Supporting Information

Stereochemistry of Isoplagiochin C, a Macrocyclic Bisbibenzyl from Liverworts

Gerhard Bringmann,[*,†] *Jörg Mühlbacher,*[†,°] *Matthias Reichert,*[†] *Michael Dreyer,*[†] *Jürgen Kolz,*[‡] *and Andreas Speicher*[‡]

Contribution from the Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany, and the FR Organische Chemie, Saarland University, Universität, D-66123 Saarbrücken, Germany

[†] University of Würzburg.

[‡] Saarland University.

° Current address: Novartis Institutes for Biomedical Research, CH-4002 Basel, Switzerland.

Experimental Section

General. Racemic isoplagiochin C (**1**) was prepared by total synthesis.[5] A sample of natural **1** from *Plagiochila deflexa* was provided by Prof. R. Mues, Saarland University. Optical activities were measured on a Perkin Elmer polarimeter 241. NMR experiments were performed using a Bruker DRX 500 spectrometer (^{1}H, 500 MHz).

HPLC Analysis on a Chiral Phase. Enantiomer resolutions were carried out on a Chiralcel OD-H column (4.6 × 250 mm, 5 μm, Daicel Chemical Ltd.) at room temp., 0.5 mL/min, using an *n*-hexane/*i*-PrOH gradient (90:10, v/v, for 16.5 min, 50:50 for 20 min, 5:95 for 13.5 min).

The HPLC system consisted of a PU 1580 pump, an LG-980-02S ternary gradient unit (all from Jasco), and a 7215 single wavelength detector (ERC).

CD Measurements Offline and in Hyphenation with HPLC. Offline CD investigations[30] were performed on a J-715 spectropolarimeter (Jasco) in a 1 mm quartz cuvette, while online measurements were done with a 5 mm standard flow cell at 254 nm. Full CD spectra were recorded in the stop-flow mode at a scan speed of 500 nm/min, with a response time of 0.5 sec and a band width of 0.5 nm. For further experimental details, see refs. 28–30.

Kinetic Experiments. A solution of 0.30 mg (0.71 μmol) of isoplagiochin C (**1**) (from *Plagiochila deflexa,* initial enantiomeric ratio *P*:*M* = 85:15) in 2 mL of decaline (mixture of *cis* and *trans*) was stirred under Ar at 85 °C, 105 °C, 125 °C, or 145 °C. Analytical 100 µL samples were taken at defined times, cooled, and diluted by addition of 100 µL of isopropanol/*n*-hexane (1:1 v/v). From the enantiomeric ratios measured by HPLC on a chiral phase, the kinetic data for a first order reaction leading to an equilibrium (50:50 in this case, $[P]_e = 0.5$: equilibrium concentration of the *P*-enantiomer) were approximated: $\ln\{[P]-[P]_e\}$ vs t resulting in $k_1+k_{-1} = 2\ k_1$ as slope. From the resulting Arrhenius plot $[\ln(k_1+k_{-1})]$ vs 1/T, see Figure S1, the racemization barrier was calculated as 101.6 ± 1.0 kJ/mol.[31]

NMR Experiments at Variable Temperature. (a) 10 mg of racemic **1** were dissolved in CD_3OD (0.6 mL) and ^1H NMR spectra were taken at +25 °C, 0 °C, –10 °C, –20 °C, –30 °C, –40 °C, –50 °C, –60 °C, –70 °C, +25 °C, +40 °C, +50 °C, +60 °C, +25 °C. No additional or disappearing signals were observed upon cooling or heating and the spectra subsequently obtained at 25 °C were identical to those before cooling or heating. (b) 10 mg of racemic **1** were dissolved in d_6-DMSO (0.6 mL) and ^1H NMR spectra were measured at +25 °C, +40 °C, +50 °C, +60 °C, +70 °C, +80 °C, +90 °C, +100 °C, +25 °C. Again, in no case the appearance or disappearance of any proton signals was observed.

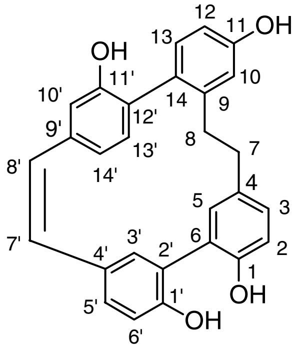
Computational Methods. The conformational analysis of isoplagiochin C (**1**) was performed on Silicon Graphics OCTANE R10000 workstations by means of the semiempirical AM1[19] method as implemented in the program package VAMP 6.5,[32] starting from preoptimized geometries generated by the TRIPOS[33] force field.

To calculate the rotational barriers **A**–**C**, the respective transition structures were located and optimized using the STQN[34,35] method as implemented in the Gaussian 98[36] package starting from a global minimum geometry. To verify that the particular transition state corresponds to the respective isomerization step, a frequency analysis was performed in each case resulting in one imaginary frequency according to a first-order saddle point.

The MD simulations were performed using the TRIPOS force field implemented in the molecular modelling package Sybyl 6.5,[33] using a timestep of 0.5 fs. The molecule was weakly coupled to a thermal bath,[37] with a temperature relaxation time $\tau = 0.1$ s.

The wave functions for the calculation of the rotational strengths for the electronic transitions from the ground state to excited states were obtained by CNDO/S-CI[24,38] calculations, in which the CI expansion takes into account the ground state and all n and π orbitals. The calculations were carried out using the BDZDO/MCDSPD[38] program package. For better comparison of the theoretical CD spectrum with the experimental one, a Gaussian band shape function was generated over the calculated rotational strength values.

Table S1. ^{1}H NMR Data (Chemical Shifts in ppm) of NMR Experiments at Variable Temperatures (Performed on a Bruker DRX 500 Spectrometer, 500 MHz)



Position	CD_3OD	d_6-DMSO
1	-	-
2	6.72 d (8.0 Hz)	6.72 d (8.0 Hz)
3	6.97 dd (2.3/8.0 Hz)	7.00 dd (2.2/8.1 Hz)
4	-	-
5	6.57 d (2.2 Hz)	6.47 d (2.1 Hz)
6	-	-
7	2.70-2.45 m	2.65-2.39 m
8	2.70-2.45 m	2.65-2.39 m
9	-	-
10	6.76 d (2.5 Hz)	6.73 d (2.4 Hz)
11	-	-
12	6.68 dd (2.4/8.2 Hz)	6.65 dd (2.6/8.1 Hz)
13	7.00 d (8.4 Hz)	6.92 d (8.2 Hz)
14	-	-
1'	-	-
2'	-	-
3'	7.21 d (2.3 Hz)	7.09 d (2.2 Hz)
4'	-	-
5'	7.13 dd (2.3/8.0 Hz)	7.18 dd (2.2/8.3 Hz)
6'	6.85 d (8.2 Hz)	6.87 d (8.3 Hz)

7'	6.55 d (12.0 Hz)	6.56 d (11.9 Hz)
8'	6.63 d (12.0 Hz)	6.62 d (11.9 Hz)
9'	-	-
10'	6.83 d (not resolved)	6.82 d (not resolved)
11'	-	-
12'	-	-
13'	7.08 d (7.5 Hz)	7.07 d (7.6 Hz)
14'	6.80 dd (not resolved)	6.72 dd (superposed)
OH at C-11/11'	not observed	9.26 s, 2 H
OH at C-1	not observed	9.49 s
OH at C-1'	not observed	9.57 s

In $CDCl_3$ only one signal at 7.60 ppm was observed for all four OH-protons indicating a position as expected for non-chelated OH-protons.[39]

Table S2. Idealized Dihedral Angles in the Eight Hypothetical Conformers of 1

		α		β		γ
$\mathbf{1}_{\mathrm{C1}}$	P_{A}	270°	P_{B}	270°	P_{C}	225°
ent-$\mathbf{1}_{\mathrm{C1}}$	M_{A}	90°	M_{B}	90°	M_{C}	135°
$\mathbf{1}_{\mathrm{C2}}$	P_{A}	270°	P_{B}	270°	M_{C}	315°
ent-$\mathbf{1}_{\mathrm{C2}}$	M_{A}	90°	M_{B}	90°	P_{C}	45°
$\mathbf{1}_{\mathrm{C3}}$	P_{A}	270°	M_{B}	90°	P_{C}	225°
ent-$\mathbf{1}_{\mathrm{C3}}$	M_{A}	90°	P_{B}	270°	M_{C}	135°
$\mathbf{1}_{\mathrm{C4}}$	P_{A}	270°	M_{B}	90°	M_{C}	315°
ent-$\mathbf{1}_{\mathrm{C4}}$	M_{A}	90°	P_{B}	270°	P_{C}	45°

Table S3. Dihedral Angles in the Two Global Minimum Structures $\mathbf{1}_{\mathrm{C2}}$ and $\mathbf{1}_{\mathrm{C3}}$

		α		β		γ
1$_{C2}$	P_A	86°	P_B	49°	M_C	130°
1$_{C3}$	P_A	71°	M_B	130°	P_C	68°

Table S4. Experimental Data from the Thermal Racemization Experiments

T (°C)	k_1+k_{-1} (s^{-1})	repetitive error	$\ln(k_1+k_{-1})$	1/T
85	1.03×10^{-5}	$\pm 7.8 \times 10^{-7}$	–11.486	0.00279
105	5.83×10^{-5}	$\pm 3.1 \times 10^{-6}$	–9.750	0.00265
125	3.11×10^{-4}	$\pm 2.4 \times 10^{-5}$	–8.075	0.00251
145	1.36×10^{-3}	$\pm 8.4 \times 10^{-5}$	–6,600	0.00239

extrapolated for 50 °C: $k = 2.48 \times 10^{-7}\ s^{-1}$

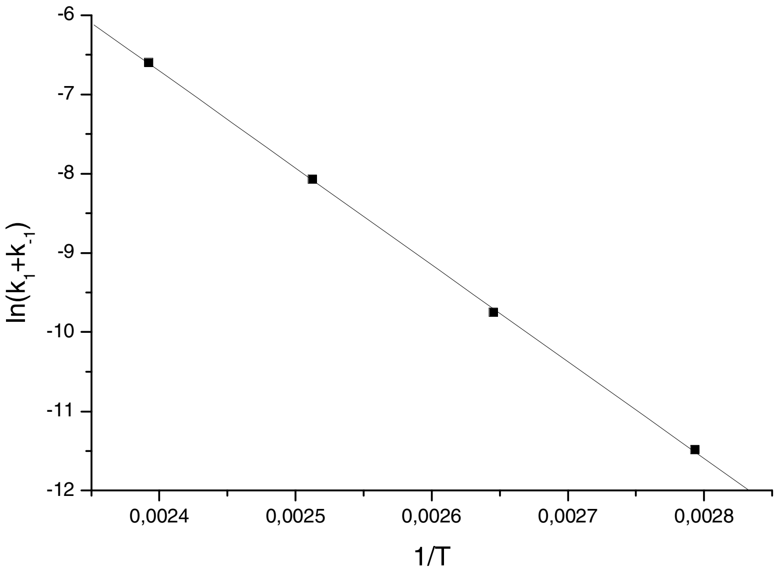


Figure S1. Kinetic studies on the racemization of **1** (Arrhenius plot).

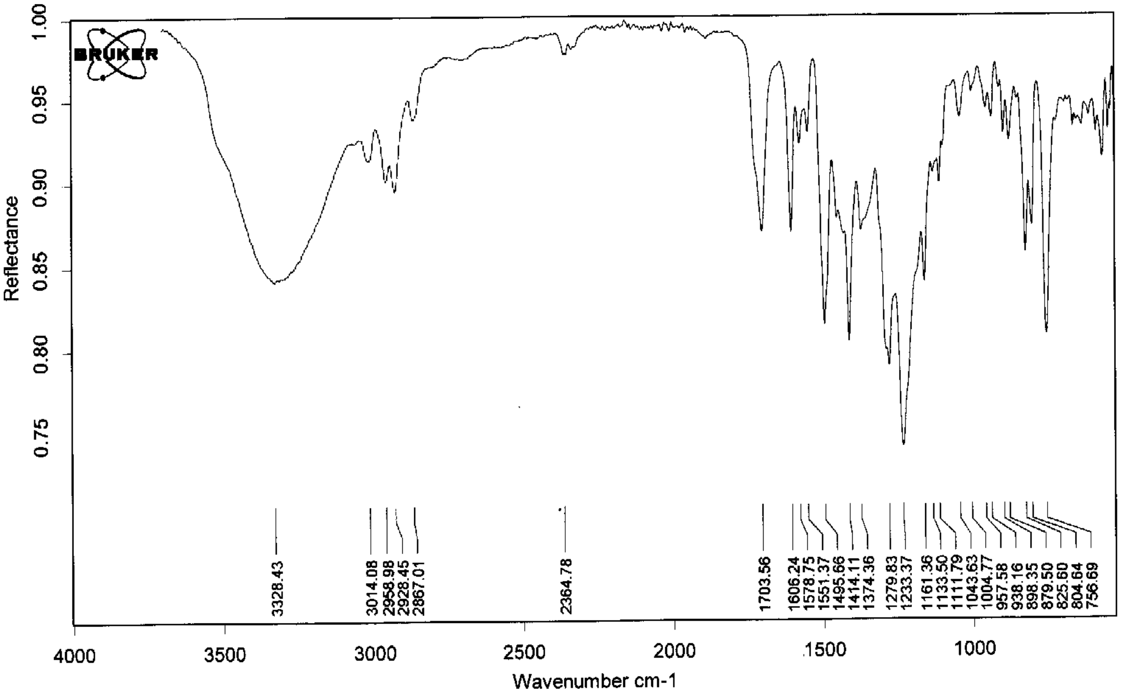


Figure S2. FT-IR spectrum of **1** (taken on a Bruker Tensor 27, Diamond ATR: Golden Gate A531XPM).

References

(32) Rauhut, G.; Chandrasekhar, J.; Alex, A.; Beck, B.; Sauer, W.; Clark, T. VAMP 6.5, available from Oxford Molecular Ltd., The Medawar Centre, Oxford Science Park, Sandford-on-Thames, Oxford, OX4 4GA, England.

(33) SYBYL 6.5: Tripos Associates, 1699 Hanley Road, Suite 303, St. Louis, MO, 63144.

(34) Peng, C.; Schlegel, H. B. *Israel J. Chem.* **1994**, *33*, 449–454.

(35) Peng, C.; Ayala, P. Y.; Schlegel, H. B.; Frisch, M. J. *J. Comp. Chem.* **1996**, *17*, 49–56.

(36) Gaussian 98, Revision A.7, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K.

N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, 1998.

(37) Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; DiNola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684–3690.

(38) Downing, J. W. Program package BDZDO/MCDSPD, Department of Chemistry and Biochemistry, University of Colorado, Boulder, USA; modified by Fleischhauer, J.; Schleker, W.; Kramer, B.; ported to Linux by Gulden, K.-P.

(39) (a) Didi, M. A.; Maki, A. K. T.; Mostafa, M. M. *Spectrochim. Acta* **1991**, *47A,* 667–670. (b) Kanala, A.; Solcaniova, E.; Kovac, S. *Chem. Zvesti* **1975**, *29,* 392–396.