Supporting Information: Unbiased Determination of Absolute Configurations by vis-à-vis Comparison of Experimental and Simulated Spectra: the Challenging Case of Diplopyrone

Marco Fusè,[†,#] Giuseppe Mazzeo,[¶,#] Giovanna Longhi,[¶,§] Sergio Abbate,[*,¶,§] Marco Masi,[‡] Antonio Evidente,[*,‡] Cristina Puzzarini,[&] and Vincenzo Barone[*,†]

†*Scuola Normale Superiore, Piazza dei Cavalieri 7, I-56126 Pisa, Italy*

¶*Dipartimento di Medicina Molecolare e Traslazionale, Università di Brescia, Viale Europa 11, 25123 Brescia, Italy*

§*Consiglio Nazionale delle Ricerche-I.N.O. c/o CSMT via Branze, 45 – 25123 Brescia, Italy*

‡*Dipartimento di Scienze Chimiche, Università di Napoli Federico II, Complesso Universitario Monte S. Angelo, Via Cintia 4, 80126 Napoli, Italy*

&*Dipartimento di Chimica "Giacomo Ciamician", Università di Bologna, Via Selmi 2, I-40126 Bologna (Italy)*

#*These authors contributed equally to this work.*

E-mail: sergio.abbate@unibs.it; antonio.evidente@unina.it; vincenzo.barone@sns.it

Contents

1 Preliminary Conformational Analysis **S-3**

2 ECD **S-5**

3 Optical Rotation **S-6**

4 Harmonic IR and VCD spectra **S-7**

5 Anharmonic Calculations **S-9**

5.1 Resonances Thresholds S-9

5.1.1 Fermi Resonances S-9

5.1.2 Intensity Specific Fermi Resonances S-9

5.1.3 Darling-Dennison resonances S-10

5.1.4 Intensity Specific Darling-Dennison resonances S-10

5.2 LAMs and Added Resonance in the GVPT2 calculations. S-11

5.2.1 Diastereomer *R-R-SS*: S-11

5.2.2 Diastereomer *R-S-SS* Conformer 1 . . . . . S-11

5.2.3 Diastereomer *R-S-SS* Conformer 2 . . . . . S-12

5.2.4 Diastereomer *R-S-SS* Conformer 3 . . . . . S-13

5.2.5 Diastereomer *R-S-SS* Conformer 4 . . . . . S-14

5.2.6 Diastereomer *R-S-SS* Conformer 5 . . . . . S-15

5.2.7 Diastereomer *S-R-SS* S-17

5.2.8 Diastereomer *S-S-SS* S-17

6 Optimized structures in XYZ **S-20**

References **S-28**

1 Preliminary Conformational Analysis

Table S1: Conformer relative free energies (ΔG, in kJ/mol units) and percent population factors (%pop, computed from the Boltzmann distribution) for all diplopyrone diastereomers calculated at the B3LYP-D3/TZVP level of theory.

R-R-SS	ΔG	%pop	*R-S-SS*	ΔG	%pop	*S-R-SS*	ΔG	%pop	*S-S-SS*	ΔG	%pop
1	0.00	51.6	1	0.00	37.6	1	0.00	16.9	2	0.00	56.6
5	3.26	13.9	2	0.84	27.0	4	0.63	13.0	1	1.97	25.6
4	3.77	11.2	3	2.22	15.3	5	0.84	12.1	3	5.27	6.8
2	4.73	7.7	5	3.14	10.7	3	1.38	9.6	5	5.90	5.3
3	5.06	6.7	4	4.35	6.5	8	1.51	9.2	4	6.44	4.2
6	7.95	2.1	6	6.95	2.3	6	1.51	9.2	8	10.42	0.8
7	8.16	1.9	7	10.29	0.6	9	1.97	7.7	7	11.25	0.6
8	8.83	1.5	8	20.88	0.0	2	2.51	6.2	6	17.74	0.0
9	10.38	0.8	9	21.76	0.0	10	3.47	4.2	9	22.18	0.0
14	10.42	0.8	10	22.59	0.0	11	3.47	4.2	10	24.31	0.0
13	11.80	0.4	11	23.89	0.0	12	3.81	3.7	12	26.74	0.0
11	11.92	0.4	14	24.39	0.0	7	5.19	2.1	11	27.28	0.0
10	12.13	0.4	12	25.23	0.0	13	7.45	0.8			
16	12.72	0.3				14	8.37	0.6			
12	15.06	0.1				16	10.29	0.3			
18	15.06	0.1				19	10.29	0.3			
17	16.69	0.1				15	12.18	0.1			

All density functional theory calculations have been corrected for dispersion effects according to Grimme's DFT-D3[S1] scheme employing the Becke-Johnson damping function.[S2] The levels of theory considered are: the hybrid B3LYP[S3,S4] functional in conjunction with the jun-cc-pVDZ[S5] basis set and the double-hybrid B2PLYP[S6] functional in conjunction with the jun-cc-pVTZ basis set.[S5] All computations have been performed using the Gaussian suite of programs.[S7]

Table S2: Relative energy, free energy and free energy in $CDCl_3$(PCM) in kJ/mol and percent population factors (%pop, computed from the Boltzmann distribution) at 298K of the five most populated conformers of the *R-S-SS* diastereomer. The values computed at the B3LYP-D3/jun-cc-pVDZ (B3) and B2PLYP-D3/jun-cc-pVTZ (B2) levels of theory are reported.

	B3		B2	
Conf.	ΔE	%pop.	ΔE	%pop.
Conf.1	0.8124	37.57	0.0225	41.57
Conf.2	0.0000	52.22	0.0000	41.95
Conf.3	5.6493	5.29	3.9136	8.59
Conf.4	6.5450	3.68	5.0145	5.50
Conf.5	9.2328	1.24	7.0597	2.40
Conf.	ΔG	%pop.	ΔG	%pop.
Conf.1	0.6890	35.51	0.1326	35.95
Conf.2	0.0000	46.95	0.0000	37.94
Conf.3	3.8896	9.70	2.4076	14.30
Conf.4	5.6134	4.82	4.0378	7.38
Conf.5	6.7704	3.02	5.2988	4.43
Conf.	ΔG PCM	%pop.	ΔG PCM	%pop.
Conf.1	0.2177	39.94	0.0000	39.88
Conf.2	0.0000	43.62	0.2195	36.48
Conf.3	4.5201	6.98	3.3325	10.33
Conf.4	5.2462	5.20	4.1437	7.44
Conf.5	5.7427	4.25	4.7267	5.87

2 ECD

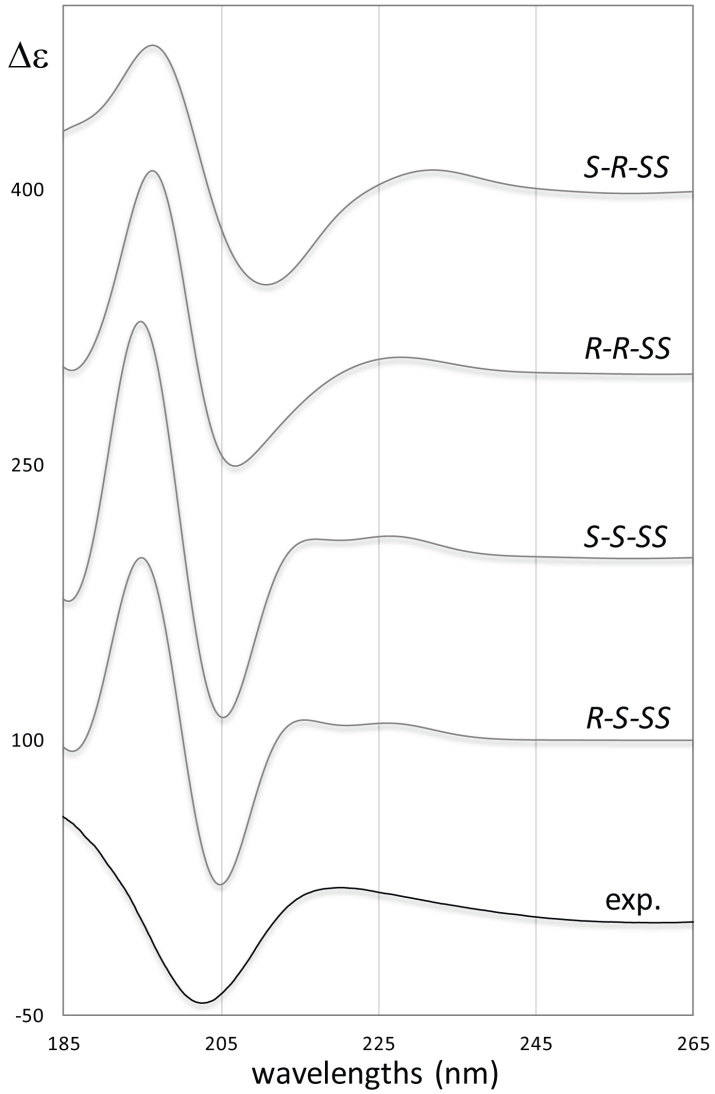

Figure S1: Comparison of the experimental ECD spectrum of diplopyrone (recorded in acetonitrile solution at concentration of ca. 10^{-3} M in a 0.1 mm quartz cuvette) with the calculated ECD spectra of possible diastereomers (calculated at the TD-DFT/CAM-B3LYP/TZVP level of theory; 0.2 eV as Gaussians bandwidth; first 50 excited states were considered).

3 Optical Rotation

Table S3: Specific Rotation ($[\alpha]_D$) in $CDCl_3$ (PCM) for all diplopyrone diastereomers calculated at different levels of theory.

Diastereomers	B3LYP-D3/jun-cc-pVDZ (B3)	B3LYP-D3/jun-cc-pVTZ[a] // B2PLYP-D3/jun-cc-pVTZ
R-R-SS	314.08	323.64
R-S-SS	55.23	51.09
S-R-SS	105.55	148.59
S-S-SS	185.29	186.10
Diastereomers	**CAM-B3LYP-D3/jun-cc-pVDZ[b] // B3LYP-D3/jun-cc-pVDZ**	**CAM-B3LYP-D3/jun-cc-pVTZ[c] // B2PLYP-D3/jun-cc-pVTZ**
R-R-SS	257.84	267.50
R-S-SS	51.41	44.58
S-R-SS	98.83	145.09
S-S-SS	162.98	161.13

[a] Since optical rotation can not be computed at B2 level of theory, the calculations have been performed using the B3LYP-D3/jun-cc-pVTZ level of theory on the B2 geometries;
[b] Optical rotation computed at CAM-B3LYP-D3/jun-cc-pVDZ level of theory on B3 geometries;
[c] Optical rotation computed at CAM-B3LYP-D3/jun-cc-pVTZ level of theory on B2 geometries.

4 Harmonic IR and VCD spectra

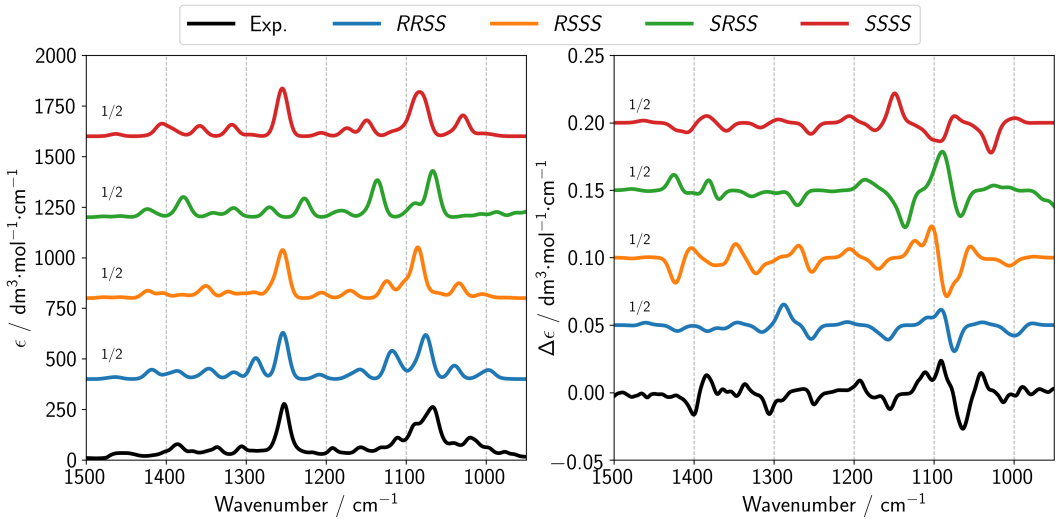

Figure S2: Experimental and simulated harmonic IR and VCD spectra of the four diastereoisomers. The spectra were simulated assigning a Gaussian band shape of 8 cm^{-1} half-width at half-height. Levels of theory reported: B3LYP-D3/jun-cc-pVDZ level of theory.

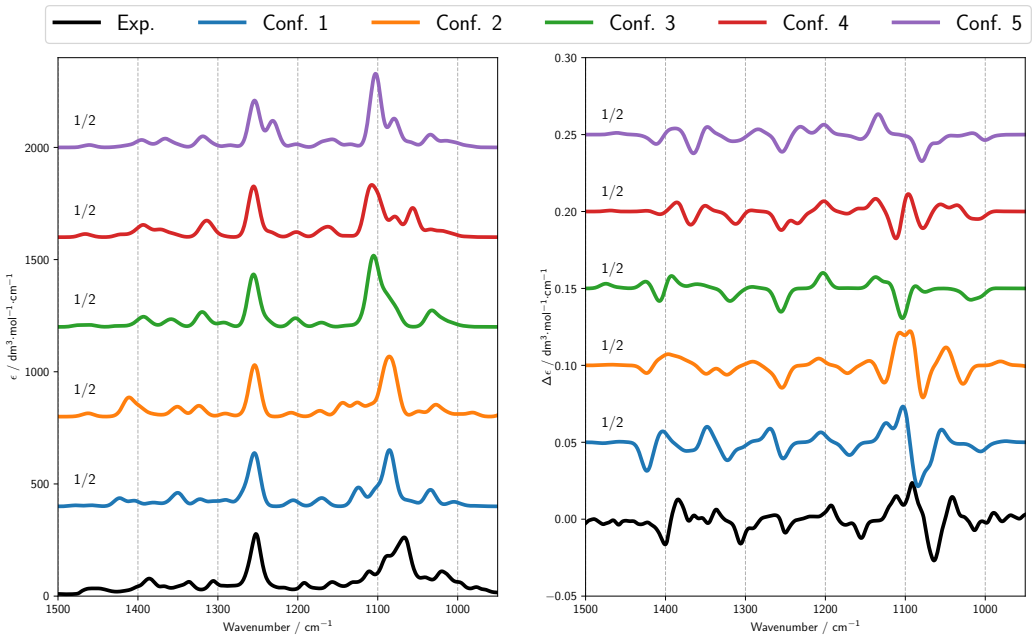

Figure S3: Experimental and simulated harmonic IR and VCD spectra of the five most populated conformers of the *R*-*S*-*SS* diastereomer. The spectra were simulated assigning a Gaussian band shape of 8 cm^{-1} half-width at half-height. Levels of theory reported: B3LYP-D3/jun-cc-pVDZ level of theory.

5 Anharmonic Calculations

5.1 Resonances Thresholds

5.1.1 Fermi Resonances

Identification of Fermi resonances (FRs) is done through a two step procedure: first, states differing in energies by less than 200 cm^{-1} are collected (step 1); then, the Martin's test[S8] is performed on the selected states to identify the resonant modes using a threshold of 1 cm^{-1} (step 2):

$$Step1 : |\omega_i - (\omega_j + \omega_k)| \leq \Delta_{\omega}^{1-2} \tag{1}$$

$$Step2 : |\langle v + 1_i|\hat{\mathcal{H}}'|v + 1_j + 1_k\rangle| - |\frac{k_{ijk}^2}{2\left[\omega_i - (\omega_j + \omega_k)\right]}| \geq K^{1-2} \tag{2}$$

5.1.2 Intensity Specific Fermi Resonances

In table S4 the specific threshold employed for IR and VCD spectroscopies, according to the two-step procedure introduced in subsection **Anharmonic calculations** in main text, are reported.

Table S4: Summary of Intensity specific FRs threshold values employed in this work.

	IR	VCD
$\Delta_{\omega I}^{1-2}$	15 cm^{-1}	15 cm^{-1}
test	$\frac{DS}{\lvert\Delta\omega\rvert}$	$\frac{RS}{\lvert\Delta\omega\rvert}$
K_I^{1-2}	150 $10^{-40}esu^2cm^3$	50 $10^{-44}esu^2cm^3$

DS is the dipole strength and
RS is the rotatory strength.

5.1.3 Darling-Dennison resonances

Other types of resonance can occur between states of equal symmetry and close in energy. They are generically denoted as Darling-Dennison resonances (DDRs) and are classified on the basis of the number of quanta involved ($1-1$, $1-3$, $2-2$). Analogously to intensity specific resonances, the DDRs are identified using a two step procedure: first, only states with energy differences lower than 100 cm^{-1} are considered; then, within threshold tuned on the type of DDRs, the terms are considered as resonant on the basis of the magnitude of the associated variational term ($1-1$: 1 cm^{-1}; $1-3$ and $2-2$: 10 cm^{-1}):

$$Step1 : |\Delta\omega| \leq \Delta_{\omega}^{DD} \tag{3}$$

$$Step2 : |\langle v'|\hat{\mathcal{H}}'|v''\rangle| \geq K^{DD} \tag{4}$$

5.1.4 Intensity Specific Darling-Dennison resonances

Smaller off-diagonal terms with low impact on the energy corrections can have a significant impact on the transition intensities.[S9,S10] To address this issue, a further test specific for intensity has been added to the second step of the DDRs identification, where the off-diagonal term is scaled down by the inverse squared wave number difference:

$$\left|\frac{\langle v'|\hat{\mathcal{H}}'|v''\rangle}{\Delta\omega^2}\right| \geq K_I^{A-B} \tag{5}$$

where A-B can be either $1-1$ and $1-3$, which are the only resonances involved in the intensity calculations (K_I^{A-B} $1-1$: 1 cm^{-1}).

5.2 LAMs and Added Resonance in the GVPT2 calculations.

5.2.1 Diastereomer *R-R-SS*:

Level of Theory: B3LYP-D3/jun-cc-pVDZ

Removed lam: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16.

Added FRs:

```
1-2 36 18 17
1-2 43 22 17
1-2 48 23 19
1-2 52 25 17
1-2 53 25 17
1-2 54 27 17
1-2 56 26 19
1-2 56 22 22
1-2 60 27 27
1-2 60 28 26
1-2 60 29 25
1-2 60 33 23
1-2 60 44 17
1-2 60 51 12
1-2 60 52 12
1-2 60 43 18
1-2 67 59 53
```

5.2.2 Diastereomer *R-S-SS* Conformer 1

Level of Theory: B3LYP-D3/jun-cc-pVDZ

Removed lam: 1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 13.

Added FRs:

```
1-2 54 22 22
1-2 60 45 16
1-2 60 37 21
1-2 54 21 21
1-2 60 37 22
1-2 49 28 14
1-2 57 25 19
1-2 58 31 22
1-2 26 14 14
```

Level of Theory: hybrid scheme B2PLYP-D3/jun-cc-pVTZ//B3LYP-D3/jun-cc-pVDZ

Removed lam: 1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 13.

Added FRs:

```
1-2 70 58 57
1-2 54 38 10
1-2 53 25 18
1-2 48 28 14
1-2 60 38 20
1-2 43 29 10
1-2 58 26 23
1-2 54 23 19
1-2 48 34 10
1-2 60 27 26
1-2 37 18 17
1-2 60 43 17
1-2 57 23 22
1-2 64 59 46
1-2 32 18 14
1-2 58 41 16
1-2 45 30 10
1-2 54 29 16
1-2 37 18 17
1-2 39 19 16
1-2 58 33 20
1-2 43 19 19
```

5.2.3 Diastereomer *R-S-SS* Conformer 2

Level of Theory: B3LYP-D3/jun-cc-pVDZ

Removed lam:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12.

Added FRs:

```
1-2 27 15 13
1-2 32 17 15
1-2 37 18 16
1-2 39 19 16
1-2 40 22 14
1-2 43 20 19
1-2 46 21 19
1-2 47 21 19
1-2 47 25 15
1-2 48 22 20
1-2 51 30 13
1-2 54 26 17
1-2 58 31 21
1-2 60 27 27
1-2 60 36 21
1-2 60 36 22
1-2 60 41 19
1-2 70 60 53
```

Level of Theory: hybrid scheme B2PLYP-D3/jun-cc-pVTZ//B3LYP-D3/jun-cc-pVDZ

Removed lam:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12.

Added FRs:

```
1-2 56 32 15
1-2 53 26 17
1-2 32 19 13
1-2 30 16 15
1-2 44 21 18
1-2 56 26 19
1-2 58 27 23
1-2 38 22 13
1-2 23 13 13
1-2 31 18 14
1-2 35 18 15
1-2 36 18 16
1-2 40 18 18
1-2 40 19 17
1-2 44 26 13
1-2 54 25 18
1-2 54 29 15
1-2 54 33 13
1-2 58 40 17
1-2 60 27 26
1-2 60 27 27
1-2 60 28 25
1-2 60 35 22
1-2 60 39 20
1-2 60 40 19
1-2 60 43 16
1-2 60 46 14
1-2 60 47 14
1-2 60 48 13
1-2 60 49 13
1-2 64 58 48
```

5.2.4 Diastereomer *R-S-SS* Conformer 3

Level of Theory: B3LYP-D3/jun-cc-pVDZ

Removed lam:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13.

Added FRs:

```
1-2 57 26 19
1-2 28 14 14
1-2 29 15 15
1-2 44 23 15
1-2 35 18 18
1-2 60 28 26
1-2 60 35 22
1-2 28 15 15
```

```
1-2 57 33 14
1-2 47 23 17
1-2 58 41 18
1-2 55 27 18
1-2 47 25 15
1-2 60 27 26
1-2 60 29 26
```

Level of Theory: hybrid scheme B2PLYP-D3/jun-cc-pVTZ//B3LYP-D3/jun-cc-pVDZ

Removed lam:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13.

Added FRs:

```
1-2 28 15 14
1-2 35 19 16
1-2 41 20 18
1-2 47 23 18
1-2 60 26 26
1-2 60 29 24
1-2 60 39 20
1-2 60 41 19
1-2 60 45 14
1-2 60 45 15
1-2 72 66 22
```

5.2.5 Diastereomer *R-S-SS* Conformer 4

Level of Theory: B3LYP-D3/jun-cc-pVDZ

Removed lam: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11.

Added FRs:

```
1-2 23 13 12
1-2 25 16 12
1-2 37 20 15
1-2 44 22 18
1-2 44 23 15
1-2 44 26 12
1-2 46 25 14
1-2 49 22 20
1-2 50 28 15
1-2 50 29 14
1-2 54 21 21
1-2 60 28 26
1-2 60 42 19
1-2 60 44 18
1-2 60 45 16
1-2 60 50 13
1-2 60 55 12
1-2 72 65 21
```

Level of Theory: hybrid scheme B2PLYP-D3/jun-cc-pVTZ//B3LYP-D3/jun-cc-pVDZ

Removed lam:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11.

Added FRs:

```
1-2 35 18 17
1-2 36 19 16
1-2 37 20 15
1-2 43 26 12
1-2 44 22 18
1-2 44 24 13
1-2 44 27 12
1-2 47 24 16
1-2 47 26 14
1-2 53 26 17
1-2 60 26 26
1-2 60 29 24
1-2 60 34 22
1-2 60 35 21
1-2 60 40 19
1-2 60 41 19
1-2 60 45 14
1-2 60 45 15
1-2 60 51 12
1-2 60 52 12
```

5.2.6 Diastereomer *R-S-SS* Conformer 5

Level of Theory: B3LYP-D3/jun-cc-pVDZ

Removed lam:1, 2, 3, 4, 5, 6, 7, 8, 9.

Added FRs:

```
1-2 23 16 10
1-2 26 15 13
1-2 28 16 13
1-2 36 19 16
1-2 37 20 15
1-2 38 20 15
1-2 43 20 19
1-2 43 21 17
1-2 44 22 18
1-2 44 23 15
1-2 44 27 12
1-2 49 22 20
1-2 50 24 17
1-2 50 31 12
1-2 52 23 19
1-2 54 26 17
1-2 59 39 19
```

```
1-2 60 28 26
1-2 60 29 25
1-2 60 31 23
1-2 60 36 22
1-2 60 40 20
1-2 60 42 19
1-2 60 44 18
1-2 60 46 16
1-2 60 50 13
1-2 60 51 13
1-2 60 55 12
```

Level of Theory: hybrid scheme B2PLYP-D3/jun-cc-pVTZ//B3LYP-D3/jun-cc-pVDZ

Removed lam:1, 2, 3, 4, 5, 6, 7, 8, 9.

Added FRs:

```
1-2 23 16 10
1-2 24 16 11
1-2 26 15 13
1-2 27 17 12
1-2 27 18 11
1-2 37 20 15
1-2 37 23 10
1-2 43 21 18
1-2 43 23 14
1-2 43 27 11
1-2 44 22 18
1-2 44 23 15
1-2 44 24 13
1-2 44 27 12
1-2 48 22 20
1-2 48 31 11
1-2 49 33 11
1-2 50 24 18
1-2 50 32 12
1-2 53 30 13
1-2 60 26 26
1-2 60 29 24
1-2 60 35 21
1-2 60 41 19
1-2 60 43 17
1-2 60 45 15
1-2 60 51 12
1-2 60 52 12
1-2 60 53 11
```

5.2.7 Diastereomer *S-R-SS*

Level of Theory: B3LYP-D3/jun-cc-pVDZ

Removed lam: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14.

Added FRs:

```
1-2  28 15 15
1-2  36 18 16
1-2  37 19 16
1-2  39 18 17
1-2  46 20 20
1-2  46 24 16
1-2  48 22 19
1-2  51 24 17
1-2  54 21 21
1-2  60 29 26
1-2  60 30 25
1-2  60 34 23
1-2  60 35 22
1-2  60 37 21
1-2  60 39 20
1-2  60 43 18
1-2  60 45 16
1-2  60 49 15
1-2  61 59 43
```

5.2.8 Diastereomer *S-S-SS*

Level of Theory: B3LYP-D3/jun-cc-pVDZ

Removed lam: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13.

Added FRs:

```
1-2  31 16 15
1-2  36 18 16
1-2  37 20 14
1-2  38 18 17
1-2  38 19 15
1-2  40 19 17
1-2  42 22 15
1-2  47 21 19
1-2  49 21 20
1-2  49 25 16
1-2  51 25 17
1-2  55 22 21
1-2  55 28 16
1-2  60 28 26
1-2  60 30 23
1-2  60 31 23
```

1-2	60	36	22
1-2	60	37	21
1-2	60	41	19
1-2	60	43	17
1-2	60	44	17
1-2	60	48	14
1-2	60	49	14
1-2	61	57	57
1-2	65	60	43
1-2	66	60	46

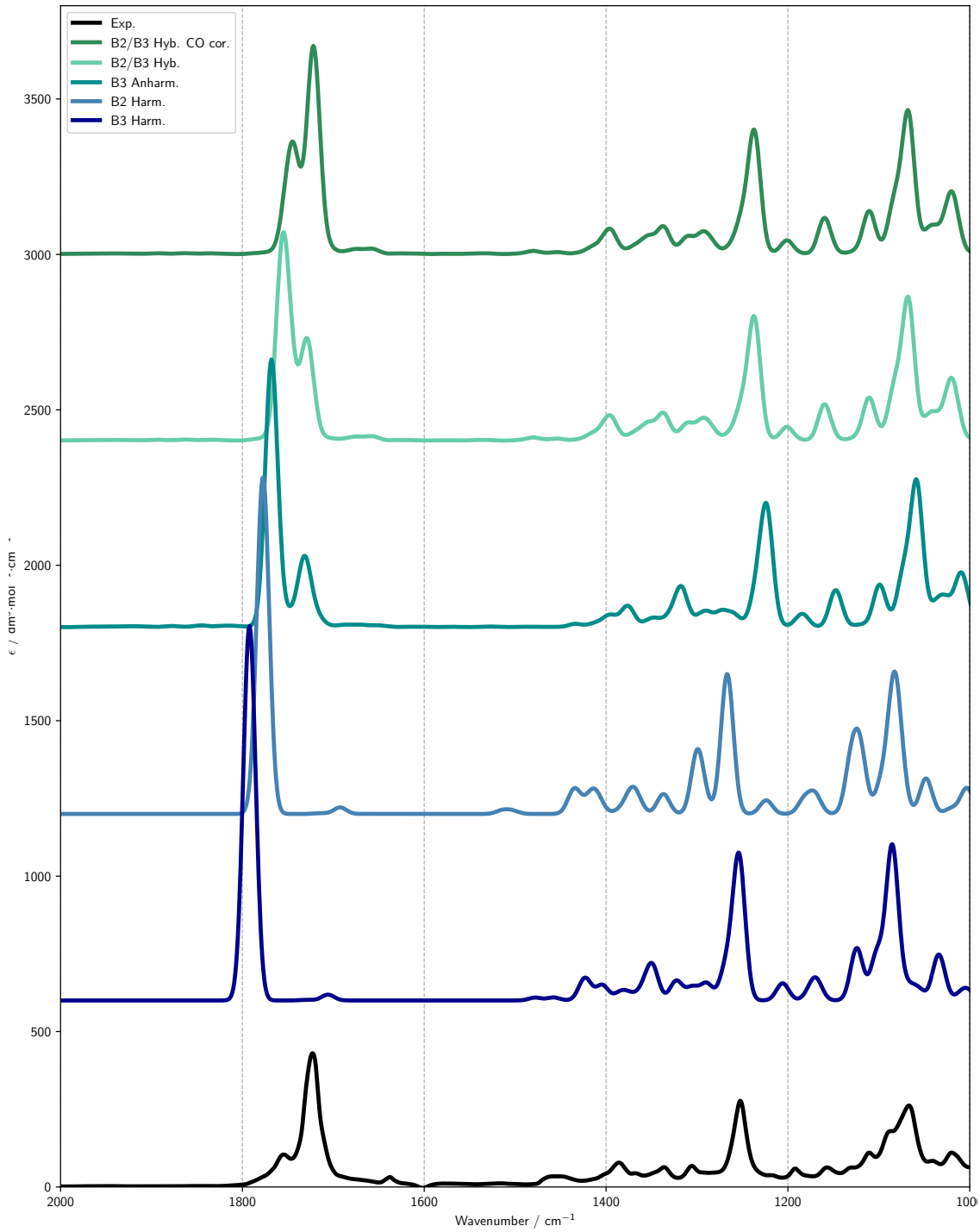

Figure S4: Comparison of the different methods employed in the simulation of IR spectra. The most abundant conformer of the *R*-*S*-*SS* diastereomer is shown. All the spectra were simulated assigning a Gaussian band shape of 8 cm^{-1} half-width at half-height. Since the νCO was still overestimated at the B2/B3 hybrid level, a further shift of 12 cm^{-1} was applied, thus completely recovering the observed discrepancy.

6 Optimized structures in XYZ

: Diastereomer *R-R-SS* at the B2PLYP-D3/jun-cc-pVTZ level

```
26
Diplopyrone_R-R-SS
O          -0.46720        -0.66683        -0.56858
C          -1.15712         1.63210        -0.18151
C           0.98117         0.81665         0.73405
C           0.00861         1.89984         0.40133
C           0.34065        -0.55534         0.60284
C          -1.56520         0.25752        -0.60509
H          -0.27675        -0.70207         1.49573
H           1.32266         0.92397         1.76749
H          -1.85995         0.27806        -1.65637
H          -1.85094         2.43213        -0.39947
H           0.29238         2.91380         0.64453
C          -2.74839        -0.31670         0.18733
C          -4.01391         0.50068         0.02599
H          -4.25509         0.62536        -1.02932
H          -3.91329         1.48086         0.48771
H          -4.84141        -0.01936         0.50317
C           1.37524        -1.62987         0.53538
H           1.06976        -2.64585         0.74484
C           2.63129        -1.34209         0.19740
H           3.40174        -2.09474         0.13206
O           2.13721         1.01000        -0.11388
C           3.04722         0.01065        -0.23089
O           4.12309         0.23536        -0.72897
H          -2.47376        -0.34816         1.24866
O          -3.02312        -1.63234        -0.27532
H          -2.17243        -2.05418        -0.44601
```

: Diastereomer *R-S-SS* conformer 1 at the B2PLYP-D3/jun-cc-pVTZ level

```
26
Diplopyrone_R-S-SS conf1
O          0.49339       -0.98500       -0.27816
C          1.41428        1.20473       -0.73280
C         -1.01525        0.82625       -0.90582
C          0.18767        1.70866       -0.83949
C         -0.61083       -0.62604       -1.10000
C          1.68550       -0.26310       -0.60089
H         -0.32577       -0.74301       -2.15327
H         -1.64941        1.11558       -1.74847
H          2.27044        1.86412       -0.72488
H          0.02404        2.77585       -0.88615
C          2.66879       -0.60434        0.52193
C          4.06683       -0.07391        0.28021
H          4.07828        1.01405        0.27810
H          4.46182       -0.43573       -0.66827
H          4.72369       -0.41162        1.07829
C         -1.73908       -1.54987       -0.77850
H         -1.69291       -2.56189       -1.15614
C         -2.75394       -1.14019       -0.01860
H         -3.58133       -1.78236        0.24125
O         -1.78584        1.05854        0.29855
C         -2.77095        0.18808        0.63153
O         -3.57564        0.48800        1.47969
H          2.69969       -1.69815        0.56787
O          2.21827       -0.08164        1.76208
H          1.29669       -0.34247        1.87203
H          2.09525       -0.65521       -1.54302
```

: Diastereomer *R-S-SS* conformer 2 at the B2PLYP-D3/jun-cc-pVTZ level

```
26
Diplopyrone_R-S-SS conf2
O          0.67877       -0.66092       -0.48765
C          1.29573        1.68128       -0.46370
C         -1.06436        1.02592       -0.71838
C          0.01210        2.03123       -0.46562
C         -0.47829       -0.28435       -1.22184
C          1.75375        0.26711       -0.63803
H         -0.20527       -0.13259       -2.27390
H         -1.75542        1.40007       -1.47900
H          2.06696        2.42882       -0.32665
H         -0.29176        3.05432       -0.29578
C          2.82170       -0.14444        0.38027
C          2.34822       -0.02950        1.82102
H          2.07481        0.99572        2.06694
H          3.14506       -0.34848        2.48865
H          1.47554       -0.65828        1.98747
C         -1.47052       -1.39503       -1.11220
H         -1.31019       -2.28348       -1.70716
C         -2.50227       -1.29954       -0.27463
H         -3.23212       -2.08603       -0.15960
O         -1.82126        0.89077        0.50833
C         -2.66658       -0.15968        0.65319
O         -3.46905       -0.16355        1.55475
H          3.68597        0.50170        0.22095
O          3.27973       -1.45739        0.08012
H          2.51204       -2.03920        0.11051
H          2.19198        0.13824       -1.63731
```

: Diastereomer *R-S-SS* conformer 3 at the B2PLYP-D3/jun-cc-pVTZ level

```
26
Diplopyrone_R-S-SS conf3
O          0.53047       -0.74025       -0.31540
C          1.24143        1.57444       -0.30811
C         -1.13170        1.01283       -0.66212
C         -0.02672        1.97327       -0.36775
C         -0.57585       -0.33042       -1.10798
C          1.64484        0.13723       -0.44276
H         -0.24888       -0.21204       -2.14915
H         -1.76254        1.39980       -1.46740
H          2.04236        2.27965       -0.14020
H         -0.29570        3.00915       -0.21705
C          2.64715       -0.27309        0.63672
C          3.03122       -1.73734        0.53638
H          3.46769       -1.94636       -0.43997
H          2.16043       -2.37217        0.67893
H          3.76544       -1.98703        1.30314
C         -1.61483       -1.39982       -1.02561
H         -1.45537       -2.31000       -1.58707
C         -2.68794       -1.24304       -0.25185
H         -3.45312       -1.99835       -0.15962
O         -1.96488        0.93658        0.52085
C         -2.85969       -0.07385        0.63737
O         -3.71528       -0.02365        1.48808
H          2.18914       -0.07200        1.60978
O          3.77459        0.58349        0.43793
H          4.45631        0.33973        1.06981
H          2.12755       -0.02109       -1.41857
```

: Diastereomer *R-S-SS* conformer 4 at the B2PLYP-D3/jun-cc-pVTZ level

```
26
Diplopyrone_R -S - SS conf4
O          0.53255       -0.73926       -0.31128
C          1.23813        1.57587       -0.29626
C         -1.13300        1.01184       -0.66181
C         -0.03060        1.97246       -0.35810
C         -0.57436       -0.33100       -1.10549
C          1.64522        0.14065       -0.43431
H         -0.24504       -0.21245       -2.14600
H         -1.75846        1.39935       -1.47107
H          2.03621        2.28117       -0.11407
H         -0.30309        3.00588       -0.19719
C          2.65951       -0.26049        0.64625
C          3.02760       -1.72939        0.57230
H          3.46690       -1.96352       -0.40063
H          2.14850       -2.35446        0.70309
H          3.75274       -1.96834        1.34759
C         -1.61153       -1.40212       -1.02572
H         -1.44728       -2.31321       -1.58433
C         -2.68909       -1.24613       -0.25804
H         -3.45302       -2.00301       -0.16845
O         -1.97352        0.93561        0.51551
C         -2.86896       -0.07511        0.62711
O         -3.73135       -0.02341        1.47057
H          2.22063       -0.03351        1.61743
O          3.80846        0.58030        0.54065
H          4.39245        0.21288       -0.13008
H          2.12289       -0.01627       -1.41549
```

: Diastereomer *R-S-SS* conformer 5 at the B2PLYP-D3/jun-cc-pVTZ level

```
26
Diplopyrone_R -S - SS conf5
O          0.52285       -0.75339       -0.32600
C          1.24449        1.55407       -0.38014
C         -1.13485        0.99769       -0.68994
C         -0.02147        1.96110       -0.43885
C         -0.58828       -0.35496       -1.11732
C          1.64552        0.11346       -0.46340
H         -0.27234       -0.25821       -2.16394
H         -1.77775        1.37085       -1.49222
H          2.04326        2.27510       -0.27374
H         -0.28001        3.00494       -0.33066
C          2.63206       -0.28737        0.64570
C          3.07002       -1.72999        0.50689
H          3.60655       -1.86323       -0.43249
H          2.21006       -2.39392        0.51997
H          3.73878       -1.99304        1.32317
C         -1.63106       -1.41775       -1.00118
H         -1.48501       -2.33805       -1.54950
C         -2.69002       -1.24292       -0.21176
H         -3.45658       -1.99311       -0.09322
O         -1.94473        0.94785        0.50881
C         -2.84134       -0.05820        0.66007
O         -3.67994        0.01170        1.52561
H          2.13056       -0.13823        1.60478
O          3.80421        0.52704        0.56305
H          3.67221        1.32291        1.08340
H          2.14086       -0.07240       -1.42785
```

: Diastereomer *S-R-SS* at the B2PLYP-D3/jun-cc-pVTZ level

```
26
Diplopyrone_S-R-SS
O          0.86116        0.73454        0.99472
C          0.88535       -0.79345       -0.89044
C         -0.96725       -0.82351        0.75054
C         -0.21617       -1.37207       -0.42338
C         -0.55766        0.62225        1.02933
C          1.46533        0.43832       -0.27191
H         -0.83011        0.90109        2.04834
H         -0.79090       -1.43287        1.63494
H          1.31475        1.28916       -0.95020
H          1.39069       -1.19760       -1.75594
H         -0.62164       -2.26624       -0.87683
C          2.96465        0.34703        0.02763
H          3.23380        1.29891        0.49779
O          3.23631       -0.72221        0.92200
H          2.65354       -0.61203        1.68132
C          3.81375        0.14009       -1.20899
H          3.61977        0.91563       -1.94900
H          3.61970       -0.83299       -1.65505
H          4.86586        0.17905       -0.93727
C         -1.22592        1.55459        0.06617
H         -0.77078        2.52586       -0.08058
C         -2.35148        1.21114       -0.55743
H         -2.86678        1.86723       -1.24158
O         -2.39239       -0.95541        0.53149
C         -3.03304       -0.06979       -0.27933
O         -4.14049       -0.32725       -0.68184
```

: Diastereomer *S-S-SS* at the B2PLYP-D3/jun-cc-pVTZ level

```
26
Diplopyrone_S-S-SS
C          1.26646        1.70789       -0.42347
C         -1.08075        1.01966       -0.70701
C         -0.02205        2.03694       -0.43273
C         -0.46912       -0.27918       -1.20718
C          1.75372        0.30345       -0.61335
H         -0.19021       -0.12034       -2.25656
H         -1.76696        1.38640       -1.47546
H          2.02340        2.46181       -0.25181
H         -0.34365        3.05089       -0.24269
C          2.81298       -0.07686        0.42478
H          3.62477        0.64693        0.33670
O          2.30311        0.08854        1.73979
H          1.45609       -0.37040        1.78247
C          3.35756       -1.47968        0.20182
H          3.81021       -1.56940       -0.78622
H          2.56072       -2.21615        0.28285
H          4.11386       -1.69883        0.95177
C         -1.44142       -1.40831       -1.11013
H         -1.25335       -2.29521       -1.69923
C         -2.49045       -1.32995       -0.29248
H         -3.20818       -2.12923       -0.18998
O         -1.85461        0.86698        0.50807
C         -2.69184       -0.19236        0.63102
O         -3.51513       -0.20805        1.51355
O          0.69228       -0.64136       -0.46961
H          2.19752        0.19502       -1.61380
```

References

(S1) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *The Journal of Chemical Physics* **2010**, *132*, 154104.

(S2) Grimme, S.; Ehrlich, S.; Goerigk, L. Effect of the damping function in dispersion corrected density functional theory. *Journal of Computational Chemistry* **2011**, *32*, 1456–1465.

(S3) Becke, A. D. Density-Functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

(S4) Perdew, J. P.; Burke, K.; Wang, Y. Generalized gradient approximation for the exchange-correlation hole of a many-electron system. *Phys. Rev. B* **1996**, *54*, 16533–16539.

(S5) Papajak, E.; Zheng, J.; Xu, X.; Leverentz, H. R.; Truhlar, D. G. Perspectives on Basis Sets Beautiful: Seasonal Plantings of Diffuse Basis Functions. *Journal of Chemical Theory and Computation* **2011**, *7*, 3027–3034, PMID: 26598144.

(S6) Grimme, S. Semiempirical hybrid density functional with perturbative second-order correlation. *The Journal of Chemical Physics* **2006**, *124*, 034108.

(S7) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.;

Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian 16 Revision B.01. 2016; Gaussian Inc. Wallingford CT.

(S8) Martin, J. M. L.; Lee, T. J.; Taylor, P. R.; Francois, J. The anharmonic force field of ethylene, C_2H_4, by means of accurate ab initio calculations. *The Journal of Chemical Physics* **1995**, *103*, 2589–2602.

(S9) Bloino, J.; Biczysko, M.; Barone, V. Anharmonic Effects on Vibrational Spectra Intensities: Infrared, Raman, Vibrational Circular Dichroism, and Raman Optical Activity. *The Journal of Physical Chemistry A* **2015**, *119*, 11862–11874.

(S10) Bloino, J.; Baiardi, A.; Biczysko, M. Aiming at an accurate prediction of vibrational and electronic spectra for medium-to-large molecules: An overview. *International Journal of Quantum Chemistry* **2016**, *116*, 1543–1574.