A Modified Procedure for the Synthesis of C_3-Symmetric 'Mixed-Tail' Triphenylenes

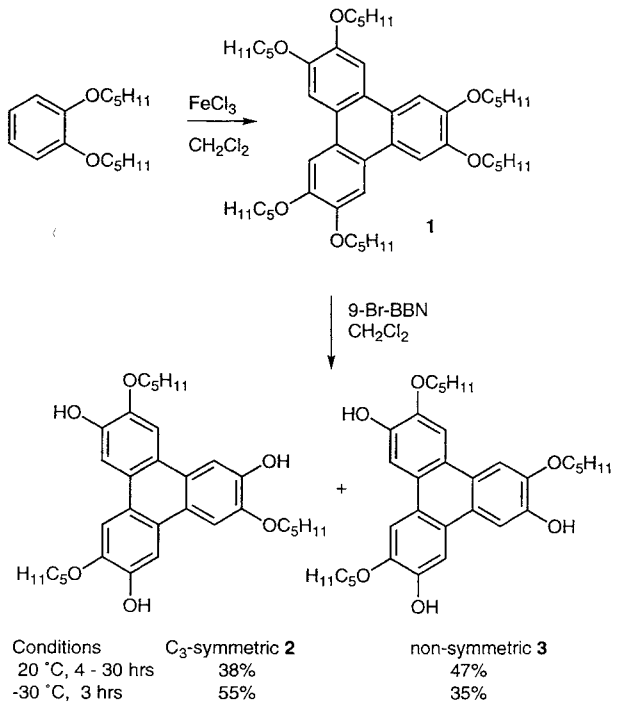
Paul T. Wright,[a] Iain Gillies,[b] Jeremy D. Kilburn*[a]

[a] Department of Chemistry, University of Southampton, Southampton, SO17 1BJ, UK
Fax +44(1703)593781; E-mail: jdk1@soton.ac.uk
[b] Chemical Development Laboratory, Glaxo Wellcome Ltd, Temple Hall, Dartford, Kent, DA1 5AH, UK

Received 3 March 1997; revised 1 April 1997

A modified procedure of the selective cleavage of three of the pentyloxy groups from 2,3,6,7,10,11-hexapentyloxytriphenylene **(1)** to give C_3-symmetric 2,6,10-trihydroxy-3,7,11-tripentyloxytriphenylene **(2)** is described. The methodology has been extended to provide a convenient route to the C_3-symmetric triphenylene derivative **8**, with orthogonally protected carboxylic acid groups.

We are interested in using the triphenylene system as a rigid base for new macrocyclic receptors and to this end we required access to C_3-symmetric 2,6,10-trihydroxytriphenylenes. 2,3,6,7,10,11-Hexaalkoxytriphenylenes (HATs) have been extensively studied because of their discotic liquid crystalline properties[1] and there is now considerable interest in more heavily functionalised and 'mixed tail' triphenylenes.[2] Hexaalkoxytriphenylenes are readily prepared by an oxidative trimerisation of a dialkoxybenzene using ferric chloride.[3] However, the reaction conditions used are incompatible with many other substituents so that access to more functionalised triphenylenes requires subsequent manipulation of the alkoxy substituents, or the use of lengthier coupling procedures to access the triphenylene core.[4] Ringsdorf et al.[5] have recently described a very effective method for selective cleavage of three of the pentyloxy groups from 2,3,6,7,10,11-hexapentyloxytriphenylene **(1)**, using the hindered Lewis acid 9-bromo-9-borabicyclo[3.3.1]nonane (9-Br-BBN), which gives a mixture of the C_3-symmetric trihydroxytripentyloxytriphenylene **2** (38% yield), which we required, as well as the non-symmetric trihydroxytripentyloxytriphenylene **3** (47% yield) (Scheme 1).

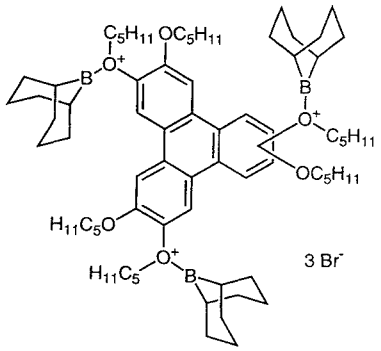


Scheme 1

In our hands the selective deprotection of hexapentyloxytriphenylene, using the methodology described by Ringsdorf, initially gave a mixture of **2** and **3** exactly as described, but subsequently we have experienced difficulties in reproducing the result and on scale up we generally obtained **2** in yields of less than 10%, accompanied by considerable degradation of the triphenylene core. We have found a modified procedure which has proved more reliable, gives improved selectivity in favour of the C_3-symmetric triphenylene **2**, and uses a simpler workup procedure. In addition, we have extended the procedure to the selective deprotection of hexabenzyloxytriphenylene **5** which subsequently allows for further manipulation of the triphenylene unit and access to differentially functionalised triphenylenes such as **8**.

Our failure to obtain reproducible yields of **2** using the Ringsdorf procedure led us to investigate the effect of temperature on the reaction. Pleasingly, reducing the reaction temperature and careful attention to the reaction time gave a consistent improvement of the yield of the reaction. An optimal reaction temperature of −30 °C and a reaction time of 4.5 hours gave a yield of 55% for the C_3-symmetric isomer **2** and 35% for the non C_3-symmetric isomer **3** on a 2 mmol scale. Even better yields (up to 65%) of the symmetric isomer **2** were obtained on larger scale reactions (4–5 mmol). Longer reaction times were found to give reduced yields and reducing the temperature further (to −40 °C) retarded the reaction too much and led to an incomplete reaction. We also used a modified workup procedure, which avoided the need to add stoichiometric ethanolamine to the reaction mixture, and instead involved cannulation of the reaction mixture at −30 °C directly into a well stirred mixture of saturated sodium bicarbonate and dichloromethane. The increase in the yield of the C_3-symmetric isomer **2** with reducing temperature indicates that steric effects in the presumed intermediate **4** are felt not just by substituents in the 2,3 relationship around the triphenylene ring, but also by substituents in the 3,6 relationship.

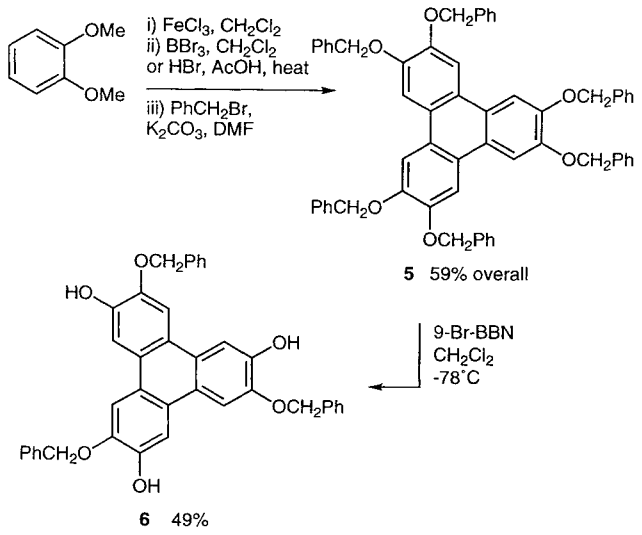
The symmetric trihydroxytripentyloxytriphenylene can be readily derivatised through the hydroxy groups, however most of the functionality we introduced precluded the easy removal of the other pentyl groups which would have allowed further functionalisation of the triphenylene



4

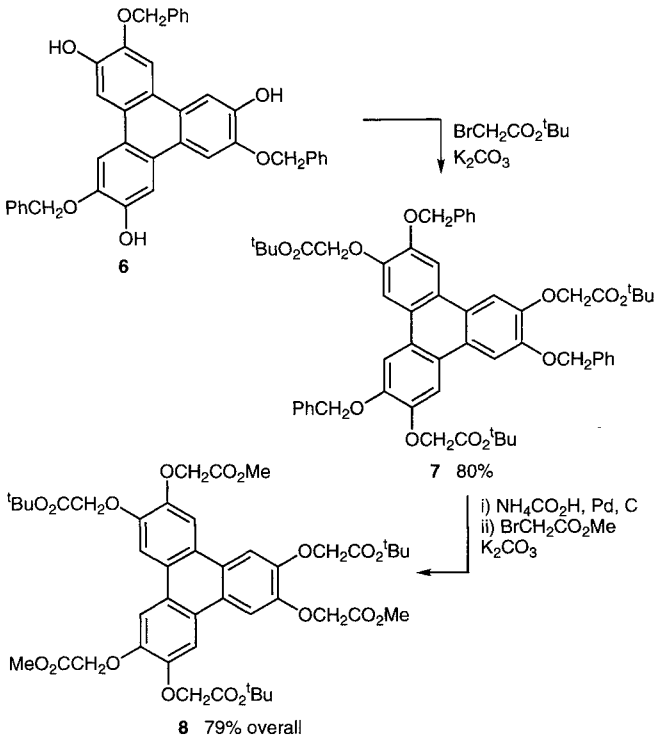
core. We have therefore extended the selective deprotection procedure to hexabenzyloxytriphenylene **5** (Scheme 2).

In this case, best yields of the desired C_3-symmetric product **6** were obtained with a reaction temperature of $-78\,^{\circ}C$, with the reaction completed in less than 1 hour. Purification by chromatography on silica gave **6** in 49% yield on a ~2 mmol scale. Comparable yields of **6** were obtained using up to 10 g of starting hexabenzyloxytriphenylene **5**. Alkylation with *tert*-butyl bromoacetate gave triester **7** and hydrogenolysis successfully removed the second set of benzyl groups. The resulting triol was then alkylated with methyl bromoacetate to give the triphenylene derivative **8** with orthogonally protected carboxylic acids suitable for further elaboration (Scheme 3). Clearly this procedure can be adapted to produce a range of C_3-symmetric 'mixed-tail' triphenylenes.



Scheme 2

Melting points were recorded on a Gallenkamp melting point apparatus (MF-370). IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. ^1H NMR spectra were recorded on JEOL JNM-GX 270 and Bruker AC300 instruments; chemical shifts are given relative to residual solvent references. ^{13}C NMR data were recorded on a Bruker AC300 instrument; the numbers in parenthesis indicate the number of protons attached to the carbon as revealed by DEPT experiments. Mass spectra were recorded on a Micromass Platform quadrupole mass analyser with an electrospray (ES) ion source.



Scheme 3

Hexapentyloxytriphenylene **1** and hexamethoxytriphenylene were prepared according to the literature[3] from the corresponding dialkoxybenzene. Complete demethylation of hexamethoxytriphenylene to give hexahydroxytriphenylene was carried out according to the literature, using either BBr_3 in CH_2Cl_2[6] or HBr/HOAc.[7] Light petrol used had bp 40–60 °C.

2,6,10-Trihydroxy-3,7,11-tripentyloxytriphenylene (2) and 3,6,10-Trihydroxy-2,7,11-tripentyloxytriphenylene (3):

9-Bromo-9-borabicyclo[3.3.1]nonane (9 mL of a 1.0 M solution in CH_2Cl_2) was pre-cooled to $-30\,^{\circ}C$, and added to a solution of 2,3,6,7,10,11-hexapentyloxytriphenylene (**1**; 1.5 g, 2.0 mmol) in CH_2Cl_2 (15 mL) under argon at $-30\,^{\circ}C$. The mixture was stirred at $-30\,^{\circ}C$ for 4.5 h and then cannulated directly into a vigorously stirred mixture of sat. aq $NaHCO_3$ solution (25 mL) and CH_2Cl_2 (50 mL) at r.t. The organic solvents were removed in vacuo and the aqueous residue extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo to give a yellow oil. Column chromatography on silica gel eluting with 60% CH_2Cl_2/light petrol, then CH_2Cl_2 gave the C_3-symmetric isomer **2** (596 mg, 55%) and the non-C_3-symmetric isomer **3** (373 mg, 35%) both of which were recrystallised from MeOH.

C_3-isomer **2**: mp 157–8 °C (MeOH) (Lit.[5] mp 140 °C); R_f 0.5 (CH_2Cl_2/light petrol).

Non-C_3-isomer **3**: mp 119–120 °C (MeOH) (Lit.[5] mp 146 °C); R_f 0.2 (CH_2Cl_2/light petrol).

For both isomers ^1H NMR and IR data are in accordance with literature.[5]

2,3,6,7,10,11-Hexabenzyloxytriphenylene (5):

2,3,6,7,10,11-Hexahydroxytriphenylene (9.45 g, 25 mmol) and benzyl bromide (32.5 g, 190 mmol) were dissolved in DMF (230 mL) and anhyd K_2CO_3 (55 g, 398 mmol) was added. The mixture was stirred under a N_2 atmosphere for 18 h at r.t. and then poured into 2 N HCl (500 mL). The resulting light brown solid was collected by filtration, washed with H_2O and recrystallised from CH_2Cl_2/Et_2O to give hexabenzyloxytriphenylene **5** as an off-white solid; yield: 19.82 g (92%); mp 196–196.5 °C.

IR (Nujol): $\nu = 1615, 1510\ cm^{-1}$.

^{1}H (300 MHz, $CDCl_3$): δ = 7.69 (6H, s, ArH), 7.57 (12H, d, J = 7 Hz, ArH), 7.43 (12H, t, J = 7 Hz, ArH), 7.35 (6H, t, J = 7 Hz, ArH), 5.31 (12H, s, OCH_2).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 148.5, 137.4, 128.7(1), 128.0(1), 127.4(1), 123.6, 108.1(1), 71.6(2).

MS (ES): m/z = 865 $[M+H]^+$.

$C_{60}H_{48}O_6$	calc.	C	83.31	H 5.59
(865.0)	found		83.18	5.50

2,6,10-Tribenzyloxy-3,7,11-trihydroxytriphenylene (6):
9-Bromo-9-borabicyclo[3.3.1]nonane (8.3 mL of a 1.0 M solution in CH_2Cl_2) was pre-cooled to −78 °C, and added to a solution of **5** (2 g, 2.31 mmol) in CH_2Cl_2 (15 mL) under argon at −78 °C. The mixture was stirred at −78 °C for 40 min and then cannulated directly into a vigorously stirred mixture of sat. aq $NaHCO_3$ (60 mL) and CH_2Cl_2 (60 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give an orange gum (3.90 g). Column chromatography on silica gel eluting with CH_2Cl_2 gave the product as a light brown solid; yield: 0.67 g (49%), mp 221 °C (dec); R_f 0.4 (CH_2Cl_2).

IR (Nujol): ν = 3520, 1620, 1595 cm^{-1}.

^{1}H (300 MHz, DMSO-d_6): δ = 9.34 (3H, s, ArO*H*), 7.90 (3H, s, ArH), 7.89 (3H, s, ArH), 7.62 (6H, d, J = 7 Hz, ArH), 7.44 (6H, t, J = 7 Hz, ArH), 7.35 (3H, t, J = 7 Hz, ArH), 5.38 (6H, s, OCH_2).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 146.6, 146.5, 137.3, 128.3(1), 127.8(1), 127.7(1), 123.5, 121.2, 108.5(1), 106.5(1), 69.7(2).

MS (ES): m/z = 630 $[M+Cl]^-$.

$C_{39}H_{30}O_6 \cdot 0.5H_2O$	calc.	C	77.60	H 5.18
(603.7)	found		77.68	5.03

2,6,10-Tribenzyloxy-3,7,11-tri(*tert*-butyloxycarbonylmethoxy)triphenylene (7):
K_2CO_3 (0.90 g, 6.5 mmol) was added to a solution of **6** (0.50 g, 0.8 mmol) and *tert*-butyl bromoacetate (0.625 g, 3.2 mmol) in DMF (8 mL). The mixture was stirred at r.t. for 19 h under a N_2 atmosphere then poured into 2 N HCl (20 mL). The resulting yellow precipitate was collected by filtration, washed with water and recrystallised from EtOH; yield: 0.627 g (80%), mp 103–104 °C.

IR (Nujol): ν = 1745, 1640, 1510 cm^{-1}.

^{1}H (300 MHz, $CDCl_3$): δ = 7.81 (3H, s, ArH), 7.66 (3H, s, ArH), 7.62 (6H, d, J = 7.0 Hz, ArH), 7.45 (6H, t, J = 7 Hz, ArH), 7.35 (3H, t, J = 7 Hz, ArH), 5.37 (6H, s, OCH_2Ph), 4.76 (6H, s, OCH_2CO_2), 1.52 (27H, s, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.1, 148.4, 147.8, 137.2, 128.7(1), 128.1(1), 127.5(1), 124.2, 123.5, 108.3(1), 107.9(1), 82.4, 71.7(2), 67.3(2), 28.2(3).

MS (ES): m/z = 954 $[M+NH_4]^+$, 959 $[M+Na]^+$, 1423 $[3M+2NH_4]^{2+}$, 1890 $[2M+NH_4]^+$, 1895 $[2M+Na]^+$.

$C_{57}H_{60}O_{12}$	calc.	C	73.06	H 6.45
(937.1)	found		73.18	6.20

2,6,10-Tri(*tert*-butyloxycarbonylmethoxy)-3,7,11-tri(methoxycarbonylmethoxy)triphenylene (8):
A mixture of **7** (500 mg, 0.53 mmol) and 10% Pd/C (50 mg) in MeOH (10 mL) was stirred at r.t. for 17 h under atmospheric pressure of H_2. CH_2Cl_2 (30 mL) was added, the catalyst was removed by filtration and the solvent removed in vacuo to give a grey powder (363 mg). The resulting trihydroxytriphenylene was dissolved in DMF (5 mL) and stirred with methyl bromoacetate (318 mg, 2.08 mmol) and K_2CO_3 (575 mg, 4.16 mmol) under N_2 at r.t. for 4.5 h. The mixture was poured into 2 N HCl, a white precipitate was recovered by filtration, washed with H_2O and recrystallised from acetone/light petrol; yield: 372 mg (79% over two steps); mp 176.5–177 °C.

IR (Nujol): ν = 1753, 1621, 1511 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (3H, s, ArH), 7.72 (3H, s, ArH), 4.93 (6H, s, OCH_2), 4.80 (6H, s, OCH_2), 3.87 (9H, s, OCH_3), 1.51 [27H, s, $C(CH_3)_3$].

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 169.4, 167.7, 148.1, 147.4, 124.7, 123.9, 109.9(1), 107.7(1), 82.5, 67.4(2), 66.9(2), 52.3(3), 28.1(3).

MS (ES): m/z = 905 $(M+Na)^+$.

HRFABMS (MNOBA): m/z calcd. for $C_{45}H_{54}O_{18}$ (M^+) 882.3310; found: 882.3239.

We thank Glaxo Wellcome and the EPSRC for a CASE studentship for PTW.

(1) Chandrasekhar, S.; Sadashiva, B.K.; Suresh, K.A. *Pramana* **1977**, *9*, 471.
(2) See, for example: Rego, J.A.; Kumar, S.; Dmochowski, I.J.; Ringsdorf, H. *J. Chem. Soc. Chem. Commun.* **1996**, 1031.
Henderson, P.; Kumar, S.; Rego, J.A.; Ringsdorf, H.; Schuhmacher, P. *J. Chem. Soc., Chem. Commun.* **1995**, 1059.
(3) Naarmann, H.; Hanack, M.; Mattmer, R. *Synthesis* **1994**, 477.
Boden, N.; Borner, R.C.; Bushby, R.J.; Cammidge, A.N.; Jesudason, M.V. *Liquid Crystals* **1993**, *15*, 851.
Bengs, H.; Karthaus, O.; Ringsdorf, H.; Baehr, C.; Ebert, M.; Wendorff, J.M. *Liquid Crystals* **1991**, *10*, 161.
(4) Boden, N.; Bushby, R.J.; Cammidge, A.N.; Headdock, G. *Synthesis* **1995**, 31.
Goodby, J.W.; Hird, M.; Toyne, K.J.; Watson, T. *J. Chem. Soc., Chem. Commun.* **1994**, 1701.
Borner, R.C.; Jackson, R.F.W. *J. Chem. Soc., Chem. Commun.* **1994**, 845.
Boden, N.; Bushby, R.J.; Cammidge, A.N. *J. Chem. Soc., Chem. Commun.* **1994**, 465.
(5) Closs, F.; Häußling, L.; Henderson, P.; Ringsdorf, H.; Schuhmacher, P. *J. Chem. Soc. Perkin Trans. 1* **1995**, 829.
(6) Beattie, D.R.; Hindmarsh, P.; Goodby, J.W.; Haslam, S.D.; Richardson, R.M. *J. Mater. Chem.* **1992**, *2*, 1261.
(7) Piattelli, M.; Fattorusso, E.; Nicolaus, R.A.; Magno, S. *Tetrahedron* **1965**, 3229.