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LETTERS

Benzylidene Protected Bis-MPA
A Convenient Dendrimer Building Block

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Abstract: Benzylidene protected bis-MPA, 2,2-bis(hydroxymethyl)propanoic acid, was synthesised and evaluated as building block in the construction of dendrimers. It was found that the anhydride of benzylidene protected bis-MPA reacts with neopentylic alcohols to give high yields of acylated products. Purification is facilitated by the crystalline nature of most ester products. Deprotection by hydrogenolysis gives polyol dendrimers in good yields.

Compounds with a highly branched, tree-like, molecular structure have been known for long[1], but have only during the last decade attracted general attention. Synthesis of perfect dendritic material is a challenging task as high yield and selectivity is requested in all reaction steps. Various applications have been suggested for dendrimers, but complex and inefficient synthesis is still an obstacle to technical use.[2]

Acid catalysed condensation of bis-MPA (2,2-bis-(hydroxymethyl)propanoic acid) and ethoxylated pentaerythritol (PP50) with azeotropic removal of water, gives inexpensive polydisperse polyols.[3] Although not perfect dendrimers, they may nevertheless possess properties related to these, such as low viscosity relative to molecular mass.[4] Functionalisation with fatty acids, acrylic acids etc. modulates important technical properties e.g. rheology, curing characteristics, and dimensional stability of epoxy resins and UV-polymers, respectively.[5]

To obtain reference material for analytical and comparative application studies, we initiated a program dedicated to the synthesis of bis-MPA based dendrimers (perfect structures), with terminal hydroxyl groups available for derivatisation.

Exploring various routes to dendrimers based on pentaerythritol and bis-MPA we have found that the benzaldehyde acetal of bis-MPA (**1**) is a highly reactive reagent for the formation of esters. Sterically congested alcohols, e.g. pentaerythritol, are peracylated in good yields. Acetal **1** was readily synthesised from benzaldehyde (1 eq), bis-MPA (1 eq), and a small amount of *p*-TsOH. The reactants were mixed and set aside for a few days and aqueous $NaHCO_3$ was added. Acetal **1**[6] (89.4 g, 82%) was isolated after washing with ether, acidification (tartaric acid), and filtration.

The synthesis of the 1G (generation) dendrimer **2** commenced by acylation of pentarerythritol. Pentaerythritol (1 eq), acetal **1** (8 eq), DMAP (0.5 eq), and DCC (7.5 eq) were allowed to react in methylene

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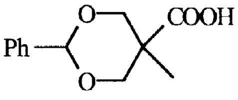
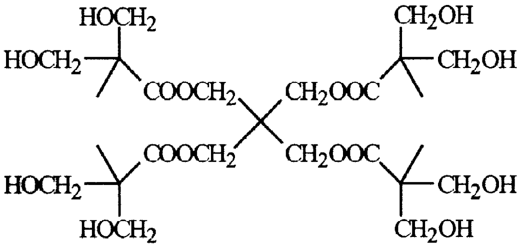
chloride at room temperature for 4 days. Removal of DCU by filtration followed by washing ($NaHCO_3$(*aq*)), and crystallisation (EtOAc) gave a protected tetraester[7] (8.23 g, 83%). Hydrogenolysis (Pd/C, DME/MeOH 1:1, 3 d), filtration, and removal of solvent furnished octaol **2**[8] (2.7 g, 96%).



1

$C[CH_2O(CH_2)_3OR]_4$ **3**, R = H
5, R = Bn

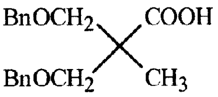
$BnOCH_2CH_2CH_2O$*p*Ts **4**



2

The same procedure was equally successful with the less sterically congested tetrol **3** to give the octaol[9] homologous to **2**. The tetrol **3**[10,11] (1.68 g, 61%) was synthesised by alkylation of pentaerythritol (1 eq) with tosylate **4**[12] (6 eq) (NaH/DMF), followed by chromatography and hydrogenolysis (Pd/C, EtOH) of the intermediary benzyl ether **5**[13].

By repeated acylation and deprotection procedures we have synthesised the 2-4th generation dendrimers of pentaerythritol and tetrol **3**, respectively.[14,15] Isolated yields in each acylation/deprotection sequence were 81-92%.



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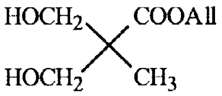

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Attempts using bisbenzylether **6**[16] in acylation reactions were less successful, e.g. oxalyl chloride or DCC activation gave tetraesters of tetrol **3** in yields below 50%. The bisbenzyl ether **6** (85.7 g, 59 %) was synthesised from bis-MPA (1 eq), benzyl chloride (7 eq), and potassium hydroxide (10 eq) in refluxing toluene (16 h).

A convergent synthesis was evaluated as an alternative route. A dendron trimer was synthesised by acylation of bis-MPA allyl ester **7**[17] with the acid chloride of bisbenzyl ether **6**, followed by palladium catalysed deallylation.[18] Condensation of the trimer and ester **7** gave the next higher homologue. Acylation of tetrol **3** with these dendrons gave poor yields of dendrimers and/or purification was more complex compared to the divergent sequence using acetal **1**.

In summary, we have presented a route to bis-MPA derived dendrimers emanating from tetrafunctional core molecules. The use of inexpensive materials and simple procedures should promote the protocol based on acetal **1** to be further developed into large scale preparation of perfect dendritic materials.

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6. 5-Metyl-2-phenyl-1,3-dioxane-5-carboxylic acid, ^{1}H-NMR (DMSO-d$_6$): δ = 0.94 (s, 3H), 3.66 (d, *J* = 11.0 Hz, 2H), 4.43 (d, J = 10.7 Hz, 2H), 4.49 (s, 1H), 7.32-7.42 (m, 5H); ^{13}C-NMR (DMSO-d6): δ= 17.5, 41.5, 72.6, 100.3, 126.0, 127.9, 128.6, 138.3, 175.5.
7. 1G-Benzylidene protected dendrimer, ^{1}H-NMR (CDCl$_3$): δ= 1.85 (s, 12H), 3.58 (d, J = 10.8 Hz, 8H), 4.30 (s, 8H), 4.58 (d, J = 10.8 Hz, 8H), 5.42 (s, 4H), 7.21-7.32 (m, 12H), 7.37-7.44 (m, 8H); ^{13}C-NMR (CDCl$_3$): δ =17.6, 42.7, 43.6, 61.6, 73.6, 101.7, 126.2, 128.1, 128.8, 137.8, 173.0.
8. 1G-Hydroxy dendrimer **2**, ^{1}H-NMR (DMSO-d$_6$): δ= 1.02 (s, 12H), 3.40 (d, J = 10.6 Hz, 8H), 3.48 (d, J = 10.6 Hz, 8H), 4.07 (s, 8H); ^{13}C-NMR (DMSO-d$_6$): δ= 16.5, 42.4, 50.3, 61.7, 63.6, 174.2.
9. 1G-Hydroxy dendrimer based on tetrol **3**: ^{1}H-NMR (pyridine-d5): δ= 1.55 (s, 12H), 1.9 (p, 8H), 3.35-3.55 (m, 16H), 4.2 (m, 16H), 4.35 (t, 8H,), 6.3 (br s, 8H). ^{13}C-NMR (pyridine-d5): δ= 17.58, 29.18, 45.54, 51.19, 61.59, 65.15, 67.83/69.75, 175.75. HRMS (CI): (*m/z*) Calc. for $C_{37}H_{68}O_{20}$ (M$^+$): 832.4304, Found 833.4373 (M$^+$+1).
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11. *O,O',O'',O'''*,-Tetrakis(3-hydroxypropyl)pentaerythritol, the ^{1}H-NMR spectrum is in accordance with published data.[10] ^{13}C-NMR (CDCl$_3$): δ= 31.8, 44.7, 60.8, 69.8, 70.7.
12. 3-(Benzyloxy)propyl *p*-toluenesulfonate, prepared according to Buttler, C. L.; Renfrew, A. G.; Clapp, M. *J. Am. Chem.*, **1938**, *60*, 1472. ^{1}H-NMR (CDCl$_3$): δ 1.95 (p, 2H), 2.43 (s, 3H), 3.51 (t, 2H), 4.18 (t, 2H), 4.41 (s, 2H), 7.1-7.4 (m, 7H), 7.80 (d, 2H). ^{13}C-NMR (CDCl$_3$): δ= 21.6, 29.4, 65.7, 67.8, 73.0, 127.6, 127.7, 127.9, 128.4, 129.9, 133.0, 138.2, 144.8.
13. *O,O',O'',O'''*,-Tetrakis(3-benzyloxypropyl)pentaerythritol, the ^{1}H-NMR spectrum is in accordance with published data.[10] ^{13}C-NMR (CDCl$_3$): δ= 30.2, 45.6, 67.6, 68.3, 69.9, 73.1, 127.6, 127.7, 128.5, 138.8.
14. 4G-Hydroxy dendrimer based on pentaerythritol: ^{1}H-NMR (D$_2$O): δ= 1.03 (s, 96H), 1.20 (s, 48H), 1.21 (s, 24H), 1.26 (s, 12H), 3.49 (d, J = 11.2 Hz, 64H), 3.58 (d, J =11.2 Hz, 32H), 3.58 (d, J = 11.2 Hz, 32H), 3.59 (d, J = 11.2 Hz, 32H), 4.12-4.32 (m, 120H). ^{13}C-NMR (D$_2$O): δ= 16.7, 17.48, 17.54, 17.71, 17.73, 46.9, 47.0, 47.2, 50.8, 64.7, 65.6, 66.2, 172.6, 172.9, 173.7, 176.0. Size exclusion chromatography (M_w/M_n = 1.007) and MALDITOF (MS) confirmed monodispersity and identity. Dr Magnus Karlsson, Astra Draco AB, is greatly acknowledged for recording the MALDITOF (MS) spectra.
15. Benzylidene protected 4G-dendrimer based on tetrol **3**: ^{1}H-NMR (CDCl$_3$): δ= 0.88 (s, 96H), 1.01 (s, 24H), 1.11 (s, 12H), 1.18 (s, 48H), 1.85 (p, J = 7 Hz, 8H), 3.39 (t, J = 7 Hz, 8 H), 3.41 (s, 8H), 3.53 (d, J = 10 Hz, 32H), 3.54 (d, J = 10 Hz, 32H); 4.01-4.21 (m, 56H), 4.33 (d, J = 10 Hz, 32H), 4.36 (d, J = 10 Hz, 32H), 4.53 (d, J = 10 Hz, 64H), 5.36 (s, 32H), 7.24-7.32 (m, 96H), 7.36-7.41 (m, 64H). ^{13}C-NMR (CDCl$_3$): δ 17.3, 17.6, 17.67, 17.68, 29.0, 42.6, 46.0, 46.4, 46.5, 46.9, 63.2, 65.0, 65.2, 65.5, 68.0, 70.4, 73.4, 171.4, 171.8, 172.0, 173.2. ^{1}H- and ^{13}C-NMR spectra of the corresponding deprotected derivative are in agreement with the proposed structure but less detailed due to overlapping signals. Size exclusion chromatography (M_w/M_n = 1.006) confirmed monodispersity of the hydroxy derivative.
16. 2,2-Bis(benzyloxymethyl)propanoic acid, ^{1}H-NMR (CDCl$_3$): δ= 1.3 (s 3H), 3.6-3.7 (m, 4H), 4.55 (s, 4H), 7.2-7.4 (m, 10H). ^{13}C-NMR (CDCl$_3$): δ= 18.1, 48.4, 72.0, 73.5, 127.6, 127.7, 128.4, 138.3, 180.9.
17. Allyl 2,2-bis(hydroxymethyl)propanoate, ^{1}H-NMR (CDCl$_3$): δ= 1.1 (s, 3H), 3.2 (t, 2H), 3.7 (dd, 2H), 3.9 (dd, 2H), 4.6 (dm, 2H), 5.2 (dm, 1H), 5.3 (dm, 1H), 5.8-6.0 (m, 1H).
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