A fast double-stage convergent synthesis of dendritic polyethers

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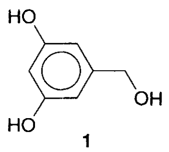
Two *tert*-butyldiphenylsilyl-protected synthons 7 and 9 are prepared in excellent yields and used in a one-pot synthesis of higher generation polyether dendrons.

The convergent synthesis of dendritic polyethers, based on the AB_2 monomer 3,5-dihydroxybenzyl alcohol **1**, has been developed by Hawker and Fréchet[1] and successfully used by his[2] and other groups[3] to construct monodisperse macromolecules. The drawbacks of the method, however are that the build-up of the dendritic wedges is time-consuming and the increasing steric hindrance, which occurs at the focal functional group with dendron growth, may inhibit its anchoring to a central core. Fréchet and coworkers[4] circumvented these problems by using hypercores constructed from 4,4-bis(4-hydroxyphenyl)pentanol **2** as the building block. During the convergent growth the phenol functions at the periphery were protected with benzyl groups, which were removed by catalytic hydrogenolysis after the dendrons had been attached to a central polyfunctional molecule. These hypercores were then alkylated with polyether benzylic bromides derived from the monomer **1** to give dendrimers with nominal molecular weights up to 84 219 Da. The dendrimers thus obtained possess a two-layered structure.

Another approach can be envisaged to accelerate the synthesis, and consists of using the appropriate AB_4 (see **7**, R = H) or AB_8 monomer (see **9**, R = H) in the assembly of the higher generation polyether dendrons. Fréchet and coworkers[5] have already explored this possibility, however, without much success. We have now developed a double-stage synthesis of dendritic wedges, built uniformly from the monomer **1**, by protecting the phenol functions at the periphery with *tert*-butyldiphenylsilyl groups.[6] This group was chosen both for its stability under the reaction conditions and its easy and selective removal with fluoride ion. The *tert*-butyldimethylsilyl protecting group, which was checked as an alternative, is unsuitable since it was partially removed in the $LiAlH_4$ reduction step of our synthesis (Scheme 1).

Thus, methyl 3,5-dihydroxybenzoate **3** was converted into the bis(*tert*-butyldiphenylsilyl)-protected ester **4** and reduced with lithium aluminium hydride to the protected alcohol **5**, isolated as a white crystalline solid (mp 105.0–105.7 °C) in 87% overall yield. Coupling of the monomeric alcohol **5** with the precursor **3** under Mitsunobu conditions ($EtO_2C{-}N{=}N{-}CO_2Et$, PPh_3)[7] afforded the trimeric ester **6** (85%) which was reduced to the protected trimeric alcohol **7** (white foam, 94%). This sequence was repeated to give the heptameric ester **8** (79%) and the heptameric alcohol **9** (colourless glass, 90%). The structures of the products were fully characterized by ^1H and ^{13}C NMR spectroscopy, FAB MS and microanalyses.



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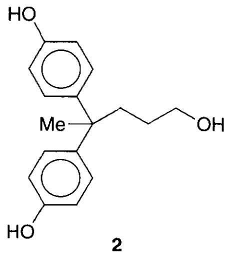

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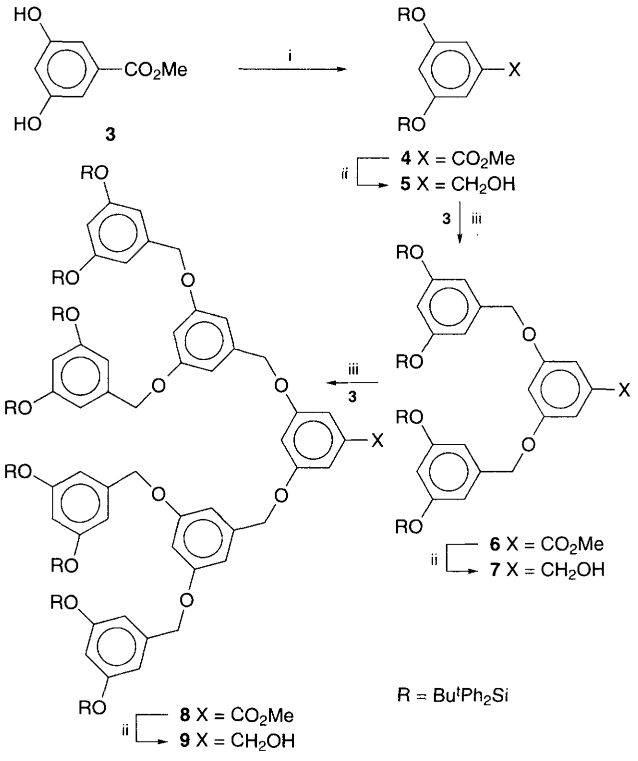
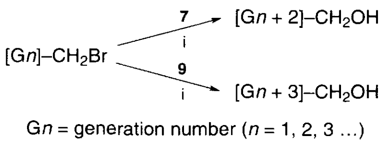
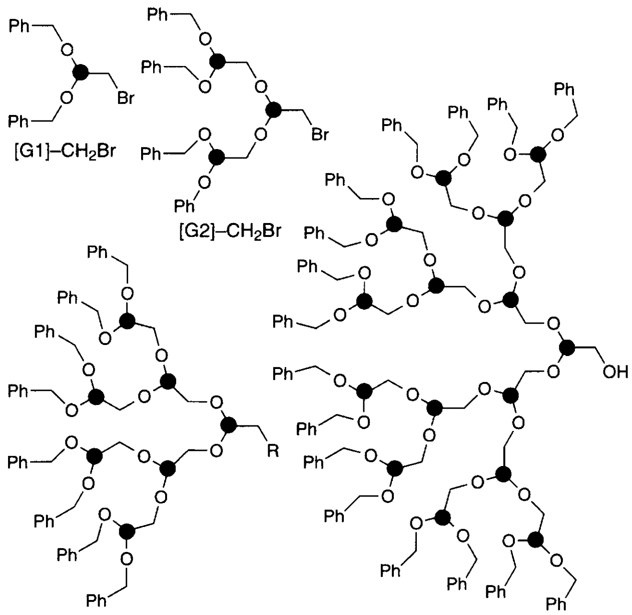
With the synthons **7** and **9** at hand, higher generation dendrons can now be prepared easily in a one-pot reaction by simultaneous deprotection and alkylation according to Scheme 2. This approach is illustrated by reacting the alcohol **7** with potassium fluoride–18-crown-6 and Fréchet's benzylic bromides [G*n*]–CH_2Br of the first (*n* = 1), second (*n* = 2) and third generation (*n* = 3), which yielded dendritic wedges [G*n* + 2]–CH_2OH of the third (92%), fourth (90%) and fifth generation (82%) respectively; thus increasing the generation number by two units in each case. Similar transformations were achieved with the heptameric alcohol **9**, where the higher dendrons [G4]–CH_2OH (82%) and [G5]–CH_2OH (83%) were obtained directly from Fréchet's benzylic bromides of the first and second



Scheme 1 *Reagents*: i, Bu^tPh_2SiCl, imidazole, DMF; ii, $LiAlH_4$, THF; iii, $EtO_2CN{=}NCO_2Et$, PPh_3, THF



Scheme 2 *Reagents and conditions*: i, KF, 18-crown-6, acetone, reflux, 24 h

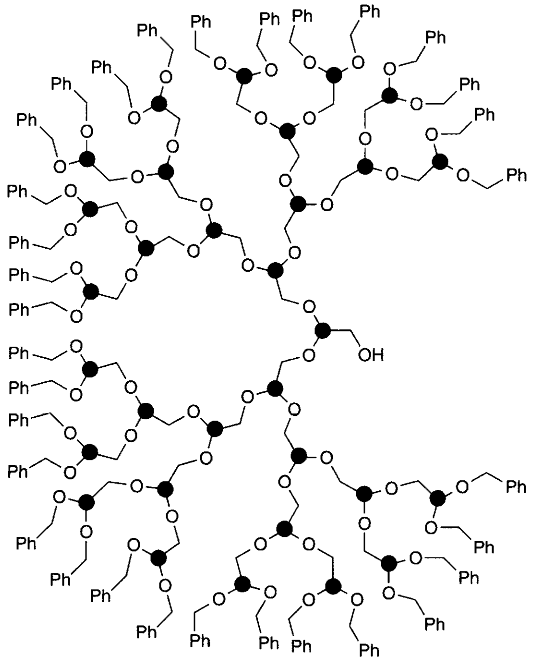


[G1]–CH_2Br

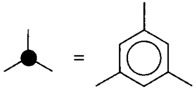
[G2]–CH_2Br

[G3]-CH_2Br (R = Br)
[G3]-CH_2OH (R = OH)

[G4]–CH_2OH



[G4]–CH_2OH



generation; here, a growth of three generations is made in each case. The reactions were carried out in refluxing acetone for 24 h under a nitrogen atmosphere, and the products were purified by chromatography and identified by comparison of the ^{1}H and ^{13}C NMR spectroscopic data with those of Hawker and Fréchet.[1]

The strategy outlined above represents a simplified and fast method for the synthesis of polyether dendrons as compared with the classical approach,[1] where two separate steps are required for each generation growth. Moreover, the silylated oligoethers offer two additional advantages for the construction of dendrimers. Firstly, they can be attached to a core reagent and then used as a hypercore for the elaboration of high molecular weight dendrimers. Secondly, with *tert*-butyldiphenylsilyl as a protecting group, the periphery can be functionalized at a later stage of the synthesis, which is especially useful for labile functions or groups which are inconvenient to carry along during the multistep convergent synthesis. These topics are currently being investigated.

Financial support from the NFWO, the University and the Ministerie voor Wetenschapsbeleid is gratefully acknowledged. This work has been accomplished with fellowships from the IWT (for B. F.) and the University (for W. D.), and with the enthusiastic collaboration of Kurt Desmedt.

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Received, 5th July 1996; Com. 6/04715G