Supporting Information

for

# RDC-based Determination of the Relative Configuration of the Fungicidal Cyclopentenone 4,6-Diacetylhygrophorone A[12]

*Volker Schmidts,[†] Maic Fredersdorf,[†] Tilo Lübken,[‡] Andrea Porzel,[‡] Norbert Arnold,[‡] Ludger Wessjohann,*[‡] and Christina M. Thiele*[†]*

[†] Clemens Schöpf Institute for Organic Chemistry and Biochemistry, Technische Universität Darmstadt, Petersenstr. 22, D-64287 Darmstadt, Germany.

[‡] Department of Bioorganic Chemistry, Leibniz Institute of Plant Biochemistry, Weinberg 3, D-06120 Halle/Saale, Germany.

## *Table of Contents*

## *NMR Spectra of 4,6-Diacetylhygrophorone A[12] (3)*

Spectra were acquired on a Bruker Avance II 700MHz US spectrometer equipped with a TXI 700S4 cryo probe. Relevant delays and durations are given, were appropriate. Unless otherwise noted experiments were performed at 300K.

### Assignment of Chemical Shifts

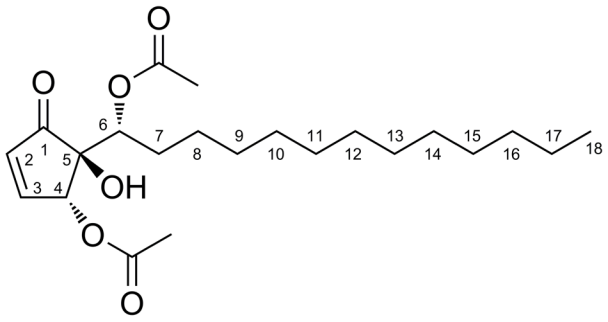
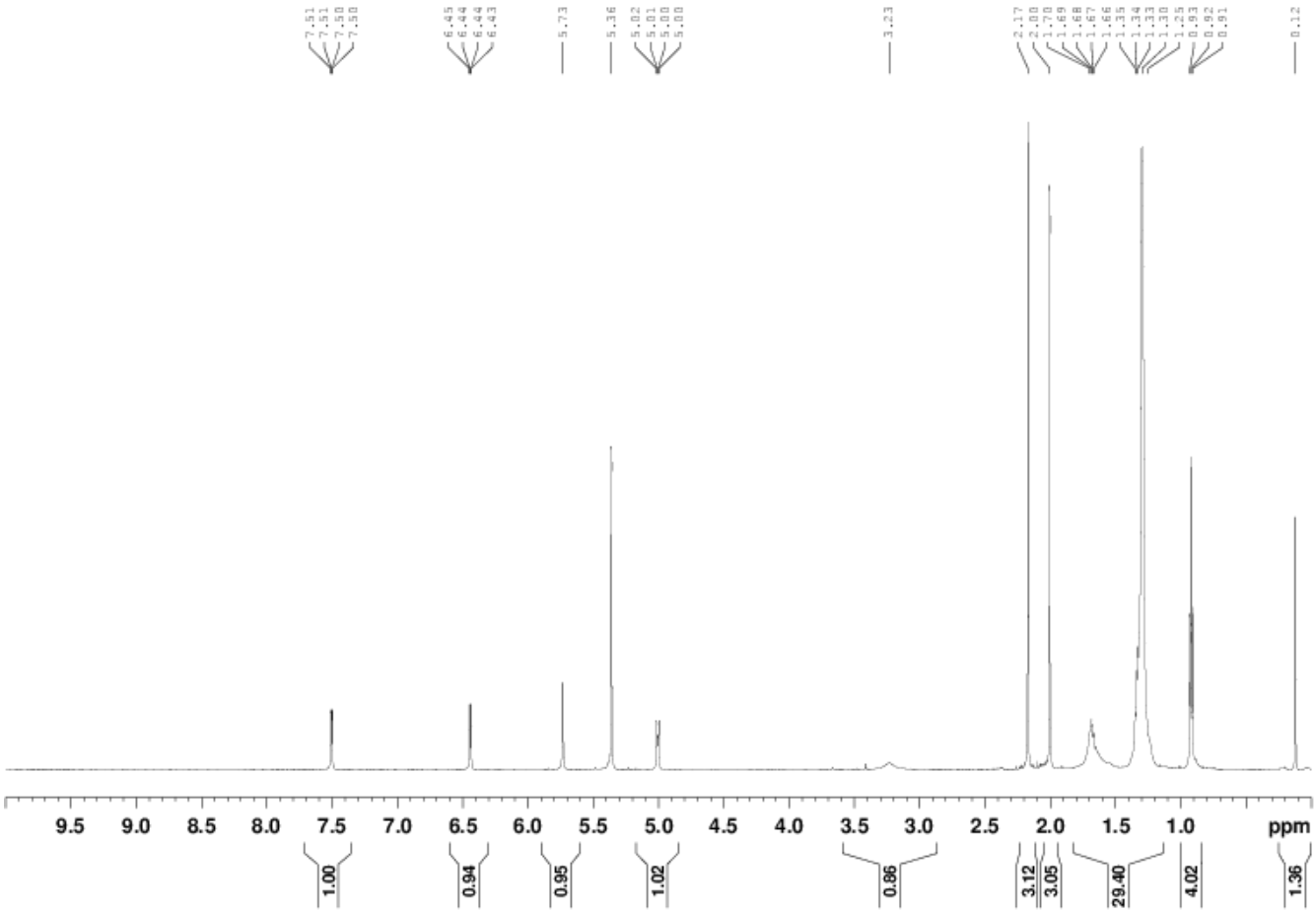


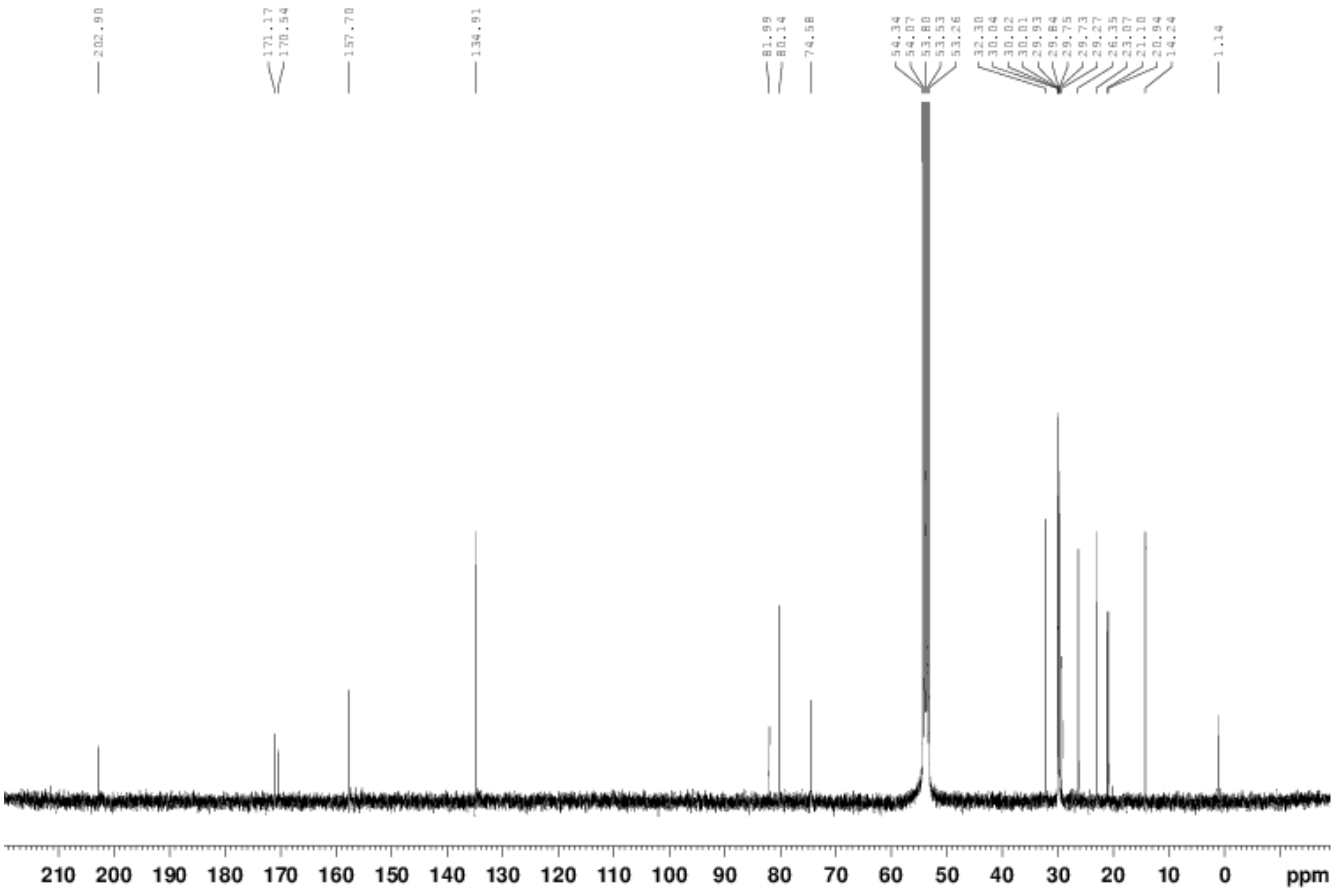

Table SI 1: Assignment of $^{1}H$ and $^{13}C$ chemical shifts of 4,6-diacetylhygrophorone A[12] (**3**) in isotropic solution ($CD_2Cl_2$). Numbering scheme see above.

| Position | $^{1}H$ (ppm) | $^{13}C$ (ppm) |
|---|---|---|
| 1 | – | 202.9 |
| 2 | 6.4 (dd) | 134.9 |
| 3 | 7.5 (dd) | 157.7 |
| 4 | 5.7 (dd) | 80.2 |
| 4-OAc | – | 171.2 |
| 4-OAc | 2.1 (s) | 21.1 |
| 5 | – | 80.2 |
| 6 | 5.0 (dd) | 74.6 |
| 6-OAc | – | 170.5 |
| 6-OAc | 2.0 | 20.9 |
| 7 | 1.6 (m) | 32.3 |
| 8-17 | 1.1 – 1.3 (m) | 26.0 – 30.0 |
| 18 | 0.9 (t) | 14.2 |

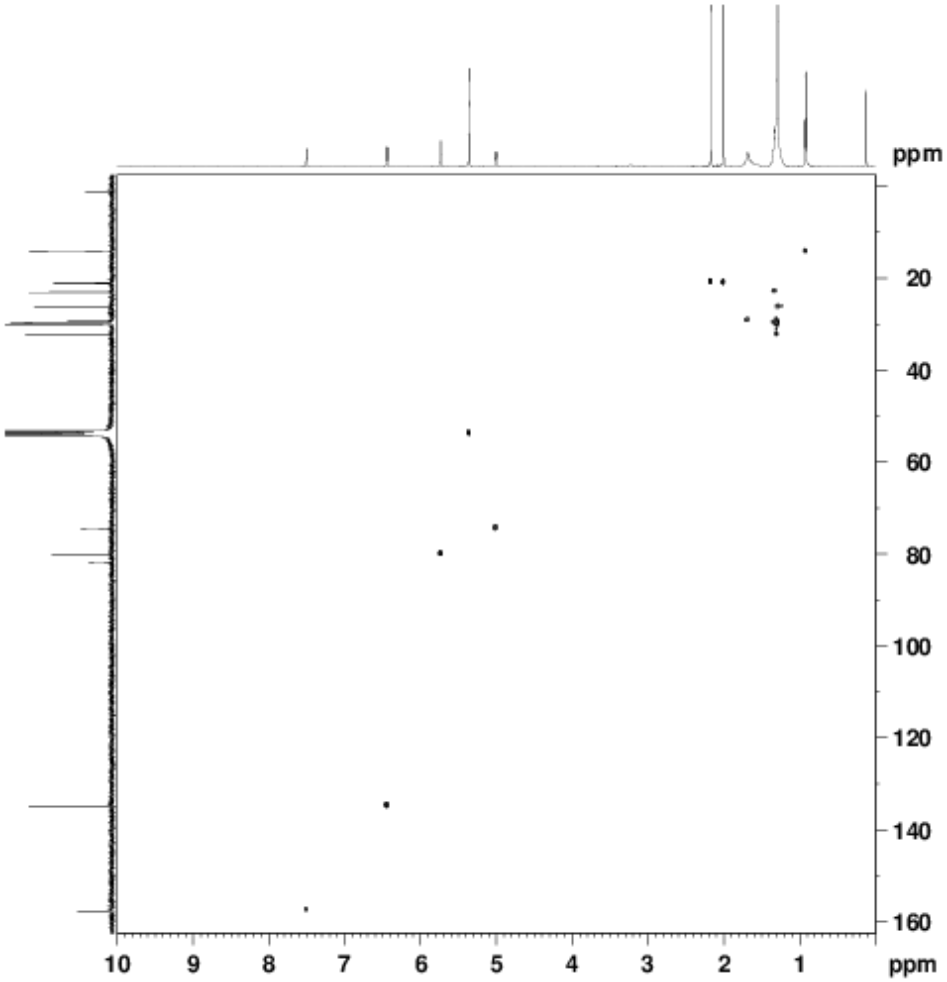
$^{1}$H, 300K, isotropic



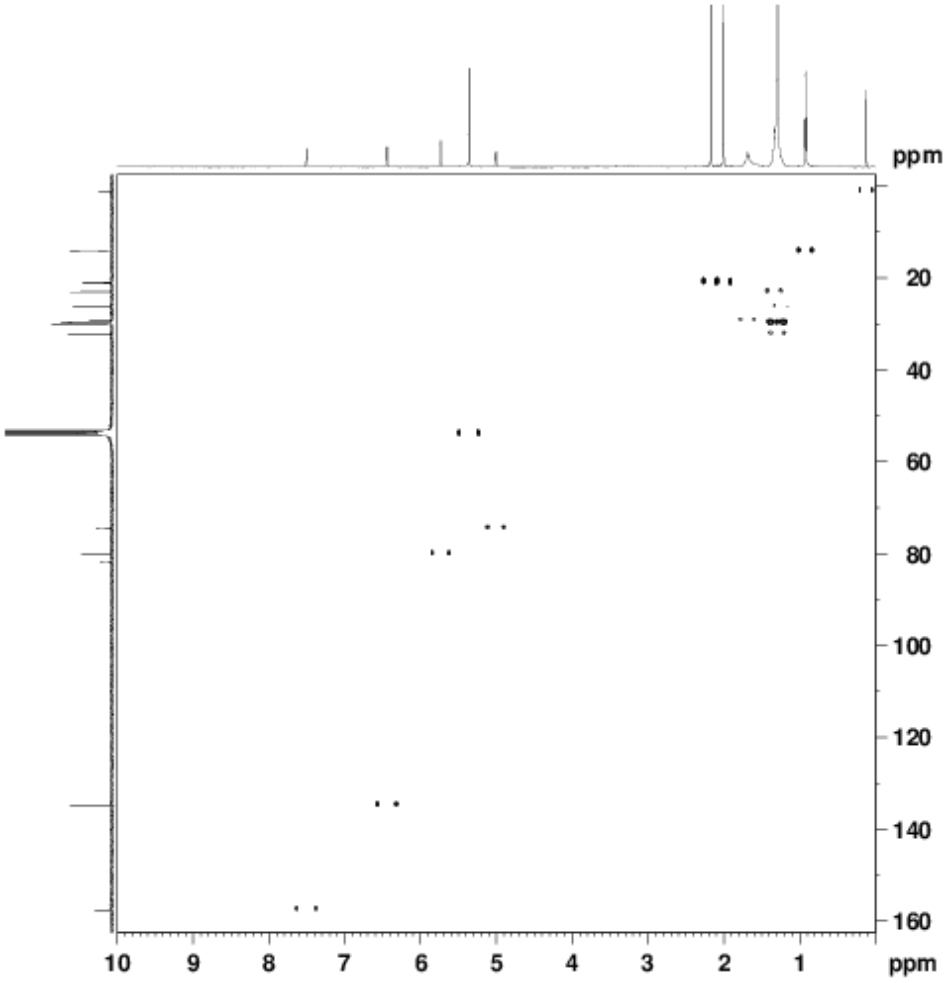
$^{13}C$, 300K, isotropic



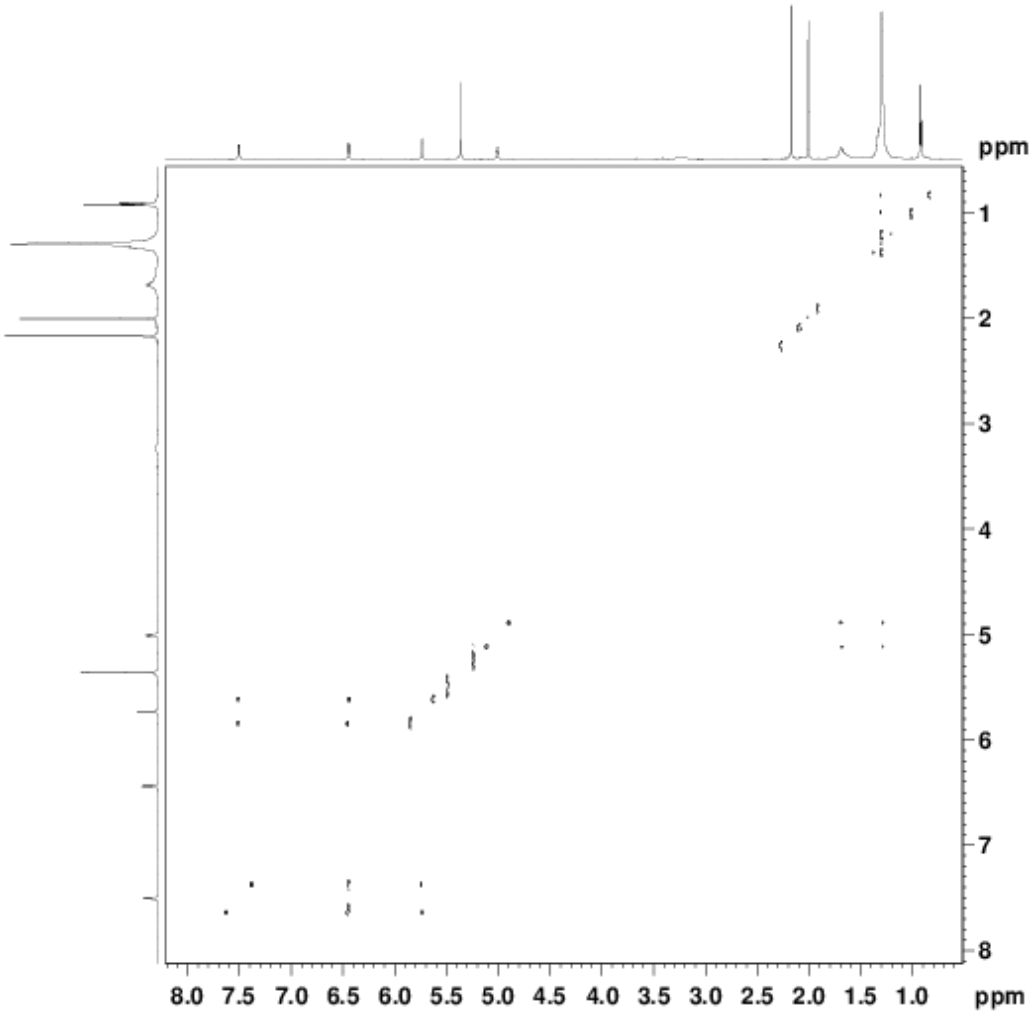
$^{1}H$-$^{13}C$ HSQC, 300K, INEPT delay optimized for 145 Hz, isotropic



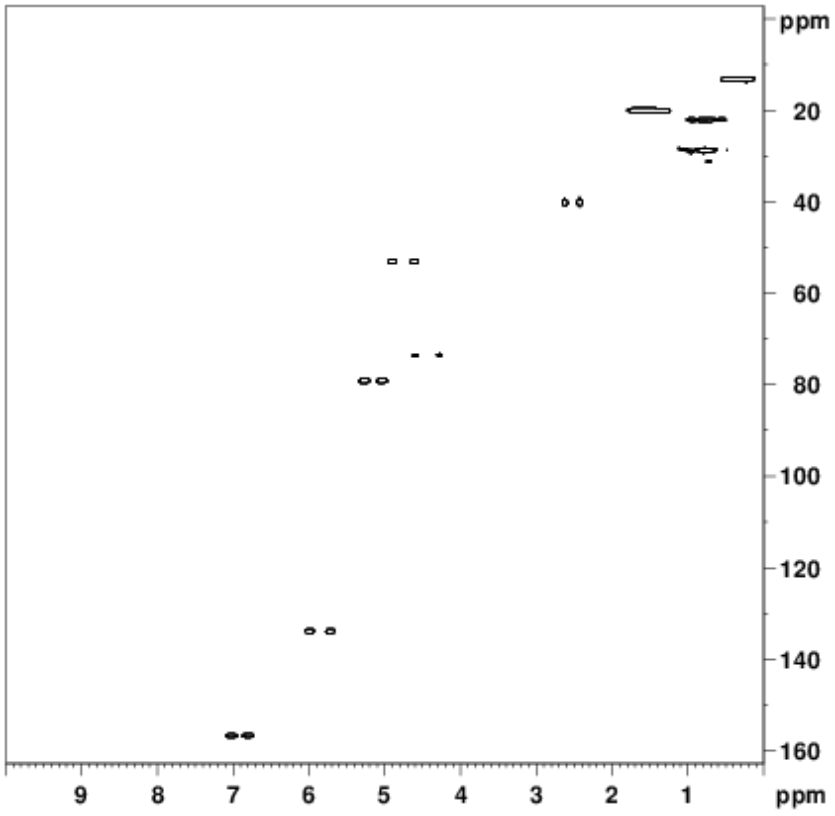
$^{1}H$-$^{13}C$ CLIP-HSQC,[1] 300K, INEPT delay optimized for 145 Hz, isotropic



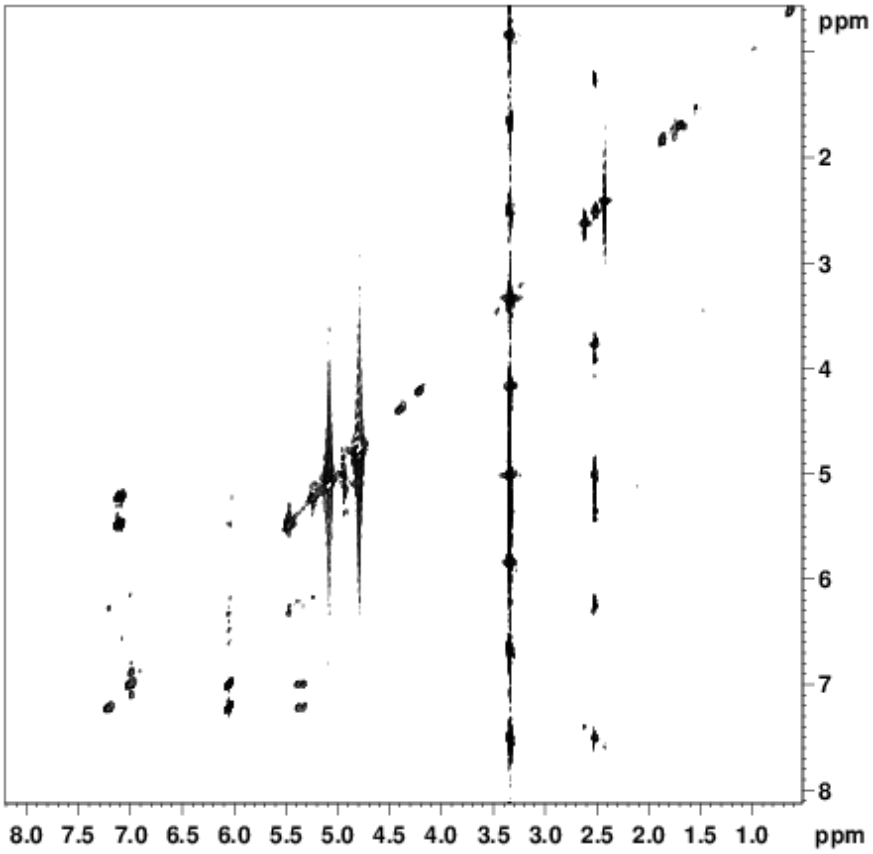
$^{1}H$-$^{13}C$ HETLOC,[2,3] 300K, INEPT delay optimized for 145 Hz, TOCSY mixing 50ms, isotropic



$^{1}H$-$^{13}C$ CLIP-HSQC,[1] 300K, INEPT delay optimized for 145 Hz, anisotropic



$^{1}H$-$^{13}C$ HETLOC,[2,3] 300K, INEPT delay optimized for 145 Hz, TOCSY mixing 50ms, anisotropic



## *Cartesian coordinates of calculated structure models*

Structure calculations were performed on a model system, where the alkyl chain on C5 was truncated after the third carbon atom. Using conventional force field methods (SYBYL, Tripos 7.0) several low energy conformers were found and further optimized by DFT methods (Gaussian 03,[4] B3LYP/6-311+G**). The coordinates of these optimized geometries were then used as structure models in the SVD-based RDC fit with the software hotFCHT.[5,6]

## 4R5R6R

```
34
4r5r6r
  C3          -0.470     -2.478     -1.139
  H3          -0.949     -2.938     -1.995
  C4          -0.713     -1.029     -0.804
  H4          -0.526     -0.351     -1.639
  C5           0.231     -0.739      0.413
  C1           0.789     -2.153      0.774
  C2           0.331     -3.097     -0.266
  H2           0.627     -4.138     -0.280
  O1           1.485     -2.391      1.733
  O4          -2.103     -0.932     -0.443
  C6           1.432      0.174      0.054
  H6           1.988      0.341      0.981
  C7           2.380     -0.368     -1.018
  H7a          2.712     -1.364     -0.711
  H7b          1.837     -0.490     -1.961
  O6           0.963      1.458     -0.437
  Oh          -0.514     -0.228      1.494
  HOh         -0.032      0.507      1.905
  C8           3.605      0.524     -1.237
  H8a          3.316      1.518     -1.583
  H8b          4.180      0.639     -0.313
  H8c          4.267      0.086     -1.987
  C6O          0.662      2.436      0.442
  C6OC         0.242      3.691     -0.265
  H6OCa        0.950      3.945     -1.056
  H6OCb       -0.729      3.506     -0.730
  H6OCc        0.162      4.505      0.453
  O6CO         0.713      2.291      1.646
  C4O         -2.682      0.295     -0.477
  C4OC        -4.062      0.242      0.120
  H4OCa       -4.611     -0.624     -0.251
  H4OCb       -3.967      0.135      1.204
  H4OCc       -4.596      1.162     -0.109
  O4CO        -2.146      1.275     -0.931
```

## 4R5R6S

```
34
4r5r6s
  C3          -1.749      2.243      0.036
  H3          -2.599      2.790      0.427
  C4          -1.525      0.801      0.400
  H4          -1.467      0.650      1.479
  C5          -0.182      0.402     -0.326
  C1           0.156      1.682     -1.158
  C2          -0.824      2.729     -0.796
  H2          -0.777      3.732     -1.202
  O1           1.051      1.774     -1.963
  O4          -2.651      0.055     -0.082
  C6           0.927      0.092      0.716
  H6           0.624     -0.820      1.239
  C7           1.230      1.209      1.717
  H7a          1.662      2.057      1.177
  H7b          0.296      1.560      2.162
  O6           2.198     -0.165      0.051
  Oh          -0.383     -0.669     -1.214
  HOh          0.103     -1.451     -0.902
  C8           2.179      0.764      2.835
  H8a          1.756     -0.070      3.403
  H8b          3.143      0.447      2.432
  H8c          2.361      1.585      3.532
  C6O          2.484     -1.397     -0.404
  C6OC         3.884     -1.464     -0.947
  H6OCa        3.947     -0.830     -1.835
  H6OCb        4.598     -1.079     -0.216
  H6OCc        4.124     -2.492     -1.210
  O6CO         1.698     -2.321     -0.389
  C4O         -2.808     -1.192      0.434
  C4OC        -3.934     -1.917     -0.248
  H4OCa       -4.811     -1.272     -0.336
  H4OCb       -3.616     -2.183     -1.259
  H4OCc       -4.177     -2.820      0.307
  O4CO        -2.117     -1.629      1.322
```

## 4R5S6R (OH5 and H6 antiperiplanar)

```
34
4r5s6r antiperiplanar
  C3           -2.565      0.143     -1.095
  H3           -3.272      0.826     -1.553
  C4           -1.089      0.465     -1.072
  H4           -0.705      0.619     -2.080
  C5           -0.417     -0.834     -0.499
  C1           -1.647     -1.630      0.065
  C2           -2.864     -1.013     -0.503
  H2           -3.843     -1.455     -0.384
  O1           -1.594     -2.585      0.800
  O4           -0.832      1.760     -0.455
  C6            0.686     -0.680      0.573
  H6            0.193     -0.408      1.505
  C7            1.518     -1.944      0.792
  H7a           2.115     -2.155     -0.097
  H7b           0.810     -2.769      0.896
  O6            1.575      0.487      0.379
  Oh           -0.022     -1.630     -1.609
  HOh           0.820     -1.256     -1.927
  C8            2.411     -1.861      2.034
  H8a           1.817     -1.701      2.939
  H8b           3.138     -1.048      1.963
  H8c           2.967     -2.793      2.163
  C6O           2.268      0.673     -0.746
  C6OC          3.171      1.875     -0.650
  H6OCa         2.572      2.774     -0.824
  H6OCb         3.939      1.814     -1.418
  H6OCc         3.618      1.955      0.341
  O6CO          2.169     -0.014     -1.746
  C4O          -1.165      1.995      0.837
  C4OC         -0.882      3.428      1.206
  H4OCa         0.199      3.579      1.252
  H4OCb        -1.316      3.641      2.182
  H4OCc        -1.282      4.109      0.453
  O4CO         -1.605      1.156      1.582
```

## 4R5S6R (OH5 and H6 (+)-synclinal)

```
34
4r5s6r plus synclinal
  C3            1.832      1.759      0.585
  H3            2.858      1.878      0.912
  C4            1.440      0.674     -0.383
  H4            1.795      0.920     -1.385
  C5           -0.117      0.693     -0.411
  C1           -0.434      2.081      0.238
  C2            0.804      2.557      0.894
  H2            0.832      3.449      1.506
  O1           -1.497      2.647      0.183
  O4            1.965     -0.630     -0.035
  C6           -0.751     -0.461      0.418
  H6           -0.450     -1.401     -0.050
  C7           -0.425     -0.487      1.912
  H7a          -0.863      0.397      2.385
  H7b           0.656     -0.415      2.034
  O6           -2.201     -0.365      0.340
  Oh           -0.592      0.698     -1.739
  HOh          -0.951     -0.172     -1.968
  C8           -0.935     -1.754      2.604
  H8a          -0.486     -2.652      2.168
  H8b          -2.020     -1.842      2.523
  H8c          -0.681     -1.738      3.667
  C6O          -2.853     -0.970     -0.669
  C6OC         -4.341     -0.823     -0.519
  H6OCa        -4.660     -1.146      0.473
  H6OCb        -4.844     -1.404     -1.290
  H6OCc        -4.602      0.233     -0.622
  O6CO         -2.296     -1.544     -1.583
  C4O           3.244     -0.900     -0.415
  C4OC          3.613     -2.322     -0.085
  H4OCa         3.388     -2.543      0.960
  H4OCb         4.671     -2.477     -0.284
  H4OCc         3.021     -3.004     -0.701
  O4CO          3.959     -0.089     -0.947
```

## 4R5S6R (OH5 and H6 (–)-synclinal)

```
34
4r5s6r minus synclinal
  C3           -1.399     -1.100     -1.795
  H3           -1.143     -1.423     -2.798
  C4           -0.499     -1.406     -0.632
  H4           -0.606     -2.460     -0.359
  C5           -1.066     -0.576      0.558
  C1           -2.489     -0.191      0.022
  C2           -2.527     -0.487     -1.423
  H2           -3.369     -0.227     -2.051
  O1           -3.362      0.286      0.702
  O4            0.871     -1.195     -1.015
  C6           -0.383      0.771      0.975
  H6           -1.167      1.249      1.569
  C7            0.853      0.707      1.874
  H7a           1.723      0.313      1.356
  H7b           0.598      0.010      2.676
  O6           -0.314      1.646     -0.194
  Oh           -1.246     -1.377      1.711
  HOh          -0.421     -1.865      1.849
  C8            1.192      2.065      2.498
  H8a           0.336      2.475      3.044
  H8b           1.499      2.794      1.746
  H8c           2.018      1.959      3.206
  C6O           0.800      1.968     -0.890
  C6OC          0.437      2.917     -2.008
  H6OCa        -0.319      2.464     -2.653
  H6OCb         1.329      3.154     -2.585
  H6OCc         0.007      3.831     -1.593
  O6CO          1.917      1.576     -0.660
  C4O           1.801     -1.790     -0.230
  C4OC          3.185     -1.585     -0.769
  H4OCa         3.259     -2.005     -1.776
  H4OCb         3.908     -2.063     -0.111
  H4OCc         3.379     -0.513     -0.842
  O4CO          1.509     -2.391      0.781
```

## 4S5R6R

```
34
4s5r6r
  C3            2.248      1.811     -0.001
  H3            2.436      2.855      0.221
  C4            0.881      1.354     -0.434
  H4            0.624      1.732     -1.426
  C5            0.992     -0.193     -0.524
  C1            2.514     -0.454     -0.315
  C2            3.153      0.826      0.037
  H2            4.206      0.915      0.269
  O1            3.034     -1.535     -0.473
  O4           -0.088      1.857      0.506
  C6            0.181     -1.037      0.487
  H6            0.404     -2.080      0.244
  C7            0.465     -0.803      1.971
  H7a           1.545     -0.895      2.123
  H7b           0.191      0.217      2.243
  O6           -1.228     -0.817      0.239
  Oh            0.639     -0.552     -1.853
  HOh           0.789     -1.501     -1.967
  C8           -0.256     -1.809      2.874
  H8a          -1.340     -1.731      2.767
  H8b           0.033     -2.837      2.636
  H8c          -0.010     -1.627      3.923
  C6O          -1.890     -1.703     -0.555
  C6OC         -3.301     -1.240     -0.798
  H6OCa        -3.793     -0.995      0.146
  H6OCb        -3.277     -0.332     -1.406
  H6OCc        -3.854     -2.018     -1.320
  O6CO         -1.397     -2.711     -0.995
  C4O          -1.272      2.324      0.016
  C4OC         -2.177      2.736      1.145
  H4OCa        -2.488      1.844      1.695
  H4OCb        -1.648      3.387      1.843
  H4OCc        -3.053      3.242      0.744
  O4CO         -1.532      2.388     -1.157
```

## *RDC Fits with hotFCHT*

Experimental RDCs are fitted using the SVD-based approach outlined by Losonczi et al.,[7] as implemented in a self-written module of the software hotFCHT.[5,6] Based on a proposed (rigid) geometry, an alignment tensor is calculated, and used to back-calculate the RDCs. Through a user controlled flag an automated normalization of RDCs before SVD can be performed within hotFCHT. Comparison of experimental and back-calculated RDCs give quality factors, showing the goodness-of-fit.[8] Derived parameters describing the magnitude, eigenvalues and orientation of the alignment tensor[9] are also given below.

The weighting factor is determined by normalizing the magnetogyric ratios and distances of each coupling to the respective values of the largest coupling. Each row of the coefficient matrix is multiplied by the weighting factor $w_i$ of the respective coupling before SVD, and then renormalized after the alignment tensor is calculated.

$$w_i = \left| \frac{max\left(\gamma_j\gamma_k / r^3\right)}{\gamma_{i,j}\gamma_{i,k} / r_i^3} \right| \qquad (1)$$

Table SI 2: Fits of experimental RDCs to the calculated structure models without additional weighting.

| RDC | $w_i$ | $D_{exp}$ (Hz) | *4R5R6R* $D_{calc}$ (Hz) | *4R5R6S* $D_{calc}$ (Hz) | *4R5S6R* antiperip. $D_{calc}$ (Hz) | *4R5S6R* (+)-syncl. $D_{calc}$ (Hz) | *4R5S6R* (–)-syncl. $D_{calc}$ (Hz) | *4S5R6R* $D_{calc}$ (Hz) |
|---|---|---|---|---|---|---|---|---|
| C2 – H2 | 1.00 | 5.85 | 4.52 | 8.62 | 5.61 | 7.59 | 4.41 | 2.67 |
| C3 – H3 | 1.00 | -15.02 | -13.91 | -15.04 | -15.05 | -15.14 | -14.78 | -14.63 |
| C4 – H4 | 1.00 | 4.93 | 5.97 | 4.86 | 4.93 | 4.10 | 4.74 | 3.35 |
| C6 – H6 | 1.00 | 44.39 | 16.97 | 26.60 | 43.31 | 27.50 | 35.58 | 29.96 |
| C4 – H3 | 1.00 | 0.52 | -5.75 | -3.31 | 0.41 | -2.90 | -3.33 | -3.44 |
| C4 – H2 | 1.00 | 0.09 | 1.00 | 0.76 | 0.01 | 0.81 | 0.76 | 0.72 |
| C3 – H2 | 1.00 | -0.88 | 8.09 | 5.14 | -1.25 | 5.18 | 5.30 | 5.25 |
| C3 – H4 | 1.00 | 4.12 | 2.38 | 3.88 | 4.46 | 4.03 | 4.26 | 5.65 |
| Quality Factor | | $Q$ | 0.62 | 0.41 | 0.03 | 0.39 | 0.24 | 0.35 |
| Condition Number | | cond. | 11.54 | 10.45 | 4.12 | 10.77 | 7.05 | 2.95 |
| Tensor Magnitude | | GDO ($*10^{-3}$) | 4.35 | 3.57 | 3.30 | 3.22 | 3.58 | 5.23 |
| Axial Component | | $D_a$ ($*10^{-3}$) | 1.94 | 1.77 | -1.56 | 1.59 | 1.78 | 2.57 |
| Rhombic Component | | $D_r$ ($*10^{-3}$) | 1.13 | 0.24 | -0.63 | 0.25 | 0.22 | 0.55 |
| Tensor Orientation – Euler Angles | | α (°) | 66.58 | 162.42 | 82.70 | 161.18 | 158.52 | 120.64 |
| | | β (°) | 33.22 | 51.76 | 59.61 | 97.79 | 50.57 | 116.88 |
| | | γ (°) | 52.35 | 83.14 | 33.14 | 132.77 | 123.96 | 127.36 |

Table SI 3: Fits of experimental RDCs to the calculated structure models with additional weighting according to eq. (1).

| RDC | $w_i$ | $D_{exp}$ (Hz) | *4R5R6R* $D_{calc}$ (Hz) | *4R5R6S* $D_{calc}$ (Hz) | *4R5S6R* antiperip. $D_{calc}$ (Hz) | *4R5S6R* (+)-syncl. $D_{calc}$ (Hz) | *4R5S6R* (–)-syncl. $D_{calc}$ (Hz) | *4S5R6R* $D_{calc}$ (Hz) |
|---|---|---|---|---|---|---|---|---|
| C2 – H2 | 1.00 | 5.85 | 6.19 | 9.95 | 6.76 | 7.01 | -0.03 | 0.23 |
| C3 – H3 | 1.01 | -15.02 | -12.01 | -15.17 | -15.03 | -15.58 | -13.26 | -13.45 |
| C4 – H4 | 1.02 | 4.93 | 7.56 | 4.75 | 4.99 | 3.13 | 3.65 | -0.20 |
| C6 – H6 | 1.02 | 44.39 | -20.75 | 2.29 | 38.67 | 1.62 | -9.81 | -0.93 |
| C4 – H3 | 9.17 | 0.52 | 0.06 | 0.55 | 0.36 | 0.72 | -0.01 | 0.00 |
| C4 – H2 | 31.82 | 0.09 | 0.06 | 0.16 | 0.06 | 0.13 | 0.01 | -0.01 |
| C3 – H2 | 8.04 | -0.88 | -0.58 | -0.63 | -0.94 | -0.56 | -0.26 | -0.60 |
| C3 – H4 | 7.93 | 4.12 | 4.05 | 4.11 | 4.15 | 4.10 | 4.15 | 4.21 |
| Quality Factor | | $Q$ | 1.37 | 0.89 | 0.12 | 0.90 | 1.15 | 0.96 |
| Condition Number | | cond. | 2.86 | 13.33 | 3.78 | 1.33 | 3.43 | 3.31 |
| Tensor Magnitude | | GDO ($*10^{-3}$) | 3.26 | 2.76 | 2.93 | 3.41 | 4.24 | 4.22 |
| Axial Component | | $D_a$ ($*10^{-3}$) | -1.51 | -1.29 | -1.38 | 1.51 | 1.84 | -1.85 |
| Rhombic Component | | $D_r$ ($*10^{-3}$) | -0.70 | -0.57 | -0.58 | 0.92 | 1.22 | -1.17 |
| Tensor Orientation – Euler Angles | | $\alpha$ (°) | 114.84 | 68.89 | 84.31 | 66.12 | 117.60 | 99.75 |
| | | $\beta$ (°) | 93.95 | 125.92 | 59.18 | 109.83 | 55.61 | 28.30 |
| | | $\gamma$ (°) | 130.66 | 29.85 | 32.02 | 161.17 | 92.90 | 96.00 |

## *Back-Calculation of the C6-H6 RDC*

To cross-validate the rigid model of the exocyclic C5-C6 bond, RDC fits were performed without the C6-H6 RDC for each conformer of the 4R5S5R relative configuration. The three conformers are denoted according to their OH5-C5-C6-H6 torsion: antiperiplanar, (+)-synclinal and (–)-synclinal. The resulting tensors were then used to back-calculate the C6-H6 RDC. In the absence of conformational flexibility this approach should give a value close to the experimental one, whereas conformational averaging would strongly reduce the observed RDC.

Table SI 4: Fits of experimental RDCs without the C6-H6 RDC with and without additional weighting before SVD. The resulting tensor is used to back-calculate the value for the C6-H6 RDC.

| | | no weighting | | | with SVD weighting | | |
|---|---|---|---|---|---|---|---|
| RDC | $D_{exp}$ (Hz) | *4R5S6R* antiperip. $D_{calc}$ (Hz) | *4R5S6R* (+)-syncl. $D_{calc}$ (Hz) | *4R5S6R* (–)-syncl. $D_{calc}$ (Hz) | *4R5S6R* antiperip. $D_{calc}$ (Hz) | *4R5S6R* (+)-syncl. $D_{calc}$ (Hz) | *4R5S6R* (–)-syncl. $D_{calc}$ (Hz) |
| C2 – H2 | 5.85 | 5.89 | 5.82 | 5.82 | 7.30 | 4.99 | 4.97 |
| C3 – H3 | -15.02 | -15.02 | -15.02 | -15.02 | -14.93 | -15.15 | -15.17 |
| C4 – H4 | 4.93 | 4.93 | 4.93 | 4.93 | 4.94 | 5.16 | 5.25 |
| C4 – H3 | 0.52 | 0.25 | 0.82 | 0.78 | 0.41 | 0.68 | 0.70 |
| C4 – H2 | 0.09 | 0.04 | 0.07 | 0.08 | 0.08 | 0.06 | 0.06 |
| C3 – H2 | -0.88 | -0.94 | -0.80 | -0.81 | -0.90 | -0.81 | -0.80 |
| C3 – H4 | 4.12 | 4.12 | 4.11 | 4.11 | 4.12 | 4.12 | 4.11 |
| Condition Number | cond. | 20.62 | 14.59 | 15.92 | 3.78 | 11.60 | 3.61 |
| Tensor Magnitude | GDO ($*10^{-3}$) | 2.99 | 3.62 | 3.58 | 2.85 | 3.41 | 3.69 |
| Axial Component | $D_a$ ($*10^{-3}$) | -1.40 | 1.59 | 1.45 | -1.34 | 1.48 | 1.62 |
| Rhombic Component | $D_r$ ($*10^{-3}$) | -0.60 | 1.00 | 0.94 | -0.56 | 0.97 | 1.03 |
| Tensor Orientation – Euler Angles | $\alpha$ (°) | 82.78 | 118.14 | 67.40 | 85.26 | 66.52 | 118.32 |
| | $\beta$ (°) | 59.21 | 57.42 | 109.69 | 59.17 | 109.45 | 57.14 |
| | $\gamma$ (°) | 32.90 | 84.56 | 161.87 | 31.45 | 161.18 | 82.26 |
| C6 – H6 | 44.39 | 39.26 | -0.40 | -20.61 | 37.73 | -0.67 | -19.94 |

## *References*

(1) Enthart, A.; Freudenberger, J. C.; Furrer, J.; Kessler, H.; Luy, B., *J. Magn. Reson.* **2008,** *192*, 314-322.
(2) Kurz, M.; Schmieder, P.; Kessler, H., *Angew. Chem. Int. Ed.* **1991,** *30*, 1329-1331.
(3) Uhrín, D.; Batta, G.; Hruby, V. J.; Barlow, P. N.; Kövér, K. E., *J. Magn. Reson.* **1998,** *130*, 155-161.
(4) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Jr., J. A. M.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision 6.0*, Gaussian Inc.: Pittsburgh, PA, 2003.
(5) Berger, R.; Fischer, C.; Klessinger, M., *J. Phys. Chem. A* **1998,** *102*, 7157-7167.
(6) Schmidts, V.; Berger, R.; Thiele, C. M.,
(7) Losonczi, J. A.; Andrec, M.; Fischer, M. W. F.; Prestegard, J. H., *J. Magn. Reson.* **1999,** *138*, 334-342.
(8) Cornilescu, G.; Marquardt, J. L.; Ottiger, M.; Bax, A., *J. Am. Chem. Soc.* **1998,** *120*, 6836-6837.
(9) Zweckstetter, M., *Nat. Protoc.* **2008,** *3*, 679-690.