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Characterization of stereoisomeric 5-(2-nitro-1-phenylethyl)furan-2(5*H*)-ones by computation of <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts and electronic circular dichroism spectra

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# Abstract

In the present work we describe the preparation of two diastereomers from the enantioselective Michael addition of furan-2(5H)-one to (*E*)-(2-nitrovinyl)benzene catalyzed by a dinuclear Zn-complex. The relative configurations of the diastereomeric products were assigned by comparing NMR experimental chemical shift data with those computed by DFT methods. Corrected mean absolute error (CMAE) and CP3 analyses were used to compare the data sets. The absolute configuration of each diastereomer was initially assigned by analysis of electronic circular dichroism (ECD) data, which was consistent with that of the known X-ray crystallographic structure of the product of a related reaction, namely (R)-5-((R)-1-(4-chlorophenyl)-2-nitroethyl)furan-2(5H)-one.

# Keywords

DFT, MAE, CP3, ECD, NMR, Michael addition

## HIGHLIGHTS

Relative configuration determination by computation of NMR properties. Absolute configuration analysis by electronic circular dichroism (ECD).

# **1. Introduction**

One challenge for synthetic chemists is achieving the preparation of compounds having high levels of excess of one stereoisomer among others. Chiral auxiliaries or asymmetric catalysts often drive the new methodologies used to perform enantioselective and/or diastereoselective reactions. The need for such methods is often motivated by the differences in biological activity possessed by different stereoisomers.<sup>1-3</sup>

Conjugated  $\gamma$ -lactones have been used as the Michael donor upon activation to engage a suitable acceptor.<sup>6</sup> It should be noted that lactones are found in many biologically active compounds and are, additionally, precursors for the further synthesis of a range of other such compounds.<sup>7</sup>

NMR spectroscopy is the primary tool used to assign the constitution and relative configuration of new chemical structures. However, unequivocal assignment of structure can sometimes be challenging. In these instances, quantum chemical calculation of NMR properties can be helpful as an auxiliary tool. Different protocols can be used to compare experimental data with that computed for various candidate structures; among them is CP3, an approach that results in a statistic parameter for comparison of two sets of experimental vs. two sets of computed data of NMR chemical shifts.<sup>8</sup>

Another significant aspect of structure determination is assigning the correct absolute configuration (AC) to enantioenriched compounds. For crystalline compounds, X-ray diffraction can often allow for the determination of AC.<sup>9,10</sup> However a suitable single crystal is not always attainable, making the use of NMR-based techniques such as Mosher's ester analysis an alternative.<sup>11</sup> In addition, quantum chemical calculations have emerged in the last decade as a tool to predict with good accuracy spectroscopic parameters,<sup>12–18</sup> including chiroptical properties like electronic circular dichroism (ECD) spectra.<sup>19–22</sup>

The ECD technique can be employed to determine the absolute configuration of compounds containing suitable chromophores that absorb in the UV-visible spectrum. The experimental ECD spectra associated with quantum mechanical calculations using the appropriate functional and basis set have been used to establish the absolute configurations with good accuracy, and non-racemic samples of chiral compounds have been studied by this method.<sup>23–26</sup>

As part of a program directed towards the synthesis of bioactive compounds, we were interested in preparing substances with potential insecticidal and herbicidal activities. Lactone compounds are known to present diverse biological activities. Therefore, we decided to use the known<sup>4</sup> Michael addition of furan-2(5*H*)-one (1) to (*E*)-(2-nitrovinyl)benzene (2) to prepare a compound that could be further converted into various derivatives. From this reaction we obtained two diastereomers, one known and one new, whose relative and

absolute configurations were determined by comparison of the experimental with the computed NMR and ECD data. This analysis is the subject of the current manuscript.

### 2. Materials and Methods

## 2.1 General

THF was dried by refluxing over sodium wire in the presence of benzophenone as indicator and oxygen and water scavenger. The THF was distilled and stored over molecular sieves 4Å overnight. The reaction was followed by thin layer chromatography coated in silica-gel plates in a ultraviolet chamber at 254 nm<sup>27</sup> and subsequent staining with vanillin. Column chromatography was performed over silica gel (60-230 mesh). NMR spectra were recorded on a Bruker AVANCE III nanobay 400 MHz using deuterated chloroform as solvent. Both proton and carbon chemical shifts are reported relative to internal TMS ( $\delta = 0.00$  ppm). Carbon chemical shift assignments are based on analysis of the HMBC and HSQC spectra. The term "nfom" in a proton resonance is used to indicate a non-first order multiplet.

The experimental ECD curves were recorded on a J-815 Jasco spectropolarimeter. Each compound was analyzed at a concentration of 0.1 mg/mL in a solution of acetonitrile at ambient temperature in a 10 mm long cell from 200–500 nm. The data were saved in the .txt format and then processed in Origin 2017 using the option: analysis > signal processing > smooth > open dialog and selecting the FFT (fast Fourier transform) filter method and a window of 136.

# 2.2 Procedure for preparation of the diastereomeric Michael adducts.

Products **4a** and **4b** were prepared using a modification of the reported methodology.<sup>4</sup> The (*S*,*S*)-enantiomer of the bis-prophenol ligand (400 mg, 0.6 mmol, 1 equiv) was added to a flask under nitrogen atmosphere, and anhydrous THF (6.2 mL) was added followed by slow addition of a 1.0 M solution of  $Et_2Zn$  in hexanes (1.2 mL, 1.2 mmol, 2 equiv). The resulting mixture was stirred at rt for 20 min and subsequently used, assuming it to be a 0.1 M solution of catalyst **3**.

*trans*- $\beta$ -Nitrostyrene (**2**, 0.950 mg, 6.3 mmol, 1 equiv) was added to a round-bottomed flask containing dry THF (18.7 mL) under nitrogen atmosphere. The freshly prepared solution of catalyst **3** in THF (6.2 mL, 0.63 mmol, 0.10 equiv) and furan-2(5*H*)-one (**1**, 0.9 mL, 0.01 mmol, 2 equiv) were successively added to the reaction mixture. The mixture was stirred at room temperature for 22 h and diluted with EtOAc (50 mL). The reaction mixture

was filtered through a pad of Celite<sup>®</sup> and washed with water (62.5 mL). The aqueous layer was separated and extracted with EtOAc (3 x 62.5 mL); the combined organic layers was dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by flash silica gel column chromatography (hexanes:EtOAc 1.5:1) gave, in order of elution, isomer **4a** (or **4a-ent**), a mixture of **4a** (or **4a-ent**) and **4b**, and isomer **4b**. After 24 hours, crystals were formed from the mixture in diethyl ether, which were separated to leave, predominantly, the diastereomer **4b**. The final isolated yields of pure **4a** and **4b** were (349.1 mg, 23%) and (208.7 mg, 14%) respectively.

#### (*R*)-5-((*S*)-2-Nitro-1-phenylethyl)furan-2(5H)-one (4a)

 $R_f$  = 0.48 (hexane:EtOAc 1.5:1); yellow solid (mp 119.9-122.7 °C); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.6 (C2), 154.0 (C4), 134.5 (Ph<sub>ipso</sub>), 129.6 (Ph<sub>m</sub>), 129.1 (Ph<sub>p</sub>), 127.9 (Ph<sub>o</sub>), 122.8 (C3), 83.0 (C5), 76.8 (C2'), and 48.1 (C1'); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.44-7.34 (m, 3H, H5', H6' and H7'), 7.25-7.30 (dd, *J* = 7.6, 2.0 Hz, 2H, H4' and H8'), 7.18 (dd, *J* = 5.7, 1.7 Hz, 1H, H4), 6.18 (dd, *J* = 5.7, 1.7 Hz, 1H, H3), 5.21 (ddd, *J* = 9.0, 1.7, 1.7 Hz, 1H, H5), 4.95 (dd, *J* = 13.3, 5.3 Hz, 1H, H2'a or H2'b), 4.82 (dd, *J* = 13.3, 9.0 Hz, 1H, H2'a or H2'b), and 3.62 (ddd, *J* = 9.0, 9.0, 5.3 Hz, 1H, H1'); *m*/*z* (EI, 70 eV) 233 (0.16 M<sup>+</sup>, C<sub>12</sub>H<sub>11</sub>NO<sub>4</sub>), 186 (15), 150 (36), 104 (99), and 55 (100%); IR (ATR, thin film) v 3092 (C<sub>sp2</sub>-H), 2922 (C<sub>sp3</sub>-H), 1788 and 1749 (C=O), 1602 (C=C), 1548 (N=O), 1156 and 1086 (=C-O-C), and 893 (C-N) cm<sup>-1</sup>.

### (*R*)-5-((*R*)-2-Nitro-1-phenylethyl)furan-2(5H)-one (**4b**)

 $R_f$  = 0.39 (hexane:EtOAc 1.5:1); colorless crystals (mp 152.2-153.4 °C); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.8 (C2), 153.4 (C4), 132.5 (Ph<sub>ipso</sub>), 129.2 (Ph<sub>m</sub>), 128.8 (Ph<sub>p</sub>), 128.3 (Ph<sub>o</sub>), 123.1 (C3), 81.9 (C5), 75.8 (C2'), and 46.0 (C1'); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.27-7.35 (m, 4H, H4, H5', H7' and H6'), 7.11-7.19 (nfom, 2H, H4' and H8'), 5.93 (dd, *J* = 5.8, 2.0 Hz, 1H, H3), 5.38 (ddd, *J* = 3.3, 2.0, 1.6 Hz, 1H, H5), 4.98 (dd, *J* = 13.7, 7.6 Hz, 1H, H2'a or H2'b), 4.82 (dd, *J* = 13.7, 7.6 Hz, 1H, H2'a or H2'b), and 4.05 (ddd, *J* = 7.6, 7.6, 3.2 Hz, 1H, H1'); *m*/*z* (EI, 70 eV) 233 (0.15 M<sup>+</sup>, C<sub>12</sub>H<sub>11</sub>NO<sub>4</sub>), 186 (13), 150 (38), 104 (93), and 55 (100%); IR (ATR, solid state) v 3106 (C<sub>sp2</sub>-H), 2919 (C<sub>sp3</sub>-H), 1772 and 1737 (C=O), 1600 (C=C), 1546 (N=O), 1167 and 1105 (=C-O-C), and 884 (C-N) cm<sup>-1</sup>.

### 2.3 Computation

<u>Conformational search</u>. A molecular mechanics "Conformer search" was used to identify a suitable set of starting candidate structures for further DFT geometry optimization. This initial search was performed using the optimized potentials for liquid simulations (OPLS3)<sup>28,29</sup> parameter set as implemented in Maestro 2018-1 (Maestro version 11.5.011).<sup>30</sup> The OPLS3 force field includes systematic generation of torsional parameters previously missing from earlier versions of this force field. The "Energy window for saving structures" was kept at 5.02 kcal mol<sup>-1</sup>, "100 steps per rotatable bond" and the "Maximum number of steps" was 1000. The number of conformers found for (R)-5-((S)-2-nitro-1phenylethyl)furan-2(5H)-one (4a) and (R)-5-((R)-2-nitro-1-phenylethyl)furan-2(5H)-one (4b) were 10 and 12, respectively. As an internal check on the computational methodology, the enantiomeric (S)-5-((R)-2-nitro-1-phenylethyl)furan-2(5H)-one (4a-ent) and (S)-5-((S)-2nitro-1-phenylethyl)furan-2(5H)-one (4b-ent) were also computed in the same fashion and, as they should, gave rise to an entirely analogous set of 10 and 12, mirror image conformers. Chemical shift calculations. All candidate conformers from the molecular mechanics conformational search were subjected to geometry optimization and frequency calculation using Gaussian  $16^{31}$  at the M06-2X<sup>32</sup>/6-31+G(d,p) level of theory. NMR shielding tensors were calculated for each optimized conformer using B3LYP<sup>33</sup> functional and 6-311+G(2d,p) basis set. The Boltzmann weighting factors were calculated from the relative free energies obtained from the frequency calculations. The shielding constants were Boltzmann averaged for each nucleus of each isolated conformer. Solvation was addressed using integrated equation formalism polarized continuum model (IEFPCM)<sup>34</sup> during optimization and shielding constants calculations. Chemical shifts were then calculated according to  $\delta_{calc}^{x}$  =  $\frac{\sigma^o - \sigma^x}{1 - \sigma^o / 10^6}$ , where  $\delta_{calc}^x$  is the calculated shift for nucleus x (in ppm),  $\sigma^x$  is the shielding constant for nucleus x and  $\sigma^{o}$  is the shielding constant for the proton in tetramethylsilane (TMS), which was obtained using the same level of theory ( ${}^{1}H = 31.8816$ ;  ${}^{13}C = 183.7262$ ). Some systematic differences between experimental and calculated chemical shifts were then reduced by using linear regression. This was done in MS Excel for all the experimental (y axis) versus computed (x axis) chemical shifts. The linear regression was performed for chemical shifts grouped into a set of (5) C<sub>sp2</sub>-bound and (4) C<sub>sp3</sub>-bound protons (Tables S1-S4). The linear regression was done also without separating C<sub>sp2</sub>-bound and C<sub>sp3</sub>-bound protons. The <sup>1</sup>H NMR chemical shifts of C<sub>sp2</sub>-bound and C<sub>sp3</sub>-bound protons were all grouped together for the linear regression (Tables S26-S29).

<u>CMAE analysis</u>. The corrected mean absolute error (CMAE) is the average difference between the calculated ( $\delta_{calc}$ ) chemical shift, corrected by linear regression, and the experimental ( $\delta_{exp}$ ) chemical shift for each of the unique protons in the candidate pairs of structures ( $\Sigma_n |\delta_{calc} - \delta_{exp}|/n$ ). Better r<sup>2</sup> fits were seen when the corrected shifts were separately binned into a set of (5) C<sub>sp2</sub>-bound and (4) C<sub>sp3</sub>-bound protons as opposed to including all (9) protons in a single regression set.

<u>MAE analysis</u>. Mean absolute error (MAE) data are those from the uncorrected chemical shifts. No linear correction was carried out on the chemical shifts.

<u>CP3 analysis</u>. The computed chemical shifts used in the CMAE calculation were also used in CP3 analyses. CP3 analyses were performed with uncorrected chemical shifts (no linear correction, **Figure S19-S22**) and after linear correction (**Figure S23-S25**). The calculated and experimental <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts for both of the diastereomeric structures were transferred to the CP3 analysis tool located at <u>http://wwwjmg.ch.cam.ac.uk/tools/nmr/CP3.html</u>.

Electronic Circular Dichroism (ECD) calculations. The geometry was optimized for all (10 or 12) candidate conformers using Gaussian  $16^{31}$  at the APFD<sup>35</sup>/6-311+G(2d,p) level of theory. The electronic spectrum was also computed using this basis set with acetonitrile as solvent (IEFPCM).<sup>34</sup> For the calculated spectra the results were processed in GaussView 16<sup>31</sup> software. All six conformers of each candidate structure were opened as a single new molecule group. In the "Results" dialog the "UV-vis" option was selected; a plot of the weighted ECD spectrum was created by selecting "mixture spectra in the plot menu". In the "mixture editor" dialog, under "Weight", "assign Boltzmann population weights" was selected. In the "combination region," "curve" was selected from the "plot style" drop-down menu. In the "plot style" column, the option none was selected for each conformer. "Ok" returns one to the spectrum; in the "plot" drop-down menu, in properties the scale the "UVvis" option was deselected leaving only the ECD spectrum showing. In "Properties" the "fixed range" for the x axis was set from 225 to 280 nm and y axis from -8 to 8  $\Delta\epsilon$  (units of 10-40  $esu^2 cm^2$ ) for structures *R*,*R* and *S*,*S* (4b and 4b-ent). For candidate structures *R*,*S* and SR (4a and 4a-ent) the x axis was set to the same wavelength of 225 and 280 nm and to -4 to 4  $\Delta \varepsilon$  (units of 10-40 esu<sup>2</sup> cm<sup>2</sup>) for the y axis. "Save data" was used to save the spectrum as a \*.txt file, which was opened in Origin to combine with the experimental curve(s) to then superimpose on the computed spectra.

#### 3. Results and discussion

Lactones are of interest because of their biological activity as well as their uses in synthetic chemistry. Among the latter is a variant of the Michael reaction in which a butenolide anion acts as a nucleophile that adds to an appropriately electrophilic Michael acceptor. Asymmetric catalysts have been used to promote this reaction. In the study reported here, we used the method of Trost and Hitce<sup>4</sup> to effect the addition of furan-2(5*H*)-one (**1**) to *trans*- $\beta$ -nitrostyrene (**2**) in the presence of the zinc (*S*,*S*)-bis-Pro-Phenol-based complex **3**. This afforded two diastereomeric products: the faster eluting compound (on silica gel) was presumed to be either (*R*)-5-((*S*)-2-nitro-1-phenylethyl)furan-2(5*H*)-one (**4a**) or its enantiomer (**4a-ent**); the slower eluting isomer had NMR spectral data that were essentially identical with those reported for the known isomer<sup>4</sup> (*R*)-5-((*R*)-2-nitro-1-phenylethyl)furan-2(5*H*)-one (**4b**) (Fig. 1).



**Figure 1**: Asymmetric Michael reaction of *trans-\beta*-nitrostyrene (2) and furan-2(5*H*)-one (1), catalyzed by the asymmetric zinc complex 3. Candidate structures 4a (*R*,*S*), 4a-ent (*S*,*R*), 4b (*R*,*R*), and 4b-ent (*S*,*S*) for the two diastereomeric products.

The relative and absolute configurations of **4b** were originally assigned based on the consistency of its NMR spectral data within a series of related compounds made by this methodology, one of whose structures was verified by a single crystal x-ray diffraction analysis.<sup>4</sup> Having both (**4b**) and (either **4a** or **4a-ent**) diastereomers in hand, we further analyzed these isomers using computational NMR methods. More specifically, the proton and carbon chemical shifts were computed for each and compared with the experimental values. Subsequently, all four stereoisomers were further studied by comparing their experimental

and computed ECD spectra to confirm (for 4b) and establish (for 4a) their absolute configuration.

All <sup>1</sup>H and <sup>13</sup>C NMR signals were assigned for both candidate structures by interpretation of the NMR spectral data. However, the relative configurations of the isolated diastereomers could not be definitively assigned based only on the interpretation of their NMR spectra. To achieve that, we computed the NMR chemical shifts for the ( $R^*,S^*$ ) and ( $R^*,R^*$ ) diastereomers (i.e., **4a** and **4b**) in order to compare these to the experimental values for each compound. For the computations, the geometries for the set of conformations, identified by an initial molecular mechanics conformational search,<sup>36</sup> for each of **4a** and **4b** were optimized at the M06-2X/6-31+G(d,p) level of theory and then subjected to NMR chemical shift calculation using the B3LYP functional and 6-311+G(2d,p) basis set. The shifts for each diastereomer were Boltzmann averaged according to the M06-2X energies of the full set of conformers. The experimental proton chemical shifts for each of the two diastereomers as well as the computed shifts (linearly corrected, see Supporting Information (SI)) for each of the isomeric **4a** and **4b** are shown in Table 1. The experimental carbon chemical shifts for each of the two diastereomers as well as the computed shifts after linear correction (SI) for each of the isomeric **4a** and **4b** are shown in Table 2.

The corrected mean absolute error (CMAE) and the CP3 statistical analysis were then used to identify the better match between the experimental and computed data sets. CP3 is calculated according to **Equation S1** (SI) and it is based on comparing differences in calculated chemical shifts with differences in experimental data for equivalent atoms. Some systematic errors in calculated data are cancelled by comparing the differences between two calculated shifts and two experimental chemical shifts. A large positive value for CP3 points to a correct assignment, whereas a large negative value indicates poor agreement. Nuclei which are not useful for discriminating between structures are automatically given a low weighting. The probability that the assignment combination is correct (4a = R, S, 4b = R, R) is calculated by the Bayes' theorem (**Equation S2**, SI).<sup>37</sup>

The results of these approaches are summarized in **Table 3**. Both CMAE and CP3 analyses of the proton data clearly indicate a better correlation between the experimental and computed shifts for the pairs of structures  $4a_{expt}$  vs.  $4a_{calc}$  and  $4b_{expt}$  vs.  $4b_{calc}$  (cf. green highlighted values).

MAE analysis was carried out for the <sup>1</sup>H NMR chemical shifts without linear correction (**Tables S30-S33**). CMAE analyses were performed for the <sup>1</sup>H NMR after linear correction of the chemical shifts without separating the  $C_{sp2}$ -bound and  $C_{sp3}$ -bound protons (**Tables S26-S29**).

CMAE calculation after linear regression of the <sup>1</sup>H NMR chemical shifts of  $4a_{exp}+4b_{exp}$  vs.  $4a_{calc}+4b_{calc}$  and  $4a_{exp}+4b_{exp}$  vs.  $4b_{calc}+4a_{calc}$  was carried out (Tables S34-S35). Linear correction done using the new Python scripts created by Willoughby-Hoye <sup>1</sup>H<sub>stope</sub> = -1.0767; <sup>1</sup>H<sub>intercept</sub>= 31.9477; <sup>13</sup>C<sub>stope</sub> = -1.0522; <sup>13</sup>C<sub>intercept</sub>= 181.2412 followed by CMAE calculation was also evaluated. All MAE and CMAE analyses were consistent except for the method employing intercet-slope from the literature.<sup>36</sup> Incorrect matching  $4b_{exp} \neq 4a_{calc}$  presented smaller CMAE (0.11 ppm) than the correct matching  $4b_{exp}=4b_{calc}$  (0.18 ppm). However, except for the approach intercept-slope from the literature, the outcome of the other calculations agreed as summarized in Table 4. The literature intercept-slope was created using a large set of molecules with a wide range of chemical shifts, and the molecules in the present work contain atoms with NMR shielding constant properties (through-space effects and anisotropy) different from those in the literature. Therefore, the use of literature intercept-slope tends to inadequately correct the chemical shifts in the present work.

The CMAE analysis of the carbon shift data (after linear correction; Tables S7-S10) is far less clear. Previous work has shown that <sup>13</sup>C shifts are sometimes less reliable than <sup>1</sup>H in identifying the correct relative configuration within sets of diastereomers.<sup>38</sup> The two lowest CMAE fits for the carbon data are both to the same calculated data set (i.e., that for 4b<sub>calc</sub>; cf. blue vs. gray highlighted CMAE values). Since it is, of course, impossible for both diastereomers to have the same relative configuration(!), we also looked at the use of a "match ratio,"<sup>39</sup> an approach that recently has been statistically validated for identification of the better of two possible pairwise correlations for over 200 pairs of diastereomers.<sup>38</sup> In that approach, greater weight is placed on any pair of CMAE values having a higher match ratio. Applying that concept here leads to the correct conclusion, but the difference in the match ratio values (1.34 vs. 1.21) is quite small and that criterion alone does not lend sufficient confidence in guiding the assignment of relative configuration. Linear regression of the <sup>13</sup>C NMR chemical shifts of 4aexp+4bexp vs. 4acalc+4bcalc and 4aexp+4bexp vs. 4bcalc+4acalc followed by CMAE analysis of the corrected shifts are summarized in Table 4 (cf. green highlighted values). Linear regression was carried out in MS Excel and transferred to the SM (Tables S36-S37). The assignment of relative configuration is more conclusive when linear

correction of the calculated  ${}^{13}$ C NMR chemical shifts is done for the entire set of chemical shifts (4a+4b) than when it is carried out separately.

However, the CP3 analysis method for the carbon data is definitive, just as it was for the proton data sets.

After using the above NMR methods to validate the relative configurations of the two diastereomers as (4a or 4a-ent) and (4b), we decided to examine the ability of ECD calculations to validate the known absolute configuration of 4b and then, if encouraging, to assign the absolute configuration of the second diastereomer. The experimental ECD spectrum (dashed) of the isomer 4b was compared to the calculated electronic spectra for each of the enantiomers 4b and 4b-ent (Fig. 2, panel A). For each isomer, the calculated spectrum was merged from the Boltzmann-weighted spectra from the six individual, lowest energy conformers. We judged there to be a sufficiently good match (cf. red vs. dashed spectra) to warrant using the same approach for the comparison of the computed ECD spectra for 4a and 4a-ent with the experimental spectrum for the second diastereomer (Fig. 2, panel B). In this case, there was a very close similarity between the blue and dashed spectra, leading us to confidently assign the absolute configuration of the second isomer as 4a. In other words, the major enantiomer in each of these two Michael addition products has arisen from approach of the electrophilic nitrostyrene to the same enantiotopic face of C5 in the enolized furanone nucleophile (cf. Fig. 1).

B)



**Figure 2**: Panel A) Experimental electronic circular dichroism (ECD) spectrum of **4b** (dotted line) and the calculated spectra of the (R,R)- and (S,S)-enantiomers **4b** (red) and **4b-ent** (orange). Panel B) ECD spectrum of the minor isomer (dotted line) and the calculated spectra for the (R,S)- and (S,R)-enantiomers **4a** (blue) and **4a-ent** (green).

# 4. Conclusion

The enantioselective Michael addition of furan-2(5*H*)-one (1) to *trans-* $\beta$ -nitrostyrene (2) provided two diastereomeric products **4a** and **4b**. The relative configurations of these two diastereomers were distinguished by comparing the experimental <sup>1</sup>H NMR chemical shift values with the shifts computed for each of the two candidate structures. The validity of using the computed ECD spectrum to discern the correct absolute configuration for this class of compound was established using the known (*R*,*R*)-stereoisomer **4b** as a benchmark. This approach was then used to assign the absolute configuration of the second diastereomer as the (*R*,*S*)-isomer **4a**.

# **Supporting Information**

Further details of the NMR assignments, CMAE analyses, and CP3 analyses. The DFT energies and optimized geometries for the individual conformers as well as copies of the <sup>1</sup>H and <sup>13</sup>C 1D and 2D (HSQC and HMBC) NMR spectra for the isomers **4a** and **4b** may be found in the online version of this article at the publisher's website.

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	<u> </u>	<u> ठीम</u> Calculated corrected <sup>a</sup>			
Proton	$ \begin{array}{c}     "R,S" \\     4a \text{ or } 4a\text{-ent} \\     \delta(\text{ppm})^b \end{array} $	$egin{array}{c} ``R,R"\ 4b^4\ \mathcal{\delta}(\mathrm{ppm})^b \end{array}$	" <i>R,S"</i> 4a δ(ppm) <sup>c</sup>	${}^{\prime\prime}\!$	
3	6.18 (dd, 5.7, 2.7)	5.93 (dd, 5.8, 2.0)	6.18	5.93	
4	7.18 (dd, 5.7, 1.7)	7.31 (m)	7.21	7.30	
5	5.21 (dt, 9.0, 1.7)	5.38 (m)	5.18	5.31	
1'	3.62 (ddd, 9.0, 9.0, 5.4)	4.05 (ddd, 7.6, 3.2)	3.61	4.02	
2'a	4.82 (dd, 13.3, 9.0)	4.82 (dd, 13.7, 7.6)	4.84	4.86	
2'b	4.95 (dd, 13.3, 5.3)	4.98 (dd, 13.7, 7.6)	4.97	5.03	
Phipso	n/a	n/a	n/a	n/a	
Pho	7.28 (m)	7.15 (m)	7.35	7.25	
Ph <sub>m</sub>	7.40 (m)	7.31 (m)	7.36	7.27	
$Ph_p$	7.40 (m)	7.31 (m)	7.34	7.27	

Table 1. Experimental vs. computed <sup>1</sup>H NMR chemical shifts of diastereomers 4a and 4b.

<sup>*a*</sup>After linear correction (see SI). <sup>*b*</sup>Data in parentheses following the shift value is the multiplicity and *J* values (in Hz) for each proton. <sup>*c*</sup>Data taken from " $\partial$ H Calc *R*,*S* Corrected" Table S1. <sup>*d*</sup>Data taken from " $\partial$ H Calc *R*,*R* Corrected" Table S4.

	<u> бн</u> Ехр	erimental	<u> бн</u> Calculated Corrected <sup>a</sup>		
Carbon	4a or 4a-ent $\delta$ (ppm)	$4b^4$ $\delta$ (ppm)	$4 { m a} \delta { m (ppm)^b}$	$4 extbf{b}$ $\delta( extbf{ppm})^ extbf{c}$	
2 (C=O)	171.6	171.8	171.9	171.9	
3	122.8	123.1	121.0	121.5	
4	154.0	153.4	158.2	157.8	
5	83.0	81.9	82.8	81.0	
1'	48.1	46.0	49.9	48.1	
2'	76.8	75.8	77.3	76.2	
Phipso	134.5	132.5	135.3	133.0	
$Ph_o$	127.9	128.3	126.8	126.7	
$Ph_m$	129.6	129.2	127.2	127.6	
$\mathrm{Ph}_p$	129.1	128.8	127.0	127.0	

Table 2. Experimental vs. computed <sup>13</sup>C NMR chemical shifts of diastereomers 4a and 4b.

"After linear correction (see SI). <sup>b</sup>Data taken from "ALC" Table S7. <sup>c</sup>Data taken from "ALC" Table S8.

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pairwise comparisons	<sup>d</sup> CMAE <sub>proton</sub>	<sup>e</sup> CMAE <sub>carbon</sub>	match ratio	CP3proton	CP3carbon	CP3 all data <sup>c</sup>
4aexpt VS. 4acalc	0.03 ppm	1.53 ppm		98.3%	100%	100%
4aexpt VS. 4bcalc	0.06 ppm	1.26 ppm	$\int^{1.21}$	1.7%	0%	0
4bexpt vs. 4bcalc	0.04 ppm	1.48 ppm		98.3%	100%	100%
4bexpt vs. 4acalc	0.09 ppm	1.98 ppm	$\int^{1.34}$	1.7%	0%	0

Table 3. Methods used for comparison of experimental and calculated chemical shift data.<sup>a,b</sup>

<sup>a</sup>The chemical shifts used in the CP3 analyses were not corrected by linear regression.

<sup>b</sup>The CP3 analyses were performed before and after assignment of the signals. The probabilities were identical in both situations (print screens of the CP3 analyses are shown in the SI).

<sup>c</sup>CP3 analysis was performed with proton and carbon data.

<sup>d</sup>The linear regression was performed for chemical shifts grouped into a set of (5) Csp2bound and (4) Csp3-bound protons (**Tables S1-S4**).

<sup>e</sup>After linear correction (ALC) of the calculated <sup>13</sup>C NMR chemical shifts (**Tables S7-S10**).



Pairwise	<sup>a</sup> CMAE <sub>proton</sub>	<sup>b</sup> CMAE <sub>proton</sub>	<sup>c</sup> MAE <sub>proton</sub>	<sup>d</sup> CMAE <sub>proton</sub>	<sup>e</sup> CMAE <sub>proton</sub>	<sup>f</sup> CMAE <sub>carbon</sub>
comparisons	i i					
4a <sub>exp</sub> vs. 4a <sub>calc</sub>	0.03 ppm	0.05 ppm	0.29 ppm	0.07 ppm	0.09 ppm	1.51 ppm
4aexp vs. 4bcalc	0.06 ppm	0.16 ppm	0.35 ppm	0.15 ppm	0.24 ppm	1.93 ppm
4b <sub>exp</sub> vs. 4b <sub>calc</sub>	0.04 ppm	0.08 ppm	0.28 ppm	0.07 ppm	0.18 ppm	1.51 ppm
4bexp vs. 4acalc	0.09 ppm	0.11 ppm	0.33 ppm	0.15 ppm	0.11 ppm	1.93 ppm

**Table 4.** MAE and CMAE analyses calculated before and after linear correction of the calculated <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts, respectively.

<sup>a</sup>The linear regression was performed for chemical shifts grouped into a set of (5) Csp2bound and (4) Csp3-bound protons (**Tables S1-S4**).

<sup>b</sup>The linear regression was done without separating Csp2-bound and Csp3-bound protons. The <sup>1</sup>H NMR chemical shifts were all grouped together for the linear regression (**Tables S26-S29**).

<sup>c</sup>Without linear correction of the calculated <sup>1</sup>H NMR chemical shifts (**Tables S30-S33**).

<sup>d</sup>The linear correction was done using the <sup>1</sup>H NMR chemical shifts of **4a+4b**. The CMAE was calculated using (**4a+4b**)<sub>calc</sub> vs. (**4a+4b**)<sub>exp</sub>. and (**4b+4a**)<sub>calc</sub> vs. (**4a+4b**)<sub>exp</sub>. (**Tables S34-35**)

<sup>e</sup>The linear correction was done using the new Python scripts created by Willoughby-Hoye  ${}^{1}H_{slope} = -1.0767$ ;  ${}^{1}H_{intercept} = 31.9477$ ;  ${}^{13}C_{slope} = -1.0522$ ;  ${}^{13}C_{intercept} = 181.2412$ ;<sup>36</sup>

<sup>f</sup>The linear correction was done using the <sup>13</sup>C NMR chemical shifts of **4a+4b**. The CMAE was calculated using (**4a+4b**)<sub>calc</sub> vs. (**4a+4b**)<sub>exp</sub>. and (**4b+4a**)<sub>calc</sub> vs. (**4a+4b**)<sub>exp</sub>. (**Tables S36-37**)

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