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Synthesis of New Amphiphilic Dendrons Bearing Aliphatic Hydrocarbon Surface Sectors and a Monocarboxylic or Dicarboxylic Acid Focal Point

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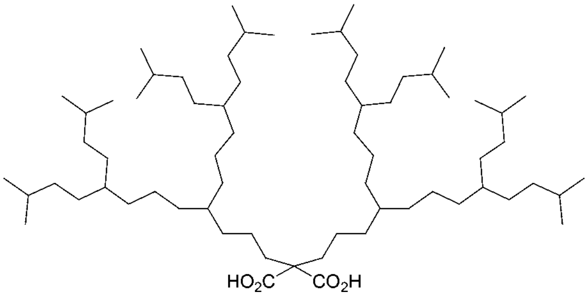
ABSTRACT



A new series of amphiphilic G1–G3 dendrons containing purely aliphatic hydrocarbon dendritic surface sectors and one or two carboxylic acid group(s) at the focal point was synthesized in good yields. The key branching steps involve diallylation reactions of diethyl malonate or Meldrum's acid. These dendrons are highly soluble in hexane despite having highly polar carboxylic acid groups at the focal point.

Amphiphilic dendrimers are a new subclass of dendrimers possessing interesting self-assembling,[1] gene transfection,[2] and catalyst properties.[3] They were generally prepared either by grafting linear hydrophilic chains (e.g., oligoethyleneglycols or alkyl carboxylates) to the surface of a hydrophobic dendrimer[4] or by attaching linear aliphatic hydrocarbon chains [e.g., $-(CH_2)_n-$] to the surface of a hydrophilic core.[1b,5] However, hydrophobic dendrons based on a highly branched aliphatic hydrocarbon skeleton are scarcely known.[6] Herein, we report the synthesis of a new series of amphiphilic dendrons **1**−**6** based on an "inverted" architecture wherein the hydrophobic hyperbranched aliphatic hydrocarbon dendrons were anchored onto a hydrophilic carboxylic or

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(1) (a) Laufersweiler, M. J.; Rohde, J. M.; Chaumette, J.-L.; Sarazin, D.; Parquette, J. R. *J. Org. Chem.* **2001**, *66*, 6440. (b) Cho, B.-K.; Jain, A.; Nieberle, J.; Mahajan, S.; Wiesner, U.; Gruner, S. M.; Türk, S.; Räder, H. J. *Macromolecules* **2004**, *37*, 4227. (c) Vutukuri, D. R.; Basu, S.; Thayumanavan, S. *J. Am. Chem. Soc.* **2004**, *126*, 15636.

(2) (a) Bielinska, A.; Kukowska-Latallo, J. F.; Johnson, J.; Tomalia, D. A.; Baker, J. R., Jr. *Nucl. Acids Res.* **1996**, *24*, 2176. (b) Loup, C.; Zanta, M.-A.; Caminade, A.-M.; Majoral, J.-P.; Meunier, B. *Chem. Eur. J.* **1999**, *5*, 3644. (c) Joester, D.; Losson, M.; Pugin, R.; Heinzelmann, H.; Walter, E.; Merkle, H. P.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1486.

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(4) For examples, see: (a) Newkome, G. R.; Moorefield, C. N.; Baker, G. R.; Saunders, M. J.; Grossman, S. H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1178. (b) Pan, Y.; Ford. W. T. *Macromolecules* **2000**, *33*, 3731.

(5) For examples, see: (a) Schenning, A. P. H. J.; Elissen-Román, C.; Weener, J.-W.; Baars, M. W. P. L.; van der Gaast, S. J.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 8199. (b) Luman, N. R.; Grinstaff, M. W. *Org. Lett.* **2005**, *7*, 4863.

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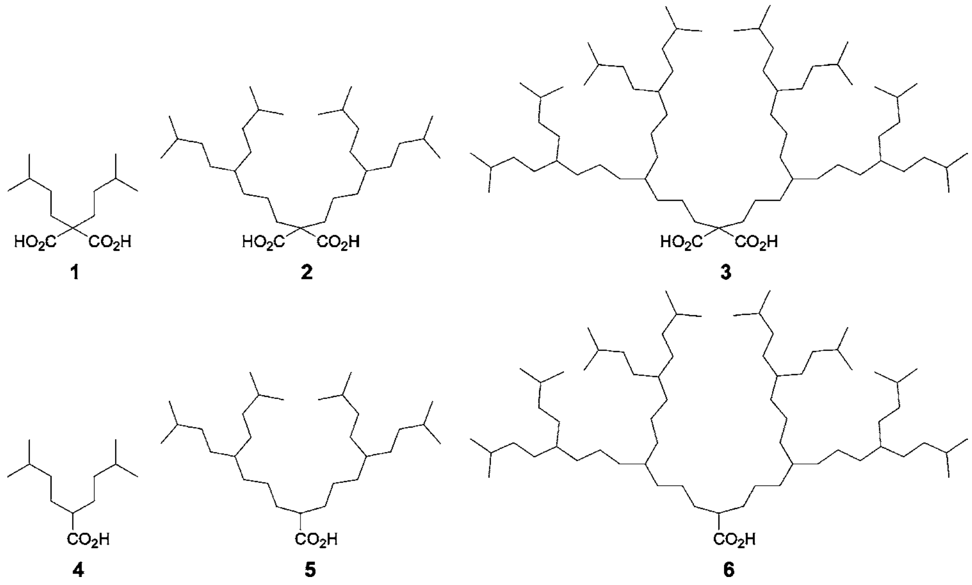


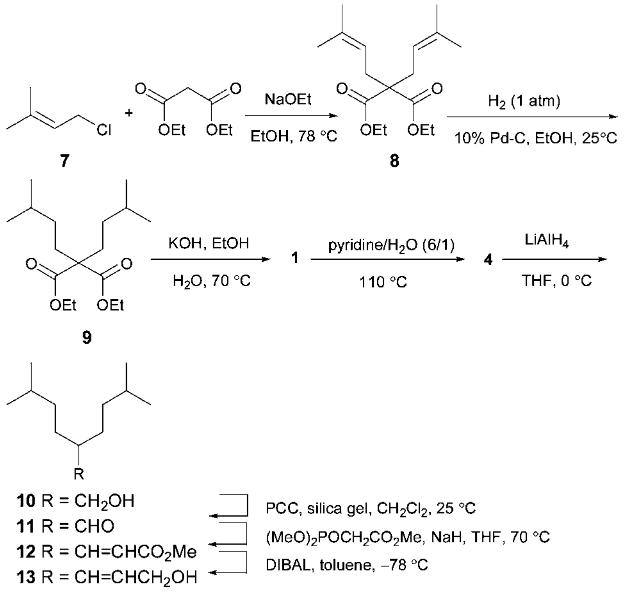
Figure 1. Structure of aliphatic hydrocarbon dendrons **1**−**6**.

dicarboxylic acid focal point group (Figure 1). Hydrocarbon dendrimers such as oligo(arylene),[7] oligo(phenylenevinylene),[8] and oligo(phenylene-ethynylene)[9] dendrimers had all been reported before, but these were systems constructed based on sp^2- or sp-hybridized carbon atoms. Hydrophobic dendrimers or dendrons constructed solely from sp^3-hybridized carbon systems are therefore of special interest because they are expected to possess even higher hydrophobicity and should be soluble in nonpolar aliphatic hydrocarbon solvents. For the present series of amphiphilic dendrons **1**−**6**, the availability of the focal point carboxylic acid functionality also facilitates their attachment to other functional molecules. Hence, these dendrons have the ability to solubilize poorly soluble molecular fragments and to facilitate catalytic systems to dissolve and function in nonpolar aliphatic hydrocarbon solvents.

Despite their structural simplicity, the synthesis of aliphatic hydrocarbon dendrons is not a trivial task. First, aliphatic hydrocarbons are inherently inert and therefore lack reactive functionalities for their controlled iterative growth. Second, formation of C−C bonds between sp^3- and sp^3-hybridized carbons is strongly deterred by steric congestion and this problem is particularly acute during the branching process. Third, the structures of such dendrons are overwhelmed by the nonpolar surface sectors, and hence, the differences of the chromatographic mobilities of such dendrons bearing different focal point group are diminished and this could create additional problems in product separation.

In our synthetic scheme, we chose the diallylation reaction of diethyl malonate or Meldrum's acid as the pivotal step in the branching growth of such dendrons. The starting materials for the synthesis of the G1 series of dendrons were 4-chloro-2-methylbut-2-ene **7** and diethyl malonate (Scheme 1).

Scheme 1. Synthesis of G1 Dendrons



Hence, diallylation of diethyl malonate with 2.2 equiv of **7** in the presence of NaOEt (2.2 equiv) at 78 °C afforded the desired di-*C*-allylation product **8** in 83% yield. The C═C double bonds in product **8** were then saturated in the presence

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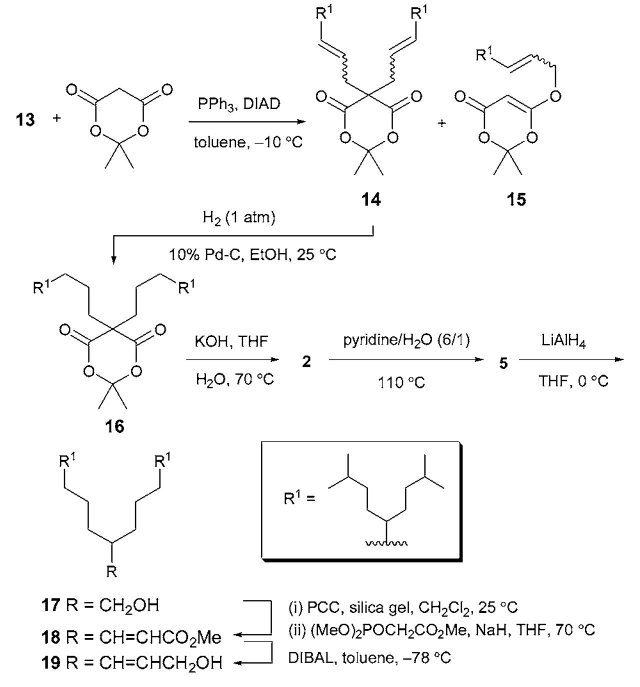
(9) Xu, Z.; Moore, J. S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 2, 246.

of 10% Pd−C under H_2 atmosphere (1 atm) to give the saturated diester **9** in 94% yield. Base hydrolysis (KOH, EtOH, H_2O, 78 °C) of the two ester groups then gave the G1-diacid **1** as a crystalline solid (mp 138−140 °C) in 94% yield. This diacid could be cleanly decarboxylated[10] in refluxing/H_2O (v/v = 6/1) to produce the G1-monoacid **4** as a solid (mp 49−50 °C) in 94% yield. On the other hand, the classical Krapcho decarboxylation[11] of compound **9** or the acid-catalyzed (concd H_2SO_4) decarboxylation of diacid **1** resulted in substantial decomposition. The monoacid **4** was converted to the corresponding alcohol **10** by $LiAlH_4$ in 96% yield. The alcohol was oxidized to the corresponding aldehyde **11** with PCC/silica gel in CH_2Cl_2, and was intermediately reacted with 1.1 equiv of the sodium salt of trimethylphosphonoacetate to give an *E*/*Z* (4:1) mixture of α,β-unsaturated ester **12** (81% overall yield from compound **10**). This mixture was then reduced to the corresponding allylic alcohol **13** by DIBAL in 96% yield. This alcohol **13** could be used in the next iterative cycle without the need to convert it into the corresponding allylic halide. This series of reactions then completed the first iterative synthetic cycle. There are eight steps in this cycle;[12] however, all of them are efficient, and the products formed could be carried to the next step without chromatographic purifications.[13] The overall yield of the G1-allylic alcohol **13** from the G0-allylic chloride (i.e., **7**) was 51%, and the reactions could be carried out in 50 g scale.

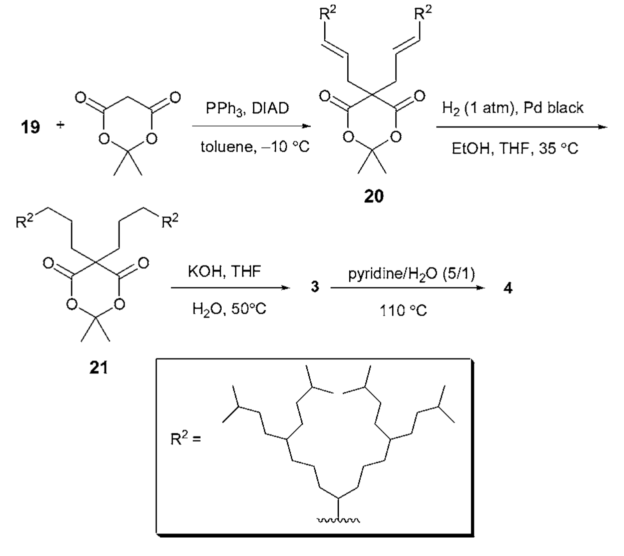
Scheme 2. Synthesis of G2 Dendrons



For the synthesis of the G2-dendrons, compound **13** was found to react smoothly with Meldrum's acid[14] in toluene according to Shing's[15] procedure (Scheme 2) to produce the di-*C*-allylation product **14** in 85% yield together with a mono-*O*-allylation product **15** (10%).[16] Hydrogenation of the C═C bonds in the presence of 10% Pd−C gave the saturated product **16** which was subsequently hydrolyzed with aqueous KOH to produce the G3-diacid **2** as a solid (mp 80−82 °C) in overall 87% yield. Similarly, decarboxylation of compound **2** in aqueous pyridine afforded the G2-monoacid **5** in 93% yield. The monoacid **5** was then converted to the alcohol **17** in 94% yield by $LiAlH_4$. The alcohol **17** was then treated with PCC in CH_2Cl_2 to give the corresponding aldehyde, which was immediately reacted with the sodium salt of trimethylphosphonoacetate to produce α,β-unsaturated ester **18** as a separable mixture of *E*/*Z* isomers in a ratio of 8.5:1. Finally, DIBAL reduction of compound **18** gave the allylic alcohol **19** in 61% overall yield from the G2-alcohol **17**.

The G2-allylic alcohol **19** was again subjected to the Mitsunobu reaction (Scheme 3) with Meldrum's acid in toluene to produce the G3-diallylation product **20** in 72% together with a small amount (19%) of mono-*O*-allylation product. Despite the larger size of the G2-allylic alcohol **19**, the reaction still went smoothly, indicating the versatility of this diallylation reaction. The C═C bonds were similarly

Scheme 3. Synthesis of G3 Dendrons



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[10] Cocker, W.; Geraghty, N. W. A.; McMurry, B. H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2245.

[11] Krapcho, A. P. *Synthesis* **1982**, 893.

[12] The number of steps in the iterative cycle could have been shortened to five if we were to use a dialkylation reaction of diethyl malonate with a saturated alkyl halide instead of the allylic chloride **7** in the synthesis. By doing so, the hydrogenation reaction, Wittig olefination and DIBAL reduction steps could be removed from the iterative cycle. However, we found that dialkylations of diethyl malonate with saturated bromides were extremely sluggish and conversion was low even after prolonged reaction time.

[13] Column chromatographic purification was needed only for the isolation of compound **12**. The other compounds could go to the next step without purification.

[14] Reactions using Meldrum's acid directly purchased from vendors without prior recrystallization from aqueous acetone resulted in poor product yields and the formation of a substanital amount of a mono-*O*-allylation product **15**. The presence of trace amount of acetic acid (<0.5%) in the reaction also significantly lowered the yield of the diallylation product **14**.

[15] Shing, T. K. M.; Li, L.-H.; Narkunan, K. *J. Org. Chem.* **1997**, *62*, 1617.

[16] Reaction of Meldrum's acid and the G1-allylic alcohol in THF as an alternative solvent, however, gave 65% yield of compound **14** and 26% of the mono-*O*-allylation product **15**.

hydrogenated in the presence of Pd black to give the saturated G3-Meldrum's acid **21** (99% yield) that could be conveniently converted to the target G4-diacid dendron **3** (88% yield) and the G3-monoacid dendron **6** (88% yield) using the reactions described earlier. All synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, exact mass measurement (Table 1), and/or elemental analysis (Table 2).

Table 1. High-Resolution Mass Spectral Data of Synthesized Compounds

compd	found	calcd
2	519.4388 (M + Na$^+$)	519.4384
3	1024.0028 (M + Na$^+$)	1024.0018
5	475.4484 (M + Na$^+$)	475.4486
6	980.0125 (M + Na$^+$)	980.0120
10	185.1901 (M − H$^+$)	185.1900
11	185.1911 (M + H$^+$)	185.1900
13	211.2052 (M − H$^+$)	211.2056
16	559.4707 (M + Na$^+$)	559.4697
17	461.4697 (M + Na$^+$)	461.4693

The influence of the highly hydrophobic dendrons on the solubility of focal point dicarboxylic acid functional group was of special interest. For example, while the G1-diacid **1** is sparingly soluble (<2 mg/mL) in hexane at 20 °C, both the G2- and G3-diacids (**2** and **3**) are highly soluble/miscible in hexane in all proportions at 20 °C. Rather surprisingly, both the unsaturated G3-Meldrum's acid **20** as well as the saturated one **21** are immiscible (at concentration of 100 mg/mL) with EtOH in a temperature range from 20 to 60 °C. They are, however, fully miscible with hexane in all proportions at 20 °C, suggesting that the polarity of the Meldrum's acid focal point group was completely masked by the highly nonpolar aliphatic hydrocarbon dendrons. Hence these dendrons are capable of bringing highly polar functional group into nonpolar solutions. The dicarboxylic acid moieties here could also be converted into other functionalities such as bis(oxazoline)s, metal complexes of which are known to be excellent catalysts for a wide variety of reactions.[17]

Table 2. Elemental Analysis Data of Synthesized Compounds

compd	found	calcd
1	C 63.85, H 9.89	C 63.91, H 9.90
4	C 71.92, H 12.17	C 71.95, H 12.08
8	C 69.06, H 9.64	C 68.89, H 9.52
9	C 67.71, H 10.41	C 67.96, H 10.74
12	C 74.88, H 11.75	C 74.95, H 11.74
14	C 76.60, H 11.34	C 76.64, H 11.35
18	C 80.68, H 12.70	C 80.42, H 13.09
19	C 82.49, H 13.78	C 82.68, H 13.88
20	C 80.96, H 13.02	C 81.01, H 12.82
21	C 80.90, H 13.23	C 80.70, H 13.16

In summary, we report a high-yielding, large-scale synthesis of a new class of hyperbranched dendrons based on an aliphatic hydrocarbon skeleton. These dendrons are highly nonpolar and are capable of solubilizing hydrophilic groups even in hexane solutions. We are currently investigating the amphiphilic nature of these unusual dendritic compounds.

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Supporting Information Available: Details of synthetic procedures and ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For a review, see: Ghosh, A. K.; Mathivanan, P.; Gappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.