DOI: 10.1002/ejoc.200900121

One-Step Synthesis of Tröger's Base Hybrids Containing at Least One Halogen Atom

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Keywords: Tröger's base / Chirality / Aromatic substitution / Haloanilines / X-ray diffraction

The one-step synthesis of a series of hybrid dibenzo Tröger's base analogues bearing at least one halogen atom is described. The strategy involves a reaction between two different anilines and affords hybrid compounds in yields as high as 46%, together with the symmetric Tröger's base products. This straightforward approach requires only one chromatographic step and has the potential to replace multistep approaches to hybrid Tröger's base compounds.

Introduction

Tröger's base (**1**, Figure 1) is a chiral cleft-containing molecule that was first prepared by Tröger in 1887.[1] The compound is formed as a racemic mixture; however, its structure was not confirmed until 1935,[2] and it was resolved by Prelog in 1944, providing one of the first examples of chromatography with a chiral stationary phase.[3]

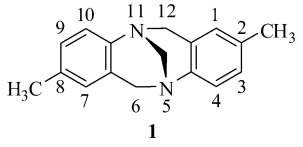

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Figure 1. Chemical structure of Tröger's base (**1**) and the conventional numbering system.

The reaction is the result of an acid-catalysed condensation of formaldehyde with *p*-toluidine, and involves electrophilic aromatic substitution and imine formation. In subsequent years, numerous researchers have published papers dealing with the synthesis and structure of Tröger's base analogues.[4–8] More recently, potential applications in the field of supramolecular chemistry provided much of the impetus for renewed interest in these compounds.[9–22]

There have been two long-held beliefs regarding the role of substituents in the direct synthesis of Tröger's base analogues from anilines, and these beliefs had limited the design of new analogues. The first of these beliefs was that electron-withdrawing substituents are poorly tolerated in the reaction. The work of Wärnmark's group on the preparation of dihalogenated compounds[23] was the first step to dismantling this misconception. There have been subsequent reports of tetrahalo,[24–26] and octafluoro analogues,[27] and diester-,[22,26,28–31] dinitro-[26,32–35] and even tetranitro-substituted[36] Tröger's base analogues have now been prepared. The second belief was that a substituent must be present in the *p*-position to prevent polymer formation, as a result of an additional condensation with formaldehyde at the activated site *para* to the aniline nitrogen atom. Wärnmark was again the first to show this was not the case by preparing a series of dihalo Tröger's base analogues, in yields as high as 59%,[37] from haloanilines unsubstituted *para* to the aniline amino group. Dinitro-[35] and diester-substituted[31] Tröger's bases substituent-free at the 2,8-positions have also been reported, and it has been shown that aniline itself can be used in the synthesis of unsubstituted Tröger's base in 78% yield.[38]

It is sometimes desirable to prepare non-symmetric, or "hybrid" Tröger's base analogues. A hybrid material here is defined as one in which the two aromatic rings are differentially substituted. These compounds can be synthesised in an unambiguous fashion by a stepwise route that initially involves the formation of a mono-linked compound.[39–43] The use of a single aniline with two unsubstituted and inequivalent positions *ortho* to the amino group can also theoretically afford a hybrid, as one of three potential Tröger's base products. Whilst this has been observed experimentally,[33,35,37] the compounds may be inseparable[13,44] and with some anilines only a single Tröger's base com-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900121.

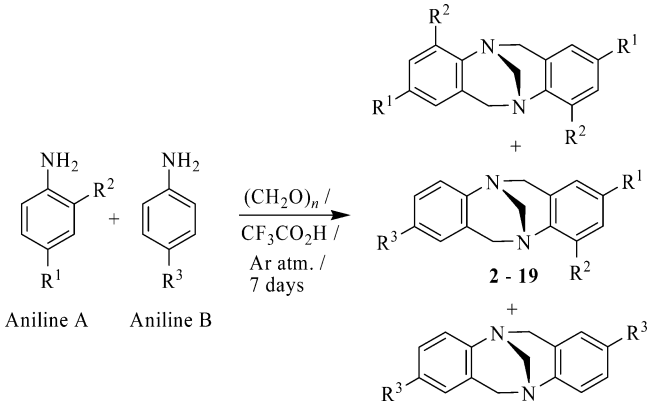
pound is formed.[31,45] Another strategy is to "desymmetrise" a symmetric Tröger's base, either by converting one of two symmetrically positioned substituents,[46,47] or introducing a substituent through either monobromination,[38,48] monochlorination[48] or monoiodination reactions.[38]

Conceptually, hybrids can be formed in a one-step reaction from a mixed condensation of two different aminoaryl units. This method has been reported previously; however, the reactions have involved either an aniline and an aminobiphenyl (no experimental details were provided),[49] or 5-aminophenanthroline and 3-aminoacridines.[50,51]

In this paper, we describe our recent efforts to expand the chemistry of dibenzo Tröger's base analogues by preparing a range of new hybrid compounds possessing at least one halogen atom.

Results and Discussion

In the present context, the reaction of two different *p*-substituted anilines (Aniline A and Aniline B) affords a mixture of three possible Tröger's base products: two symmetric compounds and a hybrid (Scheme 1). This approach yields a range of hybrid compounds in acceptable yields in a single step from readily available starting materials, providing that the symmetric product derived from aniline A has a very different R_f value from the symmetric product derived from aniline B.



Scheme 1. Synthesis of Tröger's base hybrids **2**–**19**.

This requirement was derived empirically from experimental observations. In each case examined thus far, the hybrid, not surprisingly, has an R_f value that lies between the two symmetric compounds. Thus, if the symmetric products have similar R_f values, the isolation of the hybrid by chromatographic techniques proves to be problematic.

4-Bromoaniline was chosen as one of the anilines in the first series of the reactions as its homo-coupled product, 2,8-dibromo Tröger's base, is formed in excellent yield in the absence of a second aniline. This compound is non-polar and is eluted relatively quickly from standard silica columns with a solvent system consisting of 10% ethyl acetate in dichloromethane. In addition, conditions have been established that enable the bromo group to be converted to other types of functionality (including formyl, carboxy, cyano and imino groups),[46,47,52–55] and hence each of the hybrids prepared here have the potential to give rise to other series of hybrid compounds. The hybrids were generally obtained as pure materials after chromatography (see the Experimental Section) in yields ranging from 7% to 41% (Scheme 1, Table 1).

Table 1. Yields of hybrids **2**–**11**.

Compound	R^1	R^2	R^3	Yield[a] %
2	Br	H	CH_3	35
3	Br	H	$CH_2(CH_2)_8CH_3$	13
4	Br	H	Ph	7
5	Br	H	OCH_3	23
6	Br	H	$NHCOCH_3$	33
7	Br	H	$NHCOC(CH_3)_3$	33
8	Br	Cl	Br	25
9	CH_3	Br	CH_3	35
10	Br	Br	CH_3	41
11	Br	H	H	14

[a] Analytically pure material obtained after chromatography.

By assuming equal reactivity of both anilines (which is clearly not the case, as the presence of different substituents and even the same substituents in different locations will impart different reactivity on the anilines), the theoretical yield of hybrids formed in this way is 50%, with each of the two symmetric compounds formed in 25% yield, based on a 1:2:1 product distribution (A/A, A/B, B/A, B/B).

Several reactions involving 2,4-substituted anilines were also performed to afford hybrids **8**–**10** in 25–41% yields, and these compounds include examples of hybrids in which the halogen atoms are present in the 4-, 2,4-, and 2,4,8-positions.

In each case the homo-coupled products (2,8-dibromo, 2,8-dimethyl Tröger's base, etc.) were also formed in varying yields, and in some cases (for example in the synthesis of **3** and **4**) fractions were also collected that contained mixtures of the homo-coupled product and the hybrid material (i.e., separation was not complete, and some tailing of the bands on the column had taken place), and thus the actual yield of hybrid compound in the crude reaction mixture was higher than stated in Table 1.

In fact, the poor yield of purified **3** and **4** is indicative of an insufficient difference in polarity of the symmetric Tröger's base products. Dibromo and didecyl Tröger's base, as well as dibromo and diphenyl Tröger's base have similar R_f values and are therefore difficult to separate (by using conventional column chromatography) from their hybrids **3** and **4**, respectively. In addition, the symmetric 2,8-diphenyl Tröger's base is obtained in 29% yield in our hands in a reaction involving only 4-aminobiphenyl as the aminoaryl compound (when performed on a 1 g scale with TFA and paraformaldehyde), probably as a result of condensation with formaldehyde at the activated 4′-site leading to other products. Hence, a poor yield of hybrid is also expected, even in the absence of purification problems.

Of course, as is the case in all Tröger's base reactions, other by-products, such as 3,4-dihydroquinazolines (the

products of a condensation between two anilines and two formaldehyde equivalents)[28,56–61] and related products (for example, condensation between three anilines and four formaldehyde equivalents),[6,62] can also be formed. Clearly, the use of two different anilines in the reaction can magnify these types of impurities, which may complicate purification of the desired hybrids. This appears to be the case in the synthesis of **11**, in which the poor yield is the result of a significant loss of desired product during purification as it co-elutes with other (non-Tröger's base) compounds with similar R_f values. The preferable route to this compound is by bromination of unsubstituted Tröger's base and affords **11** in 44% yield over two steps, as this avoids the problematic impurities formed in the one-step reaction of **11**.[38] However, if the synthesis of a Tröger's base bearing a single bromo substituent in the 2-position is desired, the one-step synthesis of **2** (or **5**) is more direct and requires a single chromatographic step during purification. Compound **2** has also been prepared by a stepwise procedure (3 steps) from 5-bromoisatoic anhydride in 49% overall yield.[43]

X-ray crystal structures were obtained for compounds **2** and **4** (Figures 2 and 3). The dihedral angle (formed by the intersection of the least-squares planes that pass through the aryl rings connected to the diazocine bridge) in these compounds was measured to be 92.6° and 101.4°, respectively.

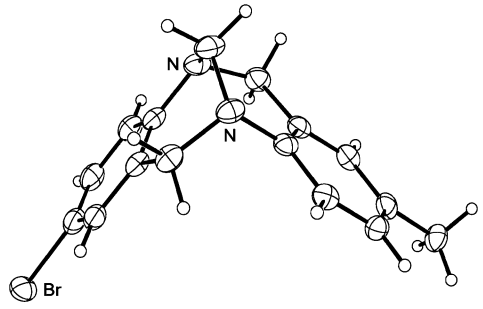


Figure 2. ORTEP diagram of **2** with 50% probability ellipsoids.

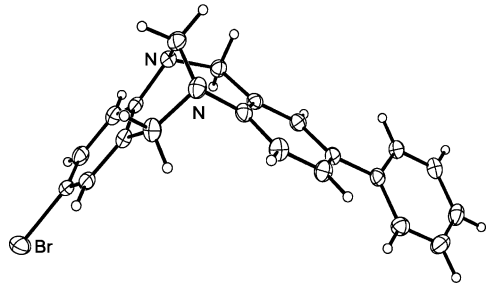


Figure 3. ORTEP diagram of **4** with 50% probability ellipsoids.

An X-ray crystal structure of **7** showed the presence of two crystallographically independent molecules in the unit cell, with dihedral angles of 94.2° and 99.0° (Figure 4).

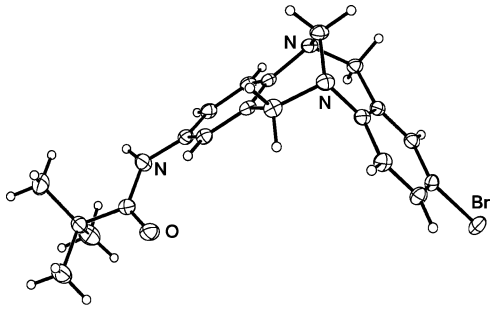


Figure 4. ORTEP diagram of one of the two crystallographically independent molecules present in the unit cell of **7**, with 50% probability ellipsoids.

A series of reactions were then carried out with iodo-substituted anilines, by using the same conditions as outlined in Scheme 1, and the results are summarised in Table 2.

Table 2. Yields of hybrids 1**2**–**19**.

Compound	R^1	R^2	R^3	Yield[a]%
12	I	H	CH_3	31
13	I	H	OCH_3	46
14	Br	CH_3	I	42
15	CH_3	Br	I	42
16	Br	Cl	I	20
17	Br	Br	I	20
18	I	CH_3	Br	34
19	I	H	H	15

[a] Analytically pure material obtained after chromatography.

The use of iodoanilines was again based on the demonstrated utility of the halogen atom as a substituent on Tröger's base analogues, in which the iodo group has been used to introduce methoxy,[52] formyl,[63] aryl,[47,63] and alkyne[23,52,64,65] substituents.

A reaction involving 4-iodoaniline and 4-aminobiphenyl yielded an inseparable mixture of the desired hybrid and the two symmetric compounds, as anticipated, because 2,8-diiodo and 2,8-diphenyl Tröger's base have a similar R_f value. A similar outcome resulted from a reaction with 4-bromoaniline and 4-iodoaniline, i.e., an inseparable mixture of the three possible Tröger's base compounds was formed.

An X-ray structure was obtained of **12** (Figure 5) and the dihedral angle was found to be 92.3°, essentially the same as that in **2**.

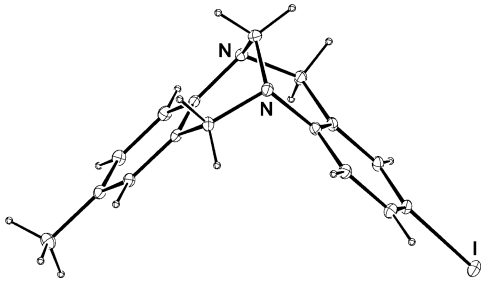


Figure 5. ORTEP diagram of **12** with 10% probability ellipsoids.

Compounds **12** and **13** may be regarded as analogues of **19** in the sense that they are mono-iodo compounds with the iodo group in the 2- (or 8-)position; however, by using this approach the compounds bearing methyl or methoxy groups in the 8- (or 2-)positions are available in higher yields than those in which the second aryl ring lacks a substituent. As was the case with compound **11**, at least part of the reason for the poor yield of **19** is the loss of hybrid material due to co-elution with other (non-Tröger's base) compounds with similar R_f values. A more efficient route to **19** involves iodination of unsubstituted Tröger's base, which reportedly affords the hybrid in 43% yield over two steps.[38]

In terms of the position of halogen atoms, compounds **14** and **18** may be regarded as equivalent to one another as they are both essentially "2-bromo-8-iodo Tröger's base", which is available in 29% yield from a three-step process (that also requires three chromatographic separation steps).[38] As stated above, the R_f values of 2,8-dibromo and 2,8-diiodo Tröger's base are similar to one another in a variety of solvents, and this rendered the attempted isolation of 2-bromo-8-iodo Tröger's base unsuccessful by using the mixed condensation strategy outlined here. However, from the examination of Table 2 it is apparent that this problem was readily overcome by incorporating a methyl group at the 2-position of either 4-bromoaniline or 4-iodoaniline, as the symmetric Tröger's base analogues produced in hybrid-forming reactions exhibit markedly different R_f values to one another.

Compound **15** (Figure 6) is an isomer of **14**, in which the bromo group is in the 4-position, rather than the 2-position. Compounds **16** and **17** are trihalo-substituted analogues.

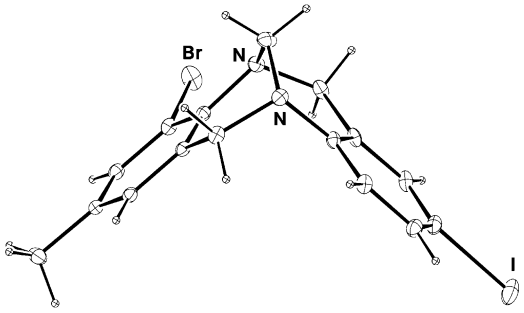


Figure 6. ORTEP diagram of **15** with 10% probability ellipsoids.

All X-ray structures obtained in this work contained equal numbers of both enantiomers in the unit cell, which is not surprising as the crystals were grown from racemic solutions.

Conclusions

We have shown that hybrid Tröger's base compounds can be obtained in reasonable yields in a single step from a reaction involving two anilines, negating the need for multistep syntheses. The reaction works well provided that the two homo-coupled compounds have significantly different R_f values. This criterion can be easily assessed qualitatively by comparing the R_f values of the corresponding symmetric Tröger's base compounds by TLC analysis. There are clearly many other substituted anilines that could be used; however, the results detailed here provide a sample of the substitution type and patterns that are possible by using this one-step approach to hybrids. The synthesis of Tröger's base analogues bearing different halogens presents the opportunity to capitalise on their different reactivities in subsequent transformations, and these studies are being actively pursued in our laboratory.

Experimental Section

General: All starting materials were commercially available and were used without further purification or were obtained according to literature procedures. All solvents were distilled prior to use, with the exception of trifluoroacetic acid. NMR spectra were measured with a Bruker 400 MHz spectrometer and referenced to residual protio peaks ($CHCl_3$: δ = 7.26 ppm for ^1H and δ = 77.0 ppm for ^{13}C).

General Procedure for the Synthesis of Hybrids: The two anilines (5.8 mmol of each) and paraformaldehyde (558 mg, 18.6 mmol, 1.6 equiv. with respect to the total mmol amount of the anilines) were dissolved in trifluoroacetic acid (25 mL), and the mixture was stirred under argon in the dark for 60 h. The reaction mixture was then basified with a solution of concentrated ammonia (30 mL) in water (60 mL), followed by the addition of a saturated sodium hydrogen carbonate solution (100 mL) and extracted into dichloromethane (3 × 75 mL). 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 chromatographed (silica gel) to afford the desired hybrid as one of three Tröger's base products.

2-Bromo-8-methyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (2): With 4-bromoaniline (1.0 g, 5.8 mmol), *p*-toluidine (0.62 g, 5.8 mmol) and paraformaldehyde (558 mg, 18.6 mmol), chromatography (silica gel; ethyl acetate/dichloromethane, 1:9) afforded (±)-**2** (647 mg, 35%) as a pale yellow solid; m.p. 118–120 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.20 (s, 3 H, CH_3), 4.05–4.15 (m, 2 H, CH_2), 4.22–4.33 (m, 2 H, CH_2), 4.63 (d, J = 16.8 Hz, 1 H, CH_2), 4.65 (d, J = 16.6 Hz, 1 H, CH_2), 6.70–6.72 (m, 1 H, ArH), 6.96–7.05 (m, 4 H, ArH), 7.25 (dd, J = 2.3, 8.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.8, 58.3, 58.7, 66.8, 116.5, 124.7, 126.7, 127.1, 127.2, 128.4, 129.7, 130.0, 130.4, 133.8, 144.9, 147.1 ppm. HRMS: calcd. for $C_{16}H_{15}BrN_2$ [M + H]$^+$ 315.049138; found 315.049497. $C_{16}H_{15}BrN_2$ (315.21): calcd. C 60.97, H 4.80, N 8.89; found C 61.10, H 4.85, N 8.91. Crystals suitable for X-ray diffraction were obtained by recrystallisation from dichloromethane.

2-Bromo-8-decyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (3): With 4-bromoaniline (1.0 g, 5.8 mmol), 4-decylaniline (1.35 g, 5.8 mmol) and paraformaldehyde (557 mg, 18.56 mmol), chromatography (silica gel; ethyl acetate/dichloromethane, 1:9) afforded (±)-**3** (300 mg, 13%) as a pale yellow solid; m.p. 44–46 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.85–0.90 (m, 3 H, CH_3), 1.22–1.31 (m, 14 H, CH_2), 1.48–1.58 (m, 2 H, CH_2), 2.43–2.50 (m, 2 H, CH_2), 4.03–4.13 (m, 2 H, CH_2), 4.22–4.34 (m, 2 H, CH_2), 4.61–4.70 (m, 2 H, CH_2), 6.69–6.73 (m, 1 H, ArH), 6.96–7.06 (m, 4 H, ArH), 7.26 (dd, J = 2.3, 8.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.1, 22.7, 29.3, 29.4, 29.5, 29.6, 29.7, 31.5, 31.9, 35.4, 58.2, 58.7, 66.8, 116.5, 120.8, 124.7, 126.5, 126.7, 127.0, 127.7, 129.7, 130.0, 130.4, 139.1, 147.1 ppm. HRMS:

calcd. for $C_{25}H_{33}BrN_2$ [M + Na]$^+$ 463.171933; found 463.172469. $C_{25}H_{33}BrN_2$ (441.45): calcd. C 68.02, H 7.53, N 6.35; found C 68.46, H 7.60, N 6.33.

2-Bromo-8-phenyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (4): With 4-bromoaniline (1.00 g, 5.8 mmol), 4-aminobiphenyl (0.98 g, 5.8) and paraformaldehyde (560 mg, 18.6 mmol), chromatography (silica gel; ethyl acetate/dichloromethane, 1:9) afforded (±)-**4** (158 mg, 7%) as a pale yellow solid; m.p. 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.15–4.23 (m, 2 H, CH_2), 4.28–4.38 (m, 2 H, CH_2), 4.69 (d, J = 16.8 Hz, 1 H, CH_2), 4.75 (d, J = 16.7 Hz, 1 H, CH_2), 7.04 (d, J = 8.6 Hz, 1 H, ArH), 7.06–7.08 (m, 1 H, ArH), 7.11–7.13 (m, 1 H, ArH), 7.19 (d, J = 8.3 Hz, 1 H, ArH), 7.25–7.33 (m, 2 H, ArH), 7.36–7.42 (m, 3 H, ArH), 7.46–7.50 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 58.8, 59.2, 67.2, 117.1, 125.8, 125.9, 126.8, 127.2, 127.3, 127.5, 128.2, 129.1, 130.2, 130.4, 130.9, 137.7, 141.0, 147.3, 147.5 ppm. HRMS: calcd. for $C_{21}H_{17}BrN_2$ [M + H]$^+$ 377.064788, found 377.064504. $C_{21}H_{17}BrN_2$ (377.28): calcd. C 66.85, H 4.54, N 7.43; found C 66.62, H 4.53, N 7.35. Crystals suitable for X-ray diffraction were obtained by recrystallisation from dichloromethane.

2-Bromo-8-methoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (5): With 4-bromoaniline (5.00 g, 29.1 mmol), *p*-anisidine (2.58 g, 29.1 mmol) and paraformaldehyde (2.79 g, 93.1 mmol), chromatography (silica gel; ethyl acetate/dichloromethane, 1:9) afforded (±)-**5** (2.18 g, 23%) as a pale orange solid; m.p. 114–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.71 (s, 3 H, OCH_3), 4.07 (d, J = 16.6 Hz, 1 H, CH_2), 4.10 (d, J = 16.6 Hz, 1 H, CH_2), 4.21–4.32 (m, 2 H, CH_2), 4.57–4.68 (m, 2 H, CH_2), 6.42 (d, J = 2.8 Hz, 1 H, ArH), 6.75 (dd, J = 2.8, 8.7 Hz, 1 H, ArH), 7.00–7.06 (m, 3 H, ArH), 7.26 (dd, J = 2.3, 8.7 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 55.3, 58.3, 58.9, 66.9, 110.8, 114.1, 116.5, 125.9, 126.7, 128.2, 129.7, 130.0, 130.3, 140.4, 147.1, 156.1 ppm. HRMS: calcd. for $C_{16}H_{15}BrN_2O$ [M + Na]$^+$ 353.025997; found 353.026771. $C_{16}H_{15}BrN_2O$ (331.21): calcd. C 58.02, H 4.56, N 8.46; found C 57.85, H 4.50, N 8.43.

8-Acetamido-2-bromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (6): With 4-bromoaniline (1.0 g, 5.8 mmol), 4-aminoacetanilide (0.87 g, 5.8 mmol) and paraformaldehyde (558 mg, 18.59 mmol), chromatography (silica gel; ethanol/dichloromethane, 1:9) afforded (±)-**6** (680 mg, 33%) as a pale yellow solid; m.p. 132–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.10 (s, 3 H, CH_3), 4.04–4.12 (m, 2 H, CH_2), 4.19–4.29 (m, 2 H, CH_2), 4.58–4.66 (m, 2 H, CH_2), 6.99 (d, J = 8.6 Hz, 1 H, ArH), 7.02–7.06 (m, 2 H, ArH), 7.10 (dd, J = 2.2, 8.6 Hz, 1 H, ArH), 7.21–7.25 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 24.4, 58.3, 58.7, 66.7, 116.5, 118.4, 119.6, 125.3, 126.7, 128.1, 129.6, 129.8, 130.4, 133.9, 143.9, 147.0, 168.2 ppm. HRMS: calcd. for $C_{17}H_{16}BrN_3O$ [M + Na]$^+$ 380.036896; found 380.035812. $C_{17}H_{16}BrN_3O$ (358.23): calcd. C 57.00, H 4.50, N 11.73; found C 56.57, H 4.70, N 11.83.

2-Bromo-8-(2′,2′-dimethylpropionamido)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7): With *N*-(4-aminophenyl)pivalamide (8.35 g, 43.44 mmol), 4-bromoaniline (7.47 g, 43.44 mmol) and paraformaldehyde (4.17 g, 139 mmol), chromatography (silica gel, ethyl acetate) afforded (±)-**7** (5.90 g, 33%) as a white solid; m.p. 190–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.26 [s, 9 H, $C(CH_3)_3$], 4.06–4.14 (m, 2 H, CH_2), 4.22–4.24 (m, 2 H, CH_2), 4.62 (d, J = 16.7 Hz, 1 H, CH_2), 4.65 (d, J = 16.7 Hz, 1 H, CH_2), 7.00 (d, J = 8.6 Hz, 1 H, ArH), 7.03 (d, J = 2.3 Hz, 1 H, ArH), 7.07 (d, J = 8.6 Hz, 1 H, ArH), 7.13 (dd, J = 2.3, 8.6 Hz, 1 H, ArH), 7.17–7.21 (br. s, 1 H, NH), 7.25 (dd, J = 2.3, 8.6 Hz, 1 H, ArH), 7.33 (d, J = 2.3 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.5, 39.4, 58.8, 58.7, 66.8, 116.7, 118.4, 119.6, 125.2, 126.7, 128.0, 129.7, 130.5, 134.2, 146.8, 176.5 ppm. HRMS: calcd. for $C_{20}H_{22}BrN_3O$ [M + H]$^+$ 400.101901; found 400.100561. $C_{20}H_{22}BrN_3O$ (400.31): calcd. C 60.01, H 5.54, N 10.50; found C 59.78, H 5.64, N 10.47. Crystals suitable for X-ray diffraction were obtained by recrystallisation from dichloromethane.

2,8-Dibromo-4-chloro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (8): With 4-bromoaniline (505 mg, 2.9 mmol), 4-bromo-2-chloroaniline (605 mg, 2.9 mmol) and paraformaldehyde (560 mg, 18.6 mmol), chromatography (silica gel; dichloromethane) afforded (±)-**8** (298 mg, 25%) as a white solid; m.p. 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.10 (d, J = 16.8 Hz, 1 H, CH_2), 4.20–4.32 (m, 3 H, CH_2), 4.55 (d, J = 17.4 Hz, 1 H, CH_2), 4.61 (d, J = 16.8 Hz, 1 H, CH_2), 6.97–7.01 (m, 2 H, ArH), 7.08 (d, J = 2.3 Hz, 1 H, ArH), 7.27 (dd, J = 2.3, 8.6 Hz, 1 H, ArH), 7.39 (d, J = 2.3 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 54.3, 58.2, 66.9, 116.8, 117.0, 126.7, 128.3, 129.8, 129.9, 130.1, 130.6, 131.0, 131.6, 142.8, 146.2 ppm. HRMS: calcd. for $C_{15}H_{11}Br_2ClN_2$ [M + H]$^+$ 412.905028; found 412.906131. $C_{15}H_{11}Br_2ClN_2$ (414.52): calcd. C 43.46, H 2.67, N 6.76; found C 43.57, H 2.70, N 6.96.

4-Bromo-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (9): With 2-bromo-4-methylaniline (1.00 g, 5.37 mmol), *p*-toluidine (0.58 g, 5.37 mmol) and paraformaldehyde (516 mg, 17.2 mmol), chromatography (silica gel; ethyl acetate/dichloromethane, 1:9) afforded (±)-**9** (618 mg, 35%) as an off-white solid; m.p. 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.20 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 4.11 (d, J = 16.7 Hz, 1 H, CH_2), 4.27–4.39 (m, 3 H, CH_2), 4.56 (d, J = 17.2 Hz, 1 H, CH_2), 4.62 (d, J = 16.7 Hz, 1 H, CH_2), 6.66–6.69 (m, 1 H, ArH), 6.75–6.78 (m, 1 H, ArH), 6.96–7.00 (m, 1 H, ArH), 7.04 (d, J = 8.2 Hz, 1 H, ArH), 7.24–7.26 (m, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.5, 20.9, 55.2, 58.8, 67.4, 119.5, 124.7, 126.7, 127.3, 127.6, 128.2, 130.2, 132.0, 133.8, 135.1, 142.4, 144.8 ppm. HRMS: calcd. for $C_{17}H_{17}BrN_2$ [M + Na]$^+$ 351.046732; found 351.046953. $C_{17}H_{17}BrN_2$ (329.23): calcd. C 62.02, H 5.20, N 8.51; found C 62.25, H 5.25, N 8.50.

2,4-Dibromo-8-methyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (10): With 2,4-dibromoaniline (1.00 g, 3.99 mmol), *p*-toluidine (0.43 g, 3.99 mmol) and paraformaldehyde (383 mg, 12.8 mmol), chromatography (silica gel; dichloromethane) afforded (±)-**10** (641 mg, 41%) as an off-white powder; m.p. 156–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.24 (s, 3 H, CH_3), 4.12 (d, J = 16.9 Hz, 1 H, CH_2), 4.22–4.38 (m, 3 H, CH_2), 4.53–4.64 (m, 2 H, CH_2), 6.74–6.76 (m, 1 H, ArH), 6.89–7.03 (m, 3 H, ArH), 7.56 (d, J = 2.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.8, 55.0, 58.5, 67.2, 117.0, 120.5, 124.7, 127.2, 127.3, 128.4, 129.0, 132.4, 133.7, 134.0, 144.4, 144.5 ppm. HRMS: calcd. for $C_{16}H_{14}Br_2N_2$ [M + Na]$^+$ 414.941560; found 414.941595. $C_{16}H_{14}Br_2N_2$ (394.10): calcd. C 48.76, H 3.58, N 7.11; found C 48.74, H 3.65, N 6.95.

2-Bromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (11): With 4-bromoaniline (860 mg, 5.0 mmol), aniline (465 mg, 5.0 mmol) and paraformaldehyde (480 mg, 16 mmol), chromatography (silica gel; ethyl acetate/dichloromethane, 1:19 then 1:9) afforded (±)-**11** (217 mg, 14%) as white solid; m.p. 123–124 °C (ref.[38] 119–121 °C; ref.[46] 123.5–125 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.12 (d, J = 16.5 Hz, 1 H, CH_2), 4.16 (d, J = 16.5 Hz, 1 H, CH_2), 4.23–4.35 (m, 2 H, CH_2), 4.62–4.73 (m, 2 H, CH_2), 6.88–6.92 (m, 1 H, ArH), 6.96–7.01 (m, 1 H, ArH), 7.00 (d, J = 8.6 Hz, 1 H, ArH), 7.04 (d, J = 2.2 Hz, 1 H, ArH), 7.09–7.13 (m, 1 H, ArH), 7.14–7.20 (m, 1 H, ArH), 7.25 (dd, J = 2.2, 8.6 Hz, 1 H, ArH) ppm. ^{13}C

NMR (100 MHz, $CDCl_3$, 25 °C): δ = 58.4, 58.7, 66.7, 116.6, 124.2, 125.1, 126.8, 127.0, 127.6, 129.7, 130.1, 130.4, 147.2, 147.7 ppm.

2-Iodo-8-methyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (12): With 4-iodoaniline (410 mg, 1.9 mmol), *p*-toluidine (200 mg, 1.9 mmol) and paraformaldehyde (180 mg, 6.0 mmol), chromatography (silica gel; ethyl acetate/dichloromethane, 1:9) afforded (±)-**12** (204 mg, 31%) as a white solid; m.p. 171–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.22 (s, 3 H, CH_3), 4.08 (d, J = 16.6 Hz, 1 H, CH_2), 4.10 (d, J = 16.4 Hz, 1 H, CH_2), 4.21–4.32 (m, 2 H, CH_2), 4.61 (d, J = 16.6 Hz, 1 H, CH_2), 4.65 (d, J = 16.4 Hz, 1 H, CH_2), 6.66–6.72 (m, 1 H, ArH), 6.88 (d, J = 8.5 Hz, 1 H, ArH), 6.97 (dd, J = 1.6, 8.2 Hz, 1 H, ArH), 7.01 (d, J = 8.2 Hz, 1 H, ArH), 7.23 (d, J = 2.0 Hz, 1 H, ArH), 7.44 (dd, J = 2.0, 8.5 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.8, 58.1, 58.7, 66.8, 87.3, 124.8, 126.7, 127.0, 127.1, 127.2, 128.4, 130.6, 133.7, 135.8, 136.2, 145.0 ppm. $C_{16}H_{15}IN_2$ (362.21): calcd. C 53.06, H 4.17, N 7.73; found C 53.08, H 3.84, N 7.73. Crystals suitable for X-ray diffraction were obtained by recrystallisation from dichloromethane.

2-Iodo-8-methoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (13): With 4-iodoaniline (410 mg, 1.9 mmol), *p*-anisidine (230 mg, 1.9 mmol) and paraformaldehyde (180 mg, 6.0 mmol), chromatography (silica gel; ethyl acetate/dichloromethane, 1:9) afforded (±)-**13** (315 mg, 46%) as a pale brown solid; m.p. 133–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.71 (s, 3 H, OCH_3), 4.06 (d, J = 16.5 Hz, 1 H, CH_2), 4.10 (d, J = 16.5 Hz, 1 H, CH_2), 4.23 (d, J = 12.6 Hz, 1 H, CH_2), 4.29 (d, J = 12.6 Hz, 1 H, CH_2), 4.60 (d, J = 16.5 Hz, 1 H, CH_2), 4.66 (d, J = 16.5 Hz, 1 H, CH_2), 6.42 (d, J = 2.9 Hz, 1 H, ArH), 6.74 (dd, J = 2.9, 8.8 Hz, 1 H, ArH), 6.88 (d, J = 8.5 Hz, 1 H, ArH), 7.04 (d, J = 8.8 Hz, 1 H, ArH), 7.23 (d, J = 2.1 Hz, 1 H, ArH), 7.44 (dd, J = 2.1, 8.5 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 55.4, 58.1, 58.9, 66.9, 87.4, 110.9, 114.1, 125.9, 127.0, 128.2, 130.5, 135.8, 136.2, 140.5, 148.0, 156.2 ppm. $C_{16}H_{15}IN_2O$ (378.21): calcd. C 50.81, H 4.00, N 7.41; found C 50.80, H 4.17, N 7.13.

2-Bromo-8-iodo-4-methyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (14): With 4-iodoaniline (410 mg, 1.87 mmol), 4-bromo-2-methylaniline (347 mg, 1.87 mmol) and paraformaldehyde (180 mg, 5.98 mmol), chromatography (silica gel; dichloromethane) afforded (±)-**14** (347 mg, 42%) as a pale yellow solid; m.p. 149–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.35 (s, 3 H, CH_3), 3.89 (d, J = 16.9 Hz, 1 H, CH_2), 4.08 (d, J = 16.9 Hz, 1 H, CH_2), 4.21–4.28 (m, 2 H, CH_2), 4.51 (d, J = 16.9 Hz, 1 H, CH_2), 4.61 (d, J = 16.9 Hz, 1 H, CH_2), 6.85–6.90 (m, 2 H, ArH), 7.16–7.18 (m, 1 H, ArH), 7.22–7.25 (m, 1 H, ArH), 7.45 (dd, J = 2.0, 8.4 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.8, 54.3, 58.4, 66.9, 87.6, 116.8, 127.07, 127.11, 129.6, 130.5, 131.9, 135.3, 135.7, 136.2, 144.6, 147.7 ppm. $C_{16}H_{14}BrIN_2$ (441.10): calcd. C 43.57, H 3.20, N 6.35; found C 43.38, H 2.86, N 6.19.

4-Bromo-8-iodo-2-methyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (15): With 4-iodoaniline (410 mg, 1.87 mmol), 2-bromo-4-methylaniline (348 mg, 1.87 mmol) and paraformaldehyde (183 mg, 5.98 mmol), chromatography (silica gel; dichloromethane) afforded (±)-**15** (348 mg, 42%) as an off-white solid; m.p. 176–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.21 (s, 3 H, CH_3), 4.08 (d, J = 16.8 Hz, 1 H, CH_2), 4.24–4.34 (m, 3 H, CH_2), 4.53 (d, J = 17.4 Hz, 1 H, CH_2), 4.61 (d, J = 16.8 Hz, 1 H, CH_2), 6.66–6.72 (m, 1 H, ArH), 6.89 (d, J = 8.5 Hz, 1 H, ArH), 7.27–7.31 (m, 2 H, ArH), 7.45 (dd, J = 2.0, 8.5 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.5, 54.6, 58.8, 67.2, 87.6, 119.5, 126.6, 127.0, 129.9, 130.6, 132.2, 135.4, 135.9, 136.3, 142.0, 147.5 ppm. $C_{16}H_{14}BrIN_2$ (441.10): calcd. C 43.57, H 3.20, N 6.35; found C 43.82, H 2.83, N 6.18. Crystals suitable for X-ray diffraction were obtained by recrystallisation from dichloromethane.

2-Bromo-4-chloro-8-iodo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (16): With 4-bromo-2-chloroaniline (389 mg, 1.87 mmol), 4-iodoaniline (410 mg, 1.87 mmol) and paraformaldehyde (189 mg, 6.30 mmol), chromatography (silica gel; dichloromethane) afforded (±)-**16** (168 mg, 20%) as a pale yellow solid; m.p. 142–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.10 (d, J = 16.9 Hz, 1 H, CH_2), 4.21–4.33 (m, 3 H, CH_2), 4.52 (d, J = 17.2 Hz, 1 H, CH_2), 4.62 (d, J = 16.9 Hz, 1 H, CH_2), 6.88 (d, J = 8.5 Hz, 1 H, ArH), 6.99 (d, J = 2.2 Hz, 1 H, ArH), 7.28 (d, J = 2.2 Hz, 1 H, ArH), 7.40 (d, J = 2.2 Hz, 1 H, ArH), 7.47 (dd, J = 2.2, 8.5 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 54.2, 58.3, 67.0, 87.9, 116.9, 127.0, 128.3, 130.1, 130.2, 131.0, 131.6, 135.8, 136.5, 142.8, 147.1 ppm. $C_{15}H_{11}BrClIN_2$ (461.52): calcd. C 39.04, H 2.40, N 6.07; found C 39.25, H 2.23, N 5.85.

2,4-Dibromo-8-iodo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (17): With 4-iodoaniline (410 mg, 1.87 mmol) 2,4-dibromoaniline (474 mg, 1.87 mmol) and paraformaldehyde (180 mg, 5.98 mmol), chromatography (silica gel; dichloromethane) afforded (±)-**17** (192 mg, 20%) as a pale yellow solid; m.p. 162–163 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.09 (d, J = 16.9 Hz, 1 H, CH_2), 4.22 (d, J = 12.8 Hz, 1 H, CH_2), 4.28 (d, J = 17.4 Hz, 1 H, CH_2), 4.30 (d, J = 12.8 Hz, 1 H, CH_2), 4.53 (d, J = 17.4 Hz, 1 H, CH_2), 4.61 (d, J = 16.9 Hz, 1 H, CH_2), 6.88 (d, J = 8.5 Hz, 1 H, ArH), 7.02 (d, J = 2.2 Hz, 1 H, ArH), 7.28 (d, J = 2.0 Hz, 1 H, ArH), 7.46 (dd, J = 2.0, 8.5 Hz, 1 H, ArH), 7.58 (d, J = 2.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 54.5, 58.5, 66.9, 87.9, 117.3, 120.6, 127.0, 129.0, 130.2, 132.0, 134.0, 135.8, 136.5, 144.0, 147.1 ppm. $C_{15}H_{11}Br_2IN_2$ (505.97): calcd. C 35.61, H 2.19, N 5.54; found C 35.77, H 1.97, N 5.35.

8-Bromo-2-iodo-4-methyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (18): With 4-bromoaniline (323 mg, 1.88 mmol), 4-iodo-2-methylaniline (438 mg, 1.88 mmol) and paraformaldehyde (216 mg, 7.2 mmol), chromatography (silica gel; dichloromethane) afforded (±)-**18** (281 mg, 34%) as an off-white solid; m.p. 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.32 (s, 3 H, CH_3), 3.90 (d, J = 16.9 Hz, 1 H, CH_2), 4.06 (d, J = 16.9 Hz, 1 H, CH_2), 4.22 (d, J = 17.7 Hz, 1 H, CH_2), 4.25 (d, J = 17.7 Hz, 1 H, CH_2), 4.51 (d, J = 16.9 Hz, 1 H, CH_2), 4.60 (d, J = 16.9 Hz, 1 H, CH_2), 6.99 (d, J = 8.4 Hz, 1 H, ArH), 7.05 (d, J = 2.3 Hz, 1 H, ArH), 7.07–7.09 (m, 1 H, ArH), 7.27 (dd, J = 2.3, 8.4 Hz, 1 H, ArH), 7.36–7.39 (m, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.7, 54.5, 58.1, 66.9, 88.0, 116.8, 126.8, 129.7, 130.0, 130.5, 133.2, 135.5, 137.9, 147.0 ppm. $C_{16}H_{14}BrIN_2$ (441.10): calcd. C 43.57, H 3.20, N 6.35; found C 43.94, H 2.95, N 6.01.

2-Iodo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (19): With 4-iodoaniline (1.09 g, 5.0 mmol), aniline (465 mg, 5.0 mmol) and paraformaldehyde (480 mg, 16 mmol), chromatography (silica gel; dichloromethane/ethyl acetate, 50:1) afforded (±)-**19** (268 mg, 16%) as a white solid; m.p. 124–125 °C (ref.[38] 121–123 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.12 (d, J = 16.7 Hz, 1 H, CH_2), 4.14 (d, J = 16.7 Hz, 1 H, CH_2), 4.23–4.34 (m, 2 H, CH_2), 4.64 (d, J = 16.7 Hz, 1 H, CH_2), 4.68 (d, J = 16.7 Hz, 1 H, CH_2), 6.89 (d, J = 8.5 Hz, 1 H, ArH), 6.90 (d, J = 7.6 Hz, 1 H, ArH), 6.96–7.01 (m, 1 H, ArH), 7.11 (d, J = 7.9 Hz, 1 H, ArH), 7.14–7.20 (m, 1 H, ArH), 7.22–7.25 (m, 1 H, ArH), 7.44 (dd, J = 2.0, 8.5 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 58.2, 58.7, 66.7, 87.4, 124.2, 125.1, 127.0, 127.1, 127.6, 130.6, 135.7, 136.3, 147.7, 148.0 ppm.

CCDC-713412 (for **2**), -713413 (for **4**), -713414 (for **7**), -713415 (for **12**) and -713416 (for **15**), contain the supplementary crystallo-

graphic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): ^{1}H NMR spectra for compounds **2**–**19**.

Acknowledgments

We thank the Australian Research Council for a Discovery Project grant to A. C. T. (DP0345180) and Macquarie University for research support.

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Received: February 4, 2009
Published Online: July 16, 2009

