*n→π** Interactions are Competitive with Hydrogen Bonds

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General Experimental. Commercial chemicals were of reagent grade or better, and were used without further purification. Fluoroproline starting materials were obtained from OmegaChem (Lévis, Canada). All other chemicals were obtained from Sigma–Aldrich (St. Louis, MO). Anhydrous solvents were obtained from CYCLE-TAINER® solvent delivery systems from J. T. Baker (Phillipsburg, NJ). Reactions were monitored by thin-layer chromatography with visualization by UV light or staining with $KMnO_4$. The removal of solvents and other volatile materials "under reduced pressure" refers to the use of a rotary evaporator at water-aspirator pressure (<20 torr) and a water bath of <45 °C. All procedures were performed at ambient temperature (~22 °C) unless indicated otherwise. All yields are unoptimized.

Instrumentation. NMR spectra were acquired at ambient temperature with a Bruker DMX 500 MHz spectrometer (^{1}H, 500 MHz; ^{13}C, 125 MHz) in the National Magnetic Resonance Facility at Madison (NMRFAM). ^{13}C spectra were proton-decoupled. Mass spectrometry was performed with a Micromass LCT (electrospray ionization, ESI) instrument in the Mass Spectrometry Facility of the Department of Chemistry at the University of Wisconsin–Madison. Preparative and analytical HPLC were performed with a Shimadzu LC-20 HPLC on a preparative NucleoSil C18 column from Macherey–Nagel (Bethlehem, PA) using 0.1% v/v TFA in H_2O (A) and 0.1% v/v TFA in MeCN (B) as eluents.
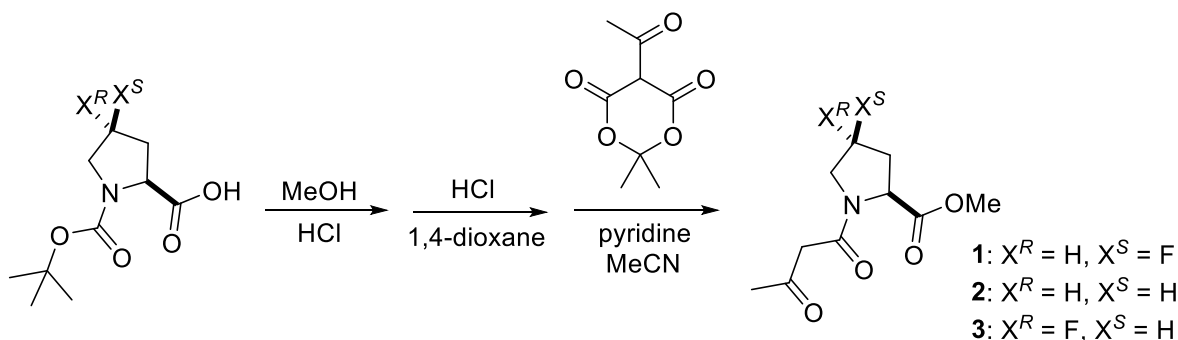
N-(3-Oxobutanoyl)-(2S,4S)-fluoroproline methyl ester (1). N-Boc-(2S,4S)-fluoroproline (1.0 g, 4.3 mmol) was dissolved in 50 mL of methanol containing three drops of concentrated aqueous hydrochloric acid, and the resulting solution was heated at reflux overnight. Following removal of solvent under reduced pressure, the resulting oil was dissolved in 10 mL of 4 M hydrochloric acid in dioxane, and the resulting solution was allowed to stir 1 h. Solvent was removed under reduced pressure. The resulting oil was dissolved in 30 mL of acetonitrile containing 5-acetyl-2,2-dimethyl-1,3-dioxane-4,6-dione^{S1} (0.80 g, 4.3 mmol) and excess pyridine. After heating at reflux overnight, the solvent was removed under reduced pressure, and the product was purified by reverse-phase HPLC using a 30–95% v/v gradient of B applied over 30 min. Lyophilization afforded 10 mg of a colorless oil, the purity of which was confirmed by HPLC. **^{1}H NMR** (500 MHz, CDCl$_3$, δ): mixture of two tautomers and two rotamers, 14.20 (s), 13.96 (s), 5.40–5.16 (m, 1H), 5.00 (s, 0.25H), 4.81 (s, 0.07H), 4.62 (m, 1H), 3.95–3.35 (m, 6H, singlets at 3.78, 3.77, 3.52), 2.82–2.56 (m, 1H), 2.44–1.92 (m, 4H, singlets at 3.30, 3.29, 1.96, 1.94); **^{13}C NMR** (125 MHz, CDCl$_3$, δ): 201.7, 201.5, 175.9, 172.6, 172.0, 170.8, 165.7, 92.5, 92.4, 91.0, 91.0, 90.8, 89.4, 88.5, 87.9, 58.1, 57.7, 57.4, 57.03, 54.3, 54.1, 53.3, 53.2, 53.1, 52.7, 52.7, 51.5, 50.4, 38.2, 38.0, 36.2, 36.1, 36.0, 35.9, 30.2, 30.1, 22.0, 21.9. HRMS-ESI: [M+H]$^+$ calculated 232.0980, observed 232.0978.

***N*-(3-Oxobutanoyl)-(2*S*)-proline methyl ester (2).** *N*-Boc-(2*S*)-proline (1.0 g, 4.6 mmol) was dissolved in 50 mL of methanol containing three drops of concentrated aqueous hydrochloric acid, and the resulting solution was heated at reflux overnight. Following removal of solvent under reduced pressure, the resulting oil was dissolved in 10 mL of 4 M hydrochloric acid in dioxane, and the resulting solution was allowed to stir for 1 h. Solvent was removed under reduced pressure. The resulting oil was dissolved in 30 mL of acetonitrile containing 5-acetyl-2,2-dimethyl-1,3-dioxane-4,6-dione (0.86 g, 4.6 mmol) and excess pyridine. After heating at reflux overnight, the solvent was removed under reduced pressure, and the product was purified by reverse-phase HPLC using a 5–95% v/v gradient of B applied over 30 min. Lyophilization afforded 10 mg of a colorless oil, the purity of which was confirmed by HPLC. **^{1}H NMR** (500 MHz, CDCl$_3$, δ): mixture of two tautomers and two rotomers, 14.24 (s), 13.61 (s), 5.04 (s, 0.21H), 4.79 (s, 0.04H), 4.54–4.45 (m, 1H), 3.75–3.25 (m, 7.2H, singlets at 3.74, 3.52), 2.44–1.75 (m, 7.5H, singlets at 2.31, 1.96); **^{13}C NMR** (125 MHz, CDCl$_3$, δ): 202.5, 202.3, 175.2, 173.1, 172.5, 172.4, 170.6, 165.8, 165.6, 88.7, 88.5, 60.0, 58.9, 58.2, 52.9, 52.5, 51.4, 51.1, 48.3, 47.8, 47.3, 46.7, 46.7, 45.8, 31.3, 30.5, 30.4, 30.3, 29.4, 28.4, 27.8, 24.9, 24.6, 22.7, 21.9. HRMS–ESI: [M+H]$^+$ calculated 214.1074, observed 214.1073.

***N*-(3-Oxobutanoyl)-(2*S*,4*R*)-fluoroproline methyl ester (3).** *N*-Boc-(2*S*,4*R*)-fluoroproline (1.0 g, 4.3 mmol) was dissolved in 50 mL of methanol containing three drops of concentrated aqueous hydrochloric acid, and the resulting solution was heated at reflux overnight. Following removal of solvent under reduced pressure, the resulting oil was dissolved in 10 mL of 4 M hydrochloric acid in dioxane, and the resulting solution was allowed to stir for 1 h. Solvent was removed under reduced pressure. The resulting oil was dissolved in 30 mL of acetonitrile containing 5-acetyl-2,2-dimethyl-1,3-dioxane-4,6-dione (0.80 g, 4.3 mmol) and excess pyridine. After heating at reflux overnight, the solvent was removed under reduced pressure, and the product was purified by reverse-phase HPLC using a 30–95% v/v gradient of B applied over 30 min. Lyophilization afforded 10 mg of a colorless oil, the purity of which was confirmed by HPLC. **^{1}H NMR** (500 MHz, CDCl$_3$, δ): mixture of two tautomers and two rotomers, 14.23 (s), 14.16 (s), 5.35–5.24 (m, 1H), 5.00 (s, 0.18H), 4.83–4.58 (m, 1H), 3.95–3.35 (m, 6.7H, singlets at 3.78, 3.75), 2.75–1.92 (m, 5.4H, singlets at 2.33, 2.31, 1.98, 1.95); **^{13}C NMR** (125 MHz, CDCl$_3$, δ): 202.4, 201.9, 175.9, 175.5, 171.3, 171.2, 170.7, 170.6, 165.9, 165.5, 92.7, 92.6, 91.4, 91.3, 91.2, 90.0, 88.5, 88.3, 58.3, 57.5, 57.2, 56.9, 56.4, 54.0, 53.8, 53.4, 53.3, 53.1, 53.0, 52.9, 52.9, 52.6, 51.3, 50.9, 38.1, 38.0, 37.9, 37.9, 36.1, 36.1, 36.0, 35.9, 30.5, 30.3, 22.3, 21.8. HRMS–ESI: [M+H]$^+$ calculated 232.0980, observed 232.0978.

NMR spectroscopy. Compounds were dissolved to a final concentration of 5 mM in CDCl$_3$ and allowed to equilibrate for approximately one week. All spectra were acquired at 25 °C. ^{1}H NMR spectra for quantitative integration were acquired by averaging 16 scans collected at 30-s intervals to allow for complete relaxation. Alkene protons were identified by their chemical shift (δ ~5.0 ppm), multiplicity (singlet), and coupling to the terminal acetyl carbon (δ ~20 ppm) and amide carbonyl carbon (δ ~175 ppm) in ^{1}H–^{13}C HMBC spectra.

Computational methodology. Preferred conformations were obtained by optimizing the respective compounds at the B3LYP/6-311+G(2d,p) level of theory as implemented by Gaussian 09.[S2] Frequency calculations of optimized structures yielded no imaginary frequencies, indicating

a true minimum on the potential energy surface. Energies were corrected by the zero-point vibrational energy. Optimized geometries were subjected to analysis with NBO 5.9 at the B3LYP/6-311+G(2d,p) level of theory implemented in Gaussian 09.[S3] Proline has been shown to populate both the *endo* pucker and the *exo* pucker of the pyrrolidine ring in an approximately 2:1 ratio.[S3] The reported energy of the $n{\rightarrow}\pi^*$ interaction for compound **2** was determined by a weighted average of the second-order perturbation theory energies calculated for those two optimized geometries. As (4*R*)- and (4*S*)-4-fluoroproline, respectively, populate the *exo* and *endo* puckers almost exclusively,[S4] the reported energy of the $n{\rightarrow}\pi^*$ interaction for compounds **1** and **3** reflects only the relevant ring pucker.

References

S1   Gopalsamy, A.; Shi, M. *Org. Lett.* **2003**, *5*, 3707–3709.

S2   Gaussian 09, Revision **A.1**, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.

S3   NBO 5.9. Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Weinhold, F. Theoretical Chemistry Institute, University of Wisconsin–Madison, Madison, WI, 2012.

S4   DeRider, M. L.; Wilkens, S. J.; Waddell, M. J.; Betscher, L. E.; Weinhold, F.; Raines, R. T.; Markley, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 2497–2505.
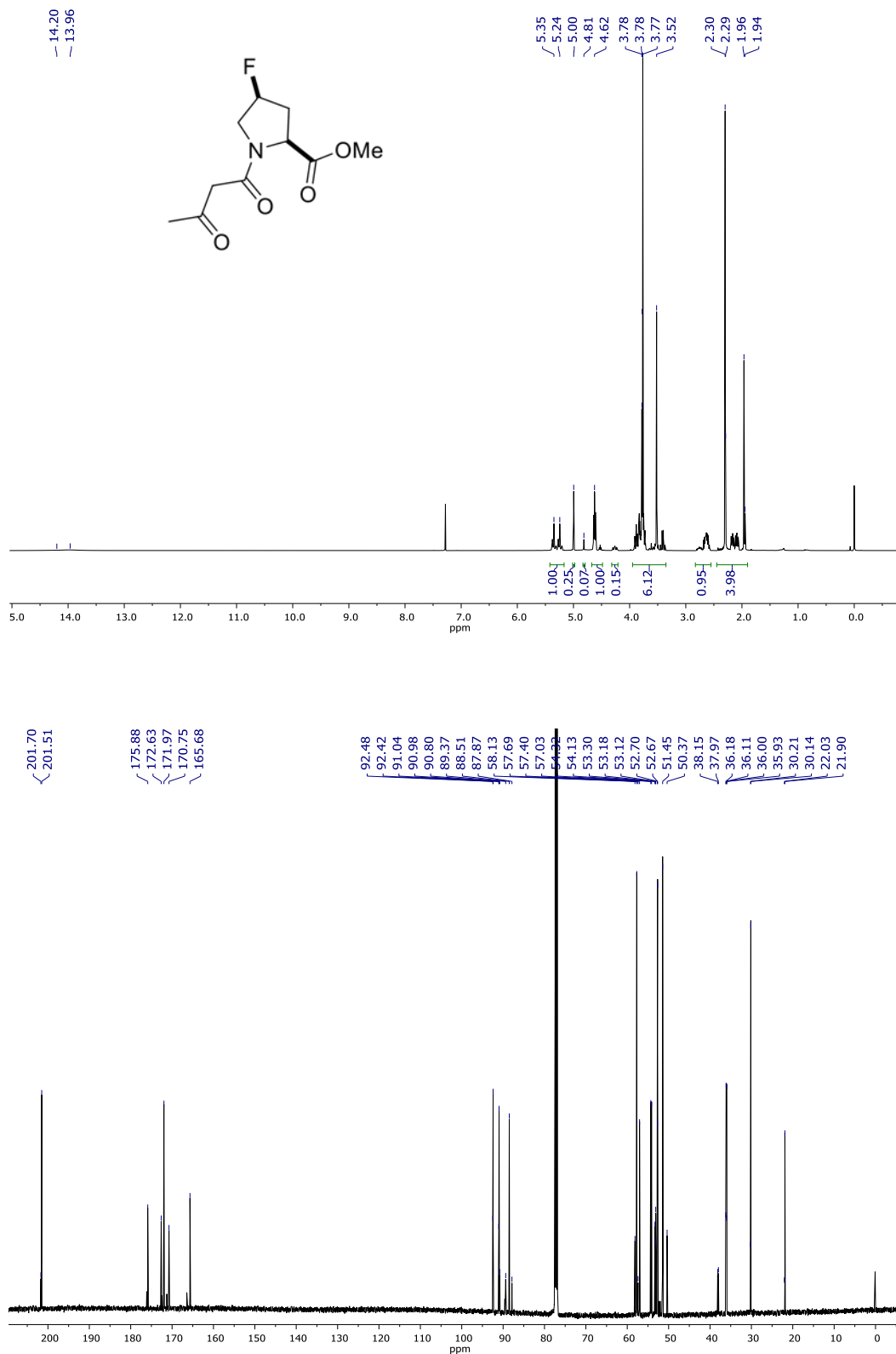
Figure S1. ^{1}H and ^{13}C NMR spectra of compound **1** in CDCl$_3$.
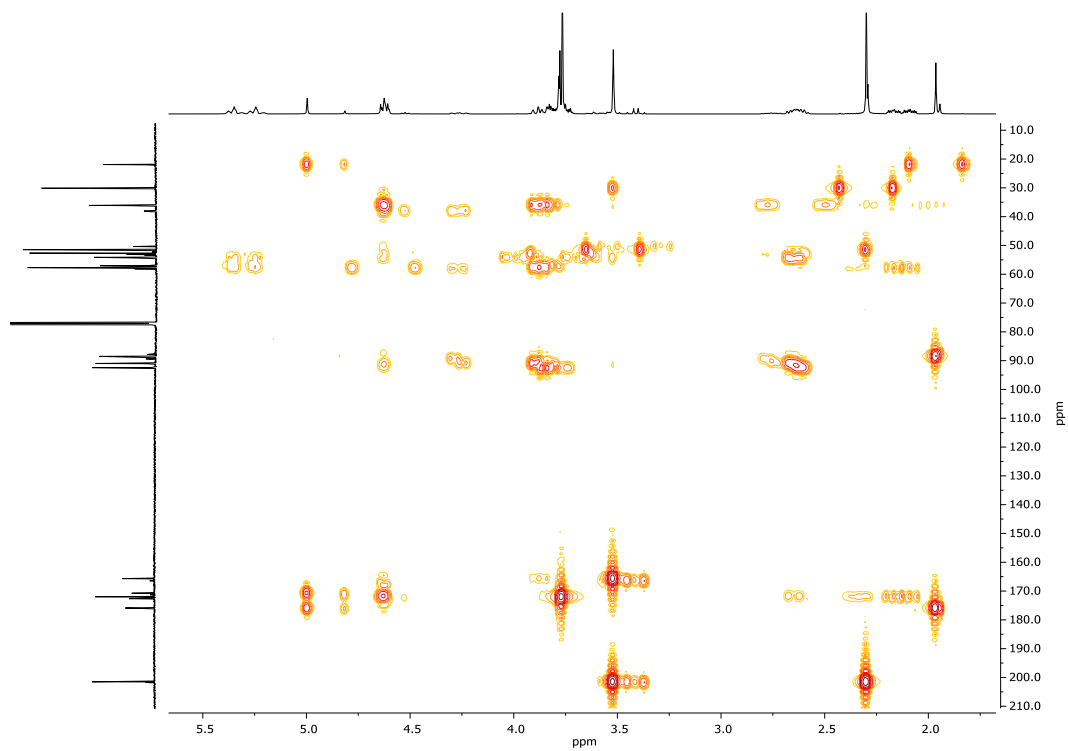
Figure S2. ^{1}H–^{13}C HMBC spectrum of compound **1** in CDCl$_3$.
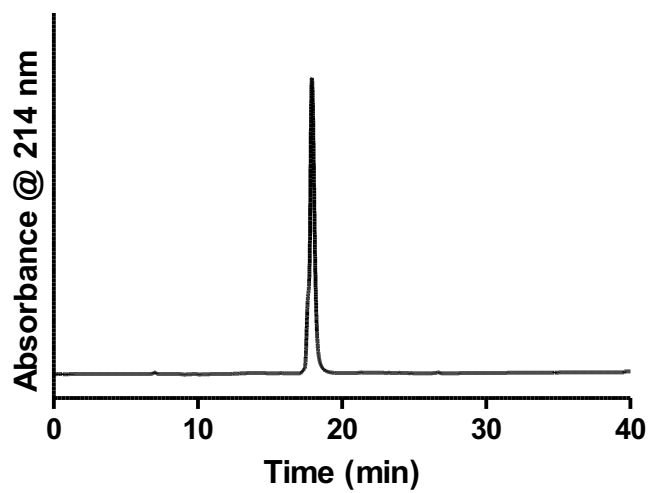
Figure S3. HPLC chromatogram of purified compound **1**.
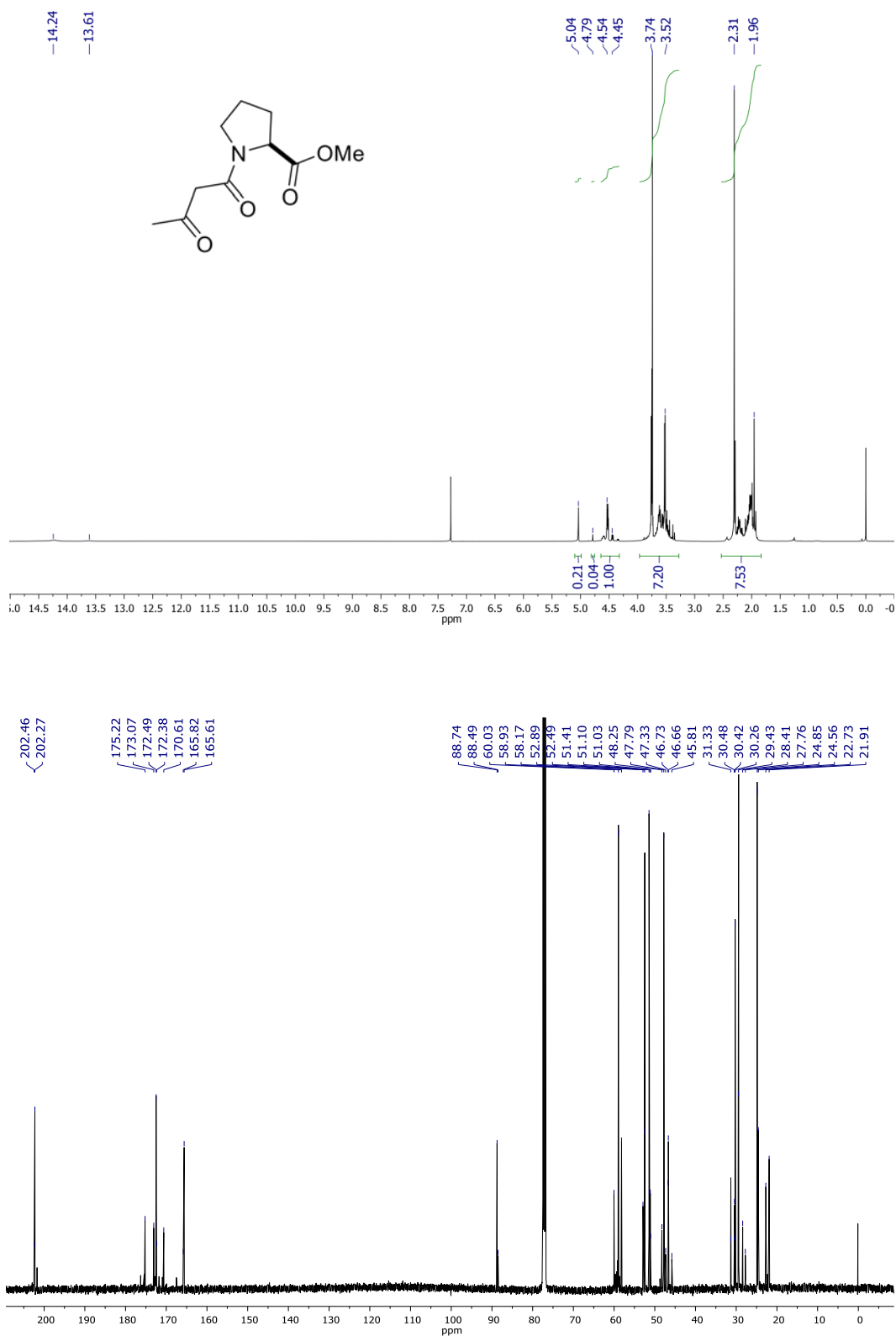
Figure S4. ^{1}H and ^{13}C NMR spectra of compound **2** in CDCl$_3$.

Figure S5. ^{1}H–^{13}C HMBC spectrum of compound **2** in CDCl$_3$.
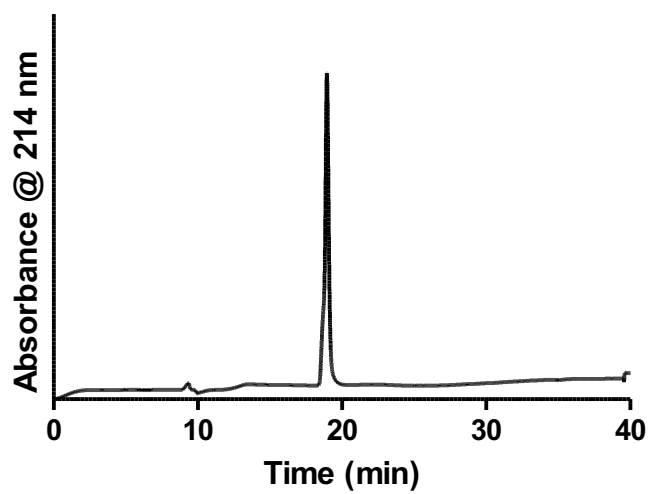
Figure S6. HPLC chromatogram of purified compound **2**.

Figure S7. ^{1}H and ^{13}C NMR spectra of compound **3** in CDCl$_3$.
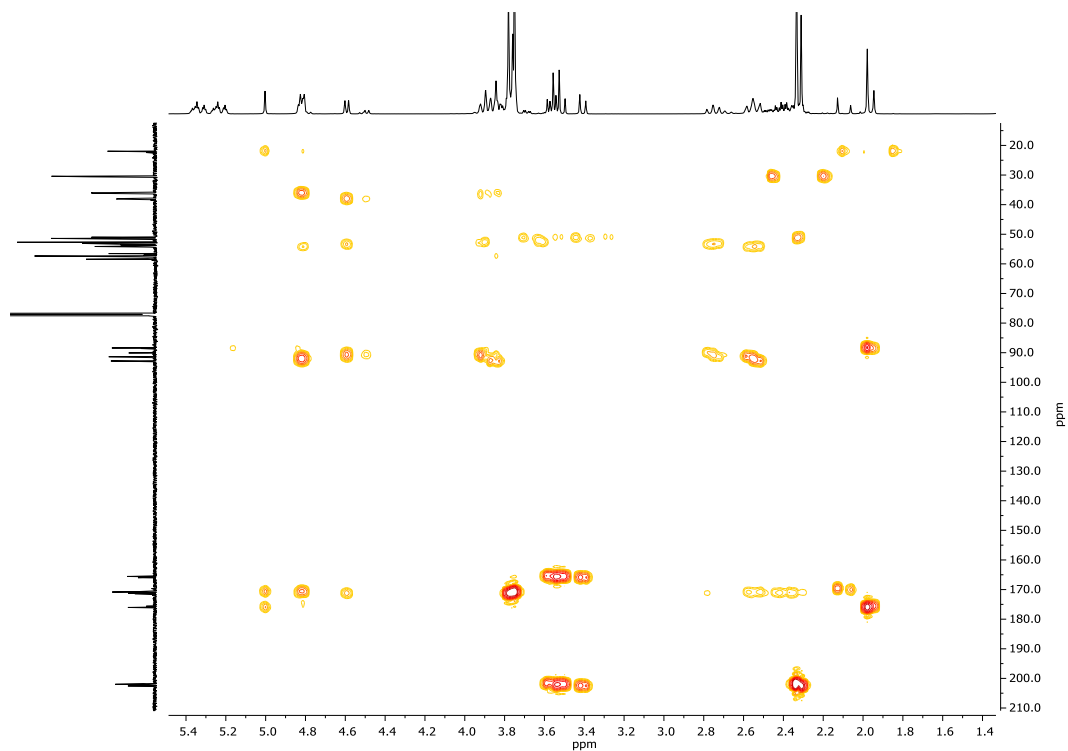
Figure S8. ^{1}H–^{13}C HMBC spectrum of compound **3** in CDCl$_3$.

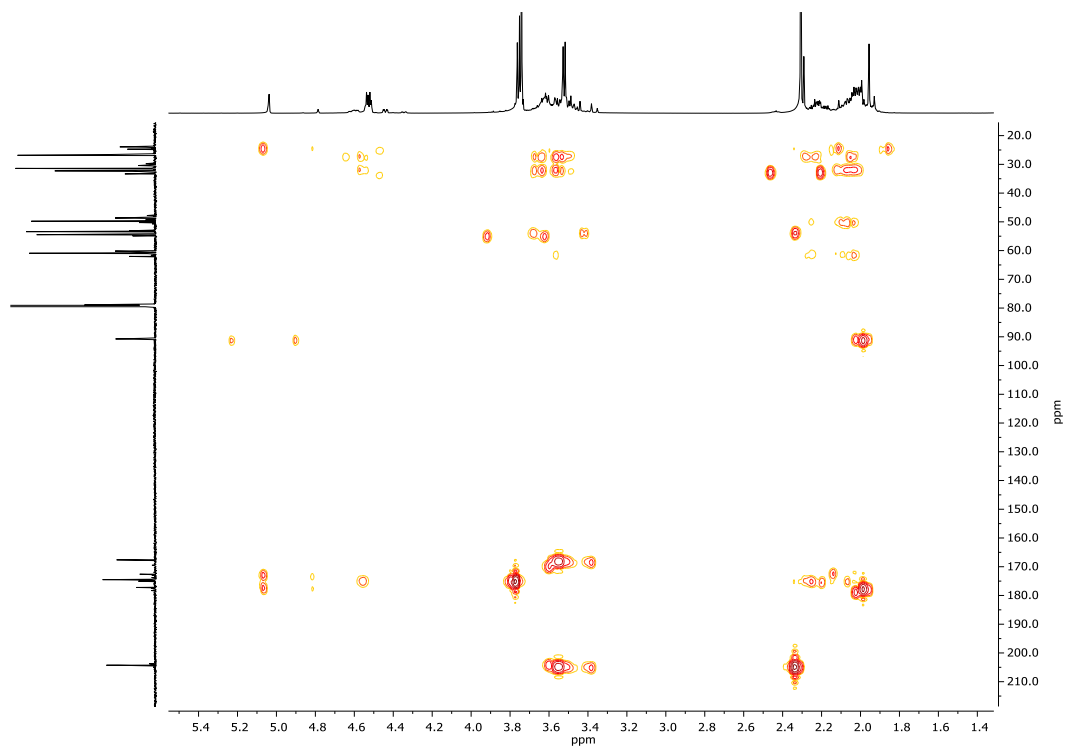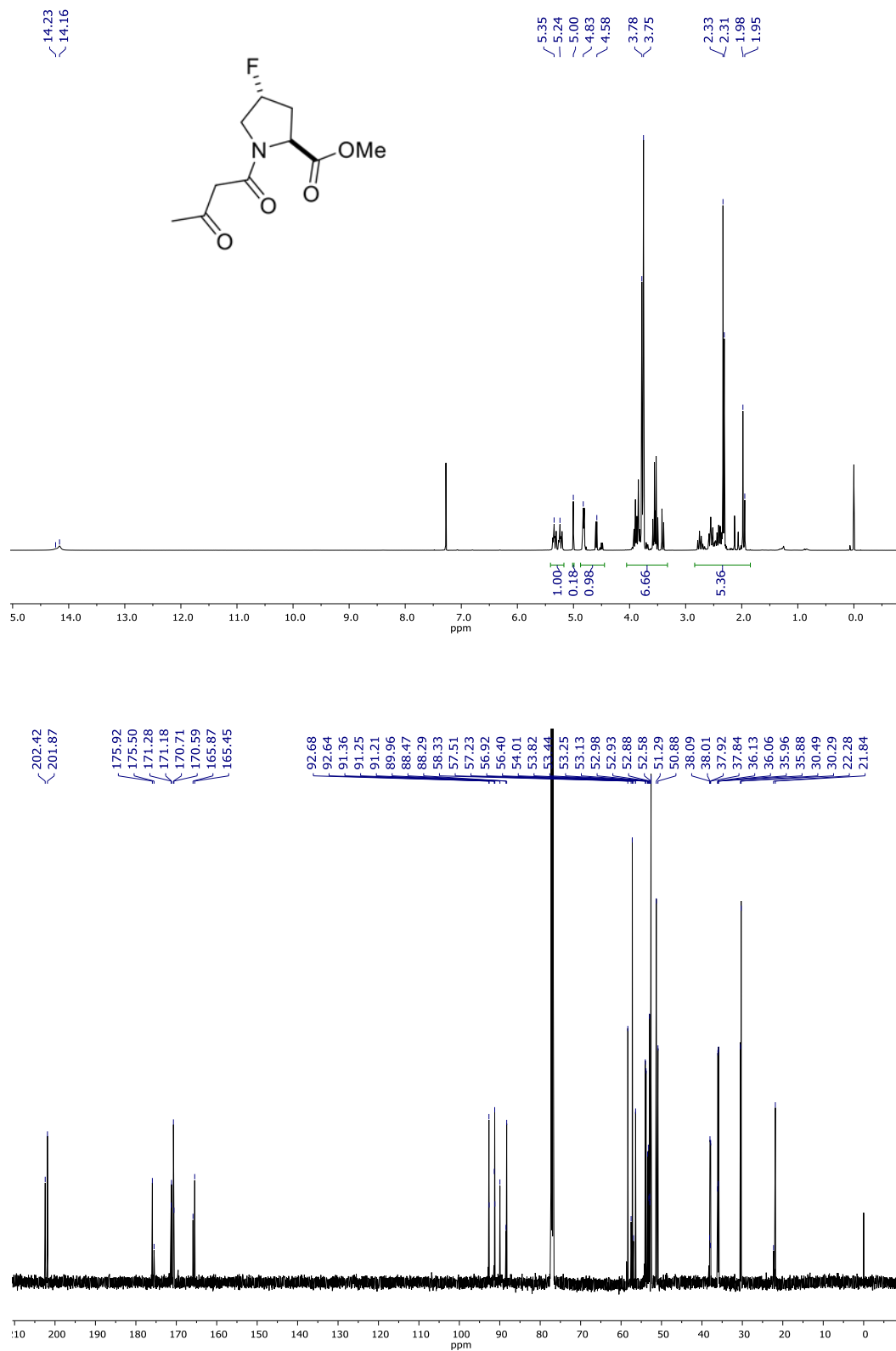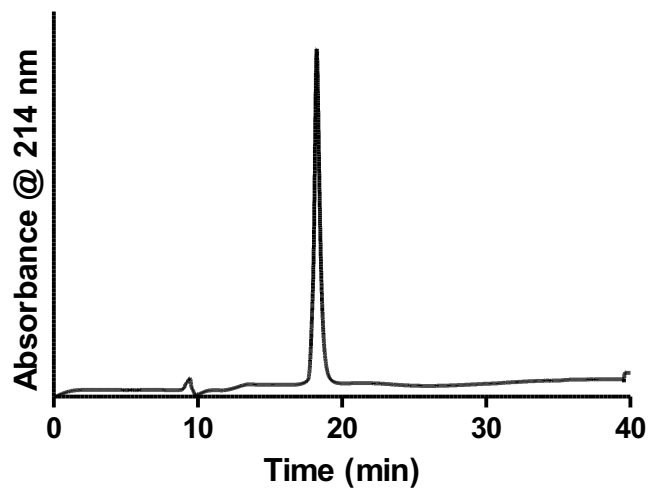**Figure S9.** HPLC chromatogram of purified compound **3**.

Table S1. Cartesian coordinates of the optimized *trans endo* conformation of compound **1**.
Energy = −845.040000 Hartree

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C            1.15156400      0.01885200     -0.84938400
H            0.96212000     -0.60229300     -1.72427800
C            0.04971800      1.95897400      0.11148900
H           -0.13896000      2.05984100      1.18231500
H           -0.62975700      2.62294700     -0.43052900
C            1.50702600      2.31341300     -0.18675000
H            1.63285800      3.34274300     -0.52245700
C            1.97194200      1.27477200     -1.19922700
H            1.70821200      1.60741300     -2.20561500
H            3.04829400      1.12104500     -1.15754100
N           -0.09343600      0.57646700     -0.35102600
C           -1.24211300     -0.15483400     -0.35619500
O           -1.22596900     -1.31737700     -0.82478900
C            1.83332300     -0.87740100      0.19190000
O            1.47131600     -1.03900100      1.32471000
O            2.91117300     -1.47077200     -0.35661400
C            3.64885300     -2.34859600      0.51577900
H            3.01142800     -3.16461000      0.85420200
H            4.47329500     -2.72749000     -0.08245600
H            4.01938500     -1.79807700      1.37985300
C           -2.45921900      0.43926700      0.16491900
C           -3.62283800     -0.26973900      0.15502100
H           -2.45969400      1.43360000      0.58250400
C           -4.91938500      0.25424200      0.67875700
H           -4.81650900      1.26758900      1.06350900
H           -5.66969200      0.24459500     -0.11590900
H           -5.28480200     -0.39796500      1.47600300
O           -3.70144600     -1.50479300     -0.32557800
H           -2.76925700     -1.73553000     -0.62849600
F            2.26814500      2.18808500      0.98737700
```

Table S2. Cartesian coordinates of the optimized *trans endo* conformation of compound **2**.
Energy = −745.761681 Hartree

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C            1.35378300     0.44091200    -0.72790500
H            1.27970500    -0.04215900    -1.70058400
C            0.02638700     2.21604900     0.29912200
H           -0.42510300     2.22553100     1.29211000
H           -0.54728800     2.88964800    -0.34673200
C            1.51004200     2.60415800     0.33970400
H            1.93845800     2.32014100     1.30177700
H            1.65838600     3.67574800     0.20378600
C            2.13817900     1.76875300    -0.78448700
H            1.96721900     2.23714600    -1.75654900
H            3.21230600     1.62548800    -0.66817000
N            0.03905700     0.85772800    -0.25924100
C           -1.01102200    -0.00151600    -0.31852100
O           -0.82716800    -1.15904100    -0.76968100
C            2.01141300    -0.54492900     0.23819300
O            1.84510200    -0.56311800     1.43107200
O            2.85624000    -1.35736200    -0.41986900
C            3.56261300    -2.31343000     0.39239900
H            2.85503800    -2.96093400     0.90865900
H            4.17428200    -2.88658400    -0.29931400
H            4.18577300    -1.80276300     1.12635600
C           -2.32050900     0.43984000     0.12725200
C           -3.38105500    -0.41354100     0.08014500
H           -2.47267500     1.44073200     0.49882600
C           -4.76073500    -0.04952400     0.52125800
H           -4.80934800     0.97784800     0.87867000
H           -5.45995500    -0.17571900    -0.30927300
H           -5.08242200    -0.72341900     1.31942100
O           -3.27582000    -1.65989500    -0.36759400
H           -2.30918800    -1.77010000    -0.62868400
```

Table S3. Cartesian coordinates of the optimized *trans exo* conformation of compound **2**.
Energy = −745.761681 Hartree

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C           1.44821800      0.56835900     -0.50942700
C           2.28594500      1.82861900     -0.19362800
C           1.26509200      2.97256900     -0.23982000
C          -0.00045100      2.33664200      0.34066400
H           1.47923100      0.31617900     -1.57087700
H           2.70524200      1.74530800      0.81143200
H           3.10872400      1.95189200     -0.89674200
H           1.58632100      3.84923900      0.32346600
H           1.08409200      3.28132400     -1.27241300
H          -0.00546600      2.38683300      1.43518800
H          -0.90957900      2.80880100     -0.03086600
C          -0.92595600      0.05917800     -0.25077000
C           1.95472600     -0.63443400      0.28139100
O          -0.68033000     -1.07110500     -0.74041200
O           1.74706500     -0.82261800      1.45204800
O           2.73324600     -1.41451000     -0.48641800
C           3.29234000     -2.56848100      0.16725300
H           3.91100700     -2.26594700      1.01180900
H           2.49386900     -3.22019200      0.51991400
H           3.89086100     -3.06936300     -0.58911700
N           0.09169300      0.94795800     -0.11749600
C          -2.26586100      0.42655200      0.17155200
C          -3.29109200     -0.45989700      0.03651700
H          -2.46449700      1.38596100      0.62179400
O          -3.12594100     -1.67044700     -0.48539700
H          -2.14552600     -1.73525800     -0.70644200
C          -4.69555700     -0.17580000      0.45764500
H          -5.36553100     -0.27200300     -0.40058600
H          -5.01376300     -0.91224100      1.19992900
H          -4.79358500      0.82335900      0.87916400
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Table S4. Cartesian coordinates of the optimized *trans exo* conformation of compound **3**.
Energy = –845.041570 Hartree

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C               1.41579700      0.27369500     -0.34233300
C               2.34115700      1.41260400      0.13986200
C               1.42850900      2.62427200      0.23690100
C               0.08728200      2.05237800      0.66740500
H               1.44796200      0.15649600     -1.42602900
H               2.72767700      1.18357100      1.13569100
H               3.18029300      1.58793900     -0.53083100
H               1.79747500      3.40767000      0.89901300
H               0.02076300      2.01829900      1.76079100
H              -0.72885900      2.66249900      0.28110800
C              -0.99875400     -0.06667100     -0.16513500
C               1.81071400     -1.05291100      0.30296300
O              -0.83110000     -1.15931800     -0.75822300
O               1.60375500     -1.33738100      1.45457300
O               2.48932200     -1.82100400     -0.56110900
C               2.93268000     -3.09179300     -0.04892400
H               3.58777600     -2.94866100      0.80996000
H               2.07396100     -3.69294100      0.24725500
H               3.46787700     -3.56390800     -0.86839500
N               0.08750000      0.71208800      0.08441200
C              -2.31338200      0.37538700      0.26048900
C              -3.40750400     -0.39685700      0.00910100
H              -2.44438500      1.30206900      0.79619800
O              -3.33060700     -1.56015600     -0.62662800
H              -2.35461800     -1.69321100     -0.83020200
C              -4.79576800     -0.02705400      0.41595800
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H              -5.20746000     -0.80152900      1.06798100
H              -4.82056900      0.92972000      0.93504800
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