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Synthesis of Symmetric Diester-Functionalised Tröger's Base Analogues

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The yields of ester-functionalised Tröger's base analogues are dramatically improved by incorporating an electron-donating group on the aromatic ring and/or enhancing solubility of the aniline unit. In addition to 2,8-diester compounds, 1,7-, 3,9- and 4,10-diester-functionalised Tröger's base analogues have been prepared for the first time.

Introduction

Tröger's base **1** is a C_2-symmetric chiral diamine that was first prepared in 1887 from the acid-catalysed reaction of *p*-toluidine and formaldehyde (Figure 1).[1] Compounds based on this framework are of interest because of their potential to function as artificial receptors[2–9] and catalysts in asymmetric transformations.[10,11]

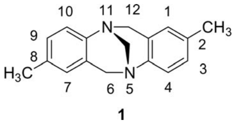

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Figure 1. Chemical structure of Tröger's base **1** and the conventional numbering system.

The syntheses of a large number of Tröger's base analogues have been reported from anilines with different substituents, however the yields are generally poor when the aniline is substituted with an electron-withdrawing group and this has greatly restricted the type of available functionality. In fact, for over 100 years it was widely believed that various analogues of Tröger's base could not be made. Wärnmark and co-workers were the first to bring this belief into question with the synthesis of a range of halogen-substituted Tröger's base compounds from halogen-substituted anilines in very good yields.[12–14] Interestingly, the synthesis of a 2,8-difluoro compound in 5–10% yield and the successful use of 3-chloro-4-methylaniline in the preparation of Tröger's bases was reported in the early 1960s, although the resulting mixture of isomers was unable to be separated at the time.[15] More recently the syntheses of tetrabromo[16] and octafluoro[17] analogues of Tröger's base in 60% and 37% yield, respectively, have been reported.

In addition to halogenated analogues becoming accessible from haloanilines, a wide range of dinitro-substituted Tröger's base analogues were recently reported from a variety of nitroanilines[18] and a tetranitro Tröger's base has also been prepared.[19]

In contrast, examples of diester-functionalised analogues, where the carbonyl group of the ester is directly attached to the benzene ring, are scarce. Only three ester-substituted anilines have been converted into Tröger's base compounds, and all bear the esters at the 2,8-positions.[9,20–23] One of these reactions involved the synthesis of a highly substituted Tröger's base (dimethyl 4,10-dichloro-1,7-dimethoxy-2,8-dicarboxylate) in 16% yield via a stepwise procedure that employed harsh reaction conditions (DMSO, 185–195 °C, 9 h).[20] A 2,8-diethyl ester Tröger's base analogue was prepared on a small scale ($<$ 200 mg) in 37% yield from the reaction of ethyl 4-aminobenzoate with DMSO and hydrogen chloride.[21] In addition to anilines, methyl and benzyl ester functionalised *N*-methylpyrroles have also been used to prepare heterocyclic analogues of Tröger's base.[24]

Given the synthetic utility of esters, we were interested in obtaining ester-functionalised analogues of Tröger's base in higher yields and also in preparing compounds with the esters located in a variety of positions on the Tröger's base framework. It is noteworthy that reported attempts to prepare Tröger's base analogues from methyl 2-amino-5-methylbenzoate and methyl 5-amino-2-methylbenzoate were unsuccessful.[25]

Results and Discussion

There are four possible arrangements of symmetrically disubstituted Tröger's base derivatives, as depicted for diester analogues in Figure 2. These different substitution patterns have been classified into groupings of Type I–IV,

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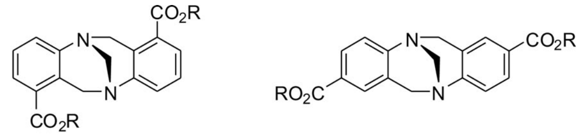
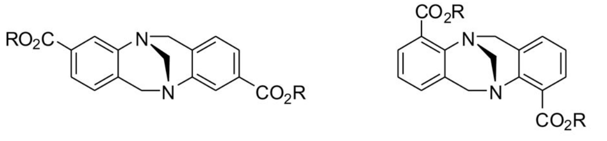
primarily for ease of discussion and they are expected to possess different electronic properties and afford different architectures when used as supramolecular building blocks.

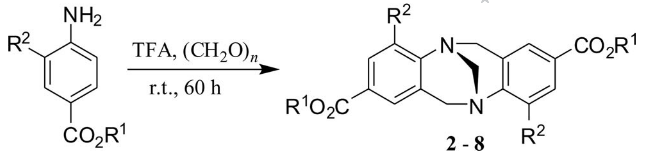


Type I (1,7-disubstituted) Type II (2,8-disubstituted)



Type III (3,9-disubstituted) Type IV (4,10-disubstituted)

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



Scheme 1. Synthesis of Type II compounds with various substituents.

Table 1. Yields of the Tröger's base 2,8-diesters **2**–**8**.

	R^1	R^2	Yield (%)[a]
2	CH_3	H	23
3	CH_2CH_3	H	31
4	CH_2CH_3	CH_3	71
5	CH_2CH_3	OCH_3	76
6	CH_2CH_3	Br	48
7	$CH_2(CH_2)_4CH_3$	H	84
8	$CH_2(CH_2)_4CH_3$	Br	88

[a] Isolated yields after column chromatography or recrystallisation.

Type II Compounds (2,8-Diesters)

We initially investigated the preparation of 2,8-diester functionalised analogues. In our hands the preparation of the methyl ester **2** on a small scale (1 g) was reasonably successful, and a yield of 23% was obtained when employing paraformaldehyde as the formaldehyde equivalent and TFA as the acid source and as a solvent.[22] However, when the reaction was performed on a multigram scale, work-up and purification became problematic due to the poor solubility of the desired material in organic solvents, and the yields were typically 10–15%.

In an effort to improve the solubility we carried out the analogous reaction with the ethyl ester on a 30 mmol (5 g) scale, which resulted in a slight improvement in the yield of the final product **3**. In fact, Goswami et al. report the synthesis of **3** in 23% yield using HMTA as the formaldehyde equivalent and TFA as the acid and solvent.[9] Their reaction was carried out on a 100 mg scale and they were reportedly frustrated by the poor yield. Other researchers report a 74% yield of **3** using paraformaldehyde/TFA when the reaction is carried out on a 5 mmol scale ($<$ 1 g).[23]

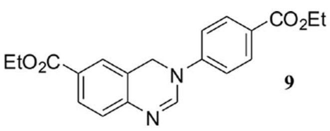
These results suggest that the poor yields of these reactions, at least when carried out on a moderate scale, may be the result of relatively poor solubility in organic solvents. We therefore sought to enhance the solubility by placing other substituents on the aryl ring. The use of electron-donating groups on the aniline was also expected to enhance their reactivity. To this end, we looked at the reaction of ethyl 4-amino-3-methylbenzoate and ethyl 4-amino-3-methoxybenzoate (Scheme 1, Table 1). In both cases the desired Tröger's base analogues **4** and **5** were produced in good yields (71% and 76%, respectively) on greater than 25 mmol scales, with reaction times of 60 h.

We next examined the reaction of ethyl 4-amino-3-bromobenzoate. Whilst the bromo group is generally regarded as a deactivating substituent, we felt that we could expect to see some improvement in the yield of the ester-functionalised Tröger's analogues, if only from improved solubility of the desired product in organic solvents. Tröger's base **6** was obtained in 48% yield, and the solubility of the desired product was greatly enhanced in comparison with compound **3** that lacks the bromo groups. Simple hydrogenolysis of **6** afforded **3** in quantitative yield. This provides a readily scalable methodology to afford 2,8-diester functionalised Tröger's base analogues and we have performed the reaction on a multigram scale.

The increased length of the ester chain from one to two carbons was found to result in an 8% increase of the yield of Tröger's base product (cf. **2** vs. **3**). This encouraged us to examine the effect of further increasing the length of the ester chain. The use of a hexyl ester in place of the simple ethyl ester led to the formation of **7** in 84% yield.

The incorporation of a bromo substituent at the 2-position of hexyl 4-aminobenzoate had a negligible effect on the yield of Tröger's base product, with **8** obtained in 88% yield. The large increase in yield that was observed in changing the length of the ester chain (cf. **3** vs. **7**), in the case of the larger scale reactions, can only be attributed to an increase in the solubility of the Tröger's base product in the organic solvents used in the work-up procedures, facilitating its isolation and purification (both ethyl and hexyl 4-aminobenzoate were readily soluble in TFA). In light of this result, it is not clear if the increased yields of compounds **4**, **5**, and to a lesser extent **6**, in relation to **3**, is the result of a change in the electron-richness of the starting aniline or an increase in the solubility of the products in organic solvents, or a combination of both.

It is noteworthy that 3,4-dihydroquinazolines were observed in the synthesis of **3**, **6** and **7**, although in the case of **7**, only when the reaction was performed on a multigram scale. The presence of such compounds is readily apparent by inspection of the ^{1}H NMR spectra of crude material obtained after work-up as the methylene protons adjacent to nitrogen resonate at ca. 5 ppm as a two-proton singlet. We have isolated and fully characterised the 3,4-dihydroquinazoline product **9** that was obtained from the reaction involving ethyl 4-aminobenzoate and we have previously reported its X-ray crystal structure.[26]



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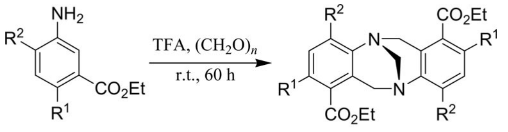
A related compound was reported in the synthesis of Tröger's base[27] and subsequently other 3,4-dihydroquinazolines have been observed in the synthesis of Tröger's base analogues.[20,28]

Type I Analogues (1,7-Diesters)

Several anilines that were capable of affording Type I Tröger's base compounds, i.e., those with esters in the 1,7-positions, were then subjected to the Tröger's base forming reaction. The most obvious manner to achieving this goal involved the use of anilines bearing a substituent at the 2-position and the ester at the 5-position, as illustrated in Scheme 2.



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

The first two anilines examined lacked a substituent at the R^1 site (*para*- to the amino group) (Table 2). Prior to the work of Wärnmark and co-workers that showed *o*-halo anilines successfully undergo the Tröger's base reaction, it was believed that the presence of a *p*-substituent on the aniline unit was essential (the highest yield of a *p*-free dihalogenated Tröger's base compound obtained by the Wärnmark group was 59 %).[14] We found that surprisingly good yields of Tröger's base products **10** and **11** were obtained, exceeding those of **2**, **3** and **6**, where a *p*-substituent was present on the starting aniline.

Table 2. Yields of the Tröger's base 1,7-diesters **10**–**13**.

	R^1	R^2	Yield (%)[a]
10	H	CH_3	52
11	H	OCH_3	61
12	CH_3	H	41
13	H	H	34

[a] Isolated yields after column chromatography or recrystallisation.

The reactivity of two anilines bearing two inequivalent sites *ortho* to the amino group were then studied (i.e., R^2 = H in Scheme 2). Anilines with this substitution pattern may be regarded as "ambiguous" anilines as they could give rise to three possible Tröger's base products as depicted in Figure 3. In fact, on the previous occasions that anilines of this type have been subjected to a Tröger's base forming reaction, at least two of the three possible isomers have been observed[25] and in the case of 3-haloanilines all three isomers were generally isolated.[14] In contrast, Type I products were formed exclusively from several 3-nitroanilines with two unsubstituted positions *ortho* to the amino group, and two 3-nitroanilines afforded both Type I and hybrid products.[18]

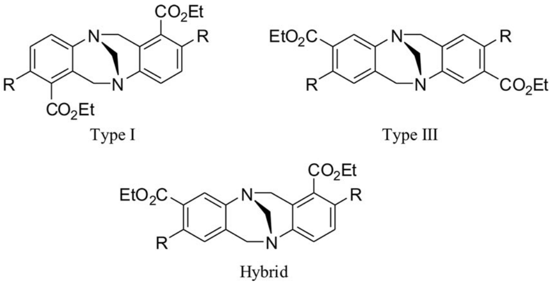


Figure 3. Three Tröger's base products that could be made from aminobenzoates with two inequivalent unsubstituted sites *ortho* to the amino group.

Both ethyl 5-amino-2-methylbenzoate and ethyl 3-aminobenzoate afforded single Tröger's base isomers **12** and **13**, respectively, as evident from examination of ^{1}H NMR spectra of the reaction mixtures after work-up and prior to chromatography. The number of signals in the ^{1}H NMR spectra established that the Tröger's base product was symmetric and the magnitude of the coupling constants for the signals of the aryl protons were sufficient to enable the assignment of compounds as Type I compounds.

This observation was somewhat unexpected as formaldehyde has reacted at the more hindered of the two sites *ortho* to the amino group at the exclusion of the less hindered site. A model is proposed in Figure 4 to rationalise the observed regioselectivity. It is possible that the ester group serves as an anchoring point to preferentially position the incoming protonated formaldehyde molecule in the proximity of the more hindered *ortho* site for an electrophilic substitution reaction. A similar model may be proposed for 3-nitroanilines to account for their analogous behaviour, with the nitro group functioning in a similar manner to the carbonyl group depicted below.

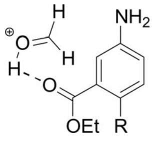


Figure 4. Proposed interaction between a protonated formaldehyde molecule and the ester functionality.

It is noteworthy that an earlier attempt to form the methyl ester analogue of **12** was unsuccessful and no Tröger's base product was obtained.[25]

The structure of compounds **12** (Figure 5) and **13**[29] were subsequently confirmed by X-ray crystallography. The two aryl rings of all Tröger's base analogues are offset with respect to one another by virtue of the methano-strapped diazocine bridge and they generally subtend a dihedral angle of approximately 90°. The dihedral angle has been found to vary between 82°[30] and 110°[31] for simple dibenzo Tröger's base analogues and is dependant upon the nature of the substituents. In the present case, the dihedral angle of **12** was measured as 88.6°, smaller than the values of 96.5°, 98.2° and 93.2° previously reported for **2**,[22] **6**[32] and **13**,[29] respectively.

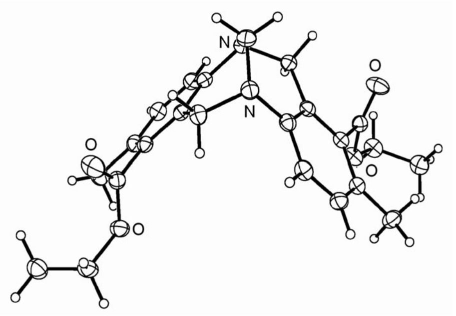
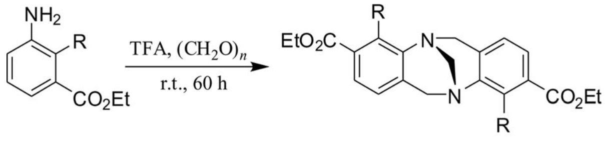


Figure 5. An ORTEP diagram of **12** with 50% probability ellipsoids.

Type III & IV Analogues (3,9- and 4,10-Diesters)

Two unambiguous anilines were used to prepare examples of Type III compounds (Scheme 3), with the ester located in the 3,9-positions. In both cases the starting anilines were also devoid of a substituent at the *para* position, however the Tröger's base products **14** and **15** were obtained in good yields.

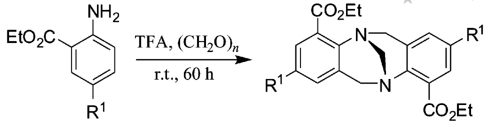


14 R = CH_3 50%
15 R = OCH_3 61%

Scheme 3. Synthesis of Type III compounds.

Two Type IV compounds **16** and **17** were prepared in relatively poor yields from 5-substituted 2-aminobenzoates (Scheme 4). As was the case with compound **12**, an unsuccessful attempt had previously been made to synthesise a dimethyl ester analogue of **16** by employing formalin, ethanol and hydrochloric acid as the reagents.[25]

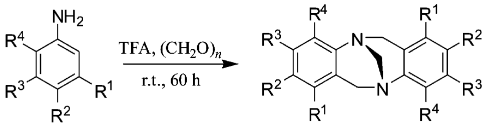
The low yields obtained for Type IV compounds may be a result of steric hindrance from the close proximity of the esters to the amino group.



16 $R^1 = CH_3$ 17%
17 $R^1 = OCH_3$ 11%

Scheme 4. Synthesis of Type IV compounds.

In light of dramatic increase in yield of **7** (hexyl ester) in comparison with **3** (ethyl ester), when the reactions were carried out on a large scale, and to a lesser extent **8** in comparison with **6**, we decided to examine the effect of this change with several other hexyl aminobenzoates. Depending upon the substituton pattern present, Type I, III and IV dihexyl ester Tröger's base analogues **18**–**26** were obtained (Scheme 5). The results are presented in Table 3.



18 - 25

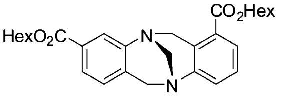
Scheme 5. Synthesis of Type I, III and IV dihexyl ester compounds.

Table 3. Yields of Type I, III and IV dihexyl Tröger's base diesters **18**–**25**.

	R^1	R^2	R^3	R^4	Yield (%)[a]
18	CO_2Hex	H	H	CH_3	68
19	CO_2Hex	H	H	OCH_3	41
20	CO_2Hex	CH_3	H	H	14
21	CO_2Hex	H	H	H	25[b]
22	H	H	CO_2Hex	CH_3	37
23	H	H	CO_2Hex	OCH_3	30
24	H	CH_3	H	CO_2Hex	16
25	H	OCH_3	H	CO_2Hex	16

[a] Isolated yields after column chromatography or recrystallisation. [b] Hybrid **26** was also isolated in 7% yield.

"Ambiguous" aminobenzoates were used in the synthesis of **20** and **21**, however, as was the case with the ethyl ester analogues **12** and **13**, respectively, no Type III compounds were observed. In the present case, the Type III compounds would be the product of a reaction with formaldehyde at the considerably less sterically hindered site *ortho* to the amino group. It is noteworthy that the use of hexyl 3-aminobenzoate resulted in at least some reactivity at this less hindered site, with the formation of hybrid **26** in 7% yield.



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Although no clear trend emerges, it is apparent that when either methyl or methoxy groups are present as substituents, no dramatic increase in yield is observed in replacing the ethyl ester with the more organic solvent soluble hexyl ester. Indeed, in several of the reactions, a decrease in yield of Tröger's base product is observed. This, in at least some cases, may be the result of steric hindrance arising from the proximity of the hexyl chain to either the amino group or a reactive site *ortho* to the amino group. In some cases (notably **20** and **24**) a loss of Tröger's base material was evident during chromatography as a result of contaminated fractions due to the presence of 3,4-dihydroquinazolines, analogous in structure to **9**, with similar R_f values.

The results are not unexpected, as the presence of hexyl ester groups improve the poor solubility exhibited by ethyl ester Tröger's base analogues otherwise lacking methyl, methoxy or bromo groups. However if these groups are present, the "extra solubility" effect is not significant, as the products formed with ethyl esters have sufficient solubility such that product loss is not observed upon work-up. Essentially, the replacement of ethyl esters with hexyl esters is not expected to have an electronic effect in terms of enhancing reactivity of the aromatic ring, and if the ethyl esters are already readily soluble in the solvents being employed, the use of hexyl esters offers no significant advantages.

Conclusions

We have shown that 2,8-diester-functionalised Tröger's base compounds can be produced in good to excellent yields, and in some instances in even higher yields than analogues bearing substituents traditionally regarded as favourable for the Tröger's base reaction. In addition, we have prepared the first examples of 1,7-, 3,9- and 4,10-diester functionalised Tröger's base analogues. We have also prepared several Tröger's base compounds from anilines lacking a substituent in the *para* position. We are currently exploring the chemistry of these compounds. We are also investigating the origin of the increased yields, in an attempt to determine the role played by the electron-donating ability of substituents on the anilines vs. enhanced solubility of the Tröger's base products. The results of these studies will be reported in due course.

Experimental Section

General: Melting points were recorded on either a Reichert melting point stage or a TA Instruments DSC 2010 Differential Scanning Calorimeter. Microanalyses were performed by the Microanalytical Unit, University of Otago, New Zealand. High resolution mass spectrometry (HRMS) was obtained at the School of Chemistry, University of New South Wales (FAB+) or at Macquarie University (ESI-MS). ^{1}H NMR spectra were recorded on a Bruker WM AMX 400 spectrometer (400 MHz) at 300 K unless otherwise stated. Signals were recorded in terms of chemical shifts and are expressed in parts per million (δ), multiplicity, coupling constants (in Hz, rounded to one decimal place) and assignments in that order. The following abbreviations for multiplicity are used: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets; br., broad; q, quartet; qn, quintet. Solvents and reagents were purified using standard techniques (see the supplementary data for the preparation of several anilines used as starting materials). All commercial solvents were routinely distilled prior to use. Hexane refers to the fraction of b.p. 60–80 °C. Where solvent mixtures are used, the portions are given by volume. Column chromatography was routinely carried out using the gravity feed column techniques on Merck silica gel type 9385 (230–400 mesh) with the stated solvent systems. Analytical thin layer chromatography (TLC) analyses were performed on precoated plates (Merck aluminium sheets, silica gel 60 F_{254}, 0.2 mm). Visualisation of compounds was achieved by illumination under ultraviolet light (254 nm).

General Method: The alkyl aminobenzoate (27.6 mmol) and paraformaldehyde (44.16 mmol) were dissolved in ice-cold trifluoroacetic acid (75 mL) and the mixture was stirred under an argon atmosphere in the dark for 60 h. The reaction mixture was then basified with an ice-cold solution of concentrated ammonia (80 mL) in water (120 mL). A saturated sodium hydrogen carbonate solution (100 mL) was added and the crude material was extracted into ethyl acetate (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 to yield an orange solid. The crude material was chromatographed (silica gel) to afford the desired Tröger's base analogue.

Type II Compounds

Dimethyl 6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine-2,8-dicarboxylate (2): With methyl 4-aminobenzoate (4.17 g, 27.59 mmol), paraformaldehyde (1.32 g, 44.16 mmol) and trifluoroacetic acid (75 mL). The crude material was chromatographed (silica gel; ethyl acetate/dichloromethane, 1:4) to afford (±)-**2** (1.08 g, 23%) as a white solid; m.p. 230–231 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.84 (s, 6 H, 2× OCH_3), 4.25 (d, J = 16.7 Hz, 2 H, CH_2), 4.32 (s, 2 H, CH_2), 4.74 (d, J = 16.7 Hz, 2 H, CH_2), 7.17 (d, J = 8.4 Hz, 2 H, ArH), 7.63 (app. s, 2 H, ArH), 7.82 (dd, J = 1.6, 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 51.7, 52.0, 58.6, 66.6, 124.9, 125.8, 127.3, 128.8, 152.2, 166.5 ppm. $C_{19}H_{18}N_2O_4$ (338.36): calcd. C 67.44, H 5.36, N 8.28; found C 67.24, H 5.32, N 8.25.

Diethyl 6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine-2,8-dicarboxylate (3) and Ethyl 3-[4-(Ethoxycarbony)phenyl]-3,4-dihydroquinazoline-6-carboxylate (9): With ethyl 4-aminobenzoate (5.00 g, 30.26 mmol), paraformaldehyde (1.46 g, 48.66 mmol) and trifluoroacetic acid (75 mL). The crude material was chromatographed (silica gel; ethyl acetate/dichloromethane, 1:9) to afford (±)-3 (1.7 g, 31%) as a white solid; m.p. 151–152 °C (ref.[9] 126–128 °C, ref.[21] 152–153 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.34 (t, J = 7.1 Hz, 6 H, 2× CH_3), 4.22–4.32 (m, 8 H, CH_2), 4.75 (d, J = 16.6 Hz, 2 H, CH_2), 7.15 (d, J = 8.4 Hz, 2 H, ArH), 7.63 (d, J = 1.9 Hz, 2 H, ArH), 7.83 (dd, J = 1.9, 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3, 58.6, 60.7, 66.6, 124.8, 126.0, 127.3, 128.7, 128.8, 152.2, 166.0 ppm. HRMS (FAB$^+$): m/z calcd. for $C_{21}H_{22}N_2O_4$ [M + Na]$^+$, 389.147170; found 389.147110. $C_{21}H_{22}N_2O_4$ (366.41): calcd. C 68.84, H 6.05, N 7.65; found C 69.13, H 5.90, N 7.72.

A second compound was subsequently eluted from the column and identified as **9** (722 mg, 14%) as a white solid; m.p. 190–191 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.36–1.42 (m, 6 H, 2× CH_3), 4.32–4.40 (m, 4 H, 2× CH_2), 4.99 (s, 2 H, CH_2), 7.20 (d, J = 8.9 Hz, 1 H, ArH), 7.23 (d, J = 8.3 Hz, 1 H, ArH), 7.71 (s, 1 H, CH), 7.73 (d, J = 1.5 Hz, 1 H, ArH), 7.92 (dd, J = 1.5, 8.3 Hz, 1 H, ArH), 8.11 (d, J = 8.9 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2, 14.3, 46.8, 60.9, 61.1, 116.9, 120.8, 122.5, 124.5, 126.7, 127.4, 127.8, 130.4, 131.3, 144.3, 145.3, 145.7, 147.2, 165.7, 165.9 ppm. LCMS: m/z calcd. for $C_{20}H_{20}N_2O_4$ [M + H]$^+$, 353.4; found 353.4. $C_{20}H_{20}N_2O_4$ (352.38): calcd. C 68.17, H 5.72, N 7.95; found C 68.18, H 5.78, N 7.82.

Diethyl 4,10-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-2,8-dicarboxylate (4): With ethyl 4-amino-3-methylbenzoate

(5.00 g, 27.90 mmol), paraformaldehyde (1.34 g, 44.64 mmol) and trifluoroacetic acid (75 mL). The crude material was purified by recrystallisation from a mixture of ethyl acetate/hexane, 1:3 to afford (±)-**4** (3.91 g, 71%) as a white solid; m.p. 133–134 °C. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.34 (t, J = 7.1 Hz, 6 H, CH$_3$), 2.44 (s, 6 H, 2× CH$_3$), 4.06 (d, J = 16.9 Hz, 2 H, CH$_2$), 4.27–4.33 (m, 6 H, 3× CH$_2$), 4.62 (d, J = 16.9 Hz, 2 H, CH$_2$), 7.48 (app. s, 2 H, ArH), 7.72 (app. s, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.3, 17.1, 54.9, 60.7, 67.3, 125.6, 126.1, 127.6, 130.2, 133.0, 150.2, 166.4 ppm. HRMS (FAB$^+$): *m/z* calcd. for $C_{23}H_{26}N_2O_4$ [M + Na]$^+$, 417.178478; found 417.177973. $C_{23}H_{26}N_2O_4$ (394.46): calcd. C 70.03, H 6.64, N 7.10; found C 69.89, H 6.73, N 7.08.

Diethyl 4,10-Dimethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-2,8-dicarboxylate (5): With ethyl 4-amino-3-methoxybenzoate (5.00 g, 25.61 mmol), paraformaldehyde (1.23 g, 40.95 mmol) and trifluoroacetic acid (75 mL). The crude material was chromatographed (silica gel; ethyl acetate) to afford (±)-**5** (4.18 g, 76%) as a white solid; m.p. 181–183 °C. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.34 (t, J = 7.1 Hz, 6 H, 2× CH$_3$), 3.98 (s, 6 H, 2× OCH$_3$), 4.28–4.38 (m, 8 H, 4× CH$_2$), 4.59 (d, J = 17.2 Hz, 2 H, CH$_2$), 7.31 (app. s, 2 H, ArH), 7.37 (app. s, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.3, 54.2, 55.8, 60.9, 67.7, 109.4, 120.9, 126.3, 128.7, 139.7, 152.6, 166.2 ppm. $C_{23}H_{26}N_2O_6$ (426.46): calcd. C 64.78, H 6.15, N 6.57; found C 64.59, H 6.15, N 6.49.

Diethyl 4,10-Dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-2,8-dicarboxylate (6): With ethyl 4-amino-3-bromobenzoate (2.00 g, 8.19 mmol), paraformaldehyde (395 mg, 13.10 mmol) and trifluoroacetic acid (30 mL). The crude material was chromatographed (silica gel; hexane/dichloromethane, 1:49) to afford (±)-**6** (1.02 g, 48%) as a white solid; m.p. 190–191 °C. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.33 (t, J = 7.1 Hz, 6 H, 2× CH$_3$), 4.27–4.34 (m, 6 H, 3× CH$_2$), 4.43 (d, J = 17.4 Hz, 2 H, CH$_2$), 4.64 (d, J = 17.4 Hz, 2 H, CH$_2$), 7.63 (d, J = 1.7 Hz, 2 H, ArH), 8.09 (d, J = 1.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.2, 55.2, 61.2, 67.3, 119.7, 127.6, 127.7, 130.2, 132.7, 148.6, 164.8 ppm. HRMS (FAB$^+$): *m/z* calcd. for $C_{21}H_{20}Br_2N_2O_4$ [M + Na]$^+$, 544.968203; found 544.967435. $C_{21}H_{20}Br_2N_2O_4$ (524.20): calcd. C 48.12, H 3.85, N 5.34; found C 48.24, H 3.89, N 5.41.

Hydrogenolysis of 6: Diester (±)-**6** (260 mg, 0.50 mmol) was dissolved in ethanol (25 mL) and dichloromethane (5 mL), hydrogenated at room temperature under atmospheric pressure over 10% palladium on carbon (50 mg). The reaction mixture was stirred in the dark for 2 d. The catalyst was filtered off, the solvent was removed in vacuo, and the residue was dissolved in dichloromethane. The organic layer was washed with saturated sodium hydrogen carbonate solution, and then brine, dried with anhydrous sodium sulfate, filtered and the solvents evaporated to dryness. The crude solid was chromatographed (silica gel; dichloromethane) to afford (±)-**3** as a white solid (180 mg, 98%); m.p. 151–152 °C (ref.[9] 126–128 °C, ref.[21] 152–153 °C). The spectroscopic data were identical to those of an authentic sample.

Dihexyl 6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine-2,8-dicarboxylate (7): With hexyl 4-aminobenzoate (5.00 g, 22.59 mmol), paraformaldehyde (1.12 g, 36.2 mmol) and trifluoroacetic acid (80 mL). The crude material was chromatographed (silica gel; ethyl acetate/hexane, 1:3) to afford (±)-**7** (4.54 g, 84%) as a white solid; m.p. 99–100 °C. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.88 (t, J = 7.0 Hz, 6 H, 2× CH$_3$), 1.28–1.40 (m, 12 H, 6× CH$_2$), 1.70 (quin, J = 6.8 Hz, 4 H, 2× CH$_2$), 4.22–4.29 (m, 6 H, 3× CH$_2$), 4.35 (s, 2 H, CH$_2$), 4.76 (d, J = 16.7 Hz, 2 H, CH$_2$), 7.19 (d, J = 8.4 Hz, 2 H, ArH), 7.63 (d, J = 1.8 Hz, 2 H, ArH), 7.84 (dd, J = 1.8, 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 13.9, 22.5, 25.6, 28.6, 31.4, 58.6, 65.0, 66.6, 124.8, 126.4, 127.2, 128.8, 128.9, 151.8, 166.1 ppm. $C_{29}H_{38}N_2O_4$ (478.62): calcd. C 72.77, H 8.00, N 5.85; found C 72.66, H 8.06, N 5.88.

Dihexyl 4,10-Dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-2,8-dicarboxylate (8): With hexyl 4-amino-3-bromobenzoate (500 mg, 1.7 mmol), paraformaldehyde (80 mg, 2.7 mmol) and trifluoroacetic acid (30 mL). The crude material was chromatographed (silica gel; ethyl acetate/hexane, 1:3) to afford (±)-**8** (467 mg, 88%) as a white solid; m.p. 111–113 °C. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.88 (t, J = 6.8 Hz, 6 H, 2× CH$_3$), 1.30–1.38 (m, 12 H, 6× CH$_2$), 1.71 (quin, J = 6.8 Hz, 4 H, 2× CH$_2$), 4.25 (t, J = 6.8 Hz, 4 H, 2× CH$_2$), 4.37 (s, 2 H, CH$_2$), 4.45 (d, J = 17.4 Hz, 2 H, CH$_2$), 4.66 (d, J = 17.4 Hz, 2 H, CH$_2$), 7.63 (app s, 2 H, ArH), 8.11 (d, J = 1.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 13.9, 22.5, 25.6, 28.6, 31.4, 55.3, 65.5, 67.3, 119.8, 127.6, 127.7, 130.2, 132.8, 148.7, 164.9 ppm. $C_{29}H_{36}Br_2N_2O_4$ (636.42): calcd. C 54.73, H 5.70, N 4.40; found C 54.78, H 5.77, N 4.37.

Type I Compounds

Diethyl 4,10-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-1,7-dicarboxylate (10): With ethyl 3-amino-4-methylbenzoate (527 mg, 2.95 mmol), paraformaldehyde (142 mg, 4.71 mmol) and trifluoroacetic acid (20 mL). The crude material was chromatographed (silica gel; ethyl acetate/hexane, 1:3) to afford (±)-**10** (303 mg, 52%) as a white solid; m.p. 160–162 °C. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.35 (t, J = 7.1 Hz, 6 H, 2× CH$_3$), 2.49 (s, 6 H, 2× CH$_3$), 4.25–4.29 (m, 6 H, 3× CH$_2$), 4.52 (d, J = 18.3 Hz, 2 H, CH$_2$), 4.83 (d, J = 18.3 Hz, 2 H, CH$_2$), 7.12 (d, J = 8.0 Hz, 2 H, ArH), 7.65 (d, J = 8.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.3, 17.9, 55.1, 60.6, 65.6, 120.7, 125.9, 126.6, 128.7, 130.8, 138.7, 146.9, 166.7 ppm. $C_{23}H_{26}N_2O_4$ (394.46): calcd. C 70.03, H 6.64, N 7.10; found C 70.05, H 6.69, N 7.11.

Diethyl 4,10-Dimethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-1,7-dicarboxylate (11): With ethyl 3-amino-4-methoxybenzoate (1.40 g, 7.10 mmol), paraformaldehyde (345 mg, 11.5 mmol) and trifluoroacetic acid (40 mL). The crude material was chromatographed (silica gel; ethyl acetate) to afford (±)-**11** (923 mg, 61%) as a white solid; m.p. 212–214 °C. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.34 (t, J = 7.1 Hz, 6 H, 2× CH$_3$), 3.97 (s, 6 H, 2× OCH$_3$), 4.21–4.32 (m, 6 H, 3× CH$_2$), 4.74 (d, J = 18.6 Hz, 2 H, CH$_2$), 4.80 (d, J = 18.6 Hz, 2 H, CH$_2$), 6.75 (d, J = 8.7 Hz, 2 H, ArH), 7.78 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.3, 54.5, 55.9, 60.4, 66.1, 107.9, 120.5, 128.3, 132.1, 136.1, 156.3, 166.4 ppm. $C_{23}H_{26}N_2O_6$ (426.46): calcd. C 64.78, H 6.15, N 6.57; found C 65.04, H 6.21, N 6.65.

Diethyl 2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-1,7-dicarboxylate (12): With ethyl 5-amino-2-methylbenzoate (1.30 g, 7.30 mmol), paraformaldehyde (350 mg, 11.6 mmol) and trifluoroacetic acid (50 mL). The crude material was chromatographed (silica gel; ethyl acetate/dichloromethane, 1:4) to afford (±)-**12** (580 mg, 41%) as a white solid; m.p. 174–176 °C. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.38 (t, J = 7.1 Hz, 6 H, 2× CH$_3$), 2.21 (s, 6 H, 2× CH$_3$), 4.13 (d, J = 17.0 Hz, 2 H, CH$_2$), 4.22 (app. s, 2 H, CH$_2$), 4.28 (q, J = 7.1 Hz, 4 H, 2× CH$_2$), 4.76 (d, J = 17.0 Hz, 2 H, CH$_2$), 7.13 (d, J = 8.2 Hz, 2 H, ArH), 7.18 (d, J = 8.2 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.2, 19.5, 57.3, 61.0, 65.8, 125.3, 126.7, 129.8, 131.4, 131.7, 145.7, 168.4 ppm. $C_{23}H_{26}N_2O_4$ (394.46): calcd. C 70.03, H 6.64, N 7.10; found C 69.92, H 6.70, N 7.10.

Diethyl 6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine-1,7-dicarboxylate (13): With ethyl 3-aminobenzoate (2.0 g, 12.1 mmol), paraformaldehyde (582 mg, 19.38 mmol) and trifluoroacetic acid (75 mL). The crude material was purified by recrystallisation from hexane to afford (±)-**13** (760 mg, 34%) as a white solid; m.p. 168–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.36 (t, *J* = 7.1 Hz, 6 H, 2× CH_3), 4.25–4.34 (m, 6 H, 3× CH_2), 4.67 (d, *J* = 18.0 Hz, 2 H, CH_2), 4.97 (d, *J* = 18.0 Hz, 2 H, CH_2), 7.22 (app. t, *J* = 8.0 Hz, 2 H, ArH), 7.37 (d, *J* = 8.0 Hz, 2 H, ArH), 7.69 (d, *J* = 8.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3, 59.1, 60.8, 65.2, 126.9, 127.0, 128.6, 129.7, 130.2, 148.8, 166.5 ppm. $C_{21}H_{22}N_2O_4$ (366.41): calcd. C 68.84, H 6.05, N 7.65; found C 69.11, H 6.06, N 7.78.

Type III Compounds

Diethyl 4,10-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-3,9-dicarboxylate (14): With ethyl 3-amino-2-methylbenzoate (1.65 g, 9.21 mmol), paraformaldehyde (442 mg, 14.73 mmol) and trifluoroacetic acid (30 mL). The crude material was chromatographed (silica gel; dichloromethane) to afford (±)-**14** (907 mg, 50%) as a white solid; m.p. 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.37 (t, *J* = 7.1 Hz, 6 H, 2× CH_3), 2.63 (s, 6 H, 2× CH_3), 3.96 (d, *J* = 16.8 Hz, 2 H, CH_2), 4.30–4.36 (m, 6 H, 3× CH_2), 4.61 (d, *J* = 16.8 Hz, 2 H, CH_2), 6.80 (d, *J* = 8.0 Hz, 2 H, ArH), 7.49 (d, *J* = 8.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3, 14.5, 55.5, 60.8, 67.4, 124.0, 125.4, 130.2, 131.9, 134.8, 146.6, 167.9 ppm. $C_{23}H_{26}N_2O_4$ (394.46): calcd. C 70.03, H 6.64, N 7.10; found C 70.22, H 6.70, N 7.24.

Diethyl 4,10-Dimethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-3,9-dicarboxylate (15): With ethyl 3-amino-2-methoxybenzoate (638 mg, 3.23 mmol), paraformaldehyde (160 mg, 5.23 mmol) and trifluoroacetic acid (30 mL). The crude material was chromatographed (silica gel; ethyl acetate/dichloromethane, 1:4) to afford (±)-**15** (420 mg, 61%) as a white solid; m.p. 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.37 (t, *J* = 7.1 Hz, 6 H, 2× CH_3), 4.02 (s, 6 H, 2× OCH_3), 4.29–4.41 (m, 8 H, 4× CH_2), 4.55 (d, *J* = 17.5 Hz, 2 H, CH_2), 6.69 (d, *J* = 8.0 Hz, 2 H, ArH), 7.40 (d, *J* = 8.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2, 54.9, 60.9, 61.2, 67.6, 122.1, 123.7, 125.7, 134.2, 153.8, 166.1 ppm. $C_{23}H_{26}N_2O_6$ (426.46): calcd. C 64.78, H 6.15, N 6.57; found C 64.92, H 6.13, N 6.65.

Type IV Compounds

Diethyl 2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-4,10-dicarboxylate (16): With ethyl 2-amino-5-methylbenzoate (4.40 g, 24.55 mmol), paraformaldehyde (1.18 g, 39.28 mmol) and trifluoroacetic acid (70 mL). The crude material was chromatographed (silica gel; dichloromethane) to afford (±)-**16** (824 mg, 17%) as a white solid; m.p. 188–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.39 (t, *J* = 7.1 Hz, 6 H, 2× CH_3), 2.33 (s, 6 H, 2× CH_3), 4.28–4.39 (m, 8 H, 4× CH_2), 4.74 (d, *J* = 17.5 Hz, 2 H, CH_2), 6.81 (d, *J* = 1.5 Hz, 2 H, ArH), 7.45 (d, *J* = 1.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3, 20.6, 57.6, 60.9, 67.3, 125.8, 129.4, 130.3, 131.6, 132.3, 133.2, 166.2 ppm. $C_{23}H_{26}N_2O_4$ (394.46): calcd. C 70.0, H 6.64, N 7.10; found C 70.21, H 6.84, N 7.18.

Diethyl 2,8-Dimethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-4,10-dicarboxylate (17): With ethyl 2-amino-5-methoxybenzoate (2.00 g, 10.25 mmol), paraformaldehyde (492 mg, 16.40 mmol) and trifluoroacetic acid (55 mL). The crude material was chromatographed (silica gel; ethyl acetate/dichloromethane, 1:1) to afford (±)-**17** (250 mg, 11%) as a white solid; m.p. 132–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.41 (t, *J* = 7.1 Hz, 6 H, 2× CH_3), 3.73 (s, 6 H, 2× OCH_3), 4.35–4.44 (m, 8 H, 4× CH_2), 4.70 (d, *J* = 17.6 Hz, 2 H, CH_2), 6.63 (d, *J* = 3.0 Hz, 2 H, ArH), 7.27 (d, *J* = 3.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3, 55.5, 57.8, 61.1, 67.6, 115.5, 115.6, 127.2, 130.8, 155.4, 165.8 ppm. $C_{23}H_{26}N_2O_6$ (426.46): calcd. C 64.78, H 6.15, N 6.57; found C 64.65, H 6.29, N 6.88.

Type I, III and IV Dihexyl Ester Compounds

Dihexyl 4,10-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-1,7-dicarboxylate (18): With hexyl 3-amino-4-methylbenzoate (444 mg, 1.89 mmol), paraformaldehyde (91 mg, 3.03 mmol) and trifluoroacetic acid (10 mL). The crude material was chromatographed (silica gel; hexane/dichloromethane, 1:1) to afford (±)-**18** (326 mg, 68%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.89 (t, *J* = 6.7 Hz, 6 H, 2× CH_3), 1.30–1.38 (m, 8 H, 4× CH_2), 1.39–1.46 (m, 4 H, 2× CH_2), 1.71 (quin, *J* = 6.8 Hz, 4 H, 2× CH_2), 2.49 (s, 6 H, 2× CH_3), 4.16–4.27 (m, 4 H, 2× CH_2), 4.30 (s, 2 H, CH_2), 4.53 (d, *J* = 18.3 Hz, 2 H, CH_2), 4.83 (d, *J* = 18.3 Hz, 2 H, CH_2), 7.12 (d, *J* = 8.0 Hz, 2 H, ArH), 7.65 (d, *J* = 8.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.03, 18.01, 22.57, 25.83, 28.72, 31.49, 55.23, 64.84, 65.69, 126.04, 126.61, 128.75, 130.84, 138.78, 147.15, 166.83 ppm. $C_{31}H_{42}N_2O_4$ (506.68): calcd. C 73.49, H 8.36, N 5.53; found C 73.40, H 8.25, N 5.46.

Dihexyl 4,10-Dimethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-1,7-dicarboxylate (19): With hexyl 3-amino-4-methoxybenzoate (395 mg, 1.57 mmol), paraformaldehyde (76 mg, 2.51 mmol) and trifluoroacetic acid (10 mL). The crude material was chromatographed (silica; ethyl acetate/dichloromethane, 1:9) to afford (±)-**19** (174 mg, 41%) as a white solid; m.p. 143–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.90 (t, *J* = 7.1 Hz, 6 H, 2× CH_3), 1.30–1.35 (m, 8 H, 4× CH_2), 1.38–1.46 (m, 4 H, 2× CH_2), 1.72 (quin, *J* = 6.8 Hz, 4 H, 2× CH_2), 3.98 (s, 6 H, 2× OCH_3), 4.15–4.30 (m, 4 H, 2× CH_2), 4.31 (s, 2 H, CH_2), 4.75 (d, *J* = 18.6 Hz, 2 H, CH_2), 4.81 (d, *J* = 18.6 Hz, 2 H, CH_2), 6.77 (d, *J* = 8.7 Hz, 2 H, ArH), 7.79 (d, *J* = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.02, 22.54, 25.77, 28.70, 31.47, 54.60, 55.94, 64.74, 66.14, 107.97, 120.61, 128.34, 132.19, 136.34, 156.38, 166.55 ppm. $C_{31}H_{42}N_2O_6$ (538.68): calcd. C 69.12, H 7.86, N 5.20; found C 69.18, H 7.82, N 5.29.

Dihexyl 2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-1,7-dicarboxylate (20): With hexyl 5-amino-2-methylbenzoate (443 mg, 1.89 mmol), paraformaldehyde (91 mg, 3.04 mmol) and trifluoroacetic acid (15 mL). The crude material was chromatographed (silica; ethyl acetate/dichloromethane, 1:20 then 1:10) to afford (±)-**20** (68 mg, 14%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.90 (t, *J* = 6.7 Hz, 6 H, 2× CH_3), 1.30–1.43 (m, 12 H, 6× CH_2), 1.71 (quin, *J* = 6.8 Hz, 4 H, 2× CH_2), 2.24 (s, 6 H, 2× CH_3), 4.12 (d, *J* = 17.0 Hz, 2 H, CH_2), 4.24–4.32 (m, 6 H, 3× CH_2), 4.69 (d, *J* = 17.0 Hz, 2 H, CH_2), 7.01 (d, *J* = 8.3 Hz, 2 H, ArH), 7.06 (d, *J* = 8.3 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.07, 19.64, 22.58, 25.78, 28.61, 31.45, 57.45, 65.33, 65.94, 125.43, 126.70, 129.77, 131.58, 131.67, 145.85, 168.72 ppm. $C_{31}H_{42}N_2O_4$ (506.68): calcd. C 73.49, H 8.36, N 5.53; found C 73.52, H 8.26, N 5.93.

Dihexyl 6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine (21) and 1,9-Bis(hexoxycarbonyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-1,7-dicarboxylate (26): With hexyl 3-aminobenzoate (444 mg, 2.0 mmol), paraformaldehyde (96 mg, 3.2 mmol) and trifluoroacetic acid. The crude material was chromatographed (silica gel; dichloromethane/ethyl acetate, 9:1) to afford to afford an mixture of (±)-21 and (±)-26 which was rechromatographed (silica gel; dichloromethane/ethyl acetate/hexane, 1:1:3) to afford (±)-21 (120 mg, 25%) as a pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.90 (t, J = 7.1 Hz, 6 H, 2× CH$_3$), 1.29–1.36 (m, 8 H, 4× CH$_2$), 1.36–1.45 (m, 4 H, 2× CH$_2$), 1.72 (quin, J = 6.8 Hz, 4 H, 2× CH$_2$), 4.20–4.27 (m, 4 H, 2× CH$_2$), 4.33 (s, 2 H, CH$_2$), 4.68 (d, J = 18.0 Hz, 2 H, CH$_2$), 4.97 (d, J = 18.0 Hz, 2 H, CH$_2$), 7.23 (app ppm. t, 2 H, ArH), 7.37 (dd, J = 1.2, 7.8 Hz, 1 H, ArH), 7.70 (dd, J = 1.2, 7.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.02, 22.56, 25.78, 28.65, 31.45, 59.19, 65.09, 65.24, 127.03, 127.07, 128.76, 130.00, 130.21, 148.85, 166.60 ppm. $C_{29}H_{38}N_2O_4$ (478.62): calcd. C 72.77, H 8.00, N 5.85; found C 72.52, H 7.98, N 6.06.

(±)-**26** (31 mg, 7%) was eluted as the second fraction as a pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.88–0.91 (m, 6 H, 2× CH$_3$), 1.30–1.36 (m, 8 H, 4× CH$_2$), 1.37–1.45 (m, 4 H, 2× CH$_2$), 1.69–1.78 (m, 4 H, 2× CH$_2$), 4.21–4.40 (m, 7 H, 4× CH$_2$), 4.68 (d, J = 18.0 Hz, 1 H, CH$_2$), 4.75 (d, J = 17.1 Hz, 1 H, CH$_2$), 5.00 (d, J = 18.0 Hz, 1 H, CH$_2$), 6.98 (d, J = 8.0 Hz, 1 H, ArH), 7.25 (app ppm. t, 1 H, ArH), 7.34–7.38 (m, 1 H, ArH), 7.64 (dd, J = 1.6, 8.0 Hz, 1 H, ArH), 7.72 (dd, J = 1.3, 7.7 Hz, 1 H, ArH), 7.86 (d, J = 1.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.01, 14.03, 22.55, 25.70, 25.76, 28.62, 28.69, 31.45, 31.47, 58.82, 59.07, 65.20, 65.23, 66.02, 125.02, 126.73, 126.94, 127.18, 127.36, 129.09, 129.58, 130.13, 130.27, 166.26, 166.47 ppm. HRMS (ESI-MS) *m*/*z* calcd. for $C_{29}H_{39}N_2O_4$ $[M + H]^+$, 479.2910; found 479.2935.

Dihexyl 4,10-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-3,9-dicarboxylate (22): With hexyl 3-amino-2-methylbenzoate (485 mg, 2.06 mmol), paraformaldehyde (99 mg, 2.51 mmol) and trifluoroacetic acid (10 mL). The crude material was chromatographed (silica gel; dichloromethane) to afford (±)-**22** (194 mg, 37%) as a pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.89 (t, J = 7.1 Hz, 6 H, 2× CH$_3$), 1.31–1.35 (m, 8 H, 4× CH$_2$), 1.39–1.46 (m, 4 H, 2× CH$_2$), 1.73 (quin, J = 6.9 Hz, 4 H, 2× CH$_2$), 2.63 (s, 6 H, 2× CH$_3$), 3.97 (d, J = 17.4 Hz, 2 H, CH$_2$), 4.22–4.30 (m, 4 H, 2× CH$_2$), 4.32 (s, 2 H, CH$_2$), 4.61 (d, J = 17.4 Hz, 2 H, CH$_2$), 6.81 (d, J = 8.0 Hz, 2 H, ArH), 7.49 (d, J = 8.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 13.89, 14.43, 22.47, 25.72, 28.70, 31.41, 55.56, 64.95, 67.53, 124.02, 125.42, 130.41, 131.88, 134.85, 146.85 ppm. 168.05 ppm. $C_{31}H_{42}N_2O_4$ (506.68): calcd. C 73.49, H 8.36, N 5.53; found C 73.48, H 8.47, N 5.63.

Dihexyl 4,10-Dimethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-3,9-dicarboxylate (23): With hexyl 3-amino-2-methoxybenzoate (425 mg, 1.51 mmol), paraformaldehyde (73 mg, 2.42 mmol) and trifluoroacetic acid (10 mL). The crude material was chromatographed (silica gel; ethyl acetate/dichloromethane, 1:50, then ethyl acetate/hexane/dichloromethane, 1:2:7) to afford (±)-**23** (121 mg, 30%) as a pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.89 (t, J = 7.1 Hz, 6 H, 2× CH$_3$), 1.28–1.35 (m, 8 H, 4× CH$_2$), 1.38–1.46 (m, 4 H, 2× CH$_2$), 1.73 (quin, J = 6.9 Hz, 4 H, 2× CH$_2$), 4.02 (s, 6 H, 2× CH$_3$), 4.25–4.30 (m, 6 H, 3× CH$_2$), 4.39 (d, J = 17.6 Hz, 2 H, CH$_2$), 4.54 (d, J = 17.6 Hz, 2 H, CH$_2$), 6.70 (d, J = 8.1 Hz, 2 H, ArH), 7.39 (d, J = 8.1 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.02, 22.55, 25.69, 28.68, 31.47, 54.97, 61.15, 65.17, 67.59, 122.10, 123.81, 125.67, 134.30, 141.15, 153.88, 166.19 ppm. $C_{31}H_{42}N_2O_6$ (538.68): calcd. C 69.12, H 7.86, N 5.20; found C 69.30, H 7.97, N 5.24.

Dihexyl 2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-4,10-dicarboxylate (24): With hexyl 2-amino-5-methylbenzoate (320 mg, 1.36 mmol), paraformaldehyde (65 mg, 2.18 mmol) and trifluoroacetic acid (10 mL). The crude material was chromatographed (silica gel; ethyl acetate/dichloromethane, 1:19) to afford (±)-**24** (60 mg, 16%) as a pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.91 (t, J = 7.0 Hz, 6 H, 2× CH$_3$), 1.32–1.38 (m, 8 H, 4× CH$_2$), 1.41–1.50 (m, 4 H, 2× CH$_2$), 1.79 (quin, J = 6.9 Hz, 4 H, 2× CH$_2$), 2.25 (s, 6 H, 2× CH$_3$), 4.30–4.35 (m, 6 H, 3× CH$_2$), 4.41 (d, J = 17.6 Hz, 2 H, CH$_2$), 4.68 (d, J = 17.6 Hz, 2 H, CH$_2$), 6.89 (d, J = 1.5 Hz, 2 H, ArH), 7.51 (d, J = 1.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.04, 20.72, 22.60, 25.78, 28.71, 31.51, 57.80, 65.16, 67.37, 126.04, 129.55, 130.19, 131.56, 133.11, 145.72, 166.46 ppm. $C_{31}H_{42}N_2O_4$ (506.68): calcd. C 73.49, H 8.36, N 5.53; found C 73.24, H 8.20, N 5.42.

Dihexyl 2,8-Dimethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-4,10-dicarboxylate (25): With hexyl 5-methoxy-2-aminobenzoate (2.40 g, 9.54 mmol), paraformaldehyde (462 mg, 15.4 mmol) and trifluoroacetic acid (45 mL). The crude was chromatographed (silica gel; dichloromethane/ethyl acetate, 1:1) to afford (±)-**25** (420 mg, 16%) as a white solid; m.p. 91–93 °C. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.90 (t, J = 7.3 Hz, 6 H, 2× CH$_3$), 1.33–1.37 (m, 8 H, 4× CH$_2$), 1.45–1.47 (m, 4 H, 2× CH$_2$), 1.78 (quin, J = 6.8 Hz, 4 H, 2× CH$_2$), 3.74 (s, 6 H, 2× OCH$_3$), 4.31–4.35 (m, 6 H, 3× CH$_2$), 4.42 (d, J = 17.6 Hz, 2 H, CH$_2$), 4.69 (d, J = 17.6 Hz, 2 H, CH$_2$), 6.63 (d, J = 2.8 Hz, 2 H, ArH), 7.26 (d, J = 2.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.0, 22.6, 25.6, 28.6, 31.5, 55.5, 57.9, 65.3, 67.6, 115.5, 115.6, 127.3, 130.9, 155.4, 166.0 ppm. $C_{31}H_{42}N_2O_6$ (538.68): calcd. C 69.12, H 7.86, N 5.20; found C 69.19, H 7.78, N 5.19.

Supporting Information (see also the footnote on the first page of this article): Experimental details for the synthesis of all non-commercially available anilines used in this work.

CCDC-629732 (for **12**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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