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Synthesis of Carbohydrate Functionalised n-Propoxy-Calix[4]arenes

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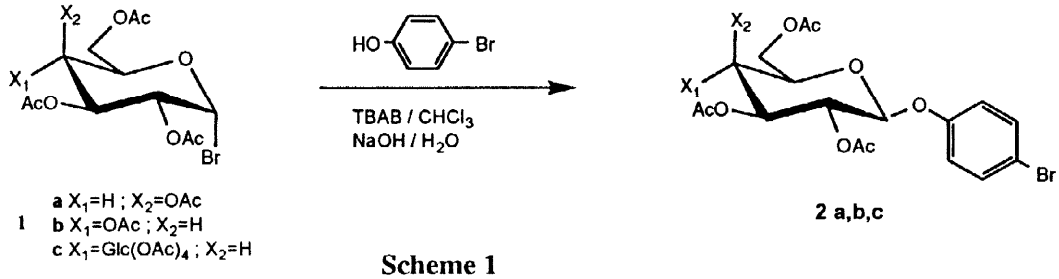
Abstract : The Suzuki reaction has been used to couple para-bromophenyl glycosides to boronic acid derivatives of n-propoxy-Calix[4]arene ; " a one-pot " methodology eliminates the need to isolate the boronic acids and increases the overall yield. The synthesis provides a new class of carbohydrate containing calixarenes with a deepened cavity.

In order to enlarge the cavity of calix[4]arene derivatives, Atwood et al[1] have prepared a p-phenylcalix[4]arene tetramethylether. Such calix[4]arene derivative should be capable of binding organic guest molecules. However the methyl derivatives are present in the semi-cone conformation, which is neither optimised for guest binding nor for increasing carbohydrate recognition by cooperative interaction.[2] In view of this, the tetra-propyl derivatives blocked in the cone conformation are of great interest.

Bearing in mind the significant role played by sugars in many biological events, the coupling of carbohydrate antennae to the calix[4]arenes may provide a new class of molecular vectors. To this end, Dondoni and Ungaro[3,4] et al have described the synthesis of calix[4]arenes substituted by carbohydrate units at the upper and at the lower rim. Roy[5] et al have prepared a water soluble α-thiosialoside-*p-tert*-butylcalix[4]arene derivative used for protein binding studies.

The aim of our work consists both of increasing the size of the cavity and incorporating the specificity of the transport and recognition properties of the calix[4]arenes by the formation of derivatives substituted by phenylglycoside antennae. The key step of the synthesis is the coupling reaction between a glycoside and a boronic acid derivative of a tetrapropoxy-calix[4]arene using a Suzuki type reaction in the presence of palladium (0)[6].

The saccharide antennae were obtained by methods analogous to those of the literature.[7] Glycosylation of p-bromophenol with tetra-O-acetyl-α-D-glycopyranosylbromide **1a**, **1b** or **1c** catalysed by tetrabutylammonium bromide (TBAB) leads to 4-bromophenyl-β-O-D-tetra-O-acetylglycoside **2a**, **2b** and **2c** in yields of 44 %, 22 % and 10 % respectively. (scheme 1).



1 a X_1=H ; X_2=OAc
b X_1=OAc ; X_2=H
c X_1=Glc(OAc)$_4$; X_2=H

2 a,b,c

Scheme 1

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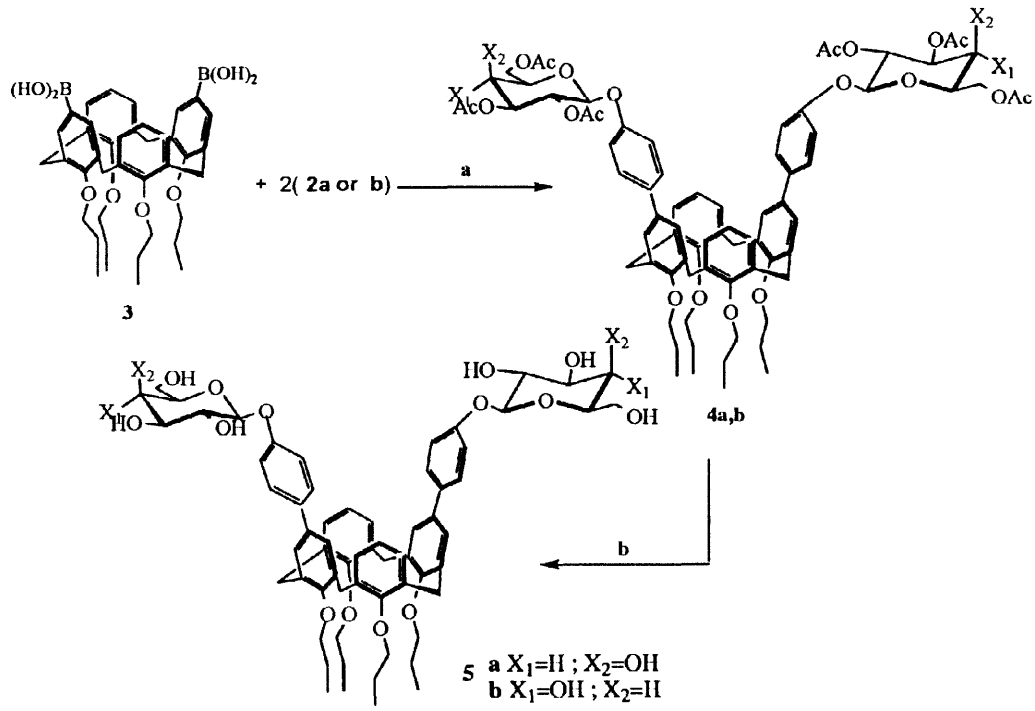
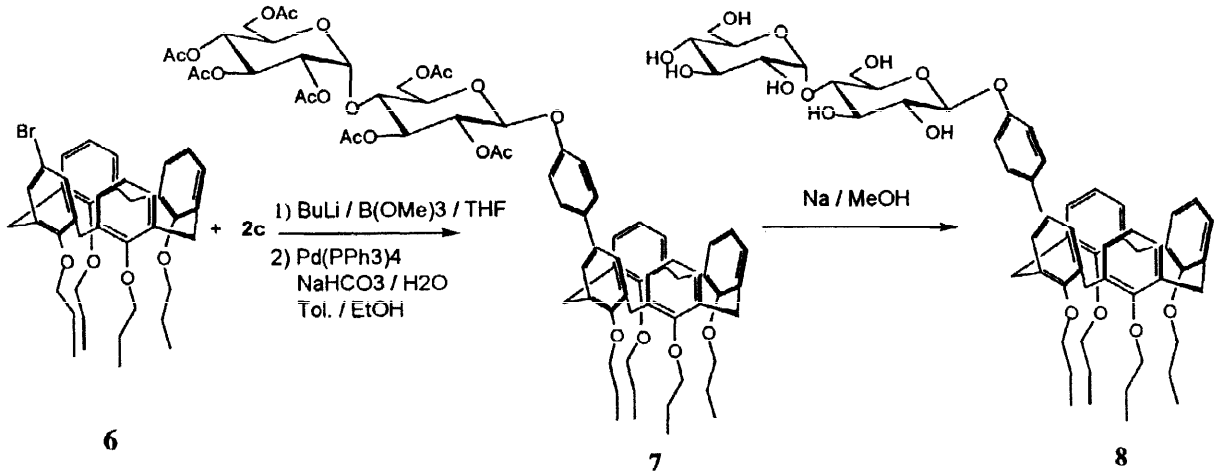
The 25,26,27,28-tetrapropoxy-calix[4]arene-5,17-diboronic acid **3**[8] was syntesised from 5,17-dibromo-25,26,27,28-tetrapropoxy-calix[4]arene with an excess of n-BuLi in THF at -78°C for 15 min, reaction with $B(OCH_3)_3$ gave the diboronic acid derivative **3**. Use of a Suzuki type reaction between **2** and **3** represents a novel and highly effective route to carbohydrate functionalised calix[4]arenes. Coupling of glycosylbromides **2a, 2b** (1.5 mmol) with the calix[4]arene diboronic acid **3** (0.75 mmol) in the presence of the Pd_2dba_3 (0.05 mmol), PPh_3 (0.18mmol) and a 1M aqueous solution of sodium hydrogenocarbonate (4ml) was carried out in 1,2-dimethoxyethane. The mixture was stirred at 60°C during 24h and hydrolysed with water and extracted with CH_2Cl_2. The new products were purified by column chromatography (eluent: $CHCl_3$).The derivatives **4a,b** were obtained in rather low yields (32 % and 42 % respectively).[9] Removal of the acetyl groups yielded the unprotected derivatives **5a,b** (11 % and 10 % respectively). It was difficult to purify **5a,b** due to their amphiphilic character (Scheme 2).



Scheme 2 : a) Pd(PPh3)4 / 1,2-dimethoxyethane / $NaHCO_3$ / H_2O ; b) Na / MeOH

In order to reduce the number of synthetic steps and increase overall yields, we have developed a one-pot process[10] which involves the use of similar reactants from the 5-monobromo-25,26,27,28-tetrapropoxy-calix[4]arene **6**[11] and the 4-bromophenyl-β-O-D-tetra-O-acetylmaltoside **2c**[9](scheme 3). The calix[4]arene derivative 7 was prepared with 35 % yield and the removal of the protecting groups yielded **8** [9](32 %). Full 500 MHz ^1H NMR analyses (COSY, TOCSY and ROESY) are consistent with all the carbohydrate containing calix[4]arene derivatives being in the *all-syn* (cone) conformation.



Scheme 3

The inclusion, lectin recognition and liquid crystal and amphiphilic properties of these products are currently under investigation.

References and notes

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9 **Selected data : p-bromophenylhepta-O-acetyl-β-D-maltoside 2c:** 10% yield. Mp = 168-172°C. $[\alpha]_D$=+49 (c 0.2, $CHCl_3$). ^1H NMR COSY (300 MHz, $CDCl_3$) δ_H ppm, 2.03 ; 2.05 ; 2.06 ; 2.07 ; 2.08 ; 2.11 ; 2.13 (7s, 21H, 7 CH_3) ; 3.86-3.90 (m, 1H, H_5) ; 3.96-4.01 (m, 1H, H_5) ; 4.08 (dd, ^{2}J=12.6 Hz, ^{3}J=1.9 Hz, 1H, $H_{6'}$) ; 4.11 (dd, ^{3}J=9.2 Hz, 1H, H_4) ; 4.27 (dd, ^{2}J=12.6 Hz, ^{3}J=4.7 Hz, 2H, 2 H_6) ; 4.50 (dd, ^{2}J=12.6 Hz, ^{3}J=2.8 Hz, 1H, $H_{6'}$) ; 4.89 (dd, ^{3}J=10.4 Hz, ^{3}J=3.8 Hz, 1H, H_2) ; 5.08 (dd, ^{3}J=10.1 Hz, 1H, H_4) ; 5.10-5.16 (m, 1H, H_2) ; 5.12 (d, ^{3}J=7.6 Hz, 1H, H_1) ; 5.31-5.35 (m, 1H, H_3) ; 5.39 (dd, ^{3}J=10.1 Hz, 1H, H_3) ; 5.46 (d, ^{3}J=3.8 Hz, 1H, H_1) ; 6.89 (d, ^{3}J=8.8 Hz, 2H, phenyl) ; 7.43 (d, ^{3}J=8.8 Hz, 2H, phenyl). ES-MS : m/z,790-792 [M+].

5,17-Bis-[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)oxyphenyl]-25,26,27,28-tetrapropoxy-calix[4]arene 4a: 32 % yield. ^1H NMR (300 MHz, $CDCl_3$) δ_H ppm, 0.95 (t, ^{3}J=7.4 Hz, 6H, 2 CH_3-CH_2); 1.07 (t, ^{3}J=7.4 Hz, 6H, 2 CH_3-CH_2); 1.9-2.1 (m, 8H, 4 CH_2-CH_3); 2.02; 2.07; 2.09; 2.20 (4s, 12H, 4 CH_3-CO); 3.20 (d, ^{2}J=13.3 Hz, 4H, 4 CH_2-Ar); 3.78 (t, ^{3}J= 7.0 Hz, 4H, 2 CH_2-O); 3.98 (t, ^{3}J= 7.8 Hz, 4H, 2 CH_2-O); 4.07-4.31 (m, 6H, 2 H_6 2 $H_{6'}$ 2 H_5); 4.50 (d, ^{2}J=13.3 Hz, 4H, 4 CH_2-Ar); 5.03 (d, ^{3}J=8.0 Hz, 2H, 2 H1); 5.16 (dd, ^{3}J=3.4 Hz, ^{3}J=10.4 Hz, 2H, 2 H_3); 5.48-5.57 (m, 4H, 2 H_2, 2 H_4); 6.37 (brd, H, phenyl); 6.97 (d, ^{3}J=8.6 Hz, 4H, phenyl); 7.09 (d, ^{4}J=2.8Hz, 4H, phenyl) ; 7.37 (d, ^{3}J=8.6 Hz, 4H, phenyl).

5,17-Bis-[(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)oxyphenyl]-25,26,27,28-tetrapropoxy-calix[4]arene 4b: 42 % yield. ^1H NMR (300 MHz, $CDCl_3$) δ_H ppm, 0.96 (t, ^{3}J=7.4 Hz, 6H, 2 CH_3-CH_2); 1.02 (t, ^{3}J=7.4 Hz, 6H, 2 CH_3-CH_2); 1.86-2.05 (m, 8H, 4 CH_2-CH_3); 2.02, 2.04, 2.05, 2.08 (4s, 12H, 4 CH_3-CO); 3.17 (d, ^{2}J=13.2 Hz, 4H, 4 CH_2-Ar); 3.81 (t, ^{3}J= 7.4 Hz, 4H, 2 CH_2-O); 3.90 (t, ^{3}J= 7.4 Hz, 4H, 2

CH_2-O); 4.15-4.35 (m, 6H, 2 H_6 2 $H_{6'}$ 2 H_5); 4.47 (d, ^{2}J=13.0 Hz, 4H, 4 CH_2-Ar); 5.03 (d, ^{3}J=7.0 Hz, 2H, 2 H_1); 5.1-5.4 (m, 6H, 2 H_2 2 H_3 2 H_4); 6.4-6.5 (m, 6H, phenyl); 6.82 (d, ^{3}J=8.5 Hz, 4H, phenyl); 6.92 (s, 4H, phenyl); 7.15 (d, ^{3}J=8.5 Hz, 4H, phenyl)

5,17-Bis-[(β-D-galactopyranosyl)oxyphenyl]-25,26,27,28-tetrapropoxy-calix[4]arene 5a: 11 % yield. Mp= 174-202°C. ^{1}H NMR COSY (500 MHz, Pyr-d_5) δ_H ppm, 0.97 (t, ^{3}J=7.2 Hz, 6H, 2 CH_3-CH_2); 1.08 (t, ^{3}J=7.2 Hz, 6H, 2 CH_3-CH_2); 1.92 (tq, ^{3}J=7.2 Hz, 4H, 2 CH_2-CH_3); 2.12 (tq, ^{3}J=7.5 Hz, 4H, 2 CH_2-CH_3); 3.43 (d, ^{2}J=13.4 Hz, 4H, 4 CH_2-Ar) ; 3.76 (t, ^{3}J=6.7 Hz, 4H, 2 CH_2-O) ; 4.17 (t, ^{3}J=7.9 Hz, 4H, 2 CH_2-O) ; 4.32-4.41 (m, 4H, 2 H_3 2 H_5) ; 4.51 (dd, ^{2}J=11.0 Hz, ^{3}J=4.9 Hz, 2H, 2 H_6); 4.58 (dd, ^{2}J=11.0 Hz, ^{3}J=6.7 Hz, 2H, 2 $H_{6'}$); 4.67 (d, ^{2}J=13.4 Hz, 4H, 4 CH_2-Ar) ; 4.63-4.71 (m, 2H, 2 H_4); 4.86(dd, ^{3}J=8.5 Hz, 2H, 2 H_2); 5.1 (bs, 8H, 8 OH); 5.68 (d, ^{3}J=8.9 Hz, 2H, 2 H_1); 6.55 (t, ^{3}J=7.5 Hz, 2H, phenyl); 6.61-6.66 (m, 4H, phenyl); 7.50 (d, ^{3}J=9.0 Hz, 4H, phenyl); 7.56 (s, 4H, phenyl); 7.71 (d, ^{3}J=9.0 Hz, 4H, phenyl). ES-MS : m/z, 1123[M+ Na^+].

5,17-Bis-[(β-D-glucopyranosyl)oxyphenyl]-25,26,27,28-tetrapropoxy-calix[4]arene 5b: 10 % yield. Mp = 161-193°C. ^{1}H NMR (500 MHz, Pyr-d_5) δ_H ppm, 0.96 (t, ^{3}J=7.5 Hz, 6H, 2 CH_3-CH_2); 1.04 (t, ^{3}J=7.5 Hz, 6H, 2 CH_3-CH_2); 1.89 (tq, ^{3}J=7.4 Hz, 4H, 2 CH_2-CH_3); 2.09 (tq, ^{3}J=7.4 Hz, 4H, 2 CH_2-CH_3); 3.40 (d, ^{2}J=13.2 Hz, 4H, 4 CH_2-Ar); 3.73 (t, ^{3}J=6.8 Hz, 4H, 2 CH_2-O); 4.13-4.17 (m, 2H, 2 H_5); 4.15 (t, ^{3}J=7.7 Hz, 4H, 2 CH_2-O); 4.37-4.56 (m, 8H, 2 H_2, 2 H_3, 2 H_6,2 $H_{6'}$); 4.62 (m, 2H, 2 H_4); 4.64(d, ^{2}J=12.8 Hz, 4H, 4 CH_2-Ar); 5.02 (brd, 8H, 8 OH); 5.73 (d, ^{3}J=6.8 Hz, 2H, 2 H_1); 6.49 (dd, ^{3}J=7.5 Hz, 2H, phenyl); 6.59 (d, ^{3}J=8.2 Hz, 4H, phenyl); 7.48 (d, ^{3}J=8.7 Hz, 4H, phenyl) ; 7.55 (s, 4H, phenyl); 7.70 (d, ^{3}J=8.7 Hz, 4H, phenyl). ES-MS : m/z, 937[M- Glc]$^{+\cdot}$; 775 [M- 2Glc]$^{+\cdot}$

Mono-[(hepta-O-acetyl-β-D-maltopyranosyl)oxyphenyl]25,26,27,28-tetrapropoxy-calix[4]arene 7: 35 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H ppm, 0.96 (t, ^{3}J=7.5 Hz, 6H, 2 CH_3-CH_2); 1.02 (t, ^{3}J=7.5 Hz, 3H, CH_3-CH_2); 1.04 (t, ^{3}J=7.5 Hz, 3H, CH_3-CH_2);1.85-2.07 (m, 8H, 4 CH_2-CH_3); 2.01, 2.03, 2.04, 2.05, 2.06, 2.09, 2.10 (7s, 21H, 7 CH_3-CO); 3.14 (d, ^{2}J=12.9 Hz, 2H, 2 CH_2-Ar); 3.19 (d, ^{2}J=12.5 Hz, 2H, 2 CH_2-Ar); 3.76-4.28 (m, 13H, 4 CH_2-O, 2 H_6, 2 $H_{6'}$, H_5); 4.45 (d, ^{2}J=12.9 Hz, 2H, 2 CH_2-Ar); 4.48 (d, ^{2}J=12.9 Hz, 2H, 2 CH_2-Ar); 4.84-4.89 (m, 1H, H_5); 5.02-5.10 (m, 2H, H_2, H4); 5.10 (d, ^{3}J=7.0 Hz, 1H, H1); 5.30-5.37 (m, 2H, 2 H_3); 5.44 (d, ^{3}J=4.0 Hz, 1H, H_1); 6.59 (s, 2H, phenyl); 6.65-6.90 (m, 9H, phenyl); 7.12 (d, ^{3}J=8.8 Hz, 2H, phenyl); 7.41 (d, ^{3}J=9.0 Hz, 2H, phenyl).

Mono-[(β-D-maltopyranosyl)oxyphenyl]-25,26,27,28-tetrapropoxy-calix[4]arene 8: 32 % yield. Mp=187-202°C. ^{1}H NMR (500 MHz, Pyr-d_5) δ_H ppm, 0.95-1.02 (m, 12H, 4 CH_3-CH_2); 1.92-1.97 (m, 8H, 4 CH_2-CH_3); 3.23 (dd, ^{2}J=13.2 Hz, J=4.4 Hz, 2H, 2 CH_2-Ar); 3.35 (d, ^{2}J=13.9 Hz, 2H, 2 CH_2-Ar); 3.78 (t, ^{3}J=7.6 Hz, 2H, CH_2-O); 3.89 (t, ^{3}J=7.6 Hz, 4H, 2 CH_2-O); 3.93 (t, ^{3}J=7.6 Hz, 2H, CH_2-O); 4.22-4.24 (m, 2H, 2 H_2); 4.25-4.35 (m, 1H, H_4); 4.39-4.66 (m, 9H, 2 H_3, H_4, 2 H_5, 2 H_6, 2 $H_{6'}$); 4.54(d, ^{2}J=13.9 Hz, 2H, 2 CH_2-Ar); 4.60 (d, ^{2}J=13.2 Hz, 2H, 2 CH_2-Ar); 5.02 (brd, 7H, 7 OH); 5.57 (d, ^{3}J=7.6 Hz, 1H, H_1); 5.99 (d, ^{3}J=3.2 Hz, 1H, H_1); 6.64-6.94 (m, 9H, phenyl); 7.10 (s, 2H, phenyl); 7.35 (d, ^{3}J=8.5 Hz, 2H, phenyl); 7.47 (d, ^{3}J=8.5 Hz, 2H, phenyl). ES-MS : m/z, 1031[M+ Na^+].

10 **Procedure for the one pot synthesis of the 7.** Solvents are oxygen free. To a solution of 5-bromotetrapropoxy-calix[4]arene **6** (0.54 g, 0.8 mmol) in dry THF (10 mL) at -78 °C was added 1.0 equiv. of n-BuLi followed by 3.0 equiv. of $B(OMe)_3$. The resulting solution was warmed to rt over a 4 h period and subsequently stirred over night under an inert atmosphere. To the solution were then added the compound **2c** (0.64 g, 0.8 mmol), Pd_2dba_3 (0.02 mmol), PPh_3 (0.08 mmol), toluene (10 mL), ethanol (10 mL) and an aqueous solution of Na_2CO_3 2M (4 mL). The resulting mixture was warmed at 50 °C during 24 h under a N_2 atmosphere. The reaction contents were cooled to rt and after the addition of water (10 mL) extracted with CH_2Cl_2. The organic layers were dried (Na_2SO4), filtered and concentrated *in vacuo* to afford the crude product which was further purified by column chromatography on silica gel (SiO_2, Merck) with($CHCl_3$ / CH_3COCH_3 (95 : 5) (v : v)) as eluent. 7 was obtained with 35 % yield.

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