Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Structural Insight into the Aggregation of L-Prolyl Dipeptides and its Effect on Organocatalytic Performance

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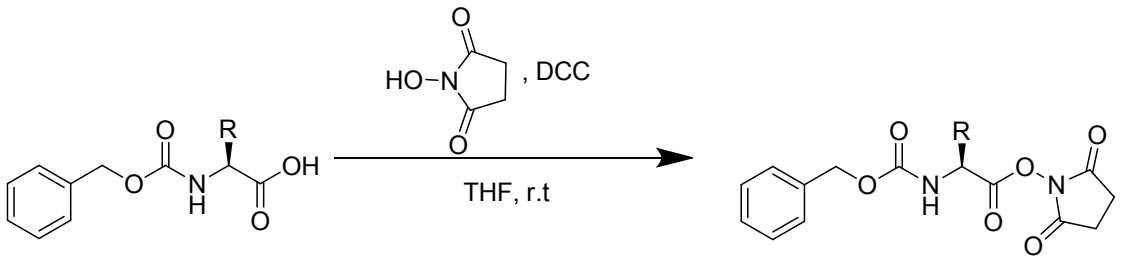
Contents

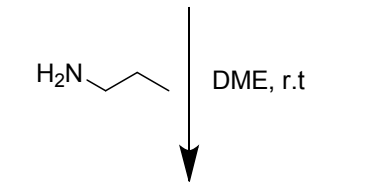
Synthetic procedures

The compound **ProValPr** was synthetized as reported previously[1,2]

Compounds, **ProIlePr**, **ProAlaPr** and **ProPhePr** were prepared as shown in the below.



ZPheOsu R= -CH_2Ph
ZIleOsu R= -$CH(CH_3)CH_2CH_3$



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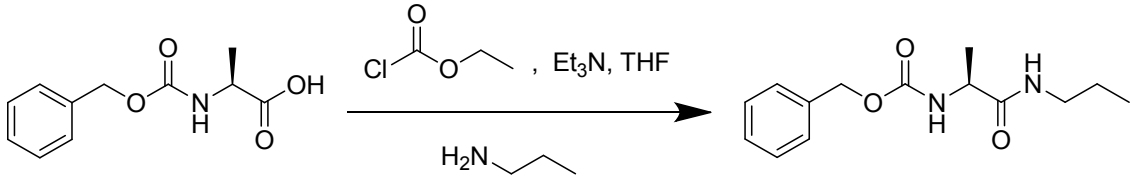

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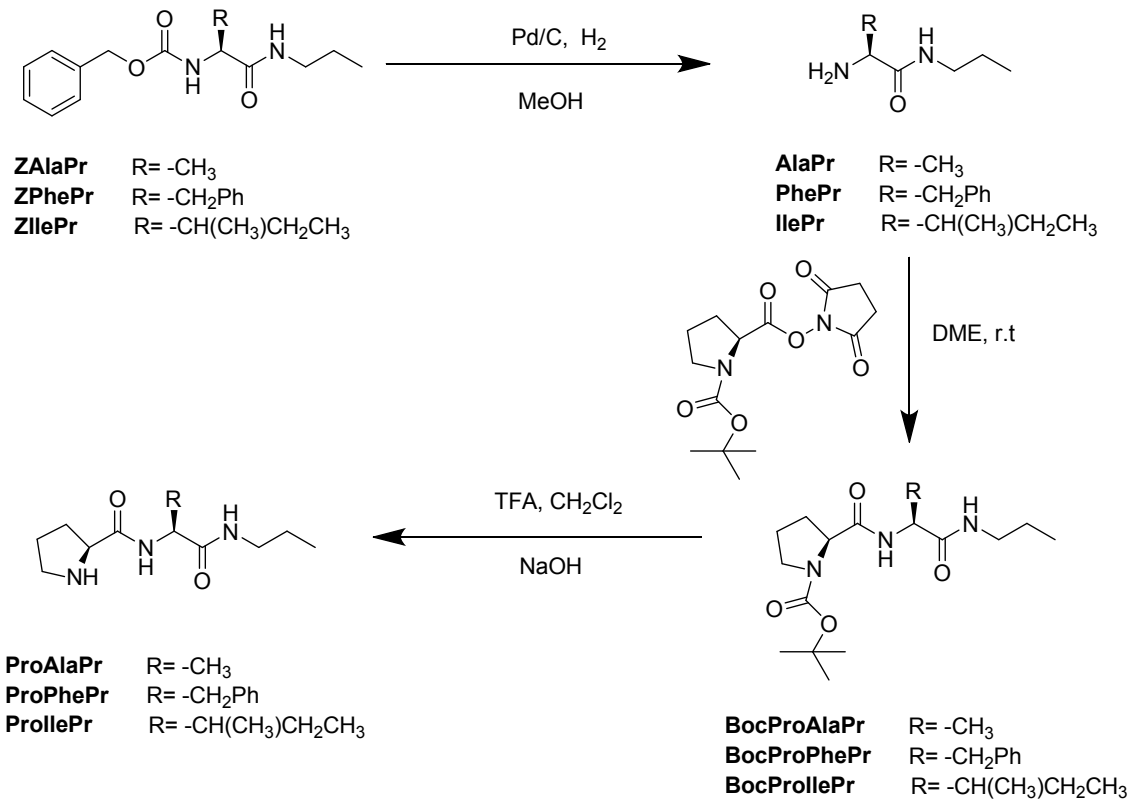


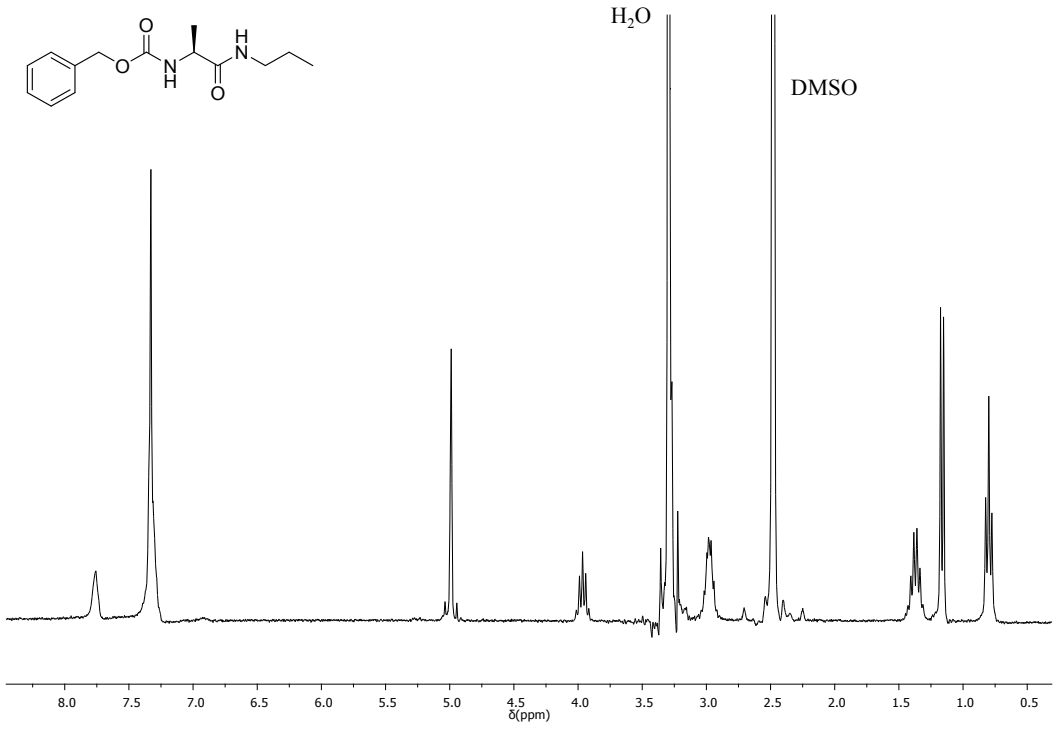
ZAlaPr R= -CH_3
ZPhePr R= -CH_2Ph
ZIlePr R= -$CH(CH_3)CH_2CH_3$

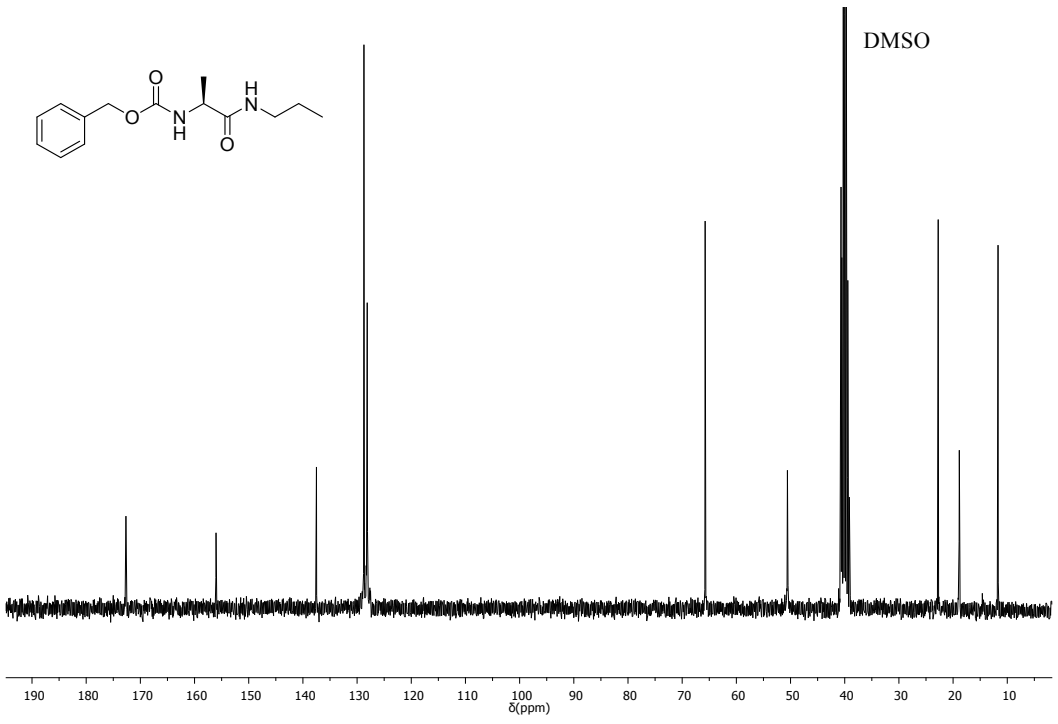
AlaPr R= -CH_3
PhePr R= -CH_2Ph
IlePr R= -$CH(CH_3)CH_2CH_3$

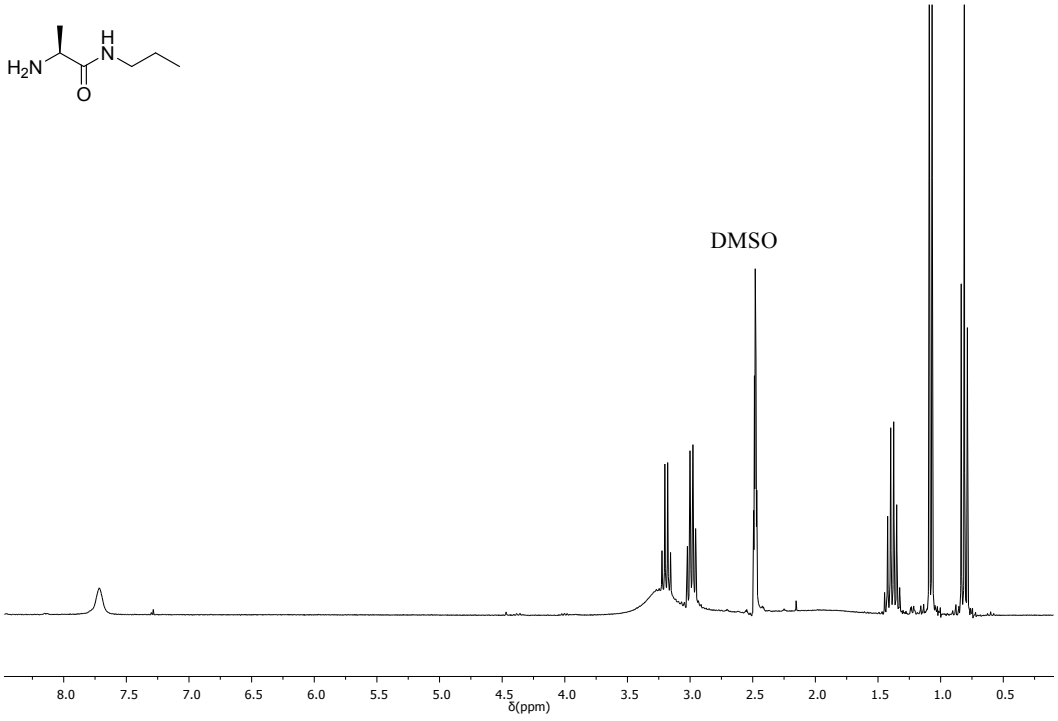
ProAlaPr R= -CH_3
ProPhePr R= -CH_2Ph
ProIlePr R= -$CH(CH_3)CH_2CH_3$

BocProAlaPr R= -CH_3
BocProPhePr R= -CH_2Ph
BocProIlePr R= -$CH(CH_3)CH_2CH_3$

^{1}H and ^{13}C NMR spectra.



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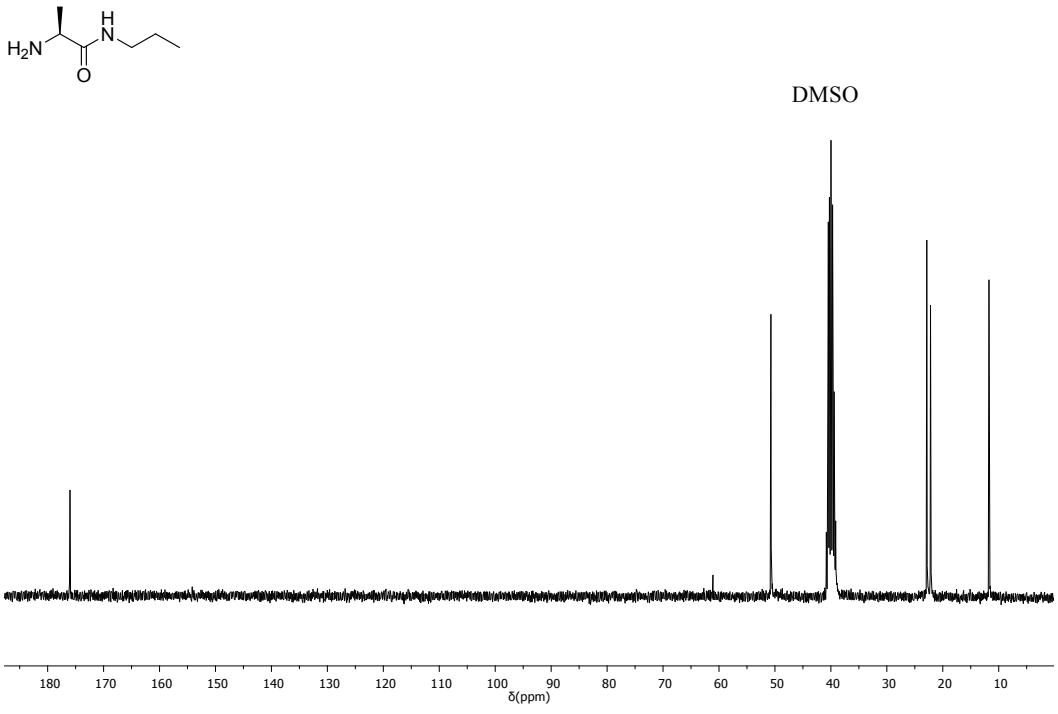
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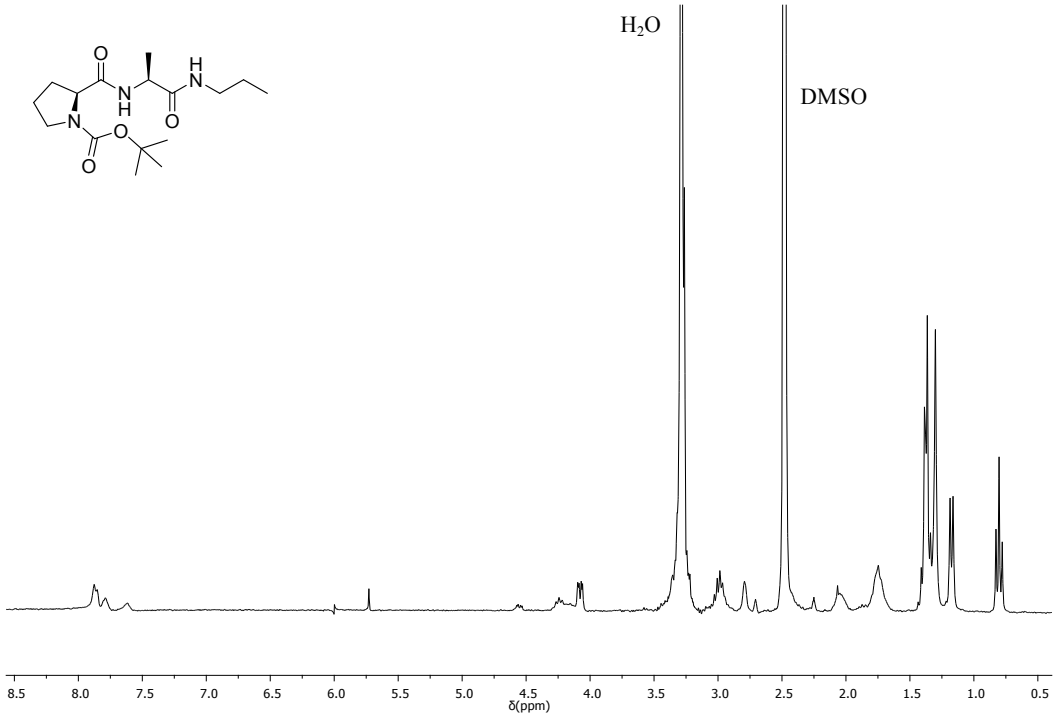
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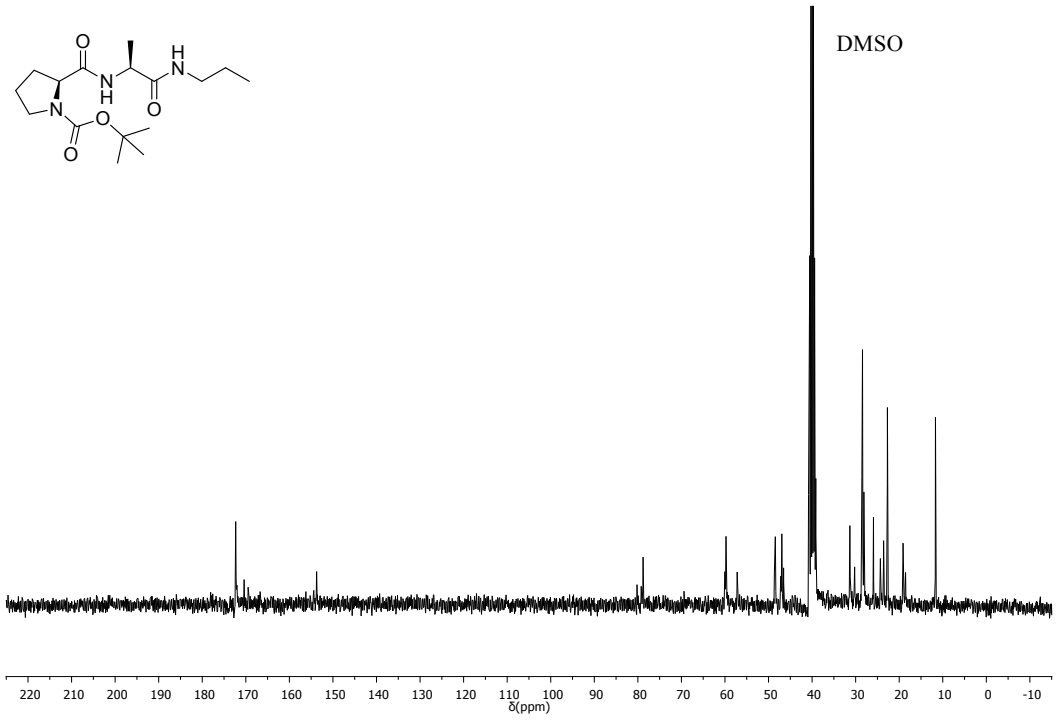
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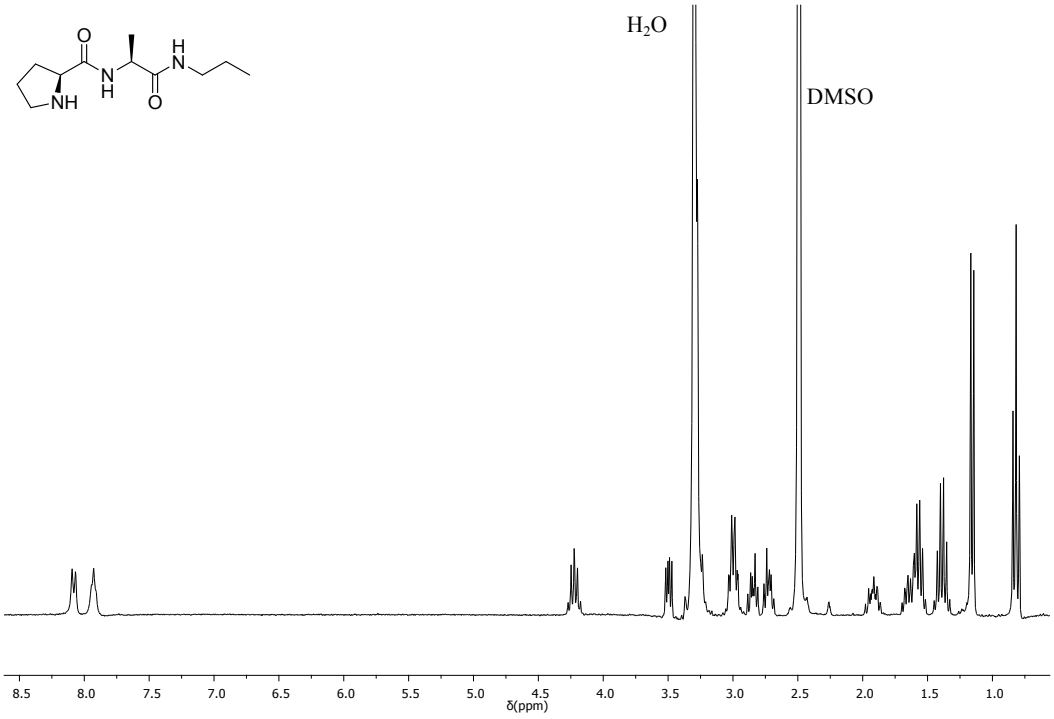
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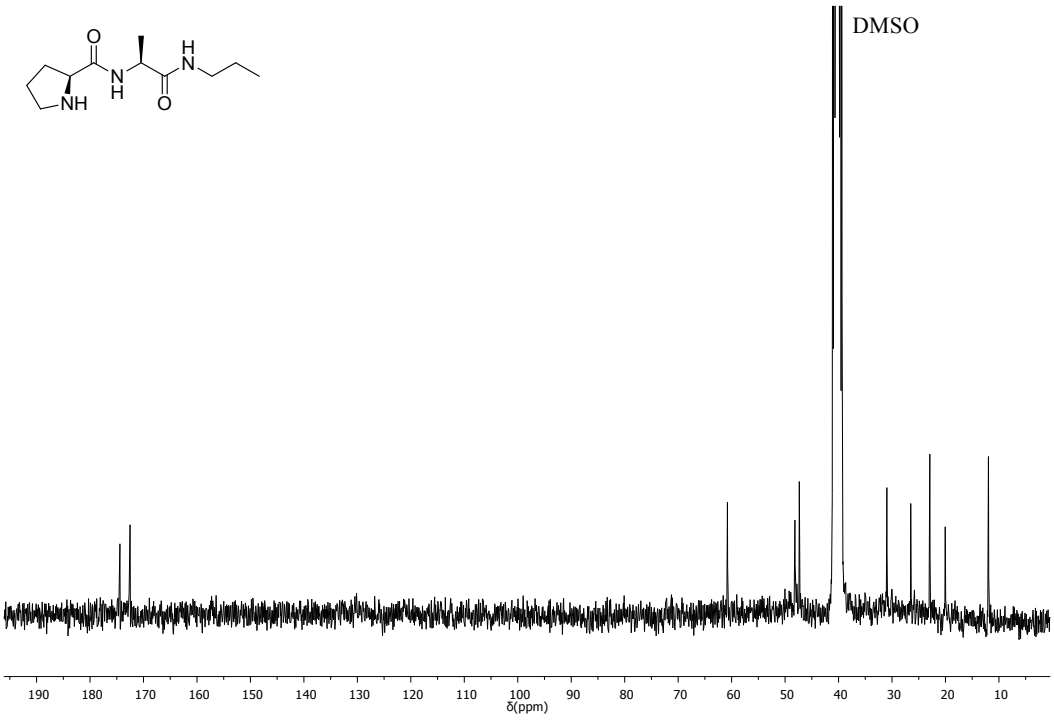
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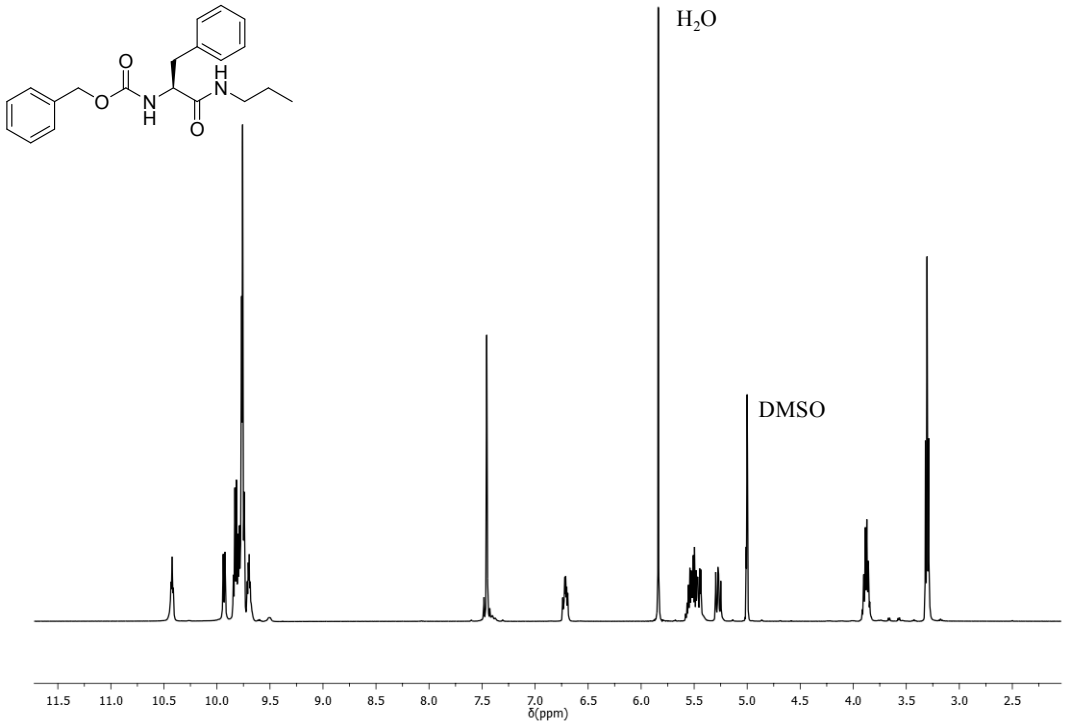
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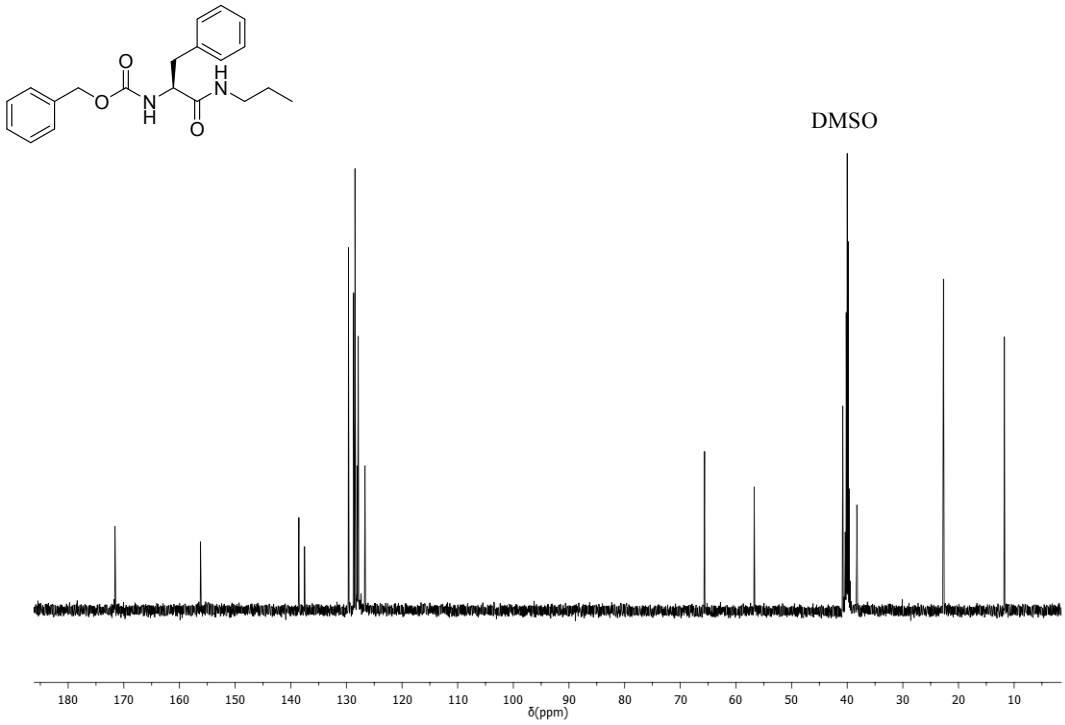
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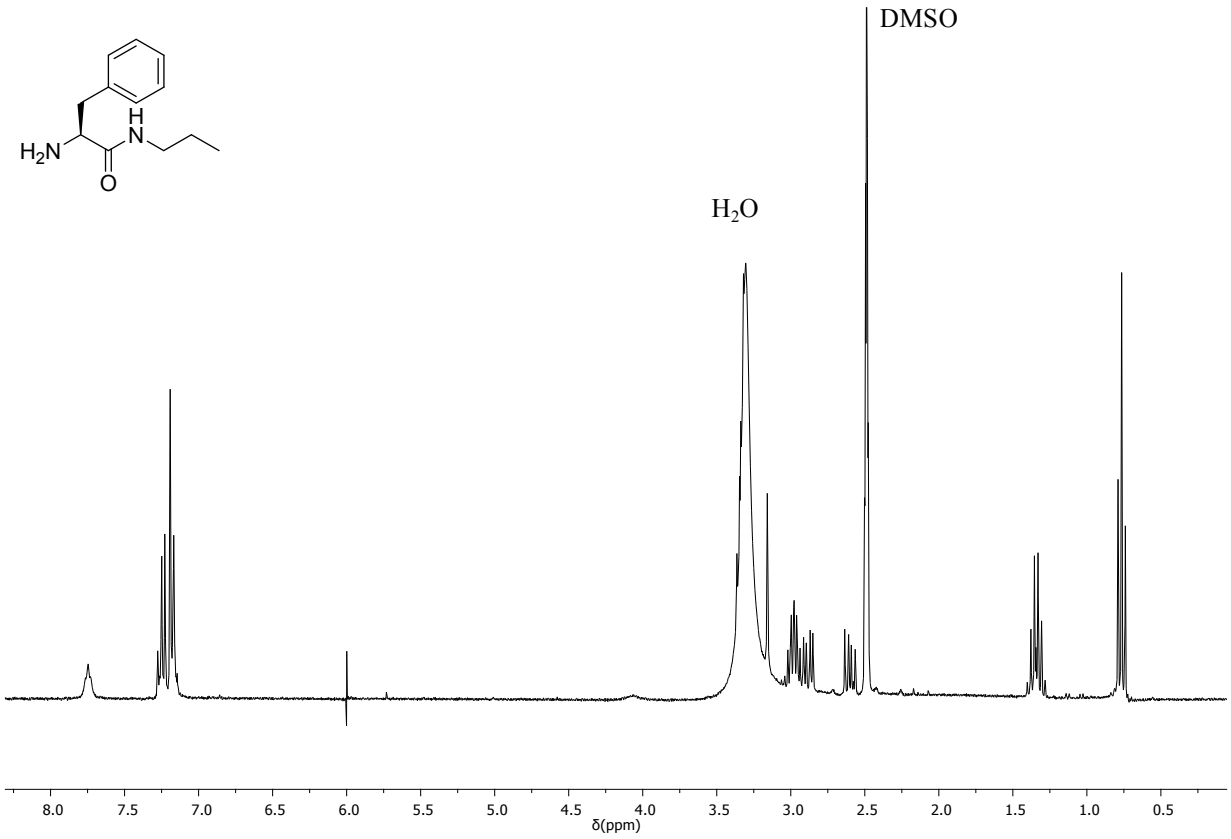
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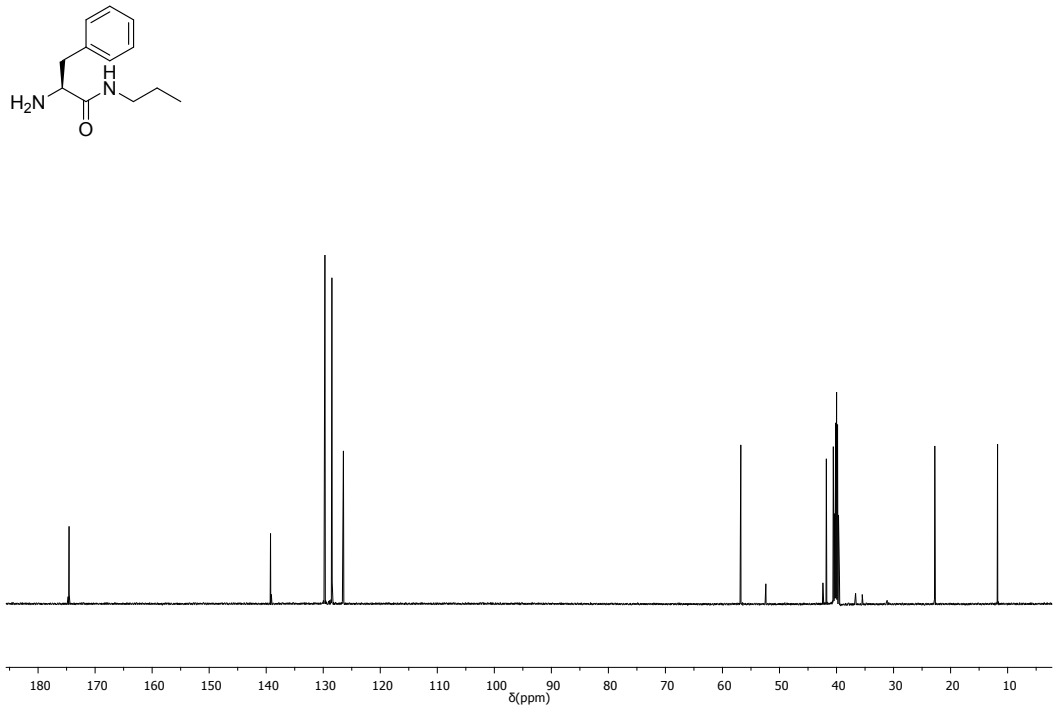
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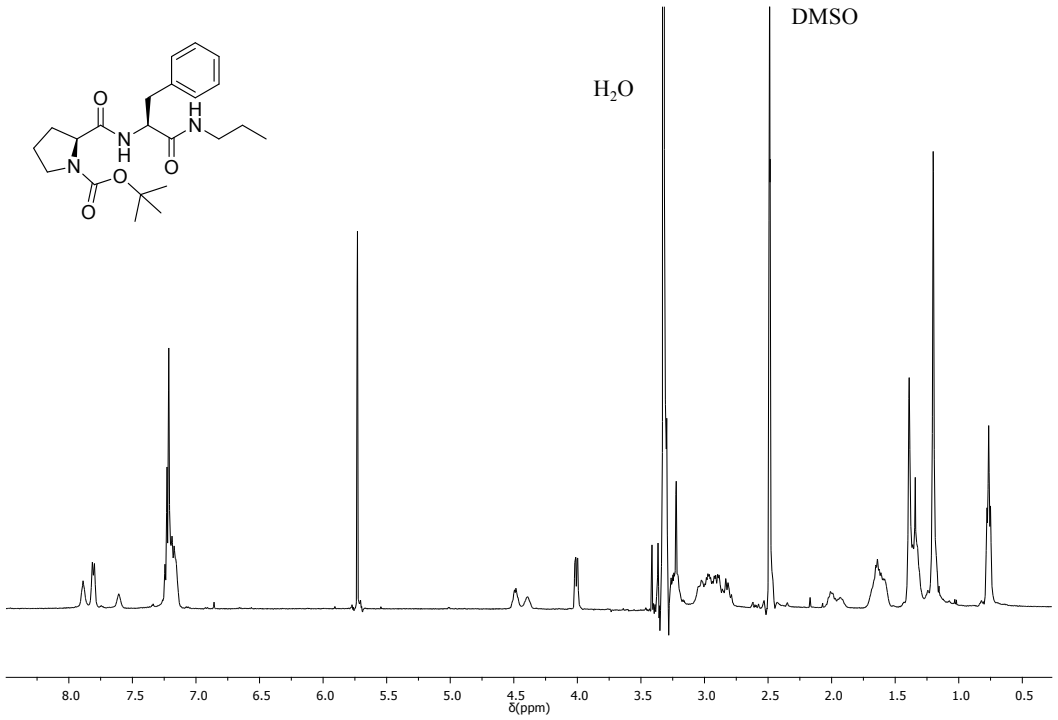
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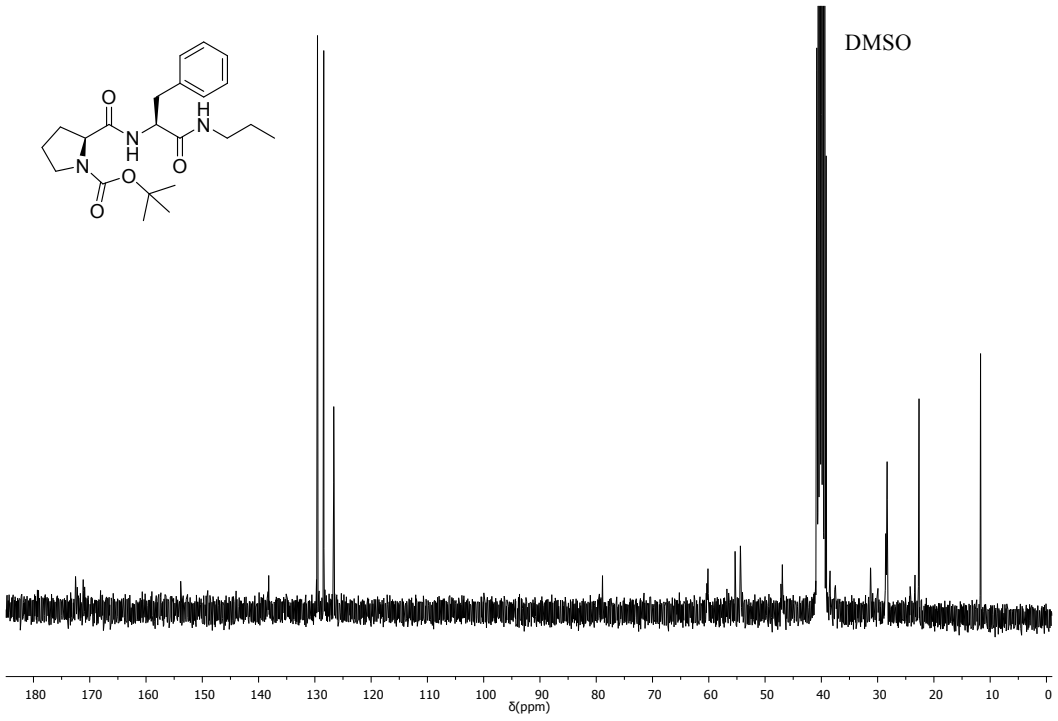
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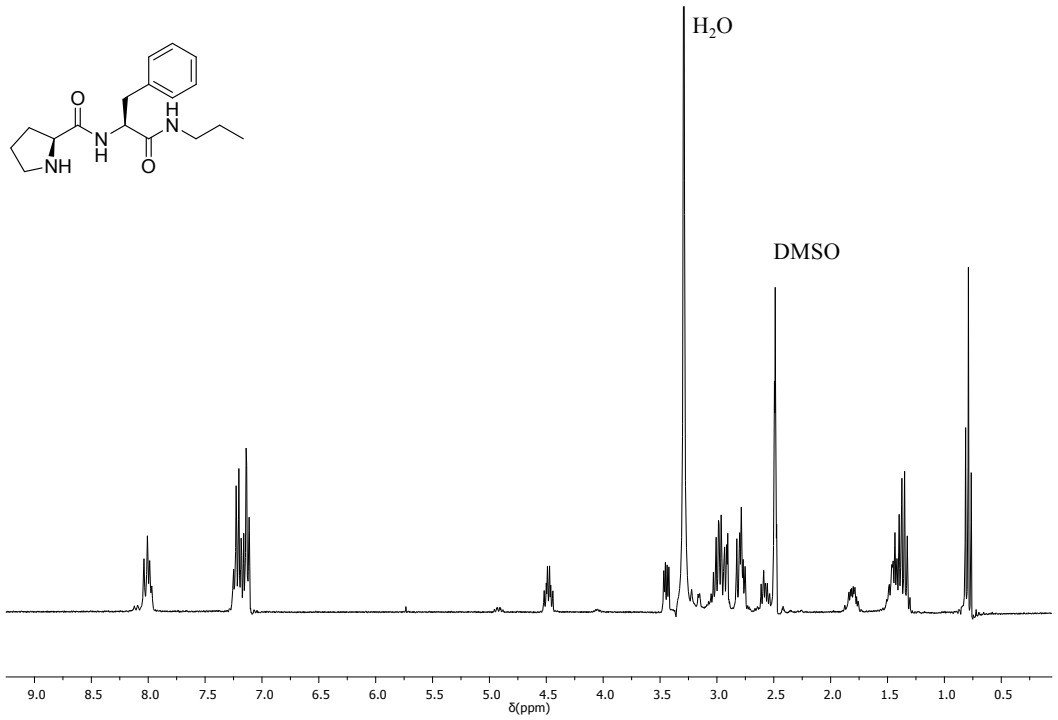
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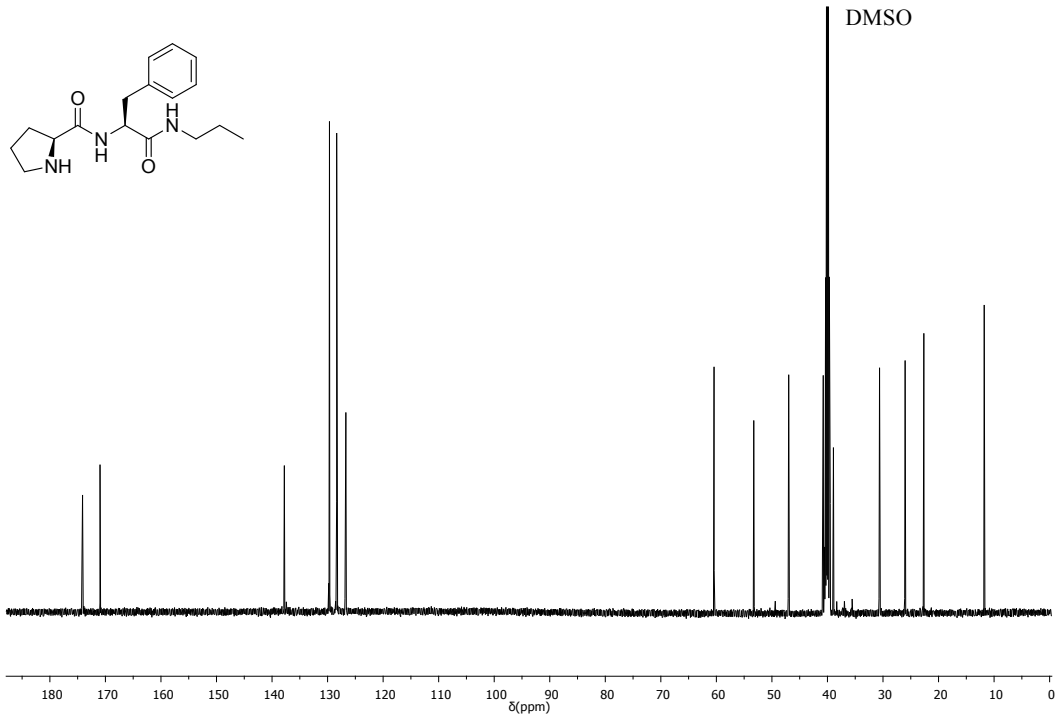
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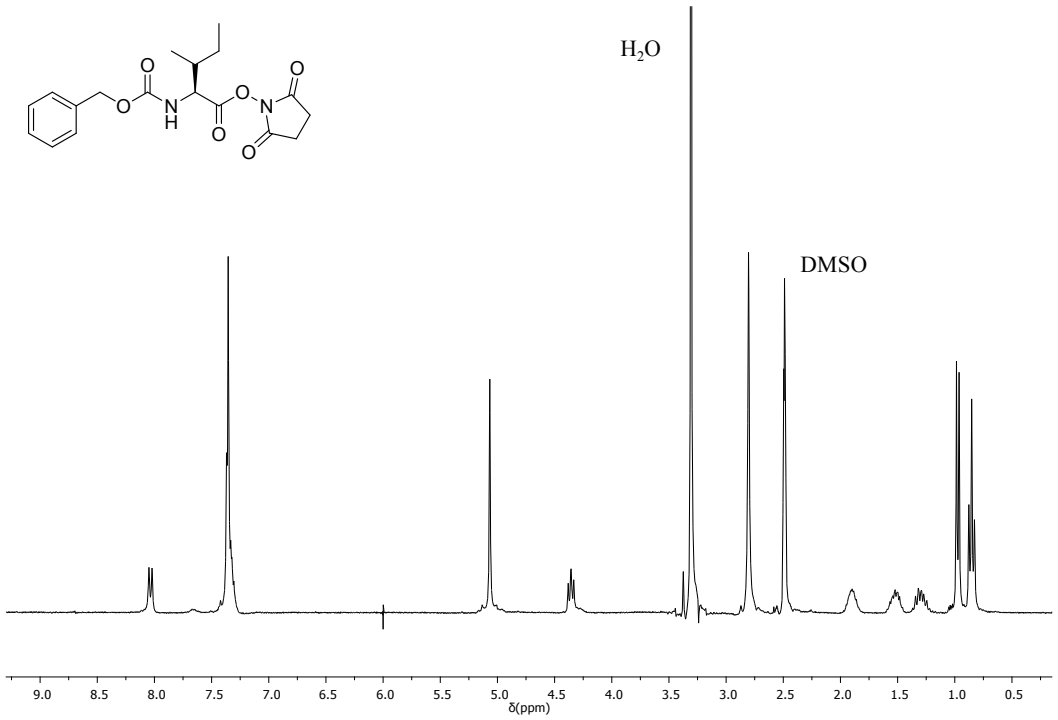
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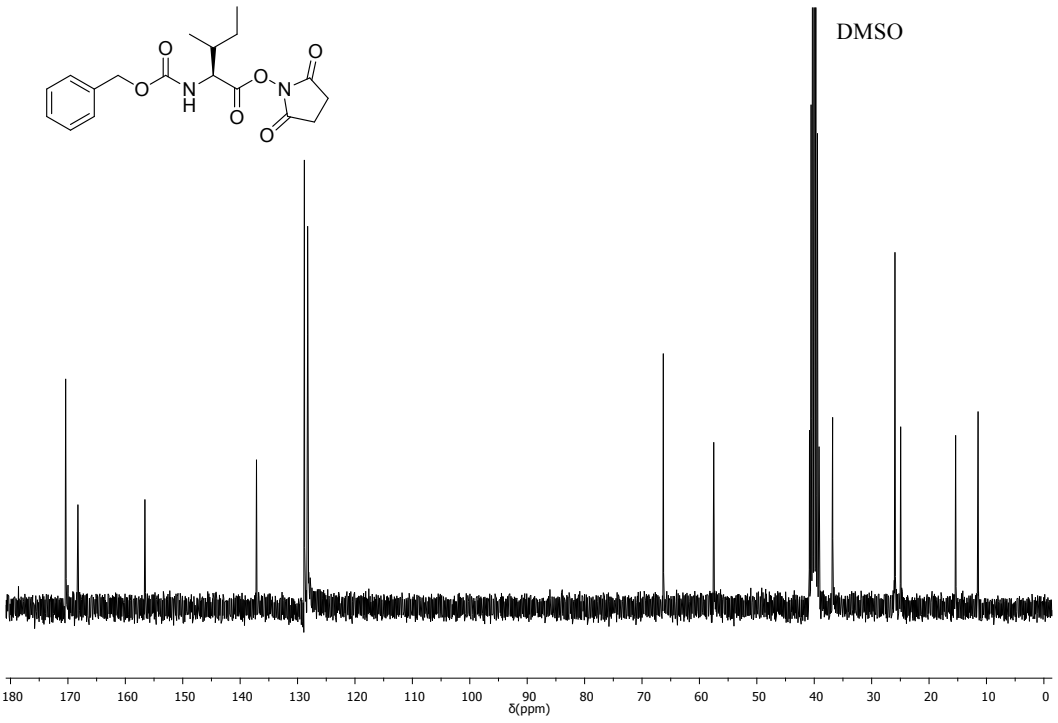
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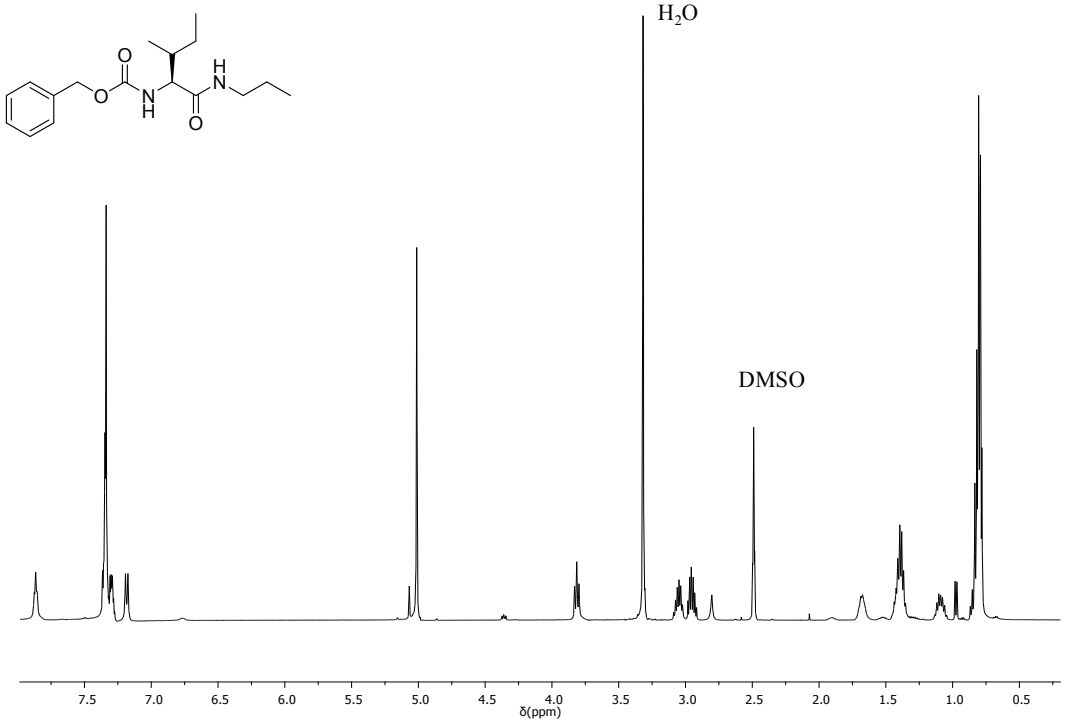
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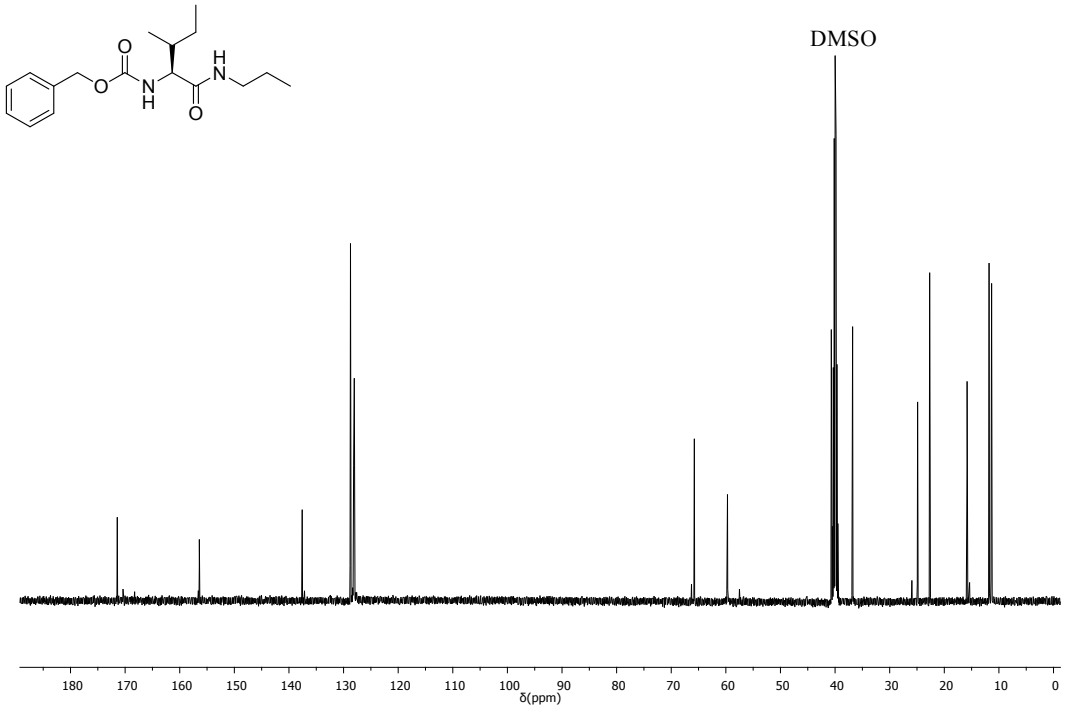
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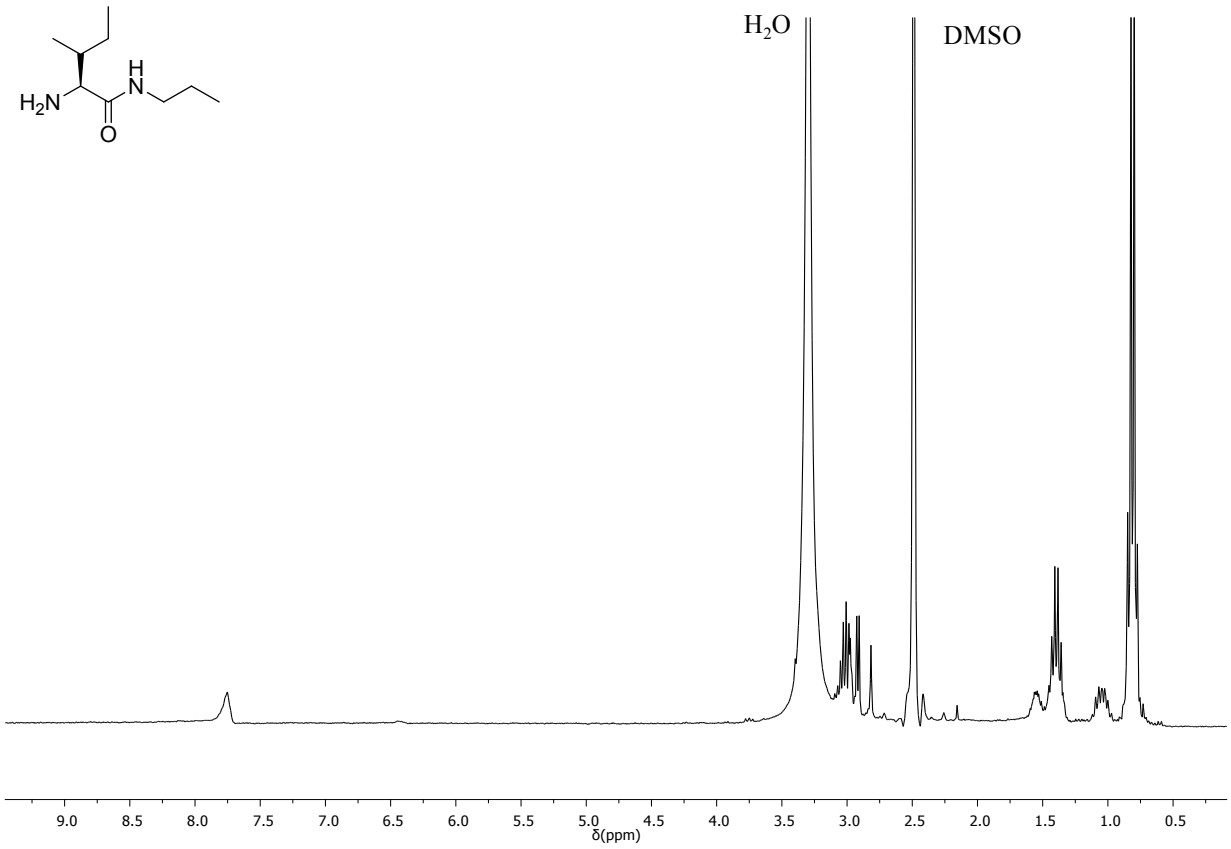
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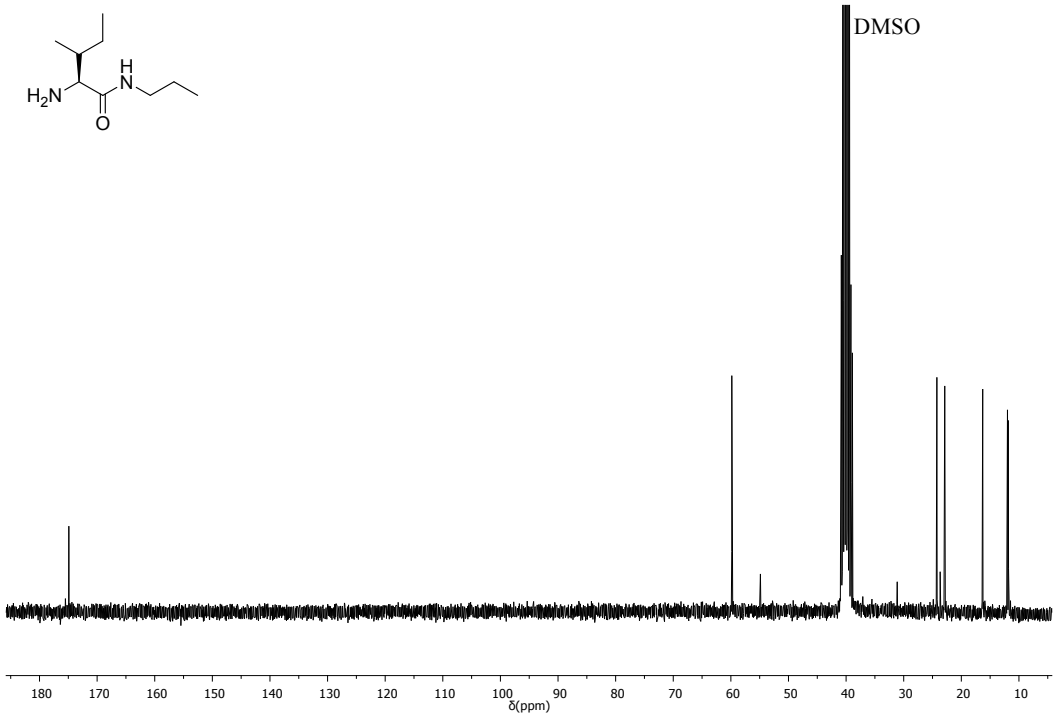
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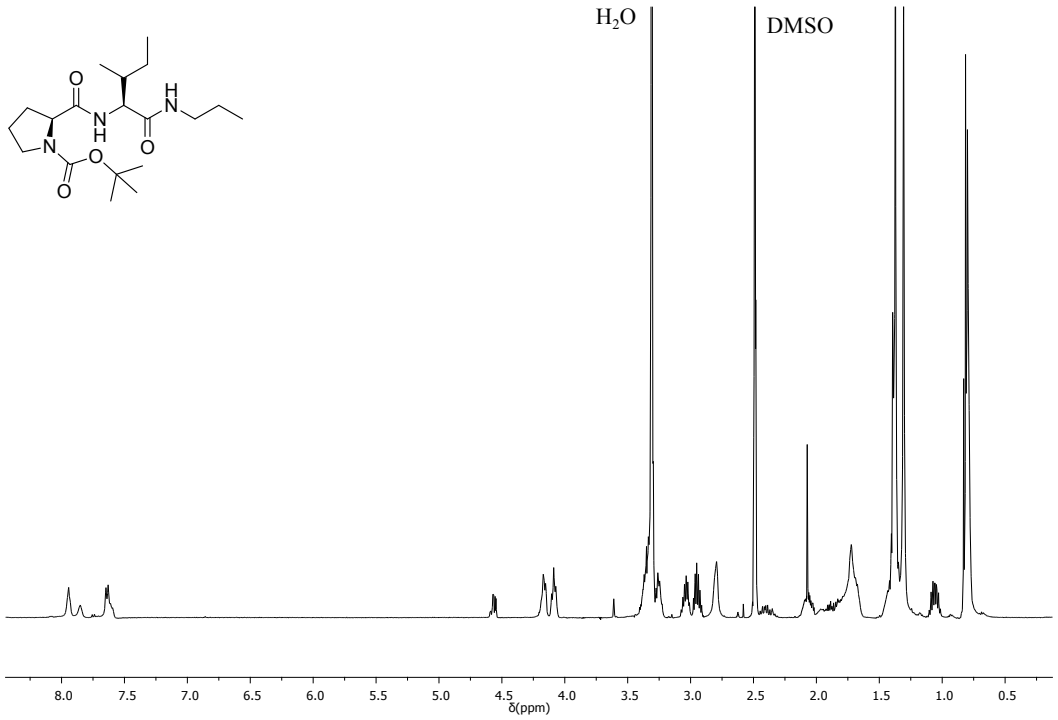
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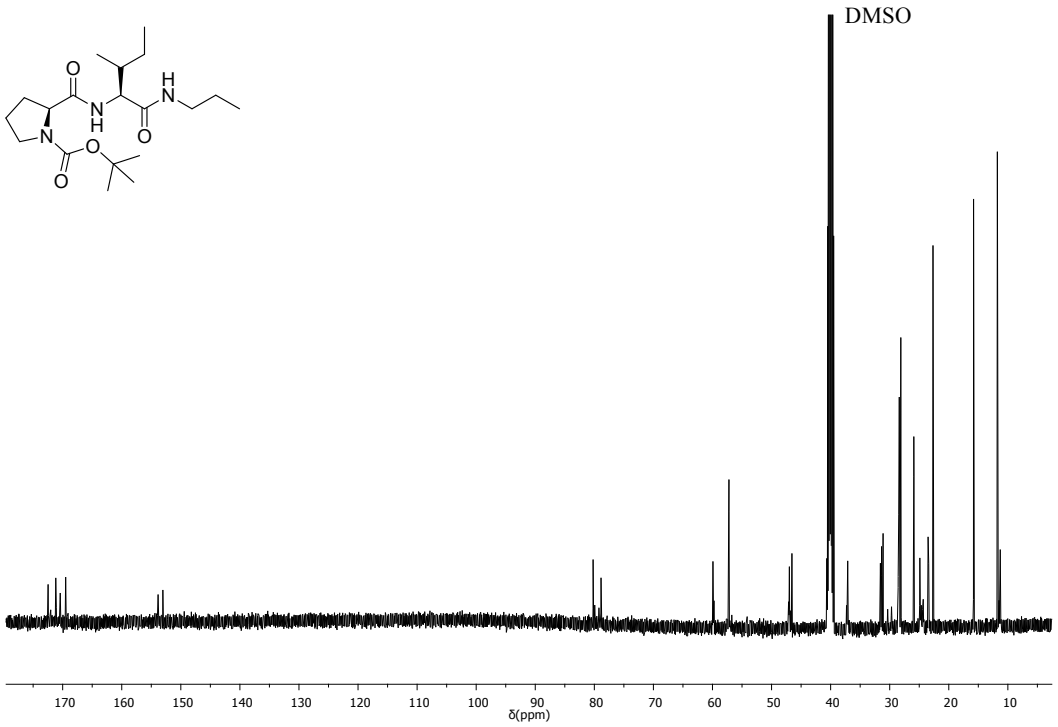
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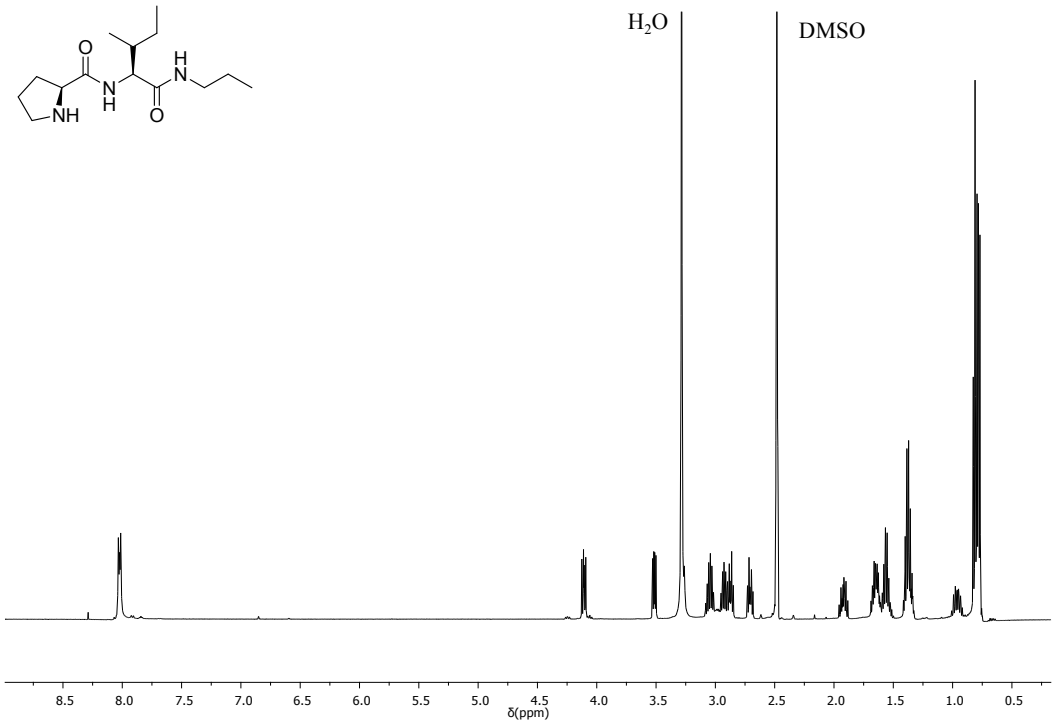
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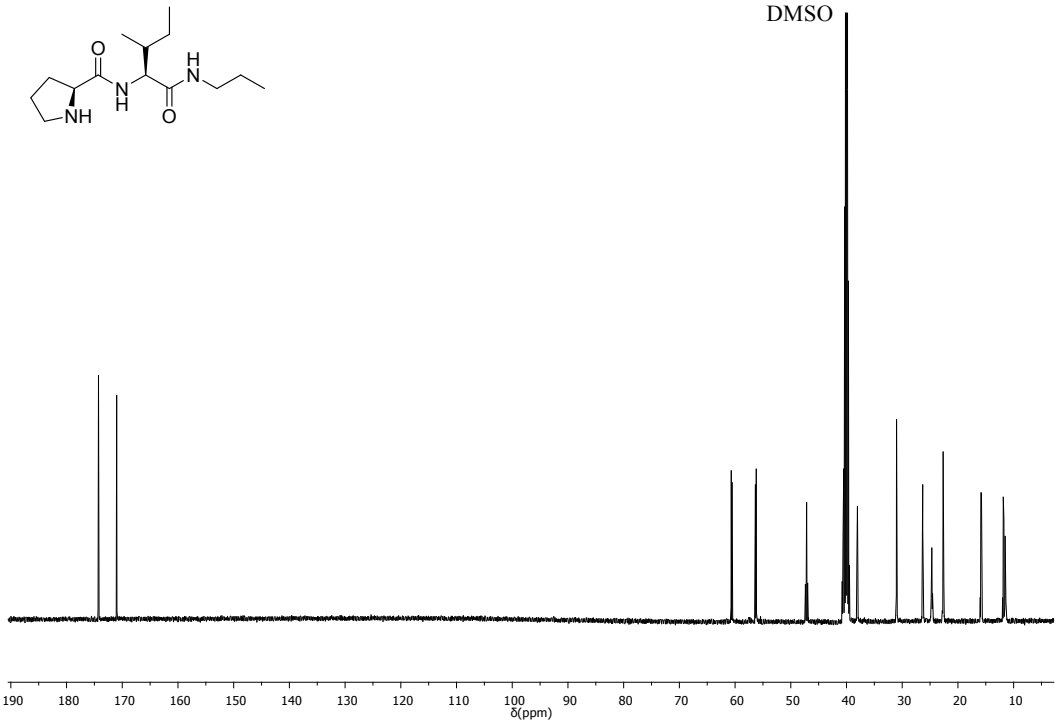
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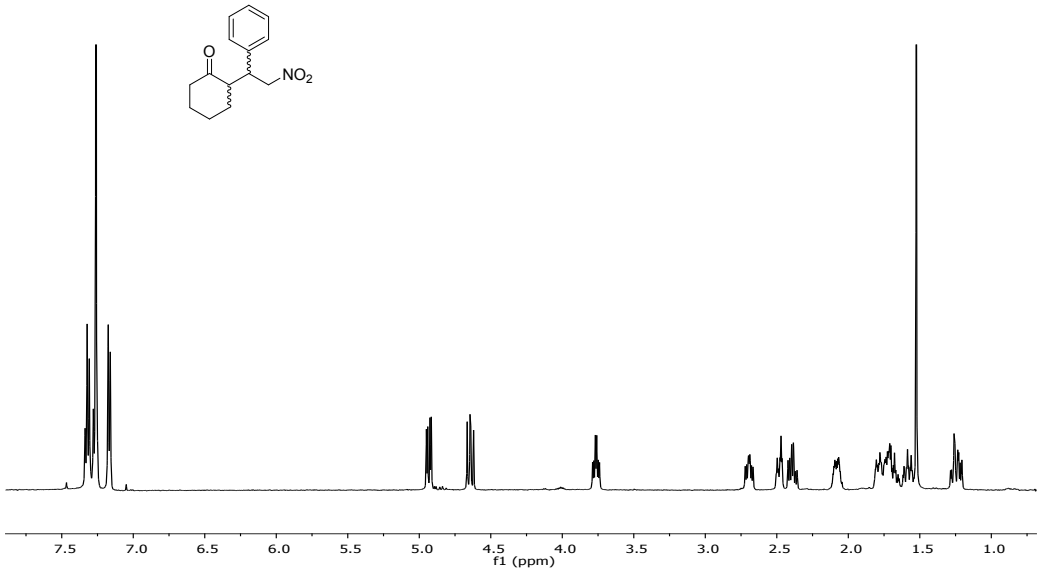
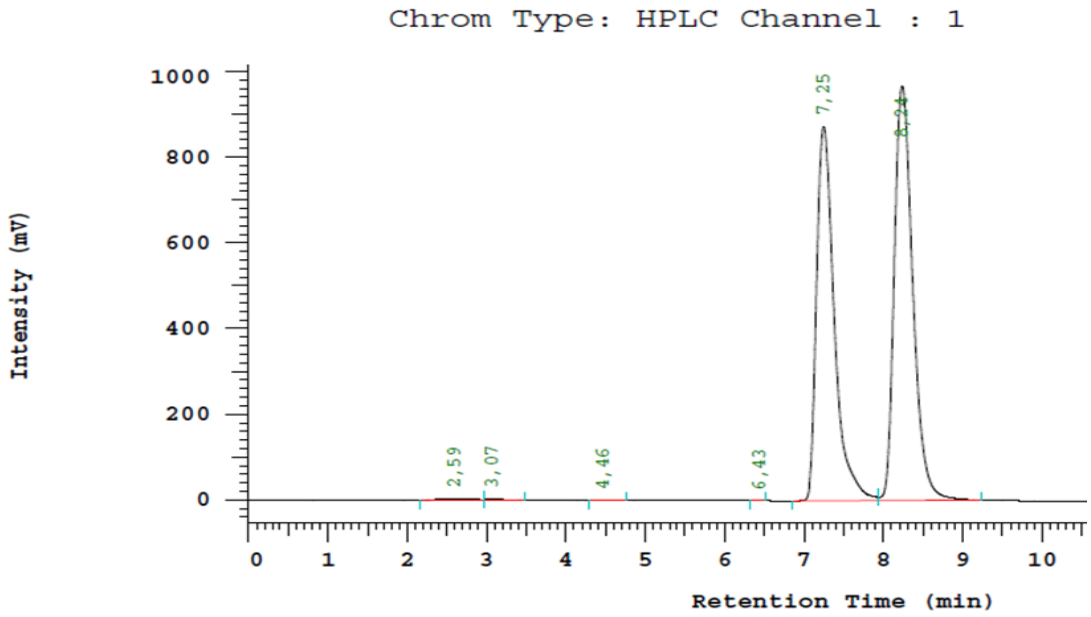
Product analysis of the conjugated addition reaction.

^{1}H-NMR of the product reaction after column chromatography



Representative HPLC chromatogram used for determination of enantiomeric excess. Chiral Pack IA column, hexane/IPA (v/v: 85/15), flow rate= 1 mL/min, λ= 210 nm.



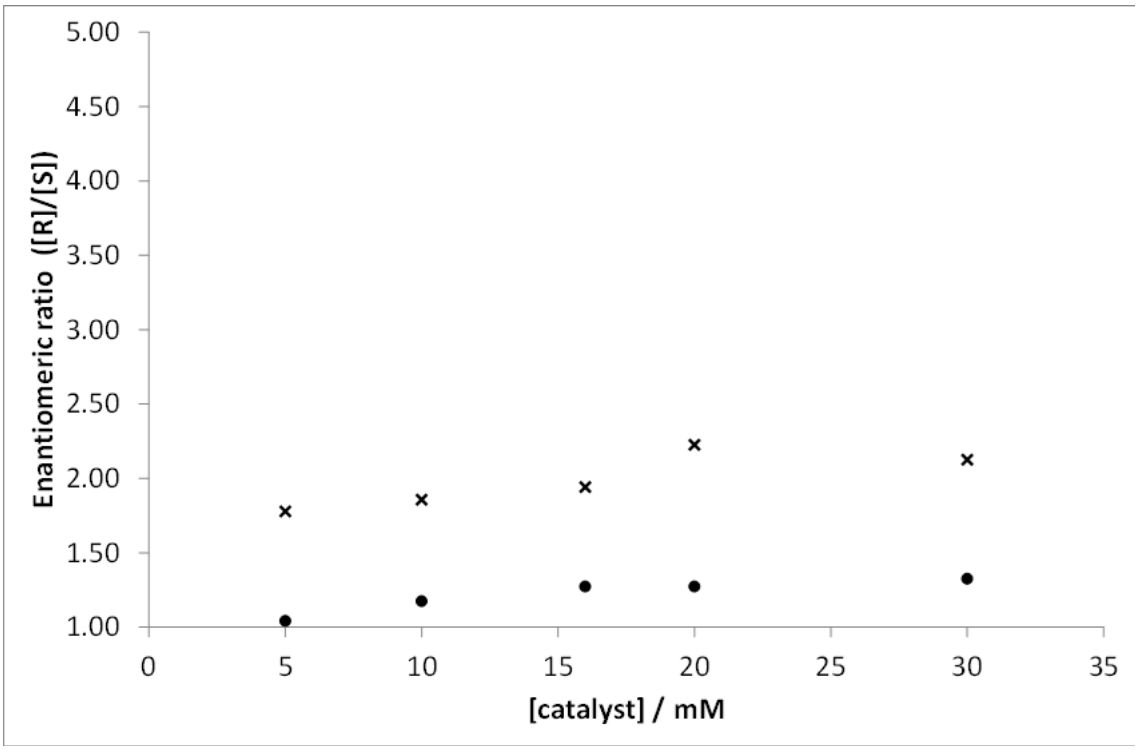
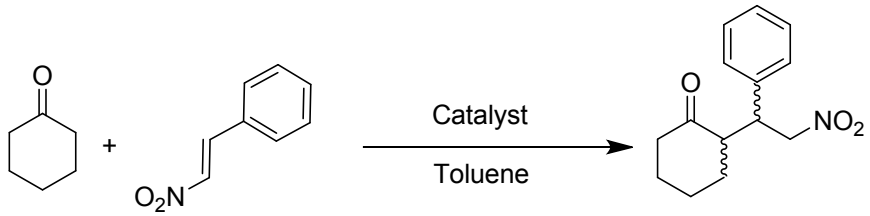


Figure S1. Effect of the concentration catalyst on the enantiomeric ratio.(x) **ProIlePr**, (•) **ProPhePr**.

Determination of kinetic constants



As described in the main text, the reactions were carried in the presence of an excess of cyclohexanone and therefore by means of simplicity the system was analysed in terms of pseudo first order kinetics (see equations 1-3; in equation (3) $[alkene]_f$ = concentration at the end of the reaction time, $[alkene]_0$ = initial concentration, k' = k [ketone][catalyst]).

$$\frac{d[alkene]}{dt} = k[catalyst][ketone][alkene] \quad (1);$$

$$\frac{d[alkene]}{dt} = k'[alkene] \quad (2); \textit{(pseudo first order kinetics)}$$

$$\ln \frac{[alkene]_f}{[alkene]_0} = k't \quad (3); \textit{(integrated rate equation)}$$

The experimental results used for the calculation of the constants cited in the main text are the following:

catalyst	[catalyst] / M	[ketone] / M	[olefine] / M	reaction time / h	yield / %	K / M^{-2} h^{-1}
ProValPr	0,0058	0,580	0,029	72	99	18,86
	0,001	0,548	0,026	24	3	2,31
ProIlePr	0,005	0,506	0,025	72	99	24,97
	0,001	0,458	0,026	24	2	1,53
ProPhePr	0,005	0,506	0,025	72	78	8,18
	0,001	0,548	0,026	24	1	0,76
ProAlaPr	0,005	0,506	0,025	72	70	6,5
	0,001	0,548	0,026	24	1	0,76

To check the feasibility of using a pseudo first order kinetic analysis, the reaction catalysed by ProIlePr was monitored by NMR at regular time intervals for 3 days. Data fit well to a first order kinetics as shown in Figure S2.

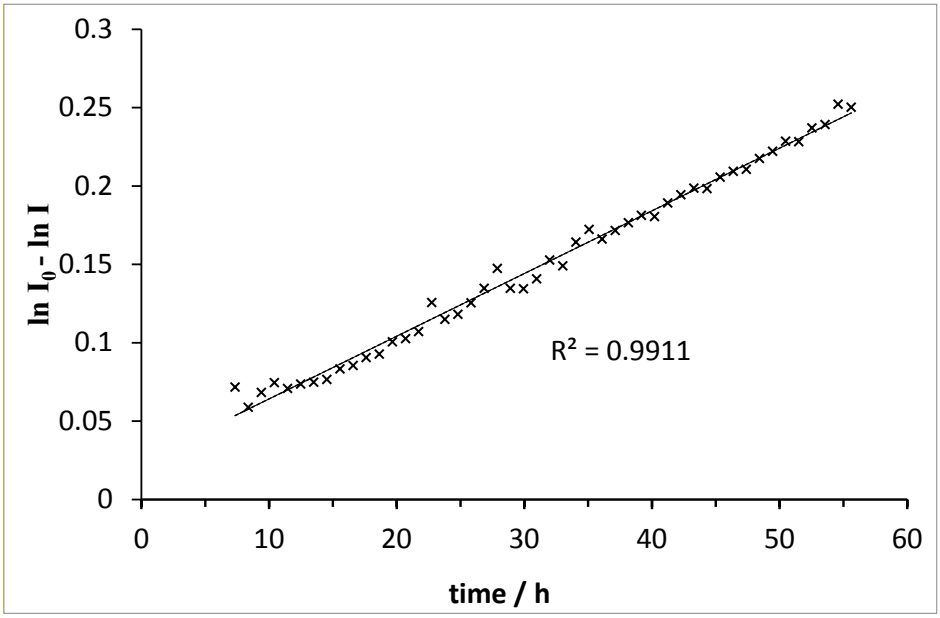


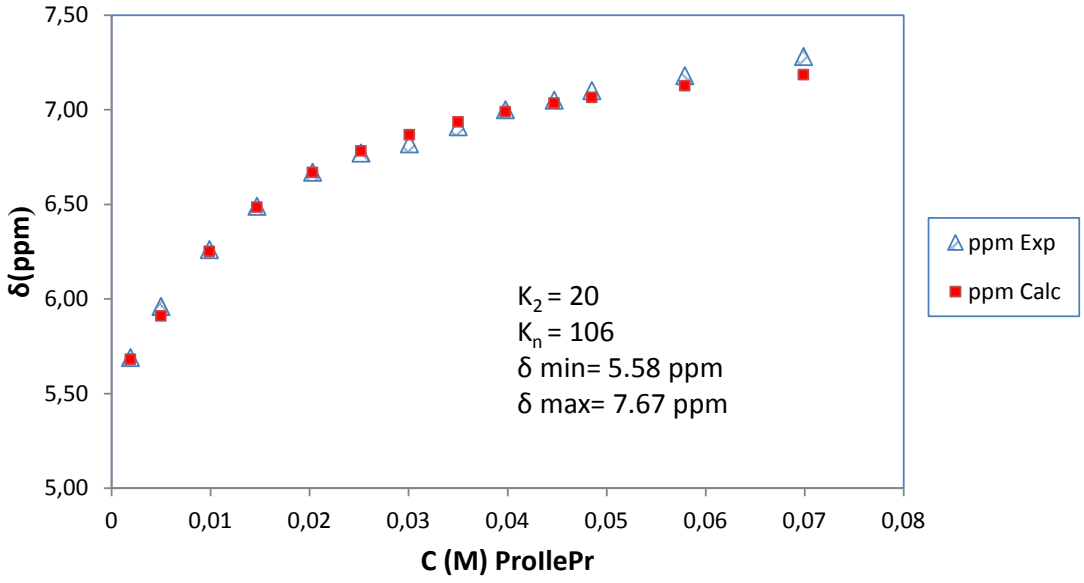
Figure S2. Pseudo first-order fit of the reaction catalysed by **ProIlePr.** Experimental data correspond to variation of NMR intensity of alkene protons of β-*trans*-nitrostyrene with time. [β-*trans*-nitrostyrene] =25 mM, [cyclohexanone] = 500 mM, [ProIlePr] = 5 mM. D_8-toluene as solvent.

Determination of aggregation constants

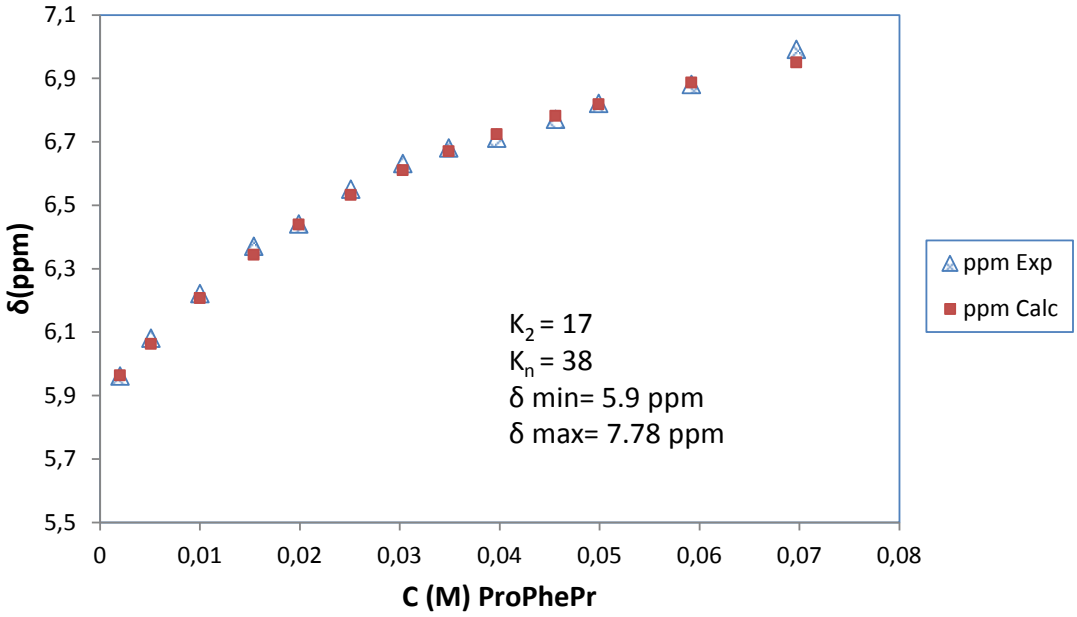
The chemical shift of NH from the propylamide moiety was used as a probe and its value was measured at different concentrations. "X" in the following equation was minimized by non-linear squares fitting using as variables δ_{max} (maximum chemical shift expected), K_2 and K_n (dimerization and oligomerization constants). Experimental data correspond to δ_{exp} (observed chemical shift), c (concentration) and δ_{min} (chemical shift in the absence of aggregation, obtained by extrapolation to c = 0).

$$X = K_2^{1/2} + K\frac{P_f[(1-P_f)c]^{1/2}}{2P_f - 1} - \frac{(1-P_f)^{1/2}}{(2P_f-1)c^{1/2}} \qquad P_f = \frac{\delta_{máx} - \delta_{exp}}{\delta_{min} - \delta_{exp}}$$

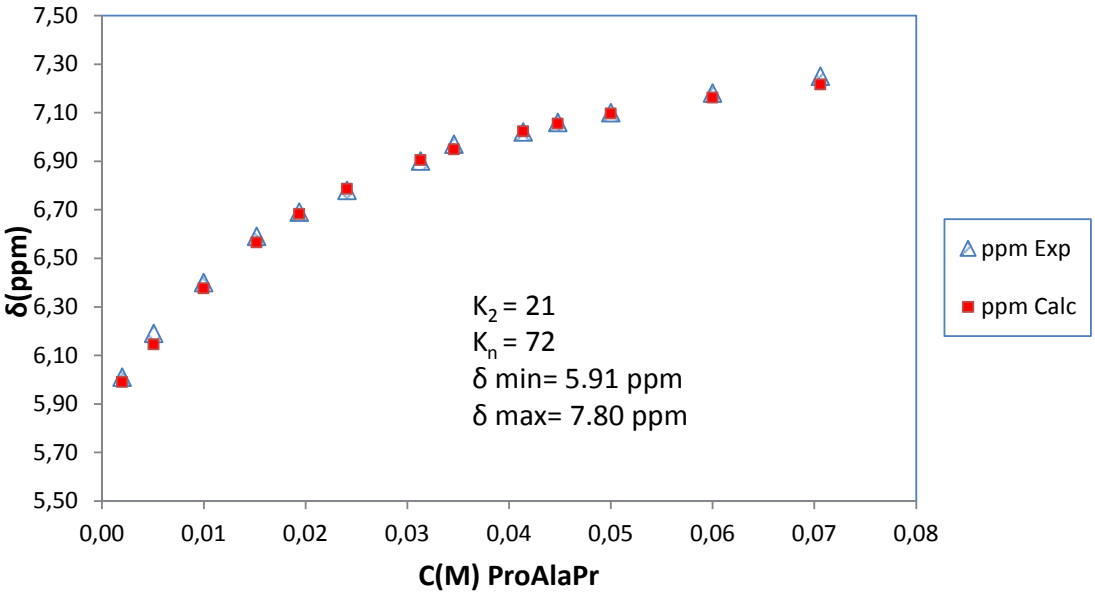
Experimental data used for constant determinations and graphical representation of the quality of the fittings.



C (M)ProllePr	ppm Exp	ppm Calc
0,0699	7,28	7,18
0,0579	7,18	7,13
0,0485	7,10	7,06
0,0447	7,05	7,03
0,0398	7,00	6,99
0,035	6,91	6,93
0,0301	6,82	6,87
0,0252	6,77	6,78
0,0203	6,67	6,67
0,0147	6,49	6,48
0,0099	6,26	6,25
0,005	5,96	5,91
0,0019	5,69	5,68



C(M)ProPhePr	ppm Exp	ppm Calc
0,0697	6,99	6,95
0,0592	6,88	6,89
0,0499	6,82	6,82
0,0456	6,77	6,78
0,0397	6,71	6,72
0,0349	6,68	6,67
0,0303	6,63	6,61
0,0251	6,55	6,53
0,0199	6,44	6,44
0,0154	6,37	6,34
0,0100	6,22	6,21
0,0051	6,08	6,06
0,0020	5,96	5,96



C (M)ProAlaPr	ppm Exp	ppm Cal
0,0706	7,25	7,22
0,0600	7,18	7,16
0,0500	7,10	7,10
0,0448	7,06	7,05
0,0414	7,02	7,02
0,0346	6,97	6,95
0,0313	6,90	6,90
0,0241	6,78	6,79
0,0194	6,69	6,68
0,0152	6,59	6,57
0,0100	6,40	6,38
0,0051	6,19	6,15
0,0020	6,01	5,99

NMR studies

-VT-NMR

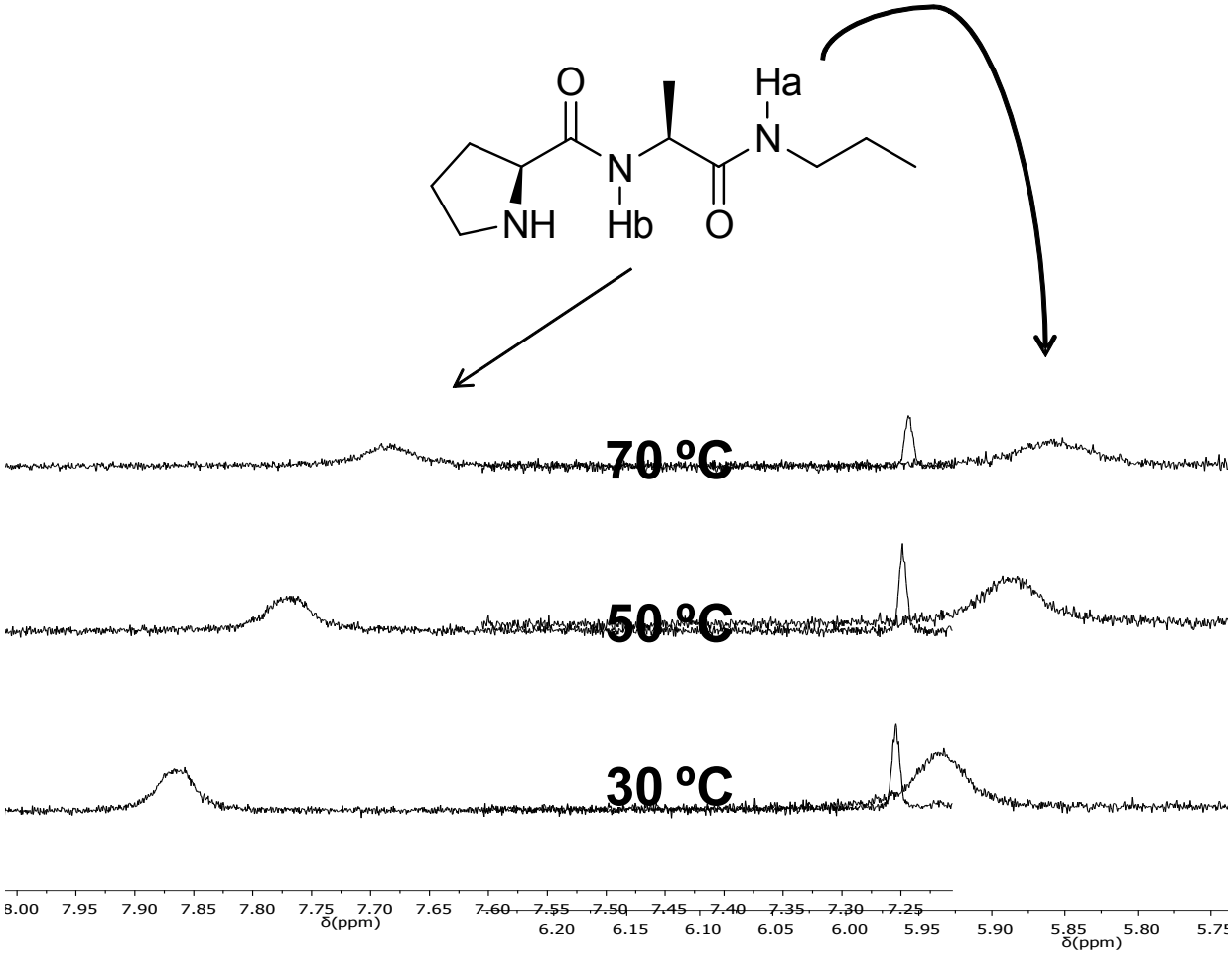


Figure S3. ^{1}H-NMR variation of the amide signal with the temperature for a sample of **ProAlaPr** 1 mM in D_8-toluene.

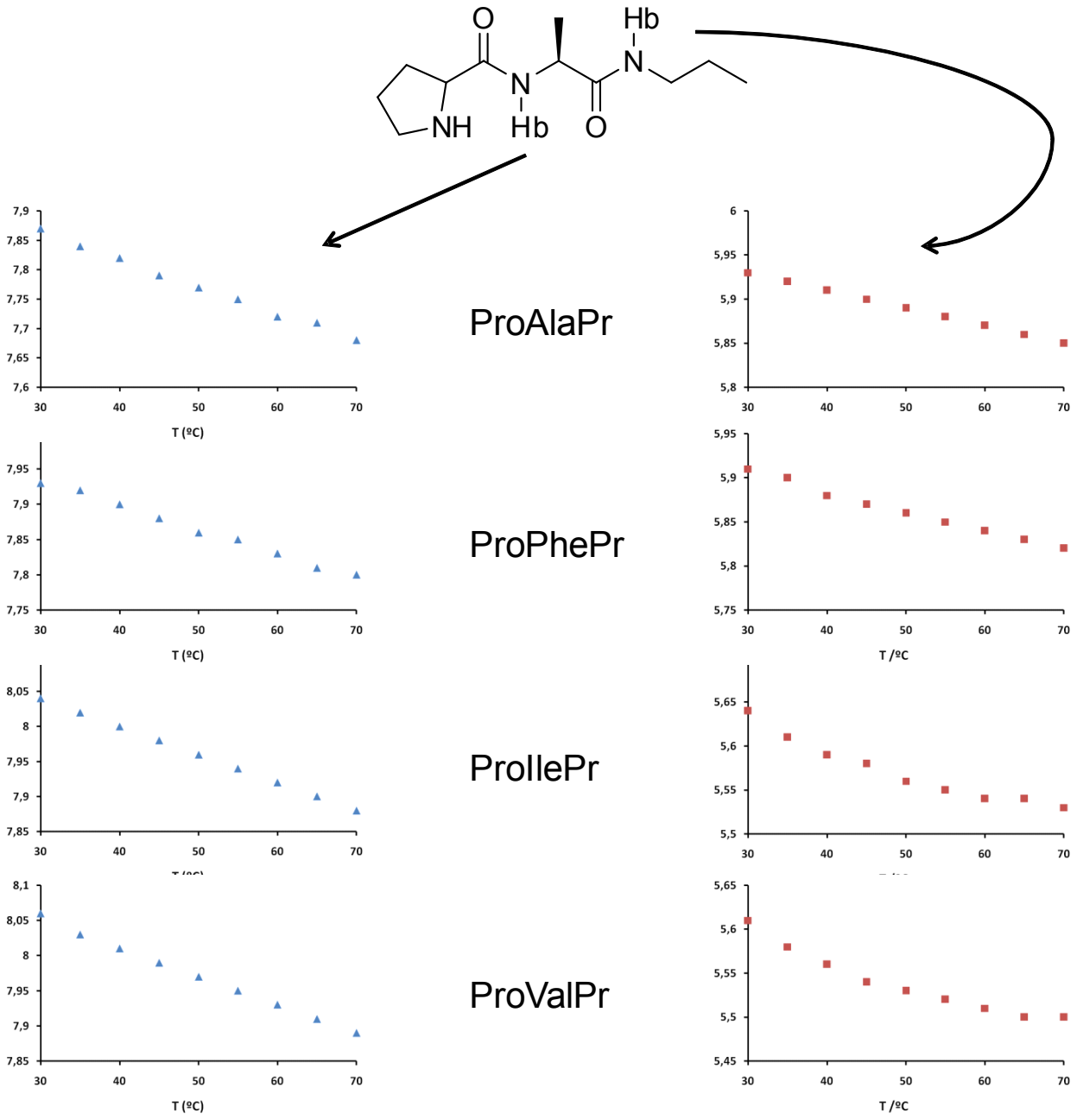


Figure S4. Variation of the amide signals with the temperature. Dipeptides 1 mM in D_8-toluene.

-NOE experiments

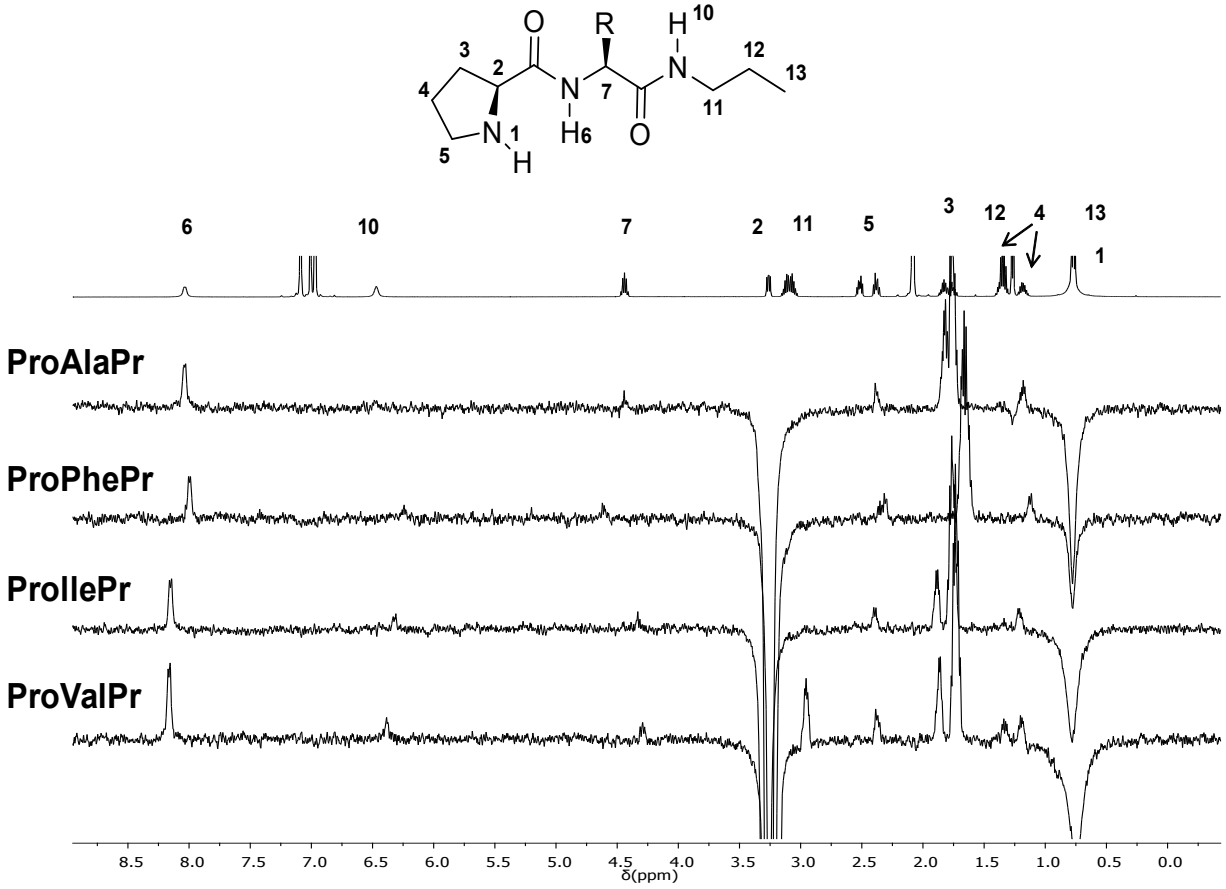


Figure S5. NOESY-1D spectra for all the compounds at 8 mM in D_8-toluene at 30ºC.

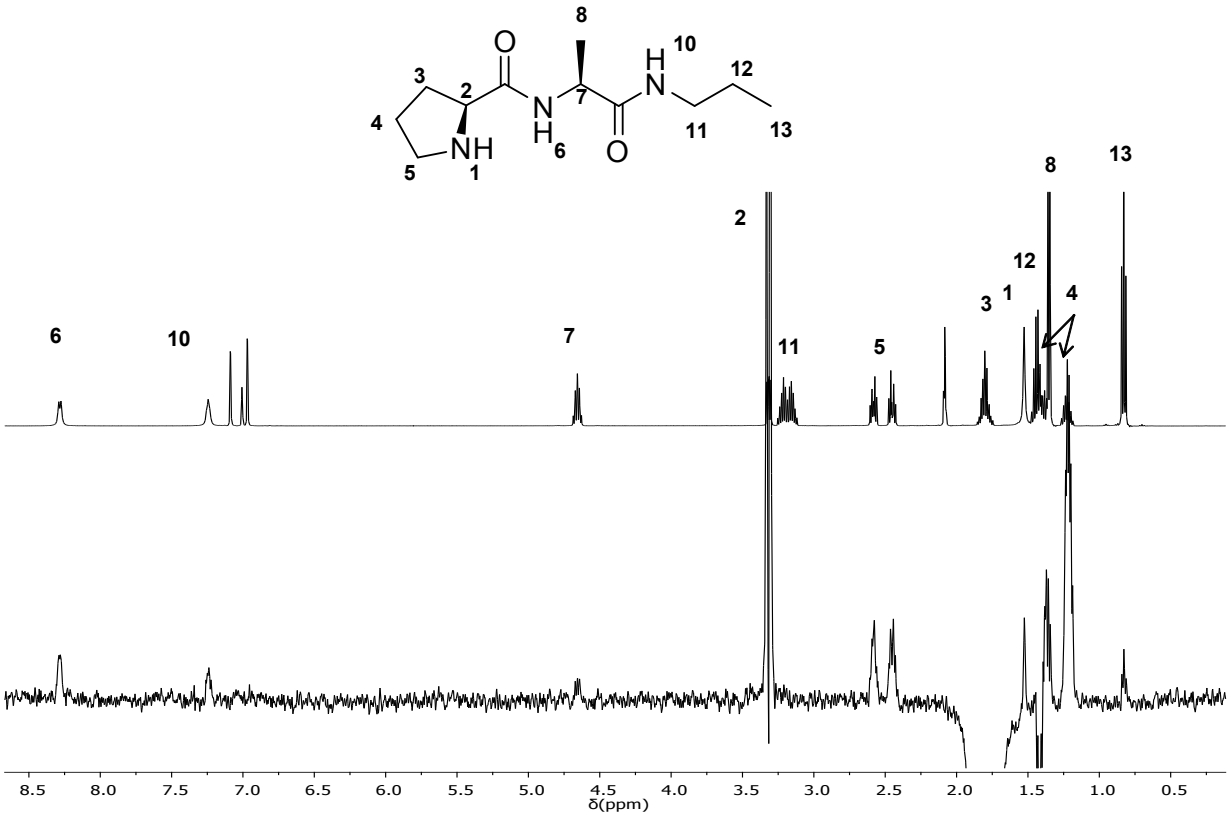


Figure S6. NOESY-1D spectrum for **ProAlaPr** at 70 mM in D_8-toluene at 30 ºC.

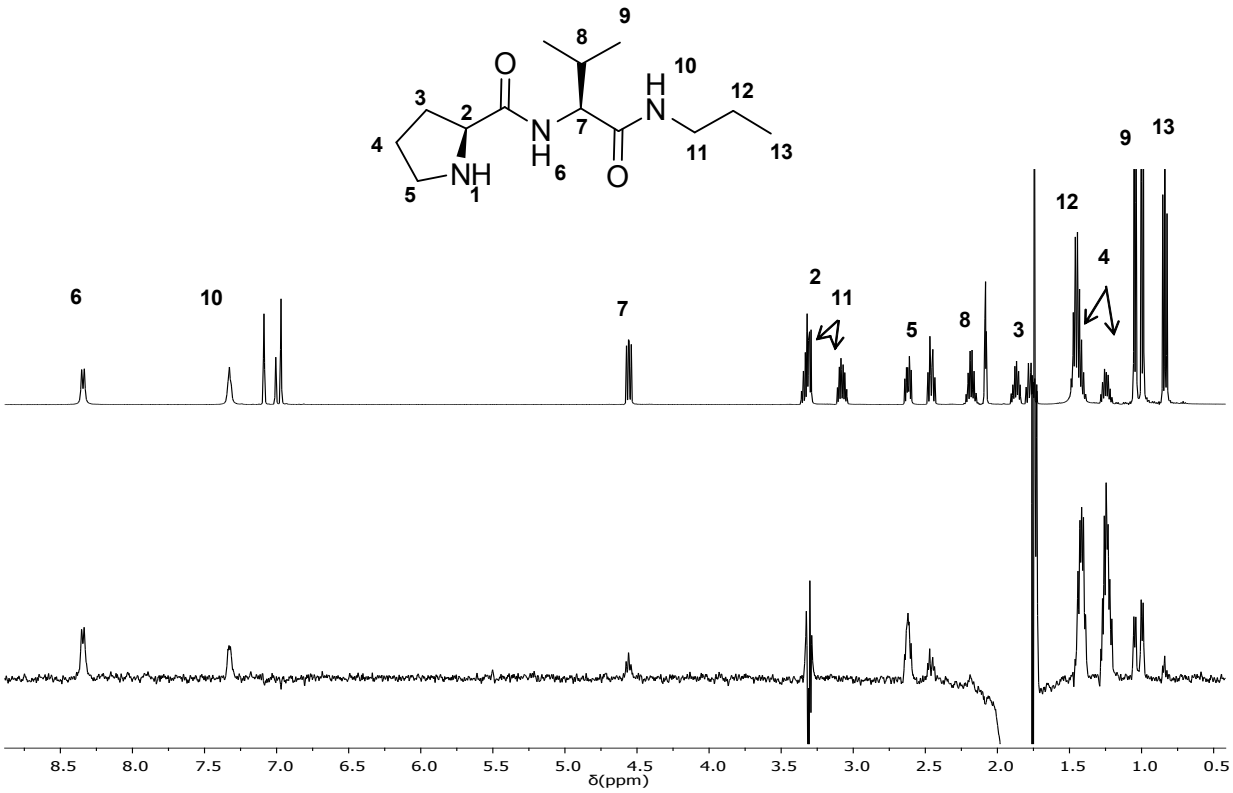


Figure S7. NOESY-1D spectrum for **ProValPr** at 70 mM in D_8-toluene at 30 ºC.

Molecular modelling studies

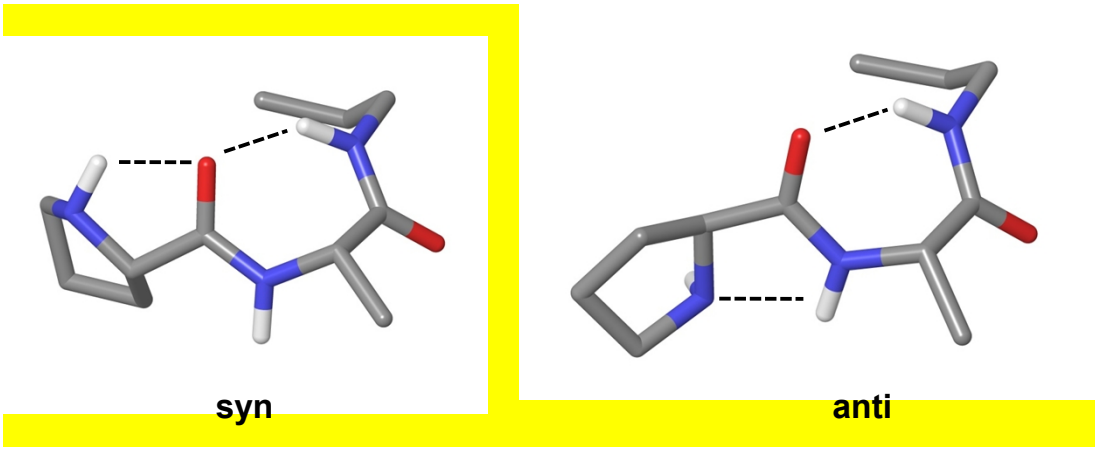


Figure S8. Molecular models (energy minimized, AMBER*) for folded conformations of **ProAlaPr.** $E_{anti} - E_{syn} = -7.4$ kJ mol^{-1}

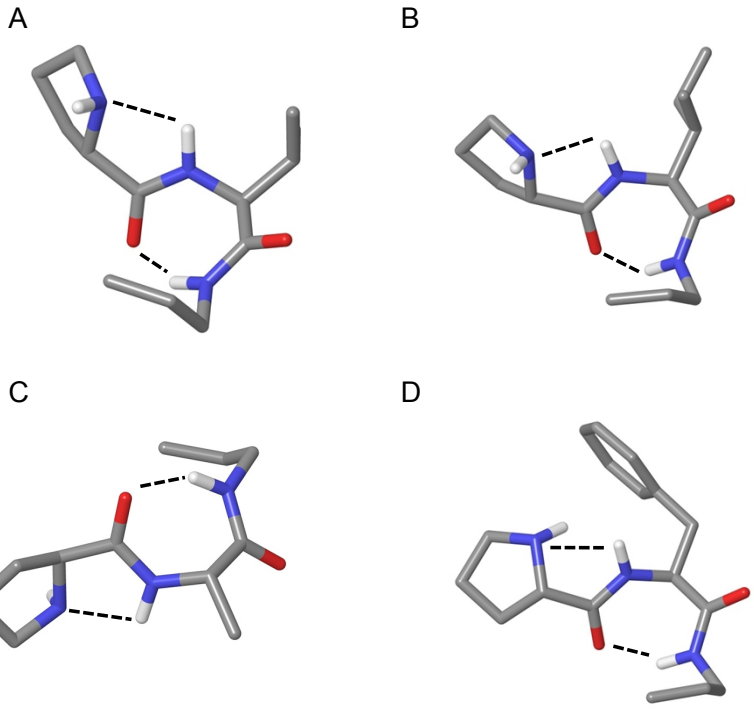


Figure S9. Molecular models for the folded *anti* conformers . (A) **ProValPr**, (B) **ProIlePr**, (C). **ProAlaPr** and (D) **ProPhePr**.

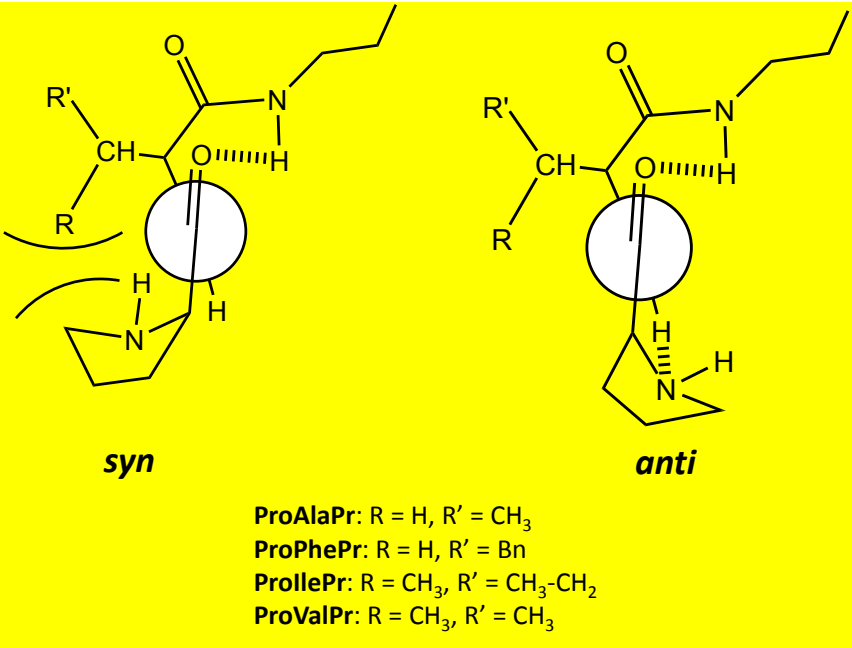


Figure S10. Schematic Newman projection of *anti* and *syn* conformers found for the dipeptides.

References

(1) Escuder, B.; Marti, S.; Miravet, J. F. *Langmuir* **2005**, *21*, 6776.
(2) Rodriguez-Llansola, F.; Escuder, B.; Miravet, J. F. *J Am Chem Soc* **2009**, *131*, 11478.