# Supporting Information Appendix

## Crystal-Structures of Proline Derived Enamines

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## I. General Experimental

### Synthesis of 1-(4,4,4-Trifluoro-3-oxo-1-buteny)-*(S)*-Proline Derivates 3a-g

To a solution of amino acids **1a-g** (1 mmol) in 1 N NaOH (1 mL) was added ketone **2** (168.177 mg, 1 mmol) and the mixture was stirred for 1-3 h at room temperature until the solution became homogeneous. The mixture was then acidified using 6 N aq HCl to pH 3.0 and extracted with $Et_2O$ (3 x 1 mL). The ethereal layer was dried ($MgSO_4$) and filtered. Hexane (0.5 mL) was added and the solvent removed by evaporation. The solids are crystallized from $Et_2O$.

### Synthesis of 1-(5-Methyl-3-oxo-1-cyclohexen-1-yl)-*(S)*-Proline and 1-(4,4-Dimethyl-3-oxo-1-cyclohexen-1-yl)-*(S)*-Proline 5a-b

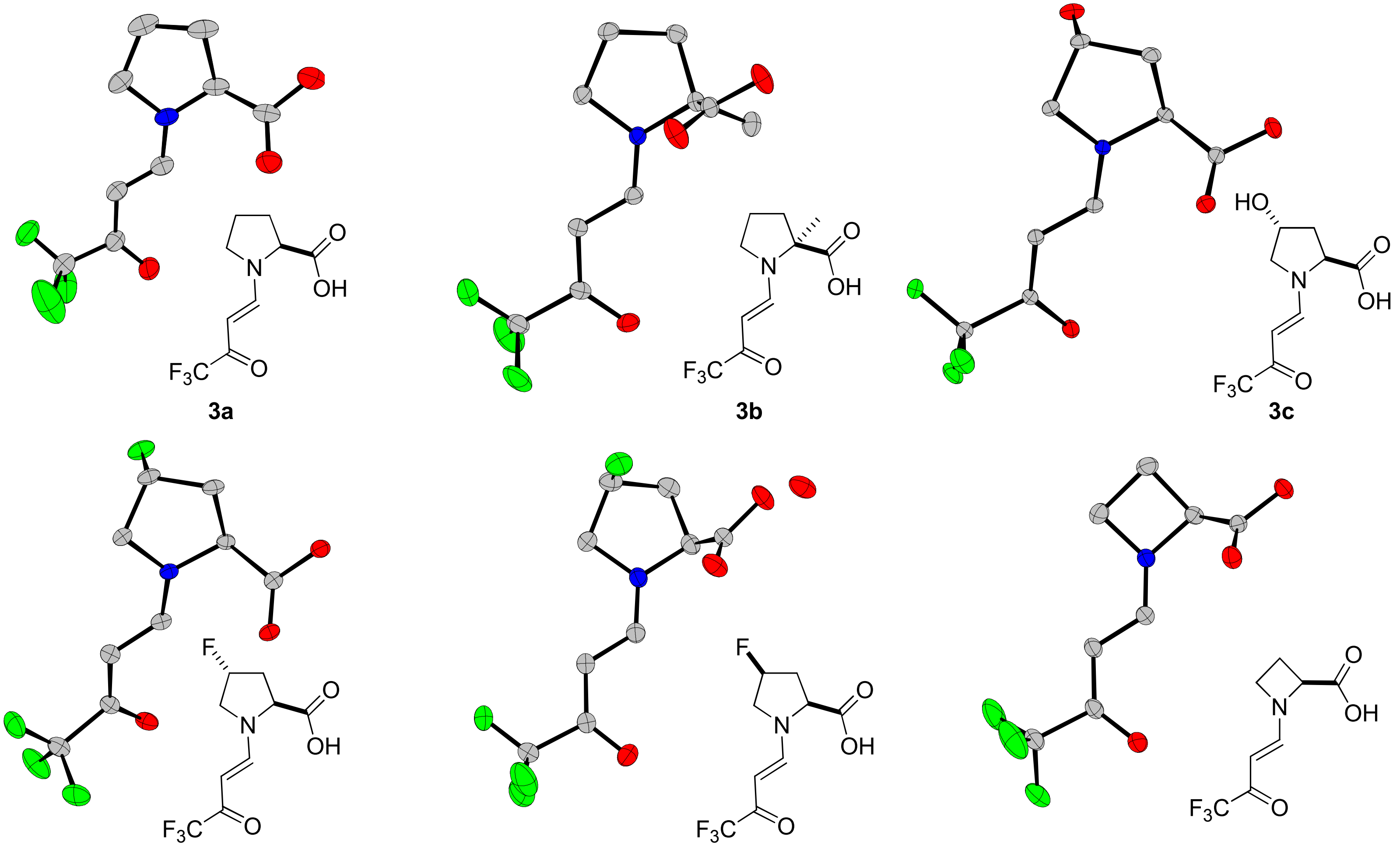
To a solution of (*S*)-proline (5 mmol) in methanol (5 mL) was added diketone **4a** or **4b** (5 mmol) and the mixture was stirred for 5 h at room temperature. The solids are crystallized from methanol.

## II. X-Ray Crystallography

**General Procedure.** Crystal were mounted on a MiTeGen loop using Perfluoropolyether PFO-XR75 and frozen immediately in a cold nitrogen gas stream at 100 K.

Data were collected on a Bruker-AXS Smart APEX-II (Bruker AXS Enraf-Nonius KappaCCD for **3b**, **3f** and **3g**) with Mo-Kα radiation (λ=0.71073 Å) utilizing both Φ and Ω scans. The data were scaled with SADABS.

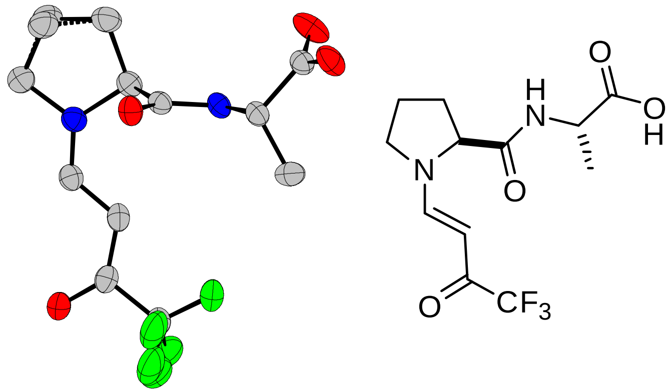
Collection and refinement data are given in SI Table 1. ORTEP´s are shown in SI Fig. 18. Data for the hydrogen bonds in the molecules are listed in SI Table 2.

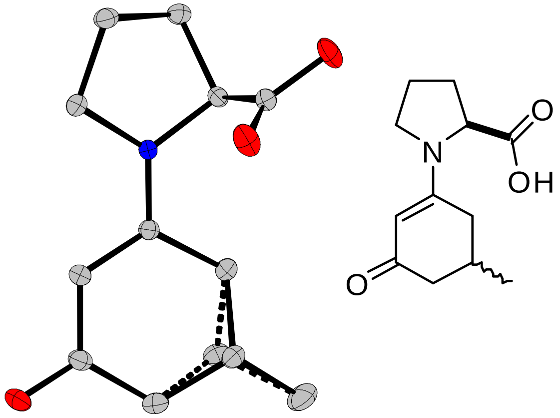


**3a** **3b** **3c**

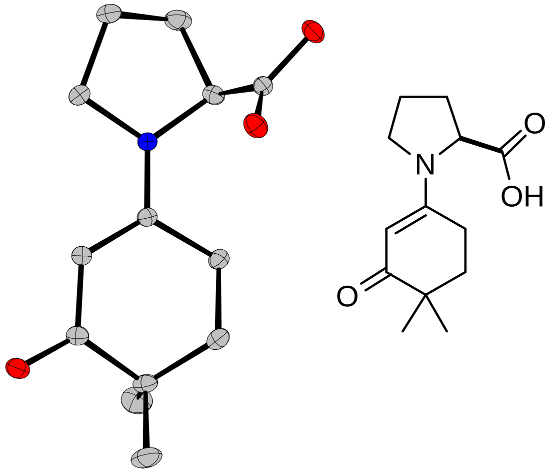
**3d** **3e** **3f**

**Figure 18.** X-Ray crystal structures of enamines **3a-g** and **5a-b**.





**5a**



**5b**

**Figure 18 (cont).** X-Ray crystal structures of enamines **3a-g** and **5a-b**.

**Table 1.** Collection and refinement data **3a-f**.

| | **3a** | **3b** | **3c** | **3d** | **3e** | **3f** |
|---|---|---|---|---|---|---|
| Empirical formula | $C_9H_{10}F_3NO_3$ | $C_{10}H_{12}F_3NO_3$ | $C_9H_{10}F_3NO_4$ | $C_9H_9F_4NO_3$ | $C_9H_{11}F_4NO_4$ | $C_8H_8F_3NO_3$ |
| $Mr$/g · mol$^{-1}$ | 237.18 | 251.21 | 253.18 | 255.17 | 273.19 | 223.15 |
| Temperature/K | | | 100 | | | |
| Wavelength/ Å | | | 0.7173 | | | |
| Crystal description | needle | block | needle | needle | needle | plate |
| Colour | colorless | colorless | colorless | colorless | colorless | colorless |
| Crystal system | monoclinic | tetragonal | orthorhombic | orthorhombic | orthorhombic | monoclinic |
| Space group | $C2$ | $P4_3$ | $P2_12_12_1$ | $P2_12_12_1$ | $P2_12_12_1$ | $P2_1/c$ |
| Unit cell dimension | | | | | | |
| $a$/Å | 29.760(9) | 7.75320(10) | 4.6943(5) | 5.0081(9) | 4.9549(9) | 13.9430(9) |
| $b$/Å | 5.0297(15) | 7.75320(10) | 12.2402(12) | 9.2071(17) | 8.8283(16) | 6.8267(5) |
| $c$/Å | 24.504(8) | 19.5272(2) | 18.8040(19) | 23.483(4) | 26.186(5) | 10.2624(7) |
| $\alpha$/° | 90 | 90 | 90 | 90 | 90 | 90 |
| $\beta$/° | 122.921(9) | 90 | 90 | 90 | 90 | 109.032(2) |
| $\gamma$/° | 90 | 90 | 90 | 90 | 90 | 90 |
| $V$/Å$^3$ | 3078.8(16) | 1173.82(2) | 1080.46(19) | 1082.8(3) | 1145.45 | 923.477 |
| Z | 12 | 4 | 4 | 4 | 4 | 4 |
| $D_{calc}$/g · cm$^3$ | 1.535 | 1.421 | 1.556 | 1.565 | 1.584 | 1.605 |
| Absorption coefficient/mm$^{-1}$ | 0.149 | 0.134 | 0.153 | 0.160 | 0.163 | 0.160 |
| $F$(000) | 1464 | 520 | 520 | 520 | 520 | 456 |
| Crystal size/mm$^3$ | 0.08 x 0.02 x 0.02 | 0.31 x 0.30 x 0.25 | 0.11 x 0.04 x 0.02 | 0.09 x 0.02 x 0.02 | 0.06 x 0.03 x 0.02 | 0.36 x 0.23 x 0.07 |

| | | | | | | |
|---|---|---|---|---|---|---|
| θ range for data collection/° | 0.99-27.68 | 3.36-37.88 | 1.99-33.24 | 1.73-30.50 | 1.56-33.28 | 6.17-38.57 |
| Index ranges | $-38 \le h \le 38$ | $-13 \le h \le 13$ | $-7 \le h \le 7$ | $-7 \le h \le 7$ | $-7 \le h \le 7$ | $-24 \le h \le 24$ |
| | $-6 \le k \le 6$ | $-13 \le k \le 13$ | $-18 \le k \le 18$ | $-12 \le k \le 13$ | $-13 \le k \le 13$ | $-11 \le k \le 11$ |
| | $-31 \le l \le 31$ | $-33 \le l \le 33$ | $-28 \le l \le 28$ | $-33 \le l \le 33$ | $-40 \le l \le 40$ | $-18 \le l \le 18$ |
| Reflections collected | 34216 | 125576 | 36090 | 29945 | 37479 | 19309 |
| Unique refelctions | 7098 | 6298 | 4154 | 3289 | 4411 | 5181 |
| $R_{int}$ | 0.1461 | 0.0404 | 0.0282 | 0.0784 | 0.1052 | 0.0448 |
| Reflections with $I>2\sigma(I)$ | 4234 | 5836 | 3936 | 2738 | 3003 | 3603 |
| Completeness to θ/% | 99.7 | 99.8 | 100 | 99.9 | 99.4 | 99.5 |
| Absorbtions correction | | | Gaussian | | | |
| Max/min transmission | 0.99894/0.99592 | 1.00/0.99 | 1.00/0.99 | 1.00/0.99 | 0.99894/0.99592 | 0.99894/0.99592 |
| Refinement method | | | Full-matrix least- | squares on $F^2$ | | |
| Data/restrains/parameters | 7098/37/464 | 6298/1/156 | 4154/0/156 | 3289/0/155 | 4411/3/170 | 5181/0/137 |
| Goodness of fit on $F^2$ | 1.048 | 1.101 | 0.886 | 1.099 | 1.020 | 0.998 |
| $F^2$ *to* $R_1$ $[I > 2\sigma(I)]$ | 0.0644 | 0.0477 | 0.0279 | 0.0454 | 0.0505 | 0.0642 |
| $wR_2$ $[I > 2\sigma(I)]$ | 0.1588 | 0.1244 | 0.0904 | 0.1287 | 0.1304 | 0.1688 |
| Absolute structutre parameter | 0.3(12) | 0.1(4) | 0.3(3) | 0.1(8) | -0.2(8) | |
| Largest diff. peak and hole/ $e \cdot A^{-3}$ | 0.770 and -0.605 | 0.531 and -0.624 | 0.420 and -0.223 | 0.493 and -0.331 | 0.502 and -0.312 | 0.623 and -0.621 |

**Table 1 (cont).** Collection and refinement data **3a-g** and **5a-b**.

| | | **3g** | **5a** | **5b** |
|---|---|---|---|---|
| Empirical formula | | $C_{12}H_{15}F_3N_2O_4$ | $C_{12}H_{17}NO_3$ | $C_{13}H_{19}NO_3$ |
| $Mr$/g · mol$^{-1}$ | | 308.25 | 223.27 | 237.29 |
| Temperature/K | | | 100 | |
| Wavelength/ Å | | | 0.71073 | |
| Crystal description | | plate | block | isometric |
| Colour | | colorless | colorless | colorless |
| Crystal system | | hexagonal | orthorhombic | orthorhombic |
| Space group | | $P6_5$ | $P2_12_12_1$ | $P2_12_12_1$ |
| Unit cell dimension | | | | |
| | $a$/Å | 9.35140(10) | 5.0422(6) | 10.1374(11) |
| | $b$/Å | 9.35140(10) | 12.3512(15) | 10.9893(12) |
| | $c$/Å | 27.8697(3) | 18.194(2) | 11.2612(12) |
| | α/° | 90 | 90 | 90 |
| | β/° | 90 | 90 | 90 |
| | γ/° | 120 | 90 | 90 |
| $V$/Å$^3$ | | 2110.65(4) | 1133.0(2) | 1254.5(2) |
| Z | | 6 | 4 | 4 |
| $D_{calc}$/g · cm$^3$ | | 1.455 | 1.309 | 1.256 |
| Absorption coefficient/mm$^{-1}$ | | 0.134 | 0.094 | 0.089 |
| $F$(000) | | 960 | 480 | 512 |
| Crystal size/mm$^3$ | | 0.150 x 0.121x 0.052 | 0.04 x 0.02 x 0.02 | 0.04 x 0.02 x 0.02 |

| | | | |
|---|---|---|---|
| θ range for data collection/° | 2.91-29.65 | 1.99-34.96 | 3.56-31.12 |
| Index ranges | $-12 \leq h \leq 12$ | $-8 \leq h \leq 8$ | $-26 \leq h \leq 26$ |
| | $-12 \leq k \leq 12$ | $-19 \leq k \leq 19$ | $-17 \leq k \leq 17$ |
| | $-38 \leq l \leq 38$ | $-29 \leq l \leq 28$ | $-27 \leq l \leq 27$ |
| Reflections collected | 43788 | 41486 | 113076 |
| Unique refelctions | 3941 | 4960 | 6494 |
| $R_{int}$ | 0.0550 | 0.0338 | 0.0678 |
| Reflections with $I>2\sigma(I)$ | 3291 | 4651 | 4531 |
| Completeness to θ/% | 99.8 | 100 | 96.6 |
| Absorbtions correction | | Gaussian | |
| Max/min transmission | 0.99/0.98 | 0.99894/0.99592 | 0.99894/0.99592 |
| Refinement method | | Full-matrix least-squares on $F^2$ | |
| Data/restrains/parameters | 3941/1/203 | 4960/0/161 | 5982/0/157 |
| Goodness of fit on $F^2$ | 1.079 | 1.143 | 0.966 |
| $F^2$ *to* $R_1$ $[I > 2\sigma(I)]$ | 0.0497 | 0.0369 | 0.0298 |
| $wR_2$ $[I > 2\sigma(I)]$ | 0.1200 | 0.1005 | 0.0971 |
| Absolute structutre parameter | 0.0(8) | -0.6(7) | -0.4(4) |
| Largest diff. peak and hole/ e · $A^{-3}$ | 0.250 and -0.264 | 0.428 and -0.261 | 0.535 and -0.510 |

**Table 2.** Collection and refinement data **3a-g** and **5a-b**. Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and Angle DHA > 110 deg.

| Compound | D-H…A | d(D-H)/Å | d(H…A) /Å | d(D…A) /Å | Angle DHA/° | symm |
|---|---|---|---|---|---|---|
| **3a** | O1A-H1A…O3C | 0.820 | 1.829 | 2.631 | 165.24 | [ x, y+1, z ] |
| | O1C-H1C…O3A | 0.709 | 1.882 | 2.552 | 157.78 | [ x, y-1, z ] |
| | O1B-H1B…O3B | 0.950 | 1.640 | 2.584 | 172.20 | [ -x+1/2, y-1/2, -z ] |
| **3b** | O1-H1...O3 | 0.820 | 1.788 | 2.598 | 169.05 | [ y, -x+2, z+1/4 ] |
| **3c** | O1-H1...O4 | 0.820 | 1.995 | 2.810 | 172.43 | [ -x+3/2, -y+2, z-1/2 ] |
| | O2-H2...O4 | 0.820 | 1.806 | 2.609 | 165.86 | [ x-1/2, -y+5/2, -z ] |
| **3d** | O1-H1...O3 | 0.820 | 1.833 | 2.605 | 156.48 | [ x-1/2, -y+3/2, -z-2 ] |
| **3e** | O2-H2A...O1 | 0.820 | 1.779 | 2.580 | 164.90 | |
| | O1-H1A...O3 | 0.817 | 1.946 | 2.751 | 168.25 | [ x+1/2, -y+3/2, -z+2 ] |
| | O1-H1B...O4 | 0.866 | 1.913 | 2.746 | 160.93 | [ x+3/2, -y+3/2, -z+2 ] |
| **3f** | O2-H2A...O1 | 0.820 | 1.775 | 2.566 | 161.56 | [ -x+1, -y, -z+1 ] |
| **3g** | N1-H1...O3 | 0.860 | 2.019 | 2.848 | 161.50 | [ y-1, -x+y, z+1/6 ] |
| | O1-H1A…O4 | 0.820 | 1.828 | 2.641 | 170.48 | [ y, -x+y, z+1/6 ] |
| **5a** | O1-H1...O3 | 0.840 | 1.710 | 2.528 | 164.21 | [ -x+5/2, -y+2, z+1/2 ] |
| **5b** | O1-H1...O3 | 0.820 | 1.743 | 2.526 | 159.11 | [ -x+1/2, -y-3, z+1/2 ] |

## III. Cambridge Structural Database (CSD) research for enamine bond lengths

The enamine bond lengths observed in the compounds of this study can be compared to the average values found in the Cambridge Structural Database for a substructure consisting of a saturated five-membered N-heterocycle bound to an acyclic olefin. There are 30 refcodes representing 36 entries (Table 3) in the latest version of the CSD which contain the search motif (**Search 1**). With the exception of two structures (27,28) the carbon-carbon double bond is part of a larger conjugated electron system in all other hits. The C=C bond averages 1.38(3) Å and the C—N bond averages 1.336(16) Å. In addition, the nitrogen pyramidalization derived from this search yields values in the range 0.0 to 0.1 (average 0.03(2) Å). An alternative search (**Search 2**) for conjugated keto enamines yielded 56 hits, 62 observations (Table 4). The search criteria required a planar π-system. Cyclic links for the diene were not excluded. Average bond lengths for C-N, C=C, C-C and C=O are 1.337(11), 1.38(3), 1.44(2) and 1.225(16) Å. Average pyramidality of N is 0.06(4).

For comparison a classical amine, consisting of the same heterocycle with an N-alkyl group results in a C—N averaged bond length of 1.464(18) Å and a pyramidalization of 0.43(6) Å.

**Figure 19.** Search motif for **search 1** (left) and **search 2** (right)

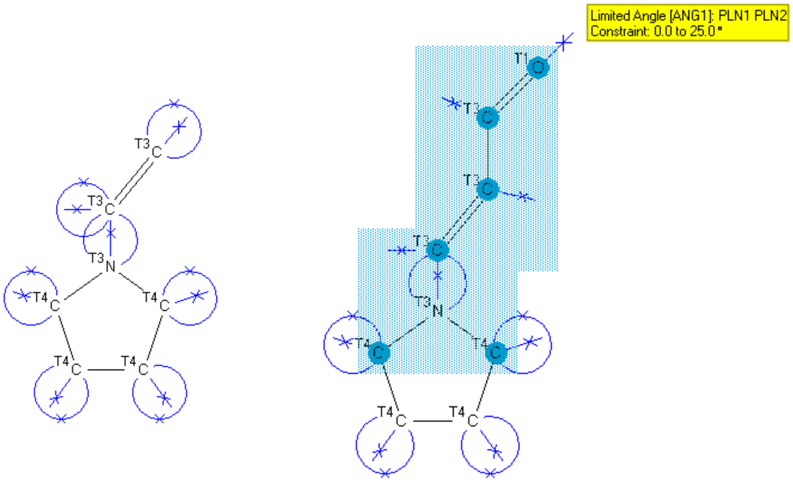


**Table 3.** List of the 30 refcodes for **search 1**

| | |
|---|---|
| ACUPET | AKIQAM |
| DPYTMC10 | FAZNOJ |
| FUDYUY | GAWPAV |
| HIHCIL | HOFBAG |
| JALCUU | KAXLOK |
| KOTNEM | NIGQOK |
| NOCVEH | NURXIH |
| ODOTIK | QAGLIU |
| QECKUE | QECLAL |
| QUSKEU | QUSKIY |
| ROGFUP | SAFPEU |
| SIPBIC | SIPBUO |
| TITKUC | TONXOK |
| UHASEB | UHASIF |
| UHASUR | WAPHEB |

**Table 4.** List of the 56 refcodes for **search 2**

| | |
|---|---|
| ACULOZ | JALCUU |
| AHIMIN | LUSWOL |
| AHIMOT | NEPTUY |
| AJIXEW | OBICIL |
| ATOYOX | OCIPEV |
| ATOYUD | OCIPIZ |
| ATOZAK | PAQWAG |
| BIDSEM | PEBWAU |
| BOSMAX | PUNXEB |
| BOSMAX10 | PYAZPC |
| BPYRRM | PYRBZR |
| CETZAC | QAKXOQ |
| DOYHUU | QAKXUW |
| DOYJAC | QAKYAD |
| DPYBTX | QORQEU |
| DUCKUH | QORQIY |
| FAZNOJ | RUGFOO |
| FEYMOM | SAFPEU |
| FISJAT | SIPBUO |
| FIVTUZ | TADTOI |
| FUDYUY | UHASEB |
| GAHMEH | UHASIF |
| GAMMAI | UHASUR |
| GAWPAV | UNOFEI |
| GEFVET | WIRWEZ |
| GEFVIX | XEGWIP |
| ICOWUS | YEYTUR |
| IJULEE | YEYVAZ |

## IV. Intramolecular carbon oxygen distances and angles

The intramolecular carbon oxygen distance between the carbonyl oxygen atom of the carboxy group and the α’ carbon atom of the double bond varies between 2.829 and 3.394 Å (Table 5). In all cases, the closest distance is between the double bond and the carbonyl oxygen not the hydroxyl oxygen. The average distance for the nine *anti* conformers is 3.02(15) Å. Notably, there is a strong correlation between the sum of two dihedral angles and the carbon-oxygen distance (Fig. 20). The first one of these dihedral angles is defined by the four atoms N1-C2-C=O, the second dihedral angle is defined by exo-cyclic $sp^2$-carbon atom, N1, C2 and the carbon atom of the carboxy group.

While the intramolecular C···O distances are up to0.4 Å shorter than the sum of the van der Waals radii (1.70 + 1.52 = 3.22 Å), there is a rather acute angle for the approaching oxygen towards the carbon atom of the double bond. This angle ε has been defined as the angle between the line connecting Cα' and O and the normal of the plane defined by N Cα' and Cα'. At the same time there is no pyramidalization of Cα' (measured for **5a** and **5b**, as the only examples with three non-hydrogen substituents). The angle ε is related to the angle of attack as introduced by Dunitz and Bürgi in 1973 (29) by adding 90°.

**Table 5:** Distance between the carbonyl oxygen and the α' carbon atom of the double bond together with the dihedral angles and the angle ε.

| Compound | C=O···Cα'=C | $\tau_1$ = O=C-C-N | $\tau_2$ = C-Cα-N-$Csp^2$ | $\tau_1 + \tau_2$ | ε |
|---|---|---|---|---|---|
| **3a** | 3.184 | -22.12 | -64.61 | -86.73 | 43.4 |
| **3a** | 2.890 | 10.73 | -55.11 | -44.38 | 49.2 |
| **3a** | 2.829 | 11.32 | -41.4 | -30.08 | 56.5 |
| **3c** | 2.972 | -12.39 | -52.42 | -64.81 | 45.9 |
| **3d** | 2.866 | 13.3 | -55.13 | -41.83 | 44.8 |
| **3e** | 3.127 | 15.13 | -75.81 | -60.68 | 45.4 |
| **3g** | 3.394 | -43.93 | -63.38 | -107.31 | 41.7 |
| **5a** | 3.188 | -0.52 | -78.95 | -79.47 | 39.2 |
| **5b** | 3.123 | 14.75 | -78.46 | -63.71 | 49.4 |

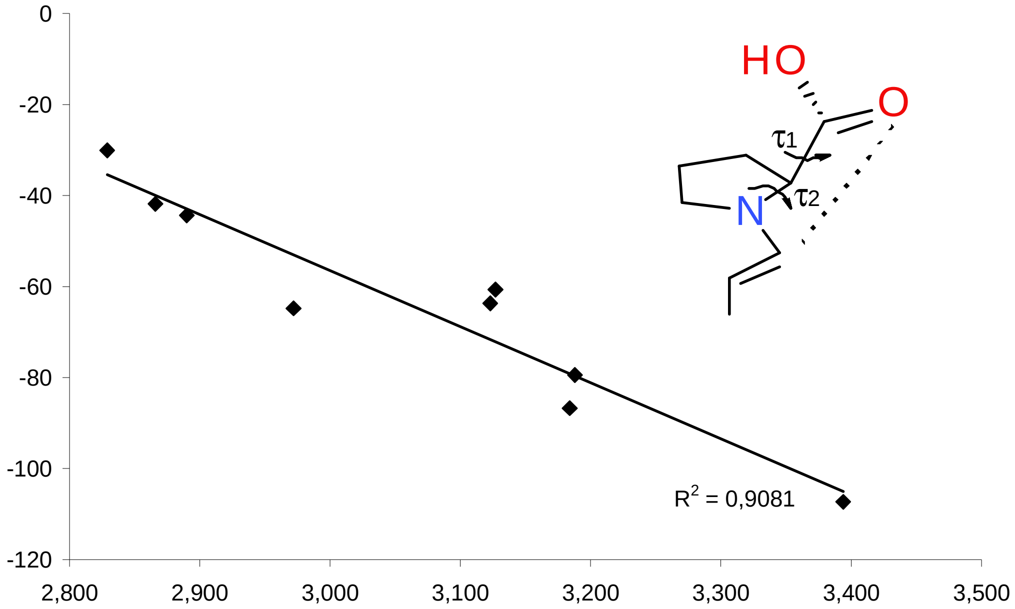


**Figure 20:** Diagram of the correlation between the two dihedral angles ($\tau_1$ and $\tau_2$) and the carbon-oxygen distance. The x-axis represents the distance in Å between O and C, the y-axis is the sum of $\tau_1$ and $\tau_2$.

## V. NMR-Measurement

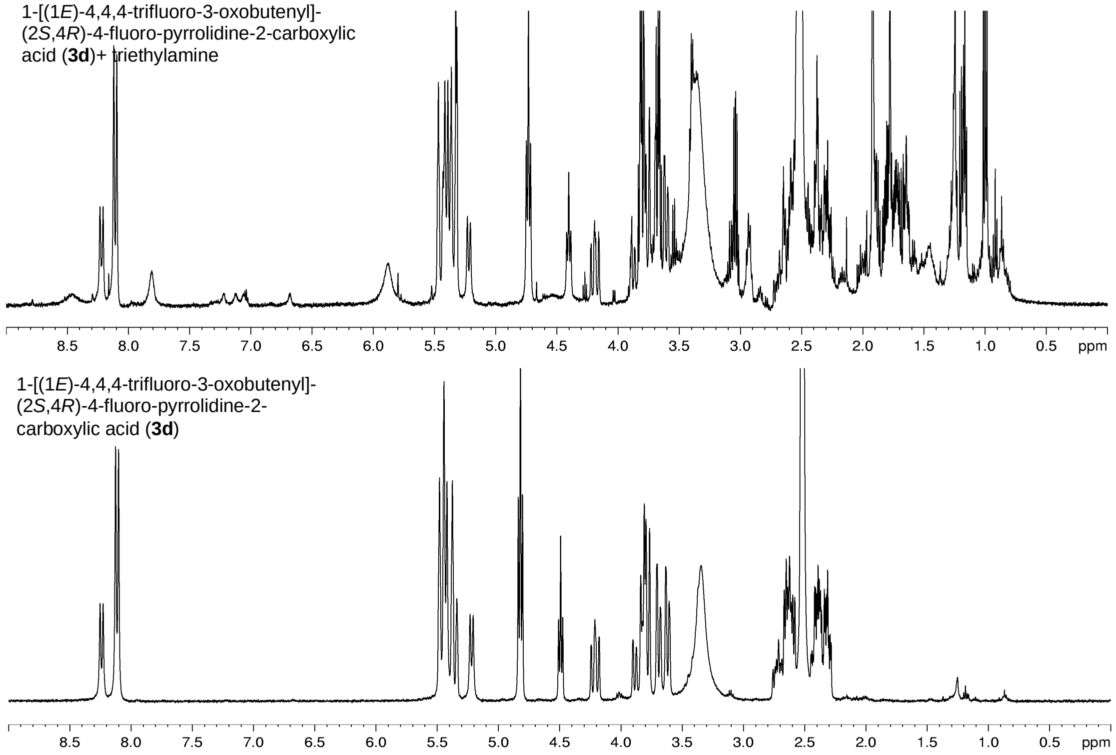


**Figure 21:** $^1$H-NMR-Measurement (in DMSO) of 1-[(1*E*)-4,4,4-trifluoro-3-oxobutenyl]-(2*S*,4*R*)-4-fluoro-pyrrolidine-2-carboxylic acid (**3d**) with or without triethylamine.

## VI. References

28. Fuji K, Node M, Nagasawa H, Naniwa Y, Taga T, Machida K, Snatzke G (1989) Direct asymmetric synthesis of quaternary carbon centers by the addition-elimination process: nitroolefination of α-substituted δ-lactones. *J Am Chem Soc* 111: 7921-7925.

29. Begum NS, Venkatesan K (1992) Studies on nonlinear optical materials:  structure of diphenylmethyl (Z)-1-(1-methylthio-2-nitrovinyl)tetrahydropyrrole-2-carboxylate. *Acta Cryst C* C48: 902-905.

30. Bürgi HB, Dunitz JD, Shefter E (1973) Geometrical reaction coordinates. II. Nucleophilic addition to a carbonyl group. *J Am Chem Soc* 95: 5065-5067.