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Reactivity of Dipyrromethanes towards Azoalkenes: Synthesis of Functionalized Dipyrromethanes, Calix[4]pyrroles, and Bilanes

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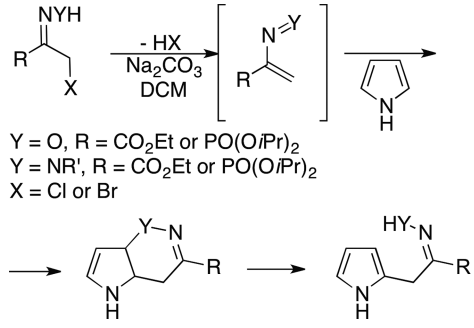
The introduction of side chains at the 1- and 9-positions of dipyrromethanes was explored by using the hetero-Diels–Alder reaction of azoalkenes. New 5,5′-diethyldipyrromethanes and 5-phenyldipyrromethanes that were functionalized with open-chain hydrazone moieties, including derivatives with tetrazolyl groups, were prepared. Furthermore, the synthesis of new calix[4]pyrroles and bilanes was achieved by employing the bis(hetero-Diels–Alder) reaction of azoalkenes with 5,5′-diethyldipyrromethane.

Introduction

The research of dipyrromethanes has mainly been carried out by groups that are focused on porphyrin chemistry, as dipyrromethanes are particularly important building blocks in the preparation of porphyrins and porphyrin analogues, such as *meso*-substituted corroles, chlorins, expanded porphyrins, and calix[4]pyrroles.[1] More recently, there has been a growing interest in the various other applications of dipyrromethanes, and this has led to a search for efficient strategies to functionalize dipyrromethanes, such as the synthesis of its 1,9-disubstituted derivatives. Dipyrromethanes are precursors to 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) dyes, the photophysical properties of which make them ideal fluorescent scaffolds for the development of high performance imaging probes.[2] Functionalized dipyrromethanes can function as photonic organic based materials, are potentially attractive structures in the development of new optical anion sensors, and have applications in biological systems and the resolution of environmental problems.[1,3] In addition, calix[4]pyrroles can act as anion sensors.[4] These macrocycles are interesting structures and can be used as anion molecular carriers to allow anions to cross lipid bilayer membranes, a topic that is particularly relevant with regard to channelopathies.[4b]

The 1,9-functionalization of dipyrromethanes can be achieved by exploring the rich electron density of the pyrrole units. Thus, these heterocyclic compounds can undergo acylation reactions, Vilsmeier reactions, Mannich reactions, and addition reactions to electron-poor heterocycles.[1a,1b] The dicyanation of 5-monosubstituted and 5-unsubstituted dipyrromethanes with chlorosulfuryl isocyanate has been reported.[5] In addition, 5,5-dialkyldipyrromethanes can undergo a reaction with phenyl isocyanate to afford monoamide derivatives, and 1,9-bis(diazo)dipyrromethanes can be obtained by a reaction with diazonium salts.[6] Pyrrole can undergo a reaction with conjugated nitrosoalkenes and azoalkenes to give open-chain oximes and hydrazones, respectively. The formation of these products can be explained by the rearomatization of the primarily formed cycloadduct, the bicyclic 1,2-oxazine or pyridazine (see Scheme 1).[7]



Scheme 1. Functionalization of pyrrole through hetero-Diels–Alder reactions (DCM = dichloromethane).[7]

This chemistry was explored as a new strategy for the functionalization of dipyrromethanes (see Scheme 2).[8] In a preliminary communication, we reported that 5,5′-diethyl- and 5-phenyldipyrromethanes participate in hetero-Diels–Alder reactions with nitrosoalkenes and azoalkenes to give dipyrromethanes with side chains that contain oxime and hydrazone groups, respectively. By controlling the stoichiometry of the reaction, it is possible to obtain monosubstituted or 1,9-disubstituted derivatives. More recently, we described a new one-pot approach to 5-substituted dipyrro-

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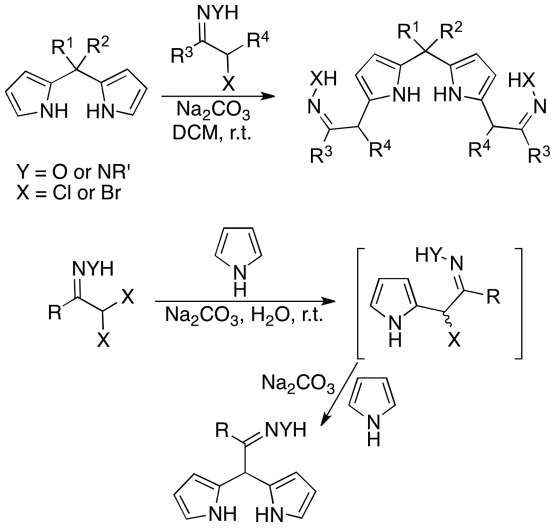
methanes by using an on water bis(hetero-Diels–Alder) reaction of azo- and nitrosoalkenes with pyrrole.[9] The base-mediated dehydrohalogenation of α,α-dihalohydrazones or α,α-dihalooximes in the presence of pyrrole led to two consecutive Diels–Alder reactions to give the target dipyrromethanes.



Scheme 2. Functionalization and synthesis of dipyrromethanes through hetero-Diels–Alder reactions.[8,9]

The hetero-Diels–Alder reaction of 3-(1*H*-tetrazol-5-yl)-nitrosoalkenes and 3-(1*H*-tetrazol-5-yl)azoalkenes was also studied as an approach to functionalized 5-substituted-1*H*-tetrazoles, which is a particularly interesting class of compounds, several derivatives of which have displayed a wide variety of biological activities.[10]

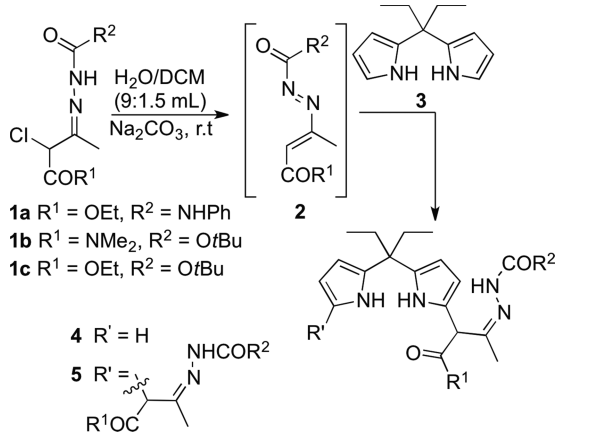
As part of our continuing investigation, we herein describe the optimization and evaluation of the scope of this strategy to functionalize dipyrromethanes by employing the hetero-Diels–Alder reactions of azoalkenes, including 3-tetrazolyl-1,2-diaza-1,3-butadienes. Furthermore, the bis-(hetero-Diels–Alder) reaction of azoalkenes with 5,5′-diethyldipyrromethane was also explored as a route for the preparation of calix[4]pyrroles.

Results and Discussion

Usually, nitroso and azoalkenes are generated in situ by treating the corresponding α-halooximes and α-halohydrazones with sodium carbonate, which has a low solubility in dichloromethane to ensure a slow rate of 1,4-dehydrohalogenation, thus preventing side reactions. These conditions were used for the previously described Diels–Alder reactions of these heterodienes with dipyrromethanes.[8] However, the bis(hetero-Diels–Alder) reaction of pyrrole with nitrosoalkenes and azoalkenes, which were generated by the base-mediated dehydrohalogenation of α,α-dihalooximes and α,α-dihalohydrazones to give 5-substituted dipyrromethanes, was accelerated and gave higher yields by using water as the solvent than carrying out the reaction in dichloromethane or in the absence of solvent.[9] In this context, the on water cycloaddition of dipyrromethanes with azoalkenes was explored.

Initially, we looked at the reactivity of 5,5′-diethyldipyrromethane (**3**) towards 1,2-diaza-1,3-butadienes **2a**–**2c** (see Table 1). Monofunctionalized dipyrromethanes **4** were preferentially obtained as the major product by using an excess amount of dipyrromethane **3** (0.5 equiv. of hydrazone), whereas the use of an excess amount of hydrazone **1** led to bis(functionalized) dipyrromethane **5** as the only product. Hydrazone **1a** (0.5 equiv.) was treated with sodium carbonate in water at room temperature for 2.5 h to give the transient 1,2-diaza-1,3-butadiene **2a**, which was trapped in situ by dipyrromethane **3** to afford open-chain hydrazone **4a** in 21% yield along with bis(functionalized) dipyrromethane **5a** in an isolated yield of 3% (see Table 1, Entry 1). The target products, however, were obtained in higher yields when dichloromethane was used as a cosolvent (see Table 1, Entries 2 and 3). Carrying out the reaction with 0.5 equiv. of hydrazone **1a** afforded open-chain hydrazones **4a** and **5a** in 81 and 17% yield, respectively, and the use of 2.3 equiv. of hydrazone **1a** allowed for the isolation of 1,9-disubstituted dipyrromethane **5a** in 90% yield as the only product. 1,2-Diaza-1,3-butadiene **2a** was isolated by following a general synthetic procedure,[11] and we carried out its reaction with an excess amount of dipyrromethane **3** (see Table 1, Entry 4). This process was less efficient than the in situ generation of the heterodiene in the presence of dipyrromethane **3**.

Table 1. Hetero-Diels–Alder reaction of 5,5′-diethyldipyrromethane (**3**) with 1,2-diaza-1,3-butadiene **2**.



Entry	Hydrazone [equiv.]	Time [h]	Products [% yield]	
1	**1a** (0.5)[a]	2.5	**4a** (21)	**5a** (3)
2	**1a** (0.5)	2	**4a** (81)	**5a** (17)
3	**1a** (2.3)	3	–	**5a** (90) (49)[8]
4	**1a** (0.5)[b]	2	**4a** (45)	**5a** (8)
5	**1b** (0.5)	2	**4b** (27)	**5b** (31)
6	**1b** (2.3)	3	–	**5b** (76) (59)[8]
7	**1c** (0.5)	2	**4c** (53) (28)[7]	**5c** (13)
8	**1c** (2.3)	3	–	**5c** (73) (68)[8]

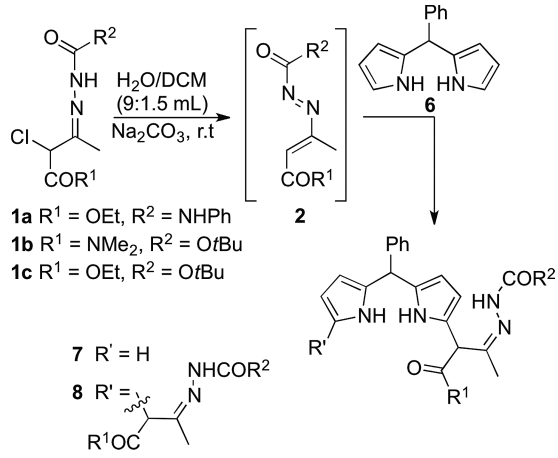
[a] Without CH_2Cl_2 as cosolvent. [b] Reaction of isolated azoalkene **2a** with dipyrromethane **3**.

The optimized reaction conditions were then applied to the Diels–Alder reactions of dipyrromethane **3** and heterodienes **2b** and **2c** (see Table 1, Entries 5–8). The expected 1,9-disubstituted dipyrromethanes **5b** and **5c** were again obtained as single products (73–76% yield) by using 2.3 equiv. of the corresponding hydrazone **1**. The use of an excess amount of the hydrazone afforded the bis(functionalized) dipyrromethanes in good overall yields. All of these reactions were carried out at room temperature for 2 to 3 h to give good yields of the desired products (see Table 1). In dichloromethane, the Diels–Alder reaction of dipyrromethane **3** required significantly longer reaction times (48–80 h)[8] and led to lower yields.

This work was extended to the cycloaddition of the 1,2-diaza-1,3-butadienes **2** with 5-phenyldipyrromethane (**6**), which showed the same chemical behavior as that of the reaction with 5,5′-diethyldipyrromethane (**3**, see Table 2). Using the optimized reaction conditions with an excess amount of hydrazones **1** afforded 1,9-disubstituted dipyrromethanes **8** in high yields (71–92%) in only 3 h (see Table 2, Entries 2, 5, and 7). By carrying out the reaction with an excess amount of dipyrromethane **6**, we obtained monofunctionalized derivatives **7** in good isolated yields (42–68%) along with 1,9-disubstituted dipyrromethanes **8** as the minor products (5–18% yield, see Table 2, Entries 1, 4, and 6). The results confirmed the advantage of using water/dichloromethane as the solvent system over dichloromethane, as significantly higher yields were obtained with shorter reaction times. On the other hand, the Diels–Alder reaction of hydrazone **1b** and dipyrromethane **6** with water as the solvent led to product **7b** in very low yield (see Table 2, Entry 3).

The reactivity of dipyrromethane **3** towards tetrazolyl-1,2-diaza-1,3-butadiene **10** was also explored (see Table 3). The transient 1,2-diaza-1,3-butadiene **10** was generated in situ by treating bromohydrazone **9**[10c] with sodium carbonate in either dichloromethane or water/dichloromethane. The Diels–Alder reaction was first carried out at room temperature for 24 h in dichloromethane to afford the two monofunctionalized dipyrromethanes **11** and **12** in 16 and 53% yield, respectively (see Table 3, Entry 1).

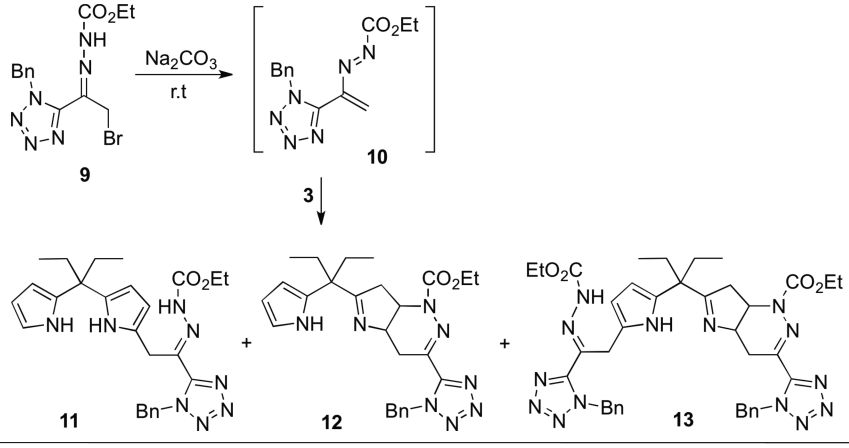
Table 2. Hetero-Diels–Alder reaction of 5-phenyldipyrromethane (**6**) with 1,2-diaza-1,3-butadiene **2**.



Entry	Hydrazone [equiv.]	Time [h]	Products [% yield]	
1	**1a** (0.5)	2	**7a** (42)	**8a** (18)
2	**1a** (2.3)	3	–	**8a** (71)
3	**1b** (0.5)[a]	24	**7b** (trace)	–
4	**1b** (0.5)	2	**7b** (58) (31)[7]	**8b** (18)
5	**1b** (2.3)	3	–	**8b** (92) (56)[8]
6	**1c** (0.5)	2	**7c** (64)	**8c** (5)
7	**1c** (2.3)	3	–	**8c** (71)

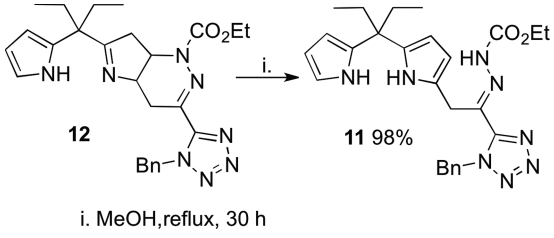
[a] Without CH_2Cl_2 as cosolvent.

Table 3. Hetero-Diels–Alder reaction of 5,5′-diethyldipyrromethane (**3**) with tetrazolyl-1,2-diaza-1,3-butadiene **10**.



Entry	**9** [equiv.]	Reaction conditions	**11**	**12**	**13**
1	0.5	DCM, 24 h	16%	53%	–
2	0.5	H_2O/DCM (9:1.5 mL), 2 h	14%	38%	7%
3	0.5	H_2O, 24 h	trace	–	–
4	2.3	DCM, 7 d	–	–	44%
5	2.7	H_2O/DCM (9:1.5 mL), 4 h	–	–	33%

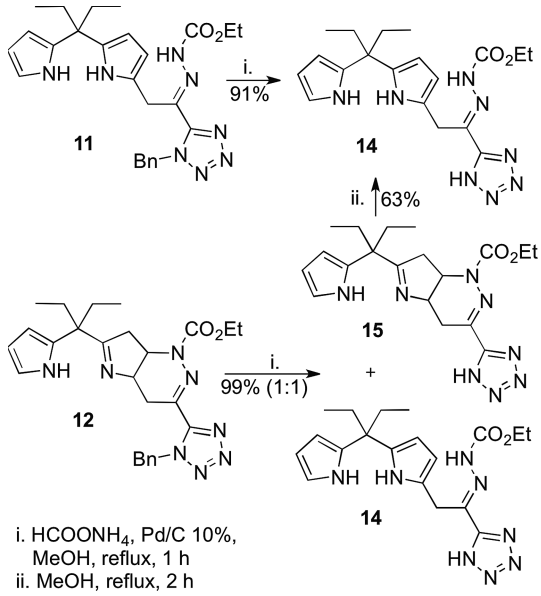
The ^{1}H NMR spectrum of compound **12** shows signals that indicate a bicyclic structure. In particular, four double doublets (δ = 2.50, 2.78, 3.05, and 3.30 ppm) are present, and their chemical shifts and coupling constants are consistent with those expected for the geminal protons in the six-membered ring and those of the five-membered ring. Two additional multiplets are present at δ = 4.42–4.47 and δ = 4.53–4.58 ppm, which correspond to the methine protons that are attached to the ring-fused carbons (see Supporting Information). Compound **12**, with a 1,4,5,6-tetrahydropyridazine ring incorporated into it, is formed by a prototropic rearrangement of the primary cycloadduct. This result indicates that compound **11** is also formed through the Diels–Alder reaction followed by an opening of the 1,4,5,6-tetrahydropyridazine ring. In fact, the conversion of **12** into **11** was quantitative by heating **12** in methanol at reflux for 30 h (see Scheme 3). This type of bicyclic imine has been obtained from the reaction of 2,5-dimethylpyrrole and azoalkenes, as the rearomatization to give a functionalized pyrrole is blocked. However, open-chain hydrazones are usually obtained by using pyrrole. Only in the case of the reaction of pyrrole with a heterodiene that was derived from bromopyruvate *tert*-butoxycarbonylhydrazone was the same type of bicyclic structure detected by NMR, although its lack of stability precluded its isolation.[7e]



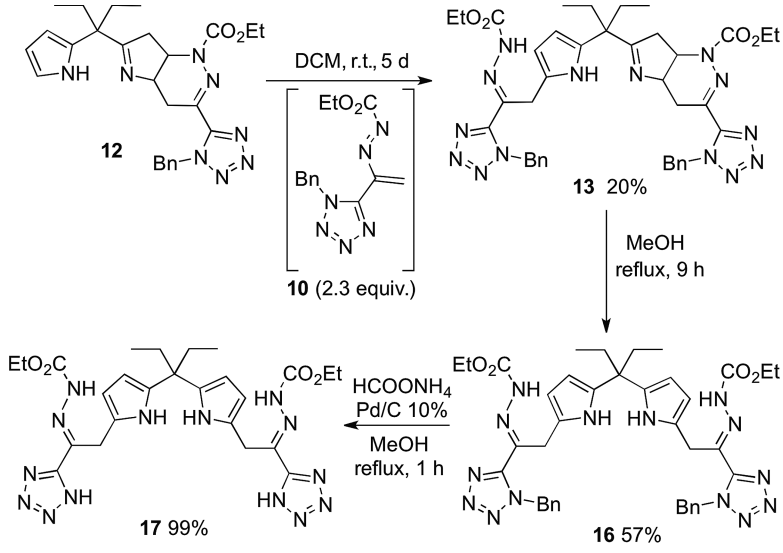
Scheme 3. Ring opening of compound **12** to afford hydrazone **11**.

The reaction of dipyrromethane **3** with 1,2-diaza-1,3-butadiene **10** in water/dichloromethane for 2 h gave the same products, compounds **11** (14%) and **12** (38%) along with difunctionalized dipyrromethane **13** (7%, see Table 3, Entry 2). The employment of water as the solvent afforded trace amounts of compound **11** (see Table 3, Entry 3). Disubstituted dipyrromethane **13**, which incorporating an open-chain hydrazone and a 1,4,5,6-tetrahydropyridazine unit, was isolated as a single product by using an excess amount of hydrazone **9** (see Table 3, Entries 4 and 5). In this case, the reaction that was performed in dichloromethane gave a higher product yield (44%) than the one in water/dichloromethane (33%), although a longer reaction time was required.

The deprotection of the tetrazolyl group of dipyrromethane **11** was efficiently carried out by using ammonium formate in the presence of 10% Pd/C as a catalytic hydrogen



Scheme 4. Deprotection of the tetrazolyl group in dipyrromethanes **11** and **12**.



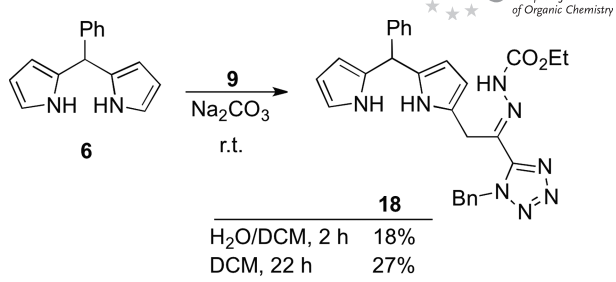
Scheme 5. Synthesis of dipyrromethane **17**.

transfer system, according to a reported procedure.[6] The deprotection of compound **12** gave a mixture (1:1) of dipyrromethanes **14** and **15**. However, by heating the mixture in methanol at reflux for 2 h, we were able to convert it into open-chain hydrazone **14** in an isolated yield of 63% (see Scheme 4).

Bis(functionalized) dipyrromethane **13** was also obtained from the Diels–Alder reaction of dipyrromethane **12** with an excess amount of 1,2-diaza-1,3-butadiene **10** to give bis(hydrazone) **16**. The deprotection of the tetrazolyl groups gave 1,9-bis(2′-ethoxycarbonylhydrazono-2′-1*H*-tetrazol-5-ylethyl)-5,5′-diethyldipyrromethane (**17**) in 99% yield (see Scheme 5). Compound **17** was very unstable upon standing at room temperature.

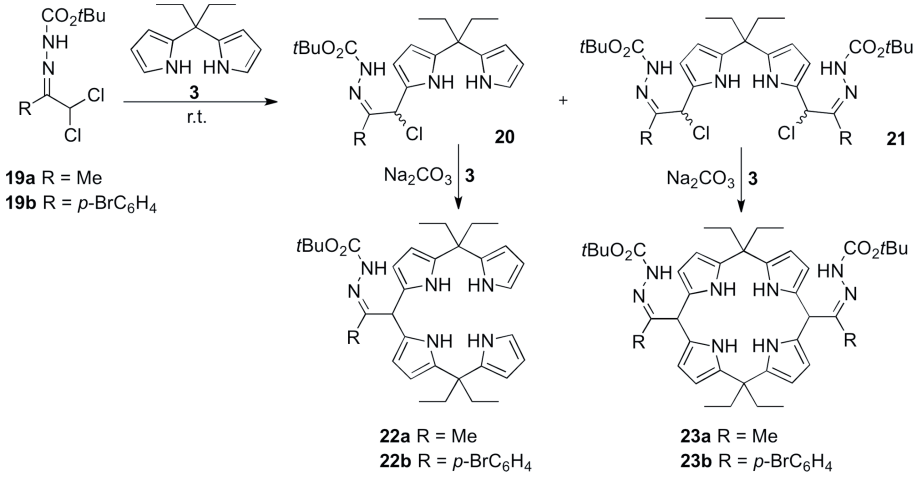
Monofunctionalized dipyrromethane **18** was obtained in low yield (18–27%) by employing the Diels–Alder reaction of hydrazone **6** with 5-phenyldipyrromethane (**6**) in either dichloromethane or water/dichloromethane as the solvent (see Scheme 6). Unfortunately, all attempts to obtain the bis(functionalized) dipyrromethane derivatives were unsuccessful.

The possibility to access tetrapyrrolic macrocycles by using the bis(hetero-Diels–Alder) approach was also investigated (see Table 4). Thus, the base-mediated dehydrohalogenation of α,α-dichlorohydrazones **19** in the presence of dipyrromethane **3** was carried out. Interestingly, when the reactions were performed at room temperature in the presence of sodium carbonate, two products were obtained, the expected calix[4]pyrroles **23** along with bilanes **22**. By starting from hydrazine **19a** (0.5 equiv.), we achieved the best overall yield (32%) with a reaction time of 96 h (see Table 4, Entry 3). Performing the reaction at room temperature for 2 h in water/dichloromethane afforded bilane **22a** and calix[4]pyrrole **23a** in 15 and 5% yield, respectively (see Table 4, Entry 4). Increasing the amount of hydrazone **19a** (2 equiv.) provided only trace amounts of bilane **22a**, and compound **24** was formed as a result of the self-condensation reaction of hydrazone **19a** (see Table 4, Entry 5). In fact, hydrazone **19a** was converted into compound **24** in 90% yield by employing triethylamine (see Scheme 7). A similar result was obtained by carrying out the reaction of hydrazone **19a** and dipyrromethane **3** in the presence of tri-



Scheme 6. Hetero-Diels–Alder reaction of hydrazone **9** with 5-phenyldipyrromethane (**6**).

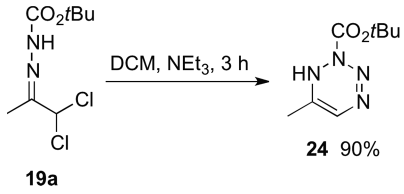
Table 4. Synthesis of bilanes **22** and calix[4]pyrroles **23** through the bis(hetero-Diels–Alder) reaction of azoalkenes with dipyrromethane **3**.



Entry	Hydrazone [equiv.]	Reaction conditions	Products [% yield]	
1	**19a** (0.5)	DCM, Na_2CO_3, r.t, 47 h	**22a** (7)	**23a** (13)
2	**19a** (0.5)	DCM, Na_2CO_3, r.t, 72 h	**22a** (14)	**23a** (11)
3	**19a** (0.5)	DCM, Na_2CO_3, r.t, 96 h	**22a** (16)	**23a** (16)
4	**19a** (0.5)	H_2O/DCM (6:1 mL), Na_2CO_3, r.t, 2 h	**22a** (15)	**23a** (5)
5	**19a** (2.0)	H_2O/DCM (6:1 mL), Na_2CO_3, r.t, 2 h	**22a** (<2)[a]	–
6	**19a** (0.5)	DCM, NEt_3, r.t, 1.5 h	**22a** (2)[a]	–
7	**19b** (0.5)	DCM, Na_2CO_3, r.t, 96 h	**22b** (8)	**23b** (7)
8	**19b** (1.0)	DCM, Na_2CO_3, r.t, 96 h	**22b** (5)	**23b** (6)

[a] Azoalkene self-condensation product **24** was also isolated.

ethylamine (see Table 4, Entry 6). Bilane **22b** and calix[4]pyrrole **23b** could also be obtained from hydrazone **19b**, although in low yields (see Table 4, Entries 7 and 8).



Scheme 7. Self-condensation of azoalkene **19a**.

The synthesis of calix[4]pyrroles **23** can be explained by the initial formation of bis(functionalized) dipyrromethane **21** followed by dehalogenation to give the corresponding azoalkenes, which can undergo a reaction with another molecule of dipyrromethane **3** through a hetero-Diels–Alder reaction. Bilanes **22** are formed through monofunctionalized dipyrromethane **20**. Bilanes are interesting heterocycles, as they are important precursors of corroles and asymmetrically-substituted porphyrins.[12]

Conclusions

The synthetic strategy to introduce side chains at the 1- and 9-positions of dipyrromethanes was further explored by employing the hetero-Diels–Alder reaction of dipyrromethanes with azoalkenes. Employing water as the solvent and dichloromethane as the cosolvent allowed for the synthesis of new 5,5′-diethyldipyrromethanes and 5-phenyldipyrromethanes with side chains that contained open-chain hydrazones.

The reaction of ethyl 3-(1-benzyl-1*H*-tetrazol-5-yl)-1,2-diaza-1,3-butadiene-1-carboxylate with 5,5′-diethyldipyrromethane afforded the corresponding dipyrromethane, but bicyclic derivatives that contained a 1,4,5,6-tetrahydropyridazine ring were also obtained by a prototropic rearrangement of the primary cycloadduct. Under thermolysis these compounds were converted into the corresponding open-chain hydrazones, and deprotection of the tetrazolyl group of the functionalized dipyrromethane was successfully carried out. The base-mediated dehydrohalogenation of α,α-dichlorohydrazones in the presence of 5,5′-diethyldipyrromethane allowed for the syntheses of new calix[4]pyrroles and bilanes through this hetero-Diels–Alder reaction.

Experimental Section

General Methods: The ^{1}H NMR spectroscopic data were recorded with an instrument that operated at 400 MHz. The ^{13}C NMR spectroscopic data were recorded with an instrument that operated at 100 MHz. The NMR solvent was deuterochloroform, except where indicated otherwise. The chemical shifts are reported in parts per million relative to TMS (δ = 0 ppm) as the internal standard, and the coupling constants (J) are reported in Hz. IR spectra were recorded with a Nicolet 6700 FTIR spectrometer. HRMS spectra were recorded with a Finnigan MAT95 S instrument. Melting points were recorded on a Melting Point Device Falc R132467. Flash column chromatography was performed with Merck 9385 silica gel as the stationary phase. Hydrazones **1a**–**1c**,[13] 1-(1-benzyl-1*H*-tetrazol-5-yl)-2-bromoethanone ethoxycarbonyl hydrazone (**9**),[10c] 1,1-dichloroacetone *tert*-butoxycarbonyl hydrazone (**19a**),[14] 2,2-dichloro-4′-bromoacetophenone *tert*-butoxycarbonyl hydrazone (**19b**),[9] 5,5′-diethyldipyrromethane,[15] and 5-phenyldipyrromethane[16] were prepared as described in the literature.

General Procedure for the Difunctionalization of Dipyrromethanes

Method A – On-Water: Dipyrromethane **3** or **6** (0.335 mmol) and a solution of hydrazone **1** or **9** (0.67 mmol) in dichloromethane (1.5 mL) were added to a solution of Na_2CO_3 (3.35 mmol) in water (9 mL). The reaction mixture was stirred at room temperature for 2 h. After this time, additional hydrazone **1** (0.1 mmol) or **9** (0.23 mmol) was added in three portions. The reaction mixture was stirred for the time indicated, and the progress of the reaction was monitored by TLC. Upon completion, the mixture was extracted with dichloromethane (3 × 20 mL), and the combined extracts were dried with Na_2SO_4. The solvent was evaporated to give the crude product, which was purified by flash chromatography.

Method B – In Dichloromethane: Dipyrromethane **3** (0.23 mmol) and hydrazone **9** (0.54 mmol) were added to a suspension of Na_2CO_3 (2.3 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature for the time indicated. The progress of the reaction was monitored by TLC. Upon completion, the mixture was filtered through a pad of Celite, which was washed with dichloromethane. The solvent was evaporated, and the product was purified by flash chromatography.

1,9-Bis(2′-phenylcarbamoylhydrazono-1′-ethoxycarbonylpropyl)-5,5′-diethyldipyrromethane (5a): Hydrazone **1a** (229 mg, 0.77 mmol) and dipyrromethane **3** (67 mg, 0.335 mmol) were employed as described in the general procedure for method A (reaction time of 3 h). Purification by flash chromatography (ethyl acetate/hexane, 1:1) afforded compound **5a**[9] (215.4 mg, 90%) as a white solid.

1,9-Bis(2′-*tert*-butoxycarbonylhydrazono-1′-dimethylaminocarbonylpropyl)-5,5′-diethyldipyrromethane (5b): Hydrazone **1b** (214 mg, 0.77 mmol) and dipyrromethane **3** (67 mg, 0.335 mmol) were employed as described in the general procedure for method A (reaction time of 3 h). Purification by flash chromatography (ethyl acetate/hexane, 3:1) afforded compound **5b**[9] (174 mg, 76%) as a white solid.

1,9-Bis(2′-*tert*-butoxycarbonylhydrazono-1′-ethoxycarbonylpropyl)-5,5′-diethyldipyrromethane (5c): Hydrazone **1c** (215 mg, 0.77 mmol) and dipyrromethane **3** (67 mg, 0.335 mmol) were employed as described in the general procedure for method A (reaction time of 3 h). Purification by flash chromatography (ethyl acetate/hexane, 1:2) afforded compound **5c**[9] (168 mg, 73%) as a white solid.

1,9-Bis(2′-phenylcarbamoylhydrazono-1′-ethoxycarbonylpropyl)-5-phenyldipyrromethane (8a): Hydrazone **1a** (229 mg, 0.77 mmol) and dipyrromethane **6** (74 mg, 0.335 mmol) were employed as described in the general procedure for method A (reaction time of 3 h). Purification by flash chromatography (ethyl acetate/hexane, 1:2) afforded compound **8a** (177 mg, 71%) as a red foam. IR (KBr): $\tilde{\nu}$ = 754, 1448, 1533, 1595, 1685, 1731, 3369 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.18 (m, 6 H, 16-H and 27-H), 1.80–1.81 (m, 6 H, 17-H and 28-H), 4.10–4.13 (m, 4 H, 15-H and 26-H), 4.48–4.50 (m, 2 H, 13-H and 24-H), 5.33 (s, 1 H, 5-H), 5.71 (s, 1 H, 3-H), 5.72 (s, 1 H, 7-H), 5.90 (s, 2 H, 2-H and 8-H), 6.95 (t, J = 8.0 Hz, 2 H, ArH), 7.11–7.20 (m, 9 H, ArH), 7.31–7.34 (m, 4 H, ArH), 7.98 (s, 2 H, NH, 22-H and 33-H), 8.55–8.61 (m, 2 H, NH, 10-H

and 11-H), 8.88–8.91 (m, 2 H, NH, 20-H and 31-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (C-16 and C-27), 14.4 (C-17 and C-28), 44.2 (C-5), 53.4 (C-13 and C-24), 61.7 (C-15 and C-26), 107.5 (C-3), 107.6 (C-7), 108.6 (C-2 and C-8), 119.2 (CH-Ar), 119.3 (CH-Ar), 123.4 (CH-Ar), 123.5 (C-1), 123.6 (C-9), 127.0 (CH-Ar), 128.3 (CH-Ar), 128.6 (CH-Ar), 129.0 (CH-Ar), 133.6 (C-4), 133.7 (C-6), 138.0 (C-23 and 34), 141.8 (C-12), 146.5 (C-18 and C-29), 153.8 (C-21 and C-32), 170.2 (C-14 and C-25) ppm. HRMS (ESI): calcd. for $C_{41}H_{45}N_8O_6$ [M + H]$^+$ 745.34566; found 745.34690.

1,9-Bis(2′-*tert*-butoxycarbonylhydrazono-1′-dimethylaminocarbonylpropyl)-5-phenyldipyrromethane (8b): Hydrazone **1b** (214 mg, 0.77 mmol) and dipyrromethane **6** (74 mg, 0.335 mmol) were employed as described in the general procedure for method A (reaction time of 3 h). Purification by flash chromatography (ethyl acetate/hexane, 3:1) afforded compound **8b**[9] (218 mg, 92%) as a pink solid.

1,9-Bis(2′-*tert*-butoxycarbonylhydrazono-1′-ethoxycarbonylpropyl)-5-phenyldipyrromethane (8c): Hydrazone **1c** (215 mg, 0.77 mmol) and dipyrromethane **6** (74 mg, 0.335 mmol) were employed as described in the general procedure for method A (reaction time of 3 h). Purification by flash chromatography (ethyl acetate/hexane, 1:2) afforded compound **8c** (168 mg, 71%) as a red solid; m.p. 98.5–100.1 °C (from diethyl ether/hexane). IR (KBr): $\tilde{\nu}$ = 769, 1161, 1244, 1369, 1496, 1728, 1732, 1979, 3352 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.2 Hz, 6 H), 1.46 and 1.50 (s, 18 H), 1.79 (s, 6 H), 4.17 (q, J = 7.2 Hz, 4 H), 4.69 (s, 2 H), 5.34–5.39 (m, 1 H), 5.74–5.82 (m, 2 H), 5.97 (s, 2 H), 7.17–7.31 (m, 5 H), 7.53 and 7.56 (s, 2 H, NH), 8.55 and 8.63 (br. s, 2 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 14.1, 28.3, 44.2, 53.3, 61.5, 81.3, 107.6, 108.0, 124.0, 126.9, 128.4, 128.5, 133.3, 141.8, 148.4, 152.6, 170.1 ppm. HRMS (ESI): calcd. for $C_{37}H_{51}N_6O_8$ [M + H]$^+$ 707.37629; found 707.37519.

Ethyl 3-(1-Benzyl-1*H*-tetrazol-5-yl)-6-[3-(5-{2-(1-benzyl-1*H*-tetrazol-5-yl)-2-[2-(ethoxycarbonyl)hydrazono]ethyl}-1*H*-pyrrol-2-yl)pentan-3-yl]-4,4a,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridazine-1-carboxylate (13): Hydrazone **9** [method A (332 mg, 0.90 mmol), method B (194 mg, 0.53 mmol)] and dipyrromethane **3** [method A (67 mg, 0.335 mmol), method B (47 mg, 0.23 mmol)] were employed as described in the general procedure for method A (reaction time of 4 h) and method B (reaction time of 7 d). Purification by flash chromatography (ethyl acetate/hexane, 1:1 and 1:2) afforded compound **13** [method A (86 mg, 33%), method B (79 mg, 44%)] as a white solid; m.p. 102.4–103.5 °C (diethyl ether/hexane). IR (KBr): $\tilde{\nu}$ = 723, 1136, 1201, 1226, 1321, 1412, 1631, 1680, 1728, 2979, 3263, 3411 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61–0.64 (m, 6 H, 16-H and 18-H), 1.29 (t, J = 8.0 Hz, 6 H, 10-H and 33-H), 1.88–1.95 (m, 4 H, 15-H and 17-H), 2.63–2.68 (m, 1 H, 7-H), 2.78 (dd, ^1J = 20.0 Hz, ^2J = 8.0 Hz, 4-H), 3.15–3.20 (m, 1 H, 7-H), 3.33–3.38 (m, 1 H, 4-H), 4.03 (d, J = 16.0 Hz, 1 H, 24-H), 4.14 (d, J = 16.0 Hz, 1 H, 24-H), 4.26–4.35 (m, 4 H, 9-H and 32-H), 4.58 (br. s, 2 H, 4a-H and 7a-H), 5.81 (s, 1 H, 21-H), 5.85 (s, 1 H, 20-H), 5.95–6.06 (m, 4 H, 12-H and 27-H), 7.27–7.43 (m, 10 H, ArH), 8.93 (s, 1 H, NH, 30-H), 10.4 (br. s, 1 H, NH, 23-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.2 (C-16), 8.3 (C-18), 14.4 (C-10), 14.4 (C-33), 25.6 (C-4), 26.5 (C-24), 27.2 (C-15), 27.3 (C-17), 41.8 (C-7), 48.7 (C-14), 52.4 (C-12 and C-27), 52.8 (C-7a), 61.6 (C-4a), 62.6 (C-31), 63.6 (C-8), 107.3 (C-20), 107.5 (C-21), 123.1 (C-22), 128.3 (CH-Ar), 128.4 (CH-Ar), 128.6 (CH-Ar), 128.7 (CH-Ar), 128.7 (CH-Ar), 131.6 (C-19), 134.5 (C-13 and C-28), 136.8 (C-25), 137.2 (C-3), 149.5 (C-11), 150.7 (C-26), 153.2 (C-31), 154.0 (C-8), 187.7 (C-6) ppm. HRMS (ESI): calcd. for $C_{39}H_{47}N_{14}O_4$ [M + H]$^+$ 775.38992; found 775.38795.

1,9-Bis(2′-ethoxycarbonylhydrazono-1′-benzyl-1*H*-tetrazol-5-yl)-5,5′-diethyldipyrromethane (16): Compound **13** (78 mg, 0.100 mmol) was dissolved in dry methanol (20 mL), and the resulting mixture was heated at reflux for 9 h. The solvent was evaporated, and the crude product was purified by flash chromatography (ethyl acetate/hexane, 1:1) to give compound **16** (44 mg, 57%) as a white solid; m.p. 114.6–116.1 °C (diethyl ether/hexane). IR (KBr): $\tilde{\nu}$ = 723, 1064, 1221, 1412, 1498, 1616, 1720, 1751, 2968, 3267, 3342, 3409 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61 (t, J = 8.0 Hz, 6 H, 13-H and 15-H), 1.32 (t, J = 8.0 Hz, 6 H, 22-H and 32-H), 1.80 (q, J = 8.0 Hz, 4 H, 12-H and 14-H), 4.00 (s, 4 H, 16-H and 26-H), 4.32 (q, J = 8.0 Hz, 4 H, 21-H and 31-H), 5.74 (s, 2 H, 2-H and 8-H), 5.86 (s, 2 H, 3-H and 7-H), 6.01 (s, 4 H, 24-H and 34-H), 7.28–7.29 (m, 6 H, ArH), 7.42 (br. s, 4 H, ArH), 8.25 (br. s, 2 H, NH, 10-H and 11-H), 8.89 (s, 2 H, NH, 19-H and 29-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.3 (C-13 and C-15), 14.4 (C-22 and C-32), 26.7 (C-16 and C-26), 29.4 (C-12 and C-14), 43.5 (C-5), 52.8 (C-24 and C-34), 62.7 (C-21 and C-31), 106.5 (C-3 and C-7), 106.8 (C-2 and C-8), 121.0 (C-1 and C-9), 128.6 (CH-Ar), 128.7 (CH-Ar), 134.4 (C-25 and C-35), 136.8 (C-17 and C-27), 137.3 (C-4 and C-6), 150.7 (C-23 and C33), 153.3 (C-20 and C-30) ppm. HRMS (ESI): calcd. for $C_{39}H_{47}N_{14}O_4$ [M + H]$^+$ 775.38992; found 775.38906.

General Procedure for the Monofunctionalization of Dipyrromethanes

Method A – On-Water: Dipyrromethane **3** or **6** (1.08 mmol) and a solution of hydrazone **1** or **9** (0.54 mmol) in dichloromethane (1.5 mL) were added to a solution of Na_2CO_3 (2.7 mmol) in water (9 mL). The reaction mixture was stirred at room temperature for 2 h. The mixture was then extracted with dichloromethane (3 × 20 mL), and the combined extracts were dried with Na_2SO_4. The solvent was evaporated to give the crude product, which was purified by flash chromatography.

Method B – In Dichloromethane: Dipyrromethane **3** or **6** (1.08 mmol) and hydrazone **1** or **9** (0.54 mmol) were added to a suspension of Na_2CO_3 (2.7 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature for the time indicated, and the progress of the reaction was monitored by TLC. Upon completion, the mixture was filtered through a pad of Celite, which was washed with dichloromethane. The solvent was evaporated, and the product was purified by flash chromatography.

1-(2′-Phenylcarbamoylhydrazono-1′-ethoxycarbonylpropyl)-5,5′-diethyldipyrromethane (4a) and 1,9-Bis(2′-phenylcarbamoylhydrazono-1′-ethoxycarbonylpropyl)-5,5′-diethyldipyrromethane (5a): Hydrazone **1a** (161 mg, 0.54 mmol) and dipyrromethane **3** (218 mg, 1.08 mmol) were employed as described in the general procedure for method A. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:1) gave, in order of elution, **4a** (204 mg, 81%) as a yellowish solid and **5a**[9] (65 mg, 17%) as a white solid. Data for **4a**: M.p. 72.5–74.2 °C (diethyl ether/hexane). IR (KBr): $\tilde{\nu}$ = 754, 1034, 1228, 1448, 1533, 1689, 1728, 2968, 3371 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70 (t, J = 7.6 Hz, 6 H), 1.26 (t, J = 7.2 Hz, 3 H), 1.88 (s, 3 H), 1.93 (q, J = 7.6 Hz, 4 H), 4.19–4.22 (m, 2 H), 4.57 (s, 1 H), 6.01 (dd, ^1J = 9.2 Hz, ^2J = 2.8 Hz, 2 H), 6.08–6.11 (m, 2 H), 6.60 (d, J = 0.8 Hz, 1 H), 7.05 (t, J = 7.6 Hz, 1 H), 7.29 (t, J = 7.6 Hz, 2 H), 7.45 (d, J = 7.6 Hz, 2 H), 7.78 (br. s, 1 H, NH), 8.07 (s, 1 H, NH), 8.23 (br. s, 1 H, NH), 8.78 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.4, 14.1, 29.5, 43.6, 53.5, 61.6, 105.9, 106.2, 107.6, 107.8, 116.8, 119.3, 123.1, 123.3, 128.9, 136.3, 137.8, 138.0, 146.4, 153.7, 170.1 ppm. HRMS (ESI): calcd. for $C_{26}H_{34}N_5O_3$ [M + H]$^+$ 464.26562; found 464.26458.

1-(2′-*tert*-Butoxycarbonylhydrazono-1′-dimethylaminocarbonylpropyl)-5,5′-diethyldipyrromethane (4b) and 1,9-Bis(2′-*tert*-Butoxycarbonylhydrazono-1′-dimethylaminocarbonylpropyl)-5,5′-diethyldipyrromethane (5b): Hydrazone **1b** (150 mg, 0.54 mmol) and dipyrromethane **3** (218 mg, 1.08 mmol) were employed as described in the general procedure for method A. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 3:1) gave, in order of elution, **4b** (65 mg, 27%) as yellowish solid and **5b**[9] (115 mg, 31%) as a white solid. Data for **4b**: M.p. 136.3–136.9 °C (diethyl ether/hexane). IR (KBr): $\tilde{\nu}$ = 761, 1169, 1241, 1511, 1643, 1724, 2971, 3303, 3384 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68–0.73 (m, 6 H), 1.50 (s, 9 H), 1.73 (s, 3 H), 1.90–1.97 (m, 4 H), 2.92 (s, 3 H), 3.03 (s, 3 H), 4.98 (s, 1 H), 5.97 (br. s, 2 H), 6.04 (br. s, 1 H), 6.10 (d, J = 2.8 Hz, 1 H), 6.61 (br. s, 1 H), 7.44 (br. s, 1 H, NH), 7.91 (br. s, 1 H, NH), 8.62 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.4, 12.9, 28.3, 29.5, 29.6, 35.8, 37.8, 43.6, 50.4, 81.2, 105.7, 106.1, 107.3, 107.5, 116.6, 124.2, 136.4, 137.2, 150.6, 152.7, 170.0 ppm. HRMS (ESI): calcd. for $C_{24}H_{38}N_5O_3$ [M + H]$^+$ 444.29692; found 444.29605.

1-(2′-*tert*-Butoxycarbonylhydrazono-1′-ethoxycarbonylpropyl)-5,5′-diethyldipyrromethane (4c) and 1,9-Bis(2′-*tert*-butoxycarbonylhydrazono-1′-ethoxycarbonylpropyl)-5,5′-diethyldipyrromethane (5c): Hydrazone **1c** (151 mg, 0.54 mmol) and dipyrromethane **3** (218 mg, 1.08 mmol) were employed as described in the general procedure for method A. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:2) gave, in order of elution, **4c**[9] (127 mg, 53%) as yellow solid and **5c**[9] (48 mg, 13%) as a white solid.

1-(2′-Phenylcarbamoylhydrazono-1′-ethoxycarbonylpropyl)-5-phenyldipyrromethane (7a) and 1,9-Bis(2′-phenylcarbamoylhydrazono-1′-ethoxycarbonylpropyl)-5-phenyldipyrromethane (8a): Hydrazone **1a** (161 mg, 0.54 mmol) and dipyrromethane **6** (240 mg, 1.08 mmol) were employed as described in the general procedure for method A. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:2) gave, in order of elution, **7a** (110 mg, 42%) as a red solid and **8a** (72 mg, 18%) as a red foam. Data for **7a**: M.p. 83.3–84.8 °C (diethyl ether/hexane). IR (KBr): $\tilde{\nu}$ = 727, 1448, 1533, 1595, 1685, 1728, 3369 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.27 (m, 3 H, 15-H), 1.90 (s, 3 H, 16-H), 4.19–4.21 (m, 2 H, 14-H), 4.59 (s, 1 H, 12-H), 5.42 (s, 1 H, 5-H), 5.80 (d, J = 4.0 Hz, 1 H, 2-H), 5.89 (s, 1 H, 8-H), 6.00 (s, 1 H, 3-H), 6.11 (t, J = 4.0 Hz, 1 H, 7-H), 6.63 (s, 1 H, 9-H), 7.04 (t, J = 8.0 Hz, 1 H, ArH), 7.17–7.29 (m, 7 H, ArH), 7.41 (d, J = 8.0 Hz, 2 H, ArH), 7.96 (br. s, 1 H, NH, 10-H), 8.05 (s, 1 H, NH, 21-H), 8.61 (d, J = 8.0 Hz, 1 H, NH, 11-H), 8.91 (d, J = 4.0 Hz, 1 H, NH, 19-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (C-15), 14.4 (C-16), 44.1 (C-5), 53.5 (C-12), 61.7 (C-14), 107.2 (C-8), 107.6 (C-2), 108.4 (C-7), 108.6 (C-3), 117.3 (C-9), 119.3 (CH-Ar), 123.3 (CH-Ar), 123.5 (C-1), 127.0 (CH-Ar), 128.4 (CH-Ar), 128.6 (CH-Ar), 128.7 (CH-Ar), 129.0 (CH-Ar), 132.4 (C-6), 133.8 (C-23), 138.0 (C-22), 142.0 (C-4), 146.4 (C-17), 153.8 (C-20), 170.1 (C-13) ppm. HRMS (ESI): calcd. for $C_{28}H_{30}N_5O_3$ [M + H]$^+$ 484.23432; found 484.23368.

1-(2′-*tert*-Butoxycarbonylhydrazono-1′-dimethylaminocarbonylpropyl)-5-phenyldipyrromethane (7b) and 1,9-Bis(2′-*tert*-butoxycarbonylhydrazono-1′-dimethylaminocarbonylpropyl)-5-phenyldipyrromethane (8b): Hydrazone **1b** (150 mg, 0.54 mmol) and dipyrromethane **6** (240 mg, 1.08 mmol) were employed as described in the general procedure for method A. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 3:1) gave, in order of elution, **7b**[9] (145 mg, 58%) as a purple solid and **8b**[9] (69 mg, 18%) as a pink solid.

1-(2′-*tert*-Butoxycarbonylhydrazono-1′-ethoxycarbonylpropyl)-5-phenyldipyrromethane (7c) and 1,9-Bis(2′-*tert*-butoxycarbonylhydrazono-1′-ethoxycarbonylpropyl)-5-phenyldipyrromethane (8c): Hydrazone **1c** (151 mg, 0.54 mmol) and dipyrromethane **6** (240 mg, 1.08 mmol) were employed as described in the general procedure for method A. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:2) gave, in order of elution, **7c** (161 mg, 64%) as a red solid and **8c** (19 mg, 5%) as a red solid. Data for **7c**: M.p. 68.9–70.4 °C (diethyl ether/hexane). IR (KBr): $\tilde{\nu}$ = 727, 1161, 1244, 1369, 1496, 1724, 2979, 3367 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.26 (m, 3 H), 1.46 and 1.50 (s, 9 H), 1.78 and 1.81 (s, 3 H), 4.11–4.19 (m, 2 H), 4.66 (s, 1 H), 5.41 (d, J = 3.6 Hz, 1 H), 5.76–5.83 (m, 1 H), 5.87 (br. s, 1 H), 5.98 (br. s, 1 H), 6.12 (br. s, 1 H), 6.69 (br. s, 1 H), 7.18–7.38 (m, 5 H), 7.51 (s, 1 H, NH), 8.25 (br. s, 1 H, NH), 8.66 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 14.1, 28.3, 44.1, 53.3, 61.6, 81.5, 107.1, 107.3, 108.0, 108.2, 117.4, 123.8, 126.8, 128.4, 128.5, 132.4, 133.5, 142.3, 152.6, 170.1 ppm. HRMS (ESI): calcd. for $C_{26}H_{33}N_4O_4$ [M + H]$^+$ 465.24963; found 465.24934.

1-(2′-Ethoxycarbonylhydrazono-1′-benzyl-1*H*-tetrazol-5-yl)-5,5′-diethyldipyrromethane (11), Ethyl 6-[3-(1*H*-Pyrrol-2-yl)pentan-3-yl]-3-(1-benzyl-1*H*-tetrazol-5-yl)-4,4a,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*c*]-pyridazine-1-carboxylate (12), and Ethyl 3-(1-Benzyl-1*H*-tetrazol-5-yl)-6-[3-(5-{2-(1-benzyl-1*H*-tetrazol-5-yl)-2-[2-(ethoxycarbonyl)-hydrazono]ethyl}-1*H*-pyrrol-2-yl)pentan-3-yl]-4,4a,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridazine-1-carboxylate (13): hydrazone **9** (200 mg, 0.54 mmol) and dipyrromethane **3** (218 mg, 1.08 mmol) were employed as described in the general procedure for method A or B (reaction time of 24 h). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:2) gave, in order of elution, **11** [method A (36 mg, 14%), method B (43 mg, 16%)] as a white solid, **12** [method A (101 mg, 38%), method B (139 mg, 53%)] as a white solid, and **13** [method A (29 mg, 7%)] as a white solid. Data for **11**: M.p. 154.2–154.7 °C (diethyl ether/hexane). IR (KBr): $\tilde{\nu}$ = 723, 1064, 1187, 1319, 1430, 1600, 1691, 3388 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.65 (t, J = 8.0 Hz, 6 H, 13-H and 15-H), 1.33 (t, J = 8.0 Hz, 3 H, 22-H), 1.88 (q, J = 8.0 Hz, 4 H, 12-H and 14-H), 4.05 (s, 2 H, 16-H), 4.32 (q, J = 8.0 Hz, 2 H, 21-H), 5.81 (s, 1 H, 2-H), 5.92 (d, J = 4.0 Hz, 1 H, 3-H), 5.99 (s, 2 H, 24-H), 6.03 (s, 1 H, 7-H), 6.08 (d, J = 4.0 Hz, 1 H, 8-H), 6.56 (s, 1 H, 9-H), 7.29–7.30 (m, 3 H, ArH), 7.41 (br. s, 2 H, ArH), 7.74 (br. s, 1 H, NH, 10-H), 8.24 (br. s, 1 H, NH, 11-H), 8.57 (br. s, 1 H, NH, 19-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.2 (C-13 and C-15), 14.5 (C-22), 27.0 (C-16), 29.1 (C-12 and C-14), 43.4 (C-5), 52.8 (C-24), 62.8 (C-21), 105.9 (C-7), 106.4 (C-3), 106.9 (C-2), 107.5 (C-8), 116.9 (C-9), 121.1 (C-1), 128.5 (CH-Ar), 128.6 (CH-Ar), 128.7 (CH-Ar), 134.4 (C-25), 136.1 (C-6), 136.8 (C-17), 138.3 (C-4), 150.6 (C-23), 153.1 (C-20) ppm. HRMS (ESI): calcd. for $C_{26}H_{33}N_8O_2$ [M + H]$^+$ 489.27210; found 489.27107. Data for **12**: M.p. 149.4–150.9 °C (ethyl acetate/hexane). IR (KBr): $\tilde{\nu}$ = 723, 1126, 1322, 1381, 1406, 1624, 1720, 2966, 3250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.60 (t, J = 8.0 Hz, 3 H, 15-H), 0.63 (t, J = 8.0 Hz, 3 H, 17-H), 1.30 (t, J = 8.0 Hz, 3 H, 20-H), 1.87–1.91 (m, 4 H, 14-H and 16-H), 2.50 (dd, ^1J = 16.0 Hz, ^2J = 4.0 Hz, 1 H, 7-H), 2.78 (dd, ^1J = 20.0 Hz, ^2J = 4.0 Hz, 1 H, 4-H), 3.05 (dd, ^1J = 16.0 Hz, ^2J = 4.0 Hz, 1 H, 7-H), 3.30 (dd, ^1J = 16.0 Hz, ^2J = 4.0 Hz, 1 H, 4-H), 4.33 (q, J = 8.0 Hz, 2 H, 19-H), 4.42–4.47 (m, 1 H, 4-Ha), 4.53–4.58 (m, 1 H, 7-Ha), 5.95 (s, 1 H, 10-H), 6.01 (s, 2 H, 22-H), 6.10 (d, J = 4.0 Hz, 1 H, 11-H), 6.60 (d, J = 4.0 Hz, 1 H, 12-H), 7.27–7.29 (m, 3 H, ArH), 7.37–7.38 (m, 2 H, ArH), 9.16 (br. s, 1 H, NH, 13-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.5 (C-15), 8.6 (C-17), 14.5 (C-20), 26.6 (C-4), 29.0 (C-14), 29.1 (C-16), 41.9 (C-7), 48.1 (C-8), 52.3 (C-22), 53.6 (C-7a), 63.2 (C-4a), 63.3 (C-19), 105.3 (C-10), 107.8 (C-11), 116.6 (C-12), 128.3 (CH-Ar), 128.5 (CH-Ar), 128.8 (CH-Ar), 133.4 (C-9), 134.6 (C-23), 137.9 (C-

3), 149.8 (C-21), 154.2 (C-18), 183.2 (C-6) ppm. HRMS (ESI): calcd. for $C_{26}H_{33}N_8O_2$ [M + H]$^+$ 489.27210; found 489.27075.

1-(2′-Ethoxycarbonylhydrazono-1′-benzyl-1*H*-tetrazol-5-yl)-5-phenyldipyrromethane (18): Hydrazone **9** (200 mg, 0.54 mmol) and dipyrromethane **6** (240 mg, 1.08 mmol) were employed as described in the general procedures for methods A and B (reaction time of 22 h). Purification by flash chromatography (ethyl acetate/hexane, 1:2) gave **18** [method A (49 mg, 18%), method B (74 mg, 27%)] as a yellow solid; m.p. 107.4–109.1 °C (diethyl ether/hexane). IR (KBr): $\tilde{\nu}$ = 723, 1064, 1223, 1430, 1685, 1701, 1709, 3340 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.2 Hz, 3 H), 4.06 (s, 2 H), 4.34 (q, J = 7.2 Hz, 2 H), 5.34 (s, 1 H), 5.75 (s, 1 H), 5.84 (s, 1 H), 5.87 (s, 1 H), 5.99 (s, 2 H), 6.11 (d, J = 2.8 Hz, 1 H), 6.66 (s, 1 H), 7.13–7.16 (m, 2 H), 7.23–7.30 (m, 6 H), 7.44 (br. s, 2 H), 7.88 (br. s, 1 H, NH), 8.50 (br. s, 1 H, NH), 8.59 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 26.7, 44.0, 52.8, 62.9, 107.3, 107.5, 107.6, 108.4, 117.3, 121.5, 127.1, 128.3, 128.6, 128.7, 128.8, 132.1, 134.1, 134.3, 141.7, 150.7 ppm. HRMS (ESI): calcd. for $C_{28}H_{29}N_8O_2$ [M + H]$^+$ 509.24080; found 509.24052.

General Procedure for *N*-Deprotection of Compounds 11 and 16: Anhydrous ammonium formate (2.5 mmol) was added in a single portion under nitrogen to a stirred suspension of compound **11** or **16** (0.25 mmol) and an equal mass of 10% Pd/C in dry methanol (20 mL). The resulting mixture was stirred, heated at reflux for 1 h, and then cooled to room temperature. The catalyst was removed by filtration through a pad of Celite, which was washed with methanol. The combined filtrates were concentrated under reduced pressure to give a residue that was triturated with diethyl ether and filtered to give the final product.

1-(2′-Ethoxycarbonylhydrazono-1′-1*H*-tetrazol-5-yl)-5,5′-diethyldipyrromethane (14): Compound **11** (122 mg, 0.25 mmol) was employed as described in the general procedure to give **14** (91 mg, 91%) as grey solid; m.p. >160 °C (dec., diethyl ether). IR (KBr): $\tilde{\nu}$ = 771, 1051, 1248, 1385, 1523, 1720, 2968, 3411 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.53–0.58 (m, 6 H), 1.24–1.28 (m, 3 H), 1.86–1.90 (m, 4 H), 3.99 (s, 1 H), 4.17 (s, 1 H), 4.19–4.23 (m, 2 H), 5.50 (s, 1 H), 5.65 (s, 1 H), 5.80 (s, 1 H), 5.87–5.89 (m, 1 H), 6.55–6.57 (m, 1 H), 9.96–10.05 (m, 1 H, NH), 10.13 (s, 1 H, NH), 10.74 (s, 1 H, NH), 11.86 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 8.4, 14.4, 25.7, 28.7, 42.8, 61.2, 104.8, 105.0, 105.2, 106.2, 116.6, 122.2, 136.4, 153.4 ppm. HRMS (ESI): calcd. for $C_{19}H_{27}N_8O_2$ [M + H]$^+$ 399.22515; found 399.22437.

1,9-Bis(2′-ethoxycarbonylhydrazono-1′-1*H*-tetrazol-5-yl)-5,5′-diethyldipyrromethane (17): Compound **16** (194 mg, 0.25 mmol) was employed as described in the general procedure to give **17** (147 mg, 99%) as grey solid; m.p. >140 °C (dec., diethyl ether). IR (KBr): $\tilde{\nu}$ = 771, 1038, 1257, 1400, 1539, 1593, 1724, 2981, 3163 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.48–0.58 (m, 6 H), 1.21–1.26 (m, 6 H), 1.80–1.82 (m, 4 H), 3.94 (s, 4 H), 4.08–4.18 (m, 4 H), 5.51–5.54 (m, 1 H), 5.57 (br. s, 2 H), 5.62 (br. s, 1 H), 8.41 (s, 3 H, NH), 10.06 (br. s, 2 H, NH), 12.84 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 8.5, 14.4, 14.5, 24.8, 26.1, 28.6, 29.1, 33.0, 42.6, 42.8, 60.0, 60.4, 61.0, 64.9, 104.6, 104.8, 104.9, 126.7, 126.8, 135.3, 135.4, 157.6, 160.6, 165.5 ppm. HRMS (ESI): calcd. for $C_{25}H_{35}N_{14}O_4$ [M + H]$^+$ 595.29602; found 595.29584.

General Procedure for the Synthesis of Bilanes and Calix[4]pyrroles: Dipyrromethane **3** (0.82 mmol) and hydrazone **19a** or **19b** (0.41 mmol) were added to a suspension of Na_2CO_3 (4.1 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 96 h. The mixture was then filtered through a pad of Celite, which was washed with dichloromethane. The solvent was evaporated, and the product was purified by flash chromatography.

5,5′,15,15′-Tetraethyl-10-(1′-*tert*-butoxycarbonylhydrazonoethyl)-bilane (22a) and 5,5′,15,15′-Tetraethyl-10,20-bis(1′-*tert*-butoxycarbonylhydrazonoethyl)calix[4]pyrrole (23a): Hydrazone **19a** (100 mg, 0.41 mmol) and dipyrromethane **3** (167 mg, 0.82 mmol) were employed as described in the general procedure. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:4) gave, in order of elution, **22a** (38 mg, 16%) as yellow solid and **23a** (49 mg, 16%) as yellow solid. Data for **22a**: M.p. 58.6–59.4 °C (ethyl acetate/hexane). IR: $\tilde{\nu}$ = 714, 764, 1039, 1157, 1234, 1367, 1491, 1717, 2964, 3360 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.66–0.72 (m, 12 H), 1.51 (s, 9 H), 1.71 (s, 3 H), 1.87–1.92 (m, 8 H), 4.85 (s, 1 H), 5.81 (s, 2 H), 5.95 (t, J = 2.8 Hz, 2 H), 6.03 (s, 2 H), 6.10 (d, J = 2.8 Hz, 2 H), 6.62 (s, 2 H), 741 (s, 1 H, NH), 8.02 (br. s, 2 H, NH), 8.09 (br. s, 2 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.4, 28.3, 29.5, 29.6, 43.5, 47.0, 81.3, 105.6, 105.8, 106.3, 107.3, 116.8, 128.1, 136.6, 136.8, 152.0, 152.8 ppm. HRMS (ESI): calcd. for $C_{34}H_{48}N_6NaO_2$ [M + Na]$^+$ 595.37310; found 595.37324. Data for **23a**: M.p. >160 °C (dec., ethyl acetate/hexane). IR: $\tilde{\nu}$ = 763, 1045, 1156, 1239, 1367, 1491, 1708, 2967, 3306 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.62 (t, J = 7.2 Hz, 6 H), 0.71 (t, J = 7.2 Hz, 6 H), 1.50 (s, 18 H), 1.81 (s, 6 H), 1.84–1.89 (m, 8 H), 4.96 (s, 2 H), 5.85 (s, 4 H), 5.91 (s, 4 H), 7.38 (s, 2 H, NH), 8.18 (br. s, 4 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.28, 8.32, 28.3, 43.1, 46.9, 81.3, 105.4, 106.1, 128.6, 137.3, 151.7, 153.1 ppm. HRMS (ESI): calcd. for $C_{42}H_{61}N_8O_4$ [M + H]$^+$ 741.48103; found 741.47976.

5,5′,15,15′-Tetraethyl-10-[1′-*tert*-butoxycarbonylhydrazono-1′-(*p*-bromophenyl)methyl]bilane (22b) and 5,5′,15,15′-Tetraethyl-10,20-bis[1′-*tert*-butoxycarbonylhydrazono-1′-(*p*-bromophenyl)methyl]-calix[4]pyrrole (23b): Hydrazone **19b** (157 mg, 0.41 mmol) and dipyrromethane **3** (167 mg, 0.82 mmol) were employed as described in the general procedure. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:5) gave, in order of elution, **23b** (29 mg, 7%) as yellow solid and **22b** (23 mg, 8%) as yellow solid. Data for **22b**: M.p. 72.6–74.2 °C (ethyl acetate/hexane). IR: $\tilde{\nu}$ = 714, 753, 1086, 1154, 1232, 1480, 1731, 2963, 3362 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68 (t, J = 7.2 Hz, 12 H), 1.46 (s, 9 H), 1.85–1.92 (m, 8 H), 5.14 (s, 1 H), 5.76 (s, 2 H), 5.92 (s, 2 H), 6.02 (s, 2 H), 6.10 (d, J = 2.4 Hz, 2 H), 6.63 (br. s, 4 H), 7.37 (br. s, 1 H, NH), 7.46 (d, J = 8.0 Hz, 2 H), 7.96 (br. s, 2 H, NH), 8.10 (br. s, 2 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.4, 28.2, 29.1, 43.3, 46.6, 81.7, 105.5, 105.9, 107.0, 107.3, 116.8, 127.4, 129.1, 132.5, 136.7, 137.1, 151.9, 152.5 ppm. HRMS (ESI): calcd. for $C_{39}H_{50}BrN_6O_2$ [M + H]$^+$ 713.31731; found 713.31697. Data for **23b**: M.p. >180 °C (dec., ethyl acetate/hexane). IR: $\tilde{\nu}$ = 750, 1091, 1154, 1226, 1482, 1739, 2969, 3362 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.63 (t, J = 7.2 Hz, 12 H), 1.44 (s, 18 H), 1.70–1.83 (m, 8 H), 5.18 (s, 2 H), 5.87 (s, 4 H), 5.89 (s, 4 H), 6.90 (d, J = 8.4 Hz, 4 H), 7.43 (s, 2 H, NH), 7.49 (d, J = 8.4 Hz, 4 H), 8.20 (br. s, 4 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.3, 28.2, 28.7, 43.1, 46.6, 81.6, 105.4, 106.7, 123.9, 128.2, 129.2, 131.7, 132.6, 137.4, 150.9, 152.6 ppm. HRMS (ESI): calcd. for $C_{52}H_{63}Br_2N_8O_4$ [M + H]$^+$ 1021.33335; found 1021.33080.

***tert*-Butyl 6-Methyl-1,2-dihydro-1,2,3,4-tetrazine-2-carboxylate (24):** Triethylamine (1.23 mmol) was added to a solution of hydrazone **19a** (0.41 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 3 h. The mixture was then extracted with dichloromethane (3× 20 mL), and the combined extracts were dried with Na_2SO_4. The solvent was evaporated, and the resulting residue was purified by flash chromatog-

raphy (ethyl acetate/hexane, 1:3) to give compound **24** (73 mg, 90%) as a white solid; m.p. 113.4–115.2 °C (from ethyl acetate/hexane). IR: $\tilde{\nu}$ = 1012, 1138, 1238, 1533, 1696, 3189 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.57 (s, 9 H), 1.93 (s, 3 H), 8.27 (br. s, 1 H, NH), 9.52 (s, 1 H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.7, 28.1, 83.3, 147.7, 151.3, 191.3 ppm.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra of all new compounds; COSY, NOESY, HMQC and HMBC spectra of compounds **7a**, **8a**, **11**, **12**, **13** and **16**.

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