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Synthesis of Symmetric Dinitro-Functionalised Tröger's Base Analogues

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The synthesis of six new examples of 2,8-dinitro-substituted Tröger's base analogues are reported, together with the first examples of 1,7-, 3,9- and 4,10-dinitro Tröger's base analogues and the first example of a tetranitro Tröger's base compound. Several of these dinitro compounds lack substituents at the 2- and 8-positions and therefore provide further examples of Tröger's base analogues derived from anilines lacking a *para* substituent.

Introduction

Tröger's base (**1**, Figure 1) is a chiral, concave-shaped molecule that is prepared by the acid-catalysed condensation of *p*-toluidine and formaldehyde.[1] It was the first compound whose chirality is due solely to asymmetric nitrogen atoms to be resolved and additionally was probably the first compound to be resolved with the aid of a chiral stationary phase.[2]

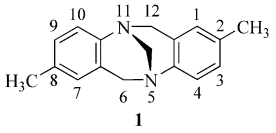

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Figure 1. Chemical structure of Tröger's base **1** and the conventional numbering system.

Numerous analogues of **1** have been prepared, however until very recently the type of substitution available on the benzene rings was limited by the belief that electron-withdrawing groups on the starting aniline units were poorly tolerated, if at all. The synthesis of dihalogenated Tröger's base compounds[3–5] provided inspiration that other electron-withdrawing substitutents may also be incorporated on aniline precursors.

The synthesis of Tröger's base analogues bearing the more strongly electron-withdrawing nitro group has remained a challenge due to the fact that it is difficult to form the necessary aryl-methylene bond on a ring bearing a nitro group. Tröger's base compounds bearing a nitro group on *one* of the aromatic rings have been prepared, but their synthesis avoided the difficult bond-forming process by having it in place in one of the starting materials.[6,7] Only two dinitro-substituted Tröger's base compounds have previously been prepared. The first of these was 2,8-dinitro Tröger's base **2**, that was synthesised using two different methodologies. The initial report described the synthesis of **2** in 56% yield as an unexpected product of a reaction aimed at producing a cyclic imide **4**, that was not observed at the time. The reaction utilised 4-nitroaniline, diglycolic acid and polyphosphoric acid (PPA) as the reagents.[8] In the second report, **2** was obtained in 23% yield from the reaction of 4-nitroaniline, hydrogen chloride and DMSO.[9] The synthesis of a second dinitro analogue, 4,10-dimethyl-2,8-dinitro Tröger's base **3**, in 80% yield, was reported more recently from a reaction of 2-methyl-4-nitroaniline and paraformaldehyde in trifluoroacetic acid (TFA).[10]

Results and Discussion

In light of the synthetic utility of the nitro group, we chose to further investigate the synthesis of dinitro Tröger's

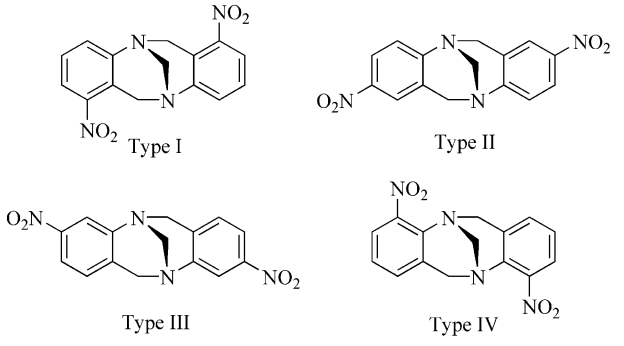

Figure 2. The four possible symmetric dinitro Tröger's base analogues.

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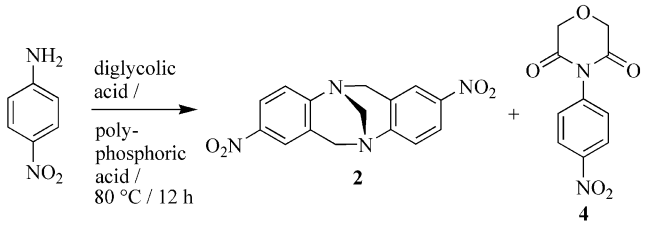
base analogues and 4 types of symmetrically substituted isomers were targeted as depicted in Figure 2.

Reagent Investigation

As a starting point, several reagent combinations with 4-nitroaniline were examined in attempts to form **2**. The first of these was a reproduction of the published methodology, in which a mixture of 4-nitroaniline, polyphosphoric acid and diglycolic acid were mixed together and heated at 80 °C for 12 h; this will be referred to as Method A (Scheme 1).[8] However, a yield of greater than 22% was never achieved and the cyclic imide, 4-(4′-nitrophenyl)morpholine-3,5-dione (**4**) was always present as a co-eluting and inseparable product after all attempted chromatographic separations. No mention of **4** was made in the literature, although it was the anticipated product.



Scheme 1. Synthesis of 2,8-dinitro Tröger's base **2** and morpholine dione **4**.

A slight modification to the published procedure (polyphosphoric acid and diglycolic acid were stirred together at 80 °C for 2 h prior to the addition of 4-nitroaniline, which will be referred to as Method B) resulted in the formation of **2** in 28% yield. Whilst this yield was again substantially lower than the reported yield of 56%, the crude sample produced after work-up was devoid of **4** when this methodology was employed.

It was subsequently found that for a variety of nitroanilines examined (see below) essentially the same yields were obtained using either Method A or B, however the crude samples obtained after work-up were easier to purify, and generally free of any cyclic imide products, if Method B was employed. It was also found that with some of the nitroanilines investigated, cyclic imides were not produced regardless of whether Method A or Method B was employed. When the reaction was conducted at 50 °C over the same time period only unreacted starting material was recovered. In contrast, when the reaction was performed at 70 °C the desired product was obtained, although in lower yields than reactions performed at 80 °C, and unreacted starting material was also recovered. The use of temperatures greater than 80 °C resulted in the formation of polymeric material which made the isolation of the desired products more difficult.

In order to learn more about the mechanism of the reaction, glycolic anhydride was employed in place of diglycolic acid. The use of 1.5 equiv. of diglycolic anhydride in polyphosphoric acid (Method C) resulted in the formation of the cyclic imide **4** that co-eluted with the desired Tröger's base **2**, as confirmed by examination of ^{1}H NMR spectrum of the crude product and ^{1}H NMR spectra obtained after repeated attempts of separation. The ratio of 2,8-dinitro Tröger's base **2**/cyclic imide **4** was found to be 86:14 from integration of signals in a ^{1}H NMR spectrum after chromatography, which was essentially the same product distribution observed when Method A was employed (83:17). In the case of Method C, unreacted 4-nitroaniline was also recovered in a 21% yield.

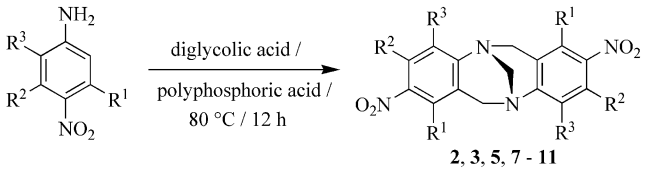
The fact that very similar product distributions were observed with both diglycolic acid (Method A) and glycolic acid anhydride (Method C) suggests that the reaction proceeds via the anhydride (that in the case of diglycolic acid could be formed from a dehydration reaction with polyphosphoric acid). Method C was not employed with any other nitro anilines.

The use of paraformaldehyde and trifluoroacectic acid (TFA) (Method D, a reagent mixture that proved to be successful in the synthesis of **3**[10]) lead to the recovery of some unreacted 4-nitroaniline, together with significant amounts of intractable material. A similar result was obtained when PPA was used in place of TFA. There was no trace of **2** present in the ^{1}H NMR spectrum of the crude material obtained after work-up in either case.

In light of these results in the synthesis of **2**, and those obtained by other researchers in the synthesis of **3**, a study on the generality of the reaction was conducted where two types of reagents and reactions conditions were used; in the first, diglycolic acid was employed as the formaldehyde equivalent in PPA at 80 °C and in the second set of conditions, paraformaldehyde was used with TFA at room temperature.

Type II Compounds (2,8-Dinitro)

The initial point of variation in the nitroanilines was based on Type II compounds and involved the incorporation substituents at the 2-position. It was anticipated that the substituents would increase the yield of Tröger's base products by either enhancing the electron-richness of the aniline, or increasing the solubility of the products, thereby facilating their isolation and purification (Scheme 2, Table 1).



Scheme 2. Synthesis of Type II compounds with various substitution patterns.

As mentioned previously, **2** was obtained in a 28% yield in our hands. The presence of a substituent *ortho* to the amino group afforded several new 2,8-dinitro Tröger's base compounds, however the substituent had a negligible effect

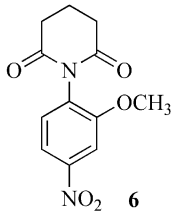
Table 1. Yields of the 2,8-dinitro Tröger's base compounds **2**, **3**, **5** and **7**–**11**.

	R^1	R^2	R^3	Yield (%)[a]	Method
2	H	H	H	28	B
2	H	H	H	trace[b]	D
3	H	H	CH_3	34	B
3	H	H	CH_3	78	D
5	H	H	OCH_3	20[c]	A
5	H	H	OCH_3	27	B
5	H	H	OCH_3	68	D
7	H	H	Br	28	B
7	H	H	Br	–[d]	D
8	CH_3	H	CH_3	16	B
8	CH_3	H	CH_3	92	D
9	Br	H	CH_3	23	B
9	Br	H	CH_3	71	D
10	CH_3	H	H	13[e]	A
10	CH_3	H	H	14[f]	D
11	Br	H	H	14	B
11	Br	H	H	–[d]	D

[a] Isolated yields after column chromatography. [b] Only a trace of a Tröger's base product was observed in the ^{1}H NMR spectrum of the crude material after work-up. [c] When Method A was employed, a 34% yield of the 2′-methoxy analogue of **4**, compound **6**, was also obtained. [d] No Tröger's base product was detected in the ^{1}H NMR spectrum of the crude material after work-up. [e] Small amounts of the other two isomers were evident in a ^{1}H NMR spectrum of the crude material. [f] The combined yield of an inseparable mixture of all 3 possible isomers.

on yields when either Method A or B was used. It is noteworthy that the solubility of **3**, **5** and **7** was considerably improved over that of **2** and in this regard the incorporation of the substituents exhibited the desired effect. The use of method D results in a considerable improvement in the yields of **3** and **5**, with methyl and methoxy groups, respectively, *ortho* to the amine. However, the inclusion of a bromo group at this position failed to afford any trace of the desired product, Tröger's base **7**, when Method D was employed.

When Method A was employed in the synthesis of **5**, 4-(2′-methoxy-4′-nitrophenyl)morpholine-3,5-dione **6** was also isolated in a 34% yield,[11] however this product was not observed in a ^{1}H NMR spectrum of the crude material after work-up when Method B was employed.



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An X-ray crystal structure of **5** is shown in Figure 3. The dihedral angle between the least-squares planes of the two aryl rings in this molecule is 103.4°, at the upper end of the range of 82[12] – 110°[13] that has been reported for a wide variety of simple dibenzo Tröger's base analogues.

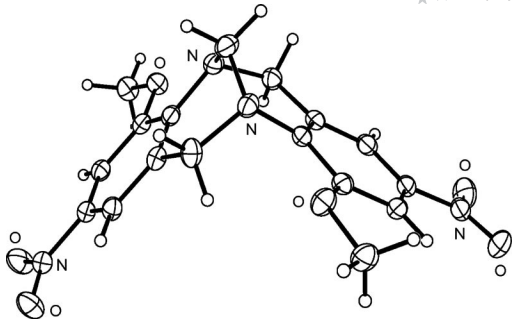


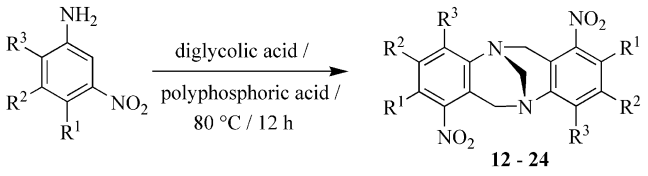
Figure 3. An ORTEP diagram of **5** with 50% probability ellipsoids.

As was observed in the case of **3**, **5** and **7**, the presence of substituents on compounds **8**–**11** increased their solubility in organic solvents in comparison with **2**, without increasing the yields of the desired products when Methods A or B were used, whilst yield of **8** and **9** were dramatically enhanced with Method D.

Compounds **10** and **11** were the products of anilines that could each theoretically afford three different Type II Tröger's base products as they have two inequivalent positions *ortho* to the amino group (due to the presence of a substituent at the R^1 site in Scheme 2). Indeed, all three isomers were formed, however the use of Method A led to the formation of **10** as the major product which facilitated its purification. In contrast, Method D resulted in the formation of all three isomers in approximately equal amounts and the Tröger's base products proved to be inseparable by either chromatography or recrystallisation, although the latter technique did lead to partial separation with considerable loss of material. As was the case in the attempted synthesis of **7** using Method D, no trace of **11** was observed using these conditions (the aniline employed in these two reactions are isomers of one another).

Type I Compounds (1,7-Dinitro)

The reaction of *m*-nitroanilines was then examined (Scheme 3, Table 2). In order to investigate the effect of the presence of other substituents on the aromatic ring, four different types of substitution patterns were studied; those with *ortho* and *para* substituents, those with an *ortho* substituent only, those with a *para* substituent and lacking an *ortho* substituent, and finally 3-nitroaniline. No single method stands out as being superior for this group of anilines.



12 - 24

Scheme 3. Synthesis of Type I compounds with various substitution patterns.

Table 2. Yields of the 1,7-dinitro Tröger's base compounds 1**2**–**24**.

	R^1	R^2	R^3	Yield (%)[a]	Method
12	CH_3	H	CH_3	51	B
12	CH_3	H	CH_3	45	D
13	Br	H	CH_3	46	A
13	Br	H	CH_3	45	D
14	CH_3	H	Br	12	A
14	CH_3	H	Br	trace[b]	D
15	H	H	CH_3	6	A
15	H	H	CH_3	56	D
16	H	H	$CH(CH_3)_2$	23	A
16	H	H	$CH(CH_3)_2$	34	D
17	H	H	OCH_3	5	A
17	H	H	OCH_3	22	D
18	H	H	Br	10	A
18	H	H	Br	–[c]	D
19	CH_3	H	H	32[d]	B
19	CH_3	H	H	–[c]	D
20	$CH(CH_3)_2$	H	H	8	A
20	$CH(CH_3)_2$	H	H	45	D
21	$CH_2(CH_3)_2CH_3$	H	H	18	B
21	$CH_2(CH_3)_2CH_3$	H	H	trace[b]	D
22	Br	H	H	6	B
22	Br	H	H	–[c]	D
23	Br	CH_3	H	18	A
23	Br	CH_3	H	trace[b]	D
24	H	H	H	22[e]	B
24	H	H	H	–[c]	D

[a] Isolated yields after column chromatography. [b] Only a trace of the symmetric Type I Tröger's base product was observed in the ^{1}H NMR spectrum of the crude material after work-up. [c] No Tröger's base product was detected in the ^{1}H NMR spectrum of the crude material after work-up. [d] Hybrid **25** was also isolated in 9% yield. [e] Hybrid **26** was also isolated in 5% yield.

Tröger's base compounds **12** and **13** were formed in acceptable yields. They were the result of reactions of anilines that bear a substituent at the *para* position and that could only afford a single Tröger's base isomer as they had only one vacant site *ortho* to the amino group. The yield of **14** was quite low, however the reason for this is unknown.

Four reactions involving 2-substituted-5-nitroanilines afforded Tröger's base compounds **15**–**18** in poor to moderate yields. In addition to halogen compounds,[5] the molecules provide further examples of the successful synthesis of Tröger's base analogues from anilines lacking a substituent in the *p*-position. A factor that may contribute to the poor yields in these cases is the possibility that the formaldehyde equivalent may condense at the *p*-position of such anilines and then undergo subsequent reactions with amino groups to afford non-Tröger's base products. Indeed it was this possibility that gave rise to the belief that a substituent at the *para*-position was a necessity if Tröger's base compounds were to be obtained.

It is apparent from inspection of Table 2 that the yields of **15**, and to a lesser extent **17**, are dramatically enhanced with the use of Method D, but this method is not consistently superior to Method A, even within this group of nitroanilines bearing the same pattern of substitution.

The structure of **15** was confirmed by X-ray crystallography (Figure 4). The dihedral angle between the least-squares planes of the two aryl rings in this compound is 99.1°.

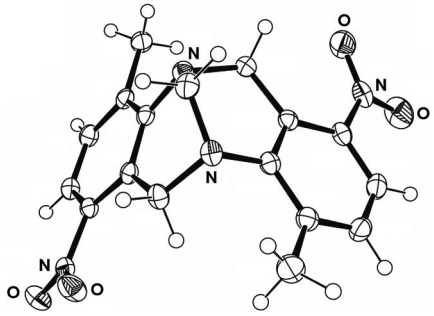


Figure 4. An ORTEP diagram of **15** with 50% probability ellipsoids.

Compounds **19**–**24** were the products of anilines that could each theoretically afford three different Tröger's base products (Type I, Type III and a Type I/III hybrid) as they have two inequivalent positions *ortho* to the amino group (i.e., R^3 = H in Scheme 3). The anticipated different reactivities of the two vacant *ortho* sites is expected to be greatest in the case of the anilines used to produce compounds **19**–**22** and **24**, where one of the vacant *ortho* sites is more sterically hindered than the other, as illustrated in Figure 5.

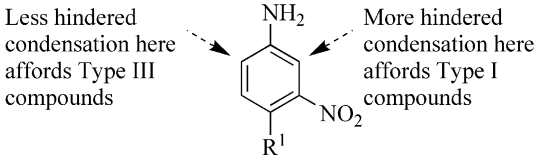
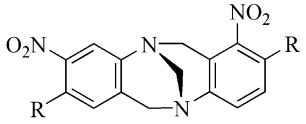


Figure 5. The two possible sites for diazocine bridge formation.

Anilines where a halogen atom is present in the place of the nitro group and R^1 = H or CH_3 have been reported to afford all three possible Tröger's base isomers (with the exception of when the halogen is a fluorine atom).[5] In an earlier report, 3,4-dimethylaniline was observed to form a Type III compound together with a hybrid, in a 72:28 ratio, with no evidence of a Type I compound.[14]

In these reactions, no Type III products where observed, despite the fact that they would be the product of a reaction at the less hindered *ortho* position. Infact, Type I compounds were observed as the exclusive Tröger's base products, with the exception of two anilines; 4-methyl-3-nitroaniline and 3-nitroaniline, which also afforded hybrids **25** and **26** in 9% and 5% yields, respectively, when Method B was employed. No Tröger's base products were formed when these two anilines where used in Method D.



25 R = CH_3 9%
26 R = H 5%

The identification of **25** and **26** as hybrid systems was possible based solely upon examination of ^{1}H NMR spectra as the bridging region of both compounds lacked the characteristic splitting pattern that reflects the C_2-symmetry

present in all symmetrically substituted Tröger's base analogues. The structure of **25** was also confirmed by X-ray crystallography.[15]

Interestingly, the use of 4-bromo-5-methyl-3-nitroaniline, an aniline with two vacant *ortho* sites, and two inequivalently substituted *meta* sites, afforded a single Tröger's base product **23**, as evident from examination of the ^{1}H NMR spectrum of the crude material after work-up when Method A was employed. The structural assignment of this compound was only possible with the aid of two-dimensional NMR experiments, which revealed the presence of an nOe between the methyl group and an adjacent aryl proton (Figure 6) (see Supporting Information), as splitting patterns in the aromatic region could not be used to provide an unambiguous assignment.

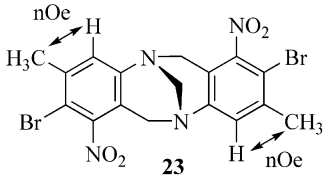


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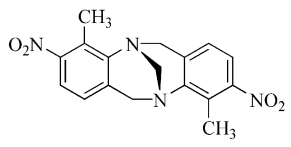
Figure 6. The observed nOe that was use to confirm the structure of **23**.

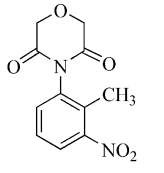
The observed nOe would not be possible if the diazocine bridge were formed at the site *ortho* to the methyl group as this would result in the aryl proton in a Tröger's base product that was positioned *para* to the methyl group.

Type III Compound (3,9-Dinitro)

A single example of a Type III compound was prepared from 2-methyl-3-nitroaniline. Unlike many of the 3-nitroanilines used in the synthesis of Type II compounds, 2-methyl-3-nitroaniline could only afford a Type III Tröger's base analogue as the position *ortho* to both the amino and nitro groups was not available for substitution. Compound **27** was prepared in 33% yield, together with another example of an *N*-phenylmorpholine dione, **28** (cf. **4** and **6**). In this instance the two compounds were readily separable by column chromatography. The use of Method D resulted in the formation of **27** in 43% yield.



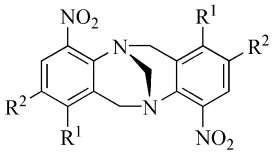
27 33% (Method B)
43% (Method D)



28 11% (Method B)

Type IV Compounds (4,10-Dinitro)

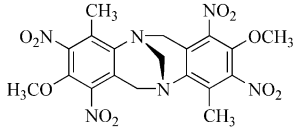
The use of 2-nitroanilines in the Tröger's base forming reaction should theoretically result in the formation of Type IV compounds. This was found to be the case for 4-methyl-2-nitroaniline and 4,5-dimethyl-2-nitroaniline, that afforded **29** (Method B) and **30** (Method A) in 36% and 8% yields, respectively, whilst the use of Method D conditions was unsuccessful with both anilines. In contrast, the use of 2-nitroaniline failed to result in the formation of a Tröger's base product under any of the examined conditions.



29 $R^1 = H$, $R^2 = CH_3$ 36%
30 $R^1 = CH_3$, $R^2 = CH_3$ 8%

A Tetranitro Compound (1,3,7,9-Tetranitro)

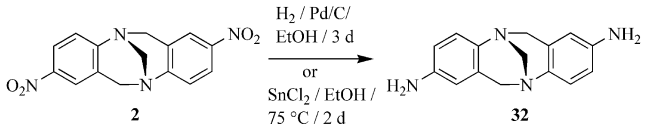
In light of the success achieved with various nitroanilines, a reaction was carried out with a dinitroaniline, 4-methoxy-2-methyl-3,5-dinitroaniline, to yield the tetranitro Tröger's base analogue **31** in 11% yield with the use of Method B, whilst Method D afforded **31** in a 4% yield. The structure of **31** was confirmed by X-ray crystallography.[16] This is yet another example of a Tröger's base compound that is multiply-substituted with electron-withdrawing substituents, the others being analogues with substituent patterns like 4,10-dichloro-1,7-dimethoxy-2,8-dimethyl ester,[17] 4,10-dibromo-2,8-diethyl ester,[18] tetrahalo,[9,13,19] and octafluoro[20]. In the present case, it is thought that the electron-withdrawing nature of the two nitro groups in the aniline should be offset somewhat by the methyl and methoxy groups that are also expected to aid in the solubility of **31**.



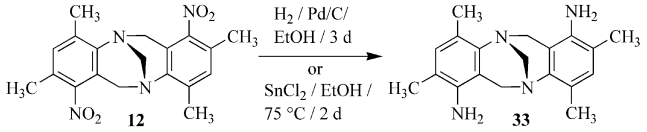
31 11% (Method B)
4% (Method D)

Amino Tröger's Base Analogues

Three amino-substituted dibenzo analogues of Tröger's base have recently been reported; two of these were obtained from a two-step reaction involving catalytic amination of preformed halogenated Tröger's base compounds and subsequent hydrolysis of the resultant imine[21] and the third diamine was obtained from reduction of dinitro Tröger's base **3** with iron powder in acetic acid and ethanol.[10] We sought access to diamino Tröger's base compounds via reduction of the nitro groups using two different reagent combinations, in order to establish the feasibility of this general approach to diamino Tröger's base analogues. Toward this end, compounds **2** and **12** were subjected to two different sets of reduction conditions (Schemes 4 and 5).



Scheme 4. Synthesis of a Type II diamine.



Scheme 5. Synthesis of a Type I diamine.

Compound **32** was produced in 92% yield from the hydrogenolysis reaction, however no Tröger's base material was recovered from the reaction involving tin(II) chloride. We believe that the reduction did take place, however we could not extract **32** from the aqueous environment during the work-up procedure.

In contrast, hydrogenolysis of **12** failed, presumably as a result of the increased steric hindrance around the nitro groups. **33** was obtained in 55% yield from the tin(II) chloride reduction. In this case, the hydrophilicity of the diamine is reduced by the presence of the methyl groups.

Both **2** and **12** were also subjected to continuous-flow hydrogenation, (see Exp. Sect. for complete details) to afford **32** and **33** in 85% and 97% yield, respectively, in drastically reduced reaction times.

Conclusions

We have prepared examples of all four types of symmetrically substituted dinitro Tröger's base compounds. In addition, we have synthesised the first example of a tetranitro Tröger's base analogue. We expect that these molecules will become useful building blocks, via conversion to the corresponding diamines, in the synthesis of more highly functionalised compounds such as bis-,[22–25] tris-[26–28] or higher-order fused Tröger's base analogues and in the synthesis of new double-stranded helicates.[10,29]

Experimental Section

General: Melting points were recorded with either a Reichert melting-point stage and are uncorrected or a TA Instruments DSC 2010 Differential Scanning Calorimeter. Microanalyses were performed by the Microanalytical Unit, University of Otago, New Zealand. High-resolution mass spectrometry (HRMS) was obtained either at the School of Chemistry, University of New South Wales (FAB) or The Research School of Chemistry, Australian National University (EI, Fissons VG-Autospec, or ESI; Bruker Apex 3). ^{1}H NMR spectra were recorded with a Bruker WM AMX 400 spectrometer (400 MHz) at 300 K unless otherwise stated. Signals were recorded in terms of chemical shifts and are expressed in parts per million (δ), multiplicity, coupling constants (in Hz, rounded to one decimal place) and assignments in that order.

Solvents and reagents were purified using standard techniques (see the Supporting Information for the preparation of several anilines used as starting materials in the work). All commercial solvents were routinely distilled prior to use. Hexane refers to the fraction of b.p. 60–80 °C. Where solvent mixtures are used, the portions are given by volume.

Column chromatography was routinely carried out using the gravity feed column techniques on Merck silica gel type 9385 (230–400 mesh) with the stated solvent systems. Analytical thin-layer chromatography (TLC) analyses were performed on precoated plates (Merck aluminium sheets, silica gel 60 F_{254}, 0.2 mm). Visualisation of compounds was achieved by illumination under ultraviolet light (254 nm).

Continuous-flow hydrogenation was carried out on a H-Cube (ThalesNano), using a 30 mm 10% Pd on C catalyst cartridge, at the conditions specified in the relevant sections.

General Procedures

Method A: The nitroaniline (14.5 mmol), diglycolic acid (3.06 g, 23.3 mmol) and polyphosphoric acid (86%, d = 1.90 g/cm^3, 20.0 g) were heated at 80 °C for 12 h under a drying tube. After cooling, water (100 mL) was added and the reaction mixture was neutralised with sodium hydroxide (3 M). The mixture was extracted with dichloromethane (2 × 150 mL) and the combined organic layers were washed with brine (100 mL), dried with anhydrous sodium sulfate, filtered and the solvents evaporated to dryness. The crude material was then purified as detailed below.

Method B: A mixture of diglycolic acid (3.06 g, 23.3 mmol) and polyphosphoric acid (86%, d = 1.90 g/cm^3, 20.0 g) was heated at 80 °C for 2 h under a drying tube. The nitroaniline (14.5 mmol) was added to this clear solution and the mixture was heated at 80 °C for another 12 h. After cooling, water (100 mL) was added and the reaction mixture was neutralised with sodium hydroxide (3 M). The mixture was extracted with dichloromethane (3 × 100 mL) and the combined organic layers were washed with brine (100 mL), dried with anhydrous sodium sulfate, filtered and the solvents evaporated to dryness. The crude material was then purified as detailed below.

Method D: The nitroaniline (6.57 mmol) and paraformaldehyde (414 mg, 13.8 mmol, 2.1 equiv.) were dissolved in TFA (15 mL) and stirred in the dark under argon for the time specified below. The reaction mixture was then poured onto ice (150 g), basified by the addition of sodium hydroxide (6 M, 100 mL) and extracted with dichloromethane (3 × 50 mL). The organic layers were combined, washed with brine (100 mL), dried with anhydrous sodium sulfate, filtered and the solvents evaporated to dryness. The crude material was then purified as detailed below.

Type II Compounds

2,8-Dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (2) and 4-(4′-Nitrophenyl)morpholine-3,5-dione (4)

Method A: Starting with 4-nitroaniline (2.00 g, 14.5 mmol), the crude material was chromatographed (silica gel, dichloromethane) to afford a mixture of (±)-**2** and **4** (468 mg) as a yellow solid in a ratio of 83:17, as determined by integration of the ^{1}H NMR spectrum.

Method B: Starting with 4-nitroaniline (2.00 g, 14.5 mmol), the crude material was chromatographed (silica gel, dichloromethane) to afford (±)-**2** (585 mg, 28%) as a pale yellow solid; m.p. 258–260 °C (ref.[8] 258–260 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.32 (d, J = 17.4 Hz, 2 H, CH_2), 4.42 (app. s, 2 H, CH_2), 4.82 (d, J = 17.1 Hz, 2 H, CH_2), 7.27 (d, J = 8.9 Hz, 2 H, ArH), 7.88

(d, J = 2.6 Hz, 2 H, ArH), 8.23 (dd, J = 2.6, 8.9 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 58.6, 66.4, 122.9, 123.2, 125.7, 128.1, 143.9, 153.9 ppm.

Method D: Starting with 4-nitroaniline (500 mg, 3.62 mmol) and stirring for 7 d, ^{1}H NMR of the crude material obtained upon work-up (530 mg) indicated that no Tröger's base product was present.

4,10-Dimethyl-2,8-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (3)

Method B: Starting with 2-methyl-4-nitroaniline (2.00 g, 13.15 mmol), the crude material was chromatographed (silica gel, dichloromethane) to afford (±)-**3** (750 mg, 34%) as a pale yellow solid; m.p. >312 °C (dec.) (ref.[10] >300 °C). ^{1}H NMR (400 MHz, DMSO, 25 °C): δ = 2.47 (s, 6 H, 2 × CH_3), 4.30 (d, J = 17.2 Hz, 2 H, CH_2), 4.35 (app. s, 2 H, CH_2), 4.68 (d, J = 17.2 Hz, 2 H, CH_2), 7.81 (d, J = 2.6 Hz, 2 H, ArH), 7.96 (d, J = 2.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, DMSO, 25 °C): δ = 16.8, 54.0, 66.1, 120.2, 123.4, 129.3, 134.5, 142.7, 151.9 ppm. $C_{17}H_{16}N_4O_4$ (340.33): calcd. C 59.99, H 4.74, N 16.46; found C 59.74, H 4.78, N 16.31.

Method D: Starting with 2-methyl-4-nitroaniline (6.00 g, 39.45 mmol) the isolation procedure described in the literature[10] was followed to afford (±)-**3** (5.25 g, 78%) as a pale yellow solid; m.p. >312 °C (dec.). The spectroscopic data on this material were identical to those obtained for (±)-**3** isolated from Method B.

4,10-Dimethoxy-2,8-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine (5) and 4-(2′-Methoxy-4′-nitrophenyl)morpholine-3,5-dione (6)

Method A: Starting with 2-methoxy-4-nitroaniline (1.00 g, 5.95 mmol), the crude material was chromatographed (silica gel, dichloromethane) to afford **6** (546 mg, 34%) as a white solid; m.p. 212–214 °C. ^{1}H NMR (400 MHz, DMSO, 25 °C): δ = 3.89 (s, 3 H, OCH_3), 4.54 (d, J = 16.3 Hz, 2 H, CH_2), 4.62 (d, J = 16.3 Hz, 2 H, CH_2), 7.56 (d, J = 8.8 Hz, 1 H, ArH), 7.94–7.96 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, DMSO, 25 °C): δ = 57.6, 68.1, 108.1, 116.5, 128.7, 132.3, 149.6, 156.6, 169.9 ppm. $C_{11}H_{10}N_2O_6$ (266.21): calcd. C 49.63, H 3.79, N 10.52; found C 49.67, H 3.85, N 10.46.

A second compound, (±)-**5** (224 mg, 20%), was subsequently eluted from the column as a yellow solid; m.p. >290 °C (dec.). ^{1}H NMR (400 MHz, DMSO, 25 °C): δ = 3.95 (s, 6 H, OCH_3), 4.28 (app. s, 2 H, CH_2), 4.36 (d, J = 17.4 Hz, 2 H, CH_2), 4.60 (d, J = 17.4 Hz, 2 H, CH_2), 7.56 (d, J = 2.3 Hz, 2 H, ArH), 7.71 (d, J = 2.3 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, DMSO, 25 °C): δ = 36.3, 53.7, 56.2, 104.0, 115.0, 129.9, 142.0, 143.3, 152.9 ppm. $C_{17}H_{16}N_4O_6$ (372.33): calcd. C 54.84, H 4.33, N 15.05; found C 54.53, H 4.46, N 14.76. Crystals suitable for X-ray diffraction were obtained by crystallisation from dichloromethane.

Method B: Starting with 2-methoxy-4-nitroaniline (2.00 g, 11.89 mmol), the crude material was chromatographed (silica gel, ethyl acetate/dichloromethane, 1:3) to afford (±)-**5** (605 mg, 27%) as a yellow solid; m.p. >290 °C (dec.). The spectroscopic data on this material were identical to those obtained for (±)-**5** isolated from Method A.

Method D: Starting with 2-methoxy-4-nitroaniline (1.00 g, 5.95 mmol) and stirring for 5 d, the crude material was chromatographed (silica gel, ethyl acetate/dichloromethane, 1:3) to afford (±)-**5** (755 mg, 68%) as a yellow solid; m.p. >290 °C (dec.). The spectroscopic data on this material were identical to those obtained for (±)-**5** isolated from Method A.

4,10-Dibromo-2,8-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7)

Method B: Starting with 2-bromo-4-nitroaniline (2.00 g, 9.21 mmol), the crude material was chromatographed (silica gel, dichloromethane) to afford (±)-**7** (600 mg, 28%) as a pale yellow solid; m.p. >298 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$/DMSO, 25 °C): δ = 4.41 (app. s, 2 H, CH_2), 4.52 (d, J = 17.5 Hz, 2 H, CH_2), 4.77 (d, J = 17.5 Hz, 2 H, CH_2), 8.10 (d, J = 2.5 Hz, 2 H, ArH), 8.29 (d, J = 2.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/DMSO, 25 °C): δ = 30.7, 54.8, 119.5, 122.3, 126.1, 131.8, 143.6, 150.6 ppm. $C_{15}H_{10}Br_2N_4O_4$ (470.07): calcd. C 38.33, H 2.14, N 11.92; found C 38.38, H 1.96, N 11.72.

Method D: Starting with 2-bromo-4-nitroaniline (500 mg, 2.30 mmol) and stirring for 6 d, ^{1}H NMR of the crude material obtained upon work-up (480 mg) indicated that no Tröger's base product was present.

1,4,7,10-Tetramethyl-2,8-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*]-[1,5]diazocine (8)

Method B: Starting with 2,5-dimethyl-4-nitroaniline (800 mg, 4.81 mmol), the crude product was chromatographed (silica gel, dichloromethane) to afford (±)-**8** (140 mg, 16%) as a yellow solid; m.p. >277 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.24 (s, 6 H, 2 × CH_3), 2.46 (s, 6 H, 2 × CH_3), 4.01 (d, J = 17.0 Hz, 2 H, CH_2), 4.21 (app. s, 2 H, CH_2), 4.51 (d, J = 17.0 Hz, 2 H, CH_2), 7.63 (s, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.6, 17.1, 53.9, 65.4, 125.0, 127.8, 128.3, 131.8, 146.1, 150.2 ppm. $C_{19}H_{20}N_4O_4$ (368.39): calcd. C 61.95, H 5.47, N 15.21; found C 62.21, H 5.59, N 15.18.

Method D: Starting with 2,5-dimethyl-4-nitroaniline (1.00 g, 6.21 mmol) and stirring for 11 d, (±)-**8** (1.05 g, 92%) was obtained as a yellow solid that required no further purification; m.p. (dec.) >277 °C. The spectroscopic data on this material were identical to those obtained for (±)-**8** isolated from Method B.

1,7-Dibromo-4,10-dimethyl-2,8-dinitro-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine (9)

Method B: Starting with 5-bromo-2-methyl-4-nitroaniline (560 mg, 2.42 mmol), the crude product was chromatographed (silica gel, ethyl acetate/hexane, 1:4) to afford (±)-**9** (139 mg, 23%) as a yellow solid; m.p. >288 °C (dec.). ^{1}H NMR (400 MHz, DMSO, 25 °C): δ = 2.43 (s, 6 H, 2 × CH_3), 4.04 (d, J = 17.3 Hz, 2 H, CH_2), 4.31 (app. s, 2 H, CH_2), 4.56 (d, J = 17.3 Hz, 2 H, CH_2), 7.82 (s, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.6, 55.9, 64.5, 111.3, 125.2, 129.5, 134.2, 145.9, 150.4 ppm. HRMS (FAB$^+$): m/z calcd. for $C_{17}H_{14}Br_2N_4O_4$ [M + Na]$^+$, 518.927401; found 518.926126. $C_{17}H_{14}Br_2N_4O_4$ (489.13): calcd. C 40.99, H 2.83, N 11.25; found C 40.90, H 2.89, N 10.97.

Method D: Starting with 5-bromo-2-methyl-4-nitroaniline (1.00 g, 4.33 mmol) and stirring for 9 d, the crude product was recrystallised from dichloromethane to afford (±)-**9** (765 mg, 71%) as a yellow solid; m.p. >288 °C (dec.). The spectroscopic data on this material were identical to those obtained for (±)-**9** isolated from Method B.

1,7-Dimethyl-2,8-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (10)

Method A: Starting with 3-methyl-4-nitroaniline (800 mg, 5.26 mmol), the crude material was chromatographed (silica gel, dichloromethane) to afford (±)-**10** (112 mg, 13%) as a yellow solid; m.p. 269–271 °C. ^{1}H NMR (400 MHz, DMSO, 25 °C): δ = 2.21 (s, 6 H, 2 × CH_3), 4.23 (app. s, 2 H, CH_2), 4.36 (d, J = 17.0 Hz, 2 H, CH_2), 4.67 (d, J = 17.0 Hz, 2 H, CH_2), 7.26 (d, J = 8.9 Hz, 2 H, ArH), 7.72 (d, J = 8.9 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, DMSO, 25 °C): δ = 13.7, 56.9, 64.2, 123.1, 123.4, 128.4, 130.9,

145.3, 152.1 ppm. HRMS (FAB$^+$): *m*/*z* calcd. for $C_{17}H_{16}N_4O_4$ [M + H]$^+$, 341.124431; found 341.124252. $C_{17}H_{16}N_4O_4$ (340.33): calcd. C 59.99, H 4.74, N 16.46; found C 59.72, H 4.81, N 16.43.

Method D: Starting with 3-methyl-4-nitroaniline (1.00 g, 6.58 mmol) and stirring for 9 d, the crude material was chromatographed (silica gel, dichloromethane) to afford a mixture of Tröger's base isomers (155 mg, 14%) that were inseparable.

1,7-Dibromo-2,8-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (11)

Method B: Starting with 3-bromo-4-nitroaniline (1.00 g, 4.60 mmol), the crude product was chromatographed (silica gel, dichloromethane) to afford (±)-**11** (150 mg, 14%) as a yellow solid; m.p. >258 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.13 (app. s, 2 H, CH_2), 4.43 (d, J = 17.1 Hz, 2 H, CH_2), 4.57 (d, J = 17.1 Hz, 2 H, CH_2) 7.21 (d, J = 8.8 Hz, 2 H, ArH), 7.79 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 53.4, 64.2, 106.1, 120.9, 122.4, 128.8, 133.4, 147.6 ppm. HRMS (FAB$^+$): *m*/*z* calcd. for $C_{15}H_{10}Br_2N_4O_4$ [M + Na]$^+$, 490.896101; found 490.894969. $C_{15}H_{10}Br_2N_4O_4$ (470.07): calcd. C 38.33, H 2.14, N 11.92; found C 38.62, H 2.17, N 11.62.

Method D: Starting with 3-bromo-4-nitroaniline (500 mg, 2.30 mmol) and stirring for 7 d, ^{1}H NMR of the crude material obtained upon work-up (507 mg) indicated that no Tröger's base product was present.

Type I Compounds

2,4,8,10-Tetramethyl-1,7-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (12)

Method B: Starting with 2,4-dimethyl-5-nitroaniline (2.44 g, 15.04 mmol), the crude product was chromatographed (silica gel, hexane/ethyl acetate, 3:1) to afford (±)-**12** (1.37 g, 51%) as a pale yellow solid; m.p. 226–227 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.24 (s, 6 H, 2×CH_3), 2.37 (s, 6 H, 2×CH_3), 3.86 (d, J = 17.4 Hz, 2 H, CH_2), 4.26 (app. s, 2 H, CH_2), 4.61 (d, J = 17.4 Hz, 2 H, CH_2), 7.02 (s, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 17.3, 17.7, 51.9, 66.3, 120.3, 120.8, 126.2, 132.1, 136.8, 144.3 ppm. HRMS (FAB$^+$): *m*/*z* calcd. for $C_{19}H_{20}N_4O_4$ [M + Na]$^+$, 391.137676; found 391.137560. $C_{19}H_{20}N_4O_4$ (368.39): calcd. C 61.95, H 5.47, N 15.21; found C 62.22, H 5.60, N 15.39.

Method D: Starting with 2,4-dimethyl-5-nitroaniline (500 mg, 3.01 mmol) and stirring for 6 d, the crude product was chromatographed (silica gel, hexane/ethyl acetate, 3:1) to afford (±)-**12** (251 mg, 45%) as a pale yellow solid; m.p. 226–227 °C. The spectroscopic data on this material were identical to those obtained for (±)-**12** isolated from Method B.

2,8-Dibromo-4,10-dimethyl-1,7-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (13)

Method A: Starting with 4-bromo-2-methyl-5-nitroaniline (1.00 g, 4.32 mmol), the crude material was chromatographed (silica gel, ethyl acetate/hexane, 1:3) to afford (±)-**13** (495 mg, 46%) as a pale yellow solid; m.p. >304 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.38 (s, 6 H, CH_3), 3.85 (d, J = 17.4 Hz, 2 H, CH_2), 4.24 (app. s, 2 H, CH_2), 4.57 (d, J = 17.4 Hz, 2 H, CH_2), 7.41 (s, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 23.3, 55.0, 65.8, 110.2, 118.6, 120.9, 128.5, 139.9, 147.3 ppm. HRMS (FAB$^+$): *m*/*z* calcd. for $C_{17}H_{14}Br_2N_4O_4$ [M + Na]$^+$, 518.927401; found 518.927064. $C_{17}H_{14}Br_2N_4O_4$ (498.13): calcd. C 40.99, H 2.83, N 11.25; found C 41.10, H 2.91, N 11.00.

Method D: Starting with 4-bromo-2-methyl-5-nitroaniline (1.06 g, 4.59 mmol) and stirring for 13 d, the crude material was recrystallised from acetone to afford (±)-**13** (515 mg, 45%) as a pale yellow solid; m.p. >304 °C (dec.). The spectroscopic data on this material were identical to those obtained for (±)-**13** isolated from Method A.

4,10-Dibromo-2,8-dimethyl-1,7-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (14)

Method A: Starting with 2-bromo-4-methyl-5-nitroaniline (2.00 g, 8.70 mmol), the crude material was chromatographed (silica gel, hexane/dichloromethane, 2:3) to afford (±)-**14** (266 mg, 12%) as a pale yellow solid; m.p. 190–191 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.25 (s, 6 H, CH_3), 4.24 (d, J = 17.9 Hz, 2 H, CH_2), 4.31 (app. s, 2 H, CH_2), 4.62 (d, J = 17.9 Hz, 2 H, CH_2), 7.48 (s, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 17.4, 52.3, 66.4, 122.7, 122.8, 128.2, 134.4, 143.2, 148.4 ppm. HRMS (FAB$^+$): *m*/*z* calcd. for $C_{17}H_{14}Br_2N_4O_4$ [M + Na]$^+$, 518.927401; found 518.927064. $C_{17}H_{14}Br_2N_4O_4$ (498.13): calcd. C 40.99, H 2.83, N 11.25; found C 41.75, H 3.01, N 11.00.

Method D: Starting with 2-bromo-4-methyl-5-nitroaniline (1.80 g, 7.80 mmol) and stirring for 5 d, ^{1}H NMR of the crude material obtained upon work-up (1.78 g) indicated that only a trace of Tröger's base product was present.

4,10-Dimethyl-1,7-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (15)

Method A: Starting with 2-methyl-5-nitroaniline (2.00 g, 13.15 mmol), the crude material was chromatographed (silica gel, ethyl acetate/hexane, 1:4) to afford (±)-**15** (126 mg, 6%) as a yellow solid; m.p. >274 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$/DMSO, 25 °C): δ = 2.27 (s, 6 H, CH_3), 4.06–4.14 (m, 4 H, 2×CH_2), 4.67 (d, J = 18.7 Hz, 2 H, CH_2), 7.01 (d, J = 8.4 Hz, 2 H, ArH), 7.53 (d, J = 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/DMSO, 25 °C): δ = 17.5, 53.5, 64.6, 120.3, 123.8, 129.0, 140.4, 144.9, 146.8 ppm. HRMS (FAB$^+$): *m*/*z* calcd. for $C_{17}H_{16}N_4O_4$ [M + Na]$^+$, 363.106376; found 363.106387. $C_{17}H_{16}N_4O_4$ (340.33): calcd. C 59.99, H 4.74, N 16.46; found C 59.98, H 4.79, N 16.50. Crystals suitable for X-ray diffraction were obtained by crystallisation from ethyl acetate/dichloromethane.

Method D: Starting with 2-methyl-5-nitroaniline (1.00 g, 6.57 mmol) and stirring for 5 d, the crude material was chromatographed (silica gel, ethyl acetate/hexane, 1:4) to afford (±)-**15** (653 mg, 56%) as a yellow solid; m.p. >274 °C (dec.). The spectroscopic data on this material were identical to those obtained for (±)-**15** isolated from Method A.

4,10-Diisopropyl-1,7-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (16)

Method A: Starting with 2-isopropyl-5-nitroaniline (1.00 g, 5.55 mmol), the crude material was chromatographed (silica gel, ethyl acetate/hexane, 1:3) to afford (±)-**16** (251 mg, 23%) as a pale yellow solid; m.p. 241–242 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.23 (d, J = 6.8 Hz, 6 H, CH_3), 1.34 (d, J = 7.0 Hz, 6 H, CH_3), 3.73 (m, 2 H, CH), 4.32–4.41 (m, 4 H, 2×CH_2), 5.01 (d, J = 18.0 Hz, 2 H, CH_2), 7.33 (d, J = 8.6 Hz, 2 H, ArH), 7.88 (d, J = 8.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.6, 24.9, 27.1, 56.3, 65.1, 121.8, 124.5, 125.7, 145.3, 146.4, 151.7 ppm. HRMS (FAB$^+$): *m*/*z* calcd. for $C_{21}H_{24}N_4O_4$ [M + Na]$^+$, 419.168976; found 419.16.168593. $C_{21}H_{24}N_4O_4$ (396.44): calcd. C 63.62, H 6.10, N 14.13; found C 63.76, H 6.15, N 14.15.

Method D: Starting with 2-isopropyl-5-nitroaniline (1.90 g, 10.50 mmol) and stirring for 14 d, the crude material was recrystallised from acetone to afford (±)-**16** (708 mg, 34%) as a pale yellow solid; m.p. 241–242 °C. The spectroscopic data on this material

were identical to those obtained for (±)-**16** isolated from Method A.

4,10-Dimethoxy-1,7-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine (17)

Method A: Starting with 2-methoxy-5-nitroaniline (2.00 g, 11.90 mmol), the crude material was chromatographed (silica gel, dichloromethane) to afford (±)-**17** (103 mg, 5%) as a pale yellow solid; m.p. >308 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.04 (s, 6 H, OCH_3), 4.34 (app. s, 2 H, CH_2), 4.67 (d, J = 18.6 Hz, 2 H, CH_2), 4.91 (d, J = 18.6 Hz, 2 H, CH_2), 6.85 (d, J = 9.2 Hz, 2 H, ArH), 7.99 (d, J = 9.2 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 53.8, 56.5, 66.0, 108.5, 123.1, 126.5, 136.3, 140.7, 157.5 ppm. HRMS (FAB$^+$): m/z calcd. for $C_{17}H_{16}N_4O_6$ [M + Na]$^+$, 395.096205; found 395.096136. $C_{17}H_{16}N_4O_6$ (372.33): calcd. C 54.84, H 4.33, N 15.05; found C 54.91, H 4.44, N 14.98.

Method D: Starting with 2-methoxy-5-nitroaniline (1.00 g, 5.95 mmol) and stirring for 5 d, the crude material was chromatographed (silica gel, dichloromethane) to afford (±)-**17** (254 mg, 22%) as a pale yellow solid; m.p. >308 °C (dec.). The spectroscopic data on this material were identical to those obtained for (±)-**17** isolated from Method A.

4,10-Dibromo-1,7-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (18)

Method A: Starting with 2-bromo-5-nitroaniline (1.00 g, 4.61 mmol), the crude material was chromatographed (silica gel, hexane/dichloromethane, 1:9) to afford (±)-**18** (103 mg, 10%) as a pale yellow solid; m.p. >280 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.40 (app. s, 2 H, CH_2), 4.76 (d, J = 18.7 Hz, 2 H, CH_2), 4.99 (d, J = 18.7 Hz, 2 H, CH_2), 7.68 (d, J = 8.8 Hz, 2 H, ArH), 7.78 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 54.6, 65.6, 122.3, 126.9, 127.5, 132.4, 146.4, 146.7 ppm. HRMS (FAB$^+$): m/z calcd. for $C_{15}H_{10}Br_2N_4O_4$ [M + Na]$^+$, 490.896101; found 490.896087. $C_{15}H_{10}Br_2N_4O_4$ (470.07): calcd. C 38.33, H 2.14, N 11.92; found C 38.12, H 2.32, N 11.66.

Method D: Starting with 2-bromo-5-nitroaniline (500 mg, 2.30 mmol) and stirring for 7 d, ^{1}H NMR of the crude material obtained upon work-up (514 mg) indicated that no Tröger's base product was present.

2,8–Dimethyl-1,7-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (19) and 2,8-Dimethyl-1,9-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (25)

Method B: Starting with 4-methyl-3-nitroaniline (1.00 g, 6.57 mmol), the crude product was chromatographed (silica gel, dichloromethane) to afford (±)-**19** (315 mg, 32%) as an orange solid; m.p. 230–232 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.76 (s, 6 H, CH_3), 4.05 (d, J = 17.3 Hz, 2 H, CH_2), 4.29 (app. s, 2 H, CH_2), 4.71 (d, J = 17.3 Hz, 2 H, CH_2), 7.14 (d, J = 8.4 Hz, 2 H, ArH), 7.18 (d, J = 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 17.7, 55.7, 65.8, 120.2, 126.7, 127.7, 130.8, 146.4 ppm. $C_{17}H_{16}N_4O_4$ (340.33): C 59.99, H 4.74, N 16.49; found C 60.06, H 4.96, N 16.71%.

Another isomer, (±)-**25** (91 mg, 9%) was subsequently eluted from the column as a yellow solid; m.p. 242–244 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.26 (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3) 4.07 (d, J = 17.3 Hz, 1 H, CH_2), 4.17 (d, J = 17.3 Hz, 1 H, CH_2), 4.28 (app. s, 2 H, CH_2), 4.67 (d, J = 17.3 Hz, 1 H, CH_2), 4.72 (d, J = 17.3 Hz, 1 H, CH_2), 6.87 (s, 1 H, ArH), 7.14 (d, J = 8.3 Hz, 1 H, ArH), 7.20 (d, J = 8.3 Hz, 1 H, ArH), 7.75 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 17.8, 20.1, 55.7, 58.5, 66.2, 120.2, 120.9, 121.5, 126.7, 127.5, 129.3, 130.7, 130.9, 133.3, 146.1 ppm. $C_{17}H_{16}N_4O_4$ (340.33): calcd. C 59.99, H 4.74, N 16.49; found C 60.28, H 4.95, N 16.64.

Method D: Starting with 4-methyl-3-nitroaniline (1.00 g, 6.57 mmol) and stirring for 7 d, ^{1}H NMR of the crude material obtained upon work-up (1.10 g) indicated that no Tröger's base product was present.

2,8-Diisopropyl-1,7-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine (20)

Method A: Starting with 4-isopropyl-3-nitroaniline (900 mg, 4.99 mmol), the crude brown product was chromatographed (silica gel, hexane/ethyl acetate, 3:1) to afford (±)-**20** (75 mg, 8%) as a pale yellow solid; m.p. 302–303 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.19 (d, J = 6.8 Hz, 6 H, 2 × CH_3), 1.23 (d, J = 6.8 Hz, 6 H, 2 × CH_3), 2.80–2.97 (m, 2 H, CH), 4.00 (d, J = 17.1 Hz, 2 H, CH_2), 4.25 (s, 2 H, CH_2), 4.63 (d, J = 17.1 Hz, 2 H, CH_2), 7.21 (d, J = 8.5 Hz, 2 H, ArH), 7.26 (d, J = 8.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 23.4, 23.8, 28.6, 55.0, 65.8, 118.9, 126.3, 127.7, 136.2, 146.3 ppm. HRMS (FAB$^+$): m/z calcd. for $C_{21}H_{24}N_4O_4$ [M + Na]$^+$, 419.168976; found 419.16.168415.

Method D: Starting with 4-isopropyl-3-nitroaniline (1.00 g, 4.59 mmol) and stirring for 7 d, the crude material was chromatographed (silica gel, hexane/ethyl acetate, 4:1) to afford (±)-**20** (516 mg, 45%) as a pale yellow solid; m.p. 302–303 °C. The spectroscopic data on this material were identical to those obtained for (±)-**20** isolated from Method A.

2,8-Dibutyl-1,7-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (21)

Method B: Starting with 4-butyl-3-nitroaniline (950 mg, 4.89 mmol), the crude product was chromatographed (silica gel, hexane/ethyl acetate, 3:1) to afford (±)-**21** (182 mg, 18%) as a pale yellow solid; m.p. 166–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.89 (t, J = 7.3 Hz, 6 H, 2 × CH_3), 1.38–1.24 (m, 4 H, 2 × CH_2), 1.44–1.63 (m, 4 H, 2 × CH_2), 2.40–2.62 (m, 4 H, 2 × CH_2), 4.02 (d, J = 17.2 Hz, 2 H, CH_2), 4.27 (app. s, 2 H, CH_2), 4.67 (d, J = 17.2 Hz, 2 H, CH_2), 7.15 (d, J = 8.4 Hz, 2 H, ArH), 7.18 (d, J = 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2, 22.9, 31.5, 33.2, 55.9, 66.2, 120.1, 128.1, 130.4, 131.5, 146.8 ppm. HRMS (FAB$^+$): m/z calcd. for $C_{23}H_{28}N_4O_4$ [M + Na]$^+$, 447.200276; found 447.200812. $C_{23}H_{28}N_4O_4$ (424.49): calcd. C 65.08, H 6.65, N 13.20; found C 65.35, H 6.77, N 13.29.

Method D: Starting with 4-butyl-3-nitroaniline (1.00 g, 5.15 mmol) and stirring for 11 d, ^{1}H NMR of the crude material obtained upon work-up (1.20 g) indicated that only a trace of Tröger's base product was present.

2,8-Dibromo-1,7-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (22)

Method B: Starting with 4-bromo-3-nitroaniline (1.00 g, 4.61 mmol), the crude product was chromatographed (silica gel, dichloromethane) to afford (±)-**22** (57 mg, 6%) as a brown solid; m.p. >300 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.16 (d, J = 17.1 Hz, 2 H, CH_2), 4.36 (app. s, 2 H, CH_2), 4.69 (d, J = 17.1 Hz, 2 H, CH_2) 7.49 (d, J = 8.8 Hz, 2 H, ArH), 7.69 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, DMSO, 25 °C): δ = 54.4, 64.3, 106.4, 120.5, 122.0, 129.3, 132.5, 148.1 ppm. HRMS (FAB$^+$): m/z calcd. for $C_{15}H_{10}Br_2N_4O_4$ [M + Na]$^+$, 490.896101; found 490.895153. $C_{15}H_{10}Br_2N_4O_4$ (470.07): calcd. C 38.33, H 2.14, N 11.92; found C 38.33, H 2.18, N 11.68.

Method D: Starting with 4-bromo-3-nitroaniline (500 mg, 2.30 mmol); the ^{1}H NMR of the crude material obtained upon work-up (520 mg) indicated that no Tröger's base product was present.

2,8-Dibromo-3,9-dimethyl-1,7-dinitro-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine (23)

Method A: Starting with 4-bromo-3-methyl-5-nitroaniline (650 mg, 2.81 mmol), the crude material was chromatographed (silica gel, dichloromethane) to afford (±)-**23** (127 mg, 18%) as a pale yellow solid; m.p. >339 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.40 (s, 6 H, CH_3), 4.01 (d, J = 17.0 Hz, 2 H, CH_2), 4.21 (app. s, 2 H, CH_2), 4.58 (d, J = 17.0 Hz, 2 H, CH_2), 7.12 (s, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 23.3, 55.0, 65.8, 110.2, 118.6, 120.9, 128.5, 139.9, 147.3 ppm. HRMS (FAB$^+$): *m*/*z* calcd. for $C_{17}H_{14}Br_2N_4O_4$ [M + Na]$^+$, 518.927401; found 518.927064. $C_{17}H_{14}Br_2N_4O_4$ (498.13): calcd. C 40.99, H 2.83, N 11.25; found C 40.99, H 2.91, N 11.02.

Method D: Starting with 4-bromo-3-methyl-5-nitroaniline (1.00 g, 3.71 mmol) and stirring for 11 d, ^{1}H NMR of the crude material obtained upon work-up (953 mg) indicated that only a trace of Tröger's base product was present.

1,7-Dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (24) and 1,9-Dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (26)

Method B: Starting with 3-nitroaniline (2.00 g, 14.49 mmol), the crude material was chromatographed (silica gel, dichloromethane) to afford (±)-**24** (450 mg, 22%) as a pale yellow solid; m.p. 294–296 °C. ^{1}H NMR (400 MHz, DMSO, 25 °C): δ = 4.39 (app. s, 2 H, CH_2), 4.57 (d, J = 17.8 Hz, 2 H, CH_2), 4.97 (d, J = 17.8 Hz, 2 H, CH_2), 7.41 (app. t, J = 8.1 Hz, 2 H, ArH), 7.63 (dd, J = 1.2, 8.1 Hz, 2 H, ArH), 7.76 (dd, J = 1.2, 8.1 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, DMSO, 25 °C): δ = 57.1, 64.1, 120.3, 123.9, 127.8, 131.6, 147.4, 149.5 ppm. $C_{15}H_{12}N_4O_4$ (312.28): C 57.69, H 3.87, N 17.94; found C 57.76, H 3.79, N 17.88%.

Another isomer, (±)-**26** (100 mg, 5%) was subsequently eluted from the column as a pale yellow solid; m.p. 222–224 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.27–4.31 (m, 3 H, CH_2), 4.57 (d, J = 17.8 Hz, 1 H, CH_2), 4.78 (d, J = 17.8 Hz, 1 H, CH_2), 5.07 (d, J = 17.8 Hz, 1 H, CH_2), 7.09 (d, J = 8.3 Hz, 1 H, ArH), 7.36 (app. t, J = 8.1 Hz, 1 H, ArH), 7.47 (dd, J = 2.2, 8.3 Hz, 1 H, ArH), 7.82–7.85 (m, 2 H, ArH), 8.01 (d, J = 2.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 57.9, 59.1, 65.7, 118.9, 120.7, 121.4, 124.2, 127.8, 127.9, 131.1, 134.7, 148.4, 149.8 ppm. $C_{15}H_{12}N_4O_4$ (312.28): calcd. C 57.69, H 3.87, N 17.94; found C 57.80, H 3.91, N 17.66.

Method D: Starting with 3-nitroaniline (1.00 g, 7.25 mmol) and stirring for 5 d, ^{1}H NMR of the crude material obtained upon work-up (1.07 g) indicated that no Tröger's base product was present.

Type III Compound

4,10-Dimethyl-3,9-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (27) and 4-(2′-Methyl-3′-nitrophenyl)morpholine-3,5-dione (28)

Method B: Starting with 2-methyl-3-nitroaniline (2.00 g, 13.15 mmol), the crude material was chromatographed (silica gel, dichloromethane) to afford (±)-**27** (732 mg, 33%) as a pale yellow solid; m.p. 279–280 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.59 (s, 6 H, 2 × CH_3), 4.00 (d, J = 17.5 Hz, 2 H, CH_2), 4.31 (app. s, 2 H, CH_2), 4.66 (d, J = 17.5 Hz, 2 H, CH_2), 6.93 (d, J = 8.4 Hz, 2 H, ArH), 7.56 (d, J = 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.5, 55.4, 67.1, 119.8, 124.9, 128.8, 132.9, 147.3 ppm. HRMS (EI$^+$): *m*/*z* calcd. for $C_{17}H_{16}N_4O_4$ [M]$^+$, 340.1172; found 340.1172.

Another compound, **28** (350 mg, 11%), was subsequently eluted from the column as a white solid; m.p. 236–237 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.29 (s, 3 H, CH_3), 4.52–4.61 (m, 4 H, 2 × CH_2) 7.35 (dd, J = 1.0, 8.1 Hz, 1 H, ArH), 7.31–7.51 (m, 1 H, ArH), 8.00 (dd, J = 1.0, 8.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.5, 68.5, 126.1, 127.7, 132.3, 133.9, 168.9 ppm. $C_{11}H_{10}N_2O_5$ (250.21): calcd. C 52.80, H 4.03, N 11.20; found C 52.62, H 4.11, N 11.03.

Method D: Starting with 2-methyl-3-nitroaniline (1.00 g, 6.57 mmol), the crude material was recrystallised from dichloromethane to afford (±)-**27** (475 mg, 43%) as a pale yellow solid; m.p. 279–280 °C. The spectroscopic data on this material were identical to those obtained for (±)-**27** isolated from Method B.

Type IV Compounds

2,8-Dimethyl-4,10-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (29)

Method B: Starting with 4-methyl-2-nitroaniline (1.00 g, 6.57 mmol), the crude material was chromatographed (silica gel, dichloromethane) to afford (±)-**29** (400 mg, 36%) as a yellow solid; m.p. 242–243 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.32 (s, 6 H, 2 × CH_3), 4.26 (app. s, 2 H, CH_2), 4.48 (d, J = 17.8 Hz, 2 H, CH_2), 4.72 (d, J = 17.8 Hz, 2 H, CH_2), 7.02–7.06 (m, 2 H, ArH), 7.57–7.61 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.9, 57.1, 67.1, 124.5, 131.0, 132.6, 135.0, 139.5, 145.3 ppm. HRMS (FAB$^+$): *m*/*z* calcd. for $C_{17}H_{16}N_4O_4$ [M + Na]$^+$, 363.106376; found 363.105808. $C_{17}H_{16}N_4O_4$ (340.33): calcd. C 59.99, H 4.74, N 16.46; found C 60.23, H 4.96, N 16.49.

Method D: Starting with 4-methyl-2-nitroaniline (1.00 g, 6.57 mmol) and stirring for 5 d, ^{1}H NMR of the crude material obtained upon work-up (1.09 g) indicated that only a trace of Tröger's base product was present.

1,2,7,8-Tetramethyl-4,10-dinitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*]-[1,5]diazocine (30)

Method A: Starting with 4,5-dimethyl-2-nitroaniline (530 mg, 3.19 mmol), the crude material was chromatographed (silica gel, dichloromethane) to afford (±)-**30** (46 mg, 8%) as a yellow solid; m.p. 274–276 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.09 (s, 6 H, 2 × CH_3), 2.27 (s, 6 H, 2 × CH_3), 4.21 (app. s, 2 H, CH_2), 4.42 (d, J = 17.8 Hz, 2 H, CH_2), 4.64 (d, J = 17.8 Hz, 2 H, CH_2), 7.67 (s, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.6, 19.8, 56.5, 65.4, 124.8, 128.7, 133.3, 140.2, 140.8, 142.6 ppm. HRMS (FAB$^+$): *m*/*z* calcd. for $C_{19}H_{20}N_4O_4$ [M + Na]$^+$, 391.137676; found 391.137325. $C_{19}H_{20}N_4O_4$ (368.39): calcd. C 61.95, H 5.47, N 15.21; found C 62.10, H 5.94, N 15.36.

Method D: Starting with 4,5-dimethyl-2-nitroaniline (1.00 g, 6.02 mmol) and stirring for 5 d, ^{1}H NMR of the crude material obtained upon work-up (1.26 g) indicated that only a trace of Tröger's base product was present.

Tetranitro Compound

2,8-Dimethoxy-4,10-dimethyl-1,3,7,10-tetranitro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (31)

Method B: Starting with 4-methoxy-2-methyl-3,5-dinitroaniline (500 mg, 2.20 mmol), the crude product was chromatographed (silica gel, hexane/ethyl acetate, 3:1) to afford (±)-**31** (60 mg, 11%) as a yellow solid; m.p. >236 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.36 (s, 6 H, 2 × CH_3), 3.83 (d, J = 17.9 Hz, 2 H, CH_2), 3.90 (s, 6 H, OCH_3), 4.28 (app. s, 2 H, CH_2), 4.66 (d, J = 17.9 Hz,

2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.3, 51.9, 64.8, 65.9, 123.1, 130.6, 140.9, 142.2 ppm. HRMS (FAB^+): *m/z* calcd. for $C_{19}H_{18}N_6O_{10}$ $[M + Na]^+$, 513.097662; found 513.098404.

Method D: Starting with 4-methoxy-3,5-dinitro-2-methylaniline (1.00 g, 4.41 mmol) and stirring for 10 d, the crude product was chromatographed (silica gel, hexane/ethyl acetate, 3:1) to afford (±)-**31** (45 mg, 4%) as a yellow solid; m.p. >236 °C (dec.). The spectroscopic data on this material were identical to those obtained for (±)-**31** isolated from Method B.

2,8-Diamino-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (32): Reduction of (±)-**2** with Pd/C in ethanol: A mixture of (±)-**2** (100 mg, 0.32 mmol), ethanol (20 mL), dichloromethane (5 mL) and 10% palladium on carbon (50 mg) was stirred in the dark under hydrogen for 3 d. The reaction was monitored by TLC and when no evidence of the starting material was observed, the mixture was filtered through Celite and the solvents evaporated to dryness. The crude solid was chromatographed (silica gel, ethyl acetate:methanol, 4:1) to afford (±)-**32** (74 mg, 92%) as a white solid; m.p. 303,–304 °C (ref.[21] 266 °C with decomposition). ^1H NMR (400 MHz, DMSO, 25 °C): δ = 3.76 (d, *J* = 16.3 Hz, 2 H, CH_2), 4.04 (app. s, 2 H, CH_2), 4.37 (d, *J* = 16.2 Hz, 2 H, CH_2), 4.64 (br. s, 4 H, 2 × NH_2), 6.06 (d, *J* = 2.2 Hz, 2 H, ArH), 6.35 (dd, *J* = 2.2, 8.4 Hz, 2 H, ArH), 6.72 (d, *J* = 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, DMSO, 25 °C): δ = 58.3, 67.1, 110.8, 113.5, 124.9, 128.3, 137.5, 144.5 ppm. HRMS (EI^+): *m/z* calcd. for $C_{15}H_{16}N_4$ $[M]^+$, 252.1375; found 252.1377. $C_{15}H_{16}N_4 \cdot 0.5H_2O$ (261.32): calcd. C 68.94, H 6.56, N 21.44; found C 69.26, H 6.45, N 20.79.

Reduction of (±)-2 with Tin(II) Chloride: (±)-**2** (300 mg, 0.96 mmol) and tin(II) chloride (2.5 g, 11.1 mmol) were suspended in absolute ethanol (50 mL) and refluxed at 75 °C for 2 d. The reaction mixture was cooled then poured onto ice and neutralised with sodium hydrogen carbonate solution (10%). The reaction mixture was extracted with dichloromethane, ethyl acetate and finally ether, however very little organic material was present after evaporation of the solvents and no Tröger's base products were observed following ^1H NMR analysis of the crude material.

Reduction of (±)-2 with Continuous-Flow Apparatus: (±)-**2** (100 mg, 0.32 mmol) was dissolved in warm ethanol (150 mL) and the warm mixture was passed through a H-Cube equipped with a 30 mm 10% Pd/C cartridge (1 mL/min; 35 °C; 70 bar). Fractions were collected, which were monitored by TLC, and evaporation of solvent under reduced pressure afforded (±)-**32** (69 mg, 85%) as a white solid that had identical spectral properties to those listed above.

1,7-Diamino-2,4,8,10-tetramethyl-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine (33): Reduction of (±)-**12** with Pd/C in ethanol: A mixture of (±)-**12** (1.0 g, 2.7 mmol), ethanol (75 mL) and 10% palladium on carbon (50 mg) was stirred in the dark under hydrogen for 3 d. No evidence of a reaction was observed by TLC monitoring. The mixture was then filtered through Celite and unreacted (±)-**12** was recovered in quantitative yield.

Reduction of (±)-12 with Tin(II) Chloride: (±)-**12** (1.0 g, 2.7 mmol) and tin(II) chloride (7.09 g, 31.4 mmol) were suspended in absolute ethanol (75 mL) and refluxed at 75 °C for 2 d. The reaction mixture was cooled to room temperature, then poured into the ice and neutralised with sodium hydrogen carbonate. The reaction mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtered and the solvents evaporated to dryness. The crude solid was chromatographed (silica gel, ethyl acetate) to afford (±)-**33** (456 mg, 55%) as an off-white solid; m.p. 102–104 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.06 (s, 6 H, 2 × CH_3), 2.33 (s, 6 H, 2 × CH_3), 3.24 (br. s, 4 H, 2 × NH_2), 3.83 (d, *J* = 16.2 Hz, 2 H, CH_2), 4.25 (app. s, 2 H, CH_2), 4.32 (d, *J* = 16.2 Hz, 2 H, CH_2), 6.80 (s, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.4, 16.9, 51.9, 66.2, 113.1, 117.2, 120.8, 121.9, 130.5, 138.9 ppm. HRMS (ESI): *m/z* calcd. for $C_{19}H_{24}N_4$ $[M^+ H]^+$, 309.2074; found 309.2081.

Reduction of (±)-12 with Continuous-Flow Apparatus: (±)-**12** (100 mg, 0.27 mmol) was dissolved in ethyl acetate (10 mL) and ethanol (10 mL) and the mixture passed through a H-Cube equipped with a 30 mm 10% Pd/C cartridge (1 mL/min; 20 °C; 70 bar). Fractions were collected, which were monitored by TLC, and evaporation of solvent under reduced pressure afforded (±)-**33** (81 mg, 97%) as an off-white solid that had identical spectral properties to those listed above.

Supporting Information (see also the footnote on the first page of this article): Experimental details for the synthesis of all non-commercially available anilines used in this work, together with a NOESY spectrum of compound **23**.

CCDC-645980 (for **5**) and -645981 (for **15**) contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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