# Desymmetrisation of Biphenyl-Based Carbohydrate Receptors: A Nonbonding Pillar in One Corner of the Cage

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This paper is dedicated to Prof. Jack E. Baldwin on the occasion of his 70th birthday.

**Abstract:** We report a new addition to the family of biphenyl-based carbohydrate receptors, derived by replacing one out of four isophthalamide (diamide) linkages with the corresponding diester. The alteration results in lower binding constants, perhaps reflecting the entropic penalty for lowering receptor symmetry. However, the synthesis allows access to many related host molecules, with potential for restoring and raising affinities and tuning selectivities.

**Key words:** carbohydrates, supramolecular chemistry, bioorganic chemistry, esters, biaryls

Carbohydrate recognition continues to attract the interest of supramolecular chemists.[1,2] On the one hand, saccharides are challenging substrates because of their complexity and the subtle differences between their structures. On the other they hold great importance for biology, not only as fuels and structural materials but also as labels for cells and proteins.[3] We have developed a family of oligophenyl-based receptors which have successfully targeted 'all-equatorial' carbohydrates (glucose, β-glucosides, cellobiose, etc.).[4] The design strategy is illustrated in Figure 1 (a) for the monosaccharide receptors **1**.[4a–c] Two biphenyl units serve as roof and floor of a tricyclic cage, providing apolar surfaces which complement the axial CH groups of a β-glucosyl substrate **2**. The aromatic surfaces can contribute to binding through CH-π interactions in nonpolar solvents, and through hydrophobic interactions in water. The biphenyls are separated by isophthalamide pillars that can hydrogen bond to the equatorially directed polar groups of the substrate. Solubility is controlled by externally directed groups X (lipophilic for organic-soluble **1a** and **1b**,[4a,b] charged for water-soluble **1c**[4c]). The receptors show useful binding properties in a full range of solvents,[5] with good-to-excellent selectivities for their intended targets.

Given the asymmetry of the carbohydrate substrates, it seems unlikely that the highly symmetrical structure **1** is optimal for binding; a receptor which is perfectly complementary for **2** should reflect the asymmetry of **2**. Moreover, less-symmetrical cages might show altered and complementary selectivities. We have previously described the preparation of receptors in which the ends of the cage are differentiated, through the presence or absence of a pyridine nitrogen.[6] In the present work we aimed to lower symmetry still further, by changing one corner of the cage. We were also interested to test the effect of removing H-bonding functionality from a pillar. Molecular modelling[4a] suggested that, in the ground state conformation of complex **1** + **2** (R = OH), one of the isophthalamide units of **1** makes no hydrogen bonds with the carbohydrate. If so, the amides in this pillar might not be needed for strong binding. We were therefore drawn to receptor **3** (Figure 1, b), an analogue of **1b** in which one isophthalamide is replaced by a diester (isophthalate) unit. Esters cannot act as H-bond donors, and are also relatively poor H-bond acceptors. We now report the successful synthesis of **3**, and a study of its carbohydrate-binding properties.

The synthetic route to **3** is summarised in Schemes 1 and 2. The key novel component was biphenyl **9** (Scheme 1), with a free hydroxy group and two types of masked amino functionality. This required a xylyl component with differentially functionalised benzylic positions. The necessary asymmetry was established in the first step by treating dibromide **4**[4b] with one equivalent of potassium acetate, giving monobromide **5**.[7] Treatment with sodium azide gave **6**, and was followed by Suzuki–Miyaura coupling with **7**[4b] to give **8**. Notably, both the azide and the acetate in **6** survived this step. Hydrolysis of the acetate group yielded **9**,[8] which was reacted with the bispentafluorophenyl ester **10**[4b] (Scheme 2). The resulting diester **11** was treated with trimethylphosphine to reduce the azides to amino groups. Cyclisation with **10** under high dilution gave macrocycle **12**. Finally, removal of the *N*-Boc protecting groups and a [2+2] cyclisation with two equivalents of **10** gave macrotricycle **3**.[9]

Diester **3** was tested as a carbohydrate receptor in $CDCl_3$–$CD_3OD$ (92:8), the solvent system used previously for **1a** and **1b**. In organic media such as this, it is necessary to use lipophilic carbohydrate derivatives as substrates. In the present case, the experiments employed the octyl glycosides **13**–**15** (Figure 2). Complex formation could be detected by $^1H$ NMR. On addition of the glycosides to a solution of **3**, the signals from the aromatic protons of the receptor broadened and moved significantly. An example is shown in Figure 3. The broadening precluded analysis for many of the resonances, but for each substrate at least two signals could be followed throughout a titration. The data were analysed by nonlinear least-squares curve-fit-

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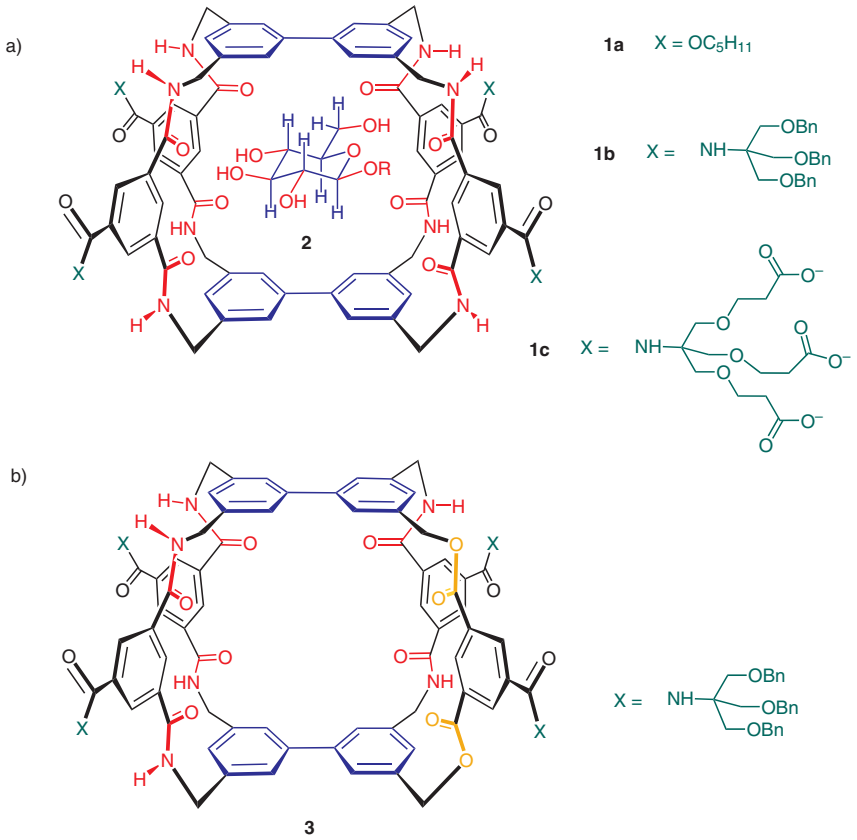
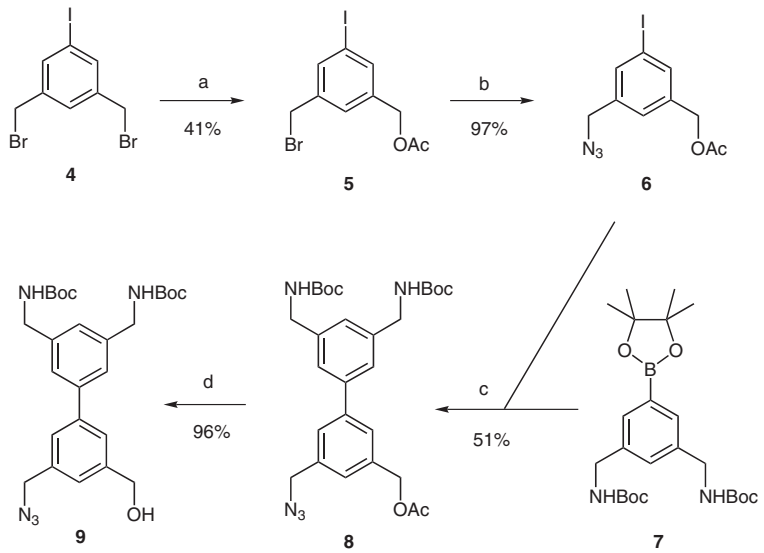



**Figure 1** a) High-symmetry biphenyl-based monosaccharide receptors **1**, and β-glucosyl substrates **2**. Apolar units are shown in blue, polar groups in red, and solubilising groups in green. b) The lower-symmetry design described in this paper. The ester groups in the isophthalate pillar are highlighted in yellow.




**Scheme 1** *Reagents and conditions*: a) KOAc, $Bu_4NBr$, DMF; b) $NaN_3$, DMF; c) $PdCl_2(dppf)$, $Na_2CO_2$ aq, DMF; d) $Cs_2CO_3$, THF–MeOH.

ting to a 1:1 binding model.[10] An example of experimental and calculated curves is given in Figure 4.

The results for the binding studies are summarised in Table 1. Given the competitive nature of the solvent system, **3** may be considered a fairly effective receptor for the β-glucosides **13** and **15**. It also shows significant selectivity for these substrates against the α-glucoside **14**. However, compared to the high-symmetry, all-amide receptors **1**, the affinities measured for **3** are quite low. For example, the binding constants of **1a** and **1b** for β-glucoside **13** were 980 and 720 $M^{-1}$, respectively. It therefore seems that all eight amide groups in **1** are important for binding. This may imply that the modelling discussed earlier was misleading, and that **2** binds simultaneously to amide

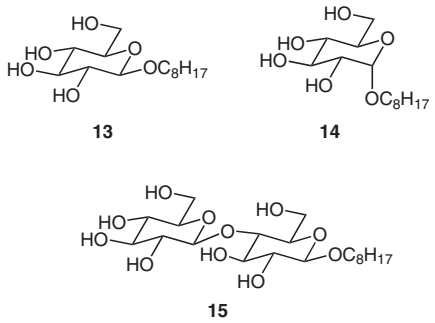
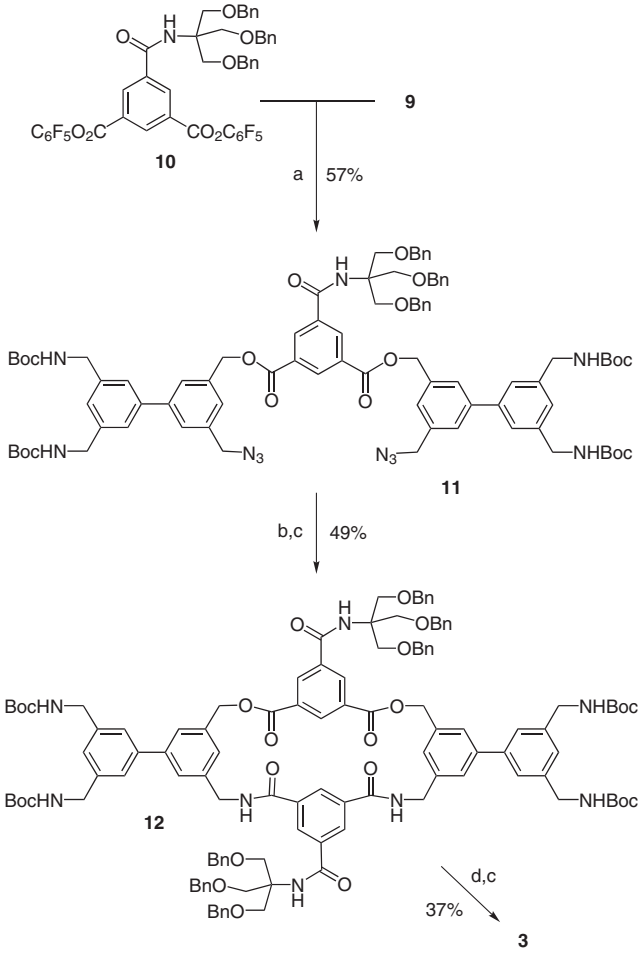



**Figure 2**




**Scheme 2** *Reagents and conditions*: a) DIPEA, DMAP, THF; b) $Me_3P$, THF, $H_2O$; c) **10**, DIPEA, THF, high dilution (0.4 mM final concentration); d) TFA, $CH_2Cl_2$.

groups in all four pillars of **1**. However, a second, more subtle factor is worth noting. In moving from the high-symmetry receptors **1** to the less symmetrical **3**, a significant entropic penalty must be paid. In the former, there are four equivalent orientations for a fully asymmetric substrate such as **2** (see Figure 5). Each strongly bound conformation can thus be formed in four distinct ways. However, if one of the pillars is altered this degeneracy is lost, so that there is only one way of assembling a given bound conformation. Even if one of the four original pillars contributed no positive binding interactions, this effect should still cause a drop in affinity. Although one might still argue that the ideal carbohydrate receptor must be asymmetric to be fully complementary to its substrate, this entropic disadvantage must be borne in mind.

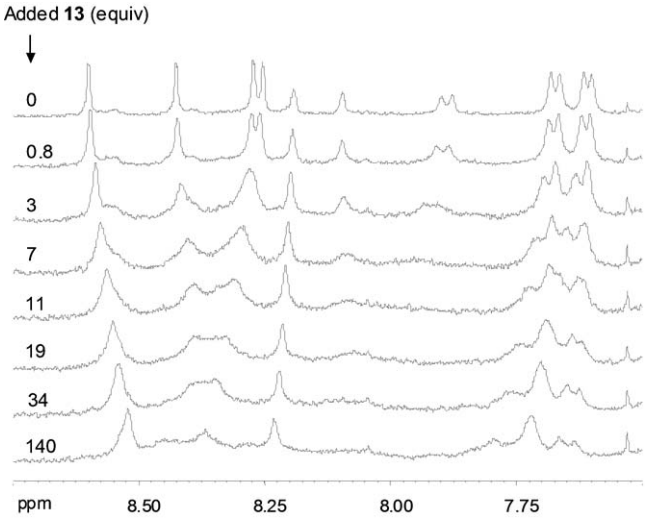



**Figure 3** $^1$H NMR spectra (aromatic region) from the titration of receptor **3** against glucoside **13** in $CDCl_3$–$CD_3OH$ (92:8).

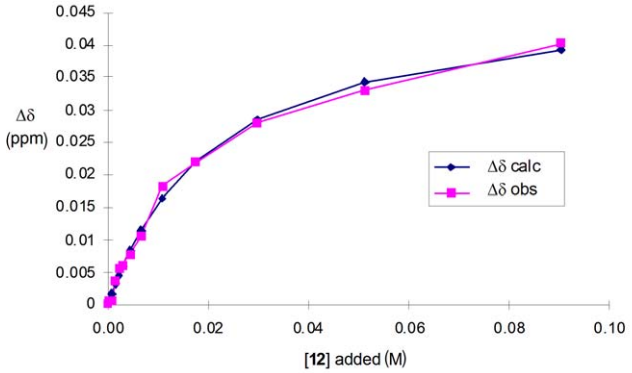



**Figure 4** Experimental and calculated values for an NMR binding study of **3** and **12** (see Figure 3; data from peak starting at δ = 8.19 ppm). Calculation assumes a 1:1 binding model; $K_a$ = 50 $M^{-1}$. Limiting Δδ = 0.048 ppm.

**Table 1** Association Constants $K_a$ between Receptor **3** and Octyl Glycosides in $CDCl_3$–$CD_3OH$ (92:8), Measured by $^1$H NMR Titration

| Glycoside | $K_a$ ($M^{-1}$) for Individual Signals[a] | $K_a$ ($M^{-1}$) (averaged) |
|---|---|---|
| Octyl β-D-glucoside (**13**) | 60 (8.6), 50 (8.19) | 55 |
| Octyl α-D-glucoside (**14**) | 9 (8.6), 11 (8.43), 10 (8.19) | 10 |
| Octyl β-D-cellobioside (**15**) | 155 (8.25), 120 (8.10) | 138 |

[a] Starting chemical shifts are shown in parentheses.

In conclusion, we have shown that our synthesis of carbohydrate receptors **1** can be modified so that one corner of the cage structure is different from the rest. The prepara-

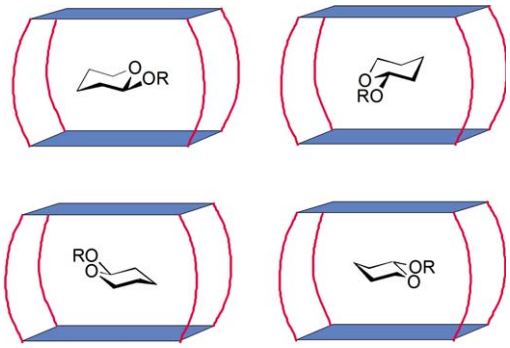



**Figure 5** Four equivalent orientations of a glycoside substrate in a $D_{2h}$ cage receptor such as **1** (shown schematically). If one corner of the cage is altered, these structures become inequivalent.

tion of diester **3** has allowed us to test the effect of removing the amide linkages from this corner. The resulting drop in affinities is perhaps disappointing, but usefully highlights the connection between receptor symmetry and binding entropy. The methodology developed during this work could be used to make a wide variety of other structures. Because the first [2+2] cyclisation (**9** → **12**, Scheme 2) is performed in stepwise fashion, there is essentially no limitation to the spacer groups (pillars) which may be introduced.[11] In future work we plan to exploit this flexibility to fine-tune the cage structure and to incorporate further binding functionality into the pillars. We may hope thereby to restore (and raise) the affinities for β-glucosides, and perhaps to develop receptors with altered selectivities.

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(7) **3-Acetyloxymethyl-5-bromomethyl-1-iodobenzene (5)** Potassium acetate (2.52 g, 25.7 mmol) was added in small portions over 1 h to a stirred solution of 1,3-bisbromomethyl-5-iodobenzene **4** (10.0 g, 25.7 mmol) and TBAB (83.0 mg, 2.57 mmol) in anhyd DMF (200 mL). The suspension was stirred at r.t. during 25 h. Ethyl acetate (600 mL) was added to the mixture and the organic solution was washed with $H_2O$ (3 × 200 mL), $NH_4Cl$ sat. solution (200 mL) and brine (200 mL), then filtered ($MgSO_4$) and concentrated under vacuum. Purification by flash chromatography (eluent: hexane–EtOAc, 90:10) afforded acetate **5** (3.92 g, 41%). $R_f$ = 0.50 ($SiO_2$; hexane–EtOAc, 80:20). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.70 (s, 1 H, Ar*H*), 7.63 (s, 1 H, Ar*H*), 7.33 (s, 1 H, Ar*H*), 5.05 (s, 2 H, $CH_2O$), 4.39 (s, 2 H, $CH_2Br$), 2.13 (s, 3 H, $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 170.6 (CO), 140.2 (Ar*C*), 138.8 (Ar*C*), 137.7 (Ar*C*H), 137.0 (Ar*C*H), 128.0 (Ar*C*H), 94.3 (Ar*C*I), 64.8 (*C*$H_2$OAc), 31.5 ($CH_2$Br), 21.0 ($CH_3$). IR: $\nu_{max}$ = 2932, 1737, 1570, 1357, 1377, 1236, 1057, 860 cm$^{-1}$. MS(CI, $NH_3$): *m/z* = 386, 388 [M + $NH_4$]$^+$. HRMS(EI): *m/z* calcd for $C_{10}H_{10}Br_1I_1O_2$ [M]$^+$: 367.8903; found: 367.8907.

(8) Data for biphenyl **9**: $R_f$ = 0.30 ($SiO_2$; hexane–EtOAc, 50:50). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.52 (s, 1 H, Ar*H*), 7.39 (s, 1 H, Ar*H*), 7.37 (s, 2 H, Ar*H*), 7.30 (s, 1 H, Ar*H*), 7.17 (s, 1 H, Ar*H*), 5.00 (br s, 2 H, NH), 4.76 (s, 2 H, C$H_2$OH), 4.39 (s, 2 H, $CH_2N_3$), 4.34 [d, $^3J$(H,H) = 5.0 Hz, 4 H, C$H_2$NH], 1.46 (s, 18 H, $CH_3$C). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 153.6 (CO), 140.0 (Ar*C*), 138.6 (Ar*C*), 138.4 (Ar*C*), 137.3 (Ar*C*), 133.4 (Ar*C*), 123.0 (Ar*C*H), 122.9 (Ar*C*H), 122.8 (Ar*C*H), 122.7 (Ar*C*H), 122.6 (Ar*C*H), 77.3 [*C*($CH_3$)$_3$], 61.7 ($CH_2$OH), 52.0 ($CH_2N_3$), 41.8 (*C*$H_2$NHBoc), 25.8 ($CH_3$). IR: $\nu_{max}$ = 3406, 3335, 2978, 2932, 2096, 1684, 1513, 1247, 1160, 852 cm$^{-1}$. MS(ES$^+$): *m/z* = 516 [M + $NH_4$]$^+$, 521 [M + Na]$^+$. MS (ES$^-$): *m/z* = 497 [M – H$^+$]$^-$. HRMS(ES$^+$): *m/z* calcd for $C_{26}H_{39}N_6O_5$ [M + $NH_4$]$^+$: 515.2976; found: 515.2971.

(9) Data for receptor **3**: $R_f$ = 0.50 ($SiO_2$; toluene–EtOAc–EtOH, 50:50:5). $^1$H NMR [400 MHz, $CDCl_3$–$CD_3OD$ (92:8)]: δ = 8.60 (s, 2 H, spacer-Ar*H*), 8.43 (s, 2 H, spacer-Ar*H*), 8.29 (s, 2 H, spacer-Ar*H*), 8.27 (s, 2 H, spacer-Ar*H*), 8.22 [t, $^3J$(H,H) = 4.8 Hz, 2 H, NH], 8.19 (s, 1 H, spacer-Ar*H*), 8.11 (s, 1 H, spacer-Ar*H*), 8.07 [t, $^3J$(H,H) = 4.8 Hz, 2 H, NH],

7.93 (s, 1 H, spacer-Ar*H*), 7.91 (s, 1 H, spacer Ar*H*), 7.83 [t, $^3J$(H,H) = 4.6 Hz, 2 H, NH], 7.69 (s, 2 H, Ar*H*), 7.67 (s, 2 H, Ar*H*), 7.62 (s, 2 H, Ar*H*), 7.61 (s, 2 H, Ar*H*), 7.52–7.05 (m, 64 H, Ar*H*), 6.85 (s, 1 H, NHC), 6.82 (s, 1 H, NHC), 6.79 (s, 1 H, NHC), 6.77 (s, 1 H, NHC), 5.46 [A part of AB system, $^2J$(H,H) = 11.7 Hz, 2 H, C$H_2$OCOAr], 5.05 [(B part of AB system, $^2J$(H,H) = 11.7 Hz, 2 H, C$H_2$OCOAr], 4.73 [A part of AB system, $^2J$(H,H) = 13.7 Hz, 2 H, C$H_2$NHCOAr], 4.50–4.45 (m, 32 H, BnC$H_2$, C$H_2$NHCOAr), 4.34 [B part of AB system, $^2J$(H,H) = 13.7 Hz, 2 H, C$H_2$NHCOAr], 3.90 (s, 6 H, CC$H_2$OBn), 3.88 (s, 18 H, CC$H_2$OBn). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.8, 166.7, 166.6, 166.0, 165.6, 165.3 (CO), 139.4, 139.3, 139.2, 139.0, 138.1 (Ar*C*), 138.0 (BnAr*C*), 136.7, 136.6, 136.5, 136.3, 136.2, 135.2, 135.1, 134.4 (Ar*C*), 133.0, 131.7 (Ar*C*H), 131.0 (Ar*C*), 129.8, 129.7, 129.6, 129.0, 128.8 (Ar*C*H), 128.4 (BnAr*C*H), 128.1, 128.0 (Ar*C*H), 127.7 (BnAr*C*H), 127.4, 126.8, 126.5, 126.4, 126.1 (Ar*C*H), 75.5 (Bn*C*$H_2$), 68.8, 68.7 (C*C*$H_2$OBn), 68.1 (*C*$H_2$OCOAr), 60.9, 60.8, 60.7, 60.6 (*C*$CH_2$OBn), 44.8 (*C*$H_2$NHCOAr). IR: $\nu_{max}$ = 3306, 3029, 2862, 1721, 1659, 1515, 1452, 1255, 1091, 1075733 cm$^{-1}$. MS (MALDI$^+$): *m/z* = 2772 [M + K]$^+$.

(10) The analysis programme was implemented as an Excel spreadsheet.

(11) In contrast, the single-step [2+2] cyclisation which forms the other end of the cage, and which is used twice in the synthesis of **1**, is limited to spacers that cannot perform [1+1] cyclisations with the diaminobiphenyl units. The rigid isophthaloyl groups fulfil this criterion but many other potential spacers do not.