A shorter synthesis of symmetrical 2,11-dimethyl-bis-Tröger's bases. A new molecular tweezer

Thierry Mas[a], Carmen Pardo*[a], and José Elguero[b]

[a] Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, E-28040 Madrid, Spain, b Centro de Química Orgánica 'Manuel Lora Tamayo', Juan de la Cierva 3, E-28006 Madrid, Spain
E-mail : chpardo@quim.ucm.es

Dedicated to Professor Enrique Meléndez on his 70th anniversary
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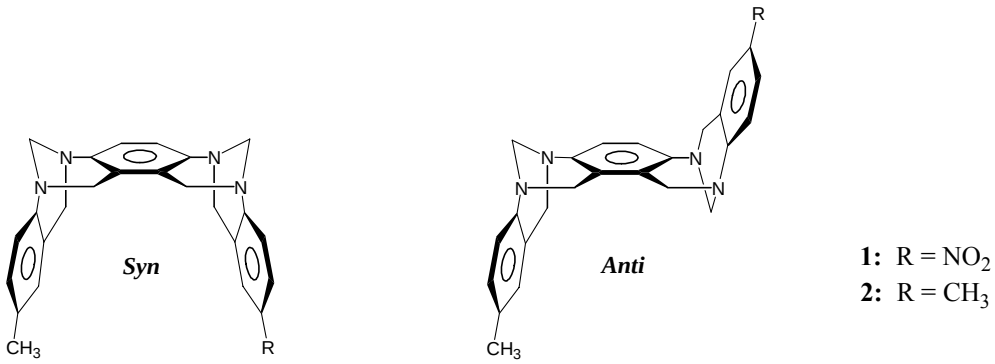
Abstract
This paper reports a new synthesis of 2,11-dimethyl-bis-Tröger´s bases starting from *p*-phenylenediamine. The new synthesis is more efficient than those previously described and yields the *anti* isomer in much higher yield. Isomerization in acidic medium of the *anti* isomer allowed us to obtain for the first time the *syn* isomer, a new molecular tweezer.

Keywords: Tröger's bases, *p*-phenylenediamine, NMR, supramolecular chemistry

Introduction

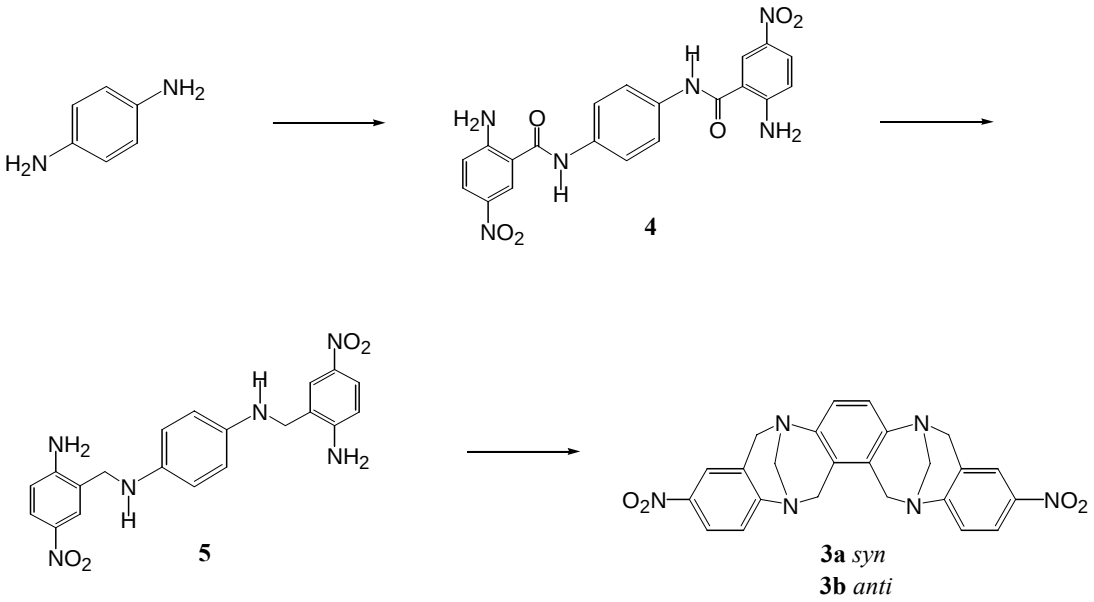
As a reasonable approach to explore and amplify the interesting properties of Tröger's base analogues,[1-6] and with the aim to use this structural framework unit as building block in the construction of new nanoporous materials and new supramolecular hosts, we have been the first to synthesize bis-Tröger's bases **1** and **2**.[7]



Scheme 1

In the case of compound **2**, an eight-step synthesis starting from *p*-toluidine, following Wilcox methodology for the synthesis of asymmetrically substituted Tröger's Bases,[8] affords only to the *anti* isomer in very low yield and with no trace of the most interesting *syn* isomer.[7] In the case of such symmetrical compounds, it is reasonable to imagine that in the absence of stabilizing π-stacking interactions between identical external phenyl rings, the *anti* stereoisomer is exclusively formed. These results and conclusions led us to disfavor this synthetic way for obtaining *symmetrical* dimethyl molecular tweezers.

Subsequently, Král and coworkers described a different and shorter procedure to prepare bis-Tröger's bases from *ortho* and *meta*-phenylenediamines[9] in four steps, both methanodiazocine rings being formed in the last one. In all cases only the *anti* isomer was isolated. Following a similar route starting from *p*-phenylenediamine, we recently succeeded in the synthesis of the symmetrical dinitro-bis-Bases **3** in only three steps (Scheme 2).[10] By treating *p*-phenylenediamine with two equivalents of 6-nitroisatoic anhydride we obtained the bis-amide **4** that was reduced with borane-SMe_2 complex in anhydrous THF to afford the tetramine **5**. Treatment of **5** with aqueous formaldehyde and conc. hydrochloric acid in ethanol at 95 ºC allowed us to obtain an almost equimolecular mixture of both *syn/anti* steroisomers **3a** and **3b**. The structure of the dinitro molecular tweezer **3a** was unambiguously determined by X-ray crystallography.

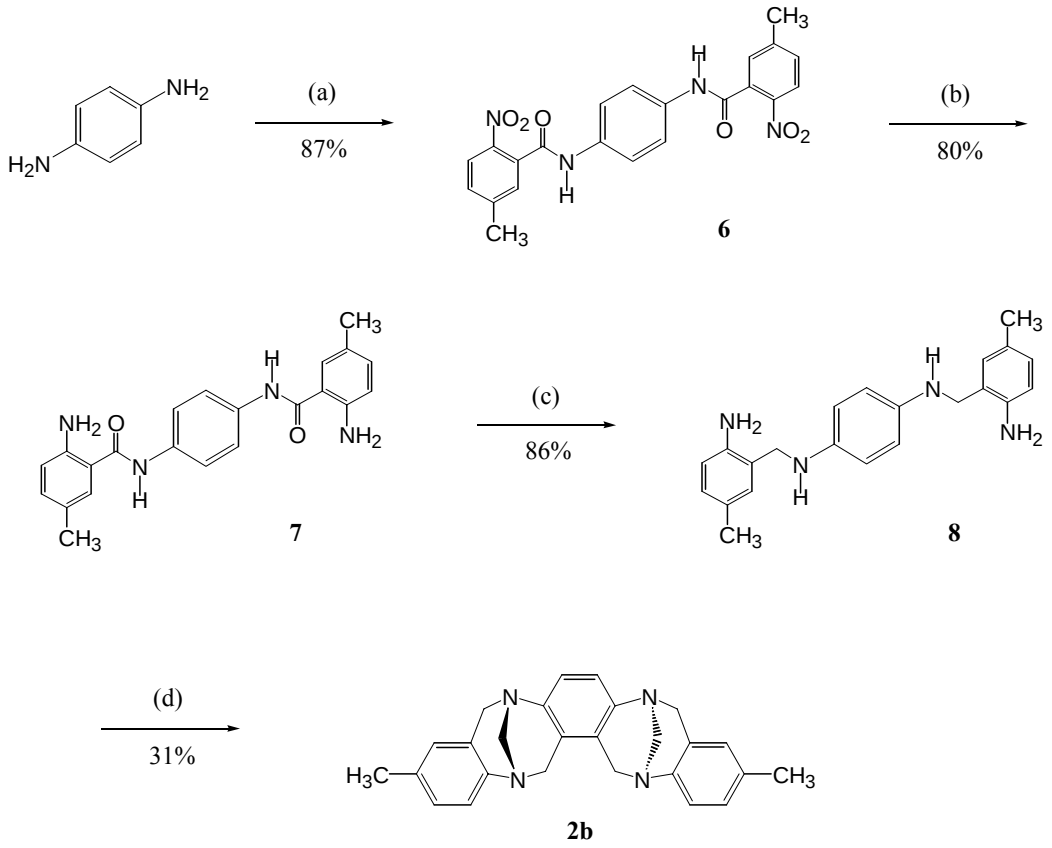


Scheme 2

The formation and isolation of this symmetrical *syn* isomer, in spite of the hypothesis earlier formulated according to which it would not be favored, have great interest and prompted us to re-evaluated the possibility to synthesize symmetrical *syn* bis-Tröger's Bases. We thus decided to examine the possibilities to obtain the *syn* isomer of the dimethyl-bis-Tröger's base **2** possessing a tweezer shape. We report herein a short and convenient synthesis of the bis-Tröger's base **2** together with the isolation of the molecular tweezer **2a**.

Results and Discussion

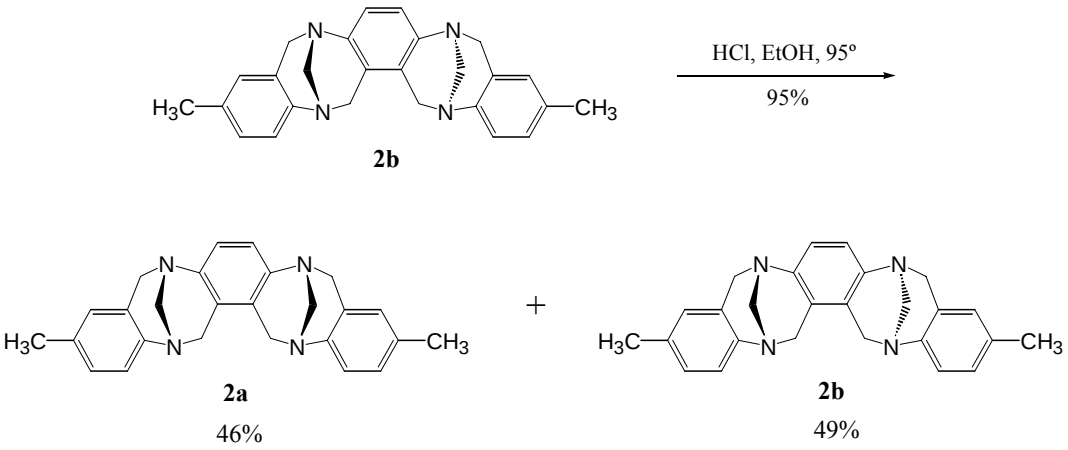
The synthesis of bis-Tröger's bases **2** was carried out using a synthetic scheme derived from that we used to synthesize compounds **3a** and **3b**. Diamide **7** could not be directly obtained by reaction of *p*-phenylenediamine with 2-amino-5-methylbenzoic acid in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC). Thus, diamide **6** is first obtained by reaction between *p*-phenylendiamine and 5-methyl-2-nitrobenzoic acid in the presence of dicyclohexylcarbodiimide (DCC) in DMF. Compound **6** is then catalytically hydrogenated over 10% palladium on charcoal to afford diamide **7**. Diamide **7** leads to tetraamine **8** through reduction with the help of borane-SMe_2 complex in anhydrous THF. Intramolecular cyclization of this latter by reaction with hexamethylene-tetraamine (HMTA) in TFA allowed us to obtain the *anti* isomer **2b** in 31% yield (18.5% global yield). However, here again, no trace of the *syn* isomer **2a** could be detected.



(a) 5-methyl-2-nitrobenzoic acid, DCC, DMF, rt; (b) H_2/Pd 10%(C), EtOH, rt;
(c) BH_3-SMe_2, THF, reflux; (d) HMTA, TFA, rt.

Scheme 3

Although these results seem disappointing, we nevertheless decided to realize different attempts to study the possible isomerisation of the *anti* isomer **2b**. In these trials, we chose to vary the experimental conditions (reaction time, temperature, HCl proportion) with the aim to found experimental conditions leading to an efficient synthesis of the *syn* isomer. After many attempts, we succeeded in preparing the *syn* isomer **2a** by treating **2b** with concentrated hydrochloric acid in ethanol at 95 ºC. A 1/1 mixture (ratio determined through ^{1}H NMR integration) of the two stereoisomers **2a** and **2b** in an almost quantitative yield was obtained. Both stereoisomers were separated by flash chromatography and identified by ^{1}H NMR.

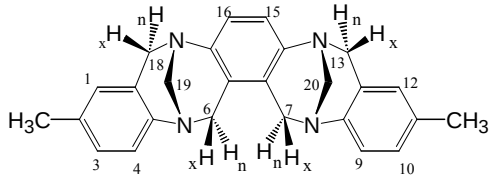


Scheme 4

The *anti* stereoisomer **2b** was identical to the previously described.[7] The *syn* stereoisomer **2a** was unambiguously identified by ^{1}H and ^{13}C NMR at 500 MHz. As reported previously,[8] we can see in Tables 1 and 2 that in the *syn* isomer the protons of the external aromatic rings are more shielded and that the Δδ between the *exo* and the *endo* protons of the methylene groups H-6(7) and H-13(18) are larger than in the *anti* arrangement.

Table 1. ^{1}H NMR data of bis-Tröger's bases **2a** and **2b** in $CDCl_3$ (δ in ppm, *J* in Hz)

	2a	**2b**
$H_{1(12)}$	6.70	6.74
		J = 1.7
$H_{3(10)}$	6.93	7.00
	J = 8.1	*J* = 8.25
$H_{4(9)}$	7.00	7.04
	J = 8.1	*J* = 8.25
$H_{6n(7n)}$	3.85	3.86
	J = 16.7	*J* = 16.5
$H_{6x(7x)}$	4.39	4.32
	J = 16.7	*J* = 16.5
$H_{13n(18n)}$	4.09	4.11
	J = 16.7	*J* = 16.9
$H_{13x(18x)}$	4.64	4.62
	J = 16.7	*J* = 16.9
$H_{15(16)}$	7.01	6.98
$H_{19a(20a)}$	4.20 / 4.29	4.14 / 4.24
	J = 12.7	*J* = 12.8



2a

Table 2. Δδ between the *exo* and *endo* protons in **2a** and **2b**

	2a	**2b**
δ-6n	3.85	3.86
δ -6x	4.39	4.32
Δδ	0.54	0.46
δ -13n	4.09	4.11
δ -13x	4.64	4.62
Δδ	0.55	0.51

Conclusions

In general, for symmetrical bis-Tröger's bases the approach using *p*-phenylenediamine as starting material is the best way of access. The isomerization of the *anti* stereoisomer in acidic medium allows to obtain the most interesting *syn* stereoisomer in good yield.

Experimental Section

General Procedures. Melting points were determined with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8300 spectrophotometer. NMR spectra were recorded with a Bruker AM-200 machine with the exception of those of compounds **2a** and **2b** which were recorded on a Bruker Avance AV-500 instrument. Chemical shifts are in ppm (internal TMS) and coupling constants in Hz. For TLC Merck silica gel 60 F524 and for chromatographic separations, flash chromatography over silica gel Merck (230-400 mesh) were used.

***N,N'*-Bis-(5-methyl-2-nitrobenzoyl)-*p*-phenylenediamine (6).** DCC (2.48 g; 12.0 mmol) was added at 0 ºC and under Ar atmosphere to a solution of *p*-phenylendiamine (542 mg; 5.0 mmol) and 5-methyl-2-nitrobenzoic acid (2.0 g; 11 mmol) in anhydrous DMF (5 mL). The temperature was allowed to reach r.t. and the reaction mixture was stirred 72 h. The dicyclohexylurea precipitate was then filtered off, washed with dichloromethane, and ethyl acetate (250 mL) was added to the filtrate. This organic solution was washed with saturated aqueous $NaHCO_3$ (2 x 100 mL), water (4 x 100 mL), and then filtered. The precipitate so obtained was washed with dichloromethane and crystallized in ethyl acetate, to afford the pure amide **6** (1.89 g). Yield 87%. mp 334-336ºC (dec.). IR (KBr) *v* (cm^{-1}): 3294, 1655, 1549, 1514, 1408, 1344, 1321, 843. ^{1}H-NMR (DMSO-d_6): δ 2.47 (s, 6H), 7.55 (bd, 2H, *J* = 8.3), 7.60 (bs, 2H), 7.65 (s, 4H), 8.06 (d, 2H, *J* = 8.3), 10.65 (s, 2H). ^{13}C-NMR (DMSO-d_6): δ 20.28, 119.54, 123.77, 129.08, 130.44, 132.37, 134.39, 143.58, 144.71, 163.52. MS (EI) m/z: 434(2) ($M^{+\cdot}$), 205(23), 172(20), 107(29), 71(27), 57(48, 56(53), 55(36), 43(100). MS (EI) m/z: 434(17) ($M^{+\cdot}$), 271 (25), 224(30), 165(36), 164(100), 134(44), 108(38), 107(92), 79(80), 56(92).

***N,N'*-Bis-(2-amino-5-methylbenzoyl)-*p*-phenylenediamine (7).** A suspension of diamide **6** (500 mg; 1.15 mmol) in ethanol (25 ml) was hydrogenated under 3-4 atm over 10% palladium on charcoal (150 mg) at r.t. during 2 h. The reaction mixture was then filtered and the precipitate, constituted by a mixture of the desired product in the solid state together with palladium on charcoal, was washed with ethanol and the filtrates eliminated. The product was then dissolved in DMSO (10-15 ml) and separated from the palladium on charcoal through filtration. Then water (50 ml) was added to the filtrate and the product isolated by filtration. The filtrate was first washed with dichloromethane and then crystallized in ethanol to afford pure diamide **7** (343 mg). Yield 80%. mp 310-312ºC (dec.). IR (KBr) ν (cm^{-1}): 3460, 3366, 3279, 1638, 1558, 1510, 1404, 822. ^{1}H-NMR (DMSO-d_6): δ 2.21 (s, 6H), 6.10 (bs, 4H), 6.67 (d, 2H, *J* = 8.3), 7.03 (dd, 2H, *J* = 8.3, 1.7), 7.44 (bs, 2H), 7.65 (s, 4H) 9.95 (s, 2H). ^{13}C-NMR (DMSO-d_6): δ 19.53, 114.95, 116.04, 120.16, 122.66, 127.98, 132.31, 134.33, 146.87, 167.15. MS (EI) m/z: 374(36) ($M^{+\cdot}$), 241(31), 134(100),108(74), 106(40),108(74), 106(40), 43(35).

***N,N'*-Bis-(2-amino-5-methylbenzyl)-*p*-phenylenediamine (8).** 10M BH_3SMe_2 (580 μL; 5.78 mmol) was added drop-wise at 0ºC and under Ar atmosphere to a suspension of amide **7** (180 mg; 0.48 mmol) in anhydrous THF (4 mL). The suspension was refluxed for 24 h and cooled to room temperature. 6M aqueous hydrogen chloride (36 mL) was then added drop-wise at 0ºC to the reaction mixture that was stirred for 3 h at r.t. The solution so obtained was basified

at 0ºC with 15M aqueous ammonia solution (p*H* = 11) and extracted with CH_2Cl_2 (3 x 25 mL). The organic layer was washed with water (25 mL), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. Crystallization in chloroform afford the pure amine **8** (144 mg). Yield 86%. mp 160-162ºC. IR (KBr) ν(cm^{-1}): 3412, 3250, 1622, 1508, 1292, 818. ^{1}H-NMR ($CDCl_3$): δ 2.26 (s, 6H), 4.16 (s, 4H), 6.64 (d, 2H, *J* = 8.3), 6.70 (s, 4H), 6.96 (bd, 2H, *J* = 8.3), 6.98 (bs, 2H). ^{13}C-NMR ($CDCl_3$): δ 20.37, 48.43, 115.34, 116.02, 123.49, 127.49, 129.20, 130.61, 141.33, 143.44. MS (EI) m/z: 346(39) ($M^{+\cdot}$), 227(28), 120(85), 108(100).

2,11-Dimethyl-5α,8β,14β,17α-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 (2b). HMTA (677 mg; 4.83 mmol) was added at r.t. and under Ar atmosphere to a suspension of diamine **8** (760 mg; 2.20 mmol) in anhydrous TFA (20 mL). The reaction mixture was stirred for 72 h and poured over 50 mL of cold water. The solution was made alkaline with 25% ammonia (p*H* = 11) and extracted with CH_2Cl_2 (3 x 100 mL). The organic layer was washed with water (150 mL), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The crude residue obtained was flash chromatographed over silica gel (eluent ethyl acetate), to afford pure compound **2b** (265 mg). Yield 31%.

2,11-Dimethyl-5α,8α,14α,17α-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 (2a). A solution of BB **2b** (150 mg; 0.38 mmol) in 95% ethanol (4 mL) containing 36% aqueous hydrogen chloride (390 µL; 4.57 mmol) was refluxed during 15 h. The reaction mixture was cooled to r. t., poured over 20 mL of water, made alkaline with 25% ammonia (p*H* = 11), and extracted with CH_2Cl_2 (3 x 15 mL). The organic layer was washed with water (20 mL), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to afford an *approx.* 1/1 mixture (ratio determined through ^{1}H NMR integration) of the two stereoisomers **2a** and **2b** (148 mg; quantitative yield). The crude so obtained was flash chromatographed over silica gel. Elution with ethyl acetate first affords the *anti* isomer **2b** (74 mg; yield 49%), and second the *syn* isomer **2a** (69 mg; yield 46%).

Anti isomer **2b**. R_f (ethyl acetate/methanol 9/1) = 0.46. mp 273-275ºC (dec.). IR (KBr) ν (cm^{-1}): 1497, 1474, 1327, 1217, 1096, 1074, 960, 839, 827. ^{13}C-NMR ($CDCl_3$): δ 20.85, 55.83, 58.19, 60.35, 124.26, 124.88, 124.90, 127.30, 127.53, 128.15, 133.77, 143.65, 145.42.

Syn isomer **2a**. R_f (ethyl acetate/methanol 9/1) = 0.17. mp 257-258ºC (dec.). IR (KBr) ν (cm^{-1}): 1497, 1475, 1325, 1213, 1107, 1069, 970, 839, 829. ^{13}C-NMR ($CDCl_3$): δ 20.80, 55.76, 57.74, 66.34, 124.21, 124.68, 125.40, 127.10, 127.48, 128.23, 133.82, 143.58, 145.36.

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