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

Giacomo Berton, a Giuseppe Borsato, a Roberta Zangrando, a,b Andrea Gambaro, c Fabrizio Fabris a and Alessandro Scarso * a

$C_3$-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 $C_3$ 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 applications 4 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 explosives 7 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 $C_3$/$C_5$ 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-tris-substituted-triphenylenes) is a highly

Fig. 1 Structures of HHTP, the $C_3$-symmetric tris-benzyl derivative $C_3$-2 and the small library of $C_2$ symmetric Mannich products 3.
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. 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. 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, simpler and convenient method based on an available and economical DIBAL-H in 48% yield for the reductive ring opening of the benzyl acetal (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$_2$-2 product, while the C$_4$-2 product could be quantitatively recycled back to HHTP by hydrogenation on Pd/C. C$_2$-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.

Results and discussion

The synthesis of C$_2$-2 started from 2,3,6,7,10,11-hexahydroxytriphenylene (HHTP) that was prepared from veratrole according to a reported procedure. Acetal 1 was obtained in 80% yield from HHTP with excess of benzaldehyde and p-toluene sulfonic 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-benzo-dioxole moieties are quite common in natural compounds. 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. 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$_2$-2 and the C$_4$-2 symmetric tris-benzyl derivatives that were separated by column chromatography eluting with dichloromethane until complete recovery of the first isomer, C$_2$-2, then with ethyl acetate to recover C$_4$-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$_2$-2 and C$_4$-2 products in a 1.0 : 1.2 ratio. The isolated yield of the desired C$_2$-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, 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, 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$_2$-2, as reported in Table 2. A large excess of the reducing agent and a prolonged reaction time (Table 2, entries 1 and 2)
turned out to be detrimental for the reaction leading to over-reduction of both C3-2 and C3-2 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 C3-2 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 C3-2, the overall yield of C3-2 calculated from veratrole increases up to 53% considering one recycle of C3-2.11

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 TPs 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) 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
possible to obtain $C_1$ symmetric Mannich products either with benzyl, alkyl or acetyl ester units on alternating catechol-like units. In detail, the alkylation with octyl bromide of $C_2$-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).

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 presence of one peak. Low temperature NMR experiments in CD$_2$Cl$_2$ on 3c (see the ESI†) did not show the splitting of the methylene units of the benzoazaine 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 obtainment 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 $C_1$-symmetric 2,6,10-tribenzoxyl-3,7,11-trihydroxytriphenylene $C_2$-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 C$_2$-2 isomer could be recycled back to the original HHTP starting material, thus increasing the efficiency of the process. Functionalization of C$_2$-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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**Notes and references**