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Reaction of Tröger's base analogues with Vilsmeier reagents

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ABSTRACT

As part of a program aimed at introducing functionality onto the Tröger's base framework post-synthesis, we investigated the formylation reaction of Tröger's base analogues with Vilsmeier reagents. We found that rather than the anticipated reaction at the aryl rings, these compounds react with Vilsmeier reagents to afford compounds with a modified strap, whereby the apical methylene group is replaced by a methylene strap bearing an *N*,*N*-disubstituted amine.

1. Introduction

Tröger's base **1** is a rigid, cleft-shaped molecule that is chiral by virtue of the two tertiary nitrogen atoms that are linked via a methano strap (Fig. 1). The compound was first prepared in 1888,[1] however a correct structural assignment was not made until 1935.[2] Analogues bearing alkoxy,[3–9] halogen,[10–16] nitro[4,14,17–20] and ester[3,21–26,14] functionality, among others, can be prepared using essentially the same chemistry, that involves the reaction of an appropriately substituted aryl amine with formaldehyde (or a formaldehyde equivalent) in an acidic medium.

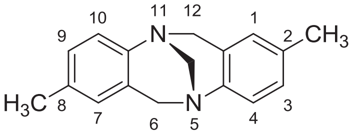

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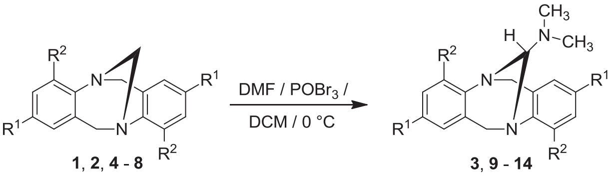
Fig. 1. The structure and numbering system of Tröger's base.

The size of the cavity present in Tröger's base analogues is largely determined by the nature of the strap between the two diazocine nitrogen atoms.[27–29]

It has recently been shown that functionality can be introduced onto the aryl rings of the Tröger's base framework via halogenation.[30,31] In this vein, we chose to explore the formylation reaction of Tröger's base analogues using Vilsmeier reagents. It should be noted that two routes for the synthesis of formyl-substituted Tröger's base analogues have been reported. The first proceeds via a lithium–halogen exchange reaction, followed by treatment with *N*,*N*-dimethylformamide at −78 °C.[32] The second uses DIBAL reduction of a cyano-substituted Tröger's base analogue.[33]

2. Results and discussion

A formylation reaction was initially performed on Tröger's base **2** in the hope of introducing the formyl group at the 2,8- or 4,10-positions (i.e., *ortho* or *para* to the bridge nitrogen atoms) (Scheme 1, Table 1).



Scheme 1.

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Table 1
Yield of products derived from Scheme 1

R^1	R^2	Starting material	Product	Yield (%)
CH_3	H	**1**	**9**	70
H	H	**2**	**3**	78
OCH_3	H	**4**	**10**	87
Br	H	**5**	**11**	82
NO_2	H	**6**	**12**	14
H	CH_3	**7**	**13**	21
H	OCH_3	**8**	**14**	24

The spectroscopic features of the resultant product **3** were quite unusual; ^{1}H NMR (Fig. 2) and mass spectrometry results (parent ion present as base peak at 266 amu) indicated that instead of formylation at the aromatic rings, the Vilsmeier reagent derived from *N*,*N*-dimethylformamide had reacted at the bridge and replaced the methylene strap with an *N*,*N*-dimethylamino-substituted methylene strap.

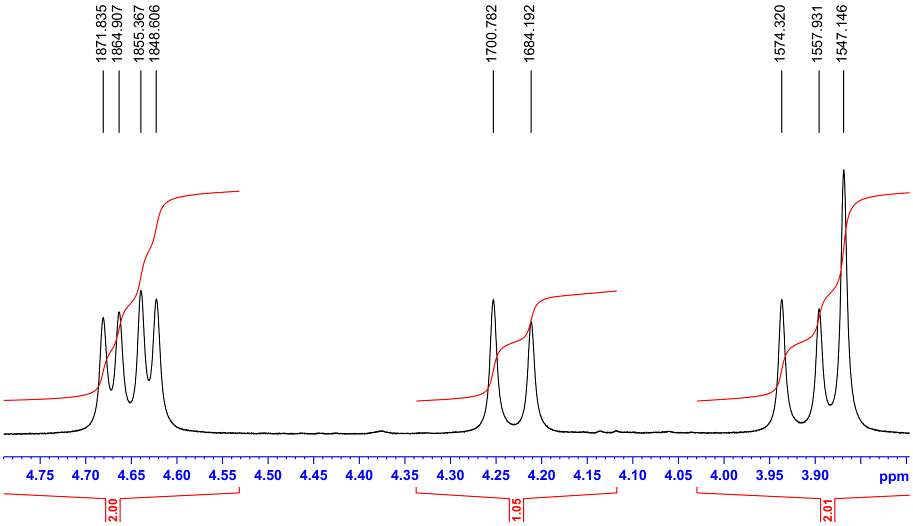


Fig. 2. 400 ^{1}H NMR spectrum ($CDCl_3$, 25 °C) showing the diazocine bridge region of **3**.

Not surprisingly, the same product is obtained if the Vilsmeier reagent is generated with either phosphorus oxychloride or thionyl chloride in the place of phosphorus oxybromide (which was used in the majority of the reactions due to its crystalline nature and ease of handling). The use of excess Vilsmeier reagent does not result in any reaction on the aryl rings.

In the present case, from examination of the diazocine bridge region of the ^{1}H NMR spectrum of **3** it is readily apparent that the compound is no longer C_2 symmetric as the four benzylic protons resonating in the region 3.5–5.0 ppm are present in unique environments. It is also clear that this compound bears two additional methyl groups, without any loss in the number of aryl protons (eight for this compound) while the signal for the apical methylene strap is absent and there is a new signal in the bridging region that integrates as one proton (at 3.86 ppm, adjacent to a geminal coupled benzylic resonance, in Fig. 2).

Strap-modified Tröger's base analogues are known, including compounds in which the strap contains two,[27,34,35] three[27] or four[27] atoms. Substituted-methylene strapped Tröger's base analogues are also known, however these are generally the result of reactions of the cyclic diamine (the Tröger's base analogue lacking the methylene strap) with either aldehydes,[36–38] ketones,[36,37,39] or 1,2-dicarboxylic acids/carboxylic acid chlorides.[40] Spirolactone-strapped Tröger's base analogues, with a single carbon atom between the two bridge nitrogen atoms, could also be prepared directly from methano-strapped Tröger's base analogues.[40] An unusual substituted-methylene strapped Tröger's base analogue can also be formed upon reaction of methano-strapped Tröger's base compounds with activated acetylenes in the presence of Lewis acids.[41]

A range of Tröger's base analogues bearing different substituents were then subjected to the same reaction conditions in order to examine the effect of pre-existing substituents in this reaction and the results are presented in Table 1.

The general ^{1}H NMR spectroscopic features present in **3** were also present in the products derived from these reactions (Scheme 1)—a loss of C_2 symmetry, the appearance of two new and equivalent methyl groups, a new singlet in the bridging region that integrates as one proton, and no chemistry having taken place at the benzylic methylene or aromatic carbons.

The yields were observed to decline in the presence of substrates bearing strongly electron-withdrawing groups (**6**) or substituents at the 4,10-positions (**7** and **8**).

A probable mechanism for the formation of the *N*,*N*-dimethylamino-substituted methano-strapped Tröger's base analogues is shown in Fig. 3. This mechanism is a modification of the one proposed to account for the observed racemisation of Tröger's base analogues bearing a single carbon strap between the two bridge nitrogen atoms,[39] and for the conversion of methano-strapped Tröger's base analogues to ethano-strapped derivatives.[34]

The structure assigned to the product of these reactions was confirmed with a crystal structure of **11** (Fig. 4).[42] The dihedral angle (formed by intersection of the least squares planes of the aryl rings) in **11** is 98.9°. The dihedral angle has been measured for over 20 methano-strapped dibenzo Tröger's base analogues and the values lie between 82°[43] and 110.9°.[16] Interestingly, **11** underwent spontaneous resolution during crystallisation, and the crystal used for the X-ray structure determination was composed of a single enantiomer. Due to the presence of the bromine atoms the absolute configuration of the enantiomer could be unambiguously determined and was found to be 5*S*,11*S*. The phenomenon of spontaneous resolution has been noted for many compounds, including some Tröger's base analogues.[4,44,45]

The reaction was also performed on two cyclic diamines, **15** and **16**, initially derived from removal of the methano-strap from the corresponding Tröger's base analogues (Scheme 2).[36–38]

In both cases the products were formed in lower yields than reactions involving the Tröger's base analogues. The mechanism

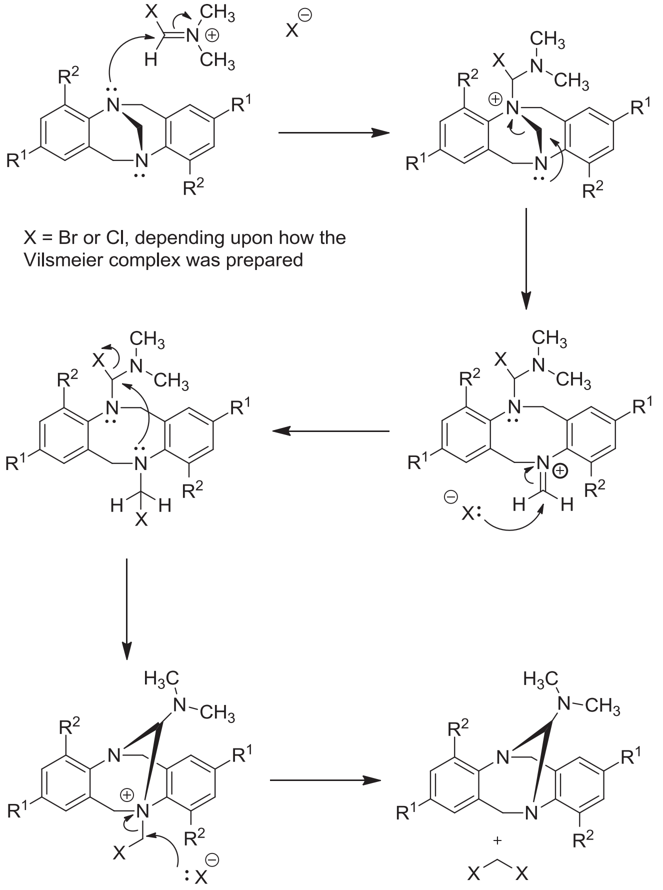


Fig. 3. Proposed mechanism to account for the experimental observations of Tröger's base analogues with Vilsmeier reagents derived from *N*,*N*-dimethylformamide.

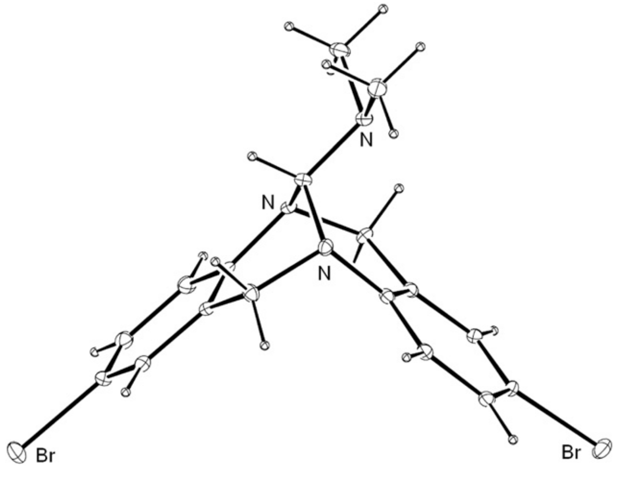
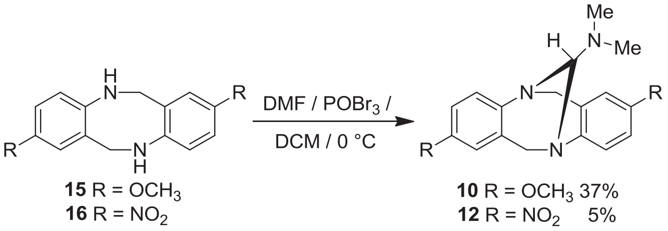


Fig. 4. An ORTEP diagram of **11**, with 10% probability ellipsoids.

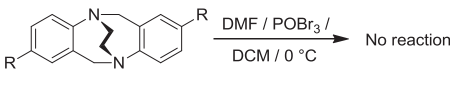


Scheme 2.

proposed in Fig. 3 is readily modified to account for the reaction of the cyclic diamines.

Analogous reactions were also carried out with **4** and **15** as substrates, in the absence of phosphorus oxybromide (i.e., just in the presence of DMF, without the possibility of forming a Vilsmeier complex). In both cases, unconverted starting material was recovered, confirming expectations that DMF itself is not sufficiently reactive.

A reaction was also investigated using ethano-strapped 2,8-dimethoxy Tröger's base **17**[34] (Scheme 3). Not unexpectedly, this reaction was unsuccessful, with the recovery of **17** in 95% yield after work-up.



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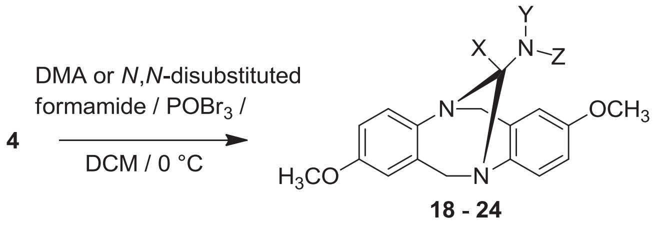
Scheme 3.

Attention was then turned away from the Tröger's base substrates, and towards the nature of the Vilsmeier reagent (Scheme 4). Compound **4** was chosen for the reactions as it afforded the product in the highest yield from reaction with the Vilsmeier adduct formed from DMF. This was presumably a result of the electron donating ability of the methoxy groups enhancing the nucleophilicity of the bridge nitrogen atoms, and a lack of steric hindrance afforded by substituents at the 4,10-positions. *N*,*N*-Dimethylacetamide (DMA), together with several *N*,*N*-disubstituted formamides were examined, as outlined in Table 2.



Scheme 4.

Table 2
Yield of products derived from Scheme 4

X	Y	Z	Product	Yield (%)
CH_3	CH_3	CH_3	**18**	0
H	CH_2CH_3	CH_2CH_3	**19**	69
H	Bn	Bn	**20**	46
H	$CHCHCH_3$	$CHCHCH_3$	**21**	77
H	Ph	Ph	**22**	77
H	CH_3	$CHCHCH_3$	**23**	42
H	CH_3	Bn	**24**	50

The reaction with DMA failed to yield any product, and unconverted **4** was recovered in near quantitative yield.

All of the *N*,*N*-disubstituted formamides examined in the current study afforded the strap-modified compounds in moderate to good yields, demonstrating that the reaction is quite general.

3. Conclusion

Attempts to formylate a range of Tröger's base analogues resulted in the discovery of a new reaction whereby the methano strap was removed and, from the product perspective, replaced by *N*,*N*-disubstituted formamides, acting as aldehydes via enhanced reactivity as the Vilsmeier complexes. The scope of the reaction was explored by firstly varying the type and pattern of substitution on the Tröger's base framework, and unsubstituted, 2,8- and the sterically demanding 4,10-substituted compounds all underwent the reaction. The nature of the *N*,*N*-disubstituted formamides, was also varied with alkyl, aryl and allyl substituted compounds all undergoing the reaction. The use of *N*,*N*-dimethylacetamide failed to yield a bridge-modified compound, and the simple methano-strapped Tröger's base analogue was recovered.

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 at Macquarie University (APAF) (ESI-MS) and high resolution mass spectral analyses were carried out at 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 a 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. The starting Tröger's base analogues and cyclic diamines were prepared as previously reported: (±)-**1**, (±)-**2**,[46] (±)-**4**,[7] (±)-**5**,[32] **6**,[17] (±)-**7** was prepared from hydrogenolysis of 2,8-dibromo-4,10-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, and (±)-**8**,[7] (±)-**15**,[36–38] (±)-**16**.[38] *N*,*N*-Dimethyl-, diethyl-, dibenzyl- and diphenyl-formamides were purchased from Sigma–Aldrich and used without further purification. The remaining *N*,*N*-disubstituted formamides were prepared from reactions of their corresponding amines with ethyl formate using a literature procedure.[47]

4.2. General procedures

Method A: The *N*,*N*-disubstituted formamide (0.31 mmol) was added to an ice-cold solution of phosphorus oxybromide (88 mg, 0.31 mmol) in dichloromethane (2 mL) whilst stirring under an atmosphere of argon. The mixture was allowed to stir for 20 min before the Tröger's base analogue (or cyclic diamine derived from the removal of the methano strap from the corresponding Tröger's base precursor) (0.31 mmol) was added and the reaction mixture allowed to warm to room temperature and stirred for a further 16 h. The reaction was quenched with saturated sodium carbonate solution (20 mL) and extracted with dichloromethane (3×50 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate and evaporated to dryness. The crude residue was purified by column chromatography over silica gel.

Method B: As for Method A, with the exception that phosphorus oxychloride was used in place of phosphorus oxybromide.

Method C: As for Method A, with the exception that thionyl chloride was used in place of phosphorus oxybromide.

*4.2.1. 13-(N,N-Dimethylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**3***. *Method A*: Starting with *N*,*N*-dimethylformamide (35 μL, 0.45 mmol) and (±)-**2** (100 mg, 0.45 mmol), the crude residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford (±)-**3** (93 mg, 78%) as an off-white solid: mp 134–136 °C; R_f (20% EtOAc/hexane) 0.59; IR (neat) ν_{max} 3062, 3022, 2949, 2918, 2818, 2766, 1484, 1447, 1356, 1100, 764 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.41 (s, 6H, CH$_3$), 3.86 (s, 1H, CH), 3.91 (d, *J* 16.4 Hz, 1H, CH$_2$), 4.23 (d, *J* 16.6 Hz, 1H, CH$_2$), 4.64 (d, *J* 16.4 Hz, 1H, CH$_2$), 4.66 (d, *J* 16.6 Hz, 1H, CH$_2$), 6.84–6.97 (m, 4H, ArH), 7.04–7.14 (m, 4H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$) δ 41.5, 51.6, 59.5, 90.2, 123.6, 123.8, 125.4, 125.7, 126.4, 126.5, 127.0, 127.1, 127.6, 128.0, 128.4, 128.7; MS (CI$^+$) *m*/*z* calcd for $C_{17}H_{19}N_3$ [M+H]$^+$ 266, observed 266; Anal. Calcd for $C_{17}H_{19}N_3$.0.2 CH_2Cl_2: C 73.17; H 6.93; N 14.88. Found: C 73.26; H 6.77; N 14.66%.

Method B: Starting with *N*,*N*-dimethylformamide (35 μL, 0.45 mmol) and (±)-**2** (100 mg, 0.45 mmol), the crude residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford (±)-**3** (83 mg, 70%) as an off-white solid. The resultant material had identical spectral properties and melting point that obtained from Method A.

Method C: Starting with *N*,*N*-dimethylformamide (35 μL, 0.45 mmol) and (±)-**2** (100 mg, 0.45 mmol), the crude residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford (±)-**3** (90 mg, 76%) as an off-white solid. The resultant material had identical spectral properties and melting point that obtained from Method A.

*4.2.2. 2,8-Dimethyl-13-(N,N-dimethylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**9***. *Method A*: Starting with with *N*,*N*-dimethylformamide (31 μL, 0.40 mmol) and (±)-**1** (100 mg, 0.40 mmol), the crude residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford (±)-**9** (82 mg, 70%) as an off-white solid: mp 89–90 °C; R_f (EtOAc) 0.80; IR (neat) ν_{max} 2990, 2955, 2904, 2859, 2821, 1494, 1141, 1107 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.19 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 2.44 (s, 6H, CH$_3$), 3.83–3.87 (m, 2H, CH and CH$_2$), 4.12 (d, *J* 16.6 Hz, 1H, CH$_2$), 4.56–4.62 (m, 2H, CH$_2$), 6.67 (s, 1H, ArH), 6.72 (s, 1H, ArH), 6.91–7.03 (m, 4H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.8, 20.9, 41.5, 51.6, 59.4, 90.3, 125.1, 125.3, 126.8, 126.9, 127.7, 127.9, 128.2, 128.6, 132.9, 133.2, 142.1, 146.3; MS (CI$^+$) *m*/*z* calcd for $C_{19}H_{23}N_3$ [M+H]$^+$ 294, observed 294; Anal. Calcd for $C_{19}H_{23}N_3$: C 77.78; H 7.90; N 14.32. Found: C 77.66; H 7.94; N 14.10%.

*4.2.3. 2,8-Dimethoxy-13-(N,N-dimethylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**10***. *Method A*: Starting with *N*,*N*-dimethylformamide (27 μL, 0.35 mmol) and (±)-**4** (100 mg, 0.35 mmol), the crude residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford (±)-**10** (99 mg, 87%) as an off-white solid: mp 98–99 °C; R_f (20% EtOAc/hexane) 0.48; IR (neat) ν_{max} 3000, 2960, 2941, 2907, 2828, 1493, 1238 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.40 (s, 6H, CH$_3$), 3.68 (s, 3H, OCH$_3$), 3.70 (s, 3H, OCH$_3$), 3.78–3.82 (m, 2H, CH and CH$_2$), 4.12 (d, *J* 16.6 Hz, 1H, CH$_2$), 4.55–4.61 (m, 2H, CH$_2$), 6.40 (d, *J* 2.8 Hz, 1H, ArH), 6.42 (d, *J* 2.8 Hz, 1H, ArH), 6.67–6.74 (m, 2H, ArH), 6.98 (d, *J* 8.7 Hz, 1H, ArH), 7.03 (d, *J* 8.7 Hz 1H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$) δ 41.5, 51.9, 55.3, 55.4, 59.6, 90.5, 110.5, 110.7, 113.6, 113.9, 126.2, 126.5, 129.1, 129.3, 137.7, 141.9, 155.8, 156.0; HRMS (EI$^+$) *m*/*z* calcd for $C_{19}H_{23}N_3O_2$ [M]$^+$ 325.1790, observed 325.1794.

Method A: Starting with *N*,*N*-dimethylformamide (29 μL, 0.37 mmol) and (±)-**15** (100 mg, 0.37 mmol), the crude residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford (±)-**10** (45 mg, 37%) as an off-white solid: mp 98–99 °C; R_f (20% EtOAc/hexane) 0.48. The resultant material had identical spectral properties and melting point that obtained from Method A when (±)-**10** was used as the starting material.

*4.2.4. 2,8-Dibromo-13-(N,N-dimethylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**11***. *Method A*: Starting with *N*,*N*-dimethylformamide (20 μL, 0.31 mmol) and (±)-**5** (100 mg, 0.26 mmol), the crude residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford (±)-**11** (90 mg, 82%) as a pale yellow crystalline solid: mp 195–196 °C; R_f (20% EtOAc/hexane) 0.69; IR (neat) ν_{max} 2989, 2955, 2919, 2866, 2825, 1669, 1472, 1403, 1201, 1107 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.37

(s, 6H, CH_3), 3.79–3.83 (m, 2H, CH and CH_2), 4.13 (d, *J* 16.7 Hz, 1H, CH_2), 4.56–4.61 (m, 2H, CH_2), 6.92–7.05 (m, 4H, ArH), 7.21–7.27 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.3, 51.2, 58.9, 89.8, 116.5, 116.7, 127.0, 127.3, 129.2, 129.3, 130.2, 130.3, 130.4, 130.7, 143.5, 147.6; Anal. Calcd for $C_{17}H_{17}Br_2N_3$: C 48.25; H 4.05; N 9.93. Found: C 47.91; H 3.92; N 9.37%.

*4.2.5. 2,8-Dinitro-13-(N,N-dimethylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**12**.* *Method A*: Starting with *N,N*-dimethylformamide (24 μL, 0.31 mmol) and (±)-**6** (98 mg, 0.31 mmol), the crude residue was purified by column chromatography (silica gel, 50% EtOAc/hexane) to afford (±)-**12** (15 mg, 14%) as a yellow solid: mp 222–223 °C; R_f (50% EtOAc/hexane) 0.34; IR (neat) ν_{max} 2966, 2919, 2876, 2838, 2793, 1579, 1511, 1474, 1329, 1204, 1087 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 6H, CH_3), 3.94 (s, 1H, CH), 4.04 (d, *J* 16.6 Hz, 1H, CH_2), 4.36 (d, *J* 16.9 Hz, 1H, CH_2), 4.79 (d, *J* 16.6 Hz, 1H, CH_2), 4.80 (d, *J* 16.9 Hz, 1H, CH_2), 7.18–7.40 (m, 2H, ArH), 7.80–7.94 (m, 2H, ArH), 8.00–8.14 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.2, 51.5, 59.1, 89.4, 122.3, 122.6, 123.0, 123.1, 126.92, 126.0, 128.6, 129.3, 143.8, 143.9, 150.7, 154.5; Anal. Calcd for $C_{17}H_{17}N_5O_4$: C 57.46; H 4.82; N 19.71. Found: C 57.32; H 4.88; N 19.58%.

Method A: Starting with *N,N*-dimethylformamide (26 μL, 0.33 mmol) and (±)-**16** (100 mg, 0.33 mmol), the crude residue was purified by column chromatography (silica gel, 50% EtOAc/hexane) to afford (±)-**12** (6 mg, 5%) as a yellow solid. The material had identical spectral properties to those obtained for (±)-**12** obtained from Method A when (±)-**6** was used as the starting material.

*4.2.6. 4,10-Dimethyl-13-(N,N-dimethylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**13**.* *Method A*: Starting with *N,N*-dimethylformamide (31 μL, 0.40 mmol) and (±)-**7** (100 mg, 0.40 mmol), the crude residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford to afford (±)-**13** (25 mg, 21%) as an off-white solid: mp 141–143 °C; R_f (20% EtOAc/hexane) 0.59; IR (neat) ν_{max} 2948, 2909, 2820, 2777, 1462, 1280, 1210, 1086, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38–2.39 (m, 12H, CH_3), 3.69 (d, *J* 16.6 Hz, 1H, CH_2), 3.87 (s, 1H, CH), 4.02 (d, *J* 16.7 Hz, 1H, CH_2), 4.47 (d, *J* 16.6 Hz, 1H, CH_2), 4.54 (d, *J* 16.7 Hz, 1H, CH_2), 6.70–6.78 (m, 2H, ArH), 6.85–6.92 (m, 2H, ArH), 6.99–7.05 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 17.4, 41.9, 48.8, 56.4, 91.1, 123.8, 124.0, 124.3, 124.4, 128.9, 129.0, 129.1, 129.2, 133.4, 133.9, 142.9, 147.3; Anal. Calcd for $C_{19}H_{23}N_3$.0.15 CH_2Cl_2: C 75.13; H 7.67; N 13.73. Found: C 75.35; H 7.60; N 13.40%.

*4.2.7. 4,10-Dimethoxy-13-(N,N-dimethylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**14**.* *Method A*: Starting with *N,N*-dimethylformamide (27 μL, 0.35 mmol) and (±)-**8** (100 mg, 0.35 mmol), the crude residue was purified by column chromatography (silica gel, 50% EtOAc/hexane) to afford (±)-**14** (27 mg, 24%) as a white solid: mp 187–189 °C; R_f (20% EtOAc/hexane) 0.52; IR (neat) ν_{max} 3042, 2927, 2911, 2835, 1590, 1485, 1227 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 6H, CH_3), 3.86–3.88 (m, 7H, CH and OCH_3), 3.93 (d, *J* 16.9 Hz, 1H, CH_2), 4.25 (d, *J* 17.3 Hz, 1H, CH_2), 4.44 (d, *J* 16.9 Hz, 1H, CH_2), 4.51 (d, *J* 17.3 Hz, 1H, CH_2), 6.52 (app d, *J* 7.8 Hz, 1H, ArH), 6.55 (app d, *J* 7.8 Hz, 1H, ArH), 6.65–6.70 (m, 2H, ArH), 6.87–6.95 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.6, 47.4, 55.3, 55.62, 90.7, 108.6, 109.1, 118.8, 123.7, 123.8, 129.7, 130.5, 132.1, 136.6, 153.1, 153.3; Anal. Calcd for $C_{19}H_{23}N_3O_2$: C 70.13; H 7.12; N 12.19. Found: C 69.82; H 7.13; N 12.06%.

*4.2.8. 2,8-Dimethoxy-13-(N,N-diethylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**19**.* *Method A*: Starting with *N,N*-dimethylformamide (27 μL, 0.35 mmol) and (±)-**4** (100 mg, 0.35 mmol), the crude residue was purified by column chromatography (silica gel, CH_2Cl_2) to afford (±)-**19** (85 mg, 69%) as a white solid: mp 118–119 °C; R_f (CH_2Cl_2) 0.86; IR (neat) ν_{max} 2962, 2917, 2827, 1495, 1238, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* 7.1 Hz, 6H, CH_3), 2.69–2.80 (m, 2H, CH_2), 2.95–3.05 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.77 (d, *J* 16.3 Hz, 1H, CH_2), 4.13 (d, *J* 16.6 Hz, 1H, CH_2), 4.34 (s, 1H, CH), 4.53–4.63 (m, 2H, CH_2), 6.39 (d, *J* 2.8 Hz, 1H, ArH), 6.43 (d, *J* 2.8 Hz, 1H, ArH), 6.70 (dd, *J* 8.7 and 2.8 Hz, 1H, ArH), 6.73 (dd, *J* 8.8 Hz, 1H, ArH), 7.00 (d, *J* 8.7 Hz, 1H, ArH), 7.08 (d, *J* 8.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 40.4, 51.7, 55.2, 55.4, 59.8, 85.7, 110.4, 110.5, 113.3, 113.7, 126.2, 126.5, 129.3, 129.7, 138.1, 142.0, 155.5, 155.8; Anal. Calcd for $C_{21}H_{27}N_3O_2$: C 71.36; H 7.70; N 11.89. Found: C 71.14; H 7.53; N 11.50%.

*4.2.9. 2,8-Dimethoxy-13-(N,N-dibenzylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**20**.* *Method A*: Starting with *N,N*-dibenzylformamide (78 mg, 0.35 mmol) and (±)-**4** (100 mg, 0.35 mmol), the crude residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford (±)-**20** (76 mg, 46%) as a white solid: mp 176–177 °C; R_f (20% EtOAc/hexane) 0.59; IR (neat) ν_{max} 3022, 2998, 2961, 2890, 2835, 2803, 1612, 1575, 1491, 1420, 1241, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.89 (m, 3H, $BnCH_2$ and CH_2), 4.03 (d, *J* 14.6 Hz, 2H, $BnCH_2$), 4.20 (d, *J* 16.7 Hz, 1H, CH_2), 4.35 (s, 1H, CH), 4.61 (d, *J* 16.7 Hz, 1H, CH_2), 4.74 (d, *J* 16.6 Hz, 1H, CH_2), 6.46 (d, *J* 2.9 Hz, 1H, ArH), 6.52 (d, *J* 2.9 Hz, 1H, ArH), 6.74–6.78 (m, 2H, ArH), 7.02 (d, *J* 8.7 Hz, 1H, ArH), 7.08 (d, *J* 8.8 Hz, 1H, ArH), 7.18–7.24 (m, 6H, ArH), 7.25–7.28 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.9, 52.5, 55.8, 59.6, 84.8, 110.9, 111.1, 113.7, 114.3, 127.0, 127.0, 127.1, 128.6, 129.9, 130.4, 138.1, 138.4, 142.3, 156.3, 156.5; Anal. Calcd for $C_{31}H_{31}N_3O_2$.0.09 CH_2Cl_2: C 76.94; H 6.48; N 8.66. Found: C 76.90; H 6.76; N 8.52%.

*4.2.10. 2,8-Dimethoxy-13-(N,N-diallylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**21**.* *Method A*: Starting with *N,N*-diallylformamide (44 mg, 0.35 mmol) and (±)-**4** (100 mg, 0.35 mmol), the crude residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford (±)-**21** (102 mg, 77%) as a white solid: mp 81–83 °C; R_f (20% EtOAc/hexane) 0.73; IR (neat) ν_{max} 3072, 3006, 2960, 2925, 2856, 2832, 2811, 1642, 1613, 1493, 1430, 1241, 922 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (dd, *J* 14.6 and 7.3 Hz, 2H, CH), 3.64 (dd, *J* 5.6 and 14.6 Hz, 2H, CH), 3.71 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.82 (d, *J* 16.4 Hz, 1H, CH_2), 4.15 (d, *J* 16.6 Hz, 1H, CH_2), 4.41 (s, 1H, CH), 4.60 (d, *J* 16.6 Hz, 1H, CH_2), 4.61 (d, *J* 16.4 Hz, 1H, CH_2), 5.12–5.20 (m, 4H, allylic CH_2), 5.80–5.92 (m, 2H, CH), 6.43 (d, *J* 2.7 Hz, 1H, ArH), 6.45 (d, *J* 2.6 Hz, 1H, ArH), 6.70–6.78 (m, 2H, ArH), 7.03 (d, *J* 8.7 Hz, 1H, ArH), 7.07 (d, *J* 8.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.2, 52.2, 55.7, 55.8, 60.1, 85.7, 110.9, 110.9, 113.8, 114.2, 117.9, 126.8, 127.0, 129.8, 130.1, 135.4, 138.2, 142.3, 156.1, 156.4; Anal. Calcd for $C_{23}H_{27}N_3O_2$: C 73.18; H 7.21; N 11.13. Found: C 72.86; H 7.29; N 11.01%.

*4.2.11. 2,8-Dimethoxy-13-(N,N-diphenylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**22**.* *Method A*: Starting with *N,N*-diphenylformamide (69 mg, 0.35 mmol) and (±)-**4** (100 mg, 0.35 mmol), the crude residue was purified by column chromatography (silica gel, 15% EtOAc/hexane) to afford (±)-**22** (121 mg, 77%) as a white solid: mp 172–173 °C; R_f (15% EtOAc/hexane) 0.85; IR (neat) ν_{max} 3410, 3059, 2953, 2904, 2830, 1588, 1491, 1241 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.92 (d, *J* 16.8 Hz, 1H, CH_2), 4.10 (d, *J* 16.7 Hz, 1H, CH_2), 4.69 (d, *J* 16.7 Hz, 2H, CH_2), 5.56 (s, 1H, CH), 6.40 (d, *J* 2.7 Hz, 1H, ArH), 6.46 (d, *J* 2.7 Hz, 1H, ArH), 6.50 (d, *J* 8.8 Hz, 1H, ArH), 6.57 (dd, *J* 2.7 and 8.2 Hz, 1H, ArH), 6.81 (dd, *J* 2.7 and 8.8 Hz, 1H, ArH), 6.80–6.91 (m, 4H, ArH), 6.92–7.09 (m, 2H, ArH), 7.12–7.20 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.7, 55.8, 55.9, 60.8, 85.3, 110.4, 110.9, 114.1, 114.5, 123.4, 125.1, 125.4, 126.8, 127.1, 128.4, 128.6, 128.9, 129.6, 129.7, 130.6, 138.2, 141.3, 147.4, 156.4, 156.7; Anal. Calcd for

$C_{29}H_{27}N_3O_2.0.1CH_2Cl_2$: C 76.31; H 5.99; N 9.17. Found: C 76.18; H 6.01; N 9.17%.

*4.2.12. 2,8-Dimethoxy-13-(N-allyl-N-methylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**23***. *Method A*: Starting with *N*-allyl-*N*-methylformamide (111 mg, 1.12 mmol) and (±)-**4** (316 mg, 1.12 mmol), the crude residue was purified by column chromatography (silica gel, 40% EtOAc/hexane) to afford (±)-**23** (164 mg, 42%) as a colourless oil; R_f (40% EtOAc/hexane) 0.54; IR (neat) ν_{max} 3009, 2941, 2911, 2833, 2767, 1611, 1491, 1272, 1241, 1044 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H, CH_3), 3.13–3.24 (m, 1H, CH), 3.55–3.64 (m, 1H, CH), 3.68 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.80 (d, *J* 16.4 Hz, 1H, CH_2), 4.08 (s, 1H, CH), 4.13 (d, *J* 16.7 Hz, 1H, CH_2), 4.55–4.64 (m, 2H, CH_2), 5.06–5.20 (m, 2H, allylic CH_2), 5.78–5.90 (m, 1H, CH), 6.40 (d, *J* 2.5 Hz, 1H, ArH), 6.43 (d, *J* 2.1 Hz, 1H, ArH), 6.66–6.75 (m, 2H, ArH), 7.00 (d, *J* 8.8 Hz, 1H, ArH), 7.05 (d, *J* 8.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.3, 51.9, 55.1, 55.3, 55.4, 59.7, 88.0, 110.4, 110.6, 113.5, 113.9, 117.3, 126.3, 126.6, 129.2, 129.6, 135.3, 137.7, 141.9, 155.7, 156.0; Anal. Calcd for $C_{21}H_{25}N_3O_2$: C 71.77; H 7.17; N 11.96. Found: C 71.44; H 7.23; N 11.80%.

*4.2.13. 2,8-Dimethoxy-13-(N-benzyl-N-methylamino)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (±)-**24***. *Method A*: Starting with *N*-benzyl-*N*-methylformamide (106 mg, 0.71 mmol) and (±)-**4** (200 mg, 0.71 mmol), the crude residue was purified by column chromatography (silica gel, 40% EtOAc/hexane) to afford (±)-**24** (142 mg, 50%) as a colourless oil that slowly crystallised to form a white solid: mp 106–107 °C; R_f (40% EtOAc/hexane) 0.68; IR (neat) ν_{max} 3025, 3000, 2961, 2892, 2837, 2800, 1612, 1577, 1491, 1422, 1241, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.84 (d, *J* 16.4 Hz, 1H, CH_2), 3.93 (br s, 2H, $BnCH_2$), 4.11 (s, 1H, CH), 4.18 (d, *J* 16.7 Hz, 1H, CH_2), 4.62 (d, *J* 16.7 Hz, 1H, CH_2), 4.68 (d, *J* 16.4 Hz, 1H, CH_2), 6.43–6.48 (m, 2H, ArH), 6.70–6.77 (m, 2H, ArH), 7.02 (d, *J* 8.7 Hz, 1H, ArH), 7.06 (d, *J* 8.8 Hz, 1H, ArH), 7.20–7.28 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.4, 52.00, 55.3, 55.4, 56.0, 59.5, 87.9, 110.4, 110.6, 113.4, 113.9, 126.3, 126.5, 126.6, 128.1, 129.0, 129.3, 129.8, 137. 7, 139.0, 141.8, 155.8, 156.0; Anal. Calcd for $C_{25}H_{27}N_3O_2$: C 74.79; H 6.78; N 10.47. Found: C 74.55; H 6.62; N 10.15%.

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Supplementary data

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