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A facile route to multi-functionalization of methyl gallate: pivotal synthons for mesomorphic materials

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Abstract—The preparation of mono-, di- and trisubstituted gallic derivatives is described using either 1-bromododecane or 12-bromo-1-dodecanol. After saponification of the methyl ester bearing the dodecanol groups, subsequent functionalization with methacryloyl chloride provides the hybrid methacrylate esters/anhydride species. Selective cleavage of the anhydride function gives rise to the corresponding acids, which have been further functionalized to the imine derivative **15** by condensation with 4-[imino-4-(toluyl)]phenol. This reaction is made possible using the acidic form of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC·HCl) and dimethylaminopyridine (DMAP). Selective hydrolysis of the imine function with a HCl-treated silica provides the targeted aniline in excellent yield.

The preparation of alkylated polyphenol derivatives from gallic and ellagic acids has attracted the attention of synthetic chemists for many years.[1] This is principally because these compounds have a variety of medicinal and industrial applications, including their use as antioxidants (radical scavengers)[2] or mediators in the modulation of the genotoxicity of food carcinogens.[3] More recently, these compounds have been used as starting materials in the engineering of mesomorphic materials.[4,5] Therefore, molecules constructed with three to six paraffinic chains attached to the termini of an extended rigid core, the so-called polycatenar[6] or swallow-tailed[7] compounds, have been synthesized. However, in this class of compounds, mesophases can only be obtained if the rigid parts are large enough to allow efficient segregation between the rigid fragments and the aliphatic chains. Furthermore, extended rigid cores constructed around transition metals (e.g. metallo-helicates), enable sufficiently strong attractive interactions to favour a columnar organization.[8] For example, pyridine,[9] 2,2′-bipyridine[10] or 2,2′:6′,2″-terpyridine[11] ligands bearing one or two imino functions provide mesomorphic complexes when a minimum of two to four chains are grafted to the scaffold. To facilitate the use of these supramolecular architectures in areas as diverse as information storage, solar cells, sensors, displays, etc., the processing of these compounds as thin films of polymeric discotic material is required.[12]

The attachment of a polymerisable group to the starting material proved to be difficult but was possible at the end of a single flexible chain using a protection/deprotection sequence of reactions.[13] Indeed, polymers containing twin dendritic benzamide side-groups generated by a terminal acrylate and novel nematic liquid–crystalline architectures created by self-organization of the polymer chain coated with cylindrical bundle have been obtained.[13] Hence, the development of mono- and disubstituted gallic derivatives seems to be a worthy task. However, this chemistry is significantly underdeveloped and their synthetic potential is relatively low due to the lack of general methods allowing the synthesis of alkylated gallic esters bearing a wide range of substituents.

At an early stage of this research program, we discovered that during the alkylation of gallic esters with an excess of 1-bromododecane in DMF with K_2CO_3 as base, the monosubstituted derivative **1** was formed very rapidly, while compounds **2** and **3** resulting from di- and trialkylation occurred slowly. Therefore, it seemed interesting to investigate more deeply this reaction in order to isolate in a convenient manner the multi-alkylated compounds. Herein we describe a practical procedure for the synthesis of mono-, di- and trialkylation of methyl gallate in the presence of ^{t}BuOK or NaH as base and the subsequent alkylation of the remaining phenol functions with bromo-derivatives.

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The most practical conditions for the preparation of these derivatives were found using anhydrous acetonitrile and ^{t}BuOK as base in the presence of the required amounts of 1-bromododecane or 12-bromo-1-dodecanol (Table 1). By varying the stoichiometry of base and alkylation reagent the mono- and disubstituted derivatives **1** and **2** were obtained on a gram-scale in acceptable yields, taking into account the availability of the starting materials.

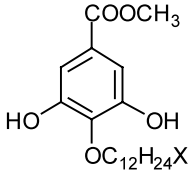
The use of anhydrous DMF did not improve significantly the yield and required the presence of catalytic amounts of KI, which favoured the bromide exchange process prior to alkylation of the phenol. NMR spectroscopy results were in keeping with the monoalkylation of methyl gallate in the 4-position, as would be expected from the acidity of the phenolic function in this position, and it is likely that the third alkylation is a slow reaction.

Interestingly, alkylation of the remaining phenolic function in **4** and **5** was straightforward and was achieved by using an excess of 1-bromododecane and K_2CO_3 in refluxing CH_3CN, providing compounds **7** and **8** in 41 and 70% yields, respectively. Alkylation of **2** with 12-bromo-1-dodecanol under similar conditions afforded the pivotal monoalcohol **9** in 63% yield.

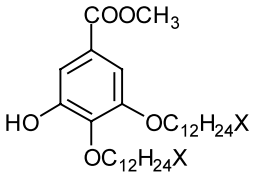
Saponification of compounds **8** and **9** with KOH gave the corresponding acids **15**[14] and **10** in 97 and 83% isolated yields, respectively. The synthesis of the methacrylate gallic acid **12** is outlined in Scheme 1 and occurs via the preparation of the mixed ester/anhydride species by reaction under anhydrous conditions of **10** with methacryloyl chloride in the presence of excess pyridine.

Compound **11** was isolated in 88% yield by flash column chromatography on silica. Treatment with aqueous pyridine resulted in the selective cleavage of the anhydride, leading to the methacrylate ester **12** after acidification with dilute HCl. Interestingly, this latter compound reacted under smooth conditions with 4-[imino-4-(toluyl)]phenol in the presence of EDC·HCl (EDC = 1 - (3 - dimethylaminopropyl) - 3 - ethylcarbodiimide) and DMPA to yield derivative **13** in good yield (90%). A similar protocol provided the hybrid-dimethacrylate/anhydride **16**[15] in 97% yield while selective hydrolysis under mild basic conditions afforded the diester/acid derivative **17**[16] in acceptable yield (84%).

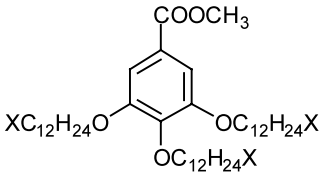
Table 1. *O*-Alkylation of methyl gallate in various anhydrous conditions at 60°C[a]



1, X = H
4, X = OH



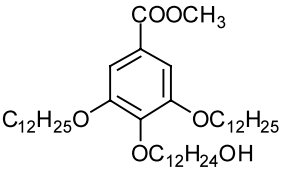
2, X = H
5, X = OH



3, X = H
6, X = OH

Experimental conditions	Cmpds **1** or **4**	Cmpds **2** or **5**	Cmpds **3** or **6**
CH_3CN/1 equiv. ^{t}BuOK/1.5 equiv. $C_{12}H_{25}Br$	24% (**1**)	10% (**2**)	Trace (**3**)
CH_3CN/2 equiv. ^{t}BuOK/5 equiv. $C_{12}H_{25}Br$	19% (**1**)	26% (**2**)	Trace (**3**)
DMF/1 equiv. NaH/1.5 equiv. $C_{12}H_{25}Br$/KI[b]	56% (**1**)	8% (**2**)	Trace (**3**)
DMF/2 equiv. NaH/5 equiv. $C_{12}H_{25}Br$/KI[c]	9% (**1**)	24% (**2**)	23% (**3**)
CH_3CN/3 equiv. ^{t}BuOK/5 equiv. $HOC_{12}H_{24}Br$	Trace (**4**)	Trace (**5**)	67% (**6**)
DMF/1 equiv. NaH/1 equiv. $HOC_{12}H_{24}Br$/KI	40% (**4**)	11% (**5**)	Trace (**6**)

[a] All compounds were characterized by NMR spectroscopies, elemental analysis and ESI-MS. 'Trace' account for <1% yield (not isolated). The average reaction time is 18 h.
[b] NaH 60% dispersed in paraffin oil.
[c] KI trace amount (≈1% in weight versus methyl gallate).



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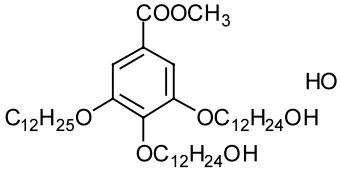

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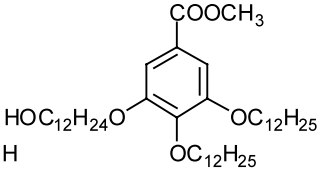

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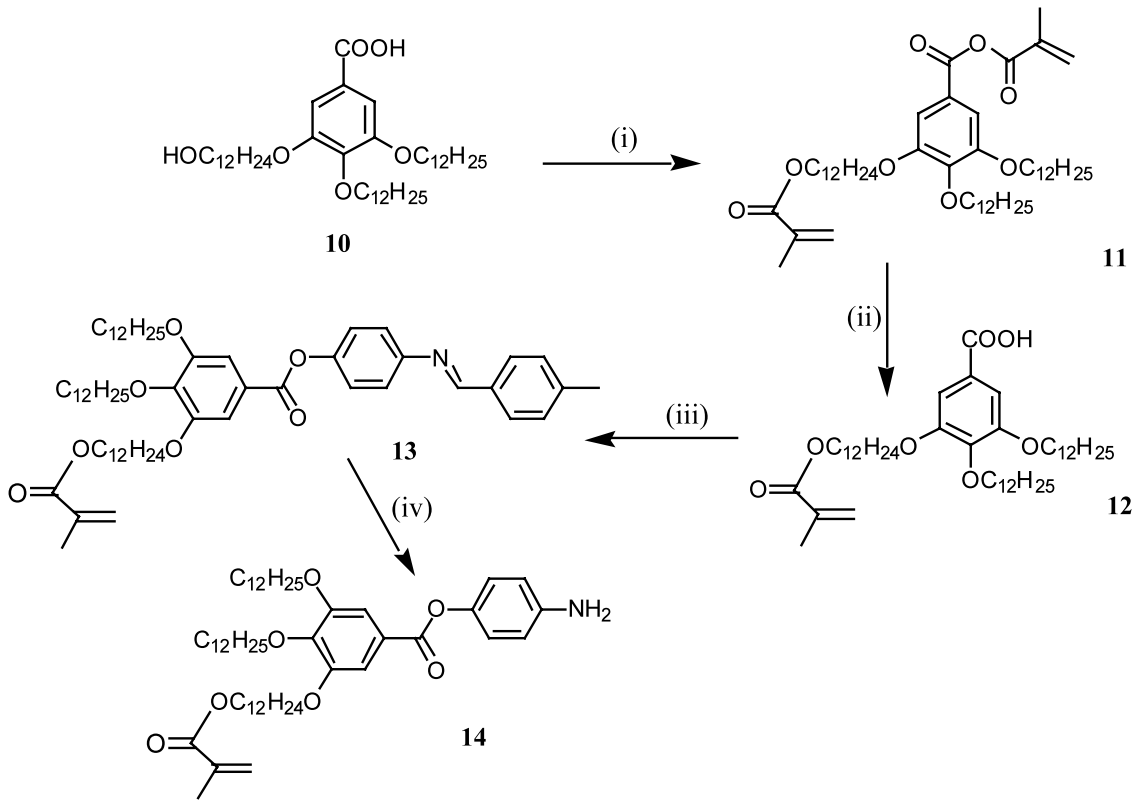
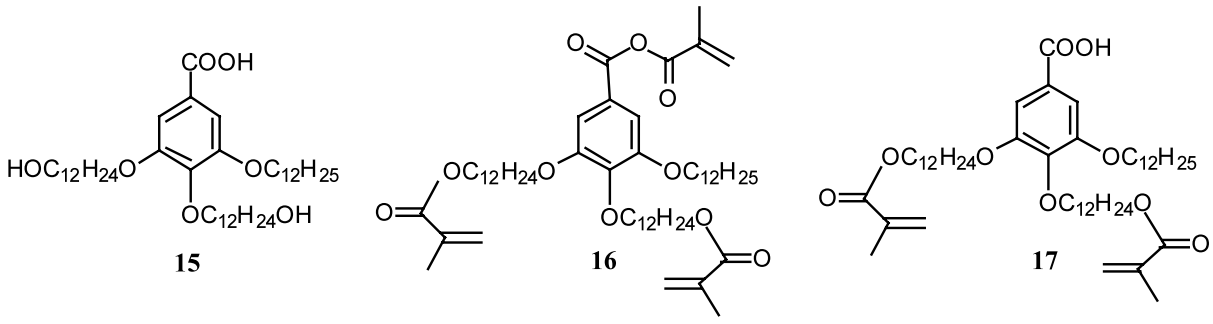


Scheme 1. *Reagents and conditions*: (i) Methacryloyl chloride (2.2 equiv.), pyridine (10 equiv.), CH_2Cl_2, rt; (ii) pyridine/H_2O (5/1, v/v), 100°C, HCl (10%); (iii) 4-[imino-4-(toluyl)]phenol (1.1 equiv.), EDC·HCl (2 equiv.), DMPA (1 equiv.), CH_2Cl_2, rt; (iv) HCl (10%) dispersed on silica (0.063–0.200 mm), rt.



Finally, selective hydrolysis of the imine in compound **13** was realized by the use of a heterogeneous procedure using silica treated with aqueous HCl (10%). The aniline derivative **14**[17] was isolated in a pure form after column chromatography (60%). All these compounds were stable when stored in a freezer for several months.

In summary, we have described the preparation of methyl gallate derivatives by selective alkylation of the phenolic functions which avoids the use of a sequence of reactions, including protection of two hydroxy functions (e.g. by a cyclic ketal[18]), followed by alkylation of the unprotected phenol, deprotection, and, finally, alkylation of the third fragment with a different reagent.[13] The grafting of one or two methacrylate groups on the molecule was ensured by esterification of the primary alcohol, leading to the key synthons **12** and **17**. Esterification of the benzoic function with an imino-phenol reagent followed by a heterogeneous hydrolysis afforded the corresponding aniline derivative **14**. Further synthetic work is directed towards the condensation of the resulting aniline derivatives with aldehyde-functionalized oligopyridine platforms in order to provide suitable synthons for polymerization of the subsequent mesomorphic metallo-complexes.

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14. Compound **15**: ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ 7.29 (s, 2H), 4.03 (m, 6H), 3.64 (m, 4H), 1.77 (m, 6H), 1.51 (m, 2H), 1.27 (m, 52H), 0.88 (t, 3H, $^3J=7.0$ Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$, 25°C): δ 172.0, 152.8, 152.8, 142.9, 123.9, 108.5, 73.5, 69.2, 63.02, 32.8, 32.7, 31.9, 30.3, 29.7, 29.6, 29.4, 26.1, 26.0, 25.8, 25.7, 22.7, 14.1. FAB$^+$-MS (*m*-NBA+3% TFA) (% rel. int.): 707.2 ([M+H]$^+$, 100). Anal. calcd for $C_{43}H_{78}O_7$ (Mr=707.08): C, 73.04; H, 11.12. Found: C, 72.72; H, 10.83%.
15. Compound **16**: ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ 7.28 (s, 2H), 6.30 (s, 1H), 6.09 (s, 1H), 5.87 (s, 1H), 5.54 (s, 1H), 5.53 (s, 1H), 5.31 (s, 1H), 4.09 (m, 10H), 2.17 (t, 9H, $^3J=6.7$ Hz), 1.77 (m, 6H), 1.51 (m, 2H), 1.27 (m, 52H), 0.88 (t, 3H, $^3J=6.5$ Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$, 25°C): δ 172.2, 167.8, 152.9, 152.8, 142.9, 136.9, 125.2, 123.6, 108.5, 73.5, 69.2, 65.6, 64.9, 32.8, 31.9, 30.7, 30.3, 29.7, 29.6, 29.1, 26.0, 25.5, 24.9, 22.7, 18.3, 18.2, 14.1. FAB$^+$-MS (*m*-NBA+3% TFA) (% rel. int.): 911.3 ([M+H]$^+$, 30), 825.2 ([M–$CH_2(CH_3)COO$]$^+$, 100). Anal. calcd for $C_{55}H_{90}O_{10}$ (Mr=911.30): C, 72.49; H, 9.95. Found: C, 72.28; H, 9.72%.
16. Compound **17**: ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ 7.31 (s, 2H), 6.09 (s, 2H), 5.53 (s, 2H), 4.12 (m, 10H), 2.01 (t, 9H, $^3J=6.0$ Hz), 1.77 (m, 6H), 1.51 (m, 2H), 1.27 (m, 52H), 0.87 (t, 3H, $^3J=6.5$ Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$, 25°C): δ 172.2, 167.8, 152.9, 142.9, 136.6, 125.2, 123.6, 108.6, 73.5, 69.2, 65.6, 64.9, 31.9, 30.7, 30.3, 29.7, 29.6, 29.1, 26.0, 25.5, 24.9, 22.7, 18.3, 18.2, 14.1. FAB$^+$-MS (*m*-NBA) (% rel. int.): 843.4 ([M+H]$^+$, 100). Anal. calcd for $C_{51}H_{86}O_9$ (Mr=843.22): C, 72.64; H, 10.28. Found: C, 72.41; H, 9.95%.
17. Compound **14**: ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ 0.88 (t, 6H, CH_3, $^3J=7.2$ Hz), 1.55 (m, 58H), 1.93 (s, 3H), 3.65 (s, 2H), 4.02 (m, 6H), 4.13 (t, 2H), 5.54 (s, 1H), 6.09 (s, 1H), 6.71 (d, 2H, $^3J=8.9$ Hz), 6.97 (d, 2H, $^3J=8.9$ Hz), 7.38 (s, 2H), 8.45 (s 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$, 25°C): δ 167.3, 165.4, 152.8, 144.3, 142.9, 142.7, 136.4, 125.0, 124.2, 122.1, 115.5, 108.4, 73.4, 69.1, 65.4, 64.7, 31.8, 30.6, 30.7, 30.2, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.2, 28.5, 26.0, 25.9, 25.6, 25.4, 24.7, 22.6, 18.2, 18.0, 14.0. FAB$^+$-MS (*m*-NBA) (% rel. int.): 874.0 ([M+H]$^+$, 100), 800.2 ([M–$CH_2(CH_3)COO$]$^+$, 25). Anal. calcd for $C_{53}H_{87}NO_7$ (Mr=872.78): C, 74.87; H, 10.31; N, 1.65. Found: C, 74.67; H, 10.07; N, 1.31%.
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