

Synthesis, Resolution, and Absolute Configuration of Difunctionalized Tröger's Base Derivatives

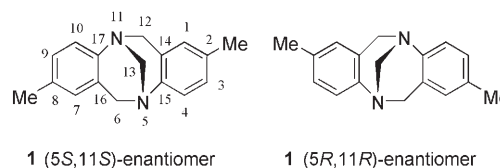
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Abstract: Two racemic derivatives of Tröger's base, the 2,8-diboronic acid ester **6** and the 3,9-dibromo-substituted derivative **5**, were synthesized and successfully resolved by HPLC on a chiral stationary Whelk-01 phase on a semipreparative scale, thereby giving rise to both enantiomers in a pure form. These functionalized C_2 -symmetric building blocks are valuable precursors for a variety of further applications. Their absolute configurations were determined by comparison of their quantum chemically calculated CD and UV/Vis spectra with the experimental ones and were independently confirmed by X-ray diffraction analysis.

Keywords: chiral resolution • circular dichroism • configuration determination • quantum chemical calculations • Tröger's base

Introduction

Tröger's base (**1**; Scheme 1) was first synthesized more than 120 years ago, in 1887, by Julius Tröger.^[1] Still, it took another 50 years to discover its N-based chirality.^[2] Only a few years later, in 1944, it became the first chiral tertiary amine to be resolved into its enantiomers,^[3] this was achieved by chromatography on D-lactose, yet led to only about 5.5% of resolved optically pure material. In the 1970s and 80s, more fruitful resolutions were developed by means of column chromatography on cellulose triacetate^[4] and by various



Scheme 1. The two enantiomers of Tröger's base (**1**).

HPLC methods applying different chiral stationary phases.^[5] Today, racemic Tröger's base itself is a standard compound for testing the efficiency of new chiral stationary phases.^[6]

The absolute configuration of **1** was first investigated in 1966, on the basis of comparative optical rotational dispersion (ORD) curves of the two pure enantiomers and (–)-argemonine, an alkaloid with a related structure: the (+)-enantiomer of **1** was attributed the (5*S*,11*S*) configuration.^[7]

Later work on the basis of circular dichroism studies, by using the exciton chirality method,^[8] came to the opposite conclusion; this, however, proved to be incorrect due to an erroneous assignment of the direction of polarization of the considered transitions. This assignment was believed to be true until 1991, when Wilen et al. finally proved by X-ray diffraction on a diastereomeric salt of (+)-**1** and (–)-1,1'-binaphthyl phosphoric acid that the initial assignment made in 1966 was correct.^[9] This salt formation was achieved in a very elegant manner by a crystallization-induced asymmetric transformation (CIAT). Tröger's base usually racemizes under acidic conditions in solution;^[10] the selective precipitation of only one of the two diastereomers of the salt, howev-

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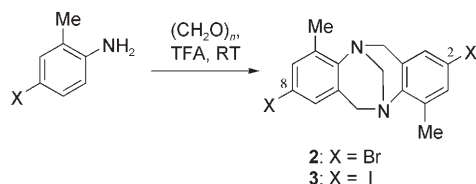
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er, shifted the equilibrium of the two enantiomers in solution towards (+)-**1** in the precipitate. By using this method, both enantiomers were accessible on a multigram scale. This is also possible by “classical” diastereomeric salt formation of racemic **1** and (+)- or (–)-di-*O,O'*-*p*-benzoyl tartaric acid (DBTA), as shown recently.^[11]

The resolution of functionalized analogues of Tröger's base, however, is limited to only a few examples: application of either enantiopure DBTA or di-*O,O'*-*p*-toluoyl tartaric acid (DTTA) resulted in diastereomeric salt formations of an acridine-substituted analogue of Tröger's base, an ethano-bridged representative, and a naphthyl-substituted derivative.^[12] Following an earlier example,^[13] and parallel to our own work described in this paper, Sergeyev and Diederich published the first study on the enantioseparation of some difunctionalized analogues of Tröger's base by HPLC on a semipreparative scale in 2006;^[14] these analogues were then used for the regio- and stereoselective tether-directed remote functionalization of fullerenes.^[15]

In the course of our studies towards the formation of diastereoselectively self-assembled metallocsupramolecular aggregates of helical shape from dissymmetrical ligands based on either substituted 1,1'-binaphthyls (for example, 1,1'-binaphthalene-2,2'-diol (BINOL)) or D-isomannide,^[16] the V-shaped rigid core of Tröger's base attracted our interest as another potential C_2 -symmetric building block. Such compounds have become even more valuable since Jensen and Wärnmark succeeded in establishing an easy access to 2,8-dihalo-substituted analogues of Tröger's base in 2001 (Scheme 2).^[17] This prompted us and other groups to apply various cross-coupling methodologies for the construction of larger architectures with extended V-shaped cores.^[18,19]



Scheme 2. Synthesis of 2,8-halogenated analogues **2** and **3** of Tröger's base (**1**). TFA: trifluoroacetic acid.

Our group has succeeded in applying these disubstituted analogues of Tröger's base for the synthesis of racemic bis(catechol) ligands and the construction of triple-stranded complexes through coordination to titanium(IV) ions^[20] and also for the preparation of racemic N-heterocyclic bis(bipyridine) and bis(2-pyridylmethanimine) ligands, which were demonstrated to form dinuclear double- and triple-stranded helicates in a (mostly) diastereoselective manner upon coordination to metal ions like Ag^+ , Cu^+ , Fe^{2+} , and Zn^{2+} .^[21]

To further pursue this concept, the availability of enantiomerically pure ligand strands is inevitably required. We have thus embarked on the development of methods to resolve racemic Tröger's base analogues at an early stage of the synthesis, which would allow us to prepare a number of more

sophisticated derivatives in an enantiomerically pure form. As the key steps of most of our routes to the ligands are transition-metal-catalyzed cross-coupling reactions, we were particularly interested in the resolution of precursors that can be applied in such reactions. Herein, we report the preparation and separation of one pair of diastereomers and the synthesis and resolution of a racemic 2,8-disubstituted diboronic acid derivative of Tröger's base as a valuable substrate for Suzuki cross-coupling reactions. Moreover, we describe the resolution of a racemic 3,9-dibromo-substituted analogue, which can also be used as a substrate for all sorts of cross-couplings. Furthermore, we have succeeded in determining the absolute configuration of the resolved enantiomers by quantum chemical circular dichroism calculations and comparison of the predicted CD spectra with the experimental ones and, independently, through anomalous X-ray diffraction.

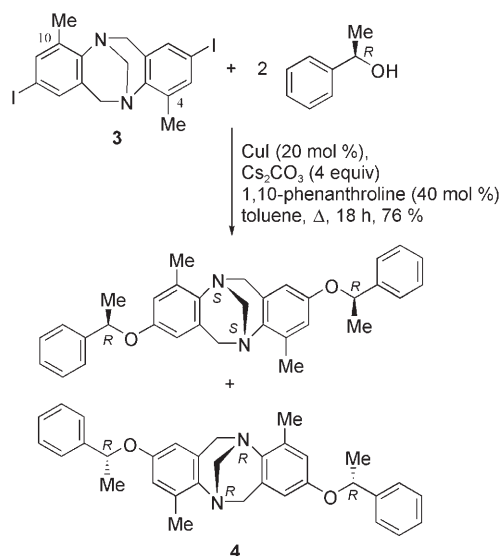
Results and Discussion

All of the Tröger's base analogues we work with possess methyl groups at the C4- and C10-positions, that is, *ortho* with respect to the nitrogen atoms. Initially, *o*-methyl-substituted anilines were used because a methyl function at this position facilitates the reaction sequence consisting of consecutive Schiff base formations and two electrophilic aromatic substitutions,^[17,22] which, as a consequence, provided better yields and furthermore resulted in the formation of only one (desired) regioisomer of the Tröger's base analogue. Recently, DFT calculations have revealed that the methyl functions at these positions provide an additional, and equally important, advantage. Usually, Tröger's bases are configurationally stable under basic and neutral conditions but tend to racemize rapidly under acidic conditions.^[10] The introduction of the methyl groups, however, gives rise to a dramatic increase of the racemization barrier in acidic media due to steric hindrance of the inversion,^[23] thereby leading to a significantly increased configurational stability in acidic solution of bis(*o*-methyl)-substituted Tröger's base analogues; this makes them much more valuable precursors than derivatives devoid of this particular substitution pattern.

Our initial attempts were aimed at the resolution of **2** and **3** through diastereomeric salt formation by following the successful approaches for other derivatives mentioned above. However, even with various conditions, such as different solvents, temperature, scale, etc., and with different chiral resolving agents, such as DBTA, DTTA, or camphor sulfonic acid, resolution of the 2,8-dibromo- or 2,8-diiodo-substituted compounds could not be achieved.

Replacement of the halogen atoms by hydroxy groups also leads to a versatile precursor for further functionalization. As shown previously,^[18] this can be achieved by means of an Ullmann coupling. However, instead of preparing the respective racemic 2,8-dihydroxy compound from **3** via its 2,8-dimethoxy derivative first and subsequently applying all

of the procedures mentioned above, a rewarding alternative was to prepare diastereomers **4** directly by diphenylether Ullmann cross-coupling of **3** with (*R*)-1-phenylethanol, by using a protocol published by Buchwald and co-workers.^[24] As shown in Scheme 3, this reaction occurred smoothly and



Scheme 3. Ullmann diphenylether cross-coupling of the racemic Tröger's base analogue **3** with enantiopure 1-phenylethanol for the synthesis of the two diastereomeric derivatives of **4**.

gave a 1:1 mixture of the diastereomeric products **4a** and **4b** in 76% yield. However, these products could not be separated by crystallization or by column chromatography on silica gel. Although diastereomers, **4a** and **4b** were finally best resolved by using methods of enantioresolution on a chiral phase. Thus, by applying an analytical (*S,S*)-Whelk-01 phase (300×4 mm) with (3*S*,4*S*)-4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydro-phenanthrene covalently attached to silica gel as a chiral selector and by using a mixture of *n*-heptane/dichloromethane (2:1) as the eluent at a flow rate of 0.3 mL min⁻¹, the resolution of the two diastereomers was achieved (Figure 1). This separation was successfully scaled up to a semipreparative level by using the (*S,S*)-Whelk-01 phase (250×10 mm) with a 3:1 mixture of *n*-heptane and dichloromethane as the eluent and a flow rate of 1.5 mL min⁻¹. Under these conditions, approximately 15 mg of the diastereomeric mixture of **4** can be resolved in a single run. Figure 1 shows the chromatogram of the two diastereomers, **4a** and **4b**, and the ¹H NMR spectra of the diastereomeric mixture and of the separated isomers.

By hydrogenolysis,^[25] the stereoisomers of **4** should be readily converted into the enantiomerically pure bisphenolic parent compounds, which could then act as versatile precursors for the elaboration of tailor-made molecular structures, either directly or after transformation into the respective *O,O'*-bistriflate derivatives.

Still, despite this successful diastereomeric resolution, the use of such a relatively expensive chromatographic tool was

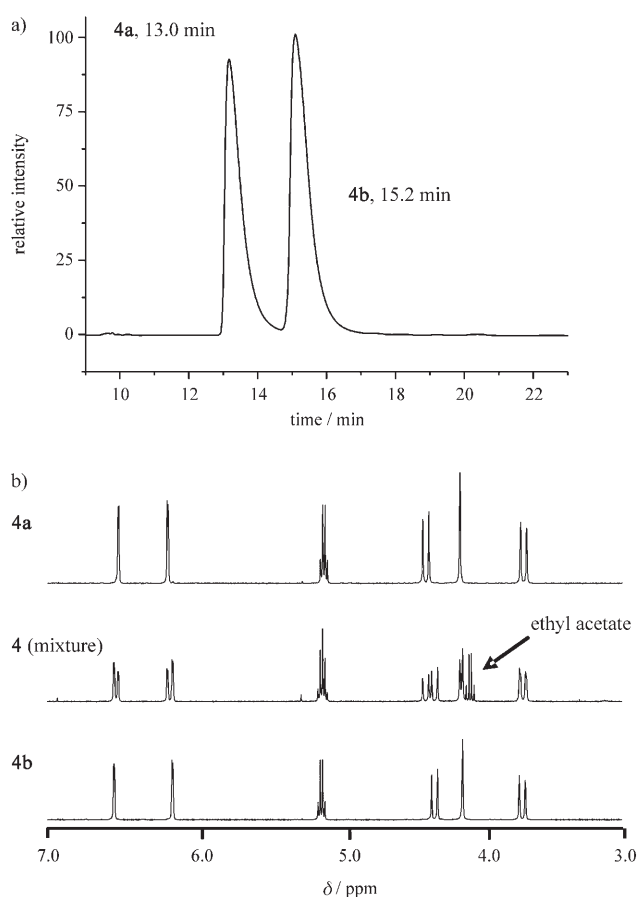
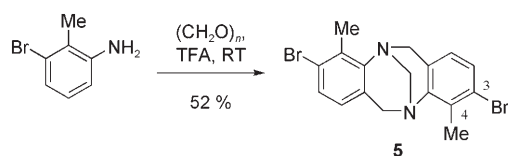


Figure 1. a) Chromatographic separation of the two diastereomers of **4** by HPLC on an analytical chiral phase, (*S,S*)-Whelk-01, with *n*-heptane/dichloromethane 2:1 as the eluent and a flow rate of 0.3 mL min⁻¹; b) relevant section of the ¹H NMR spectra of the 1:1 diastereomeric mixture of **4** and of the separated diastereomers, **4a** and **4b**.

to some extent unsatisfying and made alternative attempts, involving the use of chiral HPLC techniques for the direct enantioresolution of racemic Tröger's base analogues **2** and **3**, a rewarding option. However, despite numerous experiments, none of the chiral phases we evaluated proved to be suitable to achieve the resolution with any of the eluent mixtures and flow rates tested.^[26] Nevertheless, the successful separation of the diastereomeric mixture of **4** prompted us to consider the enantioresolution of other racemic difunctionalized Tröger's base derivatives. Our attempts to achieve the desired enantioresolution, therefore, concentrated on the 3,9-dibromo-substituted analogue **5**, which has a different substitution pattern. Racemic **5** can be prepared in one step from 3-bromo-2-methylaniline according to a published procedure (Scheme 4).^[27]

The use of this Tröger's base derivative proved to be most successful. In contrast to the 2,8-dibromo-substituted compound above, an enantioresolution was now easily achieved by using an analytical (*S,S*)-Whelk-01 phase with *n*-heptane/dichloromethane (85:15) as the eluent and a flow rate of 0.5 mL min⁻¹ (Figure 2).



Scheme 4. Synthesis of racemic 3,9-dibromo-4,10-dimethyl-6H,12H,5,11-methanodibenzodiazocine (**5**).

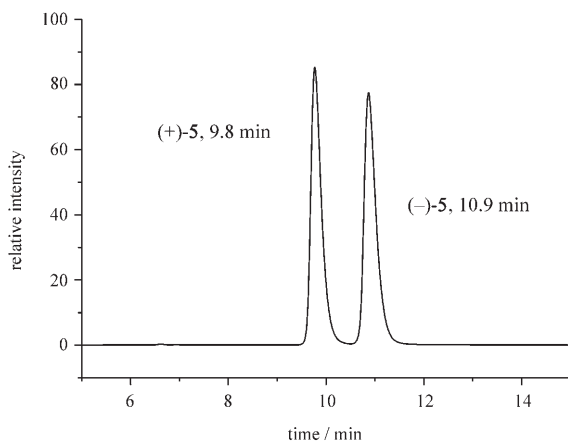
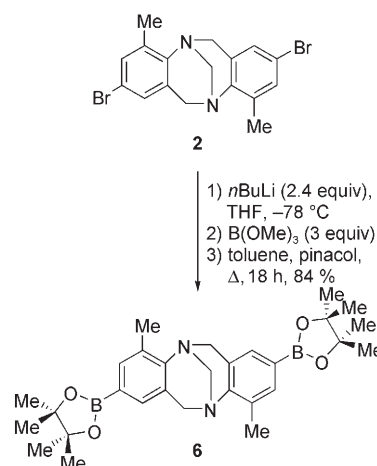


Figure 2. Chromatographic separation of racemic **5** by analytical HPLC with the (*S,S*)-Whelk-01 chiral phase, *n*-heptane/dichloromethane 85:15 as the eluent, and a flow rate of 0.5 mL min⁻¹.

Again, this separation proved to be transferable to a semi-preparative scale by applying slightly different conditions (same solvent mixture, but a flow rate of 1.5 mL min⁻¹). By using this method, approximately 10 mg of racemic **5** can be resolved into the separate enantiomers in a single run. However, due to some chromatographic tailing that occurs on the semipreparative scale, every run yields a small fraction containing both enantiomers incompletely separated. Parallel to our approach, a very elegant method for the separation of **5** has recently been developed by Kostyanovsky and co-workers, based on the discovery that racemic **5** crystallizes as a conglomerate from toluene and the enantiomorphous crystals can be isolated mechanically by manual separation and subsequent separate recrystallization.^[28]

Besides halides or pseudohalides, one could also think of other functionalities that show a somehow orthogonal reactivity in cross-coupling reactions, such as boronic acids and their derivatives, which are valuable substrates for Suzuki cross-couplings. As we still wanted to achieve the resolution of a 2,8-difunctionalized analogue of Tröger's base, we therefore prepared the racemic bis(pinacol) ester **6** from **2** by bromine–lithium exchange with subsequent borylation (Scheme 5).

The resolution of the enantiomeric bisboronates **6** could finally be achieved by again using an analytical (*S,S*)-Whelk-01 phase with a mixture of *n*-heptane/dichloromethane (85:15) as the eluent at a flow rate of 0.5 mL min⁻¹ (Figure 3). As Figure 3 indicates, substantial tailing occurs, even on an analytical scale, probably due to the presence of the boronic acid ester groups. Again, this procedure could



Scheme 5. Synthesis of racemic diboronic acid ester **6**.

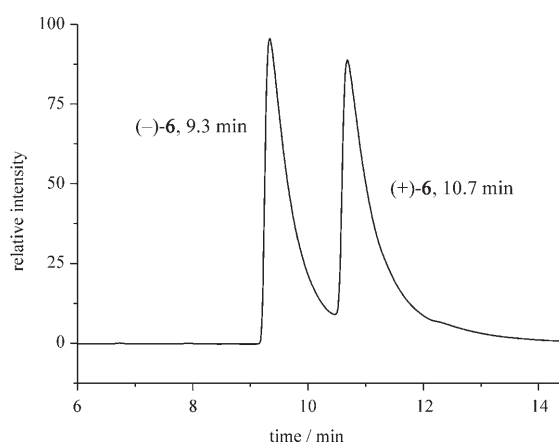


Figure 3. Chromatographic separation of racemic **6** by analytical HPLC with the (*S,S*)-Whelk-01 chiral phase, *n*-heptane/dichloromethane (85:15) as the eluent, and a flow rate of 0.5 mL min⁻¹.

be transferred to a semipreparative scale, with *n*-heptane/dichloromethane (85:15) as the eluent and a flow rate of 1.5 mL min⁻¹, yet with a more pronounced tailing. Nonetheless, as much as 6–7 mg of racemic **6** can thus be enantioseparated in a single run, although the fraction containing the unseparated enantiomers is larger than in the case of **5**. By using this method, however, around 12 runs can easily be performed within approximately 6 h to give around 30–40 mg of each of the two enantiomers, (–)-**6a** and (+)-**6b**, in an enantiopure form.

After the successful enantioseparation of **5** and **6**, the confirmation of the absolute configurations of the enantiomers of **5** and the determination of those of **6** was a rewarding task, as these building blocks were planned to act as starting materials for the formation of more sophisticated enantiomerically pure molecular architectures.

Fortunately, we succeeded in growing crystals suitable for X-ray crystal structure analysis from both enantiomers of **5** and from the more rapidly eluting enantiomer of **6**, by slow evaporation of the solvents from solutions in *n*-heptane/di-

chloromethane (3:1). Figure 4 shows the results of the analysis of the enantiomers of **5** obtained upon investigation with MoK_α radiation. Due to the presence of the two bromine

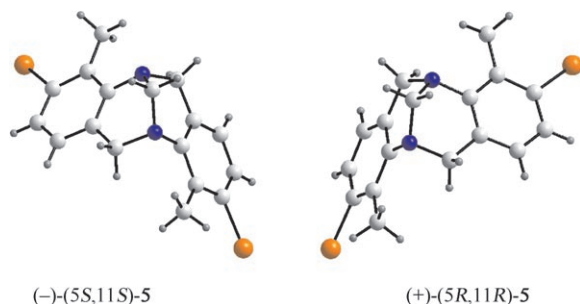


Figure 4. Crystal structures of $(-)-(5S,11S)\text{-5}$ and $(+)-(5R,11R)\text{-5}$ as determined by X-ray diffraction analysis.

atoms, the absolute configuration could be directly deduced from these experiments by analysis of the Flack parameter ($x = -0.018(7)$ for $(+)\text{-5}$, and $-0.017(6)$ for $(-)\text{-5}$). The results confirmed the $(5R,11R)$ configuration of $(+)\text{-5}$ and the $(5S,11S)$ configuration of $(-)\text{-5}$, as previously assigned by Kostyanovsky and co-workers (Figure 4).^[28]

For a first stereochemical assignment of **6**, we used CD spectroscopy as an efficient tool to elucidate the absolute configuration of our compounds. Figure 5 shows the spectra obtained from solutions of the enantiomers of **5** and **6** in

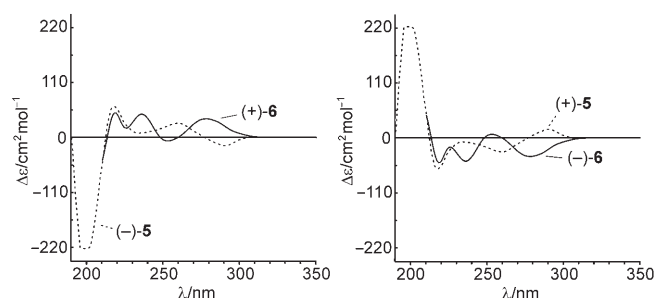


Figure 5. CD spectra of the two enantiomers of **5** (----) and **6** (—), in CH_3CN , $c = 4 \times 10^{-5} \text{ mol L}^{-1}$.

acetonitrile. From a comparison, a simple assignment of the configuration of $(+)\text{-6}$ and $(-)\text{-6}$ in analogy to $(+)\text{-5}$ and $(-)\text{-5}$ is not possible. Thus, quantum chemical calculations of the UV spectra of **5** and **6** and of the CD spectra of their enantiomers were performed to unambiguously assign the absolute configurations.

First attempts at the use of semiempirical methods (CNDO/S-CI^[29] calculations for AM1-optimized structures) showed that this level of theory is not suited for an accurate assignment of the absolute configurations of our Tröger's bases. Thus, we used time-dependent (TD) DFT calculations with the B3LYP hybrid functional and the 6-31G* basis set on B3LYP/6-31G*-optimized structures of **5** and **6**. By using this method, an excellent agreement of the experimental

UV and CD spectra of $(+)\text{-5}$ and $(-)\text{-5}$ with the calculated ones was found (Figure 6). A similar approach, yet only for the longest-wavelength band and thus for the first Cotton effect, has recently been pursued by Kostyanovsky and co-workers.^[28]

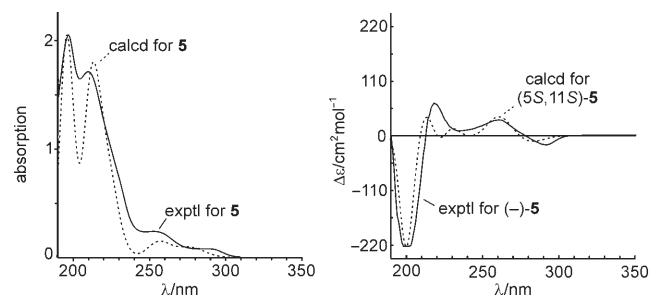


Figure 6. Calculated (B3LYP/6-31G*; ----) and experimental (—) UV spectra of **5** and corresponding experimental CD spectra of $(-)\text{-5}$ (—) and calculated CD spectra of $(5S,11S)\text{-5}$.

Application of the same approach to $(+)\text{-6}$ and $(-)\text{-6}$, however, did not lead to a similarly good agreement of the calculated spectra (10 nm red-shifted) with the experimental curves (Figure 7). Although these calculations permitted an unambiguous determination of the absolute configuration, the deviation in the region below $\lambda = 225 \text{ nm}$ was substantial.

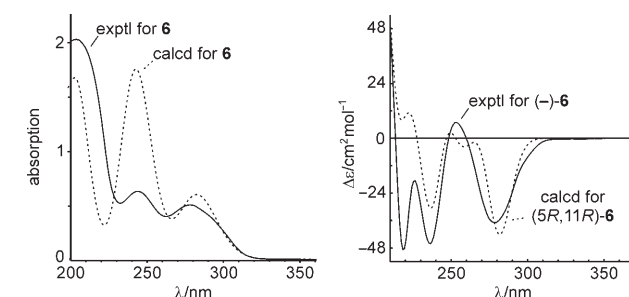


Figure 7. Calculated (TD B3LYP/6-31G*/B3LYP/6-31G*; ----) and experimental (—) UV spectra of **6** and corresponding experimental CD spectra of $(-)\text{-6}$ (—) and calculated CD spectra of $(5R,11R)\text{-6}$.

Therefore, further calculations were performed at a higher level of theory to attain a better agreement between the computed and experimental data. Interestingly, DFT/MRCI^[30] calculations gave even worse results in the region below 250 nm, thereby indicating that DFT methods are not well suited for the calculation of the rotational strengths of **6** in this wavelength region. However, MRCI calculations (UV shift of 36 nm to longer wavelengths) do reproduce the experimental data to a satisfying degree as only the first Cotton effect at approximately 280 nm is somewhat overestimated (Figure 8). These results nicely complement the assignment of $(-)\text{-6}$ as having the $5R,11R$ configuration.

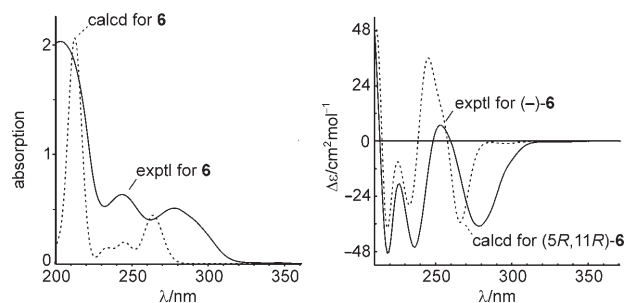


Figure 8. Calculated (MRCI/SVP//B3LYP/6-31G*; ----) and experimental (—) UV spectra of **6** and corresponding experimental CD spectra of (–)-**6** (—) and calculated CD spectra of (5*R*,11*R*)-**6**.

Independently, an X-ray diffraction analysis was performed, and a first analysis of (–)-**6** by employing $\text{MoK}\alpha$ radiation provided an excellent structural data set.^[31] However, the most important question for us, regarding the assignment of the absolute configuration, could not be answered owing to the lack of heavy atoms in this compound, which results in a nondefined Flack parameter in this case.

Therefore, we turned to $\text{CuK}\alpha$ radiation: even if the standard deviation of the Flack parameter ($x=0.0(3)$) was still quite high, this analysis clearly confirmed that the former determination of (–)-**6** as having the (5*R*,11*R*) configuration was correct (Figure 9).

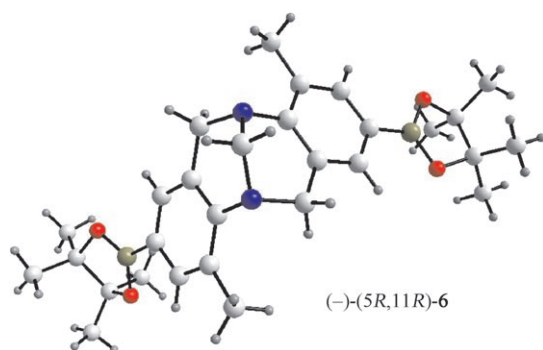
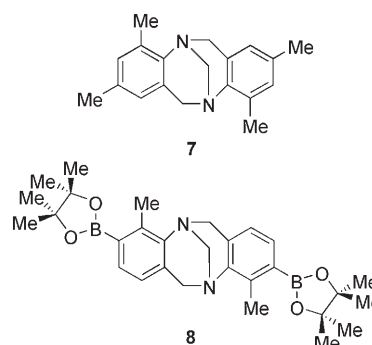


Figure 9. X-ray crystal structure of (–)-(5*R*,11*R*)-**6**.

To find out whether the divergence in the CD spectra of **5** and **6** was due to the different substitution patterns in these structures or to other reasons, the UV and CD spectra of a tetramethyl-substituted model compound **7** and the bis(boronic acid) diester **8** (Scheme 6), a regioisomer of **6**, were also calculated.

The calculated CD spectra of **5** and **7** were found to differ only slightly, but the curve of **5** is 15 nm red-shifted in comparison to that of **7** (Figure 10). The CD spectra of **6** and **7** showed a similar deviation pattern to those of **5** and **6**, with an opposite first Cotton effect, a result suggesting that the different positions of the substituents at the ring alone were not enough to explain the divergent CD spectra. This was further corroborated by the comparison with the calculated CD spectrum of model structure **8**, in which the boronic



Scheme 6. Model structures of **7** and **8**.

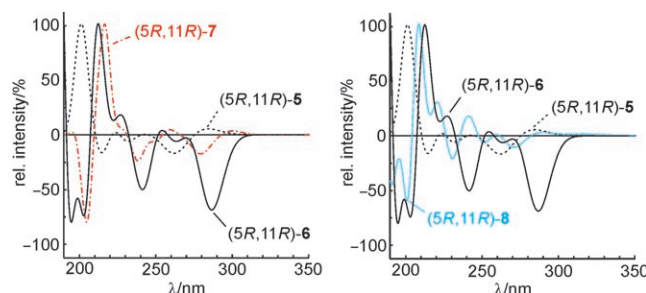


Figure 10. Comparison of the calculated (TD B3LYP/6-31G**/B3LYP/6-31G*) CD spectra of (5*R*,11*R*)-**5** (.....) and (5*R*,11*R*)-**6** (—) with those of (5*R*,11*R*)-**7** (---) and (5*R*,11*R*)-**8** (.....).

acid ester functions are in the same positions as the bromine atoms in **5**. The first Cotton effects of both **5** and **8** appear at nearly the same wavelength (≈ 290 nm), but the CD spectra as a whole are, nonetheless, not comparable, although **5** and **8** have the same absolute configuration and, formally, the same substitution pattern. As compared to the spectrum of **6**, the first Cotton effect of **8** has an opposite sign, clearly evidencing that the spectral differences are not only a consequence of the various substituents as such but result from a combination of both the electronic character of the substituent and its position.

This demonstrates the difficulties in elucidating absolute configurations of Tröger's bases just by comparison of their experimental CD spectra. Even structurally very similar derivatives of Tröger's base give rise to noticeably different CD spectra, thereby making an unambiguous elucidation impossible. Thus, for an unequivocal interpretation of these CD spectra, quantum chemical calculations constitute an indispensable tool.

For a further explanation of these differences of the experimental CD spectra, a more in-depth computational study of the first Cotton effect was performed. In the literature,^[28] the first Cotton effect found for all Tröger's bases, resulting from a highest occupied molecular orbital–lowest unoccupied molecular orbital (HOMO–LUMO) transition, has (for example, in the case of **5**) been assigned to be an $n\pi^*$ transition, and it might be possible that the first excited states in **6** result from different transitions. Computational investigations on **5** and **7** showed that the LUMO is indeed

a π^* orbital; however, a more detailed population analysis indicated that the HOMO does not only have n character from the lone pairs of the nitrogen atoms but also possesses a substantial portion of π character from the π orbitals of the aromatic rings, thereby hinting at a strong $+M$ effect of the nitrogen atoms. Thus, the HOMO–LUMO transition is better described as an $n,\pi-\pi^*$ transition for compounds such as **5** and **7** (Figure 11, top).

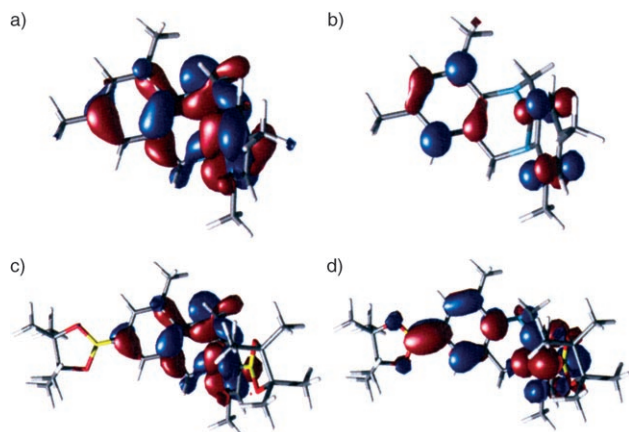


Figure 11. Calculated HOMOs (a and c) and LUMOs (b and d) of **6** (bottom) and **7** (top) obtained from B3LYP/6-31G* calculations.

While the diboronic acid esters **6** and **8** still have similar HOMOs, their LUMOs are different due to the boron atoms and are mostly formed of the empty p orbitals of the boron atoms; thus, the first Cotton effects in the CD spectra of **6** and **8** are due to an $n,\pi-p$ transition. This evidences the assumption that the properties of the different substituents also have an influence on the spectra.

Thus, we did not only succeed in elucidating the absolute configurations of the two enantiomers of **6**, but we could also establish some reasons for the difference between the spectra of the Tröger's base derivatives investigated here. One of the most important findings of the theoretical investigations is that the absolute configuration of differently substituted Tröger's bases cannot be established by just comparing their experimental CD spectra, due to the unexpectedly strong effects of the substituents on the CD spectra. Although the DFT method used here is not always able to fully reproduce the experimental CD spectra (mainly in the lower wavelength region of **6**), it does fulfill the task of distinguishing between the different enantiomers. With compound **6** as an example, this has been vigorously confirmed by higher-level calculations with the MRCI approach.

Conclusion

In summary, we have succeeded in synthesizing racemic di-substituted derivatives of Tröger's base bearing versatile functional groups for the synthesis of elaborated structures.

While the stereoisomers of a 2,8-dihydroxy derivative have only been separated in the form of their diastereomeric derivatives by using HPLC techniques on chiral stationary (*S,S*)-Whelk-01 phases, the same chromatographic approach was also applied to the resolution of the racemic 3,9-dibromo-functionalized Tröger's base derivative **5** and the 2,8-diboronic acid ester derivative **6** on a semipreparative scale. The 4,10-dimethyl substitution pattern of these compounds prevents their racemization in acidic media, which makes their successful enantioseparation even more attractive, as they are configurationally stable under basic conditions anyway, for example, in Suzuki reactions. We were also able to determine the absolute configuration of the resolved enantiomers by comparison of quantum chemically calculated CD spectra with the experimental ones and, independently, by X-ray diffraction techniques. The reliable knowledge of the absolute stereostructures of these compounds is a required precondition for the construction of more sophisticated molecular architectures, which we are currently preparing in enantiomerically pure form.

Experimental Section

General information: All reactions were performed under an argon atmosphere by using standard Schlenk techniques and glassware that was oven dried prior to use. TLC was performed on aluminum TLC plates coated with silica gel 60 F_{254} (Merck). Detection was done under UV light (254 and 366 nm). Products were purified by column chromatography on silica gel 60 (70–230 mesh; Merck). ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 spectrometer at 300 K, at 500.1 and 125.8 MHz, respectively, on a Bruker AM 400 spectrometer at 298 K, at 400.1 and 100.6 MHz, respectively, or on a Bruker Avance 300 spectrometer at 298 K, at 300.1 and 75.5 MHz, respectively. ^1H and ^{13}C NMR chemical shifts are reported on the δ scale (ppm) relative to residual non-deuterated and deuterated solvent, respectively, as the internal standards. Signals were assigned on the basis of ^1H , ^{13}C , HMQC, and HMBC NMR experiments. Mass spectra were taken on a Finnigan MAT 212 instrument with an MMS-ICIS data system (EI) or an A.E.I. MS-50 instrument (EI; high-resolution EI). Melting points were measured with a hot-stage microscope SM-Lux apparatus from Leitz and are not corrected. Elemental analyses were carried out with a Fisons Instrument EA1108 or a Heraeus Vario EL instrument. HPLC was performed by using a Prominence console from Shimadzu (binary system consisting of two pumps (LC20-AT), degasser (DGU-20A), diode array detector (SPD-M20A), and a fraction collector (FRC-10A)). Chiral analytical and semipreparative stationary phases ((*S,S*)-Whelk-01 phase from GAT) were applied and solvent mixtures of *n*-heptane and dichloromethane (HPLC quality) were used. CD spectroscopy was performed on a Jasco J-810 instrument. Crystal structures were edited with the Diamond 3.0 software (Crystal Impact GbR). Most solvents were dried, distilled, and stored under argon according to standard procedures. All chemicals were used as received from commercial sources. Racemic 3,9-dibromo-4,10-dimethyl-6*H*,12*H*-5,11-methanodibenzodiazocine (**5**),^[27] 2,8-dibromo-4,10-dimethyl-6*H*,12*H*-5,11-methanodibenzodiazocine (**2**),^[17] and 2,8-diiodo-4,10-dimethyl-6*H*,12*H*-5,11-methanodibenzodiazocine (**3**)^[20] were prepared according to published procedures. The numbering system for the ^1H and ^{13}C nuclei is indicated in Scheme 1.

2,8-Bis[(*R*)-1-phenylethoxy]-4,10-dimethyl-6*H*,12*H*-5,11-methanodibenzodiazocine (4**, mixture of two diastereomers):** A solution of **3** (600 mg, 1.20 mmol), (*R*)-(+)-1-phenylethanol (584 mg, 4.78 mmol, 4 equiv), cesium carbonate (1.56 g, 4.78 mmol, 4 equiv), copper(I) iodide (46 mg, 0.24 mmol, 20 mol %), and 1,10-phenanthroline (anhydrous; 86 mg, 0.48 mmol, 40 mol %) in toluene (10 mL) was refluxed for 18 h. It was

then filtered through silica gel and the residue was washed with CH_2Cl_2 (150 mL). The filtrate was dried with Na_2SO_4 , the solvents were evaporated, and the residue was purified by column chromatography (petroleum ether (40/60)/ethyl acetate 4:1 with 0.5% Et_3N , $R_f=0.39$). Yield: 442 mg (0.91 mmol, 76%); MS (EI): m/z (%): 490.3 (100) $[\text{C}_{33}\text{H}_{34}\text{N}_2\text{O}_2]^+$; HRMS (EI): m/z : calcd for $[\text{C}_{33}\text{H}_{34}\text{N}_2\text{O}_2]^+$: 490.2620; found: 490.2624; elemental analysis: calcd (%) for $\text{C}_{33}\text{H}_{34}\text{N}_2\text{O}_2 \cdot 0.5\text{H}_2\text{O}$: C 79.33, H 7.06, N 5.61; found: C 79.34, H 7.10, N 5.15.

Separation of the diastereomers of 4: HPLC: chiral phase (analytical): (S,S)-Whelk-01; eluent: *n*-heptane/ CH_2Cl_2 2:1; flow rate (f) = 0.3 mL min⁻¹.

Diastereomer 4a: Retention time = 13.0 min; $[\alpha]_{\text{D}}^{24} = +3.9$ ($c=0.54$ in CH_2Cl_2); m.p. 64–66 °C; ^1H NMR (400.1 MHz, CDCl_3): $\delta=1.47$ (d, $^3J=6.4$ Hz; OCH(Ph) CH_3), 2.20 (s; Ph CH_3), 3.68 (d, $^2J=-16.7$ Hz, 2H; 6-endo-H, 12-endo-H), 4.13 (s, 2H; 13-H), 4.36 (d, $^2J=-16.7$ Hz, 2H; 6-exo-H, 12-exo-H), 5.07 (q, $^3J=6.4$ Hz, 2H; OCH(Ph) CH_3), 6.16 (d, $^4J_{1,3}=^4J_{7,9}=2.6$ Hz, 2H; 1-H, 7-H), 6.50 (d, $^4J_{1,3}=^4J_{7,9}=2.6$ Hz, 2H; 3-H, 9-H), 7.14–7.18 (m, 2H; 4_{ph}-H), 7.21–7.28 ppm (m, 8H; 2_{ph}-H, 3_{ph}-H, 2'_{ph}-H, 3'_{ph}-H); ^{13}C NMR (100.8 MHz, CDCl_3): $\delta=17.2$ (Ph CH_3), 24.4 (OCH(Ph) CH_3), 55.2 (C-6, C-12), 67.7 (C-13), 76.1 (OCH(Ph) CH_3), 110.6 (C-1, C-7), 116.8 (C-3, C-9), 125.5 (C-2_{ph}, C-2'_{ph}), 127.4 (C-4_{ph}), 128.6 (C-3_{ph}, C-3'_{ph}), 128.9 (C-14, C-16), 134.2 (C-4, C-10), 139.3 (C-15, C-17), 143.5 (C-1_{ph}), 154.3 ppm (C-2, C-8).

Diastereomer 4b: Retention time = 15.3 min; $[\alpha]_{\text{D}}^{24} = +123.3$ ($c=0.48$ in CH_2Cl_2); m.p. 70–72 °C; ^1H NMR (400.1 MHz, CDCl_3): $\delta=1.47$ (d, $^3J=6.4$ Hz, 6H; OCH(Ph) CH_3), 2.23 (s, 6H; Ph CH_3), 3.69 (d, $^2J=-16.8$ Hz, 2H; 6-endo-H, 12-endo-H), 4.11 (s, 2H; 13-H), 4.30 (d, $^2J=-16.8$ Hz, 2H; 6-exo-H, 12-exo-H), 5.09 (q, $^3J=6.4$ Hz, 2H; OCH(Ph) CH_3), 6.13 (d, $^4J_{1,3}=^4J_{7,9}=2.7$ Hz, 2H; 1-H, 7-H), 6.53 (d, $^4J_{1,3}=^4J_{7,9}=2.7$ Hz, 2H; 3-H, 9-H), 7.15–7.18 (m, 2H; 4_{ph}-H), 7.19–7.27 ppm (m, 8H; 2_{ph}-H, 3_{ph}-H, 2'_{ph}-H, 3'_{ph}-H); ^{13}C NMR (100.8 MHz, CDCl_3): $\delta=17.2$ (Ph CH_3), 24.5 (OCH(Ph) CH_3), 55.3 (C-6, C-12), 67.8 (C-13), 75.8 (OCH(Ph) CH_3), 110.4 (C-1, C-7), 116.9 (C-3, C-9), 125.5 (C-2_{ph}, C-2'_{ph}), 127.3 (C-4_{ph}), 128.6 (C-3_{ph}, C-3'_{ph}), 128.8 (C-14, C-16), 134.1 (C-4, C-10), 139.2 (C-15, C-17), 143.5 (C-1_{ph}), 154.2 ppm (C-2, C-8).

3,9-Dibromo-4,10-dimethyl-6H,12H-5,11-methanodibenzodiazocine (5): Racemic **5** was synthesized according to a published procedure.^[27] The analytical and spectroscopic data were in accordance with those published.

Separation of the enantiomers of 5: HPLC: chiral phase (analytical): (S,S)-Whelk-01; eluent: *n*-heptane/ CH_2Cl_2 85:15; $f=0.5$ mL min⁻¹.

Enantiomer (–)-(5R,11R)-5: Retention time = 9.8 min; $[\alpha]_{\text{D}}^{25} = +214.8$ ($c=0.13$ in CH_2Cl_2); CD (CH_3CN): λ ($\Delta\epsilon$) = 291 (+15.9), 260 (–25.4), 219 nm (–54.6 cm² mol⁻¹).

Enantiomer (+)-(5S,11S)-5: Retention time: 10.9 min; $[\alpha]_{\text{D}}^{25} = -210.7$ ($c=0.13$ in CH_2Cl_2), 98% ee; CD (CH_3CN): λ ($\Delta\epsilon$) = 291 (–15.9), 260 (+25.4), 219 nm (+54.6 cm² mol⁻¹).

2,8-Bis[4-(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl)]-4,10-dimethyl-6H,12H-5,11-methanodibenzodiazocine (6): A solution of **2** (1 g, 2.45 mmol) in THF (10 mL) was cooled to –78 °C. *n*BuLi (1.6 M in *n*-hexane; 3.66 mL, 5.87 mmol, 2.4 equiv) was added at this temperature within 5 min and the resulting solution was stirred for another 5 min. Trimethylborate (0.82 mL, 7.35 mmol, 764 mg, 3 equiv) was added, and the reaction mixture was warmed to room temperature and stirred for another hour. The solvents were evaporated and the residue was suspended in toluene (30 mL). Pinacol (1.16 g, 9.8 mmol, 4 equiv) was added, and the resulting mixture was refluxed for 16 h. Water was added, the layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2 . The combined organic layers were dried with Na_2SO_4 , and the solvents were evaporated. The crude product was pure according to NMR spectroscopic analysis. If the product requires further purification, it can be dissolved in CH_2Cl_2 . Excessive *n*-hexane has to be added and the resulting solution has to be stored at –20 °C for 10 h. The white precipitate can be collected and is pure **6**. Yield: 970 mg (1.94 mmol, 79%); m.p. >250 °C; ^1H NMR (500.1 MHz, CDCl_3): $\delta=1.29$ (s, 24H; B[O $_2$ C $_2$ (CH $_3$) $_4$]), 2.39 (s, 6H; Ph CH_3), 4.05 (d, $^2J=-17.0$ Hz, 2H; 6-endo-H, 12-endo-H), 4.34 (s, 2H; 13-H), 4.59 (d, $^2J=-17.0$ Hz, 2H; 6-exo-H, 12-exo-

H), 7.23 (s, 2H, 1-H; 7-H), 7.48 ppm (s, 2H; 3-H, 9-H); ^{13}C NMR (125.8 MHz, CDCl_3): $\delta=16.9$ (Ph CH_3), 24.8 (B[O $_2$ C $_2$ (CH $_3$) $_4$]), 54.8 (C-6, C-12), 67.6 (C-13), 83.6 (B[O $_2$ C $_2$ (CH $_3$) $_4$]), 127.2 (C-14, C-16), 131.3 (C-1, C-7), 132.0 (C-4, C-10), 135.4 (C-3, C-9), 148.9 ppm (C-15, C-17), as a result of the high multiplicity through the ^{13}C – ^{13}B coupling, the signal for C-2 and C-8 was too weak to be detected; MS (EI): m/z (%): 502.2 (100) $[\text{C}_{29}\text{H}_{40}\text{B}_2\text{N}_2\text{O}_4]^+$; HRMS (EI): m/z : calcd for $[\text{C}_{29}\text{H}_{40}\text{B}_2\text{N}_2\text{O}_4]^+$: 502.3174; found: 502.3174; elemental analysis: calcd (%) for $\text{C}_{29}\text{H}_{40}\text{B}_2\text{N}_2\text{O}_4 \cdot \text{H}_2\text{O}$: C 66.95, H 8.14, N 5.38; found: C 66.47, H 7.82, N 5.24; UV/Vis (CH_3CN): λ_{max} ($\Delta\epsilon$) = 202 (2.0×10^4), 240 (0.6×10^4), 273 nm ($0.5 \cdot 10^4$ M⁻¹ cm⁻¹).

Separation of the enantiomers of 6: HPLC: chiral phase (analytical): (S,S)-Whelk-01; eluent: *n*-heptane/ CH_2Cl_2 85:15; $f=0.5$ mL min⁻¹.

Enantiomer (+)-(5R,11R)-6: Retention time = 9.3 min; $[\alpha]_{\text{D}}^{25} = -169.1$ ($c=0.13$ in CH_2Cl_2); CD (CH_3CN): λ ($\Delta\epsilon$) = 278 (–33.5), 236 (–41.8), 218 nm (–44.2 cm² mol⁻¹); elemental analysis: calcd (%) for $\text{C}_{29}\text{H}_{40}\text{B}_2\text{N}_2\text{O}_4 \cdot \text{H}_2\text{O}$: C 66.95, H 8.14, N 5.38; found: C 66.78, H 7.87, N 5.20.

Enantiomer (–)-(5S,11S)-6: Retention time = 10.7 min; $[\alpha]_{\text{D}}^{25} = +160.8$ ($c=0.13$ in CH_2Cl_2), 95% ee; CD (CH_3CN): λ ($\Delta\epsilon$) = 278 (+30.1), 236 (+37.6), 218 nm (+39.5 cm² mol⁻¹); elemental analysis: calcd (%) for $\text{C}_{29}\text{H}_{40}\text{B}_2\text{N}_2\text{O}_4 \cdot \text{H}_2\text{O}$: C 66.95, H 8.14, N 5.38; found: C 66.78, H 8.04, N 5.01.

Computational details: All optimizations were performed with the software package Gaussian 03,^[32] by using the AM1^[33] Hamiltonian or the DFT functional B3LYP^[34] and the basis set 6-31G*.^[35] The Tröger's bases are quite rigid structures, which could be seen by the fact that only one conformer for each base was found. To identify the found structures as energetic minima, frequency calculations were accomplished at the same level of theory. Rotational-strength values for the electronic transitions from the ground state to the singly excited states were obtained by time-dependent (TD) DFT calculations (B3LYP/6-31G*) with the Gaussian 03 software. Additionally, an MRCISVP^[36] approach was used (CAS 12,12) to calculate these values for **6** with the ab initio software package ORCA 2.6.0 developed by Prof. Dr. F. Neese (University of Bonn, Germany).^[37] $\Delta\epsilon$ values were calculated by forming sums of Gaussian functions ($\sigma=0.08$ eV for the TD DFT calculation, $\sigma=0.1$ eV for the MRCI/SVP calculations) centered at the wavelengths of the respective electronic transitions and multiplied by the corresponding rotational strengths. The CD spectra thus obtained were UV corrected^[38] and compared with the experimental ones. The HOMO and LUMO graphics were constructed by using the MOLDEN^[39] and POV-Ray 4.6 software packages.

Crystal structure determinations

X-ray crystallographic analyses of (–)-(5S,11S)-5 and (+)-(5R,11R)-5: Data were collected on a Nonius KappaCCD diffractometer equipped with a low-temperature device (Cryostream, Oxford Cryosystems) at 123(2) K by using graphite monochromated Mo $\text{K}\alpha$ radiation ($\lambda=0.71073$ Å).

X-ray crystallographic analysis of (–)-(5R,11R)-6: Data were collected on a Nonius KappaCCD diffractometer by using monochromated Cu $\text{K}\alpha$ radiation ($\lambda=1.54178$ Å). Programs used: data collection: COLLECT (Nonius B.V., 1998); data reduction: Denzo-SMN;^[40] absorption correction: Denzo.^[41] The structures were solved by direct methods (SHELXS-97) and refined by full-matrix least squares on F^2 (SHELXL-97).^[42] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms on carbon atoms were placed in calculated positions and refined isotropically by using a riding model. For some details of the crystallographic data, see Table 1. CCDC 659372 ((–)-(5R,11R)-6, employing Cu $\text{K}\alpha$ radiation), 659277 ((–)-(5R,11R)-6, employing Mo $\text{K}\alpha$ radiation), 659278 ((+)-(5R,11R)-5), and 659279 ((–)-(5S,11S)-5) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Crystallographic data for (–)-(5*R*,11*R*)-**6**, (+)-(5*R*,11*R*)-**5**, and (–)-(5*S*,11*S*)-**5**.

	(–)-(5 <i>R</i> ,11 <i>R</i>)- 6	(+)-(5 <i>R</i> ,11 <i>R</i>)- 5	(–)-(5 <i>S</i> ,11 <i>S</i>)- 5
formula	C ₂₉ H ₄₀ Br ₂ N ₂ O ₄	C ₁₇ H ₁₆ Br ₂ N ₂	C ₁₇ H ₁₆ Br ₂ N ₂
<i>M</i> _r	502.25	408.14	408.14
<i>T</i> [K]	223(2)	123(2)	123(2)
crystal system	orthorhombic	orthorhombic	orthorhombic
space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁
crystal dimensions [mm]	0.20 × 0.20 × 0.05	0.26 × 0.18 × 0.12	0.60 × 0.40 × 0.32
<i>a</i> [Å], <i>α</i> [°]	12.2311(4), 90	10.3918(2), 90	10.3918(2), 90
<i>b</i> [Å], <i>β</i> [°]	13.8425(4), 90	11.5529(3), 90	11.5541(3), 90
<i>c</i> [Å], <i>γ</i> [°]	16.9817(5), 90	12.4471(2), 90	12.4454(3), 90
<i>V</i> [Å ³]	2875.15(15)	1494.34(5)	1494.29(6)
<i>Z</i> , <i>ρ</i> [mg m ^{–3}]	4, 1.160	4, 1.814	4, 1.814
<i>μ</i> [mm ^{–1}]	0.595	5.419	5.419
<i>θ</i> range [°]	4.12–67.97	2.55–31.00	3.10–30.99
completeness [%]	93.9	99.9	99.8
reflms measured	15213	43 721	21 974
unique/observed	4736/3598	4762/3946	4756/4163
reflms (<i>R</i> _{int})	(0.0620)	(0.0979)	(0.0506)
data/restraints/parameters	4736/0/345	4762/0/192	4756/0/193
Gof on <i>F</i> ²	1.029	0.964	0.990
final <i>R</i> indices	<i>R</i> ₁ = 0.052, <i>wR</i> ₂ = 0.100	<i>R</i> ₁ = 0.028, <i>wR</i> ₂ = 0.053	<i>R</i> ₁ = 0.023, <i>wR</i> ₂ = 0.043
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.081, <i>wR</i> ₂ = 0.1183	<i>R</i> ₁ = 0.040, <i>wR</i> ₂ = 0.056	<i>R</i> ₁ = 0.030, <i>wR</i> ₂ = 0.044
absolute structure parameter <i>x</i>	0.0(3)	–0.018(7)	–0.017(6)

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- 20 < I < 22; 25 874 measured reflections, 6801 independent reflections ($R_{\text{int}} = 0.0775$); $\mu = 0.077 \text{ mm}^{-1}$; max. and min. transmissions = 0.9939 and 0.9555. Structural analysis and refinement: see the Experimental Section. GoF (F^2) = 0.886, final R indices ($[I > 2\sigma(I)]$): $R_1 = 0.0415$, $wR_2 = 0.0632$; R indices (all data): $R_1 = 0.0828$, $wR_2 = 0.0712$; max. and min. residual electron density: 0.176 and –0.169 $\text{e} \text{ \AA}^{-3}$; absolute structure parameters: 0.7(8).
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