Synthetic Routes to Linear Oligo-Tröger's Bases

Bohumil Dolenský, Martin Valík, David Sýkora, and Vladimír Král*

Department of Analytical Chemistry, Institute of Chemical Technology, Prague, Technická 5, 166 28 Praha 6, Czech Republic

kralv@vscht.cz

Received October 11, 2004

ORGANIC LETTERS 2005 Vol. 7, No. 1 67-70

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 described¹ 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 chemistry² and drug development.³ Their popularity stems from their rigid Vshape (80–120°) and their inherent chirality. Both of these structural features were utilized toward the construction of receptors for achiral⁴ and chiral⁵ analytes.

10.1021/oI047902f CCC: \$30.25 © 2005 American Chemical Society Published on Web 12/15/2004

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).

⁽¹⁾ Tröger, J. J. Prakt. Chem. 1887, 36, 225-245.

^{(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.;

^{(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.

⁽⁷⁾ Valík, M.; Dolenský, B.; Petříčková, H.; Král, V. Collect. Czech. Chem. Commun. 2002, 67, 609–621.



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 VAAis, 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 1,2,3,4substituted 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 CH₂ 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 CH₂ carbon atoms of TB units in the gHMBC (gradient-enhanced heteronuclear multiple-bond

(8) (a) Prelog, V.; Wieland, P. *Helv. Chim. Acta* 1944, 27, 1127–1134.
(b) Greenberg, A.; Molinaro, N.; Lang, M. *J. Org. Chem.* 1984, 49, 1127–1130.

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 (svn-) "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-

⁽⁹⁾ **Tris-TB 1a-a, isomer** *VVV* or *VAV*: ¹H NMR (in CDCl₃) 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*: ¹H NMR (in CDCl₃) δ 7.04 (1H, d, 8.5), 7.02 (1H, d, 8.8), 6.99 (1H, d, 8.8), 6.96 (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*: ¹H NMR (in CDCl₃; 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).



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 1,4diamino-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-TB¹⁰ **3b** (3% yield of **3b-a** and 7% yield of **3b-b**), and an

asymmetric diastereoisomer of tris-TB¹¹ 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 stepby-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.

Acknowledgment. This work was supported by grants from the Ministry of Education, Youth and Sports of the Czech Republic (Grant CEZ: MSM 223400008), the Grant Agency of the Czech Republic (Grants 203/02/0933 and 203/ 02/0420), the EU (Grant QLRT-2000-02360 and CIDNA)

⁽¹⁰⁾ **Bis-TB 3b-a:** HRMS (FAB⁺) calcd for $C_{28}H_{31}N_4$ (M + H) 423.2549, found 423.2558; ¹H NMR (in CDCl₃) 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; ¹H NMR (in CDCl₃) 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, 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; ¹H NMR (in CDCl₃) 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).

to V.K., and the Grant Agency of the Czech Republic (203/ 03/D049) to B.D.

Supporting Information Available: ¹H and ¹³C NMR and ¹H $^{-13}$ C gHMBC for **1a-a**, **1a-b**, **3b-a**, and **3b-b**, ¹H and

¹³C NMR for *VAA*-**3c**, and LC-MS and ¹H 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.

OL047902F