Synthesis of 5,6,11,12-tetrahydrodibenzo[*b*,*f*][1,5]diazocines and a demonstration of their reactivity to afford methano strap-modified Tröger's base analogues

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Abstract

Tröger's base analogues are of interest in areas such as host-guest chemistry, synthetic receptor design and asymmetric catalysis. We foresee that access to diverse functionality attached to the bridge of Tröger's base compounds will be beneficial for the development of these applications. As a starting point, we report a facile and general methodology to prepare a range of diversely functionalised 5,6,11,12-tetrahydrodibenzo[*b*,*f*][1,5]diazocines, compounds that may be viewed as "strap-clipped" Tröger's bases. As a demonstration of their reactivity, these compounds were reacted with benzaldehyde to introduce phenyl substituted straps onto a Tröger's base framework.

Keywords: Tröger's base, strap removal, diazocine, cyclic diamines, trifluoroacetic anhydride, aldehyde condensation

Introduction

Tröger's base **1** is a rigid, concave-shaped molecule with two chiral nitrogen atoms in the bridge region that are unable to undergo pyramidal inversion due to the presence of a methylene strap (Figure 1). Its rigid, chiral structure has made it an attractive scaffold for further development in areas such as asymmetric catalysis,[1, 2] DNA binding[3, 4] and synthetic receptor design.[5-9]

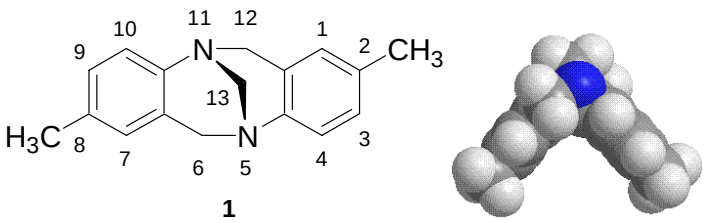

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Figure 1. Numbering scheme employed for Tröger's base and an illustration of the concave shape of **1**.

Since the first synthesis of Tröger's base **1** in 1887,[10] many structurally diverse analogues have been made, with the great majority of synthetic alterations performed on the aromatic portion of the molecule. This has been largely achieved by the use of functionalised anilines,[6, 11-14] together with other suitable aromatic amines such as amino- acridines,[15] phenanthrolines,[16, 17] pyrroles,[18] thiophenes[19] and porphyrins.[20, 21] In recent years the long-held belief that Tröger's base analogues could not be prepared from anilines bearing electron-withdrawing groups has been proven to be incorrect, with the synthesis of halo[22-25] and nitro-functionalised[26-30] Tröger's bases. Several reviews detail the major accomplishments over the past few decades with regards to Tröger's base and related chemistry.[31-33]

One aspect of Tröger's base chemistry that has been largely overlooked is the introduction of new functionality onto the methylene strap. This single-atom strap is crucial to the structural integrity of Tröger's base analogues,[34] and a potential site for generating molecular diversity. It has been previously shown that reactions of aldehydes, or a limited selection of ketones, with the two cyclic disecondary amines shown in Figure 2 results in the formation of Tröger's base analogues with the methylene strap either mono- or di-substituted.[35-37]

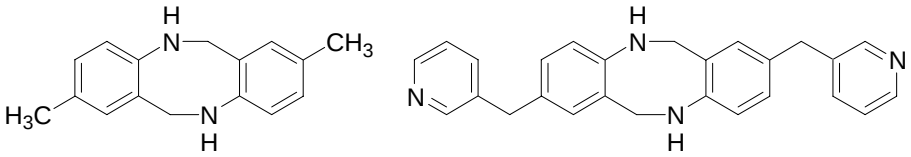


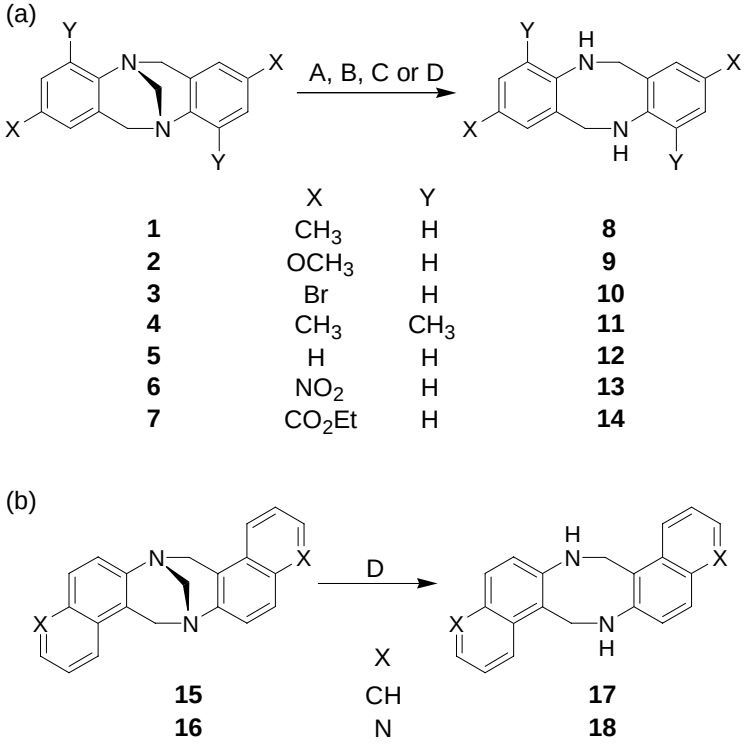
Figure 2. The two cyclic disecondary amines previously reacted with aldehydes and ketones to afford substituted methano-strapped Tröger's base analogues.

In light of the substituents that are now available on the aryl rings of Tröger's base analogues, in the present work we sought to develop a general methodology for the synthesis of functionalised cyclic disecondary amines (strap-clipped Tröger's base analogues) and demonstrate their use in a general approach toward methano-strap modified compounds.

Results and Discussion

Cyclic disecondary amines can be made from dianthranilides,[38] that in turn can be obtained from methyl anthranilates. However, in this work Tröger's base analogues **1** – **7**, **15** and **16** (Scheme 1) (all available in a one step reaction from the corresponding anilines) were used as precursors to the cyclic disecondary amines, using two different routes.

The first route investigated involved the generation of a dinitrosamine, of the general structure shown in Figure 3, following treatment of the Tröger's base analogues with sodium nitrite in acidic solution. The dinitrosamines were generally not isolated, but rather converted to the desired cyclic disecondary amines. Three variations on this general approach were utilised (Methods A – C in Scheme 1).



	X	Y	
1	CH_3	H	**8**
2	OCH_3	H	**9**
3	Br	H	**10**
4	CH_3	CH_3	**11**
5	H	H	**12**
6	NO_2	H	**13**
7	CO_2Et	H	**14**

	X	
15	CH	**17**
16	N	**18**

Scheme 1. A i. HCl, $NaNO_2$ ii. CuCl, HCl, AcOH: B i. TFA, $NaNO_2$ ii. CuCl, HCl, AcOH: C i. TFA, $NaNO_2$ ii. $NaBH_4$, $NiCl_2.H_2O$, THF: D i. TFAA, DCM ii. NaOH, EtOH.

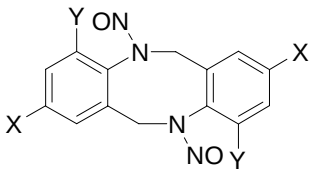


Figure 3. The general structure of the dinitrosamine intermediates obtained upon treatment of Tröger's base analogues with sodium nitrite in acidic conditions.

Initially, the generality of the literature methodology[35] (Method A) was explored, however, with the exception of compounds **1** and **2**, these reaction conditions were found to be unsuccessful. Trifluoroacetic acid was used in place of concentrated hydrochloric acid when generating the dinitrosamine (Method B and Method C) from **3** - **6** as these Tröger's base analogues were insoluble in the aqueous reaction conditions of Method A. In the case of compound **3**, reduction of the nitrosamine to afford **10** was performed using sodium borohydride in the presence of $NiCl_2.6H_2O$ in THF,[39] as the combination of CuCl-HCl was found to be ineffective (even when using sodium borohydride, reduction times of greater than 1 h resulted in greatly diminished yields). The results are summarised in Table 1.

Although the modifications employed in Method B and Method C allowed for the broader application of this route, access to several derivatives was still problematic. For example, appropriate conditions for the reduction of the dinitrosamine derived from **6** could not be found due to its poor solubility in both aqueous and organic solvents. As another example, compound **9** was afforded in poor yield and could not be fully purified due to an unidentified reaction byproduct that was inseparable by either column chromatography or recrystallisation. The poor yield of **11** was also seen to be a major drawback as 4,10-substituted Tröger's base analogues are considered potentially very useful due to a reduced susceptibility to racemisation.[40] Hence, an alternate methodology was sought.

Table 1. Yields of the various cyclic disecondary amines

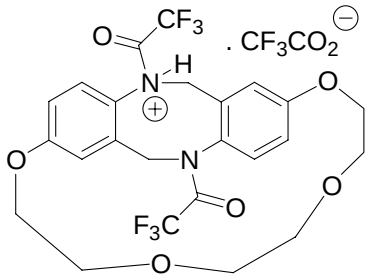
	% Yield (Method)		% Yield (Method)
8	49 (A)	**12**	55 (B)
8	64 (D)	**12**	44 (D)
9	<15[§] (A)	**13**	N/A[†] (B or C)
9	79 (D)	**13**	62 (D)
10	36 (C)	**14**	61 (D)
10	81 (D)	**17**	59 (D)
11	9 (B)	**18**	44 (D)
11	50 (D)		

[§]Yield no greater than 15% based on the amount of material recovered after column chromatography.

[†] The dinitrosamine was synthesised and identified by ^{1}H NMR analysis, however effective reduction conditions could not be found.

Miyahara *et al*.[41] used trifluoroacetic anhydride (TFAA) to generate what was reportedly a trifluoroacetate salt of a bis-trifluoroacetylated disecondary amine **19**, although no experimental details were provided. The trifluoroacetyl groups were then hydrolysed by refluxing in methanol in the presence of potassium carbonate.

We initially saw this route as a potential means to obtain **9** in an improved yield and in the absence of unwanted (and inseparable) byproducts. This proved to be the case, using TFAA (and DCM as a co-solvent), followed by ethanolysis of the crude residue in ethanolic sodium hydroxide solution (Scheme 1, Method D).



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A range of cyclic disecondary amines were obtained with improved yields (Table 1) including **13** and **14**, bearing strong electron-withdrawing groups. The cyclic disecondary amines were easily identified from their ^{1}H NMR spectra when run in DMSO-d_6, as the amine protons resonated as distinct triplets (δ 5.41 and 7.71 ppm for **9** and **13**, respectively) as illustrated in Figure 4.

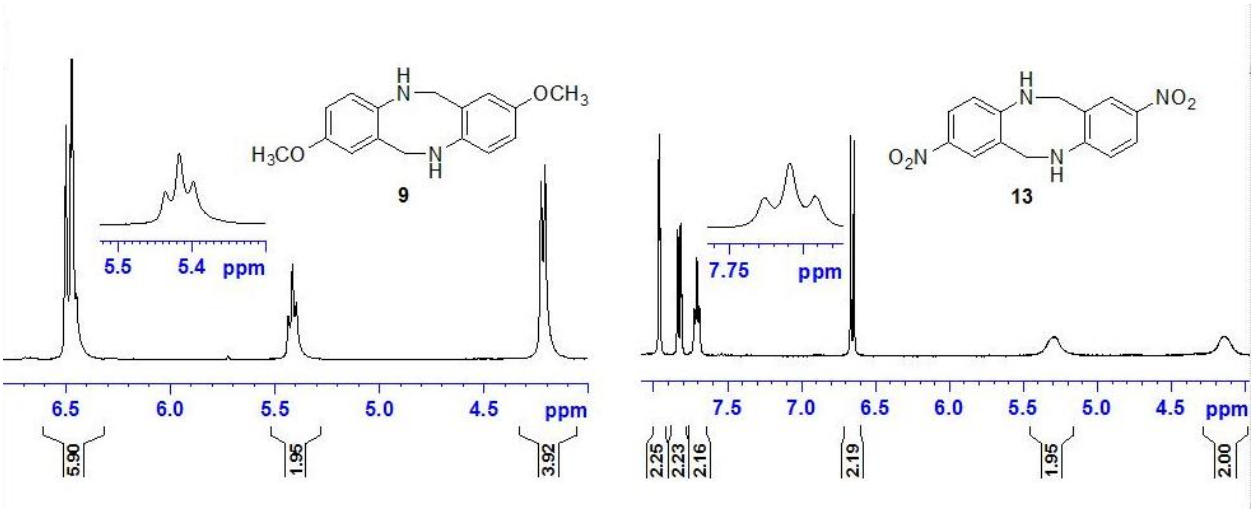
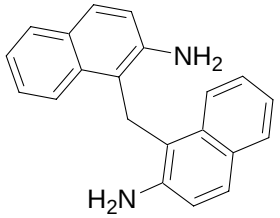


Figure 4. A portion of the 400 MHz ^{1}H NMR spectra of **9** and **13** in DMSO-d_6, illustrating the downfield shift on the amine protons of **13** relative to those of **9** (insets) as well as the different appearances of the benzylic protons (see text).

The pronounced downfield shifts of the amine protons of the cyclic disecondary amines bearing electron-withdrawing groups (**13**, **14** and, to a lesser extent, **10**) is indicative of increased H-bonding interactions with DMSO-d_6. Another interesting feature evident in Figure 4 is the contrast in the appearance of the benzylic protons. These protons appear as a four proton doublet at 4.22 ppm for **9**, whilst the corresponding protons resonate as two broad singlets, integrating as two protons each, at 4.13 and 5.30 ppm for **13**. Infact, for the nine cyclic disecondary amines

prepared in the present work, the benzylic protons in the diazocine ring appeared in one of three forms in DMSO-d_6 solution at 298 K; either a doublet integrating as four protons (**8**, **9**, **11** and **12**), or a broad singlet integrating as four protons (**10**, **17** and **18)** or two broad singlets, each integrating as two protons (**13** and **14**). In $CDCl_3$ solution, the benzylic protons of all the cyclic disecondary amines studied appeared as a single singlet, with coupling to the amino proton absent (and indeed the signal from the amino proton itself was absent in $CDCl_3$ solution). It is believed that the behaviour of the different compounds in DMSO-d_6 solution is the result of different degrees of H-bonding between the solvent and the analytes influencing the conformational dynamics of the eight-membered diazocine ring. The notion that we are observing a range of different dynamic processes within the selection of substrates at room temperature was supported by the results of a variable temperature experiment with **13** in DMSO-d_6. The variable temperature experiment showed that the two benzylic resonances, seen in Figure 4, coalesce to a single broad singlet at 358 K, and the resonance is observed as a doublet at 418 K, reminiscent of the doublet observed for **9** (4.22 ppm in Figure 4) at 298 K (see supplementary information).

In terms of the synthesis of the cyclic disecondary amines, it is noteworthy that ethanolysis of **11** had to be performed at reflux, as the room temperature reaction was very sluggish, presumably a result of steric hindrance afforded by the methyl groups at the 4,10-positions. It should also be noted that **9** and **11** tended to discolour over time if they were left open to the air above 4 ºC and that **17** decomposed to **20**, whose structure was confirmed by X-ray crystallography,[42] if left exposed to air and ambient light for prolonged periods.



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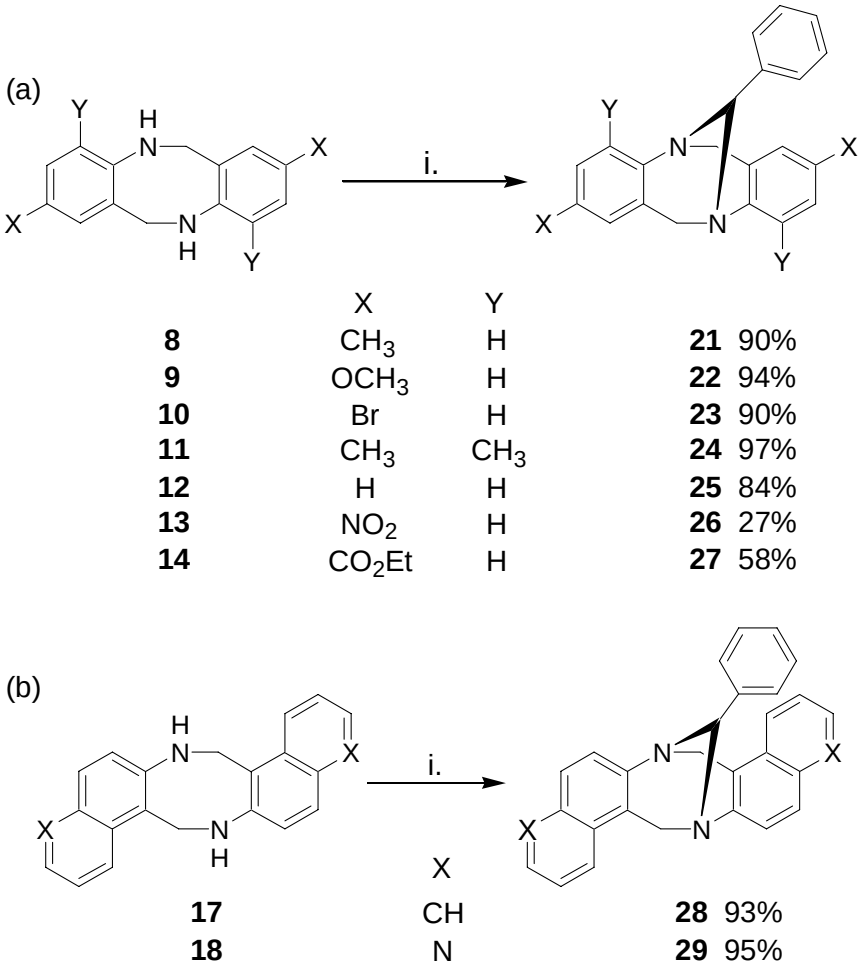
With a range of new strap-clipped Tröger's base analogues available for the first time, their ability to undergo conversion to methano-strap modified analogues of Tröger's base was evaluated. In this regard, compound **8** has previously been shown to react with a range of aldehydes and several simple, sterically unhindered ketones.[35] Rather than examine the reactions of **9** - **14**, **17** and **18** with a range of aldehydes, benzaldehyde was chosen as a representative aldehyde that was reacted with each of the cyclic disecondary amines, as shown in Scheme 2. We believe that this provides a guide to the relative reactivities of the compounds.

Reaction times of 18 h were typically employed, however longer reaction times were required for **26** and **27** (72 h and 48 h, respectively), most likely due to the lower nucleophilicity of the respective amines, whilst lower overall yields of the two compounds were attributed to difficulty during purification due to poor solubility. The yields for all other strap-modified products were approximately 85-95%.



	X	Y	
8	CH_3	H	**21** 90%
9	OCH_3	H	**22** 94%
10	Br	H	**23** 90%
11	CH_3	CH_3	**24** 97%
12	H	H	**25** 84%
13	NO_2	H	**26** 27%
14	CO_2Et	H	**27** 58%

	X	
17	CH	**28** 93%
18	N	**29** 95%

Scheme 2. i. Benzaldehyde, toluene, reflux.

An X-ray crystal structure was obtained of racemic compound **21** (Figure 5) and both enantiomers were present in the unit cell (see Supplementary Information Available). The dihedral angle (defined by the intersection of the least-squares planes of the two aryl rings fused to the diazocine ring) has been found to lie between 82°[43] and 108°[25] for over 20 simple dibenzo Tröger's base analogues with an unsubstituted methano strap. The dihedral angle at the base of **21** is 93.7°, similar to the angle present in Tröger's base **1**, where the aromatic rings in the two types of molecule present in the unit cell give rise to dihedral angles of 92.9° and 97.4°.[44] The similarity of these values suggests that the presence of the phenyl ring above the cavity in the substituted methano-strapped compounds is unlikely to impart a significant influence on the geometry of the base of the compounds.

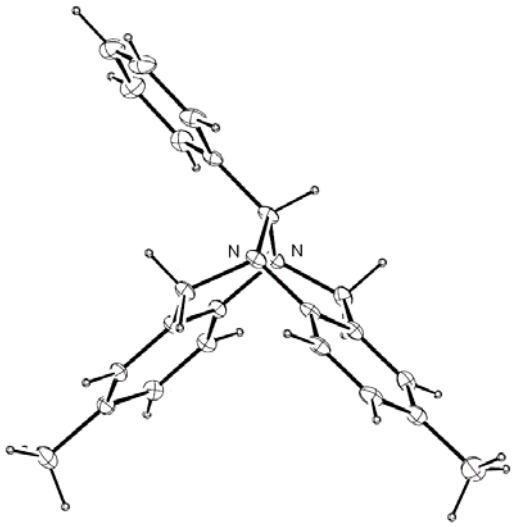


Figure 5. X-ray crystal structure of **21**.

Conclusions

We have demonstrated that cyclic disecondary amines can be produced from the removal of the apical methylene strap from a wide range of Tröger's base analogues. We have also shown that all of the diamines examined undergo reaction with benzaldehyde to afford substituted methano-strapped analogues. Investigations involving condensation reactions with functionalised aldehydes are actively underway in our laboratory and the results will be reported in due course.

Experimental Section

General Procedures. 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. NMR analyses was carried out on a Bruker DPX400 spectrometer. 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 Tröger's base starting materials were made according to literature procedures as follows: Tröger's base **1**,[45] 2,8-dimethoxy Tröger's base **2**,[45] 2,8-dibromo Tröger's base **3**,[22] 2,4,8,10-tetramethyl Tröger's base **4**,[12] unsubstituted Tröger's base **5**,[46] 2,8-dinitro Tröger's base **6**,[47] diethyl ester Tröger's base **7**,[48] dinaphthalino Tröger's base **15**,[49] and diquinolino Tröger's base **16**.[50]

General procedures for the removal of the apical methylene group

Method A/B. The Tröger's base analogue (8.0 mmol) was dissolved in concentrated hydrochloric acid (30 mL) (or trifluoroacetic acid (60 mL) for Method B) and stirred over an ice-bath for 10 min. Sodium nitrite (40 mmol, 5 equiv.) dissolved in water (25 mL), was then added dropwise over 30 min. The reaction mixture was diluted with water (100 mL) and allowed to stir for 12 h. The resultant precipitate was collected by filtration at the pump, and was suspended directly in glacial acetic acid (17 mL) with stirring at 80 °C. To the suspension was added cuprous chloride (34.8 mmol, 4.35 equiv.) dissolved in concentrated hydrochloric acid solution (40 mL). The mixture was stirred at 100 °C for 6 h and then poured onto ice and basified with 28% ammonia solution. The mixture was extracted with dichloromethane (3 x 50 mL) and the organic layers combined before washing with brine and drying over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude material was purified by column chromatography.

Method C. The Tröger's base analogue (2.66 mmol) was dissolved in trifluoroacetic acid (20 mL) and stirred over an ice-bath for 20 min. Sodium nitrite (5.85 mmol, 2.2 equiv.) dissolved in water (10 mL) was then added over a 15 min period. The mixture was stirred for 1 h and then filtered at the pump. The residue was suspended in tetrahydrofuran (36 mL) and added dropwise to a stirring suspension of nickel(II) chloride hexahydrate (15.86 mmol, 6 equiv.) and sodium borohydride (31.78 mmol, 12 equiv.) in tetrahydrofuran (20 mL) over an ice-bath. The reaction mixture was allowed to stir for 1 h before quenching with ice. A black precipitate was removed by filtration over celite that was washed with copious amounts of dichloromethane. The organic and aqueous layers were separated and the organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to dryness. The crude material was purified by column chromatography.

Method D. The Tröger's base analogue (0.45 mmol) was suspended in a mixture of trifluoroacetic anhydride (0.5 mL) and dichloromethane (1 mL) and stirred at room temperature in a closed vessel overnight. The reaction was then quenched with water and basified with saturated sodium hydrogen carbonate solution. The cloudy mixture was extracted with dichloromethane (2 x 50 mL) and the organic layers were combined and washed with brine, dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residue was dissolved in ethanol (5 mL) with sodium hydroxide (100 mg) and stirred at room temperature until completion (TLC). The reaction mixture was then concentrated under reduced pressure and the residue dissolved in a mixture of water and dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness under reduced pressure. The crude material was purified by column chromatography.

2,8-Dimethyl-5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]diazocine (8). Starting with **1** (2.00 g, 8.00 mol), column chromatography (silica gel, ethyl acetate:dichloromethane 1:4) afforded **8** (1.22 g, 64%) as a white solid, mp 205.43 °C (lit.[35] 204-205 °C); ^{1}H NMR (DMSO-d_6): δ 2.06 (6H, s), 4.24 (4H, d, J = 6.2 Hz), 5.60 (2H, t, J = 7.5Hz, NH), 6.41 (2H, d, J = 8.0 Hz), 6.64 (2H,

dd, *J* = 8.0 and 1.5 Hz), 6.68 (2H, app. s); ^{13}C NMR (DMSO-d_6): δ 50.5, 56.0, 114.2, 117.4, 118.9, 127.5, 143.8, 152.3.

2,8-Dimethoxy-5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]diazocine (9). Starting with **2** (100 mg, 0.36 mmol), column chromatography (silica gel, ethyl acetate:dichloromethane 1:1) afforded **9** (76 mg, 79%) as a white solid, mp 182.39 °C; ^{1}H NMR (DMSO-d_6) δ 3.57 (6H, s), 4.22 (4H, d, *J* = 7.5 Hz), 5.41 (2H, t, *J* = 7.5 Hz, NH), 6.40-6.52 (6H, m); ^{13}C NMR (DMSO-d_6): δ 50.5, 56.0, 114.2, 117.4, 118.9, 127.5, 143.8, 152.3. Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.45; H, 6.88; N, 10.20.

2,8-Dibromo-5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]diazocine (10). Starting with **3** (100 mg, 0.26 mmol), column chromatography (silica gel, dichloromethane) to afford **10** (77 mg, 81%) as a white solid, mp 222.90 °C; ^{1}H NMR (DMSO-d_6) δ 4.31 (4H, br s), 6.10 (2H, t, *J* = 7.2 Hz, NH), 6.51 (2H, d, *J* = 8.5 Hz), 6.98-7.02 (2H, m), 7.05 (2H, d, *J* = 2.4 Hz). ^{1}H NMR ($CDCl_3$): δ 4.44 (s, 4H), 6.48 (2H, d, *J* = 8.8 Hz), 7.07-7.12 (4H, m) ^{13}C NMR ($CDCl_3$): δ 49.7, 110.9, 119.5, 126.9, 131.1, 133.8, 146.5. Anal. Calcd. for $C_{14}H_{12}N_2Br_2$: C, 45.68; H, 3.29; N, 7.61. Found: C, 45.86; H, 3.28; 7.56.

2,4,8,10-Tetramethyl-5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]diazocine (11). Starting with **4** (100 mg, 0.36 mmol), ethanolysis was performed at reflux for 12 hr. Column chromatography (silica gel, dichloromethane) afforded **11** as a white solid 48 mg (50%), mp 172.55 °C; ^{1}H NMR (DMSO-d_6): δ 1.98 (6H, s), 2.04 (6H, s), 4.40 (4H, d, *J* = 7.2 Hz), 4.94 (2H, t, *J* = 7.2 Hz, NH), 6.58 (2H, app. s), 6.62 (2H, app. s); ^{13}C NMR (DMSO-d_6): δ 19.1, 20.8, 50.2, 123.8, 125.7, 125.9, 130.7, 130.8, 145.3. Anal. Calcd. for $C_{18}H_{22}N_2$: C, 81.16; H, 8.32; N, 10.52. Found: C, 80.79; H, 8.75; N, 10.40.

5,6,11,12-Tetrahydrodibenzo[*b,f*][1,5]diazocine (12). Starting with **5** (100 mg, 0.45 mmol), column chromatography (silica gel, ethyl acetate:dichloromethane 1:4) afforded **12** (217 mg, 44%) as a yellow crystalline solid, mp 137.80 °C; ^{1}H NMR ($CDCl_3$): δ 4.56 (4H, s), 6.92 (2H, app. d, *J* = 7.8 Hz), 6.75 (2H, app. t, *J* = 7.5 Hz), 6.99-7.10 (4H, m); ^{1}H NMR (DMSO-d_6): δ 4.33 (4H, d, *J* = 4.9 Hz), 5.86 (2H, t, *J* = 7.4 Hz, NH), 6.40-6.68 (2H, m), 6.50-6.59 (2H, m), 6.77-6.86 (4H, m); ^{13}C NMR (DMSO-d_6): δ 49.8, 117.66, 117.74, 125.7, 128.5, 132.6, 149.9. Anal. Calcd. for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.12; H, 7.05; N, 13.30.

2,8-Dinitro-5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]diazocine (13). Starting with **6** (100 mg, 0.32 mmol), purification by extraction with hot dichloromethane (10 mL) afforded **13** (60 mg, 62%) as a yellow solid, mp decomposed > 327 °C; ^{1}H NMR (DMSO-d_6): δ 4.13 (2H, br s), 5.30 (2H, br s), 6.66 (2H, d, *J* = 9.1 Hz), 7.71 (2H, t, *J* = 6.9 Hz, NH), 7.83 (2H, dd, *J* = 9.1 and 2.7 Hz), 7.96 (2H, d, *J* = 2.7 Hz); ^{13}C NMR (DMSO-d_6): δ 47.1, 116.8, 123.1, 125.5, 130.2, 136.6, 155.2. Anal. Calcd. for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.68; H, 4.19; N, 18.26.

Diethyl 5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]-diazocine-2,8-dicarboxylate (14). Starting with **7** (100 mg, 0.27 mmol), column chromatography (silica gel, ethylacetate:hexane:dichloromethane 1:1:8) afforded **14** (62 mg, 64%) as a white waxy solid, mp 266.02 °C; ^{1}H NMR (DMSO-d_6): δ 1.23 (3H, t, *J* = 7.1 Hz), 3.97 (2H, br s), 4.17 (2H, q, *J* = 7.1 Hz), 5.08 (2H, br s), 6.57 (2H, d, *J* = 8.5 Hz), 6.89 (2H, t, *J* = 6.7 Hz, NH), 7.48 (2H, dd, *J* = 8.5 and 1.3 Hz), 7.57 (2H, d, *J* = 1.3 Hz); ^{13}C NMR (DMSO-d_6): δ 15.2,

48.3, 60.5, 117.0, 117.8, 123.9, 130.3, 135.2, 153.8, 166.4. Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.61; H, 6.37; N, 7.77.

7,8,15,16-Tetrahydrodinaphthalino[*b,f*][1,5]diazocine (17). Starting with **15** (100 mg, 0.31 mol), column chromatography (silica gel, ethyl acetate:dichloromethane 9:1) afforded **17** (40 mg, 59%) as a white powdery solid, mp 176.91 °C; ^{1}H NMR (DMSO-d_6): δ 4.83 (4H, br s), 6.38 (2H, t, *J* = 7.1 Hz, NH), 6.85 (2H, d, *J* = 8.9 Hz), 7.08 (2H, app. t, *J* = 7.1 Hz), 7.30-7.39 (4H, m), 7.51 (2H, app. d, *J* = 7.4 Hz), 7.99 (2H, app. d, *J* = 8.5 Hz); ^{13}C NMR (DMSO-d_6): δ 45.8, 114.6, 121.2, 122.0, 122.1, 127.1, 128.6, 128.7, 128.8, 134.8, 149.2. Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 84.50; H, 6.20; N, 8.91.

1,1-Methylenebis(naphthalen-2-amine) (20). 20 was obtained as a decomposition product of **17** when it was left exposed to the atmosphere on the bench top. **20** could be separated from **17** by column chromatography (silica gel, dichloromethane) in variable yields (the greatest yield obtained by us was 35%, but we were more interested in **17**), depending upon the time of exposure. **20** was obtained as a white powdery solid, mp 172.06 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.34 (2H, s), 5.47 (4H, s, , NH_2), 6.95 (2H, d, *J* = 8.9 Hz,), 6.99-7.05 (2H, m), 7.10-7.14 (2H, m), 7.46 (2H, d, *J* = 8.9 Hz), 7.57 (2H, app d, *J* = 8.1 Hz,), 7.93 (2H, app d, *J* = 8.6 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 25.2, 114.0, 119.7, 121.5, 122.2, 122.5, 127.3, 128.7, 129.1, 129.5, 143.5. Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.30; H, 5.78; N, 9.22.

5,6,13,14-Tetrahydrodiquinolino[*b,f*][1,5]diazocine (18). Starting with **16** (100 mg, 0.31 mol), column chromatography (silica gel, ethyl acetate) afforded **18** (84 mg, 44%) as a pale yellow solid, mp 367.96 °C; ^{1}H NMR (DMSO-d_6): δ 4.82 (4H, br s), 6.61 (2H, t, *J* = 7.3 Hz, NH), 7.06 (2H, d, *J* = 9.1 Hz), 7.31-7.36 (2H, m), 7.47 (2H, d, *J* = 9.0 Hz), 8.39 (2H, app. d, *J* = 8.5 Hz), 8.41-8.44 (2H, m); ^{13}C NMR (DMSO-d_6): δ 44.9, 113.9, 122.2, 124.4, 129.6, 129.90, 129.95, 144.3, 146.2, 149.1. Anal. Calcd. for $C_{20}H_{16}N_4.1.1\ H_2O$: C, 72.35; H, 5.52; N, 16.87. Found: C, 72.71; H, 5.49; N, 16.96.

General procedure for the reactions of benzaldehyde with the cyclic disecondary amines

The cyclic disecondary amine (1.65 mmol) was dissolved in toluene (15 mL) and benzaldehyde (3.30 mmol, 2 equiv.) was added. The resulting solution was stirred at reflux for 18 h. The reaction mixture was then evaporated to dryness and the crude material was purified by column chromatography.

2,8-Dimethyl-13-phenyl-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine (21). Starting with **8** (389 mg; 1.63 mmol), column chromatography (silica gel, hexane:dichloromethane 1:9) afforded **21** (477 mg, 90%) as a yellow powdery solid, mp 181.23 °C (lit.[35] mp 182-183 °C); ^{1}H NMR ($CDCl_3$): δ 2.15 (3H, s), 2.26 (3H, s), 3.88 (1H, d, *J* = 16.8 Hz), 4.12 (1H, d, *J* = 16.8 Hz), 4.32 (1H, d, *J* = 16.5 Hz), 4.81 (1H, d, *J* = 16.5 Hz), 5.32 (1H, app. s), 6.46 (1H, app. s), 6.78 (1H, app. s), 6.73-7.04 (2H, m), 7.14 (1H, d, *J* = 8.3 Hz), 7.20 (1H d, *J* = 8.2 Hz), 7.21-7.32 (3H, m), 7.57-7.63 (2H, m); ^{13}C NMR ($CDCl_3$): δ 20.81, 20.85, 52.5, 60.8, 74.6, 120.8, 125.00, 125.03, 125.3, 126.9, 127.19, 127.24, 127.5, 127.7, 128.0, 128.2, 132.9, 133.3, 138.4, 143.6,

147.5. Anal. Calcd. for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.12; H, 7.05; N, 13.30.

2,8-Dimethoxy-13-phenyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (22). Starting with **9** (94 mg, 0.35 mmol), column chromatography (silica gel, dichloromethane) afforded **22** (118 mg, 94%) as a pale yellow varnish, mp 258.08 °C; ^{1}H NMR ($CDCl_3$): δ 3.63 (3H, s), 3.73 (3H, s), 3.87 (1H, d, *J* = 17.0 Hz), 4.12 (1H, d, *J* = 17.0 Hz), 4.30 (1H, d, *J* = 16.6 Hz), 4.81 (1H, d, *J* = 16.6 Hz), 5.31 (1H, s), 6.19 (1H, d, *J* = 2.7 Hz), 6.50 (1H, d, *J* = 2.7 Hz), 6.71-6.81 (2H, m), 7.12-7.33 (5H, m), 7.54-7.61 (2H, m); ^{13}C NMR ($CDCl_3$): δ 53.3, 55.6, 55.8, 61.4, 75.2, 110.8, 111.1, 114.4, 114.7, 126.7, 127.0, 127.7, 128.0, 128.6, 129.2, 129.7, 138.8, 139.5, 143.5, 156.1, 156.4. Anal. Calcd. for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 77.21; H, 6.38; N, 7.56.

2,8-Dibromo-13-phenyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (23). Starting with **10** (162 mg, 0.44 mmol), column chromatography (silica gel, hexane:dichloromethane 1:9) afforded **23** (477 mg, 90%) as a pale yellow powdery solid, mp 261.77 °C; ^{1}H NMR ($CDCl_3$): δ 3.88 (1H, d, *J* = 17.1 Hz), 4.15 (1H, d, *J* = 17.1 Hz), 4.31 (1H, d, *J* = 16.7 Hz), 4.81 (1H, d, *J* = 16.7 Hz), 5.29 (1H, s), 6.81 (1H, d, *J* = 2.1 Hz), 7.09 (1H, d, *J* = 8.6 Hz), 7.13 (1H, d, *J* = 2.1 Hz), 7.17 (1H, d, *J* = 8.6 Hz), 7.21-7.34 (5H, m), 7.51-7.53 (2H, m); ^{13}C NMR ($CDCl_3$): δ 52.7, 60.7, 74.7, 117.0, 117.2, 121.5, 127.5, 127.7, 128.1, 128.8, 129.8, 130.1, 130.3, 130.8, 130.9, 131.2, 137.7, 145.5, 149.3. Anal. Calcd. for $C_{21}H_{16}Br_2N_2$: C, 55.29; H, 3.54; N, 6.14. Found: C, 55.69; H, 3.38; N, 5.37.

2,4,8,10-Tetramethyl-13-phenyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (24). Starting with **11** (86 mg, 0.32 mmol), column chromatography (silica gel, dichloromethane) afforded **24** (110 mg, 97%) as a white powdery solid, mp 180.22 °C; ^{1}H NMR ($CDCl_3$): δ 2.11 (3H, s), 2.23 (3H, s), 2.46 (3H, s), 2.54 (3H, s), 3.70 (1H, d, *J* = 17.1 Hz), 4.06 (1H, d, *J* = 17.1 Hz), 4.13 (1H, d, *J* = 16.7 Hz), 4.70 (1H, d, *J* = 16.7 Hz), 5.33 (1H, s), 6.32 (1H, app. s), 6.66 (1H, app. s), 6.86 (1H, app. s), 6.92 (1H, app. s), 7.19-7.28 (3H, m), 7.56-7.61 (2H, m); ^{13}C NMR ($CDCl_3$): δ 17.4, 17.7, 21.2, 21.3, 49.6, 57.5, 75.6, 125.0, 125.2, 127.5, 127.8, 128.2, 128.5, 129.0, 130.0, 130.2, 133.0, 133.2, 133.3, 133.4, 139.2, 141.8, 145.9. Anal. Calcd. for $C_{25}H_{26}N_2$: C, 84.70; H, 7.39; N, 7.90. Found: C, 85.08; H, 7.38; N, 7.63.

13-Phenyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (25). Starting with **12** (123 mg, 0.59 mmol), column chromatography (silica gel, dichloromethane) afforded **25** (147 mg, 84%) as a white powder, mp 135.71 °C; ^{1}H NMR ($CDCl_3$): δ 3.98 (1H, d, *J* = 16.9 Hz), 4.20 (1H, d, *J* = 16.9 Hz), 4.41 (1H, d, *J* = 16.6 Hz), 4.87 (1H, d, *J* = 16.6 Hz), 5.37 (1H, s), 6.67 (1H, dd, *J* = 7.6 and 0.7 Hz,), 6.86-6.90 (1H, m), 6.95-7.07 (2H, m), 7.16-7.32 (7H, m), 7.57-7.63 (2H, m); ^{13}C NMR ($CDCl_3$): δ 53.0, 61.2, 74.8, 124.0, 124.3, 125.8, 126.1, 127.0, 127.4, 127.6, 127.7, 127.8, 127.9, 128.58, 128.62, 129.0, 138.6, 146.8, 150.6. Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.36; H, 6.36; N, 9.29.

2,8-Dinitro-13-phenyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (26). Starting with **13** (224 mg, 0.75 mmol), column chromatography (silica gel, dichloromethane) afforded the first fraction that was collected and the solvent was removed under reduced pressure. The residue

was then recrystallised (ethyl acetate/hexane) to afford **26** (78 mg, 27%) as a yellow powder, mp 260.03 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 3.82 (1H, d, *J* = 17.3 Hz), 4.02 (1H, d, *J* = 17.3 Hz), 4.23 (1H, d, *J* = 16.9 Hz), 4.70 (1H, d, *J* = 16.9 Hz), 5.11 (1H, s), 6.91-7.01 (3H, m), 7.06 (1H, d, *J* = 8.9 Hz), 7.14-7.20 (3H, m), 7.31 (1H, d, *J* = 2.5 Hz), 7.62 (1H, d, *J* = 2.5 Hz), 7.70-7.75 (2H, m); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ 57.6, 65.5, 79.1, 127.6, 128.2, 128.4, 131.3, 131.5, 132.2, 133.3, 133.7, 133.8, 134.3, 141.2, 148.7, 148.9, 157.6, 161.0. Anal. Calcd. for $C_{21}H_{16}N_4O_4$: C, 64.94; H, 4.15; N, 14.43. Found: C, 65.24; H, 4.16; N, 14.14.

Diethyl 13-phenyl-6*H*,12*H*-5,11-methanodibenzo[b,f][1,5]diazocine-2,8-dicarboxylate (27). Starting with **14** (135 mg, 0.38 mmol), column chromatography (silica gel, dichloromethane) afforded **27** (98 mg, 58%) as a white powder, mp 67.33 °C; ^{1}H NMR ($CDCl_3$): δ 1.29 (3H, t, *J* = 7.1 Hz), 1.35 (3H, t, *J* = 7.2 Hz), 4.04 (1H, d, *J* = 17.0 Hz), 4.21-4.29 (3H, m), 4.32 (2H, q, *J* = 7.2 Hz), 4.47 (1H, d, *J* = 16.5 Hz), 4.91 (1H, d, *J* = 16.5 Hz), 5.38 (1H, s), 7.21-7.32 (4H, m), 7.34 (1H, d, *J* = 8.4 Hz), 7.39 (1H, d, *J* = 1.6 Hz,), 7.51-7.55 (2H, m), 7.65 (1H, d, *J* = 1.6 Hz), 7.83-7.90 (2H, m); ^{13}C NMR ($CDCl_3$): δ 14.7, 14.8, 53.0, 61.0, 61.1, 61.2, 74.7, 125.6, 125.9, 126.3, 126.5, 127.7, 128.1, 128.6, 128.7, 128.8, 129.1, 129.2, 129.3, 137.5, 151.2, 154.8, 166.56, 166.60. Anal. Calcd. for $C_{27}H_{26}N_2O_4$: C,73.28; H, 5.92; N, 6.33. Found: C, 73.46; H, 5.92; N, 6.21.

17-Phenyl-8*H*,16*H*-7,15-methanodinaphthalino[*b,f*][1,5]diazocine (28). Starting with **17** (192 g, 0.62 mmol), column chromatography (silica gel, hexane:dichloromethane, 1:4) afforded **28** (229 mg, 93%) as a white powdery solid, mp sublimes > 120 °C; ^{1}H NMR ($CDCl_3$): δ 4.47 (1H, d, *J* = 17.0 Hz,), 4.58 (1H, d, *J* = 17.0 Hz), 4.97 (1H, d, *J* = 16.6 Hz), 5.19 (1H, d, *J* 16.6 = Hz), 5.57 (1H, s), 7.17-7.23 (1H, m), 7.24-7.40 (5H, m), 7.42-7.49 (3H, m), 7.51 (1H, d, *J* = 8.8 Hz), 7.64-7.76 (7H, m); ^{13}C NMR ($CDCl_3$): δ 50.1, 58.3, 74.8, 121.78, 121.83, 122.4, 124.9, 125.1, 125.5, 125.7, 126.5, 126.8, 127.78, 127.82, 128.2, 128.4, 128.7, 128.8, 129.0, 131.4, 138.4, 143.7, 148.0. Anal. Calcd. for $C_{29}H_{22}N_2$: C, 87.41; H, 5.56; N, 7.03. Found: C, 87.36; H, 5.55; N, 6.65.

17-Phenyl-5*H*,13*H*-6,14-methanodiquinolino[*b,f*][1,5]diazocine (29). Starting with **18** (63 mg, 0.20 mmol), column chromatography (silica gel, ethyl acetate) afforded **29** (77 mg, 95%) as an off-white powder, mp 265.13 °C; ^{1}H NMR ($CDCl_3$): δ 4.48 (1H, d, *J* = 17.1 Hz), 4.55 (1H, d, *J* = 17.1 Hz), 4.94 (1H, d, *J* = 16.5 Hz), 5.19 (1H, d, *J* = 16.5 Hz), 5.56 (1H, s), 7.18-7.40 (5H, m), 7.61-7.69 (3H, m), 7.74 (1H, d, *J* = 9.1 Hz), 7.91-7.99 (2H, m), 8.06 (1H, app. d, *J* = 7.7 Hz), 8.70 (1H, dd, *J* = 4.2 and 1.6 Hz), 8.81 (1H, dd, *J* = 4.2 and 1.6 Hz); ^{13}C NMR ($CDCl_3$): δ 49.7, 57.7, 74.8, 121.4, 121.6, 122.1, 122.4, 126.4, 126. 9, 127.7, 128.1, 128.8, 128.9, 129.1, 129.8, 130.05, 130.09, 130.1, 137.7, 143.8, 146.5, 146.6, 148.0, 149.2, 149.4. Anal. Calcd. for $C_{27}H_{20}N_4.0.2\ H_2O$: C, 80.08; H, 5.10; N, 13.43. Found: C, 80.08; H, 5.10; N, 13.83.

Supplementary Information Available

A section of the 400 MHz ^{1}H NMR spectrum of **13** illustrating the chemical shift change of the benzylic protons at various temperatures is shown in the supplementary information, together

with the numbering system used in the naming of the cyclic disecondary amines derived from naphthalene and quinoline Tröger's bases **15** and **16**. In addition, the crystallographic data (excluding structure factors) for compound **21** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC 672280. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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