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Synthesis of Nitrogen-, Oxygen- and Sulphur-containing Tripodal Ligands with a Trimethylbenzene Core

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Abstract. Synthetic procedures for the preparation of various nitrogen-, oxygen- and sulphur-containing tripodal ligands having a 1,3,5-trimethylbenzene core are reported.
Keywords: 1,3,5-tris(bromomethyl)benzene, ethyl-xanthate, tris-thiol, tripodal ligands, Michael additions, ligand design.

Resumen. Se describe la preparación de diferentes ligantes tripodales que contienen átomos de nitrógeno, oxígeno y azufre, así como la plataforma 1,3,5-trimetilbenceno.
Palabras clave: 1,3,5-tris(bromometil)benceno, etilxantato, tris-tiol, ligandos tripodales, adiciones de Michael, diseño de ligantes.

Introduction

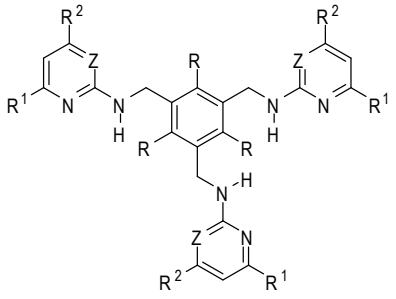
1,3,5-Tris(*N*-alkylaminomethyl)benzene derivatives have attracted much attention as efficient building blocks for the development of functional molecules such as molecular receptors, in which the benzene ring is particularly useful as a small rigid platform for receptor synthesis [1]. Recent studies have shown that 1,3,5-trimethylbenzene derivatives can act as highly efficient catalysts [2], and, additionally, they have applications in analytical chemistry [3] and for anion-templated reactions [4]. The recently reported 2-aminopyridine and 2-aminopyrimidine derivatives **I-VI** have high affinity for β-D-glucopyranosides and a marked β *vs* α anomer selectivity (Scheme 1) [5].

Conventionally, there are three methodologies for the construction of tripodal ligands based on the trisubstituted 1,3,5-benzene scaffold (Scheme 2): (i) coupling of alkyl-4-toluene sulfonamide (Ts-amide) with 1,3,5-tris(bromomethyl)benzene [6] (method A), (ii) reduction of *N,N′,N′′*-trialkyl-1,3,5-carboxamidobenzene with $LiAlH_4$ or BH_3 in THF [7] (method B), and (iii) condensation of 1,3,5-tris(aminomethyl)benzene derivatives with appropriate aldehydes through formation of the corresponding imine followed by reduction with $NaBH_4$ (method C) [8]. For method A, deprotection of the Ts-amide moieties requires harsh reaction conditions, such as Birch reduction or hydrolysis in a highly acidic medium [9].

Herein we describe a convenient synthesis of the 1,3,5-tris(*N*-alkylaminomethyl)benzene derivatives **2a-e**, and an alternative efficient synthesis of the parent 1,3,5-tris(aminomethyl)benzene **8** from the tris-azide **7** derived from the tris-bromide **4**. Compound **4** was also utilized as a precursor of the tris-sulphur containing compounds **14** and **15,** and compound **7** was converted into the tris-triazole **9**. In addition, compound **8** served as the progenitor of the Michael addition derived tris-β-amino esters **11** and **13**.

Results and discussion

Synthesis: In the first approach to synthesize 1,3,5-tris(aminomethyl)benzene, the tripodal Ts-amide **1** precursor was synthesized according to the coupling process described by Dietrich *et al* [11], and Steed *et al* [6a]. The key step of this reaction consists in the condensation of *N*-benzyl-4-methylbenzenesulfonamide (**3**) with 1,3,5-tris(bromomethyl)benzene (**4**), and requires 3 equivalent of Cs_2CO_3. Compound **4** was obtained from 1,3,5-benzenetricarboxylic acid after reaction



I: Z = CH, R = R^1 = CH_3, R^2 = H

II: Z = CH, R = R^1 = CH_3, R^2 = CH_3

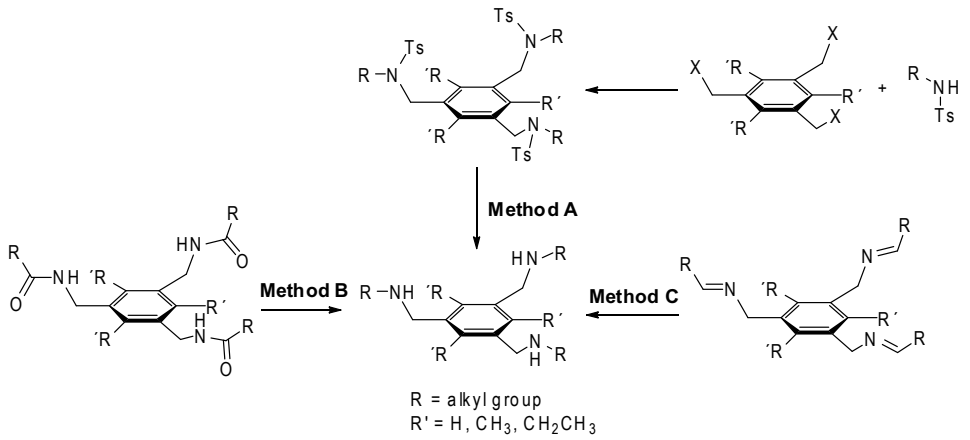
III: Z = CH, R = CH_3, R^1 = NH_2, R^2 = H

IV: Z = CH, R = CH_2CH_3, R^1 = R^2 = CH_3

V: Z = CH, R = CH_2CH_3, R^1 = NH_2, R^2 = H

VI: Z = N, R = R^1 = R^2 = CH_3

Scheme 1.



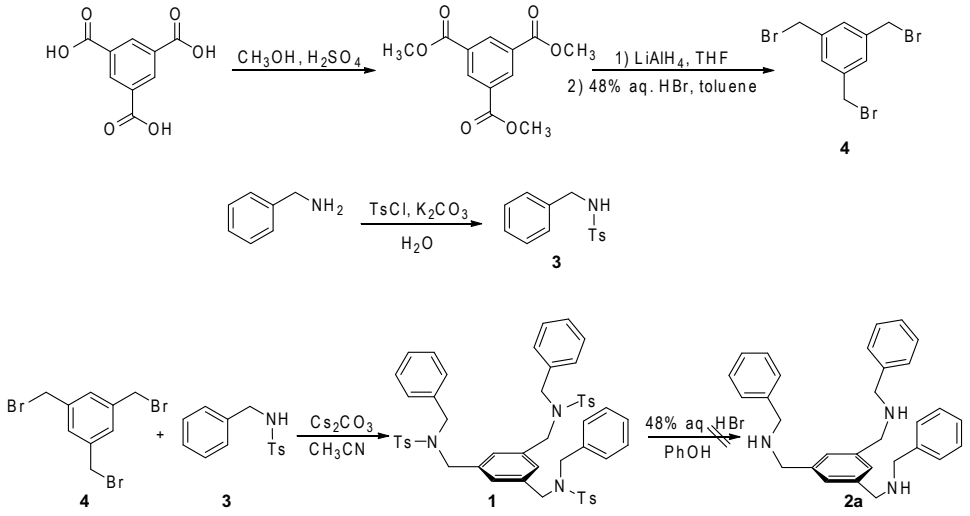
Scheme 2.

with methanol in the presence of concentrated sulfuric acid, followed by reduction with $LiAlH_4$ and hydrolysis with 48% aq. HBr. All reaction steps involved in the synthesis of compound **1** gave satisfactory yields (70% overall yield, Scheme 3). For the preparation of 1,3,5-tris(*N*-benzylaminomethyl)benzene **2a**, Prolonged heating (72 h) of a solution of the Ts-amide **1** in 48% HBr containing phenol [6a], at reflux temperature, resulted only in its destruction.

The structure of the Ts-amide **1** was examined also by single-crystal X-ray crystallography (Table 1), thus providing information about the molecular structure and conformation of this precursor. An interesting feature of this structure is that the cavity of the tripodal ligand precursor is occupied by one of the benzyl groups attached to the periphery of the molecule. The centroid distance between the central benzene core and this benzyl group is 4.09 Å (Figure 1).

In the second approach for the synthesis of 1,3,5-tris(*N*-alkylaminomethyl)benzene derivatives the protecting group was changed from Ts to Boc, which allowed us to obtain compounds **2a-2e** in three steps starting from **4** (Scheme 4). First, compound **4** was reacted with *tert*-butylbenzylcarbamate (**5a**) under basic conditions (NaH) to produce compound **6a**, which after hydrolysis under mild conditions gave the target compound **2a** in 35% yield. With this protocol in hand, we examined the scope and limitations of this method using a series of alkylcarbamate reactants (**5b-5e**). The results indicated that the reaction is effective for a range of aliphatic and aromatic amine derivatives (Table 2). The highest yield was obtained for *iso*-propyl-4-methoxyphenylcarbamate (**5e**) (entry 5). All products were characterized by common instrumental techniques such as IR, $^1H/^{13}C$ NMR spectroscopy and mass spectrometry. Removal of the Boc protecting group was achieved in high yields with 3M aq. HCl in ethyl acetate (Scheme 4) [10].

Conversion of 1,3,5-tris(bromomethyl)benzene (**4**) into compound **8** was also accomplished by an alternative two step procedure. First, 1,3,5-tris(azidomethyl)benzene (**7**) was



Scheme 3.

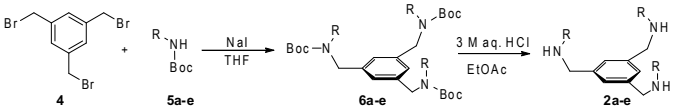
Table 1. Crystallographic data for compound **1**.

Crystal data[a]	
Formula	$C_{51}H_{51}N_3O_6S_3$
MW (g mol^{-1})	898.13
Space group	*P2$_1$/n*
a (Å)	12.5502(12)
b (Å)	11.2111(10)
c (Å)	32.038(3)
β (°)	100.497(2)
V (Å^3)	4432.3(7)
Z	4
μ (mm^{-1})	0.223
ρ_{calcd} (g cm^{-3})	1.346
R[b, c]	0.052
R_w[d, e]	0.125

[a]$\lambda_{MoK\alpha}$ = 0.71073 Å. [b]$F_o > 4\sigma(F_o)$. [c]$R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [d]All data. [e]$R_w = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.

formed in 95% yield by reaction of **4** with six equivalents of sodium azide at room temperature in dimethylformamide. Catalytic hydrogenation of **7** over 10% Pd/C then gave **8** in higher overall yield than previously reported procedures [7,12]. Additionally, we prepared 1,3,5-tris((4-phenyl-1-H-1,2,3-triazol-1-yl)methyl)benzene (**9**) by addition of three equivalents of phenylacetylene to **7** in the presence of a catalytic amount of CuI (Scheme 5) [13].

Table 2. Influence of the organic substituent in alkylcarbamates **5a-e** on the yields of compounds **2** and **6**.



Entry	Carbamate	R	**6** Yield (%)	**2** Yield (%)
1	**5a**	$PhCH_2^-$	49	91
2	**5b**	$PhCH_2CH_2^-$	43	85
3	**5c**	$CH_3CH_2^-$	34	84
4	**5d**	$(CH_3)_2CH^-$	36	60
5	**5e**	CH_3O-*p*-$C_6H_4^-$	97	74

Examination of the reactivity of compound **8** in Michael addition reactions revealed that the expected addition of the tris-amine to the β-carbons of the α,β-unsaturated carbonyl compounds **10** and **12**. β-Amine ester **11** was formed in 62% yield by reaction of **8** with methyl acrylate (**10**) in methanol at reflux temperature (Scheme 6). Compound **13** was prepared in an analogous manner, although only in 25% yield, using

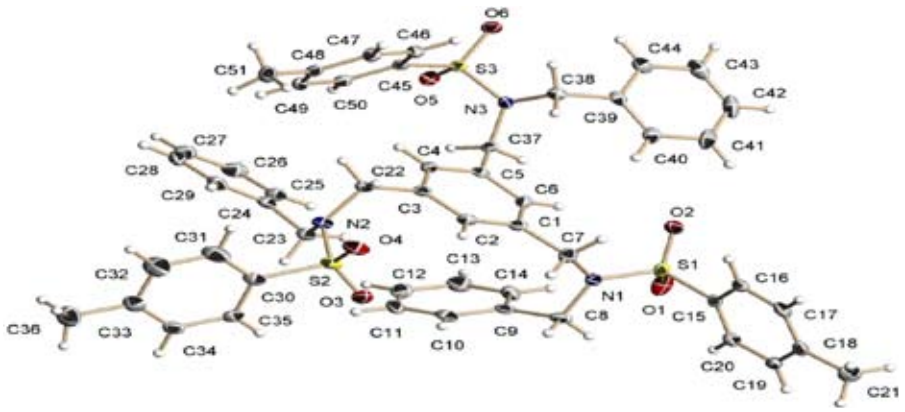
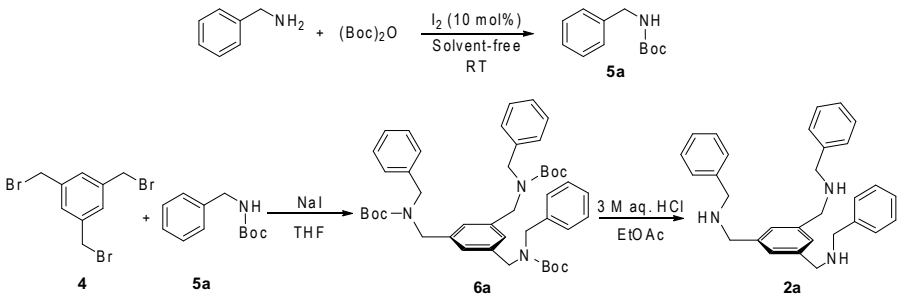
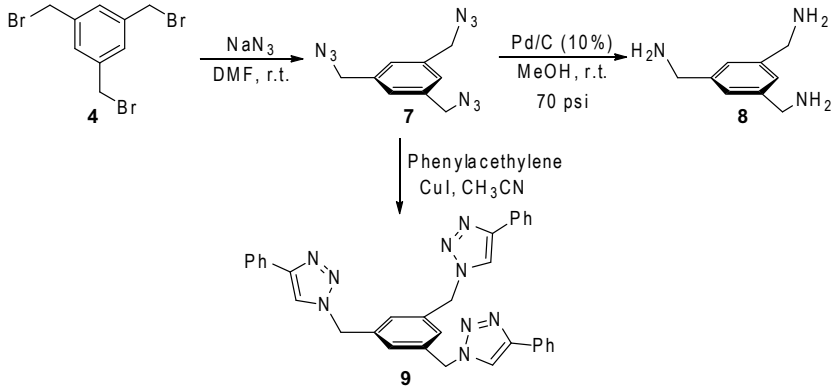


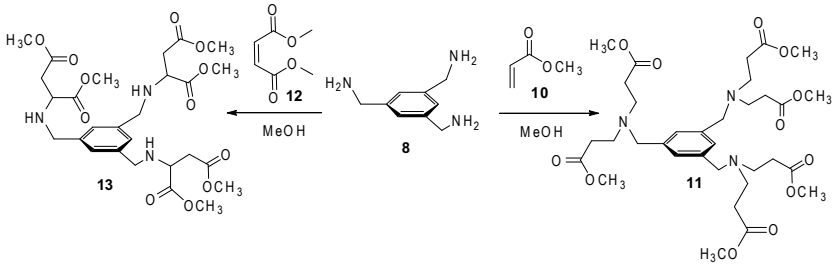
Figure 1. Perspective view of the molecular structure of compound **1**. Ellipsoids are shown at the 50% probability level.



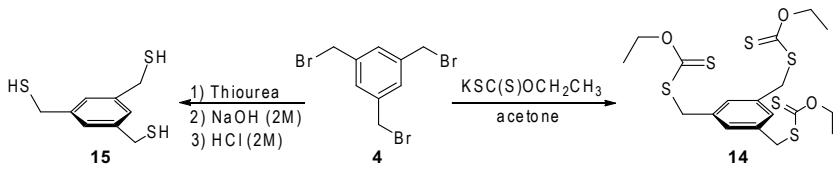
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

dimethyl fumarate (**12**) and a large excess of $LiClO_4$ as a promoter.

In recent years xanthates (dithiocarbonates) [14] have found widespread applications for the synthesis of complex structures and in living radical polymerization reactions [15]. In order to explore the possibility of preparing these types of compounds, 1,3,5-tris(bromomethyl)benzene **4** was combined with six equivalents of commercially available potassium *O*-ethyl dithiocarbonate according to previously described methodology [16]. The tris-xanthate **14** was obtained in 74% yield. 1,3,5-tris(mercaptomethyl)benzene (**15**) was prepared from **4** by reaction with thiourea followed by subsequent treatment with NaOH (1N) and HCl (2N) (Scheme 7).

Conclusions

In this contribution, starting from 1,3,5-benzenetricarboxylic acid, two alternative routes for the preparation of 1,3,5-tris(aminomethyl)benzene have devised, giving the tripodal ligand in overall yields of 29 and 72%. This tris-amine has been transformed into multidentate oxygen-containing ligand precursors by Michael-addition reactions to α,β-unsaturated carbonyl compounds. The results of this work have shown further that a whole series of tripodal ligands having triazole, thiol and xanthate functions can be easily accessed from 1,3,5-tris(bromomethyl)benzene.

Experimental

General

All starting reagents were obtained from commercial sources and used without purification. Technical grade solvents were used and freshly distilled prior to use. For TLC Merck-DC-F_{254} plates were used and flash column chromatography [17] was performed using Merck silica gel (230-240 mesh). All melting

points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL Eclipse+400 instrument. Chemical shifts (δ) are indicated in ppm using TMS as internal reference; coupling constants (*J*) are given in Hz. Elemental analyses were performed on a Perkin-Elmer Series II CHNS/O Analyzer 2400.

1,3,5-Tris[*N*-benzyl-*N*-(4-methylphenylsulfonyl) aminomethyl]benzene (1)

1.10 g (4.20 mmol) of *N*-benzyl-4-methylbenzenesulfonamide (**3**) and 1.37 g (4.20 mmol) of Cs_2CO_3 suspended in CH_3CN (35 mL) were refluxed for 1 h. Then, a solution of 0.50 g (1.40 mmol) of 1,3,5-tris(bromomethyl)benzene (**4**) [6a] in CH_3CN (25 mL) was added dropwise. After the addition was complete, the suspension was refluxed and stirred for 5h. After filtration the solvent was removed and the crude product was purified by column chromatography on silica (hexane/AcOEt, 8:2) to afford 0.89 g (70%) of **1** as white crystals, mp 151-153ºC. ^{1}H NMR ($CDCl_3$) δ: 7.70 (*d*, *J* = 8.1 Hz), 7.30 (*d*, *J* = 8.1 Hz), 7.18 (*s*, 9H), 7.0 (*s*, 6H), 6.62 (*s*,3H), 4.14 (*s*, 6H), 4.04 (s, 6H), 2.42 (*s*, 9H). ^{13}C NMR ($CDCl_3$) δ: 143.6, 137.3, 136.4, 135.7, 129.9, 128.7, 128.5, 128.0, 127.8, 127.3, 51.1, 50.6, 21.6. IR (HBr) ν_{max} 2921, 1455, 1338, 1157 cm^{-1}. HRMS (FAB$^+$) *m/z* calcd for $C_{51}H_{52}O_6N_3S_3$ $[M+H]^+$ 899.1701. Found 899.3271.

General procedure for the reaction of alkylcarbamates 5a-5e with1,3,5-tris(bromomethyl)benzene (6a-e)

The corresponding alkylcarbamate (5 equiv.) and NaH (8 equiv.) were suspended in dry THF (30 mL) and refluxed for 20 minutes. To this mixture, a solution of 1,3,5-tris(bromomethyl)benzene (**4**) [6a] (1.0 equiv.) in THF (15 mL) was added dropwise. After the addition was complete, the suspension was refluxed and stirred for 24 h. After removal of the solvent 500 mL of water was added and the product was extracted with ethyl acetate (2 × 50 mL). After drying over Na_2SO_4, the solution was evaporated under reduced pressure and the residue was purified by column chromatography.

1,3,5-Tris[(*N*-benzyl-*N*-*tert*-butoxycarbonylamino)methyl] benzene (6a)

The general procedure was followed using 1.35 g (7.0 mmol) of **5a**, 0.27 g (11.20 mmol) of NaH and 0.50 g (1.40 mmol) of 1,3,5-tris(bromomethyl)benzene (**4**) to afford 0.50 g (49%) of **6a** as colorless oil. ^{1}H NMR ($CDCl_3$; 60ºC) δ: 7.32-7.19 (*m*, 15H), 6.97 (*s*, 3H), 4.38 (*s*, 12H), 1.50 (*s*, 27H). ^{13}C NMR ($CDCl_3$; 60ºC) δ: 155.9, 138.9, 138.1, 128.5, 127.8, 127.2, 126.0, 80.10, 49.6, 49.4, 28.5. IR (CH_2Cl_2) ν_{max} 3026, 2974, 1693, 1454, 1411, 1164 cm^{-1}. Anal. Calcd for $C_{45}H_{57}N_3O_6$: C, 73.44; H, 7.81, N, 5.71. Found: C, 73.29; H, 8.14, N, 5.34.

1,3,5-Tris[*N*-*tert*-butoxycarbonyl-*N*-(2-phenylethyl)amino methyl]benzene (6b)

The general procedure was followed using 1.55 g (7.0 mmol) of **5b**, 0.27 g (11.20 mmol) of NaH and 0.50 g (1.40 mmol) of 1,3,5-tris(bromomethyl)benzene (**4**) to afford 0.47 g (43%) of **6b** as colorless oil. ^{1}H NMR ($CDCl_3$; 60ºC) δ: 7.25-7.08 (*m*, 15H), 6.94 (*s*, 3H), 4.31 (*b*, 6H), 3.36 (*b*, 6H), 2.77 (*b*, 6H), 1.44 (*s*, 27H).^{13}C NMR ($CDCl_3$; 60ºC) δ: 155.7, 139.3, 128.8, 128.5, 126.2, 125.6, 79.7, 50.6, 48.6, 34.8, 28.5. IR (CH_2Cl_2) ν_{max} 3025, 2974, 2929, 1693, 1454, 1412, 1164 cm^{-1}. Anal. Calcd for $C_{48}H_{63}N_3O_6$: C, 74.10; H, 8.16, N, 5.40. Found: C, 73.97; H, 8.38, N, 5.25.

1,3,5-Tris [(*N*-*tert*-butoxycarbonyl-*N*-ethyl)aminomethyl] benzene (6c)

The general procedure was followed using 1.02 g (7.0 mmol) of **5c**, 0.27 g (11.20 mmol) of NaH and 0.50 g (1.40 mmol) of 1,3,5-tris(bromomethyl)benzene (**4**) to afford 0.26 g (34%) of **6c** as colorless oil. ^{1}H NMR ($CDCl_3$; 60ºC) δ: 6.92 (*s*, 3H), 4.31 (*s*, 6H), 3.13 (*b*, 6H), 1.38 (*s*, 27H), 0.97 (*b*, 9H). ^{13}C NMR ($CDCl_3$; 60ºC) δ: 155.9, 155.3, 139.2, 125.3, 79.4, 49.9, 49.5, 41.3, 28.5, 13.2. IR (CH_2Cl_2) ν_{max} 2975, 2932, 1694, 1455, 1414, 1174 cm^{-1}. HRMS (FAB$^+$) *m/z* calcd for $C_{30}H_{51}N_3O_6 \cdot H_2O$ $[M+H_2O]^+$ 567.3884. Found: 567.4115.

1,3,5-Tris [(*N*-*tert*-butoxycarbonyl-*N*-isopropyl) aminomethyl]benzene (6d)

The general procedure was followed using 1.11 g (7.0 mmol) of **5d**, 0.27 g (11.20 mmol) of NaH and 0.50 g (1.40 mmol) of 1,3,5-tris(bromomethyl)benzene (**4**) to afford 0.30 g (36%) of **6d** as colorless oil. ^{1}H NMR ($CDCl_3$; 60ºC) δ: 6.97 (*s*, 3H), 4.30 (*s*, 6H), 4.11 (*b*, 3H), 1.41 (*s*, 27H), 1.06 (*d*, *J* = 7.0 Hz, 18H).^{13}C NMR ($CDCl_3$; 60ºC) δ: 155.7, 140.5, 123.9, 79.4, 48.0, 46.9, 28.5, 20.8. IR (CH_2Cl_2) ν_{max} 2975, 2932, 1694, 1455, 1414, 1174 cm^{-1}. Anal. Calcd for $C_{33}H_{57}N_3O_6$: C, 66.97; H, 9.71 N, 7.10. Found: C, 66.90; H, 9.71, N, 6.90.

1,3,5-Tris [(*N*-*tert*-butoxycarbonyl-*N*-(4-methoxyphenyl)) aminomethyl]-benzene (6e)

The general procedure was followed using 1.56 g (7.0 mmol) of **5e**, 0.27 g (11.20 mmol) of NaH and 0.50 g (1.40 mmol) of 1,3,5-tris(bromomethyl)benzene (**4**) to afford 1.00 g (92%) of **6e** as colorless oil. ^{1}H NMR ($CDCl_3$; 60ºC) δ: 6.95 (*s*, 3H), 6.85 (*b*, 6H), 6.71 (*d*, *J* = 8.4 Hz, 6H), 4.67 (*s*, 6H), 3.73 (*s*, 9H), 1.36 (*s*, 27H). ^{13}C NMR ($CDCl_3$; 60ºC) δ: 157.7, 155.1, 139.0, 135.7, 128.1, 126.2, 113.9, 80.1, 55.3, 54.0, 28.3. IR (CH_2Cl_2) ν_{max} 2975, 2930, 2838, 1698, 1457, 1162 cm^{-1}. Anal. Calcd for $C_{45}H_{57}N_3O_6$: C, 68.94; H, 7.33 N, 5.36. Found: C, 68.78; H, 7.06, N, 5.17.

General procedure for the removal of the Boc group in 2a-e

To a solution of 1 mmol of the corresponding adduct (**6a-e**) in 10 mL of ethyl acetate a solution of 3M HCl (5 mL) was added dropwise at room temperature. The mixture was allowed to react for 1 h and the solid formed was separated by filtration. After neutralization with NaOH, the product was extracted with

CH_2Cl_2 (5 × 10 mL) and the resulting solution was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure.

1,3,5-Tris(*N*-benzylaminomethyl)benzene (2a)

The general procedure was followed using 0.050 g (0.068 mmol) of **6a** and 5 mL of 3 M HCl to afford 24 mg (91%) of **2a** [7c,e] as colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.35-7.23 (*m*, 18H), 3.83 (*s*, 6H), 3.81 (*s*, 6H), 2.00 (*b*, 3H). ^{13}C NMR ($CDCl_3$) δ: 140.6, 140.2, 128.4, 127.1, 126.9, 126.8, 53.4, 53.2. IR (CH_2Cl_2) ν_{max} 3312, 2916, 2812, 1452, 1111, 735, 697 cm^{-1}.

1,3,5-Tris(*N*-(2-phenylethyl)aminomethyl)benzene (2b)

The general procedure was followed using 0.200 g (0.26 mmol) of **6b** and 12 mL of 3M HCl to afford 91 mg (85%) of **2b** [18] as colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.29-7.20 (*m*, 15H), 7.08 (*s*, 3H), 3.77 (*s*, 6H), 2.90 (*t*, *J* = 6.2 Hz, 6H), 2.84 (*t*, *J* = 6.2 Hz, 6H), 1.68 (*b*, 3H). ^{13}C NMR ($CDCl_3$) δ: 140.5, 140.1, 128.8, 128.7, 126.6, 126.3, 53.8, 50.7, 36.4. IR (CH_2Cl_2) ν_{max} 3303, 2924, 2815, 1452, 1115, 748, 698 cm^{-1}.

1,3,5-Tris(*N*-ethylaminomethyl)benzene (2c)

The general procedure was followed using 0.068 g (0.12 mmol) of **6c** and 5 mL of 3 M HCl to afford 22 mg (84%) of **2c** as colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.13(*s*, 3H), 3.74 (*s*, 6H), 2.66 (*q*, *J* = 7.3 Hz, 6H), 1.60 (*b*, 3H), 1.11 (*t*, *J* = 7.3 Hz, 9H). ^{13}CNMR ($CDCl_3$) δ: 140.7, 126.7, 54.0, 43.9, 15.3. IR (CH_2Cl_2) ν_{max} 3270, 2966, 1454, 743 cm^{-1}. HRMS (FAB$^+$) *m/z* calcd for $C_{15}H_{28}N_3$ [M+H]$^+$ 250.2283. Found 250.2284.

1,3,5-Tris(*N*-isopropylaminomethyl)benzene (2d)

The general procedure was followed using 0.208 g (0.35 mmol) of **6d** and 5 mL of 3 M HCl to afford 59 mg (60%) of **2d** as colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.13 (*s*, 3H), 3.73 (*s*, 6H), 2.83 (*m*, 3H), 1.31 (*b*, 3H), 1.08 (*d*, *J* = 6.24 Hz, 18H).^{13}C NMR ($CDCl_3$) δ: 141.1, 126.5, 51.7, 48.5, 23.0. IR (CH_2Cl_2) ν_{max} 3280, 2964, 2930, 2869, 2826, 1467, 1379, 1367, 1174, 741 cm^{-1}. HRMS (FAB$^+$) *m/z* calcd for $C_{18}H_{34}N_3$ [M+H]$^+$ 292.2753. Found: 292.2754.

1,3,5-Tris[*N*-(4-methoxyphenyl)aminomethyl]benzene (2e)

The general procedure was followed using 0.200 g (0.26 mmol) of **6e** and 5 mL of 3M HCl to afford 82 mg (74%) of **2e** as colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.28 (*s*, 3H), 6.76 (*dd*, *J* = 8.8 Hz, *J* = 3.7 Hz, 6H), 6.58 (*dd*, *J* = 8.8 Hz, *J* = 3.7 Hz, 6H), 4.24 (*s*, 6H), 3.74 (*s*, 9H). ^{13}C NMR ($CDCl_3$) δ: 152.4, 142.5, 140.7, 125.6, 115.0, 114.3, 55.9, 49.3. IR (CH_2Cl_2) ν_{max} 3399, 2931, 2831, 1513, 1234, 819 cm^{-1}.

1,3,5-Tris(azidomethyl)benzene (7)

1.00 g (2.80 mmol) of 1,3,5-tris(bromomethyl)benzene (**4**) [6a] were dissolved in 5 mL of DMF, whereupon 1.11 g (17.10 mmol) of NaN_3 were added in small portions. After stirring the mixture for 2 h at room temperature. 50 mL of ethyl acetate were added and the solution was washed with water and brine. The organic phase was dried with Na_2SO_4 and evaporated under reduced pressure to afford 0.65 g (95%) of **7** [19] as colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.24 (*s*, 3H), 4.35 (*s*, 6H). ^{13}C NMR ($CDCl_3$) δ: 137.1, 127.6, 54.4.

1,3,5-Tris(aminomethyl)benzene (8)

1.29 g (5.30 mmol) of 1,3,5-tris(azidomethyl)benzene (**7**) [19] dissolved in EtOH (70 mL), and 0.13 g of 10% Pd/C were placed in a 250 mL hydrogenation flask, and the reaction mixture was stirred for 3 h at 70 psi. Lower pressures gave only low yields. The solution was filtered and the solvent was removed under reduced pressure to afford 0.80 g (91%) of **8** [20] as a white solid. ^{1}H NMR ($CDCl_3$) δ: 7.10 (*s*, 3H), 3.80 (*s*, 6H), 1.58 (*b*, 6H). ^{13}C NMR ($CDCl_3$) δ: 143.9, 124.4, 46.4.

1,3,5-Tris[(4-phenyl-1H-1,2,3-triazol-1-yl)methyl]benzene (9)

0.20 g (0.82 mmol) of 1,3,5-tris(azidomethyl)benzene (**7**) [19] and 0.40 mL (3.70 mmol) of phenylacetylene were placed in a previously oven-dried 25 mL round-bottomed flask, followed by addition of 40 mL of CH_3CN and 0.094 g (0.049 mmol) CuI. After the addition was complete, the suspension was refluxed and stirred for 15h and then allowed to cool to room temperature. The solids formed were filtered off and washed with acetonitrile to afford 0.22 g (50%) of **9** [13] as white solid, mp 221-222°C. ^{1}H NMR ($CDCl_3$) δ: 8.61 (*s*, 3H), 7.82 (*d*, *J* = 7.3 Hz, 6H), 7.42 (*t*, *J* = 7.3 Hz, 3H), 7.32 (*m*, 6H) 5.67 (*s*, 6H). ^{13}C NMR ($CDCl_3$) δ: 147.2, 137.9, 131.2, 129.4, 128.5, 127.8, 125.7, 122.3, 122.0, 53.1.

1,3,5-Tris[*N*,*N*-di(3-methoxy-3-oxopropyl)aminomethyl] benzene (11)

0.10 g (0.60 mmol) of 1,3,5-tris(aminomethyl)benzene (**8**) [20], 7 mL of methanol and 0.38 g (4.21 mmol) of methyl acrylate were placed in a previously oven-dried 25 mL round-bottomed flask. The reaction mixture was heated for 8 h, whereupon the solvent and excess of ethyl acrylate were removed. The product was extracted with ethyl acetate (3 × 50 mL), the organic phase dried over Na_2SO_4 and concentrated under reduced pressure to afford 0.25 g (62%) of **11** as colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.04 (*s*, 3H), 3.62 (*s*, 18H), 3.54 (*s*, 6H,), 2.76 (*t*, *J* = 7.1 Hz, 12H), 2.43 (*t*, *J* = 7.1 Hz, 12H). ^{13}C NMR ($CDCl_3$) δ: 173.0, 138.9, 128.1, 58.3, 51.6, 49.3, 32.5. IR (CH_2Cl_2) ν_{max} 2952, 2830, 1737, 1437, 1197 cm^{-1}. HRMS (FAB$^+$) *m/z* calcd for $C_{33}H_{52}N_3O_{12}$ [M+H]$^+$ 682.3551. Found: 682.3525.

1,3,5-Tris[*N*-(1,4-dimethoxy-1,4-dioxobutan-2-yl) aminomethyl]benzene (13)

0.10 g (0.60 mmol) of 1,3,5-tris(aminomethyl)benzene (**8**) [20], 7 mL of methanol, 0.38 g (1.82 mmol), 0.23 mL of dimethyl maleate and 0.32 g (3.02 mmol) of $LiClO_4$ were placed into a

previously oven-dried 25 mL round-bottomed flask. The reaction mixture was heated for 24 h, and then the solvent was removed in a rotary evaporator. The solid was dissolved in 50 mL of ethyl acetate and the solution washed with water (3 × 50 mL). After drying the organic phase over Na_2SO_4 and evaporation of the solvent under reduced pressure, the residue was purified by column chromatography to afford 0.10 g (25%) of **13** as colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.14 (*s*, 3H), 3.82 (*d*, *J* = 12.8 Hz, 3H), 3.72 (*s*, 9H) 3.66 (*s*, 9H), 3.65 (*m*, 3H), 3.63 (*d*, *J* = 12.8 Hz, 3H), 2.74 (*dd*, *J* = 5.9 Hz, *J* = 16.2 Hz, 3H), 2.67 (*dd*, *J* = 6.6 Hz, *J* = 16.2 Hz, 3H), 2.1 (b, 3H). ^{13}C NMR ($CDCl_3$) δ: 174.1, 171.4, 139.85, 127.0, 57.0, 52.2, 51.9, 37.9. IR (CH_2Cl_2) ν_{max} 2953, 2847, 1737, 1437, 1204 cm^{-1}. HRMS (FAB$^+$) *m/z* calcd for $C_{27}H_{40}N_3O_{12}$ $[M+H]^+$ 598.2612. Found 598.2614.

1,3,5-Tris[(ethoxycarbonothioyl)thiomethyl]benzene (14)

1.10 g (5.60 mmol) of potassium *O*-ethyl dithiocarbonate and 30 mL of acetone were placed in an oven-dried 100 mL round-bottomed flask. Then a solution of 0.50 g (1.40 mmol) of 1,3,5-tris(bromomethyl)benzene (**4**) [6a] in acetone (5 mL) was added. The reaction mixture was allowed to react for 2 h at room temperature, and then the solvent was removed in a rotary evaporator. The solid was dissolved in 60 mL of ethyl acetate and the solution was washed with a saturated solution of NH_4Cl (3 × 50 mL). After drying the organic phase over Na_2SO_4 and evaporation of the solvent under reduced pressure, the residue was purified by column chromatography to afford 0.49 g (74%) of **14** as white crystals, mp 98-100ºC. ^{1}H NMR ($CDCl_3$) δ: 7.22 (*s*, 3H), 4.63 (*q*, *J* = 7.2 Hz, 6H), 4.30 (*s*, 6H), 1.40 (*t*, *J* = 7.2 Hz, 9H). ^{13}C NMR ($CDCl_3$) δ: 213.6, 136.9, 129.0, 70.3, 40.0, 13.9. IR (KBr) ν_{max} 2976, 2935, 1218, 1108 cm^{-1}. HRMS (FAB$^+$) *m/z* calcd for $C_{18}H_{25}O_3S_6$ $[M+H]^+$ 481.0128. Found: 481.0143.

1,3,5-Tris(mercaptomethyl)benzene (15)

1.28 g (3.59 mmol) of 1,3,5-tris(bromomethyl)benzene (**4**) [6a], 0.82 (10.77 mmol) of thiourea and 20 mL of acetone were placed in a previously oven-dried 50 mL round-bottomed flask. The reaction mixture was heated to reflux for 1 h and then allowed to cool to room temperature. The solids formed were filtered off and dried under high vacuum. After dissolving the solid in 2M NaOH (30 mL), the mixture was heated to reflux for 2 h. After acidification to pH ≈ 2 with 2M HCl, the product was extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was washed with H_2O (2 × 25 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to afford 0.63 g (81%) of **15** [21] as a colorless oil. Further purification was not required. ^{1}H NMR ($CDCl_3$) δ: 7.15 (*s*, 3H), 3.69 (*d*, *J* = 7.7 Hz, 6H), 1.79 (*t*, *J* = 7.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 142.1, 126.6, 28.8. IR (CH_2Cl_2) ν_{max} 2928, 2554, 1454, 708 cm^{-1}.

X-ray crystallography

X-ray diffraction studies were performed on a Bruker-APEX diffractometer with a CCD area detector ($\lambda_{MoK\alpha}$ = 0.71073 Å, monochromator: graphite). Frames were collected at *T* = 100 K via ω- and ϕ-rotation at 10 s per frame (SMART) [22a]. The measured intensities were reduced to F^2 and corrected for absorption with SADABS (SAINT-NT) [22b]. Corrections were made for Lorentz and polarization effects. Structure solution, refinement and data output were carried out with the SHELXTL-NT program package [22c,d]. Non hydrogen atoms were refined anisotropically, while hydrogen atoms were placed in geometrically calculated positions using a riding model. The molecular structure was illustrated by the SHELXTL-NT software package [22c,d]. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-760724. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk, www: http://www.ccdc.cam.ac.uk).

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