Beyond Optical Rotation for Frondosin B: What's Left is not Always *Right* in Total Synthesis

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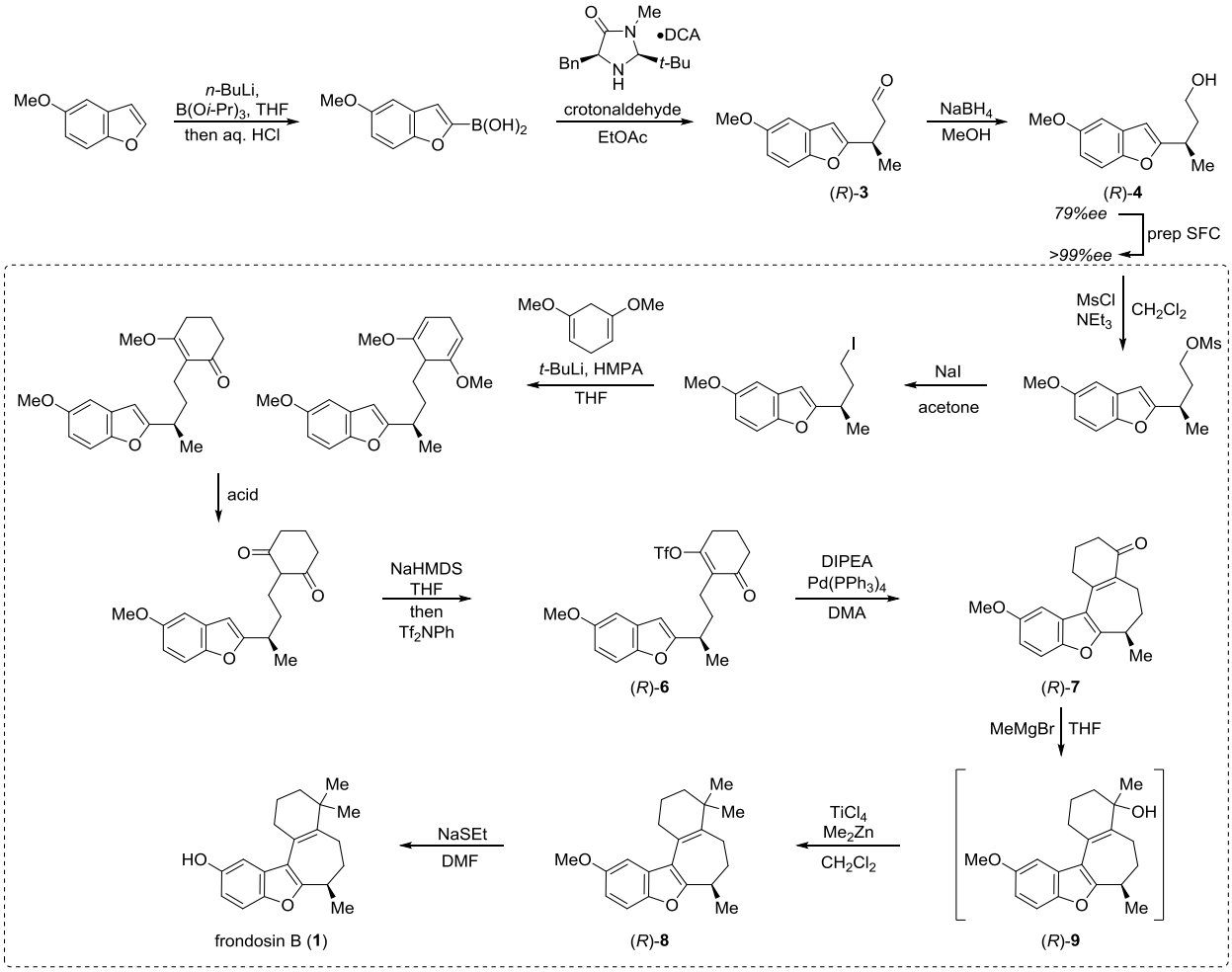
1) Materials and Methods

All reagents were purchased from commercial sources, and unless otherwise noted were used without further purification. All solvents used were of HPLC grade, and were used as received. All reactions were carried out under N_2 atmosphere unless otherwise noted. Anhydrous solvents were used from Sure/SealTM bottles without further drying or purification. All other commercial chemicals were used as received. Enantiomeric excess was measured using either chiral HPLC or SFC as described below. VCD spectra were recorded on a ChiralIR Spectrometer (Biotools, Jupiter FL), while ECD spectra were recorded using a Chirascan qCD Spectrometer (Applied Photophysics, Surrey UK). Single-crystal X-ray data were acquired on a Bruker Apex II system at 100K. ^{1}H and ^{13}C NMR spectra were recorded using a 600 MHz Bruker AVANCE III spectrometer equipped with a 1.7-mm TXI MicroCryoProbe™. NMR solvents were obtained from Cambridge Isotope Laboraties. Chemical shifts were referenced to residual deuterated

solvents, and are reported in ppm. All optical rotation measurements were taken on a Perkin Elmer polarimeter equipped with PCB 1500 water Peltier system. Measurements were recorded at 25°C at 589 nm in a jacketed 5 cm cell at a concentration of 10 mg/mL (c=1.0) unless otherwise noted.

2) Synthetic Details

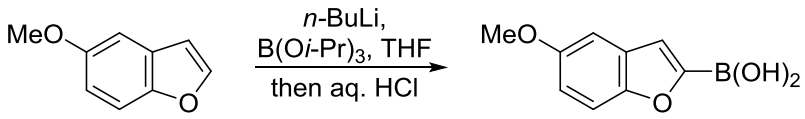
Overview of Substrate Preparation:



Reactions run according to procedures published by Trauner.[4]

Figure S1. Procedures for the preparation of aldehyde (*R*)-**3** and the synthesis and enantiopurity upgrade of alcohol (*R*)-**4** are given below. From alcohol (*R*)-**4**, enone (*R*)-**7** was prepared using the procedures previously published by Trauner.[4] NMR data obtained for all compounds matched those previously published.

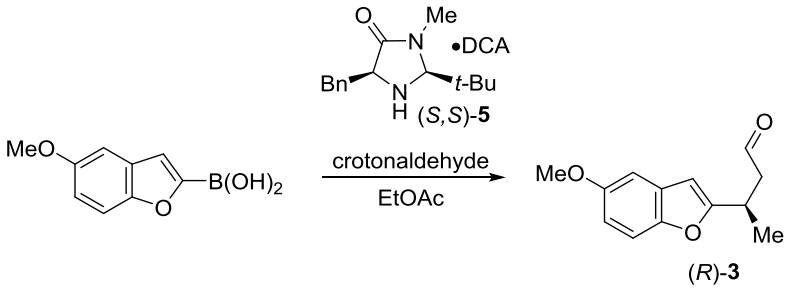
Preparation of (5-methoxybenzofuran-2-yl)boronic acid



Some commercial suppliers exist, but due to its limited availability, this compound was prepared according to a modified literature procedure.[1]

n-Butyllithium (38.6 ml, 97 mmol) was slowly added over 10 minutes to 5-methoxybenzofuran (13.0 g, 88 mmol) in THF (130 ml) at –78 °C, giving a yellow solution that quickly formed a thick tan suspension that became difficult to stir. After 1 hour, triisopropyl borate (50.9 mL, 219 mmol) was added, and the reaction mixture was stirred at –78 °C, turning dark red and becoming mobile again. After 30 minutes, the reaction mixture was quenched by addition of 2 M hydrochloric acid (50 mL) and warmed to room temperature. Water (50 mL) and ethyl acetate (50 mL) were added and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL), and the combined organic phases were washed with water (50 mL) and brine (50 mL) and dried ($MgSO_4$). The dried solution was reduced to about 50 mL in volume by concentration under reduced pressure and heptane (100 mL) was slowly added, causing a beige solid to precipitate that was collected by filtration. Further recrystallization from ethyl acetate–heptane gave (5-methoxybenzofuran-2-yl)boronic acid as a colorless solid (10.1 g, 59% yield). Data match those previously reported.[2]

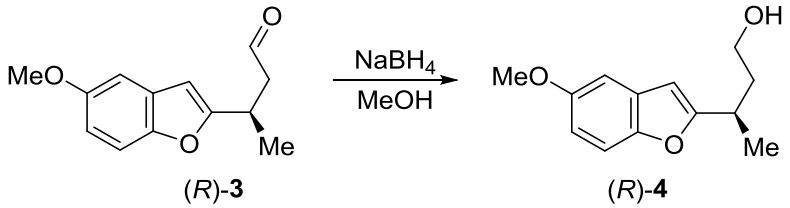
Preparation of (*R*)-3-(5-methoxybenzofuran-2-yl)butanal (*R*)-3



The protocol previously published by MacMillan and coworkers was employed,[3] but a commercially available imidazolidinone (CAS: 346440-54-8) was used in order to avoid the lengthy synthesis of organocatalyst (*S*, *S*)-**5** from the original report. This resulted in a slightly lower ee than the literature report (typically 85-89% ee using the published SFC analytical method).

Aqueous hydrofluoric acid (48%; 0.262 ml, 7.29 mmol) and dichloroacetic acid (0.120 ml, 1.459 mmol) were added to (5-methoxybenzofuran-2-yl)boronic acid (2 g, 7.29 mmol) and (2*S*,5*S*)-5-benzyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one (0.359 g, 1.459 mmol) in ethyl acetate (40 mL) in a 50 mL HDPE plastic Wheaton centrifuge tube. The resulting yellow solution was stirred for 15 minutes and then crotonaldehyde (1.813 ml, 21.88 mmol) was added, the tube was capped and the reaction mixture was stirred at room temperature. After 5 hours, water was added (20 mL) and the biphasic mixture stirred was vigorously for 15 minutes. The reaction mixture was transferred to a separating funnel and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 20 mL) and the combined organic extracts were washed water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated. The residual bright orange oil was purified by flash column chromatography on silica gel (120 g ISCO cartridge, eluting with 0–10% ethyl acetate in hexanes) to give (*R*)-3-(5-methoxybenzofuran-2-yl)butanal (1.5 g, 6.87 mmol, 94 % yield) as a very pale yellow oil. NMR data match those previously reported by MacMillan.[3]

Preparation of Alcohol (*R*)-4



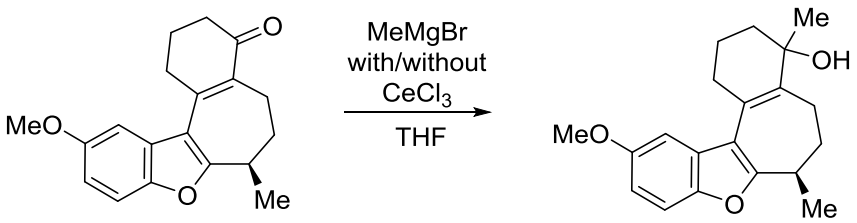
(*R*)-**3** (*R*)-**4**

Solid sodium borohydride (1.486 g, 39.3 mmol) was added portionwise over 10 minutes to (*R*)-3-(5-methoxybenzofuran-2-yl)butanal **3** (8.57 g, 39.3 mmol) in THF (40 mL) and MeOH (40 mL) and the resulting yellow suspension was stirred at room temperature for 1 hour. The reaction mixture was quenched by dropwise addition of acetic acid (until no more H_2 was produced), stirred for 5 minutes and concentrated under reduced pressure. The white solid residue obtained was dissolved in ethyl acetate (50 mL) and water (100 mL) and transferred to a separating funnel. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were washed with water (20 mL), dried ($MgSO_4$) and concentrated to give (*R*)-3-(5-methoxybenzofuran-2-yl)butan-1-ol (8.2 g, 37.2 mmol, 95 % yield) as a very pale yellow that solidified upon standing.

Analysis by SFC using a 4.6 x 250 mm Chiralcel OD column, 15% IPA/CO_2, 2.1 mL/min, 100 bar with detection at 220 and 254 nm showed an ee of 79%. Preparative separation of enantiomers was carried out

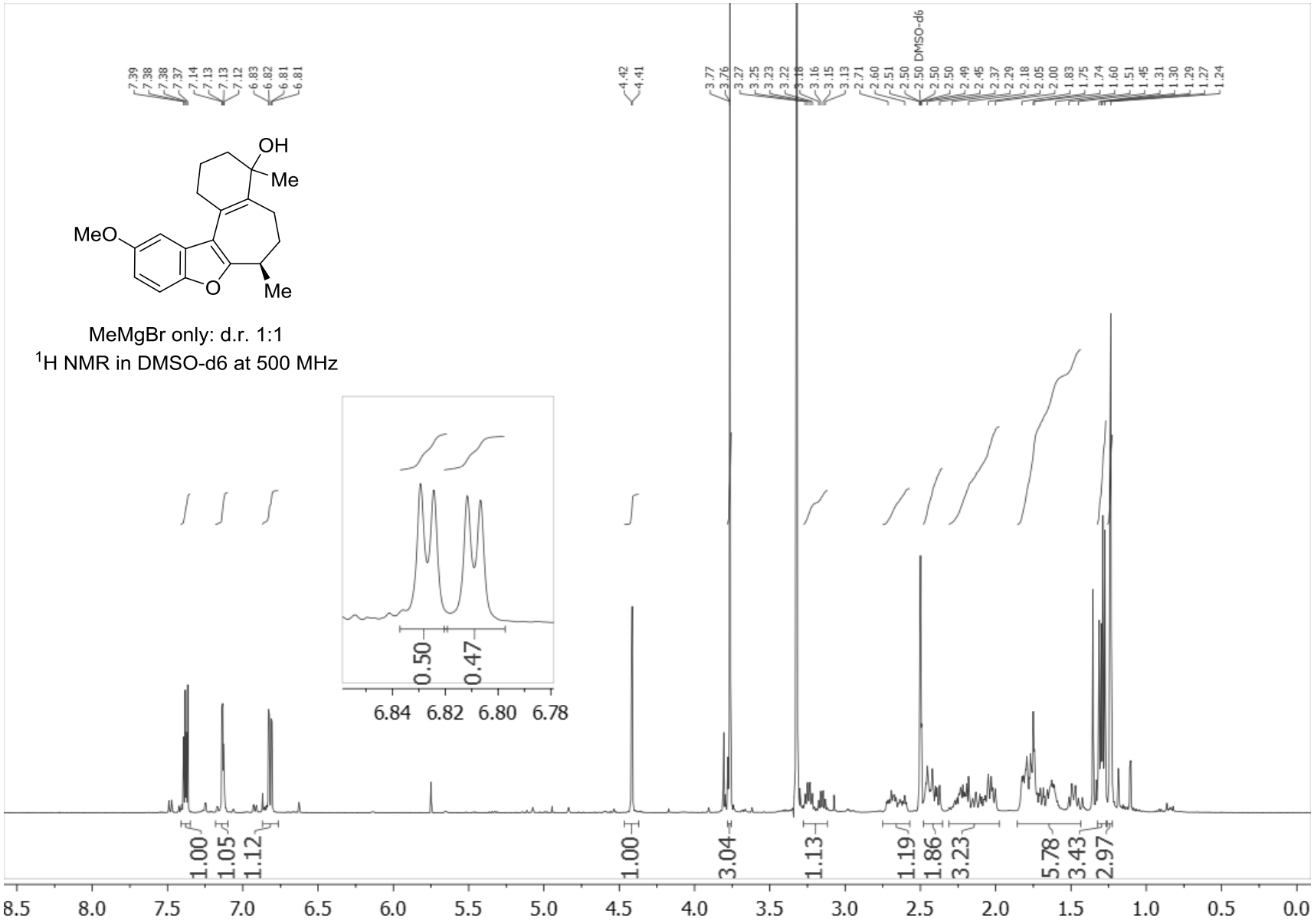
using stacked injections on a Berger MultiGram II SFC using a Kromasil-5 30x250 mm column, 15% IPA/CO_2, 70 mL/min, 100 bar with detection at 254 nm. Thus, purification of 8.5 g of alcohol (*R*)-4 (79% ee) gave 7.32 g of enantiopure material (ee > 99%). NMR data match those previously reported by Trauner.[4]

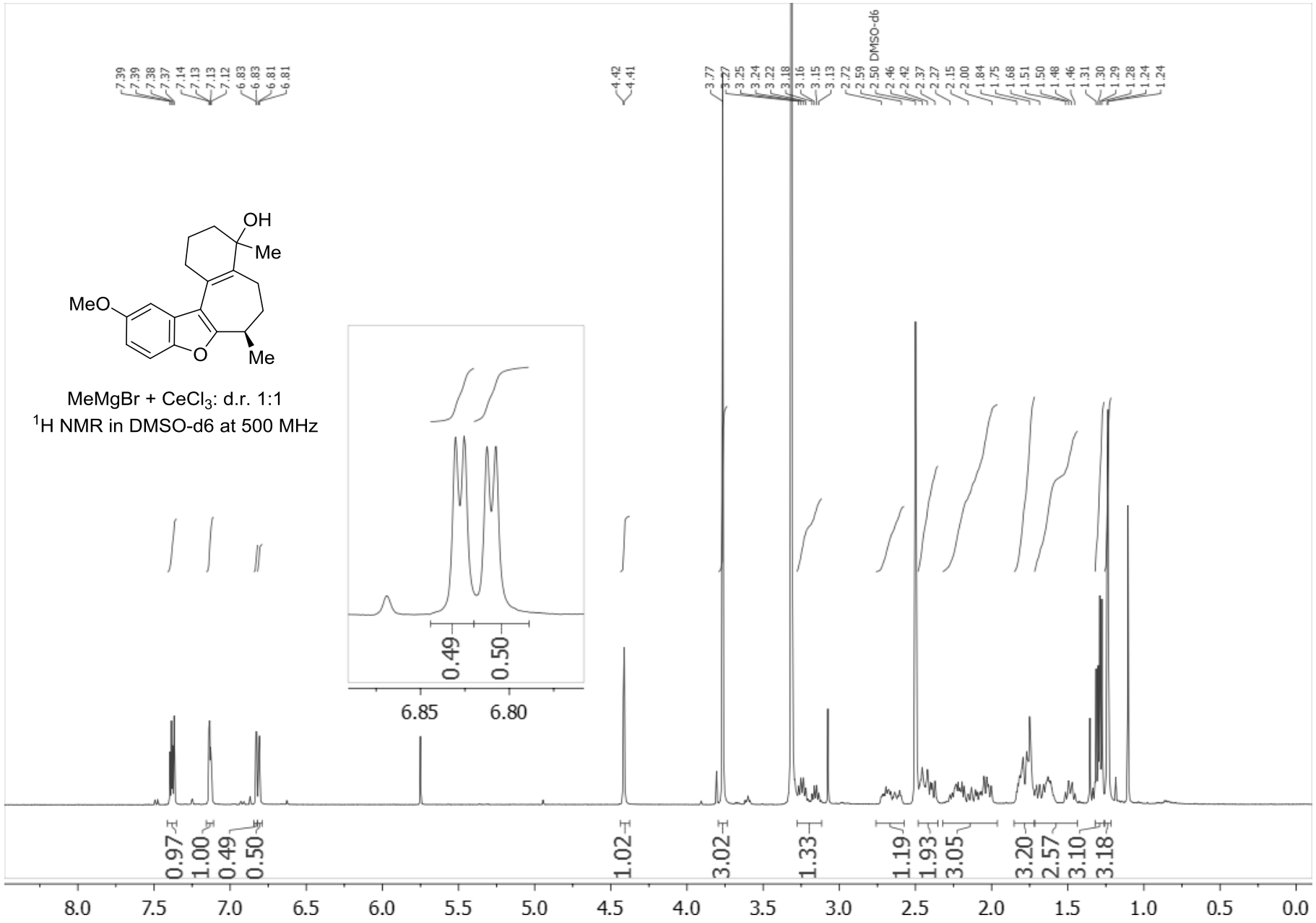
Preparation of (*R*)-9 and Diastereoselectivity of the Grignard Addition

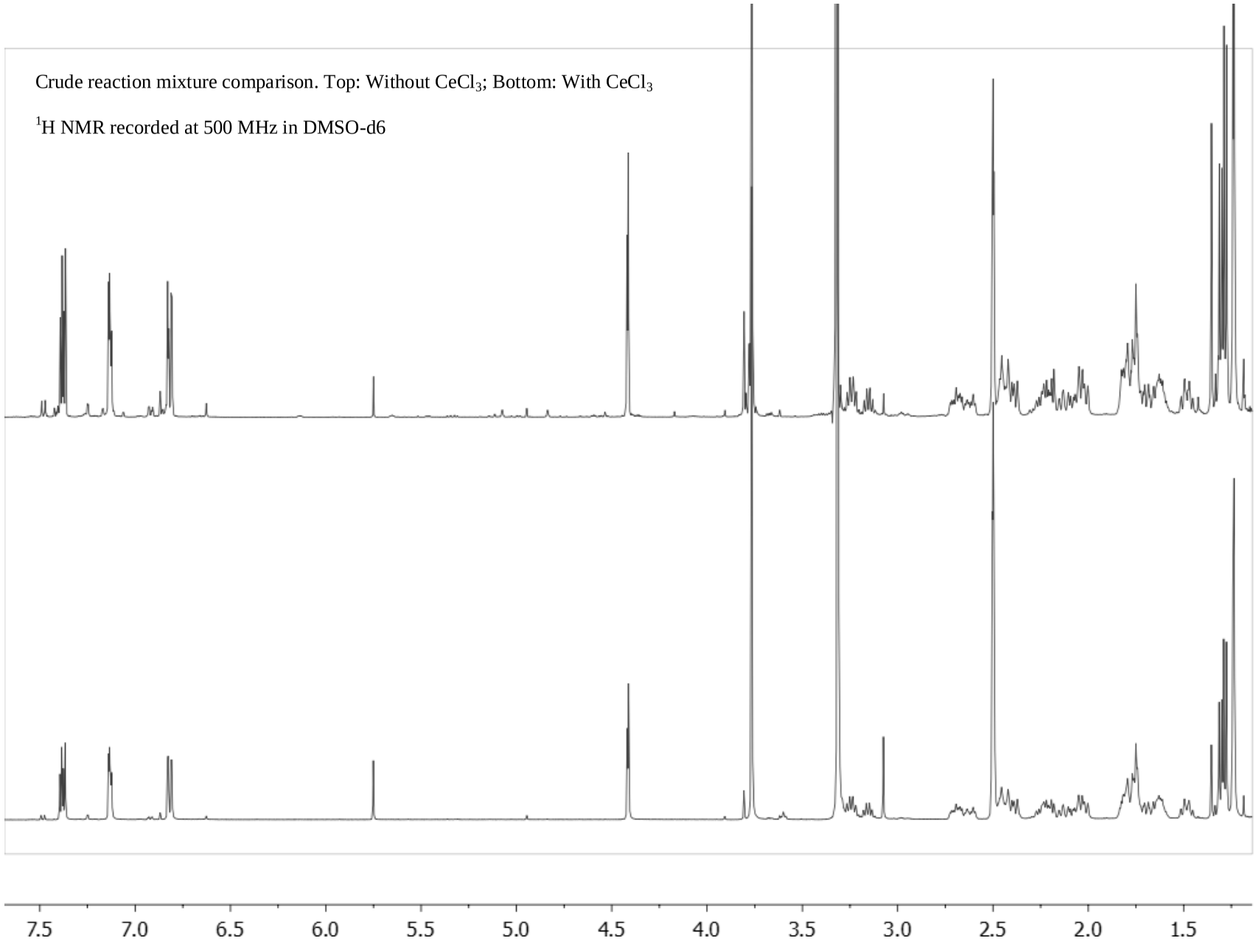


(*R*)-**7** (*R*)-**9**

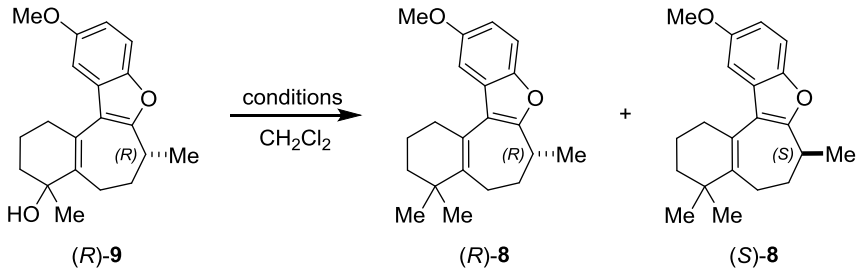
The diastereoselectivity of the Grignard addition to (*R*)-**7** and NMR data for adduct **9** have not been reported. Addition was carried out as exactly as described by Trauner[4] (without $CeCl_3$) and Wright[5] (with $CeCl_3$). Tertiary alcohol **9** was found to be unstable and could not be purified on silica gel or analyzed by HPLC, but crude ^{1}H NMR spectra shown below indicate that a 1:1 mixture of diastereomers and a similar reaction profile was obtained in both cases.


OH
Me
MeO
O
Me
MeMgBr only: d.r. 1:1
1H NMR in DMSO-d6 at 500 MHz
DMSO-d6
0.50
0.47
6.84 6.82 6.80 6.78
1.00
1.05
1.12
1.00
3.04
1.13
1.19
1.86
3.23
5.78
3.43
2.97
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


OH
Me
MeO
O
Me
MeMgBr + CeCl3: d.r. 1:1
1H NMR in DMSO-d6 at 500 MHz
DMSO-d6
0.49
0.50
6.85
6.80
0.97
1.00
0.49
0.50
1.02
3.02
1.33
1.19
1.93
3.05
3.20
2.57
3.10
3.18
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Crude reaction mixture comparison. Top: Without CeCl3; Bottom: With CeCl3
1H NMR recorded at 500 MHz in DMSO-d6
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

Effect of Stoichoimetry on Stereochemical Outcome



(*R*)-**9** (*R*)-**8** (*S*)-**8**

entry	conditions	temp	*R* : *S*	
1	2 eq. $ZnMe_2$, 1 eq. $TiCl_4$	0 °C to rt (2 h)	99.5	0.5
2	2 eq. $ZnMe_2$, 1 eq. $TiCl_4$	0 °C (30 min)	99.6	0.4
3	2 eq. $ZnMe_2$, 1 eq. $TiCl_4$	rt (3 h)	97.0	3.0
4	1 eq. $ZnMe_2$, 1 eq. $TiCl_4$	0 °C to rt (2 h)	99.0	1.0
5	1 eq. $ZnMe_2$, 2 eq. $TiCl_4$	0 °C to rt (2 h)	99.5	0.5
6	1 eq. $TiCl_4$, then 2 eq. $ZnMe_2$	–20 °C (1 h)	99.7	0.3

Figure S2. Summary of methylation reactions carried out and the enantiomeric ratios obtained using the (*R*)-enantiomer of enone starting material, including conditions by Trauner (entry 1), Wright (entry 2) and the conditions originally reported by Reetz (entry 6). The starting material for this step had an *ee* value of 99.4%.

3) Chromatography Conditions

Compound **7**:

Achiral purity of intermediate **7** was initially analyzed using UHPLC, according to the following separation details:

Instrument: Waters Acquity SQD-MS

Column: BEH C18 (150x2.1 mm, 1.8 µm)

Mobile Phase A: 2 mM NH_4HCO_2 pH 3.5 in water

Mobile Phase B: 2 mM NH_4HCO_2 pH 3.5 in 90% MeCN/water

Gradient: Time (min) %Mobile Phase B

0-4 min	5-95%
4-6 min	95%

Temperature: 50°C

Flow Rate: 0.4 mL/min

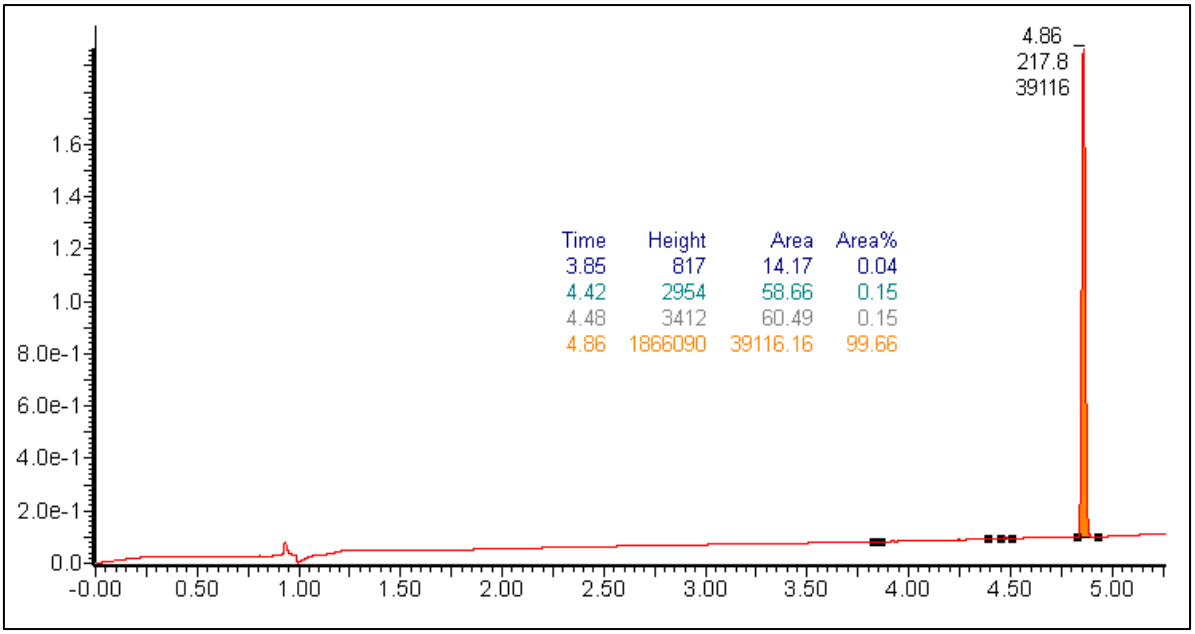


Figure S3. Results of the achiral UHPLC analysis of intermediate compound **7** at 210 nm.

Chiral purity of intermediate **7** was determined to be 99.4% ee at 254 nm using SFC, according to the following separation details:

Instrument: Waters UPC^2

Column: Chiralpak AD-3 (150x4.6 mm, 3 µm)

Mobile Phase A: CO_2

Mobile Phase B: *i*PrOH with 25 mM isobutylamine

Gradient:	Time (min)	%Mobile Phase B
	0-5 min	1-40%
	5-6 min	40%

Temperature: 40°C

Flow Rate: 3 mL/min

BPR Setting: 200 bar

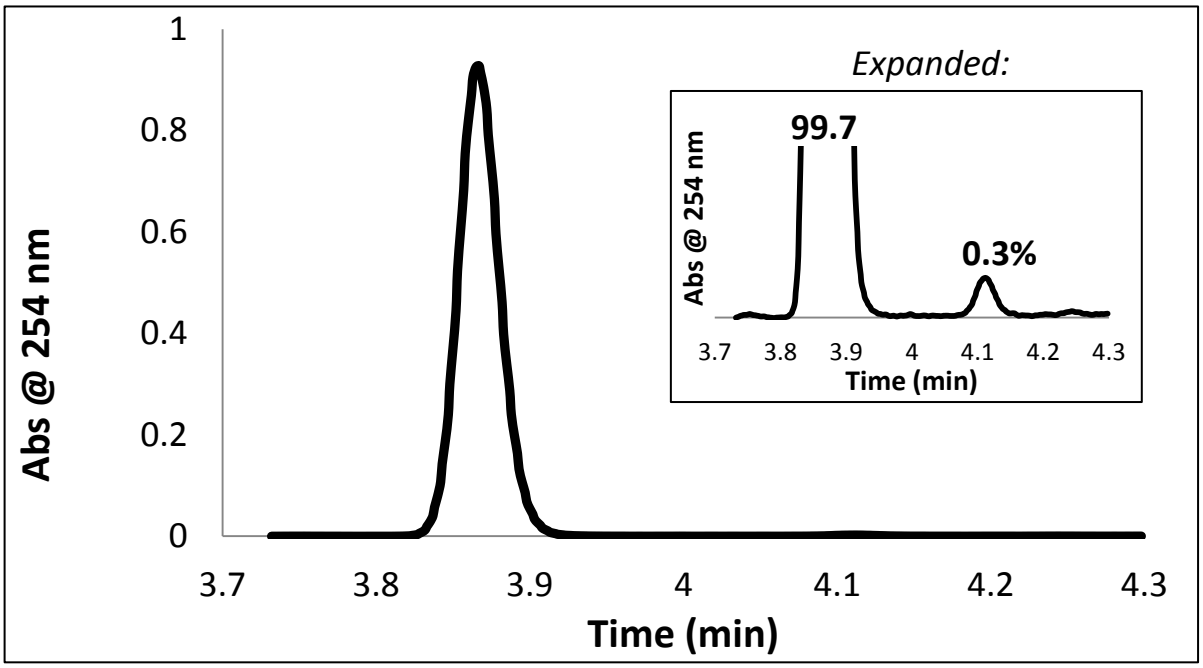


Figure S4. Results of the chiral SFC analysis of intermediate compound **7** at 254 nm.

Compound **9**:

The achiral purity of intermediate **8** was determined to be 92.9% using chiral SFC, with a single impurity identified (7.1% LCAP at 210 nm). The chiral purity of intermediate **8** was determined to be 99.4% ee using the same SFC method. The conditions for both of these separations are shown below:

Instrument: Waters UPC^2

Column: Chiralpak AD-3 (150x4.6 mm, 3 µm)

Mobile Phase A: CO_2

Mobile Phase B: ^{i}PrOH with 25 mM isobutylamine

Gradient:

Time (min)	%Mobile Phase B
0-4 min	4%
4-10 min	4-40%

Temperature: 40°C

Flow Rate: 2.5 mL/min

BPR Setting: 150 bar

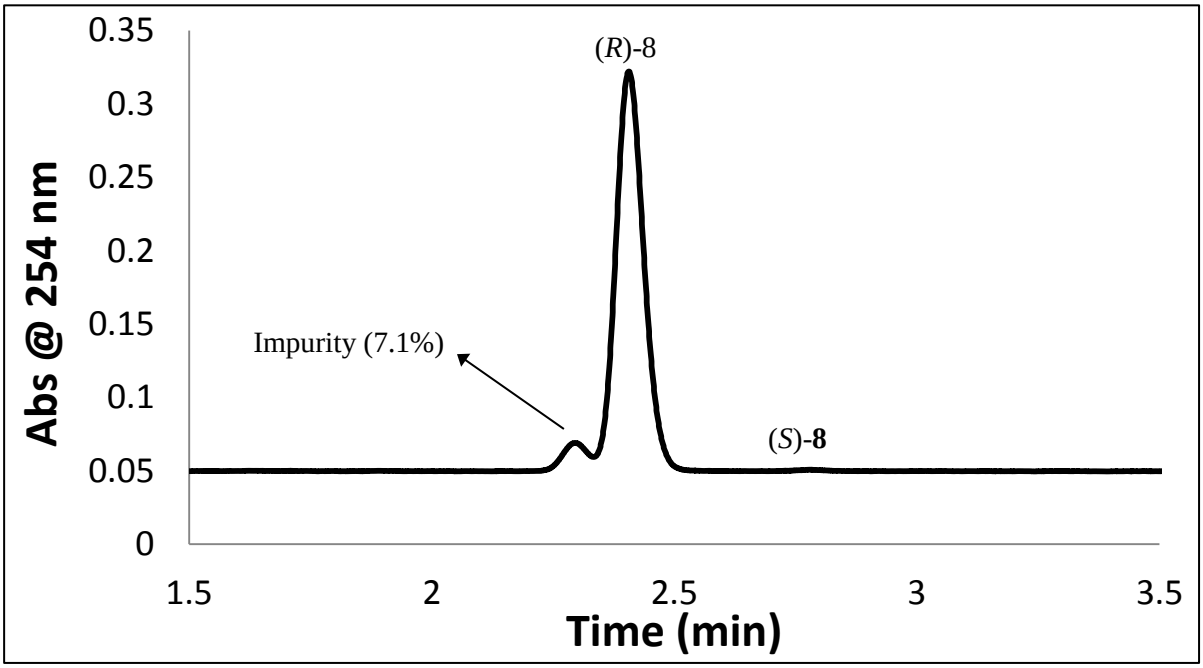


Figure S5. Results of the achiral and chiral SFC analysis of intermediate compound **8** at 254 nm, with key peaks noted.

Compound **1**:

The achiral purity of crude synthetic frondosin B **1** was determined to be 78.9% LCAP at 210 nm using chiral SFC, with multiple impurities identified (both enantiomers of intermediate **8**, impurity identified in compound **8**, and impurity **10**). The chiral purity of crude synthetic frondosin B **1** was determined to be 7.8% ee using the same chiral method. The conditions for both of these separations are shown below:

Instrument: Waters UPC^2

Column: Chiralpak AD-3 (100x4.6 mm, 3 µm)

Mobile Phase A: CO_2

Mobile Phase B: MeOH

Isocratic: Time (min) %Mobile Phase B

0-4 min 20%

Temperature: 40°C

Flow Rate: 2.0 mL/min

BPR Setting: 103 bar

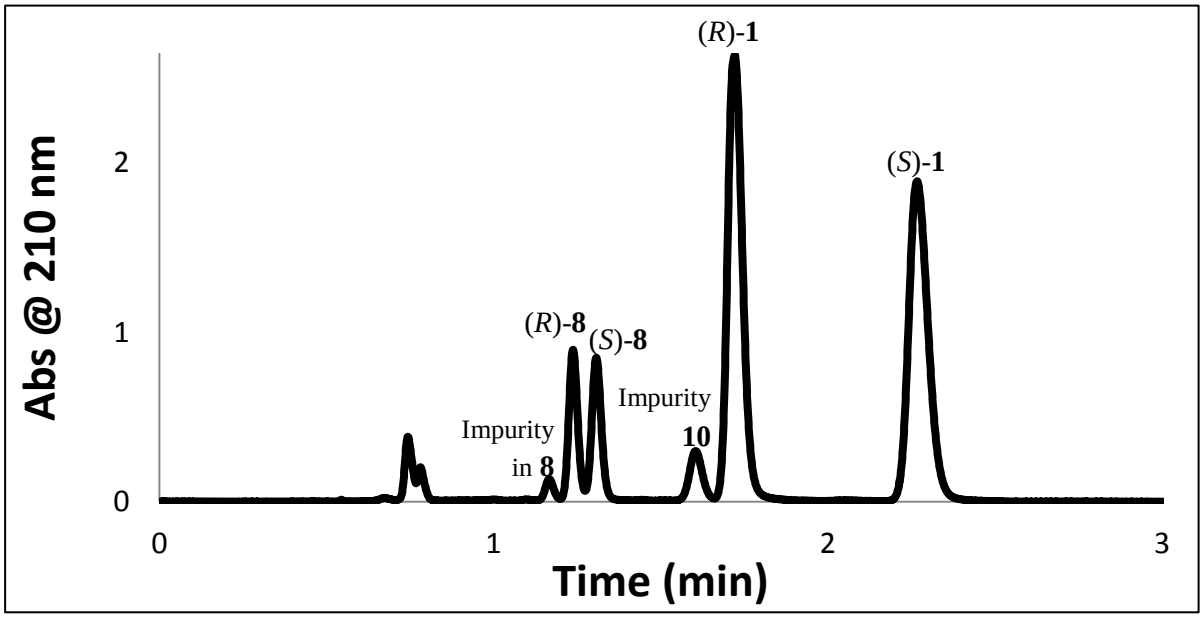


Figure S6. Results of the achiral and chiral SFC analysis of Frondosin B **1** at 210 nm, with key peaks noted.

In order to further purify the enantiomers of synthetic frondosin B **1**, a prep SFC purification was performed. This purification delivered the first eluting enantiomer, (*R*)-**1**, with 92% LCAP at 210 nm with >99.6% *ee*. The major impurity that was not removed from this sample was compound **10**. The second eluting enantiomer was >98% LCAP at 210 nm and >99.5% *ee*. The conditions used are listed below:

Instrument: Multigram 2 Prep SFC

Column: Chiralpak AD-H (250x21.2mm, 5 µm)

Mobile Phase A: CO_2 (80%)

Mobile Phase B: MeOH (20%)

Temperature: 35°C

Flow Rate: 50.0 mL/min

BPR Setting: 100 bar

Injection Volume: 150 µL (~9 mg/mL in MeOH)

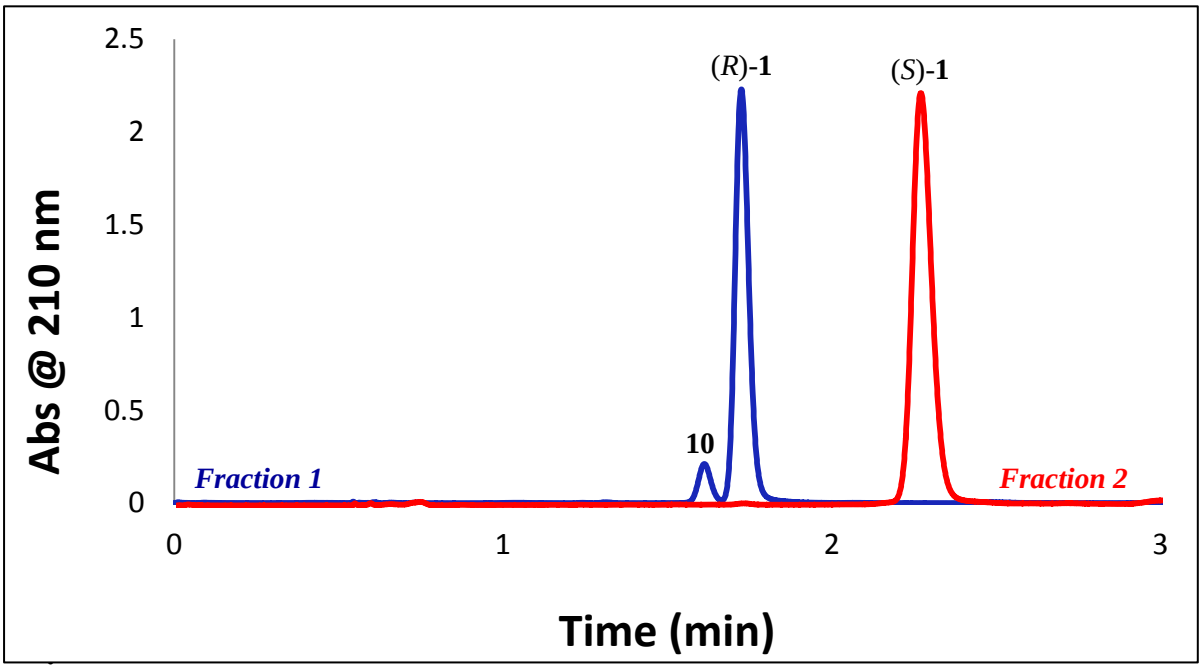


Figure S7. Results of the prep SFC separation of frondosin B **1** enantiomers at 210 nm, with key peaks noted.

An additional orthogonal preparative purification was required to separate impurity **10** from the (*R*)-**1**. This separation was achieved using RPLC, and afforded the desired compounds in high purity (4.5 mg of (*R*)-1 was isolated with >99% LCAP at 210 nm, while 1.3 mg of **10** was isolated with >90% LCAP at 210 nm). The conditions used are listed below:

Instrument: Agilent 1200 HPLC with Fraction Collector

Column: Chiralcel OJ-RH (150x4.6 mm, 5 µm)

Mobile Phase A: Water (35%)

Mobile Phase B: MeCN (65%)

Flow Rate: 1 mL/min

Temperature: RT

Fraction Collection: Time based ((*R*)-**1** eluted at 5.3 min, **10** at 6.2 min)

Injection Volume: 25 µL (~11 mg/mL in MeCN)

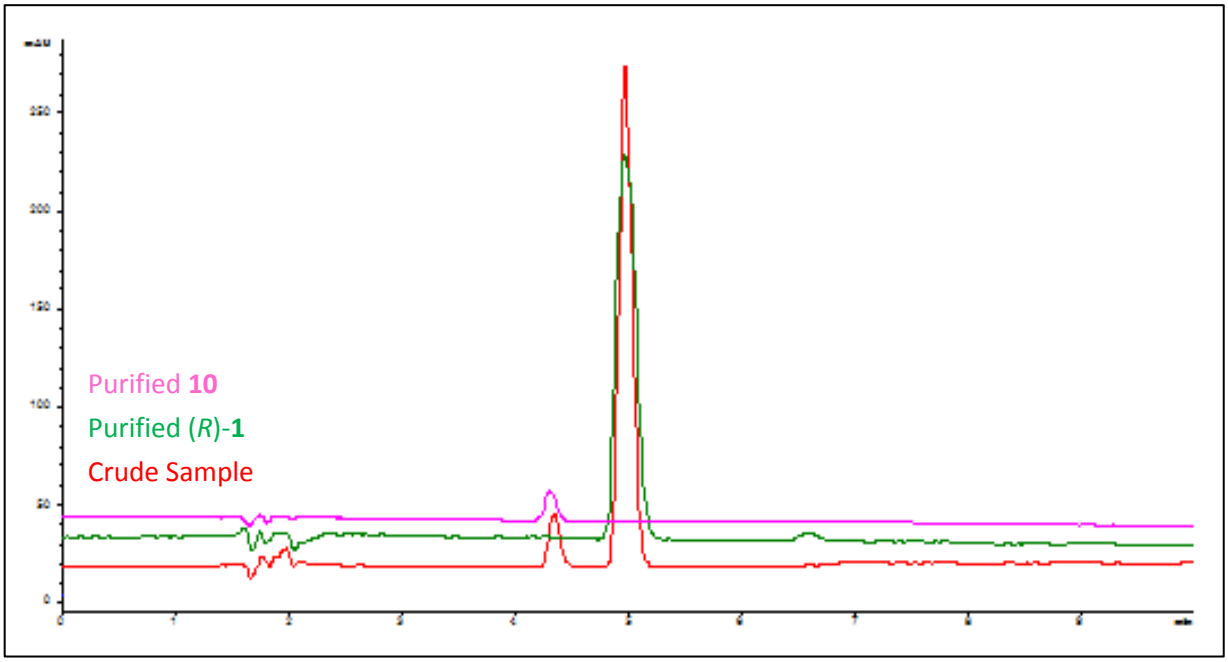


Figure S8. Results of the prep RPLC separation giving pure (*R*)-**1** and impurity 10, recorded at 210 nm.

An attempt was made to reproduce the separation conditions reported by the Danishefsky group.[1b] This consisted of a NPLC separation, but both enantiomers of (R)-1 were found to coelute under these conditions. These conditions were tried on two different previously used columns, as well as a brand new one, and all three gave the same coelution of enantiomers. Method conditions are given below:

Instrument: Agilent 1100 HPLC

Column: Chiralcel OD-H (250x4.6 mm, 5 µm)

Mobile Phase A: Hexanes (95%)

Mobile Phase B: iPrOH (5%)

Temperature: RT

Flow Rate: 1 mL/min

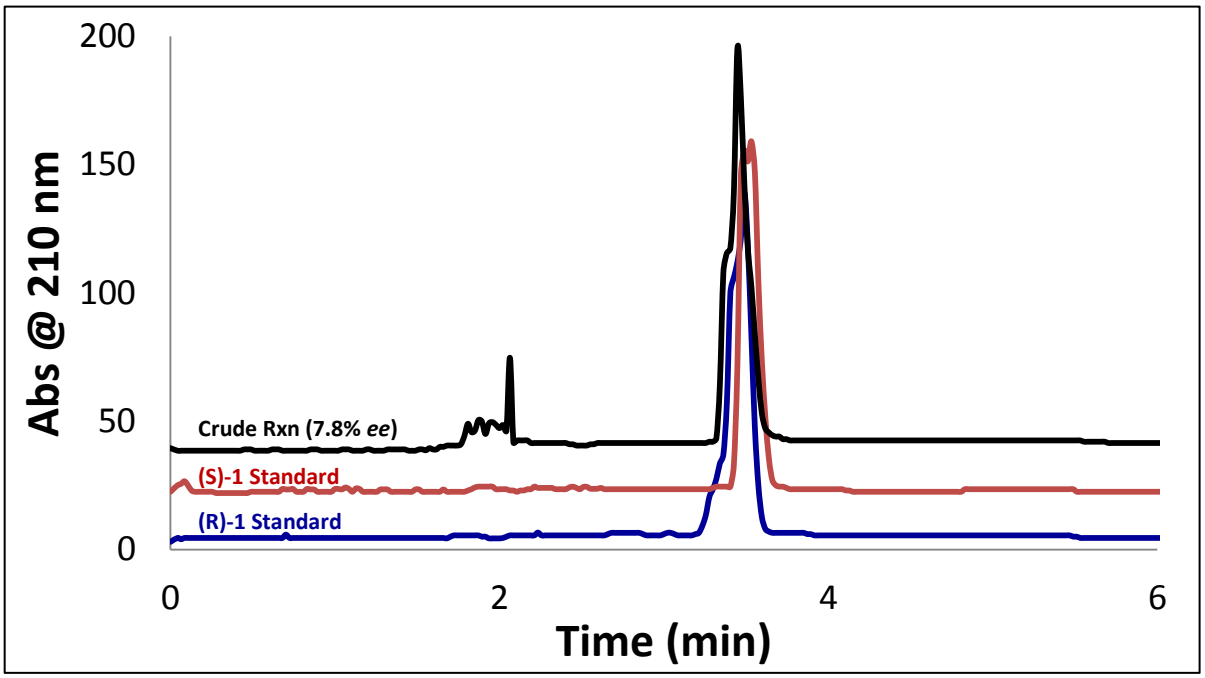


Figure S9. Results of analysis with chiral NPLC reported by Danishefsky to separate Frondosin B **1**, recorded at 210 nm.

4) Single-Crystal X-Ray Data for Compound 7

A single crystal grown from dichloromethane by solvent evaporation was selected for single crystal X-ray data analysis. The crystal was a colorless irregular cut block with dimensions of approximately 0.20 mm x 0.15 mm x 0.15 mm. Data collection was performed on a Bruker Apex II system at 100 K. The unit cell was determined to be orthorhombic in space group $P2_12_12_1$ and the structure contained one molecule of compound **7** in the crystallographic asymmetric unit. Crystallographic data is summarized in Table 1. Absolute configuration was determined by resonant-scattering effects in the diffraction measurements on the crystal and confirmed that the stereochemistry at stereogenic center was *R*. **Figure S10** shows a thermal ellipsoid representation of compound **7** with thermal ellipsoids set at the 50% probability level. Coordinates, refinement details and structure factors have been deposited with the Cambridge Crystallographic Data Center (CCDC 1553975).

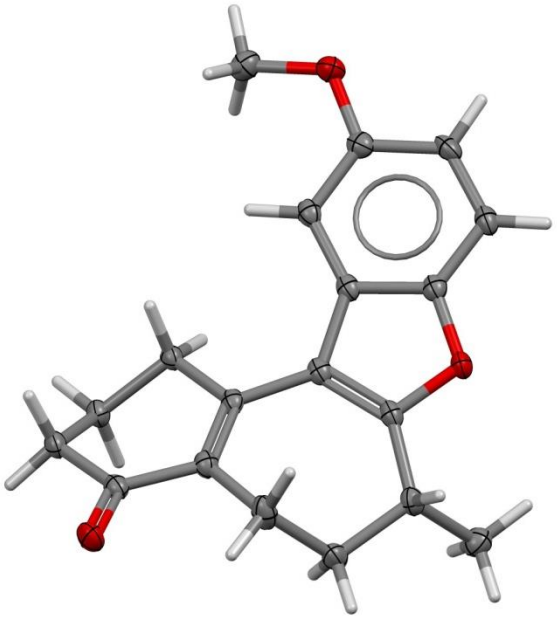


Figure S10: Thermal ellipsoid representation of compound **7** with thermal ellipsoids set at the 50% probability level.

Table S1. Crystal Data and Structure Refinement for Compound 7 (CCDC 1553975)

Identification code	mdl058	
Empirical formula	C19 H20 O3	
Formula weight	296.35	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.3146(4) Å	α= 90°.
	b = 11.1767(5) Å	β= 90°.
	c = 16.4216(7) Å	γ = 90°.
Volume	1526.06(12) $Å^3$	
Z	4	
Density (calculated)	1.290 g/cm^3	
Absorption coefficient	0.690 mm^{-1}	
F(000)	632	
Crystal size	0.20 x 0.15 x 0.15 mm^3	

Theta range for data collection	4.786 to 68.230°.
Index ranges	-10<=h<=9, -13<=k<=13, -18<=l<=19
Reflections collected	15782
Independent reflections	2757 [R(int) = 0.0246]
Completeness to theta = 68.230°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.902 and 0.857
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2757 / 0 / 202
Goodness-of-fit on F^2	1.089
Final R indices [I>2sigma(I)]	R1 = 0.0243, wR2 = 0.0622
R indices (all data)	R1 = 0.0245, wR2 = 0.0624
Absolute structure parameter (Flack)	-0.03(5)
Extinction coefficient	0.0035(5)
Largest diff. peak and hole	0.181 and -0.114 e.$Å^{-3}$

5) VCD and ECD Experimental and Calculations

Samples for VCD were dissolved in $CDCl_3$ (50-100 mg/mL for each sample) for VCD studies, and spectra acquired using a 0.10-mm path length cell with BaF_2 windows. The IR and VCD spectra were recorded using a Chiral*IR*™ VCD spectrometer equipped with the Dual PEM accessory (BioTools, Jupiter, FL), with 4 cm^{-1} resolution. A dry N_2 purge was used to eliminate water from the instrument. Data were collected in blocks, where the instrument recorded ~3000 scans over the course of 1 hour and averaged those scans into one block. Each of the runs involved averaging four blocks for each sample, as well as the solvent. The solvent background average was then subtracted from the sample average. Collection times for sample and solvent ranged were approximately five hours each. Samples for ECD were dissolved in MeCN (0.1-1 mg/mL), and spectra were acquired in a 1.0-mm pathlength Starna Quartz cuvette. The UV and ECD spectra were recorded using a Chirascan qCD Spectrophotometer with the following instrumental parameters: 185-350 nm with a 1 nm step and a 5 nm bandwidth, with data averaging over 0.5 sec per point. Only one spectral acquisition was taken without repetitions for each sample, and required approximately two minutes each. The solvent spectrum was then subtracted from the sample average to give the final compound spectrum.

The general approach for VCD assignment at Merck, including the details computational workflow, has been published elsewhere.[6,7] A subset of the details of the computational methodology is provided here. Conformers of each test structure were geometry optimized at the B3LYP/6-31G** level and stationary points were confirmed by performing frequency calculations.[8-16] All calculations were performed using Gaussian 09.[17] Frequency calculations output the IR and VCD spectra.[18] Frequencies were scaled by a value of 0.98, but owing to the secondary scaling and shifting of the calculated VCD and IR spectra (during extraction of VCD by BioTools ViewVCD and during spectra alignment detailed below) in comparison to the experimental spectra, this initial scaling was, to some extent, arbitrary.

Output conformers were ranked according to DFT energy and a clustering was performed to remove duplicates. Initial identification of duplicates was performed solely on an electronic energy basis where compounds were considered identical if the difference in Hartrees was less than 0.01. Rounding the differences led to inconsistencies in identification of duplicates. It became better to cluster the DFT minima by energy and then re-cluster each energy bucket by structure using an all atom RMS of 0.6 Å. This faithfully removed only identical compounds. Two Boltzmann distributions were calculated based on electronic energy (E) and free energy (G).

The in-house method for comparing VCD and IR spectra is based on published methodology.[19] We used the same formulas for calculating similarity for IR and VCD spectra of experimental and observed curves. Based on our experience in matching the curves by hand we introduced the following modifications to the algorithm: we scale the spectra (0 to 1 for IR, -1 to 1 for VCD) before comparing them; we isolate each peak for movement rather than groups of peaks; we isolate peaks independently for IR and VCD spectra; when looking for the best match we move the experimental peak only to higher frequencies with a maximum shift of 20 cm^{-1}; if the user sees that the baseline of the spectrum is not corrected the user can ask the program to correct the baseline. An example of the comparison of the experimental with the calculated before and after shifting are shown below for compound **1** (Figure SX and SY). For all figures contained in the manuscript, the output intensities from Gaussian for IR $\Delta\varepsilon$ (molar absorptivity) and VCD $\Delta\varepsilon$ are D (10^{-40} esu^2 cm^2) and R (10^{-44} esu^2 cm^2), respectively. However, owing to scaling all peaks the intensities are labeled only as 'normalized VCD'.

To calculate ECD spectra, B3LYP geometries were used as input for CAM-B3LYP calculations[20] using the 6-31++G** basis set[21,22] in vacuo. Only conformers which contributed more than 2.0% to the total in vacuo conformer distribution were selected for ECD calculation. Time-dependent Density Functional Theory (TDDFT)[23] methodology was employed using the following keywords: TD=full,singlet, Nstates=100, and integral=ultrafinegrid. Spectral display and Boltzmann weighting were carried out using SpecDis,[24,25] and were displayed with a band broadening sigma=0.3 eV.

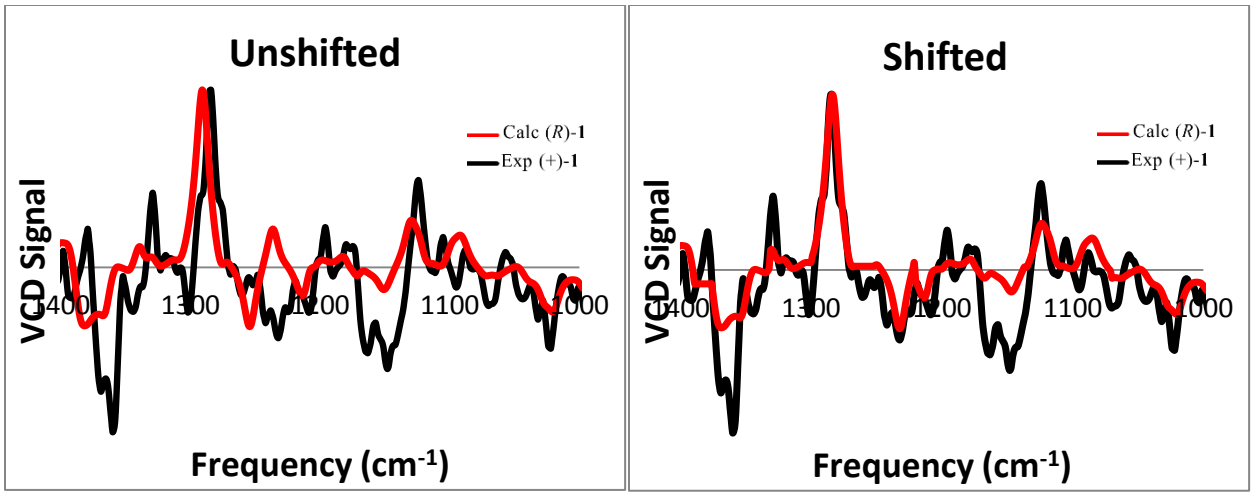


Figure S11. Comparison of experimental spectrum with the unshifted calculated spectrum (left) and shifted calculated spectrum (right), recorded in CDCl3 according to the experimental conditions listed above.

6) Atomic Coordinates for Relevant Conformers

Coordinates are listed for conformers that contribute >2% to the Boltzmann distribution.

***(R)*-Frondosin B (1)**

Conformer 1: E = -927.064818 hartrees
B3LYP/6-31G**

6 0.773602 -0.50635 -0.13826
6 1.96001 -0.122174 0.392783
6 2.09616 1.23544 1.0623
6 1.838 2.40893 0.090781
6 0.363979 2.83469 0.02975
6 -0.585014 1.67367 0.043328
6 -0.459885 0.304779 -0.021641
6 0.627245 -1.80471 -0.920501
6 1.96347 -2.3139 -1.45602
6 2.96595 -2.36295 -0.30734
6 3.24309 -0.967323 0.302091
6 3.84062 -1.19496 1.7125
6 4.29476 -0.23242 -0.566522
8 -1.9015 2.06536 0.141073
6 -2.65599 0.924401 0.142561
6 -1.8307 -0.205504 0.043158
6 -4.03985 0.871647 0.244101
6 -4.62969 -0.387279 0.248855
6 -3.83361 -1.545 0.159831
6 -2.44455 -1.47134 0.059097
8 -4.50181 -2.74357 0.179811
6 0.095598 3.77213 -1.16486
1 4.69949 -1.87254 1.64518
1 4.19364 -0.27077 2.17875
1 3.1032 -1.65109 2.38103
1 3.95525 -0.126316 -1.60146
1 4.51207 0.769809 -0.184937
1 5.23754 -0.791566 -0.57506
1 0.288056 3.25633 -2.11153
1 -0.940884 4.11745 -1.16914
1 0.750521 4.6483 -1.11502
1 3.09401 1.34277 1.49165
1 1.39434 1.31043 1.90486
1 2.18236 2.12919 -0.911516
1 2.42586 3.28663 0.385256
1 -0.086777 -1.65584 -1.73827
1 0.193612 -2.58452 -0.277499
1 2.32272 -1.65073 -2.25294
1 1.83928 -3.3067 -1.90398
1 3.91695 -2.80805 -0.624629
1 2.56189 -3.02137 0.473934
1 0.14193 3.4052 0.945004
1 -4.6308 1.7778 0.319616
1 -5.70501 -0.50323 0.32494
1 -1.86373 -2.38526 -0.001079
1 -3.85838 -3.46085 0.113753

Conformer 2: E = -927.064562 hartrees
B3LYP/6-31G**

6 0.776175 -0.507499 -0.14042
6 1.96244 -0.124554 0.391715
6 2.10017 1.23289 1.06149
6 1.84258 2.40689 0.090518
6 0.368784 2.8336 0.029719
6 -0.580842 1.67322 0.043212

6 -0.456322 0.305082 -0.022631
6 0.627432 -1.80522 -0.923006
6 1.96349 -2.31805 -1.45532
6 2.96409 -2.36799 -0.305012
6 3.24396 -0.972222 0.302848
6 4.29769 -0.240326 -0.565777
6 3.83996 -1.19935 1.714
8 -1.89789 2.06746 0.142246
6 -2.65299 0.926959 0.143449
6 -1.82766 -0.205869 0.04282
6 -4.03412 0.874292 0.244764
6 -4.62103 -0.389815 0.247663
6 -3.82496 -1.54663 0.157718
6 -2.43556 -1.47086 0.057663
8 -4.3778 -2.80355 0.1656
6 0.100652 3.7713 -1.16476
1 4.51661 0.762072 -0.185337
1 3.95913 -0.135098 -1.60111
1 5.23946 -0.801222 -0.572883
1 4.1949 -0.275412 2.17946
1 4.69726 -1.87906 1.64809
1 3.10098 -1.65309 2.38239
1 -0.935576 4.11747 -1.16882
1 0.292525 3.25534 -2.11145
1 0.756316 4.64693 -1.1151
1 1.39929 1.30853 1.90481
1 3.09852 1.3393 1.48996
1 2.43085 3.28433 0.385095
1 2.18659 2.12717 -0.911891
1 0.187992 -2.58276 -0.282274
1 -0.083894 -1.65406 -1.74261
1 1.83719 -3.31126 -1.90148
1 2.32623 -1.65729 -2.25284
1 2.55694 -3.02406 0.476496
1 3.91462 -2.81588 -0.619987
1 0.146981 3.40403 0.945105
1 -4.62766 1.77856 0.321398
1 -5.70174 -0.484127 0.323955
1 -1.87484 -2.3937 -0.001797
1 -5.33677 -2.72314 0.244186

Conformer 3: E = -927.064474 hartrees
B3LYP/6-31G**

6 -0.778928 -0.605203 -0.264936
6 -1.89541 -0.163 0.366878
6 -1.79233 1.01621 1.32984
6 -1.64854 2.41967 0.699684
6 -0.635999 2.48064 -0.476666
6 0.509477 1.5368 -0.265467
6 0.474023 0.168878 -0.175905
6 -0.758617 -1.83085 -1.15983
6 -1.98746 -2.72112 -0.971846
6 -3.24809 -1.85828 -0.953747
6 -3.26487 -0.841754 0.214156
6 -3.6427 -1.5676 1.52965
6 -4.35704 0.209179 -0.09423
8 1.78603 2.03095 -0.193113
6 2.61033 0.9402 -0.049058
6 1.85886 -0.248209 -0.031896
6 3.99225 0.97911 0.078713
6 4.65134 -0.236 0.234249
6 3.92728 -1.44414 0.268591
6 2.53862 -1.46585 0.142115
8 4.66523 -2.58808 0.437923
6 -0.198775 3.91911 -0.776174
1 -3.65708 -0.880619 2.38135
1 -2.93434 -2.36716 1.76508
1 -4.6421 -2.01023 1.4467
1 -4.4898 0.923095 0.724282
1 -5.32094 -0.287599 -0.254223
1 -4.1165 0.773324 -1.00154
1 0.433728 3.9708 -1.66654
1 0.36759 4.34 0.060047
1 -1.07723 4.55018 -0.942952
1 -2.65456 1.0324 2.00333
1 -0.914125 0.852651 1.96494
1 -2.61467 2.7825 0.327772
1 -1.33574 3.11638 1.48924
1 -0.693893 -1.50138 -2.20816
1 0.159151 -2.40315 -0.986152
1 -2.04268 -3.46563 -1.77432
1 -1.89985 -3.28055 -0.032197
1 -3.30725 -1.30866 -1.90341
1 -4.14986 -2.48083 -0.898893
1 -1.17239 2.0901 -1.3541
1 4.53212 1.91952 0.060371
1 5.72981 -0.278442 0.337288
1 2.00245 -2.4096 0.193004
1 4.06762 -3.3468 0.445893

Conformer 4: E = -927.064193 hartrees
B3LYP/6-31G**

6 -0.781338 -0.607028 -0.264268
6 -1.89843 -0.164477 0.366279
6 -1.79713 1.01566 1.3284
6 -1.65348 2.41869 0.697568
6 -0.639817 2.47872 -0.477765
6 0.505831 1.53553 -0.2646
6 0.470879 0.168206 -0.17517
6 -0.757725 -1.8357 -1.15476
6 -1.98687 -2.72557 -0.967027
6 -3.24805 -1.86351 -0.952112
6 -3.26691 -0.845185 0.214121
6 -3.64456 -1.56951 1.53055
6 -4.36015 0.20404 -0.09647
8 1.78258 2.03224 -0.191193
6 2.60748 0.94192 -0.047364
6 1.85632 -0.249613 -0.031165
6 3.98669 0.98118 0.079779
6 4.64363 -0.239197 0.233335
6 3.91989 -1.44694 0.265831
6 2.53082 -1.46688 0.140422
8 4.54742 -2.65683 0.426707
6 -0.203387 3.91698 -0.779327
1 -3.66112 -0.881191 2.38119
1 -2.93492 -2.36731 1.76787
1 -4.6431 -2.01412 1.44735
1 -4.49429 0.919207 0.720817
1 -5.32343 -0.29408 -0.256148
1 -4.11991 0.767024 -1.00464
1 0.43035 3.96771 -1.6689
1 0.361304 4.34011 0.05695
1 -1.08219 4.54694 -0.948564
1 -2.66014 1.0318 2.00087
1 -0.919645 0.853035 1.96477
1 -2.61928 2.78072 0.324019
1 -1.34181 3.11645 1.48672
1 -0.690095 -1.50969 -2.20404
1 0.159115 -2.40699 -0.975204

1 -2.04037 -3.47145 -1.76826
1 -1.89985 -3.28357 -0.026617
1 -3.30642 -1.31528 -1.9027
1 -4.14968 -2.48632 -0.89729
1 -1.17511 2.08614 -1.35492
1 4.5288 1.92024 0.062938
1 5.72627 -0.259462 0.333698
1 2.01535 -2.41862 0.19019
1 5.49805 -2.50854 0.508267

Conformer 5: E = -927.063642 hartrees
B3LYP/6-31G**

6 -0.773853 -0.537481 -0.153625
6 -1.97861 -0.07169 0.259806
6 -2.1397 1.3825 0.660858
6 -1.82748 2.35845 -0.497817
6 -0.354453 2.79759 -0.531886
6 0.589117 1.64992 -0.320705
6 0.457057 0.286318 -0.16414
6 -0.606681 -1.96012 -0.671191
6 -1.92609 -2.56736 -1.14211
6 -2.96221 -2.41254 -0.034279
6 -3.25597 -0.92985 0.299695
6 -3.88241 -0.894417 1.71554
6 -4.29266 -0.379062 -0.712329
8 1.90979 2.04018 -0.314781
6 2.65936 0.911229 -0.137698
6 1.82884 -0.214057 -0.036534
6 4.04494 0.870064 -0.051431
6 4.63281 -0.372815 0.151703
6 3.83249 -1.52496 0.269125
6 2.44218 -1.46232 0.1801
8 4.49794 -2.70703 0.4774
6 -0.075895 3.93121 0.479089
1 -4.25142 0.097198 1.99234
1 -3.15656 -1.20882 2.47252
1 -4.73535 -1.58145 1.76013
1 -4.51257 0.678747 -0.539387
1 -5.23653 -0.929114 -0.623553
1 -3.93922 -0.479628 -1.7433
1 0.972044 4.23657 0.452799
1 -0.309013 3.61538 1.50138
1 -0.696589 4.80136 0.241815
1 -3.1549 1.56351 1.01793
1 -1.47851 1.6098 1.50865
1 -2.09888 1.88421 -1.44648
1 -2.44403 3.26117 -0.412466
1 0.131034 -1.96719 -1.481
1 -0.195461 -2.60218 0.121474
1 -2.26203 -2.0625 -2.05641
1 -1.78703 -3.62425 -1.39781
1 -3.90334 -2.91257 -0.293968
1 -2.58285 -2.91571 0.86574
1 -0.144772 3.20577 -1.53213
1 4.63785 1.77408 -0.136489
1 5.70904 -0.479749 0.228116
1 1.86109 -2.37181 0.282897
1 3.85158 -3.42168 0.543205

Conformer 6: E = -927.063367 hartrees
B3LYP/6-31G**

6 0.776243 -0.53895 0.155316
6 1.98128 -0.074096 -0.258301
6 2.14469 1.38037 -0.657845
6 1.83185 2.35584 0.500999
6 0.359274 2.79659 0.533173
6 -0.584989 1.64978 0.321261
6 -0.453548 0.286824 0.165261
6 0.606015 -1.96159 0.671539
6 1.92494 -2.57324 1.13777
6 2.95951 -2.41766 0.02856
6 3.2567 -0.934802 -0.301239
6 4.29527 -0.389191 0.711641
6 3.88232 -0.896616 -1.71737
8 -1.90621 2.04288 0.313951
6 -2.65651 0.914481 0.136625
6 -1.82591 -0.213977 0.036575
6 -4.03929 0.873384 0.049936
6 -4.62425 -0.374877 -0.152434
6 -3.82393 -1.52629 -0.268186
6 -2.43334 -1.46147 -0.178875
8 -4.37335 -2.76753 -0.475825
6 0.083153 3.93039 -0.47829
1 5.23819 -0.940481 0.620076
1 4.51684 0.668933 0.542291
1 3.94257 -0.492995 1.74253
1 3.15517 -1.20694 -2.47478
1 4.25405 0.094793 -1.99159
1 4.73332 -1.5859 -1.76457
1 0.317115 3.61413 -1.50024
1 -0.964442 4.23712 -0.453227
1 0.704734 4.79977 -0.240464
1 1.48556 1.6093 -1.50684
1 3.16082 1.56047 -1.01277
1 2.44939 3.2581 0.417405
1 2.10104 1.88047 1.44969
1 0.188562 -2.60066 -0.119389
1 -0.129221 -1.96746 1.48349
1 1.78316 -3.63057 1.38964
1 2.26451 -2.07279 2.05329
1 2.57695 -2.91686 -0.872218
1 3.89993 -2.92091 0.284793
1 0.148445 3.20518 1.53305
1 -4.63485 1.77573 0.133252
1 -5.7059 -0.460364 -0.225722
1 -1.87265 -2.37993 -0.282887
1 -5.33359 -2.68031 -0.52656

Conformer 7: E = -927.063179 hartrees
B3LYP/6-31G**

6 -0.769592 -0.607417 -0.209611
6 -1.89293 -0.17812 0.419207
6 -1.82296 1.05847 1.31281
6 -1.67682 2.43391 0.624612
6 -0.609733 2.4844 -0.501846
6 0.523771 1.54009 -0.235375
6 0.477226 0.174984 -0.127017
6 -0.726919 -1.85054 -1.08258
6 -2.11753 -2.24221 -1.58177
6 -3.08487 -2.27835 -0.401116
6 -3.24104 -0.910614 0.311481
6 -4.24161 -0.024237 -0.470756
6 -3.83969 -1.20203 1.70943
8 1.80645 2.0232 -0.172751
6 2.62097 0.92583 -0.022347
6 1.85747 -0.254241 0.005058
6 4.00419 0.947001 0.095117
6 4.64842 -0.277478 0.242641
6 3.91082 -1.47774 0.275627

6 2.52094 -1.48224 0.16168
8 4.63761 -2.63131 0.428298
6 -0.157193 3.92101 -0.789337
1 -5.2295 -0.498654 -0.504843
1 -4.36199 0.955176 0.003299
1 -3.90942 0.143275 -1.49993
1 -3.11913 -1.72408 2.34764
1 -4.16276 -0.296968 2.23113
1 -4.72153 -1.84406 1.60359
1 0.37074 4.34611 0.069748
1 0.515323 3.96701 -1.65006
1 -1.0266 4.55169 -0.999454
1 -0.959448 0.936648 1.97805
1 -2.6995 1.10892 1.96326
1 -1.42098 3.16803 1.40093
1 -2.63267 2.75842 0.194586
1 -0.297098 -2.69071 -0.515207
1 -0.045721 -1.67992 -1.92415
1 -2.08509 -3.21759 -2.08108
1 -2.45669 -1.51591 -2.3313
1 -2.71298 -3.01433 0.325092
1 -4.07649 -2.62829 -0.713959
1 -1.10339 2.09202 -1.40314
1 4.55699 1.87977 0.071911
1 5.72714 -0.33365 0.336445
1 1.97004 -2.41824 0.197518
1 4.03091 -3.38271 0.440176

Conformer 8: E = -927.062723 hartrees
B3LYP/6-31G**

6 -0.773266 -0.492792 0.242907
6 -1.93084 -0.136932 -0.363117
6 -1.98649 1.1322 -1.19642
6 -1.86204 2.39308 -0.309345
6 -0.403493 2.82039 -0.045374
6 0.566656 1.67641 0.01324
6 0.464035 0.307977 0.096196
6 -0.685949 -1.69202 1.17504
6 -1.79908 -2.71026 0.935595
6 -3.14449 -1.99166 0.900161
6 -3.23961 -0.934982 -0.226271
6 -4.43547 -0.014625 0.118796
6 -3.53643 -1.63487 -1.57657
8 1.87722 2.08864 -0.081591
6 2.64821 0.957957 -0.084456
6 1.83932 -0.184767 0.009737
6 4.03151 0.924746 -0.201888
6 4.63707 -0.32609 -0.242199
6 3.85608 -1.49594 -0.181496
6 2.46761 -1.44176 -0.061102
8 4.53741 -2.68462 -0.255767
6 -0.294554 3.72806 1.19662
1 -4.66434 0.70225 -0.674648
1 -4.25232 0.546398 1.04117
1 -5.33347 -0.623594 0.273633
1 -3.58089 -0.916118 -2.4012
1 -4.50217 -2.15224 -1.53588
1 -2.76477 -2.37018 -1.82276
1 0.729493 4.08443 1.33418
1 -0.592401 3.18436 2.09928
1 -0.950136 4.59887 1.09137
1 -1.1767 1.13505 -1.93746
1 -2.91898 1.17537 -1.76353
1 -2.38047 3.2432 -0.768997
1 -2.36724 2.20669 0.645012
1 0.290948 -2.17259 1.09952
1 -0.739677 -1.32616 2.21228
1 -1.62275 -3.23636 -0.011251
1 -1.79221 -3.47173 1.72416
1 -3.97112 -2.70485 0.79073
1 -3.29299 -1.49177 1.86725
1 -0.071595 3.41607 -0.908959
1 4.6099 1.83962 -0.269153
1 5.71268 -0.426396 -0.334459
1 1.89708 -2.36528 -0.052546
1 3.90451 -3.41201 -0.19924

(*R*)-Intermediate 7

Conformer 1: E = -961.762005 hartrees
B3LYP/6-31G**

6 0.355185 -1.79553 -0.04106
8 -0.807595 -2.51871 -0.09538
6 -1.84434 -1.62356 -0.102352
6 -1.35686 -0.31357 -0.041384
6 0.102831 -0.437451 -0.002361
6 -3.19303 -1.95101 -0.175527
6 -4.09549 -0.897664 -0.191002
6 -3.6446 0.439406 -0.142477
6 -2.28459 0.746804 -0.070401
6 1.07504 0.661396 0.066198
6 2.34132 0.558518 -0.434455
6 2.88621 -0.70907 -1.04711
6 2.8988 -1.88944 -0.057684
6 1.57652 -2.66841 -0.00996
6 1.53929 -3.63839 1.1895
6 0.594202 1.94774 0.719446
6 1.73998 2.77969 1.29682
6 2.79812 3.0158 0.222765
6 3.28037 1.71134 -0.395779
8 4.40718 1.63816 -0.875388
8 -4.64266 1.37614 -0.174055
6 -4.28069 2.74531 -0.134543
1 0.628977 -4.24201 1.18465
1 1.58034 -3.0866 2.1345
1 2.40063 -4.31282 1.15268
1 -5.21583 3.30622 -0.168739
1 -3.66053 3.02696 -0.99581
1 -3.74347 2.99714 0.789489
1 2.29461 -0.983948 -1.9322
1 3.89911 -0.492447 -1.39097
1 3.68992 -2.59918 -0.325013
1 3.14649 -1.51773 0.943852
1 0.057725 2.55335 -0.027118
1 -0.135026 1.70765 1.49931
1 1.3592 3.72998 1.68707
1 2.18691 2.24295 2.14315
1 2.37528 3.62651 -0.589346
1 3.67478 3.55186 0.59642
1 1.5153 -3.28071 -0.922907
1 -3.51921 -2.98405 -0.221897
1 -5.16382 -1.07417 -0.246297
1 -1.9563 1.7749 -0.044071

Conformer 2: E = -961.761515 hartrees
B3LYP/6-31G**

6 -0.368358 1.73328 -0.037816
8 0.826569 2.40512 -0.089292

6 1.82291 1.46379 -0.089436
6 1.27245 0.173246 -0.026172
6 -0.180682 0.365984 0.005064
6 3.17975 1.72495 -0.157349
6 4.04393 0.628512 -0.164638
6 3.52788 -0.680483 -0.112038
6 2.15007 -0.917486 -0.046025
6 -1.20091 -0.688955 0.068122
6 -2.45874 -0.529188 -0.438505
6 -2.94433 0.762186 -1.05125
6 -2.90457 1.94224 -0.062299
6 -1.54869 2.66078 -0.012763
6 -1.4706 3.63103 1.18448
6 -0.777779 -1.99545 0.720398
6 -1.96124 -2.78373 1.28297
6 -3.02071 -2.96866 0.200157
6 -3.44684 -1.64079 -0.408895
8 -4.56877 -1.51535 -0.889348
8 4.3072 -1.80748 -0.122402
6 5.71383 -1.65539 -0.205275
1 -0.533562 4.19223 1.18103
1 -1.54011 3.08409 2.13061
1 -2.3002 4.34383 1.14292
1 6.12608 -2.66558 -0.205291
1 6.11618 -1.10407 0.654705
1 6.01494 -1.14491 -1.12943
1 -2.33988 1.00983 -1.93574
1 -3.96565 0.59192 -1.39633
1 -3.66215 2.68712 -0.331356
1 -3.17063 1.58281 0.938999
1 -0.256212 -2.6175 -0.022684
1 -0.047458 -1.78796 1.50853
1 -1.62214 -3.75152 1.66826
1 -2.39232 -2.23562 2.13034
1 -2.61616 -3.58781 -0.614801
1 -3.92028 -3.47322 0.563118
1 -1.45687 3.26722 -0.927061
1 3.55459 2.74126 -0.206652
1 5.11159 0.800062 -0.215735
1 1.81597 -1.94569 -0.017502

Conformer 3: E = -961.760904 hartrees
B3LYP/6-31G**

6 0.362309 1.77679 0.292703
8 -0.798654 2.50377 0.328522
6 -1.83744 1.62347 0.189688
6 -1.35562 0.315017 0.07798
6 0.105829 0.423799 0.151487
6 -3.18327 1.96798 0.147337
6 -4.09165 0.933779 -0.021067
6 -3.64799 -0.400086 -0.151337
6 -2.29065 -0.723954 -0.107437
6 1.06717 -0.687086 0.114185
6 2.36611 -0.540706 -0.284498
6 2.96893 0.786666 -0.669267
6 2.89231 1.82533 0.46746
6 1.58373 2.6316 0.469954
6 1.6104 3.76749 -0.577367
6 0.536799 -2.04506 0.549424
6 1.63575 -2.97583 1.06304
6 2.75041 -3.07814 0.026686
6 3.28636 -1.70781 -0.359849
8 4.44275 -1.58872 -0.75196
8 -4.65071 -1.31657 -0.322092
6 -4.29786 -2.68142 -0.463443
1 0.678687 4.33682 -0.569713
1 1.75723 3.37177 -1.58736
1 2.43598 4.45127 -0.356845
1 -5.23611 -3.22513 -0.583052
1 -3.77336 -3.05975 0.42402
1 -3.66944 -2.84964 -1.34799
1 4.00761 0.601968 -0.948269
1 2.46388 1.18199 -1.56185
1 3.02061 1.31379 1.42755
1 3.72106 2.53751 0.38363
1 -0.230184 -1.90483 1.31693
1 0.034662 -2.52748 -0.303237
1 2.04022 -2.57652 2.00172
1 1.21893 -3.96329 1.29004
1 3.59578 -3.68362 0.364635
1 2.36627 -3.55188 -0.889387
1 1.48278 3.11283 1.45438
1 -3.502 3.00035 0.23859
1 -5.15831 1.12359 -0.062768
1 -1.97109 -1.74853 -0.220845

Conformer 4: E = -961.760488 hartrees
B3LYP/6-31G**

6 0.37103 1.7133 0.307477
8 -0.823904 2.38534 0.350425
6 -1.82042 1.45711 0.204333
6 -1.27212 0.170215 0.081316
6 0.182963 0.351543 0.154883
6 -3.17583 1.73186 0.165445
6 -4.04375 0.653139 -0.010991
6 -3.53127 -0.650731 -0.149875
6 -2.1548 -0.900703 -0.108934
6 1.19515 -0.712648 0.102961
6 2.4856 -0.500226 -0.29326
6 3.02649 0.858881 -0.658654
6 2.89494 1.88109 0.487734
6 1.54967 2.62436 0.491335
6 1.52359 3.76606 -0.549745
6 0.726067 -2.09938 0.515813
6 1.86648 -2.99211 1.00551
6 2.98141 -3.02347 -0.035382
6 3.45764 -1.62316 -0.390225
8 4.6084 -1.44361 -0.776123
8 -4.31319 -1.76078 -0.334562
6 -5.71893 -1.5933 -0.402544
1 1.68957 3.38333 -1.56176
1 0.566042 4.2908 -0.539783
1 2.3158 4.48692 -0.324829
1 -6.01298 -0.950109 -1.24232
1 -6.13357 -2.59089 -0.555276
1 -6.12573 -1.17464 0.527357
1 2.50866 1.23952 -1.55034
1 4.07433 0.726811 -0.933479
1 3.68926 2.63263 0.415022
1 3.04263 1.36677 1.44354
1 0.237094 -2.58529 -0.341972
1 -0.041283 -2.00679 1.29011
1 1.49335 -4.00132 1.21132
1 2.25695 -2.59684 1.95192
1 2.61392 -3.49074 -0.961514
1 3.85251 -3.60082 0.286068
1 1.42304 3.09465 1.47809
1 -3.54588 2.74632 0.264096

1 -5.11043 0.834709 -0.044455

1 -1.82711 -1.92351 -0.232907

Conformer 5: E = -961.759938 hartrees
B3LYP/6-31G**

6 -0.372669 1.64237 -0.24178

8 0.742124 2.42992 -0.231303

6 1.81989 1.58235 -0.11306

6 1.39471 0.246892 -0.060582

6 -0.056626 0.305481 -0.144847

6 3.15219 1.9702 -0.038175

6 4.09434 0.960201 0.097698

6 3.70221 -0.395483 0.168479

6 2.35845 -0.766801 0.096724

6 -1.07564 -0.745611 -0.187814

6 -2.27169 -0.552914 0.444625

6 -2.50305 0.616189 1.38074

6 -2.69422 1.99449 0.716546

6 -1.7143 2.27936 -0.455821

6 -1.63262 3.77701 -0.774999

6 -0.791199 -1.98175 -1.01807

6 -1.7106 -3.1537 -0.668556

6 -3.16957 -2.69457 -0.663909

6 -3.39118 -1.51248 0.271406

8 -4.46981 -1.35179 0.832141

8 4.7376 -1.27823 0.315246

6 4.43386 -2.65974 0.401746

1 -1.02377 3.96936 -1.66241

1 -1.19443 4.33362 0.058858

1 -2.63676 4.17207 -0.955479

1 5.39052 -3.17357 0.506475

1 3.92769 -3.02166 -0.502956

1 3.80732 -2.88399 1.27505

1 -3.38304 0.392183 1.9882

1 -1.63971 0.682479 2.05352

1 -3.71411 2.09274 0.326489

1 -2.57696 2.76735 1.48737

1 -0.910872 -1.7168 -2.08042

1 0.259691 -2.2673 -0.913293

1 -1.56487 -3.97686 -1.37637

1 -1.44704 -3.53681 0.325556

1 -3.46085 -2.37449 -1.67572

1 -3.86251 -3.48773 -0.370495

1 -2.13761 1.76349 -1.33054

1 3.43889 3.01508 -0.081396

1 5.15278 1.1869 0.15986

1 2.06256 -1.80425 0.176923

Conformer 6: E = -961.759875 hartrees
B3LYP/6-31G**

6 0.365683 1.65173 0.213543

8 -0.7559 2.43189 0.214417

6 -1.82846 1.57887 0.087133

6 -1.39348 0.247819 0.021886

6 0.055967 0.31498 0.094016

6 -3.16515 1.9531 0.022227

6 -4.09721 0.932562 -0.109015

6 -3.69333 -0.419893 -0.180393

6 -2.34534 -0.778211 -0.120207

6 1.06075 -0.74582 0.124207

6 2.27518 -0.554071 -0.473543

6 2.55756 0.653288 -1.34542

6 2.73477 2.008 -0.634536

6 1.69671 2.28974 0.486588

6 1.59918 3.78718 0.803011

6 0.718159 -2.02882 0.857758

6 1.96496 -2.699 1.44326

6 3.02771 -2.8785 0.359164

6 3.33697 -1.58833 -0.392831

8 4.42337 -1.43967 -0.942045

8 -4.72208 -1.31255 -0.313518

6 -4.40526 -2.69088 -0.403663

1 1.19883 4.34382 -0.049741

1 0.95093 3.97872 1.66211

1 2.59404 4.18258 1.02859

1 -3.89194 -3.04944 0.498324

1 -5.35727 -3.2139 -0.505314

1 -3.77998 -2.90731 -1.27981

1 1.72073 0.753158 -2.04841

1 3.45685 0.441029 -1.92818

1 2.67516 2.79992 -1.39264

1 3.73321 2.07823 -0.18704

1 0.227191 -2.72427 0.158769

1 -0.014519 -1.81958 1.64395

1 1.70422 -3.66352 1.8928

1 2.36367 -2.07002 2.24906

1 2.67436 -3.60341 -0.389893

1 3.96996 -3.27074 0.751968

1 2.07643 1.7745 1.38171

1 -3.46384 2.99431 0.072161

1 -5.15838 1.14854 -0.162769

1 -2.03481 -1.81254 -0.18559

Conformer 7: E = -961.759624 hartrees
B3LYP/6-31G**

6 -0.36486 1.78675 0.000387

8 0.789414 2.52515 -0.041162

6 1.83622 1.64086 -0.040283

6 1.36333 0.324675 0.011201

6 -0.096689 0.434541 0.058766

6 3.18136 1.98272 -0.115698

6 4.09425 0.939088 -0.15589

6 3.65702 -0.403453 -0.139034

6 2.30067 -0.725133 -0.062206

6 -1.07804 -0.655535 0.154805

6 -2.30221 -0.577087 -0.44159

6 -2.76466 0.644691 -1.19953

6 -2.90867 1.86273 -0.264156

6 -1.5988 2.64157 -0.039752

6 -1.69186 3.55551 1.19999

6 -0.706246 -1.85133 1.01596

6 -1.43113 -3.13052 0.596517

6 -2.93694 -2.88007 0.551347

6 -3.30504 -1.66505 -0.289445

8 -4.41697 -1.58811 -0.801922

8 4.66326 -1.32877 -0.210788

6 4.31516 -2.7022 -0.207056

1 -0.790686 4.16306 1.31281

1 -1.82144 2.96 2.10973

1 -2.55113 4.22757 1.10917

1 5.2558 -3.25239 -0.259302

1 3.69529 -2.96692 -1.07386

1 3.78342 -2.9841 0.711437

1 -2.06326 0.883709 -2.01008

1 -3.72806 0.406367 -1.65344

1 -3.6455 2.56734 -0.666706

1 -3.30818 1.52407 0.699229

1 0.373071 -2.00256 1.02749

1 -0.969612 -1.60539 2.05701

1 -1.07835 -3.43878 -0.396067
1 -1.19463 -3.94707 1.28762
1 -3.50094 -3.73474 0.16757
1 -3.30982 -2.68842 1.56901
1 -1.44772 3.29596 -0.911566
1 3.49675 3.01956 -0.150837
1 5.16027 1.12752 -0.216047
1 1.98175 -1.75743 -0.088246

Conformer 8: E = -961.759275 hartrees
B3LYP/6-31G**

6 -0.378632 1.57527 -0.256083
8 0.775636 2.30585 -0.253774
6 1.80941 1.40407 -0.131641
6 1.31209 0.088373 -0.069241
6 -0.135293 0.224962 -0.149085
6 3.1546 1.71902 -0.062717
6 4.05467 0.660185 0.077084
6 3.58855 -0.667501 0.154216
6 2.22225 -0.961908 0.088204
6 -1.20767 -0.771925 -0.175691
6 -2.38954 -0.508638 0.458078
6 -2.55622 0.680998 1.38213
6 -2.67459 2.06096 0.705025
6 -1.68524 2.28032 -0.473145
6 -1.52632 3.76769 -0.810772
6 -0.988643 -2.03426 -0.985701
6 -1.9677 -3.15067 -0.617065
6 -3.401 -2.61663 -0.616891
6 -3.55834 -1.41007 0.300092
8 -4.62626 -1.18331 0.858815
8 4.40913 -1.75424 0.301667
6 5.80703 -1.53902 0.395676
1 -0.910738 3.91754 -1.70176
1 -1.05786 4.31099 0.015381
1 -2.50908 4.21202 -0.994157
1 6.25593 -2.5266 0.512304
1 6.06698 -0.921618 1.26544
1 6.20917 -1.06721 -0.510402
1 -3.4462 0.510416 1.9923
1 -1.68982 0.707451 2.05384
1 -3.68887 2.21046 0.316666
1 -2.51304 2.83403 1.46769
1 -1.09395 -1.78109 -2.05246
1 0.045412 -2.37274 -0.873579
1 -1.86615 -3.99092 -1.31227
1 -1.72168 -3.5319 0.382154
1 -3.67893 -2.298 -1.63296
1 -4.13328 -3.36796 -0.309148
1 -2.13797 1.77633 -1.33995
1 3.49593 2.74711 -0.112304
1 5.11418 0.875439 0.130462
1 1.91553 -1.99759 0.174256

(*R*)-Intermediate 8

Conformer 1: E = -966.369815 hartrees
B3LYP/6-31G**

6 3.82834 -0.713149 -0.143581
6 2.44598 -0.87689 -0.044256
6 1.63049 0.27282 -0.036454
6 2.24825 1.52546 -0.141893
6 3.62252 1.70851 -0.243167
6 4.41288 0.568036 -0.239739
6 0.192045 0.540985 0.025406
6 0.080219 1.91076 -0.04687
8 1.31109 2.52085 -0.146515
6 -0.885768 -0.467712 0.144694
6 -2.11878 -0.293004 -0.390567
6 -2.4798 1.01791 -1.06907
6 -2.43225 2.22238 -0.102491
6 -1.05267 2.89362 -0.036179
6 -0.524556 -1.71866 0.933642
6 -1.7581 -2.44084 1.47123
6 -2.73523 -2.66801 0.322733
6 -3.23966 -1.34418 -0.302148
6 -0.952359 3.86246 1.15914
8 4.7261 -1.74979 -0.158928
6 4.22409 -3.0705 -0.0668
6 -4.41145 -0.794487 0.550184
6 -3.7747 -1.67997 -1.71588
1 -1.05696 3.32075 2.10514
1 0.009819 4.37993 1.16663
1 -1.74743 4.6136 1.10686
1 3.564 -3.31551 -0.909668
1 5.09467 -3.72797 -0.092179
1 3.67702 -3.23389 0.87136
1 -4.10989 -0.631637 1.58971
1 -4.7895 0.156507 0.162423
1 -5.24656 -1.50447 0.548038
1 -4.5067 -2.49329 -1.651
1 -4.27464 -0.832473 -2.19319
1 -2.96339 -2.0086 -2.37361
1 -3.478 0.951112 -1.5056
1 -1.79403 1.20677 -1.90691
1 -2.72891 1.89103 0.899232
1 -3.16022 2.98506 -0.403947
1 0.153267 -1.44834 1.751
1 0.034326 -2.41832 0.295082
1 -2.22591 -1.84045 2.26149
1 -1.47039 -3.39475 1.92849
1 -3.59927 -3.26175 0.645361
1 -2.22593 -3.25884 -0.451027
1 -0.928571 3.49428 -0.950614
1 2.01375 -1.86402 0.021781
1 4.05242 2.70083 -0.324217
1 5.4927 0.632615 -0.314673

Conformer 2: E = -966.369571 hartrees
B3LYP/6-31G**

6 3.89064 -0.626806 0.182152
6 2.52246 -0.875888 0.065977
6 1.65383 0.223298 -0.074848
6 2.19523 1.51879 -0.069862
6 3.5545 1.78335 0.048481
6 4.40169 0.690184 0.170154
6 0.216873 0.406968 -0.197678
6 0.022603 1.76314 -0.254445
8 1.20084 2.46054 -0.180813
6 -0.891352 -0.562678 -0.29356
6 -2.05518 -0.327401 0.363396
6 -2.13467 0.830901 1.35366
6 -2.23652 2.25183 0.754998
6 -1.26614 2.50825 -0.43048
6 -0.684817 -1.74452 -1.22382
6 -1.74613 -2.83067 -1.04661
6 -3.13167 -2.18967 -0.985101
6 -3.29422 -1.22264 0.212404

6 -1.07826 4.00624 -0.697402
8 4.84278 -1.60324 0.31978
6 4.41667 -2.95355 0.337964
6 -3.5168 -2.03725 1.51158
6 -4.55487 -0.364537 -0.046038
1 -0.583017 4.49722 0.145789
1 -0.471166 4.18315 -1.58939
1 -2.05131 4.48498 -0.844907
1 3.90325 -3.23076 -0.592386
1 5.32112 -3.55535 0.440714
1 3.75002 -3.15915 1.18612
1 -2.68274 -2.71689 1.70848
1 -3.62238 -1.38591 2.38457
1 -4.43263 -2.63472 1.43426
1 -5.4225 -1.01394 -0.210606
1 -4.79307 0.289808 0.797719
1 -4.43097 0.260337 -0.936822
1 -1.23328 0.802076 1.97662
1 -2.97861 0.689336 2.03579
1 -2.03316 2.97384 1.55749
1 -3.25561 2.45482 0.403317
1 0.317914 -2.16102 -1.07928
1 -0.693896 -1.38024 -2.26254
1 -1.54993 -3.39444 -0.12611
1 -1.69223 -3.55121 -1.87081
1 -3.91717 -2.95397 -0.936193
1 -3.29845 -1.63164 -1.91686
1 -1.74299 2.05595 -1.31256
1 2.13376 -1.88505 0.09796
1 3.93291 2.79972 0.048138
1 5.47404 0.820472 0.264255

Conformer 3: E = -966.369154 hartrees
B3LYP/6-31G**

6 -3.72102 -0.853988 0.10064
6 -2.33088 -0.981071 0.009583
6 -1.53852 0.17381 0.014687
6 -2.18572 1.41719 0.124606
6 -3.55813 1.56831 0.217327
6 -4.33568 0.408476 0.201578
6 -0.104936 0.473815 -0.035409
6 -0.023437 1.84392 0.046281
8 -1.26745 2.43117 0.141676
6 0.99234 -0.513451 -0.152373
6 2.21771 -0.317891 0.392967
6 2.54969 0.996789 1.07911
6 2.48205 2.20526 0.118771
6 1.08957 2.84908 0.048925
6 0.657718 -1.76747 -0.947568
6 1.90744 -2.46862 -1.47526
6 2.87893 -2.68095 -0.319097
6 3.35711 -1.34971 0.310569
6 0.976232 3.82341 -1.14084
8 -4.41292 -2.03937 0.085036
6 -5.82455 -1.9962 0.18752
6 4.52489 -0.778524 -0.532925
6 3.88813 -1.67824 1.72754
1 1.09645 3.28983 -2.08957
1 0.004122 4.3219 -1.15018
1 1.75625 4.58943 -1.07954
1 -6.27966 -1.45214 -0.650891
1 -6.1608 -3.03413 0.162073
1 -6.15241 -1.53642 1.12937
1 4.22772 -0.6201 -1.57438
1 4.88287 0.178745 -0.14144
1 5.37257 -1.47344 -0.525508
1 4.63423 -2.47893 1.66659
1 4.37027 -0.823087 2.20962
1 3.078 -2.02179 2.37905
1 3.54753 0.947992 1.51889
1 1.85745 1.16782 1.91553
1 2.79017 1.8853 -0.883172
1 3.19279 2.98106 0.427898
1 -0.016079 -1.50547 -1.7709
1 0.101797 -2.47581 -0.316955
1 2.37224 -1.86023 -2.26129
1 1.6388 -3.42665 -1.93524
1 3.75517 -3.26043 -0.634847
1 2.37279 -3.28016 0.450164
1 0.947548 3.44096 0.966467
1 -1.91776 -1.97829 -0.059472
1 -4.01009 2.55048 0.302534
1 -5.41258 0.495549 0.271677

Conformer 4: E = -966.368803 hartrees
B3LYP/6-31G**

6 3.78247 -0.814752 0.148059
6 2.40236 -1.01478 0.040225
6 1.56617 0.098849 -0.096048
6 2.15018 1.38163 -0.097861
6 3.51182 1.60152 0.010425
6 4.33699 0.480457 0.130528
6 0.133997 0.328915 -0.208864
6 -0.016675 1.68955 -0.268226
8 1.18301 2.35309 -0.204744
6 -1.0036 -0.606757 -0.291234
6 -2.15423 -0.332596 0.373949
6 -2.19039 0.831786 1.35945
6 -2.25164 2.25302 0.756139
6 -1.28278 2.47429 -0.437553
6 -0.83743 -1.80159 -1.21283
6 -1.93218 -2.85211 -1.02412
6 -3.29631 -2.16744 -0.956403
6 -3.42035 -1.19142 0.238335
6 -1.05006 3.96444 -0.712662
8 4.52773 -1.95972 0.274045
6 5.93223 -1.83902 0.409218
6 -3.65438 -1.99377 1.54309
6 -4.65733 -0.297539 -0.012444
1 -0.533347 4.44301 0.124757
1 -0.444353 4.11847 -1.60985
1 -2.0086 4.47295 -0.855288
1 6.20922 -1.26963 1.30642
1 6.31478 -2.85693 0.501254
1 6.3889 -1.36337 -0.468927
1 -2.8369 -2.69406 1.73681
1 -3.73602 -1.33563 2.4136
1 -4.58624 -2.56723 1.47566
1 -5.54515 -0.921564 -0.167347
1 -4.86903 0.366542 0.830956
1 -4.52254 0.320511 -0.90644
1 -1.28612 0.77706 1.97653
1 -3.03354 0.719513 2.04804
1 -2.01941 2.9713 1.55422
1 -3.26636 2.48725 0.411026
1 0.151551 -2.24857 -1.0661
1 -0.837817 -1.44509 -2.25431
1 -1.74767 -3.41798 -0.102684
1 -1.90617 -3.57732 -1.84543

1 -4.10518 -2.90647 -0.899201
1 -3.452 -1.6078 -1.88917
1 -1.7799 2.03256 -1.31369
1 2.0238 -2.02948 0.077814
1 3.92213 2.60546 0.005632
1 5.40692 0.623394 0.214291

Conformer 5: E = -966.368641 hartrees
B3LYP/6-31G**

6 3.82867 -0.693263 0.162803
6 2.44608 -0.868725 0.093135
6 1.62879 0.267225 -0.081376
6 2.24917 1.52003 -0.160525
6 3.62384 1.71583 -0.091326
6 4.41458 0.587339 0.068811
6 0.188695 0.526072 -0.180324
6 0.08083 1.89529 -0.301411
8 1.31495 2.507 -0.298618
6 -0.882632 -0.497311 -0.179311
6 -2.14307 -0.256911 0.260333
6 -2.54719 1.13811 0.698796
6 -2.42293 2.17898 -0.438666
6 -1.04886 2.86761 -0.473891
6 -0.481756 -1.85587 -0.739687
6 -1.68348 -2.67141 -1.21018
6 -2.71129 -2.72471 -0.085095
6 -3.2527 -1.32408 0.288943
6 -0.957115 4.00841 0.562894
8 4.72582 -1.71791 0.325296
6 4.22367 -3.03846 0.418393
6 -3.85882 -1.43227 1.70986
6 -4.38061 -0.93564 -0.700132
1 -1.12386 3.63498 1.57874
1 0.023976 4.487 0.538191
1 -1.71798 4.76649 0.350036
1 3.67425 -3.33 -0.486766
1 5.09447 -3.68621 0.532333
1 3.5659 -3.16479 1.28879
1 -3.0817 -1.6431 2.4518
1 -4.38348 -0.523761 2.01864
1 -4.58543 -2.2524 1.74007
1 -5.21184 -1.64614 -0.62457
1 -4.78194 0.060948 -0.492827
1 -4.02481 -0.940396 -1.73504
1 -1.92359 1.45706 1.54558
1 -3.57394 1.13415 1.06895
1 -3.186 2.95858 -0.327564
1 -2.61813 1.68531 -1.39606
1 0.048702 -2.43707 0.028587
1 0.231733 -1.71364 -1.55867
1 -1.36726 -3.6819 -1.4943
1 -2.11772 -2.21274 -2.10744
1 -2.23295 -3.17212 0.797034
1 -3.55549 -3.37598 -0.342607
1 -0.926291 3.32992 -1.46504
1 2.01649 -1.85526 0.175085
1 4.05289 2.70959 -0.157787
1 5.49471 0.661281 0.129126

Conformer 6: E = -966.368227 hartrees
B3LYP/6-31G**

6 -3.88291 -0.662248 -0.188226
6 -2.51049 -0.894625 -0.088293
6 -1.65632 0.217104 0.033868
6 -2.21124 1.50644 0.041582
6 -3.57485 1.75376 -0.063029
6 -4.40892 0.649074 -0.175518
6 -0.22185 0.413644 0.142887
6 -0.039145 1.76947 0.219864
8 -1.22553 2.45668 0.158422
6 0.878597 -0.563259 0.233188
6 2.05026 -0.340765 -0.41448
6 2.17662 0.869479 -1.33714
6 2.26679 2.26576 -0.681931
6 1.23793 2.51937 0.452499
6 0.642943 -1.7626 1.13608
6 1.9567 -2.35814 1.64084
6 2.89356 -2.5867 0.457776
6 3.25966 -1.28575 -0.301853
6 1.03289 4.01754 0.706446
8 -4.82567 -1.65039 -0.306922
6 -4.38298 -2.99533 -0.326754
6 3.77059 -1.71409 -1.69947
6 4.40988 -0.554775 0.434035
1 0.577547 4.50501 -0.161054
1 0.383305 4.19489 1.56776
1 1.99654 4.49928 0.899136
1 -3.85728 -3.26438 0.599124
1 -5.28076 -3.60864 -0.419661
1 -3.72176 -3.19407 -1.18076
1 2.9596 -2.13131 -2.30554
1 4.22236 -0.889751 -2.25794
1 4.53939 -2.48742 -1.58911
1 5.30577 -1.18595 0.469028
1 4.68146 0.375412 -0.075344
1 4.13214 -0.30151 1.46188
1 1.2997 0.876364 -1.99599
1 3.0445 0.758729 -1.99186
1 2.12534 3.01368 -1.47413
1 3.26875 2.43764 -0.269171
1 0.082214 -2.53705 0.590299
1 0.002615 -1.46582 1.97459
1 1.77215 -3.29984 2.17092
1 2.41525 -1.67374 2.36561
1 2.40107 -3.27708 -0.240961
1 3.81939 -3.08094 0.777186
1 1.67167 2.07349 1.35984
1 -2.10634 -1.89814 -0.10702
1 -3.96739 2.76473 -0.055818
1 -5.48385 0.765922 -0.257301

Conformer 7: E = -966.368004 hartrees
B3LYP/6-31G**

6 -3.72042 -0.838338 -0.151642
6 -2.32989 -0.976087 -0.088533
6 -1.53669 0.164951 0.091005
6 -2.18733 1.40742 0.184072
6 -3.56039 1.56998 0.123704
6 -4.33742 0.422257 -0.043801
6 -0.101642 0.456502 0.185881
6 -0.025007 1.82562 0.317379
8 -1.27256 2.41312 0.326116
6 0.989822 -0.544804 0.171681
6 2.24336 -0.274751 -0.27016
6 2.61807 1.13216 -0.697118
6 2.47282 2.16223 0.447657
6 1.08426 2.82084 0.490146
6 0.61565 -1.91625 0.71857
6 1.83413 -2.71598 1.17258

6 2.85833 -2.73514 0.043041
6 3.37289 -1.32009 -0.314358
6 0.963866 3.96384 -0.541308
8 -4.41034 -2.01231 -0.325184
6 -5.82264 -1.957 -0.409741
6 3.97812 -1.39941 -1.73761
6 4.49529 -0.922159 0.677192
1 1.1355 3.59836 -1.5592
1 -0.027483 4.42047 -0.511295
1 1.70863 4.7375 -0.327689
1 -6.15814 -1.35305 -1.26338
1 -6.15706 -2.98647 -0.548919
1 -6.27265 -1.55591 0.508276
1 3.20348 -1.61496 -2.48075
1 4.48593 -0.477852 -2.03591
1 4.71915 -2.20599 -1.77926
1 5.33904 -1.61678 0.592823
1 4.87851 0.083677 0.479954
1 4.14128 -0.944302 1.71249
1 1.9885 1.44458 -1.54203
1 3.64471 1.15242 -1.06695
1 3.21831 2.95922 0.340522
1 2.68049 1.66635 1.40129
1 0.088368 -2.49642 -0.051953
1 -0.09475 -1.79573 1.54361
1 1.5371 -3.73578 1.44334
1 2.2641 -2.26249 2.07461
1 2.3847 -3.17924 -0.843203
1 3.71553 -3.37411 0.288363
1 0.954233 3.27591 1.48371
1 -1.9183 -1.97115 -0.185088
1 -4.01247 2.55276 0.200553
1 -5.41478 0.517638 -0.093147

Conformer 8: E = -966.367671 hartrees
B3LYP/6-31G**

6 3.84018 -0.665548 -0.145124
6 2.46078 -0.847424 -0.035453
6 1.63252 0.292023 0.021027
6 2.2333 1.55378 -0.078716
6 3.60451 1.75521 -0.187303
6 4.4088 0.624755 -0.211562
6 0.192181 0.543352 0.098108
6 0.059968 1.90864 0.003808
8 1.28237 2.53683 -0.089188
6 -0.891604 -0.455166 0.249502
6 -2.09251 -0.307063 -0.35856
6 -2.36641 0.928776 -1.19925
6 -2.45417 2.19926 -0.322174
6 -1.08933 2.87126 -0.069667
6 -0.604061 -1.61733 1.18824
6 -1.51584 -2.81658 0.936991
6 -2.96776 -2.3495 0.901222
6 -3.24663 -1.31557 -0.21691
6 -1.13517 3.80327 1.15804
8 4.74882 -1.69067 -0.203993
6 4.26364 -3.01941 -0.140121
6 -4.57644 -0.609522 0.142739
6 -3.43273 -2.05041 -1.56852
1 -1.33495 3.23073 2.06989
1 -0.186508 4.33068 1.2863
1 -1.92947 4.54841 1.04284
1 3.60394 -3.25391 -0.986292
1 5.14225 -3.6651 -0.18334
1 3.72175 -3.21025 0.795857
1 -4.47991 -0.027157 1.06509
1 -4.92949 0.060138 -0.646339
1 -5.3588 -1.35983 0.30471
1 -4.30403 -2.71444 -1.52609
1 -3.59313 -1.34721 -2.39197
1 -2.55547 -2.6544 -1.81854
1 -3.29515 0.809262 -1.76173
1 -1.5723 1.06364 -1.94522
1 -2.91599 1.93783 0.636482
1 -3.1121 2.94475 -0.785116
1 -0.736989 -1.26564 2.22331
1 0.443469 -1.91627 1.12785
1 -1.37582 -3.57117 1.71994
1 -1.24431 -3.29448 -0.012976
1 -3.20646 -1.8949 1.87261
1 -3.65374 -3.19713 0.780204
1 -0.863642 3.50121 -0.943327
1 2.03981 -1.84262 -0.022402
1 4.02137 2.7538 -0.259048
1 5.48699 0.704033 -0.295198

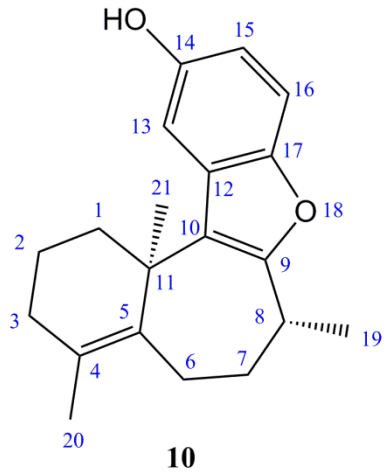
Conformer 9: E = -966.367402 hartrees
B3LYP/6-31G**

6 3.77463 -0.838958 0.160239
6 2.39137 -1.02541 0.069443
6 1.5674 0.098331 -0.05072
6 2.16157 1.37582 -0.067192
6 3.52647 1.58173 0.02678
6 4.34072 0.451466 0.139176
6 0.137704 0.33757 -0.151595
6 -0.004796 1.69694 -0.233334
8 1.20109 2.35302 -0.181806
6 -0.989771 -0.608448 -0.229827
6 -2.1505 -0.349614 0.424062
6 -2.23646 0.868329 1.34119
6 -2.29022 2.26363 0.680229
6 -1.26109 2.48285 -0.461088
6 -0.790169 -1.82142 -1.12295
6 -2.12162 -2.38995 -1.61181
6 -3.05629 -2.58099 -0.42011
6 -3.38561 -1.2622 0.325414
6 -1.01432 3.97336 -0.722648
8 4.51142 -1.99103 0.271448
6 5.91909 -1.88357 0.381447
6 -3.905 -1.66086 1.72873
6 -4.51733 -0.508741 -0.416299
1 -0.539868 4.45078 0.14019
1 -0.365049 4.12846 -1.58849
1 -1.96469 4.48216 -0.911706
1 6.21762 -1.32012 1.27549
1 6.29398 -2.90523 0.462913
1 6.36405 -1.40873 -0.50314
1 -3.10354 -2.08913 2.3397
1 -4.33763 -0.81947 2.27687
1 -4.69144 -2.41757 1.62821
1 -5.43102 -1.11446 -0.439536
1 -4.76046 0.435747 0.08122
1 -4.23651 -0.277568 -1.4485
1 -1.35571 0.853116 1.99485
1 -3.10293 0.785779 2.00187
1 -2.12306 3.01085 1.46816
1 -3.28899 2.46254 0.271902
1 -0.242554 -2.60227 -0.573722

1 -0.149603 -1.5484 -1.96933
1 -1.96366 -3.34222 -2.13133
1 -2.56849 -1.7033 -2.34183
1 -2.57643 -3.27443 0.284245
1 -3.99602 -3.05625 -0.7278
1 -1.71269 2.04526 -1.36365
1 1.99868 -2.03507 0.097964
1 3.94841 2.58076 0.013041
1 5.41296 0.58366 0.210475

7) NMR Experiments

A 1.3 mg sample of **10** was dissolved in 40 µL of $CDCl_3$ containing 0.03% TMS. Spectra were recorded using a 600 MHz Bruker AVANCE III spectrometer equipped with a 1.7-mm TXI MicroCryoProbe™. To determine the structure and assign all the resonances, the following 2D NMR experiments were performed: multiplicity-edited pure shift HSQC[26,27] (16 transients, 2048 x 128 points and linear predicted to 1024 points in F_1), IDR-HSQC-TOCSY[28] (18 ms mixing time, 48 transients, 2048 x 512 points, and 30 ppm spectral width in F_1 centered at 27.5 ppm), HMBC (J_{CH} = 8 Hz, 32 transients, 2048 x 160 points and then linear predicted to 1024 points in F_1), LR-HSQMBC[29] (J_{CH} = 3 Hz, 32 transients, 1536 x 574 points), and ROESY (400 ms mixing time, 16 transients, 1024 x 512 points and then linear predicted to 2048 points in F_1).



10

Position	^{1}H (*J* in Hz)	^{13}C	HMBC	LR-HSQMBC	ROEs
1’	1.78, td (12.6, 12.2, 2.8)	37.3, CH_2	2, 5, 10, 11	2, 3, 5, 10, 11	1’’, 2’, 8, 13
1’’	2.01, ov	--	2, 3, 5, 10, 11	2, 3, 10, 11, 21	1’, 2’, 2’’, 13, 21
2’	1.56, ov	19.4, CH_2	4, 11	1, 11	1’, 1’’, 2’’
2’’	1.72, ov	--	1, 3, 4, 11	3, 4, 11	1’’, 2’
3’	1.97, dt (17.2, 4.8, 4.5)	32.0, CH_2	1, 2, 4, 5	2	20, 3’’
3’’	2.06, ov	--	4, 5	--	20, 3’
4	--	127.7, Cq	--	--	--
5	--	134.9, Cq	--	--	--
6’	2.21, dt(13.8, 9.8, 9.6)	25.3, CH_2	4, 5, 7, 11	7, 11	6’’, 7’, 21
6’’	2.49, dd (13.7, 8.2)	--	4, 5, 7, 8, 11	4	6’, 7’’, 20
7’	1.58, ov	34.7, CH_2	5, 6, 8, 9, 19	6, 8	6’, 7’’, 8, 19
7’’	2.02, ov	--	5, 6, 8, 9	6	6’’, 7’, 8, 19, 20
8	3.23-3.14, m	29.8, CH	7, 9, 19	6, 10, 12	1’, 7’, 7’’, 19, 20
9	--	156.1, Cq	--	--	--
10	--	120.6, Cq	--	--	--
11	--	39.7, Cq	--	--	--
12	--	129.8, Cq	--	--	--
13	7.06, d (2.5)	106.5, CH	10, 15, 14, 17	9, 10, 13-17	1’, 1’’, 21, OH
14	--	150.4, Cq	--	--	--
15	6.67, dd (8.6, 2.5)	110.6, CH	13, 14, 17	10, 12-15, 17	16, OH
16	7.24, d (8.6)	111.3, CH	12, 14, 17	12-14, 17	15
17	--	149.1, Cq	--	--	--
19	1.35, d (7.1)	16.6, CH_3	7-9	6-9, 12	7’, 7’’, 8
20	1.69, s	19.8, CH_3	3-6, 11	2-7, 10, 11, 21	3’, 3’’, 6’’, 7’’, 8
21	1.55, s	26.1, CH_3	1, 5, 10, 11	1, 2, 4, 5, 9-11, 13	13, 6’, 1’’
OH	4.49, s	--	13-15	--	13, 15

^{1}H and ^{13}C spectra were referenced to TMS (0.00 ppm) and $CDCl_3$ (77.16 ppm), respectively.
ov = overlapped, m = multiplet, s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets

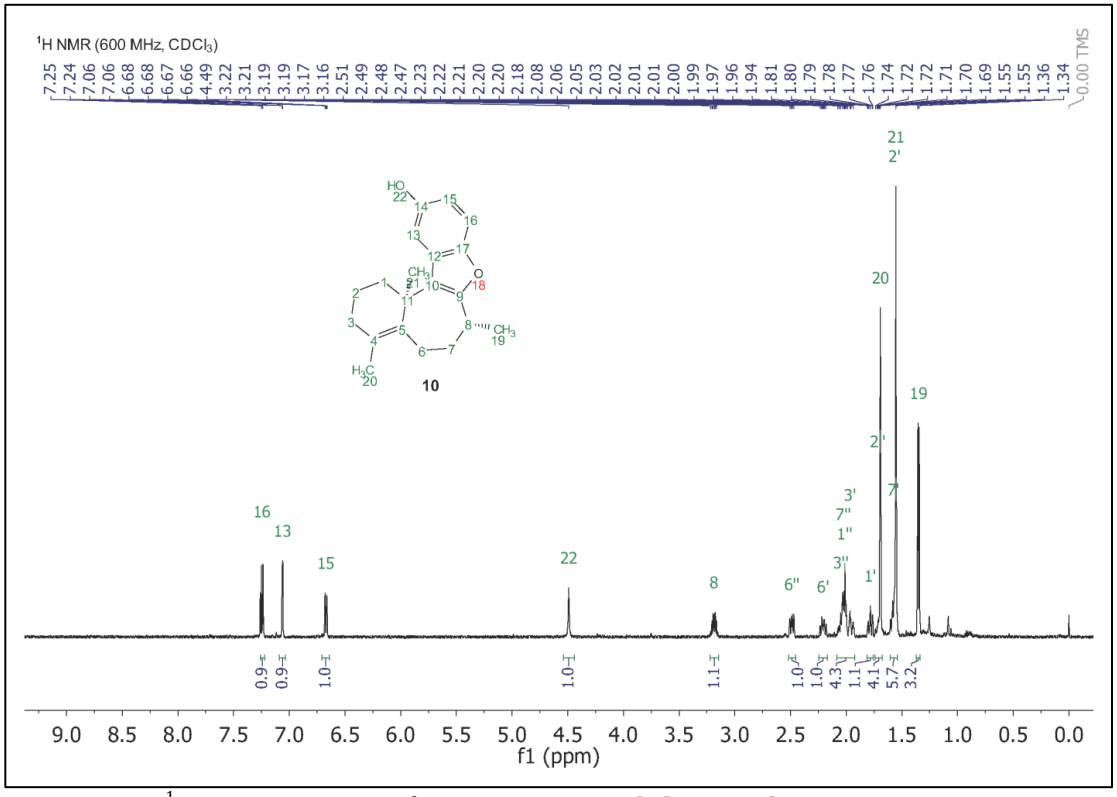


Figure S12. ^{1}H NMR spectrum of impurity **10** recorded in $CDCl_3$.

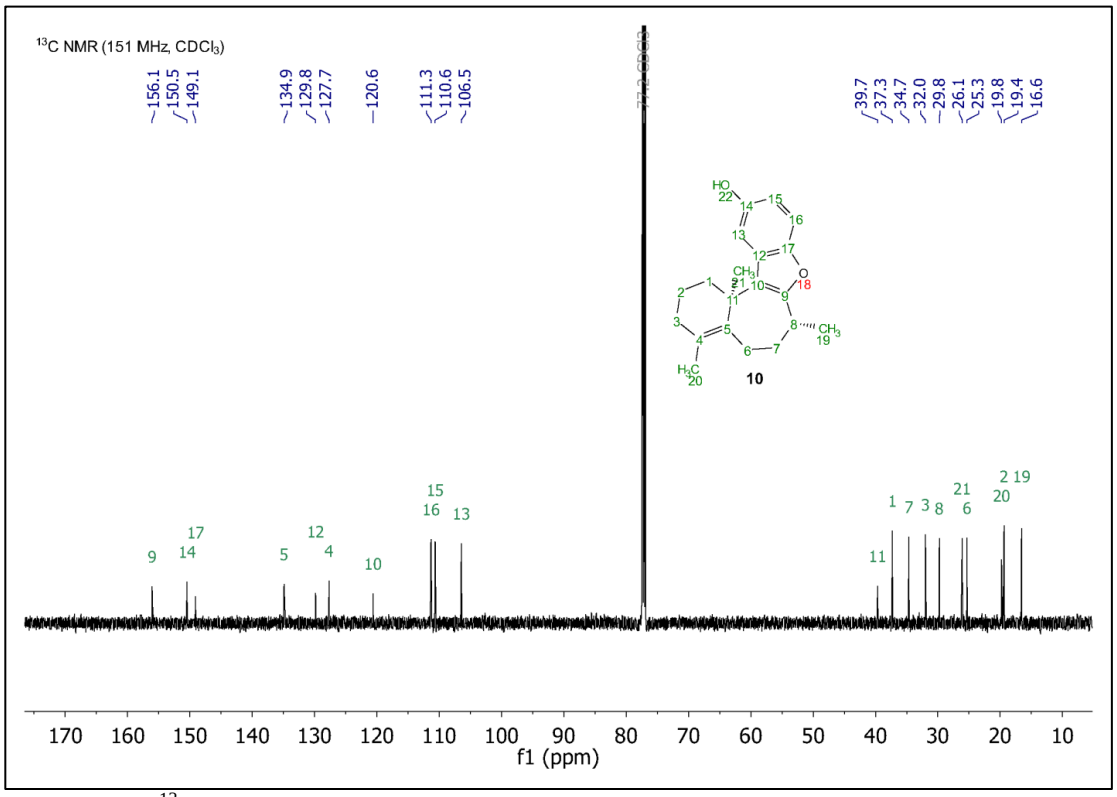


Figure S13: ^{13}C NMR spectrum of impurity **10** recorded in $CDCl_3$

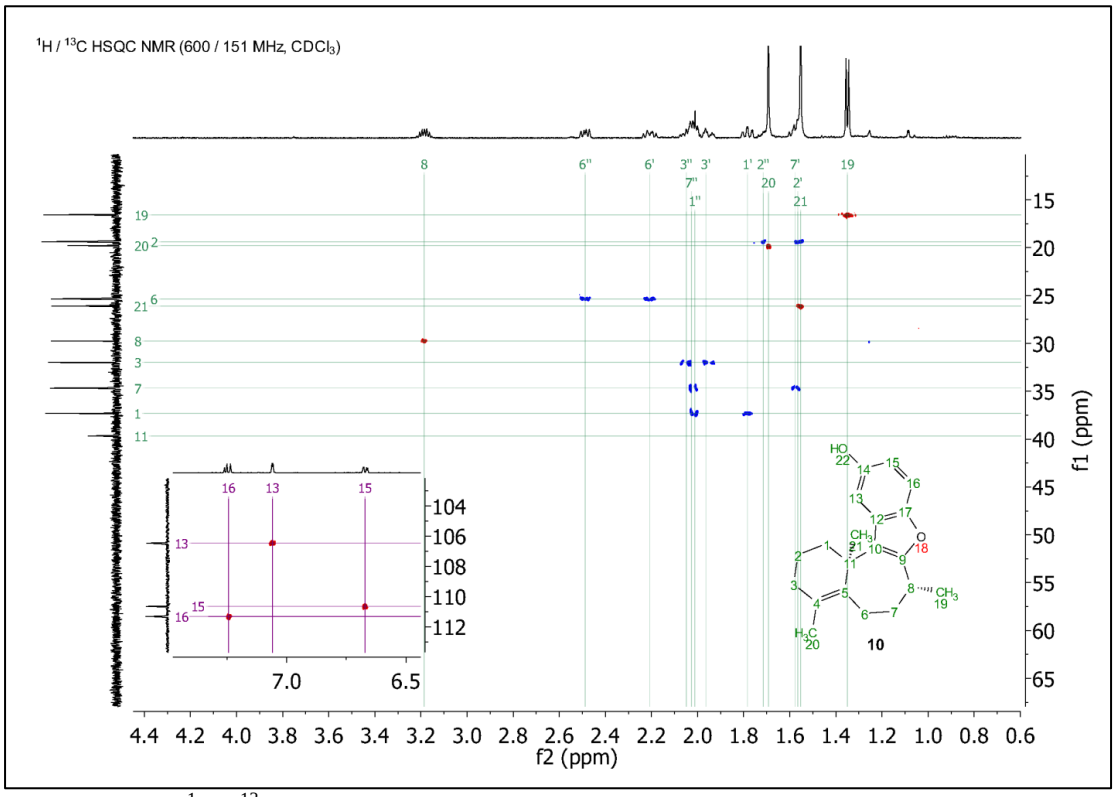


Figure S14: ^{1}H / ^{13}C HSQC NMR spectrum of impurity **10** recorded in $CDCl_3$

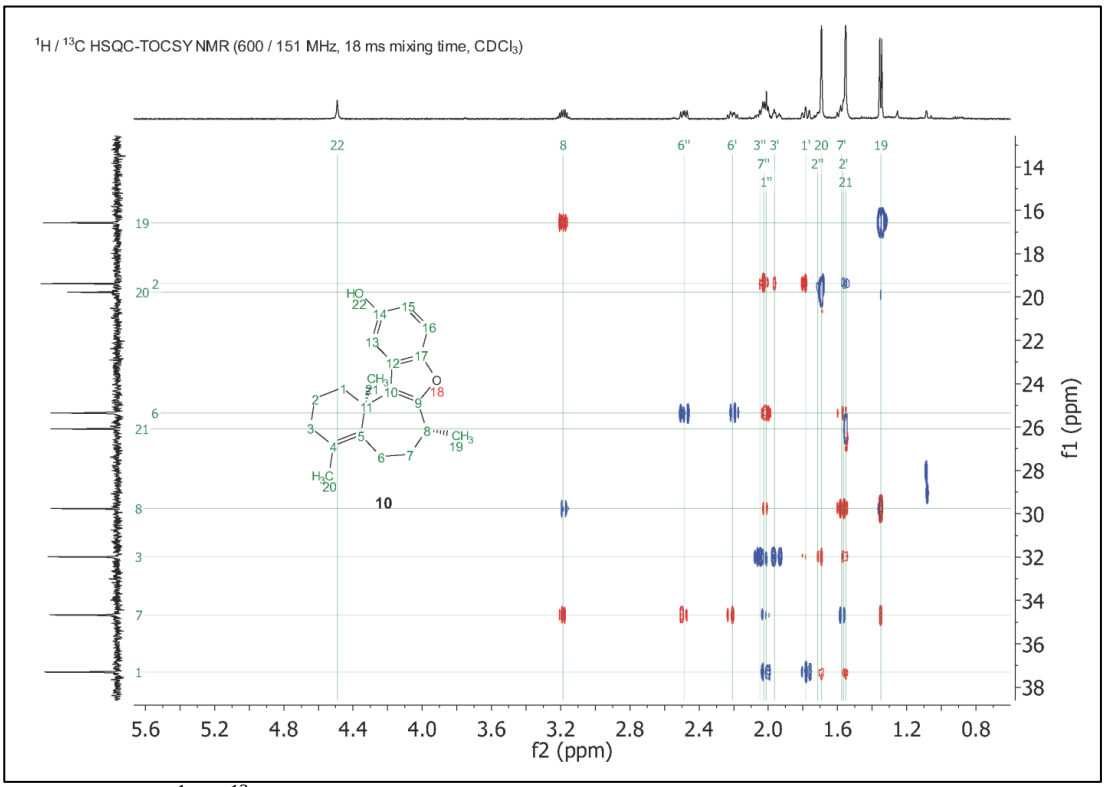


Figure S15: ^{1}H / ^{13}C HSQC-TOCSY NMR spectrum of impurity **10** recorded in $CDCl_3$

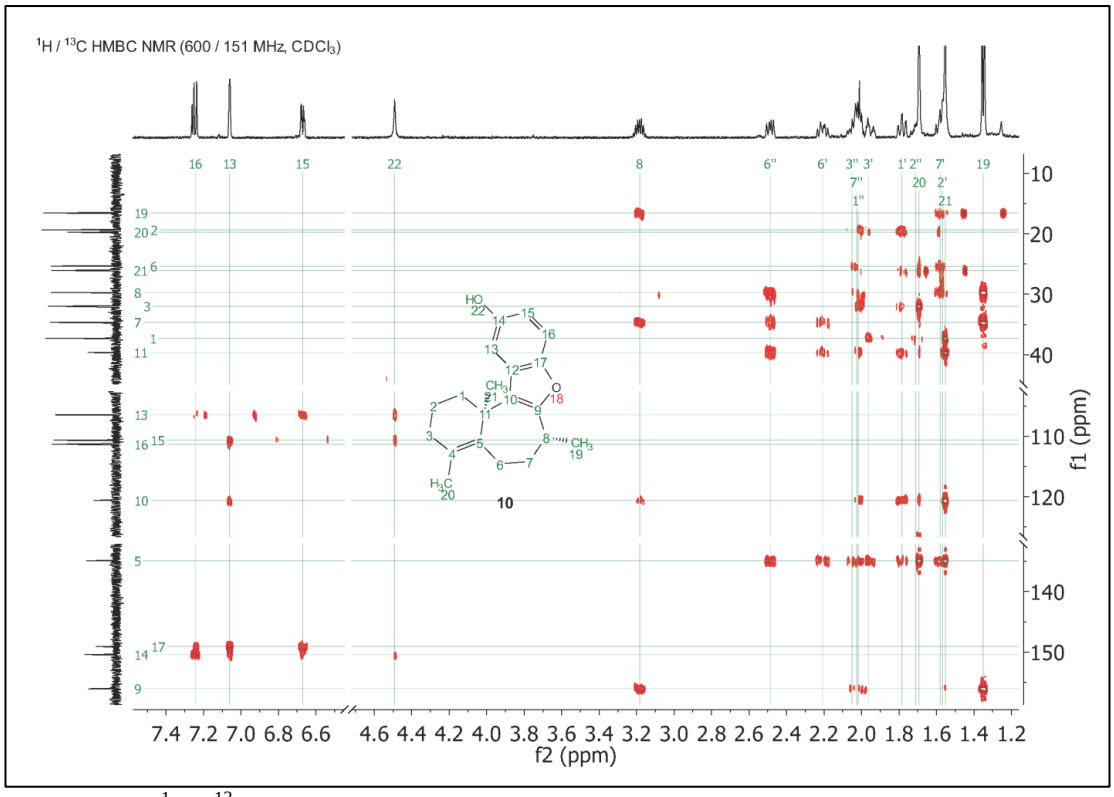


Figure S16: ^{1}H / ^{13}C HMBC NMR spectrum of impurity **10** recorded in $CDCl_3$

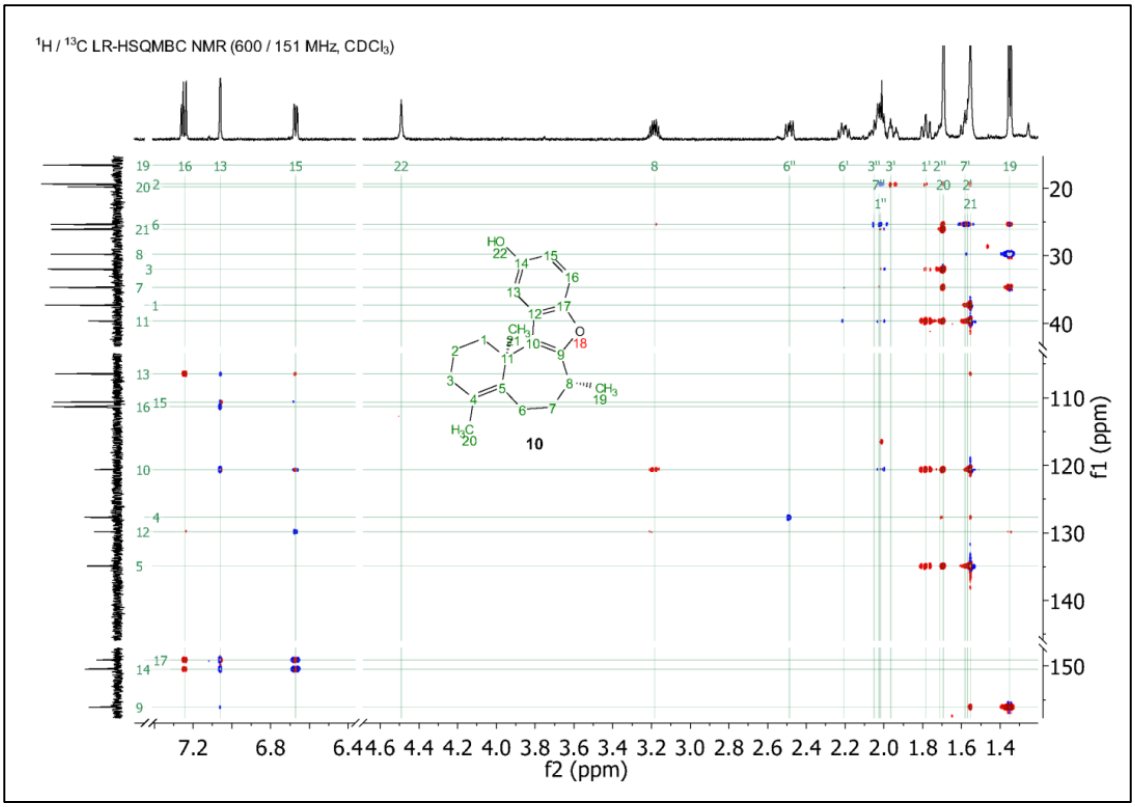


Figure S17: ^{1}H / ^{13}C LR-HSQMBC NMR spectrum of impurity **10** recorded in $CDCl_3$

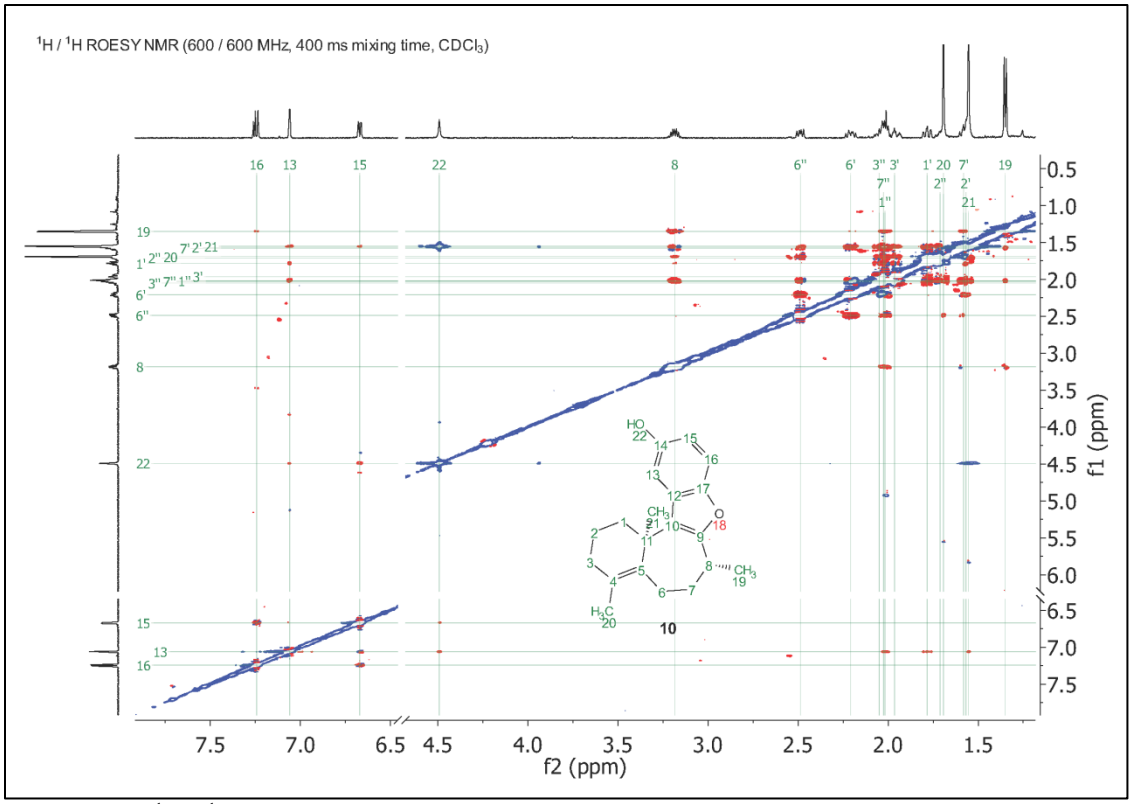


Figure S18: ^{1}H / ^{1}H ROESY NMR spectrum of impurity **10** recorded in $CDCl_3$

DFT chemical shift predictions of frondosin B impurity, 10

NMR chemical shifts, δ (ppm), were calculated using density functional theory (DFT) to provide greater confidence in the structural elucidation of **10**, and in particular, to confirm the relative stereoconfiguration. An ensemble of conformers were initially generated through simulated annealing using the MMFF94[30] force field implemented in Spartan '14[31,32]. Low energy conformers within 10 kcal/mol of the MMFF94[30] global minimum were included in the ensemble for further DFT calculations using Gaussian '09[17]. The theoretical model for DP4+ predictions was used[33]. Namely, molecular geometries were optimized at the B3LYP/6-31G(d) level followed by vibrational frequency calculations at the same level of theory to determine the thermal corrections to the energy. Conformers with negative vibrational frequencies (i.e., saddle points on the potential energy surface) and redundant structures after DFT optimization were removed from the ensemble. Magnetic shielding values, σ, were then calculated for each conformer at the mPW1PW91/6-31+G(d,p) level using the gauge-independent atomic orbital (GIAO) method[34], and implicit solvent effects from chloroform were accounted for by the polarizable continuum model (PCM)[35]. The shieldings were then Boltzmann-weighted based on the DFT calculated energies and then converted to chemical shifts using the following equations.

$$\delta_u = \sigma_0 - \sigma^x \qquad\qquad \delta_s = \frac{\delta_u - \mathrm{b}}{\mathrm{m}}$$

where:

δ_u, δ_s	=	unscaled and scaled chemical shifts (ppm), respectively
σ^x	=	Boltzmann-averaged magnetic shielding value
σ_0	=	magnetic shielding for TMS as reference calculated at the same level of theory
b, m	=	y-intercept and slope, respectively, from linear scaling

The linear scaling factors (b = 194.1824 and 31.6614 and m = -0.9738 and -1.0594 for carbon and proton, respectively) for δs were determined using a test set of 80 reference structures compiled by Rablen and coworkers (http://chesirenmr.info/MoleculeSets.htm)[36-38]. Both the unscaled and scaled proton and carbon chemical shifts were used to determine the DP4+ probabilities[33] for each relative stereoconfiguration, *i*, according to the following formula.

$$P(i) = \frac{\prod_{k=1}^{N}\left[1 - T_s^{\upsilon}\left(\frac{e_{s,k}^{i}}{\sigma_s}\right)\right]\left[1 - T_{u-spx}^{\upsilon}\left(\frac{e_{u,k}^{i} - \mu_{u-spx}}{\sigma_{u-spx}}\right)\right]}{\sum_{j=1}^{m}\prod_{k=1}^{N}\left[1 - T_s^{\upsilon}\left(\frac{e_{s,k}^{i}}{\sigma_s}\right)\right]\left[1 - T_{u-spx}^{\upsilon}\left(\frac{e_{u,k}^{i} - \mu_{u-spx}}{\sigma_{u-spx}}\right)\right]}$$

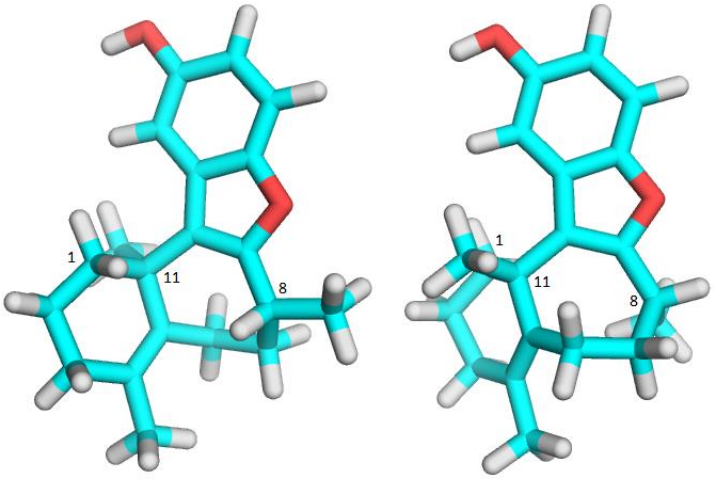
where:

$P(i)$	=	probability that structure *i* is correct
j, m	=	counter, *j*, running over each plausible structure up to *m* structures (i.e., stereoconfigurations)
k, N	=	counter, *k*, running over each chemical shift up to *N* total chemical shifts
T_s^{υ}	=	cumulative distribution function for scaled chemical shifts with υ degrees of freedom
$T_{u\text{-}spx}^{\upsilon}$	=	cumulative distribution function for unscaled chemical shifts with υ degrees of freedom
σ_s	=	variance for scaled chemical shifts
$\sigma_{u\text{-}spx}$	=	variance for unscaled chemical shifts
$e_{s,k}^{i}$	=	error in scaled chemical shift prediction versus experiment, (i.e., $\delta_s - \delta_{exp}$)
$e_{u,k}^{i}$	=	error in unscaled chemical shift prediction versus experiment, (i.e., $\delta_u - \delta_{exp}$)
$\mu_{u\text{-}spx}$	=	mean error between unscaled chemical shift prediction and experiment

The table below shows the DFT calculated (B3LYP/6-31G*) Boltzmann population for the lowest ten energy conformers for each relative stereoconfiguration, (8*R*, 11*R*) and (8*R*, 11*S*). The conformer numbering was from the initial MMFF94[30] energy ranking.

8*R*, 11*R* isomer		8*R*, 11*S* isomer	
Conformer	**Boltzmann pop. (%)**	**Conformer**	**Boltzmann pop. (%)**
2	44.04	2	35.01
1	38.62	1	32.03
4	7.32	10	11.40
3	6.41	9	10.77
6	1.52	8	2.74
5	1.37	7	2.46
10	0.29	4	2.09
9	0.28	3	1.98
8	0.08	6	0.82
7	0.08	5	0.71

For both stereoisomers, conformers 1 and 2 contribute greater than 60% of the Boltzmann population. The only difference between these two structures is the orientation of the hydroxyl group. In conformer 2, the hydroxyl hydrogen points towards the bottom ring system, while it is in the opposite direction in conformer 1. The three-dimensional structures of the global minimum energy conformers are shown in the figure below. For the 8*R*, 11*R* stereoisomer, the protons at positions 1' and 8 are separated by 3.8 Å, which is consistent with the weak ROE. In the case of 8*R*, 11*S*, they are 4.9 Å apart, which is typically too far to observe an ROE .



8*R*, 11*R* **8R, 11*S***

The Boltzmann-averaged, linearly-scaled chemical shifts are provided in the below table for each stereoconfiguration. From this data, the 8*R*, 11*R* stereoconfiguration exhibited the lowest root mean square deviations (RMSD), and the calculated DP4+ probability[33] was 100.00% for 8*R*, 11*R*.

	Expt.	**Calc. 8*R*, 11*R***	**Calc. 8*R*, 11*S***

Position	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1’	1.78	37.3	1.81	37.3	1.76	37.1
1’’	2.01	--	2.08	--	2.30	--
2’	1.56	19.4	1.53	20.6	1.58	20.5
2’’	1.72	--	1.80	--	1.86	--
3’	1.97	32.0	1.92	32.4	2.00	32.6
3’’	2.06	--	2.11	--	2.03	--
4	--	127.7	--	131.5	--	131.0
5	--	134.9	--	137.8	--	139.0
6’	2.21	25.3	2.30	27.2	2.25	28.1
6’’	2.49	--	2.52	--	2.53	--
7’	1.58	34.7	1.54	37.0	1.65	33.9
7’’	2.02	--	1.98	--	2.12	--
8	3.18	29.8	3.23	32.0	3.06	35.8
9	--	156.1	--	157.0	--	157.8
10	--	120.6	--	120.0	--	120.4
11	--	39.7	--	44.5	--	44.2
12	--	129.8	--	129.4	--	129.6
13	7.06	106.5	6.95	103.4	6.96	104.3
14	--	150.4	--	150.7	--	150.6
15	6.67	110.6	6.61	107.1	6.61	107.7
16	7.24	111.3	7.18	110.3	7.14	110.0
17	--	149.1	--	147.1	--	147.3
19	1.35	16.6	1.30	15.9	1.25	23.5
20	1.69	19.8	1.73	19.6	1.75	19.4
21	1.55	26.1	1.59	25.5	1.56	24.8
	RMSD error:		0.19	0.23	2.1	2.9

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