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Synthesis of new dendrimers—trimesic acid derivatives

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ABSTRACT

The efficient synthesis of new dendrimeric polyesters up to generation 3 that consist of 1,3,5-benzenetricarboxylic acid building blocks with potential applications in drug delivery is described. The dendrimers possess hydroxy or allyl functional groups on the surface and were prepared through a divergent approach using readily available 2-(hydroxymethyl)-2-ethylpropan-1,3-diol and 1,3,5-benzenetrimethanol as central cores, with 3,5-bis[(allyloxy)methyl]benzoic acid being an essential unit of the dendrimer. The latter compound was synthesized, in high yield, from 1,3,5-benzenetricarboxylic acid, applying selective hydrolysis of the corresponding triester as the key step.

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Dendrimers are highly branched, three dimensional monodispersed polymers made up of repeating cascade structures emanating from a central core to a polyfunctional surface. These synthetic macromolecules offer numerous applications,[1] especially in biomedical sciences as drugs in their own right,[2] or as drug and gene carriers.[3] While several types of dendrimers have been described as in vivo biomolecule delivery agents, carboxylate polyester dendrimers have proved to be the most important[4] due to their biodegradability, which causes the macromolecules, in the presence of enzymes, to hydrolyze into small molecules which can leave the body. Although the chemical synthesis of dendrimers is well-founded, the synthesis of carboxylate polyester-based dendrimers is still very much warranted.

On the other hand, trimesic acid (1,3,5-benzenetricarboxylic acid), a planar and highly symmetrical trifunctional compound, seems to be an appropriate candidate as a structural monomer of the dendrimer framework. Previously, 1,3,5-benzenetricarboxylic acid has been used as the central core in both dendrimeric polyarylesters[5] and polyarylamides.[6] A few years ago, we developed a method for the synthesis of dendrimeric polyphosphates and their analogs.[7] In continuation of our efforts, an efficient and divergent synthesis of new polyester dendrimers possessing the trimesic acid skeleton is reported herein.

The synthesis of the key monomer proceeds from 1,3,5-benzenetricarboxylic acid, which was transformed into trimethyl ester **1**.[8] Careful basic hydrolysis with dilute NaOH (2.07 equiv) in a methanol–water mixture (Scheme 1) produced almost exclusively[9] (90%, according to NMR) the corresponding monoester **2**,[10] which was spectrally pure after crystallization from ethyl acetate (79% yield from **1**).

Selective formation of the monoester can be explained due to very slow and disfavored nucleophilic attack of the hydroxy anion on the remaining ester carbonyl group in the double-negatively charged molecule. Another highly chemoselective reaction was reduction (rt, 24 h) of the two carboxylate groups in diacid monoester **2** using borane–dimethyl sulfide complex, which provided 3,5-bis(hydroxymethyl)benzoic acid methyl ester (**3**) in a high isolated yield (80% after crystallization from CH_2Cl_2–MeOH–cyclohexane). At this point, difficulties were encountered in the selection of suitable protecting group for the hydroxy functions. The first choice was the acetyl group, which worked perfectly for the synthesis of phosphoric acid polyester dendrimers.[7] Unfortunately, this actual dendrimer was not stable enough for hydrolysis and/or alcoholysis of the peripheral acetates without affecting the benzenecarboxylic acid polyester scaffold. On the other hand, the dendrimer showed an important feature—it was relatively easy to hydrolyze. After further experimentation, it turned out that allyl and *p*-methoxybenzyl (a benzylic diol cannot be protected and deprotected successfully with a benzyl group) groups were the most suitable for this synthesis. Hence, the opportunity of further functionalization, the size, and particularly the atom economy strongly supported the allyl group. Therefore, diol **3** was reacted with an excess (3 equiv) of allyl bromide [NaOH, benzene–DMF (6:1), 70 °C, 7 h]. This reaction produced a mixture of the expected diallyl ether methyl ester **4** and diallyl ether allyl ester **5** in a 7:1 ratio and 92% yield, after passing the crude mixture through a short pad of silica gel using dichloromethane as the eluent. Obviously, separation of the above mixture was not necessary as basic hydrolysis and subsequent acidification afforded the target dendrimer

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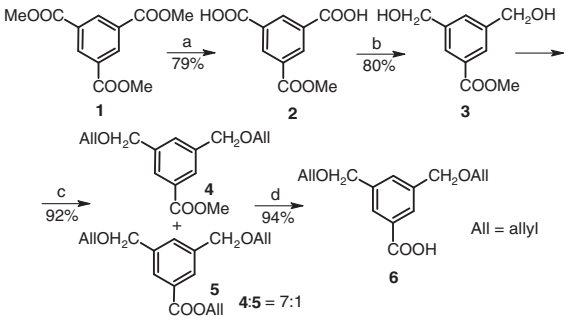


Scheme 1. Reagents and conditions: (a) NaOH, MeOH, H_2O, then HCl (aq); (b) $B_2H_6{\cdot}(CH_3)_2S$, THF; (c) NaOH, allyl bromide, benzene, DMF; (d) NaOH, MeOH, H_2O, then HCl (aq).

building block **6**[11] in 94% yield. This compound represents an AB_2-type monomer. The A group (carboxyl) is active and the B groups (hydroxy) are protected such that the A group reacts solely with the B (active) groups in the prior generation of the dendrimer.

The core triol, 2-(hydroxymethyl)-2-ethylpropane-1,3-diol, commonly known as trimethylolpropane (TMP) reacted readily (Scheme 2) with acid **6** (3.2 equiv, 12 h, CH_2Cl_2, rt), in the presence of the water-soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide[12] (EDCI) (3.3 equiv), and 4-dimethylaminopyridine (DMAP) (0.35 equiv) to furnish the first generation dendrimer **7**[13] in 93% yield.

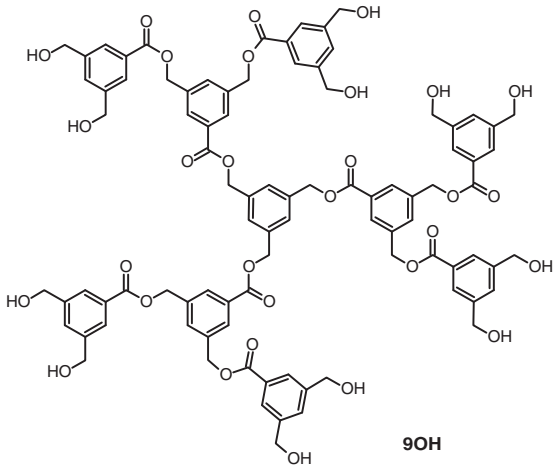
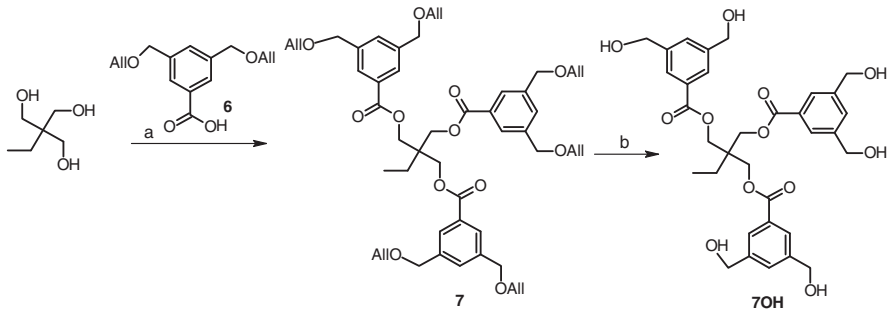
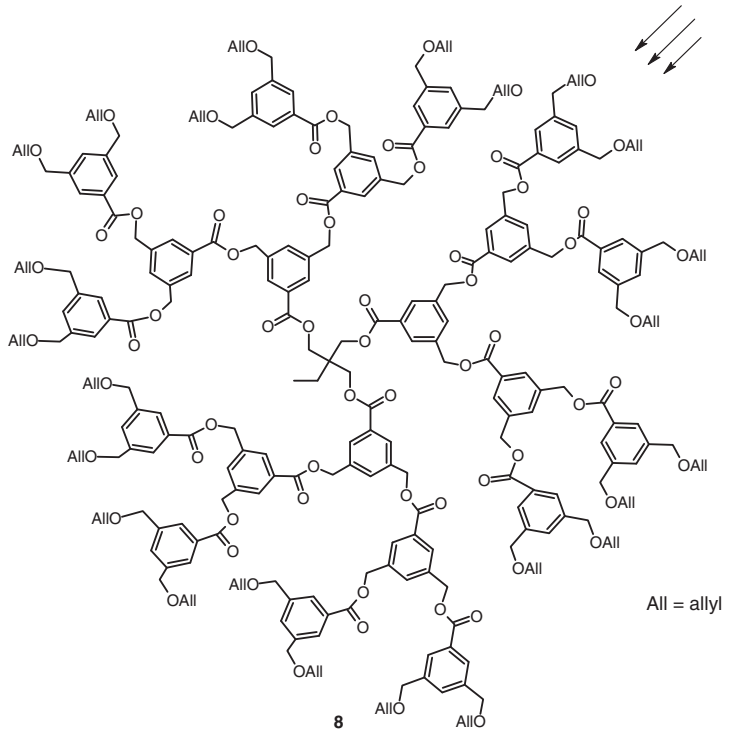


Figure 1. Structure of the hydroxy-terminated 2nd generation dendrimer **9OH** possessing a 1,3,5-benzenetrimethanol core.





Scheme 2. Reagents and conditions: (a) EDCI, DMAP, CH_2Cl_2; (b) Pd/C, AcOH–H_2O–MeOH, TsOH.

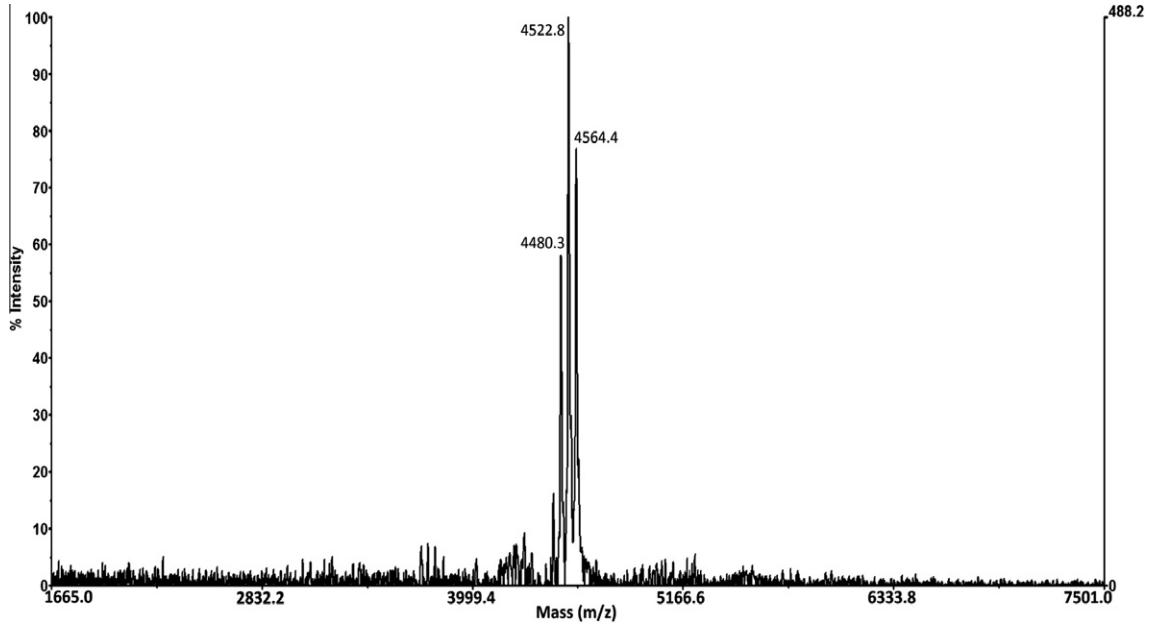


Figure 2. MALDI TOF mass spectrum of 3rd generation dendrimer **8**.

Cleavage of the terminal allyl ethers was carried out under milder (than original) conditions using a slight modification of the procedure disclosed by Boss and Scheffold.[14] Thus, hexaallyl ether **7** was stirred in acetic acid–water–methanol mixture (7:2:1), at 50 °C, in the presence of catalytic amounts of 10% Pd/C (0.4 equiv) and *p*-toluenesulfonic acid (~0.2 equiv). The reaction was monitored by ^{1}H NMR; after 40 h, no trace of vinylic protons was observed and the desired hexol **7OH** was obtained in 90% yield.[15] It is noteworthy that the only by-product, propionaldehyde, as a volatile compound, was continuously removed from the reaction mixture to avoid any undesired side reactions. Reiteration of growth and deprotection provided the 2nd (75% yield), 3rd (**8**, 45%), and 4th (<10%, not isolated) generation dendrimers.[16] Another set of polyester dendrimers[17] (Fig. 1) was prepared, starting from 1,3,5-benzenetrimethanol[18] by repeating the synthetic procedures described above.

In this case, the yields of the dendrimers were somewhat lower: 88% (1st), 63% (2nd), and 31% (3rd generation dendrimer), respectively. All allyl terminated compounds were stable, colorless oils the viscosity of which increased with increasing molecular weight. Hydroxy terminated dendrimers were white solids. The high purity of the final products was confirmed by NMR and MALDI TOF mass spectrometry. For example, Figure 2 shows the MALDI TOF mass spectrum of 3rd generation dendrimer **8** (calcd for $C_{267}H_{278}O_{66}$, M = 4539.84), where the signal at 4564.4 is attributed to the molecular ion (M+Na). All three peaks differ in mass by exactly 42 amu, most probably due to minor fragmentation via loss of one or two allyl cations.

In conclusion, new carboxylate polyester-based dendrimers have been prepared as potential candidates for drug delivery. The mild conditions of both the coupling and deprotection reactions provided highly pure macromolecular material in good overall yields. The dendrimers obtained are terminated with carbon–carbon double bonds or benzylic hydroxy groups (in contrast to the much less reactive, frequently reported phenolic hydroxy groups[5,19]). Therefore, these reactive peripheral residues could be transformed into other functions via addition, oxidation, nucleophilic substitution reactions, etc. Consequently, these hydrolysable dendrimers also possess good properties for grafting various compounds, including biomolecules, onto their surfaces.

Acknowledgment

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9. To a suspension of 1,3,5-benzenetricarboxylic acid trimethyl ester (**1**) (2.2 g, 8.8 mmol) in MeOH (100 mL), aq NaOH (22.8 mL, 0.8 M, 2.07 equiv) was added. The resulting cloudy mixture was stirred vigorously (rt) and slowly formed a solution over ~5 h. After 15 h, MeOH was removed in vacuo. H_2O (50 mL) was added and the solution acidified (pH ~2.0) with 6 M HCl, yielding a white dispersion. The organic material was extracted with EtOAc (50 mL). The solvent was removed to give **2** (impure with 7–8% of 1,3,5-benzenetricarboxylic acid dimethyl ester, according to NMR) as a white powder. Crystallization from EtOAc provided pure monoester **2** (1.6 g, 79%): mp 220–221 °C; ^{1}H NMR (200 MHz, $CD_3OD/CDCl_3$ 1:1) δ = 3.95 (s, 3H), 8.81 [d, ^4J(H,H) = 1.6 Hz, 2H], 8.83 [t, ^4J(H,H) = 1.6 Hz, 1H] ppm. ^{13}C NMR (50 MHz, $CD_3OD/CDCl_3$ 1:1) δ = 53.01 (CH_3), 131.8 (Ar), 132.6 [2C, (Ar)], 134.9 [2C, (*ipso* Ar)], 135.4 (*ipso* Ar), 166.4 (C=O), 167.4 [2C, (C=O)] ppm.

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11. *Compound* **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ = 4.04 [d, ^{3}J(H,H) = 5.7 Hz, 4H, (OCH_2CH)], 4.56 (s, 4H, $ArCH_2O$), 5.22 [dd, $^{3}J_{cis}$(H,H) = 10.3 Hz, ^{2}J(H,H) = 1.5 Hz, 2H, ($CH{=}CH_2$)], 5.29 [dd, $^{3}J_{trans}$(H,H) = 15.7 Hz, ^{2}J(H,H) = 1.5 Hz, 2H, ($CH{=}CH_2$)], 5.96 [ddd, $^{3}J_{trans}$(H,H) = 15.7 Hz, $^{3}J_{cis}$(H,H) = 10.3 Hz, ^{3}J(H,H) = 5.7 Hz, 2H, ($CH_2CH{=}CH_2$)], 7.56 (s, 1H, Ar), 7.94 [d, ^{4}J(H,H) = 0.7 Hz, 2H, Ar], 8.81–9.53 (br s, 1H, COO*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ = 70.69 [2C, (OCH_2CH)], 71.29 [2C, ($ArCH_2O$)], 117.4 [2C, ($CH{=}CH_2$)], 128.5 [2C, (Ar)], 129.6 [2C, (*ipso* Ar)], 132.0 [1C, (Ar)], 133.8 [2C, ($CH_2CH{=}CH_2$)], 139.0 [1C, (*ipso* Ar)], 171.5 [1C, (*C*=O)] ppm.
12. The use of more traditional dicyclohexyl carbodiimide (DCC) instead of EDCI resulted in a significantly lower (~63%) yield in the coupling reaction. Also, purification of the product from dicyclohexyl urea was very tedious.
13. *Compound* **7**: ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.07 [t, ^{3}J(H,H) = 6.4 Hz, 3H, (CCH_2CH_3)], 1.82 [q, ^{3}J(H,H) = 6.4 Hz, 2H, (CCH_2CH_3)], 4.05 [d, ^{3}J(H,H) = 5.5 Hz, 12H, (OCH_2CH)], 4.51 [s, 6H, (CCH_2O)], 4.55 [s, 12H, ($ArCH_2O$)], 5.22 [dd, $^{3}J_{cis}$(H,H) = 10.2 Hz, ^{2}J(H,H) = 0.7 Hz, 6H, ($CH{=}CH_2$)], 5.32 [dd, $^{3}J_{trans}$(H,H) = 16.4 Hz, ^{2}J(H,H) = 0.7 Hz, 6H, ($CH{=}CH_2$)], 5.95 [ddd, $^{3}J_{trans}$(H,H) = 16.4 Hz, $^{3}J_{cis}$(H,H) = 10.2 Hz, ^{3}J(H,H) = 5.5 Hz, 6H, ($CH_2CH{=}CH_2$)], 7.60 (s, 3H, Ar), 7.90 (s, 6H, Ar) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ = 7.36 [1C, (CCH_2CH_3)], 23.40 [1C, (CCH_2CH_3)], 41.40 {1C, [$CH_2(CH_2)CCH_2$]}, 64.53 [3C, CCH_2O)], 71.11 [12C, ($OCH_2CH{=}$) and ($ArCH_2O$)], 117.0 [3C, ($CH{=}CH_2$)], 127.6 (6C, Ar), 129.8 (3C, Ar), 131.2 (3C, *ipso* Ar), 134.3 [6C, ($CH_2CH{=}CH_2$)], 139.0 (6C, *ipso* Ar), 165.8 [3C, (*C*=O)] ppm. MALDI TOF MS calcd for $C_{51}H_{62}O_{12}$, M = 866.4. Found *m*/*z* = 889.45 (M+Na) (100%).
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15. *Deallylation procedure*: First generation dendrimer **7** (200 mg) was stirred (open flask) in AcOH–H_2O–MeOH (7:2:1) mixture (5 mL) with 10% Pd/C (100 mg) and TsOH (~10 mg) at 50 °C for 40 h. The catalyst was filtered off and all the liquids removed. The residue was washed with Et_2O (2 mL) and dissolved in saturated $NaHCO_3$ solution in MeOH (2 mL) and again concentrated in vacuo. Finally, the residue was redissolved in acetone–MeOH 4:1 (5 mL) and the sodium salts removed by filtration to yield the polyol **7OH**, 130 mg (90%).
16. Allyl protected dendrimers (after aqueous work-up) were purified through a short plug of silica gel (CH_2Cl_2/acetone from 50:1 to 10:1, depending on generation). Data for compound **8**: ^{1}H NMR (500 MHz, $CDCl_3$) (superscripts refer to generation number) δ = 0.98 [br t, 3H, (CCH_2CH_3)], 1.71 [br q, 2H, (CCH_2CH_3)], 4.01 [d, ^{3}J(H,H) = 5.2 Hz, 48H, (OCH_2CH)], 4.50 [s, 48H, (Ar^3CH_2O)], 4.52 [s, 6H, (CCH_2O)], 5.17 [d, $^{3}J_{cis}$(H,H) = 9.8 Hz, 24H, ($CH{=}CH_2$)], 5.27 [d, $^{3}J_{trans}$(H,H) = 17.1 Hz, 24H, ($CH{=}CH_2$)], 5.37 [s, 24H, (Ar^2CH_2O)], 5.39 [s, 12H, (Ar^1CH_2O)], 5.89 [m, 24H, ($CH_2CH{=}CH_2$)], 7.55 [s, 12H, (Ar^3)], 7.73 [s, 6H, (Ar^2)], 7.76 [(s, 3H, (Ar^1)], 7.92 [s, 24H, (Ar^3)], 8.05 [s, 6H, (Ar^1)], 8.11 [s, 12H, (Ar^2)] ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 7.60 (CCH_2CH_3), 29.42 (CCH_2CH_3), 41.88 [$CH_2(CH_2)CCH_2$], 64.73 (3C, CCH_2O), 66.01 [6C, (Ar^1CH_2O)], 66.33 [12C, (Ar^2CH_2O)], 71.31 [24C, ($OCH_2CH{=}$)], 71.35 [24C, (Ar^3CH_2O)], 117.0 [24C, ($CH{=}CH_2$)], 128.0 (24C, Ar^3), 129.2 (12C, Ar^2), 129.4 (12C, Ar^3), 129.9 (6C, Ar^1), 130.5 (6C, Ar^2), 131.5 (3C, Ar^1), 134.4 [24C, $CH_2CH{=}CH_2$)], 137.1 [21C, (*ipso* $Ar^{1,2,3}$)], 139.1 [42C, *ipso* $Ar^{1,2,3}$)], 165.5 [3C, (*C*=O)^{1}], 166.0 [18C, (*C*=O)^{2,3}] ppm. MALDI TOF MS calcd for $C_{267}H_{278}O_{66}$, M = 4539.84. Found *m*/*z* = 4564.4 (M+Na), 4522.8 [M–(allyl$^+$)+Na], 4480.3 [M–2·(allyl$^+$)+Na].
17. Data for the 2nd generation dendrimer **9OH** (superscripts refer to generation number): ^{1}H NMR (200 MHz, CD_3OD) δ = 4.62 [s, 24H, (Ar^2CH_2OH)], 5.23 [s, 12H, ($Ar^1CH_2OC{=}O$)], 5.42 [s, 6H ($Ar^0CH_2OC{=}O$)], 7.55 [s, 6H (Ar^2)], 7.57 [s, 3H (Ar^0)], 7.72 [s, 3H (Ar^1)], 7.93 [s, 18H, (Ar^1, Ar^2)] ppm. ^{13}C NMR (50 MHz, CD_3OD) δ = 63.38 (12C, Ar^2CH_2OH), 66.14 (3C, Ar^0CH_2O), 66.33 (6C, Ar^1CH_2O), 127.7 (3C, Ar^0), 127.9 (6C, Ar^1), 129.2 (12C, Ar^2), 129.4 (6C, Ar^2), 129.7 (3C, Ar^1), 130.2 (3C, *ipso* Ar^1), 131.3 (6C, *ipso* Ar^2), 136.8 (3C, *ipso* Ar^0), 137.7 (6C *ipso* Ar^1), 139.9 (12 C, *ipso* Ar^2), 167.2 (9C, *C*=O) ppm. MALDI TOF MS calcd for $C_{90}H_{84}O_{30}$, M = 1644. Found *m*/*z*, fragmentation: 530.6, 574.6, 727.7, 811.7, 833.6, 920.6, 1006.5, 1168.0, 1368.8, 1542.4.
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