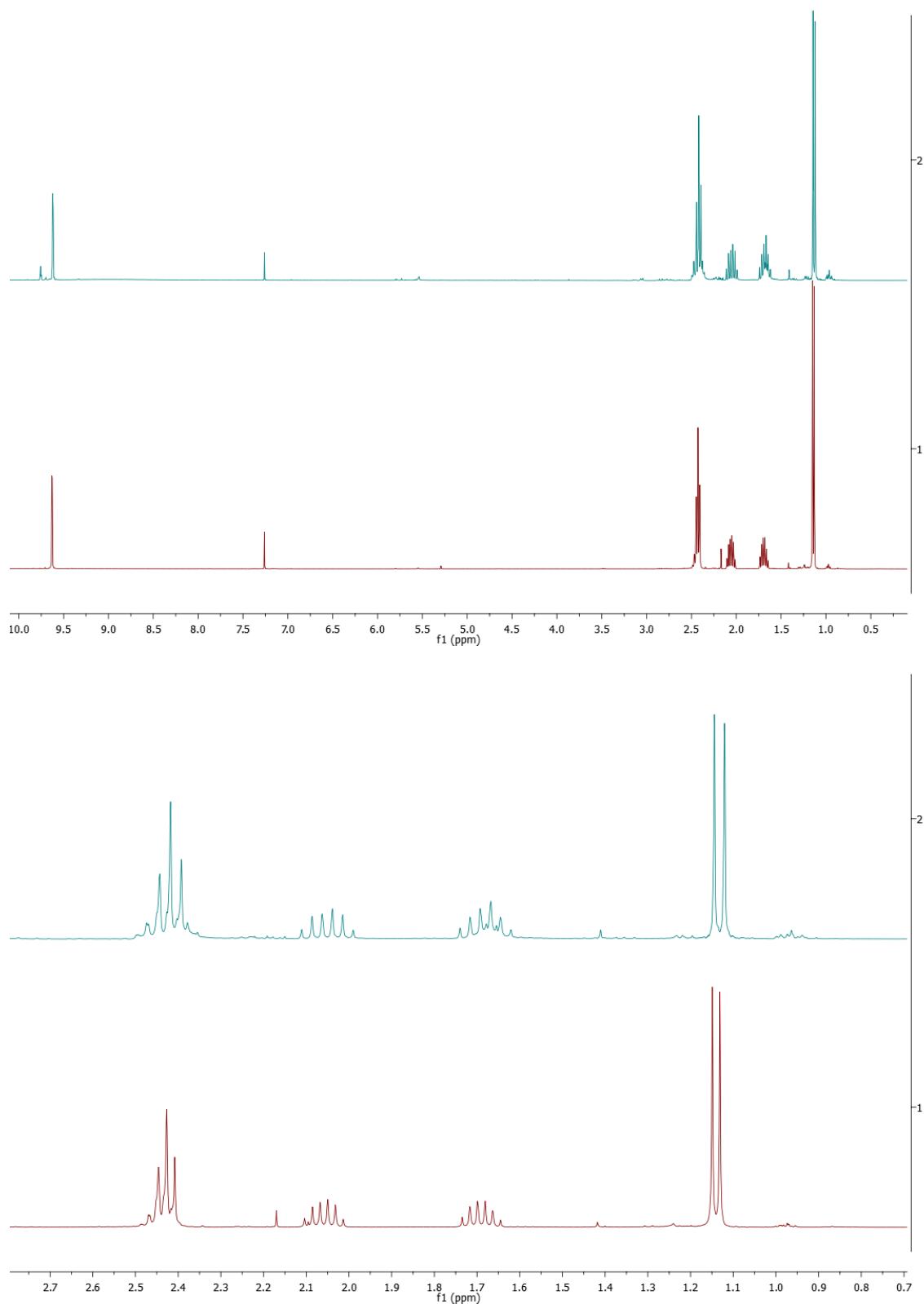


Figure S8 ^1H NMR spectrum of the isolated major product for sequential isomerisation-hydroformylation of 4-pentenoic acid in CDCl_3 (top spectrum, 300 MHz) and of the reference sample of 4-methyl-5-oxopentenoic acid (bottom spectrum, 400 MHz). For the assignment of all signals (and other analytical data), see ref. S3a.

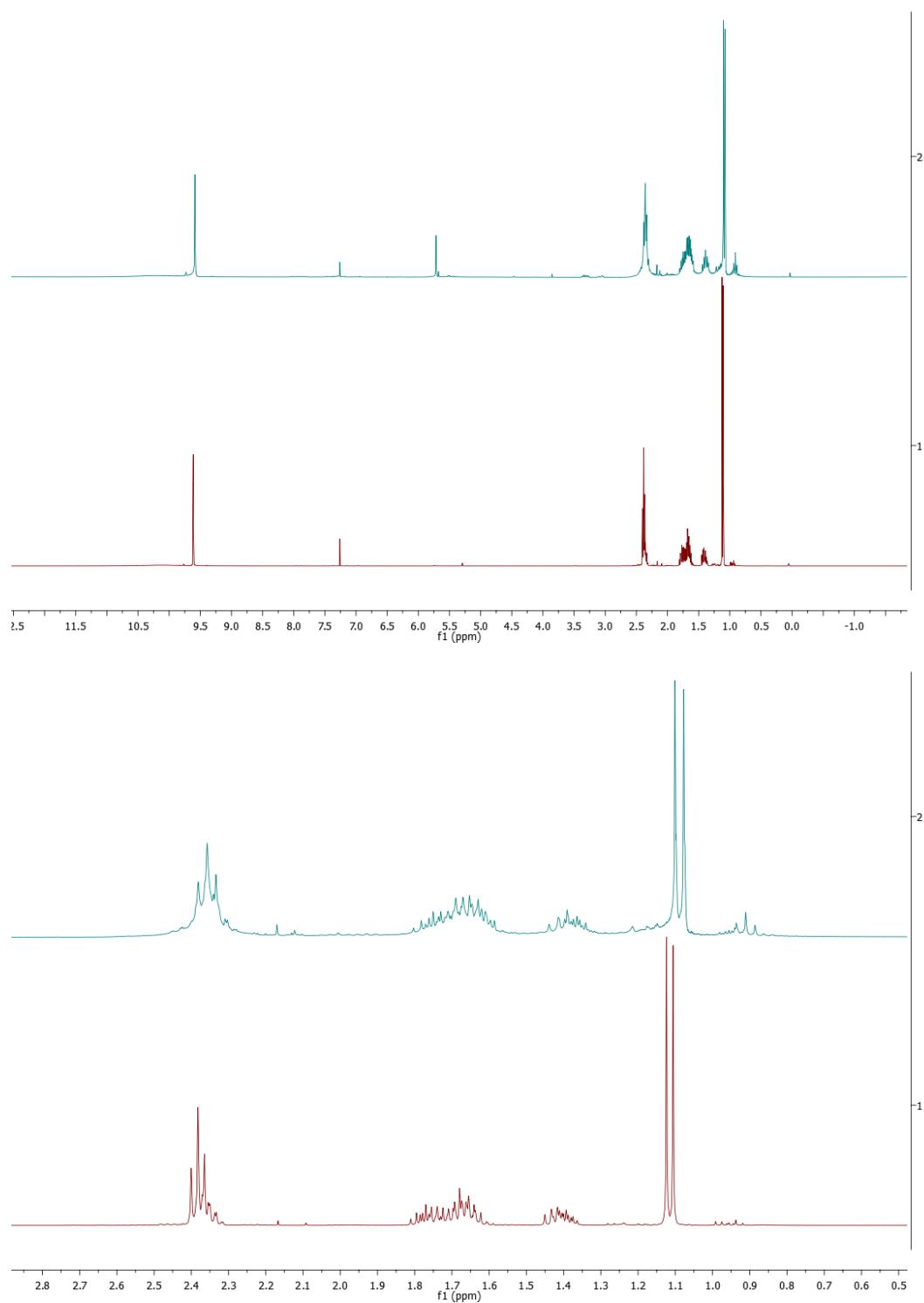


Figure S9 ^1H NMR spectra of the isolated major product for sequential isomerisation-hydroformylation of 5-hexenoic acid in CDCl_3 (top spectrum, 300 MHz) and of the reference sample of 5-methyl-6-oxohexanoic acid (bottom spectrum, 400 MHz). For the full assignment of signals (and other analytical data), see ref. S3a.

¹ Dydio, P.; Reek, J. H. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 3878-3882.

² We evaluated that there is no influence of the order of the addition of base and the catalyst on the reaction outcome.

³ (a) Dydio, P.; Detz, R. J.; Reek, J. H. N. *J. Am. Chem. Soc.* **2013**, *135*, 10817–10828. (b) Dydio, P.; Dzik, W. I.; Lutz, M.; de Bruin, B.; Reek, J. H. N. *Angew. Chem., Int. Ed.* **2011**, *50*, 396-400.