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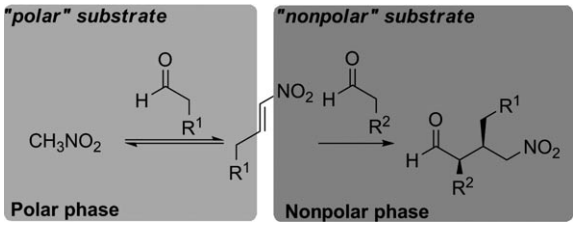
Polarity-Directed One-Pot Asymmetric Cascade Reactions Mediated by Two Catalysts in an Aqueous Buffer**

*Steven T. Scroggins, Yonggui Chi, and Jean M. J. Fréchet**

Modern organic synthesis predominately relies on functional group reactivity differences to achieve the chemoselective formation of desired products.[1] Herein we report a one-pot multistep asymmetric catalytic reaction in which substrates with similar chemical reactivities are differentiated on the basis of polarity. The one-pot reaction involves two catalysts and three substrates in the presence of water. The reaction mixture consists of two phases: a polar aqueous phase and a hydrophobic organic phase. The biphasic nature of the reaction medium and the polarity properties of the substrates and catalysts enable the selective formation of a major product instead of a statistical mixture of four possible products.

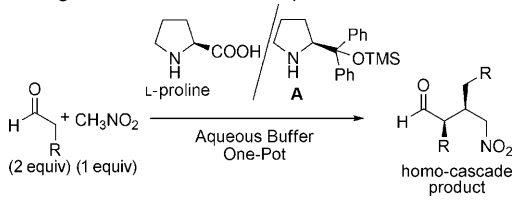
We chose a two-step reaction involving condensation[2,3] and subsequent conjugate addition as a model to develop a polarity-directed cascade reaction. Both reaction steps can involve linear aliphatic aldehydes as substrates (Scheme 1).[4,5] Our aim was to combine the two reaction steps to develop a one-pot reaction in which two different aldehyde substrates react in a controlled manner to generate the desired cross-product.[6] A typical homogeneous (one-phase) version of such one-pot reactions in organic solvents results in a statistical mixture of all four possible cascade products in an approximately a 1:1:1:1 ratio (see the Supporting Information for details), as confirmed in our preliminary studies. Therefore, we decided to focus on a water/organic biphasic system that might allow the use of substrate polarity differences to control the reaction pathways (Scheme 1).



Scheme 1. Polarity-directed chemoselective incorporation of two different aldehydes to form a major cross-cascade product in a one-pot reaction involving two aldehydes with similar reactivities but different polarities.

We first examined the condensation reaction of nitromethane and *n*-pentanal mediated by L-proline in an aqueous buffer (Table 1). The condensation reaction is reversible.[2c,d]

Table 1: Studies on the reaction of nitromethane with *n*-pentanal or *n*-decanal to generate a homo-cascade product.[a]



Entry	R	L-Proline [mol%]	**A** [mol%]	Yield [%]	e.r.[b]
1	*n*Pr	20	0	45[c]	ca. 50:50
2	*n*Pr	20	20	70[c]	93:7
3[d]	*n*Pr	0	20	trace[e]	–
4[d]	*n*-octyl	20	20	trace[e]	–
5	*n*-octyl	20	0	none[e]	–

[a] Reaction conditions: aldehyde (2 mmol 9, nitromethane (1 mmol), PBS (1 mL, pH 7.5), RT, 16 h. [b] Determined by ^{1}H NMR assay (see the Supporting Information for details).[11] Absolute and relative stereochemistry established by analogy to literature precedent.[5] [c] Yield of isolated product after column chromatography. [d] Attempted with and without added lauric acid, a co-catalyst used to promote the reactions mediated by amine **A**. [e] Estimated from ^{1}H NMR analysis of the crude reaction mixture. PBS = phosphate buffered saline.

Subsequently, the α,β-unsaturated nitroalkene formed in this step was consumed in a conjugate addition reaction to generate a homo-cascade product with 45% yield and little enantioselectivity (Table 1, entry 1). The low yield resulted from many side reactions, such as aldol reactions and the addition of nitromethane to the nitroalkene intermediate. The condensation reaction mediated by L-proline is a facile process, and the conjugate addition catalyzed by L-proline[7] appeared to be slow under the aqueous conditions.[8] Therefore, we reasoned that the formation of the cascade product could be improved by accelerating the conjugate addition step. This acceleration may be achieved through the addition of a second catalyst, such as diphenylprolinol TMS ether (**A**),[5a,9] an efficient and stereoselective catalyst for the conjugate addition of aldehydes to nitroalkenes.[5] As shown in entry 2 of Table 1, when a combination of L-proline and **A**

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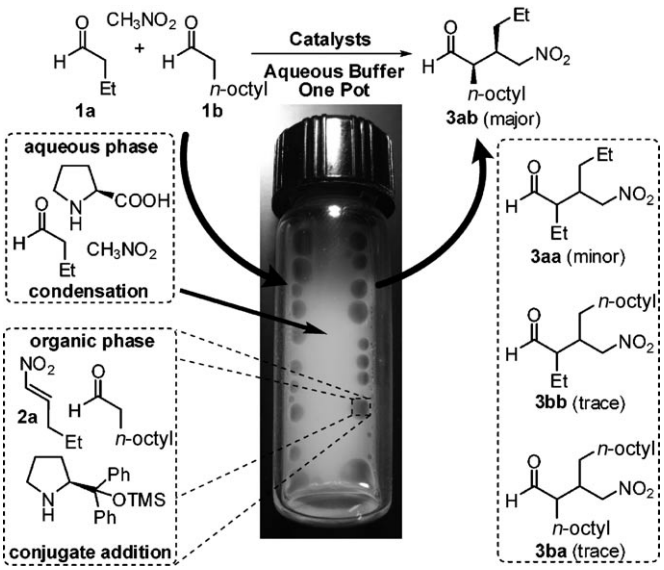
(20 mol% each) was used, the product yield was significantly improved. The cascade reaction performed in this manner had good enantioselectivity (ca. 93:7), thereby indicating that the rate of the competitive, non-stereoselective conjugate addition mediated by L-proline was negligible under these conditions. Previous reports by others[5c,10] and our own studies have indicated that the conjugate addition reaction mediated by **A** in the presence of water mainly takes place in a concentrated organic phase and not in water. When only **A** was used, there was little formation of either the nitroalkene intermediate or the final cascade product (Table 1, entry 3), which suggested that **A** was not effective in mediating the condensation step. When *n*-decanal (more hydrophobic than *n*-pentanal) was used as the substrate with L-proline or a combination of L-proline and **A** as the catalyst(s), only a small amount of the nitroalkene intermediate or the cascade product was observed (Table 1, entries 4 and 5). These results indicate that the condensation reaction requires some miscibility of the aldehyde with the aqueous solution containing L-proline and nitromethane. The hydrophobic nature of *n*-decanal explains its poor reactivity in contrast to the less hydrophobic *n*-pentanal.

The solubility properties of the reacting components and the results summarized in Table 1 suggest that the condensation reaction mainly occurs in the aqueous phase of the one-pot system. The conjugate addition catalyzed by **A** predominately takes place in the organic phase constituted by the aldehyde substrate and the nitroalkene intermediate. We next sought to perform a controlled one-pot reaction involving two different aldehydes to produce a single cross-product. We anticipated that aldehydes with different polarities, such as *n*-butanal (**1a**) and *n*-decanal (**1b**), could be distinguished and react in a programmed manner. Whereas both *n*-butanal and *n*-decanal are hydrophobic molecules, *n*-butanal should have a significantly greater miscibility with the aqueous phase than *n*-decanal. For example, in water/octanol (1:1) systems *n*-butanal partitions into the aqueous phase approximately 1000 times more favorably than *n*-decanal.[12] The condensation reaction step occurring in water mainly involves *n*-butanal and nitromethane as the substrates to produce nitroalkene **2a** as the intermediate. This hydrophobic intermediate diffuses into the organic phase consisting of catalyst **A** and the other organic components of the reaction. Under these heterogeneous conditions with 20 mol% L-proline and 20 mol% **A**, the desired cross-product **3ab** was formed as the major product (Scheme 2) when the aldehydes were used in equimolar amounts and added to the reaction mixture simultaneously. The main side product was **3aa** (the ratio of **3ab**:**3aa** being approximately 4:1), formed from aldehyde **1a** and nitroalkene **2a**. Products **3bb** and **3ba**, which would require a nitroalkene intermediate (not shown in Scheme 2) generated from *n*-decanal, were observed in only trace amounts; *n*-decanal is too hydrophobic to participate in the aqueous phase condensation reaction to form the corresponding nitroalkene intermediate.

Having demonstrated the possibility of selectively forming the cross-product **3ab**, we then adjusted several parameters to additionally improve the reaction selectivity. We first attempted to achieve an aldehyde concentration bias by the slow addition of one aldehyde component.[1a] However, undesired side reactions consumed whichever aldehyde was in excess, indicating that the simultaneous addition of the aldehydes may be the best method. The consumption of intermediate **2a** in the absence of aldehyde **1b** indicates that stepwise reactions under these conditions are not suitable for the synthesis of **3ab**, which further demonstrates the advantages of our one-pot reaction approach.[3] We found that the most productive optimization approach was to accelerate the formation of nitroalkene intermediate **2a**. Accelerating **2a** formation increases nitroalkene concentration and decreases the presence of *n*-butanal in the organic phase. This minimizes the conjugate addition reaction leading to **3aa** and avoids other significant side reactions in the organic phase. Therefore, accelerating the condensation reaction between nitromethane and *n*-butanal favors the ultimate formation of desired product **3ab**. Our methods for selectively accelerating the formation of **2a** included raising the pH of the aqueous layer,[13] increasing the concentration of nitromethane used, and lowering the ratio of catalyst **A** to L-proline. A very small amount of catalyst **A** (e.g., 1 mol%) in combination with an acid co-catalyst[4c,d,14] was optimal to perform the conjugate addition in the organic phase. Lauric (dodecanoic) acid is sufficiently hydrophobic to remain exclusively in the organic layer and was chosen as the acid co-catalyst. Importantly, even slightly water-miscible organic acids are problematic for the reaction because they lower the pH of the aqueous layer and slow the condensation step catalyzed by L-proline. For this reason, shorter-chain aldehydes were distilled and handled carefully before use as oxidation led to residual acids.

We settled on conditions employing three equivalents of nitromethane, a 0.4 M concentration of L-proline (40 mol%),

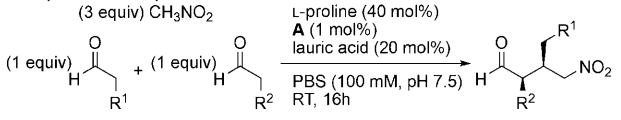


Scheme 2. A polarity-directed one-pot reaction for the selective formation of a major cascade product. The reaction mixture consists of oily droplets (organic phase) in an aqueous medium, as pictured. The relatively polar *n*-butanal is converted into nitroalkene intermediate **2a** by a reaction in the aqueous phase. This intermediate is then converted into the final product by reaction with *n*-decanal in the organic substrate phase. TMS = trimethylsilyl.

1 mol% **A**, and 20 mol% lauric acid. The ratio of products **3ab** and **3aa** observed by ^{1}H NMR analysis at full conversion of both aldehydes was around 6:1 in favor of **3ab**, and few side reaction products were observed. Under these conditions, **3ab** could be isolated in 67% yield (82% for each step) and around 9:1 d.r.; and the major diastereomer was formed with excellent enantioselectivity. The beneficial feature of the biphasic mixture was additionally confirmed by a control reaction in a homogeneous solution (DMF as the solvent) under otherwise similar conditions. Multiple side products (including those other than the cascade products) were formed, and NMR analysis of the crude reaction mixture showed that **3aa**, **3ab**, **3ba**, and **3bb** were formed in roughly equal molar amounts. Under homogeneous conditions there was no significant chemical reactivity difference between these aldehydes. This result is a further confirmation that the controlled formation of a single cascade product in our system is achieved using polarity differences.

By using the one-pot, two-phase system containing multiple catalysts and substrates, aldehyde pairs with a small size difference can be differentiated and react in a controlled manner to selectively form a single cross-product. The yield of the reaction is most sensitive to the identity of the "more polar" aldehyde component, for which a certain degree of miscibility with water is required for the condensation reaction to occur efficiently. Therefore, *n*-butanal and *n*-pentanal are much more effective as the more polar reacting partners than is *n*-hexanal. Aldehyde pairs with as little as a one carbon atom difference (such as *n*-butanal and *n*-pentanal) can react selectively (see the Supporting Information for details). A small set of examples involving several aldehyde pairs are summarized in Table 2. The highest yield is obtained with 3-methylbutanal as the more polar aldehyde component because it effectively undergoes the condensation reaction but participates very little in the conjugate addition reaction because of its steric bulk (Table 2, entry 7).

Table 2: Polarity-directed one-pot cascade reaction involving two different aliphatic aldehydes.



Entry[a]	R^1	R^2	Yield [%][b]	e.r.[c]	d.r.[d]
1	Et	*n*Bu	64[e]	>95:5	–[f]
2	Et	*n*-hexyl	62	>95:5	13:1
3	Et	*n*-octyl	67	>95:5	10:1
4	Et	*n*-decyl	65	>95:5	19:1
5	*n*Pr	*n*-octyl	63	>95:5	10:1
6	*n*Bu	*n*-octyl	40[e]	>95:5	–[f]
7	*i*Pr	*n*-octyl	77	>95:5[g]	16:1

[a] See experimental procedure for reaction conditions. [b] Yield of product isolated after column chromatography. [c] Determined for major diastereomer by ^{1}H NMR assay (see the Supporting Information for details).[11] [d] Measured by ^{1}H NMR of isolated products. [e] Estimated yield based on ^{1}H NMR analysis of incompletely separated products. [f] Diastereomeric ratio was not determined for incompletely isolated products. [g] Enantiomeric ratio confirmed by HPLC methods (see the Supporting Information for details).

In summary, we have developed a polarity-directed one-pot cascade reaction. Substrates with different hydrophobicities but similar reactivities can be differentiated to react in a programmed manner. Two catalysts were used, and each catalyst mediates an individual reaction step in either the aqueous or organic phase. The system highlights an often-ignored approach to developing chemoselective reactions by using properties other than chemical reactivity (such as polarity) inherent to the substrates or catalysts. We anticipate that these results should inspire the design of new catalytic systems, including those using enzyme-like polymer catalysts, which can achieve unusual control of reactions.[15]

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Keywords:

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Communications

Organocatalysis

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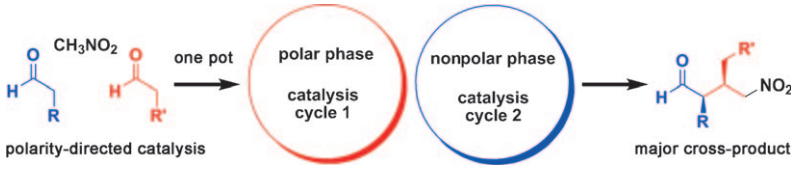
Polarity-Directed One-Pot Asymmetric Cascade Reactions Mediated by Two Catalysts in an Aqueous Buffer



A crossing between phases: Polarity makes a difference in distinguishing substrates of otherwise nearly identical chemical reactivities. A one-pot cascade reaction involving nitromethane and two aliphatic aldehydes with similar reactivities has been developed (see scheme). The use of a biphasic reaction medium with two different organic catalysts results in the controlled incorporation of both aldehyde substrates into a single major cross-product.

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Supporting Information

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Supporting Information

Polarity-Directed One-Pot Asymmetric Cascade Reactions Mediated by Two Catalysts in an Aqueous Buffer

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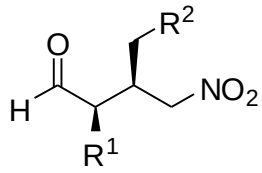
General information.

Commercial chemicals were purchased from Sigma-Aldrich except: lauric acid which was from Mathewson, Coleman and Bell; (S)-(+)-1-methoxy-2-propylamine, which was from Alfa Aesar; monobasic sodium phosphate monohydrate, which was from EMD Chemicals; and dibasic sodium phosphate heptahydrate, which was from EM Sciences. L-Proline, DL-proline, pyrrolidine (S)-(-)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (**A)**, lauric acid, and nitromethane were used as received from commercial sources. It was found that for the reactions to proceed efficiently, it was essential to minimize the presence of acid in the aldehydes as a result of oxidation. Therefore, immediately prior to use, all aldehydes (with the exception of propionaldehyde) were washed successively with 10% sodium carbonate, saturated sodium sulfite, and water, and dried over magnesium sulfate. Subsequently, the aldehydes were distilled and approximately 1 mol% hydroquinone was added to inhibit oxidation. The aldehyde/hydroquinone mixtures were used directly in the reactions as soon as possible after distillation. DMF was purchased from Fisher and used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker AVQ 400 or AVB 400

instruments. High resolution mass spectra were obtained by the mass spectrometry facility at UC Berkeley using electron impact (EI) ionization. Infra-red spectra were recorded on a Varian 3100 FT-IR spectrometer. The pH values were measured using a Fischer Accumet AB15 pH meter.

Summary of experimental results.

See below and main text for experimental details.



Compound	R^1	R^2	mol% proline	mol% **A**	Yield (%)	d.r.[a]	e.r. (major)[b]
4	*n*Pr	*n*Pr	20	0	45	11:1	50:50
4	*n*Pr	*n*Pr	20	20	70	3:1	>95:1
4	*n*Pr	*n*Pr	20	10	70	4:1	>95:1
4	*n*Pr	*n*Pr	20	20	74	3:1	93:7
4	*n*Pr	*n*Pr	0	20	trace	-	-
4	*n*Pr	*n*Pr	0	20	trace	-	-
5[d]	*n*Octyl	*n*Octyl	20	0	none	-	-
5[d]	*n*Octyl	*n*Octyl	20	20	trace	-	-
6	*n*Octyl	Me	40	1	45	9:1	>95:1
7	*n*Octyl	*n*Pr	40	1	63	10:1	>95:1
8[d]	*n*Octyl	*n*Bu	40	1	40	-	-
9[d]	*n*Pr	Et	40	1	>25	-	-
10[d]	*n*Bu	Et	40	1	64	-	-
11[d]	*n*Bu	*n*Pr	40	1	>25	-	-
12	*n*Hexyl	Et	40	1	62	13:1	>95:1
3ab	*n*Octyl	Et	40	1	67	10:1	>95:1
3ab[e]	*n*Octyl	Et	40	1	77	9:1	-
3ab[f]	*n*Octyl	Et	40	1	75	13:1	-
13	*n*Decyl	Et	40	1	65	19:1	>95:1
14	*n*Octyl	*i*Pr	40	1	77	16:1	99:1[g]

[a]Measured by ^{1}H NMR analysis of the isolated product; [b]Measured using a ^{1}H NMR ee assay (see supporting information main text); [c]No lauric acid was used; [d]The desired product was not completely isolated and was only be characterized as a mixture by ^{1}H NMR analysis; [e]2 eq of decanal were used; [f]2 eq of butanal were used; [g]Verified by chiral HPLC.

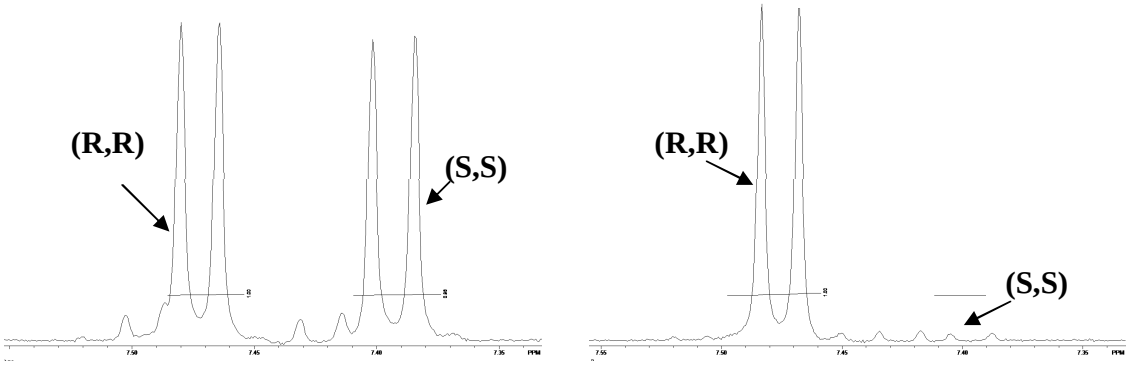
General procedure for the monitoring of the one-pot reactions using ^{1}H NMR.

Reaction optimization experiments and several reactions mentioned in the manuscript main text were monitored by ^{1}H NMR analysis of the crude reaction mixture. For the analysis of reactions in the aqueous mixture, 100 µL of the reaction mixture was mixed with 700 µL benzene-d_6 in a vial. The vial was vigorously shaken for a few seconds, and anhydrous Na_2SO_4 was added to absorb the water. The dried benzene-d_6 solution containing both reactants and products of the catalytic reaction was filtered into an NMR tube and used for ^{1}H NMR analysis. For the catalytic reaction in DMF, 100 µL of the reaction mixture was mixed with 600 µL benzene-d_6 for ^{1}H NMR analysis. An approximate estimation of the ratios of the reaction products was made using ^{1}H NMR analysis.

General procedure for measuring the ee of the cascade product by a ^{1}H NMR ee assay.

According to the method of Chi et al.,[1] the enantiomeric excess of the products could be estimated by treating the product with the chiral amine (S)-(+)-1-methoxy-2-propylamine and measuring the diastereomeric ratio of the resulting imine by ^{1}H NMR. Immediately before the ^{1}H NMR experiment, 15 µL of the chiral amine was added to the NMR tube containing about 9 mg of the sample and 1 mg of acetic acid in 670 µL of $CDCl_3$. The imine protons of all four diastereomeric products were clearly visible as separated doublets in the region of 7.6-7.4 ppm and were assigned by comparison with the corresponding racemic samples. The absolute and relative stereochemistry of the products was assumed to (R,R) by analogy to literature examples employing similar

substrates and catalysts. The figures below are the sample ^{1}H NMR spectrum of the in situ formed imine species containing the protons of interest for compound **14** in the ee assay. On the left is the racemic form of product **14** prepared using DL-proline and substituting chiral catalyst **A** with pyrrolidine. The two largest doublets are from the major enantiomers of the cascade product. The integrations of the minor peaks are consistent with the diastereomeric ratio observed in the spectrum of the corresponding cascade products (aldehyde samples). On the right is compound **14** synthesized in the one-pot reaction with a combined use of proline and catalyst **A**.



In order to verify these data, compound **14** was used as a model compound to verify the enantiomeric ratio by chiral HPLC. After purification, 10 mg of both the racemic and enantiomerically enriched samples of **14** were converted to the corresponding alcohol by treatment with 10 mg of $NaBH_4$ in 1 mL of MeOH for a few minutes. The reactions were quenched with 2 mL of ice-cold saturated NH_4Cl solution and extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. After filtering and evaporation of the solvent, the identity of the material was confirmed by ^{1}H NMR and the samples were redissolved in hexanes. The enantiomeric ratio was determined by HPLC using a Chiracel OD-H

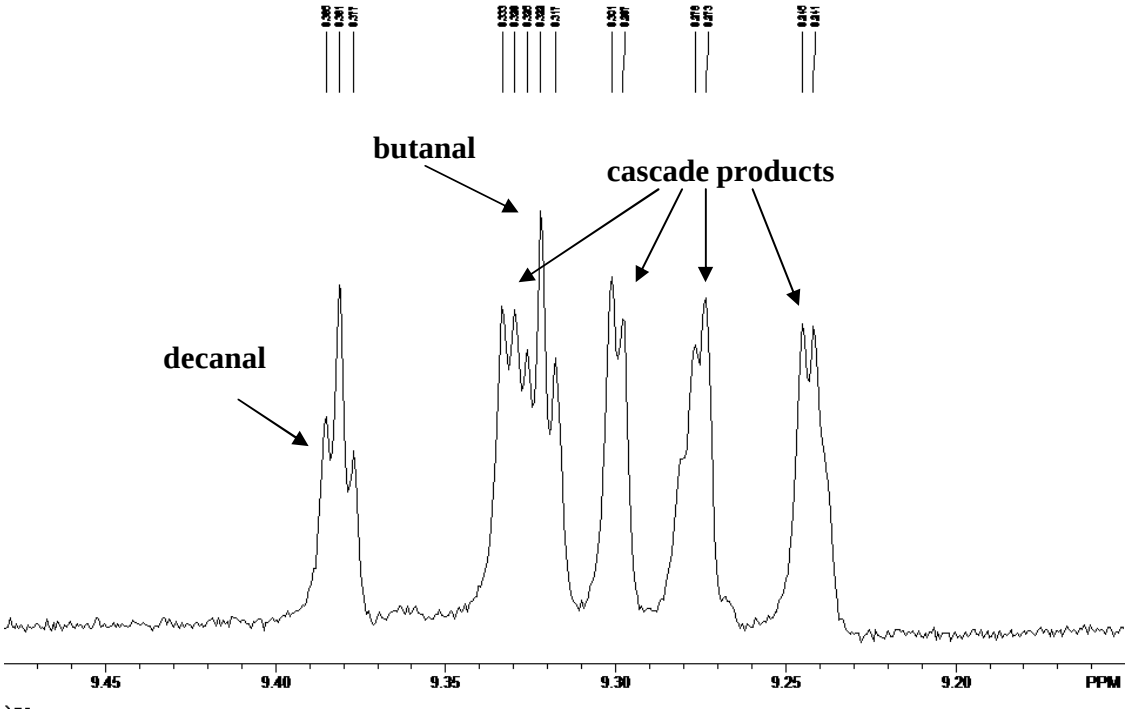
column, λ=210 nm, hexane/isopropanol (v/v: 99.75:0.25, premixed), flow rate = 0.6 mL/min; t_R = 134.5 min (major), 146.7 min (minor) (99:1 e.r.).

Sample one-pot reaction procedure.

All one-pot reactions for the synthesis of the "cross" cascade products (shown in Table 2) followed a similar procedure for the synthesis of **3ab** from butyraldehyde and decyl aldehyde: To a small vial equipped with a magnetic stir bar, was added 3.3 mg (0.010 mmol) of **A**, 46.1 mg (0.400 mmol) of L-proline, and 40.1 mg (0.200 mmol) of lauric acid. A 100 mM phosphate buffer solution (1 mL, pH 7.5) was added. The resulting cloudy mixture was stirred for a few minutes at rt and then 162 µL (183 mg, 3 mmol) of nitromethane was added via a syringe. After stirring at rt for another few minutes, the two aldehyde substrates were added via a syringe: 188 µL (156 mg, 1 mmol) of decanal was added, followed immediately by 89.6 µL (72.1 mg, 1 mmol) of butanal. The reaction mixture was stirred vigorously at rt for 16h, at which point complete consumption of decanal was observed through ^{1}H NMR and GC/MS analysis. The reaction mixture was then extracted three times with approximately 20 mL of dichloromethane. The collected organic fractions were dried over sodium sulfate and concentrated. Purification via flash chromatography (gradient of 2-4% ethyl acetate in hexanes) yielded the product (181 mg, 67% yield) as a pale yellow oil. The ^{1}H and ^{13}C NMR spectra of the compound were identical to a compound synthesized from the conjugate addition of decanal to nitroalkene **2a**.[2]

Testing the reaction in DMF as the solvent.

The one-pot reaction of decanal and butanal was performed using various catalyst combinations in DMF. ^{1}H NMR analysis of the crude reaction mixtures showed that in all cases the four possible cascade products shown in Scheme 2 were formed in roughly equal molar amounts. For example, the spectrum shown below is from a reaction in which all catalyst and substrate ratios correspond to those used in the one-pot reaction conditions. In addition to the triplet peaks corresponding to the two aldehyde starting materials, four doublets from the various cascade products are observed with roughly equal magnitudes. Under these homogeneous conditions the reactivity of the two aldehydes is nearly indistinguishable.



Optimization of the experimental conditions and parameters.

The "cross" cascade reactions were optimized extensively with respect to temperature, order of reagent addition, reagent and catalyst concentrations/loadings, and buffer pH. Reactions were monitored for selectivity by ^{1}H NMR and yields estimated by comparison of the NMR integration of the product and starting material relative to that of nitromethane. Changing the temperature or reagent addition protocol had little beneficial effect on the selectivity or yield of the reaction.

Effect of reagent substrate/catalyst loading. Increasing the amount of nitromethane resulted in greater selectivity for the formation of the desired "cross" cascade product, but other side reactions, such as conjugate addition of the nitromethane to the nitroalkene intermediate, also increased. The use of 3 eq of nitromethane was found to be optimal for reaction yield. A similar pattern was observed when increasing the amount of proline, and/or decreasing the amount of catalyst **A** or lauric acid.

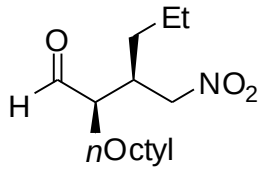
Effect of buffer pH. Decreasing the pH of the buffer from 8.0 to 7.0 resulted in greater selectivity for the desired "cross" cascade product over the undesired "homo" products, but other side reactions increased. Some examples of these side reactions are aldol-type reactions of the aldehydes and the conjugate addition of nitromethane to the nitroalkene intermediate. A pH of 7.5 was found to be optimal for reaction yield. As the buffer pH dropped below 7.0, the rate, selectivity and yield of the reaction decreased along with pH. Below a pH of approximately 6.5 (near the isoelectric point of proline), the first step of the reaction was strongly inhibited, most likely because the free amine site on proline is essential to its catalytic activity. For this reason, the reaction conditions

were carefully controlled to exclude water-miscible organic acids derived from the aldehyde substrates, which lead to undesirable lowering of the pH of the aqueous phase.

Product isolation:

In all of the reactions tested, the four cascade products (i.e. **3aa**, **3ab**, **3ba**, and **3bb**) could be easily isolated together as a mixture. In all cases under the optimized reaction conditions, approximately 80% of the theoretical mass of the final products was contained within this product mixture. For the most part, the desired product (i.e. **3ab**) could be isolated at approximately 65% of the theoretical mass. The remainder of the product mixture contained primarily homo adduct (i.e. **3aa**) and trace amounts of the other two cascade products (i.e. **3bb**, **3ba**). In the case of the reactions to form products **8**, **9**, **10**, and **11** it was difficult to completely separate the desired major cascade products from the other products without significant loss of material. In cases where complete product isolation via flash chromatography was difficult, the yield of the major products was estimated based on ^{1}H NMR and GC/MS analysis of an isolated mixture of several cascade products.

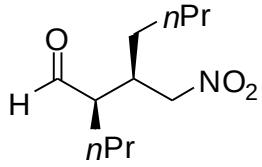
Characterization data.



3ab

2-(1-nitropentan-2-yl)decanal.

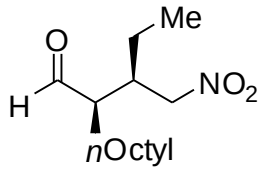
^{1}H NMR (400 MHz, C_6D_6) *d* = 9.15 (d, *J* = 1.5 Hz, 1H), 3.82 (dd, *J* = 6.8, 12.8 Hz, 1H), 3.74 (dd, *J* = 6.9 Hz, 12.5, 1H), 2.37-2.34 (m, 1H), 1.96-1.92 (m, 1H), 1.37-1.10 (m, 13H), 1.02-0.87 (m, 5H), 0.92 (t, *J* = 6.8 Hz, 3H), 0.64 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR *d* = 201.55, 76.58, 52.12, 36.55, 31.91, 31.00, 29.64, 29.38, 29.30, 27.62, 24.90, 22.75, 19.77, 14.02, 13.56 ppm; IR (neat) 2960, 2928, 2857, 2727, 1725, 1554, 1466, 1381, 723; HRMS (EI) *m/z* calculated for [M^++1] 272.2226, found 272.2230.



4

3-(nitromethyl)-2-propylheptanal.[2]

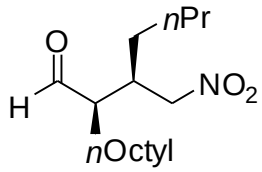
^{1}H NMR (400 MHz, C_6D_6) *d* = 9.12 (d, *J* = 1.4 Hz, 1H), 3.82 (dd, *J* = 6.9, 12.8 Hz, 1H), 3.72 (dd, *J* = 6.9, 12.5 Hz, 1H), 2.32-2.27 (m, 1H), 1.92-1.90 (m, 1H), 1.32-0.78 (m, 10H), 0.74 (t, *J* = 7.0 Hz, 3H), 0.70 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR *d* = 201.53, 76.59, 51.82, 36.68, 28.71, 28.55, 26.90, 22.41, 20.72, 13.79, 13.61 ppm; IR (neat) 2961, 2935, 2874, 2729, 1724, 1553, 1467, 1382, 731; HRMS (EI) *m/z* calculated for [M^++1] 216.1600, found 216.1597.



6

2-(1-nitrobutan-2-yl)decanal.

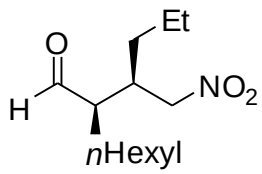
^{1}H NMR (400 MHz, C_6D_6) *d* = 9.13 (d, *J* = 1.5 Hz, 1H), 3.82 (dd, *J* = 7.1, 12.5 Hz, 1H), 3.74 (dd, *J* = 6.8, 12.7 Hz, 1H), 2.25-2.06 (m, 1H), 1.94-1.87 (m, 1H), 1.40-0.70 (m, 16H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.50 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR *d* = 201.59, 76.25, 51.81, 38.16, 31.91, 29.63, 29.37, 29.31, 27.50, 24.95, 22.75, 21.68, 14.02, 10.75 ppm; IR (neat) 2957, 2928, 2857, 2725, 1725, 1554, 1465, 1383, 723; HRMS (EI) *m/z* calculated for [M^++1] 258.2069, found 258.2074.



7

2-(1-nitrohexan-2-yl)decanal.

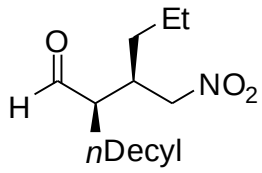
^{1}H NMR (400 MHz, C_6D_6) *d* = 9.16 (d, *J* = 1.3 Hz, 1H), 3.84 (dd, *J* = 7.2, 12.6 Hz, 1H), 3.77 (dd, *J* = 6.7, 12.5 Hz, 1H), 2.42-2.20 (m, 1H), 2.02-1.92 (m, 1H), 1.40-0.70 (m, 20H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.74 (t, *J*= 7.6 Hz, 3H) ppm; ^{13}C NMR *d* = 201.57, 76.60, 52.10, 36.74, 31.91, 29.63, 29.37, 29.32, 28.71, 28.56, 27.61, 24.91, 22.75, 22.42, 14.02, 13.62 ppm; IR (neat) 2958, 2928, 2857, 2725, 1725, 1553, 1467, 1381, 724; HRMS (EI) *m/z* calculated for [M^++1] 286.2382, found 286.2381.



12

2-(1-nitropentan-2-yl)octanal.

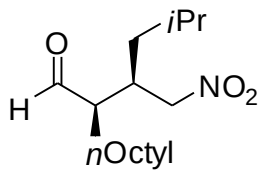
^{1}H NMR (400 MHz, C_6D_6) *d* = 9.14 (d, *J* = 1.5 Hz, 1H), 3.82 (dd, *J* = 6.9, 12.5 Hz, 1H), 3.74 (dd, *J* = 6.7, 12.7 Hz, 1H), 2.38-2.19 (m, 1H), 1.95-1.89 (m, 1H), 1.30-0.80 (m, 14H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.63 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR *d* = 201.54, 76.58, 52.11, 36.54, 31.53, 30.99, 29.28, 27.56, 24.88, 22.62, 19.77, 13.94, 13.56 ppm; IR (neat) 2960, 2931, 2860, 2723, 1723, 1554, 1466, 1382, 725; HRMS (EI) *m/z* calculated for [M^++1] 300.2539, found 300.2539.



13

2-(1-nitropentan-2-yl)dodecanal.

^{1}H NMR (400 MHz, C_6D_6) *d* = 9.14 (d, *J* = 1.4 Hz, 1H), 3.82 (dd, *J* = 7.2, 12.5 Hz, 1H), 3.74 (dd, *J* = 6.8, 12.4 Hz, 1H), 2.39-2.20 (m, 1H), 1.97-1.90 (m, 1H), 1.40-0.80 (m, 25H), 0.63 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR *d* = 201.53, 76.57, 52.12, 36.54, 31.99, 30.99, 29.72, 29.67, 29.66, 29.45, 29.44, 27.64, 24.89, 22.78, 19.77, 14.03, 13.58 ppm; IR (neat) 2959, 2927, 2856, 2722, 1725, 1554, 1466, 1381, 722; HRMS (EI) *m/z* calculated for [M^++1] 244.1913, found 244.1913.



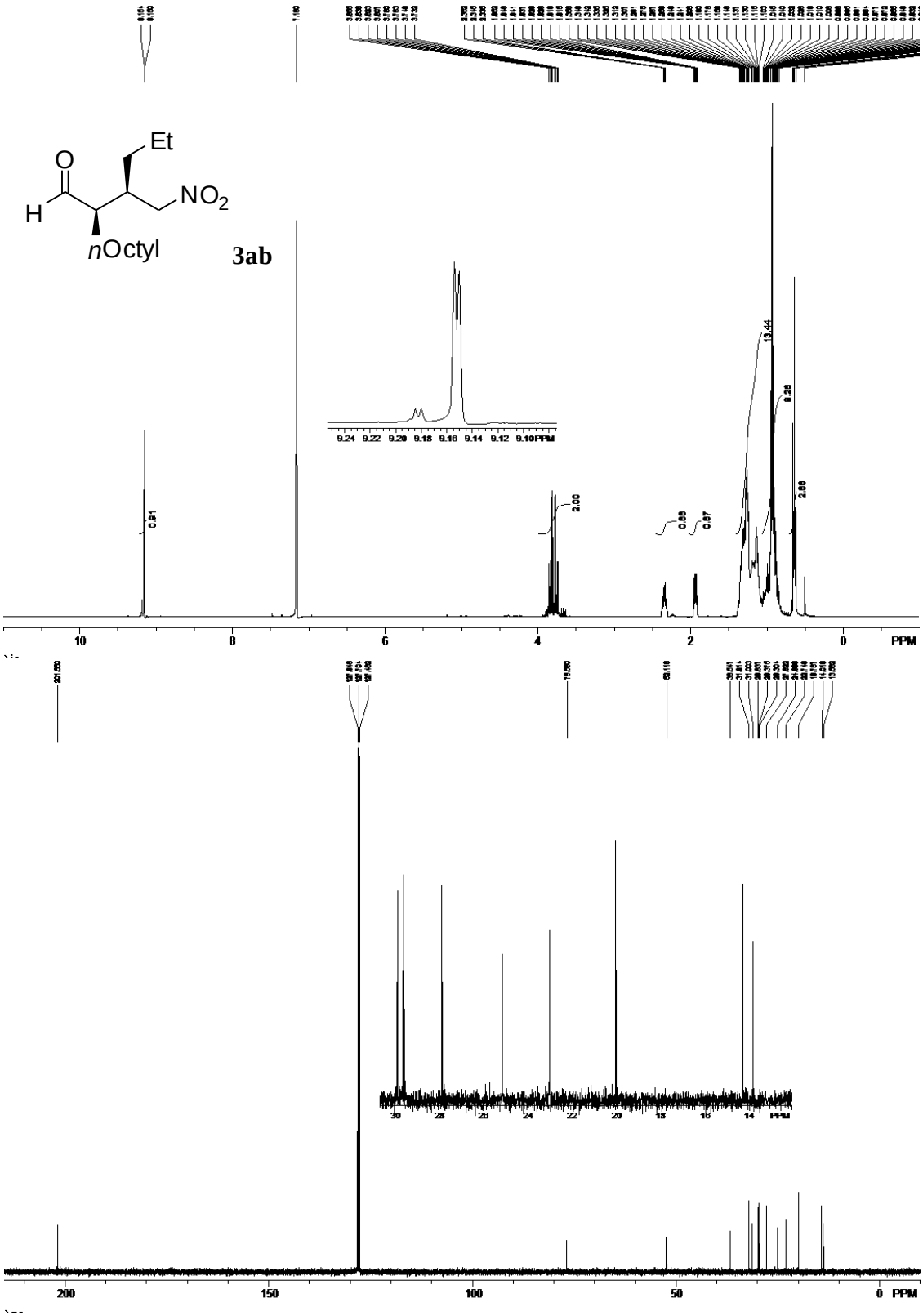
14

2-(4-methyl-1-nitropentan-2-yl)decanal.

^{1}H NMR (400 MHz, C_6D_6) *d* = 9.16 (d, *J* = 1.3 Hz, 1H), 3.85 (dd, *J* = 6.7, 12.5 Hz, 1H), 3.76 (dd, *J* = 7.1, 12.5 Hz, 1H), 2.55-2.34 (m, 1H), 2.04-1.95 (m, 1H), 1.42-0.78 (m, 17H), 0.92 (t, *J* = 6.8 Hz, 3H), 0.66 (d, *J* = 6.6 Hz, 3H), 0.65 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR *d* = 201.49, 76.66, 52.23, 37.95, 34.63, 31.91, 29.64, 29.38, 29.32, 27.71, 24.87, 24.79, 22.75, 22.24, 21.65, 14.03 ppm; IR (neat) 2959, 2929, 2723, 1725, 1555, 1467, 1382, 723; HRMS (EI) *m/z* calculated for [M^++1] 286.2382, found 286.2383

[1] Y. Chi, T. J. Peelen, S. H. Gellman, *Org. Lett.* **2005**, *7*, 3469-3472.

[2] S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555-558; *Angew. Chem. Int. Ed.* **2006**, *47*, 545-548.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NO2
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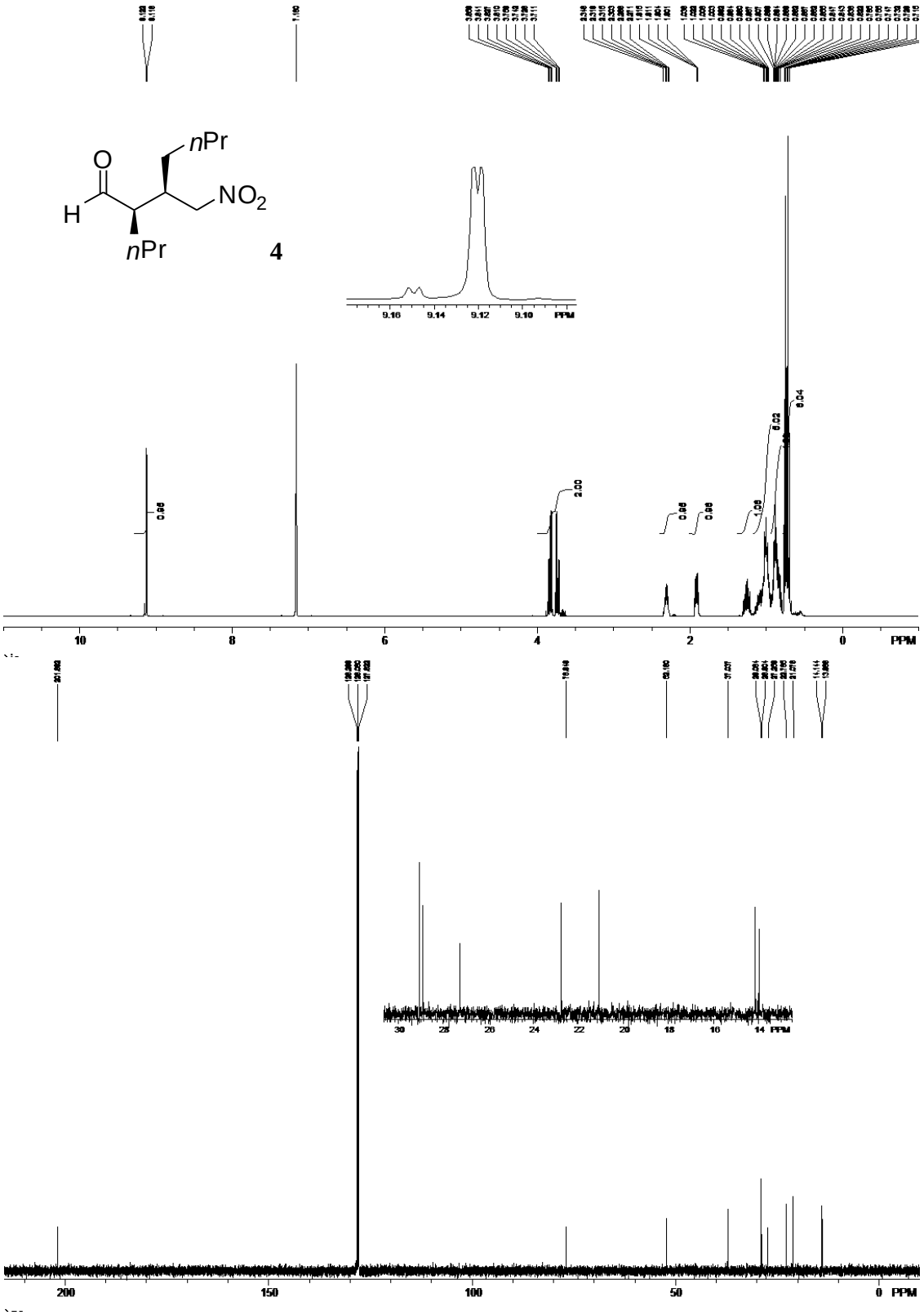
3ab
PPM
PPM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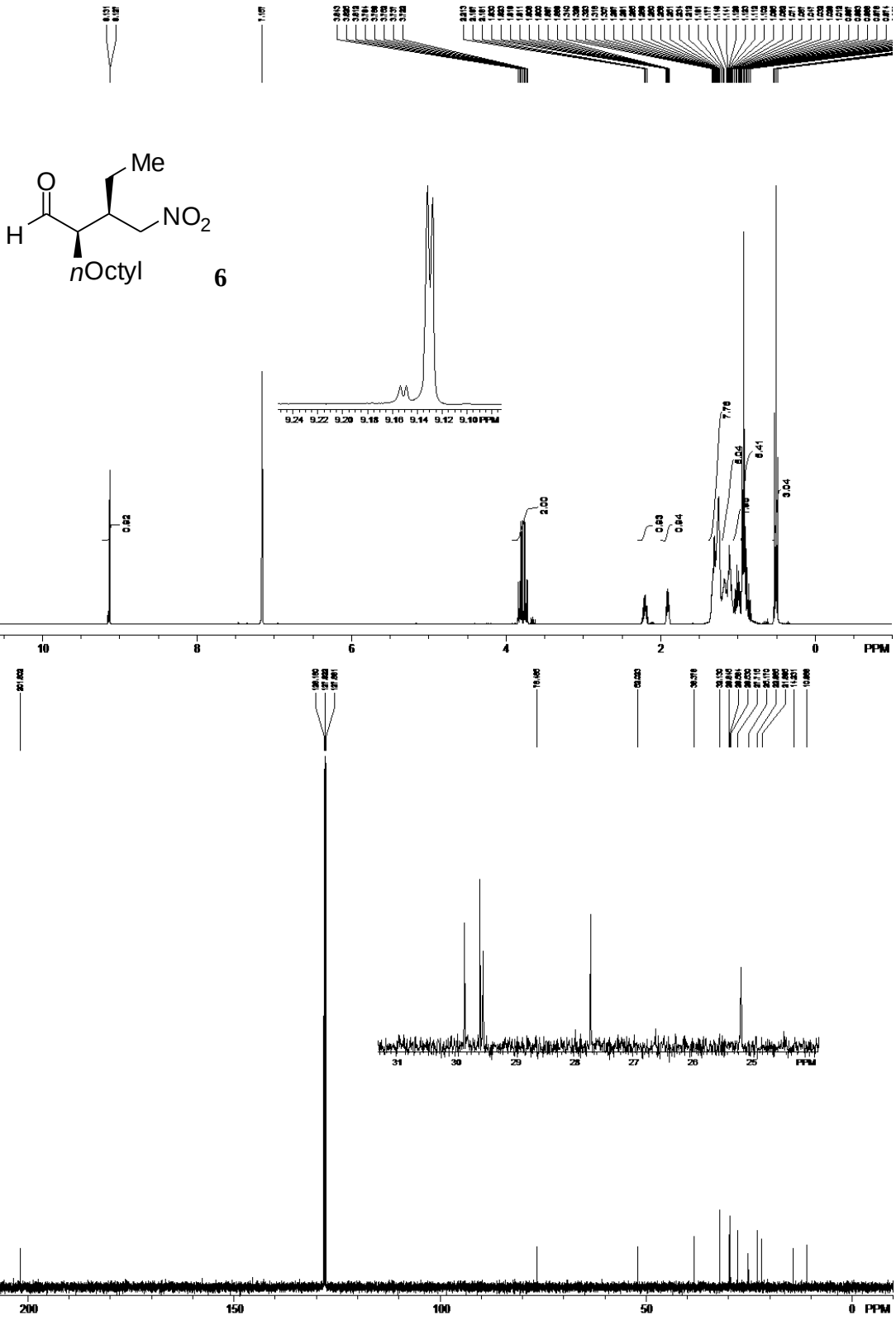
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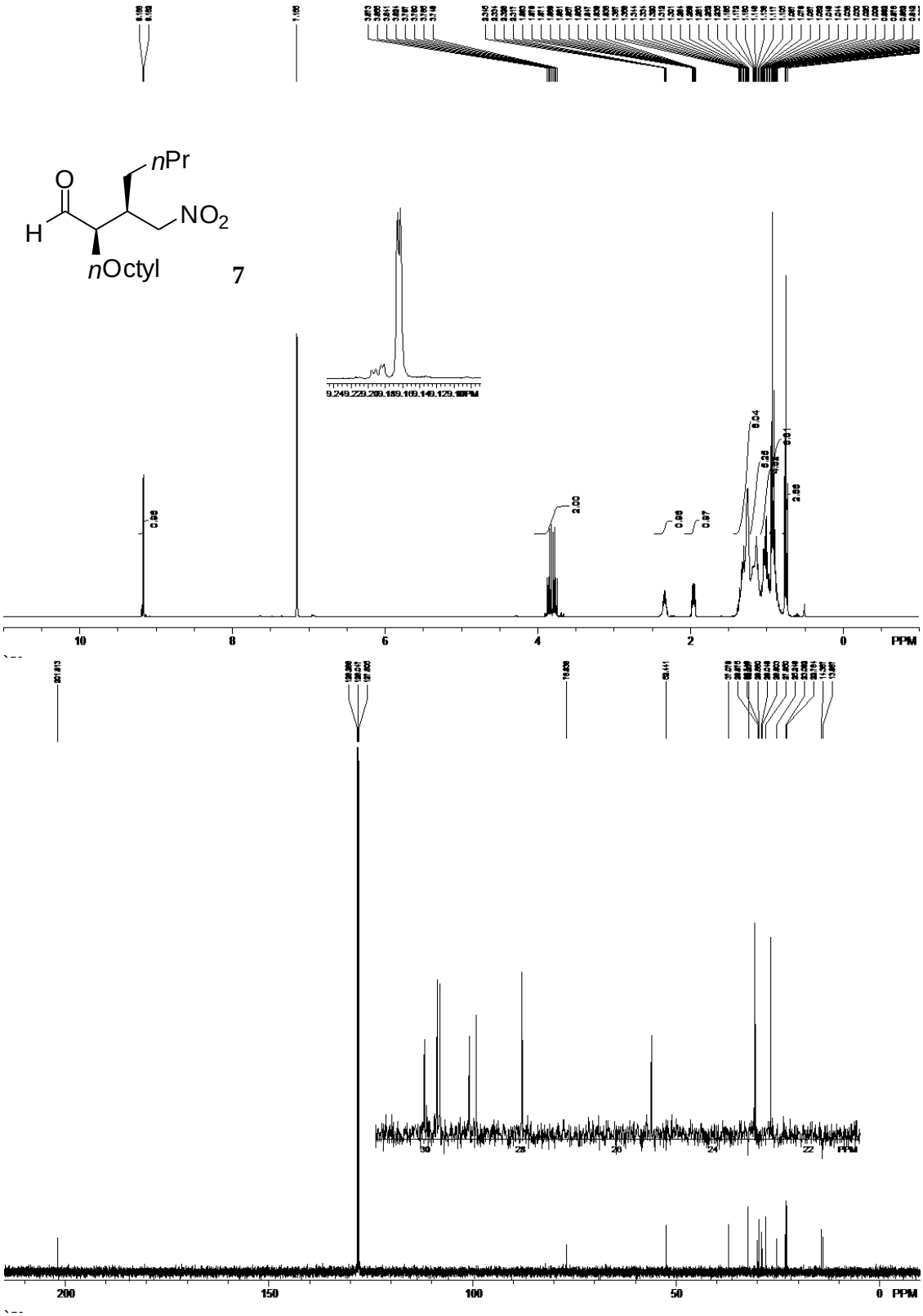
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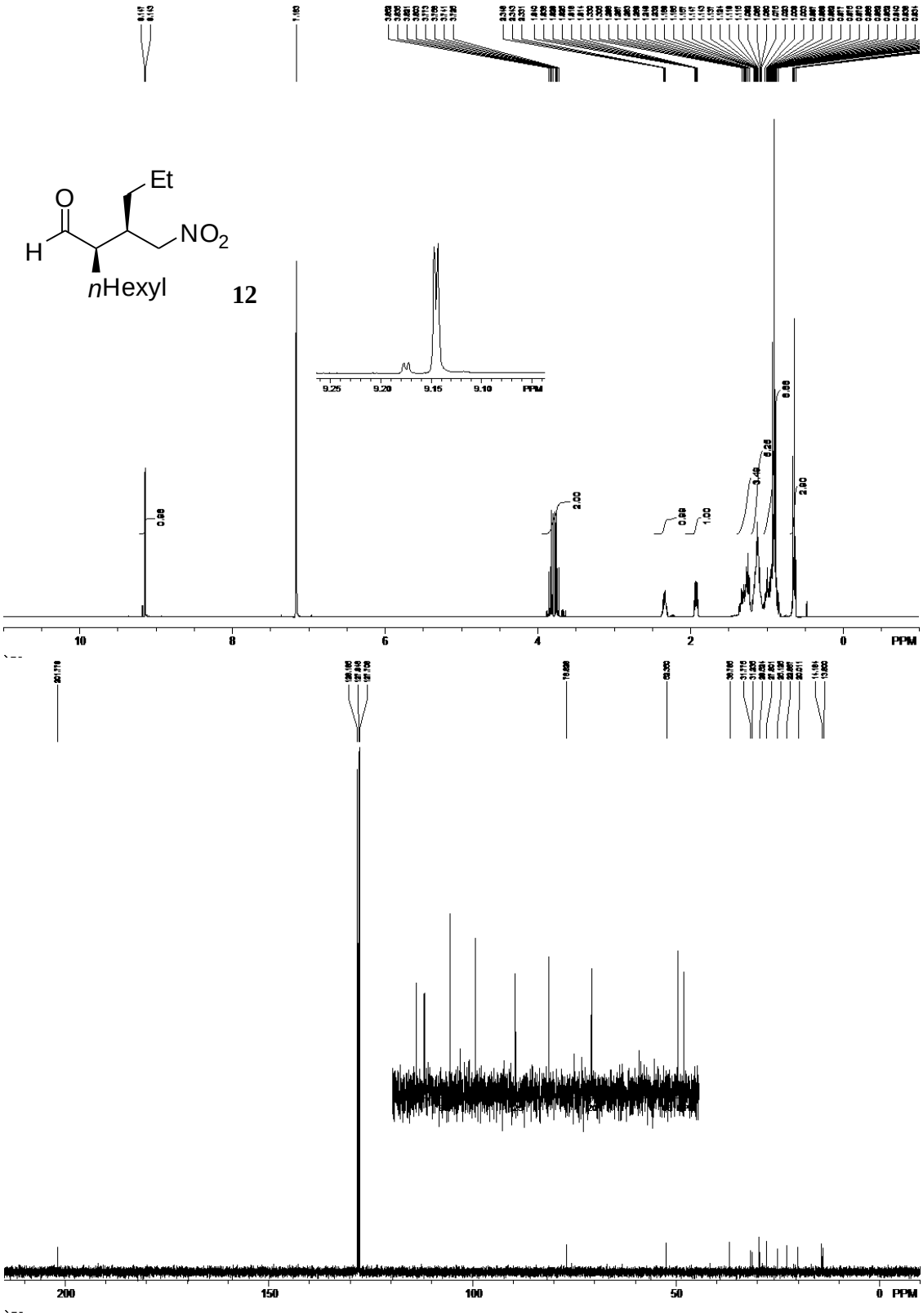
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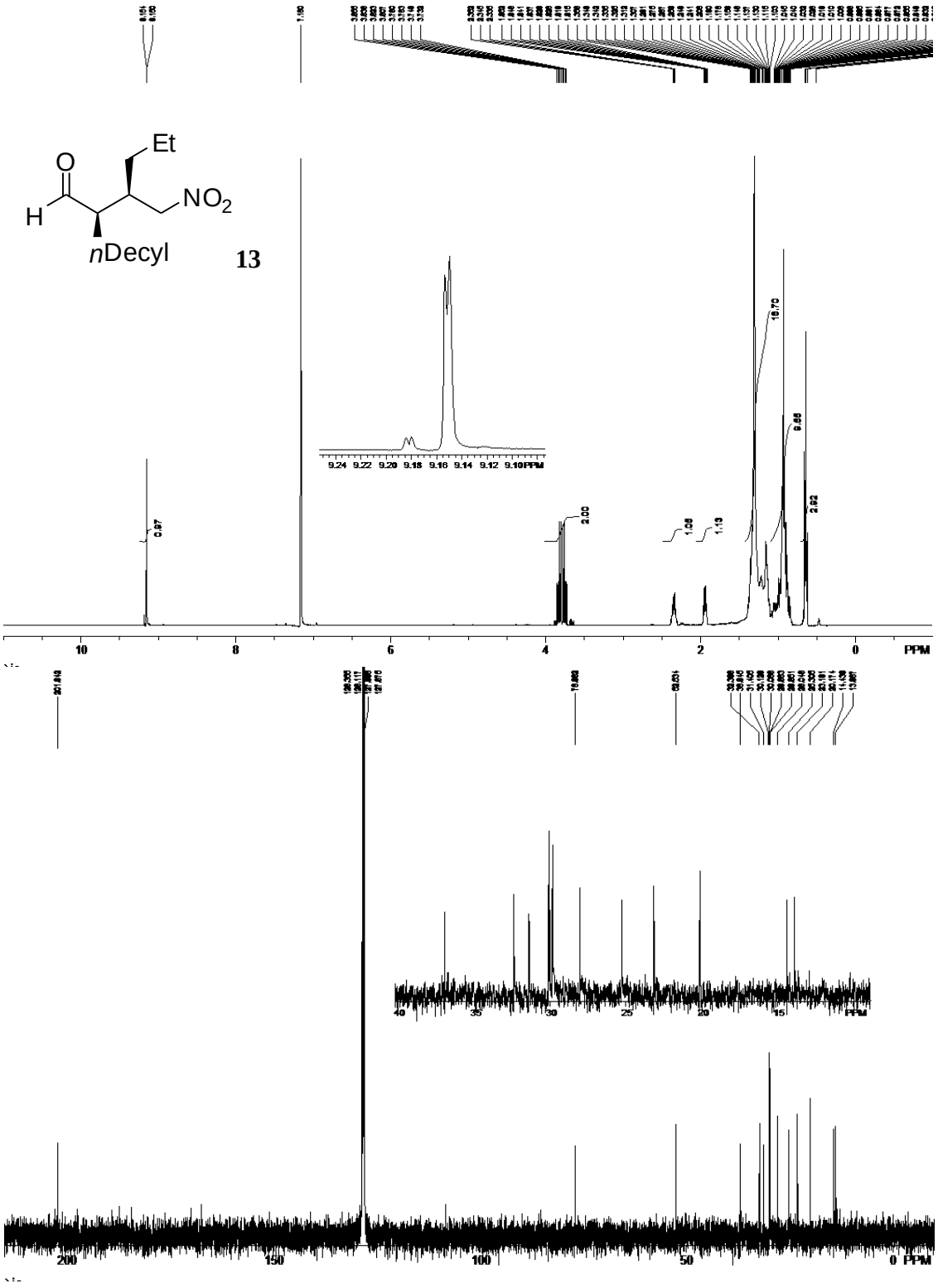
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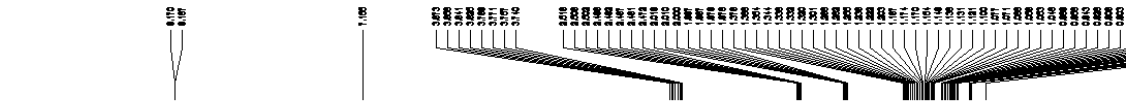

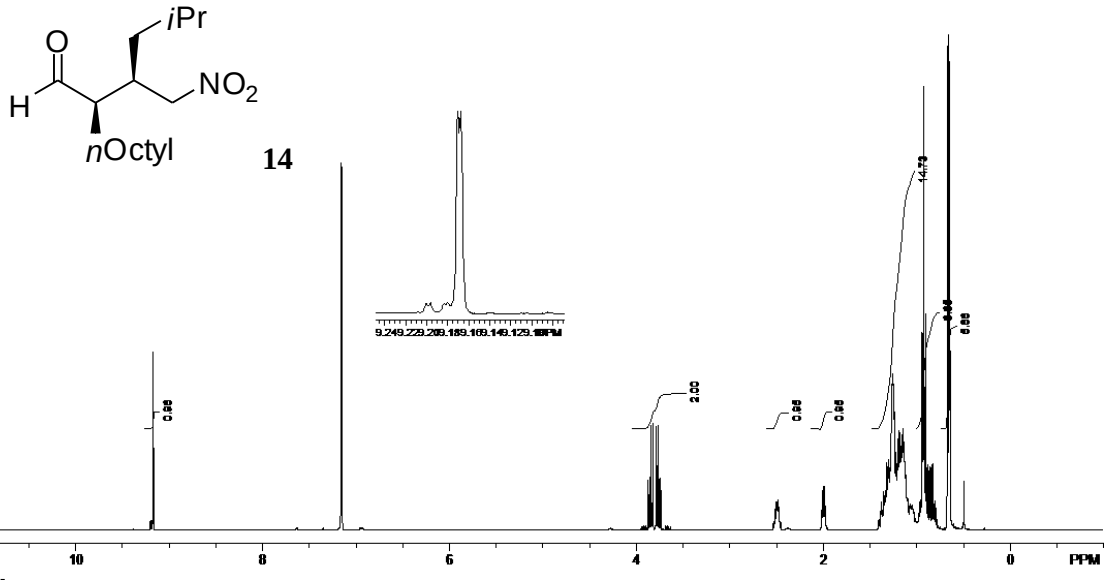

14