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Synthetic Routes to Linear Oligo-Tröger's Bases

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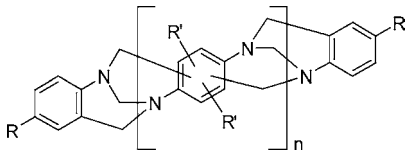
ABSTRACT



Derivatives of Tröger's base (TB) have played important roles in receptor construction due to their rigid V-shape. A new class of these compounds are the oligo-TBs, which can function as cavitands. Herein, we describe both stepwise and one-step (oligomerization) methods suitable for the preparation of linear oligo-TBs.

In 1887, Julius Tröger described[1] the condensation reaction of *p*-toluidine with formaldehyde leading to the formation of a unique structure containing nitrogen. It does not invert its tetradric arrangement of moieties and thus provides a persistent chiral center. The compound is known today as Tröger's base (TB). Many years later, TB derivatives found important applications in supramolecular chemistry[2] and drug development.[3] Their popularity stems from their rigid V-shape (80−120°) and their inherent chirality. Both of these structural features were utilized toward the construction of receptors for achiral[4] and chiral[5] analytes.

New uses for TB derivatives were made possible by the finding that more than one TB unit can be attached to a central benzene ring. Thus, bis-TB can be prepared[6,7] as a mixture of boatlike (*VV*-bis-TB) and chairlike (*VA*-bis-TB) diastereoisomers, which are mutually interconvertible under acidic conditions. Recently, we have shown that a structure with benzene substituted by three TB units can be prepared.[7] Oligo-TBs with more than two TB units around a central unit can be called calix-TB. Each of these unique oligo-TBs can function as a pH-sensitive cavity-containing scaffold for the construction of novel receptors.

In this article, we present a stepwise preparation of a new group of oligo-TB derivatives, the linear oligo-TBs. They have structural TB units that are interconnected, affording a chain structure. Additionally, for the first time, a one-pot preparation of linear oligo-TBs via an oligomerization reaction is described.

A step-by-step synthesis of linear oligo-TBs has several inherent limitations. The main drawback is the limited availability of suitable starting compounds. A five-step preparation can be designed for the synthesis of tris-TBs **1** (Scheme 1).

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(2) (a) Bag, B. G. *Curr. Sci.* **1995**, *68*, 279−288. (b) Demeunynck, M.; Tatibouet, A. Recent Development in Tröger's Base Chemistry. In *Progress in Heterocycles Chemistry*; Gribble, G. W., Cilchrist, T. L., Eds.; Pergamon: Oxford, UK, 1999; pp 1−20.
(3) (a) Baldeyrou, B.; Tardy, C.; Bailly, C.; Colson, P.; Houssier, C.; Charmantray, F.; Demeunynck, M. *Eur. J. Med. Chem.* **2002**, *37*, 315−322. (b) Johnson, R. A.; Gorman, R. R.; Wnuk, R. J.; Crittenden, N. J.; Aiken, J. W. *J. Med. Chem.* **1993**, *36*, 3202−3206. (c) Bailly, C.; Laine, W.; Demeunynck, M.; Lhomme, J. *Biochem. Biophys. Res. Commun.* **2000**, *273*, 681−685.
(4) (a) Goswami, S.; Ghosh, K.; Dasgupta, S. *J. Org. Chem.* **2000**, *65*, 1907−1914. (b) Hansson, A. P.; Norrby, P.-O.; Warnmark, K. *Tetrahedron Lett.* **1998**, *39*, 4565−4568. (c) Wilcox, C. S.; Greer, L. M.; Lynch, V. *J. Am. Chem. Soc.* **1987**, *109*, 1865−1867.
(5) (a) Allen, P. R.; Reek, J. N. H.; Try, A. C.; Crossley, M. J. *Tetrahedron: Asymmetry* **1997**, *8*, 1161−1164. (b) Webb, T. H.; Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 8554−8555. (c) Wilcox, C. S.; Adrian, J. C.; Webb, T. H.; Zawacki, F. J. *J. Am. Chem. Soc.* **1992**, *114*, 10189−10197.
(6) (a) Pardo, C.; Sesmilo, E.; Gutierrez-Puebla, E.; Monge, A.; Elguero, J.; Fruchier, A. *J. Org. Chem.* **2001**, *66*, 1607−1611. (b) Mas, T.; Pardo, C.; Salort, F.; Elguero, J.; Torres, M. R. *Eur. J. Org. Chem.* **2004**, 1097−1104.
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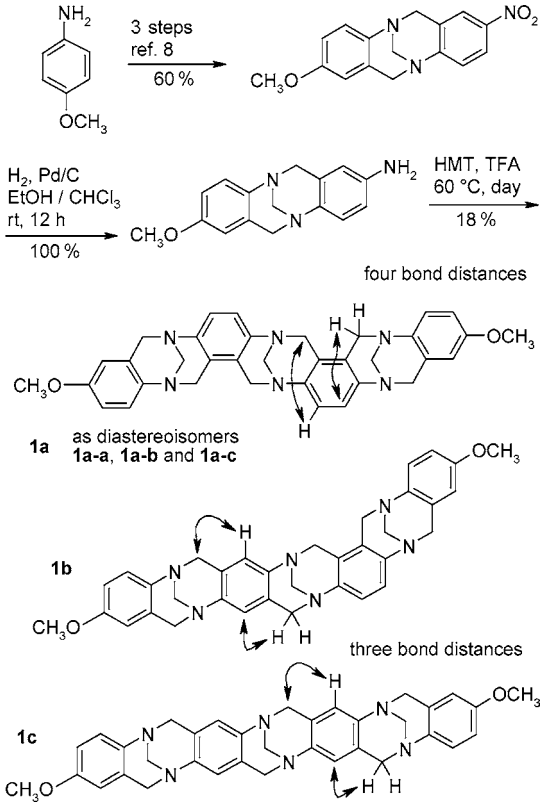
Scheme 1. Step-by-Step Preparation of Tris-TBs **1a**



Theoretically, in the final step, three regioisomers **1a**, **1b**, and **1c** can be formed (each as a mixture of four racemic diastereoisomers in the case of **1b** (*VVV*-, *VVA*-, *VAA*-, and *VAV*-) or three in the cases of **1a** and **1c**, in which the *VAA*-is, due to symmetry, an enantiomer of *VVA*-, vide infra). We isolated two tris-TBs (**1a-a** and **1a-b**) in an overall preparative yield of 11%. In addition, we found that all tris-TBs **1a** can be converted into the two other respective tris-TB diastereoisomers (LC-MS). This phenomenon is associated with the well-known racemization[6a,8] of TB units. This proves that only one of three possible regioisomers, **1a**, **1b**, and **1c**, was formed as a mixture of diastereoisomers **1a-a** and **1a-b**. This strong selectivity in the preparation might be surprising; however, it is consistent with current knowledge in this area. It has been recently found that 1,2,3,4-substituted benzene derivatives are formed exclusively. No 1,2,4,5-derivatives have been observed to date.[6,7] The above mentioned facts lead to the speculation that regioisomer **1a** is the isolated product. In addition, we studied the diastereoisomers of **1a** by NMR and assigned the structure on the basis of a missing cross-peak between the CH carbon atoms of the central benzene ring and the CH_2 proton atoms of TB units (see Scheme 1). In addition, there was a missing cross-peak between the CH proton atoms of the central benzene ring and the CH_2 carbon atoms of TB units in the gHMBC (gradient-enhanced heteronuclear multiple-bond correlation) NMR spectrum. As shown in Scheme 1, both regioisomers **1b** and **1c** have three bond distances to the aforementioned atoms. Thus, **1b** and **1c** would be expected to exhibit cross-peaks.

As the number of TB units in one molecule increases, there is a need for an easy description of the relative configuration of oligo-TB diastereoisomers that is not dependent on the nature of substituents as in (*R*,*S*)-systems. In addition, the chirality on nitrogen of a TB unit is controlled by the chirality of the second nitrogen of the unit; thus, only a one-letter assignment should be sufficient. We propose a description consistent with traditional labeling of the TB shape as the V-shape using letters *V* and *A*. By this notification, bis-TB in chair (anti-) "conformation" can be assigned as *VA*-bis-TB (or *AV*-bis-TB for the enantiomer) and the boat (syn-) "conformation" as *VV*-bis-TB (or *AA*-bis-TB for the enantiomer). The possible diastereoisomers of linear tris-TBs are shown in Figure 1. Note that symmetrically substituted linear tris-TBs can be found, due to symmetry, as only three diastereoisomers.

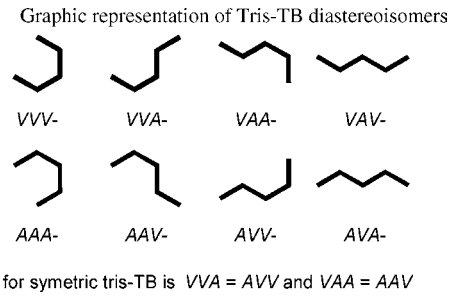


Figure 1. Graphic representation of Tris-TB diastereoisomers.

Thus, we have prepared, via a step-by-step method, the symmetric tris-TB **1a-a** (configuration *VVV* or *VAV*) as a major diastereoisomer of **1a** as well as the asymmetric tris-TB **1a-b** with the configuration *VAA*. The second symmetric isomer **1a-c** was prepared by racemization of **1a-a** or **1a-b**. It was detected by LC-MS. The three diastereoisomers of **1a** were also characterized by NMR.[9]

It is clear that the preparation of tris-TBs different from **1a**, or the preparation of tetra-TBs or higher oligo-TBs, would be tedious. A step-by-step synthesis would be time-consuming and expensive. Moreover, our overall preparative yield (11%) is low and makes the oligo-TB scaffolds labor-

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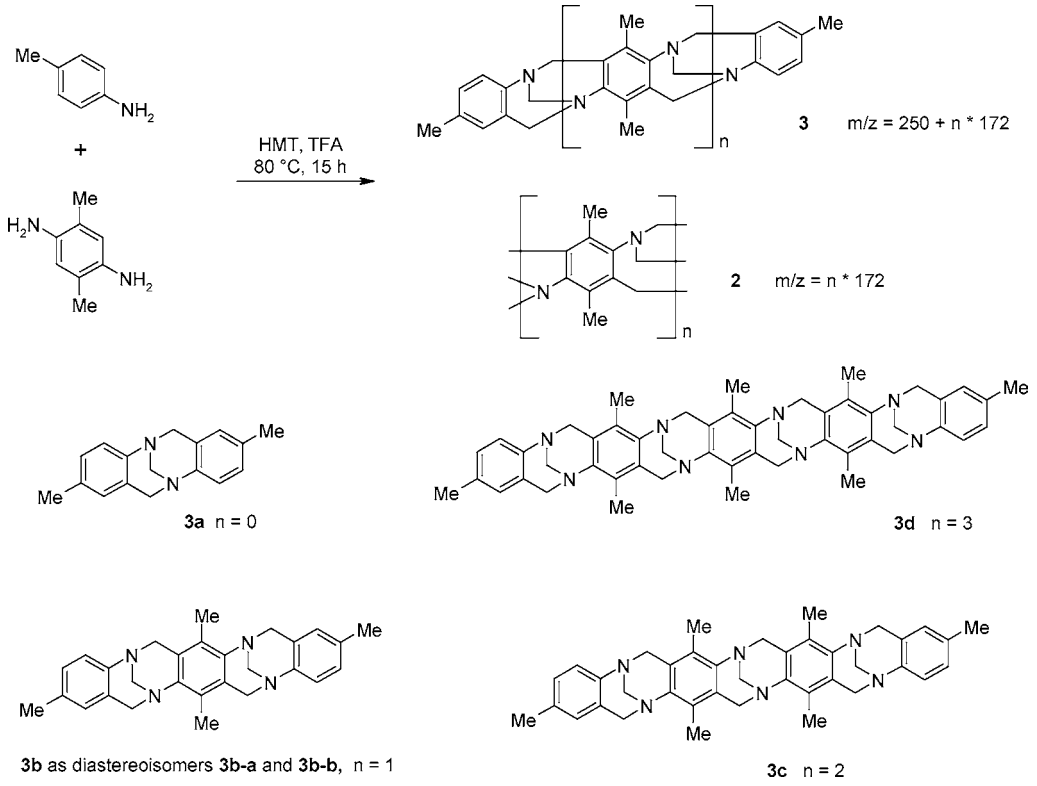
(9) **Tris-TB 1a-a, isomer *VVV* or *VAV*:** ^{1}H NMR (in $CDCl_3$) δ 7.06 (2H, d, 8.8), 6.99 (2H, d, 8.8), 6.95 (2H, d, 8.8), 6.75 (2H, dd, 8.8, 3.0), 6.43 (2H, d, 3.0), 4.62 (2H, d, 16.7), 4.38 (2H, d, 16.8), 4.18 (2H, d, 16.7), 4.13 (2H, dd, 13.1, 2.6), 4.11 (2H, d, 17.2), 4.06 (2H, s), 3.83 (2H, d, 16.6), 3.78 (2H, dd, 16.9, 1.5), 3.71 (6H, s); overall preparative yield 7%. **Tris-TB 1a-b, isomer *VVA*:** ^{1}H NMR (in $CDCl_3$) δ 7.04 (1H, d, 8.5), 7.02 (1H, d, 8.8), 6.99 (1H, d, 8.8), 6.96 (1H, d, 8.8), 6.86 (2H, s), 6.74 (1H, dd, 8.7, 2.9), 6.70 (1H, dd, 8.7, 2.9), 6.42 (1H, d, 2.5), 6.41 (1H, d, 2.5), 4.64 (1H, d, 16.8), 4.60 (1H, d, 16.8), 4.35 (1H, d, 17.1), 4.33 (1H, d, 17.1, 1H), 4.27 (2H, d, 17.3), 4.02−4.26 (8H, m), 3.81 (1H, d, 16.8), 3.79 (1H, d, 17.1), 3.78 (2H, d, 16.8), 3.70 (3H, s), 3.68 (3H, s); overall preparative yield 4%. **Tris-TB 1a-c, isomer *VVV* or *VAV*:** ^{1}H NMR (in $CDCl_3$; only noncovered characteristic signals in the mixture after racemization) δ 6.65 (2H, dd, 8.8, 2.8), 6.34 (2H, d, 2.7), 3.63 (6H, s).

Scheme 2. Oligomerization Reaction



intensive by the above-described multistep synthesis. Hence, a one-step preparation would be preferable even with a lower isolated yield. This motivated us to develop an alternative synthetic protocol for this class of compounds. We applied the oligomerization of a diamine to forming TB units. As a suitable candidate, we chose commercially available 1,4-diamino-2,5-dimethylbenzene, which gives only one route to bis-TB unit formation, thus limiting byproducts.

On the basis of molecular modeling, we predicted a possibility of forming cyclic pentakis-TB (**2**, $n = 5$) or hexakis-TB (**2**, $n = 6$). Unfortunately, we did not observe any traces of cyclo-TBs **2** in the reaction mixture of 1,4-diamino-2,5-dimethylbenzene with urotropine in TFA by MS analysis. The mass spectra showed a series of peaks differing by $m/z = 172$, which was expected (Scheme 2). This suggests the possibility of their formation via employment of an appropriate template.

Second, we tried the oligomerization of the diamine in the presence of *p*-toluidine. This led to the expected mixture of oligo-TBs **3** (Scheme 2). To date, we have isolated Tröger's base **3a** (5% yield), both diastereoisomers of bis-TB[10] **3b** (3% yield of **3b-a** and 7% yield of **3b-b**), and an asymmetric diastereoisomer of tris-TB[11] *VAA*-**3c** (1% yield) from the reaction mixture. In addition, the MS analysis shows the formation of tetra-TB **3d** ($n = 3$) and penta-TB **3e** ($n = 4$) as trace products. We have also isolated formylated and methylated derivatives of TB **3a** and their identification is in progress. The overall yield of Tröger's bases **3** (>11%) is promising. The oligomerization is thus an attractive alternative for oligo-TB preparations. We found that the degree of oligomerization can be controlled by the ratio of amine:diamine and by the order of reactant addition. Optimization of the oligomerization reaction aimed at obtaining higher oligo-TBs ($n > 2$), improving yields and decreasing side-products is in progress.

In summary, we have prepared linear tris-TBs by a step-by-step synthesis. We have additionally prepared oligo-TBs by one-step oligomerization and isolated linear bis- and tris-TBs from the reaction mixture. We have proven that tetra-TBs or higher TBs can be prepared by this synthetic protocol.

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(10) **Bis-TB 3b-a:** HRMS (FAB$^+$) calcd for $C_{28}H_{31}N_4$ (M + H) 423.2549, found 423.2558; ^{1}H NMR (in $CDCl_3$) δ 6.96 (2H, d, 8.1), 6.87 (2H, dd, 8.1, 1.6), 6.57 (2H, br s), 4.44 (2H, d, 16.6), 4.40 (2H, d, 16.7), 4.32 (2H, d, 12.5), 4.16 (2H, d, 12.5), 3.92 (2H, d, 16.6), 3.68 (2H, d, 16.7), 2.12 (6H, s), 2.02 (6H, s). **Bis-TB 3b-b:** HRMS (FAB$^+$) calcd for $C_{28}H_{31}N_4$ (M + H) 423.2549, found 423.2530; ^{1}H NMR (in $CDCl_3$) δ 7.06 (2H, d, 7.9), 6.96 (2H, dd, 8.3, 2.0), 6.70 (2H, br s), 4.46 (2H, d, 16.8), 4.33 (2H, d, 16.2), 4.20 (2H, dd, 12.5, 1.6), 4.05 (2H, dd, 12.5, 1.6), 4.05 (2H, d, >16, covered), 3.79 (2H, d, 16.8), 2.22 (6H, s), 2.10 (6H, s).

(11) **Tris-TB *VVA*-3c:** HRMS (FAB$^+$) calcd for $C_{39}H_{43}N_6$ (M + H) 595.3549, found 595.3573; ^{1}H NMR (in $CDCl_3$) δ 7.05 (1H, d, 8.1), 7.03 (1H, d, 8.0), 6.99−6.93 (2H, m), 6.69 (1H, br s), 6.64 (1H, br s), 4.52 (1H, d, 16.6), 4.51 (1H, d, 16.8), 4.48 (1H, d, 16.8), 4.41 (2H, br d, 17.0), 4.30−4.06 (8H, m), 4.01 (1H, d, 16.7), 3.83 (1H, d, 16.8), 3.75 (1H, d, 16.8), 3.72 (2H, d, 17.0), 2.21 (3H, s), 2.20 (3H, s), 2.14 (3H, s), 2.12 (3H, s), 2.09 (3H, s), 2.04 (3H, s).

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Supporting Information Available: ^{1}H and ^{13}C NMR and $^{1}H-^{13}C$ gHMBC for **1a-a**, **1a-b**, **3b-a**, and **3b-b**, ^{1}H and ^{13}C NMR for *VAA*-**3c**, and LC-MS and ^{1}H NMR for a mixture of **1a-a**, **1a-b**, and **1a-c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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