Synthesis and Functional Group Transformations of Tris(pyrazol-1-yl)methane (Tpm) and -ethane (Tpe) Derivatives for the Preparation of Sterically Hindered Chelating Macrobicycles

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Abstract: Tris(pyrazol-1-yl)methane (Tpm) and -ethane (Tpe) chelate derivatives bearing *meta*-benzonitrile groups in the position *ortho* to the coordinating nitrogen atom have been prepared from 3-(1*H*-pyrazol-3-yl)benzonitrile, and subjected to functional group transformations leading to the corresponding benzylthiol-substituted derivatives. The Tpe analogue was reacted with 1,3,5-tribromomethylbenzene in basic conditions to afford the Tpe-incorporating macrobicycle **2** in 40% yield.

Key words: chelates, heterocycles, ligands, macrobicycles, pyrazoles

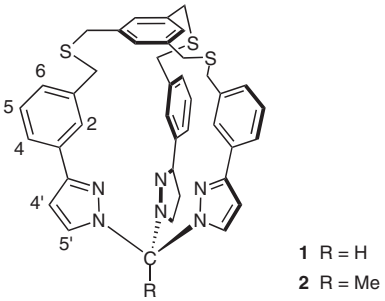

Figure 1 Macrobicycles **1** and **2**

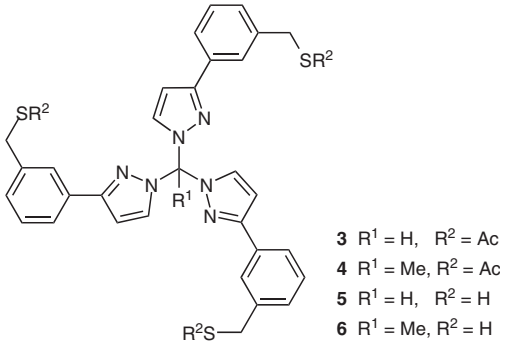

Figure 2 Benzylthiol-functionalized Tpm **5** and Tpe **6**, and their respective benzylthioacetate precursors **3** and **4**

Tris(pyrazol-1-yl)methane[2] (Tpm) chelates derive from analogous tris(pyrazol-1-yl)hydroborates[3] (Tp) by substitution of BH^- by the isoelectronic methine (CH) connector. The coordination chemistry[4] and applications[5] of these neutral nitrogen-based ligands are much less developed than those of negatively charged scorpionates, which have been used notably in transition metal catalysis[6] and metalloenzyme mimicry.[7] Such applications have required the development of a range of substituted scorpionates in order to control the steric environment and the coordination sphere of the metal cation.[8]

Rather than using Tpm ligands bearing bulky substituents ortho (position 3′) to the coordinating nitrogen atoms, we have developed a family of macrobicycles incorporating the Tpm chelate (Figure 1).[9] In these molecules, the [N3] coordinating site is capped by a benzenic fragment that restricts the space available for ancillary ligands, which leads to unusual coordination properties of the Tpm chelate. For example, reaction of **1** with $[Cu(MeCN)_4]^+$ in wet acetone ultimately leads to the helical coordination polymer $[Cu(\mathbf{1})(H_2O)]_n^{n+}$, the water molecule of which is contained inside the cavity of the macrobicycle subunits, and simultaneously bound to Cu(I) and a pyrazole nitrogen.[9b] The macrobicycles are prepared by tripod-tripod coupling reaction between benzylthiol-substituted Tpm (**5** for **1**, Figure 2), or tris(pyrazol-1-yl)ethane Tpe (**6** for **2**), and 1,3,5-tribromomethylbenzene in basic conditions.

This work reports a straightforward synthesis of the benzylthiol-functionalized Tpm **5** and Tpe **6**. By contrast to earlier studies (see below),[9] the tripodal framework is elaborated at an early stage of the macrobicycle synthesis, starting from the appropriate benzonitrile-substituted pyrazole, the function of which is not sensitive to either acidic or basic media (reaction conditions of Tpm synthesis). The preparation of macrobicycle **2**, which incorporates the rare tris(pyrazol-1-yl)ethane chelate, is presented lastly.

Homoleptic tris(pyrazolyl)methane ligands built from symmetrically-substituted pyrazoles are usually readily prepared by heating a chloroform solution of the pyrazole of interest in the presence of a base under either solid–liquid[10] or liquid–liquid[11] phase-transfer catalysis (method A). For example, tris(pyrazol-1-yl)methane and tris(3,5-dimethyl-1-pyrazolyl)methane were isolated in 63% and 65% yield, respectively, in the latter reaction conditions. When unsymmetrically substituted pyrazoles are involved (e.g., different substituents on the positions 3 and 5), a mixture of regioisomers is obtained, which can

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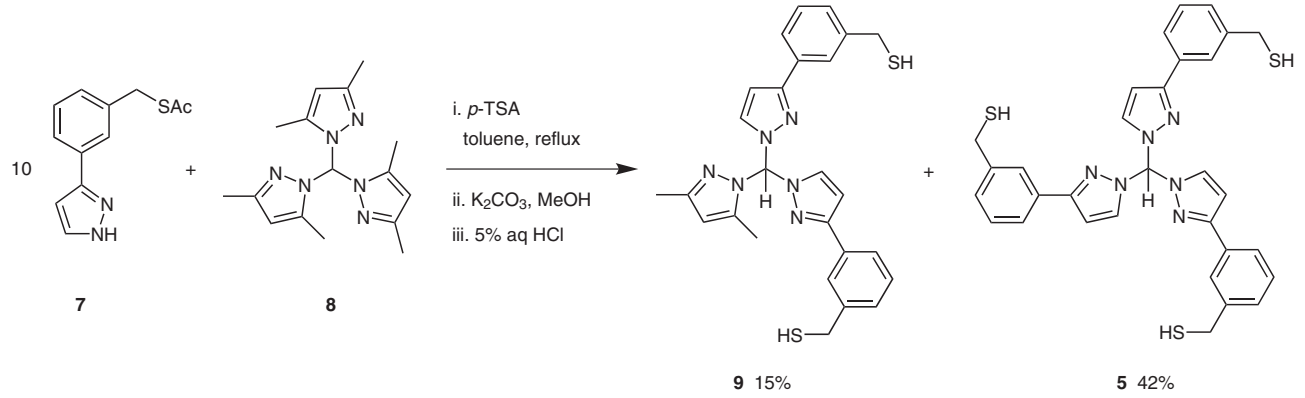
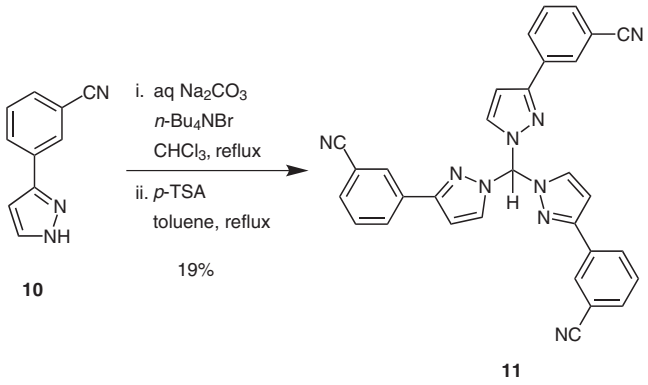


Scheme 1 One-pot formation of Tpm **5**[9a]

be converted to the less sterically hindered species by equilibration of the reaction mixture in refluxing toluene containing catalytic amounts of *p*-TSA.[11,12] Alternatively, treatment of a prototypical tris(pyrazolyl)methane (1 equiv) with an excess (10 equiv) of the pyrazole of interest in the presence of *p*-TSA (1 equiv) in refluxing toluene was shown to produce a mixture of heteroleptic and homoleptic tris(pyrazolyl)methanes (method B).[13]

In earlier studies benzylthiol-substituted Tpm **5** was synthesized from pyrazole **7** bearing a benzylthioacetate group in position 3′ and tris(3,5-dimethyl-1-pyrazolyl)methane **8**, under conditions B (Scheme 1).[9a] However, the thioacetate function was cleaved to some extent even in acidic medium (*p*-TSA in refluxing toluene), thus impeding the clean formation of the benzylthioacetate-substituted Tpm intermediate **3**. Instead, Tpm with mixed CH_2SAc and CH_2SH functions were obtained.[14] Methanolysis of the crude reaction mixture in the presence of K_2CO_3 followed by column chromatography afforded the desired homoleptic **5**, and heteroleptic **9** benzylthiol-substituted Tpm in 42% and 15% yield, respectively.[9a]

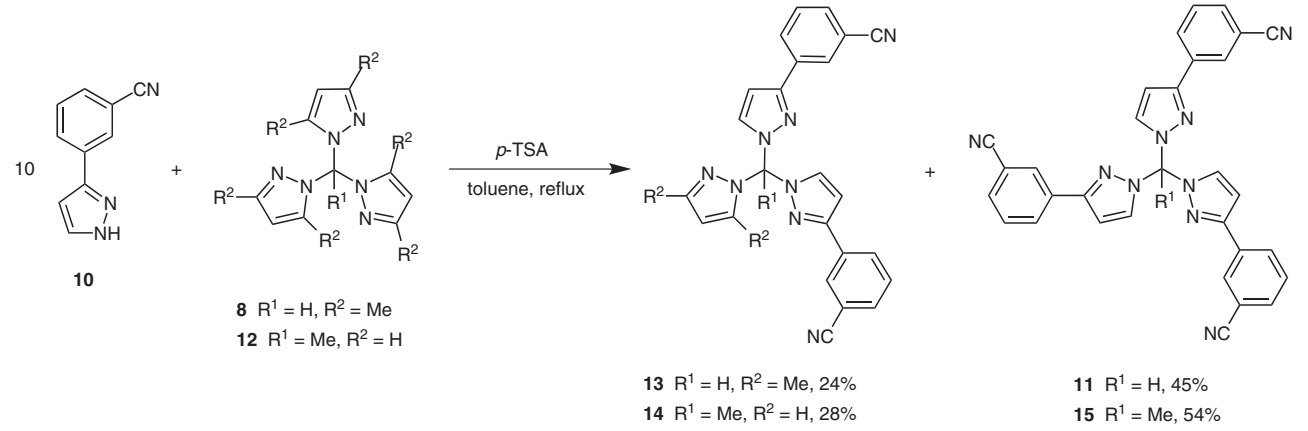
In the new synthetic strategy reported here, the chelate skeletons of macrobicycles **1** and **2** were elaborated starting from 3-(1*H*-pyrazol-3-yl)benzonitrile (**10**).[15] At first (conditions A, Scheme 2), heating **10** in a refluxing mixture of $CHCl_3$ and water for two days in the presence of Na_2CO_3 and *n*-Bu_4NBr produced a mixture of isomeric tris(pyrazolyl)methanes, which were subsequently equilibrated for 24 hours in refluxing toluene in the presence of *p*-TSA. Product **11** was separated from the starting material by chromatography and obtained in 19% yield. In conditions B (Scheme 3), a mixture of **10** (10 equiv) and Tpm **8** (1 equiv) was heated in refluxing toluene in the presence of *p*-TSA (1 equiv) for two days. Column chromatography of the crude mixture allowed to separate the desired homoleptic Tpm **11** (45%) from the heteroleptic Tpm **13** (24%). Whereas **11** can be prepared using either method A or B, this is not the case with its tris(pyrazol-1-yl)ethane homologue **15**, which obviously cannot be formed from $CHCl_3$. Therefore, conditions B, using the known tris(pyrazol-1-yl)ethane Tpe **12**[16] instead of Tpm **8** were explored. In these conditions, Tpe derivative **15** was obtained in 54% yield, alongside with heteroleptic derivative **14** (28%). Interestingly, **14** can be converted into **15** by reaction with **10** (20 equiv) and *p*-TSA (1 equiv) in refluxing toluene. The desired homoleptic Tpm **15** is obtained in 53% yield after chromatographic separation. These experiments show that the metathesis reaction that was developed for tris(pyrazol-1-yl)methanes[13] also works in the case of tris(pyrazol-1-yl)ethane.



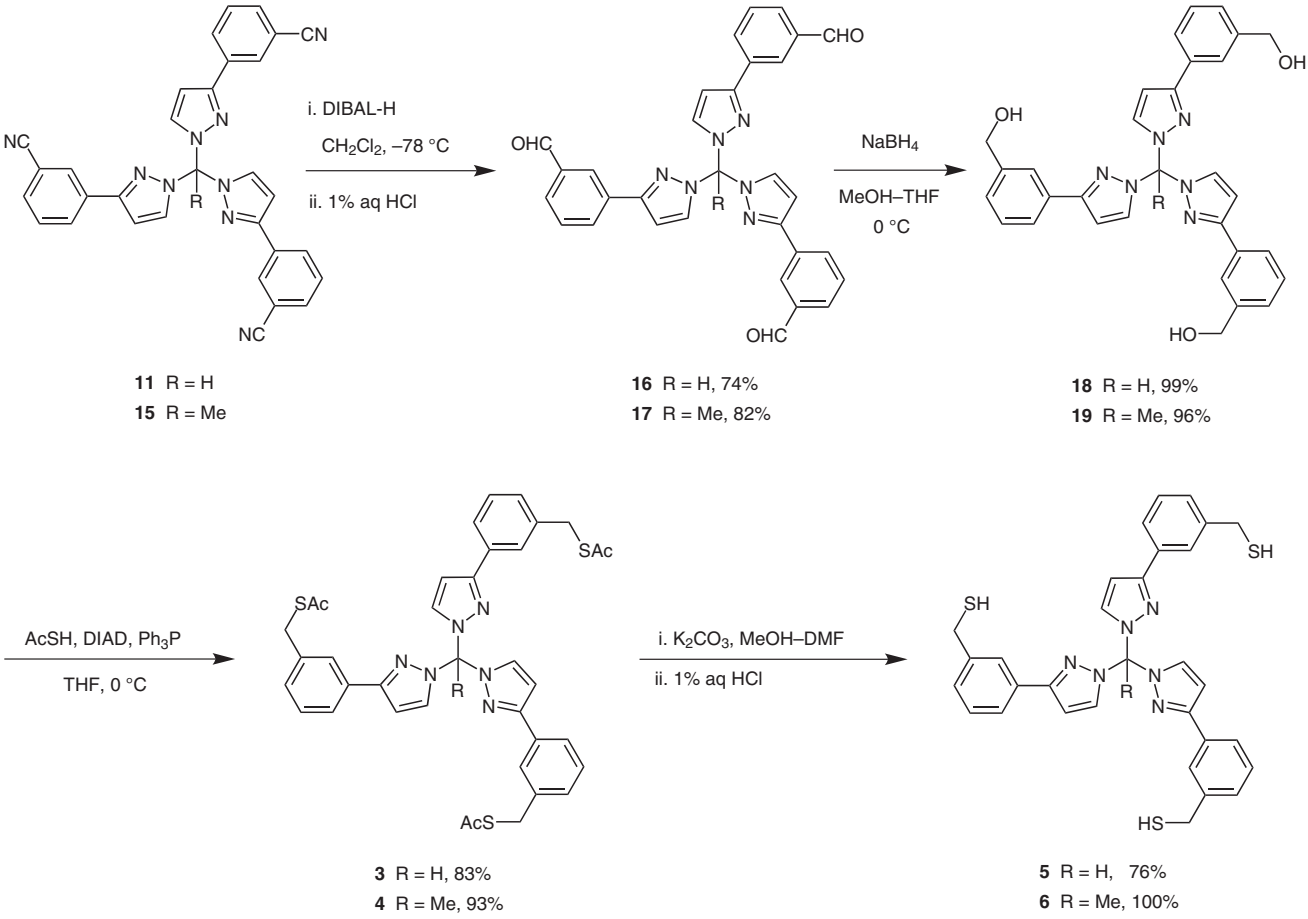
Scheme 2 One-pot synthesis of Tpm **11**

The sequences of transformations leading to Tpm **5** (or Tpe **6**) are shown in Scheme 4. At first, reaction of **11** (**15**) with DIBAL-H (3 equiv) in CH_2Cl_2 at –78 °C, followed by acidic workup (1% HCl) afforded benzaldehyde-substituted Tpm **16** (Tpe **17**) in 74% (82%) yield. The corresponding benzyl alcohol derivative **18** (**19**) was obtained in 99% (96%) yield, by $NaBH_4$ reduction in MeOH–THF at 0 °C. Subsequent treatment of **18** (**19**) with thioacetic acid (6 equiv) in Mitsunobu reaction conditions[17] (Ph_3P, DIAD, THF, 0 °C) afforded thioacetate **3** (**4**) in 83% (93%) yield after chromatography. Finally, benzylthiol-substituted Tpm **5** (Tpe **6**) was produced in 76% (ca. 100%) yield by methanolysis of **3** (**4**) using K_2CO_3 as base followed by acidic workup.

This sequence of functional group transformations has notably allowed us to obtain in preparative yield benzylthioacetate-substituted Tpm **3**, which was previously isolated in minor amounts from the metathesis reaction between **7** and Tpm **8**.[9a]



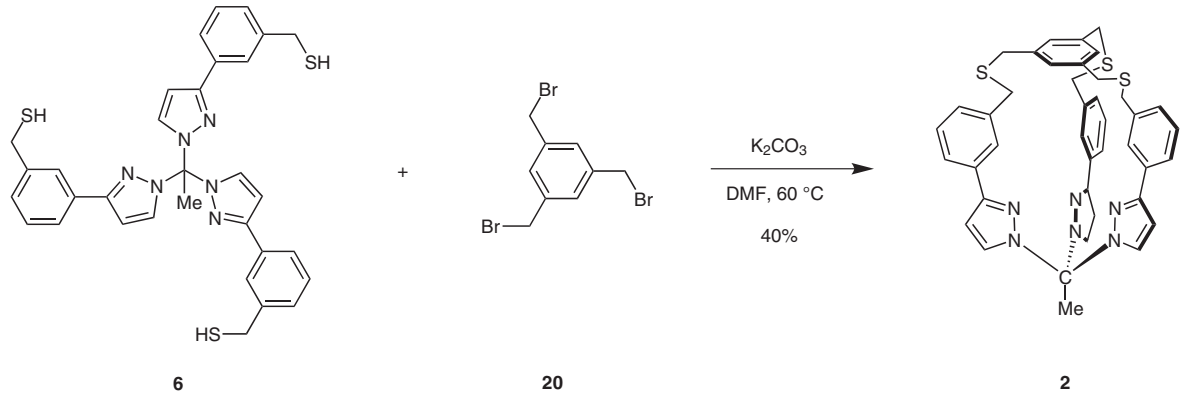
Scheme 3 Preparation of benzonitrile-functionalized Tpm **11** and Tpe **15** by metathesis reaction



Scheme 4 Sequence of functional group transformations starting from Tpm **11** and Tpe **15**, and leading to Tpm **5** and Tpe **6**, respectively

Tpe-incorporating macrobicycle **2** was prepared in the same conditions as **1**[9a] by tripod-tripod coupling reaction between benzylthiol-functionalized Tpe **6** and 1,3,5-tribromomethylbenzene (**20**) in the presence of K_2CO_3 as base in DMF at 60 °C under high dilution (1.68 mM), and obtained in 40% yield after purification by column chromatography (Scheme 5). Tpm macrobicycle **1** being isolated in 28% yield in these conditions, the higher yield of macrobicycle **2** could attest to the increased rigidity/preorganization of the Tpe framework.

The proton NMR spectra of macrobicycles **1** and **2** in CD_2Cl_2 are shown in Figure 3. They were assigned using 2D $^1H/^1H$ COSY and ROESY NMR spectroscopy. Consistency of the attributions was checked by 2D $^{13}C/^1H$ HSQC and HMBC NMR spectroscopy. Comparison of these spectra shows interesting differences. Contrary to what is observed in the case of **1**, the signals of protons H-2, H-4, H-5, and H-6 of **2** do not show first order splitting patterns (respectively s, d, t, and d in the case of **1**). In addition, the signals of the following protons are shifted up-



6 20 2

Scheme 5 Preparation of macrobicycle **2**

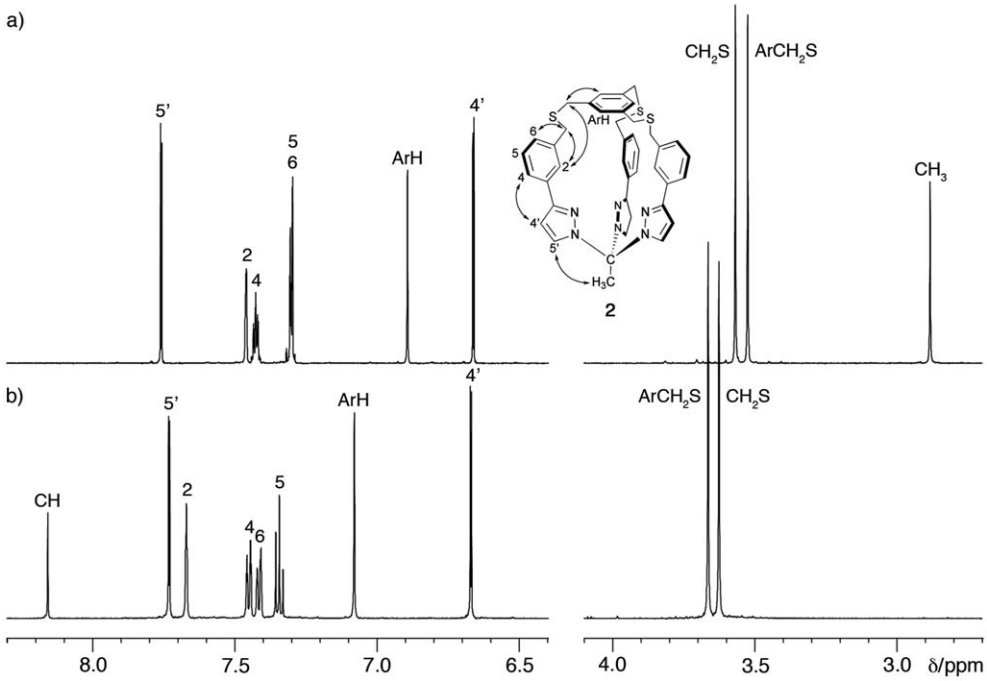


Figure 3 Comparison of the ^{1}H NMR spectra (600 MHz, CD_2Cl_2) of macrobicycles **2** (a) and **1** (b); the arrows show ROESY correlations in **2**

field significantly: H-2 (–0.21), H-6 (–0.11), ArH (–0.16), and $ArCH_2S$ (–0.14 ppm), while those of peripheral H-4, H-4′, H-5, and H-5′ are only slightly affected by changing the methine proton in **1** to a methyl group in **2**. Therefore, this substitution induces conformational changes that affect mainly protons of the aryl cap or its vicinity, that is, protons remote from the methine connector. Based on NOE correlations (e.g., H-4′/H-4) the solution structure of macrobicycle **1** is quite similar to its solid state structure,[9b] in which the phenyl substituents are coplanar with the pyrazole rings. The same NOE correlations are also observed in the case of macrobicycle **2**. This suggests that its conformation is probably very close to that of **1**.

There are quite few reports on the synthesis of functionalized Tpm and their functional group transformations. This study has developed a straightforward and clean route for the preparation of a benzylthiol-substituted Tpm from a basic Tpm precursor and a functionalized pyrazole, showing that the Tpm skeleton tolerated a range of reaction types and conditions. In addition, this route could be equally applied to a simple Tpe precursor, allowing to synthesize a benzylthiol-functionalized Tpe from which, for demonstration purposes, a Tpe-incorporating macrobicycle was prepared.

Unless otherwise stated all reactions were performed under argon using standard Schlenk techniques. DMF was filtered on alumina and stored over molecular sieves; THF and toluene were distilled over sodium/benzophenone, and CH_2Cl_2 over P_2O_5. All other chemicals were used as received. Silica gel for column chromatography was from Merck (Kieselgel 60). NMR spectra were obtained using Bruker Avance 300 and 600, and DRX 500 spectrometers. IR spectra were recorded with a Bruker IFS 66v Fourier Transform IR spectrophotometer. Mass spectra were obtained with a Bruker Daltonix Proflex III spectrometer (MALDI-TOF, dithranol matrix). Melting points were measured with a Büchi Melting Point B-545 apparatus.

Elemental analyses were run with an EA1108 CHNS Fisons Instrument analyzer.

The following compounds were prepared according to the literature: Ethanethioic acid *S*-{[3-(1*H*-pyrazol-3-yl)phenyl]methyl} ester (**7**),[9b] 3-(1*H*-pyrazol-3-yl)benzonitrile (**10**),[15] 1,1′,1″-methylidynetris[3,5-dimethyl-1*H*-pyrazole] (**8**),[11] 1,1′,1″-ethylidynetris[1*H*-pyrazole] (**12**),[16] and 1,3,5-tribromomethylbenzene (**20**).[18]

3,3′,3″-[Methylidynetris(1*H*-pyrazole-1,3-diyl)]tribenzonitrile (11)

Method A: A mixture of 3-(1*H*-pyrazol-3-yl)benzonitrile (**10**; 3.384 g, 20.07 mmol), *n*-Bu_4NBr (0.324 g, 1 mmol), and Na_2CO_3 (12.713 g, 120.12 mmol) in $CHCl_3$ (10 mL) and H_2O (40 mL) was heated at reflux for 2 days. The aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with H_2O until pH <8, and dried. The residue was redissolved in toluene (50 mL), and the mixture heated at reflux in the presence of *p*-TSA (0.060 g, 0.324 mmol) for 24 h in a Dean–Stark apparatus. The reaction mixture was washed with 5% aq $NaHCO_3$ (50 mL) and H_2O (70 mL). Flash column chromatography (silica gel, 0.5% MeOH in CH_2Cl_2) afforded **11** as a colorless solid; yield: 0.665 g (19%).

Method B: A solution of **8** (0.894 g, 3 mmol), **10** (7.5 g, 0.045 mol), and *p*-TSA (0.57 g, 3 mmol) in toluene (100 mL) was refluxed for 48 h. The reaction mixture was subsequently washed with 10% aq $NaHCO_3$ (50 mL), H_2O (3 × 50 mL), brine (50 mL), and dried ($MgSO_4$). Column chromatography (alumina, heptane 40% in CH_2Cl_2) of the crude product from two reactions run on a total of 3.7 mmol of **8** allowed to separate **13** (0.400 g, 24%) from **11** (0.860 g, 45% yield).

11

IR (KBr): 2229 (C≡N) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.74 (d, *J* = 2.6 Hz, 3 H, H-4′), 7.51 (t, *J* = 7.8 Hz, 3 H, H-5), 7.62 (td, *J* = 7.8, 1.2 Hz, 3 H, H-6), 7.79 (d, *J* = 2.6 Hz, 3 H, H-5′), 8.03 (td, *J* = 7.8, 1.2 Hz, 3 H, H-4), 8.12 (s, 3 H, H-2), 8.49 (s, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 83.9 (CH), 105.2 (C-4′), 113.0, 118.8 (CN), 129.6 (C-5), 129.7 (C-2), 130.2 (C-4), 131.6 (C-5′), 131.9 (C-6), 133.7, 151.8.

MS (MALDI-TOF): *m*/*z* = 350.61 $[M + H - C_{10}H_6N_3]^+$.

Anal. Calcd for $C_{31}H_{19}N_9$: C, 71.94; H, 3.70; N, 24.36. Found: C, 71.99; H, 3.76; N, 23.68.

13

IR (KBr): 2229 (C≡N) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 5.97 (s, 1 H, H-4″), 6.67 (d, *J* = 2.6 Hz, 3 H, H-4′), 7.50 (t, *J* = 7.8 Hz, 2 H, H-5), 7.60 (td, *J* = 7.8, 1.2 Hz, 2 H, H-6), 7.72 (d, *J* = 2.6 Hz, 2 H, H-5′), 8.03 (td, *J* = 7.8, 1.2 Hz, 2 H, H-4), 8.11 (t, *J* = 1.2 Hz, 2 H, H-2), 8.36 (s, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.0 (CH_3), 14.0 (CH_3), 81.0 (CH), 104.7 (C-4′), 107.7 (C-4″), 112.9, 118.8 (CN), 129.5 (2 s, C-2, C-5), 130.1 (C-4), 131.4 (C-5′), 131.8 (C-6), 134.2, 141.4, 150.8, 151.3.

Anal. Calcd for $C_{26}H_{20}N_8 \cdot 0.25\ H_2O$: C, 69.55; H, 4.60; N, 25.00. Found: C, 69.68; H, 4.72; N, 23.90.

3,3′,3″-[Ethylidynetris(1*H*-pyrazole-1,3-diyl)]tribenzonitrile (15)

A solution of 1,1′,1″-ethylidynetris[1*H*-pyrazole] (**12**; 0.386 g, 1.69 mmol), 3-(1*H*-pyrazol-3-yl)benzonitrile (**10**; 5.749 g, 0.034 mol), and *p*-TSA (0.355 g, 1.87 mmol) in toluene (20 mL) was refluxed for 2 h in a Dean–Stark apparatus. The reaction mixture was partitioned between CH_2Cl_2 (50 mL) and 5% aq $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$). Column chromatography of the crude product (silica gel, CH_2Cl_2) followed by flash column chromatography (silica gel, 1% EtOAc in CH_2Cl_2) afforded **15** (0.483 g, 54%) and **14** (0.203 g, 28%) as colorless solids.

14

^1H NMR (500 MHz, $CDCl_3$): δ = 3.08 (s, 3 H, CH_3), 6.38 (t, *J* = 2.0 Hz, 1 H, H-4″), 6.66 (d, *J* = 2.6 Hz, 2 H, H-4′ or H-5′), 6.95 (d, *J* = 2.6 Hz, 2 H, H-5′ or H-4′), 7.05 (d, *J* = 2.0 Hz, 1 H, H-3″ or H-5″), 7.51 (t, *J* = 7.8 Hz, 2 H, H-5), 7.61 (dt, *J* = 7.8, 1.4 Hz, 2 H, H-6 or H-4), 7.73 (d, *J* = 2.0 Hz, 1 H, H-5″ or H-3″), 8.04 (dt, *J* = 7.8, 1.4 Hz, 2 H, H-4 or H-6), 8.12 (t, *J* = 1.4 Hz, 2 H, H-2).

15

Mp 110.6–111.3 °C.

IR (KBr): 2229.8 (C≡N) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.14 (s, 3 H, CH_3), 6.69 (d, *J* = 2.6 Hz, 3 H, H-4′ or H-5′), 7.06 (d, *J* = 2.6 Hz, 3 H, H-5′ or H-4′), 7.52 (t, *J* = 7.8 Hz, 3 H, H-5), 7.62 (dt, *J* = 7.8, 1.4 Hz, 3 H, H-6 or H-4), 8.05 (dt, *J* = 7.8, 1.4 Hz, 3 H, H-4 or H-6), 8.13 (t, *J* = 1.4 Hz, 3 H, H-2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.4, 91.2, 104.6, 113.1, 118.7, 129.6 (2 s), 130.2, 131.2, 131.8, 133.9, 151.4.

MS (MALDI-TOF): *m*/*z* = 362.30 $[M + H - C_{10}H_7N_3]^+$.

Anal. Calcd for $C_{32}H_{21}N_9$: C, 72.30; H, 3.98; N, 23.71. Found: C, 72.12; H, 4.46; N, 23.07.

Conversion of 14 into 15

A solution of **14** (0.203 g, 0.457 mmol), **10** (1.600 g, 9.54 mmol), and *p*-TSA (0.090 g, 0.472 mmol) in toluene (8.5 mL) was refluxed for 48 h using a Dean–Stark apparatus. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and transferred into a separatory funnel. The organic phase was washed with 5% aq $NaHCO_3$ (50 mL), dried ($MgSO_4$), and the solvents evaporated. Column chromatography (silica gel, 0.5–2% EtOAc in CH_2Cl_2) allowed the removal of excess of **10**, unreacted **14**, and released pyrazole. Flash column chromatography (silica gel, 1% EtOAc in CH_2Cl_2) afforded pure **15** (0.132 g, 53%).

3,3′,3″-[Methylidynetris(1*H*-pyrazole-1,3-diyl)]tribenzaldehyde (16)

A 1 M solution of DIBAL-H (5 mL, 5 mmol) in hexane was added dropwise to a solution of **11** (0.695 g, 1.34 mmol) in CH_2Cl_2 (45 mL) at –78 °C. After stirring for 3 h at r.t., the reaction mixture was quenched with 1% aq HCl (200 mL), and extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were dried ($MgSO_4$). Purification of the crude product by column chromatography (silica gel, 5% EtOAc in CH_2Cl_2) afforded **16** (0.511 g, 74%) as a colorless waxy solid.

IR (KBr): 1996.0 (C=O) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 2.6 Hz, 3 H, H-4′), 7.55 (t, *J* = 7.7 Hz, 3 H, H-5), 7.79 (d, *J* = 2.6 Hz, 3 H, H-5′), 7.83 (dt, *J* = 7.7, 1.4 Hz, 3 H, H-6 or H-4), 8.09 (dt, *J* = 7.7, 1.4 Hz, 3 H, H-4 or H-6), 8.30 (t, *J* = 1.4 Hz, 3 H, H-2), 8.55 (s, 1 H, CH), 10.05 (s, 3 H, CHO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 83.9, 105.1, 127.1, 129.5, 129.7, 131.4, 131.8, 133.5, 136.9, 152.5, 192.3.

MS (MALDI-TOF): *m*/*z* = 354.62 $[M + H - C_{10}H_8N_2O]^+$.

Anal. Calcd for $C_{31}H_{22}N_6O_3 \cdot 0.5\ H_2O$: C, 69.52; H, 4.33; N, 15.69. Found: C, 70.09; H, 4.36; N, 15.52.

3,3′,3″-[Ethylidynetris(1*H*-pyrazole-1,3-diyl)]tribenzaldehyde (17)

A 1 M solution of DIBAL-H (17.50 mL, 17.50 mmol) in hexane was added dropwise to a solution of **15** (2.267 g, 4.263 mmol) in CH_2Cl_2 (140 mL) at –78 °C. After stirring for 3 h at r.t., the reaction mixture was treated with 1% aq HCl (145 mL for quenching, 750 mL for washing) and extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layers were dried ($MgSO_4$). Purification of the crude product by flash column chromatography (silica gel, 2% EtOAc in CH_2Cl_2) afforded **17** (1.896 g, 82%) as a colorless waxy solid.

IR (KBr): 1697.2 (C=O) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.19 (s, 3 H, CH_3), 6.73 (d, *J* = 2.9 Hz, 3 H, H-4′ or H-5′), 7.00 (d, *J* = 2.9 Hz, 3 H, H-5′ or H-4′), 7.86 (dt, *J* = 7.8, 1.5 Hz, 3 H, H-6 or H-4), 8.13 (dt, *J* = 7.8, 1.5 Hz, 3 H, H-4 or H-6), 8.34 (t, *J* = 1.5 Hz, 3 H, H-2), 10.08 (s, 3 H, CHO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.4, 91.4, 104.6, 127.1, 129.6, 129.8, 131.1, 131.9, 133.8, 137.0, 152.3, 192.4.

MS (MALDI-TOF): *m*/*z* = 368.17 $[M + H - C_{10}H_8N_2O]^+$.

Anal. Calcd for $C_{32}H_{24}N_6O_3 \cdot 0.25\ C_4H_8O_2$: C, 70.45; H, 4.66; N, 14.94. Found: C, 70.73; H, 5.00; N, 14.99.

3,3′,3″-[Methylidynetris(1*H*-pyrazole-1,3-diyl)]tribenzenemethanol (18)

$NaBH_4$ granules (0.0371 g, 1 mmol) were added to a solution of **16** (0.330 g, 0.627 mmol) in a mixture of MeOH (44 mL) and THF (11 mL) at 0 °C. After stirring for 1 h, the reaction mixture was quenched with 5% aq $NaHCO_3$ (75 mL). The resulting suspension was stirred for 1.5 h, diluted with H_2O (300 mL), extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic extracts were dried ($MgSO_4$). Purification of the crude product by column chromatography (silica gel, 4–7% MeOH in CH_2Cl_2) afforded **18** (0.330 g, 99%) as a colorless solid; mp 161.8–162.6 °C.

IR (KBr): 3357.9 (OH) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.75 (br s, 3 H, OH), 4.74 (s, 6 H, CH_2), 6.69 (d, *J* = 2.6 Hz, 3 H, H-4′), 7.34 (br d, *J* = 7.7 Hz, 3 H, H-6 or H-4), 7.40 (t, *J* = 7.7 Hz, 3 H, H-5), 7.69 (d, *J* = 2.6 Hz, 3 H, H-5′), 7.74 (d, *J* = 7.7 Hz, 3 H, H-4 or H-6), 7.84 (br s, 3 H, H-2), 8.49 (s, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 64.2, 84.0, 104.7, 124.6, 125.0, 127.1, 128.8, 131.8, 133.0, 142.3, 154.0.

MS (MALDI-TOF): *m*/*z* = 554.62 $[M + Na]^+$, 358.63 $[M + H - C_{10}H_{10}N_2O]^+$.

Anal. Calcd for $C_{31}H_{28}N_6O_3 \cdot 0.25\ H_2O$: C, 69.32; H, 5.35; N, 15.65. Found: C, 69.47; H, 5.62; N, 15.55.

3,3′,3″-[Ethylidynetris(1*H*-pyrazole-1,3-diyl)]tribenzenemethanol (19)

$NaBH_4$ granules (0.027 g, 0.713 mmol) were added to a solution of **17** (0.257 g, 0.475 mmol) in MeOH (40 mL) at 0 °C. After stirring for 1 h, the reaction mixture was quenched with 5% aq $NaHCO_3$ (50 mL). The resulting suspension was stirred for 1.5 h, extracted with CH_2Cl_2 (4 × 50 mL) and the combined organic layers were dried ($MgSO_4$). Purification of the crude product by column chromatography (silica gel, 7% MeOH in CH_2Cl_2) afforded **19** (0.330 g, 96%) as a colorless solid; mp 141.7–143 °C.

IR (KBr): 3360.7 (OH) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.47 (br s, 3 H, OH), 3.16 (s, 3 H, CH_3), 4.74 (s, 6 H, CH_2), 6.63 (d, *J* = 2.6 Hz, 3 H, H-4′ or H-5′), 6.88 (d, *J* = 2.6 Hz, 3 H, H-5′ or H-4′), 7.34 (ddd, *J* = 7.6, 1.6, 1.3 Hz, 3 H, H-6 or H-4), 7.40 (t, *J* = 7.6 Hz, 3 H, H-5), 7.76 (ddd, *J* = 7.6, 1.6, 1.3 Hz, 3 H, H-4 or H-6), 7.86 (br s, 3 H, 2-H).

^{13}C NMR (125 MHz, CD_3OD): δ = 25.9, 64.2, 91.2, 104.4, 124.6, 125.0, 127.1, 129.0, 131.4, 133.2, 142.3, 153.8.

MS (MALDI-TOF): *m*/*z* = 372.62 $[M + H - C_{10}H_{10}N_2O]^+$.

Anal. Calcd for $C_{32}H_{30}N_6O_3$: C, 70.31; H, 5.53; N, 15.37. Found: C, 69.85; H, 5.62; N, 15.19.

***S*,*S*′,*S*″-[Methylidynetris(1*H*-pyrazole-1,3-diyl-3,1-phenylenemethylene)] Triethanethioate (3)**

Method B: A solution of **7** (5.23 g, 0.0225 mol), **8** (0.671 g, 2.25 mmol), and *p*-TSA (0.387 g, 2.25 mmol) in toluene (60 mL) was refluxed for 48 h. After cooling to r.t., the reaction mixture was diluted with CH_2Cl_2 (150 mL) and the organic layer washed with 2% aq $NaHCO_3$ (150 mL), H_2O (3 × 50 mL), brine (50 mL), and dried ($MgSO_4$). Column chromatography of the residue (silica gel, CH_2Cl_2–heptane) allowed the separation of the pure *S*-[3-(1-acetyl-1*H*-pyrazol-3-yl)benzyl] ethanethioate (0.438 g, 7%)[14] as a crystalline product (EtOH), and **3** (0.118 g, 7%) as a waxy solid.

*From **18***: DIAD (0.433 mL, 2.183 mmol) was added to a solution of Ph_3P (0.572 g, 2.183 mmol) in THF (6 mL) at 0 °C. The resulting suspension was further stirred for 0.5 h and warmed to r.t. It was then reacted with a solution of **18** (0.310 g, 0.582 mmol) and thioacetic acid (0.248 mL, 3.492 mmol) in THF (2.5 mL) at 0 °C. After stirring for 3 h at r.t., the solvent was removed in vacuo. Flash column chromatography (silica gel, 2% EtOAc in CH_2Cl_2) of the crude mixture afforded **3** (0.342 g, 83%).

***S*-[3-(1-Acetyl-1*H*-pyrazol-3-yl)benzyl] Ethanethioate**

Mp 76.1–78.4 °C.

IR (KBr): 1728 (NCO), 1688 (SCO) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, CH_3), 2.75 [s, 3 H, NC(O)CH_3], 4.16 (s, 2 H, CH_2), 6.74 (d, 1 H, *J* = 2.9 Hz, H-4′), 7.31 (d, *J* = 7.5 Hz, 1 H, H-6), 7.36 (t, *J* = 7.5 Hz, 1 H, H-5), 7.73 (br d, *J* = 7.5 Hz, 1 H, H-4), 7.79 (s, 1 H, 2-H), 8.26 (d, 1 H, *J* = 2.9 Hz, H-5′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 [NC(O)*C*H_3], 30.4 [SC(O)*C*H_3], 33.3 (CH_2), 107.6 (4′-C), 125.3 (4-C), 126.7 (2-C), 129.2 (5-C), 129.4 (5′-C), 129.7 (6-C), 132.2, 138.4, 155.1, 169.7 (NCO), 195.0 (SCO).

Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21; S, 11.69. Found: C, 61.52; H, 5.31; N, 10.15; S, 11.10.

3

IR (KBr): 1686 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 9 H, CH_3), 4.17 (s, 6 H, CH_2), 6.69 (d, *J* = 2.6 Hz, 3 H, H-4′), 7.28 (d, *J* = 7.7 Hz, 3 H, H-6), 7.35 (t, *J* = 7.7 Hz, 3 H, H-5), 7.69 (d, *J* = 2.6 Hz, 3 H, H-5′), 7.71 (d, *J* = 7.7 Hz, 3 H, H-4), 7.76 (s, 3 H, H-2), 8.52 (s, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.4 (CH_3), 33.5 (CH_2), 83.9 (CH), 104.8 (C-4′), 125.1 (C-4), 126.5 (C-2), 128.9 (C-6), 129.1 (C-5), 130.9 (C-5′), 132.9, 138.1, 153.3, 195.2 (C=O).

Anal. Calcd for $C_{37}H_{34}N_6O_3S_3 \cdot H_2O$: C, 61.30; H, 5.00; N, 11.59; S, 13.27. Found: C, 61.31; H, 5.17; N, 11.45; S, 12.29.

***S*,*S*′,*S*″-[Ethylidynetris(1*H*-pyrazole-1,3-diyl-3,1-phenylenemethylene)] Triethanethioate (4)**

DIAD (0.6 mL, 3.05 mmol) was added to a solution of Ph_3P (0.720 g, 2.745 mmol) in THF (10 mL) at 0 °C. The resulting suspension was further stirred for 0.5 h and warmed to r.t. Next, it was reacted with a solution of **19** (0.400 g, 0.732 mmol) and thioacetic acid (0.40 mL, 5.60 mmol) in THF (3.5 mL) at 0 °C. After stirring overnight at r.t., the solvent was removed in vacuo. Repeated flash column chromatography (silica gel, 0–1% EtOAc in CH_2Cl_2) of the crude mixture afforded **4** (0.490 g, 93%) as a waxy solid.

IR (KBr): 1689.8 (C=O) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.35 [s, 9 H, $C(O)CH_3$], 3.15 (s, 3 H, CH_3), 4.16 (s, 6 H, CH_2), 6.61 (d, *J* = 2.6 Hz, 3 H, H-4′ or H-5′), 6.85 (d, *J* = 2.6 Hz, 3 H, H-5′ or H-4′), 7.27 (dt, *J* = 7.5 Hz, 3 H, H-6 or H-4), 7.34 (3 H, t, *J* = 7.5 Hz, 5-H), 7.71 (dt, *J* = 7.5, 1.5 Hz, 3 H, H-4 or H-6), 7.75 (t, *J* = 1.5 Hz, 3 H, 2-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.2, 30.4, 33.5, 91.3, 104.3, 125.1, 126.4, 128.9, 129.1, 130.7, 133.2, 138.1, 153.0, 195.2.

MS (MALDI-TOF): *m*/*z* = 488.73 $[M + H - C_{12}H_{12}N_2OS]^+$.

Anal. Calcd for $C_{38}H_{36}N_6O_3S_3 \cdot 0.25\ C_4H_8O_2$: C, 63.05; H, 5.15; N, 11.31; S, 12.94. Found: C, 62.87; H, 5.38; N, 11.47; S, 12.49.

3,3′,3″-[Methylidynetris(1*H*-pyrazole-1,3-diyl)]tribenzenemethanethiol (5)

From a Crude Mixture of Thioesters: Solid K_2CO_3 (3.53 g, 0.0256 mol) was added to the crude mixture of thioesters (obtained from 3.34 mmol of **7**) in DMF (15 mL) and MeOH (450 mL). After stirring for 4 h at r.t., the reaction mixture was quenched with 5% aq HCl (35 mL). The resulting solution was concentrated on the rotary evaporator, diluted with CH_2Cl_2 (200 mL), washed with H_2O (3 × 50 mL), brine (50 mL), and dried ($MgSO_4$). Column chromatography (silica gel, 10% heptane in CH_2Cl_2, then 1–4% EtOAc in toluene) afforded **9** (0.245 g, 15%) and **5** (0.819 g, 42%) as pale yellow oils.

*From Pure Thioester **3***: Solid K_2CO_3 (1.138 g, 8.235 mmol) was added to a solution of **3** (0.647 g, 0.915 mmol) in a mixture of DMF (8 mL) and MeOH (400 mL). After stirring for 3 h at r.t., the reaction mixture was quenched with 1% aq HCl (70 mL), extracted with CH_2Cl_2 (5 × 100 mL), and dried ($MgSO_4$). Purification of the crude product by column chromatography (silica gel, 0.5% EtOAc in CH_2Cl_2) afforded **5** (0.403 g, 76%) as a pale yellow oil.

9

IR (KBr): 2561 (SH) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.79 (t, *J* = 7.6 Hz, 2 H, SH), 2.24 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 3.77 (d, *J* = 7.6 Hz, 4 H, CH_2), 5.93 (s, 1 H, CH), 6.64 (d, *J* = 2.6 Hz, 2 H, H-4′), 7.29 (d, *J* = 7.7 Hz, 2 H, H-4 or H-6), 7.35 (t, *J* = 7.7 Hz, 2 H, H-5), 7.63 (d, *J* = 2.6 Hz, 2 H, H-5′), 7.66 (d, *J* = 7.7 Hz, 2 H, H-4 or H-6), 7.78 (s, 1 H, H-2), 8.35 (s, 1 H, CH).

MS (MALDI-TOF): *m*/*z* = 296.38 $[M + H - C_{10}H_9N_2S]^+$, 390.45 $[M - C_5H_7N_2]^+$.

5

IR (KBr): 2560 (SH) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.80 (t, *J* = 7.6 Hz, 3 H, SH), 3.78 (d, *J* = 7.6 Hz, 6 H, CH_2), 6.69 (d, *J* = 2.6 Hz, 3 H, H-4′), 7.31 (d, *J* = 7.7 Hz, *J* = 1.3 Hz, 3 H, H-6), 7.36 (t, *J* = 7.7 Hz, 3 H, H-5), 7.68 (d, *J* = 2.6 Hz, 3 H, H-5′), 7.69 (d, *J* = 7.7 Hz, *J* = 1.3 Hz, 3 H, H-4), 7.79 (s, 3 H, 2-H), 8.50 (s, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.1 (CS), 84.0 (CH), 104.9 (C-4′), 124.9 (C-4), 125.7 (C-2), 128.2 (C-6), 129.2 (C-5), 131.0 (C-5′), 133.0, 141.8, 153.5.

MS (MALDI-TOF): *m*/*z* = 390.53 $[M + H - C_{10}H_9N_2S]^+$.

Anal. Calcd for $C_{31}H_{28}N_6S_3 \cdot C_2H_6O$: C, 64.89; H, 5.61; N, 13.76; S, 15.75. Found: C, 64.83; H, 5.34; N, 13.96; S, 15.84.

3,3′,3″-[Ethylidynetris(1*H*-pyrazole-1,3-diyl)]tribenzenemethanethiol (6)

Solid K_2CO_3 (0.754 g, 5.455 mmol) was added to a solution of **4** (0.437 g, 0.606 mmol) in a mixture of DMF (14 mL) and MeOH (70 mL). After stirring for 4 h at r.t., the reaction mixture was quenched with 1% aq HCl (60 mL) at 0 °C, diluted with H_2O (100 mL), extracted with CH_2Cl_2 (3 × 100 mL), and dried ($MgSO_4$). Evaporation of the solvents afforded **6** (0.362 g; ca. 100%) as a colorless solid; mp 138.4–139.4 °C.

IR (KBr): 2540.5 (SH) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.80 (t, *J* = 7.6 Hz, 3 H, SH), 3.17 (s, 3 H, CH_3), 3.79 (d, *J* = 7.6 Hz, 6 H, CH_2), 6.63 (d, *J* = 2.6 Hz, 3 H, H-4′ or H-5′), 6.87 (d, *J* = 2.6 Hz, 3 H, H-5′ or H-4'), 7.31 (dt, *J* = 7.7 Hz, *J* = 1.4 Hz, 3 H, H-6 or H-4), 7.36 (t, *J* = 7.7 Hz, 3 H, H-5), 7.70 (dt, *J* = 7.7 Hz, *J* = 1.4 Hz, 3 H, H-4 or H-6), 7.80 (t, *J* = 1.4 Hz, 3 H, H-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 26.2, 29.0, 91.2, 104.3, 124.8, 125.6, 128.1, 129.1, 130.7, 133.2, 141.7, 153.1.

MS (MALDI-TOF): *m*/*z* = 404.93 $[M + H - C_{10}H_{10}N_2S]^+$.

Anal. Calcd for $C_{32}H_{30}N_6S_3$: C, 64.62; H, 5.08; N, 14.13; S, 16.17. Found: C, 64.32; H, 5.20; N, 14.17; S, 15.98.

Macrobicycle 2

A solution of **6** (0.100 g, 0.168 mmol) and 1,3,5-tribromomethylbenzene (**20**; 0.060 g, 0.168 mmol) in DMF (24 mL) was added dropwise to a stirred suspension of K_2CO_3 (0.139 g, 1 mmol) in DMF (75 mL) at 60 °C over 7 h. After stirring overnight, the solvent was removed in vacuo and the residue partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL). The organic phase was washed with brine (50 mL) and dried ($MgSO_4$). Purification of the crude product by flash column chromatography (silica gel, 4% EtOAc in toluene, then silica gel, CH_2Cl_2) afforded **2** (0.0474 g, 40%) as a colorless solid.

^1H NMR (600 MHz, CD_2Cl_2): δ = 2.88 (s, 3 H, CH_3), 3.53 (s, 6 H, $ArCH_2S$), 3.57 (s, 6 H, CH_2S), 6.66 (d, *J* = 2.4 Hz, 3 H, H-4′), 6.89 (s, 3 H, ArH), 7.30 (m, 6 H, H-5, H-6), 7.43 (m, 3 H, H-4), 7.46 (br m, 3 H, H-2), 7.76 (d, *J* = 2.4 Hz, 3 H, H-5′).

^{13}C NMR (150 MHz, CD_2Cl_2): δ = 28.7 (CCH_3), 36.1 ($ArCH_2S$), 36.3 (CH_2S), 89.1 (CCH_3), 105.3 (C-4′), 124.7 (C-4), 127.2 (C-2), 128.5 (CH_{arom}, C-6), 129.3 (C-5), 130.1 (C-5′), 133.9 (C-3), 139.1 (C-1), 139.3 ($ArCCH_2$), 151.4 (C-3′).

MS (MALDI-TOF): *m*/*z* = 709.60 $[M + H]^+$.

Anal. Calcd for $C_{41}H_{36}N_6S_3 \cdot CH_2Cl_2$: C, 63.54; H, 4.82; N, 10.59, S, 12.12. Found: C, 64.65; H, 4.81; N, 10.89; S, 12.21.

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