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# A Desymmetrization Route to Fused Tröger's Base Analogues: Synthesis, Isolation, and Characterization of the First Anti-Anti Diastereomer of a Fused Tris-Tröger's Base Analogue

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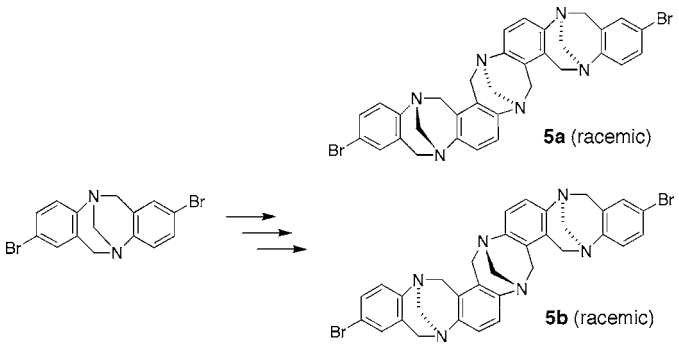
## ABSTRACT




**A desymmetrization route to fused Tröger's base analogues was developed. In this way, the synthesis of the first example of an anti-anti diastereomer of a fused tris-Tröger's base analogue was accomplished. The resulting compound 5b is a nonlinear symmetric regioisomer obtained from *p*-bromoaniline in 7% yield. The corresponding syn-anti diastereomer 5a was obtained in 4% yield.**

The recognition of unfunctionalized molecules by receptors takes place on concave surfaces and involves mainly non-directed solvophobic[1] effects and van der Waals interactions[2] between the surface and the molecule to be recognized. Particularly interesting are aromatic surfaces because of their rigidity and the possibility of additional interactions such as aromatic stacking[3] and cation−$\pi$ interactions[4] between the surface of the receptor and the ligand, the latter interaction, however, only for more functionalized ligands. One synthetic molecule containing a chiral rigid aromatic concave surface is Tröger's base, 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine,[5] obtained by the condensation of methylal and *p*-toluidine in concentrated hydrochloric acid. Analogues of Tröger's base have been used as synthetic receptors because of their aromatic cavity and the possibility to anchor recognition elements to the skeleton in a controlled spatial orientation.[6]

In a quest for receptors for relatively unfunctionalized molecules, Wilcox has extended the aromatic surface of Tröger's base by fusing the methano-diazocine core with two

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bicyclic aromatic building blocks to form chiral molecular tweezers.[7] This line has been followed by Pardo and by Král in the synthesis of chiral molecular tweezers consisting of fused bis-Tröger's base analogues.[8,9] Recently, Pardo and Král synthesized more extended analogues: fused tris-Tröger's bases (Figure 1).[10,11] There are three possible

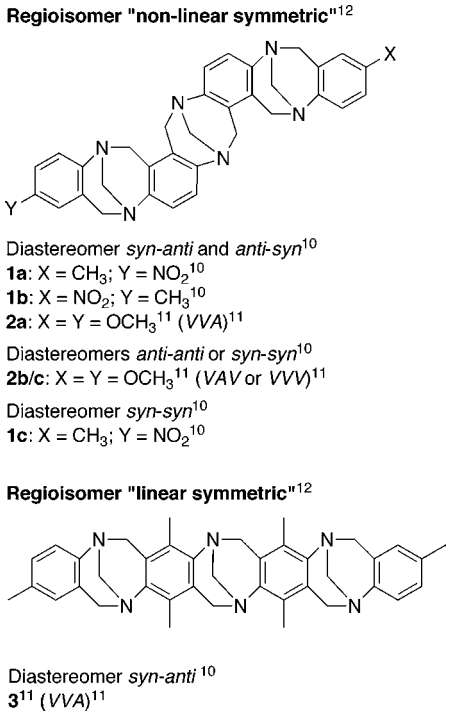


**Figure 1.** Previously synthesized fused tris-Tröger's base analogues.

regioisomers of fused tris-Tröger's base analogues, the "nonsymmetric", the "nonlinear symmetric", and the "linear symmetric" (as shown for the fused tris-Tröger's base dibromo-anlogues in Figure 2).[12] In addition, for each of these regiosisomers there are three different possible dia-

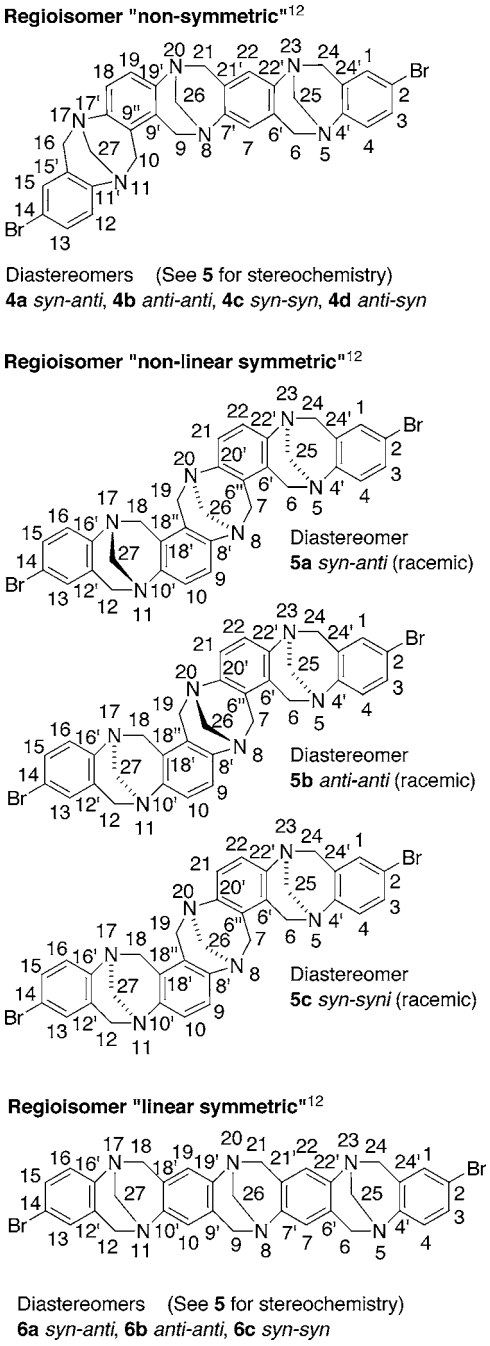


**Figure 2.** All possible regioisomers and diastereomers of fused tris-Tröger's base dibromo-analogues formed from **9**.

stereomers, syn-anti, anti-anti, and syn-syn. For the nonsymmetric regioisomer there is one additional possible diastereomer, the anti-syn (Figure 2). To date, two of the three possible regioisomers, the nonlinear symmetric and the linear symmetric have been obtained. Compounds **1**[10] and **2**[11] (Figure 1) are nonlinear symmetric. The fused Tröger's base analogue **1** was synthesized from *p*-nitroisatoic anhydride and *p*-toluidine in seven steps in a 10% overall yield, and analogue **2** was synthesized from *p*-methoxybenzene in five steps in an 18% overall yield. Compound **3**[11] (Figure 1) is linear symmetric and was isolated together with other

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(12) The name of the regioisomers refers to the symmetry of the carbon skeleton without substituents. See Figure 2 for all such regioisomers possible.

Tröger's base analogues in the condensation reaction betweeen HMT in TFA and a 1:1 mixture of 2,5-diamino-*p*-xylene and *p*-toluidine.[11] The presence of blocking methyl groups in the former starting material makes the linear symmetric regioisomer the only possible regioisomer of compound **3**. So far, the diastereomers of fused tris-Tröger's base analogues that have been synthesized, isolated, and unambigiously characterized are the syn-anti (anti-syn) isomers as in **1a**,**b**,[10] **2a**[11] (VVA[11]), and **3**[11] (VVA[11]), and the syn-syn as in **1c**.[10] However, the anti-anti diastereomer of a fused tris-Tröger's base analogue has not yet been prepared and characterized prior to the present work.[13]

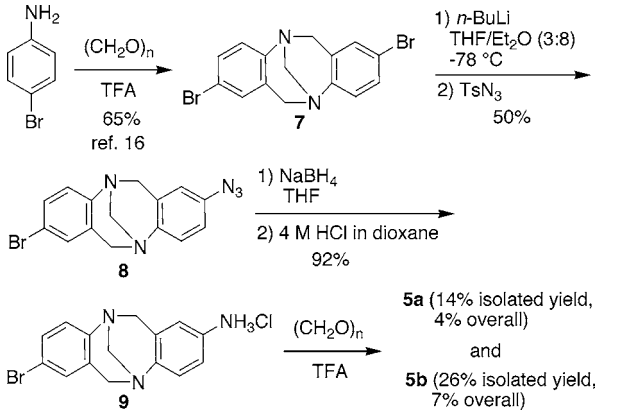
Although yielding the first fused tris-Tröger's base analogues, the synthetic methodologies leading to compounds **1**−**3** might be impossible to use for the controlled construction of higher oligomers of fused Tröger's base analogues, due to the difficulty in converting methoxy and methyl groups, present in the terminal positions of those compounds, into amino groups; these are necessary for the condensation with formaldehyde or its equivalents to generate a new Tröger's base framework.[14]

We now present a synthetic route to fused tris-Tröger's base dibromo analogues that uses desymmetrization of a $C_2$-symmetric 2,8-dibromo Tröger's base analogue as the key step. Its extension could constitute a general method for the synthesis of fused Tröger's base analogues of higher generations soon. Furthermore, we present the first example of an anti-anti fused tris-Tröger's base analogue.

The fused tris-Tröger's base dibromo analogues are presented in Figure 2. There are three possible regioisomers, the nonsymmetric, **4**, the nonlinear symmetric, **5**, and the linear symmetric **6**, and for each regioisomer there are several possible diastereomers as seen in Figure 2.[12] Especially interesting from the point of making artificial receptors are the syn-syn diastereomers because they constitute clips and tweezers and as such are ideal for the recognition of unfunctionalized molecules.[7b] The anti-anti diastereomers on the other hand have two small concave cavities that could be used for the recognition of two small molecules or representing two recognition points for a large molecule. If the fused tris-Tröger's base dibromo analogues are used as the building block for longer analogues, a receptor with multiple binding points can be envisaged. In addition, the wedged extended surfaces of the anti-anti diastereomers could be interesting as linear molecular rods and wires.[15]

The synthesis of the fused tris-Tröger's base dibromo analogues was carried out in four steps as outlined in Scheme 1 (see the Supporting Information for experimental details and characterization). Condensing *p*-bromoaniline with paraformaldehyde in TFA gave the $C_2$-symmetric 2,8-dibromo-substituted Tröger's base analogue **7** in 65% yield.[16] We have previously developed a desymmetrization protocol for the synthesis of asymmetrical 2,8-disubstituted Tröger's base analogues from **7**.[17] Thus, following a slightly modified protocol, **7** was subjected to single bromine−lithium exchange followed by quenching with $TsN_3$. This gave the 2-azido-8-bromo Tröger's base analogue **8** in 50% yield that after reduction with $NaBH_4$ and acidic workup resulted in the monoamino Tröger's base analogue **9** as its hydrochloride salt, in 92% yield. Compound **9** was reacted with paraformaldehyde in TFA and the fused tris-Tröger's base analogues **5a** and **5b** were isolated using extensive column chromatography and characterized using NMR spectroscopy as described below. In the best runs, **5a** was obtained in 14% yield[18] and **5b** in 26% yield (4 and 7% overall yield, respectively).

**Scheme 1.** Synthetic Route to **5a** and **5b**




It is worth noticing that the desymmetrization route described above for the synthesis of fused tris-Tröger's base analogues **5a** and **5b** could in its extension be a general route to fused oligo-Tröger's base analogues of higher generations: The dibromo compounds **5a** and **5b** could be converted to the corresponding monoamines using the same methodology as described above and in the next step being condensed with paraformaldehyde/TFA, alone, or together with another fused Tröger's base monoamino-monobromo analogue of a different generation. In this way, in principle, all possible oligo-fused Tröger's base dibromo analogues could be generated.

The structures of **5a**, $C_1$-symmetric, and **5b**, $C_2$-symmetric, were readily outlined from NMR data. (See the Supporting Information for NMR spectra.) Unique chemical shifts could be assigned to all nuclei in **5b**. In **5a**, the symmetrically placed aromatic carbons C-2 and C-14, C-12′ and C-24′, as well as C-10′ and C-22′ were not individually assigned. (See Figure 2 for the numbering of the atoms. In cases of symmetrically placed atoms, the discussion applies to both

(13) Král also isolated either of **2b** or **2c**.[11] Isomerization of **2a** and **2b**/**c** gave a mixture of three fused tris-Tröger's base analogues as identified by LC−MS, and according to Král, proving that all diasteromers of **2** can be obtained.

(14) Compound **1** can be used in one more condensation reaction with formaldehyde after the reduction of the nitro group to an amine.

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(18) The fraction containing **5a** consisted also of approximately 2 mol % of **5b**.

atoms and they are addressed by putting one of the atoms in parentheses.) In the HMBC spectra, all carbons in the terminal aromatic rings were correlated from the aromatic protons as well as from methylene protons H-24(12), H-25(27), and H-6(18). Protons H-6x(18x) and H-6n(18n), using x for *exo* and n for *endo*, correlated to no other carbon in the terminal aromatic ring than C-4′(16′) and thus established the position of the quaternary carbon C-4′(16′) and indirectly that of C-24′(12′). In the NOESY spectra, correlations between H-1(13) and the methylene protons H-24x(12x) and H-24n(12n) is in accordance with distances expected for benzylic protons staggering an aromatic proton. The aromatic proton H-4(16), on the other hand, is farther in distance to the methylene protons H-6(18) and can only be expected to receive NOE from the H-6n(18n), as was observed in our NOESY spectra, and not from the H-6x(18x). NOESY correlations from H-25(27) to H-24x(12x) and H-6x(18x), further established the relative orientation of the nuclei considered so far.

To determine which regioisomers were formed in **5a** and **5b**, we used the same approach as has been applied to fused bis- and tris-Tröger's base analogues previously.[8,11] The absence of NOESY correlation from the methylene protons H-6(18) in **5a** and **5b** to protons in the inner aromatic rings, H-21(9) and H-22(10), strongly indicated that the nonlinear symmetric regioisomer was at hand (Figure 3). NOESY spectra of **5a** also showed correlation between H-7x(19x) and H-26, and between H-7n(19n) and the aromatic H-9(21), a doublet coupled to H-10(22) with a coupling constant of 8.7 Hz. The latter observation further established the proposed nonlinear symmetric regioisomeri. The expected NOESY correlation between H-24n(12n) and H-22(10) was also observed. The diastereomer of **5a** must be syn-anti, which is the only $C_1$-symmetric diastereomer of a nonlinear symmetric regioisomer of a fused tris-Tröger's base analogue (Figure 2).

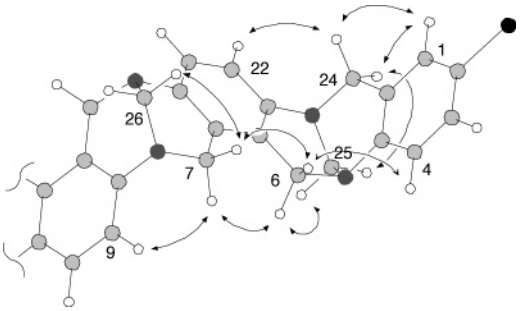


**Figure 3.** NOESY correlations of **5b** outlined with curly arrows. Only a part of **5b** is shown.

The diastereomer of the $C_2$-symmetric **5b** could have been either syn-syn or anti-anti, but was proven to be anti-anti from the NOESY spectra. An observed NOESY correlation between H-6x(18x) and H-7n(19n) and between H-7x(19x) and H-6n(18n) in **5b** proves that the diastereoisomer is anti-anti (Figure 3). The inter nuclear distances H-6x(18x) to H-7n(19n) and H-7x(19x) to H-6n(18n) are much shorter than the *exo* to *exo* and *endo* to *endo* distances in the global energy minimum conformation of an anti-anti diastereomer of a nonlinear symmetric regioisomer equivalent to **5b**. The reverse is true for the syn-syn diastereomer, in the case of which an NOE of zero to negative intensity would be expected between the mentioned *exo* and *endo* protons. Thus the observed NOESY correlations between H-6x(18x) and H-7n(19n) and between H-7x(19x) and H-6n(18n) are taken as conclusive evidence for the anti-anti diastereomer in **5b** (Figure 2).

Finally, compounds **5a** and **5b** were subjected to an isomerization study. It has been demonstrated that optically pure Tröger's base racemizes under moderately acidic conditions.[19] Thus, stirring **5a** and **5b** separately in TFA for several days at r.t gave in the first case a mixture of **5a** and **5b** in an approximately 4:1 ratio and in the second case, only **5b**. This proved as expected that the anti-anti diastereomer **5b** is the thermodynamically more stable of the two isolated isomers.

In conclusion, we have synthesized, isolated and characterized the first example of an anti-anti diastereomer of a fused tris-Tröger's base analogue, the dibromo analogue **5b** as well as a syn-anti diastereomer **5a**, both as nonlinear symmetric regioisomers. The synthetic route involving desymmetrization of Tröger's base dibromo-analogues could in principle be used to synthesize fused Tröger's base dibromo-analogues of higher genererations. We have also proven that the anti-anti isomer **5b** is the thermodynamically more stable of the two isolated isomers.

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**Supporting Information Available:** Experimental procedures and characterization data (including NMR spectra in relevant cases) for compounds **5a**,**b**, **7**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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