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Synthesis of symmetrical amino and aminomethyl derivatives of Tröger's base via Pd-catalyzed C–C and C–N bond formation

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Abstract—In this paper, we report the synthesis of amino and aminomethyl derivatives of Tröger's base (±)-**1** and (±)-**2**. The key steps in the synthesis of (±)-**1** and (±)-**2** are Pd-catalyzed amination and cyanation, respectively, of the easily accessible dihalo derivatives (±)-**3**. These compounds are important intermediates in the synthesis of new ligands and building blocks for H-bonded supramolecular architectures.

1. Introduction

Tröger's base, (±)-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (Fig. 1), was first synthesized in 1887 by the condensation of *para*-methylaniline with formaldehyde. Tröger's base is a chiral diamine with two stereogenic bridge-head nitrogen atoms. The unique set of structural features (C_2-symmetry and a rigid V-shape geometry with the two aromatic rings nearly perpendicular to each other) makes derivatives of Tröger's base very attractive for the application in supramolecular chemistry and molecular recognition.[1] In particular, the rigid scaffold of Tröger's base has been used in the design of synthetic receptors for recognition of adenine, pyrimidine, biotin derivatives,[2] and dicarboxylic acids,[3] in the 'molecular torsion balance' for the quantification of weak interactions,[4] and in the templated synthesis of functional fullerene derivatives with precisely defined geometry.[5,6] Very recently, α-amino acid conjugates of Tröger's base were suggested as novel conformationally restricted scaffolds inducing ca. 90° turn in non-natural proteins.[7]

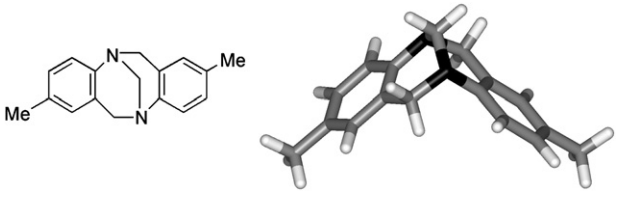

Figure 1. Tröger's base: structural formula (left) and optimized geometry of (*S*,*S*)-enantiomer (right).

All these molecular designs require the introduction of specific functional groups in certain positions of the rigid skeleton of Tröger's base. This can be achieved either by the condensation of the suitable aniline derivatives bearing the necessary functional groups with formaldehyde or its synthetic equivalent[2,3] or, alternatively, via the sequential build-up of functionality to create complex linked aniline derivatives that are finally transformed into an intact Tröger's base skeleton.[4]

In the course of our own studies on ligands for H-bonded supramolecular architectures, we became interested in the derivatives of Tröger's base bearing amide, urea, and similar H-bond donor groups connected by a σ-bond or by a CH_2 spacer to the various positions of the heterocyclic system. Amino and aminomethyl derivatives of Tröger's base are evident but not easily accessible intermediates for these molecules. Here, we report the synthesis of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine derivatives (±)-**1** and (±)-**2** bearing NH_2 and CH_2NH_2 groups via Pd-catalyzed cross-coupling reactions followed by common transformations of functional groups.

2. Results and discussion

The most practical and general synthesis of Tröger's base derivatives is the condensation of anilines with formaldehyde or its synthetic equivalent. The amino derivatives of Tröger's base are not accessible by this route since the reaction of diaminobenzenes with formaldehyde will obviously afford polymeric products. Hence, another synthetic methodology is required in order to access these amino compounds. At this point halogen-substituted derivatives of Tröger's base seemed to be a very attractive solution for two reasons. On the one hand, they can easily be prepared

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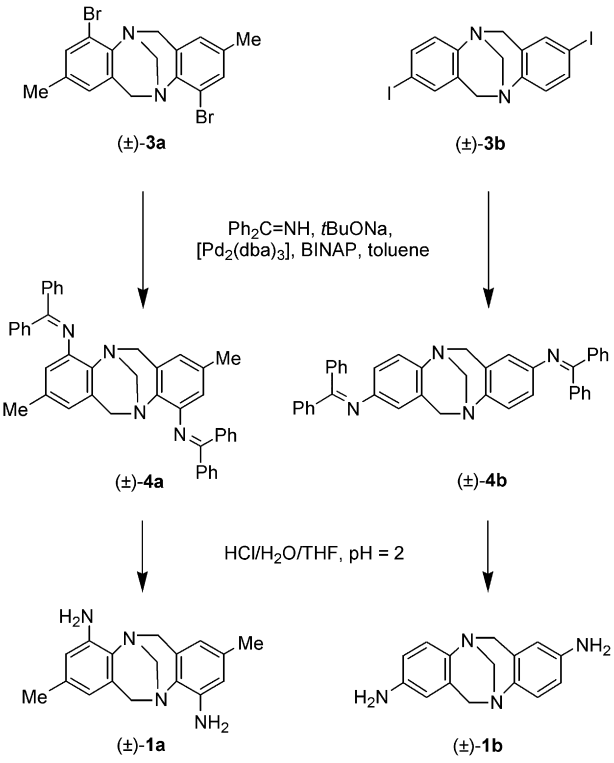
starting from the corresponding halo anilines.[6,8] On the other hand, they are versatile intermediates for many metal-catalyzed cross-coupling reactions, which have already shown their efficiency in the preparation of symmetric acetylenic and biaryl derivatives of Tröger's base.[9,10] We decided to investigate the possibility of the catalytic amination of 4,10-dibromo ((±)-**3a**) and 2,8-diiodo ((±)-**3b**) derivatives of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine.

In the recent years, the aromatic amination catalyzed by transition metal complexes became a powerful tool in organic synthesis.[11] Although direct coupling of aryl halides with NH_3 is not synthetically feasible, other nitrogen derivatives such as amines, imines, or carbamates can be successfully used as a 'masked ammonia'.[12,13] An interesting example reported on Tröger's base derivatives is the Cu-catalyzed coupling of diiodide (±)-**3b** with $BocNH_2$ (Boc=*tert*-butoxycarbonyl).[10] This reaction could be of interest for the synthesis of amino derivatives of Tröger's base since *N*-Boc group is easily cleavable upon the action of acids. However, this reaction produced only the product of the single halogen substitution in moderate yield. Although this method provides access to otherwise hardly available unsymmetrical derivatives of Tröger's base, it is clearly unsuitable for the synthesis of symmetrical derivatives. It also became obvious that a careful choice of the catalytic system is necessary for the double substitution of halogen in the deactivated aromatic rings of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine.

We have chosen the benzophenone imine ($Ph_2C{=}NH$) as a synthetic equivalent of NH_3 for Pd-catalyzed amination. Earlier, Buchwald and co-workers have reported the application of this reagent in the Pd-catalyzed coupling of various aryl halides including deactivated methoxy-substituted bromo- and iodobenzenes.[13] This methodology is quite appealing since benzophenone imine is more reactive compared to amines or carbamates, it is commercially available, and finally, the product of the cross-coupling can be conveniently isolated and transformed into a free amine by various methods.

We have found that the treatment of (±)-**3a** or (±)-**3b** with $Ph_2C{=}NH$ in the presence of $[Pd_2(dba)_3]$ (dba=dibenzylideneacetone), (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (BINAP), and ^{t}BuONa at 80 °C smoothly afforded symmetrical coupling products (±)-**4a** and (±)-**4b**, respectively (Scheme 1). TLC and ^{1}H NMR spectra of reaction mixture confirmed complete conversion of the starting dihalides. Crude diimines (±)-**4a**,**b** can be purified by column chromatography on SiO_2. However, this purification appeared to be cumbersome and resulted in a considerable loss of product, presumably, due to the lability of imine groups upon contact with the slightly acidic surface of SiO_2. Fortunately, we found that the thorough purification of diimines (±)-**4a**,**b** was not necessary. Instead, crude intermediates were subjected to the mild acidic cleavage (HCl in THF/H_2O at pH=2) to give the diamines (±)-**1a** and (±)-**1b** in a yield of 69 and 86%, respectively. The given yields correspond to the total of two steps starting from dihalides (±)-**3a**,**b**. The slightly lower yield of (±)-**1a** compared to (±)-**1b** can probably be explained by a better reactivity of the iodine derivative (±)-**3b** in the Pd-catalyzed cross-coupling step compared to the bromo analog (±)-**3a**. Notably, a simple acidic–basic work up allowed to remove the catalyst and other impurities, and afforded diamines (±)-**1a**,**b** that were sufficiently pure for the subsequent synthesis. The analytically pure products were isolated by column chromatography on SiO_2.

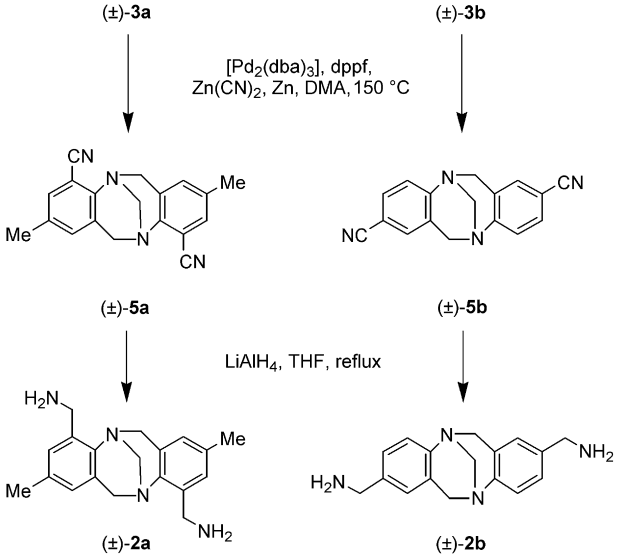


Scheme 1. Synthesis of amino derivatives of Tröger's base (±)-**1a**,**b**; dba=dibenzylideneacetone, BINAP=(±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene.

The di(aminomethyl) derivative of Tröger's base (±)-**2b** was synthesized earlier in moderate yield (33%) via the condensation of the phthalimide derivative of 4-aminobenzylamine with formaldehyde followed by deprotection with N_2H_4.[14] A more general and rapid access to variety of aminomethyl derivatives such as (±)-**2a**,**b** could be granted by the reduction of the corresponding dinitriles (±)-**5a**,**b**. Unfortunately, dicyano derivatives of Tröger's base are in general not accessible via direct condensation of amino nitriles because of the strong electron-withdrawing nature of the CN group. The only reported exception is an unusual reaction of 4-cyanoaniline with DMSO as a formaldehyde equivalent in relatively drastic conditions upon the action of the gaseous HCl to give dinitrile (±)-**5b** in low yield (21%).[15]

At the same time, the reaction of metal cyanides with aryl halides is a well-known method for the synthesis of aromatic nitriles.[16] Classically known as the Rosenmund–von Braun reaction, this useful transformation was greatly improved by application of transition metal complexes as catalysts.[17] Therefore, we developed a synthesis of dinitriles (±)-**5a**,**b** based on a double displacement of halogen by CN^- in dihalo derivatives (±)-**3a**,**b**. The Pd-catalyzed cyanation of (±)-**3b** was attempted earlier.[10] However, similar to the above discussed amination, it only gave a product of a single halogen substitution in moderate yield. The Cu-mediated cyanation catalyzed by chelating diamine ligands developed by

Buchwald and co-workers[18] also remained unsuccessful. However, we have found the method initially developed for the cyanation of challenging substrates such as deactivated aryl chlorides to be very useful in the double cyanation of the dihalo derivatives of Tröger's base. Air-stable [$Pd_2(dba)_3$] and an activating ligand dppf (1,1′-bis(diphenylphosphino)ferrocene) were used as an efficient catalytic system. The combination of $Zn(CN)_2$ as a cyanide source with catalytic amounts of Zn allows to avoid the CN^--induced deactivation of the catalyst.[19] Similar to Pd-catalyzed cross coupling with $Ph_2C{=}NH$, iodo derivative (±)-**3b** was more reactive toward Pd-catalyzed cyanation compared to its bromo analog (±)-**3a**. Indeed, (±)-**3b** afforded 98% of (±)-**5b** while (±)-**3a** gave (±)-**5a** in relatively modest yield (62%) under identical reaction conditions (Scheme 2).



Scheme 2. Synthesis of aminomethyl derivatives of Tröger's base (±)-**2a**,**b**; dba=dibenzylideneacetone, dppf=1,1′-bis(diphenylphosphino)ferrocene, DMA=*N*,*N*-dimethylacetamide.

The reduction of nitriles (±)-**5a** and (±)-**5b** to diamines (±)-**2a** and (±)-**2b**, respectively, with $LiAlH_4$ in THF was straightforward. ^{1}H NMR spectra showed complete conversion of the starting material and only traces of impurities. Amines (±)-**2a**,**b** can thus either be used in the subsequent synthesis without further purification or be purified by column chromatography. However, the purification required highly polar eluants (CH_2Cl_2/MeOH/aq NH_3). In order to demonstrate the synthetic utility of these amines, (±)-**2b** was converted to the diamide (±)-**6** by acylation with 2-nitrobenzoyl chloride in the presence of Et_3N (Scheme 3). In another example, the amino derivative (±)-**1a** was transformed to the dithiourea (±)-**7** upon the action of the corresponding isothiocyanate in THF. All synthesized compounds were characterized by ^{1}H and ^{13}C NMR and by HRMS (see Supplementary data for original spectra).

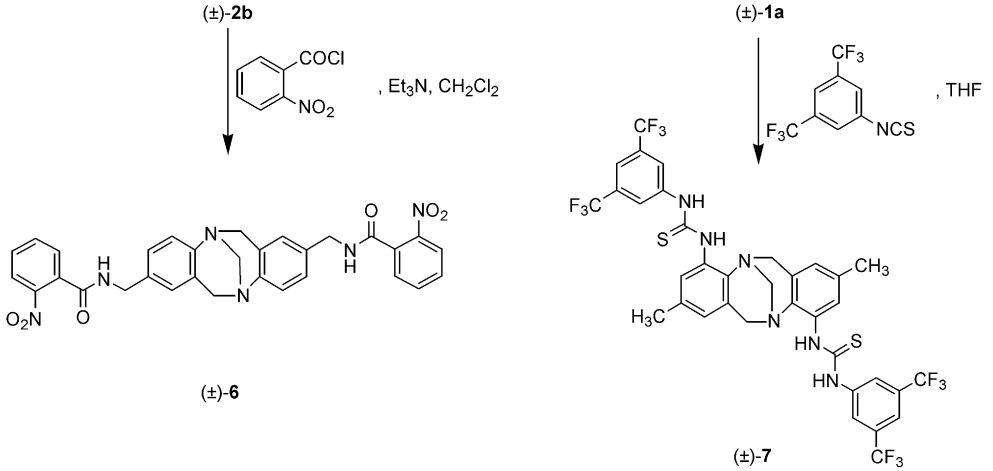
3. Conclusion

In summary, we have demonstrated the efficiency of Pd-catalyzed C–C and C–N forming reactions providing an easy access to amino and aminomethyl derivatives of Tröger's base. The identity (bromo or iodo) and the position of the halogen in the aromatic ring of the 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine scaffold have relatively little influence on the outcome of these coupling reactions. In a similar way, other symmetrical derivatives of Tröger's base bearing NH_2 or CH_2NH_2 functionalities in the different positions of the aromatic rings should be easily accessible by this method starting from known dihalo derivatives. Obviously, these diamines can be further elaborated in a variety of ways and converted into other derivatives such as amides, carbamates, sulfonamides, ureas, or thioureas. We are currently working on the studies of the self-assembly of such derivatives into hydrogen-bonded supramolecular architectures and on their application in organocatalysis. Furthermore, diamines derived from Tröger's base can be interesting as ligands for transition metal catalysis and for heterotopic metal-mediated self-assemblies, such as recently demonstrated for enantiomers of **2b** and a scissor-like zinc porphyrin.[20]

4. Experimental section

4.1. General

All chemicals were purchased from Aldrich or Acros and used without further purification unless stated otherwise.



Scheme 3. Conversion of diamines (±)-**2b** and (±)-**1a** into diamide and dithiourea derivatives.

THF was refluxed over sodium and benzophenone until a blue-violet color persisted and distilled directly into the reaction flask. All Pd-catalyzed reactions were performed in oven-dried glassware under dry Ar atmosphere. Dry *N*,*N*-dimethylacetamide and toluene were kept over 4 Å molecular sieves. Column chromatography: SiO_2 Kieselgel 60 (Macherey–Nagel, particle size 0.04–0.063 mm). TLC: precoated SiO_2 plates Kieselgel $60F_{254}$ (Merck). ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ on a Brucker Avance 300 spectrometer; chemical shifts (δ) are given in parts per million relative to Me_4Si; coupling constants (J) are given in hertz. Electron impact mass spectra (EIMS) were recorded on a Waters AutoSpec 6F instrument and electrospray ionization mass spectra (ESIMS) on a Waters QToF 2 instrument; *m*/*z* with the lowest isotopic mass are reported. IR spectra were recorded on a Shimadzu IR-470 instrument. Diiodide (±)-**3b** was prepared from 4-iodoaniline as described earlier.[6]

4.2. (±)-4,10-Dibromo-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine ((±)-3a)

2-Bromo-4-methylaniline (25.2 g, 0.135 mol) and then paraformaldehyde (8.1 g, 0.27 mol) were added in portions to CF_3COOH (250 mL) at −15 °C. The resulting mixture was allowed to reach room temperature and stirred for 20 h, then slowly added upon vigorous stirring to a mixture of ice and an excess of NH_3 solution (25% in water) at 0 °C. The resulting mixture was extracted with CH_2Cl_2 (3×200 mL), dried over $MgSO_4$, and concentrated in vacuum. The resulting solid was washed with hexane to give pure (±)-**3a** (27.2 g, 98%) as a colorless solid. Analytical data were identical with those published earlier.[21]

4.3. (±)-*N*,*N*′-Dibenzhydrylidene-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine-4,10-diamine ((±)-4a)

A mixture of bromide (±)-**3a** (399 mg, 0.977 mmol), Ph_2C=NH (0.423 mL, 2.52 mmol), ^{t}BuONa (282 mg, 2.93 mmol), $Pd_2(dba)_3$ (240 mg, 0.262 mmol), (±)-BINAP (490 mg, 0.787 mmol) and dry toluene (4 mL) were heated at 80 °C under Ar atmosphere in a Schlenk tube. After 24 h, the reaction mixture was allowed to reach room temperature and diluted with CH_2Cl_2 (40 mL). Filtration and evaporation of the solvent afforded (±)-**5a** as a red solid that was used in the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.02 (s, 6H), 3.94 (s, 2H), 4.17 (d, $^2J_{H,H}$=17.1 Hz, 2H), 4.33 (d, $^2J_{H,H}$=17.1 Hz, 2H), 6.15 (d, $^4J_{H,H}$=1.6 Hz, 2H), 6.37 (d, $^4J_{H,H}$=1.6 Hz, 2H), 7.15–7.55 (m, 16H), 7.82 (dd, $^3J_{H,H}$=8.1 Hz, $^4J_{H,H}$=1.5 Hz, 4H); EIMS: *m*/*z* (%)=608 (6), 531 (26), 453 (100), 437 (18), 221 (16).

4.4. (±)-*N*,*N*′-Dibenzhydrylidene-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-2,8-diamine ((±)-4b)

Prepared similar to (±)-**4a** from (±)-**3b** (484 mg, 1.03 mmol), Ph_2C=NH (0.508 mL, 3.03 mmol), ^{t}BuONa (283 mg, 2.94 mmol), $Pd_2(dba)_3$ (233 mg, 0.254 mmol), and (±)-BINAP (483 mg, 0.776 mmol) in dry toluene (4 mL). The product was used in the next step without further purification. Red solid; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=3.89 (d, $^2J_{H,H}$=16.5 Hz, 2H), 4.20 (s, 2H), 4.45 (d, $^2J_{H,H}$=16.5 Hz, 2H), 6.29 (d, $^4J_{H,H}$=2.4 Hz, 2H), 6.49 (dd, $^3J_{H,H}$=8.4 Hz, $^4J_{H,H}$=2.4, 2H), 6.81 (d, $^3J_{H,H}$=8.4 Hz, 2H), 7.00–7.55 (m, 16H), 7.65–7.75 (m, 4H). HREIMS *m*/*z*, calcd for $C_{41}H_{32}N_4$ ([M]$^+$): 580.2627; found: 580.2614.

4.5. (±)-2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine-4,10-diamine ((±)-1a)

A solution of HCl (2 M in water) was added to a solution of bis-imine (±)-**4a** in THF (10 mL) until pH=2 was reached. After 2 h of stirring at room temperature the reaction mixture was partitioned between hexane/AcOEt (2:1, 200 mL) and the aqueous 0.5 M HCl solution (200 mL). The aqueous phase was separated, filtered, made alkaline with an aqueous NaOH solution, and then extracted with CH_2Cl_2 (2× 100 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuum to give a pale yellow solid (189 mg, 0.674 mmol). Yield from (±)-**3a**: 69%; mp 206 °C (dec); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.14 (s, 6H), 3.95 (br s, 4H), 4.04 (d, $^2J_{H,H}$=16.8 Hz, 2H), 4.26 (s, 2H), 4.35 (d, $^2J_{H,H}$=16.8 Hz, 2H), 6.16 (d, $^4J_{H,H}$=0.9 Hz, 2H), 6.40 (d, $^4J_{H,H}$=0.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=21.1, 52.6, 67.9, 113.5, 116.8, 128.3, 131.2, 134.0, 140.6; EIMS: *m*/*z* (%)=280 (100), 265 (14), 146 (16). HREIMS *m*/*z*, calcd for $C_{17}H_{20}N_4$ ([M]$^+$): 280.1688; found: 280.1684.

4.6. (±)-6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine-2,8-diamine ((±)-1b)

Synthesized similar to (±)-**1a** from crude (±)-**4b** prepared from (±)-**3b** (484 mg, 1.03 mmol). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 9:1 to 7:3) to give a pale yellow solid (220 mg). Yield from (±)-**3b**: 85%; mp 266 °C (dec); ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.76 (d, $^2J_{H,H}$=16.5 Hz, 2H), 4.04 (s, 2H), 4.37 (d, $^2J_{H,H}$=16.5 Hz, 2H), 4.66 (br s, 4H), 6.07 (d, $^4J_{H,H}$=2.4 Hz, 2H), 6.36 (dd, $^3J_{H,H}$=8.4 Hz, $^4J_{H,H}$=2.4 Hz, 2H), 6.72 (d, $^3J_{H,H}$=8.4 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=58.3, 67.0, 110.8, 113.4, 124.9, 128.3, 137.4, 144.4. HREIMS *m*/*z*, calcd for $C_{15}H_{16}N_4$ ([M]$^+$): 252.1375; found: 252.1381.

4.7. (±)-2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine-4,10-dicarbonitrile ((±)-5a)

Bromide (±)-**3a** (5.00 g, 12.2 mmol), $Pd_2(dba)_3$ (4.50 g, 4.91 mmol), dppf (5.45 g, 9.83 mmol), Zn powder (0.192 g, 2.94 mmol), and $Zn(CN)_2$ (1.76 g, 15.0 mmol) were placed in a dry argon flushed flask. Dry *N*,*N*-dimethylacetamide (50 mL) was added via syringe. The resulting mixture was heated at 150 °C for 18 h. The reaction mixture was cooled to room temperature and diluted with AcOEt (150 mL). The organic phase was filtered through Celite, and then washed with 2 N aqueous NH_3 solution (200 mL) and with water (2×100 mL). The organic phase was then dried over $MgSO_4$ and concentrated in vacuum. Hexane (2 mL) was added to the resulting oil and the mixture was sonicated for few minutes. The resulting solid was filtered, dissolved in hexane/AcOEt (8:2), the solution was passed through a plug of SiO_2, and concentrated. Finally, crystallization of the residue from hexane/AcOEt afforded

analytically pure (±)-**5a** (2.268 g, 62%) as an off-white solid; mp 258–261 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.27 (s, 6H), 4.25–4.40 (m, 4H), 4.73 (d, $^2J_{H,H}$=17.7 Hz, 2H), 7.00 (s, 2H), 7.31 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=20.6, 56.8, 67.0, 108.7, 117.2, 128.9, 132.4, 132.6, 134.5, 148.0; EIMS: *m*/*z* (%)=300 (100), 285 (15), 272 (9), 180 (9), 170 (15). HREIMS *m*/*z*, calcd for $C_{19}H_{16}N_4$ ([M]$^+$): 300.1375; found: 300.1359.

4.8. (±)-6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine-2,8-dicarbonitrile ((±)-5b)

Prepared similar to (±)-**5a** from (±)-**3b** (1.422 g, 3.00 mmol), $Pd_2(dba)_3$ (1.106 g, 1.21 mmol), dppf (1.340 g, 2.42 mmol), Zn powder (47 mg, 0.719 mmol), and $Zn(CN)_2$ (434 mg, 3.70 mmol) in dry *N*,*N*-dimethylacetamide (9 mL). Purification by column chromatography (hexane/AcOEt gradient from 6:4 to 2:8) afforded (±)-**5b** as an off-white solid (804 mg, 98%); mp 250 °C (lit.[15] mp 248–249 °C); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=4.21, (d, $^2J_{H,H}$=16.8 Hz, 2H), 4.29 (s, 2H), 4.73 (d, $^2J_{H,H}$=16.8 Hz, 2H), 7.16–7.26 (m, 4H), 7.46 (dd, $^3J_{H,H}$=8.4 Hz, $^4J_{H,H}$=1.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=58.3, 66.3, 107.7, 118.6, 125.9, 128.6, 131.4, 152.1 (one signal missing because of overlap). HREIMS *m*/*z*, calcd for $C_{17}H_{12}N_4$ ([M]$^+$): 272.1062; found: 272.1065.

4.9. (±)-*C*-(10-Aminomethyl-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-4-yl)methylamine ((±)-2a)

$LiAlH_4$ (0.268 g, 7.06 mmol) was added at 0 °C to a stirred solution of nitrile (±)-**5a** (0.504 g, 1.68 mmol) in dry THF (25 mL). The reaction mixture was heated to reflux for 24 h, then allowed to reach room temperature, and quenched with an excess of THF/water (4:1). After 60 min of stirring the mixture was filtered, the filtrate was dried over $MgSO_4$, and concentrated in vacuum. The resulting (±)-**2a** (0.488 g, 94%) can be used without further purification. Brownish amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.0 (br, 4H, NH_2), 2.22 (s, 6H), 3.68 (d, $^2J_{H,H}$=14.4 Hz, 2H), 3.99 (d, $^2J_{H,H}$=16.8 Hz, 2H), 4.24 (d, $^2J_{H,H}$=14.4 Hz, 2H), 4.25 (s, 2H), 4.57 (d, $^2J_{H,H}$=16.8 Hz, 2H), 6.61 (s, 2H), 6.98 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=20.9, 42.3, 56.0, 67.2, 125.9, 127.4, 127.9, 133.8, 137.5, 142.9; EIMS: *m*/*z* (%)=308 (15), 274 (35), 205 (100), 174 (33), 158 (55), 130 (70), 91 (46). HREIMS *m*/*z*, calcd for $C_{19}H_{24}N_4$ ([M]$^+$): 308.2001; found: 308.1999.

4.10. (±)-*C*-(8-Aminomethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-2-yl)-methylamine ((±)-2b)

Prepared similar to (±)-**2a** from (±)-**5b** (0.276 g, 1.01 mmol) and $LiAlH_4$ (0.248 g, 6.53 mmol) in dry THF (10 mL). The resulting (±)-**2b** (0.283 g, 100%) can be used without further purification. Brownish amorphous solid; ^{1}H NMR (300 MHz, DMSO, 25 °C): δ=3.51 (br s, 4H), 3.76 (s, 4H), 4.07 (d, $^2J_{H,H}$=16.8 Hz, 2H), 4.23 (s, 2H), 4.62 (d, $^2J_{H,H}$=16.8 Hz, 2H), 7.00 (s, 2H), 7.12 (d, $^3J_{H,H}$=8.4 Hz, 2H), 7.18–7.22 (m, 2H); ^{13}C NMR (75 MHz, DMSO, 25 °C): δ=42.6, 58.2, 66.1, 124.6, 126.9, 127.2, 127.8, 131.8, 147.6. HREIMS *m*/*z*, calcd for $C_{17}H_{20}N_4$ ([M]$^+$): 280.1688; found: 280.1687.

4.11. (±)-*N*-(8-[(2-Nitrobenzoylamino)methyl]-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-2-ylmethyl)-2-nitrobenzamide ((±)-6)

Diamine (±)-**2b** (0.040 g, 0.143 mmol), 2-nitrobenzoyl chloride (0.083 g, 0.447 mmol), and Et_3N (0.225 mL, 1.61 mmol) in CH_2Cl_2 (2 mL) were stirred for 5 h at room temperature, then water (5 mL) and CH_2Cl_2 (5 mL) were added. The organic phase was washed with water (20 mL), dried over $MgSO_4$, and concentrated in vacuum. Column chromatography (gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) afforded (±)-**6** as a yellow solid (44 mg, 53%); mp 131 °C; IR (KBr) (ν_{max}/cm^{-1}): 3380 (N–H), 3255, 3050, 2910, 1644 (C=O), 1520 (N–H), 1492, 1425, 1346, 1294, 1201, 1106, 1059, 959, 834, 783, 728, 692. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=4.13 (d, $^2J_{H,H}$=16.8 Hz, 2H), 4.23 (s, 2H), 4.36–4.44 (m, 4H), 4.63 (d, $^2J_{H,H}$=16.8 Hz, 2H), 6.26 (t, $^3J_{H,H}$=5.5 Hz, 2H), 6.89 (br, 2H), 7.04–7.16 (m, 4H), 7.41 (dd, $^3J_{H,H}$=7.4 Hz, $^4J_{H,H}$=1.7 Hz, 2H), 7.46–7.62 (m, 4H), 7.96 (dd, $^3J_{H,H}$=8.0 Hz, $^4J_{H,H}$=1.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=43.7, 58.7, 66.8, 124.5, 125.3, 126.5, 127.1, 128.1, 128.6, 130.5, 132.7, 133.1, 133.6, 146.4, 147.5, 166.3. HRESIMS *m*/*z*, calcd for $C_{31}H_{26}N_6NaO_6$ ([M+Na]$^+$): 601.1812; found: 601.1805.

4.12. (±)-1-[3,5-Bis(trifluoromethyl)phenyl]-3-[10-(3-[3,5-bis(trifluoromethyl)phenyl]-thioureido)-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-4-yl]-thiourea ((±)-7)

3,5-Bis(trifluoromethyl)phenyl isothiocyanate (267 mg, 0.985 mmol) was added at 0 °C to a solution of diamine (±)-**1a** (138 mg, 0.492 mmol) in dry THF (5 mL). The mixture was stirred for 10 min at 0 °C, allowed to reach room temperature, and stirred for further 22 h. Solvent was removed in vacuum and the crude product was crystallized from CH_2Cl_2 to give analytically pure (±)-**7** as a colorless solid (244 mg, 60%); mp 280 °C (dec); IR (KBr) (ν_{max}/cm^{-1}): 3345 (N–H), 3175, 3010, 1611, 1524 (br, C=S, N–H), 1464, 1437, 1383, 1333, 1276, 1180, 1135, 1108, 919, 884, 678.^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ=2.19 (s, 6H), 3.93 (d, $^2J_{H,H}$=16.8 Hz, 2H), 4.32 (s, 2H), 4.54 (d, $^2J_{H,H}$=16.8 Hz, 2H), 6.67 (s, 2H), 7.48 (s, 2H), 7.82 (s, 2H), 8.40 (s, 4H), 9.64 (s, 2H), 10.64 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=20.5, 54.4, 66.0, 116.6–116.9 (m, *C*CCF$_3$), 123.2 (q, $^1J_{C,F}$=272.8 Hz, CF_3), 122.7–123.0 (m, *C*CCF$_3$), 124.5, 124.7, 128.5, 130.0 (q, $^2J_{C,F}$=32.9 Hz, *C*CF$_3$), 132.0, 132.6, 138.0, 141.7, 179.4. HRESIMS *m*/*z*, calcd for $C_{35}H_{27}N_6F_{12}S_2$ ([M+H]$^+$): 823.1547; found: 823.1544.

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Supplementary data

Original ^{1}H and ^{13}C NMR spectra of (±)-**1a**,**b**, (±)-**2a**, (±)-**5a**, (±)-**6**, and (±)-**7**. Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2007.02.032.

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