A New Entry to Bis-Tröger's Bases

Thierry Mas,[a] Carmen Pardo,*[a] Francisca Salort,[a] José Elguero,[b] and M. Rosario Torres[c]

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This paper reports the use of *p*-phenylenediamine to prepare bis-Tröger's bases. The methyl,nitro-substituted bis-Tröger's base **5**, already previously prepared by another procedure, was obtained in fewer steps, although with no improvement in the yield of the desired *syn* isomer. The symmetric dinitro-substituted bis-Tröger's base **17**, which cannot be prepared by the older method, was then synthesized. Its structure was determined by mass spectrometry, 2D NMR spectroscopy, and, in the case of the *syn* isomer, by X-ray crystallography.

Introduction

We were the first to synthesize bis-Tröger's bases (BTB),[1] with the aim of exploring and amplifying the interesting properties of these bases.[2−7] Wilcox methodology[8] was used to prepare the methyl,nitro-substituted compound **5**. Reduction of Tröger's base **1** with H_2/Pd afforded **2**, which can be converted to the benzamide **3** by reaction with *p*-nitroanthranilic acid and DCC in DMF. Reduction to the benzylamine **4** by borane−THF, followed by reaction with formaldehyde and HCl finally yielded **5**, as a 2:1 mixture of **5a** and **5b** (Scheme 1). Because the synthesis of **1** requires four steps, the whole process requires eight steps, and although the yields in each step are good (about 60%), the total yield is only 14%.

Subsequently, Král and co-workers described a different, shorter procedure to prepare BTBs from *o*- and *m*-phenylenediamines.[9] For instance, BTB **7** can be obtained in four steps (the last of which constructs both methanodiazocine rings) from **6**, in an overall yield of 3.2% (Scheme 2).

These results prompted us to investigate the use of *p*-phenylenediamine (**8**) as a starting material to synthesize BTBs. In our first attempt, **8** was treated with 5-nitroisatoic anhydride (**9**) in THF at room temperature, to provide the monoamide **10** almost quantitatively, without any trace of the desired diamide. An attempt to convert **10** to the diamide by treatment with 2-amino-5-methylbenzoic acid (**11**) and DCC in DMF gave only the condensation product of DCC and **11**, already reported in the literature[10] (Scheme 3).

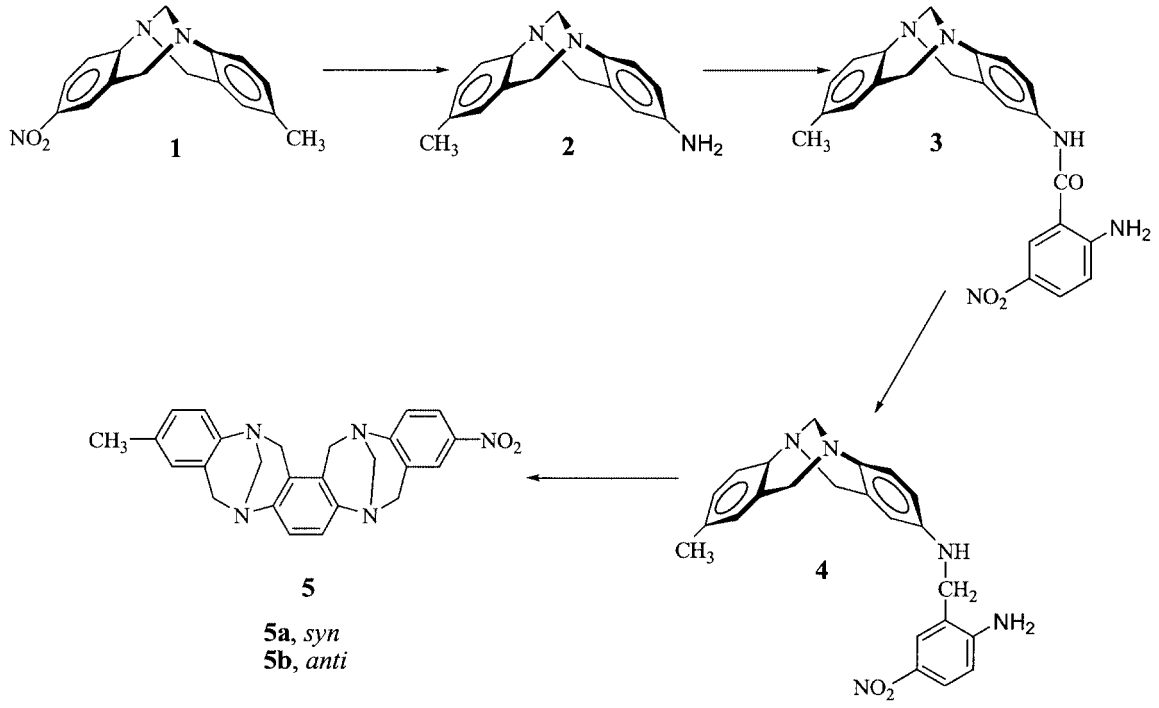
We therefore decided to invert the order of the steps, by condensing **8** and **11** in the presence of DCC, to obtain the monoamide **12** (containing a methyl group rather than a nitro group, as in **10**) in 56% yield. The subsequent reaction between **12** and **9** at room temperature led to the desired diamide **13** in 75% yield (Scheme 4).

Our first attempt at reducing the diamide **13** to the benzylic diamine **14** used a large excess of the borane−THF complex[1] (yield 56%). However, a better yield (95%) was obtained using the borane−dimethylsulfide reagent.[11] Treatment of **14** with aqueous formaldehyde and conc. hydrochloric acid in ethanol at 90 °C afforded the methyl, nitro-substituted BTB **5** in 22% yield, as a 1:1 mixture of two isomers.[1] These isomers were separated by flash chromatography on silica gel (eluting with hexane/ethyl acetate, 1:9).

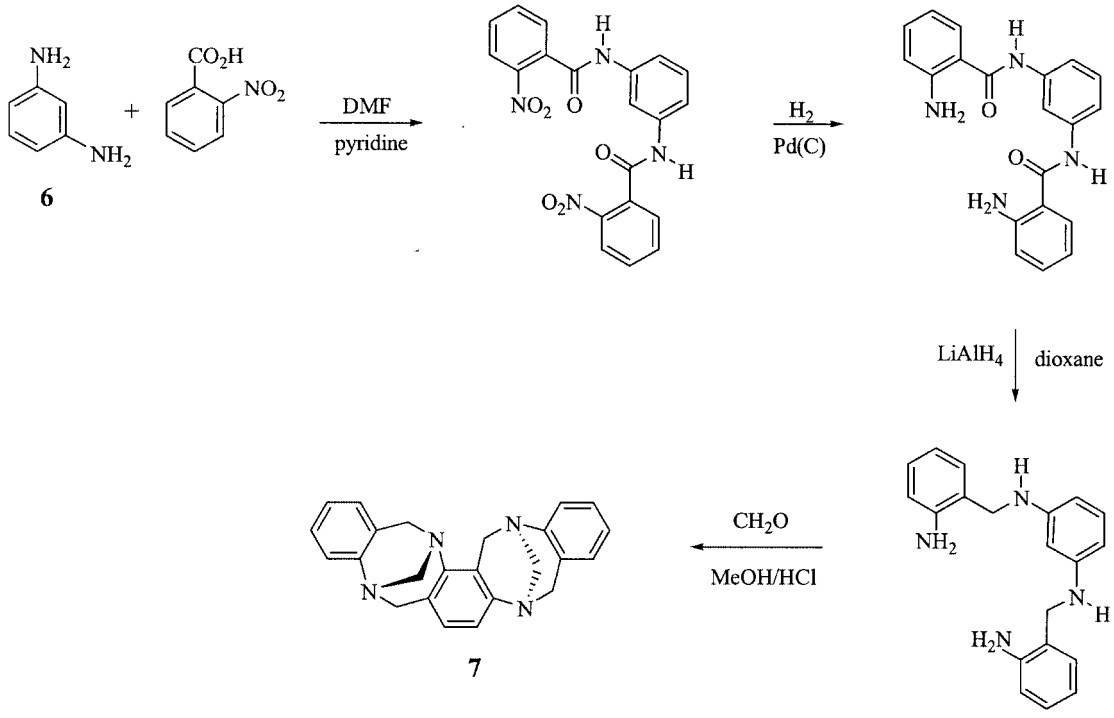
Using this procedure, **5** was obtained in an overall yield of only 8.3%. Moreover, the crude product was difficult to purify, and the most interesting BTB (the *syn* isomer **5a**, which has a "tweezer" structure) was formed in smaller amounts than with the Wilcox methodology.[1] We tested other conditions, such as aqueous formaldehyde and hydrochloric acid in ethanol at 50 °C, but the cyclization step proceeded in lower yield (10%), and only the *anti* BTB **5b** could be isolated. We also tried using hexamethylenetetramine in TFA as a source of formaldehyde,[4] but no BTB could be isolated from the crude product.

Despite these drawbacks, we decided to examine the possibility of preparing the dinitro-substituted BTB **17** by this method, because this compound cannot be prepared by the Wilcox procedure. Treatment of **8** with two equivalents of **9** yielded the diamide **15** in 97% yield. Reduction with borane-dimethylsulfide in anhydrous THF afforded the tetra-

[a] Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, 28040 Madrid, Spain
[b] Instituto de Química Médica, CSIC, Juan de la Cierva, 3, 28006 Madrid, Spain
[c] Laboratorio de Rayos X, Facultad de Ciencias Químicas, Universidad Complutense, 28040 Madrid, Spain



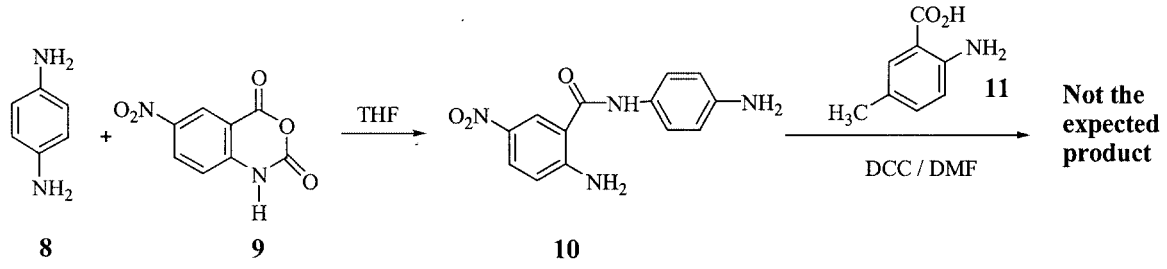
Scheme 1



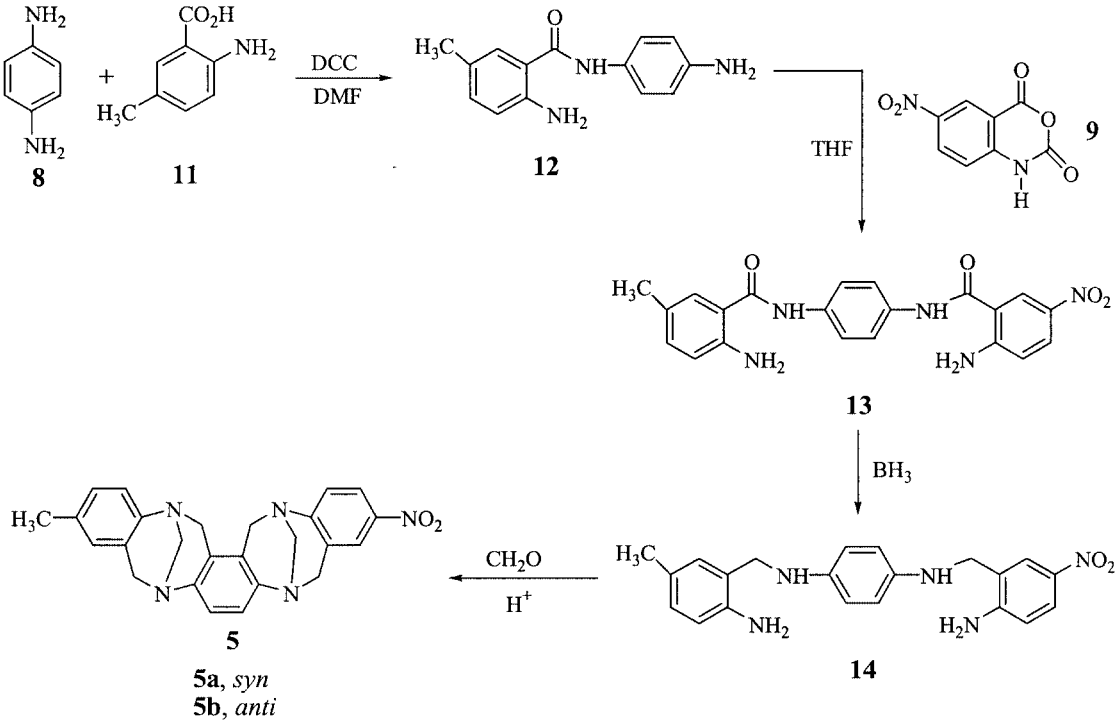
Scheme 2

amine **16** (89% yield). In the final step, we used aqueous formaldehyde and conc. hydrochloric acid in ethanol at reflux, and isolated **17** in 37% yield (overall yield 32%). The 1.2:1 mixture of *syn* and *anti* stereoisomers **17a** and **17b** could be separated by flash chromatography (Scheme 5).

Compounds **17a** and **17b** are the first BTBs with two strong electron-withdrawing substituents in the aromatic rings. In principle, the double-ring closure of **16** could lead to two regioisomers **17** and **18**, but only the former compound was isolated. The assignment was made by NOE dif-



Scheme 3



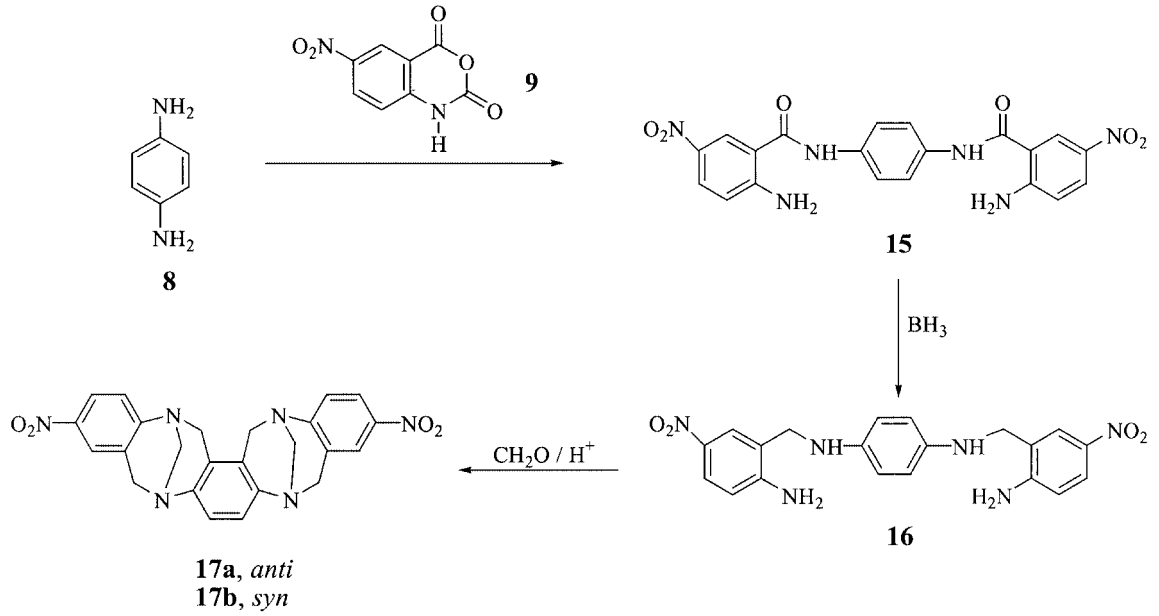
Scheme 4

ference experiments on **17a**, the less polar isomer. Irradiation of H^{15} (or H^{16}) produces a NOE effect only in the *endo* protons H^{13n} (or H^{18n}). The NOE effects that would be expected for the regioisomer **18** were not observed (Scheme 6).

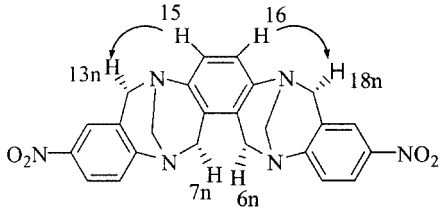
The regioselectivity in the formation of BTBs corresponds to that found previously.[1,9] On the basis of the different polarity of both stereoisomers, equilibriation experiments and ^{1}H NMR spectroscopic data,[1] we have tentatively identified **17a** as the *anti* isomer. The *syn* isomer **17b** is the first molecular tweezer described containing a bis-Tröger's base skeleton with electron-withdrawing substituents in both external aromatic rings.[1,9] Table 1 gives the ^{1}H and ^{13}C NMR spectroscopic data of the BTBs **17a** and **17b**.

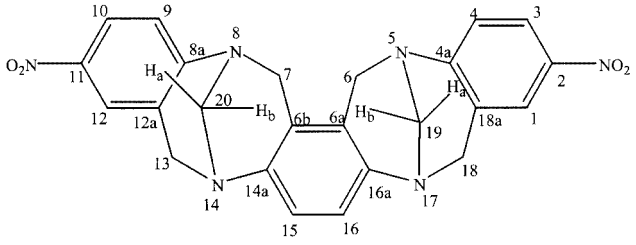
A ^{1}H COSY experiment allowed us to assign the methylene protons $H^{6(7)}$ and $H^{13(18)}$ in compound **17**. The relationship between $H^{1(12)}$ and $H^{18n(13n)}$ identifies the latter and these, in turn, identify $H^{18x(13x)}$. The assignment of the other AB system, corresponding to $H^{6(7)}$, was based on two facts: i) the *endo* proton is always more shielded than the *exo* proton, and ii) the signals due to the *endo* protons are broader than those for the *exo* protons due to a W-type ^4J coupling with the *anti* proton of the methylene bridge.[5,6] The methylene bridge protons appear as an AB system and were assigned in compound **17b** by a NOE difference experiment with proton H^{6x} (in compound **17a** these experiments failed).

HMQC (one bond) and HMBC (long distance) 2D-experiments were used to assign the signals given in Table 1. The following correlations were observed: C-2 with H^1 and H^4; C-4a with H^1, H^3, H^4, H^{6x} and H^{18}; C-6a with H^6 and H^{16}; C-12a with H^9 and H^{13}, and C-14a with H^{16}, H^7 and H^{13x}. The correlations observed between the *endo* protons and the carbon atoms of the methylene bridges, as well as between the quaternary carbon atoms adjacent to the nitrogen atoms and the *exo* protons of the nearby methylene group (for instance, between C-4a and H^{6x}), allow us to assign unambiguously these carbon atoms and protons.[6]

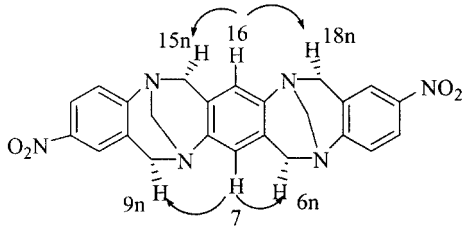


Scheme 5





Scheme 7



Scheme 6

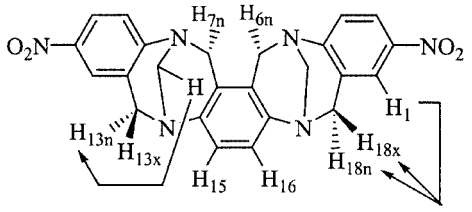
This ^{1}H NMR study allowed us to assign the stereochemistry of both **17a** and **17b** by comparison with the ^{1}H NMR spectroscopic data of the BBTs **5**. Table 2 shows that the difference in chemical shift between the *exo* and *endo* protons when the arrangement of the methylene groups at C-6(7) and C-13(18) is *syn* (**5a**) is larger than when they are *anti* (**5b**).

This configurational assignment was confirmed by X-ray diffraction analysis of **17b** (Figure 1). The X-ray structure shows that the central phenyl ring is almost orthogonal (angles 89.5° and 79.2°) to the external arms, as in most Tröger's bases, although the smaller of these two angles is lower than usual.[1,4] The external aromatic rings lie almost parallel with each other (angle 22.8°), with a distance between their centres of 6.717(8) Å. In the crystal, pairs of molecules are packed in such a way that (in the *c* direction) the arm of one molecule lies between the arms of the other (Figure 2). The nitro groups point to the central aromatic ring in an edge-to-face interaction, with a distance [4.423(8) Å], between the centres of the aromatic rings of the two molecules. This value is very close to that observed for **5a**.[1]

In conclusion, our synthetic approach,[1] although longer, affords the desired asymmetric BTBs with a high proportion of the *syn* tweezer isomer, in cleaner reactions and in a higher overall yield. When both substituents are electron-withdrawing groups, the synthesis of symmetric isomers is only possible by means of the second approach, using *p*-phenylenediamine.

Table 1. ^{1}H and ^{13}C NMR spectroscopic data of BTBs **17a** and **17b** in $CDCl_3$ (δ in ppm, J in Hz)

	^{1}H (500 MHz)		^{13}C (75 MHz)		
	17a	**17b**		**17a**	**17b**
$H^{1(12)}$	7.88, d, J = 2.4	7.79, d, J = 2.5	C-1(12)	123.05	122.80
			C-2(11)	143.71	143.74
$H^{3(10)}$	8.06, dd, J = 8.9, 2.5	7.97, dd, J = 8.8, 2.5	C-3(10)	122.84	122.89
$H^{4(9)}$	7.24, d, J = 8.9	7.19, d, J = 8.8	C-4(9)	125.56	125.62
			C-4a	154.78	154.86
$H^{6n(7n)}$	3.94, d, J = 16.6	3.92, d, J = 16.8	C-6(7)	56.13	56.18
$H^{6x(7x)}$	4.43, d, J = 16.6	4.48, d, J = 16.8	C-6a(6b)	124.41	124.19
			C-12a(18a)	128.82	128.86
$H^{13n(18n)}$	4.22, d, J = 17.0	4.18, d, J = 16.9	C-13(18)	58.09	57.77
$H^{13x(18x)}$	4.70, d, J = 17.0	4.69, d, J = 16.9	C-14a(16a)	143.32	143.36
$H^{15(16)}$	7.02	7.04	C-15(16)	124.86	124.76
$H^{19a(20a)}$	4.19 (4.22), d, J = 13.0	4.20, d, J = 12.6	C-19(20)	66.00	66.06
$H^{19b(20b)}$	4.22 (4.19), d, J = 13.0	4.24, d, J = 12.6			



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Scheme 8

Table 2. Chemical shift differences between *exo* and *endo* protons (in ppm)

	17a	**5b** (*anti*)	**17b**	**5a** (*syn*)
δ(6n)	3.94	3.93	3.92	3.93
δ(6x)	4.43	4.41	4.48	4.46
Δδ	0.49	0.48	0.56	0.53
δ(13n)	4.22	4.19	4.18	4.13
δ(13x)	4.70	4.68	4.69	4.66
Δδ	0.48	0.49	0.51	0.53

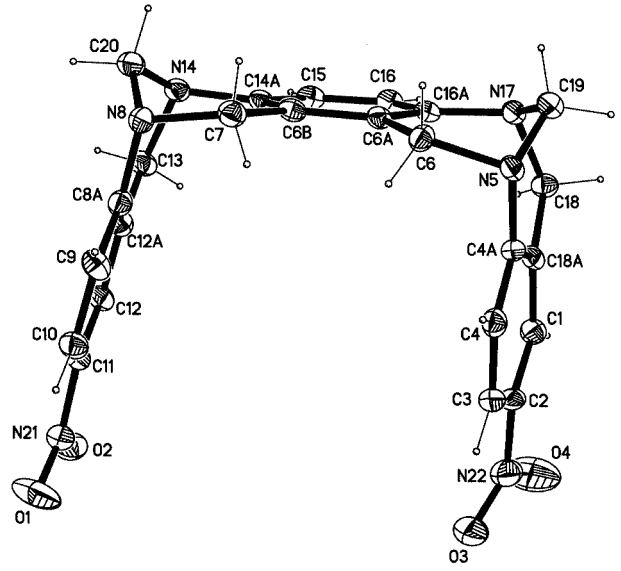

Figure 1. X-ray structure of **17b** — an ORTEP view

Experimental Section

Melting points were determined with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded with a Shimadzu FTIR-8300 spectrophotometer. NMR spectra were recorded with a Bruker AM-200 machine with the exception of the BTBs **17**, for which both 1D and 2D spectra were recorded with Bruker Avance DPX-300 and Avance AV-500 instruments. Tetramethylsilane was used as an internal standard. Merck silica gel 60 F524 was used for TLC analysis, and Merck silica gel (230−400 mesh) was used for separations by flash chromatography.

6-Nitroisatoic Anhydride (9): Prepared according to the literature procedure.[12]

2-Amino-*N*-(4-aminophenyl)-5-nitrobenzamide (10): 6-Nitroisatoic anhydride (**9**) (366 mg; 1.75 mmol) was added in small portions to a solution of *p*-phenylenediamine (**8**) (200 mg; 1.85 mmol) in anhydrous THF (25 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred at room temperature for 4 h and the solvents evaporated under reduced pressure. Crystallization from THF yielded the pure amide **10** (474 mg). Yield 94%. M.p. 243−245 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3383, 3350 and 3317 (ν_{NH}), 1628 (ν_{CO}), 1514 (ν_{NO2} asymm.), 1323 (ν_{NO2} symm.), 1256, 1128, 833 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 5.01 (br. s, 2 H, NH_2), 6.54 (AA′, 2 H, 3′-H and 5′-H), 6.82 (d, J = 9.2 Hz, 1 H, 3-H), 7.30 (BB′, 2 H, 2′-H and 6′-H), 7.64 (s, 2 H, NH_2), 8.05 (dd, J = 9.2, 2.6 Hz, 1 H, 4-H), 8.56 (d, J = 2.6 Hz, 1 H, 6-H), 10.10 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 113.90, 114.26, 115.92, 122.94, 126.30, 127.56, 127.71, 135.18, 145.66, 155.39, 165.62 ppm. $C_{13}H_{12}N_4O_3$ (272.3): calcd. C 57.35, H 4.44, N 20.58; found C 57.28, H 4.37, N 20.67.

2-Amino-*N*-(4-aminophenyl)-5-methylbenzamide (12): DCC (10.5 g; 51 mmol) was slowly added to a suspension of *p*-phenylenediamine (**8**) (9.0 g: 83 mmol) and 2-amino-5-methylbenzoic acid (**11**) (5.9 g; 39 mmol) in anhydrous DMF (30 mL) at 0 °C under argon. The

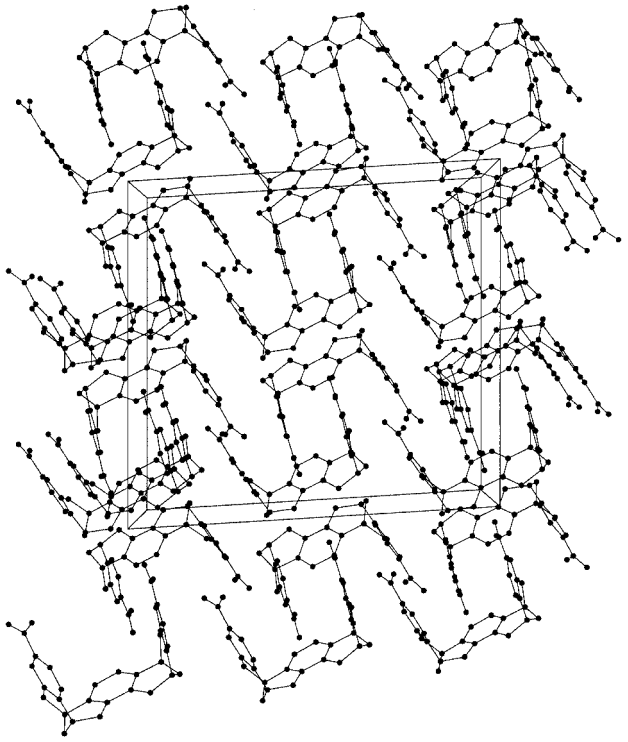

Figure 2. The unit cell of **17b**

reaction was allowed to reach room temperature and the mixture stirred overnight. The precipitate of dicyclohexylurea was then filtered off, washed with dichloromethane, and ethyl acetate (300 mL) added to the filtrate. The resulting solution was washed with saturated aqueous $NaHCO_3$ (3 × 100 mL), water (10 × 100 mL), dried with anhydrous $MgSO_4$, and the solvents evaporated under reduced pressure. Flash chromatography (eluent hexane/ethyl acetate 6:4) yielded the pure amide **12** (5.28 g). Yield 56%. M.p. 164−165 °C. IR (KBr): $\tilde{\nu}$ = 3416 and 3288 (ν_{NH}), 1639 (ν_{CO}), 1516, 1425, 1256, 1207, 822 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 2.20 (s, 3 H, CH_3), 4.88 (s, 2 H, NH_2), 6.03 (s, 2 H, NH_2), 6.53 (AA′, 2 H, 2′-H and 6′-H), 6.64 (d, *J* = 8.3 Hz, 1 H, 3-H), 6.99 (dd, *J* = 8.3, 1.5 Hz, 1 H, 4-H), 7.31 (BB′, 2 H, 3′-H and 5′-H), 7.38 (d, *J* = 1.5 Hz, 1 H, 6-H), 9.60 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 20.20, 113.81, 116.19, 116.58, 122.53, 123.26, 128.38, 128.51, 132.51, 145.11, 147.28, 167.35 ppm. $C_{14}H_{15}N_3O$ (241.3): calcd. C 69.69, H 6.27, N 17.41; found C 69.78, H 6.03, N 17.55.

***N*-(2-Amino-5-methylbenzoyl)-*N*′-(2-amino-5-nitrobenzoyl)-*p*-phenylenediamine (13):** Amide **12** (400 mg; 1.66 mmol) was added in small portions to a suspension of 6-nitroisatoic anhydride (**9**) (448 mg; 2.16 mmol) in anhydrous THF (4.5 mL) at room temperature under an argon atmosphere. The solution was refluxed for 6 h, poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water (50 mL), dried with anhydrous $MgSO_4$, and the solvents evaporated under reduced pressure. Crystallization from ethyl acetate yielded the pure amide **13** (504 mg). Yield 75%. M.p. 288−289 °C. IR (KBr): $\tilde{\nu}$ = 3458, 3371 and 3332 (ν_{NH}), 1645 and 1612 (ν_{CO}), 1520 (ν_{NO_2} asymm.), 1320 (ν_{NO_2} symm.), 820 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 2.22 (s, 3 H, CH_3), 6.10 (br. s, 2 H, NH_2), 6.67 (d, *J* = 8.3 Hz, 1 H, 3′-H), 6.85 (d, *J* = 9.3 Hz, 1 H, 3"-H), 7.03 (br. d, *J* = 8.3 Hz, 1 H, 4′-H), 7.43 (br. s, 1 H, 6′-H), 7.67 (m, 4 H, 2-H, 3-H, 5-H and 6-H), 8.08 (dd, *J* = 9.3, 2.5 Hz, 1 H, 4"-H), 8.62 (d, *J* = 2.5 Hz, 1 H, 6"-H), 9.98 (s, 1 H, NH), 10.42 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 20.22, 113.75, 115.57, 116.06, 116.74, 120.83, 121.27, 123.33, 126.50, 127.78, 128.67, 133.05, 134.30, 135.13, 135.56, 147.59, 155.40, 166.01, 167.87 ppm. $C_{21}H_{19}N_5O_4$ (405.4): calcd. C 62.22, H 4.72, N 17.27; found C 62.20, H 4.60, N 17.39.

***N*-(2-Amino-5-methylbenzyl)-*N*′-(2-amino-5-nitrobenzyl)-*p*-phenylenediamine (14):** 10 M borane-dimethylsulfide (2.1 mL; 20.7 mmol) was added dropwise to a suspension of amide **13** (700 mg; 1.73 mmol) in anhydrous THF (15 mL) at 0 °C under an argon atmosphere. The suspension was refluxed for 20 h and cooled to room temperature. A 0.7 M solution of HCl in methanol (15 mL) was then added dropwise, the reaction mixture refluxed for 1 h, and the solvents evaporated under reduced pressure. Water (50 mL) was added to the residue, the resulting solution adjusted to pH 11 with 25% aqueous ammonia solution, and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with water (50 mL), dried with anhydrous $MgSO_4$, and the solvents evaporated under reduced pressure. Flash chromatography (eluent hexane/ethyl acetate 1:1) afforded the pure amine **14** (620 mg). Yield 95%. M.p. 173−174 °C. IR (KBr): $\tilde{\nu}$ = 3481, 3452, 3406 and 3368 (ν_{NH}), 1636, 1522 (ν_{NO_2} asymm.), 1306 (ν_{NO_2} symm.), 1286, 824 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 2.11 (s, 3 H, CH_3), 3.92 (d, *J* = 5.9 Hz, 2 H, CH_2), 3.99 (d, *J* = 5.9 Hz, 2 H, CH_2), 5.09 (t, *J* = 5.9 Hz, 1 H, NH), 5.46 (t, *J* = 5.9 Hz, 1 H, NH), 6.39−6.46 (AA′BB′, 4 H, 2-H, 3-H, 5-H and 6-H), 6.47 (br. s, 2 H, NH_2), 6.53 (d, *J* = 8.1 Hz, 1 H, 3′-H), 6.60 (br. s, 2 H, NH_2), 6.67 (d, *J* = 8.8 Hz, 1 H, 3"-H), 6.75 (br. d, *J* = 8.1, 1 H, 4′-H), 6.89 (br. s, 1 H, 6′-H), 7.87 (dd, *J* = 9.0, 2.7 Hz, 1 H, 4"-H), 7.99 (d, *J* = 2.7 Hz, 1 H, 6"-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 20.22, 44.03, 45.48, 113.15, 113.87, 114.10, 114.88, 122.57, 123.36, 124.01, 124.20, 124.28, 127.64, 128.84, 135.99, 139.86, 140.85, 143.90, 153.17 ppm. $C_{21}H_{23}N_5O_2$ (377.4): calcd. C 66.83, H 6.14, N 18.55; found C 66.76, H 6.10, N 18.64.

2-Methyl-11-nitro-5,17:8,14-dimethano-5,8,14,17-tetraaza-5,6,7,8,13,14,17,18-octahydrodibenzo[*e*,*e*′]benzo[1,2-*a*:3,4-*a*′]dicyclooctene (5). Method A: 35% Aqueous formaldehyde (0.6 mL) and 35% HCl (0.6 mL) were added successively to a suspension of the diamine **14** (200 mg; 0.53 mmol) in ethanol (9 mL) at room temperature under argon. The mixture was stirred at 90 °C for 24 h, cooled to room temperature and poured inzo 17 mL of water. The solution was adjusted to pH 11 with 25% aqueous ammonia and extracted with dichloromethane (3 × 50 mL). The organic layer was washed with saturated solutions of $NaHCO_3$ and NaCl, dried with anhydrous $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. Flash chromatography (eluent hexane/ethyl acetate, 1:9) yielded first the *anti* isomer **5b** (12% yield) and then the *syn* isomer **5a** (10% yield). **Method B:** As for Method A, but with heating at 50 °C for 24 h. Only *anti* **5b** was obtained (10% yield). **Method C:** A suspension of the diamine **14** (0.40 mmol) and hexamethylenetetramine (0.8 mmol) in trifluoroacetic acid (1.5 mL) was stirred under argon at room temperature for 24 h, by which time the suspension had cleared. Trifluoroacetic acid was removed under reduced pressure, water was added to the residue and the solution adjusted to pH 11 with 25% aqueous ammonia. This solution was extracted with $CHCl_3$ (3 × 50 mL), the organic layer dried with anhydrous $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. TLC and ^1H NMR of the residue showed that there were no traces of **5**.

***N,N*′-Bis(2-amino-5-nitrobenzoyl)-*p*-phenylenediamine (15):** 6-Nitroisatoic anhydride (**9**) (1.92 g; 9.2 mmol) was added in small portions to a suspension of *p*-phenylenediamine (**8**) (482 mg; 4.5 mmol) in anhydrous THF (16 mL) at room temperature under

argon. The reaction mixture was stirred at room temperature for two days, and the solvents evaporated under reduced pressure. Crystallization from THF yielded pure **15** (1.89 g). Yield 97%. M.p. 350 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3470, 3393 and 3308 (ν_{NH}), 1612 (ν_{CO}), 1585, 1560 (ν_{NO_2} asymm.), 1514, 1329 (ν_{NO2} symm.), 1285, 833 cm^{-1}. ^1H NMR ([D_6]DMSO): δ = 6.86 (d, *J* = 9.3 Hz, 1 H, 3′-H), 7.69 (s, 4 H, 2-H and NH_2), 8.08 (dd, *J* = 9.2, 2.5 Hz, 1 H, 4′-H), 8.63 (d, *J* = 2.6 Hz, 1 H, 6′-H), 10.45 (s, 1 H, NH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 113.70, 116.09, 121.28, 126.52, 127.82, 134.86, 135.14, 155.41, 166.07 ppm. $C_{20}H_{16}N_6O_6$ (436.4): calcd. C 55.05, H 3.70, N 19.26; found C 55.00, H 3.67, N 19.36.

***N,N′*-Bis(2-amino-5-nitrobenzyl)-*p*-phenylenediamine (16):** 10 M Borane−dimethylsulfide (6.5 mL; 64.7 mmol) was added dropwise to a suspension of the amide **15** (2.35 g; 5.4 mmol) in anhydrous THF (40 mL) at 0 °C under argon. The suspension was refluxed for 12 h and cooled to room temperature. 6 M Hydrochloric acid (150 mL) was then added dropwise, and the solution stirred for 2 h at room temperature. This solution was adjusted to pH 11 with 25% aqueous ammonia, and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (100 mL), dried with anhydrous $MgSO_4$, and the solvents evaporated under reduced pressure. Crystallization from THF yielded the pure amine **16** (1.96 g). Yield 89%. M.p. 220−222 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3410, 3339 and 3292 (ν_{NH}), 1616, 1518 (ν_{NO_2} asymm.), 1374 (ν_{NO2} symm.), 1310, 820 cm^{-1}. ^1H NMR ([D_6]DMSO): δ 4.01 (br. d, *J* = 4.9 Hz, 2 H, CH_2), 5.46 (br. t, 1 H, NH), 6.45 (s, 2 H, 2-H), 6.58 (br. s, 2 H, NH_2), 6.68 (d, *J* = 9.0 Hz, 1 H, 3′-H), 7.88 (dd, *J* = 8.9, 2.7 Hz, 1 H, 4′-H), 8.00 (d, *J* = 2.6 Hz, 1 H, 6′-H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 44.29, 113.38, 114.21, 122.72, 124.30, 124.51, 136.22, 140.33, 153.40 ppm. $C_{20}H_{20}N_6O_4$ (408.4): calcd. C 58.82, H 4.94, N 20.58; found C 58.93, H 4.78, N 20.53.

2,11-Dinitro-5,17:8,14-dimethano-5,8,14,17-tetraaza-5,6,7,8,13,14,17,18-octahydrodibenzo[*e*,*e′*]benzo[1,2-*a*:3,4-*a′*]dicyclooctene (17): 37% Aqueous formaldehyde (4.3 mL; 58 mmol) and 36% hydrochloric acid (4.9 mL; 58 mmol) were added successively to a suspension of the diamine **16** (1.96 g; 4.8 mmol) in 95% ethanol (40 mL) at room temperature under argon. The reaction mixture was refluxed for 48 h, cooled to room temperature and poured into 100 mL of water. The solution was adjusted to pH 11 with 25% ammonia, and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (100 mL), dried with anhydrous $MgSO_4$, and the solvents evaporated under reduced pressure. The residue was flash chromatographed over silica gel. Elution with ethyl acetate/hexane (55:45) afforded the *anti* isomer **17a** (429 mg; yield 20%); subsequent elution with ethyl acetate/hexane (85:15) afforded the *syn* isomer **17b** (362 mg; yield 17%).

***anti* Isomer 17a:** M.p. 243−245 °C (dec.). IR (KBr): $\tilde{\nu}$ = 1611, 1580, 1512, 1472, 1337, 1221, 1084, 941, 839, 806 cm^{-1}. HRMS (FAB+) calcd. for $C_{24}H_{20}N_6O_4$ [M] 456.154588; found 456.154689, [M + 1] calcd. 457.162412, found 455.162207.

***syn* Isomer 17b:** M.p. > 380 °C (dec.). IR (KBr): $\tilde{\nu}$ = 1612, 1580, 1508, 1472, 1342, 1215, 1084, 945, 839 cm^{-1}. HRMS (FAB+) calcd. for $C_{24}H_{20}N_6O_4$ [M] 456.154588; found 456.154301, [M + 1] calcd. 457.162412, found 455.161613.

Equilibriation of 17a: A solution of BTB **17a** (8 mg; 18 μmol) in 95% ethanol (1.5 mL) containing 36% aqueous hydrogen chloride (50 μL; 600 μmol) was stirred at 80 °C for 24 h. The reaction mixture was then cooled to room temperature, poured into 10 mL of water, adjusted to pH 11 with 25% ammonia, and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with water (10 mL), dried with anhydrous $MgSO_4$, and the solvents evaporated under reduced pressure to afford a mixture of **17a** and **17b** (8 mg; quantitative yield). The ratio of the isomers was approximately 1:1, as determined by integration of signals in the ^1H NMR spectrum.

Crystal Structure of 17b: A crystal of **17b** was obtained from a saturated solution in tetrahydrofuran/dichloromethane. 11550 reflections were collected on a SMART CCD-BRUKER diffractometer, using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) operating at 50 kV and 35 mA. Data were collected over a hemisphere of reciprocal space by combination of three exposure sets. Each exposure of 30 s covered 0.3 in ω. The reflection range for the data collection was 1.98 < θ <25°. The first 50 frames were re-collected at the end of the data collection process to monitor crystal decay. 3692 reflections were observed [$I > 2\sigma(I)$], 308 refined parameters, *R* = 0.058 (*R*w = 0.1753). The structure was solved by direct methods and Fourier synthesis. The refinement was done by full-matrix least-squares procedures on F^2 (SHELXTL version 5.1).[13] The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in calculated positions. Further crystallographic details for the structure reported in this paper may be obtained from the Cambridge Crystallographic Data Centre, on quoting the depository number CCDC-220288. A summary of the fundamental crystal data is given in Table 3.

Table 3. Crystal data and structure refinement for **17b**

Molecular formula	$C_{24}H_{20}N_6O_4$
Molecular mass	456.46
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	*C*2/*c*
Unit cell dimensions	*a* = 20.574(3) Å α = 90°
	b = 10.6400(17) Å β = 93.509(4)°
	c = 19.183(3) Å γ = 90°
Volume	4191.5(11) $Å^3$
Z	8
Density (calcd.)	1.447 Mg/m^3
Absorption coefficient	0.102 mm^{-1}
F(000)	1904
Crystal size	0.08 × 0.12 × 0.30 mm
θ range for data collection	1.98 to 25.00°.
Index ranges	$-24 \le h \le 22$, $-12 \le k \le 12$, $-22 \le l \le 20$
Reflections collected	10758
Independent reflections	3692 [*R*(int) = 0.1255]
Completeness to θ = 25.00°	99.8%
Absorption correction	none
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	3692/0/308
Goodness-of-fit on F^2	0.792
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0581, *wR*2 = 0.1210
R indices (all data)	*R*1 = 0.2186, *wR*2 = 0.1753
Extinction coefficient	0.00134(19)
Largest diff. peak and hole	0.226 and −0.226 e·$Å^{-3}$

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