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Tröger's Base Twisted Amides: *Endo* Functionalization and Synthesis of an Inverted Crown Ether

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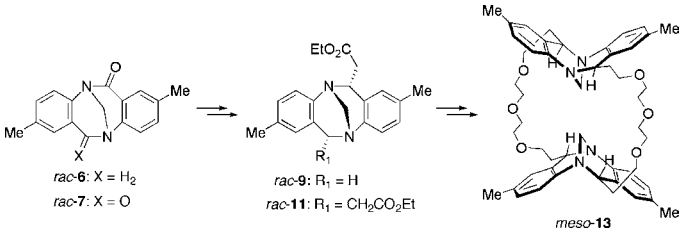
ABSTRACT



Taking advantage of the unconventional reactivity of twisted mono- and bis-amides of Tröger's base (TB), *rac*-6 and *rac*-7, respectively, the first synthesis of a 6-*endo*-monosubstituted TB analogue, *rac*-9, and the first rational synthesis of a 6,12-*endo*,*endo*-disubstituted TB analogue, *rac*-11, have been achieved. The bis-TB crown ether, *meso*-13, was prepared starting from *rac*-7. *Meso*-13 constitutes a rare example of a crown ether with an inverted methylene bridge-to-bridge bis-TB conformation both in solution and in the solid state, resulting in a reluctance to act as a receptor for cations.

Tröger's base (TB),[1] *rac*-**1** (Figure 1), is a fascinating molecule with a controversial and lengthy history of structural and stereochemical assignment.[2] TB represents a chiral diamine with two stereogenic N-atoms and is one of the first chiral compounds resolved by chiral stationary phase chromatography (on (+)-α-lactose hydrate).[3] This textbook molecule and its functionalized analogues have received considerable attention as building blocks in diverse areas such as molecular recognition, catalysis, enzyme inhibition, and optical materials.[4,5]

These applications of the structural features of TB have elicited substantial synthetic efforts that include (1) a facile synthesis of halogenated TB analogues,[6−8] which allows its aromatic ring functionalization,[9,10] (2) *N*-mono and -dialkylations,[11] and (3) replacement of the methylene bridge.[12,13] Although C-6 and C-12 functionalized TB analogues have been synthesized from substituted dibenzodiazocines,[14] the preparation of such *exo*-monosubstituted (**2**) or *exo*,*exo*-disubstituted (**3**) derivatives from the readily available TB has been feasible only by the metalation strategy developed in our laboratories (Figure 1).[15] We have previously reported on the use of *exo*-substituted analogues of TB in the catalytic asymmetric addition of diethylzinc to substituted benzaldehydes in up to 86% ee.[15b] However, it may be argued that *endo*-monosubstituted (**4**) or *endo*,*endo*-disubstituted (**5**) analogues of TB (Figure 1) are potentially more useful since the

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diazocine ring substituents are directed toward the chiral cavity of TB and are therefore especially suitably positioned for asymmetric catalysis and molecular recognition.

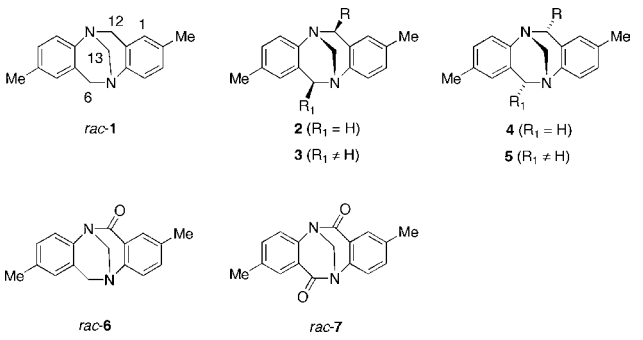


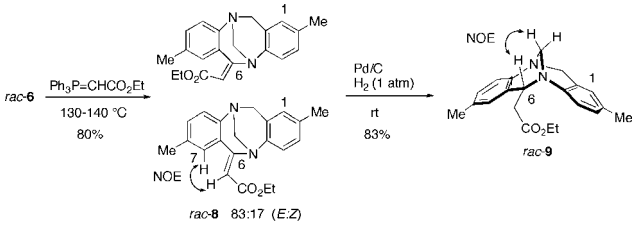
Figure 1. Possible diazocine ring substituted analogues of Tröger's base (TB) *rac*-**1**: *exo*-monosubstituted (**2**), *exo*,*exo*-disubstituted (**3**), *endo*-monosubstituted (**4**), *endo*,*endo*-disubstituted (**5**), twisted mono- (*rac*-**6**) and twisted bis- (*rac*-**7**) amides.

With these factors in mind, we prepared, by direct C-6 and C-12 oxidation reactions, mono- (*rac*-**6**) and bis-amide (*rac*-**7**) TB analogues (Figure 1),[16] the latter being the first twisted bis-amide reported to date. Twisted amides are compounds having their carbonyl π-systems out of conjugation with the nitrogen lone pairs.[17] For *rac*-**7**, the twist angle, τ,[18] describing the deviation from coplanarity between the carbonyl π orbital and the nitrogen lone pair, was determined to be $-43.7°$ as compared to being near 0° and 180° as commonly found in unconstrained *cisoid* and *transoid* amides, respectively. The twisted amide structural feature in *rac*-**7** was also reflected by its rapid acid hydrolysis.[16,19] This property suggested further possibilities for the benzylic functionalization of monoamide (*rac*-**6**) and bis-amide (*rac*-**7**) TB analogues.

Herein we report on the Wittig olefination of *rac*-**6** and *rac*-**7**, which has led to the first synthesis of *endo*-monosubstituted (*rac*-**9**) (Scheme 1) and the first rational synthesis of *endo*,*endo*-disubstituted (*rac*-**11**) TB analogues (Scheme 2). In addition, the availability of *rac*-**11** allowed the synthesis of crown ether *meso*-**13** (Scheme 2), which showed unexpected conformational properties.

While Wittig olefinations do not take place on regular amides, examples of olefinations of twisted amides[17b,c] and phthalimides[20] are known. Taking advantage of the protocol described for phthalimides,[20] *rac*-**6** was readily olefinated at 130−140 °C using the commercially available (ethoxycarbonylmethylene)-triphenylphosphorane to give the monoenamino TB adduct *rac*-**8** in high yield (Scheme 1) as an 83:17 *E*/*Z* mixture according to ^{1}H NMR analyses (see Supporting Information (SI)). The assignment of the geometrical isomers of *rac*-**8** was established by ROESY experiments (see SI), which showed a correlation between H-7 and the vinyl H (Scheme 1) for the isolated sample of the minor isomer, thus demonstrating the *Z*-geometry of this isomer. Since the outcome of the next synthetic step was indifferent to the configuration of the olefin, the *E*/*Z* mixture was subjected to hydrogenation using Pd/C at 1 atm and rt, resulting in the formation of *rac*-**9** in 83% yield after 16 h. The relative stereochemistry of *rac*-**9** was assigned by NOESY experiments (see SI), which showed a correlation between the H-6 and one of the methylene

Scheme 1. Synthesis of *endo*-Substituted TB Analogue *rac*-**9**



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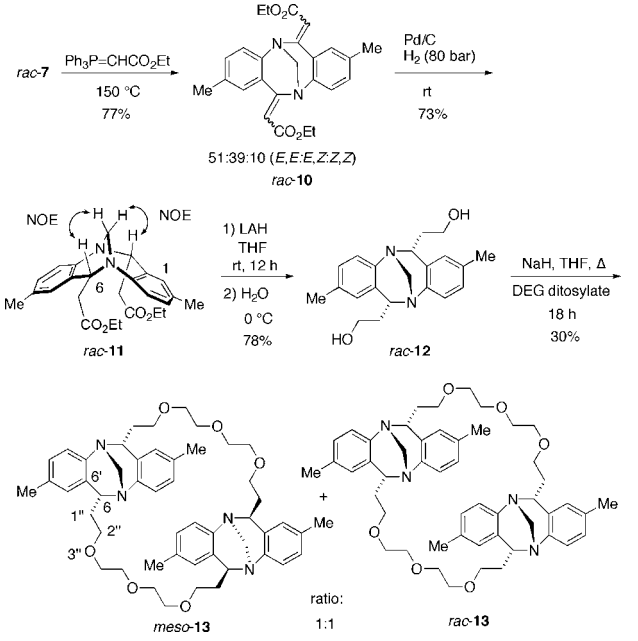
bridge protons (Scheme 1), thus establishing the *endo* configuration of the ethoxycarbonylmethylene group. The stereochemical outcome of the hydrogenation may be rationalized by consideration of the convex face of *rac*-**8** being more accessible to the catalyst surface compared to the more hindered concave face.

Next, the methodology for the synthesis of *endo*-monosubstituted TB analogue *rac*-**9** was successfully applied to the preparation of the *endo,endo*-disubstituted TB analogue *rac*-**11** (Scheme 2). Thus, *rac*-**7** was readily olefinated at 150 °C using (ethoxycarbonylmethylene)-triphenylphosphorane to give *rac*-**10** in 77% yield as a mixture of the three possible geometrical isomers in a 51:39:10 (*E*,*E*/*E*,*Z*/*Z*,*Z*) ratio, according to ^{1}H NMR analyses (see SI), differing from a 69:28:3 statistical ratio expected if the *E*/*Z* selectivity of the olefination of *rac*-**6** and *rac*-**7** had been the same. The assignment of the geometrical isomers of *rac*-**10** was established by ROESY experiments, as in the case of *rac*-**8**. This mixture of isomers was subjected to hydrogenation using Pd/C at 80 bar and rt for 24 h to give *rac*-**11**[21] in 73% yield.[22] As for *rac*-**9** (*vide supra*), the relative stereochemistry was assigned by NOESY experiments (see SI and Scheme 2).

With *rac*-**11** in hand, we recognized the potential for the preparation of derivatives with functional groups oriented toward the aromatic cavity of TB. One possibility was the introduction of an oligoethylene glycol strap. Toward this end, reduction of *rac*-**11** with LAH smoothly gave the diol *rac*-**12** in 78% yield (Scheme 2). Although attempts to bridge the two hydroxyl groups with tri- and tetraethylene glycol ditosylates to form the corresponding mono-TB crown ether failed, the use of diethylene glycol ditosylate resulted in a dimerization to give the bis-TB crown ether **13** in 30% yield as a 1:1 mixture of *meso*-**13** and *rac*-**13** (Scheme 2),

Scheme 2. Synthesis of *endo,endo*-Disubstituted TB Analogues *rac*-**11**, *rac*-**12**, and bis-TB Crown Ethers **13**



as revealed by ^{1}H NMR spectroscopy (see SI). The rest of the isolated material was assumed to be oligomeric due to the observed broad peaks in its ^{1}H NMR spectrum. Macrocycle *meso*-**13** was obtained in 9% yield by a double recrystallization of the reaction mixture, first from hexane/*i*PrOH (8:2) and then from EtOAc. Alternatively, each of the three stereoisomers was separated by semi-preparative HPLC using a cellulose-derived chiral stationary phase, giving (−)-**13**, (+)-**13**, and *meso*-**13** (see SI), respectively, as isolated pure compounds.

The structure of *meso*-**13** was unambiguously assigned by X-ray crystallography, thereby conclusively establishing the *endo,endo*-configuration of precursor TB derivatives **11**−**13**. To our surprise, the solid state structure of *meso*-**13** (Figure 2) showed that the methylene bridges of the TB framework were both directed toward and not away from each other as expected from the *endo,endo*-configuration of the starting TB analogue *rac*-**12**, resulting in an "inverted" crown ether. All efforts to grow suitable crystals for X-ray diffraction analysis of both racemic and enantiopure **13** were unsuccessful.

The conformation of *meso*-**13** was investigated by *in silico* modeling using molecular dynamics with $CHCl_3$ as solvent (see SI). The C6′−C6−C1″−C2″ structural component (Scheme 2) of the simulated structure of *meso*-**13** showed a very good correlation with the solid state structure (compare Figures S29 and S30, SI), supporting the methylene bridge-to-bridge bis-TB conformation. The conformations obtained by the X-ray crystal structure and the geometry-optimized calculated structure both agreed well with the ROESY correlations achieved for *meso*-**13** in $CDCl_3$ (see SI). The *in silico* modeling data established a dihedral angle of 160° for C6′−C6−C1″−C2″ and a dihedral angle of −70° for C6−C1′−C2″−O3″ for the (*S*,*S*)-Tröger's base structural component, and the opposite sign for the corresponding dihedral angles for the (*R*,*R*)-Tröger's base of *meso*-**13**, respectively, agreeing well with the X-ray structure. The measured ROESY cross peaks for hydrogen atoms at C1″ and C2″ to aromatic hydrogen atoms at C4 and C7 are in accordance with this geometry (see Figures S30−31, SI).

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Notably, macrocycle **13** is an uncommon example of crown ether analogues of TB.[23] It is also structurally similar to "Trögerophanes"[24] and a bis(*endo*,*endo*-dihydroxymethyl)dibenzobicyclo[3.3.1]-nonane crown ether.[25] These compounds show interesting recognition properties as receptors for benzenoid and alicyclic systems in aqueous solvents[24a,b] and are useful as chiral resolving reagents in phase-transfer systems,[25b] and as potential enzyme models.[24c]

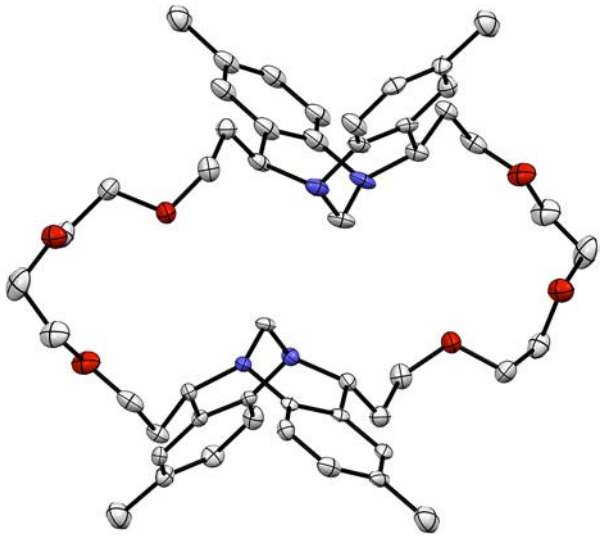

Figure 2. ORTEP representation of the crystal structure of *meso*-**13**. H-atoms have been removed for clarity.

Knowledge of these facts led to the examination of the cation recognition properties of *meso*-**13**, both in colorimetric phase transfer and in ESI-MS screening protocols,[26] which included 19 metal and ammonium salts (see SI). In the colorimetric phase transfer screening, no evidence for interactions between the salts and *meso*-**13** was found with the possible exception for Fe^{3+}. In the gas phase ESI-MS screening, only interactions between Li^+, Na^+, and Cs^+, respectively, and *meso*-**13** were established. The lack of recognition properties of *meso*-**13** strongly suggests a closed cavity in the macrocycle resulting from its methylene bridge-to-bridge bis-TB conformation as a contributing factor.

In summary, taking advantage of the enhanced reactivity of twisted mono- and bis-amide TB analogues, *rac*-**6** and *rac*-**7**, we have synthesized the first *endo*-monosubstituted and *endo*,*endo*-disubstituted TB analogues, *rac*-**9** and *rac*-**11**, respectively.[21] The diol *rac*-**12**, readily available from *rac*-**11**, was converted into *meso*-**13**, a rare example of an "inverted" crown ether, exhibiting an unexpected methylene bridge-to-bridge bis-TB conformation in both the solid state and in solution. As evidenced by phase transfer and gas phase screening experiments, the methylene bridge-to-bridge conformation of *meso*-**13** hampers the recognition of a range of cations in solution. The chemistry leading to *rac*-**9** and *rac*-**11** is expected to be general, thereby providing an opportunity for the generation of a number of *endo*-substituted TB analogues whose application in supramolecular chemistry and catalysis may be anticipated. Modification of the design of macrocycle *meso*-**13**, in which both "closed" and "open" conformations are accessible, has potential for the construction of gated hosts.[27] Further results will be reported in due course.

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Supporting Information Available. Detailed experimental procedures, characterization data for all compounds (including relevant NMR spectra), and CIF files of compound *meso*-**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.