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Synthesis and reactivity of dimethoxy-functionalised Tröger's base analogues

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ABSTRACT

Tröger's base analogues were prepared bearing methoxy groups in the 1,7-, 2,8-, 3,9- or 4,10-positions. These compounds were converted to their dihydroxy analogues in excellent yields upon treatment with boron tribromide and the 4,10-dihydroxy analogue could be prepared by directly from 4-hydroxyaniline. The synthetic utility of the dihydroxy-functionalised compounds as building blocks was demonstrated by the synthesis of a dialkoxy and a diester Tröger's base analogue.

1. Introduction

Tröger's base **1** is a chiral V-shaped compound whose chirality is the result of two stereogenic nitrogen centres being unable to invert due to the presence of a methylene strap (Fig. 1).[1] It is formed by an acid catalysed reaction of *p*-toluidine with either formaldehyde or formaldehyde equivalent.[2] In recent years, a wide variety of substituents, including the electron-withdrawing halogen,[3–9] ester[7,10–14] and nitro groups,[7,15–19] have become available on the aryl rings of the Tröger's base framework, through the use of appropriately substituted anilines.

The chiral cavity present in Tröger's base has made it an attractive scaffold for further development in areas, such as asymmetric catalysis,[20–22] DNA binding[23–27] and synthetic receptor design[11,28–34] and these investigations are set to continue as new analogues are prepared and resolved.

It was long believed that Tröger's base analogues could only be made from anilines bearing electron-donating functionality, so it comes as no surprise to learn that alkoxy Tröger's base compounds have been known for several decades. Infact the 2,8-dimethoxy and 2,8-ethoxy Tröger's bases, **2** and **3**, respectively, were the first reported Tröger's base analogues[35] and the X-ray crystal structure of **2** was one of the first Tröger's base analogues to be solved.[36] Compound **2** has been prepared from *p*-anisidine with various combinations of reagents, including ethanol/hydrochloric acid/formalin,[35] methylal/methanesulfonic acid[37] and dimethyl sulfoxide/hydrogen chloride.[7] A 4,10-dimethyl-2,8-dimethoxy Tröger's base **5** was prepared from 2,8-diiodo-4,10-dimethyl Tröger's base using a cross-coupling strategy, and converted to the corresponding 2,8-dihydroxy compound **6** in excellent yield with the use of boron tribromide.[38] Two more highly substituted 2,8-dimethoxy Tröger's base analogues, **7** (converted to the dihydroxy analogue **8** upon treatment with acetic acid and hydrochloric acid, at reflux for 48 h) and **9**, have also been reported.[39,18] A 1,7-dimethoxy Tröger's base analogue **10** was prepared in 16% yield from a highly functionalised precursor by heating in DMSO solution at 185–190 °C for 9 h.[10] Two related 1,7-dihydroxy analogues **11** and **12** were prepared directly from the corresponding aniline precursors[40] and a 2,3,8,9-tetramethoxy analogue **13** has also been reported.[41] A 2,8-dihydroxy analogue **4** is briefly discussed in the

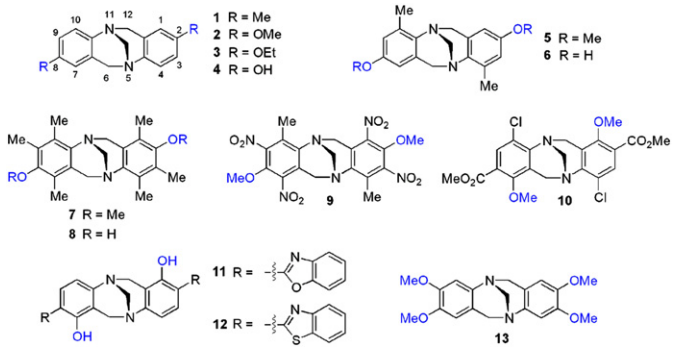

Fig. 1. The structure of Tröger's base, and the various dimethoxy and dihydroxy Tröger's base analogs previously reported in the literature.

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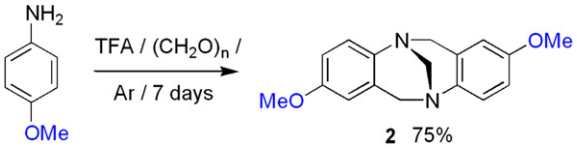
literature, however experimental details were limited to inclusion of the reagents on an experimental scheme.[42]

In terms of the placement of the methoxy/hydroxy groups, it is apparent that there is not much variation within the group. Compounds **2**–**13** were prepared as racemic mixtures and there have been no reported resolutions.

Against this background, the work described here details the synthesis of several new symmetric dimethoxy and dihydroxy Tröger's base analogues with a range of substitution patterns, and two reactions of 2,8-dihydroxy Tröger's base **4**.

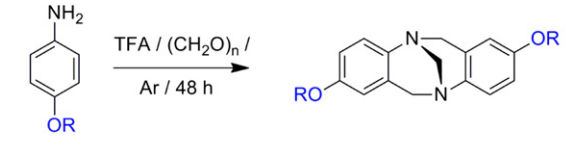
2. Results and discussion

The work commenced with the synthesis of **2** in 75% yield using TFA and paraformaldehyde (Scheme 1), conditions that have become popular in the preparation of Tröger's base analogues,[3,19,43–46] after their initial use in the synthesis of acridine analogues of Tröger's base.[47] This yield is essentially the same as that recently reported (76%) for the synthesis **2** employing $AlCl_3$ and CH_2Cl_2 as the reagents.[48]



Scheme 1.

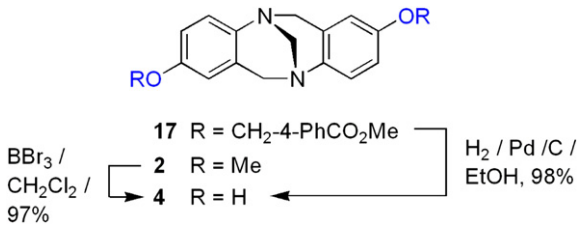
In order to realize the full potential synthetic utility of methoxy-functionalized Tröger's base compounds as building blocks, we sought access the dihydroxy compound **4**. Whilst the hexamethyl dihydroxy compound **8** was prepared from acid hydrolysis of **7**, we felt that **4** might be more difficult to isolate from an aqueous solution due to its reduced lipophilic character with respect to **8**. With this consideration, and the potential zwitterionic nature of **4** (i.e., protonated on one of the nitrogens under acidic conditions[49] and deprotonated on one or both of the hydroxyl groups at basic pH) and the associated hydrophilic nature of the charged compounds, our initial approach to **4** involved the use of a protecting group on the phenolic oxygen that could withstand TFA and be removed under neutral and non-aqueous conditions. The obvious candidate was to use a benzyl ether protected aniline, as outlined in Scheme 2. Removal of the protecting group could then be effected via a simple hydrogenolysis reaction.



Scheme 2.

Examination of the ^{1}H NMR spectrum of the crude material obtained upon work-up of a reaction involving 4-aminophenyl benzyl ether **14** did not reveal any of the desired Tröger's base product **16**. It was suspected that the aromatic ring of the benzyl group may have reacted with formaldehyde to afford a product that could then undergo oligomerisation/polymerisation reactions.

The use of the more strongly electron-withdrawing ester substituent at the 4-position of the benzyl ring (compound **15**) led to the successful formation of Tröger's base analogue **17** in 35% yield. Compound **17** was then subjected to hydrogenolysis to afford **4** in quantitative yield (Scheme 3).



Scheme 3.

With an authentic sample of **4** in hand, its acid/base properties were investigated by attempting to extract the Tröger's base material into ethyl acetate, from solutions of various pH strengths. It was found that the highest yield of compound was obtained from solutions at pH 4.5–5.5.

A demethylation reaction was then conducted on **2**, using a solution of boron tribromide in dichloromethane. This reaction afforded **4**, again in near quantitative yield, importantly from a more readily available starting material than **17** (Scheme 3).

The direct synthesis of **4** from 4-hydroxyaniline was also examined, using the conditions employed in Scheme 1, and after work-up and adjustment of the solution to pH 5, **2** was obtained in 50% yield.

The synthesis of other dimethoxy Tröger's base regioisomers was then explored using the same methodology as outlined in Scheme 1. In general terms, there are four different symmetric dimethoxy regioisomers as illustrated in Fig. 2.

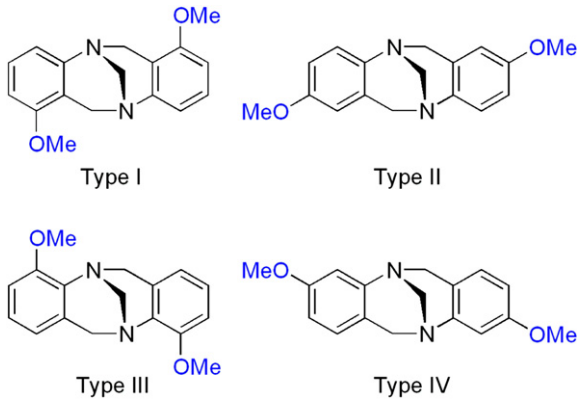


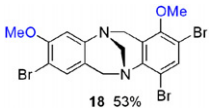
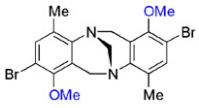
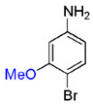
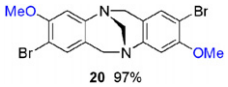
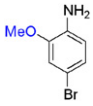
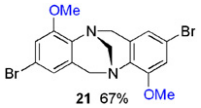
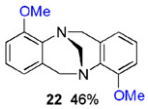
Fig. 2. The substitution pattern of the four symmetric dimethoxy Tröger's base regioisomers.

Both Type I and Type III compounds are potentially derived from *m*-methoxy substituted anilines. The synthesis of Type I compounds may be precluded by the inclusion of a substituent at the site *para* to the methoxy group, whilst the placement of a substituent *ortho* to both the amino and methoxy groups precludes the synthesis of Type III compounds. In terms of the other sites on the aniline, recent studies have shown that successful syntheses of Tröger's base analogues do not require the presence of a substituent in the *p*-position,[5,14,19,50] as was long believed to be the case.

With these features considered, the anilines listed in Table 1 were successfully reacted with paraformaldehyde in TFA to afford new Tröger's base analogues.

The reaction of 2,4-dibromo-5-methoxyaniline was anticipated to afford a symmetric Type I compound, however it was not observed and a hybrid **18** was isolated as the sole Tröger's base product (and was the only Tröger's base present in a ^{1}H NMR spectrum of the crude material obtained after work-up). The formation of **18** necessitates the loss of a bromo group *ortho* to the amino group on one of the anilines. Whilst several other *ortho*-

Table 1
The structures of Type **I**, **III** and **IV** dimethoxy Tröger's base analogues successfully prepared.

Entry	Aniline	Tröger's base[a]
1		 **18** 53%
2		 **19** 94%
3		 **20** 97%
4		 **21** 67%
5		 **22** 46%

[a] Isolated yields after column chromatography.

bromoanilines[5,6,13,51] have been subjected to the same reaction conditions, to the best of our knowledge, hybrids analogous to **18** have not been observed in those reactions. It should be noted, however, that the loss of an *ortho*-iodo group has been reported during a Tröger's base-forming reaction.[5]

An X-ray crystal structure was obtained of **18** and this confirmed the structural assignment (Fig. 3).[52] The dihedral angle (which is the angle formed by the intersecting least squares planes defined by the two aryl rings) of **18** was found to be 98.8°. This value lies in the middle of the range of dihedral angles that has been found to span from 82°[53] to 110.8°[9] (the lower and upper limits, respectively, that have been measured from the X-ray structures of almost 30 simple dibenzo Tröger's base analogues).

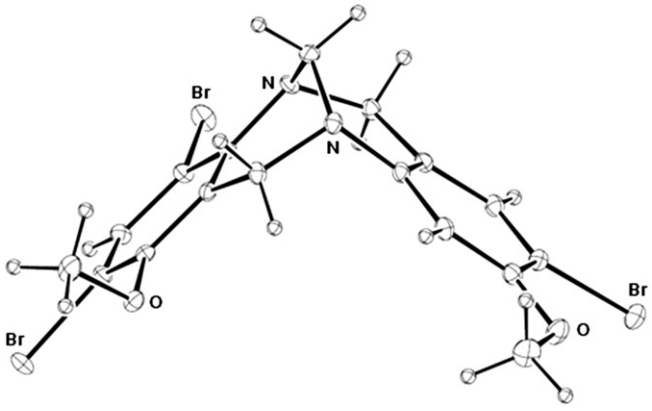


Fig. 3. An ORTEP diagram of **18**, with 10% probability ellipsoids.

m-Anisidine, as well as 2-bromo- and 2-methyl-5-methoxyaniline failed to yield any Tröger's base product, however 4-bromo-5-methoxy-2-methylaniline afforded a symmetric Type I analogue **19** in 94% yield.

In contrast, 4-bromo-3-methoxyaniline, with two inequivalent positions *ortho* to the amino group, afforded a Type III product **20** in near quantitative yield, with no evidence of a Type I or Type I/III hybrid product. This behaviour is consistent with the reaction of 3,4-dimethoxyaniline to afford **13**,[41] where C–C bond formation occurs only at the least hindered position *ortho* to the amino group.

Two Type IV compounds, **21** and **22**, were prepared in 67% and 46% yield, respectively. **21** could be converted to **22** in 61% yield via a hydrogenolysis reaction. An X-ray crystal structure was obtained for **22** and revealed the presence of two crystallographically independent molecules with dihedral angles of 104.14° and 104.64° (Fig. 4).[52]

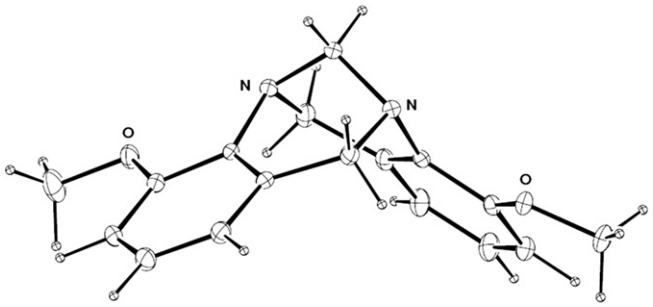


Fig. 4. An ORTEP diagram of one of the two crystallographically independent molecules that was present in the unit cell of **22**, with 10% probability ellipsoids.

Although not shown in Table 1, the behaviour of other two methyl substituted methoxyanilines 2-methoxy-4-methylaniline and 2-methoxy-5-methylaniline were also examined in the Tröger's base-forming reaction, however they both failed to afford any Tröger's base products (based on examination of the bridge region, 4–5 ppm, of the ^{1}H NMR spectra obtained on the crude material after work-up), presumably due to oxidation reactions involving the benzylic methyl group on the electron rich anilines. 2-Hydroxyaniline was also unsuccessfully trialed in the Tröger's base reaction as part of this work.

The presence of the bromine atoms on each of the anilines in entries 1–3 in Table 1 was essential for Tröger's base synthesis, however, the halogens on compounds **18**–**21** are also expected to serve as sites for further elaboration in light of the work of other researchers.[38,43,53–55]

Demethylation reactions were then attempted on **19**–**22**, (using the same methodology as employed to convert **2** to **4**, Scheme 3), however, repeated reactions on **21** led to the recovery of unchanged material. These reactions included the use of BBr_3 from different bottles, containing reagent that successfully demethylated other dimethoxy Tröger's base analogues. Compounds **23**, **24** and **25** were formed in 98%, 98% and 97% yield, respectively (Fig. 5).

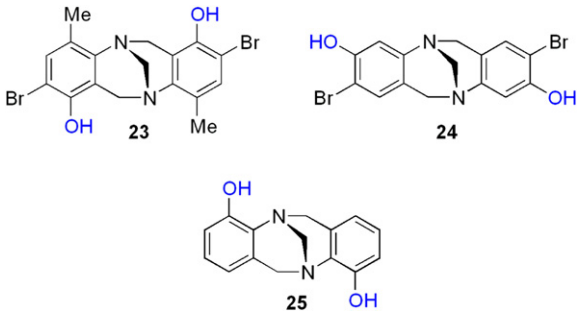
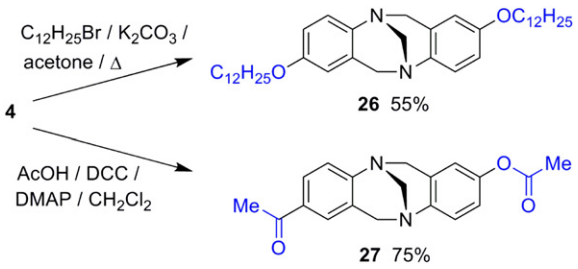


Fig. 5. Structures of three dihydroxy-substituted Tröger's base analogues.

It should be noted that dihydroxylation reactions of Tröger's base **1**, together with 2,3,8,9-, 1,2,8,9- and 2,4,8,10-tetramethyl Tröger's base were recently reported in superacidic media (HF/SbF_5, 25/1 M ratio), with sodium persulfate (2.3 equiv) at −20 °C or −40 °C for 10 or 15 min[56]

In a final part of this work, some reactions of dihydroxy Tröger's base **4** were investigated. It is known that the reaction of Tröger's base **1**, and its analogues, with alkyl halides affords mono-*N*-alkylated species, even in the presence of an excess of the alkyl halide.[36,57,58] Therefore it was of interest to determine if **4** could be alkylated on the oxygen atoms at the exclusion of a bridge nitrogen atom. A single reaction was performed as a proof-of-concept and the nucleophilic nature of the phenolic hydroxyl groups was enhanced by deprotonation with potassium carbonate in acetone. 1-Bromododecane was chosen as a 'model' long-chained alkyl halide and **26** was obtained in 55% yield (Scheme 4).



Scheme 4.

We then sought to convert **4** into a diester. A general, simple and effective way of preparing esters from alcohols involves a reaction with the appropriate acid chloride, however the reaction Tröger's base analogues with acid chlorides (or anhydrides) is known to afford strap-clipped diamides (i.e., removal of the apical methylene unit).[1,35,59–61] Therefore, we chose to react 2,8-dihydroxy Tröger's base **4** with acetic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine using dry dichloromethane as solvent, at room temperature over a period of 3 days (Scheme 4). The crude material was filtered and the filtrate evaporated to dryness. The resultant material was chromatographed to afford **27** in 75% yield.

3. Conclusion

We have demonstrated that dimethoxy Tröger's base analogues can be prepared with the methoxy groups at the 1,7-, 2,8-, 3,9- and 4,10-positions. We have also shown that these methyl ethers are readily cleaved in the presence of BBr_3 to afford dihydroxy Tröger's base analogues. The synthetic utility of the dihydroxy compounds was demonstrated by the conversion of 2,8-dihydroxy analogue to diether and diester analogues. Such analogues are expected to be of interest in the design of new catalysts and molecular receptors.

4. Experimental

4.1. General

Melting points were determined using a TA Instruments DSC 2010 Differential Scanning Calorimeter. Elemental analyses were carried out using a Perkin–Elmer 2400 Series II CHNS/O Analyzer. Mass spectral analyses were performed either at Macquarie University (APAF) (ESI-MS) or the School of Chemistry at the University of New South Wales (FAB^+). NMR analyses were carried out on a Bruker DPX400 spectrometer. IR spectra were recorded on a Nicolet iS10 IR spectrophotometer, fitted with an SMART iTR accessory that permits direct IR measurements of material. Chromatography was carried out using silica gel Merck 230–400 mesh ASTM. All solvents were freshly distilled and reagents were purchased from Sigma Aldrich. 2,4,4,6-Tetrabromocyclohexadione was prepared according to a literature procedure.[62]

4.2. Synthesis of Tröger's base precursors

4.2.1. 4-Nitrophenyl benzyl ether. 4-Nitrophenol (10.0 g, 71.4 mmol) and benzyl bromide (6.02 g, 35.2 mmol) were dissolved in acetone (150 mL) before adding potassium carbonate (19.5 g). The mixture was refluxed for 4 days under constant stirring. The reaction was monitored by TLC (dichloromethane). At the completion of the reaction acetone was evaporated under reduced pressure and the residue was taken up in a mixture of dichloromethane and water. The crude material was extracted into dichloromethane (3×40 mL) and the combined organic layers were washed with sodium hydroxide (3 M) until the aqueous layer became colourless. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude material was chromatographed (silica gel, hexane/dichloromethane 1:2) to afford 4-nitrophenyl benzyl ether (8.01 g, 99%) as white crystals: mp 102–104 °C (lit.[63] 102–105 °C, lit.[64] 105–107 °C); R_f (5% EtOAc/hexane) 0.82; IR (neat) ν_{max} 2949, 1589, 1506, 1493, 1247, 867, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.16 (s, 2H, CH_2), 7.03 (d, *J* 7.1 Hz, 2H, ArH), 7.34–7.45 (m, 5H, ArH), 8.20 (d, *J* 7.1 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.5, 114.7, 125.7, 127.3, 128.3, 128.5, 128.6, 135.4, 141.4, 163.5; Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found C, 68.02; H, 4.82; N, 5.93%.

4.2.2. 4-Aminophenyl benzyl ether ***14****.* 4-Nitrophenyl benzyl ether (4.00 g, 17.4 mmol) was dissolved in ethanol (50 mL) before adding tin(II) chloride dihydrate (19.1 g, 84.4 mmol). The mixture was stirred under an argon atmosphere at 70 °C for 6 days. The reaction was monitored by TLC using dichloromethane as solvent. At the completion of the reaction, the mixture was treated with a concentrated aqueous solution of sodium bicarbonate until the effervescence ceased. The mixture was extracted with ethyl acetate (4×50 mL), the organic layers were collected, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. **14** (3.36 g, 97%) was obtained as a brown oil and used without further purification. R_f (CH_2Cl_2) 0.60; ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (s, 2H, CH_2), 6.64 (d, *J* 6.8 Hz, 2H, ArH), 6.81 (d, *J* 6.8 Hz, 2H, ArH), 7.34–7.45 (m, 5H, ArH).

4.2.3. Methyl 4-[(4′-nitrophenoxy)methyl]benzoate. 4-Nitrophenol (2.40 g, 17.2 mmol) and methyl 4-bromomethylbenzoate (2.00 g, 8.7 mmol) were dissolved in acetone (150 mL) before adding potassium carbonate (7.0 g). The mixture was refluxed for 7 days under constant stirring. The reaction was monitored by TLC (dichloromethane). At the completion of the reaction acetone was evaporated under reduced pressure and the residue was taken up in a mixture of dichloromethane and water. The crude material was extracted into dichloromethane (3×40 mL) and the combined organic layers were washed with sodium hydroxide (3 M) until the aqueous layer became colourless. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude material was chromatographed (silica gel, hexane/dichloromethane 1:2) to afford methyl 4-[(4′-nitrophenoxy)methyl]benzoate (2.40 g, 96%) as white crystals: mp 161–162 °C; R_f (CH_2Cl_2) 0.95; IR (neat) ν_{max} 2960, 1707, 1592, 1511, 1498, 1261, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H, OCH_3), 5.22 (s, 2H, CH_2), 7.03 (d, *J* 7.1 Hz, 2H, ArH), 7.49 (d, *J* 8.4 Hz, 2H, ArH), 8.07 (d, *J* 8.4 Hz, 2H, ArH), 8.20 (d, *J* 7.1 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.4, 69.4, 114.4, 114.4, 125.2, 125.3, 126.4, 126.5, 129.3, 140.1, 162.8; Anal. Calcd for $C_{15}H_{13}NO_5$: C 62.72; H 4.56; N 4.88. Found C 62.96; H 4.71; N 4.75%.

4.2.4. Methyl 4-[(4′-aminophenoxy)methyl]benzoate ***15****.* Methyl 4-[(4′-nitrophenoxy)methyl]benzoate (2.00 g, 7.0 mmol) was

dissolved in methanol (100 mL) before adding tin(II) chloride dihydrate (7.64 g, 33.7 mmol). The mixture was stirred under an argon atmosphere at 70 °C for 8 days. The reaction was monitored by TLC using dichloromethane as solvent. At the completion of the reaction, the mixture was treated with a concentrated aqueous solution of sodium bicarbonate until the effervescence ceased. Then mixture was extracted with ethyl acetate (4×50 mL), the organic layers were collected, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. **15** (1.71 g, 95%) was obtained as a brown solid: mp 143–144 °C; R_f (CH_2Cl_2) 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H, OCH_3), 5.12 (s, 2H, CH_2), 6.63 (d, *J* 6.1 Hz, 2H, ArH), 6.78 (d, *J* 6.1 Hz, 2H, ArH), 7.49 (d, *J* 8.4 Hz, 2H, ArH), 8.07 (d, *J* 8.4 Hz, 2H, ArH).

4.2.5. 2,4-Dibromo-5-methoxyaniline and 4-bromo-3-methoxyaniline. *m*-Anisidine (5.00 g, 40.6 mmol) was dissolved in chloroform (40 mL) and the solution was chilled to 5 °C. *N*-Bromosuccinimide (7.23 g, 40.6 mmol) was added portionwise to the chilled solution over a 1 h period and the mixture was then stirred for another 4 h in an ice bath at 5–10 °C. The reaction mixture was allowed to warm at room temperature and stirring was continued overnight. The mixture was washed with sodium hydroxide (2 M, 50 mL), followed by water (60 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated to afford a dark brown viscous liquid. The crude material was chromatographed (silica gel, dichloromethane/hexane 2:1) to afford a mixture of 2-bromo-5-methoxyaniline and 2,4-dibromo-5-methoxyaniline as the first major band eluted. Subsequently, another major band was eluted to afford 4-bromo-3-methoxyaniline (860 mg, 10%) as peach coloured crystals: mp 97–98 °C (lit.[65] 93–94 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (br s, 2H, NH_2), 3.80 (s, 3H, OCH_3), 6.16 (dd, *J* 2.5, 8.4 Hz, 1H, ArH), 6.23 (d, *J* 2.5 Hz, 1H, ArH), 7.23 (d, *J* 8.4 Hz, 1H, ArH). The data are in agreement with those reported in the literature.[65] The first major band was evaporated to dryness and rechromatographed (silica gel, ethyl acetate/hexane 1:2) to afford 2-bromo-5-methoxyaniline (830 mg, 10%) as an orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H, OCH_3), 4.07 (br s, 2H, NH_2), 6.21 (dd *J* 2.9, 8.8 Hz, 1H, ArH), 6.30 (d, *J* 2.9 Hz, 1H, ArH), 7.25 (d, *J* 8.8 Hz, 1H, ArH). The data are in agreement with those reported in the literature.[65] This was followed by the elution of a second band that afforded 2,4-dibromo-5-methoxyaniline (2.66 g, 23%) as a brown liquid. R_f (80% EtOAc/CH_2Cl_2) 0.87; IR (neat) ν_{max} 3420, 3295, 3176, 2965, 2934, 1620, 1582, 1503, 1278, 1207, 1018, 805 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H, OCH_3), 4.10 (br s, 2H, NH_2), 6.31 (s, 1H, ArH), 7.49 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 99.3, 99.3, 99.7, 135.1, 144.3, 155.8; Anal. Calcd for $C_7H_7Br_2NO$: C, 29.93; H, 2.51; N, 4.99. Found: C 30.29; H 2.24; N 4.95%.

4.2.6. 4-Bromo-5-methoxy-2-methylaniline. *N*-Bromosuccinimide (0.80 g, 4.50 mmol) was added portionwise over a 1 h period to an ice-chilled solution of 5-methoxy-2-methylaniline (0.62 g, 4.50 mmol) in chloroform (10 mL). The reaction mixture was then stirred at 5–10 °C for 4 h, before it was allowed to warm at room temperature. The mixture was then washed with sodium hydroxide (2 M, 10 mL) and water (2×20 mL), dried over anhydrous sodium sulfate and filtered. The solvent was evaporated and the residue was chromatographed (silica gel, dichloromethane) to afford 4,6-dibromo-5-methoxy-2-methylaniline (0.12 g, 9%) as an orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.85 (br s, 2H, NH_2), 7.17 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 60.4, 104.0, 105.2, 120.2, 132.5, 143.0, 152.5. Another fraction was also eluted, to afford 4-bromo-5-methoxy-2-methylaniline (0.75 g, 77%) as a light grey solid: mp 103–105 °C; R_f (80% EtOAc/CH_2Cl_2) 0.75; IR (neat) ν_{max} 3462, 3402, 3332, 3223, 2965, 2932, 2854, 1633, 1602, 1574, 1500, 1454, 1398, 1296, 1211, 1051, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.81 (br s, 2H, NH_2), 6.29 (s, 1H, ArH), 7.16 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 56.2, 99.6, 100.0, 116.2, 134.2, 144.1, 154.7; Anal. Calcd for $C_8H_{10}BrNO$: C 44.47; H 4.66; N 6.48. Found: C 44.54; H 4.39; N 6.33%.

4.2.7. 4-Bromo-2-methoxyaniline. *o*-Anisidine (470 mg, 3.60 mmol) was dissolved in dichloromethane (8 mL) and cooled to −10 °C. 2,4,4,6-Tetrabromocyclohexadione (1.56 g, 3.60 mmol) was slowly added into the above stirred solution, while the temperature was kept below −5 °C. The reaction was allowed to warm to room temperature and stirring was continued overnight. The reaction mixture was washed with sodium hydroxide (10 mL, 2 M) and then water (15 mL), dried over magnesium sulfate, filtered and evaporated to dryness. The residue was chromatographed (silica gel, dichloromethane) to afford 2,4-dibromo-6-methoxyaniline (90 mg, 9%) as a dark brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H, OCH_3), 4.20 (br s, 2H, NH_2), 6.83 (d, *J* 2.1 Hz, 1H, ArH), 7.19 (d, *J* 2.1 Hz, 1H, ArH). The spectral data are in agreement with those reported in the literature.[65] Continued elution afforded 4-bromo-2-methoxyaniline (579 mg, 83%) as a brown solid: mp 57–59 °C (lit.[66] 56.5–58 °C; lit.[65] 60–61 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H, OCH_3), 3.85 (br s, 2H, NH_2) 6.60 (d, *J* 7.8 Hz, 2H, ArH), 6.88–6.90 (m, 2H, ArH). The spectral data are in agreement with those reported in the literature.[65]

4.3. Synthesis of Tröger's base analogues

*4.3.1. 2,8-Dimethoxy-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**2**.* 4-Methoxyaniline (5.00 g, 40.6 mmol) and paraformaldehyde (1.94 g, 65.0 mmol) were dissolved in trifluoroacetic acid (60 mL) and stirred under an argon atmosphere at room temperature in the dark for 48 h. The reaction mixture was basified by the addition of aqueous ammonia (25%) and washed with a saturated sodium hydrogen carbonate solution (200 mL). The crude material was extracted into dichloromethane (3×60 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The resultant material was a brown oil that was chromatographed (silica gel, ethyl acetate/dichloromethane 1:4) to afford (±)-**2** (5.72 g, 99%) as a white solid: mp 172–173 °C (lit.[35] 172–173 °C, lit.[67] 172 °C, lit.[37] 163–165 °C); R_f (EtOAc) 0.56; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 4.12 (d, *J* 16.8 Hz, 2H, CH_2), 4.27 (s, 2H, CH_2), 4.60 (d, *J* 16.8 Hz, 2H, CH_2), 6.49 (d, *J* 2.2 Hz, 2H, ArH), 6.80 (dd, *J* 6.5, 2.2 Hz, 2H, ArH), 7.14 (d, *J* 6.5 Hz, 2H, ArH).

*4.3.2. Attempted preparation of 2,8-dibenzyloxy-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine **16**.* 1-(Benzyloxy)-4-aminobenzene **14** (3.36 g, 16.8 mmol) and paraformaldehyde (806 mg, 26.8 mmol) were dissolved in trifluoroacetic acid (20 mL) and stirred under an argon atmosphere at room temperature in the dark for 48 h. The reaction mixture was basified with aqueous ammonia (25%) and saturated sodium hydrogen carbonate solution (200 mL) was added. The crude material was extracted into dichloromethane (3×50 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The resultant material was a brown viscous oil that appeared to be a polymerised material, not the desired compound, as evidenced by ^{1}H NMR analysis of a crude sample.

*4.3.3. 2,8-Bis(4′-methylcarboxyl)benzyloxy-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**17**.* Methyl 4-[(4′-aminophenoxy)methyl]benzoate **15** (2.00 g, 7.71 mmol) and paraformaldehyde (365 mg, 12.2 mmol) were dissolved in trifluoroacetic acid (20 mL) and stirred under an argon atmosphere at room temperature in the dark for 48 h. The reaction mixture was basified with aqueous ammonia (25%) and saturated sodium

hydrogen carbonate solution (200 mL) was added. The crude material was extracted into dichloromethane (3×50 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The resultant material was a brown viscous oil that was chromatographed (silica gel, ethyl acetate/dichloromethane 1:4) to afford (±)-**17** (1.12 g, 35%) as a white solid: mp 167–168 °C; R_f (15% EtOAc/CH_2Cl_2) 0.37; IR (neat) ν_{max} 2922, 2851, 1715, 1490, 1276 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 4.06 (d, *J* 16.8 Hz, 2H, CH_2), 4.28 (s, 2H, CH_2), 4.63 (d, *J* 16.8 Hz, 2H, CH_2), 5.09 (s, 2H, OCH_2), 6.49 (d, *J* 2.6 Hz, 2H, ArH), 6.79 (dd, *J* 6.0, 2.6 Hz, 2H, ArH), 7.07 (d, *J* 6.0 Hz, 2H, ArH), 7.49 (d, *J* 8.4 Hz, 4H, ArH), 8.07 (d, *J* 8.4 Hz, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 58.8, 67.1, 69.5, 112.1, 114.6, 126.0, 126.9, 128.7, 129.6, 129.8, 141.4, 142.23, 154.9, 166.8; HRMS (FAB^+) *m*/*z* calcd for $C_{33}H_{30}N_2O_6$ $[M+Na]^+$ 573.1996, observed 573.1996; Anal. Calcd for $C_{33}H_{30}N_2O_6$: C 71.99; H 5.49; N 5.09. Found C 71.77; H 5.59; N 5.34%.

*4.3.4. 2,8-Dihydroxy-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**4**.* Method 1: hydrogenolysis of **17**: compound **17** (100 mg, 0.18 mmol) was dissolved in ethanol (30 mL) before adding 10% Pd/C (60 mg). The mixture was stirred under an atmosphere of hydrogen at room temperature in the dark for 5 h. The reaction was monitored by TLC (ethyl acetate). At the completion of the reaction, the mixture was filtered and the filtrate was evaporated to dryness. The residue was chromatographed (silica gel, ethyl acetate) to afford (±)-**4** (65 mg, 98%) as a white solid: mp decomp. >302 °C; R_f (70% EtOAc/CH_2Cl_2) 0.33; IR (neat) ν_{max} 3048 (br), 1498, 1450, 1228 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.85 (d, *J* 16.9 Hz, 2H, CH_2), 4.07 (s, 2H, CH_2), 4.43 (d, *J* 16.9 Hz, 2H, CH_2), 6.27 (d, *J* 2.4 Hz, 2H, ArH), 6.52 (dd, *J* 8.6, 2.4 Hz, 2H, ArH), 6.85 (d, *J* 8.6 Hz, 2H, ArH), 9.04 (br s, 2H, OH); ^{13}C NMR (100 MHz, DMSO) δ 58.3, 66.8, 112.3, 114.5, 125.6, 128.8, 139.5, 153.3; HRMS (FAB^+) *m*/*z* calcd for $C_{15}H_{14}N_2O_2$ $[M+Na]^+$ 277.0947, observed 277.0950; Anal. Calcd for $C_{15}H_{14}N_2O_2 \cdot 0.75H_2O$: C 67.28; H 5.83; N 10.46. Found C 67.11; H 5.63; N 10.19%.

Method 2: demethylation of (±)-**2**: compound (±)-**2** (1.00 g, 3.50 mmol) was dissolved in anhydrous dichloromethane (20 mL) and boron tribromide (8.87 g, 35.4 mmol, 10 equiv) in successive portions at 0 °C. The mixture was stirred under an argon atmosphere in the dark at 0–5 °C for 5 h, then overnight at room temperature. The reaction was monitored by TLC (ethyl acetate). At the completion of reaction, the mixture was poured on to ice and extracted into ethyl acetate (5×50 mL) at pH ~ 5. The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. (±)-**4** (890 mg, 97%) was obtained as a white solid. The compound had identical spectral properties as the authentic material obtained from Method 1 (immediately above).

Method 3: direct condensation: 4-aminophenol (1.00 g, 9.10 mmol) and urotropin (1.28 g, 9.10 mmol) were dissolved in trifluoroacetic acid (15 mL) at 0 °C and stirred under an argon atmosphere in the dark for 2 h, then at room temperature for 2 days. The reaction mixture was extracted with ethyl acetate (3×40 mL) at pH ~ 5, the combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The resultant material was a brown oil that was chromatographed (silica gel, ethyl acetate) to afford (±)-**4** (557 mg, 50%) as a white solid. The compound had identical spectral properties as authentic material obtained from Method 1.

*4.3.5. 2,4,8-Tribromo-1,9-dimethoxy-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**18**.* 2,4-Dibromo-5-methoxyaniline (930 mg, 3.31 mmol) and paraformaldehyde (160 mg, 5.30 mmol) were dissolved in trifluoroacetic acid (30 mL). The reaction mixture was stirred under an argon atmosphere in dark for 48 h. The reaction mixture was then basified with a solution of concentrated ammonia (30 mL) in water (30 mL). A saturated sodium hydrogen carbonate solution (100 mL) was added and the aqueous mixture was extracted into dichloromethane (3×50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude material was chromatographed (silica, dichloromethane) to afford (±)-**18** (450 mg, 53%) as a pale off-white solid: mp 181–182 °C; R_f (CH_2Cl_2) 0.22; IR (neat) ν_{max} 2938, 2895, 2848, 1604, 1486, 1442, 1420, 1247, 1195, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.15–4.33 (m, 4H, CH_2), 4.47 (d, *J* 17.0 Hz, 1H, CH_2), 4.52 (d, *J* 17.0 Hz, 1H, CH_2), 6.66 (s, 1H, ArH), 7.09 (s, 1H, ArH), 7.61 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.1, 55.3, 56.2, 60.2, 66.5, 107.1, 108.3, 111.5, 114.7, 120.8, 125.5, 131.0, 134.6, 145.4, 147.4, 153.5, 155.0; Anal. Calcd for $C_{17}H_{15}Br_3N_2O_2.0.1$ CH_2Cl_2: C 38.93; H 2.90; N 5.31. Found: C 38.85; H 2.73; N 5.06%.

*4.3.6. 2,8-Dibromo-1,7-dimethoxy-4,10-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**19**.* 4-Bromo-5-methoxy-2-methylaniline (720 mg, 3.33 mmol) and paraformaldehyde (160 mg, 5.33 mmol) were dissolved in trifluoroacetic acid (40 mL) and stirred under argon atmosphere in dark for 48 h. The reaction mixture was then basified with a solution of concentrated ammonia (40 mL) in water (80 mL). A saturated sodium hydrogen carbonate solution (100 mL) was added and the aqueous mixture was extracted into dichloromethane (3×50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude material was chromatographed (silica gel, dichloromethane) to afford (±)-**19** (720 mg, 94%) as a white powder: mp 209–211 °C; R_f (CH_2Cl_2) 0.38; IR (neat) ν_{max} 2970, 2944, 2907, 1462, 1439, 1419, 1330, 1202, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 6H, CH_3), 3.73 (s, 6H, OCH_3), 4.12 (d, *J* 17.4 Hz, 2H, CH_2), 4.22 (s, 2H, CH_2), 4.45 (d, *J* 17.4 Hz, 2H, CH_2), 7.24 (s, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 51.4, 60.1, 66.5, 110.5, 123.2, 130.4, 132.7, 146.1, 151.9; Anal. Calcd for $C_{19}H_{20}Br_2N_2O_2$: C 48.74; H 4.31; N 5.98. Found: C 48.34; H 4.11; N 5.90%.

*4.3.7. 2,8-Dibromo-3,9-dimethoxy-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**20**.* 3-Methoxy-4-bromoaniline (1.67 g, 8.26 mmol) and paraformaldehyde (0.40 g, 13.4 mmol) were dissolved in trifluoroacetic acid (60 mL). The reaction mixture was stirred under an argon atmosphere in dark for 48 h. The reaction mixture was then basified with a solution of concentrated ammonia (60 mL) in water (12 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford (±)-**20** (1.73 g, 95%) as a slightly pinkish/off-white crystals that did not require any further purification: mp 242–243 °C; R_f (50% EtOAc/CH_2Cl_2) 0.55; IR (neat) ν_{max} 2955, 2894, 2845, 1600, 1483, 1436, 1285, 1194, 1132, 1102, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 6H, OCH_3), 4.08 (d, *J* 16.3 Hz, 2H, CH_2), 4.21 (s, 2H, CH_2), 4.58 (d, *J* 16.3 Hz, 2H, CH_2), 6.64 (s, 2H, ArH), 7.05 (s, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 57.7, 66.6, 107.0, 108.3, 120.7, 131.0, 147.8, 155.1; Anal. Calcd for $C_{17}H_{16}Br_2N_2O_2$: C 46.39; H 3.66; N 6.36. Found: C 46.71; H 3.63; N 6.26%.

*4.3.8. 2,8-Dibromo-4,10-dimethoxy-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**21**.* 4-Bromo-2-methoxyaniline (670 mg, 3.31 mmol) and paraformaldehyde (160 mg, 5.30 mmol) were dissolved in trifluoroacetic acid (30 mL) and the resulting reaction mixture was stirred under an argon atmosphere in dark for 48 h. The reaction mixture was then basified with a solution of concentrated ammonia (30 mL) in water (80 mL). A saturated sodium hydrogen carbonate solution (100 mL) was added and the aqueous mixture was extracted into dichloromethane (3×50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford a transparent light brown solid. The crude material was chromatographed (silica, ethyl acetate/hexane 1:1) to afford (±)-**21**

(570 mg, 79%) as a white solid: mp 233–234 °C; R_f (50% EtOAc/CH_2Cl_2) 0.55; IR (neat) ν_{max} 2965, 2939, 1564, 1470, 1410, 1257, 1220, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 6H, OCH_3), 4.20 (d, *J* 17.2 Hz, 2H, CH_2), 4.26 (s, 2H, CH_2), 4.47 (d, *J* 17.2 Hz, 2H, CH_2), 6.71 (d, *J* 1.7 Hz, 2H, ArH), 6.82 (d, *J* 1.7 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.8, 55.8, 67.6, 112.3, 117.1, 121.7, 130.8, 134.3, 153.5; Anal. Calcd for $C_{17}H_{16}Br_2N_2O_2$: C 46.39; H 3.66; N 6.36. Found: C 46.43; H 3.62; N 6.30%.

*4.3.9. 4,10-Dimethoxy-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**22**.* Method 1 (Debromination): compound (±)-**21** (200 mg, 0.45 mmol) was dissolved in a mixture of ethanol (25 mL) and dichloromethane (10 mL). Pd/C (10%, 10 mg) was added and the reaction mixture was stirred under a hydrogen atmosphere for 2 days and then filtered through Celite and evaporated to dryness. The residue was dissolved in dichloromethane and washed with saturated solution of sodium carbonate and extracted in dichloromethane (3×30 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated to dryness to afford an off-white solid. The crude material was chromatographed (silica, ethyl acetate/hexane 1:1) to afford (±)-**22** (73 mg, 61%) as long transparent crystals: mp 197–199 °C; R_f (80% EtOAc/CH_2Cl_2) 0.36; IR (neat) ν_{max} 2946, 2891, 1575, 1470. 1437, 1260, 1137, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 6H, OCH_3), 4.26 (d, *J* 17.0 Hz, 2H, CH_2), 4.38 (s, 2H, CH_2), 4.59 (d, *J* 17.0 Hz, 2H, CH_2), 6.57 (d, *J* 7.7 Hz, 2H, ArH), 6.72 (d, *J* 8.0 Hz, 2H, ArH), 6.97–7.02 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.1, 55.4, 67.7, 108.3, 118.8, 124.0, 129.3, 135.5, 152.8; Anal. Calcd for $C_{17}H_{18}N_2O_2$: C 72.32; H 6.43; N 9.92. Found: C 71.99; H 6.06; N 9.81%.

Method 2 (Direct condensation): *o*-anisidine (1.00 g, 8.13 mmol) and paraformaldehyde (0.39 g, 13.0 mmol) were dissolved in trifluoroacetic acid (21 mL). The reaction mixture was stirred under an argon atmosphere in dark for 14 days. The reaction mixture was then basified with a solution of concentrated ammonia (21 mL) in water (42 mL). A saturated sodium carbonate solution (100 mL) was added and the aqueous mixture was extracted into dichloromethane (3×50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford an off-white solid. The crude material was chromatographed (silica, ethyl acetate) to afford (±)-**22** (500 mg, 46%) as an off-white solid. Mp 197–199 °C. The compound possessed identical spectral properties to those reported from Method 1.

*4.3.10. 2,8-Dibromo-1,7-dihydroxy-4,10-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**23**.* Compound (±)-**19** (150 mg, 0.32 mmol) was dissolved in anhydrous dichloromethane (2 mL) and boron tribromide (0.3 mL, 3.2 mmol, 10 equiv) was added in successive portions at 0 °C. The resultant mixture was stirred under argon atmosphere in the dark at 0–5 °C for 5 h and then overnight at room temperature. Upon completion of the reaction (TLC) the mixture was poured onto ice and extracted into ethyl acetate at pH 4.3. The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford (±)-**23** (138 mg, 98%) as a light pink solid: mp decomp. >286 °C; R_f (80% EtOAc/CH_2Cl_2) 0.87; IR (neat) ν_{max} 3200 (br), 2947, 2906, 1458, 1203 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.23 (s, 6H, CH_3), 3.92 (d, *J* 17.3 Hz, 2H, CH_2), 4.10 (s, 2H, CH_2), 4.27 (d, *J* 17.3 Hz, 2H, CH_2), 7.17 (s, 2H, ArH), 8.80 (br s, 2H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 15.8, 51.4, 65.5, 104.7, 118.4, 125.4, 131.2, 146.0, 148.3; HRMS (ESI-MS^+) *m/z* calcd for $C_{17}H_{16}Br_2N_2O_2$ M+H^+440.9636, observed 440.9636.

*4.3.11. 2,8-Dibromo-3,9-dihydroxy-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**24**.* Compound (±)-**20** (1.00 g, 2.27 mmol) was dissolved in anhydrous dichloromethane and boron tribromide (5.68 g, 22.7 mmol, 10 equiv) was added in successive portions at 0 °C. The reaction mixture was stirred under an argon atmosphere in dark at 0–5 °C for 5 h, then overnight at room temperature. The reaction was monitored by TLC (ethyl acetate). At the completion of the reaction, the mixture was poured onto ice and extracted into ethyl acetate (5×50 mL) at pH ~ 4.18. The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness to yield (±)-**24** (920 mg, 98%) as a pink solid: mp decomp. >256 °C; R_f (80% EtOAc/CH_2Cl_2) 0.68; IR (neat) ν_{max} 3183 (br), 1241, 1194, 1103 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.90 (d, *J* 16.4 Hz, 2H, CH_2), 4.05 (s, 2H, CH_2), 4.42 (d, *J* 16.4 Hz, 2H, CH_2), 6.68 (s, 2H, ArH), 7.02 (s, 2H, ArH), 9.96 (br s, 2H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 52.3, 60.8, 99.2, 106.8, 115.2, 125.4, 143.1, 147.7; Anal. Calcd for $C_{15}H_{12}Br_2N_2O_2$: C 43.72; H 2.94; N 6.80. Found: C 43.68; H 3.01; N 6.78%.

*4.3.12. 4,10-Dihydroxy 6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**25**.* Method 1 (Demethylation): compound (±)-**22** (400 mg, 1.42 mmol) was dissolved in anhydrous dichloromethane (10 mL) and boron tribromide (3.53 g, 14.1 mmol, 10 equiv) was added in successive portions at 0 °C. The reaction mixture was stirred under an argon atmosphere in dark at 0–5 °C for 5 h, then overnight at room temperature. The reaction was monitored by TLC (ethyl acetate). At the completion of the reaction, the mixture was poured onto ice and extracted into ethyl acetate (5×50 mL) at pH ~ 4.70. The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness to yield (±)-**25** (350 mg, 97%) as a pinkish white solid: mp decomp. >258 °C; R_f (80% EtOAc/CH_2Cl_2) 0.65; IR (neat) ν_{max} 3301 (br), 1463,1244, 1069 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.98 (d, *J* 17.1 Hz, 2H, CH_2), 4.12 (s, 2H, CH_2), 4.32 (d, *J* 17.1 Hz, 2H, CH_2), 6.37 (d, *J* 7.9 Hz, 2H, ArH), 6.57 (d, *J* 7.9 Hz, 2H, ArH), 6.72 (app. t, *J* 7.9 Hz, 2H, ArH), 9.09 (br s, 2H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 53.7, 67.2, 113.1, 117.1, 117.4, 123.5, 129.4, 150.6. Anal. Calcd for $C_{15}H_{14}N_2O_2.1/3H_2O$: C 69.22; H 5.68; N 10.76. Found: C 69.52; H 5.40; N 10.53%.

Method 2 (Direct condensation): *o*-aminophenol (500 mg, 109.13 mmol) and paraformaldehyde (220 mg, 7.36 mmol) were dissolved in trifluoroacetic acid (20 mL). The reaction mixture was stirred under an argon atmosphere in dark for 48 h. The reaction mixture was then basified with a solution of concentrated ammonia (20 mL) in water (40 mL). It was then treated with sodium hydroxide solution (6 M) to obtain a pH of ~4.70 and then extracted with ethyl acetate solvent (3×25 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford a dark reddish solid. TLC and ^1H NMR showed a complex reaction mixture and no evidence of the Tröger's base was found.

4.4. Reactions of 2,8-dihydroxy Tröger's base (±)-4

*4.4.1. 2,8-n-Didodecyloxy-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**26**.* Compound (±)-**4** (100 mg, 0.40 mmol) and 1-bromododecane (191 mg, 0.85 mmol) were dissolved in acetone (20 mL) before adding potassium carbonate (1.00 g). The mixture was refluxed for 5 days under constant stirring. The reaction was monitored by TLC (dichloromethane). At the completion of the reaction acetone was evaporated under reduced pressure and the residue was taken up in a mixture of dichloromethane and water. The crude material was extracted into dichloromethane (3×50 mL) and the organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude compound was chromatographed (silica gel, ethyl acetate/dichloromethane 1:4) to afford (±)-**26** (130 mg, 55%) as an off-white solid: mp 59–61 °C; R_f (20% EtOAc/hexane) 0.32; IR (neat) ν_{max} 2918, 2850, 1491, 1467, 1307, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* 7.0 Hz, 6H, CH_3), 1.21–1.41 (m, 36H, CH_2), 1.70 (qn, *J* 6.7 Hz, 4H, βCH_2), 3.81 (t, *J*

6.5 Hz, 4H, αCH$_2$), 4.12 (d, *J* 16.5 Hz, 2H, CH$_2$), 4.31 (s, 2H, CH$_2$), 4.61 (d, *J* 16.5 Hz, 2H, CH$_2$), 6.40 (d, *J* 2.0 Hz, 2H, ArH), 6.70 (dd, *J* 8.9, 2.7 Hz, 2H, ArH), 7.12 (d, *J* 8.9 Hz, 2H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$); δ 14.1, 22.7, 26.0, 29.25, 29.33, 29.34, 29.55, 29.57, 29.61, 29.63, 31.9, 58.8, 67.2, 68.1, 111.5, 114.5, 125.8, 128.4, 155.7; HRMS (FAB$^+$) *m*/*z* calcd for $C_{39}H_{62}N_2O_2$ [M+Na]$^+$ 613.4703, observed 613.4701; Anal. Calcd for $C_{39}H_{62}N_2O_2$: C 79.27; H 10.58; N, 4.74. Found C 79.24; H 10.43; N 4.83%.

*4.4.2. 2,8-Acetoxy-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**27**.* Compound (±)-**4** (100 mg, 0.41 mmol), acetic acid (51 mg, 0.82 mmol), *N*,*N*′-dicyclohexylcarbodiimide (160 mg, 0.82 mmol) and 4-(dimethylamino)pyridine (50 mg, 0.41 mmol) were mixed together in dichloromethane (20 mL) at 0 °C under constant stirring for 3 h. Then the reaction mixture left under stirring for 3 days at room temperature. The crude material was filtered and the filtrate evaporated to dryness. The resultant material was chromatographed (silica gel, ethyl acetate/dichloromethane 1:9) to afford (±)-**27** (102 mg, 75%) as a white solid: mp 127–129 °C; R_f (20% EtOAc/CH$_2$Cl$_2$) 0.39; IR (neat) ν_{max} 2917, 2850, 1753, 1488, 1145 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.14 (s, 6H, CH$_3$), 4.11 (d, *J* 16.9 Hz, 2H, CH$_2$), 4.25 (s, 2H, CH$_2$), 4.67 (d, *J* 16.8 Hz, 2H, CH$_2$), 6.65 (d, *J* 2.3 Hz, 2H, ArH), 6.86 (dd, *J* 8.7, 2.3 Hz, 2H, ArH), 7.11 (d, *J* 8.7 Hz, 2H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.0, 58.4, 66.6, 119.4, 120.7, 126.0, 128.6, 145.4, 146.6, 169.6; HRMS (FAB$^+$) *m*/*z* calcd for $C_{19}H_{18}N_2O_4$ [M+Na]$^+$ 361.1159, observed 361.1155.

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Supplementary data

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