

METHODOLOGY FOR EASY ACCESS TO LARGE SIDEWALL BIS-TRÖGER'S BASES

Martin HAVLÍK¹, Vladimír KRÁL² and Bohumil DOLENSKÝ^{3,*}

Department of Analytical Chemistry, Institute of Chemical Technology, Prague,
Technická 5, 166 28 Prague 6, Czech Republic; e-mail: ¹ havlikm@vscht.cz, ² kralv@vscht.cz,
³ dolenskb@vscht.cz

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4,6-Bis(bromomethyl)-*N*¹,*N*³-bis(*tert*-butoxycarbonyl)benzene-1,3-diamine is introduced as a general starting compound for the preparation of bis-Tröger's base (bisTB) derivatives in excellent yield in just two steps. The synthetic sequence includes treatment of the above-mentioned protected diamine with an arylamine followed by in situ deprotection and the final bisTB-forming reaction. This sequence allows synthesis of bisTB derivatives, which are not accessible by known procedures. The described approach is a general new method for the preparation of bisTB derivatives from "troegerable" arylamines.

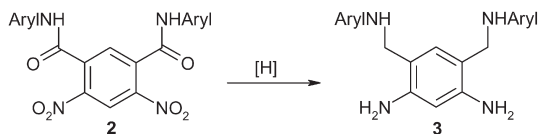
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Bis-Tröger's bases derivatives **1** (bisTB) are compounds that contain a central aromatic ring fused to two 1,5-methano-1,5-diazocines (TB units) containing annelated aromatic sidewalls. Typical TB derivatives¹ exhibit rigid V-shapes, causing bisTBs to exist as *syn*- and *anti*-diastereoisomeric forms^{2–4}. The *syn*-bisTBs embody molecular tweezers. TB derivatives¹, can isomerize in acidic media, thereby allowing, in contrast to common molecular tweezers, the possibility of switching between a tweezer and non-tweezer form^{2,3b,3c,4}. In addition, Lenev et al.⁵ recently reported that the isomerization of TB derivatives, i.e. the stability of TB derivatives in acidic condition, could be effectively tuned by the judicious choice of moieties proximal to nitrogen. The inherent chirality of TB derivatives¹ also bolsters interest in bisTB molecular architectures.

General methods for bisTB preparation are lacking. One synthetic strategy is based on the preparation of each TB unit in discreet steps^{2a,2b,2d,3b,4}. The most direct route to bisTBs is a one-pot preparation, i.e., the mixed "troegeration" of an aromatic amine and diamine^{3b,3c}. The low yield and uncontrollable regioselectivity are restrictions of this approach. Thus, new

approaches, including the preparation of useful intermediates, are of interest^{2c,3a,3c,3d}.

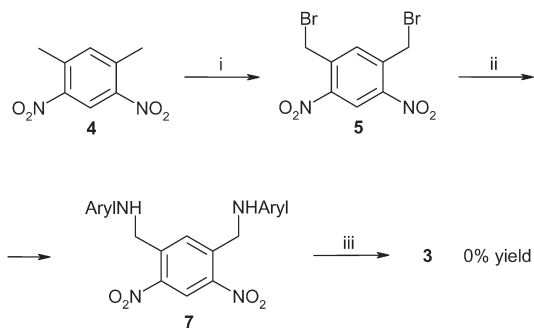
In a previous investigation, the reduction of amides **2** to tetraamines **3** (the precursors for final “troegeration”) (Scheme 1) had unexpected limitations. In the cases of aryls such as anthracene, fluorene and pyrene, the reduction was troublesome^{3d}.



SCHEME 1

The critical step in amide protocol of bisTB preparation

As an alternative route to tetraamines **3** we started from dinitroxylylene **4** (Scheme 2). Bromation afforded **5**, which, after treatment with excess of arylamines **6**, gave dinitrodiamines **7** in yields of about 90%. Unfortunately, attempts⁶ at nitro group reduction to the expected tetraamines **3** led to CH₂-NH-Aryl cleavage. Arylamines **6** were formed as the main products. Thus, the problems with amide reduction are a result of the low stability of targeted tetraamines **3** against reducing agents and not due to the amide carbonyls as reported previously⁷.

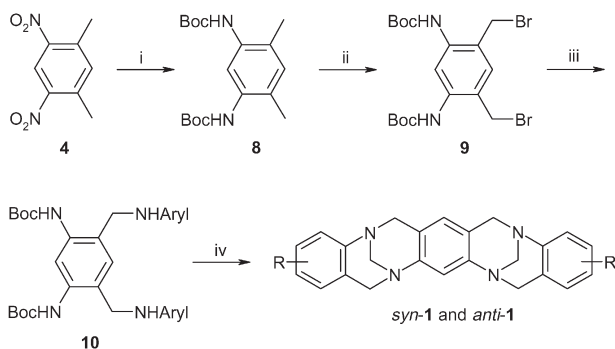


(i) NBS, **5** (20%); (ii) arylamine **6** (series: **a** naphth-2-yl, **b** anthracen-2-yl, **c** fluoren-2-yl, **d** pyren-1-yl, **e** anthracen-1-yl), **7b** (83%), **7c** (87%), **7d** (98%); (iii) reduction caused decomposition⁶

SCHEME 2

Nitrobromide synthetic pathway to bisTB.

To bypass the reduction step, the nitro groups of dinitroxylylene **4** are reduced initially to amino groups, which are protected by reaction with Boc_2O to give diamine **8** (Scheme 3). The protecting was performed to preclude potential complications with reactivity and selectivity in the following reactions. The bocylation after reduction gave better yields than bocylation during the reduction. The bocyl was chosen due to its removing in acidic condition and uninterfering byproducts, thus, in situ deprotection during the “troegeration” can be achieved. Bromination of **8** furnished diaminodibromide **9** in good yield. The purification of **9** by chromatography led to decomposition. Thus **9** was used crude (purity 80–90% by NMR) in the next reaction. The treatment of **9** with excess **6** gave corresponding tetraamines **10** in moderate yields. Dissolving tetraamines **10** in trifluoroacetic acid (TFA) gave desired tetraamines **3**. The experiment in NMR tube shown that the debocylation of tetramine **10d** in TFA-d_1 is finished in about 5 min at 23 °C, and formed tetramine **3d** in TFA-d_1 is stable for at least 24 h. Addition of paraformaldehyde started the “troegeration” process. This gave expected bisTBs in excellent yields not only in the case of naphthalene-2-amine derived bisTB **1a** (isolated 41% of isomer **1a-A** and 53% of isomer **1a-B**), which was prepared also by the amide-based protocol^{3d} (7%; so low yield cannot be explained by the small contamination of the starting tetramine **3a** with naphthalene-2-amine), but also in the case of anthracene-2-amine derived bisTB **1b** (isolated 36% of isomer **1b-A** and



(i) Pd/C , H_2 , Boc_2O , 84%; (ii) NBS, 82%; (iii) arylamine **6** (see footnote of Scheme 2), **10a** (48%), **10b** (30%), **10c** (43%), **10d** (16%), **10e** (11%); (iv) paraformaldehyde, TFA, **1a** (94%), **1b** (76%), **1c** (82%), **1d** (~0%), **1e** (~0%)

SCHEME 3
Aminobromide synthetic pathway to bisTB

40% of isomer **1b-B**) and fluorene-2-amine derived bisTB **1c** (isolated 44% of isomer **1c-A** and 38% of isomer **1c-B**), which are cannot be readily prepared via the corresponding amides^{3d}. It should be noted both diastereoisomers of bisTBs were isolated and separated, however, the determination of the relative configuration is due to symmetry impossible base on NMR, thus, the X-ray diffraction analyses will be necessary. Unfortunately, pyrene-1-amine derived bisTB **1d** and anthracene-1-amine derived bisTB **1e** were not isolated (see Experimental) from the corresponding tetraamines **10** via our new methodology.

Relatively simpler Tröger's base derivatives¹ are readily formed from precursors such as naphthalene-2-amine (67% yield)⁸ or anthracene-2-amine (30% yield); additionally, the tetraamines **10a** and **10b** give the expected bisTBs **1a** and **1b**, respectively. In contrast, "untroegerable" arylamines, such

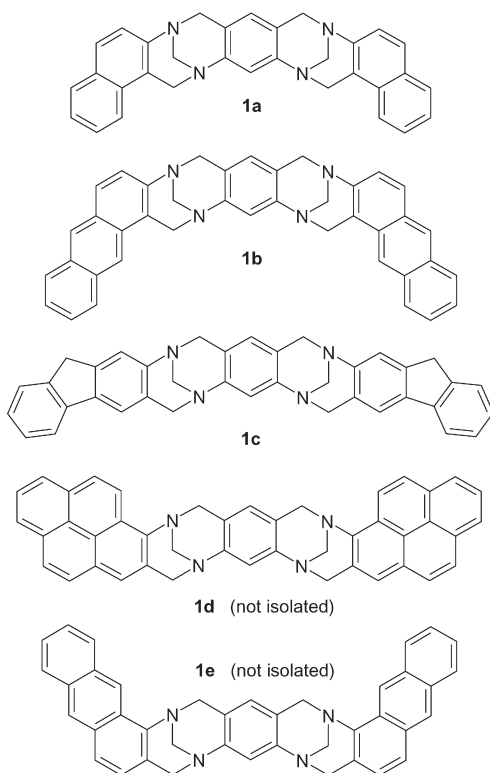


CHART 1
BisTB derivatives

as naphthalene-1-amine, anthracene-1-amine or pyrene-1-amine, do not afford TB derivatives. Thus, it is not surprising bisTB derivatives are not formed from the corresponding tetraamines **10d** and **10e** (Chart 1).

In conclusion, we have presented a new aminobromide-based protocol, which overcomes the reduction issues inherent in prior methodology. It enables the preparation of derivatives, which are not accessible via previous protocols. Thus, the first preparations of bisTB derivatives with sidewalls as large as anthracene are presented. The aminobromide protocol appears useful at least for bisTB derivatives with “troegerable” arylamines as sidewalls. The synthetic methods described herein should be readily applicable to analogous architectures beyond those wherein the central building block is benzene.

EXPERIMENTAL

Commercial solvents for chromatography were purified by distillation. NMR spectra were obtained with Varian Gemini 300 HC (300.077 MHz for ^1H and 75.460 MHz for ^{13}C) at 23 °C in deuteriochloroform CDCl_3 or deuterated dimethyl sulfoxide $\text{DMSO}-d_6$. Chemical shifts δ are presented in ppm, coupling constants J in Hz. Mass spectra were obtained by fast atom bombardment (FAB) with a VG Analytical ZAB-EQ spectrometer. Thin-layer chromatography was performed on TLC-sheet (Merck) with UV detection at 254 nm.

Preparation of Dibromide **5**

1,3-Dimethyl-4,6-dinitrobenzene (2.0 g, 10.2 mmol) was treated with *N*-bromosuccinimide (NBS, 3.8 g, 21.4 mmol) and dibenzoyl peroxide (DBP, 0.02 g, 83 μmol) in CCl_4 (200 ml) at reflux for 4 h. Then next portions of NBS (3.8 g) and DBP (0.02 g) were added and the reaction mixture was kept at reflux overnight. Precipitated solid was filtered off and washed with CCl_4 . The filtrate was evaporated to dryness in vacuo and dibromide **5** (0.71 g, 20%) and monobromide **13** (0.48 g, 17%) were isolated by column chromatography (CHCl_3 –hexane 2:1).

1,5-Bis(bromomethyl)-2,4-dinitrobenzene (5): ^1H NMR (CDCl_3): 8.69 s, 1 H; 7.80 s, 1 H; 4.80 s, 4 H. ^{13}C APT NMR (CDCl_3): 146.83 (C), 138.33 (C), 136.97 (CH), 123.09 (CH), 26.76 (CH_2). HRMS (EI^+): for $\text{C}_8\text{H}_6\text{Br}_2\text{N}_2\text{O}_4$ [M^+] calculated: 351.8694, 353.8671, 355.8653; found: 351.8681, 353.8675, 355.8637.

1-(Bromomethyl)-5-methyl-2,4-dinitrobenzene (13): ^1H NMR (CDCl_3): 8.64 s, 1 H; 7.56 s, 1 H; 4.78 s, 2 H; 2.65 s, 3 H. ^{13}C APT NMR (CDCl_3): 147.99 (C), 145.38 (C), 139.98 (C), 137.35 (C), 137.14 (CH), 122.36 (CH), 27.25 (CH_2), 20.50 (CH_3). HRMS (EI^+): for $\text{C}_8\text{H}_7\text{BrN}_2\text{O}_4$ [M^+] calculated: 273.9589, 275.9569; found: 273.9584, 275.9554.

Preparation of Diamines **7**. General Procedure

Dibromide **5** was treated with arylamine **6** in EtOH (150 ml) at 80 °C overnight. Precipitated solid filtered off and washed with EtOH, concentrated NH_3 and water, dried in vacuo to give corresponding diamine **7**.

N-(5-((Anthracen-2-ylamino)methyl)-2,4-dinitrobenzyl)anthracene-2-amine (**7b**): Dibromide **5** (0.20 g, 0.57 mmol) and anthracene-2-amine (1.09 g, 5.67 mmol) gave 0.27 g (83%) of **7b**. ^1H NMR (DMSO- d_6): 8.82 s, 1 H; 8.14 s, 1 H; 8.04 s, 2 H; 7.85 m, 2 H; 7.75 s, 2 H; 7.59 m, 2 H; 7.50 d, 2 H, $J = 9.2$; 7.29 m, 4 H; 6.89 dd, 2 H, $J = 9.1$, $J = 1.8$; 6.73 t, 2 H, $J = 5.7$; 6.52 s, 2 H; 4.78 d, 4 H, $J = 5.7$. ^{13}C APT NMR (DMSO- d_6): 146.51 (C), 144.82 (C), 141.23 (C), 133.13 (C), 131.70 (C), 130.38 (CH), 128.78 (CH), 128.57 (C), 127.97 (CH), 126.95 (CH), 126.77 (C), 125.58 (CH), 125.03 (CH), 123.22 (CH), 122.24 (CH), 121.65 (CH), 120.01 (CH), 100.05 (CH), 44.31 (CH₂). HRMS (FAB⁺): for C₃₆H₂₇N₄O₄ [MH⁺] calculated: 579.2032; found: 579.2014.

N-(5-((9H-Fluoren-2-ylamino)methyl)-2,4-dinitrobenzyl)-9H-fluorene-2-amine (**7c**): Dibromide **5** (0.20 g, 0.57 mmol), fluorene-2-amine (1.03 g, 5.66 mmol) gave 0.27 g (87%) of **7c**. ^1H NMR (DMSO- d_6): 8.74 s, 1 H; 8.06 s, 1 H; 7.40 d, 2 H, $J = 7.5$; 7.26 m, 6 H; 7.08 m, 2 H; 6.61 s, 2 H; 6.41 m, 4 H; 4.68 d, 4 H, $J = 6.2$; 3.51 s, 4 H. ^{13}C APT NMR (DMSO- d_6): 147.44 (C), 146.37 (C), 144.44 (C), 141.80 (C), 141.68 (C), 141.57 (C), 130.86 (CH), 130.48 (C), 126.37 (CH), 124.58 (CH), 124.40 (CH), 122.13 (CH), 120.26 (CH), 118.04 (CH), 111.16 (CH), 108.58 (CH), 44.68 (CH₂), 36.14 (CH₂). HRMS (FAB⁺): for C₃₄H₂₇N₄O₄ [MH⁺] calculated: 555.2032; found: 555.2042.

N-[5((Pyren-1-ylamino)methyl)-2,4-dinitrobenzyl]pyrene-1-amine (**7d**): Dibromide **5** (0.15 g, 0.43 mmol) and pyrene-1-amine (0.94 g, 4.32 mmol) gave 0.27 g (98%) of **7d**. ^1H NMR (DMSO- d_6): 8.89 s, 1 H; 8.13 s, 1 H; 7.94 d, 2 H, $J = 7.6$; 7.87 t, 2 H, $J = 7.6$; 7.70 m, 4 H; 7.54 s, 4 H; 7.53 d, 2 H, $J = 6.5$; 7.24 d, 2 H, $J = 9.4$; 7.12 t, 2 H, $J = 5.6$; 6.79 d, 2 H, $J = 8.5$; 4.94 d, 4 H, $J = 5.3$. ^{13}C APT NMR (DMSO- d_6): 146.37 (C), 141.63 (C), 141.57 (C), 131.66 (C), 131.00 (C), 129.70 (CH), 127.17 (CH), 125.91 (CH), 125.62 (CH), 124.97 (C), 124.60 (C), 124.28 (CH), 123.06 (CH), 122.64 (CH), 122.47 (CH), 122.22 (CH), 121.69 (C), 120.30 (CH), 115.54 (C), 108.15 (CH), 44.31 (CH₂). HRMS (ES⁺): for C₄₀H₂₆N₄O₄ [M⁺⁺] calculated: 626.1954; found: 626.1726.

Preparation of Dibromide **9**

1,3-Dimethyl-4,6-dinitrobenzene (2.0 g, 10.2 mmol) was dissolved in 50 ml of methanol, and catalyst (5% Pd/C, 0.2 g) was added. The reaction mixture was stirred under hydrogen atmosphere for 2 days. The catalyst was filtered off, and the filtrate was evaporated to dryness in vacuo to give 1.3 g (94%) of 4,6-dimethylbenzene-1,3-diamine (**14**). Obtained diamine **14** (1.0 g, 7.34 mmol) was treated with Boc₂O (3.4 g, 15.6 mmol) in 150 ml of MeOH at room temperature for 3 h. Reaction mixture was evaporated to dryness in vacuo, and the residue was separated by column chromatography (MeOH-CHCl₃ 975:25) to give 2.2 g (89%) of bocylamine **8**. Obtained bocylamine **8** (1.0 g, 3.0 mmol) was treated with *N*-bromosuccinimide (NBS, 1.1 g, 6.0 mmol) and α,α' -azo-bis(isobutyronitrile) (AIBN, 0.1 g, 0.6 mmol) in CCl₄ (150 ml) under irradiation by the IR lamp for 1.5 h. Precipitated solid was filtered off and washed with CCl₄. The filtrate was extracted with 2% aqueous ammonium and then with water. The organic layer was dried over Na₂SO₄ and evaporated to dryness in vacuo, dissolved in Et₂O and the precipitated solid was filtered off. The filtrate was evaporated to dryness in vacuo to give bromide **9** (1.2 g, 82%).

4,6-Dimethylbenzene-1,3-diamine (**14**): ^1H NMR (CDCl₃): 6.64 s, 1 H; 5.98 s, 1 H; 3.33 bs, 4 H; 1.98 s, 6 H. ^{13}C APT NMR (CDCl₃): 143.13 (C), 132.24 (CH), 112.86 (C), 102.37 (CH), 16.26 (CH₃). HRMS (EI⁺): for C₈H₁₂N₂ [M⁺] calculated: 136.1000; found: 136.0999. Known compound⁹.

4,6-Dimethylbenzene- N^1,N^3 -bis(*tert*-butoxycarbonyl)-1,3-diamine (**8**): ^1H NMR (CDCl_3): 7.94 s, 1 H; 6.86 s, 1 H; 6.08 bs, 2 H; 2.10 s, 6 H; 1.44 s, 18 H. ^{13}C APT NMR (CDCl_3): 153.11 (C), 134.39 (C), 131.96 (CH), 124.33 (C), 115.63 (CH), 80.24 (C), 28.34 (CH_3), 17.13 (CH_3). HRMS (EI^+): for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_4$ [M^+] calculated: 336.2049; found: 336.2059.

4,6-Bis(bromomethyl)- N^1,N^3 -bis(*tert*-butoxycarbonyl)benzene-1,3-diamine (**9**): ^1H NMR (CDCl_3): 8.35 s, 1 H; 7.20 s, 1 H; 6.68 s, 2 H; 4.44 s, 4 H; 1.53 s, 18 H. ^{13}C APT NMR (CDCl_3): 152.44 (C), 138.57 (C), 131.61 (CH), 122.29 (C), 116.25 (CH), 81.30 (C), 30.73 (CH_2), 28.26 (CH_3). HRMS: no ionization techniques (EI^+ , FAB^+ , ESI^+) gave molecular ion.

Preparations of Diamines **10**. General Procedure

Dibromide **9** was treated with arylamine **6** and K_2CO_3 in DMF at 70 °C for 5 h. The reaction mixture was evaporated to dryness in vacuo and tetraamine **10** was obtained by column chromatography to give pure tetraamine **10**.

N^1,N^3 -Bis(*tert*-butoxycarbonyl)-4,6-bis((naphthalen-2-ylamino)methyl)benzene-1,3-diamine (**10a**): Naphthalene-2-amine **6a** (2.90 g, 20.2 mmol), dibromide **9** (1.00 g, 2.0 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 100 ml of DMF; the first column chromatography (toluene–EtOAc– Et_3N 500:100:1) gave crude product, which was purified by next column chromatography (CH_2Cl_2) to give pure 0.60 g (48%) of diamine **10a**. ^1H NMR (CDCl_3): 8.29 s, 1 H; 7.63 d, 2 H, $J = 8.2$; 7.60 d, 2 H, $J = 8.2$; 7.57 d, 2 H, $J = 6.7$; 7.31 m, 4 H; 7.21 m, 3 H; 6.90 m, 4 H; 4.25 s, 4 H; 3.91 bs, 2 H; 1.41 s, 18 H. ^{13}C APT NMR (CDCl_3): 153.24 (C), 145.55 (C), 137.64 (C), 134.86 (C), 130.71 (CH), 128.99 (CH), 128.18 (C), 127.65 (CH), 126.46 (CH), 126.21 (CH), 123.78 (C), 122.71 (CH), 118.44 (CH), 115.68 (CH), 106.44 (CH), 80.68 (C), 46.7 (CH_2), 28.31 (CH_3). HRMS (FAB^+): for $\text{C}_{38}\text{H}_{43}\text{N}_4\text{O}_4$ [MH^+] calculated: 619.3284; found: 619.3275.

4,6-Bis((anthracen-2-ylamino)methyl)- N^1,N^3 -bis(*tert*-butoxycarbonyl)-1,3-diamine (**10b**): Anthracene-2-amine **6b** (3.90 g, 20.2 mmol), dibromide **9** (1.00 g, 2.0 mmol), K_2CO_3 (0.31 g, 2.2 mmol), 50 ml of DMF, column chromatography (toluene–EtOAc– Et_3N 833:167:1), 0.43 g (30%) of diamine **10b**. ^1H NMR ($\text{DMSO}-d_6$): 8.76 s, 2 H; 8.20 s, 2 H; 7.90 s, 2 H; 7.89 d, 2 H, $J = 8.1$; 7.74 d, 2 H, $J = 8.1$; 7.69 d, 2 H, $J = 8.8$; 7.54 s, 1 H; 7.48 s, 1 H; 7.31 m, 4 H; 7.02 dd, 2 H, $J = 9.2$, $J = 1.8$; 6.59 s, 2 H; 6.51 t, 2 H, $J = 5.5$; 4.27 d, 4 H, $J = 5.5$; 1.47 s, 18 H. ^{13}C APT NMR ($\text{DMSO}-d_6$): 153.67 (C), 145.74 (C), 135.02 (C), 133.46 (C), 131.84 (C), 129.09 (C), 128.58 (CH), 128.50 (C), 128.01 (CH), 127.25 (CH), 126.91 (CH), 126.74 (C), 125.66 (CH), 125.13 (CH), 123.15 (CH), 121.42 (CH), 120.97 (CH), 120.78 (CH), 99.84 (CH), 78.97 (C), 43.11 (CH_2), 28.10 (CH_3). HRMS (FAB^+): for $\text{C}_{46}\text{H}_{46}\text{N}_4\text{O}_4$ [M^+] calculated: 718.3519; found: 718.3508.

4,6-Bis((9H-fluoren-2-ylamino)methyl)- N^1,N^3 -bis(*tert*-butoxycarbonyl)benzene-1,3-diamine (**10c**): Fluorene-2-amine **6c** (3.67 g, 20.2 mmol), dibromide **9** (1.00 g, 2.0 mmol), K_2CO_3 (0.31 g, 2.2 mmol), 45 ml of DMF, column chromatography (toluene–EtOAc– Et_3N 833:167:1), 0.60 g (43%) of diamine **10c**. ^1H NMR ($\text{DMSO}-d_6$): 8.68 s, 2 H; 7.51 s, 1 H; 7.49 d, 2 H, $J = 7.9$; 7.40 d, 2 H, $J = 8.2$; 7.38 s, 1 H; 7.32 d, 2 H, $J = 7.3$; 7.23 t, 2 H, $J = 7.3$; 7.08 m, 2 H; 6.68 s, 2 H; 6.49 dd, 2 H, $J = 8.2$, $J = 1.8$; 6.18 t, 2 H, $J = 5.6$; 4.19 d, 4 H, $J = 5.3$; 3.61 s, 4 H; 1.46 s, 18 H. ^{13}C APT NMR ($\text{DMSO}-d_6$): 153.52 (C), 148.41 (C), 144.37 (C), 142.00 (C), 141.55 (C), 134.83 (C), 130.00 (C), 129.10 (C), 127.26 (CH), 126.42 (CH), 124.60 (CH), 124.30 (CH), 120.29 (2 $\times$ CH), 117.98 (CH), 111.59 (CH), 108.76 (CH), 78.94 (C), 43.64 (CH_2), 36.21 (CH_2), 28.10 (CH_3). HRMS (FAB^+): for $\text{C}_{44}\text{H}_{46}\text{N}_4\text{O}_4$ [M^+] calculated: 694.3519; found: 694.3492.

N^1,N^3 -Bis(*tert*-butoxycarbonyl)-4,6-bis((pyren-1-ylamino)methyl)benzene-1,3-diamine (**10d**): Pyrene-1-amine **6d** (1.4 g, 6.4 mmol), dibromide **9** (0.8 g, 1.6 mmol), K_2CO_3 (0.2 g, 1.6 mmol), 50 ml of DMF; the first column chromatography (toluene–EtOH–Et₃N 800:200:1) gave crude product, which was purified by next column chromatography (CH_2Cl_2) to give pure 0.2 g (16%) of diamine **10d**. ¹H NMR (DMSO-*d*₆): 8.90 s, 2 H; 8.08 d, 2 H, *J* = 9.4; 7.94 m, 6 H; 7.61 m, 8 H; 7.48 d, 2 H, *J* = 7.6; 7.16 bs, 2 H; 6.82 d, 2 H, *J* = 8.2; 4.44 s, 4 H; 1.47 s, 18 H. ¹³C APT NMR (DMSO-*d*₆): 153.72 (C), 142.88 (C), 134.74 (C), 131.92 (C), 131.35 (C), 129.42 (C), 127.53 (CH), 126.20 (CH), 126.11 (CH), 125.83 (CH), 125.24 (C), 124.92 (C), 124.43 (CH), 123.00 (CH), 122.55 (CH), 121.96 (CH), 121.24 (C), 121.00 (2 × CH), 115.62 (C), 108.58 (CH), 78.94 (C), 42.98 (CH₂), 28.10 (CH₃). HRMS (FAB⁺): for C₅₀H₄₇N₄O₄ [MH⁺] calculated: 767.3597; found: 767.3617.

4,6-Bis((anthracen-1-ylamino)methyl)- N^1,N^3 -bis(*tert*-butoxycarbonyl)benzene-1,3-diamine (**10e**): Anthracene-1-amine **6e** (0.97 mg, 5.0 mmol), dibromide **9** (0.50 mg, 1.0 mmol), K_2CO_3 (0.14 mg, 1.0 mmol), 50 ml of DMF; the first column chromatography (toluene–CH₂Cl₂–Et₃N 100:900:1) gave crude product, which was purified by next column chromatography (CH_2Cl_2) to give pure 80 mg (11%) of diamine **10e**. ¹H NMR (CDCl₃): 8.43 s, 1 H; 8.31 s, 4 H; 7.91 m, 4 H; 7.55 s, 2 H; 7.44 d, 2 H, *J* = 8.5; 7.38 m, 5 H; 7.29 m, 2 H; 6.63 d, 2 H, *J* = 7.3; 4.56 bs, 2 H; 4.40 s, 4 H; 1.36 s, 18 H. ¹³C APT NMR (CDCl₃): 153.48 (C), 142.74 (C), 138.12 (C), 132.29 (C), 131.64 (C), 131.48 (CH), 131.10 (C), 128.41 (CH), 127.78 (CH), 126.72 (CH), 125.79 (CH), 125.65 (CH), 125.30 (CH), 124.12 (C), 123.91 (C), 119.36 (CH), 118.88 (CH), 116.05 (CH), 104.21 (CH), 80.75 (C), 46.82 (CH₂), 28.27 (CH₃). HRMS (FAB⁺): for C₄₆H₄₆N₄O₄ [M⁺] calculated: 718.3519; found: 718.3526.

Preparation of Tröger's Bases **1**. General Procedure

Diamine **10** was dissolved in of TFA and paraformaldehyde (37 mg) was added. The reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with ice water, and alkalized by concentrated aqueous ammonia. The product was extracted into $CHCl_3$ or CH_2Cl_2 , washed with water, with brine, dried over Na₂SO₄, and evaporated to dryness in vacuo. The residue was separated by chromatography to obtain corresponding bisTB **1**, wherein the diastereoisomer eluted as the first one is marked as **1-A** while the slower one is marked as **1-B**.

Naphthalene-2-amine derived bisTB 1a: Diamine **10a** (80 mg, 0.13 mmol), 10 ml of TFA, 37 mg (0.77 mmol of CH₂O equiv.) of paraformaldehyde; by preparation TLC (CH_2Cl_2 –CH₃OH 95:5) were obtained 25 mg (41%) of **1a-A** and 32 mg (53%) of **1a-B**. The NMR characteristics was identical with the ones observed previously^{3d}.

Anthracene-2-amine derived bisTB 1b: Diamine **10b** (250 mg, 0.35 mmol), 25 ml of TFA, 134 mg (2.79 mmol of CH₂O equiv.) of paraformaldehyde; by column chromatography (CH_2Cl_2 –CH₃OH 97:3) were obtained 71 mg (36%) of **1b-A** and 79 mg (40%) of **1b-B**.

BisTB 1b-A: ¹H NMR (CDCl₃): 8.21 s, 2 H; 8.07 s, 2 H; 7.89 d, 2 H, *J* = 8.9; 7.86 d, 2 H, *J* = 8.9; 7.73 d, 2 H, *J* = 9.1; 7.38 m, 4 H; 7.11 d, 2 H, *J* = 9.1; 7.09 s, 1 H; 6.40 s, 1 H; 4.99 d, 2 H, *J* = 16.6; 4.71 d, 2 H, *J* = 16.6; 4.46 d, 2 H, *J* = 16.6; 4.31 d, 2 H, *J* = 12.5; 4.18 d, 2 H, *J* = 12.5; 4.17 d, 2 H, *J* = 16.6. ¹³C APT NMR (CDCl₃): 147.56 (C), 144.13 (C), 131.96 (C), 130.81 (C), 129.77 (C), 129.57 (C), 128.29 (CH), 128.04 (CH), 127.97 (CH), 126.98 (CH), 125.74 (CH), 125.24 (CH), 125.04 (CH), 124.64 (CH), 123.83 (C), 121.07 (CH), 120.40 (C), 119.31 (CH), 66.73 (CH₂), 57.30 (CH₂), 56.34 (CH₂). HRMS (FAB⁺): for C₄₀H₃₁N₄ [MH⁺] calculated: 567.2549; found: 567.2563.

BisTB 1b-B: ^1H NMR (CDCl_3): 8.06 s, 2 H; 7.98 s, 2 H; 7.79 d, 2 H, $J = 8.0$; 7.71 d, 2 H, $J = 8.0$; 7.60 d, 2 H, $J = 9.0$; 7.25 m, 4 H; 7.06 d, 2 H, $J = 9.0$; 7.05 s, 1 H; 6.48 s, 1 H; 5.02 d, 2 H, $J = 16.7$; 4.58 d, 2 H, $J = 16.7$; 4.47 d, 2 H, $J = 16.7$; 4.33 d, 2 H, $J = 12.9$; 4.32 d, 2 H, $J = 12.9$; 4.19 d, 2 H, $J = 16.7$. ^{13}C APT NMR (CDCl_3): 147.74 (C), 144.21 (C), 131.80 (C), 130.67 (C), 129.63 (C), 129.42 (C), 128.10 (CH), 127.92 (CH), 127.84 (CH), 126.84 (CH), 125.56 (CH), 125.09 (CH), 124.83 (CH), 124.54 (CH), 124.06 (C), 121.65 (CH), 120.21 (C), 119.20 (CH), 66.84 (CH_2), 56.91 (CH_2), 56.21 (CH_2). HRMS (FAB^+): for $\text{C}_{40}\text{H}_{31}\text{N}_4$ [MH^+] calculated: 567.2549; found: 567.2570.

Fluorene-2-amine derived bisTB 1c: Diamine **10c** (0.50 g, 0.35 mmol), 50 ml of TFA, 275 mg (5.72 mmol of CH_2O equiv.) of paraformaldehyde; by column chromatography (CH_2Cl_2 – CH_3OH 97:3) were obtained 173 mg (44%) of **1c-A** and 146 mg (38%) of **1c-B**.

BisTB 1c-A: ^1H NMR (CDCl_3): 7.56 d, 2 H, $J = 7.3$; 7.40 d, 2 H, $J = 7.3$; 7.24 s, 2 H; 7.24 td, 2 H, $J = 7.3$, $J = 1.1$; 7.19 s, 2 H; 7.16 td, 2 H, $J = 7.3$, $J = 1.1$; 6.93 s, 1 H; 6.39 s, 1 H; 4.73 d, 2 H, $J = 16.5$; 4.50 d, 2 H, $J = 16.5$; 4.27 d, 2 H, $J = 16.5$; 4.24 d, 2 H, $J = 12.5$; 4.16 d, 2 H, $J = 12.5$; 4.07 d, 2 H, $J = 16.5$; 3.80 d, 2 H; 21.7, 3.70 d, 2 H, $J = 21.7$. ^{13}C APT NMR (CDCl_3): 147.27 (C), 146.92 (C), 143.04 (C), 142.54 (C), 141.28 (C), 138.07 (C), 126.72 (CH), 126.25 (CH), 126.14 (C), 125.03 (CH), 124.89 (CH), 123.87 (C), 121.47 (CH), 120.84 (CH), 119.43 (CH), 117.88 (CH), 66.93 (CH_2), 59.44 (CH_2), 58.63 (CH_2), 36.60 (CH_2). HRMS (FAB^+): for $\text{C}_{38}\text{H}_{31}\text{N}_4$ [MH^+] calculated: 543.2549; found: 543.2542.

BisTB 1c-B: ^1H NMR (CDCl_3): 7.46 d, 2 H, $J = 7.3$; 7.30 d, 2 H, $J = 7.3$; 7.17 s, 2 H; 7.15 td, 2 H, $J = 7.3$, $J = 1.2$; 7.13 s, 2 H; 7.06 td, 2 H, $J = 7.3$, $J = 1.2$; 6.87 s, 1 H; 6.37 s, 1 H; 4.71 d, 2 H, $J = 16.6$; 4.57 d, 2 H, $J = 16.6$; 4.25 d, 2 H, $J = 12.5$; 4.23 d, 2 H, $J = 12.5$; 4.12 d, 2 H, $J = 16.6$; 4.03 d, 2 H, $J = 16.5$; 3.71 d, 2 H, $J = 21.7$; 3.58 d, 2 H, $J = 21.7$. ^{13}C APT NMR (CDCl_3): 147.53 (C), 146.96 (C), 142.95 (C), 142.40 (C), 141.13 (C), 137.89 (C), 126.56 (CH), 126.13 (CH), 126.09 (C), 124.87 (CH), 124.79 (CH), 123.99 (C), 121.41 (CH), 120.87 (CH), 119.27 (CH), 117.77 (CH), 66.90 (CH_2), 59.15 (CH_2), 58.52 (CH_2), 36.47 (CH_2). HRMS (FAB^+): for $\text{C}_{38}\text{H}_{31}\text{N}_4$ [MH^+] calculated: 543.2549; found: 543.2527.

Pyrene-1-amine derived bisTB 1d: Diamine **10d** (40 mg, 52 μmol), 5 ml of TFA, 20 mg (416 μmol of CH_2O equiv.) of paraformaldehyde. ^1H NMR spectrum of crude product confirms a formation of very complex mixture, in which mass spectroscopy found very low intensity of the expected peak of **1d**. HRMS (FAB^+): for $\text{C}_{44}\text{H}_{31}\text{N}_4$ [MH^+] calculated: 615.2549; found: 615.2574.

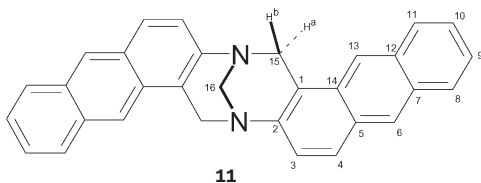
Anthracene-1-amine derived bisTB 1e: Diamine **10e** (20 mg, 28 μmol), 2 ml of TFA, 8 mg (167 μmol of CH_2O equiv.) of paraformaldehyde. ^1H NMR spectrum of crude product confirms a formation of very complex mixture, in which mass spectroscopy found very low intensity of the expected peak of **1e**. HRMS (FAB^+): for $\text{C}_{40}\text{H}_{31}\text{N}_4$ [MH^+] calculated: 567.2549; found: 567.2564.

Preparations of Tröger's Bases **11** from Anthracene-2-amine

The flask was charged with 783 mg (4.05 mmol) of anthracene-2-amine and 400 ml of methanol. Then 10 ml of formol (37%) were added, followed by 10 ml of concentrated aqueous HCl. The mixture was stirred at room temperature for 3 days. The mixture was poured into 1.3 l of water, alkalinized by 30 ml of concentrated aqueous NH_3 , and extracted by CH_2Cl_2 . The organic parts were collected and filtrated through 40 g of silica and evaporated to dryness. The obtained solid was macerated with warm CHCl_3 to obtain yellowish solid compound **12** (98 mg) of unknown structure, and solution containing expected

Tröger's base **11**. The solution was concentrated in vacuo and separated by column chromatography (350 g, silica, CHCl_3) to give 261 mg (30%) of Tröger's base **11**.

Tröger's base 11: The chemical shifts were assigned based on g-COSY, g-HMBC, g-HMQC, 1D NOEDIF NMR experiments and geometric data (dihedral angles and distances) from the computer model (geometry optimized by PM3) of the compound. ^1H NMR ($\text{DMSO}-d_6$): 8.39 s, 2 H (H-6); 8.35 s, 2 H (H-13); 8.04 d, 2 H, $J = 8.2$ (H-11); 7.96 d, 2 H, $J = 8.0$ (H-8); 7.86 d, 2 H, $J = 9.1$ (H-4); 7.47 dd, 2 H, $J = 8.2$, $J = 6.3$ (H-10); 7.42 dd, 2 H, $J = 8.0$, $J = 6.3$ (H-9); 7.40 d, 2 H, $J = 9.1$ (H-3); 5.06 d, 2 H, $J = 17.0$ (H-15b); 4.87 d, 2 H, $J = 17.0$ (H-15a); 4.53 s, 2 H (H-16). ^{13}C NMR ($\text{DMSO}-d_6$): 144.71 (C-2), 131.47 (C-12), 130.21 (C-7), 129.49 (C-14), 129.13 (C-5), 127.95 (C-11), 127.86 (C-8), 127.70 (C-4), 126.68 (C-6), 125.75 (C-10), 125.19 (C-3), 125.08 (C-9), 120.24 (C-1), 119.39 (C-13), 66.32 (C-16), 54.62 (C-15). HRMS (FAB^+): for $\text{C}_{31}\text{H}_{23}\text{N}_2$ $[\text{MH}^+]$ calculated: 423.1861; found: 423.1868.



Compound 12: ^1H NMR ($\text{DMSO}-d_6$): 10.83 s, 1 H; 10.05 s, 2 H; 8.69 s, 2 H; 8.40 dd, 2 H, $J = 8.1$, $J = 1.0$; 8.32 d, 2 H, $J = 9.3$; 8.24 dd, 2 H, $J = 8.1$, $J = 1.0$; 7.96 d 2 H, $J = 9.3$; 7.81–7.68 m, 4 H.

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