Supporting Information

Mixed Phosphane η^5-CpRuCl$(PR_3)_2$ Complexes as Ambifunctional Catalysts for anti-Markovnikov Hydration of Terminal Alkynes

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Content

1. General

Syntheses of and with air-sensitive materials were performed under argon, using freshly distilled and degassed solvents. The catalyst is not particularly sensitive to oxygen, but oxidation of the aldehyde product may be problematic when working in air.

TLC were performed on coated plates (Merck, Kieselgel 60, F254 indicator) and detected by UV and molybdenum stain solution (10 g of $(NH_4)_6[Mo_7O_{24}]\cdot 4\ H_2O$ + 0.1 g of $Ce(SO_4)_2\cdot 4\ H_2O$ + 200 mL H_2O +10 mL of H_2SO_4 conc.). Preparative chromatography (CC, column chromatography) was performed using Acros silica gel 60 (0.040–0.063 mm) using pressured air (0.1-0.3 bar) for flash elution.

Analytical data:

Analytical data were obtained from in-house services at the Institute of Organic Chemistry, RWTH Aachen University and at the Department of Chemistry, TU München. **MS:** *m/z* (% *relative abundance). **^{1}H NMR**: δ/ppm, *J*/Hz, referenced to tetramethylsilane as internal standard. **^{13}C NMR:** δ/ppm, *J*/Hz, referenced to tetramethylsilane as internal standard. **IR**: ν/cm^{-1}, intensity: vs = very strong, s = strong, m = medium, w = weak, vw = very weak. Melting points (**MP**) were measured in a metal block using a digital thermometer, therefore represent "corrected" values.[1]

Materials:

Unless otherwise mentioned, chemicals were obtained from commercial suppliers and used as received. Solvents: DMF, DCM and acetone were bought in 99% purity and used without purification.

The following substances were prepared according to literature procedures:

ISIPHOS;[2] 4,4-Dimethyl-6-heptyn-2-one;[3] 3-(Methoxymethoxy)oct-1-yne;[4] 1-Phenylbut-3-yn-1-yl acetate;[5] 10,11-Didehydrocinchonine.[6]
$CpRuCl(PPh_3)_2$ was obtained commercially, or synthesized according to the literature.[7]

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[1] G. V. D. Tiers, *J. Chem. Educ.* **1990**, *67*, 258.

[2] L. Hintermann, T. T. Dang, A. Labonne, T. Kribber, L. Xiao, P. Naumov, *Chem. – Eur. J.* **2009**, *15*, 7167.

[3] D. Felix, J. Schreiber, G. Ohloff, A. Eschenmoser, *Helv. Chim. Acta* **1971**, *54*, 2896.

[4] L. Hintermann, T. Kribber, A. Labonne, E. Paciok, *Synlett* **2009**, 2412.

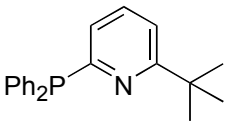
[5] T. Kribber, A. Labonne, L. Hintermann, *Synthesis* **2007**, 2809.

[6] K. M. Kacprzak, W. Lindner, N. M. Maier, *Chirality* **2008**, *20*, 441.

[7] M. I. Bruce, C. Hameister, A. G. Swincer, R. C. Wallis, *Inorg. Syntheses* **1990**, *28*, 270.

AZARYPHOS ligands[2] used in this study:

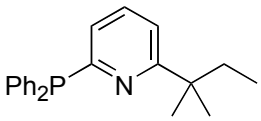
The AZARYPHOS ligands used were prepared according to the detailed procedures in ref.[2] The ligands **L^b** and **L^d** are also commercially available from Aldrich.



L^a

^{t}BuPyPPh$_2$

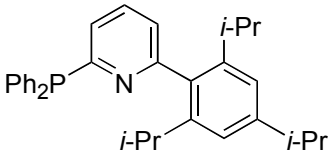
BUPYPHOS



L^b

^{t}AmPyPPh$_2$

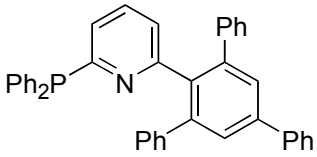
TAMPYPHOS



L^c

^{2,4,6}*i*-Pr$_3$C$_6$H$_2$PyPPh$_2$

ISIPHOS

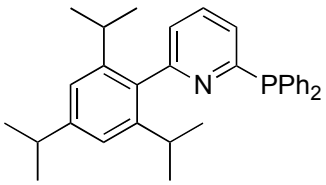


L^d

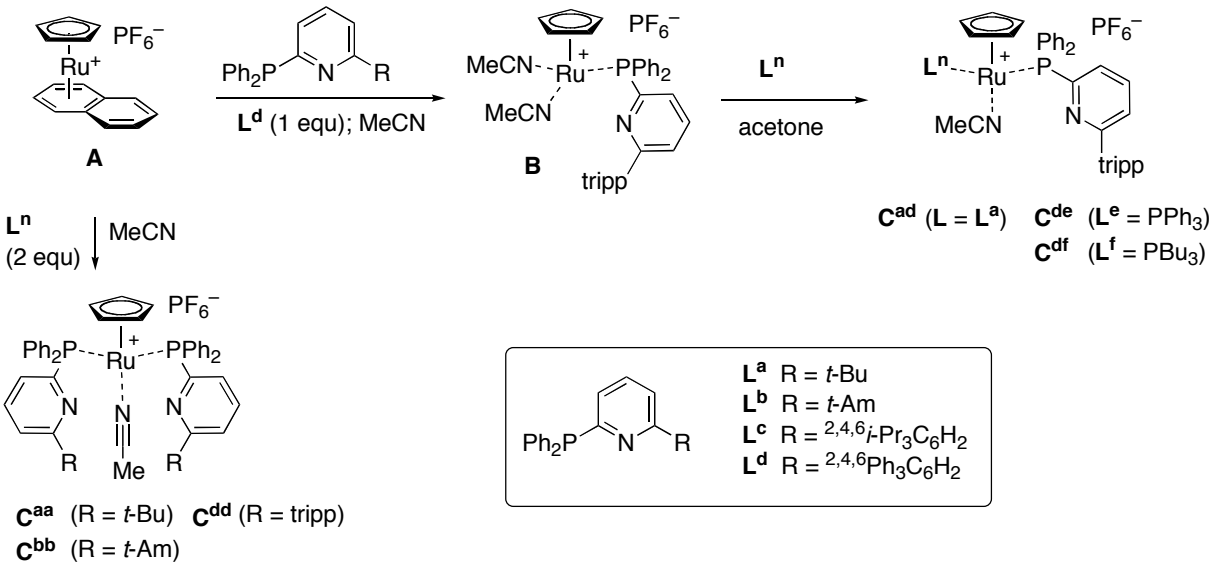
^{2,4,6}Ph$_3$C$_6$H$_2$PyPPh$_2$

TRIPPYPHOS

Abbreviations:

AMH	anti-Markovnikov hydration (of terminal alkynes)
aq	aqueous solution
CC	column chromatography
C_{Ar}	carbon in an aryl group
Cp	η^5-cyclopentadienyl
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCM	dichloromethane
DMAP	4-*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
ISIPHOS	
MP	melting point
NHS	*N*-hydroxysuccinimide
rt	room temperature
sat.	saturated
TBME	*tert*-butylmethylether, *t*-BuOMe
TLC	thin layer chromatography

2. Synthesis of catalyst complexes



For the synthesis of homoleptic complexes [CpRu($\mathbf{L^n}$)$_2$(MeCN)]PF$_6$, see refs.[8,9]

General procedure for preparing complexes [CpRu($\mathbf{L^c}$)($\mathbf{L^n}$)(MeCN)]PF$_6$ (GP1)

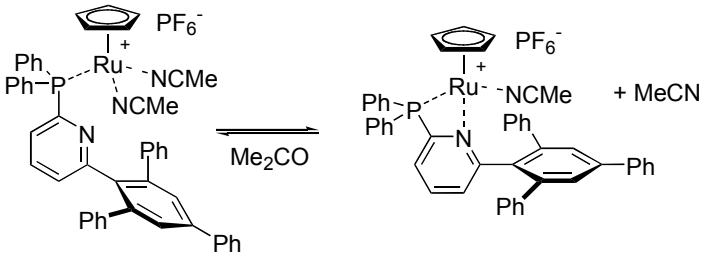
In a Schlenk tube, a mixture of solid [CpRu($\mathbf{L^c}$)(MeCN)$_2$]PF$_6$ (**B**; 1 equiv) and ligand $\mathbf{L^n}$ (1 equivalent) was placed under argon. Degassed acetone (50 mL/mmol) was added by syringe and the mixture was stirred for 3.5 h at r.t. The solvents were removed in vacuum, until a resinous residue remained. To this was added degassed hexanes (= petroleum ether fraction; 50 mL/mmol) and the vessel placed in a warm (ca 40 °C) water bath. The resinous residue slowly transformed into a microcrystalline yellow solid, which was ground to a powder by means of a spatula. The resulting yellow suspension was stirred magnetically for 10 min. The supernatant liquid was removed via steel cannula and/or a filter stick. The remaining yellow powder (yield >90%) was washed twice with hexanes, dried in high vacuum and stored under argon.

The homogeneity of the mixed phosphane complexes [CpRu($\mathbf{L^1}$)($\mathbf{L^2}$)(MeCN)]PF$_6$ with respect to complex impurities ([CpRu($\mathbf{L^1}$)$_2$(MeCN)]PF$_6$ and [CpRu($\mathbf{L^2}$)(MeCN)]PF$_6$, and [CpRu($\mathbf{L^1}$)(MeCN)$_2$]) was determined by ^{31}P NMR and found to be ≥95%. In cases where the homoleptic complex [CpRu($\mathbf{L^2}$)$_2$(MeCN)]PF$_6$ was found in the product, the complex synthesis was repeated with an adjusted (smaller) amount of $\mathbf{L^2}$.

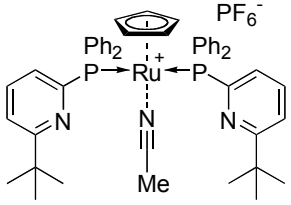
[8] L. Hintermann, L. Xiao, A. Labonne, U. Englert, *Organometallics* **2009**, *28*, 5739–5748.

[9] A. Labonne, T. Kribber, L. Hintermann, *Org. Lett.* **2006**, *8*, 5853.

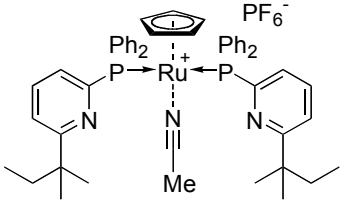
[CpRu(2,4,6-$Ph_3C_6H_2PyPPh_2$-κP)-$(MeCN)_2$]PF_6 (B): This material was synthesized as described earlier from **A** and **L[d]** in MeCN solution.[8]



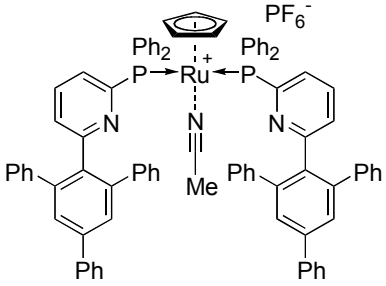
[CpRu(2-^{t}BuPyPPh$_2$)$_2$(MeCN)]PF_6 (IIa = C[aa]): Synthesized from **A** and **L[a]** in MeCN solution as described earlier.[9] This complex has earlier been synthesized by Grotjahn.[10]



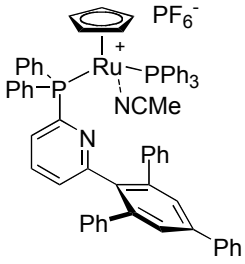
[CpRu(2-^{t}AmPyPPh$_2$)$_2$(MeCN)]PF_6 (C[bb]): Synthesized from **A** and **L[a]** in MeCN solution as described earlier.[9]



[CpRu(2,4,6-$Ph_3C_6H_2PyPPh_2$)$_2$(MeCN)]PF_6 (C[dd]): This complex was synthesized as described earlier from **A** and **L[d]** in MeCN solution.[8,9]



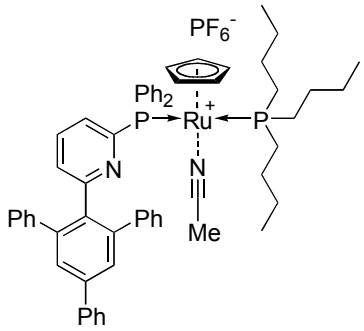
[η^5-CpRu(2,4,6-$Ph_3C_6H_2PyPPh_2$)(PPh_3)(MeCN)]PF_6 (C[de]): Synthesized according to the **GP1** from [η^5-CpRu(2,4,6-$Ph_3C_6H_2PyPPh_2$)$(MeCN)_2$]PF_6 (100 mg, 0.104 mmol) and PPh_3 (27.3 mg, 0.104 mmol).



^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (t, J = 1.4 Hz, 3 H, MeCN), 4.17 (s, 5 H, Cp), 6.57–6.66 (m, 2 H_{Arl}), 6.86–6.94 (m, 6 H_{Arl}), 6.96–7.17 (m, 20 H_{Arl}), 7.19–7.35 (m, 8 H_{Arl}), 7.37–7.44 (m, 3 H_{Arl}), 7.46–7.52 (m, 2 H_{Arl}), 7.69–7.76 (m, 4 H_{Arl}). ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.23 (t, J_{PH} = 1.4 Hz, 3 H, *Me*CN), 4.29 (s, 5 H, Cp), 6.72–6.79 (m, 2 H_{Arl}), 6.99–7.07 (m, 6 H_{Arl}), 7.09–7.49 (m, 29 H_{Arl}), 7.51–7.57 (m, 4 H_{Arl}), 7.75–7.78 (m, 2 H_{Arl}), 7.87–7.90 (m, 2 H_{Arl}). ^{31}P NMR (120 MHz, $CDCl_3$): δ = –144.4 (sept, J_{PF} = 712 Hz, PF_6^-), 40.1 (d, J_{PP} = 35.3 Hz), 45.8 (d, J_{PP} = 35.3 Hz). ^{31}P NMR (120 MHz, acetone-d_6): δ = 44.6 (d, J_{PP} = 35.8 Hz), 40.7 (d, J_{PP} = 36.0 Hz), –144.4 (sept, J_{PF} = 708 Hz, PF_6^-). MS (ESI, $CHCl_3$): *m*/*z* = 1036.67 [M^+], 996.27, 734.60.

[10] D. B. Grotjahn, D. A. Lev, *J. Am. Chem. Soc.* **2004**, *126*, 12232–12233.

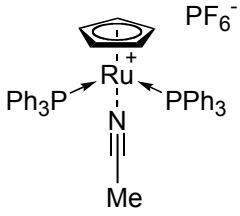
CpRu(^{2,4,6}Ph$_3$C$_6$H$_2$PyPPh$_2$)(PBu$_3$)(MeCN)]PF$_6$ (Cdf): Synthesized according to the **GP1** from [η^5-CpRu(^{2,4,6}Ph$_3$C$_6$H$_2$PyPPh$_2$)-(MeCN)$_2$]PF$_6$ (96.1 mg, 0.10 mmol) and tributylphosphane (25 μL, 0.10 mmol).



^{1}H NMR (400 MHz, acetone-d_6): δ = 0.80 (t, J = 7.2 Hz, 9 H, 3 × CH_3), 1.13–1.40 (m, 15 H, CH_2), 1.62–1.74 (m, 3 H, PCH_2) 2.43 (t, J_{PH} = 1.3 Hz, 3 H, *Me*CN), 4.53 (s, 5 H, Cp), 7.01–7.06 (m, 1 H_{Arl}), 7.13–7.59 (m, 25 H_{Arl}), 7.72 (d, J = 2.1 Hz, 1 H_{Arl}), 7.78 (d, J = 2.0 Hz, 1 H_{Arl}), 7.84–7.89 (m, 2 H_{Arl}) ppm. ^{31}P NMR (162 MHz, acetone-d_6): δ = 46.5 (d, J = 37.8 Hz), 22.6 (d, J = 37.8 Hz), –144.4 (sept, J = 708 Hz, PF_6) ppm. MS (ESI, $CHCl_3$): m/z = 935.96 [CpRu(^{2,4,6}Ph$_3$C$_6$H$_2$PyPPh$_2$)(PBu$_3$)]$^+$, 734.23.

X-ray analysis: Crystals suitable for an X-ray analysis were obtained from a solution of the complex in acetone by overlayering with hexanes and standing for 2 d in a fridge at 4 °C. (κ*N*-Acetonitrile)(η^5-cyclopentadienyl)(κ*P*-2-diphenylphosphanyl-6-(2,4,6-triphenylphenyl)pyridine)-(κ*P*-tributylphosphane)ruthenium(II) hexafluorophosphate; $C_{60}H_{65}F_6N_2P_3Ru$; unit cell parameters: *a* 18.3756(11), *b* 14.6058(9), *c* 22.0886(13); β 111.7290(10); space group P21/n. CCDC 813354 contains the supplementary crystallographic data.

[CpRu(PPh$_3$)$_2$(MeCN)]PF$_6$ (**C^{ee}**): In a dry Schlenk vessel under argon, [CpRu(η^6-naphthalene)]PF$_6$ (**A**; 87.9 mg, 0.20 mmol) and PPh_3 (105 mg, 0.40 mmol) were dissolved in degassed MeCN (5 mL) and stirred for 43 h at 60 °C. The solvent was removed in vacuum. To the resinous residue, hexanes (5 mL) were added and the vessel kept for 1 h at 50 °C.

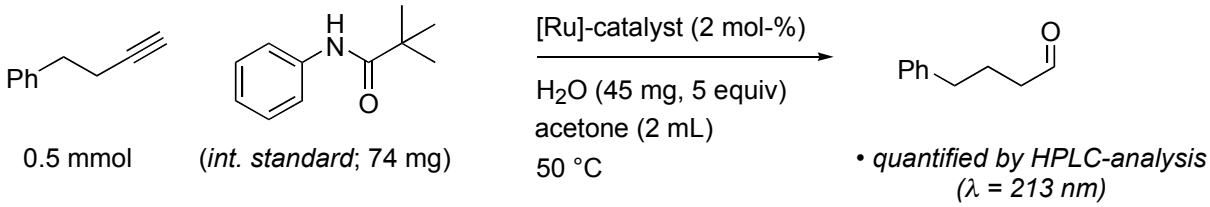


The residue, which had converted to a microcrystalline yellow solid, was ground to a powder by means of a spatula. After stirring the yellow suspension for another 30 min at 50 °C, the supernatant was removed via cannula and/or a filter stick, the residual powder was washed twice with hexanes and then dried in vacuum to give fine, bright-yellow powder.

$C_{43}H_{38}F_6NP_3Ru$ (M_r 876.75). ^{1}H NMR (400 MHz, acetone-d_6): δ = 2.36 (t, J_{PH} = 1.4 Hz, 3 H, *Me*CN-Ru), 4.60 (s, 5 H), 7.18–7.23 (m, 12 H_{Ph}), 7.33–7.37 (m, 12 H_{Ph}), 7.43–7.48 (m, 6 H_{Ph}). ^{31}P NMR (162 MHz, acetone-d_6): δ = 41.9 (s), –144.4 (sept, J = 708 Hz, PF_6). MS (ESI, $CHCl_3$): m/z = 731.3 (10) [M$^+$], 691.1 (100).

3. Kinetics of the catalytic anti-Markovnikov hydration

General procedure for recording hydration kinetics with HPLC quantification (GP2)



0.5 mmol (*int. standard*; 74 mg)

• *quantified by HPLC-analysis (λ = 213 nm)*

Setup: Into a 10 mL Schlenk-tube with rubber septum, the internal standard *N*-pivaloylaniline (74 mg, 0.42 mmol) and the ruthenium(II)-complex catalyst (2 mol%) were placed under an atmosphere of argon. The solvent mixture, consisting of acetone and water (2 mL [→ c = 0.25 mol·L^{-1}] containing 45 mg H_2O, 2.5 mmol, 5 equivalents), was added by syringe from a degassed (argon) stock-solution. After addition of 4-phenyl-1-butyne (70 µL, 0.5 mmol; micro-syringe), the Schlenk tube was placed in a metal block heated to 50 °C.

Sampling: Using a micro syringe, 20 µL were removed from the reaction mixture and diluted with HPLC mobile phase (5 mL; *t*-BuOMe/hexanes 1:5). The diluted sample was analyzed by HPLC with UV-detection (stationary phase: Kromasil® 100 Si-5µ; mobile phase: *t*-BuOMe/-hexanes = 1:5, flow = 1 mL/min, T = 20 °C; UV-detection λ = 213 nm).

Analysis: Integration of the peak areas for 4-phenylbutanal (t_R = 5.0 min) and internal standard (*N*-pivaloylaniline; t_R = 7.5 min) and multiplication of the relative peak area ($\int_{product}/\int_{int.\ standard}$) with a response factor and the mass of int. standard (74 mg) gave the time-dependent product yield (in mg). The response factor was determined as follows: 10 mg each of product and internal standard was dissolved in 10 mL of mobile phase and analyzed by HPLC. The relative peak areas were: $\int_{int.\ standard}/\int_{product}$ = 0.62 (λ = 213 nm).

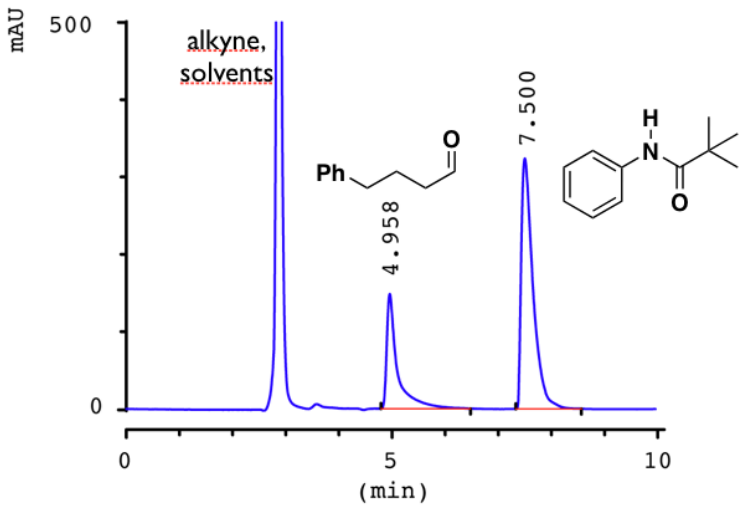


Figure S1. Example for an HPLC-trace of a catalytic AMH reaction.

A) Effect of AZARYPHOS ligand structure on catalytic activity

Experiments were performed according to the GP2.

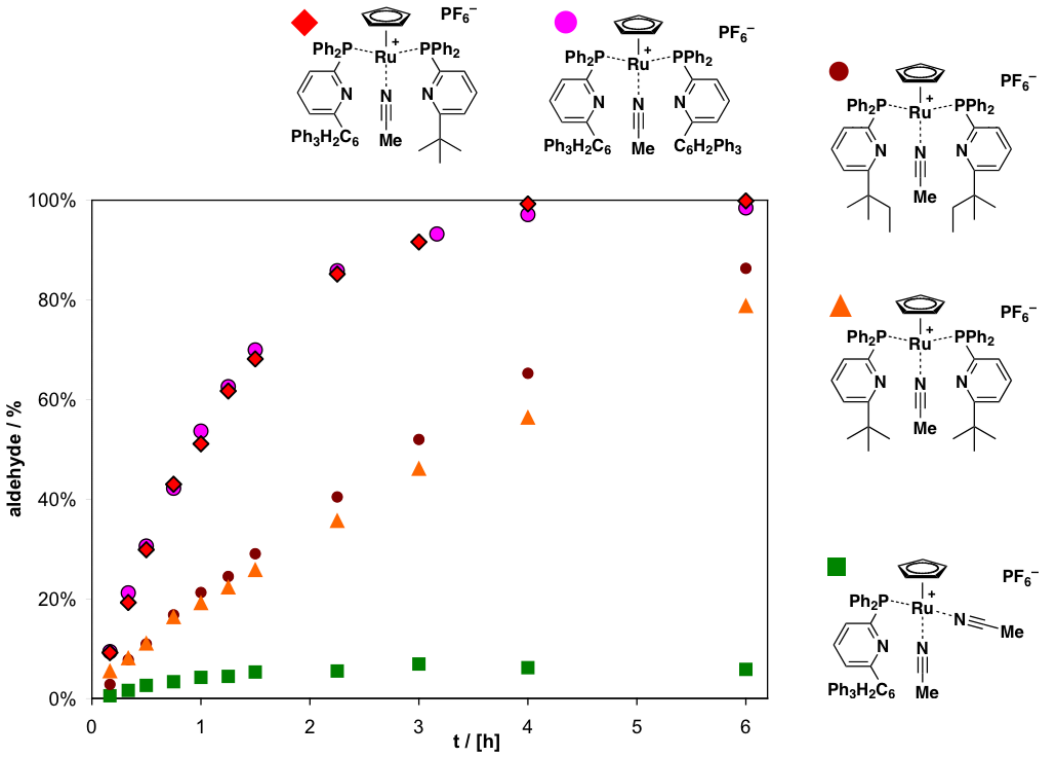


Figure S2. Effect of the ligand structure on the kinetics of catalytic AMH

B) Effect of the ligand structure and combination in mixed ligand catalyst complexes on kinetics of catalytic anti-Markovnikov hydration of alkynes

Kinetic curves were recorded according to the GP2. Mixed phosphane complexes have been prepared according to the GP1.

The results with mixed phosphane complexes [CpRu(TRIPPYPHOS)(PAr_3)(MeCN)]PF_6 incorporating substituted triphenylphosphane ligands (PAr_3; Ar = 4-fluorophenyl, 4-chlorophenyl, 4-methylphenyl, 4-trifluoromethyl) are also shown in the graph. The results with those mixed species were not substantially different (within the limits of accuracy of the analytical method) from those with the mixed complex with PPh_3.

Aside the triarylphosphane and the tributylphosphane (**C**^{df}) containing complexes, only the mixed complex incorporating triethyl phosphite (and, to a lesser degree, triphenylphosphite; *not shown*) displayed some activity. Other mixed complexes incorporating tri-cyclohexylphosphane, tris-ortho-tolylphosphane, tris-1-naphthylphosphane, tris-2,6-dimethoxyphenylphosphane or 4-*tert*-butylpyridine displayed no activity; some of the sterically more hindered phosphane ligands failed to form stable mixed complexes.

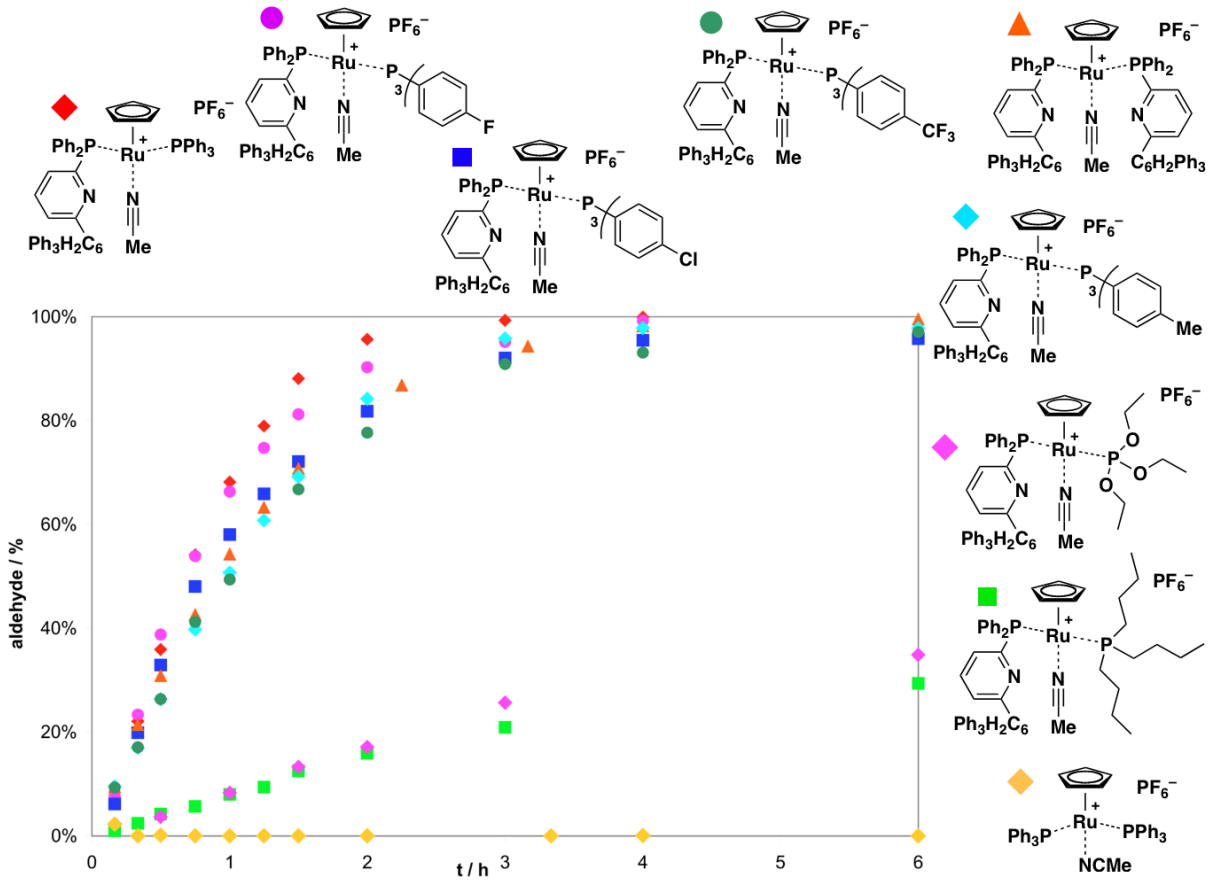


Figure S3. Performance of mixed phosphane catalyst complexes in catalytic AMH.

C) Effect of the water concentration on the kinetics of anti-Markovnikov alkyne hydration

Reactions were performed according to GP2 with complex **C**^{dd}, but using a reaction medium prepared from acetone (2.0 mL) and variable amounts of water:

• 10 equivalents = 5 mmol = 0.1 mL H_2O for 2 mL acetone (20:1)

• 20 equivalents = 10 mmol = 0.18 mL H_2O for 2 mL acetone (10:1)

• 36.65 equivalents = 18.325 mmol = 0.33 mL H_2O for 2 mL acetone (6:1)

• 55.5 equivalents = 27.75 mmol = 0.50 mL H_2O for 2 mL acetone = (4:1).

In the reaction with „0 equivalents“, reagent grade acetone was used straight from the bottle. According to the label, it may have contained water in excess of 1000 ppm (>0.1%).

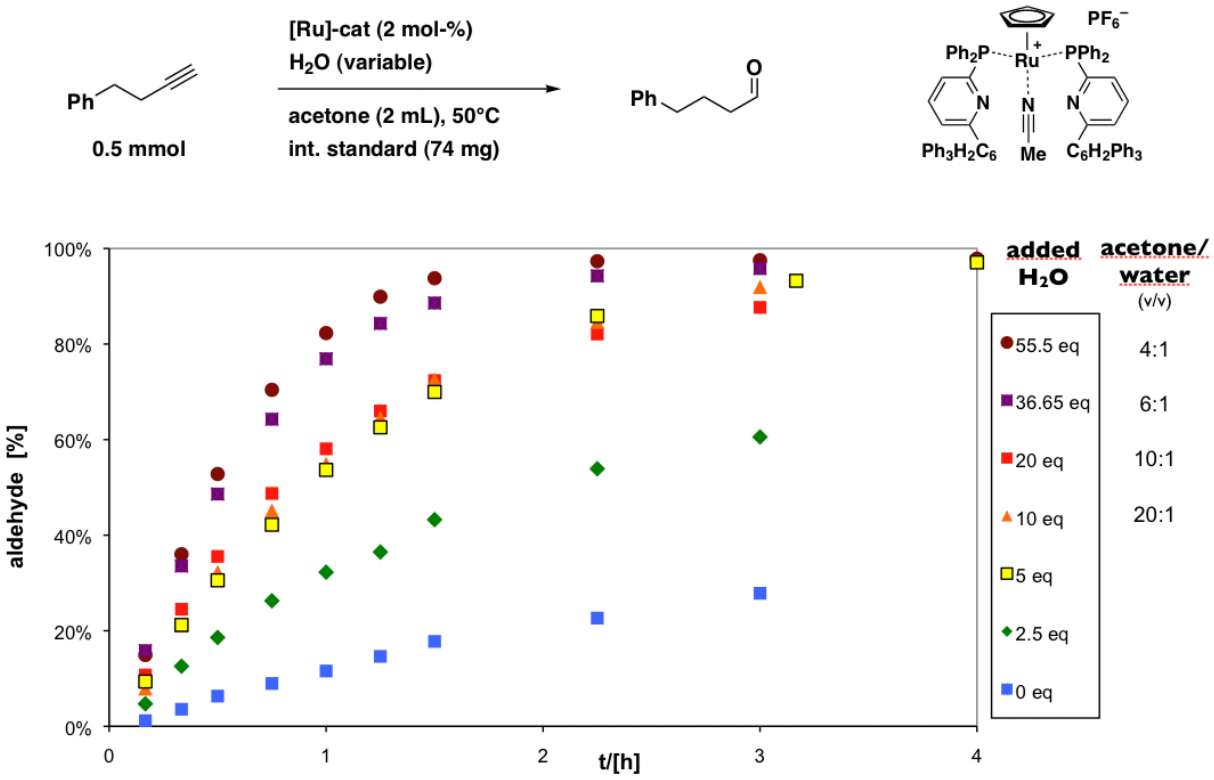


Figure S4. Effect of the water concentration on the catalytic AMH.

D) Inhibitory effect of acetonitrile on the kinetics of anti-Markovnikov alkyne hydration

Experiments were performed according to the GP2, with complex **C**^{dd} and additional MeCN ([mol-%] relative to substrate). Since the catalyst complex incorporates coordinated MeCN, an additional 2 mol-% of MeCN is present in all runs.

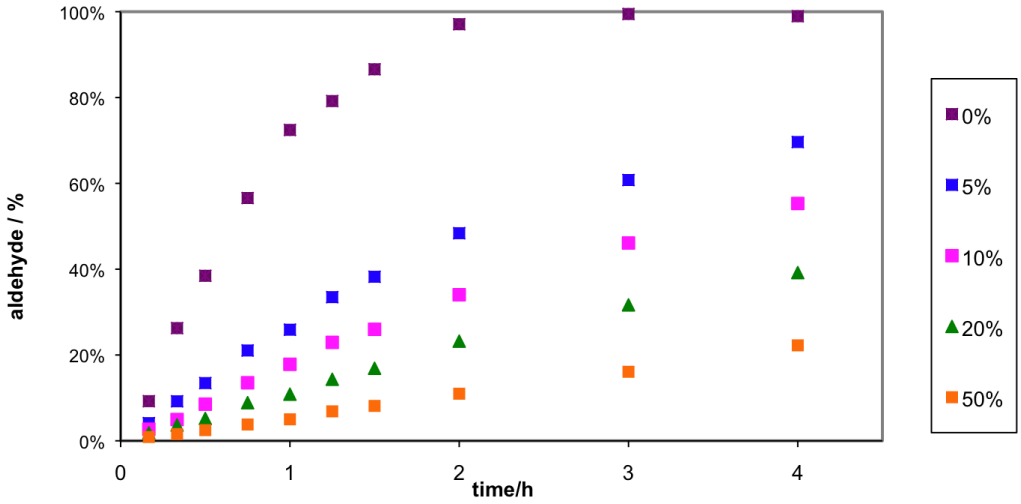
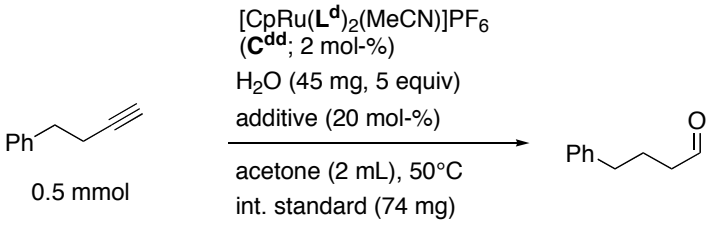


Figure S5. Inhibitory effect of added MeCN on the catalytic AMH.

E) Effect of various additives on the kinetics of anti-Markovnikov alkyne hydration



The standard hydration reaction (GP2) with complex $\mathbf{C}^{\mathbf{dd}}$ was performed in the presence of a range of additives at the 20 mol-% level. None of the additives increased the rate of the catalytic reaction, however, several additives, including benzoic and anthranilic acid, were compatible with the hydration reaction.

On the other hand, coordinating counter-ions like chloride and acetate reduced catalytic activity considerably. The reaction does not proceed in the presence of bases (*tert*-amine).

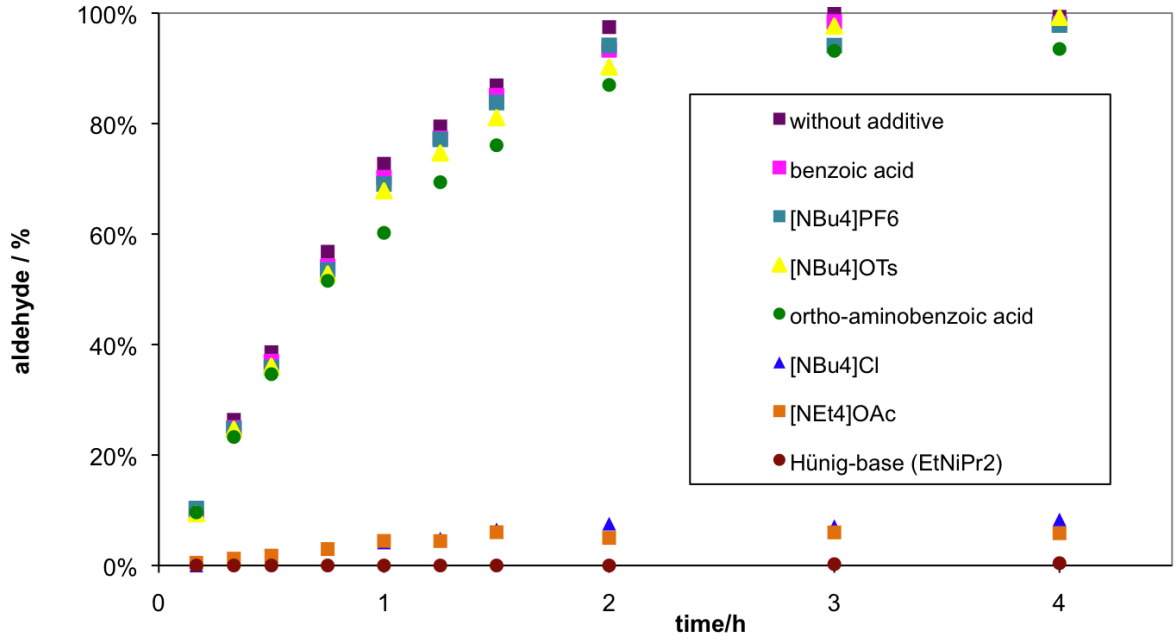
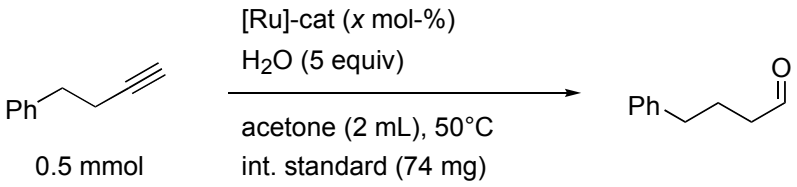


Figure S6. Effect of various additives on the kinetics of the AMH.

F) Effect of catalyst loading on hydration kinetics



Experiments performed according to the GP2, with $[CpRu(TRIPPYPHOS)_2(MeCN)]PF_6$ (**C^{dd}**).

The reactions with 2 mol-% of catalyst loading are, as expected, faster than reactions with 1 mol-% of catalyst loading. However, further increasing the catalyst loading to 3 or 4 mol-% has only a small effect on the reaction kinetics. This is presumably due to the equilibrium:

$$Ru(MeCN)^+ = Ru^+_{(active)} + MeCN$$

The precursor $Ru(MeCN)^+$ dissociates to give the catalytically active Ru^+-species and the inhibitor MeCN reversibly. Therefore, a linear increase of the concentration of $Ru(MeCN)^+$ does not lead to a linear increase of the active species Ru^+.

Catalyst loadings below 1 mol-% do not give reliable results, because catalyst deactivation (due to generation of inactive ruthenium carbonyl complexes) becomes notable. Catalysis may stop before the substrate is consumed.

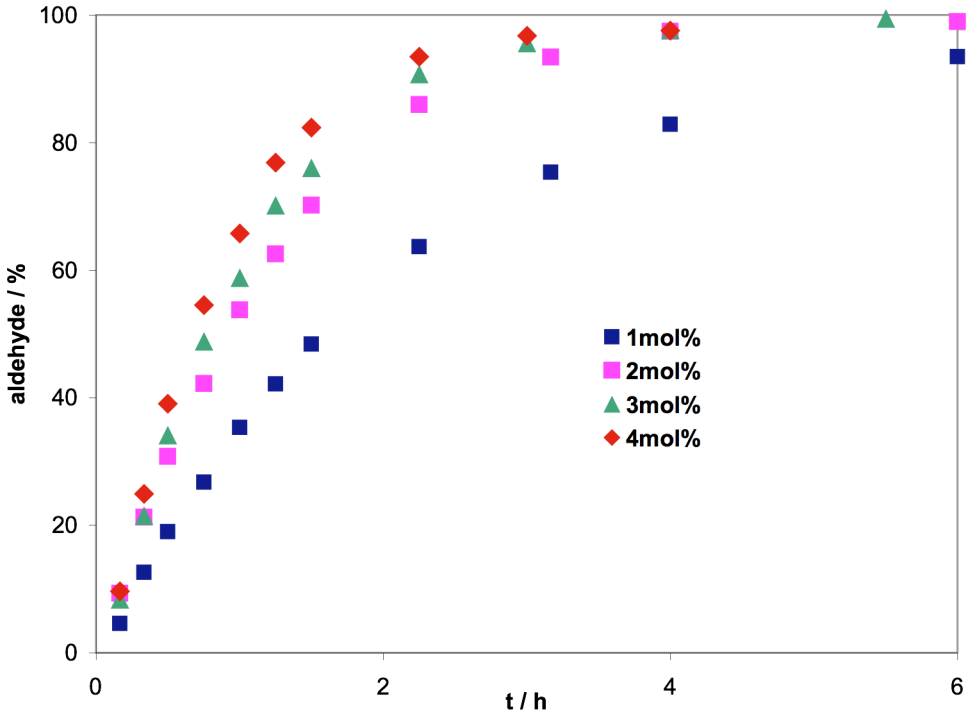
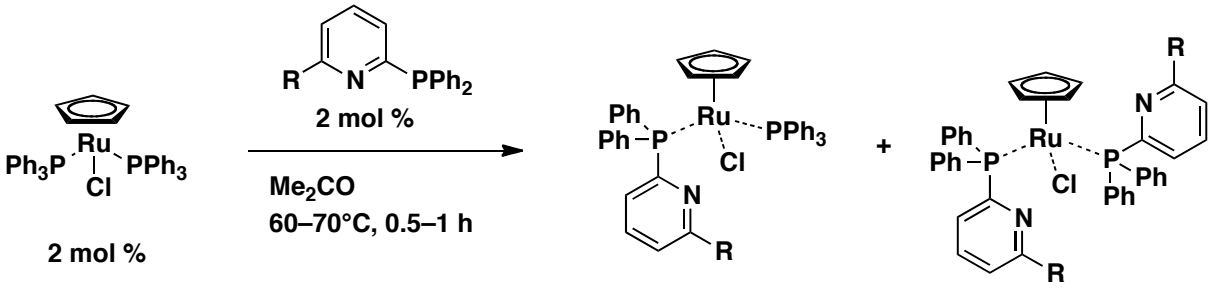
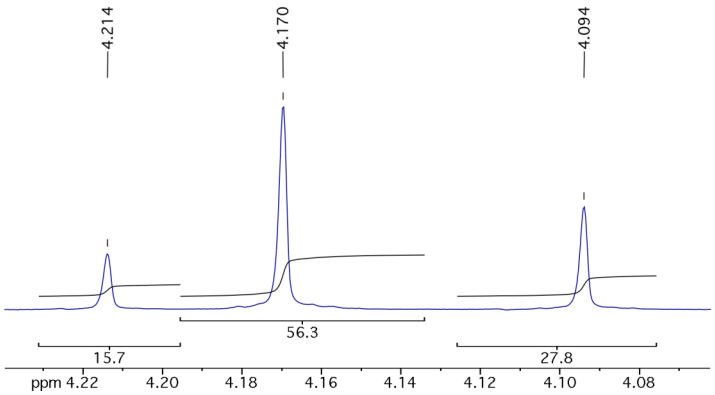


Figure S7. Effect of the catalyst loading on catalytic AMH.

4. NMR in situ ligand exchange experiment

BUPYPHOS (*t*-BuPyPPh$_2$) (15.9 mg, 0.05 mmol, 1.0 eq) and CpRuCl(PPh$_3$)$_2$ (28.6 mg, 0.05 mmol, 1.0 eq) were dissolved in 1.5 mL of degassed acetone-d_6 containing two drops of D_2O. The mixture was heated to 50 °C for 3 hours and cooled to rt (*the ligand exchange is actually much faster and appears to be completed within 30 min at 50 °C*). A sample of 0.5 mL was removed for NMR-analysis. At higher D_2O-contents, spectra became more complex with additional and broadened lines due to chemical exchange with aquo-complexes.





^{1}H NMR (360 MHz, acetone-d_6, r.t.); *η^5-Cp signal region.*

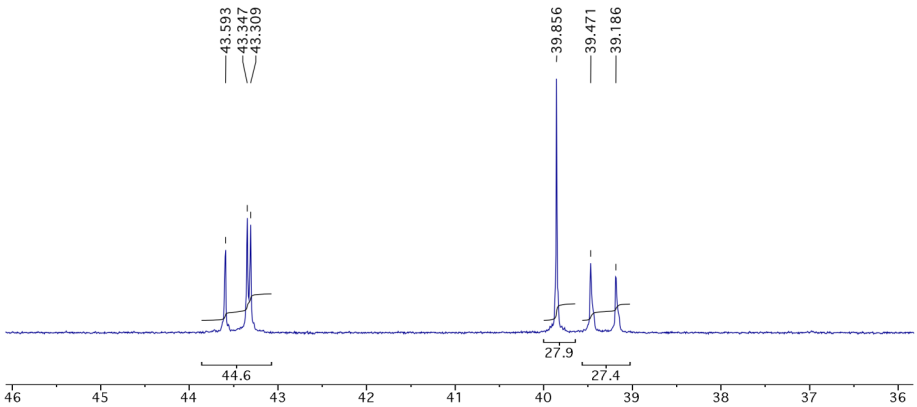


Figure S8. ^{31}P NMR (145.8 MHz, acetone-d_6, r.t.); *excerpt, coordinated phosphane signals.*

***Table S1**. NMR data and population analysis:*

	$\delta(^{31}P)$		$\int {}^{31}P$	$\delta(^{1}H)_{Cp}$	$\int (^{1}H)_{Cp}$
$CpRuCl(PPh_3)_2$	39.9 ppm (s)		28%	4.09 (s)	28%
$CpRuCl(PPh_3)(t\text{-}BuPyPPh_2)$	39.3 (d, J = 41.4 Hz)	(27.4%)	55%	4.17 (s)	56%
	43.5 (d, J = 41.4 Hz)	(27.4%)			
$CpRuCl(t\text{-}BuPyPPh_2)_2$	43.3 (s)		17%	4.21 (s)	16%
Σ (mol-%)			100%		100%

5. General procedures for preparative alkyne hydration

General procedure for catalytic anti-Markovnikov hydration of terminal alkynes (GP3)

Reactions were performed on a scale of 0.25–4.0 mmol: Freshly degassed solvent (acetone/water = 4:1 (*v*/*v*); 2.5 mL/mmol) was added to a Schlenk-tube (*not* dried) equipped with a magnetic stirring bar under argon, containing $CpRuCl(PPh_3)_2$ (2–10 mol-%; typically 2 mol-%) and AZARYPHOS ligand (2–10 mol-%, 1–1.2 equiv. relative to Ru; typically 2 mol-%). The mixture was heated to 65 °C for 30 min.* The substrate was added at once and the reaction mixture heated to 70 °C with stirring.** Reaction progress was checked by TLC- or GC/MS-analysis. After completion of the reaction (2–16 h), acetone was removed under reduced pressure (e.g., rotatory evaporator). The aqueous/organic mixture was extracted with *t*-BuOMe (3 x 5 mL). The combined organic phase was washed with brine (5 mL) and dried over $MgSO_4$. Filtration and evaporation afforded the crude product, which was purified by Kugelrohr distillation or column chromatography (CC).

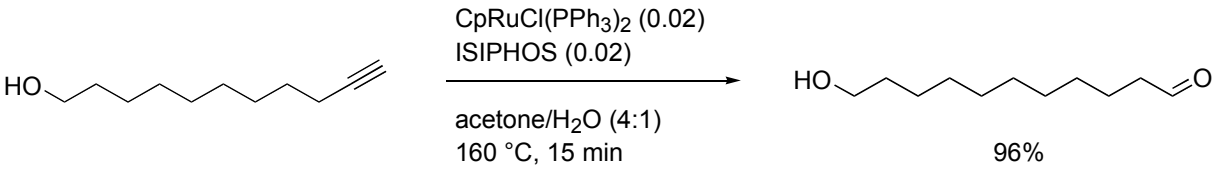
*Notes: * This ligand exchange phase may be omitted (compare also GP4), but it appeared that slightly better results were obtained with it, particularly at lower catalyst loadings. ** The mixture may be cooled to r.t., prior to addition of the substrate, in order to prevent evaporation losses of the solvent (if the substrate is added in a counter-stream of argon).*

General procedure for catalytic anti-Markovnikov hydration of terminal alkynes at elevated temperature, with microwave heating (GP4)

Reactions were typically performed on a 0.5 mmol scale: In a 20 mL microwave vessel under argon, $CpRuCl(PPh_3)_2$ (2 mol-%), AZARYPHOS ligand (2 mol-%) and substrate (1 equiv.) were combined with a freshly degassed solvent mixture (acetone/water = 4:1 (*v*/*v*);1.25 mL/mmol) and heated to 160 °C for 2–15 min (*focused microwave irradiation with external IR-temperature sensor; the heating power is variable and regulated by the microwave unit so as to keep the temperature constant at 160 °C; see next page for a representative experiment protocol*). After cooling to r.t., acetone was removed under reduced pressure and the aqueous/organic mixture extracted with *t*-BuOMe (3 x 5 mL). The combined organic phase was washed with brine (5 mL) and dried over $MgSO_4$. Filtration and evaporation afforded the crude product, which was purified by Kugelrohr distillation or column chromatography (CC).

Microwave heating protocol for a representative catalytic hydration

Reaction: (Table 1, entry 3b)

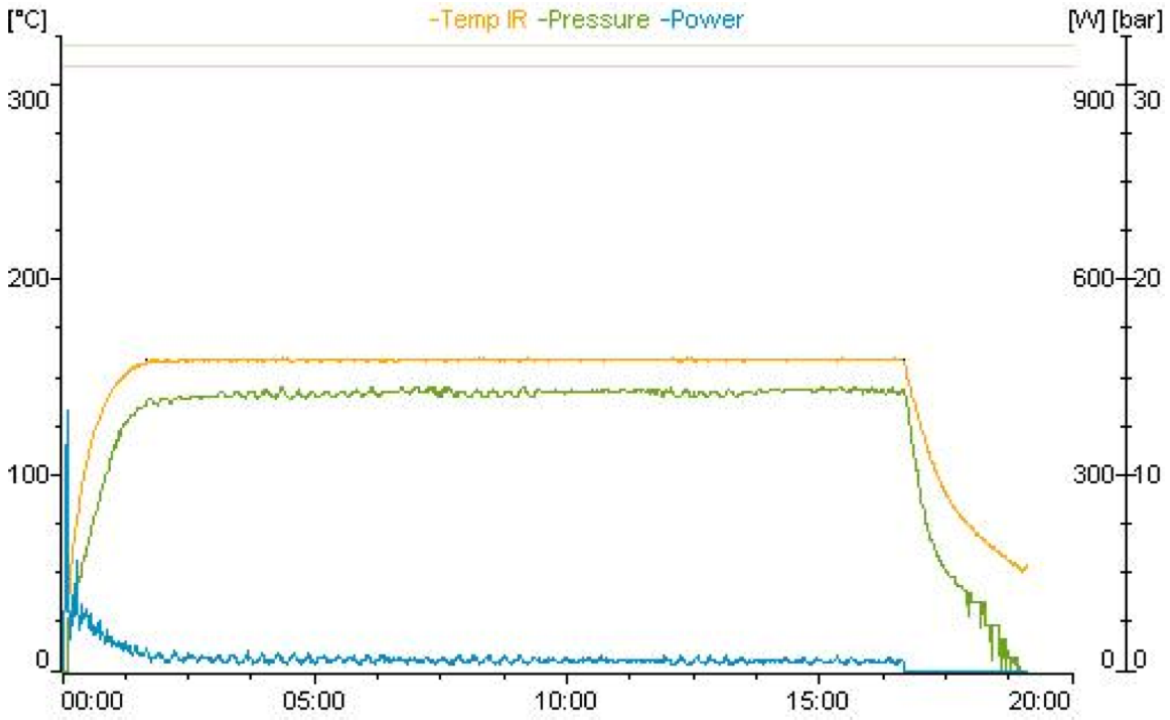


Experiment Information:

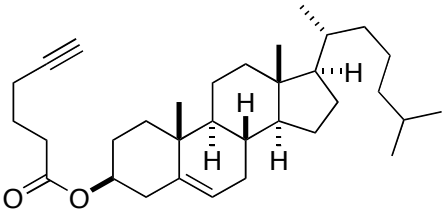
Name: **fb-064**
Temperature Control: **IR**
Program

Step	Program	Temperature	Time	Stirrer Speed
		°C	mmm:ss	rpm
1	Heat to temperature	160	-	600
2	Hold	-	15:00	600
3	Cool down	55	0:00	600

Date: **Friday, October 08, 2010 1:48 PM**
User: **Administrator**
Date of last IR sensor adjustment: **Wednesday, October 06, 2010 10:03 AM**
User name of last IR sensor adjustment: **Administrator**
Result: **OK**

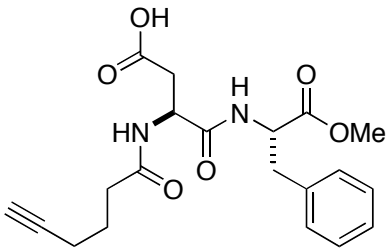


6. Substrates for catalytic anti-Markovnikov hydration



Cholesteryl 5-hexynoate. To a solution of cholesterol (10 mmol, 3.87 g) and 5-hexynoic acid (12 mmol, 1.35 g) in DCM (20 mL) at 0 °C, DCC (15 mmol, 15 mL of a 1 M solution in DCM) and DMAP (5 mmol, 611 mg) was added successively. The mixture was warmed to r.t. (23 °C) and stirred for 20 h. The suspension was filtered and the solid washed with TBME. The combined filtrate was evaporated and the residue purified by CC (TBME/*n*-pentane 1:100–1:30) to give 4.74 g (99%) of a white solid.

CAS-Nr.: 949584-05-8, **MP:** 75–76 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.67 (s, 3H), 0.85 (d, *J* = 1.8 Hz, 3H), 0.87 (d, *J* = 1.8 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 1.02 (s, 6H), 1.07-1.21 (m, 7H), 1.25-1.39 (m, 4H), 1.42-1.64 (m, 7H), 1.77-1.89 (m, 5H), 1.92-2.06 (m, 3H), 2.26 (dt, *J* = 2.6, 7.0 Hz, 2H), 2.31 (d, *J* = 7.6 Hz, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 4.55-4.64 (m, 1H), 5.37 (d, *J* = 4.6 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 12.1 (CH_3), 18.1 (CH_2), 19.0 (CH_3), 19.6 (CH_3), 21.3 (CH_2), 22.8 (CH_3), 23.1 (CH_3), 24.0 (CH_2), 24.1 (CH_2), 24.5 (CH_2), 28.0 (CH_2), 28.3 (CH), 28.5 (CH_2), 32.1 (CH), 32.1 (CH_2), 33.5 (CH_2), 36.0 (CH), 36.4 (CH_2), 36.8 (C), 37.2 (CH_2), 38.4 (CH_2), 39.7 (CH_2), 39.9 (CH_2), 42.5 (C), 50.2 (CH), 56.3 (CH), 56.9 (CH), 69.2 (C≡CH), 74.1 (CHOR), 83.5 (C≡C), 122.7 (C=CH), 139.7 (C=C), 172.5 COOR) ppm. **IR** (ATR) $\tilde{\nu}$ = 3262 (m), 2940 (vs), 2968 (s), 1718 (vs), 1462 (s), 1375 (s), 1323 (s), 1263 (vs), 1240 (s), 1196 (m), 1152 (m), 1062 (w), 959 (vw), 923 (w), 839 (w), 801 (m), 732 (w), 689 (vs) cm^{-1}. **MS** (EI, 70 eV): *m/z* (%) = 480 (3), 369 (55), 368 (100), 353 (24), 260 (18), 255 (14), 247 (15), 147 (25), 145 (19), 107 (11), 105 (12), 95 (15), 81(14), 67 (11), 57 (10), 55 (14). **Elemental analysis**: calc. (%) for $C_{33}H_{52}O_2$: C 82.44, H 10.90; found: C 82.63, H 10.98.



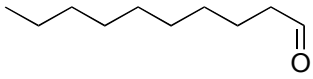
***N*-(*N'*-Hex-5-ynoyl-L-α-aspartyl)-L-phenylalanine 1-methyl ester (*N'*-Hex-5-ynoyl-aspartame)**. DCC (3.35 mmol, 691 mg) and *N*-hydroxysuccinimide (3.35 mmol, 385 mg) were added to a solution of 5-hexynoic acid (3.04 mmol, 341 mg) in DCM (5 mL). The mixture was stirred at 40 °C for 3 h, cooled to rt, and filtered. The solid material was rinsed thoroughly with DCM. The combined filtrate was evaporated under reduced pressure and the resulting crude material dissolved in DMF (3 mL). *N*-(L-α-Aspartyl)-L-phenylalanine 1-methyl ester (*aspartame*) (1.52 mmol, 0.448 mg) was added and the solution heated to 60 °C for 16 h. After cooling to rt, the mixture was diluted with DCM (10 mL) and washed with HCl (aq) (2 M, 10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification of

the crude product by CC (DCM/MeOH = 20:1+1% AcOH) gave 385 mg (65%) of a white solid.

MP: 119–120 °C. **^{1}H NMR** (250 MHz, $CDCl_3$): δ = 1.80 (quint., *J* = 6.9 Hz, 2H), 1.98 (t, *J* = 2.6 Hz, 1H), 2.22 (dt, *J* = 2.6, 6.8 Hz, 2H), 2.32 (dd, *J* = 6.5, 7.8 Hz, 2H), 2.68 (dd, *J* = 6.5, 17.2 Hz, 1H), 2.91 (dd, *J* = 4.6, 16.1 Hz, 1H), 3.03 (dd, *J* = 6.9, 13.9 Hz, 1H), 3.15 (dd, *J* = 5.7, 13.9 Hz, 7H), 3.70 (s, 3H), 4.72-4.90 (m, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 2.31 (d, *J* = 7.6 Hz, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 4.55-4.64 (m, 1H), 5.37 (d, *J* = 4.6 Hz, 1H), 7.08-7.16 (m, 2H), 7.18-7.32 (m, 3H), 7.25 (br s, 1H) ppm. **^{13}C NMR** (63 MHz, $CDCl_3$): δ = 17.9 (CH_2), 24.0 (CH_2), 34.9 (CH_2), 35.9 (CH_2), 37.8 (CH_2), 49.2 (CH_3), 52.6 (CH), 53.8 (CH), 69.7 (C≡CH), 83.3 (C≡C), 127.3 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 129.4 ($C_{Ar}H$), 135.9 (C_{Ar}), 170.5 (CONR), 171.7 (COOMe), 173.1 (COOH), 174.6 (CONR) ppm. **IR** (ATR) $\tilde{\nu}$ = 2916 (m), 2844 (w), 1707 (s), 1686 (vs), 1468 (m), 1437 (w), 1408 (w), 1387 (vw), 1345 (w), 1314 (vw), 1284 (m), 1254 (w), 1224 (m), 1194 (vw), 1109 (vw), 1038 (vw), 919 (m), 751 (vw), 724 (w), 690 (w), 667 (vw), 657 (vw) cm^{-1}. **MS** (EI, 70 eV): *m/z* (%) = 370 (4), 310 (4), 293 (4), 225 (24), 224 (94), 181 (6), 167 (10), 166 (12), 149 (17), 143 (89), 120 (23), 111 (16), 100 (30), 99 (95), 98 (79), 83 (48), 70 (67), 61 (81), 56 (100), 55 (76), 43 (64); MALDI-TOF: *m/z* = 410.863 $[M+Na]^+$ **Elemental analysis**: calc. (%) for $C_{20}H_{24}N_2O_6$: C 61.84, H 6.23, N 7.21; found: C 61.77, H 6.47, N 7.32.

7. Products of anti-Markovnikov alkyne hydration

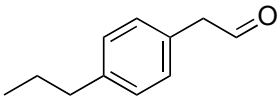
Decanal. a) *(Table 1, entry 1a)* Synthesis according to **GP3** with 1-decyne (2 mmol, 277 mg), $CpRuCl(PPh_3)_2$ (30 mg, 2.0 mol-%) and ISIPHOS (24 mg, 2.5 mol-%) at 60 °C for 18 h. Purification by CC (TBME/*n*-pentane = 1:50) gave 310 mg (99%) of a colorless liquid.



b) *(Table 1, entry 1b)* Synthesis according to **GP4** with 1-decyne (1 mmol, 138 mg), $CpRuCl(PPh_3)_2$ (14.5 mg, 2.0 mol-%) and ISIPHOS (9.3 mg, 2.0 mol-%) at 160 °C for 15 min. Purification by CC (TBME/*n*-pentane = 1:50) gave 145 mg (93%) of a colorless liquid.

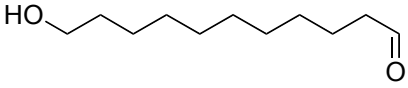
Known compound: **CAS-Nr.:** 112-31-2, **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.1 Hz, 3H), 1.22-1.37 (m, 12H), 1.63 (quint, *J* = 7.3 Hz, 2H), 2.42 (dt, *J* = 1.9, 7.3 Hz, 2H), 9.76 (t, *J* = 1.9 Hz, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.1 (CH_2), 22.6 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 43.9 (CH_2), 202.8 (CHO) ppm. Analytical data agree with those reported in literature.[11]

(4-*n*-Propylphenyl)acetaldehyde. *(Table 1, entry 2)* Synthesis according to **GP3** with (4-*n*-propylphenyl)acetylene (5 mmol, 720 mg), $CpRuCl(PPh_3)_2$ (73 mg, 2 mol-%) and ISIPHOS (58 mg, 2.5 mol-%) at 60 °C for 17 h. Kugelrohr distillation at 120 °C gave 709 mg (87%) colorless liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.3 Hz, 3H), 1.63 (s, *J* = 7.4 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 3.65 (d, *J* = 2.4 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 9.73 (t, *J* = 2.4 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 24.7 (CH_2), 37.8 (CH_2), 50.4 (CH_2), 129.0 (C_{Ar}), 129.1 (2 x $C_{Ar}H$), 129.5 (2 x $C_{Ar}H$), 141.9 (C_{Ar}), 199.6 (CHO) ppm. **IR** ($CHCl_3$) $\tilde{\nu}$ = 3432 (w), 3091 (w), 3051 (w), 3022 (m), 3259 (vs), 2929 (vs), 2870 (s), 2723 (w) 1725 (vs), 1514 (s), 1461 (m), 1420 (m), 1382 (w), 1118 (vw), 1039 (w), 1022 (w), 995 (vw), 935 (vw), 802 (m), 536 (w), 513 (w) cm^{-1}. **MS** (EI, 70 eV): *m/z* (%) = 162 (29), 133 (100), 105 (22), 91 (35), 77 (11). **Elemental analysis**: calc. (%) for $C_{11}H_{14}O$: C = 81.44, H = 8.70; found: C = 81.17, H = 8.74.

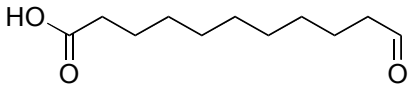
11-Hydroxyundecanal. a) *(Table 1, entry 3a)* Synthesis according to **GP3** with 10-undecyn-1-ol (1 mmol, 168 mg), $CpRuCl(PPh_3)_2$ (15 mg, 2 mol-%) and ISIPHOS (12 mg, 2.5 mol-%) at 60 °C for 3 h. Purification by CC (TBME/*n*-pentane = 1:1) gave 175 mg (94%) of white solid.



b) *(Table 1, entry 3b)* Synthesis according to **GP4** with 10-undecyn-1-ol (1 mmol, 168 mg), $CpRuCl(PPh_3)_2$ (14.5 mg, 2.0 mol-%) and ISIPHOS (9.3 mg, 2.0 mol-%) at 160 °C for 15 min. Purification by CC (TBME/*n*-pentane = 1:1) gave 179 mg (96%) of colorless liquid.

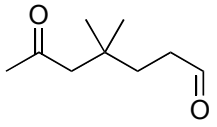
[11] X. -Q. Li, C. Zhang, *Synthesis* **2009**, 1163.

Known compound: **CAS-Nr.:** 22054-16-6, **MP:** 76–77 °C **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.27-1.36 (m, 12H), 1.40-1.51 (m, OH), 1.56 (quint, *J* = 7.0 Hz, 2H), 1.63 (quint, *J* = 7.1 Hz, 2H), 2.42 (ddt, *J* = 1.0, 1.9, 7.3 Hz, 2H), 3.64 (dt, *J* = 1.0, 6.6 Hz, 2H), 9.77 (dt, *J* = 0.9, 1.9 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.3 (CH_2), 25.9 (CH_2), 29.4 (CH_2), 29.5 (2 x CH_2), 29.6 (CH_2), 29.7 (CH_2), 33.0 (CH_2), 44.1 (CH_2), 63.2 (CH_2), 202.9 (CHO) ppm. Analytical data agree with those reported in literature.[12]

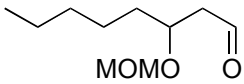
11-Oxo-undecanoic acid. *(Table 1, entry 4)* Synthesis according to **GP3** with 10-undecynoic acid (2 mmol, 365 mg), 

$CpRuCl(PPh_3)_2$ (30 mg, 2 mol-%) and ISIPHOS (24 mg, 2.5 mol-%) at 60 °C for 3 h. Purification by CC (TBME/*n*-pentane = 1:5 + 2% AcOH) gave 388 mg (97%) off-white solid.

MP: 46–47 °C **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.25-1.37 (m, 10H), 1.56 (quint, *J* = 7.0 Hz, 2H), 1.63 (quint, *J* = 7.4 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.42 (dt, *J* = 1.9, 7.4 Hz, 2H), 9.76 (t, *J* = 1.9 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.3 (CH_2), 24.9 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 34.2 (CH_2), 44.1 (CH_2), 180.0 (COOH), 203.0 (CHO) ppm. **IR** (ATR): $\tilde{\nu}$ = 3432 (w), 3091 (w), 3051 (w), 3022 (m), 3259 (vs), 2929 (vs), 2870 (s), 2723 (w) 1725 (vs), 1514 (s), 1461 (m), 1420 (m), 1382 (w), 1118 (vw), 1039 (w), 1022 (w), 995 (vw), 935 (vw), 802 (m), 536 (w), 513 (w) cm^{-1}.

4,4-dimethyl-6-oxoheptanal. *(Table 1, entry 5)* Synthesis according to **GP3** with 4,4-dimethyl-6-heptyn-2-one (0.5 mmol, 69 mg), $CpRuCl(PPh_3)_2$ (14.5 mg, 4 mol-%) and ISIPHOS (9.3 mg, 4 mol-%) at 65 °C for 4 h. Purification by CC (Et_2O/*n*-pentane = 1:4) gave 75 mg (96%) colorless liquid. 

Known compound: **CAS-Nr.:** 919091-25-1, **^{1}H NMR** (360 MHz, $CDCl_3$): δ = 1.01 (s, 6H), 1.66-1.73 (m, 2H), 2.14 (s, 3H), 2.34 (s, 2H), 2.38-2.45 (m, 2H), 9.77 (t, *J* = 1.8 Hz, 1H) ppm. **^{13}C NMR** (90 MHz, $CDCl_3$): δ = 27.1 (CH_3), 32.5 (CH_3), 33.0 (C), 33.4 (CH_2), 39.4 (CH_2), 53.5 (CH_2), 202.5 (CHO), 208.3 (CO) ppm. Analytical data agree with those reported in literature.[9]

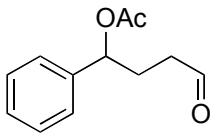
3-(Methoxymethyloxy)-octanal. *(Table 1, entry 6)* Synthesis according to **GP3** from 3-(methoxymethyloxy)-1-octyne (1 mmol, 170 mg), 

$CpRuCl(PPh_3)_2$ (36.3 mg, 5 mol-%) and ISIPHOS (29.3 mg, 6.5 mol-%) at 60 °C for 20 h. Purification CC (TBME/*n*-pentane = 1:10) gave 103 mg (55%) as colorless liquid.

Known compound: **CAS-Nr.:** 108383-17-1, **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.1 Hz, 3H), 1.24-1.39 (m, 6H), 1.47-1.58 (m, 1H), 1.59-1.69 (m, 1H), 2.56 (ddd, *J* = 1.8, 4.8, 16.3 Hz, 1H), 2.64 (ddd, *J* = 2.8, 7.0, 16.3 Hz, 1H), 3.35 (s, 3H), 4.08 (quin, *J* = 6.0 Hz, 1H), 4.66 (d, *J* = 7.0 Hz, 1H), 4.69 (d, *J* = 7.0 Hz, 1H), 9.81 (dd, *J* = 1.9, 2.8 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6 (CH_2), 25.0 (CH_2), 31.8 (CH_2), 35.0 (CH_2),

[12] M. Marchetti, C. Botteghi, S. Paganelli, M. Taddei, *Adv. Synth. Catal.* **2003**, *345*, 1229.

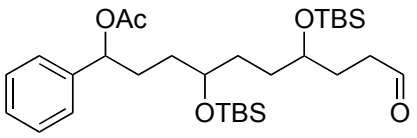
48.8 (CH_2), 55.7 (OCH_3), 73.2 (CHOR), 95.8 (CH_2O_2), 201.3 (CHO) ppm. Analytical data agree with those reported in literature.[4]



4-Acetoxy-4-phenylbutanal. a) *(Table 1, entry 7a)* Synthesis according to **GP3** with 1-phenylbut-3-yn-1-yl acetate (1 mmol, 188 mg), $CpRuCl(PPh_3)_2$ (15 mg, 2 mol-%) and ISIPHOS (9.3 mg, 2 mol-%) at 65 °C for 4 h. Purification CC (Et_2O/*n*-pentane = 1:4) gave 188 mg (92%) colorless liquid.

b) *(Table 1, entry 7b)* Synthesis according to **GP4** with 1-phenyl-3-butyn-1-yl acetate (1 mmol, 188 mg), $CpRuCl(PPh_3)_2$ (14.5 mg, 2.0 mol-%) and ISIPHOS (9.3 mg, 2.0 mol-%) at 160 °C for 2 min. Purification by CC (Et_2O/*n*-pentane = 1:4) gave 203 mg (99%) colorless liquid.

Known compound: **CAS-Nr.:** 76698-68-5, **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.00 (s, 3H), 2.04-2.21 (m, 2H), 2:39 (t, 1H *J* = 7.1 Hz, 2H), 5.70 (dd, *J* = 6.0, 7.5 Hz, 1H), 7.15-7.38 (m, 5H), 9.65 (s, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.3 (CH_3), 28.8 (CH_2), 40.0 (CH_2), 75.1 (CH), 126.4 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 139.7 (C_{Ar}), 170.3 (COOR), 201.1 (CHO) ppm. Analytical data agree with those reported in literature.[5]

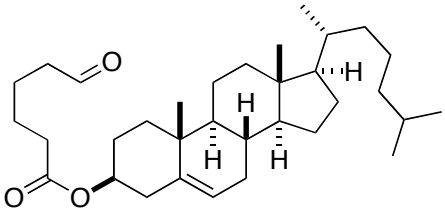


10-Acetoxy-4,7-bis(*tert*-butyldimethylsilyloxy)-10-phenyldecanal. a) *(Table 1, entry 8a)* Synthesis according to **GP3** from 10-Acetoxy-4,7-bis((*tert*-butyldimethylsilyl)oxy)-10-phenyl-1-decyne (0.25 mmol, 133 mg), $CpRuCl(PPh_3)_2$ (7.3 mg, 4 mol-%) and ISIPHOS (4.7 mg, 4 mol-%) at 65 °C in acetone/water = 8:1 (*v*/*v*) (2.5 mL) for 16 h. Purification by CC (Et_2O/*n*-pentane = 1:4) gave 98 mg (71%) colorless oil.

b) *(Table 1, entry 8b)* Synthesis according to **GP4** from 10-acetoxy-4,7-bis((*tert*-butyldimethylsilyl)oxy)-10-phenyl-1-decyne (0.5 mmol, 266 mg), $CpRuCl(PPh_3)_2$ (14.5 mg, 4.0 mol-%) and ISIPHOS (9.3 mg, 4.0 mol-%) at 160 °C in acetone/water = 8:1 (*v*/*v*) (2.5 mL) for 2 min. Purification by CC (Et_2O/*n*-pentane = 1:4) gave 253 mg (92%) colorless oil.

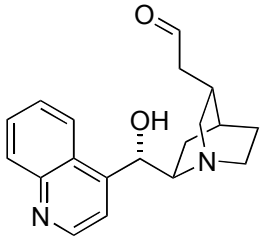
^{1}H NMR (360 MHz, $CDCl_3$): δ = -0.04–0.05 (m, 12 H), 0.84-0.89 (m, 18H), 1.23-1.98 (m, 12H), 2.06 (s, 3H), 2.46 (t, *J* = 7.4 Hz, 2H,), 3.57-3.73 (m, 2H), 5.70 (t, *J* = 6.9 Hz, 1H), 7.24-7.39 (m, 5H), 9.77 (t, J = 1.3 Hz, 1H) ppm. **^{13}C-NMR** (90 MHz, $CDCl_3$): (interpreted as 1 compound, multiple shift values and ranges given for diastereomeric signals) δ = -4.45 – -4.27 (4 x $SiCH_3$), 18.05/18.08 (2 C), 21.3 (CH_3), 26.0 (2 CH_3), 28.8–28.9 (CH_2), 31.42/31.59/31.61/31.75 (CH_2), 32.11/32.18/32.29/32.40 (CH_2), 32.48–32.80 (2 CH_2), 39.69/39.70/39.76/39.77 (CH_2), 71.17/71.18/71.25/71.27 (CH), 71.53/71.63/71.65/71.75 (CH), 76.10/76.12/76.16 (CH), 126.6 (CH), 127.9 (CH), 128.5 (CH), 140.7 (C), 170.3 (C), 202.5 (CH) ppm. **MS** (ESI, 70 eV, MeCN/H_2O): *m/z* (%) = 573.4 (100, $[M + Na]^+$). **IR** (ATR) $\tilde{\nu}$ = 2952 (s), 2929 (s), 2857 (m), 1731 (s), 1472 (w), 1462 (vw), 1372 (w), 1236 (vs) 1023 (m), 1005 (m), 834 (vs), 773 (vs), 700 (w), 666 (vw) cm^{-1}. **Elemental analysis**: To prevent

oxidation in air, a sample was reduced by $NaBH_4$ to the primary alcohol: calc. (%) for $C_{30}H_{56}O_5Si_2$: C 65.17, H 10.21; found: C 65.21, H 10.00.



Cholesteryl 6-oxohexanoate. *(Table 1, entry 9)* Synthesis according to the **GP3** from cholesteryl 5-hexynoate (0.5 mmol, 240 mg), $CpRuCl(PPh_3)_2$ (36.3 mg, 5 mol-%) and ISIPHOS (29.3 mg, 6.5 mol-%) in acetone/water (4:1) (20 mL) with added DCM (1.5 mL) to increase solubility, at 60 °C for 18 h. Purification by CC (TBME/*n*-pentane = 1:20–1:5) afforded 217 mg (88%) white crystalline solid.

MP: 81–82 °C, **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.68 (s, 3H), 0.86 (d, *J* = 1.8 Hz, 3H), 0.87 (d, *J* = 1.8 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 1.02 (s, 6H), 1.05-1.23 (m, 7H), 1.24-1.40 (m, 4H), 1.42-1.63 (m, 8H), 1.65-1.72 (m, 4H), 1.78-1.89 (m, 2H), 1.92-2.06 (m, 2H), 2.27-2.33 (m, 4H), 2.44-2.49 (m, 2H), 4.57-4.66 (m, 1H), 5.38 (d, *J* = 3.8 Hz, 1H), 9.77 (t, *J* = 1.6 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 12.0 (CH_3), 18.8 (CH_3), 19.4 (CH_3), 21.1 (CH_2), 21.6 (CH_2), 22.7 (CH_3), 22.9 (CH_3), 23.9 (CH_2), 24.4 (CH_2), 24.6 (CH_2), 27.9 (CH_2), 28.1 (CH), 28.3 (CH_2), 31.9 (CH), 32.0 (CH_2), 34.4 (CH_2), 35.9 (CH), 36.3 (CH_2), 36.7 (CH_2), 37.1 (CH_2), 38.2 (C), 39.6 (CH_2), 39.8 (CH_2), 42.4 (C), 43.6 (CH_2), 50.1 (CH), 56.2 (CH), 56.7 (CH), 74.0 (CHOR), 122.6 (C=CH), 139.5 (C=C), 172.5 (COOR), 201.9 (CHO) ppm. **IR** (ATR) $\tilde{\nu}$ = 2937 (vs), 2885 (s), 2718 (w), 1728 (vs), 1464 (s), 1368 (s), 1320 (vw), 1242 (w), 1172 (vs), 1087 (m), 1026 (m), 997 (s), 957 (w), 921 (vw), 882 (vw), 841 (w), 801 (m), 736 (w) cm^{-1}. **MS** (EI, 70 eV): *m/z* (%) = 499 (3), 369 (100), 368 (98), 353 (45), 260 (31), 247 (27), 213 (16), 159 (14), 147 (39), 133 (16), 105 (19), 95 (20), 81 (26), 67 (21), 57 (25). **Elemental analysis**: calc. (%) for $C_{33}H_{54}O_3$: C 79.46, H 10.91; found: C 79.24, H 10.71.

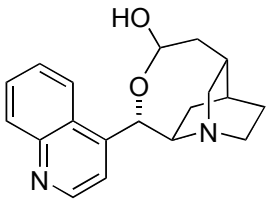


2-((1*S*,4*S*,6*R*)-6-((*S*)-Hydroxy(quinolin-3-yl)methyl)quinuclidin-3-yl) acetaldehyde. *(Table 1, entry 10)* Synthesized according to the **GP3** from 10,11-didehydrocinchonine (0.5 mmol, 146 mg), *p*-toluenesulfonic acid (0.5 mmol, 95 mg; *this additive is necessary to neutralize the tertiary amine functionality*), $CpRuCl(PPh_3)_2$ (36.3 mg, 10 mol-%) and ISIPHOS (23.3 mg, 6.5 mol-%) in acetone/water (4:1) (2.5 mL) at 65 °C for 16 h. Heating was stopped and the reaction mixture was treated with sat. aq. Na_2CO_3 (5 mL). The mixture was extracted with EtOAc (3 x 5 mL). The combined organic solvents were dried over $MgSO_4$ and filtered. Evaporation afforded a crude product, which was purified by CC (EtOAc/MeOH/-NEt_3 = 50:1:1–5:1:1) to give 95 mg (61%) off-white crystalline solid.

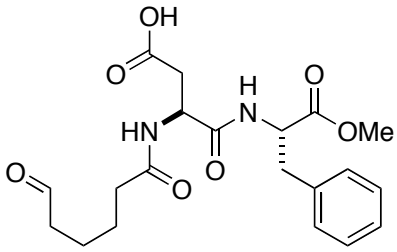
MP: 223–225 °C (dec.),**^{1}H NMR** (360 MHz, $CDCl_3$): δ = 1.10-1.16 (m, 1H), 1.22-1.38 (m, 1H), 1.47-1.65 (m, 2H), 1.67-1.73 (m, 1H), 1.95-2.06 (m, 1H), 2.12-2.24 (m, 1H), 2.65 (ddd, *J* = 1.3, 6.3, 17.4 Hz, 1H), 2.75 (dd, *J* = 8.1, 17.1 Hz, 1H), 2.82-2.91 (m, 1H), 2.93-3.03 (m,

1H), 3.06-3.17 (m, 2H), 3.22-3.31 (m, 1H), 5.87 (s, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.62-7.69 (m, 2H), 7.94 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 8.90 (d, *J* = 4.5 Hz, 1H), 9.80 (s, 1H) ppm. **^{13}C NMR** (90 MHz, $CDCl_3$): δ = 19.6 (CH_2), 26.2 (CH_2), 26.5 (CH), 29.2 (CH), 47.2 (CH_2), 49.9 (CH_2), 50.4 (CH_2), 59.8 (CH_2), 70.9 (CH), 77.2 (CH), 118.1 ($C_{Ar}H$), 122.6 ($C_{Ar}H$), 125.2 (C_{Ar}), 126.8 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 130.3 ($C_{Ar}H$), 148.1 (C_{Ar}), 148.3 (C_{Ar}), 150.1 ($C_{Ar}H$), 201.7 (CHO) ppm. **IR** (ATR) $\tilde{\nu}$ = 3065 (w), 2931 (m), 2877 (m), 2715 (w), 2113 (vw), 1941 (vw), 1909 (vw), 1716 (vs) 1591 (m), 1569 (m), 1508 (m), 1459 (m), 1387 (w), 1333 (m), 1235 (w), 1209 (w), 1169 (w), 1114 (vs), 1059 (s), 1030 (s), 994 (s), 952 (m), 885 (s), 834 (m), 761 (vs), 687 (m) cm^{-1}. **MS** (EI, 70 eV): *m/z* (%) = 311 (20), 310 (100), 282 (14), 281 (44), 172 (14), 159 (31), 158 (11), 153 (13), 152 (68), 143 (23), 142 (10), 140 (22), 130 (21), 125 (13), 124 (54), 82 (13), 56 (13), 55 (19). **Elemental analysis**: calc. (%) for $C_{19}H_{22}N_2O_2$ + 0.8 H_2O: C 70.26, H 7.32, N 8.62; found: C 70.23, H 7.66, N 8.26. **HRMS** (ESI): calc. for $C_{19}H_{23}N_2O_2^+$: 311.17540; found: 311.17556.

Note: In $CDCl_3$, the compound exists almost entirely in the hydroxyaldehyde form; in MeOH-d_4 solution, the hemiacetal form is favored (acetal/hydroxyaldehyde = 94:6). The silyl ether of a related quinidine-derived hemiacetal has been described in the literature.[13]



^{1}H NMR (360 MHz, MeOH-d_4): δ = 1.08–1.19 (m, 1 H), 1.51–1.62 (m, 2 H), 1.69–1.75 (m, 1 H), 1.79–1.92 (m, 2 H), 2.11–2.22 (m, 1 H), 2.74–3.00 (m, 3 H), 3.05–3.14 (m, 1 H), 3.36–3.46 (m, 1 H), 4.53–4.60 (m, 1 H), 5.71 (br s, 1 H), 7.63–7.70 (m, 1 H_{Ar}), 7.72–7.82 (m, 2 H_{Ar}), 8.06 (d, *J* = 8.5 Hz, 1 H_{Ar}), 8.19 (d, *J* = 8.3 Hz, 1 H_{Ar}), 8.83 (d, *J* = 4.6 Hz, 1 H_{Ar}) ppm. Selected signal for the aldehyde form: 9.75–9.77 (br s, 1 H, CHO)



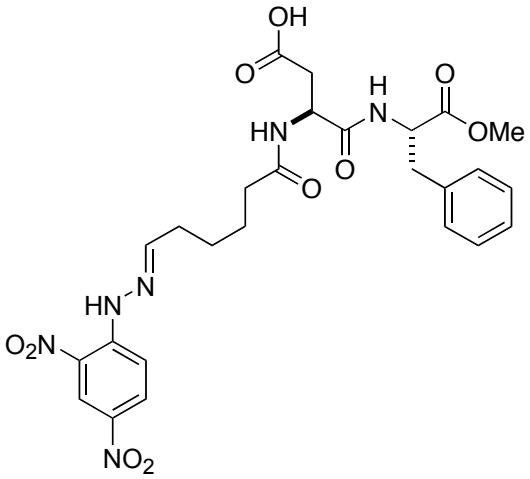
6-Oxohexanoyl-aspartame: *(Table 1, entry 11)* Synthesis according to **GP3** from *N´*-5-hexynoyl-aspartame (0.5 mmol, 194 mg), $CpRuCl(PPh_3)_2$ (7.3 mg, 2 mol-%) and ISIPHOS (4.7 mg, 2.0 mol-%) at 70 °C for 7 h. NMR of the crude compound indicated complete and selective conversion to product, with a high degree of purity, aside of catalyst components still present (>96% crude yield; *see NMR spectra of crude product further below*), but the compound was not readily purified by the standard chromatographic methods at our disposal (i.e., SiO_2, normal phase). Therefore, a 2,4-dinitrophenylhydrazone was prepared for analysis (see below).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.53-1.62 (m, 4H), 1.63 (s, *J* = 7.4 Hz, 2H), 2.26-2.23 (m, 2H), 2.37-2.44 (m, 2H), 2.70 (dd, *J* = 6.0, 16.9 Hz, 1H), 2.85 (dd, *J* = 5.6, 17.0 Hz, 1H), 3.02 (dd, *J* = 6.7, 13.9 Hz, 1H), 3.11 (dd, *J* = 5.6, 13.9 Hz, 1H), 3.65 (s, 3H), 4.76 (dd, *J* = 6.6, 13.4 Hz, 1H), 4.86 (dd, *J* = 5.9, 13.7 Hz, 1H), 7.10 (d, *J* = 6.7 Hz, 2H), 7.16-7.29 (m, 2H),

[13] W. Braje, J. Frackenpohl, P. Langer, H. M. R. Hoffmann, *Tetrahedron* **1998**, *54*, 3495.

7.37 (d, *J* = 7.7 Hz, 1H), 9.68 (s, 1H), 10.50 (br, 1H) ppm. **^{13}C NMR** (90 MHz, $CDCl_3$): δ = 21.4 (CH_2), 24.8 (CH_2), 35.7 (CH_2), 35.8 (CH_2), 35.8 (CH_2), 43.4 (CH_2), 49.3 (CH), 52.4 (CH), 53.7 (CH), 127.0 ($C_{Ar}H$), 128.5 (2 x $C_{Ar}H$), 129.3 (2 x $C_{Ar}H$), 135.8 (C_{Ar}), 170.5 (CONR), 171.6 (COOMe), 173.6 (COOH), 174.0 (CONR), 202.9 (CHO) ppm.

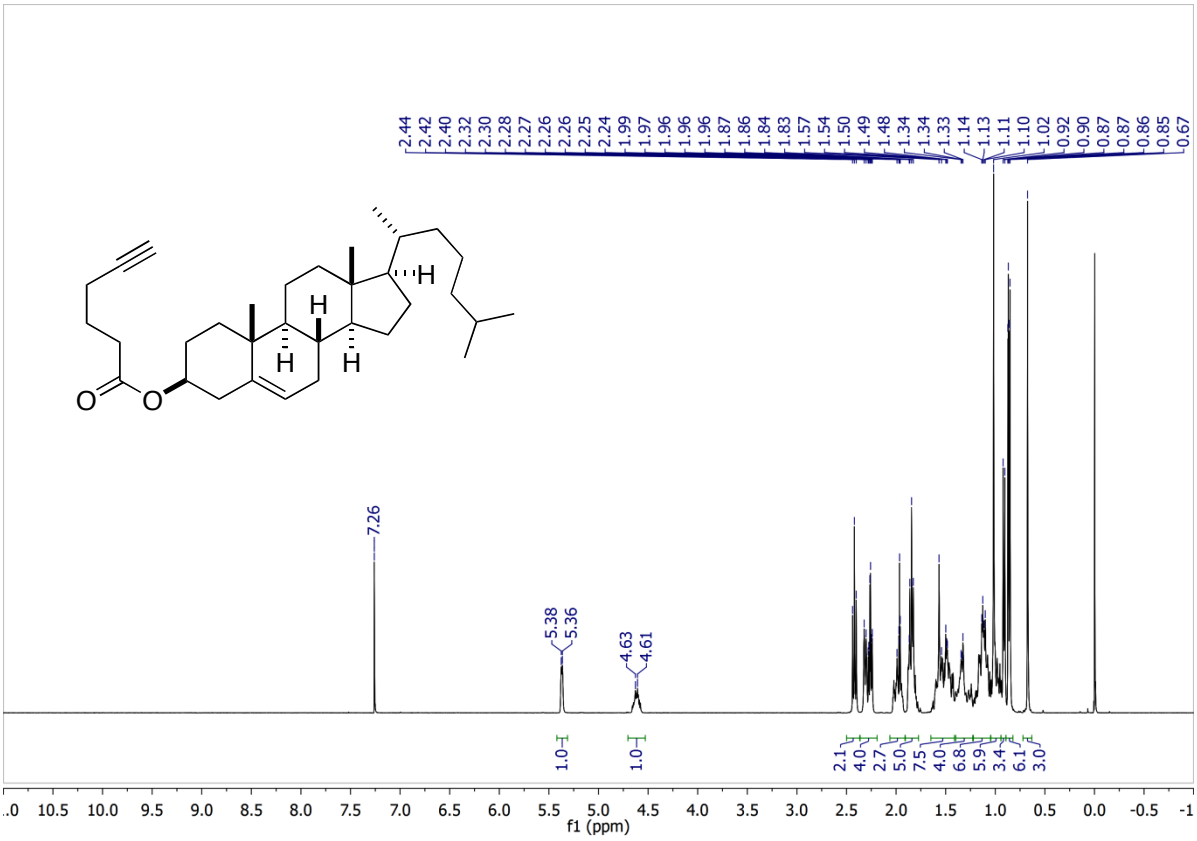
2,4-Dinitrophenylhydrazone of 6-oxohexanoyl-aspartame: *(Table 1, entry 11)* A sample of 6-oxo-hexanoyl-aspartame was prepared as described above. The organic solvent was removed under reduced pressure. To the aqueous slurry was added DCM (3 mL), *p*-toluenesulfonic acid (5 mg, 5 mol-%) and (2,4-dinitrophenyl)hydrazine (99 mg, 0.5 mmol, 1.0 eq). The mixture was heated for 10 min under reflux (40–50 °C), cooled to r.t., diluted with more DCM, washed with aqueous $NH_4Cl_{(sat.)}$ and dried over $MgSO_4$. Filtration and evaporation gave a crude product, which was purified by CC (DCM/MeOH = 10:1) to give 277 mg (94%) of a yellow crystalline solid.



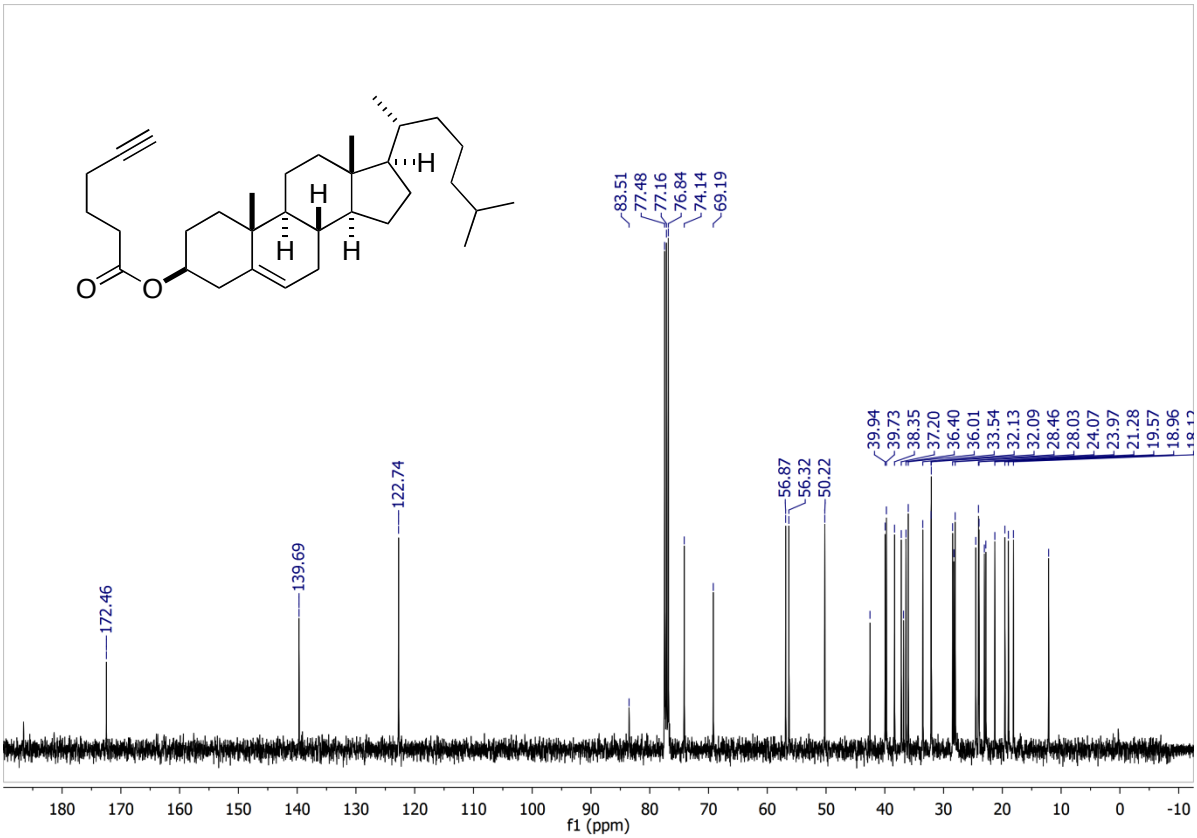
^{1}H NMR (360 MHz, DMSO-d_6): δ = 1.47-1.61 (m, 4H), 1.63 (s, *J* = 7.4 Hz, 2H), 2.08-2.17 (m, 2H), 2.34 (dd, *J* = 6.4, 11.9 Hz, 1H), 2.41 (dd, *J* = 8.5, 16.4 Hz, 1H), 2.62 (dd, *J* = 4.4, 15.5 Hz, 1H), 2.93 (dd, *J* = 8.3, 13.8 Hz, 1H), 3.00 (dd, *J* = 5.9, 13.8 Hz, 1H), 3.58 (s, 3H), 4.44 (dd, *J* = 7.8, 13.7 Hz, 1H), 4.62 (td, *J* = 5.6, 8.2 Hz, 1H), 7.15-7.29 (m, 5H), 7.87 (d, *J* = 9.7 Hz, 1H), 8.01 (t, *J* = 5.3 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 7.5 Hz, 1H), 8.32 (dd, *J* = 2.7, 9.7 Hz, 1H), 8.84 (1H, *J* = 2.7 Hz, 1H), 11.36 (br, 1H), 12.24 (br, 1H) ppm. **^{13}C NMR** (90 MHz, DMSO-d_6): δ = 25.1 (CH_2), 25.7 (CH_2), 32.3 (CH_2), 35.3 (CH_2), 36.7 (CH_2), 37.0 (CH_2), 49.5 (CH), 52.3 (CH), 54.1 (CH), 116.8 ($C_{Ar}H$), 123.5 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 129.1 (C_{Ar}), 129.5 ($C_{Ar}H$), 130.2 ($C_{Ar}H$), 136.9 (C_{Ar}), 137.4 (C_{Ar}), 145.2 (C_{Ar}), 155.4 (C=NR), 171.4 (CONR), 172.1 (COOMe + COOH), 172.5 (CONR) ppm. **IR** (ATR) $\tilde{\nu}$ = 3302 (vw), 2938 (vw), 2436 (vw), 2164 (w), 2023 (w), 1733 (w), 1616 (s), 1518 (s) 1427 (w), 1328 (vs), 1218 (m), 1139 (m), 1078 (w), 918 (vw), 834 (vw), 761 (vw), 744 (m), 705 (w), 697 (w), 675 (vw), 666 (w), 657 (vw) cm^{-1}. **MS** (ESI, 70 eV, MeCN/H_2O): *m/z* (%) = 1781 [3 x M+Na]$^+$ (6), 1211 [2 x M+K]$^+$ (16), 1195 [2 x M+Na]$^+$ (44), 1273 [2 x M+H]$^+$ (8), 625 [M + K]$^+$ (17), 609 [M+Na]$^+$ (100), 587 [M+H]$^+$ (30), 411 (12), 389 (10), 255 (10), 180 (22). **HRMS** (ESI): calc. for $C_{26}H_{31}N_6O_{10}^+$: 587.20962; found: 587.20870.

8. NMR Spectra

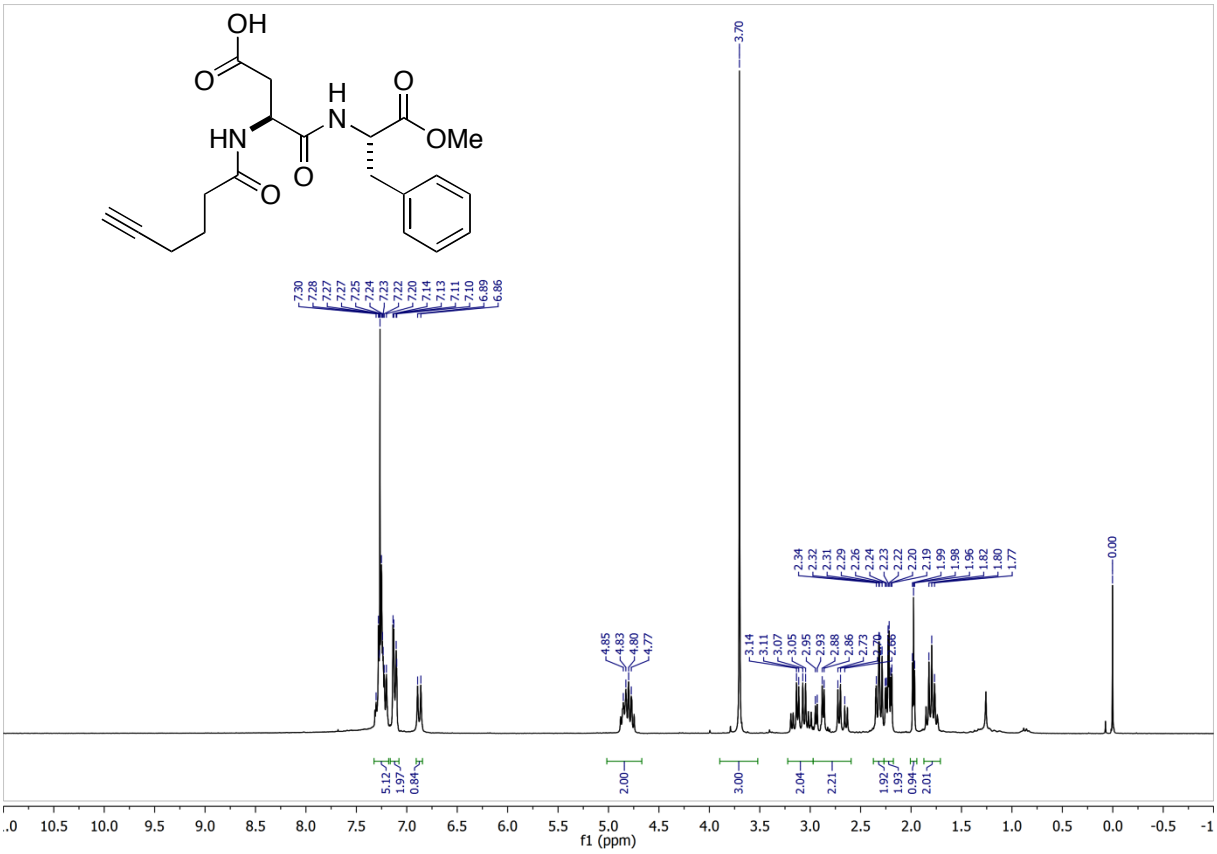
^{1}H-NMR (400 MHz, $CDCl_3$) *(Table 1, entry 9, starting material)*



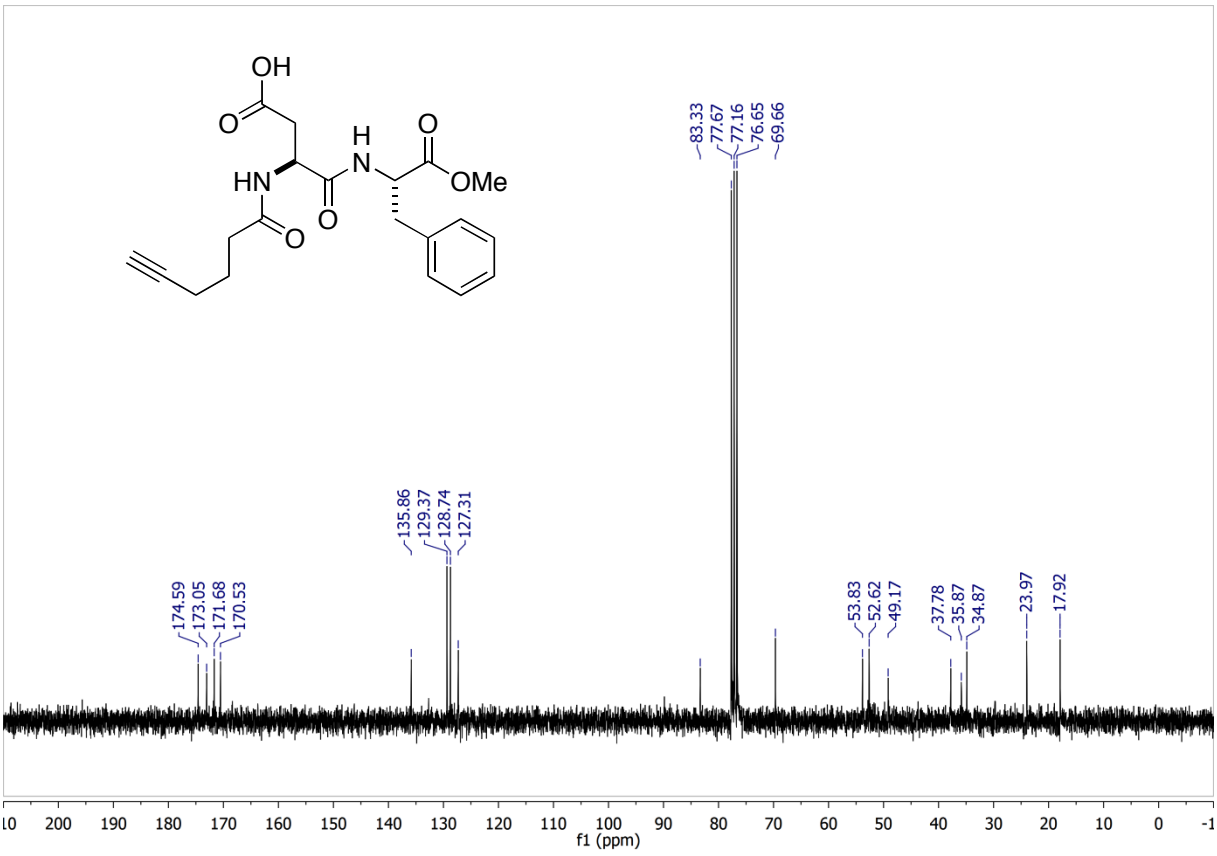
^{13}C-NMR (100 MHz, $CDCl_3$) *(Table 1, entry 9, starting material)*



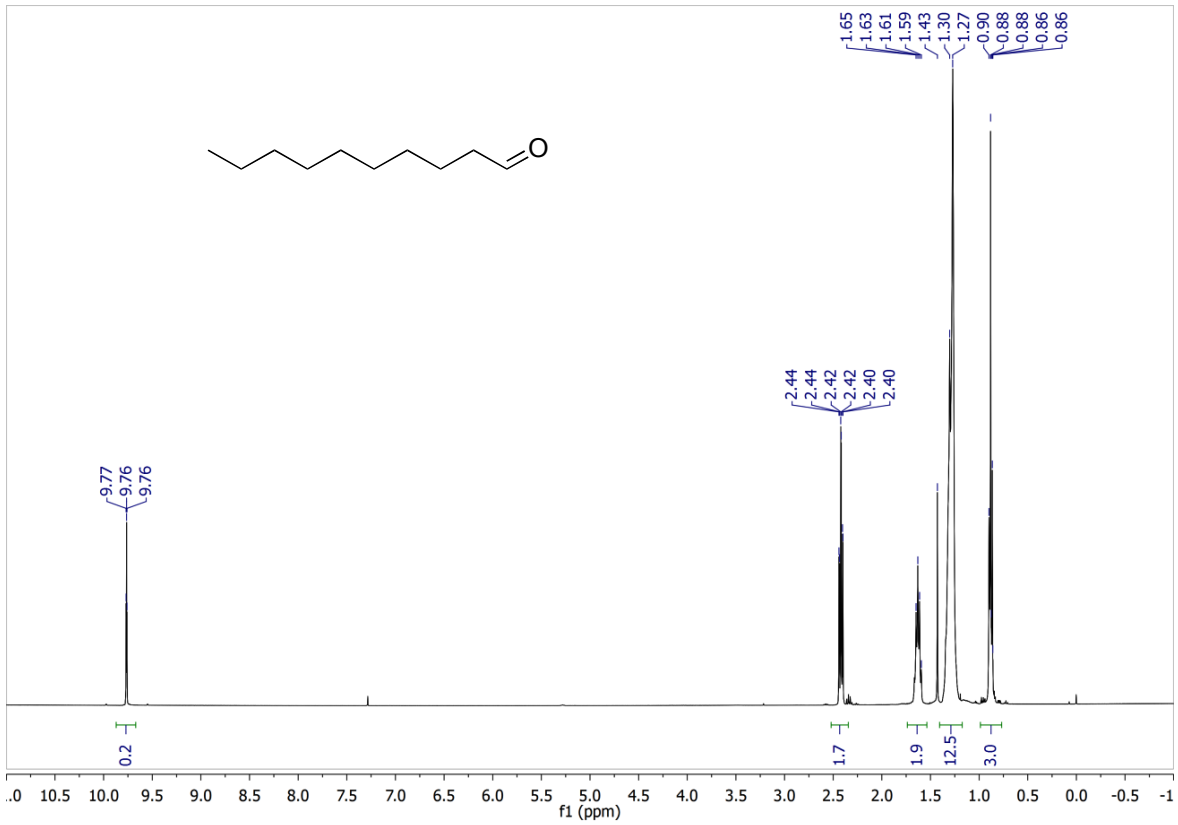
^{1}H-NMR (360 MHz, $CDCl_3$) *(Table 1, entry 11, starting material)*



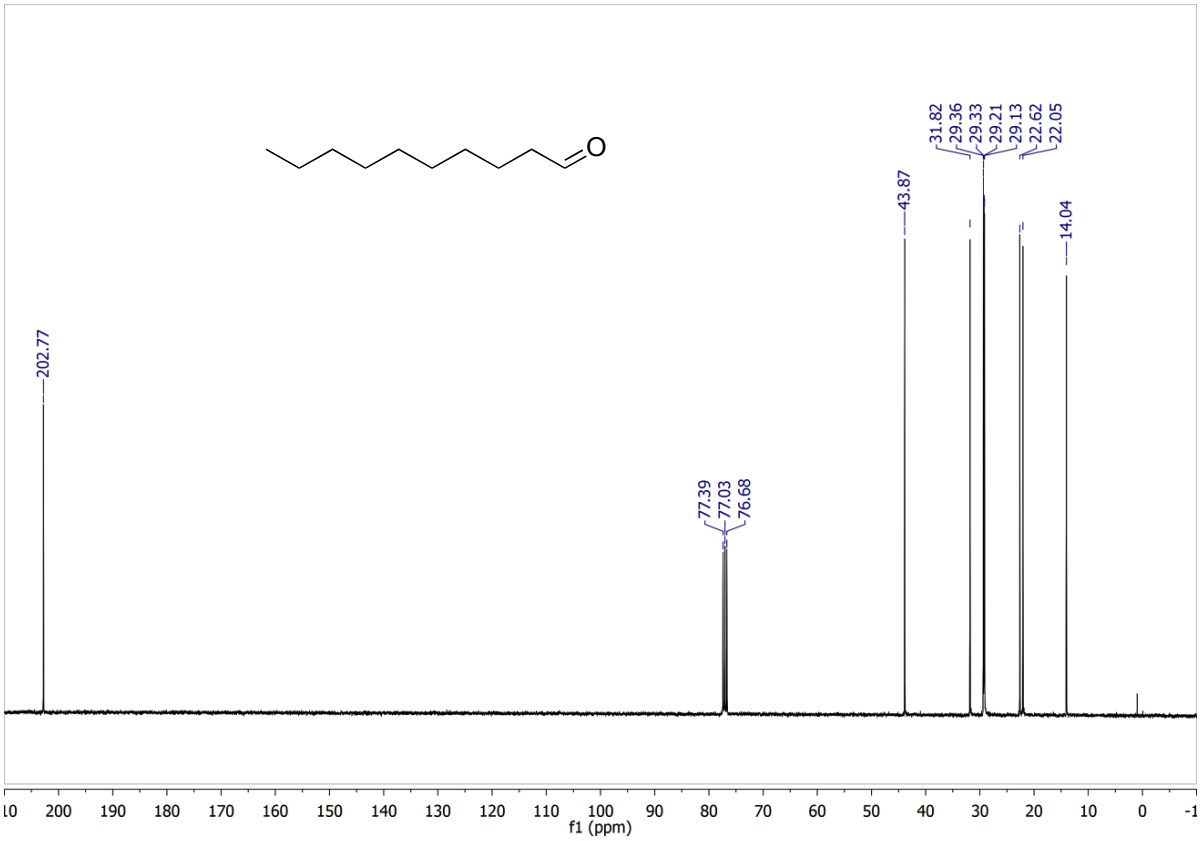
^{13}C-NMR (90 MHz, $CDCl_3$) *(Table 1, entry 11, starting material)*



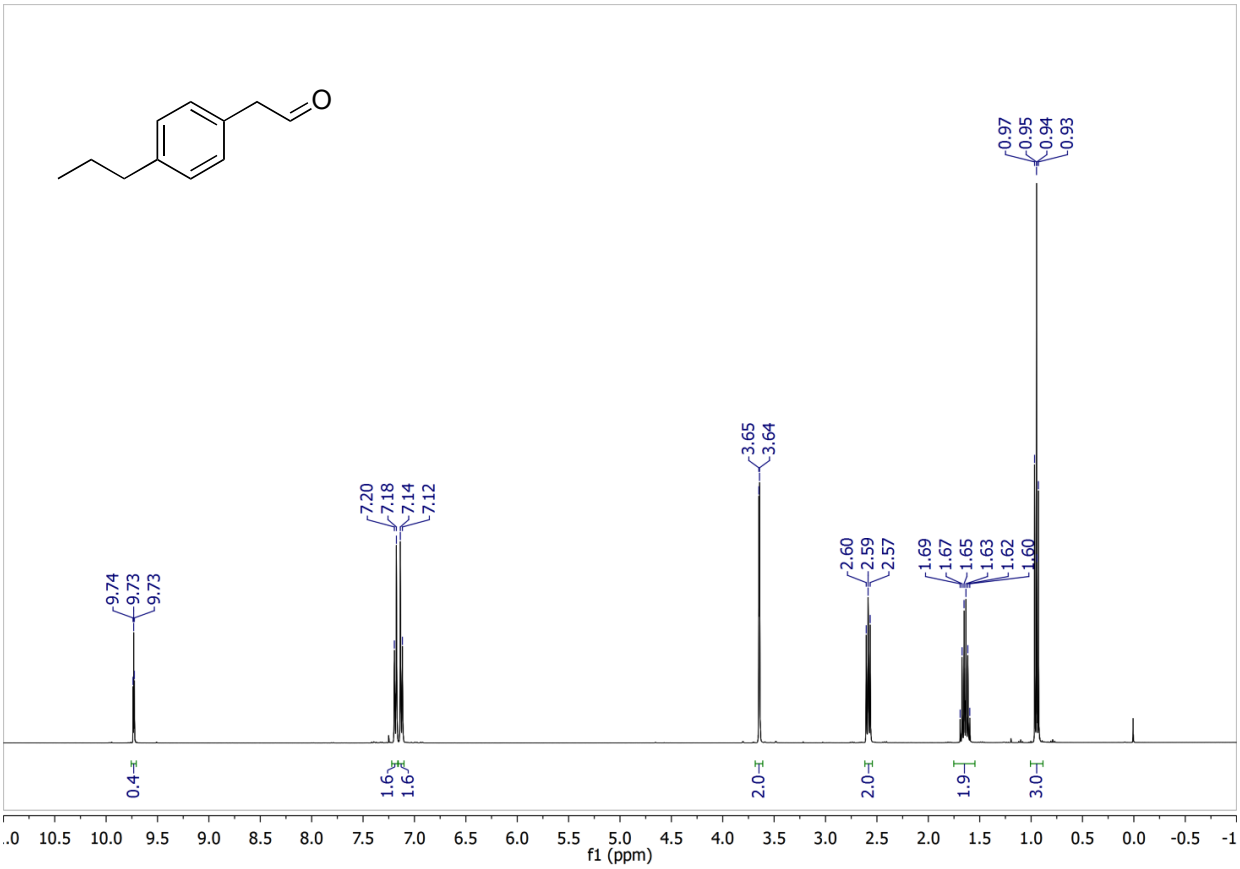
^{1}H-NMR (300 MHz, $CDCl_3$) *(Table 1, entry 1)*



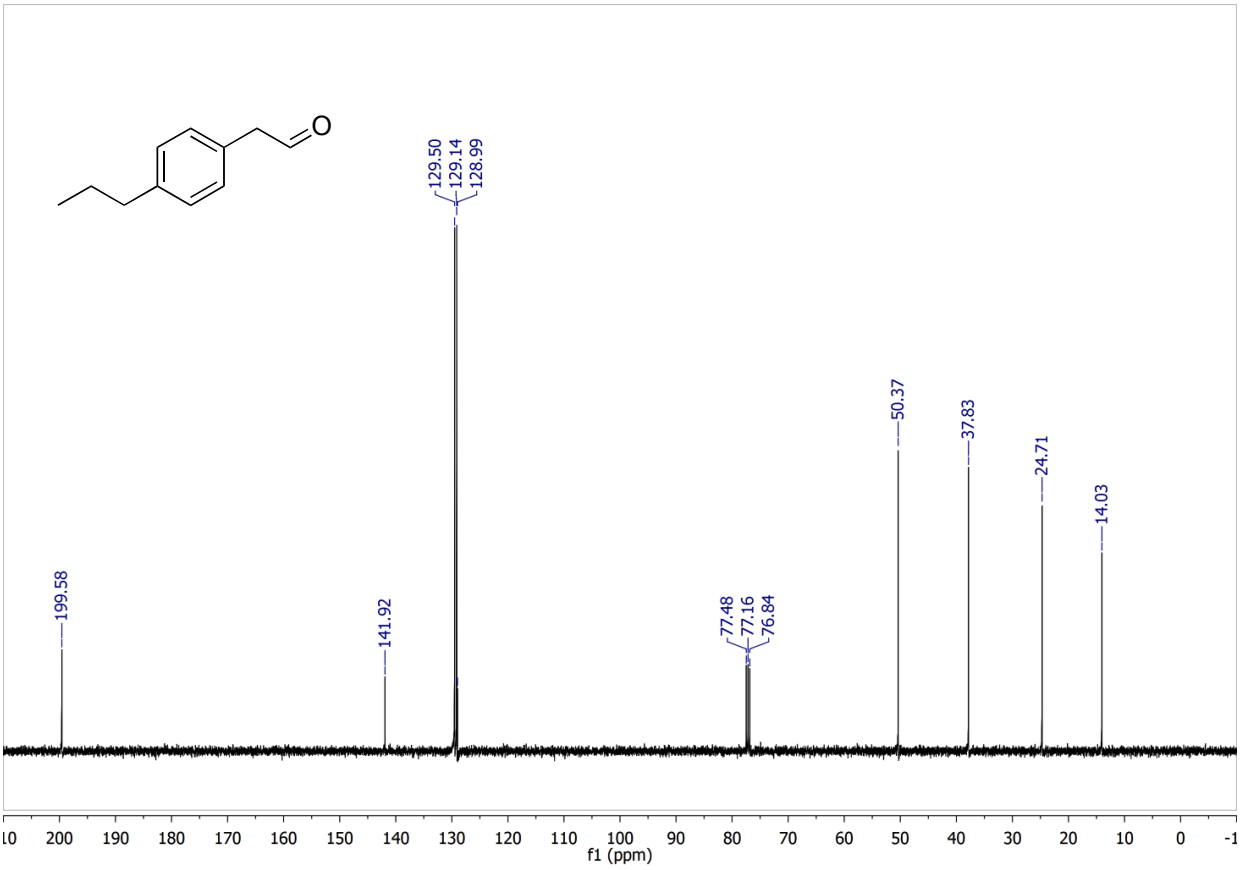
^{13}C-NMR (76 MHz, $CDCl_3$) *(Table 1, entry 1)*



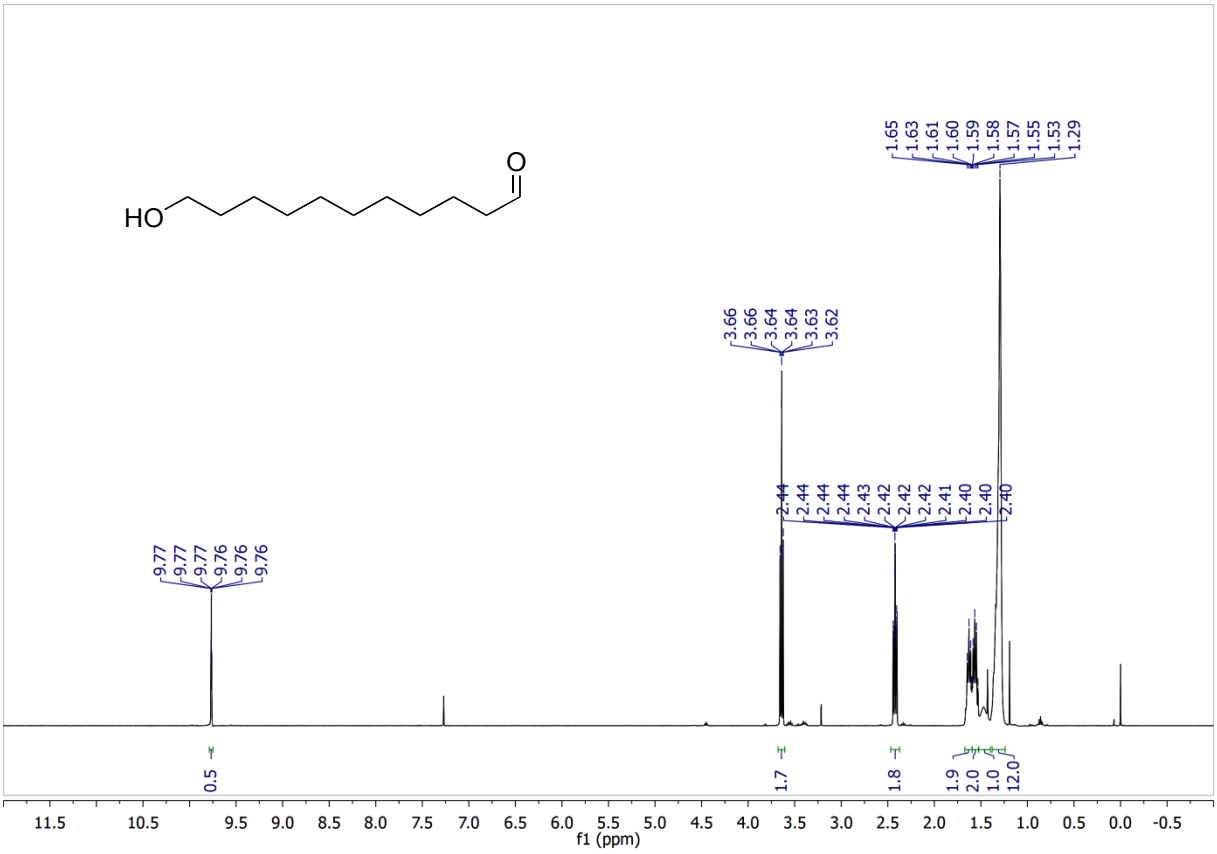
^{1}H-NMR (400 MHz, $CDCl_3$) *(Table 1, entry 2)*



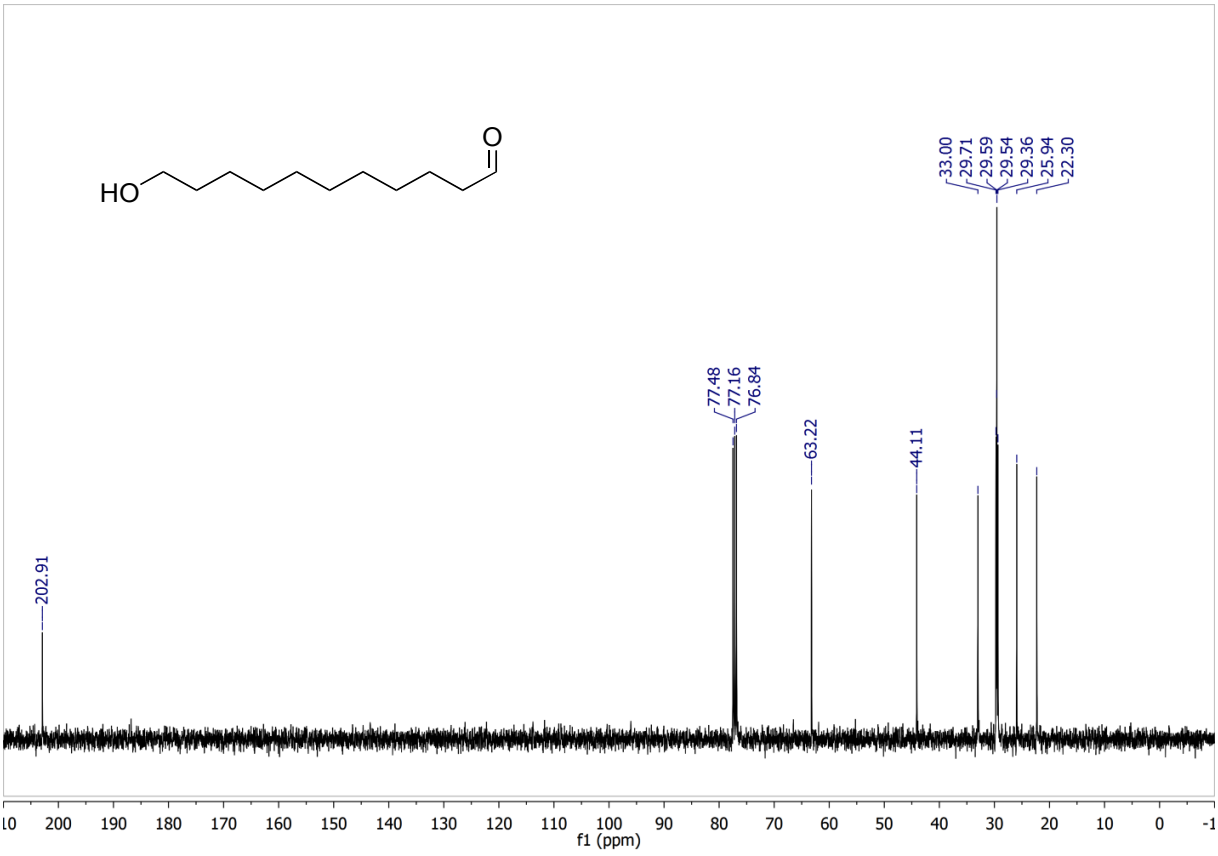
^{13}C-NMR (100 MHz, $CDCl_3$) *(Table 1, entry 2)*



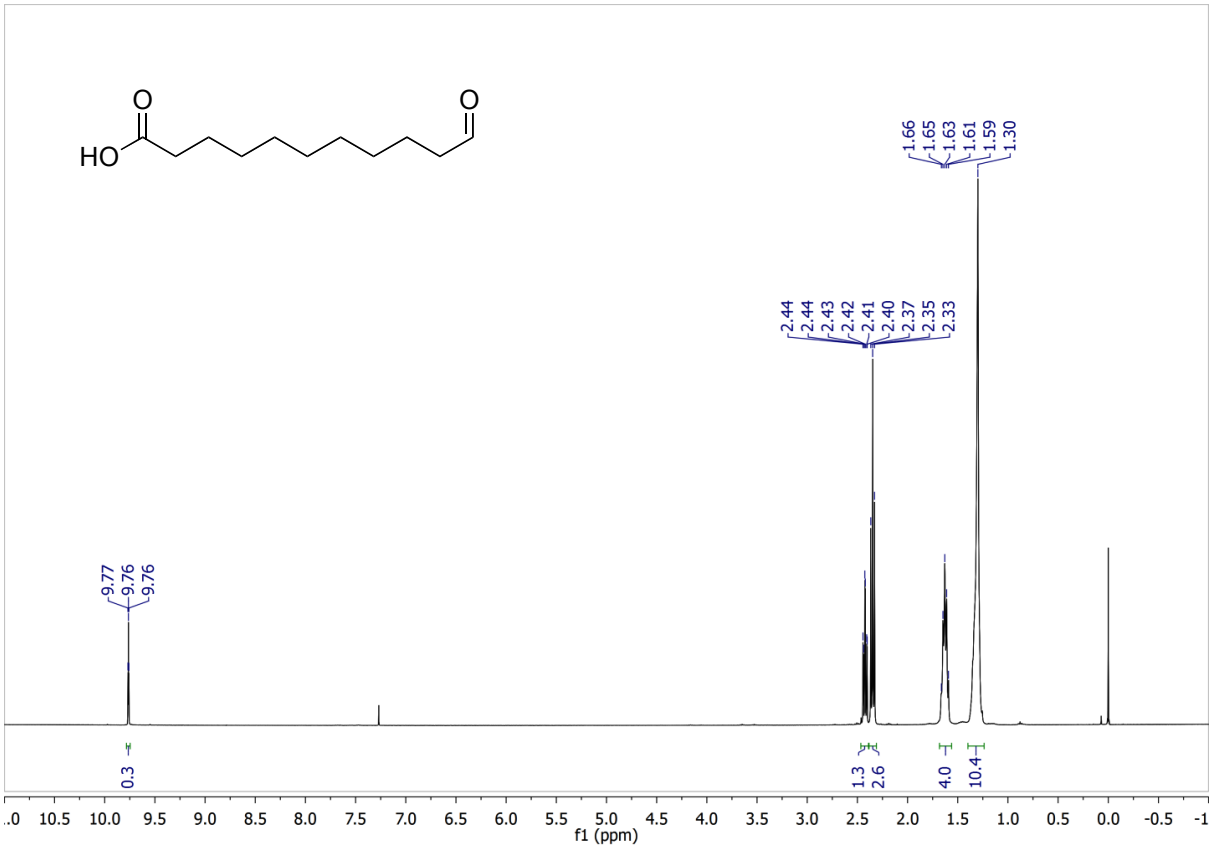
^{1}H-NMR (400 MHz, $CDCl_3$) *(Table 1, entry 3)*



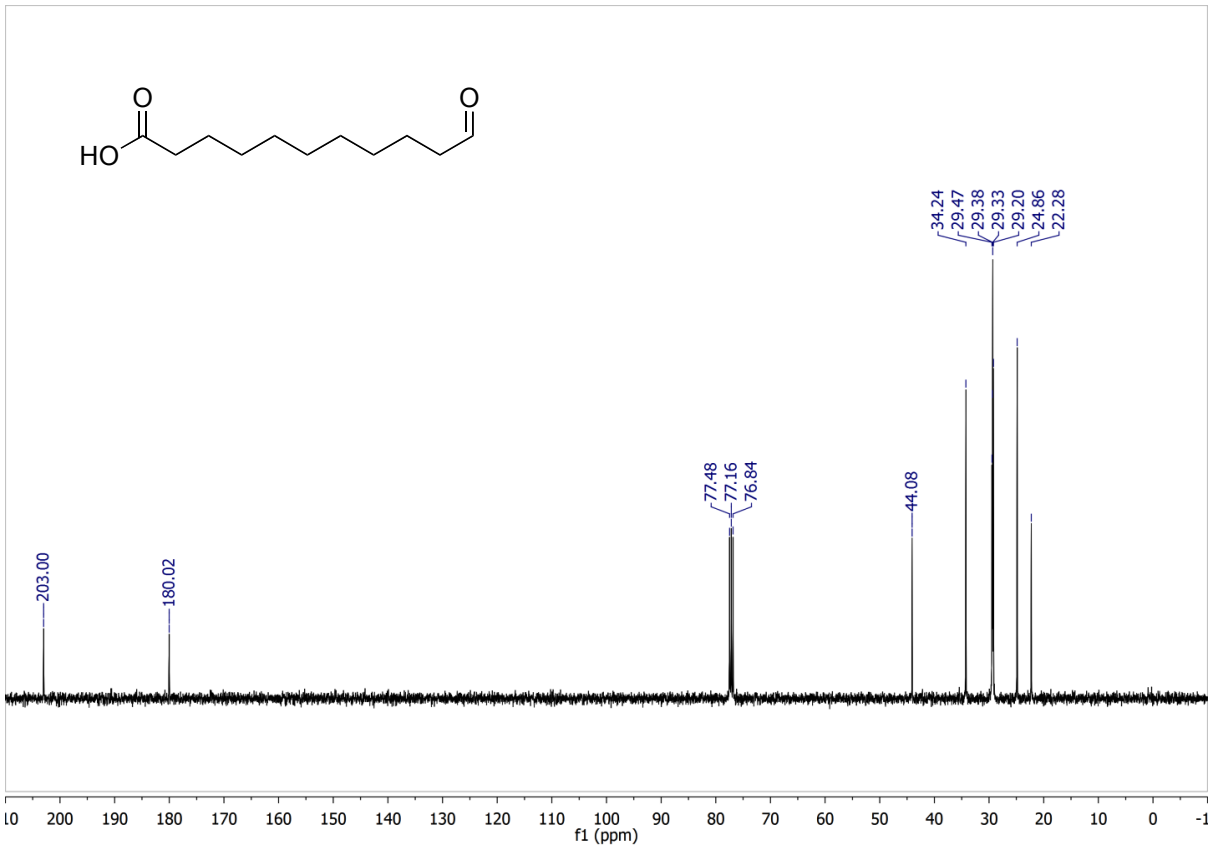
^{13}C-NMR (100 MHz, $CDCl_3$) *(Table 1, entry 3)*



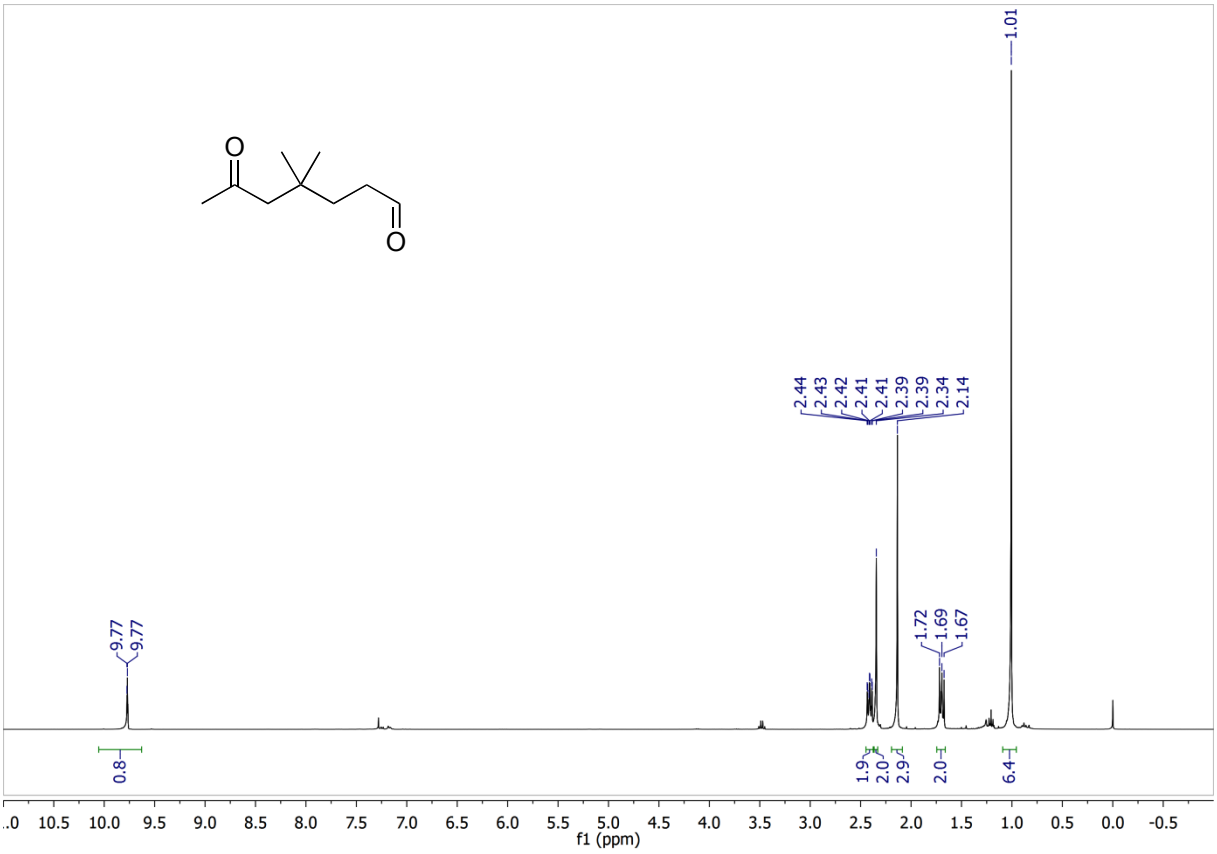
^{1}H-NMR (400 MHz, $CDCl_3$) *(Table 1, entry 4)*



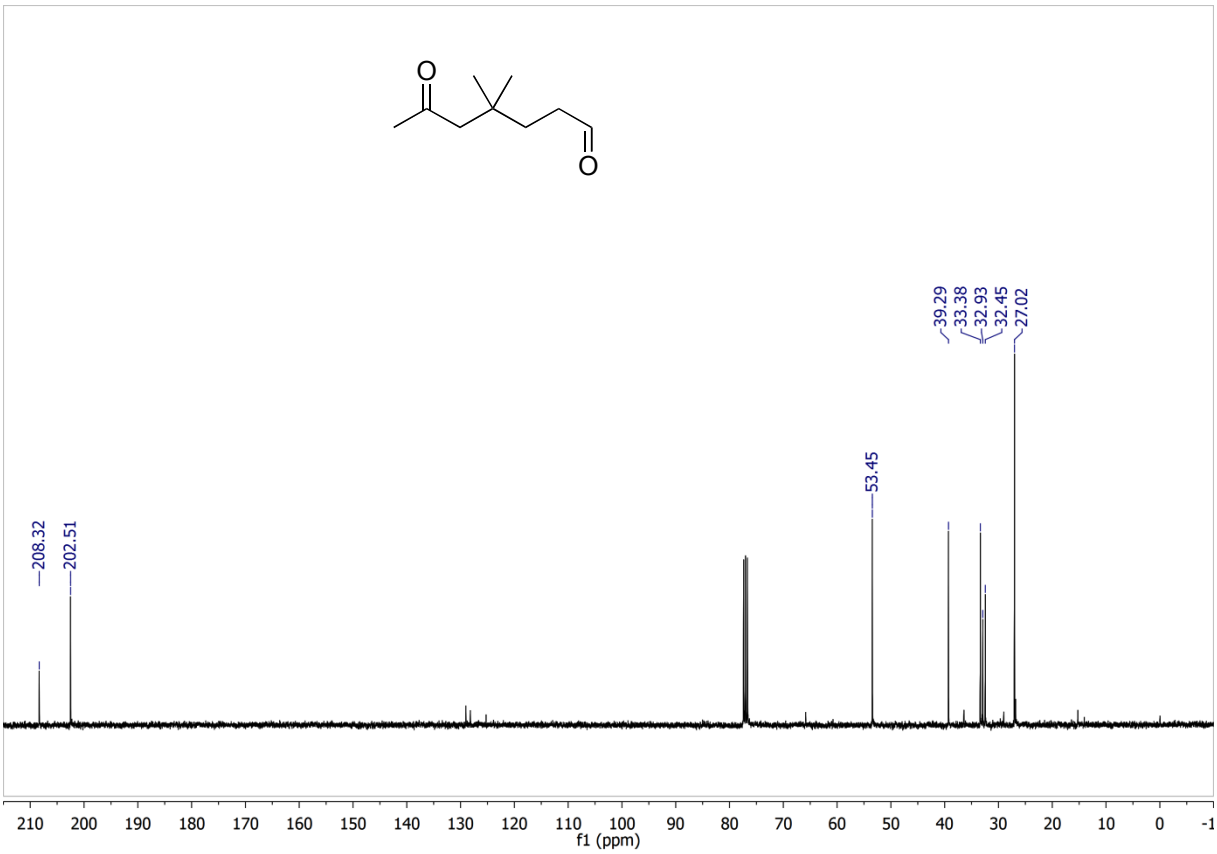
^{13}C-NMR (100 MHz, $CDCl_3$) *(Table 1, entry 4)*



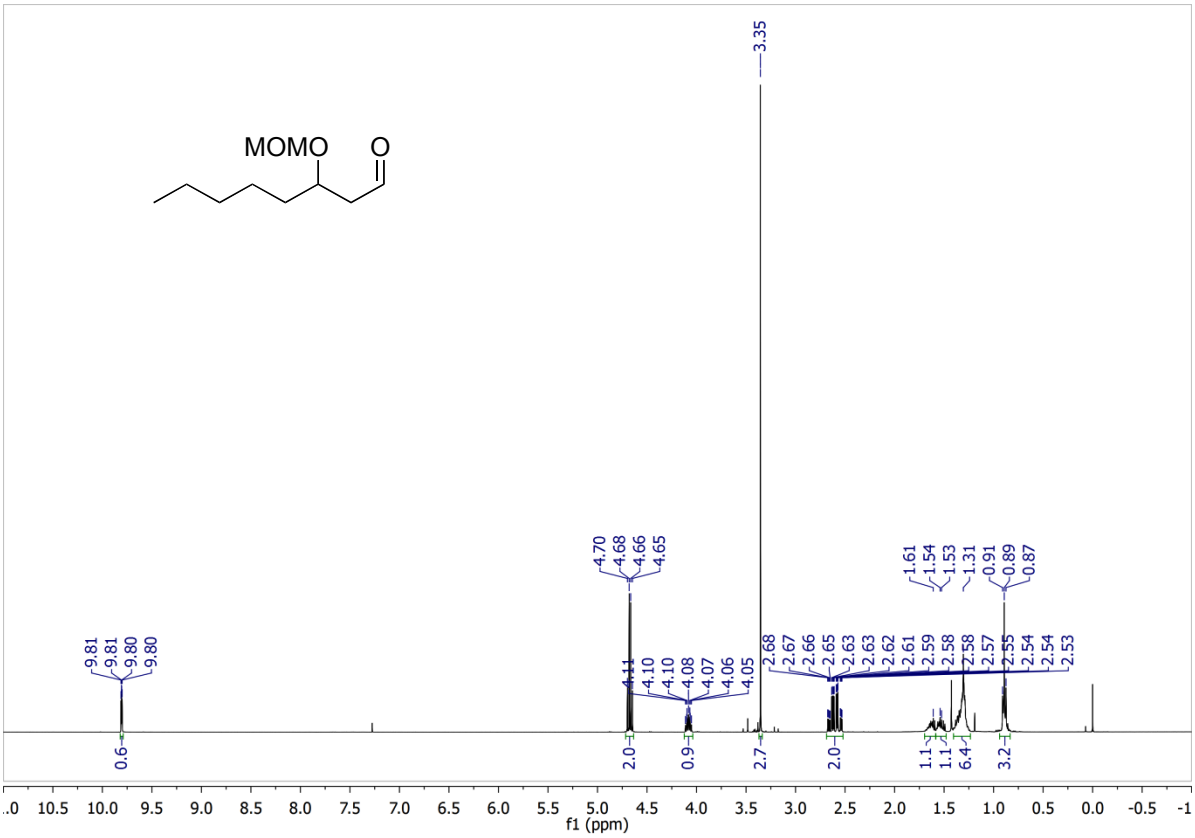
^{1}H-NMR (360 MHz, $CDCl_3$) *(Table 1, entry 5)*



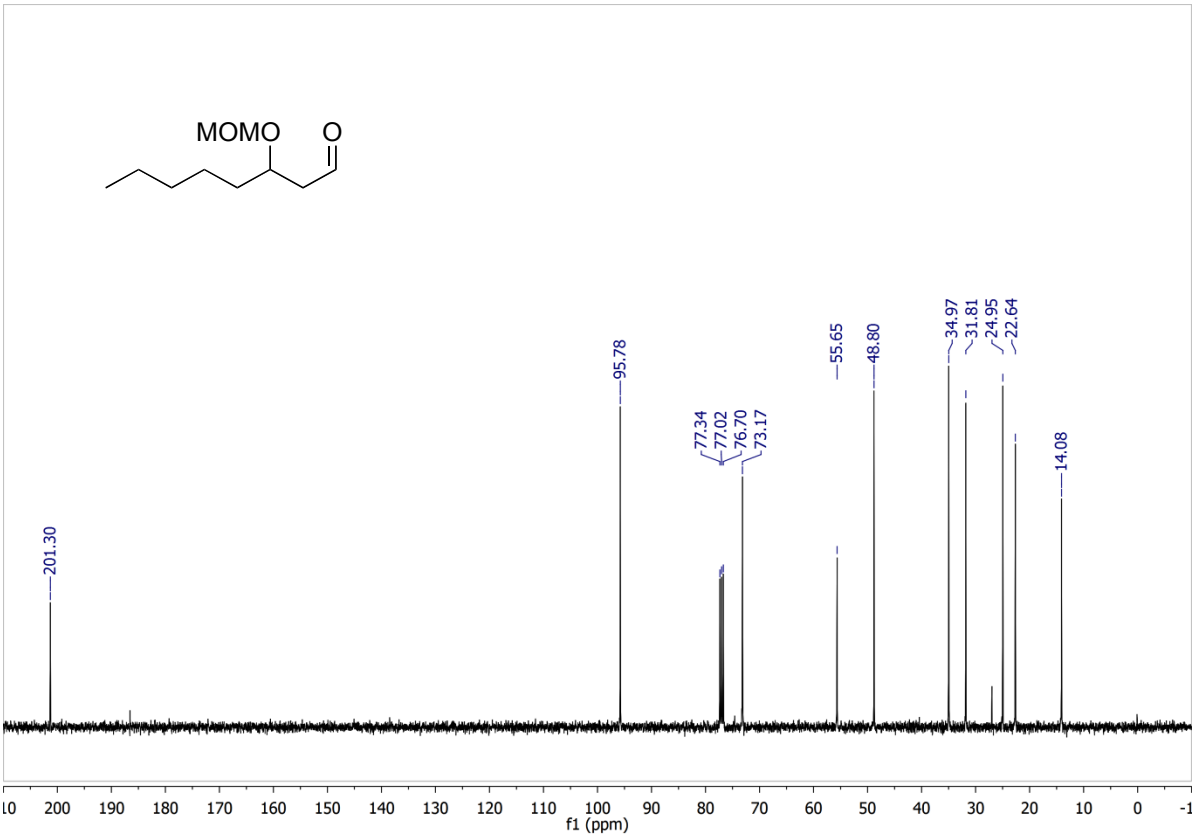
^{13}H-NMR (90 MHz, $CDCl_3$) *(Table 1, entry 5)*



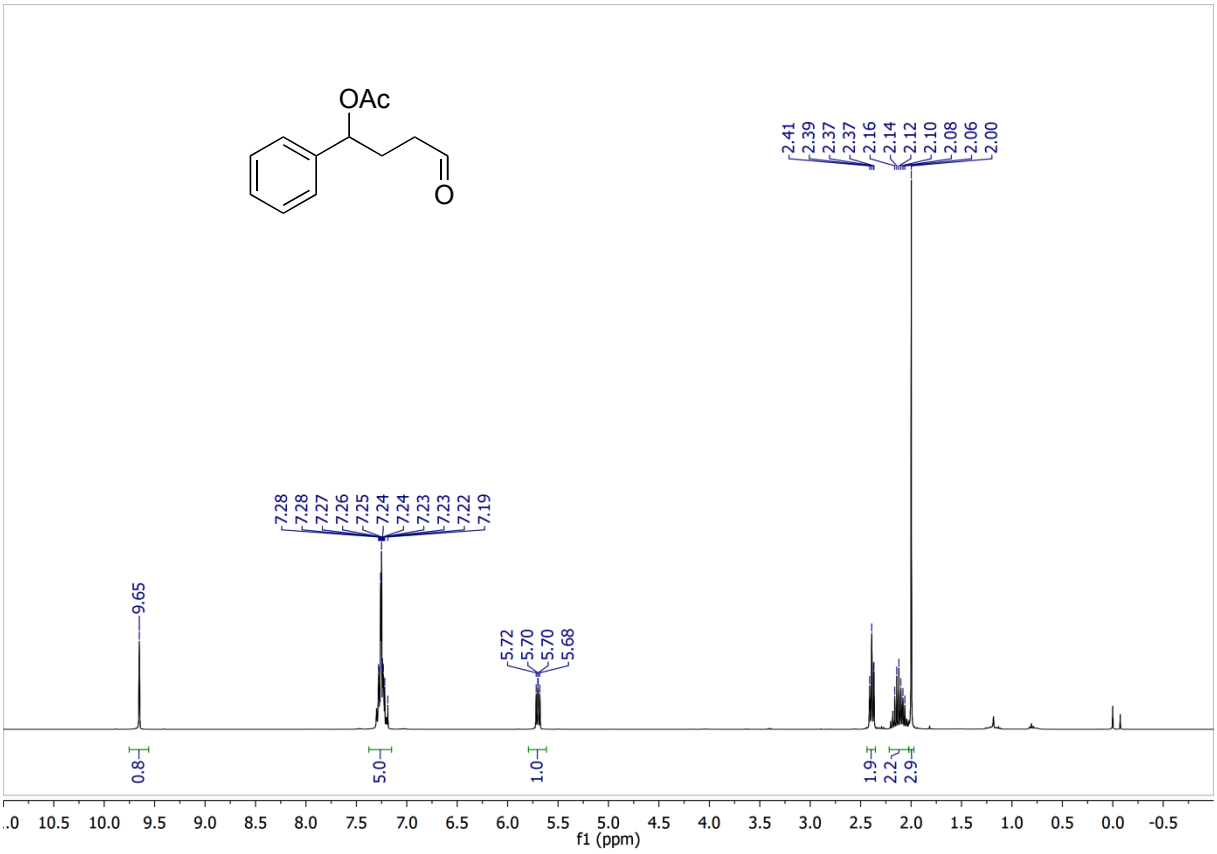
^{1}H-NMR (400 MHz, $CDCl_3$) *(Table 1, entry 6)*



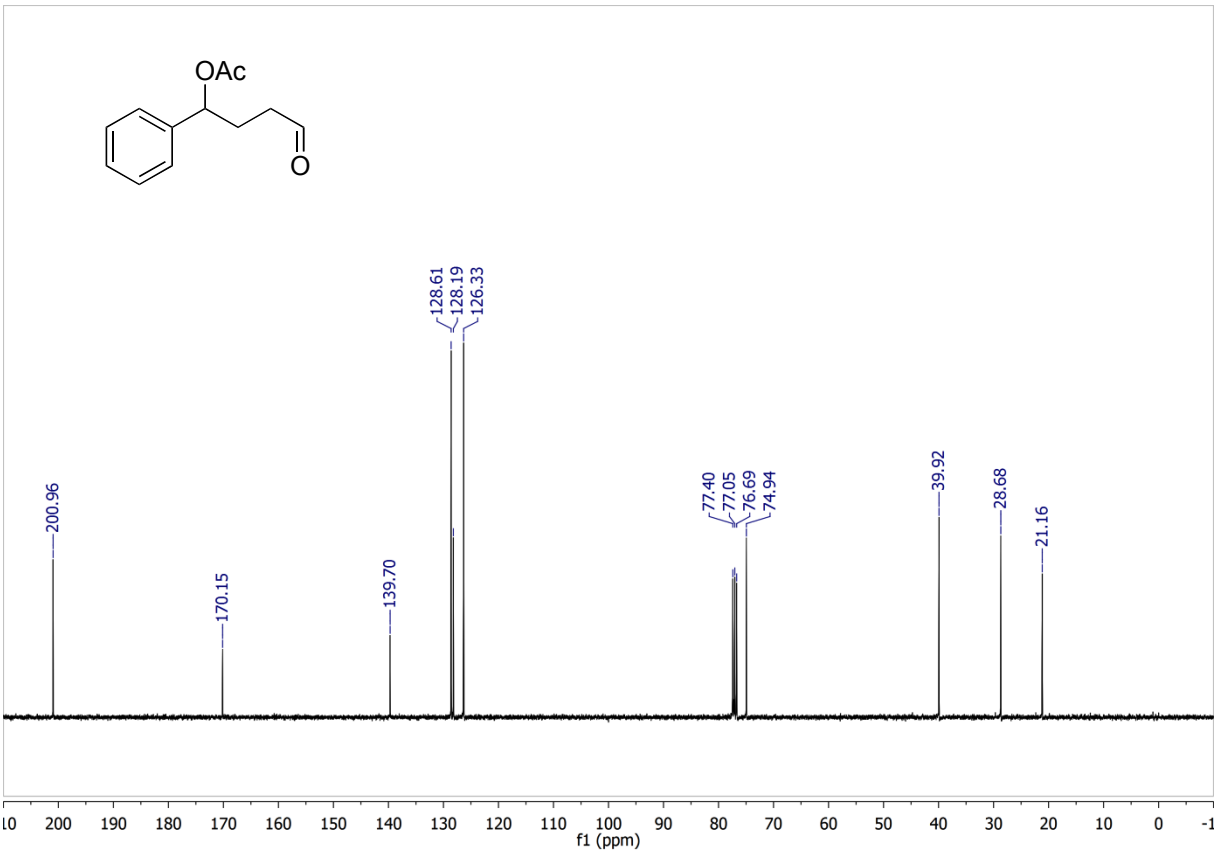
^{13}C-NMR (100 MHz, $CDCl_3$) *(Table 1, entry 6)*



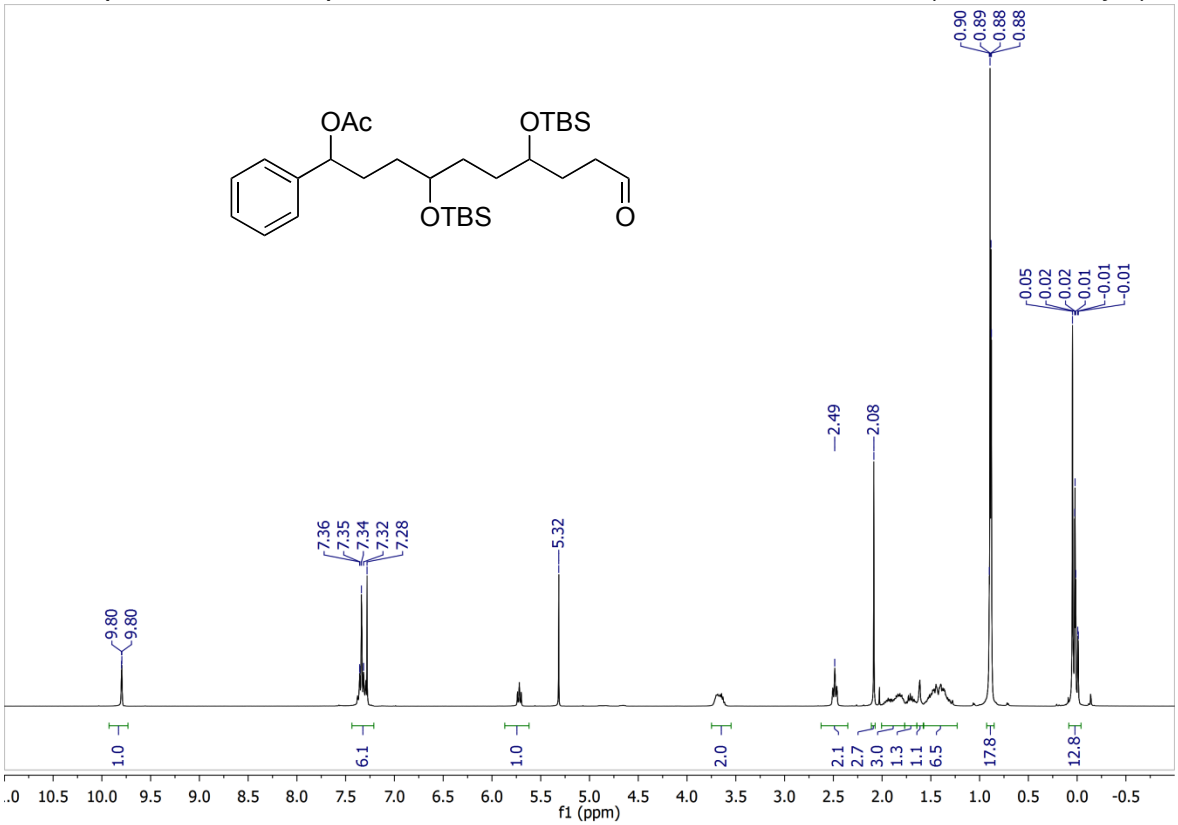
^{1}H-NMR (360 MHz, $CDCl_3$) *(Table 1, entry 7)*



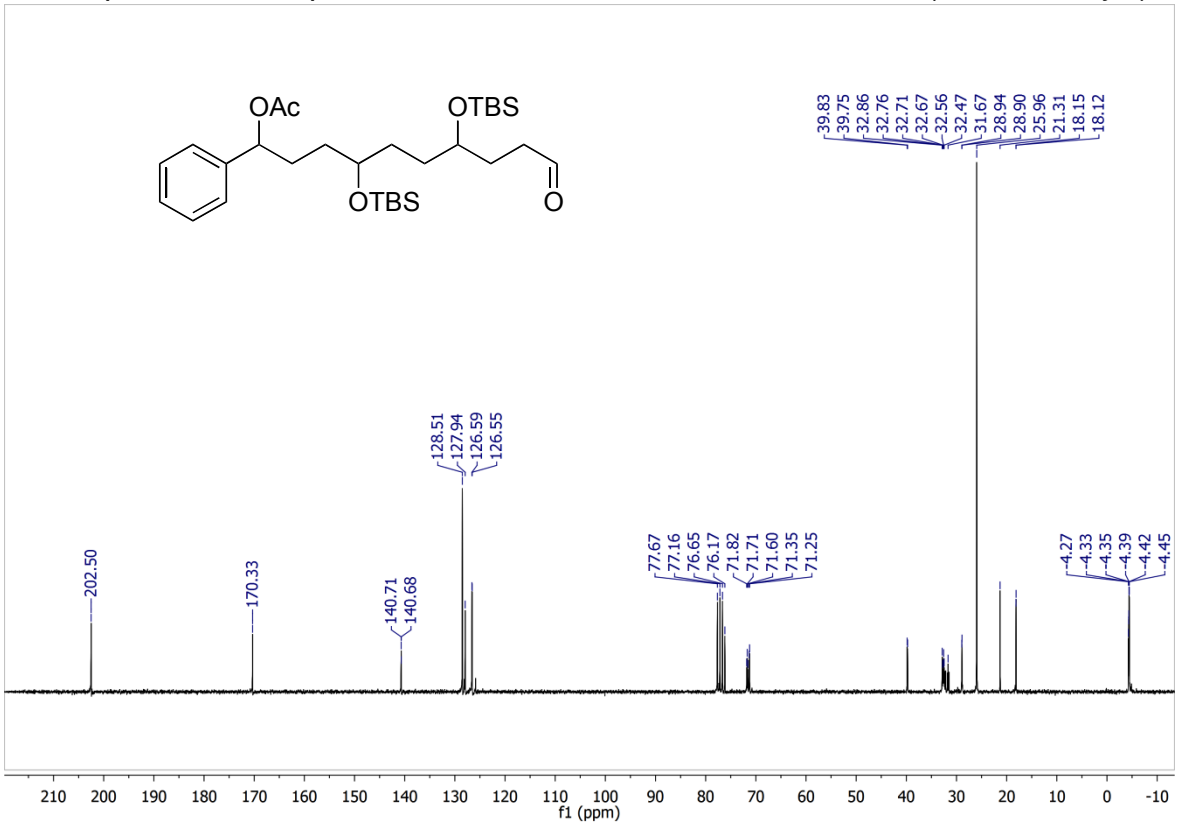
^{1}H-NMR (90 MHz, $CDCl_3$) *(Table 1, entry 7)*



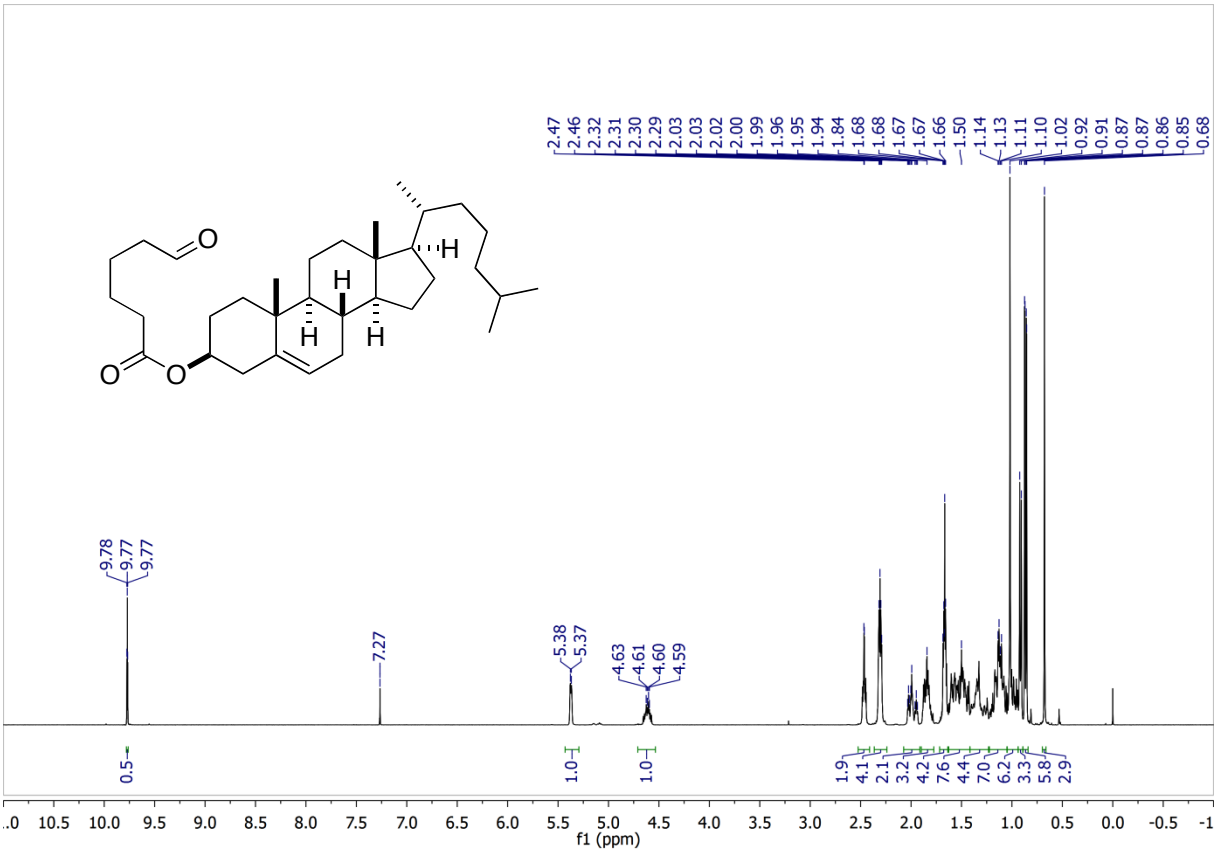
^{1}H-NMR (360 MHz, $CDCl_3$) *(Table 1, entry 8)*



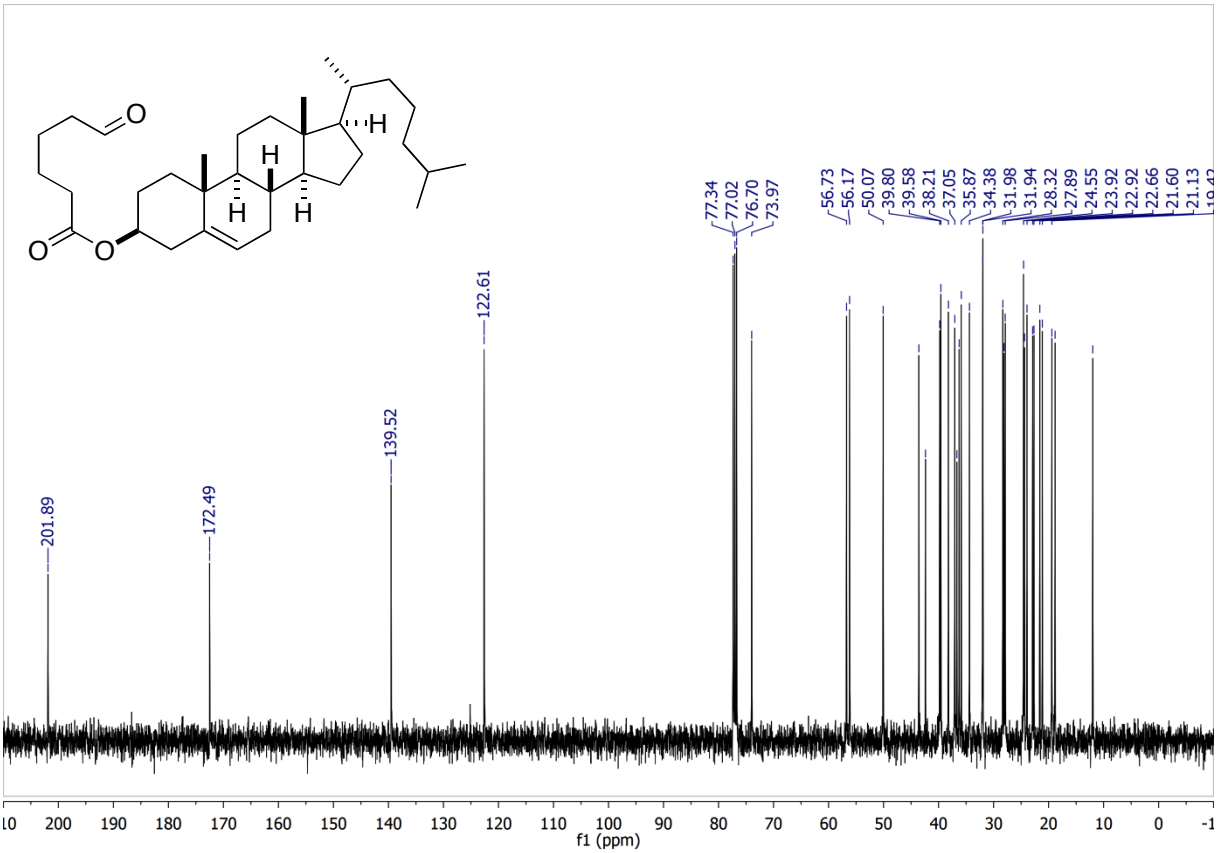
^{1}H-NMR (90 MHz, $CDCl_3$) *(Table 1, entry 8)*



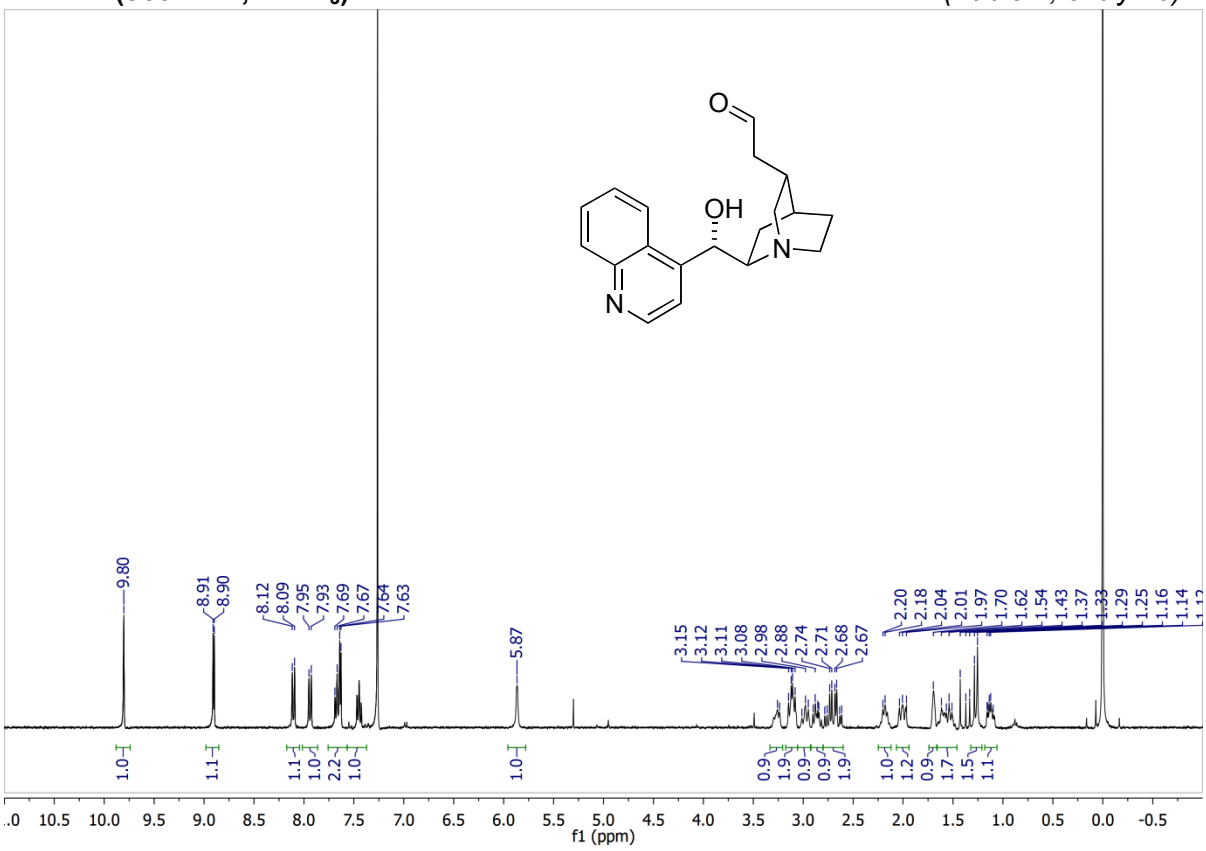
^{1}H-NMR (400 MHz, $CDCl_3$) *(Table 1, entry 9)*



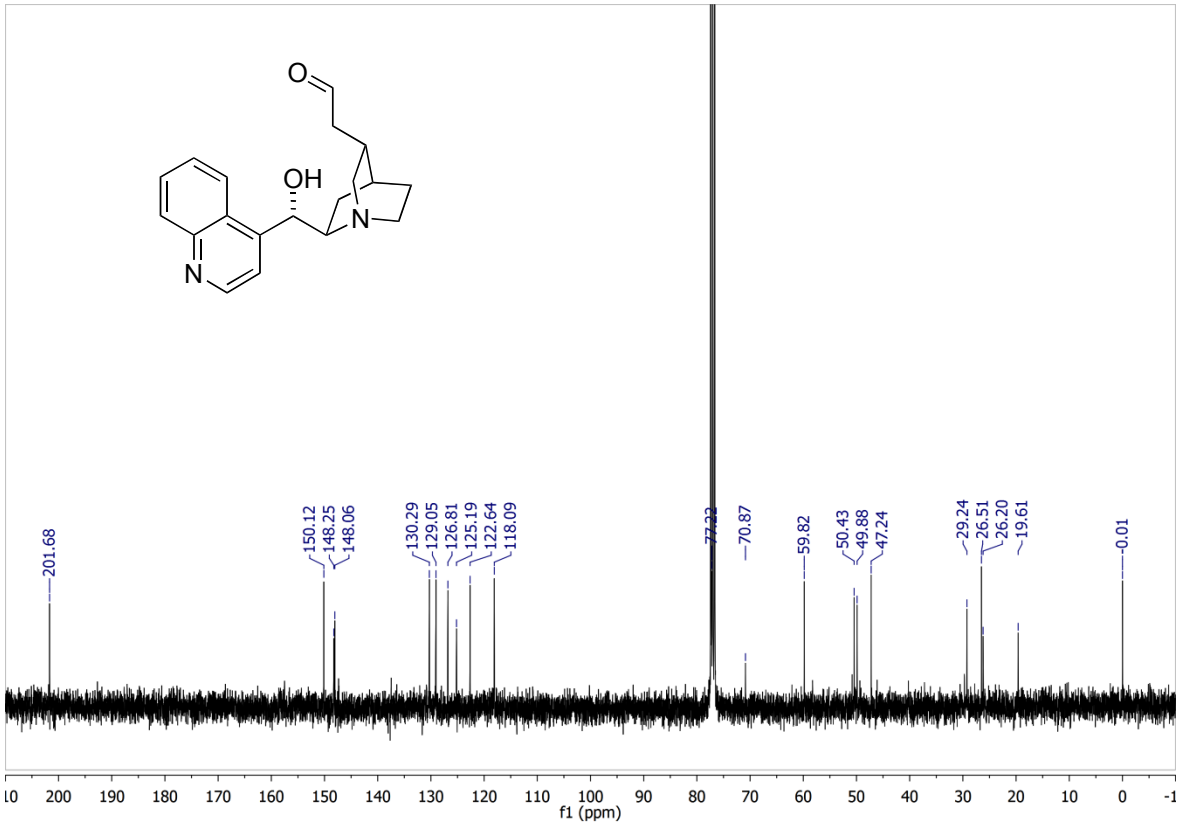
^{13}C-NMR (100 MHz, $CDCl_3$) *(Table 1, entry 9)*



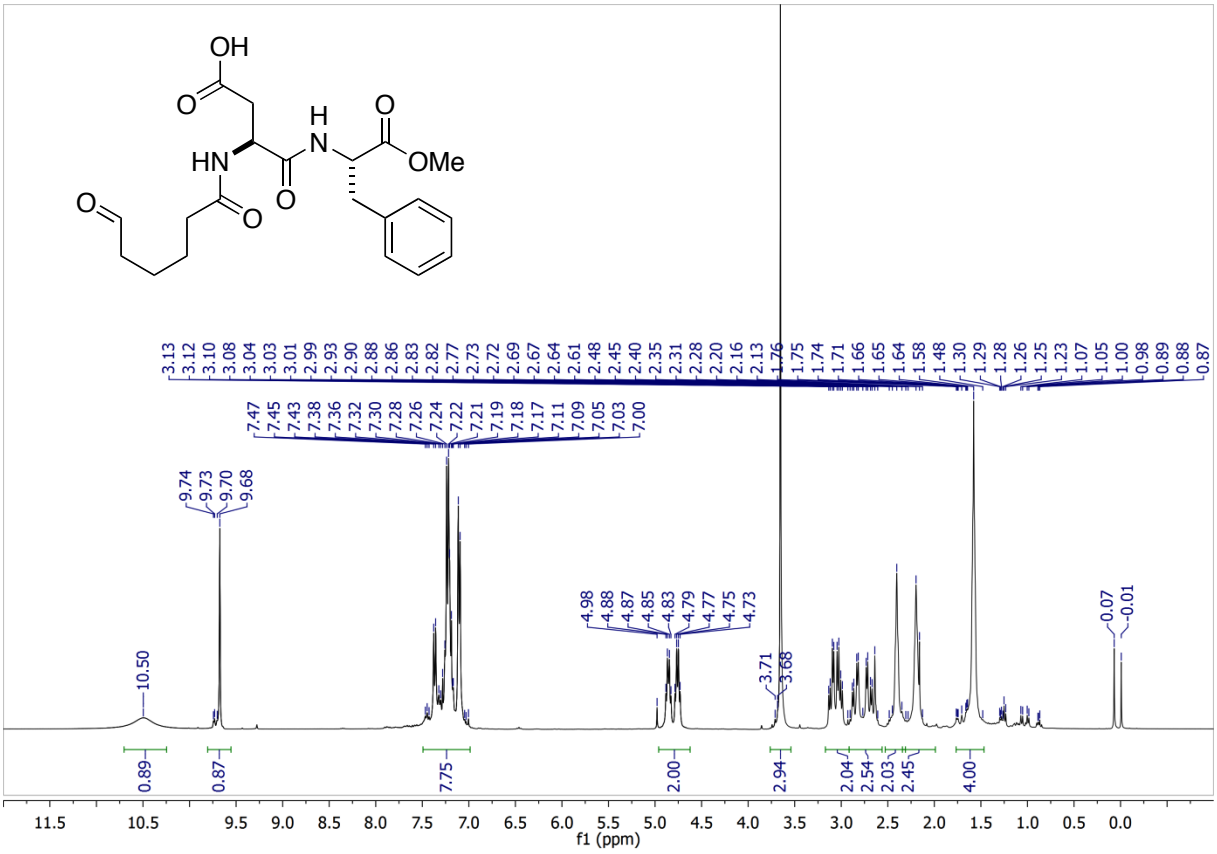
^{1}H-NMR (360 MHz, $CDCl_3$) *(Table 1, entry 10)*



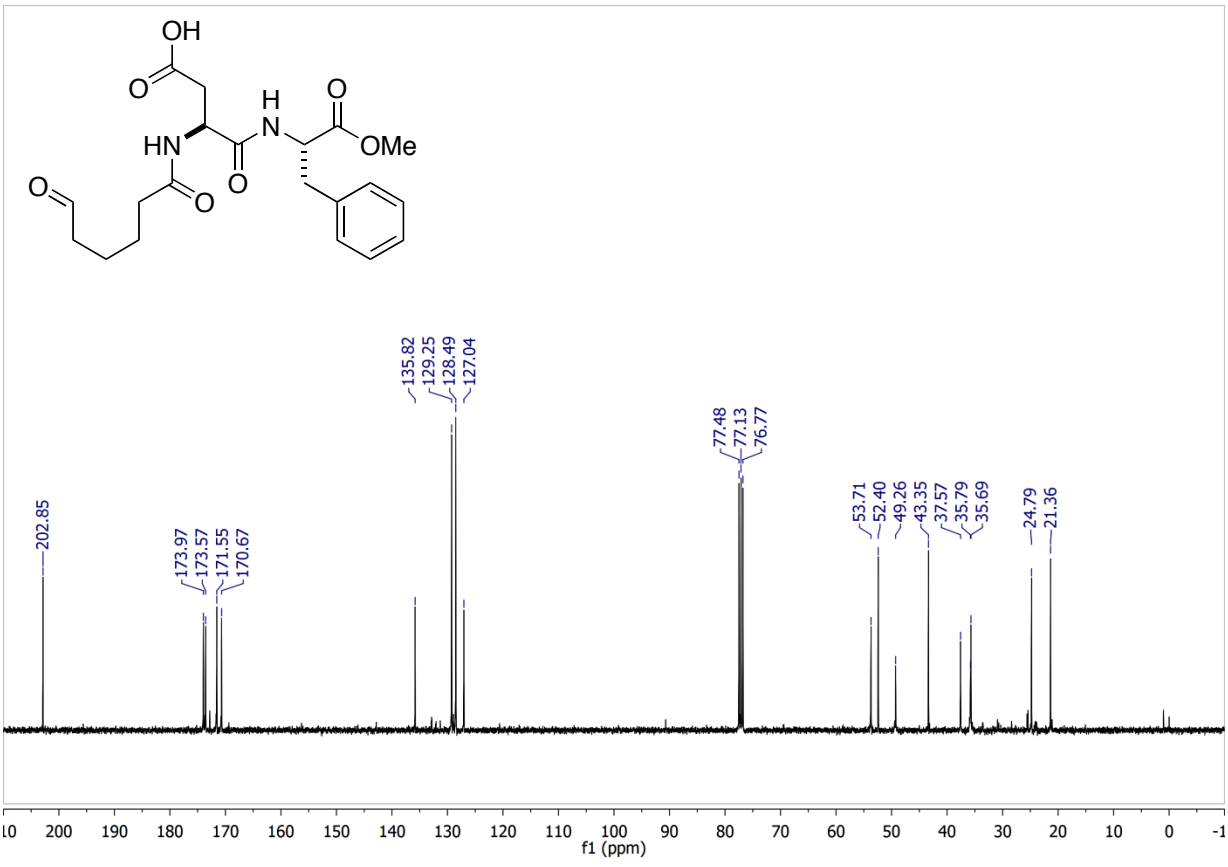
^{13}C-NMR (90 MHz, $CDCl_3$) *(Table 1, entry 10)*



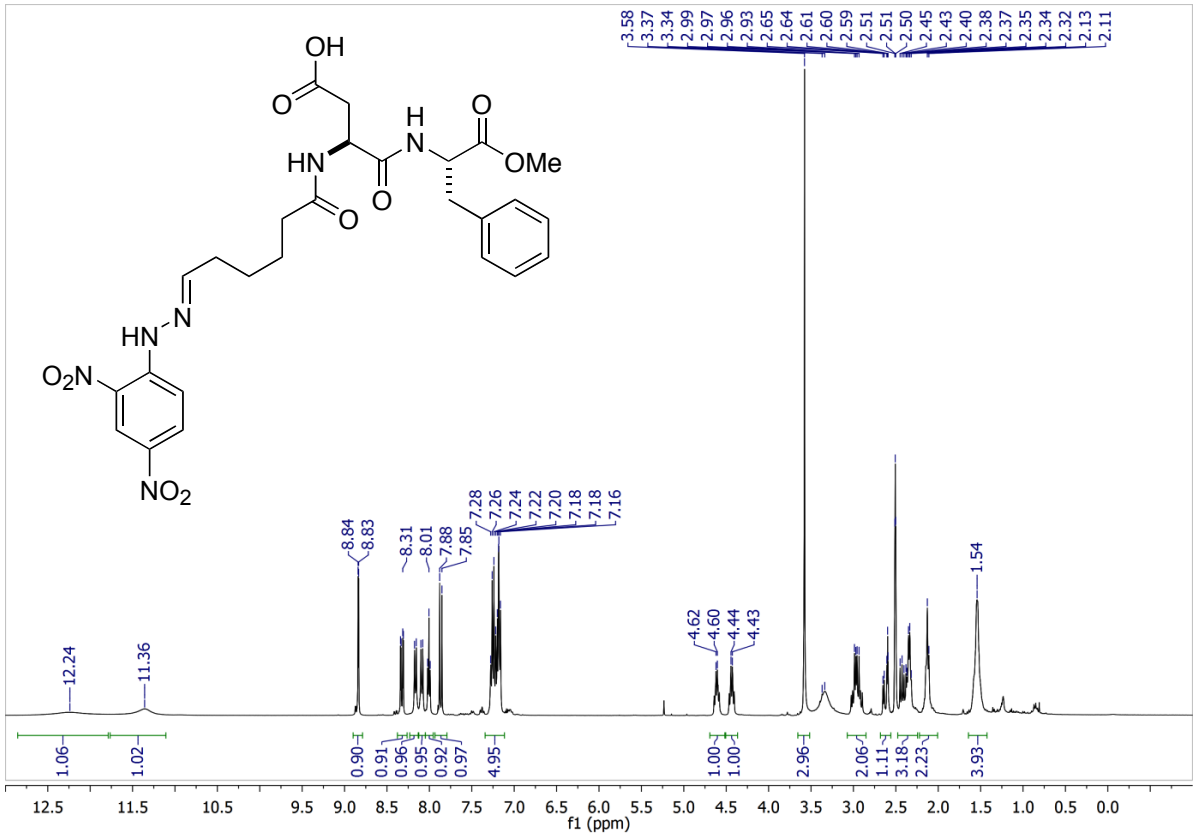
^{1}H-NMR (360 MHz, $CDCl_3$) (crude product) *(Table 1, entry 11)*



^{13}C-NMR (90 MHz, $CDCl_3$) (crude product) *(Table 1, entry 11)*



^{1}H-NMR (360 MHz, DMSO) *(Table 1, entry 11)*



^{13}C-NMR (90 MHz, DMSO) *(Table 1, entry 11)*