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

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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.

**Keywords**: Bis-Tröger's bases; Molecular tweezers; Synthetic methodology.

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 derivatives[1] exhibit rigid V-shapes, causing bisTBs to exist as *syn*- and *anti*-diastereoisomeric forms[2–4]. The *syn*-bisTBs embody molecular tweezers. TB derivatives[1], 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 at 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 derivatives[1] 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

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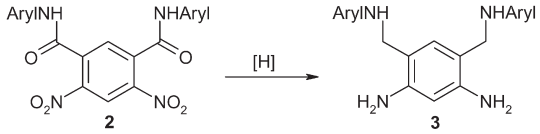
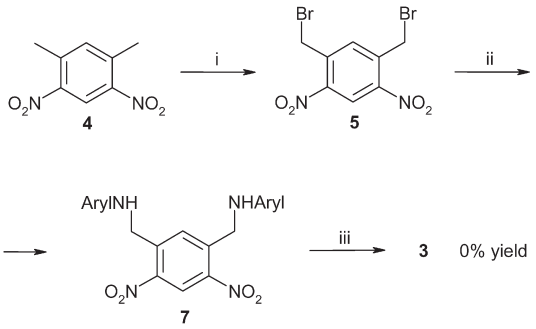
approaches, including the preparation of useful intermediates, are of interest[2c,3a,3c,3d].

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

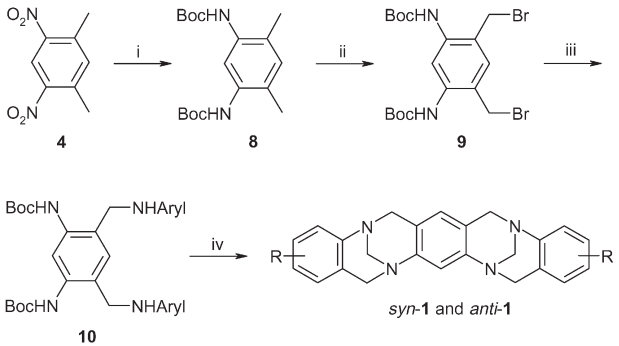
As an alternative route to tetraamines **3** we started from dinitroxylene **4** (Scheme 2). Bromation afforded **5**, which, after treatment with excess of arylamines **6**, gave dinitrodiamines **7** in yields of about 90%. Unfortunately, attempts[6] at nitro group reduction to the expected tetraaamines **3** led to $CH_2$–NHAryl 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 previously[7].




(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 decomposition[6]

SCHEME 2
Nitrobromide synthetic pathway to bisTB.

To bypass the reduction step, the nitro groups of dinitroxylene **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 tetraamine **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 derivatives[1] 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

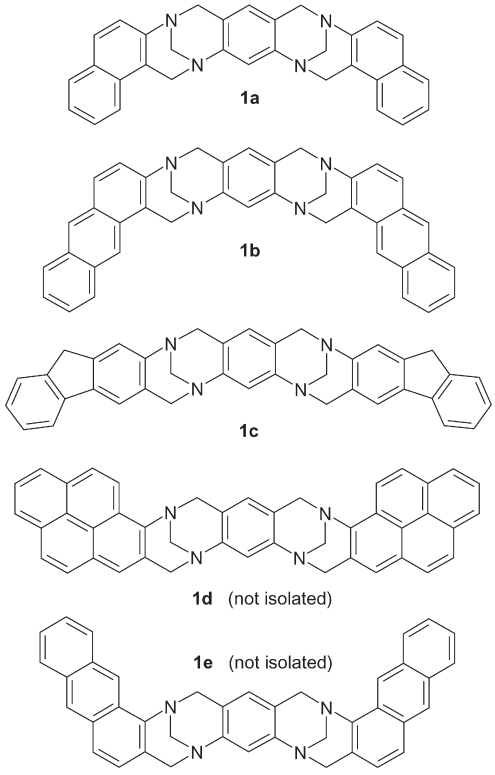



CHART 1
BisTB derivatives

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 $^{1}$H and 75.460 MHz for $^{13}$C) at 23 °C in deuteriochloroform $CDCl_3$ or deuterated dimethyl sulfoxide 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**): $^{1}$H 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 $C_8H_6Br_2N_2O_4$ [M$^+$] calculated: 351.8694, 353.8671, 355.8653; found: 351.8681, 353.8675, 355.8637.

*1-(Bromomethyl)-5-methyl-2,4-dinitrobenzene* (**13**): $^{1}$H 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 $C_8H_7BrN_2O_4$ [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**. $^1$H 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 ($CH_2$). HRMS (FAB$^+$): for $C_{36}H_{27}N_4O_4$ [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**. $^1$H 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 ($CH_2$), 36.14 ($CH_2$). HRMS (FAB$^+$): for $C_{34}H_{27}N_4O_4$ [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**. $^1$H 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 ($CH_2$). HRMS (ES$^+$): for $C_{40}H_{26}N_4O_4$ [M$^{+\bullet}$] 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 $Boc_2O$ (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–$CHCl_3$ 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 $CCl_4$ (150 ml) under irradiation by the IR lamp for 1.5 h. Precipitated solid was filtered off and washed with $CCl_4$. The filtrate was extracted with 2% aqueous ammonium and then with water. The organic layer was dried over $Na_2SO_4$ and evaporated to dryness in vacuo, dissolved in $Et_2O$ 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**): $^1$H NMR ($CDCl_3$): 6.64 s, 1 H; 5.98 s, 1 H; 3.33 bs, 4 H; 1.98 s, 6 H. $^{13}$C APT NMR ($CDCl_3$): 143.13 (C), 132.24 (CH), 112.86 (C), 102.37 (CH), 16.26 ($CH_3$). HRMS (EI$^+$): for $C_8H_{12}N_2$ [M$^+$] calculated: 136.1000; found: 136.0999. Known compound[9].

*4,6-Dimethylbenzene-$N^1$,$N^3$-bis(tert-butoxycarbonyl)-1,3-diamine* (**8**): $^1$H 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 $C_{18}H_{28}N_2O_4$ [$M^+$] calculated: 336.2049; found: 336.2059.

*4,6-Bis(bromomethyl)-$N^1$,$N^3$-bis(tert-butoxycarbonyl)benzene-1,3-diamine* (**9**): $^1$H 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 tetramine **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**. $^1$H 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 $C_{38}H_{43}N_4O_4$ [$MH^+$] 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 (toluen–EtOAc–$Et_3N$ 833:167:1), 0.43 g (30%) of diamine **10b**. $^1$H NMR (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 (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 $C_{46}H_{46}N_4O_4$ [$M^+$] 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 (toluen–EtOAc–$Et_3N$ 833:167:1), 0.60 g (43%) of diamine **10c**. $^1$H NMR (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 (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 × 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 $C_{44}H_{46}N_4O_4$ [$M^+$] 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–$Et_3N$ 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**. $^1$H 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. $^{13}$C 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 ($CH_2$), 28.10 ($CH_3$). HRMS (FAB$^+$): for $C_{50}H_{47}N_4O_4$ [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–$CH_2Cl_2$–$Et_3N$ 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**. $^1$H NMR ($CDCl_3$): 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. $^{13}$C APT NMR ($CDCl_3$): 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 ($CH_2$), 28.27 ($CH_3$). HRMS (FAB$^+$): for $C_{46}H_{46}N_4O_4$ [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 alkalinized by concentrated aqueous ammonia. The product was extracted into $CHCl_3$ or $CH_2Cl_2$, washed with water, with brine, dried over $Na_2SO_4$, 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 $CH_2O$ equiv.) of paraformaldehyde; by preparation TLC ($CH_2Cl_2$–$CH_3OH$ 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 $CH_2O$ equiv.) of paraformaldehyde; by column chromatography ($CH_2Cl_2$–$CH_3OH$ 97:3) were obtained 71 mg (36%) of **1b-A** and 79 mg (40%) of **1b-B**.

*BisTB* **1b-A**: $^1$H NMR ($CDCl_3$): 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. $^{13}$C APT NMR ($CDCl_3$): 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 ($CH_2$), 57.30 ($CH_2$), 56.34 ($CH_2$). HRMS (FAB$^+$): for $C_{40}H_{31}N_4$ [MH$^+$] calculated: 567.2549; found: 567.2563.

*BisTB* **1b-B**: $^1$H 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 $C_{40}H_{31}N_4$ [$MH^+$] 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**: $^1$H 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 $C_{38}H_{31}N_4$ [$MH^+$] calculated: 543.2549; found: 543.2542.

*BisTB* **1c-B**: $^1$H 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 $C_{38}H_{31}N_4$ [$MH^+$] 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. $^1$H 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 $C_{44}H_{31}N_4$ [$MH^+$] calculated: 615.2549; found: 615.2574.

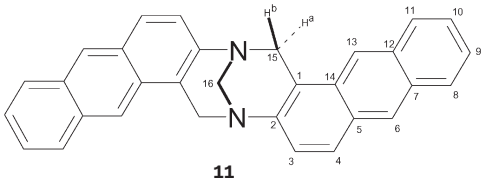
*Anthracene-1-amine derived bisTB* **1e**: Diamine **10e** (20 mg, 28 μmol), 2 ml of TFA, 8 mg (167 μmol of $CH_2O$ equiv.) of paraformaldehyde. $^1$H NMR spectrum of crude product confirms a formation of very complex mixture, in which mass spectroscopy found very low intensity of the expected peak of **1e**. HRMS ($FAB^+$): for $C_{40}H_{31}N_4$ [$MH^+$] 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, alkalized 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 optimalized by PM3) of the compound. $^1$H NMR (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 (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 $C_{31}H_{23}N_2$ [MH$^+$] calculated: 423.1861; found: 423.1868.




**11**

*Compound* **12**: $^1$H NMR (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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## REFERENCES AND NOTES

1. a) Demeunynck M., Tatibouët A. in: *Progress in Heterocycles Chemistry* (G. W. Gribble and T. L. Cilchrist, Eds), Vol. 11, pp. 1–20. Pergamon, Oxford 1999; b) Valík M., Strongin R. M., Král V.: *Supramol. Chem.* **2005**, *17*, 347; c) Dolenský B., Elguero J., Král V., Pardo C., Valík M.: *Adv. Heterocycl. Chem.* **2007**, in press.
2. a) Pardo C., Sesmilo E., Gutierrez-Puebla E., Monge A., Elguero J., Fruchier A.: *J. Org. Chem.* **2001**, *66*, 1607; b) Mas T., Pardo C., Salort F., Elguero J., Torres M. R.: *Eur. J. Org. Chem.* **2004**, 1097; c) Mas T., Pardo C., Elguero J.: *Arkivoc* **2004**, 86; d) Mas T., Pardo C., Elguero J.: *Helv. Chim. Acta* **2005**, *88*, 1199.
3. a) Valík M., Dolenský B., Petříčková H., Král V.: *Collect. Czech. Chem. Commun.* **2002**, *67*, 609; b) Dolenský B., Valík M., Sýkora D., Král V.: *Org. Lett.* **2005**, *7*, 67; c) Valík M., Matějka P., Herdtweck E., Král V., Dolenský B.: *Collect. Czech. Chem. Commun.* **2006**, *71*, 1278; d) Havlík M., Král V., Dolenský B.: *Org. Lett.* **2006**, *8*, 4867.
4. a) Hansson A., Wixe T., Bergquist K.-E., Wärnmark K.: *Org. Lett.* **2005**, *7*, 2019; b) Artacho J., Nilsson P., Bergquist K.-E., Wendt O. F., Wärnmark K.: *Chem. Eur. J.* **2006**, *12*, 2692.

5. Lenev D. A., Lysenko K. A., Golovanov V. B., Kostyanovsky R. G.: *Chem. Eur. J.* **2006**, *12*, 6412.
6. The reductions were performed on **7c** and **7d**. a) $SnCl_2 \cdot 2H_2O$/HCl, EtOH, 1 h, reflux; b) Zn/AcOH; c) Pd/C, MeOH, DMF; d) LAH, dioxane, 100 °C, 5 h; e) PMHS/KF/$Pd(OAc)_2$, THF, 1 h, r.t.; Rahaim R. J., Jr., Maleczka R. E., Jr.: *Synthesis* **2006**, 3316.
7. Mičovič V. M., Mihailovič M. L.: *J. Org. Chem.* **1953**, *18*, 1190.
8. Tálas E., Margitfalvi J., Machytka D., Czugler M.: *Tetrahedron: Asymmetry* **1998**, *9*, 4151.
9. Kato Y., Toledo L. M., Rebek J., Jr.: *J. Am. Chem. Soc.* **1996**, *118*, 8575.