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Supporting Information

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Bijvoet in Solution Reveals Unexpected Stereoselectivity in a Michael Addition

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Carlos Kleber Z. Andrade,^{*[c]} Rafael Oliveira Rocha,^{*[c]} and Christian Griesinger^{*[a]}**

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Supporting Information
for
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Michael addition

by

Han Sun, Edward James d’Auvergne, Uwe Michael Reinscheid, Luiz Carlos
Dias, Carlos Kleber Z. Andrade, Rafael Oliveira Rocha, Christian Griesinger

Contents:

Part I: Chemical synthesis and general information

- | | |
|--|----|
| 1. Experimental procedures | S1 |
| 2. Determination of the relative configuration of the two
unknown stereocenters using a chemical approach | S6 |
| 3. Atom numbering of (R)-3 | S9 |

**Part II: Determination of the relative configuration using RDC-
enhanced NMR spectroscopy**

- | | |
|--|-----|
| 4. Setup of the NMR experiments | S10 |
| 5. Assignment of (R)-3-anti in DMSO- <i>d</i> ₆ | S11 |
| 6. <i>J</i> -coupling constants of (R)-3-anti | S13 |
| 7. Quantitative ROE data of (R)-3-anti | S14 |
| 8. Alignment media and RDC data | S15 |
| 9. Ensemble evaluation by NMR data | S17 |
| 10. Analysis of configuration using ROE and RDC data | S18 |
| 11. Structures of the best ensemble of (RRR)-3 and (RSS)-3 | S20 |
| 12. Cross-validation of <i>J</i> -coupling constants | S22 |
| 13. Alignment tensor analysis | S22 |
| 14. Conformational analysis of the C ¹ -N ³³ torsion angle
using RDC data | S23 |

**Part III: Determination of the absolute configuration using a
combination of ORD and NMR spectroscopy**

Part IV: References

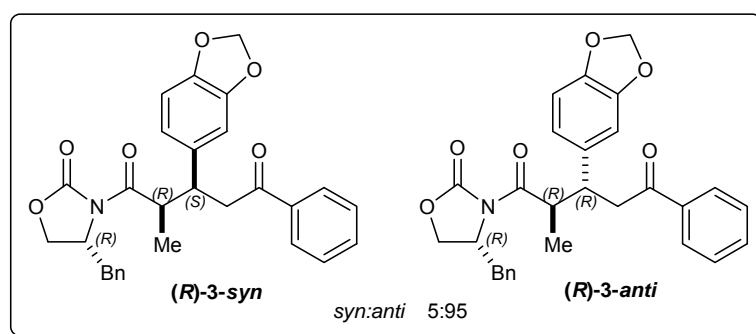
Part I: Chemical synthesis and general information

1. Experimental procedures

IR spectra were recorded on an FT-IR BOMEM Hartmann & Braun-Michelson MB-100 spectrometer. HRMS spectra were recorded on a GCT Premier Waters Spectrometer, EI (70 eV). ^1H NMR (300 and 500 MHz) and ^{13}C NMR (75 and 125 MHz) spectra were recorded on a Varian 300 Mercury Plus 7.04 T or Varian 300 Gemini and Varian 500 Inova spectrometers. The spectra were obtained using CDCl_3 , benzene- d_6 or $\text{DMSO}-d_6$ and referenced to internal TMS ($\delta = 0.0$) for ^1H NMR and CDCl_3 ($\delta = 77.0$) for ^{13}C NMR. Data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; ddd, double-double-doublet; dt, double triplet; td, triple doublet; hp, heptet. All reactions were conducted under an argon atmosphere in anhydrous solvents. THF was dried over sodium and benzophenone. CH_2Cl_2 and AcOEt were dried over calcium hydride and freshly distilled prior to use. Methanol was dried using magnesium and iodine, distilled and stored under activated 3 Å molecular sieves.

Procedure for the addition of niobium enolate of oxazolidinone to chalcones

Michael Product (**R**)-3-*anti*



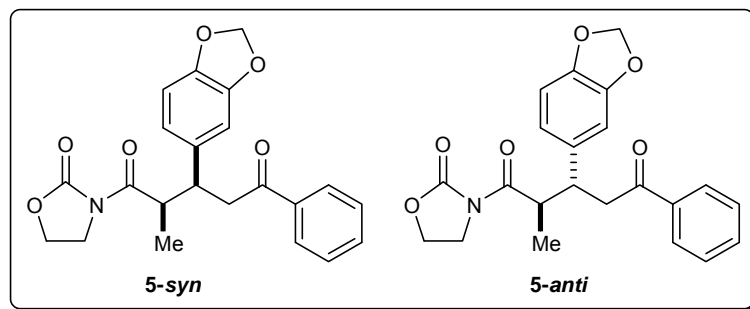
To a suspension of 0.35 g (1.3 mmol) of NbCl_5 in 1.0 mL of dry dichloromethane at 0 °C, 0.23 g of oxazolidinone **1** (1.0 mmol) diluted in 1.0 mL of dry dichloromethane was added. The reaction was vigorously stirred for 5 minutes. Then 0.35 mL (2.5 mmol) of triethylamine was added, dropwise, resulting in a dark brown solution. After stirring for 5 minutes at 0 °C, a solution of 1.1 mmol of chalcone **2** in 1.0 mL of dry dichloromethane was added and the reaction was monitored by TLC. The reaction was stirred for 3 h at 0 °C and 72 h at room temperature. Then 10 mL of saturated ammonium chloride solution (NH_4Cl) were added. The reaction mixture was extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were washed with 10 mL of brine, dried over Na_2SO_4 and concentrated in vacuum. Flash chromatography (hexanes:EtOAc = 60:40) afforded pure Michael product (**R**)-**3** in 72% yield as a yellow oil (*syn:anti* ratio = 5:95).

Spectroscopic data:

IR (film): 1775, 1688, 1488, 1385, 1238, 1210, 1038, 703. **^1H NMR** (300 MHz, CDCl_3): δ 1.02 (d, 3H, $J = 6.8$ Hz, *syn*); 1.28 (d, 3H, $J = 6.8$ Hz, *anti*); 2.20 (dd, 1H, $J = 9.8$ and 13.6 Hz, *anti*); 2.67 (dd, 1H, $J = 10.3$ and 13.1 Hz, *syn*); 2.79 (dd, 1H, $J = 3.5$ and 13.7 Hz, *anti*); 3.19 (dd, 1H, $J = 4.0$ and 15.6 Hz, *syn*); 3.33 (dd, 1H, $J = 5.0$ and 17.0 Hz, *anti*); 3.43 (dd, 1H, $J = 9.0$ and 17.0 Hz, *anti*); 3.83-3.90 (m, 1H, *anti*); 4.02 (dd, 1H, $J = 3.1$ and 9.0 Hz, *anti*); 4.08-4.13 (m, 1H, *anti*); 4.16-4.23 (m, 1H, *syn*); 4.34 (dq, 1H, $J = 6.6$ and 9.0 Hz, *anti*); 4.53-4.61 (m,

1H, *anti*); 4.67-4.75 (m, 1H, *syn*); 5.79 (d, 1H, $J = 1.4$ Hz); 5.85 (d, 1H, $J = 1.4$ Hz); 6.68 (d, 1H, $J = 8.1$ Hz); 6.81 (dd, 1H, $J = 1.8$ and 8.2 Hz); 6.89 (d, 1H, $J = 1.8$ Hz); 7.00-7.03 (m, 1H); 7.22-7.31 (m, 5H); 7.40-7.46 (m, 2H); 7.51-7.57 (m, 1H); 7.85-7.91 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 15.0; 37.3; 41.1; 42.6; 43.2; 54.9; 65.6; 100.8; 108.0; 109.1; 121.4; 127.2; 128.0; 128.1; 128.6; 128.9; 129.0; 129.2; 129.3; 133.0; 135.3; 136.4; 137.0; 146.1; 147.4; 153.1; 175.7; 198.2. The observed HRMS (ESI TOF-MS): calc. 485.1838, obs. 485.1953.

Racemic mixture of the two diastereomers of compound 5



This compound was prepared according to the general procedure described for compound (**R**)-**3** in 70-80% yield as a yellow oil (*syn:anti* ratio = 30:70). The enantiomers of the two drawn compounds were formed in identical amounts yielding a racemic mixture of the two diastereomers. In this case, the reaction was stirred for 3 hours at 0 °C and then worked up as above.

Racemic mixture of the Michael adduct 5-*anti*

Spectroscopic data:

IR (film): 2982; 2917; 1775; 1689; 1488; 1388; 1247; 1039; 761. ^1H NMR (300 MHz, CDCl_3): δ 7.87-7.90 (m, 2H); 7.51-7.57 (m, 1H); 7.40-7.47 (m, 2H); 6.83 (d, 1H, $J = 1.8$ Hz); 6.75 (dd, 1H, $J = 2.1$ and 8.4 Hz); 6.68 (d, 1H, $J = 8.0$ Hz); 5.88 (m, 2H); 4.20-4.38 (m, 3H); 3.82-3.95 (m, 2H); 3.69-3.77 (m, 1H); 3.29-3.44 (m, 2H); 1.20 (d, 3H, $J = 6.9$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 13.5; 39.8; 42.1; 42.3; 42.6; 61.7; 100.6; 100.7; 107.8; 108.5; 120.8; 127.7; 128.4; 132.8; 136.2; 136.9; 145.9; 147.2; 153.1; 198.0.

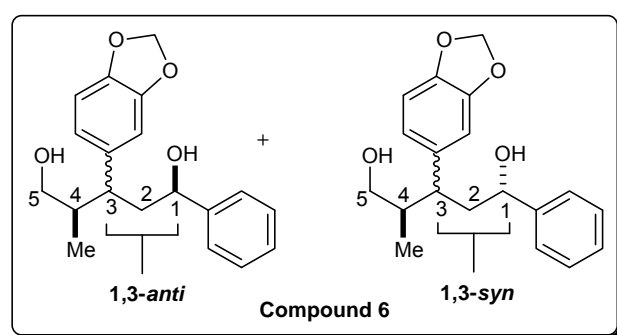
Racemic mixture of the Michael adduct 5-*syn*

Spectroscopic data:

^1H NMR (300 MHz, CDCl_3): δ 7.85-7.90 (m, 2H); 7.50-7.56 (m, 1H); 7.40-7.46 (m, 2H); 6.74 (s, 1H); 6.68-6.69 (m, 2H); 5.90 (m, 2H); 4.24-4.43 (m, 3H); 3.95-4.07 (m, 2H); 3.56-3.64 (m, 1H); 3.31 (dd, 1H, $J = 8.7$ and 15.6 Hz); 3.22 (dd, 1H, $J = 5.2$ and 15.6 Hz); 1.00 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 16.7; 42.3; 42.7; 43.7; 44.5; 61.8; 100.8; 104.7; 108.1; 108.2; 121.5; 128.1; 128.5; 132.9; 135.2; 136.7; 146.2; 147.6; 153.3; 176.4; 198.1.

Determination of the relative configuration of C2-C3 by derivatization of the racemic mixtures of 5-*anti* and 5-*syn*.

3-(Benzo[d][1,3]dioxol-6-yl)-4-methyl-1-phenylpentane-1,5-diol (**6**)

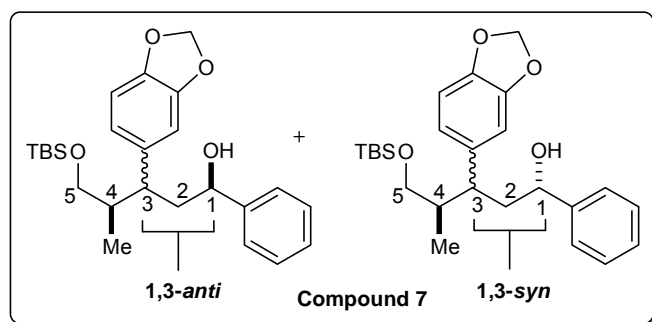


To a solution of the racemic mixture of the Michael adducts **5-anti** and **5-syn** as obtained in the previous reaction (0.6 g, 1.52 mmol) in 5.0 mL of dry THF and 0.1 mL of dry methanol at 0 °C, 3.8 mL of a 2 M solution of LiBH₄ in THF (7.60 mmol), was added dropwise, observing the gas evolution. The reaction mixture was stirred for 1 hour at 0 °C. After this time, 20 mL of a saturated sodium and potassium tartrate solution were added and the reaction was stirred for 30 minutes, followed by extraction with dichloromethane (4 x 20 mL). The organic layers were washed with 15 mL of brine, dried over sodium sulfate, filtered and concentrated in vacuum, furnishing the mixture of the racemic mixture of the 4 diastereomers of diol **6**, as a colourless oil, which was used without further purification.

Spectroscopic data:

¹H NMR (300 MHz, CDCl₃): δ 7.20-7.36 (m, 5H); 6.74 (d, 1H, *J* = 8.1 Hz); 6.65 (d, 1H, *J* = 1.2 Hz); 6.53 (dd, 1H, *J* = 1.5 and 7.8 Hz); 5.94 (s, 2H); 4.35-4.39 (m, 1H); 3.32 (dd, 1H, *J* = 5.1 and 10.8 Hz); 3.13 (dd, 1H, *J* = 6.0 and 10.6 Hz); 2.12-2.24 (m, 1H); 1.72 (hp, 1H, *J* = 6.3 Hz); 0.93 (d, 3H, *J* = 6.9 Hz, *anti*); 0.71 (d, 3H, *J* = 6.9 Hz, *syn*). ¹³C NMR (75 MHz, CDCl₃): δ 14.9; 41.3; 41.6; 44.6; 66.1; 73.4; 100.8; 108.1 (2C); 121.3; 126.4; 127.8; 128.4; 137.0; 143.5; 145.9; 147.7. HRMS (*m/z*): calc. 314.1518, obs. 314.1519.

Selective protection of the racemic mixture of the 4 diastereomers of diol **6**



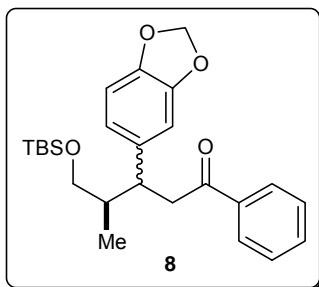
To a solution of 0.56 g of the racemic mixture of the 4 diastereomers of diol **6** (1.52 mmol) in 8.0 mL of dry dichloromethane at room temperature, 0.16 g of imidazole (2.28 mmol), 0.02 g (0.15 mmol) of 4,4-dimethylaminopyridinium (DMAP) and 0.28 g (1.82 mmol) of *tert*-butyldimethylsilyl chloride (TBSCl) were added. The reaction mixture was stirred for 1 hour at room temperature and then diluted with ethyl acetate (20 mL) and H₂O (20 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and filtered. Concentration in vacuum furnished the crude product, which was purified by column chromatography (5-10% AcOEt and hexanes) giving the racemic mixture of the 4 diastereomers of the mono protected alcohol **7** as colourless oil, in 72% yield for the two-step sequence.

Spectroscopic data:

IR (film): 3422; 3029; 2955; 2932; 2857; 1504; 1488; 1441; 1246; 1092; 1041; 837; 776; 701.
¹H NMR (300 MHz, CDCl₃): δ -0.11 (s, 6H); 0.64 (d, 3H, *J* = 6.9 Hz, 1,2-*syn*); 0.79 (s, 9H);

0.85 (d, 3H, $J = 6.8$ Hz, 1,2-*anti*); 1.67 (hp, 1H, $J = 5.5$ Hz); 1.98 (bs, 1H, OH); 2.03-2.28 (m, 3H); 2.46-2.53 (m, 1H, 1,2-*syn*); 3.09 (dd, 1H, $J = 6.2$ and 9.9 Hz, 1,2-*anti*); 3.26 (dd, 1H, $J = 5.1$ and 9.8 Hz, 1,2-*anti*); 3.27 (dd, 1H, $J = 6.5$ and 10.1 Hz, 1,2-*syn*); 3.37 (dd, 1H, $J = 5.4$ and 10.0 Hz, 1,2-*syn*); 4.35-4.42 (m, 1H); 5.91-5.93 (m, 2H); 6.53 (dd, 1H, $J = 1.6$ and 7.9 Hz); 6.64 (d, 1H, $J = 1.6$ Hz); 6.73 (d, 1H, $J = 7.9$ Hz); 7.18-7.34 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3 , 1,2-*anti* isomer): δ -5.6 (2C); 14.6; 25.8; 40.6; 41.6; 43.8; 65.7; 73.5; 100.7; 107.9; 108.4; 121.5; 126.5; 127.6; 128.3; 137.6; 143.8; 145.7; 147.5. ^{13}C NMR (75 MHz, CDCl_3 , 1,2-*syn* isomer): δ -5.5 (2C); 13.6; 25.8; 40.8; 42.2; 42.4; 65.6; 73.2; 100.7; 107.7; 109.0; 122.1; 126.4; 127.6; 128.3; 135.8; 143.9; 145.7; 147.4.

Oxidation of the racemic mixture of the 4 diastereomers of alcohol 7

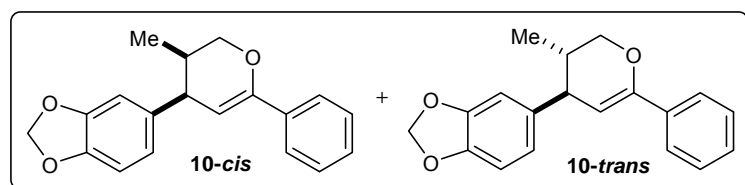


To a solution of the racemic mixture of the 4 diastereomers of mono protected alcohol **7** (0.14 g, 0.32 mmol) in 1.0 mL of dry dichloromethane were added activated 4 Å molecular sieves (0.16 g, 0.5 g/mol), NMO (0.06 g, 0.47 mmol) and a catalytic amount of TPAP (10 mol%). The reaction mixture was stirred for 18 hours at room temperature and monitored by TLC. The reaction mixture was filtered in a plug of silica gel to remove the reduced TPAP and concentrated in vacuum to furnish 0.12 g of pure racemic mixture of the 2 diastereomers of ketone **8**, as a colourless oil, in 98% yield.

Spectroscopic data:

IR (film): 2956; 2932; 2857; 1687; 1504; 1488; 1249; 1088; 1041; 939; 837; 776; 691. ^1H NMR (300 MHz, C_6D_6): δ 0.01 (s, 3H); 0.02 (s, 3H); 0.81 (d, 3H, $J = 7.2$ Hz, 1,2-*syn*); 0.99 (s, 9H); 1.00 (d, 3H, $J = 7.5$ Hz, isomer 1,2-*anti*); 1.90 (hp, 1H, $J = 6.6$ Hz); 3.09-3.33 (m, 3H); 3.42-3.71 (m, 2H); 5.31 (s, 2H, 1,2-*anti*); 5.33 (s, 2H, 1,2-*syn*); 6.61-6.67 (m, 2H); 6.84-6.87 (m, 1H); 7.05-7.17 (m, 3H); 7.84-7.89 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6 , isomer 1,2-*anti*): δ -5.4 (2C); 15.4; 26.1; 41.3; 42.5; 43.5; 66.4; 100.8; 108.1; 109.0; 121.8; 128.3; 132.5; 137.8; 137.9; 146.4; 148.1. ^{13}C NMR (75 MHz, C_6D_6 , isomer 1,2-*syn*): δ -5.3 (2C); 14.3; 26.1; 40.6; 42.7; 43.15; 66.4; 100.8; 108.1; 109.3; 122.1; 128.5; 132.5; 136.7; 137.6; 146.4; 148.0.

Deprotection of TBS group



Method A: CSA/MeOH

To a solution of 0.12 g of the racemic mixture of the 2 diastereomers of ketone **8** in 5 mL of dry methanol a little amount of camphorsulfonic acid (CSA) was added. The reaction mixture was stirred for 1 hour at room temperature. The solvent was removed under reduced pressure and the residue was diluted in 10 mL of dichloromethane and washed with 10 mL of

brine. The organic layer was dried over MgSO_4 , filtered and concentrated in vacuum, furnishing the racemic mixture of the two diastereomers of the labile dihydropyran **10** as a colourless oil in 90% yield after chromatographic purification (5% AcOEt in hexanes).

Method B: HF_{aq} and CH_3CN

In a polyethylene flask containing 0.06 g (0.14 mmol) of the racemic mixture of the 2 diastereomers of ketone **8** in 3.0 mL of acetonitrile, aqueous hydrogen fluoride 48% was added (around 20 drops) and the reaction was stirred for 3 days at room temperature. Then, a few portions of solid sodium bicarbonate were carefully added to neutralize (until pH = 7). The reaction mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuum. The resultant oil was purified by column chromatography (5% AcOEt/hexanes), giving the racemic mixture of the two diastereomers of the labile dihydropyran **10** in 95% yield as a colourless oil.

Racemic mixture of 5-((3R,4S)-3,4-Dihydro-3-methyl-6-phenyl-2H-pyran-4-yl)benzo[d][1,3]dioxole (10-cis)

Spectroscopic data:

IR (film): 2961; 2921; 2881; 1502; 1486; 1441; 1244; 1039; 935; 805. **$^1\text{H NMR}$** (500 MHz, C_6D_6): δ 0.46 (d, 3H, $J = 7.0$ Hz); 1.86-1.91 (m, 1H); 3.30 (t, 1H, $J = 5.0$ Hz); 3.69 (dd, 1H, $J = 8.0$ and 11.0 Hz); 3.78 (dd, 1H, $J = 3.0$ and 11.0 Hz); 5.32 (s, 3H, -O-CH₂-O- and -C=C-H); 6.48-6.52 (m, 1H); 6.63 (d, 1H, $J = 7.5$ Hz); 6.70 (s, 1H); 6.98-7.20 (m, 3H); 7.69 (d, 2H, $J = 7.4$ Hz). **$^{13}\text{C NMR}$** (125 MHz, C_6D_6): δ 14.1; 32.5; 36.3; 42.5; 69.6; 99.9; 101.5; 108.6; 110.8; 123.3; 125.6; 129.0; 136.9; 137.2; 147.3; 148.5; 152.8.

Racemic mixture of 5-((3S,4S)-3,4-Dihydro-3-methyl-6-phenyl-2H-pyran-4-yl)benzo[d][1,3]dioxole (10-trans)

Spectroscopic data:

$^1\text{H NMR}$ (500 MHz, C_6D_6): δ 0.61 (d, 3H, $J = 7.0$ Hz); 1.66-1.69 (m, 1H); 2.80 (dd, 1H, $J = 2.5$ and 8.5 Hz); 3.50 (t, 1H, $J = 10.5$ Hz); 3.93 (dd, 1H, $J = 3.5$ and 10.5 Hz); 5.26 (d, 1H, $J = 2.5$ Hz, -C=C-H); 6.63 (d, 1H, $J = 7.5$ Hz); 6.70 (s, 1H); 6.98-7.20 (m, 3H); 7.65 (t, 2H, $J = 7.5$ Hz). **$^{13}\text{C NMR}$** (125 MHz, C_6D_6): δ 16.1; 30.8; 40.6; 47.1; 71.5; 101.5; 101.7; 108.8; 109.4; 121.9; 122.3; 124.4; 136.8; 139.9; 147.4; 148.9; 152.0.

2. Determination of the relative configuration of the two unknown stereocenters using a chemical approach

The relative stereochemistry of the carbon C2 and C3 was established after the Michael products derivatization to cyclic compounds as described below.

First, we investigated the addition of the niobium enolate generated from achiral oxazolidinone **4** to chalcone **2**. The racemic mixture of the two diastereomeric Michael products **5** were isolated in good yields (68-80%) and moderate diastereoselectivities (Figure S1). A slight decrease in diastereoselectivity (*syn:anti* = 40:60) was observed when the enolate was generated at room temperature compared to its generation at 0 °C (*syn:anti* = 30:70).

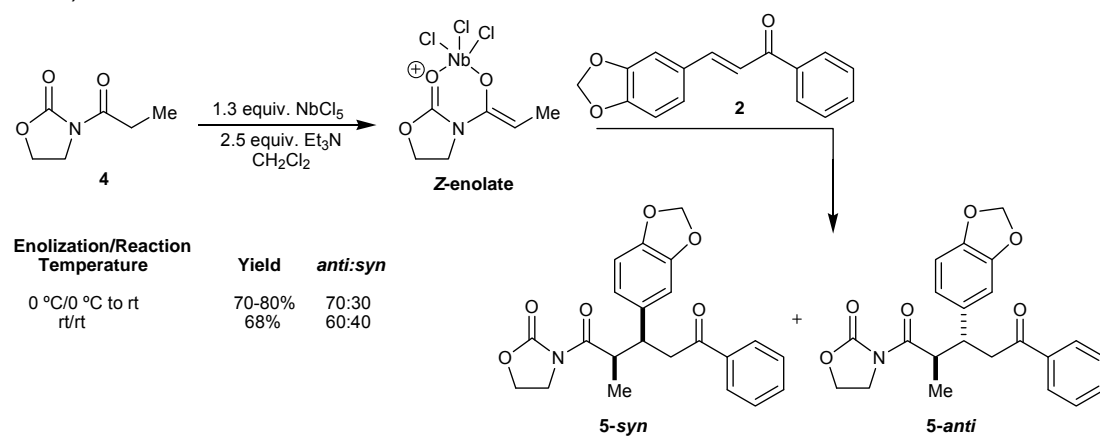


Figure S1. Conjugated addition of the niobium enolate of oxazolidinone **4** to chalcone **2**.

The relative configuration of the major product was established after derivatization to cyclic compounds as shown in Figures S2 and S3. All formulae represent only one enantiomer of the racemic mixture.

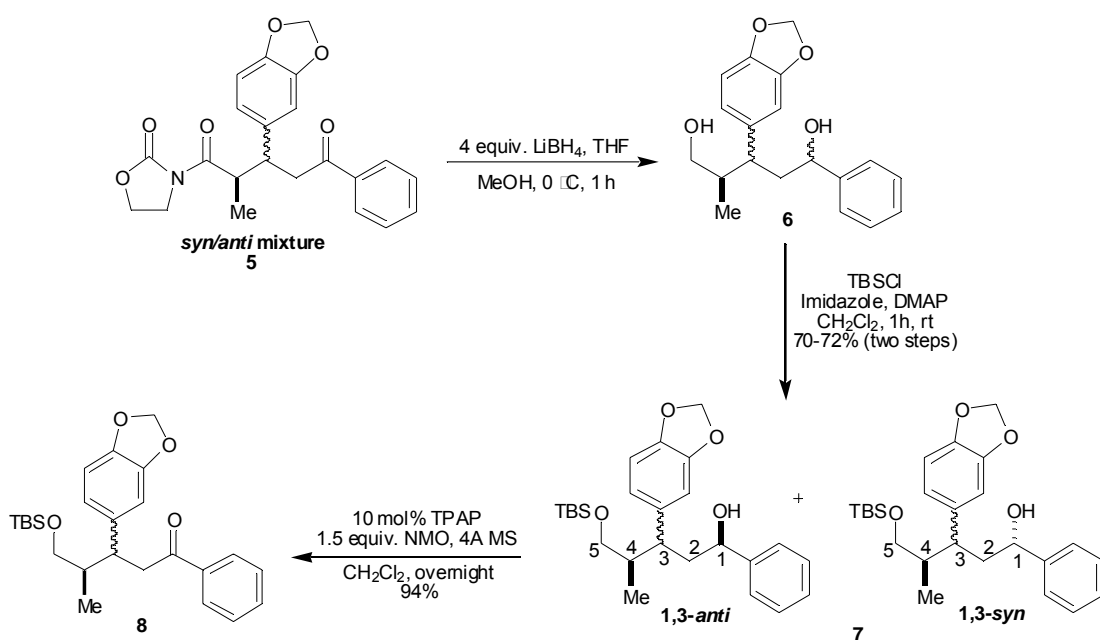


Figure S2. Synthesis of racemic mixture of the two diastereomeric ketones **8**.

Two methods to remove the silyl group of compound **8** were investigated and neither furnished the expected hemiacetal **9** (Figure S3). Instead, racemic mixtures of the labile

dihydropyrans **10** were isolated as a mixture of *cis/trans* isomers in 90% and 95% yield, respectively, in which **10-trans** is derived from **3-syn** and **10-cis** from **3-anti**. A possible mechanism to account for this observation involves tandem reactions of deprotection/cyclization/elimination by which the hemiacetals **9a** and/or **9b** are formed as non-isolated intermediates.

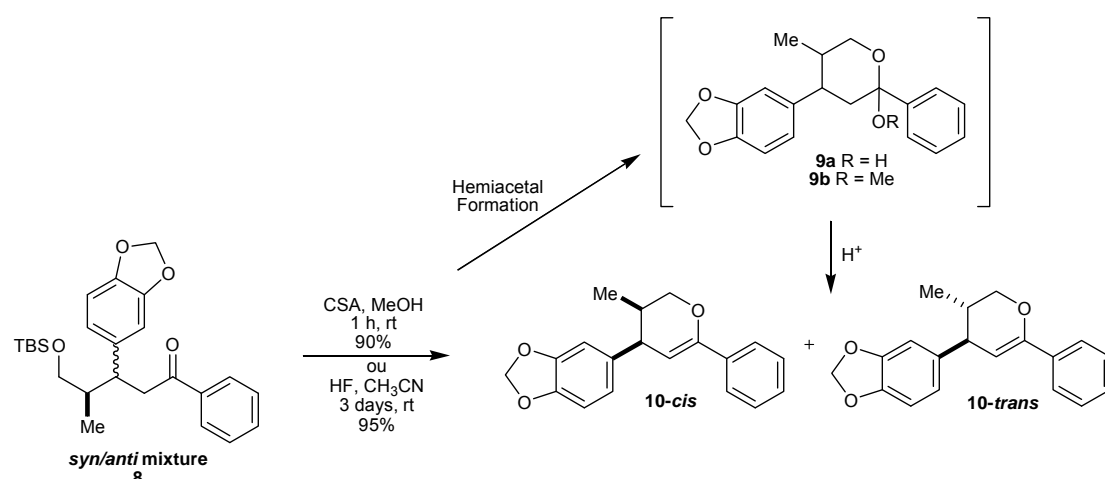


Figure S3. Synthesis of dihydropyrans **10**.

The coupling constants of Hd were decisive for the correct assignment of the relative configuration of the cyclic dihydropyrans **10** (Figure S4). Since in a six-membered ring, a 5 Hz coupling cannot arise from a *trans* configuration of the two involved protons, we can assign the major configuration to **10-cis** and the minor to **10-trans**. This constitutes **3-anti** to be the major and **3-syn** the minor product of the reaction in Figure S1.

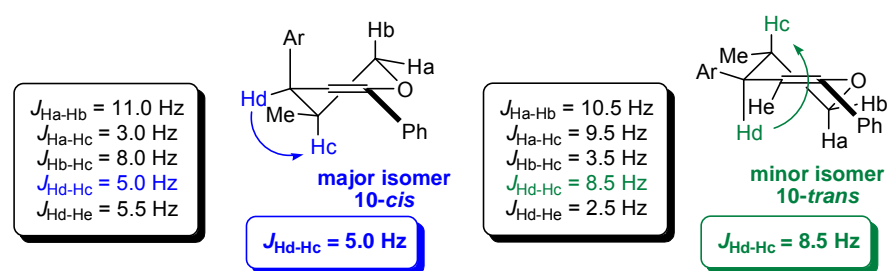


Figure S4. Coupling constants for the hydrogens of dihydropyrans **10**.

The complete conformational analysis of **10-cis** and **10-trans** is shown here focussing not only on the Hc-Hd coupling, but also on the other couplings (Figure S5). The conformation of **10-trans** brings all bulky substituents into the equatorial orientation. The expected and experimental couplings agree excellently for this relative configuration. For the conformation of **10-cis**, either the aromatic or the methyl group will be in the axial position. A DFT calculation of **10-cis** shows that the represented conformation with the aromatic ring axial is optimal. Then, the coupling constants to Hc are fairly well reproduced: $J_{\text{Ha-Hc}}^{\text{predicted}} = 3.1 \text{ Hz}$ compared to $J_{\text{Ha-Hc}}^{\text{experimental}} = 3.0 \text{ Hz}$, $J_{\text{Hb-Hc}}^{\text{predicted}} = 9.9 \text{ Hz}$ compared to $J_{\text{Hb-Hc}}^{\text{experimental}} = 8.0 \text{ Hz}$, and $J_{\text{Hc-Hd}}^{\text{experimental}} = 5.0 \text{ Hz}$, $J_{\text{Hc-Hd}}^{\text{predicted}} = 5.9 \text{ Hz}$ respectively.

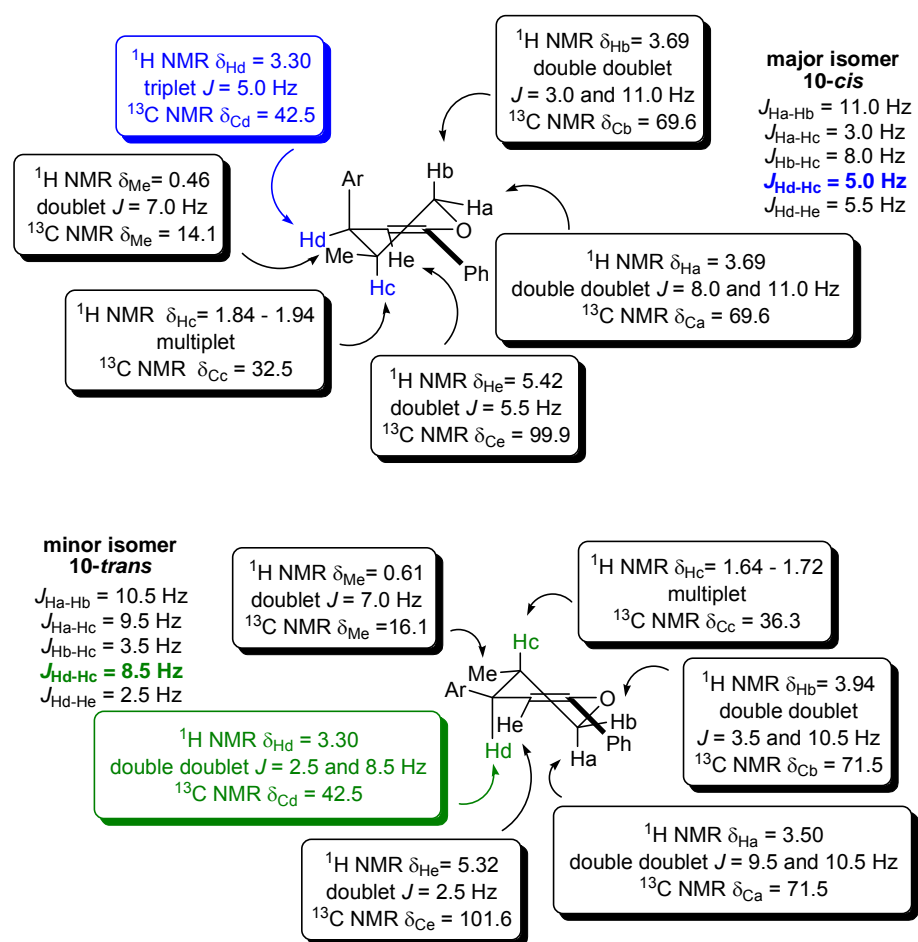


Figure S5. Chemical shifts and coupling constants for each hydrogen of dihydropyrans 10.

Part II: Determination of the relative configuration using RDC-enhanced NMR spectroscopy

4. Setup of the NMR experiments

All NMR measurements for the assignment of **(R)-3-anti** in DMSO- d_6 were performed at 298 K using a Bruker Avance 400 MHz NMR spectrometer (400.13 MHz for ^1H) equipped with a TXI probe head. The t_2 -coupled ^1H , ^{13}C -HSQC-spectra obtained in anisotropic PH-gel and the respective isotropic spectra were measured on a Bruker Avance 600 MHz spectrometer (599.90 MHz for ^1H) using a 5 mm cryo probe head. The spectra in PAN-gel and the respective isotropic spectra were acquired at an 800 MHz Bruker spectrometer (799.85 MHz for ^1H) with a 5 mm cryo probe head.

Unless otherwise indicated, the following were used: 0.12 mmol of **(R)-3-anti** in 0.6 mL DMSO- d_6 ; 4k points collected in the ^1H dimension; 512 points collected in the ^{13}C dimension; Zero-filling to double the number of collected points; Apodization with a sine squared window function with 0.3 Hz line width for both dimensions; Number of scans per FID set to 16; Relaxation delay between scans of 2 s.

NMR spectra for the assignment in isotropic phase

^1H 1D: Time domain = 16k points, apodized by exponential function with 0.3 Hz line width, number of scans = 4.

^{13}C 1D: Time domain = 32k points, apodized by exponential function with 1 Hz line width,, number of scans = 4096.

^1H - ^{13}C HSQC: Number of scans = 12.

^1H - ^{13}C HMBC: Number of scans = 24.

^1H - ^{15}N HMBC: Number of scans = 512.

^1H - ^{13}C HECADE^[30]: Number of scans = 36, 60 ms TOCSY-mixing time.

^1H - ^{13}C robust-HMBC^[31]: Standard settings were used.

^1H - ^{13}C reference-HSQC^[31]: Standard settings were used.

^1H - ^1H E.COSY^[32]: Number of scans = 24.

^1H - ^1H ROESY: Time domain (f_1) = 256 points.

NMR spectra for RDC measurements in isotropic phase and in PH-gel

t_2 -coupled ^1H - ^{13}C HSQC: 0.04 mmol of **(R)-3-anti** in 0.6 mL DMSO- d_6 .

t_2 -coupled ^1H - ^{13}C HSQC: 0.04 mmol of **(R)-3-anti** in PH-gel/DMSO- d_6 .

NMR spectra for RDC measurements in isotropic phase and in PAN-gel

t_2 -coupled ^1H - ^{13}C HSQC: 0.04 mmol of **(R)-3-anti** in 0.6 ml DMSO- d_6 . Time domain (t_2) = 1k points, (t_1) = 512 points.

t_2 -coupled ^1H - ^{13}C HSQC: 0.04 mmol of **(R)-3-anti** in PAN-gel/DMSO- d_6 . Time domain (t_2) = 1k points, (t_1) = 512 points.

5. NMR assignment of (*R*)-3-*anti* in DMSO-*d*₆

Table S1. ¹H chemical shift (δ, ppm) of (*R*)-3-*anti* in DMSO-*d*₆.

Atom number	Proton chemical shift [ppm]
1	-
2	4.13
3	3.75
4a	3.34
4b	3.62
6	1.15
7a	4.26
7b	4.05
8	4.59
9a	2.50
9b	2.63
11	6.95
12	6.77
13	6.77
14a	5.92
14b	5.88
19	7.95
19'	7.95
20	7.50
20'	7.50
21	7.61
23	6.86
23'	6.86
24	7.20
24'	7.20
25	7.22

Table S2. ^{13}C chemical shift (δ , ppm) of **(R)-3-anti** in $\text{DMSO-}d_6$.

Atom number	Carbon chemical shift [ppm]
1	175.3
2	42.8
3	42.4
4	39.9
5	198.7
6	14.8
7	65.9
8	54.4
9a	36.6
10	153.3
11	108.9
12	121.8
13	108.0
14	100.9
15	137.2
16	147.2
17	145.8
18	137.1
19	128.2
19'	128.2
20	128.9
20'	128.9
21	133.4
22	135.7
23	129.6
23'	129.6
24	127.0
24'	127.0
25	128.6

Table S3. ^{15}N chemical shift (δ , ppm) of **(R)-3-anti** in $\text{DMSO-}d_6$.

Nitrogen	Nitrogen chemical shift [ppm]
N	149.9

6. *J*-coupling constants of (*R*)-3-*anti*

To elucidate the relative configuration of the two unknown stereocenters in the major product, *J*-coupling analysis was carried out for the C2-C3 bond. $^3J_{CH}$ couplings were measured by HECAD^E^[30] and robust-HMBC experiments^[31], whereas the $^3J_{HH}$ coupling was extracted from both an E.COSY^[32] spectrum and a ¹H spectrum apodized with a Lorentz-to-Gauss window function. All *J*-couplings were then translated into dihedral angles with the calibration of an Altona-equation. Comparison of the dihedral angles obtained with possible conformations in Newman projections of the C2-C3 bond establishes, in agreement with the chemical approach, the *anti* relative configuration for compound (*R*)-3-*anti*.

Table S4. $^3J_{HH}$ coupling constants of (*R*)-3-*anti*. All couplings were extracted from an E.COSY^[32] spectrum, except for the couplings involving H2 and H3, which were taken from a 1D-¹H spectrum apodized with a Lorentz-to-Gauss window function.

Atoms	$^3J_{HH}$ [Hz]
H9a-H8	7.31
H9b-H8	3.42
H8-H7a	8.03
H8-H7b	2.98
H2-H3	8.56
H3-H4b	9.98
H3-H4a	4.02

Table S5. $^3J_{CH}$ coupling constants of (*R*)-3-*anti*, derived from HECAD^E^[30] and robust HMBC sequence^[31].

Atoms	$^3J_{CH}$ [Hz]	Experiment
H9a-C7	4.90	HECADE
H9b-C7	6.53	HECADE
H8-C22	3-4	robust-HMBC-sequence
H2-C4	2.70	HECADE
H2-C15	1-2	robust-HMBC-sequence
H3-C1	1-2	robust-HMBC-sequence
H3-C6	3.68	HECADE
H3-C5	1-2	robust-HMBC-sequence
H4a-C2	1.01	HECADE
H4b-C2	2.00	HECADE

7. Quantitative ROE data of (*R*)-3-*anti*

For deriving proton distances we integrated the volume of the cross peaks in the $^1\text{H},^1\text{H}$ -ROESY spectrum with the mixing time of 400 ms. The integrated intensities were calibrated using the two geminal protons at C9, assuming the distances between two geminal protons in a chain to be 1.78 Å. The uncertainty of the experimentally derived distances was assumed as 0.5 Å.

Table S6. Proton distance information derived from ROESY spectrum at 400 ms mixing time. All distances were referenced to H9a/H9b.

Proton 1	Proton 2	Distance [Å]
H6	H4a	2.21
H6	H4b	3.61
H6	H4	2.47
H6	H2	1.95
H6	H12	3.76
H6	H11	3.76
H6	H19/H19'	4.25
H6	H8	4.76
H9a	H8	2.70
H9a	H23/H23'	2.73
H9a	H9b	1.78
H9b	H7b	3.34
H9b	H8	2.70
H9b	H23/H23'	2.74
H4a	H4b	1.84
H4a	H19/H19'	2.71
H4a	H2	3.46
H4a	H11	4.72
H4b	H2	3.06
H4b	H11	2.93
H4b	H19/H19'	2.85
H4b	H12	2.93
H3	H2	2.67
H3	H12	2.60
H3	H11	2.72
H3	H19/H19'	3.40
H7b	H7a	1.70
H7b	H8	3.06
H7b	H23/H23'	2.84
H2	H9a	4.09
H2	H12	3.08
H2	H11	3.32
H7a	H8	2.57
H14b	H14a	1.87
H14a	H11	4.32
H2	H8	4.60
H14a	H24/H24'	4.04

H12	H19/H19'	4.67
H11	H19/H19'	4.03
H8	H23/H23'	3.16

8. Alignment media and RDC data

Table S7. Characteristics of the polymer media used to align (*R*)-3-*anti*.

	Polymer	Preparation	2D splitting [Hz]
Medium I (PH gel)	Polyacrylamide	Preparation following [23], washed in HCl; monomer concentration 0.75 mol/L; gel cylinder diameter 5.4 mm.	6.5 Hz
Medium II (PAN gel)	Polyacrylonitrile	Preparation following [24], monomer concentration 280 g/L, irradiation with 440 kGy. Polymer molecular weight: 231000 g/mol	18.2 Hz

For the RDC analysis we assumed an error of experimental RDCs of 0.5 Hz, which could not influence the analysis significantly. Therefore the uncertainty of RDCs was not included in the analysis

Table S8. Residual dipolar couplings of (*R*)-3-*anti* in the two alignment media. The RDCs were taken from t_2 -coupled ^1H - ^{13}C HSQC spectra by superimposing and fitting ω_2 traces from isotropic and anisotropic spectrum.

CH-vector	RDC [Hz] in medium I	RDC [Hz] in medium II
H25-C25	3.11	-15.08
H9a-C9	-3.20	–
H9b-C9	5.15	–
H8-C8	5.21	21.93
H7a-C7	-5.45	-3.3
H7b-C7	7.12	-25.45
H2-C2	-1.98	26.44
H3-C3	0	26.92
H11-C11	-0.37	19.37
H14a-C14	-2.50	-7.54
H14b-C14	2.07	-16.29
H13-C13	-0.51	17.49
H12-C12	1.67	10.76
H21-C21	1.63	-17.45

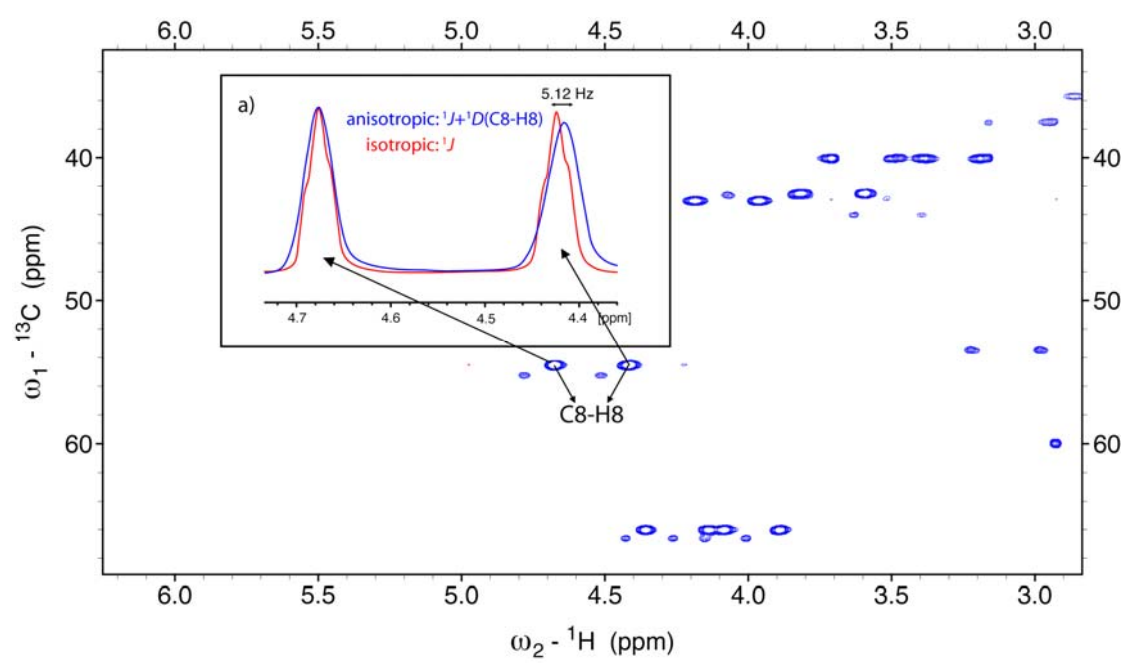


Figure S7. A section of the anisotropic t_2 -coupled ^1H , ^{13}C -HSQC spectrum of **(R)-3-anti**. a) Superimposed the lower field traces through the anisotropic HSQC section (blue line) and the isotropic HSQC section (red line). The shift between the two higher field traces is the determined RDC $^1D_{\text{CH}}$.

10. Analysis of configuration using ROE and RDC data

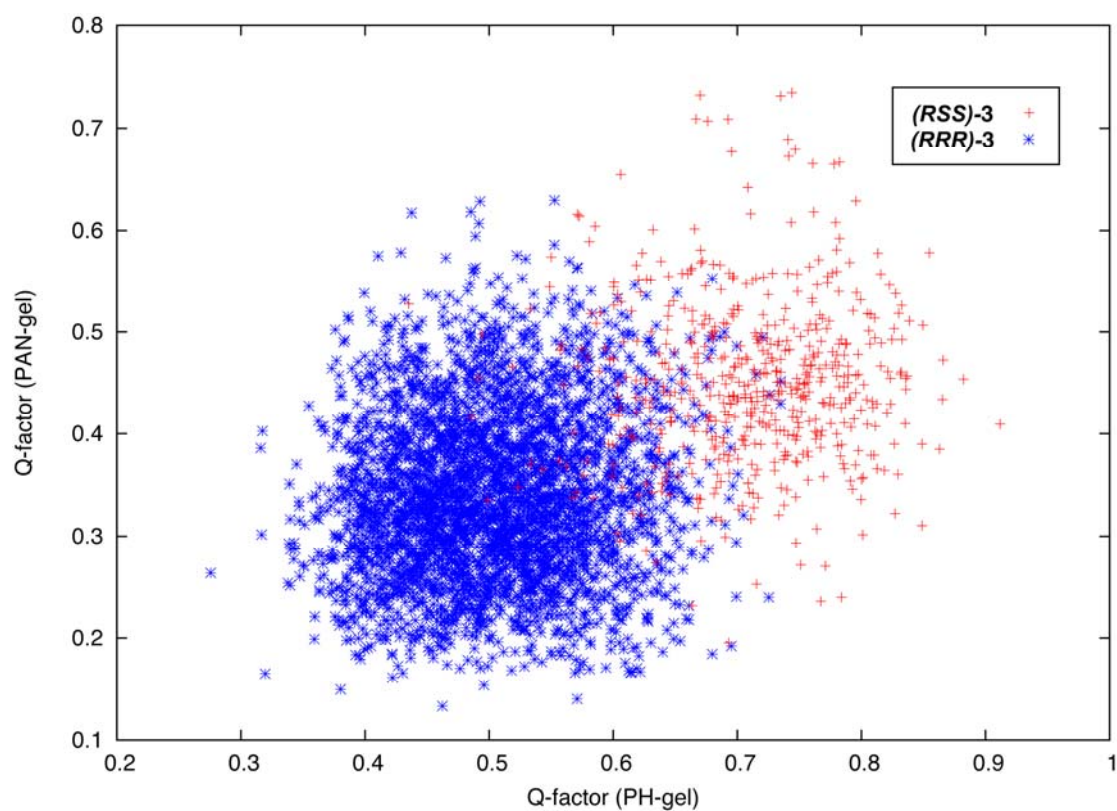


Figure S8. The projection of Figure 3 onto the PAN/PH Q-factor plane, only including ROE violations between 0 and 3.5 \AA^2 . In this plot, less **(RSS)-3** ensembles are present than **(RRR)-3** ones as the **(RRR)-3** ensembles violate ROE less than **(RSS)-3**. This 2D projection clearly demonstrates that **(RRR)-3** configuration is better supported by the NMR data. For all conformations and for both diastereomers, the C¹-N bond is *antiperiplanar*.

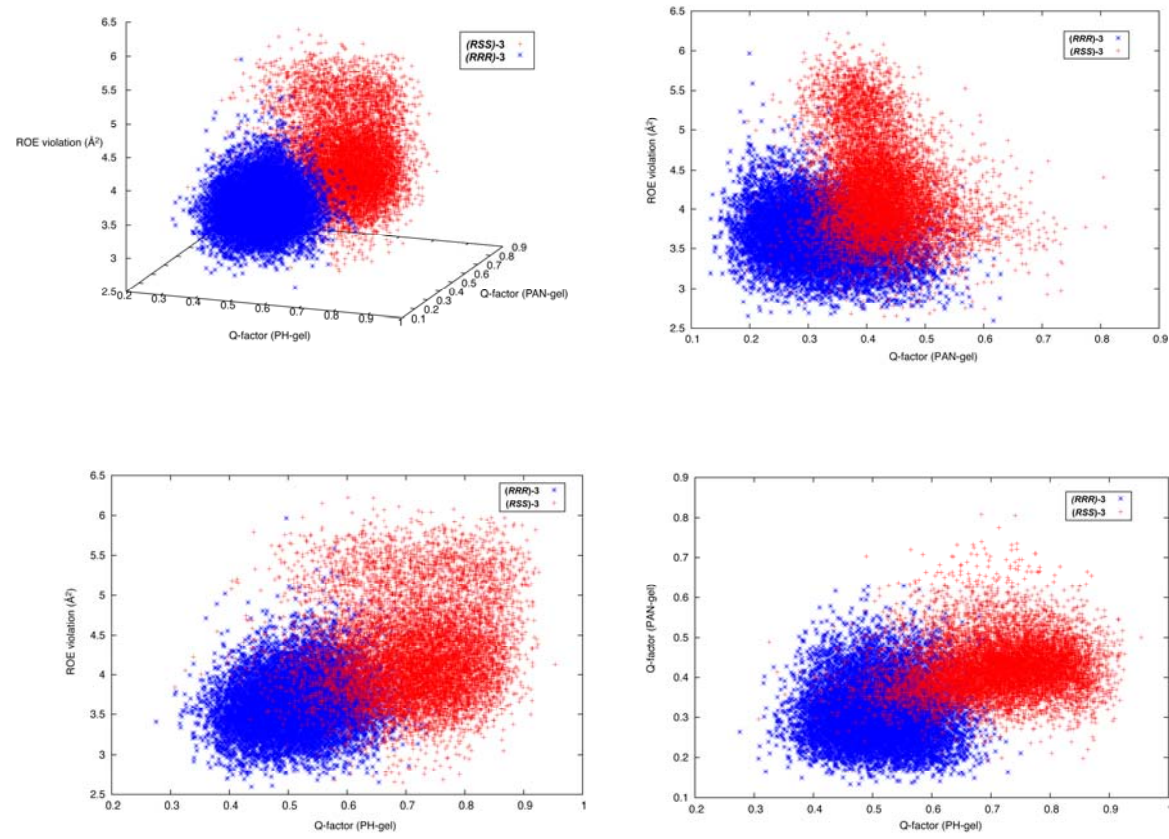


Figure S9. The three 2D projections of Figure 2 from the text.

12. Cross-validation of *J*-coupling constants

Table S9. The measured coupling constants versus the back-calculated coupling constants of the five best ensembles of (*RRR*)-**3** and (*RSS*)-**3**. For both diastereomers, the C¹-N bond is *antiperiplanar*.

Coupled proton	Calculated coupling constants for (<i>RRR</i>)- 3 [Hz]	Calculated coupling constants for (<i>RSS</i>)- 3 [Hz]	Measured coupling constants [Hz]
H2-H3	9.8-10.7	8.1-9.3	8.54
H3-H4a	8.3-10.8	10.3-11.1	9.98
H3-H4b	3.1-4.7	3.3-3.8	4.02

Part III: Determination of the absolute configuration using a combination of ORD and NMR spectroscopy

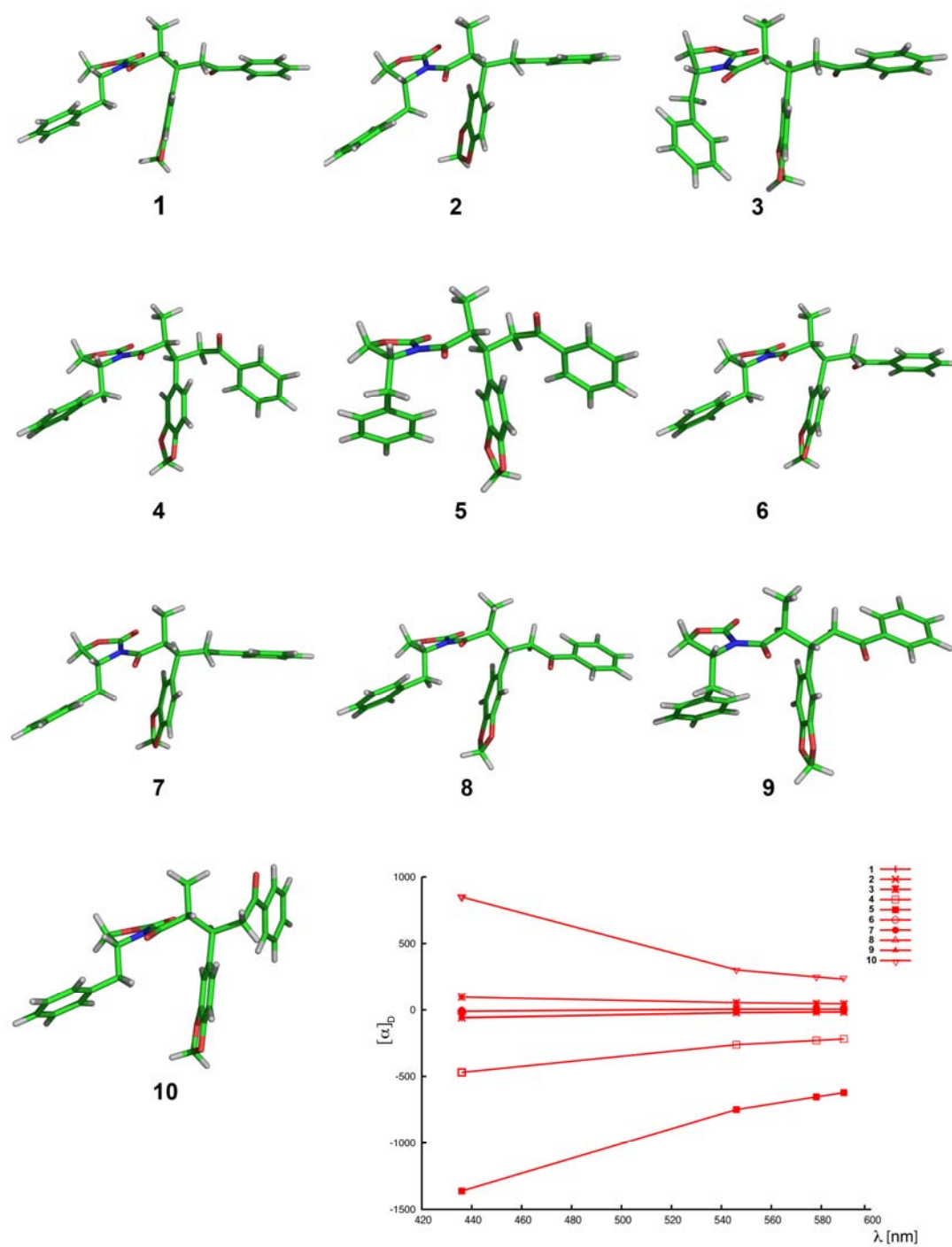


Figure S14. Optimized structures of the best ensemble of (RRR)-3 and plot of the calculated ORD values of each conformation. For all conformations, the C¹-N bond is *antiperiplanar*.

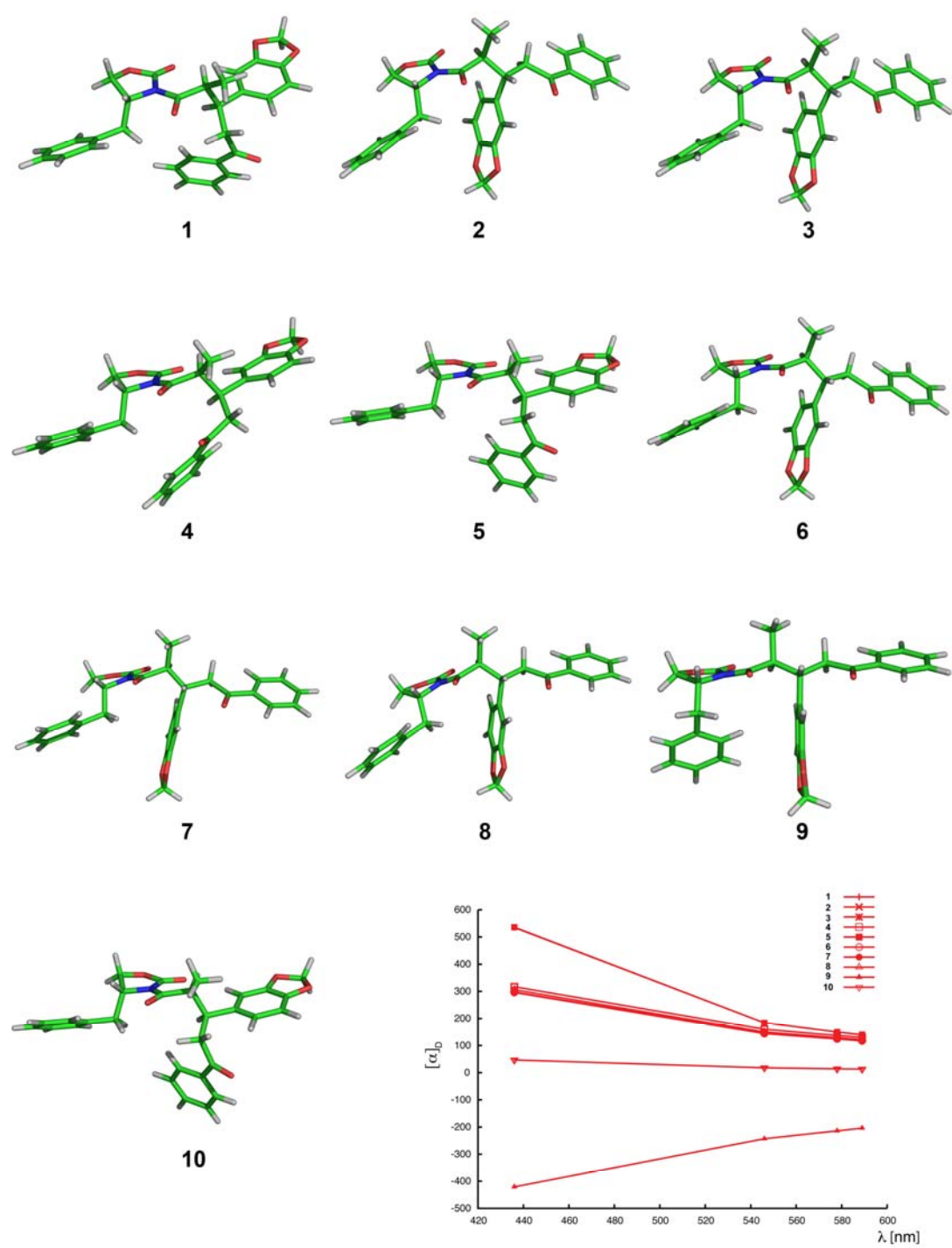


Figure S15. Optimized structures of the best ensemble of **(RSS)-3** and plot of the calculated ORD values of each conformation. For all conformations, the C¹-N bond is *antiperiplanar*.

Table S11. Calculated ORD values of each conformation for the best ensemble (**RRR**)-3 at four different wavelengths. For all conformations, the C¹-N³³ bond is *antiperiplanar*.

(RRR)-3	λ [nm]			
	436	546	578	589
1	-60	-21	-18	-16
2	-60	-22	-17	-17
3	96	54	47	45
4	-470	-262	-230	-219
5	-1362	-749	-654	-622
6	-10	6	6	6
7	-11	5	6	6
8	-11	5	6	6
9	-58	-20	-16	-15
10	850	302	249	233

Small uncertainty of the conformational changes is tolerable in the ORD calculation as one can see from Figs. S14 and S15 for the best ensembles of (**RRR**)-3 and (**RSS**)-3. Focussing on the RRR-3 ensemble, structures 5 and 10 have the largest difference in ORD. At the same time they are quite different with respect to the conformation of the two aromatic rings that are considered to dominate the ORD effect. Thus, obviously, ORD changes only dramatically if certain conformational features change from conformation to conformation.

Table S12. Calculated ORD values of each conformation for the best ensemble (**RSS**)-3 at four different wavelengths. For all conformations, the C¹-N³³ bond is *antiperiplanar*.

(RSS)-3	λ [nm]			
	436	546	578	589
1	545	184	150	139
2	306	150	129	122
3	306	150	129	122
4	316	160	137	130
5	536	184	150	140
6	296	144	124	117
7	298	146	125	118
8	306	149	129	122
9	-421	-243	-214	-204
10	47	18	14	13

Part IV: References

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