Electronic Supplementary Information

Imidazolidinone Intermediates in Prolinamide-Catalyzed Aldol Reactions

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1. General Information

^{1}H spectra were recorded at room temperature at 400 and 200 MHz and ^{13}C NMR were recorded at 100 and 50 MHz. Chemical shifts (δ) are given in ppm with the solvent signal as internal standard ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR; CH_3COCH_3, 2.05 ppm for ^{1}H NMR, CD_3COCD_3, 205.1 ppm for ^{13}C NMR; CH_3OH, 3.31 ppm for ^{1}H NMR, CD_3OD, 49.0 ppm for ^{13}C NMR) and coupling constants are reported in Hz. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet.
Melting points are uncorrected. Optical rotations were determinated for solutions in chloroform. IR were recorded as films. Mass spectra were obtained using electron impact (EI) or electron spray techniques (ESI).
Suitable single crystals of the **4**, **10a** and **10b** compounds were mounted on glass fibre for data collection on a Bruker Kappa APEX II CCD diffractometer. Data were collected at 298 K using Cu K_α radiation (λ = 1.54178 Å) and ω scan technique, and were corrected for Lorentz and polarization effects. Structure solution, refinement and data output were carried out with the SHELXTL^{TM} program package. The structures were solved by direct methods combined with difference Fourier synthesis and refined by full-matrix least-squares procedures, with anisotropic thermal parameters in the last cycles of refinement for all non-hydrogen atoms. H atoms of SP^3 hybridized carbons were located directly in a difference Fourier map and freely refined. The rest of the hydrogen atoms were positioned geometrically. Crystallographic data (excluding structure factors) for the structures reported in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary material nº. CCDC 741181-741183.

Reagents were purchased at the highest commercial quality and used without further purification unless otherwise noted[1]. Analytical thin layer chromatography was performed using pre-coated aluminium-backed plates and visualized by UV. For column chromatography silica gel (70-200 μm) was used.

The enantiomeric excess (ee) of the products was determined by chiral HPLC in an Agilent 1100 HPLC. Detection was done by UV at 210 nm. A Daicel Chiralpak IC column was used, with a length of 250 mm, and a width of 4.6 mm. Hexane/isopropanol 8:2 was used as eluent.

2. General Procedures

A. Reaction of acetone and 4-nitrobenzaldehyde

Aldol reaction in deuteroacetone: 4-nitrobenzaldehyde (60.65 mg, 0.4 mmol) and aniline prolinamide **1** (76.55 mg, 0.4 mmol) were dissolved in CD_3COCD_3 (0.4 cm^3, 5.44 mmol) at room temperature. The reaction was monitored by ^{1}H NMR.

Aldol reaction in deuterochloroform: 4-nitrobenzaldehyde (75.28 mg, 0.5 mmol), aniline prolinamide **1** (94.15 mg, 0.5 mmol) and acetone (0.037 cm^3, 0.5 mmol) were dissolved in 0.463 cm^3 of $CDCl_3$ at room temperature. The reaction was monitored by ^{1}H NMR.

B. Reaction of acetone imidazolidinone 4 and 4-nitrobenzaldehyde

Aldol reaction in deuteromethanol: 4-nitrobenzaldehyde (37.75 mg, 0.25 mmol) and acetone imidazolidinone **4** (57.50 mg, 0.25 mmol) were dissolved in 0.5 cm^3 of deuteromethanol at room temperature. The reaction was monitored by ^{1}H NMR.

Aldol reaction in deuteroacetone: 4-nitrobenzaldehyde (76.45 mg, 0.51 mmol) and acetone imidazolidinone **4** (116.83 mg, 0.51 mmol) were dissolved in 0.5 cm^3 of deuteroacetone at room temperature. The reaction was monitored by ^{1}H NMR.

[1] 4-Nitrobenzaldehyde was purified by sublimation.

C. Reaction of acetone and 4-nitrobenzaldehyde in presence of trifluoroacetic acid catalyzed by compounds 1, 12-16

4-nitrobenzaldehyde (51.3 mg, 0.34 mmol), catalyst (0.034 mmol) and trifluoroacetic acid (2.6 cm^3, 0.034 mmol) were dissolved in deuteroacetone (0.5 cm^3) at room temperature. The reaction was monitored by ^1H NMR and the enantiomeric excesses were determinated by HPLC analysis from the reaction mixture.

D. Reaction between butyraldehyde and prolinamide 1

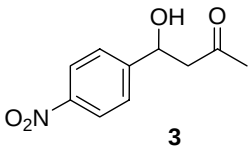
Aniline prolinamide **1** (9.58 mg, 0.05 mmol) and butyraldehyde (4.5 cm^3, 0.05 mmol) were dissolved in $CDCl_3$ (0.5 cm^3) at room temperature. The reaction was monitored by ^1H NMR.

E. Reaction between pyrrolidine cyclohexanone enamine and 4-nitrobenzaldehyde

Pyrrolidine cyclohexanone enamine[2] (11.25 mg, 0.075 mmol) and 4-nitrobenzaldehyde (11.33 mg, 0.075 mmol) were dissolved in $CDCl_3$ (0.45 cm^3) at room temperature. The reaction was monitored by ^1H NMR.

[2] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.* 1963, **85**, 207.

Figure S1. ^{1}H NMR (200MHz, $CDCl_3$) spectrum of the aldol product **3** of the reaction between acetone and 4-nitrobenzaldehyde.



3

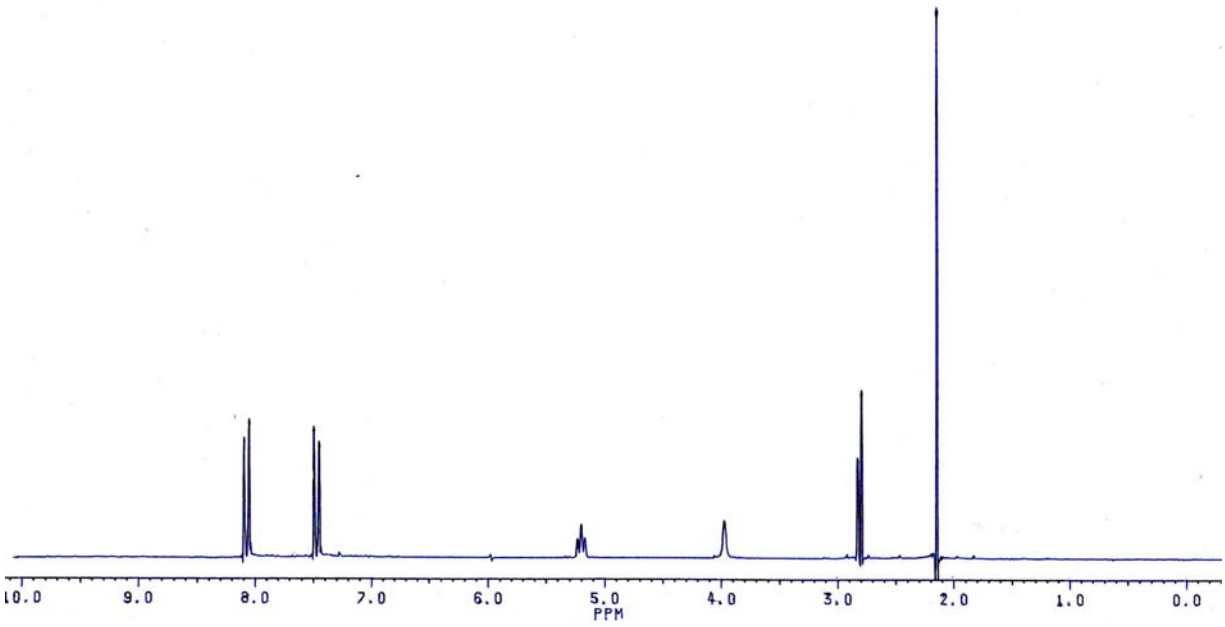


Figure S2. Chemical shifts for some relevant protons in acetone imidazolidinone **4** compared to prolinamide **1.**

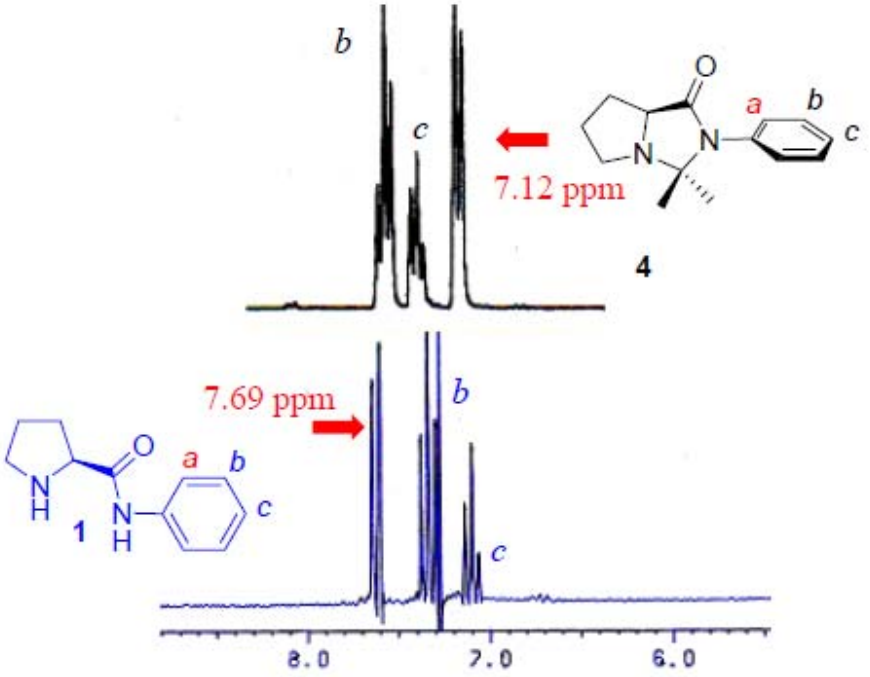
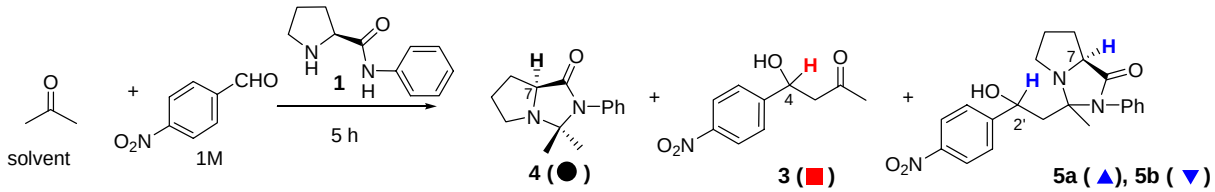


Figure S3. ^{1}H NMR spectrum of the reaction between acetone (solvent) and 4-nitrobenzaldehyde catalyzed by prolinamide **1**, after 5 hours (corresponds to Scheme1).



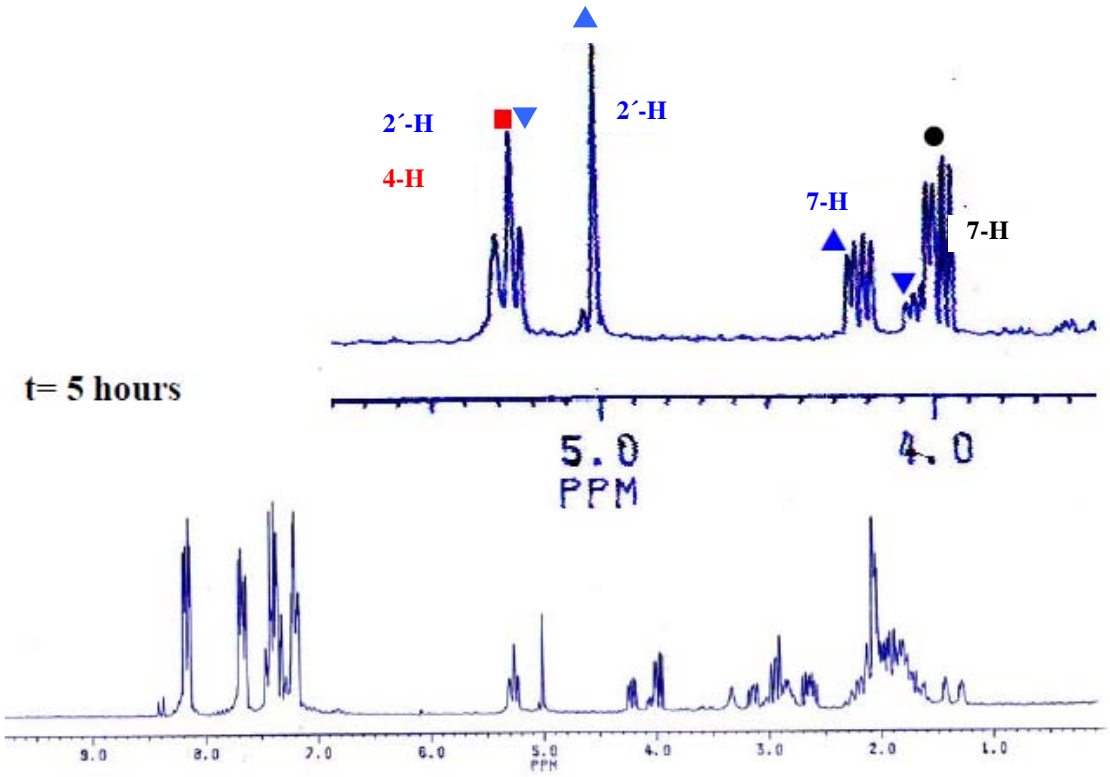
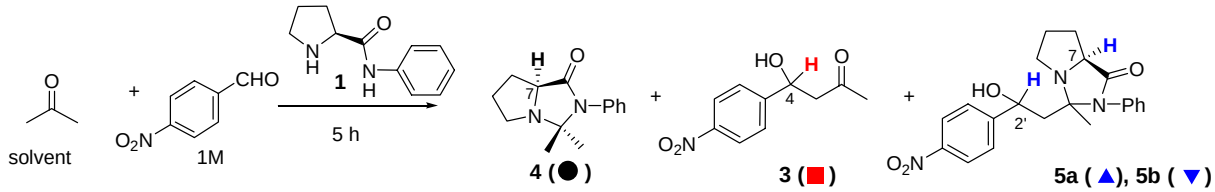
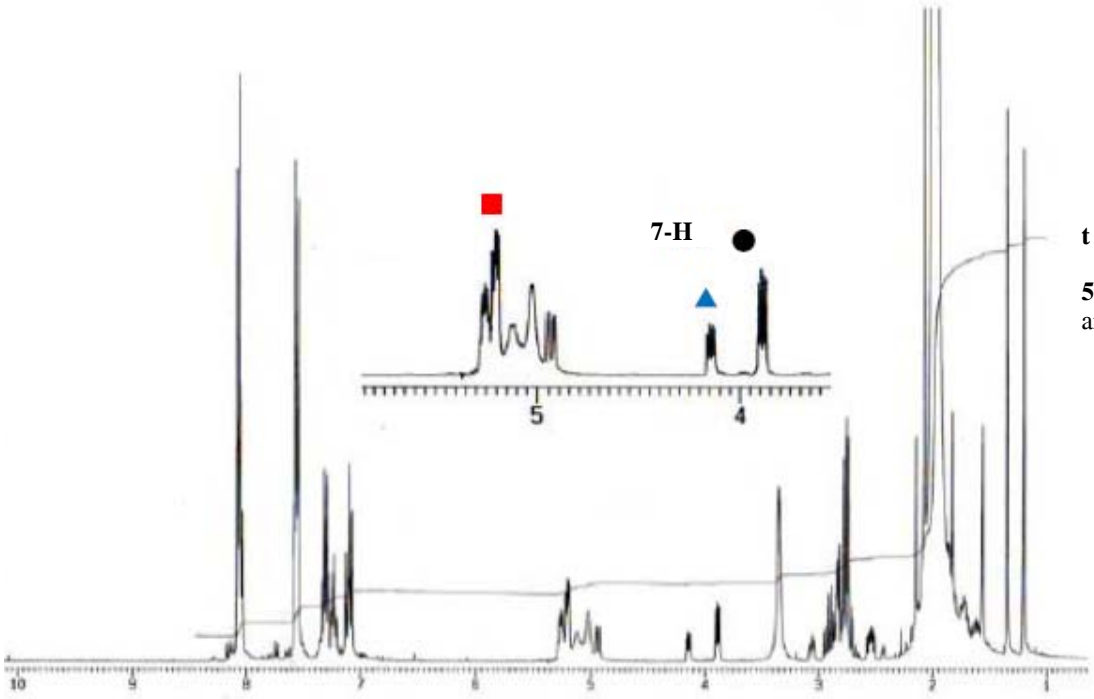


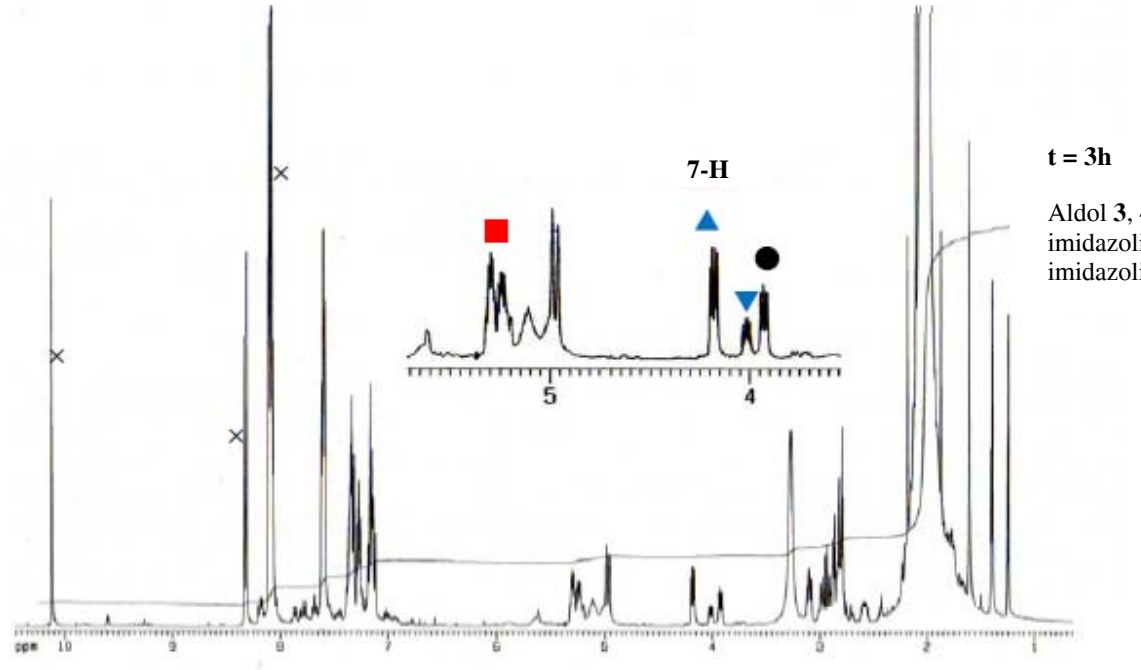
Figure S4. Aldol imidazolidinones **5a** and **5b** as intermediates in aldol condensation between acetone (solvent) and 4-nitrobenzaldehyde (×) catalyzed by prolinamide **1:** ^{1}H NMR spectra at different times.





t =20h

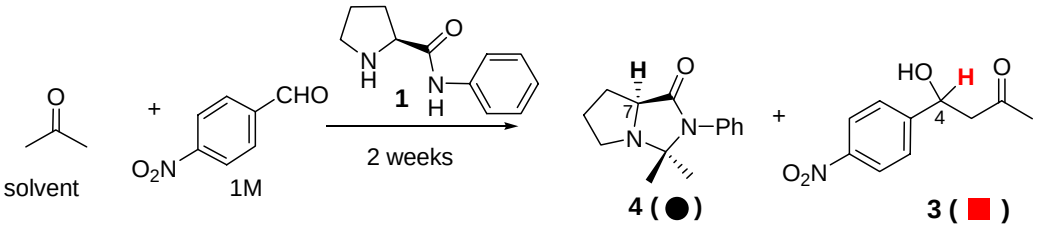
5b and 4-nitrobenzaldehyde are no longer detected



t = 3h

Aldol **3**, 4-nitrobenzaldehyde, imidazolidinone **4** and aldol imidazolidinones **5a** and **5b**

Figure S5. ^{1}H NMR spectrum of the reaction between acetone (solvent) and 4-nitrobenzaldehyde catalyzed by prolinamide **1**, after 2 weeks (corresponds to Scheme 1).



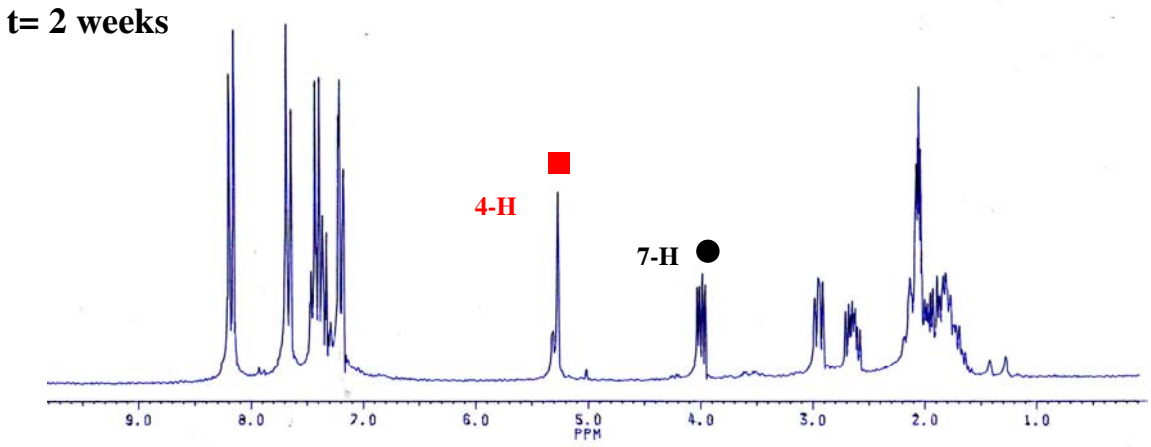


Figure S6. COSY spectrum (region 1.5-8.0 ppm) of acetone imidazolidinone **4** in deuteroacetone.

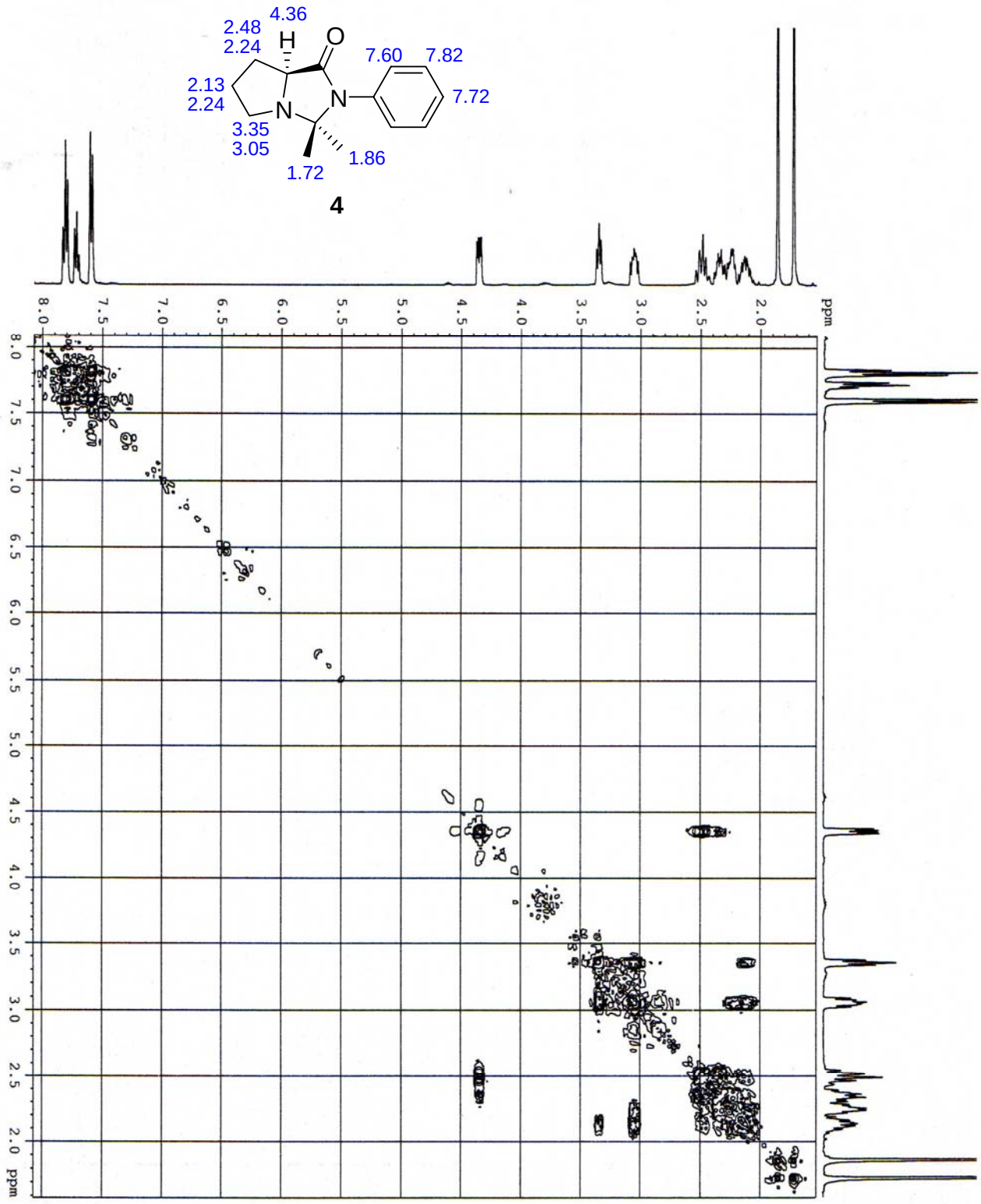


Figure S7. HMQC spectrum of acetone imidazolidinone **4** in deuteroacetone.

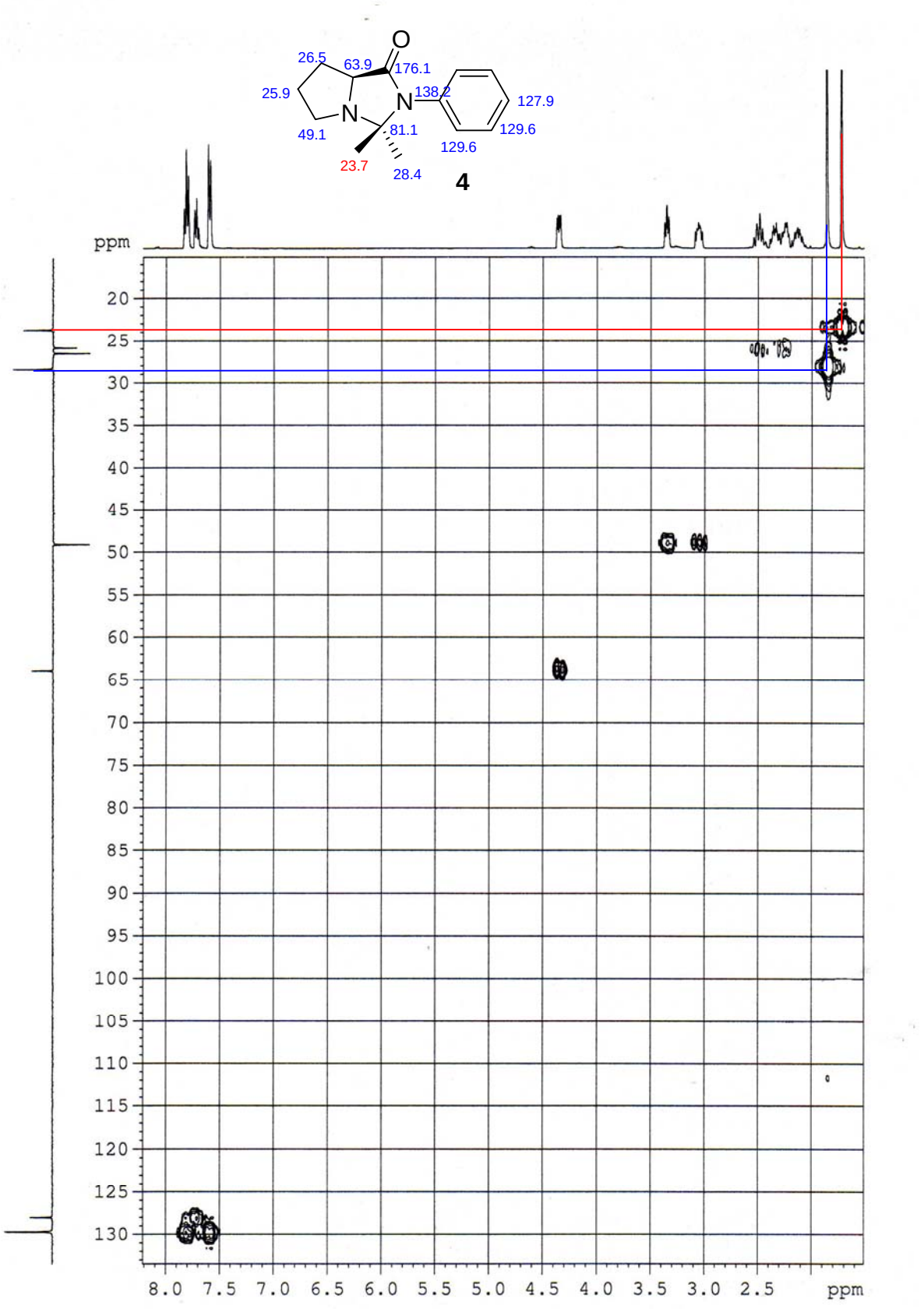
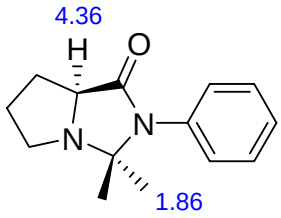


Figure S8. ROESY spectrum of acetone imidazolidinone **4** in deuteroacetone.



4

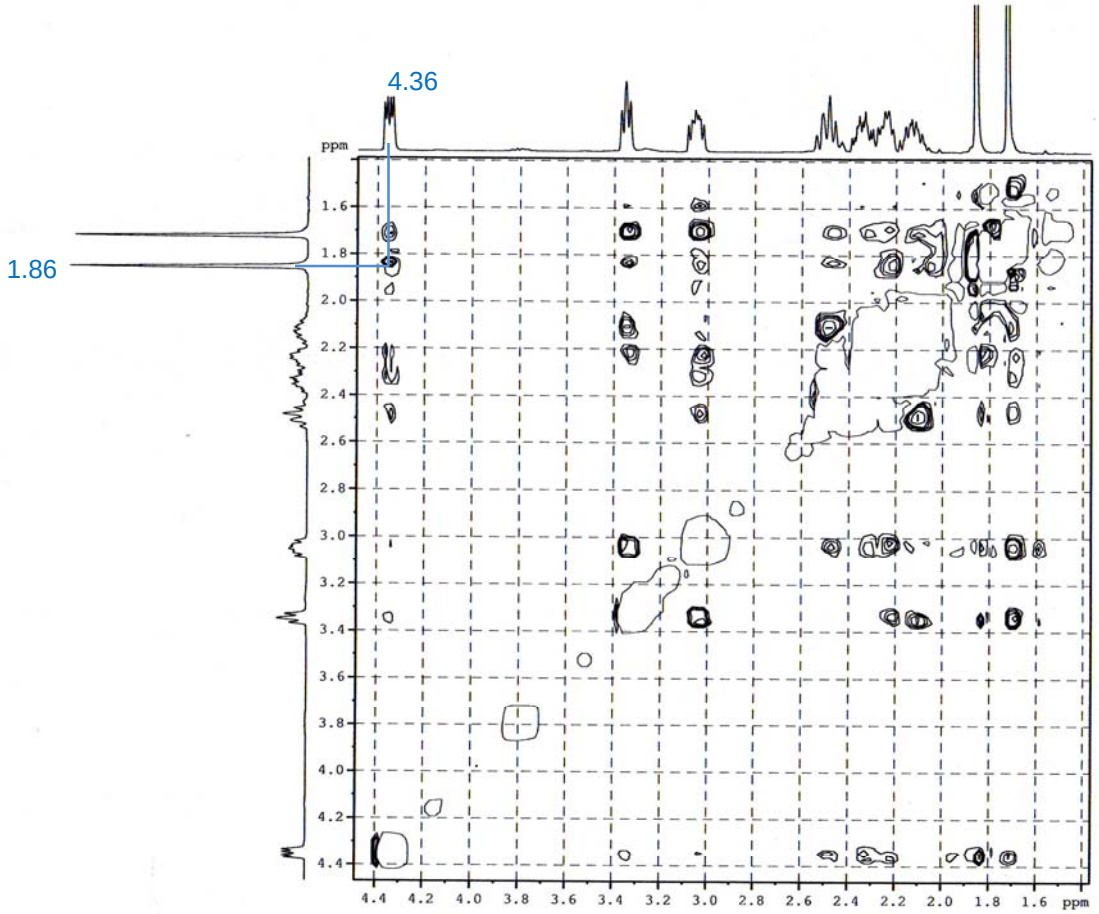


Figure S9. ^{13}C NMR spectrum of the reaction mixture corresponding to aldol condensation between acetone and 4-nitrobenzaldehyde catalyzed by prolinamide **1,** after 3 hours. Signals for the aldol imidazolidinones **5a** and **5b** are shown.

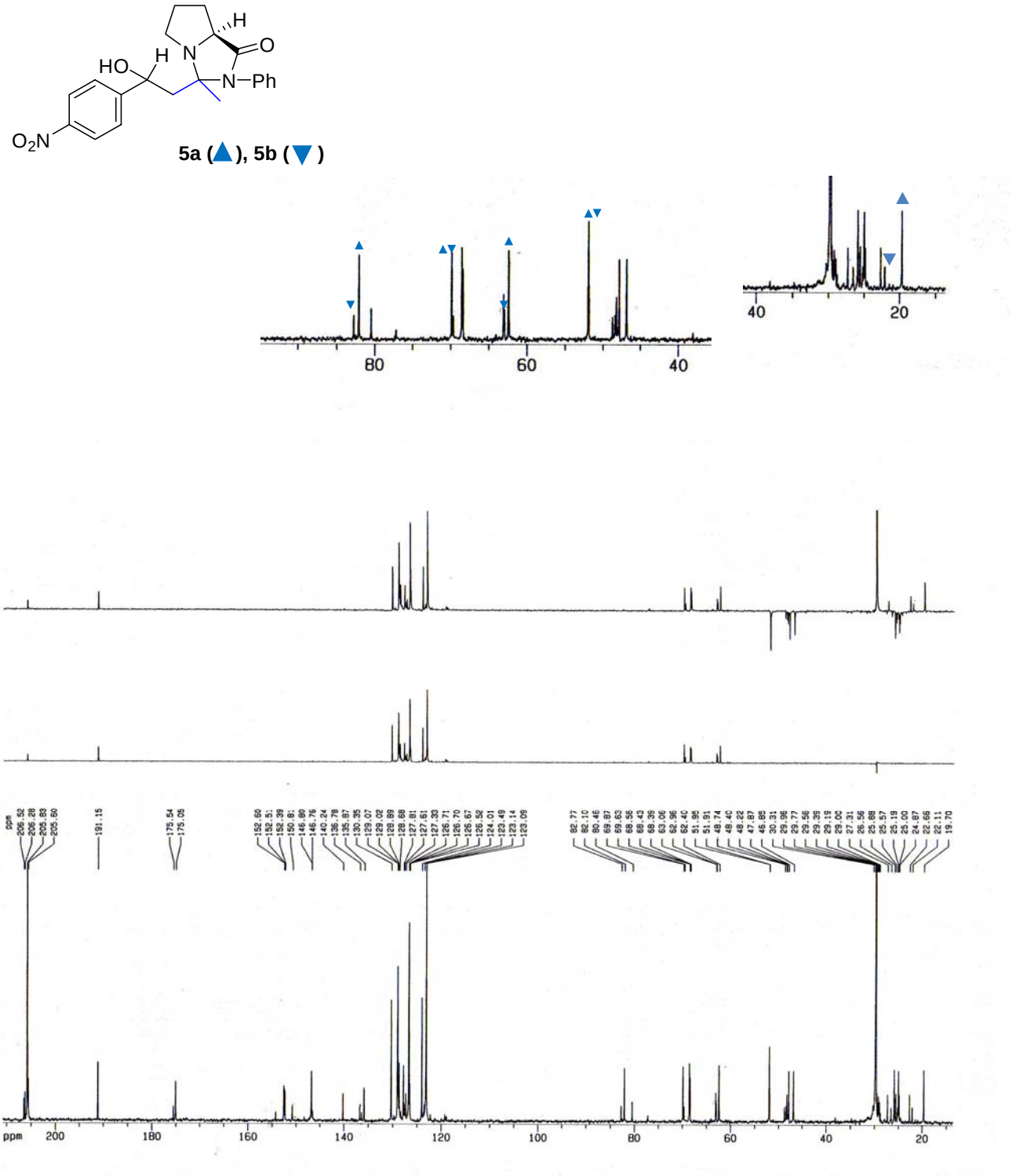


Figure S10. ^{13}C NMR spectrum of the reaction mixture corresponding to aldol condensation between acetone and 4-nitrobenzaldehyde catalyzed by prolinamide **1,** after 20 hours. Signals for the aldol imidazolidinone **5a** and acetone imidazolidinone **4** are shown.

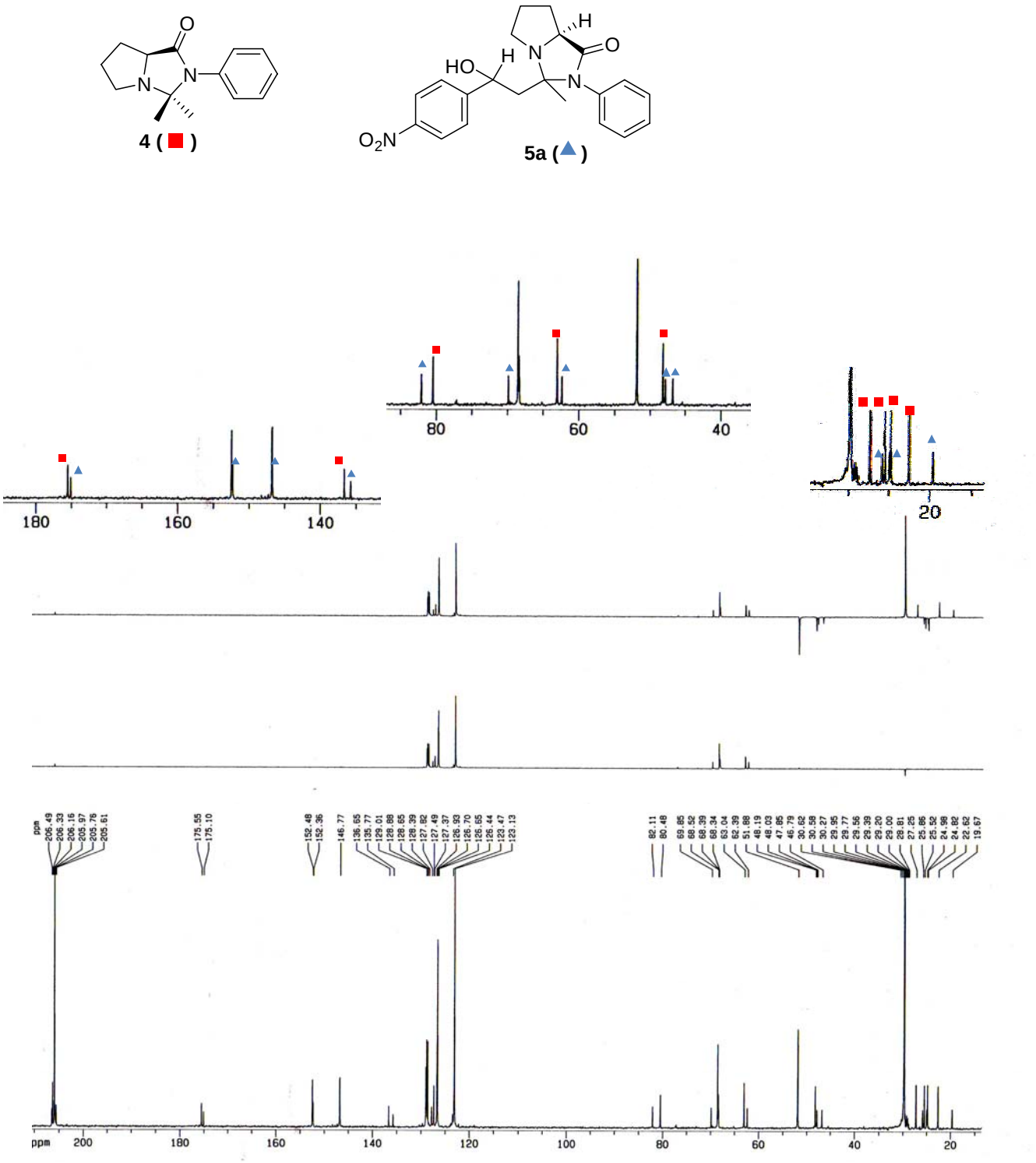
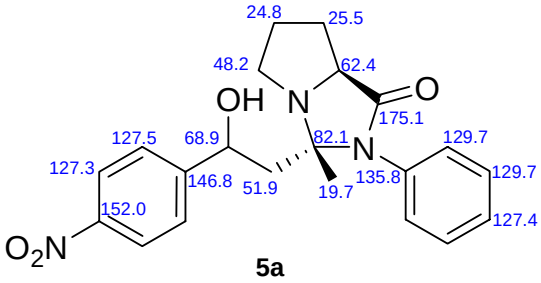
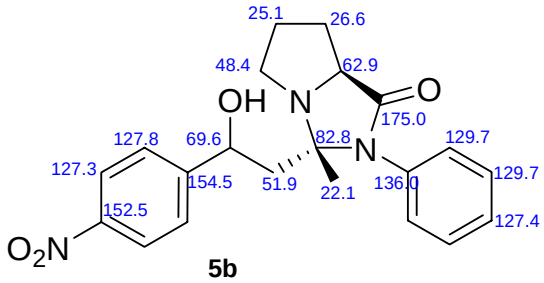


Figure S11. ^{13}C NMR assignments (tentative) for aldol imidazolidinones **5a** and **5b**.



5a



5b

Figure S12. [1]H NMR spectra (region 4.4 ppm-0.6 ppm) at different times for the reaction between prolinamide **1** and 4-nitrobenzaldehyde in deuteroacetone in which it is shown the different deuteration process of imidazolidinone **4** (Scheme 2).

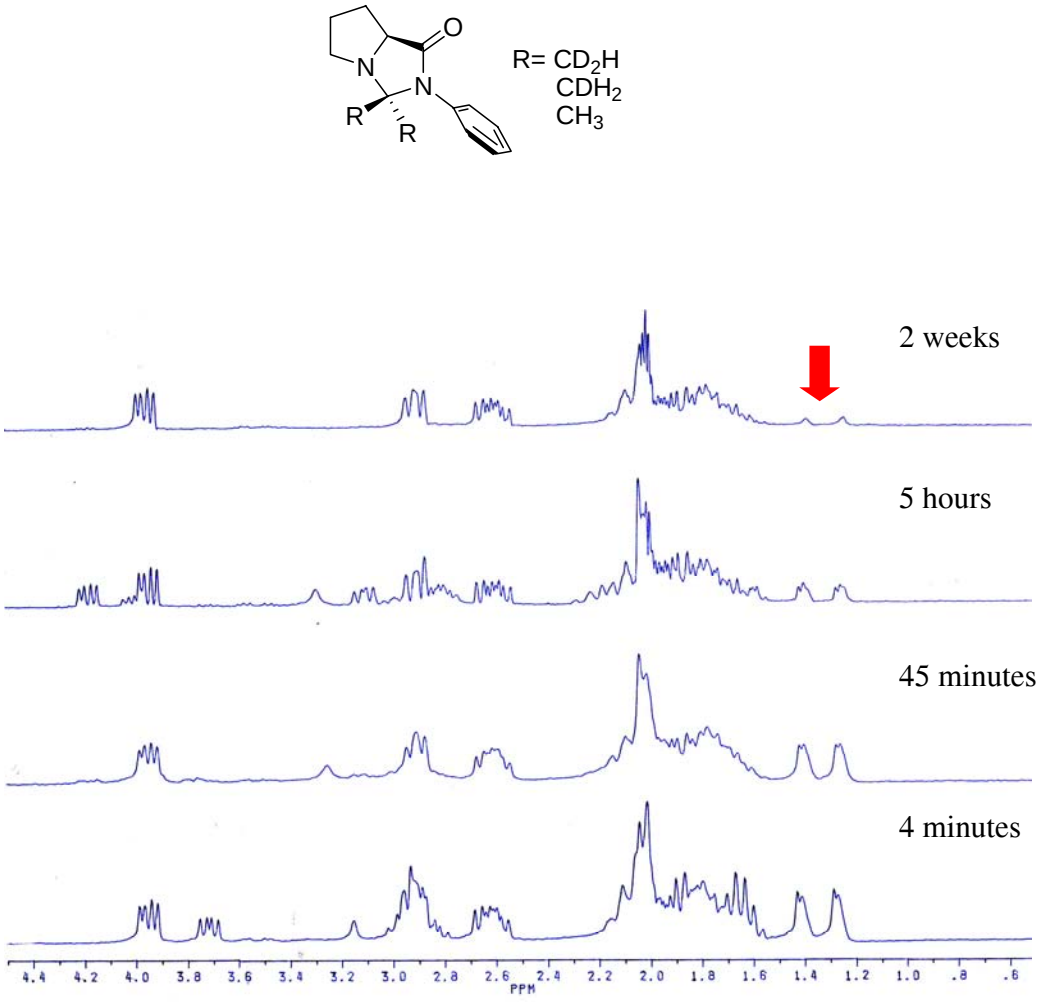
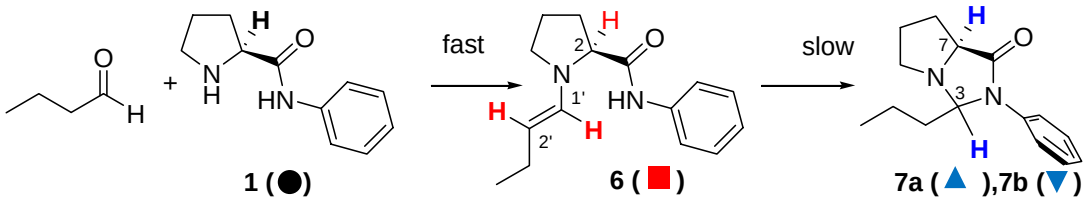


Figure S13. ^{1}H NMR spectra (200 MHz, region 3.6 ppm-6.2 ppm) at different times for the reaction corresponding to Scheme 3 (reaction of the prolinamide **1** with n-butyraldehyde in deuterochloroform).



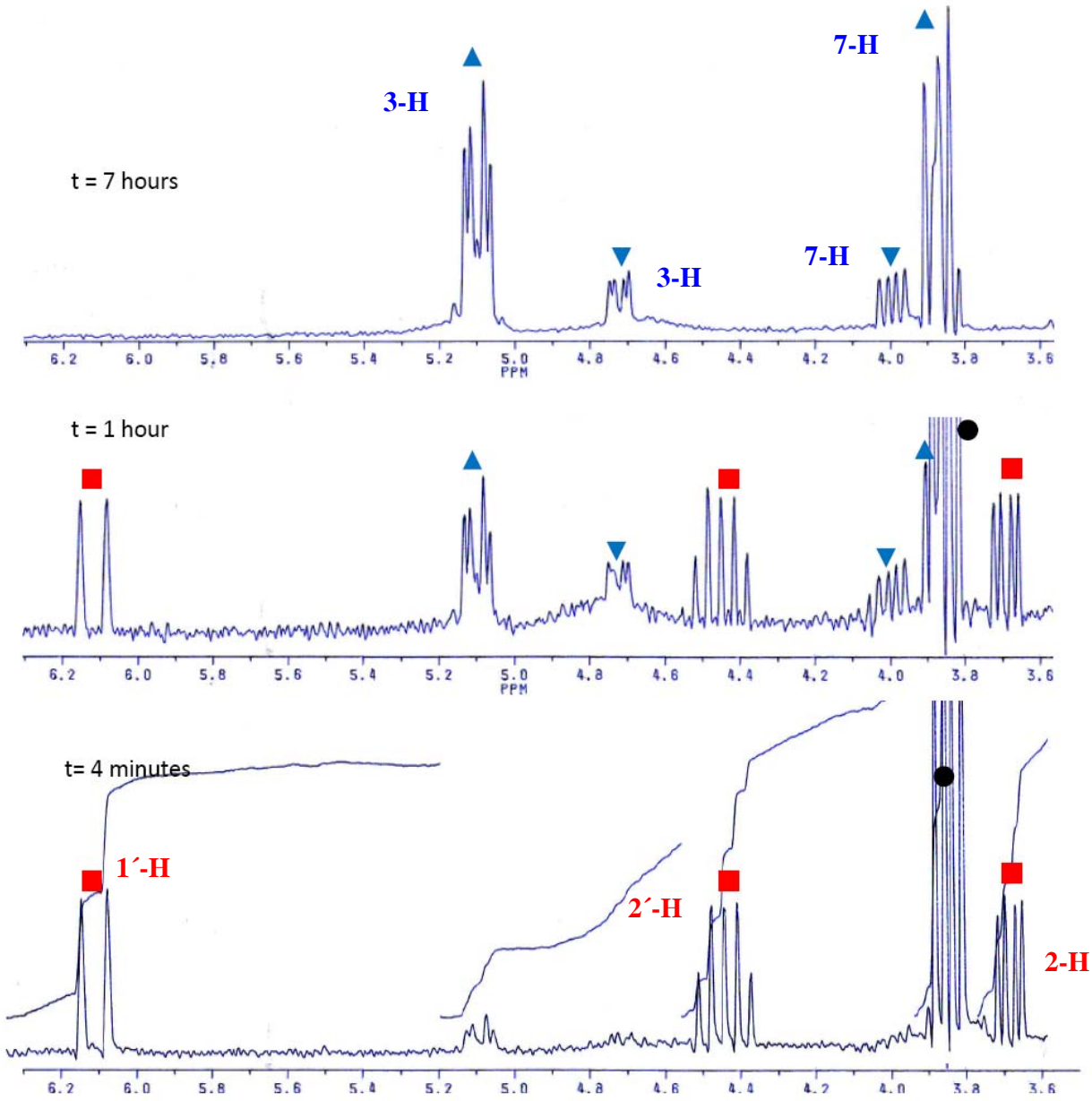
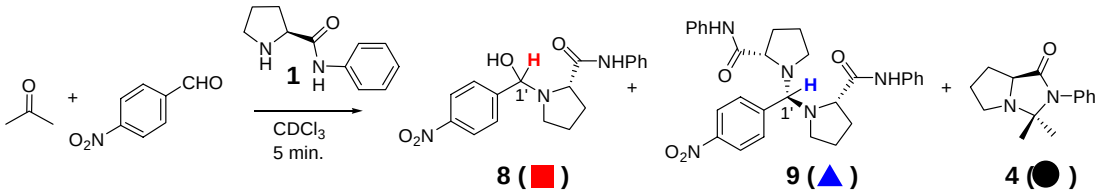


Figure S14. ^{1}H NMR spectrum of the reaction between acetone and 4-nitrobenzaldehyde in $CDCl_3$ catalyzed by prolinamide **1** after 5 minutes (corresponds to Scheme 4).



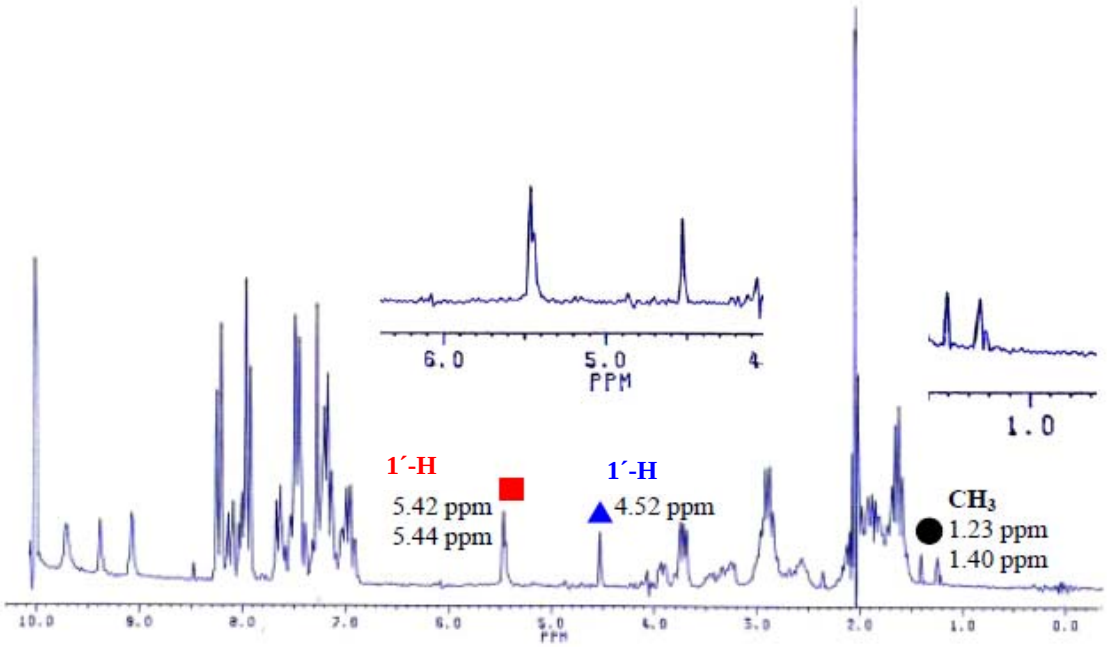
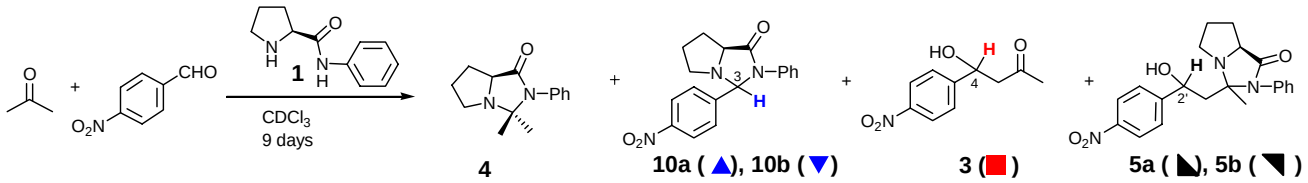


Figure S15. ^{1}H NMR spectrum of the reaction between acetone and 4-nitrobenzaldehyde in $CDCl_3$ catalyzed by prolinamide **1** after 9 days (corresponds to Scheme 4).



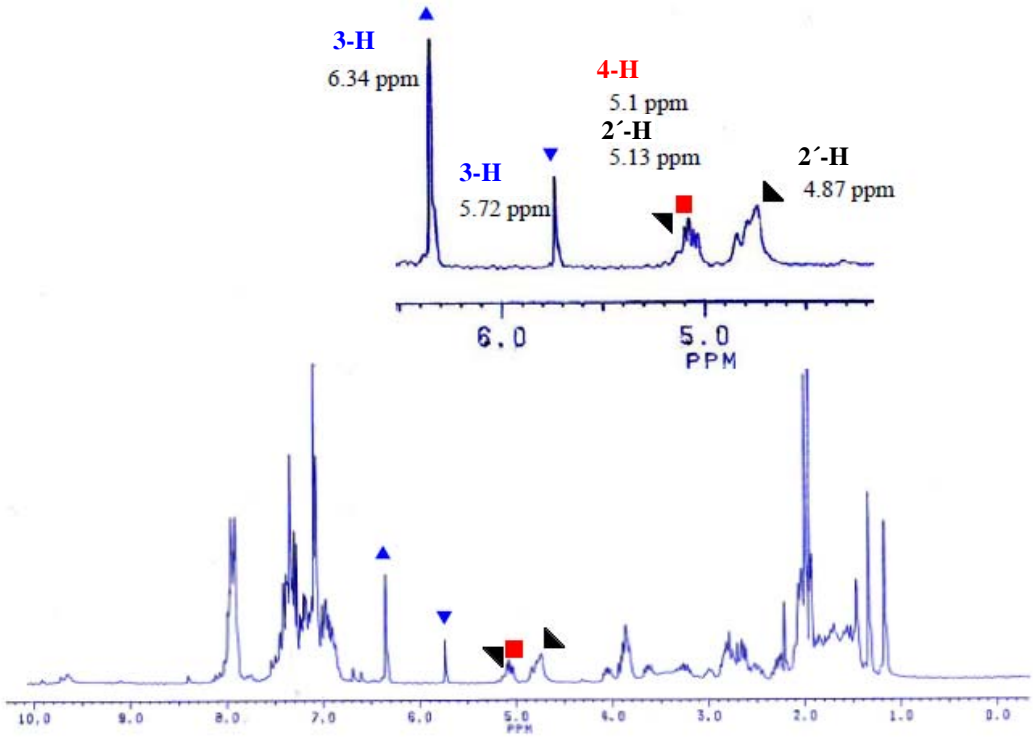
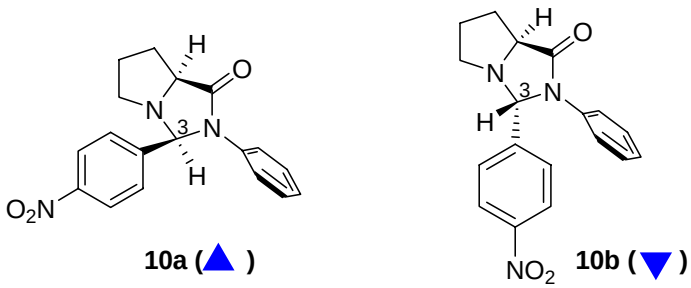


Figure S16. ^{1}H NMR spectrum for the mixture of imidazolidinones **10a** and **10b** formed in the reaction between 4-nitrobenzaldehyde and prolinamide **1** in $CDCl_3$ after nine days.



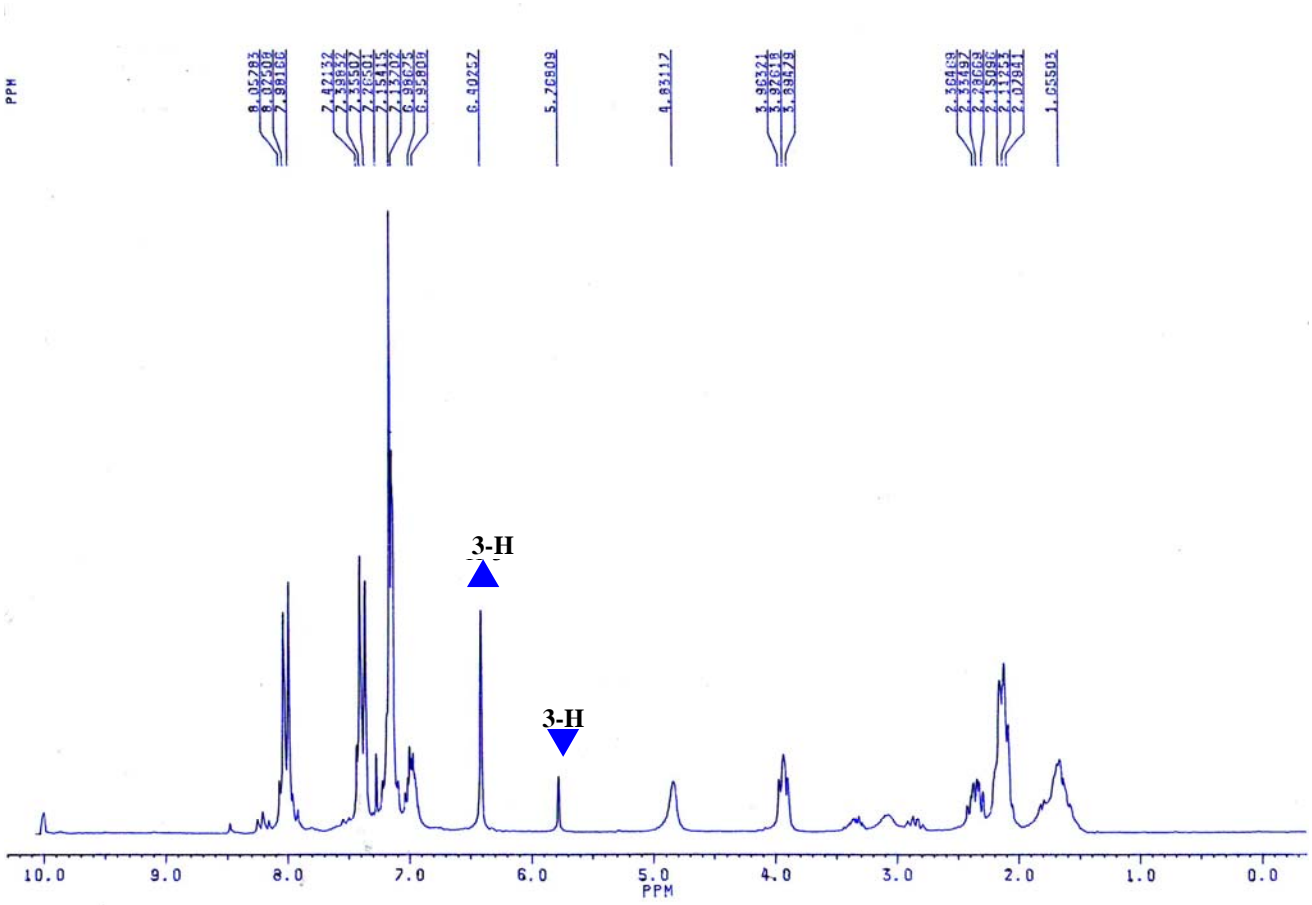


Figure S17. Chemical shifts for some relevant protons in aldehyde imidazolidinone **10a** compared to prolinamide **1.**

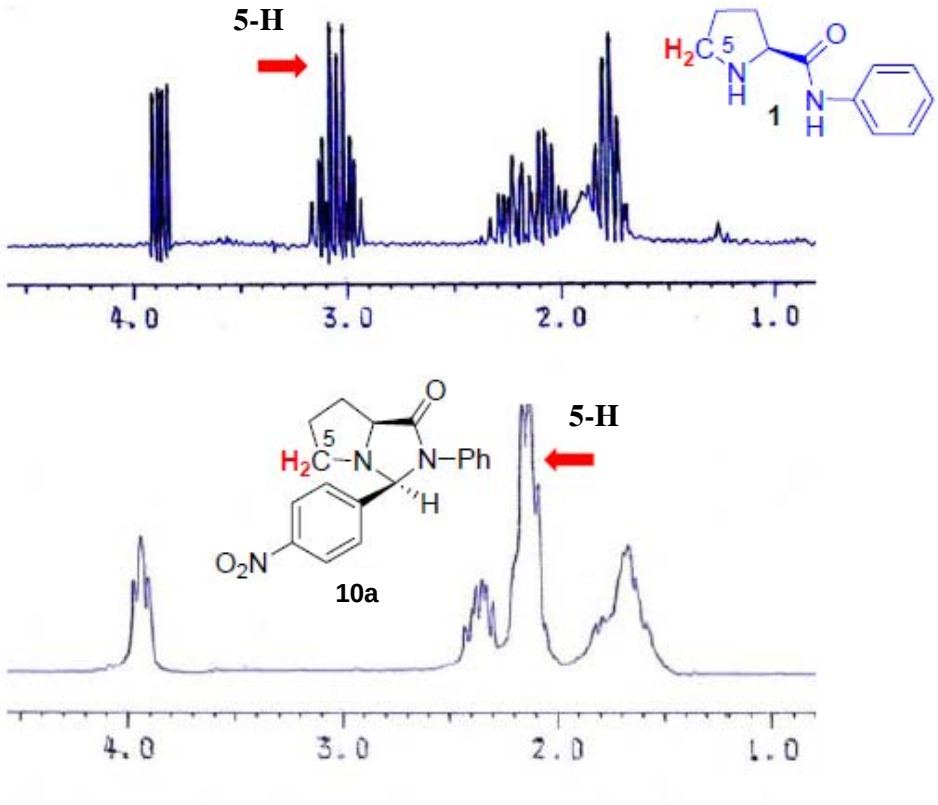
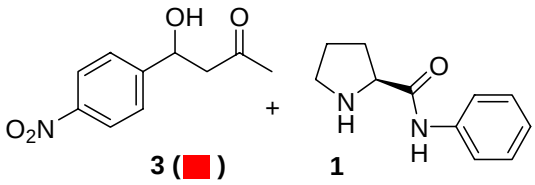


Figure S18. ^{1}H NMR spectrum for the reaction mixture of aldol **3** with prolinamide **1** in deuterochloroform (68 h).



complex mixture:
acetone imidazolidinone **4** (●)
aldehyde imidazolidinones **10a, 10b** (▲ , ▼)
aldol imidazolidinone **5a** (×)
4-nitrobenzaldehyde, acetone

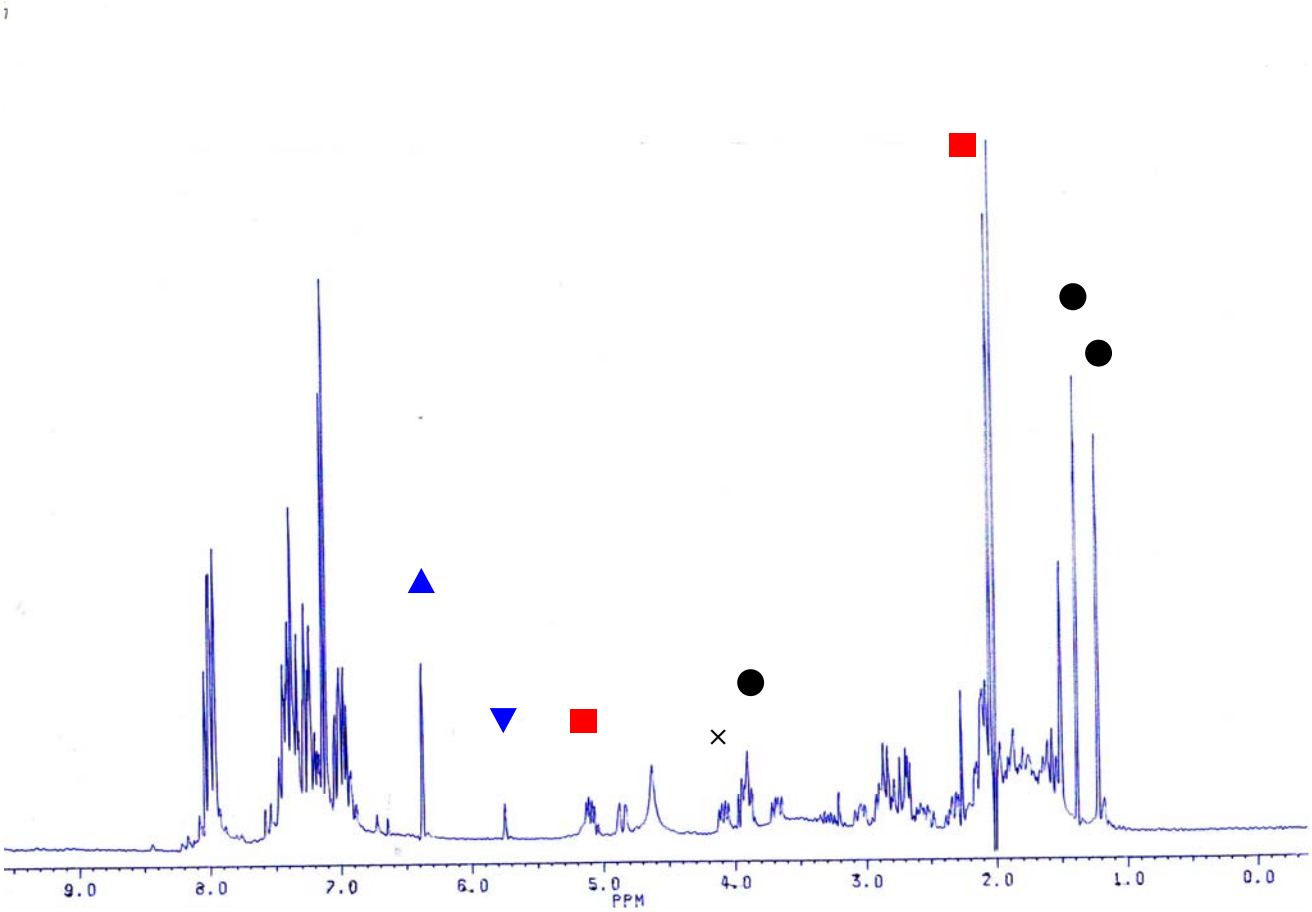
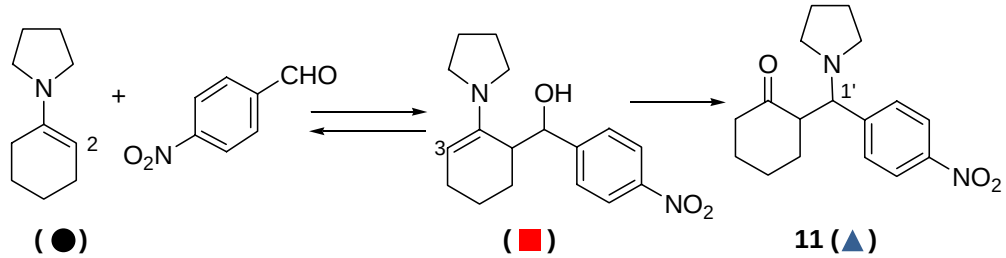
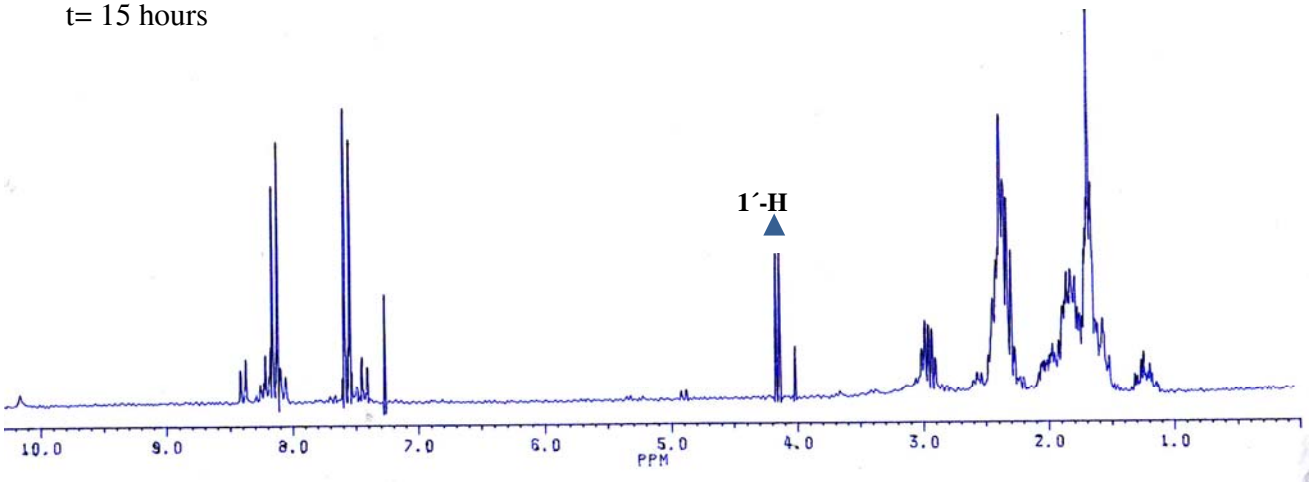


Figure S19. ^{1}H NMR spectra of the reaction between pyrrolidine cyclohexanone enamine and 4-nitrobenzaldehyde in deuterochloroform.



t= 15 hours



t= 2 minutes

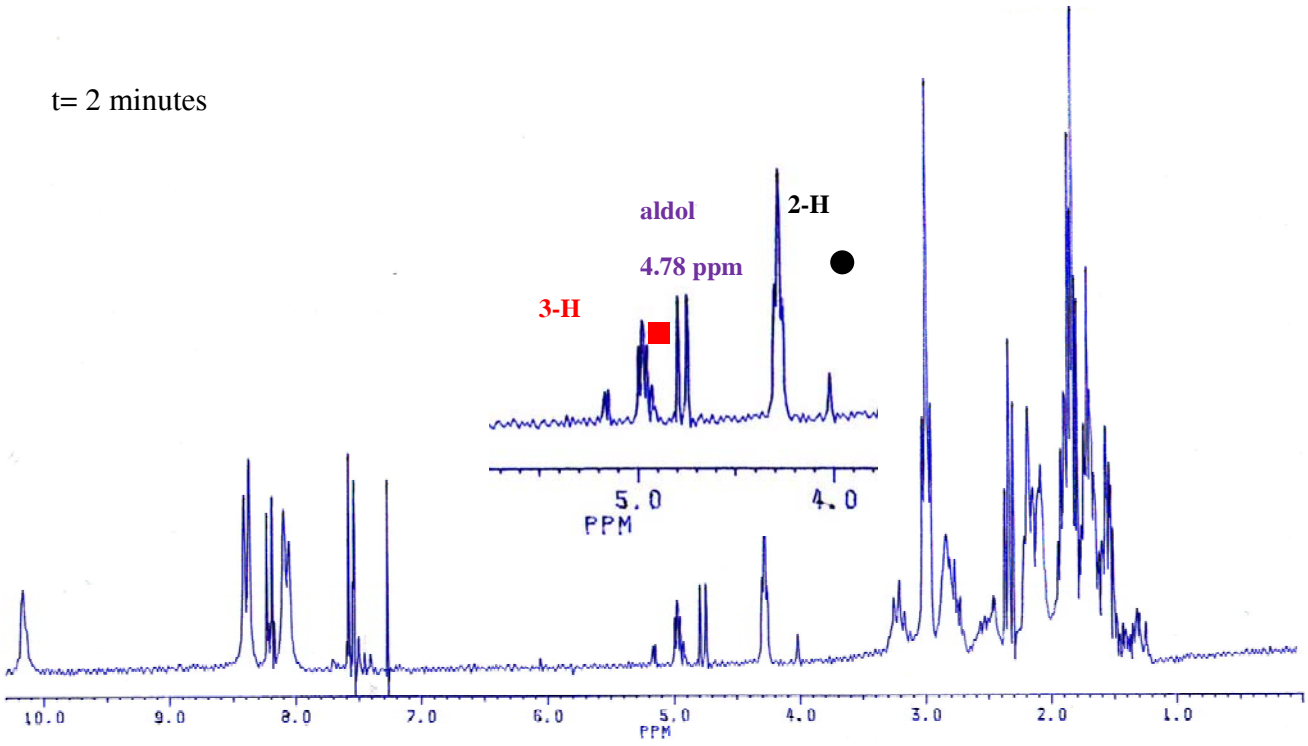


Figure S20. ^{1}H NMR spectra of the reaction between imidazolidinone **4** (0.5M) and 4-nitrobenzaldehyde (0.5M) in deuteromethanol at different times (t_1<t_2) showing deuteration exchange.

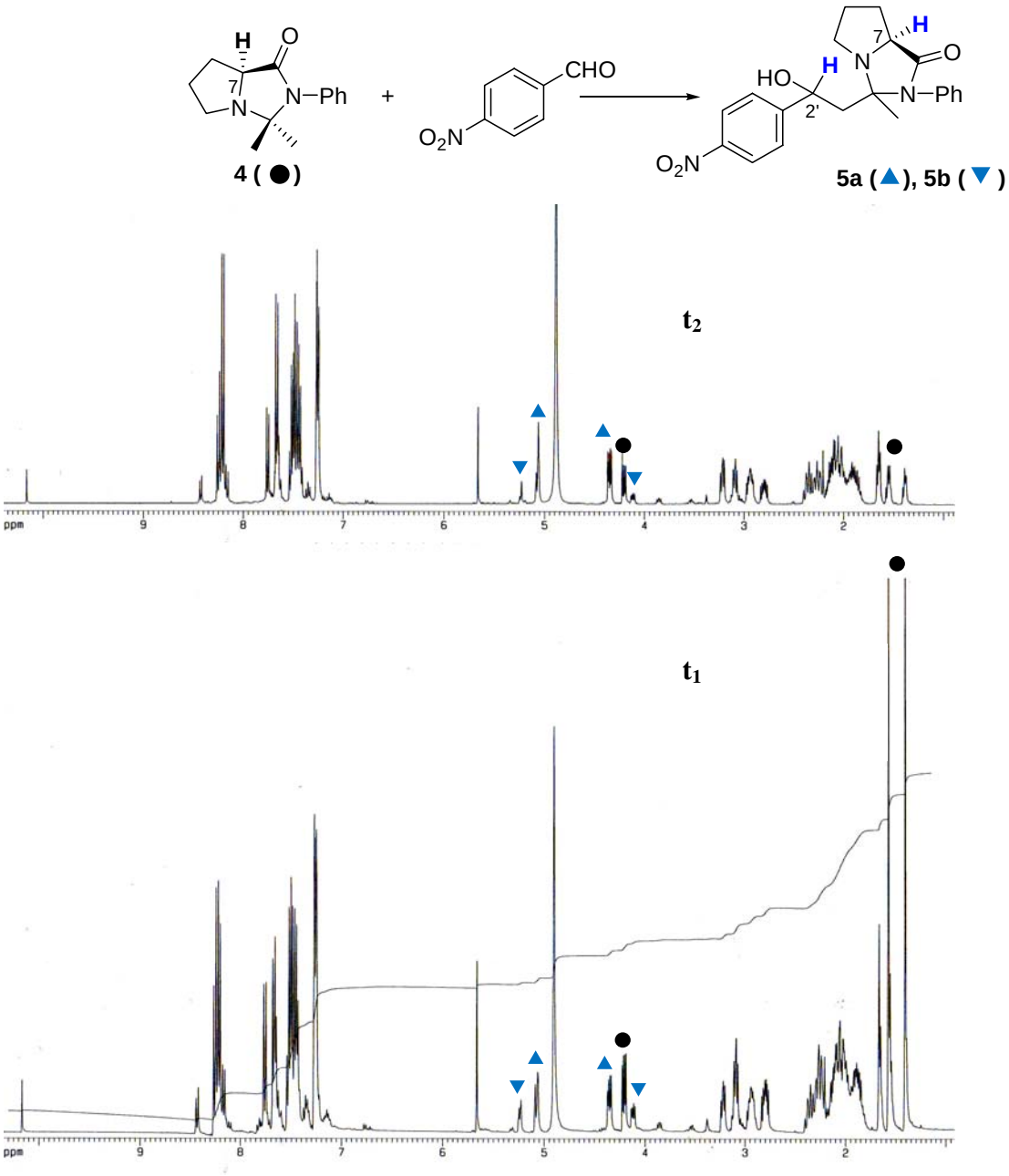
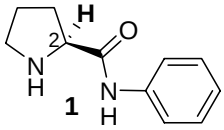
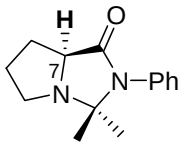


Figure S21. Competitive titration of a mixture of acetone imidazolidinone **4** and aniline prolinamide **1** with camphorsulfonic acid in deuterochloroform.

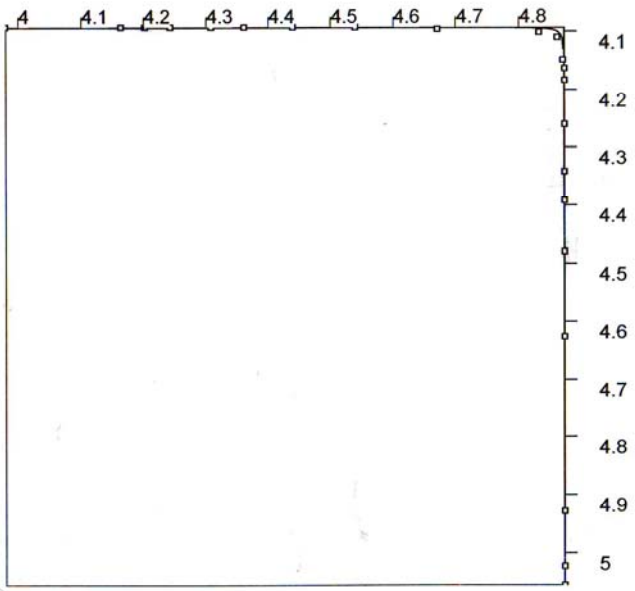


1



4

Relative constant: 1e+04 1/M
Max. Chemical Shift (H-7, 4): 5.0548
Max. Chemical Shift (H-2, 1): 4.8731



Chemical shifts (ppm)

H-2 prolinamide **1**	H-7 imidazolidinone **4**
3.9786	4.093
4.1633	4.093
4.2015	4.093
4.2425	4.093
4.307	4.093
4.3598	4.093
4.439	4.093
4.5387	4.093
4.6707	4.0959
4.8319	4.1018
4.8613	4.1106
4.8701	4.1487
4.873	4.1633
4.873	4.1839
4.873	4.2601
4.873	4.3422
4.873	4.3921
4.873	4.4801
4.873	4.6267
4.873	4.9287
4.873	5.0226
4.873	5.0548

Figure S22. ^{1}H NMR and ^{13}C spectra of imidazolidinone **4**

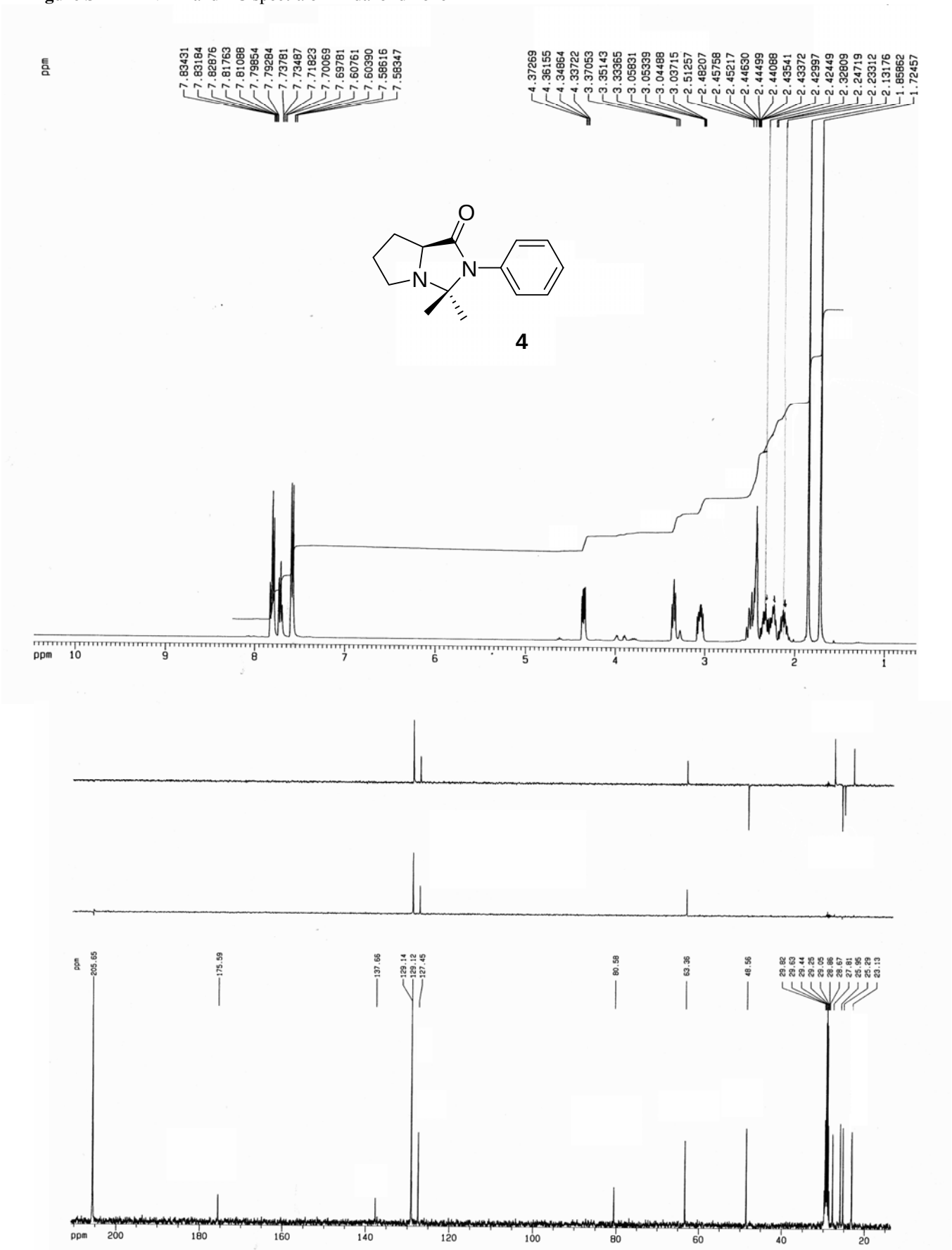


Figure S23. ^{1}H NMR and ^{13}C spectra of imidazolidinone **10a**

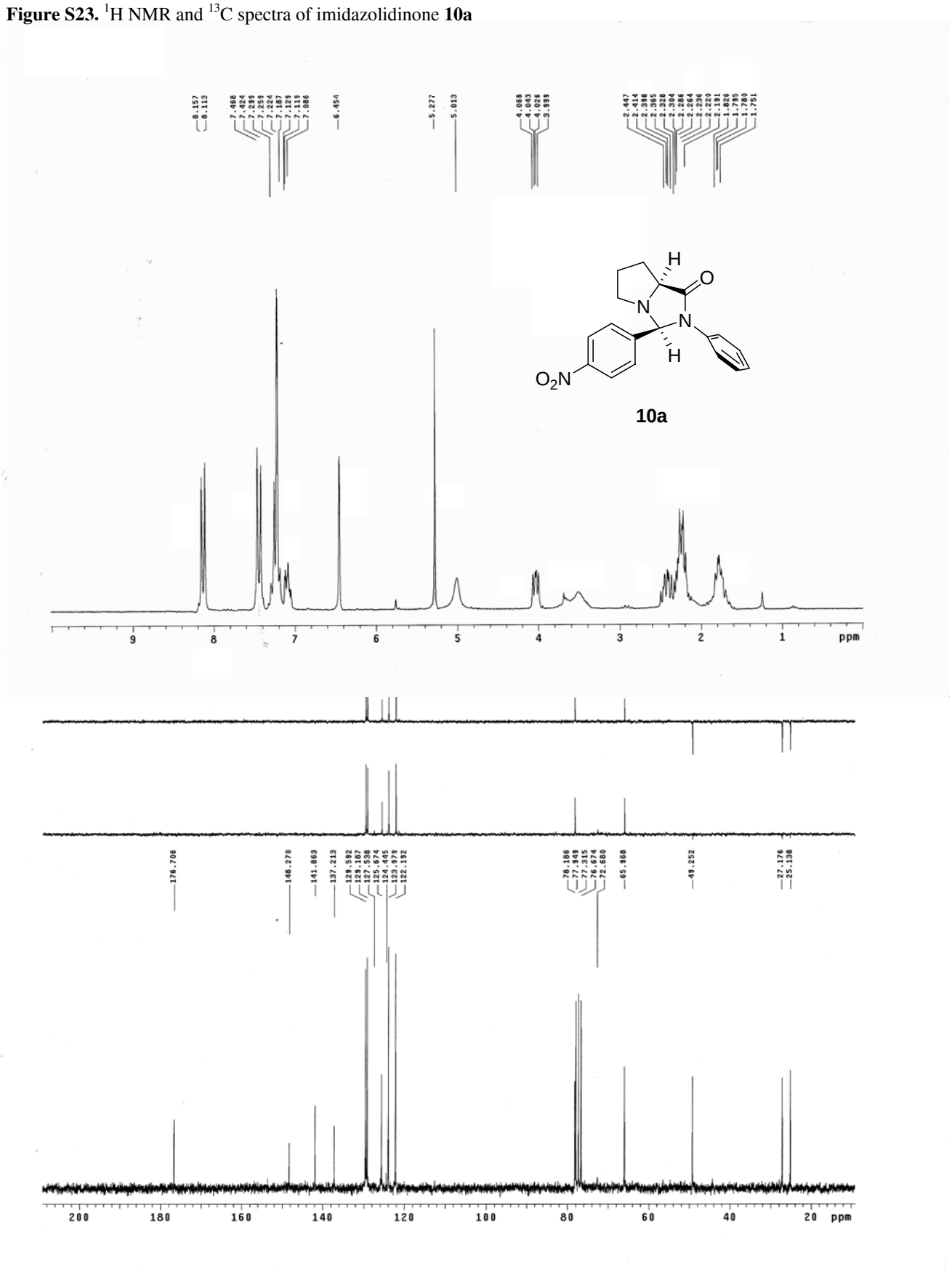


Figure S24. ^{1}H NMR and ^{13}C spectra of imidazolidinone **10b**

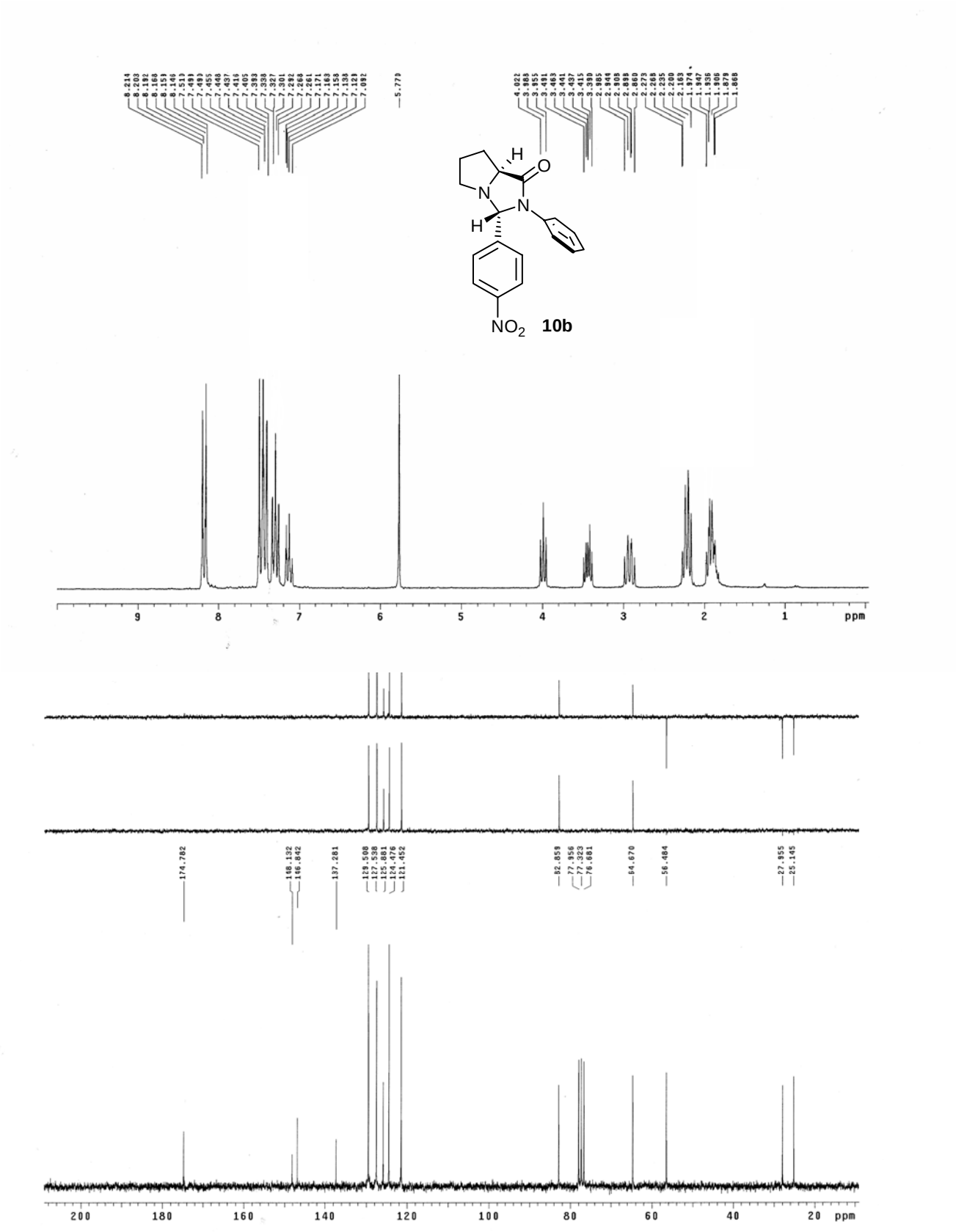


Figure S25. ^{1}H NMR and ^{13}C spectra of imidazolidinone **7b**