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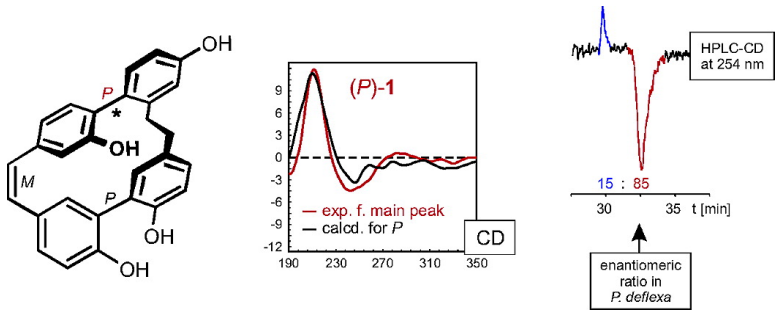

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Stereochemistry of Isoplagiochin C, A Macrocyclic Bisbibenzyl from Liverworts

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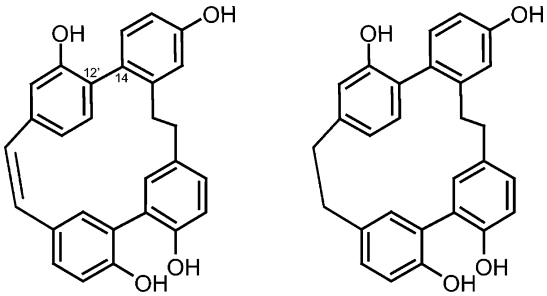
Abstract: Cyclic bisbibenzyls, like isoplagiochins C (**1**) and D (**2**), are stereochemically intriguing molecules: Although not equipped with any of the traditional stereogenic elements that render molecules conformationally stable per se, they are sometimes isolated in an optically active form and are thus chiral at room temperature. The paper describes quantum chemical calculations, in particular investigations of the conformational space and molecular dynamics simulations, showing that the helicity is a property of the *entire* molecule, whose ring strain makes the molecule configurationally stable overall, with (formally) three stereogenic elements (two biaryl axes and one helical stilbene unit). Only one of the biaryl axes (the 'upper' one, joining C-12′ and C-14) has a stable configuration, leading to a population of four interconverting diastereomers, yet without racemization at room temperature. On the basis of these conformational and dynamic calculations, the circular dichroism spectrum of isoplagiochin C (**1**) was calculated, leading to the first assignment of the absolute configuration of a cyclic bisbibenzyl. Accordingly, **1** has the *P*-configuration at the stereochemically stable biaryl axis and constitutes a mixture of diastereomers with respect to the other biaryl axis and the helical stilbene unit. From the temperature dependence of the racemization rates, an enantiomerization barrier of 101.6 kJ/mol was determined. Likewise, for the first time for cyclic bisbibenzyls, the enantiomeric ratio of this natural product was determined, by chromatography on a chiral phase with CD-coupling. Accordingly, **1** from *Plagiochila deflexa* is not enantiomerically pure, but occurs in a 85:15 ratio in favor of the enantiomer that has the *P*-configuration at the stereochemically stable axis.

Introduction

Macrocyclic bisbibenzyls, like isoplagiochins C (**1**, Figure 1) and D (**2**), from bryophytes[1,2] exhibit remarkable antitumoral, antibacterial, and antimycotic activities.[2,3] Biosynthetically, they originate from two units of lunularin, which can be joined together by 2-fold phenol-oxidative *C,C*-coupling, resulting in two biphenyl axes.[4] Several such cyclic bisbibenzyls have been prepared by total synthesis (see ref 5 and literature cited therein). Isoplagiochins C (**1**) and D (**2**) might be considered achiral at first sight: They do possess two biaryl axes, which, however, appear configurationally unstable (Figure 1). Therefore, it was not unexpected that both compounds, **1** and **2**, as isolated from the liverwort *Plagiochilla fruticosa* were optically inactive.[6] Isoplagiochin C (**1**) from *Lepidozia incurvata*, by contrast, showed a significant optical rotatory power, with an $[\alpha]_D = +42.5$ (*c* 0.2, MeOH).[7] More recently, **1** and **2** were isolated in an optically active form from *Herbertus sakuraii*, this time with $[\alpha]_D$ values of +74.8 and +47.5, respectively (*c* 0.67, MeOH).[8] Although CD spectra were recorded suggesting the presence of atropisomers, the absolute configurations could not be



Isoplagiochin C (**1**) Isoplagiochin D (**2**)

Figure 1. Macrocyclic bisbibenzyl constituents from bryophytes.

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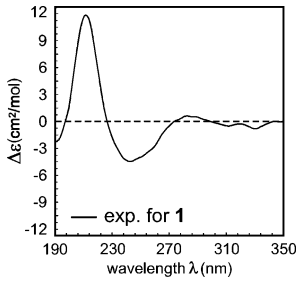

Figure 2. Experimental CD spectrum of isoplagiochin C (**1**) as isolated from *P. deflexa*.

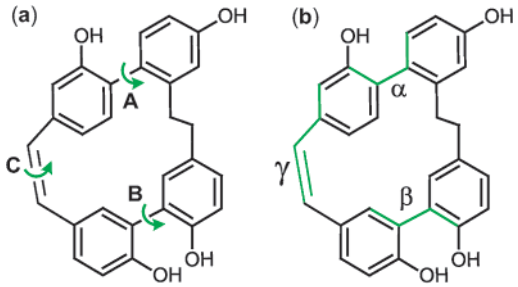

Figure 3. (a) Possible conformational barriers **A**, **B**, and **C**, in isoplagiochin C (**1**) and (b) the corresponding dihedral angles of **1**, α, β, and γ.

established.[9] Furthermore, isoplagiochins C (**1**) and D (**2**) were also isolated from a *Plagiochila* species[10] (now redefined as *Plagiochila deflexa* Mont. & Gottsche),[11] but in this case, their $[\alpha]_D$ values were not even measured. In this paper, we report the first assignment of the absolute configuration of a cyclic bisbibenzyl, isoplagiochin C (**1**), by quantum chemical CD calculations, and the investigation of its enantiomeric purity by HPLC−CD analysis.[12]

Results and Discussion

Chiroptical Properties. Our own sample of isoplagiochin C (**1**) from *Plagiochila deflexa* was laevorotatory ($[\alpha]_D = -49.0$, *c* 0.75, MeOH), opposite to that from the *Lepidozia* and *Herbertus* species investigated earlier (see above). Furthermore, **1** showed a distinct circular dichroism (CD) spectrum (Figure 2), with a minimum at ca. 240 nm and a maximum at ca. 210 nm as the most prominent peaks.

Analysis of Stereogenic Elements. The molecular structure of **1** shows three possible rotational barriers: two biaryl axes **A** and **B** and a helical double bond as part of a distorted stilbene unit **C** (Figure 3a). The respective dihedral angles α, β, and γ are defined in Figure 3b. A fourth possible stereogenic element, the helical 1,2-diarylethano unit, was not taken into account due to its anticipated high flexibility in comparison to those of the other ones, combined with the fact that this C_2 entity is, as such, not part of a chromophore.

Of the two biaryl axes, **A** and **B**, neither should be configurationally stable as such, since both possess only two (small) *ortho*-substituents in the proximity of the coupling sites, viz an OH group and an alkyl substituent in the case of **A** and two hydroxy functions for **B**. According to literature precedent,[13−15] these substituents should not provide a sufficiently high atropisomerization barrier to guarantee configurational stability. The corresponding dihedral angles α and β can take the values 90° and 270° in the two possible—idealized—atropisomers. The helical and thus likewise chiral stilbene subunit **C** should be able to adopt two stereoisomeric helicene-like distorted arrays with (P_C)- and (M_C)-configuration (stereodescriptors derived from the denotation of helicenes[16] like, e.g., hexahelicene, **6**, see Figure 4). Calculations on *cis*-stilbene[17] (**7**) suggested that an interconversion between the two possible conformations of this structural entity **C** should occur smoothly at room temperature. The observed chirality of **1**, giving rise to the Cotton effect described above, thus does not derive from isolated stereogenic elements. Structures such as **1** might also be considered as a special form of planar chirality, here in combination with formal axial and helical chirality.[18] In the idealized structures of the two possible isomers, the corresponding angle γ can adopt the values 45° (= M_A,P_C) and 135° (= M_A,M_C) for the M_A-configuration or 225° (= P_A,P_C) and 315° (= P_A,M_C) for the P_A-configuration. Since the motion of the helical stilbene subunit **C** is coupled to the biaryl unit **A**, four values of γ instead of two are necessary to describe the position of **C**.

Assuming the existence of the three aforementioned formal stereogenic subunits, **A**, **B**, and **C**, whose barriers are increased by the cyclic array, a total of up to $2^3 = 8$ conformers (viz four diastereomers and their enantiomers) might in principle be possible (see Table S2 in Supporting Information and Figure 5).

Flexibility of the Molecule by NMR Investigations. NMR spectra of **1**, taken at different temperatures from −70 °C to +100 °C, starting at 25 °C in each series, gave no additional or disappearing signals upon cooling or heating and the spectra remeasured at 25 °C were always identical. These spectra showed only one set of signals and hence did not provide any evidence for the existence of different diastereomers configurationally stable within the NMR time scale. The NMR experiments thus hinted at the existence of either only one configurationally stable stereoisomer or, rather, at the presence of the thermodynamically controlled equilibrium mixture of possibly all of the four imaginable, rapidly interconverting diastereomers.

Conformational Analysis. To gain insight into the energetic order of these barriers **A**, **B**, and **C**, we investigated the confor-

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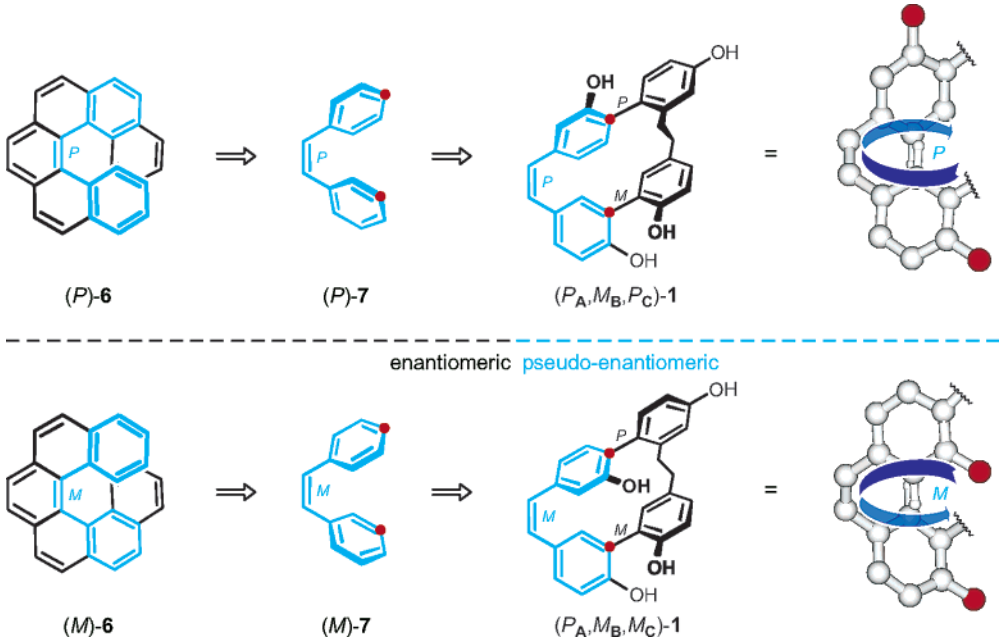

Figure 4. Determination of the stereodescriptors of the two possible epimeric helical conformations of **1** by evolution from hexahelicene (**6**): Formal abstraction of annulated benzo rings in the two enantiomers of **6** leads to the enantiomeric conformers of *cis*-stilbene (**7**), which are, as such, conformationally unstable. Embedded into the molecular frameworks of **1**, these stilbene entities are near-enantiomorphous to each other (middle-right, both with identical axial configurations). The helical orientation becomes evident from the ball-and-stick presentation of these parts (right) (- - -: mirror plane, separating enantiomers; blue - - -: pseudo-mirror plane, only concerning the 'blue' part of the molecule, separating near-enantiomorphous entities).

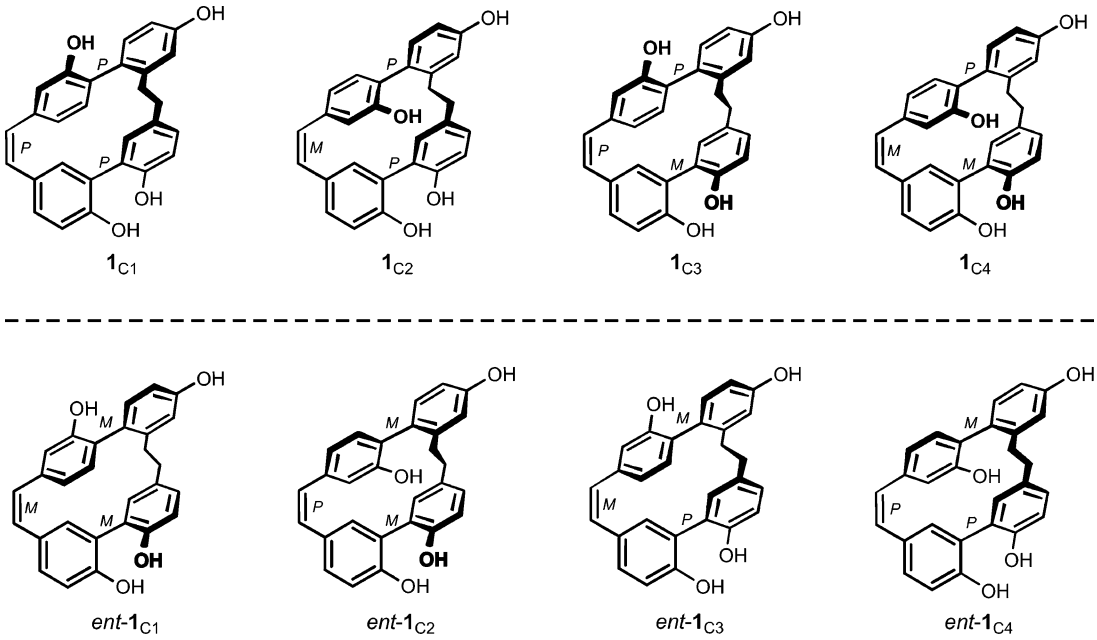

Figure 5. Eight possible stereoisomers of isoplagiochin C (**1**) (- - -: mirror plane).

mational properties of the molecule **1** by computational methods, arbitrarily starting with the (P_A,M_B,P_C)-isomer of isoplagiochin C ($\mathbf{1}_{C3}$). For this purpose we calculated, by means of the semi-empirical AM1 method,[19] reaction coordinates for the dihedral angles α, β, and γ defined above (Figure 3b), for the ethylene bridge and the four hydroxy functions, thus covering all of the flexible parts of **1** that contribute to the chromophores. The resulting rotational barrier **A** for the 'upper' biaryl axis thus obtained, was calculated as 115.1 kJ/mol, revealing its configurational stability at room temperature. For the other stereogenic elements, **B** and **C**, the calculations gave rotational barriers of 29.5 and 21.2 kJ/mol, respectively, proving their significantly higher flexibility. From these calculations, only one stereogenic element of **1**, the 'upper' biaryl axis **A**, should be stable at room temperature and was thus identified as the 'stereochemical anchor' of the molecule, which thus explained the above-mentioned single set of NMR signals, now interpreted as an array of rapidly interconverting diastereomers at room temperature.

In the course of this investigation of the conformational space, 96 minimum structures were obtained, with two conformers corresponding to $\mathbf{1}_{C2}$ and $\mathbf{1}_{C3}$ as the global minima (Figure 6a), having virtually identical heats of formation. These conformers

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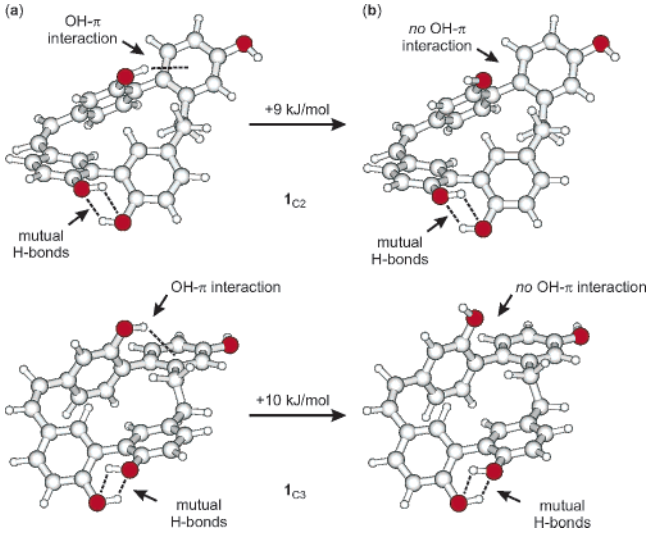

Figure 6. Global minima of **1** (a) obtained by conformational analysis (see also Table S3 in Supporting Information) and the respective structures without the stabilizing OH-π interactions (b); all structures are stabilized by mutual H-bonds in the 'lower' biarylic systems.

are stabilized by mutual H-bonds of the respective two hydroxy functions in the 'lower' biarylic systems and by OH-π interactions[20] in the 'upper' ones, energetically favoring $\mathbf{1}_{C2}$ and $\mathbf{1}_{C3}$ over the corresponding structures without these stabilizing interplays (Figure 6b) by 9 to 10 kJ/mol.

If in the structures displayed in Figure 6 one or both 'lower' H-bonds were missing, the energies were increased by about 8 and 23 kJ/mol (average values), respectively. Probably due to ring strain effects, the conformers $\mathbf{1}_{C1}$ and $\mathbf{1}_{C4}$ (Figure 5) were not found among the minimum structures.

Calculation of the CD Spectrum. The above conformational analysis furthermore paved the way for the determination of the absolute configuration of isoplagiochin C (**1**) by quantum chemical CD calculations.[21−23] For this purpose, all conformers within an energetic interval of 13 kJ/mol above the global minima were taken into consideration, because their respective CD spectra would contribute to the overall one. For each of the remaining 30 conformers, the particular single CD spectra were computed by applying the semiempirical CNDO/S-CI[24] approach. The resulting curves were then summed and weighted according to the Boltzmann statistics, i.e., with respect to the heat of formation of the particular conformer. The overall theoretical CD spectrum expected for the set of rapidly interconverting conformers with the *P*-configuration at the stable axis **A**, henceforth collectively addressed as (P_A)-**1**, is shown in Figure 7a. In a similar way the theoretical curve for the set of the respective diastereomers of the enantiomeric series, (M_A)-**1**, was also computed (Figure 7b). The comparison of the calculated CD spectra with the experimental one showed a good

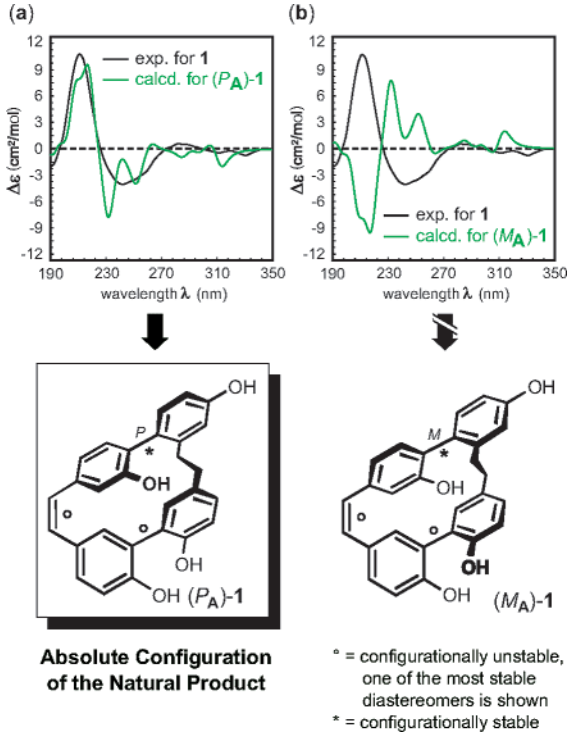

Figure 7. Assignment of the absolute configuration of (−)-isoplagiochin C (**1**) from *P. deflexa* as P_A, by comparison of its experimental CD spectrum with those calculated (a) for (P_A)-**1** and (b) for (M_A)-**1**.

agreement in the case of (P_A)-**1**, whereas the theoretical spectrum predicted for the *M*-atropo-enantiomer, (M_A)-**1**, gave an almost opposite CD curve. The configuration at the stable 'upper' biaryl axis **A** of isoplagiochin C (**1**) was thus clearly assigned as *P*.

Flexibility of the Molecule by MD Investigations. To confirm this first assigned absolute configuration of a cyclic bisbibenzyl, isoplagiochin C (**1**), and to further investigate the conformational behavior of **1**, the molecule was submitted to a molecular dynamics (MD) simulation. The calculations arbitrarily started this time with *ent*-$\mathbf{1}_{C2}$, the (M_A,M_B,P_C)-isomer of isoplagiochin C, with a simulation length of 500 ps at a virtual temperature of 300 K. The resulting trajectories were analyzed for the appearance of conformers diastereomeric to the chosen starting geometry of isoplagiochin C. As seen in Figure 8, none of the barriers was overcome at 300 K, so that in this case all four diastereomeric pairs of enantiomers shown in Figure 5 and listed in Table S2 would, if present, be stable without interconversion, thus constituting possible absolute stereostructures of isoplagiochin C (**1**). Hence, only one of the four possible diastereomers and/or its enantiomer should be present at the virtual temperature chosen in the calculations, indicating that the duration of the MD run was too short or that the temperature chosen was too low to surmount any of the existing barriers in question.

For computational economy, we increased the simulation temperature (in 100-K-steps) rather than to extend the simulation length. Still, the situation remained the same up to 600 K and only at 700 K, the helical barrier **C** was surmounted (red arrow at 700 K in Figure 8) so that just two pairs of diastereomers should be possible at this temperature. At 1000 K, the second biaryl barrier **B** was overcome (red arrow at 1000 K in Figure 8), leaving only the 'upper' biaryl axis **A** configurationally

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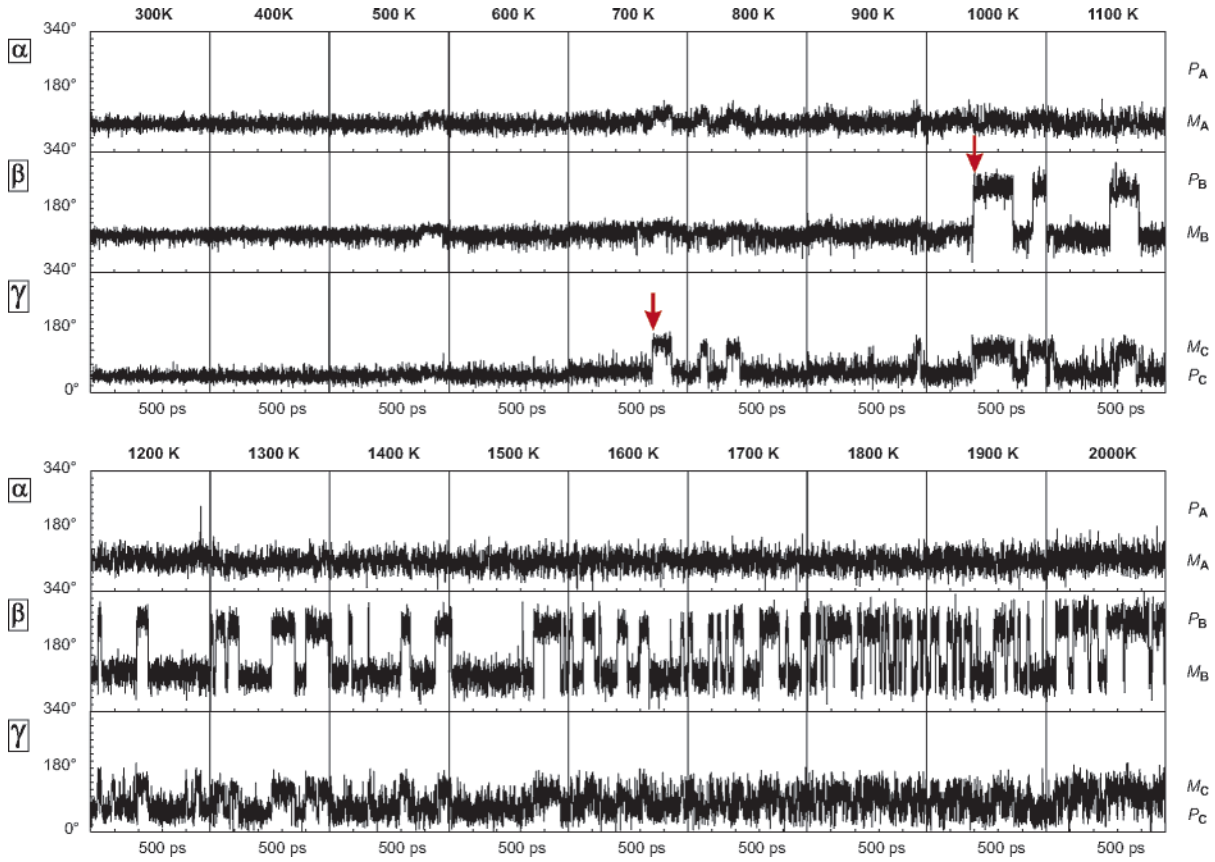

Figure 8. Analysis of the dihedral angles α, β, and γ of all of the calculated MD simulations of **1**. The red arrows indicate where the barriers **B** and **C** are surmounted for the first time.

stable, so that at this temperature, just one pair of possible enantiomers remained: the set of the rapidly interconverting diastereomers $\mathbf{1}_{C1}$, $\mathbf{1}_{C2}$, $\mathbf{1}_{C3}$, and $\mathbf{1}_{C4}$, (P_A)-**1**, and/or the set of the respective diastereomers of the enantiomeric series, (M_A)-**1**. The biaryl barrier **A** was stable up to a virtual simulated temperature of 2000 K.

From these MD investigations, the most stable chiral element is confirmed to be the 'upper' axis **A**, followed by the 'lower' biaryl linkage **B**, whereas the helical element **C** is subject to the least hindered interconversion. This result is in accordance with the outcome of the above presented AM1-based conformational analysis and the computational determination of the rotational barriers.

Verification of the Absolute Configuration by MD-Based CD Calculations. According to the temperature experiments, the barrier of **A** is not overcome at room temperature, so that the MD simulations at 1000 K and above should come close to the 'real' situation at ambient temperature. Thus, to verify the absolute configuration of isoplagiochin C (**1**) by quantum chemical CD calculations,[21−23] now based on the MD results, we chose the simulation at 1200 K as a basis for all further investigations. At this virtual temperature, all barriers are surmounted, except for that of **A** as the 'stereochemical anchor', thus guaranteeing chiral stability of **1** during the simulation process—just as found experimentally at room temperature and computationally, by the conformational analysis. Moreover, the virtual temperature should not be chosen too high since this would lead to increasingly equal conformational populations, regardless of the actual potential energy surface. Starting this time with *ent*-$\mathbf{1}_{C2}$ [(M_A,M_B,P_C)-**1**], geometries were extracted from this MD trajectory every 0.5 ps. For the 1000 structures collected, single CD spectra were calculated, and averaged arithmetically to yield the overall theoretical CD spectrum of

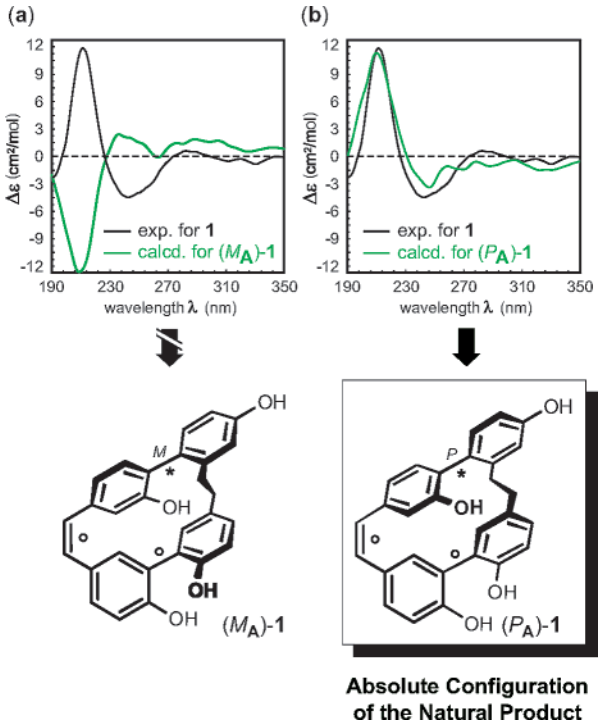

Figure 9. Absolute configuration of (−)-isoplagiochin C (**1**) from *P. deflexa* as P_A, by comparison of its experimental CD spectrum with those calculated (a) for (M_A)-**1** and (b) for (P_A)-**1**.

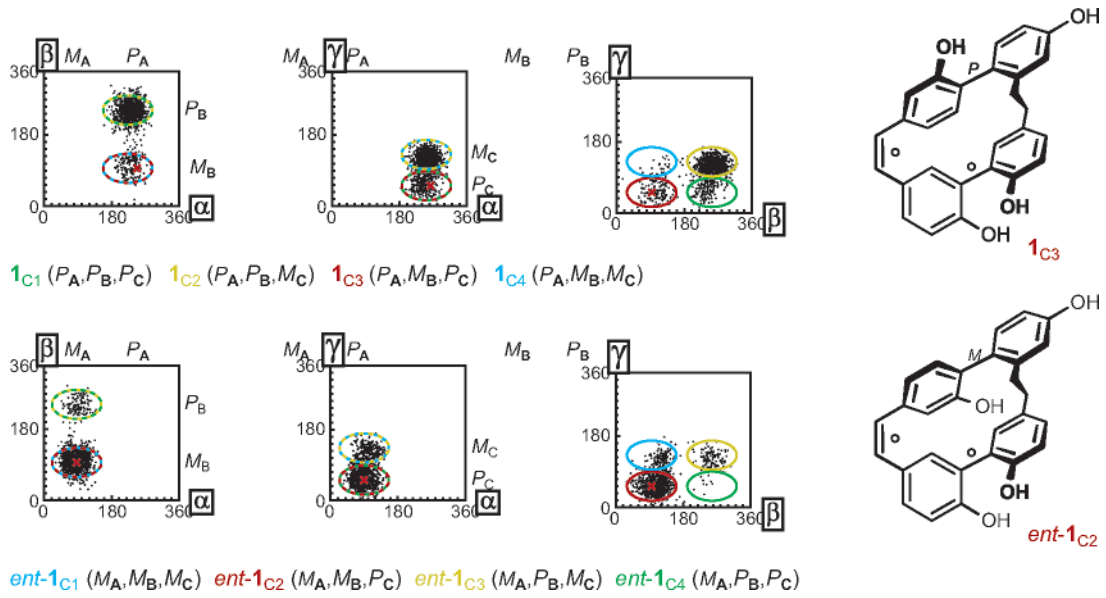

Figure 10. MD trajectories of (P_A)-**1** (top) and (M_A)-**1** (bottom) at 1200 K: correlation of α, β, and γ (°) and starting points (red ×) $\mathbf{1}_{C3}$ and *ent*-$\mathbf{1}_{C2}$ of the trajectories (conformers with the same colors have identical stereodescriptors at **B** and **C**); the formula drawings (right) show the starting stereostructures.

(M_A)-**1** (Figure 9a). In the same way, now (likewise arbitrarily) starting with $\mathbf{1}_{C3}$, the (P_A,M_B,P_C)-diastereomer of isoplagiochin C, the CD spectrum of (P_A)-**1** was calculated. The now even excellent agreement of the spectrum calculated for (P_A)-**1** with the experimental one (Figure 9b) permitted unequivocal attribution of the absolute configuration of **1** as P_A, thus confirming the results of the conformational analysis approach and showing the reliability of the method. The even better consistency and the higher degree of smoothness of the MD-based predicted overall CD spectrum as compared to the one resulting from the conformational analysis approach, is possibly due to the fact that within this method 1000 instead of 'only' 30 single spectra are taken into account, thus reflecting the 'real' situation more precisely—although being based on force field calculations.

Still, another question remained: What is the reason in the molecular structure of **1** to provide such a marked CD spectrum as shown in Figure 2? To answer this, we investigated the MD trajectories of (P_A)-**1** and (M_A)-**1** more closely. In Figure 10 the three dihedral angles α, β, and γ are correlated to deliver information about the distribution of the conformers of (P_A)-**1** and (M_A)-**1**, showing their frequencies of formation, and hence their relative stabilities.

These results provided valuable information about the conformational behavior:

•During the MD run every enantiomer populates its respective pattern of diastereomeric conformers as can be seen in Figure 10, in particular when looking at the graphs β vs γ.

•Analyzing single geometries of each region one can see that $\mathbf{1}_{C1}$ & $\mathbf{1}_{C4}$ and $\mathbf{1}_{C2}$ & $\mathbf{1}_{C3}$ [for (P_A)-**1**] as well as *ent*-$\mathbf{1}_{C1}$ & *ent*-$\mathbf{1}_{C4}$ and *ent*-$\mathbf{1}_{C2}$ & *ent*-$\mathbf{1}_{C3}$ [for (M_A)-**1**] are pseudo-enantiomeric to each other: The molecular frameworks are mirror-image like as shown in Figure 11 for the most frequently populated and thus most stable species, $\mathbf{1}_{C2}$ & *ent*-$\mathbf{1}_{C2}$, and their pseudo enantiomers, $\mathbf{1}_{C3}$ & *ent*-$\mathbf{1}_{C3}$. The only difference between conformers with the same molecular framework (same color in Figure 11) is the hydroxy group at C-11′ marked in green in Figure 11.

This difference is responsible for the dynamic behavior of **1** and thus decisive for the asymmetric geometry obtained computationally (by the MD simulations) and experimentally (by the CD spectrum).

The influence of the hydroxy group at C-11′ (marked in green in Figures 11 and 12) on the geometry of **1**, and thus on the CD behavior, is shown in Figure 12, where the opposite molecular shape of $\mathbf{1}_{C2}$ and $\mathbf{1}_{C3}$—despite their identical *P*-configuration at the stereochemically stable axis **A**—becomes evident. Due to this hydroxy function, the molecule is forced to populate mainly one of two possible pseudo-enantiomeric geometries in the MD run. In these geometries, the aromatic chromophores are arranged in the form of two near-enantiomorphous helices. These helices seem to be responsible for the strong CD bands in the measured spectra.

Thus, the MD simulations with subsequent quantum chemical CD calculations gave insight into the mobility of the molecule and its conformational restriction. Moreover, from the detailed chiroptical analysis of these species and their molecular dynamics, the calculations permitted the first elucidation of the absolute configuration of a cyclic bisbibenzyl, isoplagiochin C (**1**)—in the laevorotatory form (as isolated from *Plagiochila deflexa)* with *P*-configuration at the configurationally most stable—and thus stereochemically deciding—'upper' biaryl axis **A**.

Enantiomer Analysis by HPLC−CD Coupling. Isoplagiochin C (**1**) has also been described as dextrorotatory in some cases and as optically inactive in others (see Introduction). This warranted the development of an analytical device for the stereoanalysis of the enantiomeric ratios of these compounds from natural sources. For this reason, an HLPC analysis on a chiral phase was established, for the first time in this field of natural products.[26−29]

(25) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem., Int. Ed. Engl*. **1966**, *5*, 385−415.
(26) For method-oriented work on LC−CD coupling, see: Mannschreck, A. *Chirality* **1992**, *4*, 163−169.
(27) For LC−CD analysis of synthetic compounds, see: Mino, T.; Tanaka, Y.; Yabusaki, T.; Okumura, D.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2503−2506.

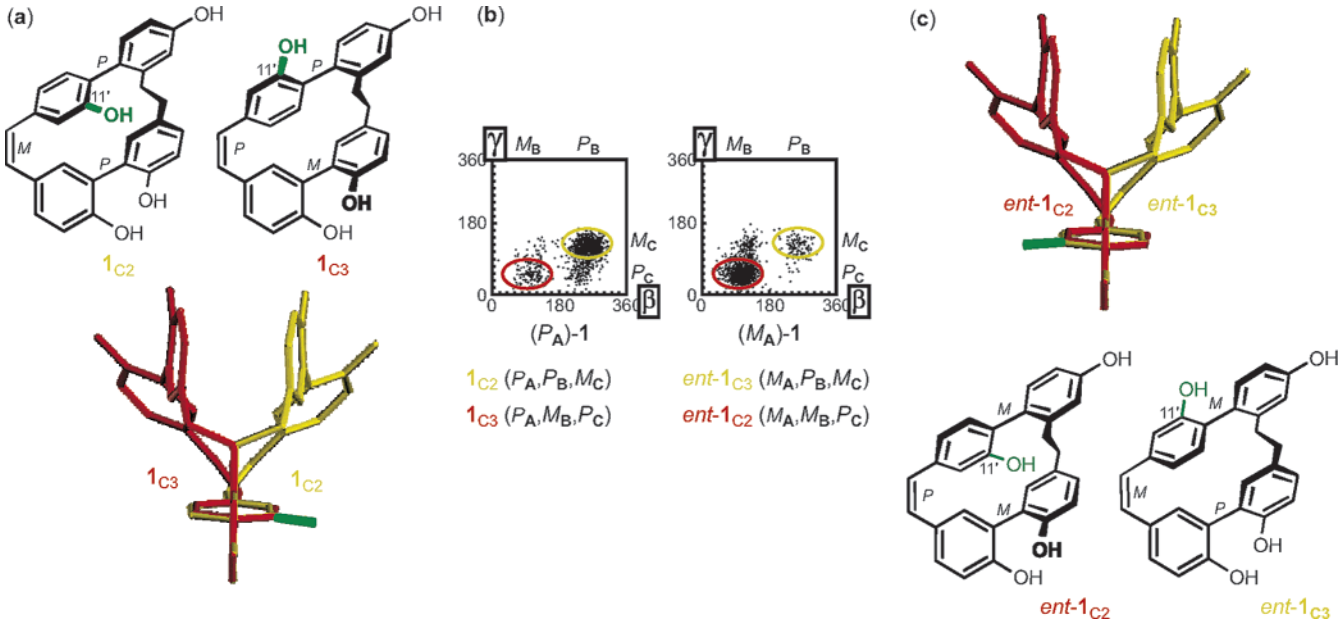

Figure 11. Influence of the hydroxy function at C-11′: comparison of the MD trajectories at 1200 K of (P_A)-**1** (b, left: $\mathbf{1}_{C2}$ & $\mathbf{1}_{C3}$) and (M_A)-**1** (b, right: *ent*-$\mathbf{1}_{C2}$ & *ent*-$\mathbf{1}_{C3}$) together with the matches of $\mathbf{1}_{C2}$ (yellow) & $\mathbf{1}_{C3}$ (red) (a) and of *ent*-$\mathbf{1}_{C3}$ (yellow) and *ent*-$\mathbf{1}_{C2}$ (red) (c); as in the formula drawings, the hydroxy function in the matchplots (a, c) is marked in green.

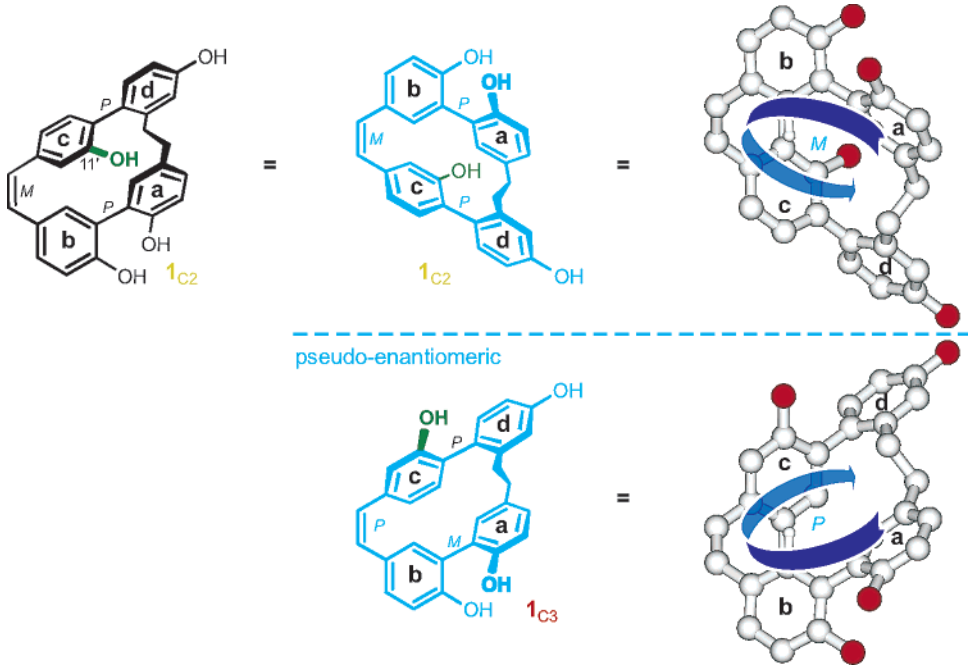

Figure 12. Comparison of the pseudo-enantiomeric conformers $\mathbf{1}_{C2}$ and $\mathbf{1}_{C3}$: rotating the molecule from the commonly used view of $\mathbf{1}_{C2}$ (top, left) to the one shown in the middle of the graphic and using a ball-and-stick presentation (right) reveal a helical arrangement of the aromatic entities **a**−**b**−**c**−**d** that is left-handed (= *M* in the helicene-conventional denotion[16,25]) for $\mathbf{1}_{C2}$ and right-handed (= *P*) for $\mathbf{1}_{C3}$.

For developing the method, a racemic sample of **1** was used, prepared by nonenantioselective total synthesis.[5] The best results were obtained on a Chiralcel OD-H phase, yielding two peaks in the expected 50:50 ratio (Figure 13), while the laevorotatory natural product from *P. deflexa* showed a 15:85 ratio in favor of the P_A-enantiomer. That the two observed peaks indeed corresponded to the two enantiomers of **1**, (P_A)-**1** and (M_A)-**1** (plus the interconverting diastereomers), was proven by online CD analysis of the peaks. This HPLC−CD coupling technique,[26,27] which has been introduced into phytochemical analysis by our group recently,[28−30] indeed resulted in near-opposite CD spectra for the two HPLC peaks (Figure 13), and thus likewise permitted the first observation of the CD spectrum of both pure isoplagiochin C enantiomers from one natural sample.

(28) Bringmann, G.; Messer, K.; Wohlfarth, M.; Kraus, J.; Dumbuya, K.; Rückert, M. *Anal. Chem.* **1999**, *71*, 2678−2686.
(29) Bringmann, G., Lang, G. In *Marine Mol. Biol.*; Müller, W. E. G., Ed.; Springer: Berlin, 2003; pp 89−116.
(30) For further experimental details of LC−CD coupling, see: (a) Bringmann, G.; Tasler, S.; Endress, H.; Kraus, J.; Messer, K.; Wohlfarth, M.; Lobin, W. *J. Am. Chem. Soc.* **2001**, *123*, 2703−2711. (b) Bringmann, G.; Messer, K.; Saeb, W.; Peters, E.-M.; Peters, K. *Phytochemistry* **2001**, *56*, 387−391. (c) Bringmann, G.; Messer, K.; Wohlfarth, M.; Kraus, J.; Dumbuya, K.; Rückert, M. *Anal. Chem.* **1999**, *71*, 2678−2686.

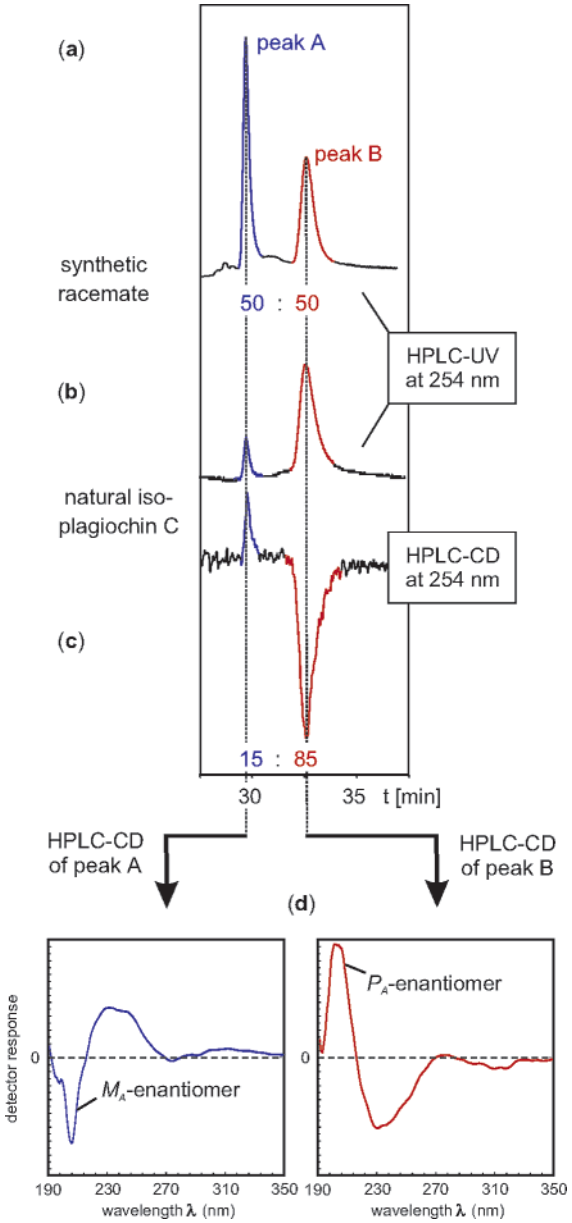

Figure 13. Resolution (a) of the two enantiomeric components of synthetic racemic isoplagiochin C (*rac*-**1**) and (b) of the natural product from *P. deflexa* on a chiral OD-H phase; HPLC-CD coupling (c) monitoring one wavelength (254 nm) and (d) with measurement of full online CD spectra.

Determination of the Overall Enantiomerization Barrier. The varying degrees of enantiomeric purity of **1** in samples from different liverworts might be due to differing chiral discriminating effects in the biosynthesis of **1** (e.g., by an atropo-enantioselective, ring-closing second phenol-oxidative coupling) or to a loss of enantiomeric purity under too harsh isolation conditions. The latter possibility necessitated kinetic studies on the temperature-dependent racemization of **1**. Changes in the enantiomeric ratio were determined by the aforementioned analysis by HPLC on a chiral phase.

The racemization rates of **1** from *Plagiochila deflexa* were determined at different temperatures from 85 °C up to 145 °C. From the corresponding Arrhenius plot (see Figure S1 in Supporting Information), an activation energy of 101.6 kJ/mol for the racemization was calculated,[31] in good accordance with the theoretically predicted value of 115.1 kJ/mol, and high enough to prevent racemization at room temperature. Some characteristic half-life values were ca. 18.7 h at 85 °C and 32 d at 50 °C (extrapolated). Nevertheless, a decrease in the enantiomeric purity might occur during standard isolation procedures with temperatures above 50 °C.

Conclusions

The present computational and experimental study has shown that isoplagiochin C (**1**) owes its chirality to the presence of two biaryl axes and a helical subunit whose configurational stability is largely increased by its cyclic array. Due to the conformational analysis, including the computation of the rotational barriers, the 'upper' biaryl axis, **A**, was identified to be the most stable stereogenic element, which was confirmed by MD studies. Its atropisomerization barrier is not surmounted at room temperature, whereas those of the other two stereogenic elements, the second biaryl axis (**B**) and the helical stilbene unit (**C**), are distinctly lower, leading to a mixture of interconverting diastereomers for each of the two enantiomeric series of molecules. On the basis of both, conformational analysis and MD investigations, quantum chemical CD calculations permitted assignment of the absolute configuration of isoplagiochin C (**1**) and established the main stereoisomeric form of **1** to be *P*-configured at the stereochemically most stable axis, **A**. The calculations further revealed the helical structure of the molecule to be responsible for the distinct CD spectrum of **1**. Moreover, an analytical method for the determination of the enantiomeric ratio of **1** was elaborated, for the first time in the field of cyclic bisbibenzyls. Application of this analysis revealed that in *P. deflexa*, **1** occurs in a 85:15 ratio in favor of the enantiomer with *P*-configuration at the most stable axis, **A**. The experimental overall-enantiomerization barrier of 101.6 kJ/mol and the theoretically calculated one of 115.1 kJ/mol confirmed the expectation of a molecule that is configurationally stable at room temperature.

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Supporting Information Available: Full experimental details together with the analytical and spectroscopic data of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) The formal value of the standard deviation for the linear regression was determined as ±1.0 kJ/mol; this, however, does not yet take into account systematic errors, so that an overall deviation of ~±10 kJ/mol was estimated.