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Highly efficient synthesis of C_3 -symmetric O-alkyl substituted triphenylenes and related Mannich derivatives†

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C_3 -Symmetric tris-benzyl-O-substituted hexahydroxytriphenylene (**HHTP**) was prepared through selective ring opening with DIBAL-H in 48% yield (38% from **HHTP** in a two-step synthesis) avoiding the use of noxious, expensive and limited market availability reagents, with complete recovery of the undesired C_s co-product that is quantitatively recovered and converted back into **HHTP**. The C_3 -symmetric triphenylene product was further functionalized through substitution, deprotection and Mannich condensation reactions affording a series of C_3 -symmetric functionalized scaffolds in good yields for supramolecular applications.

Introduction

Materials such as organic photovoltaic devices (OPVs),¹ organic field-effect transistors (OFETs)² and organic light-emitting diodes (OLEDs)³ have been recently developed taking advantage of the peculiar properties of triphenylenes (TPs) that are prepared from the common scaffold 2,3,6,7,10,11-hexahydroxytriphenylene (**HHTP**, Fig. 1). In particular, this class of self-assembling molecules can provide columnar aggregates forming hexagonal, rectangular and nematic phases with important optical applications⁴ as well as high charge-carrier transportation capacity.⁵ In recent years, the interest in TP scaffolds, apart from applications in optical devices, has increased steadily focusing on their supramolecular properties, especially for sensing purposes.⁶ Recently, systems based on C_3 -symmetric TPs have been developed for the detection of explosives⁷ or to create trans-membrane molecular devices for chloride transport.⁸

While TPs bearing the same substitution on all six O atoms are more easily prepared,⁹ the synthesis of TP derivatives bearing two different substituents on each catechol moiety is a more challenging synthetic target, especially if the C_3 -symmetric functionalized TP derivatives are required. In particular,

the presence of alternating benzyl moieties on the C_3 -symmetric triphenylene scaffold (C_3 -2, Fig. 1) provides a useful and versatile building block for further derivatization through alkylation or acylation and subsequent mild hydrogenolysis. The preparation of these alternating substituted TPs is not feasible in good yields by direct synthesis from **HHTP** due to an unfavourable 1 : 3 C_3/C_s statistical mixture of isomers that is usually observed.¹⁰ For all the above mentioned applications, the development of efficient methods for the preparation of C_3 -symmetric TPs bearing substituents on alternating positions (2,6,10-trisubstituted-triphenylenes) is a highly

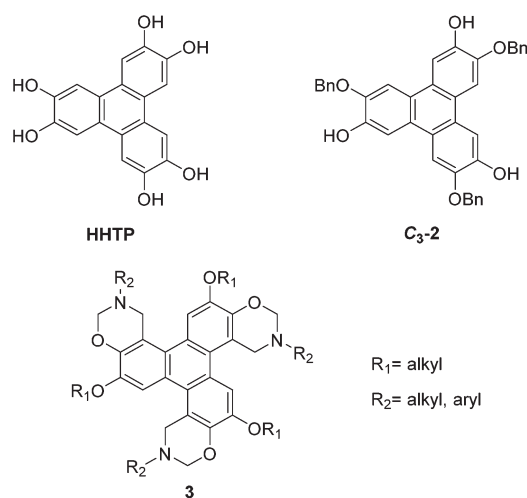


Fig. 1 Structures of **HHTP**, the C_3 -symmetric tris-benzyl derivative **C₃-2** and the small library of C_3 symmetric Mannich products **3**.

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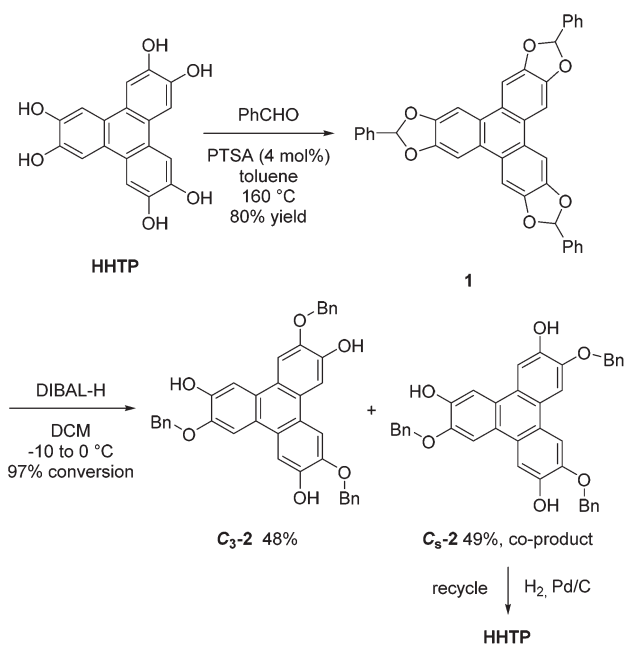
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desirable target and only two methodologies for the selective synthesis of these molecules are reported in the literature.

In the first method, 9-bromo-borabicyclo[3.3.1]nonane (9-Br-BBN) was employed as a sterically hindered ether-cleaving reagent to promote the selective de-benzylation of the hexa-benzyl substituted triphenylene affording the C_3 -symmetric tris-benzyl target product in 49% yield.¹¹ In the second methodology, hexa-*n*-pentyl substituted triphenylene was partially de-alkylated using B-bromocatecholborane with good selectivity towards the C_3 -trisubstituted triphenylene, which was obtained in 60% yield.¹² However, these methodologies are characterized by the use of toxic and expensive reagents like B-bromocatecholborane and 9-Br-BBN with rather limited availability on the market.

According to the general interest in the preparation of C_3 -symmetric hexa-substituted TPs and looking for a much simpler and convenient method based on an available and economical reducing agent, herein we present a new efficient synthesis of 2,6,10-tribenzyloxy-3,7,11-trihydroxytriphenylene C_3 -2 in high overall yield over two steps from HHTP (Scheme 1). The method is based on the controlled reductive ring opening of the benzyl acetal **1** with the safe and economical DIBAL-H in 48% yield for the C_3 -2 product, while the C_5 -2 product could be quantitatively recycled back to HHTP by hydrogenation on Pd/C. C_3 -2 was further functionalized by alkylation and de-benzylation and further elaborated including an original Mannich reaction to provide a small library of 11 compounds overall, endowed with typical functionalities for supramolecular aggregation applications.



Scheme 1 Two-step synthesis of C_3 -2 from HHTP via acetalization with benzaldehyde forming **1** and its selective cleavage with DIBAL-H.

Results and discussion

The synthesis of C_3 -2 started from 2,3,6,7,10,11-hexahydroxytriphenylene (HHTP) that was prepared from veratrole according to a reported procedure.¹³ Acetal **1** was obtained in 80% yield from HHTP with excess of benzaldehyde and *p*-toluenesulfonic acid (PTSA) as a catalyst (Scheme 1). It is worth noting that the acetalization of simple catechol with benzaldehyde has not been extensively studied in the literature even though 1,3-benzodioxole moieties are quite common in natural compounds.¹⁴ When applied to HHTP, the reaction turned out to be quite difficult and it was optimized in terms of the amount of PTSA (4 mol%) and, to drive the equilibrium to the right, it required a large amount of benzaldehyde. The latter could be easily recovered at the end of the reaction by distillation, providing **1** by precipitation with diethyl ether.

A limited number of examples of nucleophilic ring opening of ketals using hydrides have been reported in the literature, confirming the peculiarity of this moiety as a protecting group under nucleophilic or basic conditions.^{15,16} On the other hand, the presence of a Lewis acid can activate the acetal group, promoting the ring opening with the cleavage of a carbon–oxygen bond. Several combinations of reducing agent and Lewis acid were tested, as reported in Table 1, observing in all cases a mixture of the two possible isomers: the desired C_3 -2 and the C_5 -2 symmetric tris-benzyl derivatives that were separated by column chromatography eluting with dichloromethane until complete recovery of the first isomer, C_3 -2, then with ethyl acetate to recover C_5 -2. When borane in THF with $AlCl_3$ as a Lewis acid was used, it was not possible to isolate any C_3 -2, even after complete conversion of the substrate indicating the difficulty in controlling the reaction, observing the formation of further de-benzylation products. Using $LiAlH_4$ as a hydride source, the reaction turned out to be more effective in the presence of $AlCl_3$ as a Lewis acid rather than BF_3 etherate (Table 1, entries 2–7). After optimization of the solvent (use of diethyl ether turned out to be critical, Table 1, entries 3 and 4) and the ratio of $LiAlH_4$ and $AlCl_3$, it was possible to observe the formation of an encouraging 20% yield mixture of C_3 -2 and C_5 -2 products in a 1.0 : 1.2 ratio. The isolated yield of the desired C_3 -2 product was never higher than 11%, even when quantitative conversion of reagent **1** was observed. A possible cause was attributed to the high reactivity of $LiAlH_4$ with $AlCl_3$, which is known to provide the formation of alane,¹⁷ a reagent that could lead to complete removal of the benzyl moieties.

To mitigate this over-reactivity and to increase the selectivity of the process, the use of a more hindered alane was considered this time in the absence of Lewis acids. The best results were obtained using commercial diisobutylaluminum hydride (DIBAL-H) in toluene,¹⁶ which, conversely to the previous reducing agents, could be added at once. The reaction between substrate **1** and DIBAL-H was further investigated aiming at the optimization of the yield of the C_3 product, C_3 -2, as reported in Table 2. A large excess of the reducing agent and a prolonged reaction time (Table 2, entries 1 and 2)

Table 1 Selective cleavage of **1** with different combinations of reducing agent and Lewis acid

Entry	Hydride (eq.)	Lewis acid (eq.)	Solvent	Temperature [°C]	Time [h]	Conversion ^a [%]	Yield ^b [%]	C ₃ /C _s ^a	C ₃ -2 Yield ^b [%]
1	BH ₃ ·THF (20.2)	AlCl ₃ (21)	THF	66	15	100	0	—	—
2	LiAlH ₄ (3.0)	BF ₃ ·OEt ₂ (12)	Et ₂ O/DCM	0 to 60	4.0	50	0	—	—
3	LiAlH ₄ (14.5)	AlCl ₃ (12)	DCM	60	0.75	100	0	—	—
4	LiAlH ₄ (14.5)	AlCl ₃ (12)	Et ₂ O/DCM	60	2.5	100	24	1.0 : 1.2	11
5	LiAlH ₄ (14.5)	AlCl ₃ (6)	Et ₂ O/DCM	60	3.0	100	22	1.0 : 1.2	10
6	LiAlH ₄ (14.5)	AlCl ₃ (3)	Et ₂ O/DCM	60	1.0	97	19	1.0 : 1.2	8
7	LiAlH ₄ (4.0)	AlCl ₃ (4)	Et ₂ O/DCM	60	4.5	68	20	1.0 : 1.2	8

^a C₃/C_s ratio calculated by ¹H-NMR. ^b Isolated yield.

Table 2 Optimization of the selective cleavage of **1** with DIBAL-H in DCM/toluene leading to C₃-2

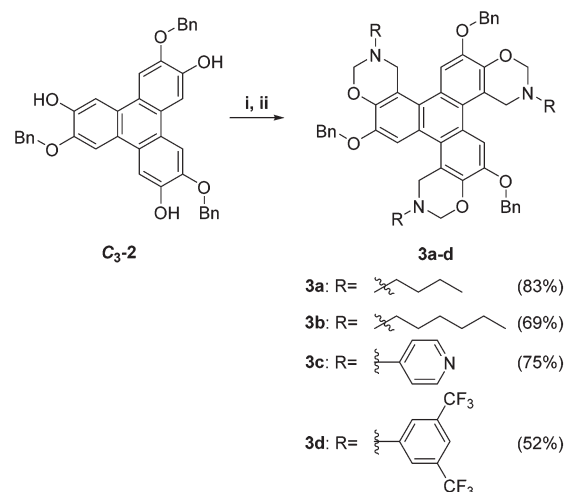
Entry	DIBAL-H (mol. ratio)	Temp. [°C]	Time [h]	Total yield ^b [%]	C ₃ /C _s ^a	C ₃ -2 Yield ^b [%]
1	15	0 to r.t.	15.0	45	1.0 : 1.4	19
2	4	0 to r.t.	0.83	79	1.0 : 1.0	40
3	4	0	1.0	53	1.0 : 0.8	30
4	4	0	1.3	76	1.0 : 0.8	42
5	4	0	4.0	86	1.0 : 0.9	43
6	5	0	3.0	95	1.0 : 1.0	47
7	5	-10	8.0	82	1.0 : 0.8	38
8	6	-10 to 0	5.5	97	1.0 : 1.0	48

^a C₃/C_s ratio calculated by ¹H-NMR. ^b Isolated yield.

turned out to be detrimental for the reaction leading to over-reduction of both C₃-2 and C_s-2 products; moreover the reaction temperature turned out to influence heavily the yield of the C₃-2 product. As reported in Table 2, entries 3–5, the reaction at 0 °C showed a maximum yield for C₃-2 after 1.3–4 h and an increase was observed operating with 5 eq. of DIBAL-H with respect to **HHTP** (1.7 eq. per acetal unit) at lower temperature (Table 2, entry 6). The use of 6.0 moles of DIBAL-H per mole of substrate at -10 to 0 °C proved to be the best option (Table 2, entry 8), enabling a favourable lowering of reaction time and the formation of the desired C₃-2 product in a 48% isolated yield after purification by flash chromatography. Similarly, the previously unknown in the literature product C_s-2 was isolated and fully characterized.¹¹ This compound can be conveniently recycled through Pd/C catalyzed hydrogenation and removal of the benzyl moieties, affording quantitatively the starting material **HHTP**. Through this recycling step of C_s-2, the overall yield of C₃-2 calculated from veratrole increases up to 53% considering one recycle of C_s-2.¹¹

To demonstrate the robustness of the synthetic method proposed, the synthesis of C₃-2 was scaled up starting from 5.6 g of **HHTP** obtaining at the end 3.2 g of the desired highly symmetric product with an overall unaltered yield of 48% over two steps.

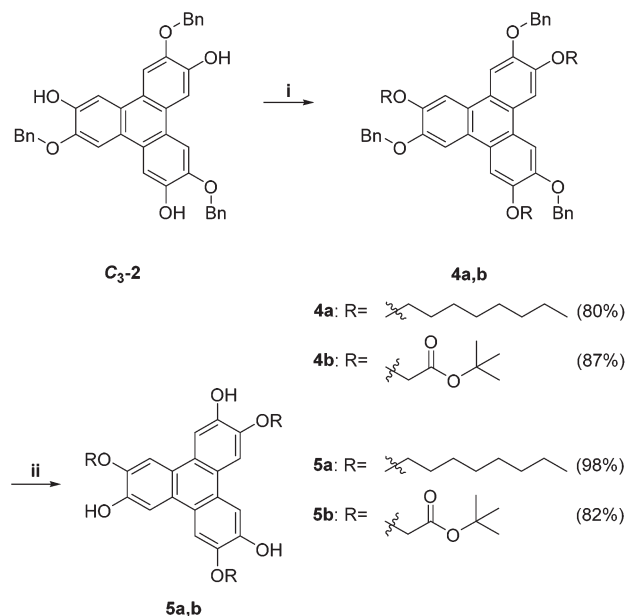
In order to implement on the TP scaffold new functionalities, the Mannich reaction¹⁸ between C₃-2 and paraformaldehyde in the presence of (i) aliphatic electron rich amines (butylamine and hexylamine) and (ii) aromatic electron poor anilines (4-aminopyridine and 3,5-bis(trifluoromethyl)aniline)



Scheme 2 Mannich reaction on C₃-2. (i) Butylamine, hexylamine or 3,5-bis(trifluoromethyl)aniline, paraformaldehyde and acetic acid, overnight in toluene at 100 °C; (ii) 4-aminopyridine, paraformaldehyde and acetic acid in butanol, refluxed overnight, then C₃-2 and paraformaldehyde, overnight in toluene at 100 °C.

was investigated to afford an unprecedented functionalization of the triphenylene scaffold (Scheme 2). In the first case, simple heating of the reagents in a sealed test tube afforded the desired products in good yields after simple precipitation from ethanol and filtration. In the second case, for 4-aminopyridine a two-step synthesis was required, since the previous approach led only to complex mixtures of intermediates. The hemiaminal between 4-aminopyridine and *n*-butanol was previously prepared by heating both in the presence of paraformaldehyde and the latter, as a more reactive species, reacted more favourably in the second step with C₃-2 together with a second portion of paraformaldehyde, eventually leading to the isolation of the desired C₃ symmetric product with the formation of three new heterocyclic units in good yield, by simple precipitation from ethanol (Scheme 2).

The presence of the benzylic moieties on C₃-2 enabled the preparation of another class of C₃-symmetric TPs which were obtained by a first alkylation of the free phenol units, followed by de-benzylation through hydrogenolysis with Pd/C to afford the three phenolic groups that can undergo further functionalization (Scheme 3). Through this approach it was



Scheme 3 Alkylation and de-benzylation of substrate **C₃-2**. (i) Alkyl bromide, K_2CO_3 , in DMF overnight at r.t.; (ii) H_2 and Pd/C in methanol, overnight at room temperature.

possible to obtain C_3 symmetric Mannich products either with benzyl, alkyl or acetyl ester units on alternating catechol-like units. In detail, the alkylation with octyl bromide of **C₃-2** led to the formation of the corresponding product **4a** in 80% isolated yield and the alkylation with bromoacetyl-*t*-butyl ester enabled the isolation of product **4b** in 87% yield (Scheme 3). Both products were subjected to de-benzylation with 1 bar of H_2 on Pd/C at room temperature obtaining the corresponding products **5a** and **5b** in 98% and 82% yield, respectively (Scheme 3).⁵

These products were further functionalized through Mannich reactions as reported in Table 3 using butylamine, hexylamine, 4-pyridyl aniline and 3,5-bis-trifluoromethyl-aniline. The corresponding products **6a**, **6b**, **6d**, **7a**, **7b** and **7c** were obtained in good yields after flash chromatography, while product **6c** was obtained in pure form by simple precipitation from diethyl ether (Table 3).

Unfortunately, the reaction between **5b** and 4-aminopyridine did not provide the desired product, but led to a mixture of by-products probably due to the 4-aminopyridine acting as a promoter of nucleophilic attack on the *t*-butyl ester moiety, similarly to the well-known action of 4-dimethylaminopyridine (DMAP).

On the basis of the structure of the Mannich derivatives **3**, **6** and **7**, we investigated the possible chirality of such molecules due to steric interactions between the benzyl methylene unit bound to the N atom and the neighbouring aromatic C-H. The 1H NMR spectra of all derivatives **3**, **6** and **7** showed singlets for those methylene units indicative of a rapid exchange on the NMR timescale. To further investigate this point, we performed some chiral HPLC analyses (see the ESI†) on selected **3b** and **6a** derivatives, observing in all cases the

Table 3 Mannich reaction on **5a** and **5b** leading to the heterocyclic compounds **6a-d** and **7a-c**

Reagent	R	Product	R'	Yield ^a [%]
5a	C_8H_{17}	6a	Butyl	98
5a	C_8H_{17}	6b	Hexyl	98
5a	C_8H_{17}	6c	4-Pyridyl	83
5a	C_8H_{17}	6d	3,5-Bis(trifluoromethyl)phenyl	53
5b	$CH_2CO_2^tBu$	7a	Butyl	50
5b	$CH_2CO_2^tBu$	7b	Hexyl	50
5b	$CH_2CO_2^tBu$	7c	3,5-Bis(trifluoromethyl)phenyl	52

(i) Butylamine, hexylamine or 3,5-bis(trifluoromethyl)aniline, paraformaldehyde and acetic acid, **C₃-2** overnight in toluene at 100 °C. (ii) 4-Aminopyridine, paraformaldehyde and acetic acid in butanol, refluxed overnight, then **C₃-2** and paraformaldehyde, overnight in toluene at 100 °C. ^a Isolated yield.

presence of one peak. Low temperature NMR experiments in CD_2Cl_2 on **3c** (see the ESI†) did not show the splitting of the methylene units of the benzoxazine units ruling out possible chirality of the molecule. Finally, we repeated the synthesis of the corresponding product **3** using enantiopure (*R*)-1-phenylethylamine to obtain two possible diastereoisomers of the product. Unfortunately, due to steric interactions, the reaction did not provide the expected product in sufficient yield.

In order to investigate possible liquid crystal properties of some of the products prepared, DSC analyses of the solid samples (**3a**, **3b**, **3c**, **3d**, **6c**, **6d** and **7c**) were carried out in the temperature range between 20–180 °C. Unfortunately, none of the synthesized molecules showed liquid crystal behaviour; most of them demonstrated typical crystalline properties, and in some cases thermal decomposition occurred. However, observing that the melting point of the products decreases as a function of the increased presence of aliphatic chains on the TP structure, we believe that the obtaining of one of these derivatives possessing a true liquid crystal behaviour is a matter of delicate balance between the aliphatic and aromatic moieties, which can be easily attached to the TP core throughout the method efficiently developed and herein described.

Conclusions

In conclusion, herein we reported a new efficient synthetic pathway to C_3 -symmetric 2,6,10-tribenzyloxy-3,7,11-trihydroxy-triphenylene **C₃-2**, with an overall 38% yield over two steps from **HHTP** through the reductive ring opening of aromatic

benzylidene acetals with commercially available and safe reagent DIBAL-H representing a substantial improvement with respect to known procedures avoiding the use of noxious reagents also suffering from limited commercial availability. The undesired C₃-2 isomer could be recycled back to the original HHTP starting material, thus increasing the efficiency of the process. Functionalization of C₃-2 and its derivatives through Mannich reactions led to the synthesis of a small library of eleven new molecules overall endowed with additional six membered ring units containing N atoms, useful for the possible preparation of new liquid crystal cores and photovoltaic materials or for the development of receptors and polydentate ligands.

Conflicts of interest

The authors declare no competing financial interest.

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