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Assignment of the Absolute Configuration and Total Synthesis of (+)-Caripyrin

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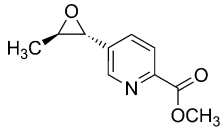
Keywords: Natural products / Total synthesis / Configuration determination / Density functional calculations / Vibrational spectroscopy

The antifungal secondary metabolite (+)-caripyrin was studied by vibrational circular dichroism spectroscopy. Analysis of the recorded data, with the Boltzmann weighted-average of the spectra calculated at the B3LYP/6-311G(d,p) level of theory for all relevant conformers, unequivocally proved the (*R*,*R*)-configuration for the dextrorotatory natural product. Based on this finding, a short enantioselective synthesis of (+)-caripyrin was developed.

Introduction

The complete characterization of chiral non-racemic natural products includes the determination of their respective absolute configuration because this information is crucial for synthetic efforts as well as for the analysis of their interaction with biological targets.

In 2010 Rieger et al. reported the flat structure of the fungal secondary metabolite (+)-caripyrin (**1**; Figure 1), which they isolated from submerged cultures of the basidiomycete *Caripia montagnei*. The compound exhibits selective and strong inhibition of conidial germination in the rice blast fungus *Magnaporthe oryzae*, the causal agent of blast, a devastating disease in cultivated rice.[1] However, the absolute configuration of its two stereogenic centers remained unknown. Herein we report the determination of the full stereostructure of **1** by vibrational circular dichroism spectroscopy by using density functional theory (DFT) calculations at the B3LYP/6-311G(d,p) level. Moreover, a short enantioselective total synthesis of **1** is presented.



(+)-(2′*R*,3′*R*)-caripyrin (**1**)

Figure 1. Structure of (+)-(2′*R*,3′*R*)-caripyrin **1**.

Results and Discussion

To elucidate the absolute configuration of **1**, the IR and vibrational circular dichroism (VCD) spectra of a sample (9.8 mg) were recorded in CCl_4 solution by using a low dead volume BaF_2 sample cell and were analyzed against Boltzmann averaged spectra from DFT calculations. For non-rigid molecules, a thorough conformational analysis is required in this context because circular dichroism spectra are generally sensitive to conformational changes. This analysis was done by using the systematic algorithm as implemented in Spartan′10[2] in combination with the MMFF force field.[3] From this procedure four candidate conformers were obtained. All of these were used as starting geometries for a geometry optimization performed at the B3LYP/6-31G(d,p)[4–7] level of theory (Gaussian09).[8] The final coordinates from this first geometry optimization were then further optimized at the B3LYP/6-311G(d,p)[9] level and solvation was treated with the integral equation formalism polarizable continuum model[10] (IEFPCM) for CCl_4. The conformer distribution, which includes the relative Gibbs energies and the dihedral angles, is given in Table 1 and the geometries are shown in Figure 2. For both side chains attached to the pyridine core, two preferred orientations were found. In the lowest energy conformer, conformer **1**, the dipole moments of the carbonyl oxygen atom, the nitrogen atom and the epoxide oxygen atom compensate each other to the largest extent.

Subsequently, a frequency analysis at B3LYP/6-311G(d,p) level with IEFPCM solvation for CCl_4 was performed for all four conformers to obtain the vibrational absorption and VCD spectra. The spectra of each conformer, the resulting Boltzmann weighted sum and the experimental data are shown in Figure 3 (IR) and Figure 4 (VCD).

The Boltzmann weighted IR spectrum is in excellent agreement with the experimental spectrum of **1**, the frequencies and the intensities of nearly all bands are correctly predicted. It should be noted that the high-frequency shoulder of the ester carbonyl stretch results from conformers **3** and **4**, in which the dipole moments of the C=O and the endocyclic C(2)=N-bond do not cancel each other.

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Table 1. Conformer distribution at B3LYP/6-311G(d,p) IEFPCM CCl_4 level of theory, relative Gibbs energies and dihedral angles of **1**.

	Dihedral N–C2–C1′–O	Dihedral C6–C5–C2′–O	Relative energy[a]	Population
Conformer 1	179.8°	167.5°	0.0	0.545
Conformer 2	179.8°	348.9°	2.1	0.236
Conformer 3	1.1°	168.7°	3.2	0.150
Conformer 4	357.2°	347.8°	5.2	0.068

[a] Values in kJ/mol.

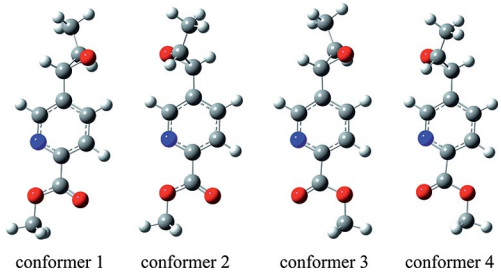


Figure 2. Geometries of all four B3LYP/6-311G(d,p)-optimized conformers of **1**.

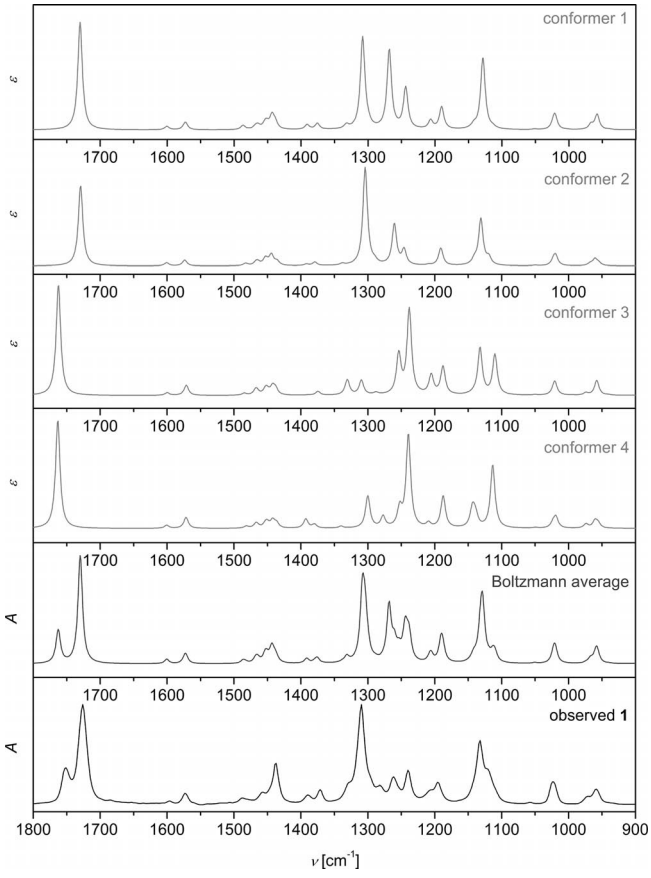


Figure 3. Vibrational absorption spectra of all four conformers, Boltzmann average and experimental spectrum of **1** in CCl_4 solution.

The same good agreement is observed with the VCD spectra. Only the smaller carbonyl band at 1753 cm^{-1} and the band at 1058 cm^{-1} have the wrong sign. This might be a consequence of a small difference in the conformer weighting or a incorrectly predicted sign in the VCD spectrum of a single conformer. The negative band at 1730 cm^{-1} in the experimental spectrum at c = 1 mol/L is a saturation artifact of the detector as can be seen from the somewhat noisier spectrum recorded at c = 0.5 mol/L.

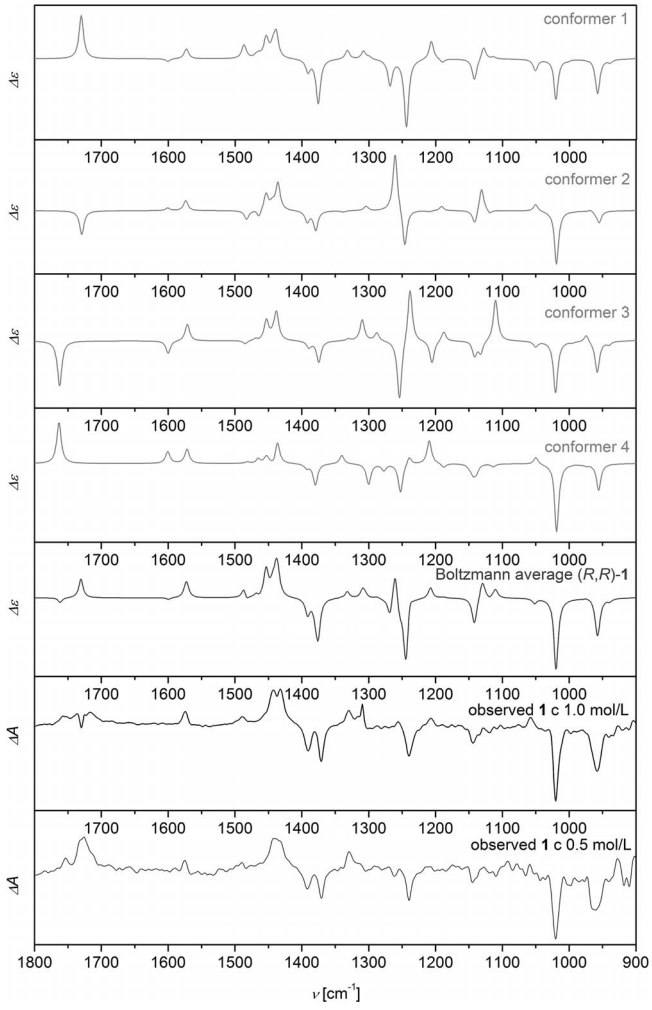
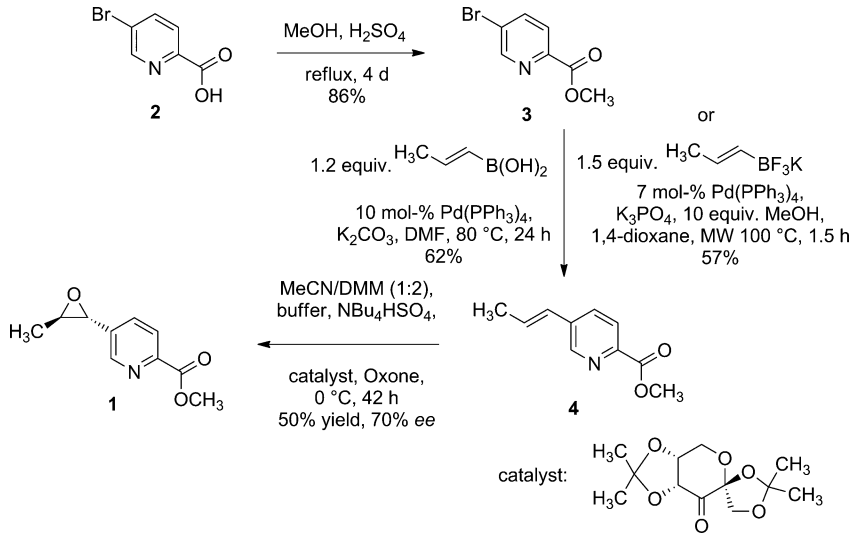


Figure 4. VCD spectra of all four conformers, Boltzmann average and experimental spectrum of **1** in CCl_4 solution in two different concentrations.

Some predicted band intensities, e.g. at 1306, 1254 and 1130 cm^{-1}, do not agree well with the experimental spectrum. In most cases, the reason for this is the small frequency difference between absorption bands with opposite signs in different conformers. However, there is clearly no doubt that the absolute configuration of **1** is (*R*,*R*). Fristrup et al. reported very similar results for their VCD study on (1*R*,2*R*)-2-methylphenyloxirane.[11]



Scheme 1. Total synthesis of (+)-(*R*,*R*)-caripyrin **1**.

With the knowledge about the absolute configuration of natural occurring **1**, an asymmetric synthesis was developed (Scheme 1). The key step is the asymmetrical epoxidation of the disubstituted (*E*)-olefin by using Shi's method.[12–14] Gratifyingly, the commercially available D-fructose-based catalyst should produce the desired enantiomer. *trans*-Olefin **4** was prepared by a Suzuki–Miyaura cross-coupling reaction of (*E*)-1-propen-1-ylboronic acid with methyl 5-bromopicolinate (**3**) as described by Aoyagi et al.[15] Ester **3** was obtained by acidic esterification of commercial 5-bromopicolinic acid (**2**).

Because (*E*)-1-propen-1-ylboronic acid is quite expensive (>250 € per g in 2014) two other boronic acid derivatives, namely (*E*)-1-propenylboronic acid *N*-methyliminodiacetic acid (MIDA) ester and potassium (*E*)-1-propenyltrifluoroborate, were tested as precursors for the propenyl side chain. The use of the MIDA ester (ca. 35 € per g in 2014; 3 equiv. used) gave olefin **4** in 67% yield as an inseparable mixture with its (*Z*)-isomer (ratio 1:0.25, *E*/*Z*, see Supporting Information). The MIDA ester already contained the same percentage of the (*Z*)-isomer. With potassium (*E*)-1-propenyltrifluoroborate (ca. 52 € per g in 2014; 1.5 equiv. used) olefin **4** was obtained in 57% yield as the pure (*E*)-isomer. Thus, the latter method is most cost-effective despite the slightly lower yield.

The epoxidation reaction with the reaction conditions described for (*E*)-prop-1-en-1-ylbenzene was found to be sluggish.[12–14] When the addition of the oxone and potassium carbonate solution was complete after 2 h, TLC indicated only very low conversion. This is presumably caused by the electrophilic nature of the intermediate dioxirane species, which reacts faster with electron-rich double bonds. The conversion could be increased by longer reaction times and the addition of more oxidant and base. After 42 h at 0 °C, **1** was isolated in 50% yield and 70% *ee* (chiral HPLC). By performing the reaction at –20 °C, near to the freezing point of the solvent mixture, produced **1** in only 11% yield after 92 h but with an appreciable *ee* of 89% (see Supporting Information). The HPLC chromatograms of natural and synthetic **1** (70% *ee*) as well as of the racemate are shown in Figure 5. As predicted, the naturally occurring enantiomer of **1** was the major product.

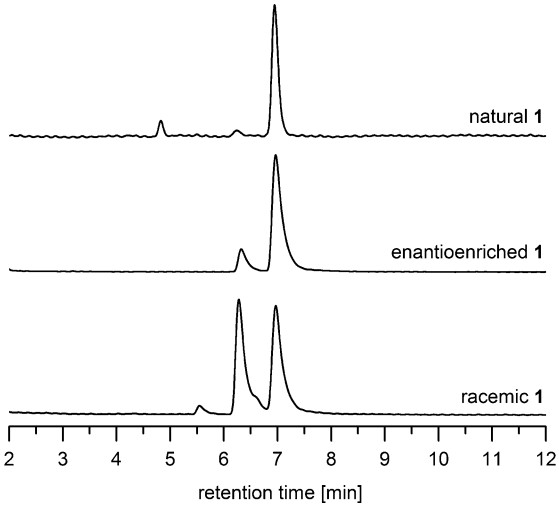


Figure 5. HPLC chromatograms of natural **1**, synthetic **1** (70% *ee*) and the racemate.

Conclusions

We unambiguously determined the absolute configuration of (+)-caripyrin (**1**) to be (2′*R*,3′*R*) by VCD spectroscopy in combination with DFT calculations. Based on this knowledge, the first asymmetric total synthesis of this antifungal natural product was performed in 26.6% overall yield. At the expense of the conversion, an enantiomeric excess of up to 89% could be achieved.

Experimental Section

Vibrational Spectroscopy: The IR (16 scans, 4000–400 cm^{-1}) and VCD (240 min accumulation time, 1800–875 cm^{-1}) spectra were re-

corded on a Bruker Tensor 27 IR spectrometer equipped with a PMA 50 module containing a single photoelastic modulator, with 4 cm^{-1} resolution and the instrument optimized at 1400 cm^{-1}. A 100 μm BaF_2 cell and CCl_4 solutions of **1** with concentrations of 0.5 mol/L and 1.0 mol/L were used. All solution spectra were solvent subtracted. Routine IR spectra were measured on the same spectrometer with a diamond ATR unit.

Computational Methods: All calculations were performed on standard desktop computers with Intel Core i7 CPUs by using Spartan′10[2] and Gaussian09 rev. A.02.[8] The calculations were preceded by a thorough conformer search by using the MMFF force field[3] and the algorithm to analyze conformer distributions as implemented in Spartan′10. All four obtained low-energy conformers were optimized at the B3LYP/6-31G(d,p)[4–7] level of theory by using Gaussian09. Subsequently, they were further optimized at the B3LYP/6-311G(d,p)[9] level treating solvation with the IEFPCM model[10] for CCl_4. A frequency analysis with the same DFT settings was done with all four further optimized structures to obtain the vibrational spectra. Boltzmann weighting with the relative Gibbs energies from the thermochemical output of the frequency calculations was carried out to receive the averaged spectra. The calculated vibrational frequencies were scaled by an empirically determined factor of 0.9805.

Synthesis: Melting points were determined in open capillary tubes with a Krüss KSP-1N apparatus. The optical rotation was measured on a Jasco P-2000 polarimeter at 589 nm with a temperature-controlled cuvette with 10 cm path length. NMR spectra were recorded with a Bruker Avance-II 400 MHz spectrometer (400 MHz ^1H and 101 MHz ^{13}C) equipped with a 5 mm BBFO probe by using standard pulse sequences. Chemical shifts were referenced by using the solvent signals of $CHCl_3/CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm).[16] HRMS (ESI) spectra were recorded with a *Waters QTof-Ultima 3*-Instrument with *LockSpray*-Interface and a suitable external calibrant. Microwave reactions were carried out in a CEM Discover monomode apparatus at the indicated maximum temperature and power setting. Chiral HPLC for enantiomeric excess determination was performed by using a Knauer HPLC system with a K-1001 pump, a column oven, a K-2800 diode array UV detector and a Chiralpak IB-3 column (250 mm × 4.6 mm, 3 μm, Daicel Corp.) with a flow rate of 2 mL/min hexane/ethanol 95:5. TLC experiments were performed on alumina sheets coated with silica gel (60 F_{254}, Merck). For flash chromatography silica gel (35–70 μm, 60 Å, Acros) was used. Automated flash chromatography was done by using a Biotage Isolera One equipped with a diode array detector (200–400 nm). All solvents, starting materials and reagents were purchased from commercial suppliers and used as received unless otherwise noted. The solvents for chromatography were distilled before use. The tetrakis(triphenylphosphine)palladium(0) was prepared according to literature methods.[17,18]

Methyl 5-[(2*R*,3*R*)-3-Methyloxiran-2-yl]picolinate (1): Olefin **4** (60 mg, 0.34 mmol), tetrabutylammonium hydrogen sulfate (5 mg, 14 μmol) and 1,2:4,5-di-*O*-isopropylidene-D-*erythro*-2,3-hexodiuro-2,6-pyranose (26 mg, 0.10 mmol) were dissolved under vigorous stirring in a mixture of acetonitrile/dimethoxymethane (5.6 mL, 1:2, v/v) and a solution of $Na_2B_4O_7 \cdot 10\ H_2O$ (0.05 M) in aqueous Na_2(EDTA) (4×10^{-4} M, 4.0 mL, pH 9.0) and cooled to –10 °C. Over a period of 2 h, a solution (6 mL) of Oxone (867 mg, 2.82 mmol) in aqueous Na_2(EDTA) (4×10^{-4} M, 18 mL) and a solution (6 mL) of potassium carbonate (817 mg, 6.27 mmol) in deionized water (18 mL) were added through syringe pumps. After stirring for 16 h, a further amount (3 mL each) of the two solutions was added through syringe pumps over 1 h. After another hour the temperature was raised to 0 °C and the reaction mixture stirred for 4 h at that temperature. Then, another portion (2 mL each) of the two solutions was added over 40 min through syringe pumps. After 18 h, the mixture was quenched by adding water (20 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 1:1 v/v) to give **1** as white microcrystalline solid (33 mg, 0.17 mmol, 50% yield, 70% *ee*). R_f = 0.10 cyclohexane/ethyl acetate, 2:1, m.p. 40–42 °C. ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 8.64 (d, J = 2.1 Hz, 1 H, 6-H), 8.07 (d, J = 8.1 Hz, 1 H, 3-H), 7.65 (dd, J = 8.1, 2.1 Hz, 1 H, 4-H), 3.98 (s, 3 H, OCH_3), 3.66 (d, J = 2.0 Hz, 1 H, 2′-H), 3.04 (qd, J = 5.1, 2.0 Hz, 1 H, 3′-H), 1.47 (d, J = 5.1 Hz, 3 H, 3′-CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ = 165.5 (C=O), 147.8 (C-6), 147.6 (C-2), 137.5 (C-5), 133.8 (C-4), 125.0 (C-3), 59.8 (C-3′), 56.9 (C-2′), 53.0 (OCH_3), 17.9 (3′-CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{10}H_{11}NO_3Na$ $[M + Na]^+$ 216.0637; found 216.0634. IR (ATR): $\tilde{\nu}_{max}$ = 2955, 1742, 1722, 1437, 1310, 1241, 1132, 1122, 859, 709 cm^{-1}.

The analytical data are consistent with the values from the literature.[1]

With the same procedure as described above carried out at –20 °C over 92 h reaction time, **1** was obtained in 11% yield and 89% *ee*. $[a]_D^{25}$ = +20.9 (c = 0.43, $CDCl_3$).

Methyl 5-(3-Methyloxiran-2-yl)picolinate (*rac*-1): Olefin **4** (48 mg, 0.27 mmol) and 3-chloroperbenzoic acid (95 mg, 0.55 mmol) were heated at reflux in dry dichloromethane (10 mL) for 6 h. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 1:1 v/v) to give *rac*-**1** (12 mg, 0.06 mmol, 22% yield).

Methyl 5-Bromopicolinate (3): 5-Bromopicolinic acid (2.56 g, 12.7 mmol) was dissolved in methanol (100 mL), sulfuric acid (0.5 mL) was added and the reaction mixture heated at reflux for 117 h. After cooling to room temperature saturated sodium carbonate solution was added until the pH was above 9. The mixture was extracted with dichloromethane. The organic layer was dried with Na_2SO_4 and the volatiles were removed under reduced pressure to give **3** as an off-white solid (2.37 g, 11.0 mmol, 86% yield). R_f = 0.30 cyclohexane/ethyl acetate, 2:1, m.p. 99–100 °C. ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 8.78 (dd, J = 2.2, 0.8 Hz, 1 H, 6-H), 8.02 (dd, J = 8.3, 0.8 Hz, 1 H, 3-H), 7.98 (dd, J = 8.3, 2.2 Hz, 1 H, 4-H), 4.00 (s, 3 H, OCH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ = 165.2 (C=O), 151.2 (C-6), 146.4 (C-2), 139.9 (C-4), 126.4 (C-3), 125.2 (C-5), 53.2 (OCH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_7H_6BrNO_2Na$ $[M + Na]^+$ 237.9480; found 237.9490. IR (ATR): $\tilde{\nu}_{max}$ = 3059, 2957, 1715, 1438, 1364, 1308, 1235, 1133, 1008, 697 cm^{-1}.

The analytical data are consistent with the values from the literature.[19]

(*E*)-Methyl 5-(Prop-1-en-1-yl)picolinate (4). Method A: Under a nitrogen atmosphere, ester **3** (2.10 g, 9.70 mmol), (*E*)-1-propen-1-ylboronic acid (1.00 g, 11.6 mmol), potassium carbonate (1.61 g, 11.6 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.12 g, 0.97 mmol) were dissolved in dry dimethylformamide (DMF; 40 mL) and heated at reflux for 5 h. Subsequently, the solvent was removed in vacuo. The crude product was coevaporated with diethyl ether (18 mL) and afterwards dissolved in chloroform and washed with aqueous NaOH (1 M), dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 2:1 v/v) to give **4** as white micro-

crystalline solid (1.10 g, 6.23 mmol, 62% yield). R_f = 0.20 cyclohexane/ethyl acetate, 2:1, m.p. 67–68 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 8.62 (dd, J = 2.2, 0.6 Hz, 1 H, 6-H), 8.02 (dd, J = 8.2, 0.6 Hz, 1 H, 3-H), 7.72 (dd, J = 8.2, 2.2 Hz, 1 H, 4-H), 6.48–6.37 (m, 2 H, 2′-H, 3′H), 3.96 (s, 3 H, OCH_3), 1.92–1.90 (m, 3 H, 3′-CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ = 165.7 (C=O), 147.7 (C-6), 145.7 (C-2), 136.7 (C-5), 133.0 (C-4), 131.4 (C-3′), 126.9 (C-2′), 125.1 (C-3), 53.2 (OCH_3), 18.9 (3′-CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{10}H_{11}NO_2Na$ $[M + Na]^+$ 200.0687; found 200.0678. IR (ATR): $\tilde{\nu}_{max}$ = 2954, 1706, 1436, 1305, 1256, 1205, 1138, 1119, 967, 703 cm^{-1}.

The analytical data are consistent with the values from the literature.[15]

Method B: In a glovebox filled with nitrogen a microwave vial was charged with ester **3** (103 mg, 0.477 mmol), potassium (*E*)-1-propenyltrifluoroborate (81 mg, 0.547 mmol), potassium phosphate (202 mg, 0.954 mmol) and tetrakis(triphenylphosphine)palladium(0) (38 mg, 3.28 μmol) and closed with a septum. Outside the glovebox, methanol (0.1 mL, 2.47 mmol) and 1,4-dioxane (6 mL) were added and the internal atmosphere changed to argon. The septum was replaced by a microwave tube cap. The sealed reaction vessel was heated in the microwave apparatus with a maximum power of 300 W for 90 min to 100 °C. Then the volatiles were removed in vacuo and the crude product was purified by automated flash chromatography (10 g cartridge, flow rate 20 mL/min, gradient cyclohexane/ethyl acetate, 94:6 to 25:75 in 15 column volumes) to give **4** as white microcrystalline solid (48 mg, 0.27 mmol, 57% yield).

Supporting Information (see footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **3**, and **4**, chiral HPLC chromatogram of compound **1** as well as atom coordinates and DFT energies for all four conformers of **1**.

Acknowledgments

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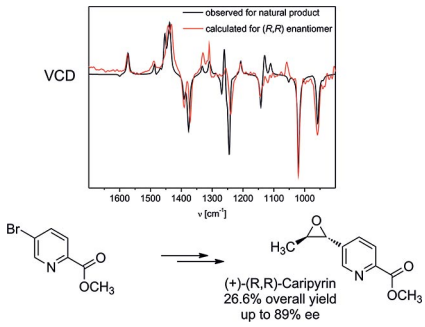
Configuration Determination

The absolute configuration of the natural product (+)-caripyrin was determined by vibrational circular dichroism spectroscopy and density functional theory calculations. Based on this information, the compound was prepared in a short asymmetric synthesis.



L. Andernach, T. Opatz* **1–6**

Assignment of the Absolute Configuration and Total Synthesis of (+)-Caripyrin

Keywords: Natural products / Total synthesis / Configuration determination / Density functional calculations / Vibrational spectroscopy

