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Highly efficient synthesis of polyfluorinated dendrons suitable for click chemistry†

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A highly efficient convergent synthesis of C_{2v}-symmetric dendrons is presented. The generation build-up was achieved by copper(I)-catalyzed azide–alkyne cycloadditions. The resulting G2-dendron consists of 72 magnetically equivalent fluorine atoms and displays a single sharp resonance in its ^{19}F NMR spectrum.

Nowadays, magnetic resonance imaging (MRI) is an established and very versatile, non-invasive, non-destructive imaging technique for diagnosis in human medicine.[1] MRI provides high resolution between soft tissues (few millimeters for human scanners and up to 50 μm for ultra high-field animal scanners), but without the need for ionizing and thus damaging radiation.[2] Besides ^{1}H, other NMR active heteronuclei could be used as well for MRI, which allows for adding a second "color" to anatomical scans obtained by classical ^{1}H MRI.[3] However, most nuclei are unfit for MRI applications, because of their inherent physical, chemical and biological properties. But ^{19}F has been shown to be exceptionally suitable for MRI as it is the second most sensitive, stable nucleus for MR spectroscopy (directly after ^{1}H) and has 100% natural abundance.[4,5] Furthermore, the resonance frequency of ^{19}F differs by only 6% from the frequency of ^{1}H, which allows creating ^{19}F MR images on common ^{1}H MRI devices.[3]

The conventional ^{1}H MRI makes use of the nuclear spin of the ubiquitous water molecules within organic tissues to enable visualization. On the contrary, fluorine is virtually absent in the biosphere.[5] The external addition of a suitable, fluorinated compound (called probe or tracer) is thus mandatory for ^{19}F MRI.[6] Only teeth and the bone matrix contain considerable amounts of endogenous fluorine. However, immobilized fluorine exhibits a very short spin–spin relaxation time and is therefore not detectable by ^{19}F MRI.[5] Consequently, ^{19}F MR images of biological samples do not have an intrinsic background signal, which results in an extremely high contrast.[5] In summary, the information obtained from ^{1}H and ^{19}F MRI is complementary: ^{1}H MRI collects morphological data (anatomy) and ^{19}F MRI enables tracking of a fluorinated, exogenous compound (*e.g.* drugs).[7]

Suitable probes for ^{19}F MRI should preferably fulfill several requirements. Of course, the probe must be chemically inert and biologically compatible.[3] Most organofluorine compounds easily match these requirements because of the extraordinary strength of the C–F bond.[8] The probe should also have a large number of fluorine atoms to provide a high spin density.[3] This is often accomplished by using perfluorinated compounds, like perfluorooctyl bromide (PFOB).[9] But perfluorinated molecules typically have the drawback of displaying multiple, split ^{19}F signals, which reduces signal intensity and leads to image artefacts.[10] This problem can be overcome by applying ^{19}F MRI probes with high symmetry, like perfluoro[15]crown-5 ether (PF15C5).[11] Finally, it would be advantageous, if the probe is water-soluble to allow for easy application without the need for complex formulation.[12] This is challenging since highly fluorinated molecules are in general very hydrophobic.[13] As a consequence, many probes have to be applied as stable emulsions, *e.g.* by mixing with a surfactant like lecithin.[9,11] In some cases, amphiphilic polyfluorinated polymers have also been shown to self-assemble into micelles in aqueous solution, which allowed for direct application without the need for stabilizing additives.[14] Nevertheless, a more elegant approach would be to acquire the requested water solubility *via* conjugation with hydrophilic compounds.[12] Hence, ^{19}F MRI probes that follow a rational design, should also provide a conjugation site for tuning their water solubility.

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Inspired by the spherically symmetric ^{19}F MRI tracers from Yu *et al.*[12,15] and owing our own interest in fluorine chemistry,[16] we set out to find an easy access to dendrimeric molecules, which can meet the aforementioned requirements. Herein, we present an efficient three-step procedure for the preparation of C_{2v}-symmetric polyfluorinated dendrons by applying the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC),[17] which is a common reaction for the preparation of various dendrimers and MRI probes,[18] as a key reaction.

Since perfluoro-*tert*-butanol already has nine magnetically equivalent fluorine atoms and displays neither interfering ^{1}H–^{19}F nor ^{19}F–^{19}F coupling,[15a] this molecule was chosen as a fluorinated precursor. Furthermore, Horváth *et al.* have shown that the sodium salt of this perfluorinated alcohol reacts with various benzyl bromides *via* nucleophilic substitution in moderate to good yields.[19] After a twofold substitution of dibromide **1**-Br[20] the polyfluorinated aryl iodide **1**-OC$(CF_3)_3$ was accessible in excellent yield (Scheme 1). Next, silylalkyne **2**-$SiMe_3$ was synthesized *via* Sonogashira coupling[21] and upon subsequent deprotection with K_2CO_3 in methanol terminal alkyne **2**-H was obtained. Notably, both silane **2**-$SiMe_3$ and alkyne **2**-H were poorly soluble in the reaction mixture, although methanol is known to be a good fluorophilic solvent.[13] However, the deprotection proceeded quantitatively and alkyne **2**-H could be isolated by simple filtration without the need for further purification. The first-generation dendron (G1-dendron) **3** was build up by twofold CuAAC of alkyne **2**-H with diazide **1**-N_3.[20] The three-step generation build-up (Sonogashira reaction, deprotection, CuAAC) for the G1-dendron **3** had a total yield of 82% and could be done easily on a gram scale.

During this sequence the ^{19}F NMR spectrum of every compound showed just one sharp singlet. This proved that all fluorine atoms are indeed magnetically equivalent. Moreover, iodide **1**-OC$(CF_3)_3$ and alkyne **2**-H could be crystallized from perfluorohexane or cyclohexane, respectively, to obtain single crystals suitable for X-ray crystallography. The molecular structures of those perfluoro-*tert*-butyl ethers are depicted in Fig. 1.

The generation build-up sequence was repeated once more to afford the second-generation dendron **5** (Scheme 2). Expectedly, the overall yield for this second cycle decreased slightly (67%), which can be explained by increased steric hindrance.[15b] Nevertheless the yields for each step were still quite high (77–94%). The 72 fluorine atoms of dendron **5** resulted in just one sharp singlet in the respective ^{19}F NMR spectrum. Hence,

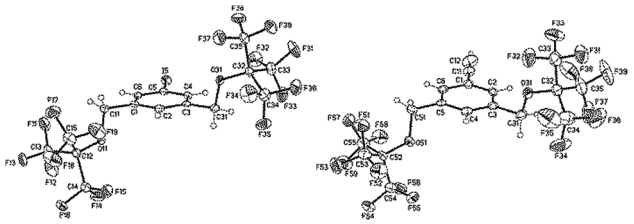
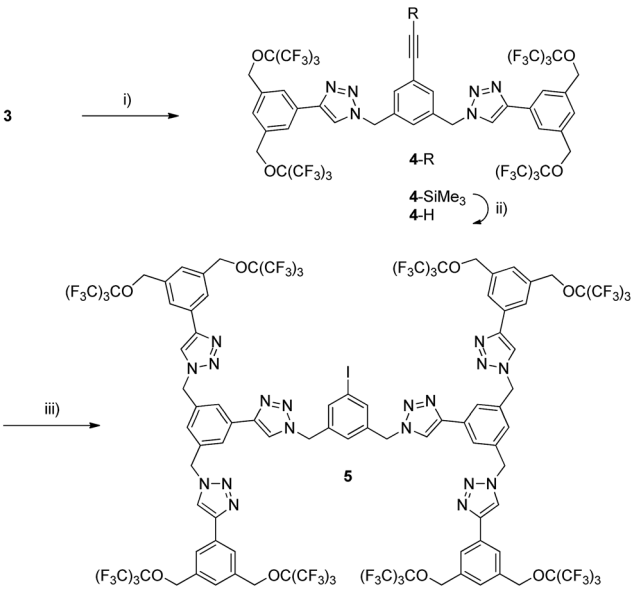


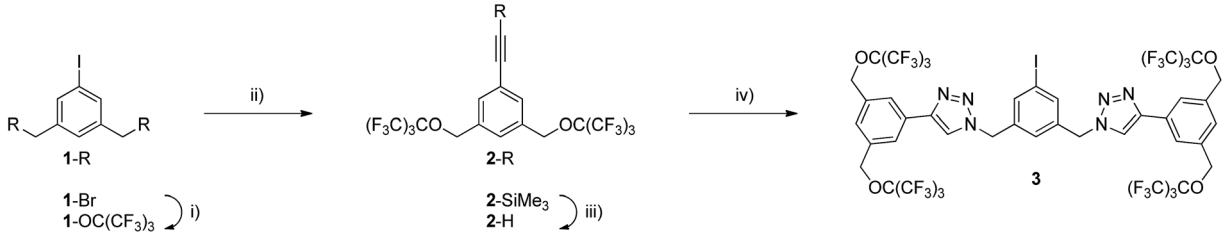
Fig. 1 Molecular structure of iodide **1**-OC$(CF_3)_3$ (left side) and alkyne **2**-H (right side) with displacement ellipsoids drawn at 50% probability level.[22]

dendron **5** has considerably more magnetically equivalent fluorine atoms than typical, commercially available ^{19}F MRI probes (*e.g.* PF15C5).

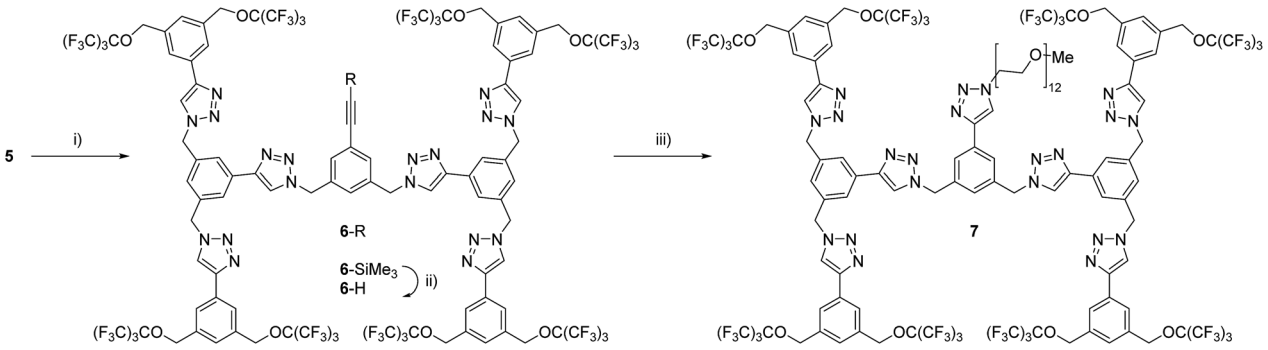
To provide dendron **5** with an appropriate conjugation site, the sequence of Sonogashira coupling with trimethylsilylacetylene and subsequent desilylation with K_2CO_3 was repeated one last time (Scheme 3). Alkyne **6**-H was obtained in 37% overall yield after 9 steps from dibromide **1**-Br. Finally, we tried to



Scheme 2 Synthesis of G2-dendron **5**. Reagents and conditions: (i) trimethylsilylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, THF, 45 °C, overnight, 94%; (ii) K_2CO_3, MeOH, rt, 1.5 day, 93%; (iii) **1**-N_3, $Cu(CH_3CN)_4PF_6$, 2,6-lutidine, THF, 40 °C, 2 days, 77%.



Scheme 1 Synthesis of G1-dendron **3**. Reagents and conditions: (i) $NaOC(CF_3)_3$, DMF, rt, 18 h, 88%; (ii) trimethylsilylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, THF, 45 °C, 4 h, 89%; (iii) K_2CO_3, MeOH, rt, 1.5 day, >99%; (iv) **1**-N_3, $Cu(CH_3CN)_4PF_6$, 2,6-lutidine, THF, 40 °C, 2 days, 92%.



Scheme 3 Synthesis of conjugate **7**. Reagents and conditions: (i) trimethylsilylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, THF, 45 °C, overnight, 82%; (ii) K_2CO_3, MeOH, rt, 1.5 day, 92%; (iii) *O*-(2-azidoethyl)-*O*′-methylundecaethylene glycol, $Cu(CH_3CN)_4PF_6$, 2,6-lutidine, THF, rt, 2.5 days, 31%.

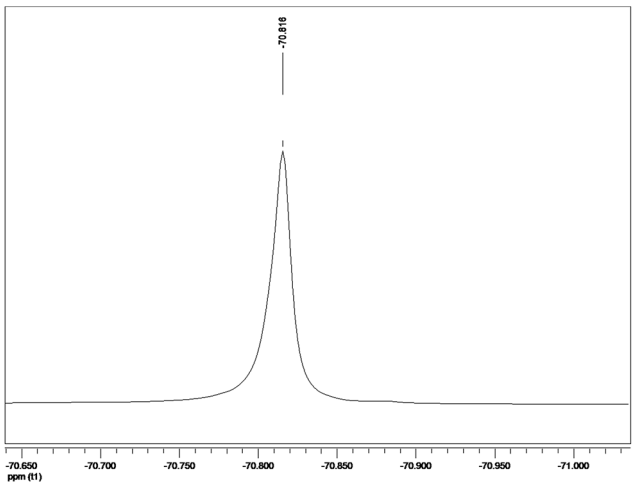


Fig. 2 ^{19}F NMR spectrum (377 MHz) of dendron **7** in $CDCl_3$ (trifluoroacetic acid was used as internal standard).

convert dendron **6**-H into a more hydrophilic form *via* conjugation with an azide-functionalized undecaethylene glycol derivative. This strategy of tethering unpolar molecules to hydrophilic ethylene glycols is commonly used in medicine to improve the water solubility.[23] In addition, poly(ethylene glycol) moieties have also been used to improve the biocompatibility of highly fluorinated hyperbranched polymers.[24] However, conjugate **7** was still too hydrophobic to dissolve in water. But overall this is just a minor drawback as ^{19}F MRI probes can also be applied in emulsified form.[9,11,14]

The ^{19}F NMR spectrum of conjugate **7** expectedly showed a sharp singlet (Fig. 2). At a magnetic flux density of 9.4 T, the resonance signal had a narrow full width at half maximum of 7 Hz. This clearly demonstrates the potential applicability of the synthesized dendron as ^{19}F MRI probe.

In summary, conjugate **7** could overcome most of the challenges that should be met by appropriate ^{19}F MRI probes. It exhibits 72 fluorine atoms and has just one single, sharp resonance in the ^{19}F NMR spectrum. As a result conjugate **7** features a high spin density without the disadvantage of causing chemical shift artefacts. The only remaining challenge would be the lack of water solubility. To address this issue, dendron **6**-H could be conjugated with other more hydrophilic (bio)molecules.[25] Hence, alkyne **6**-H is a versatile precursor for the generation of various ^{19}F MRI agents.

Conclusions

We described a facile and highly efficient procedure for the preparation of C_{2v}-symmetric dendrons that are well suited for ^{19}F MRI. This dendron synthesis is comprised of three steps that are repeated iteratively: Sonogashira coupling, alkyne deprotection and CuAAC for the generation build-up. After 9 steps the second-generation dendron **6**-H was obtained in excellent overall yield. This molecule displays 72 magnetically equivalent fluorine atoms and exhibits a terminal alkyne moiety, which serves as a tether. The latter is an important feature, because it could be used for adjusting the water solubility of a potential ^{19}F MRI probe *via* conjugation with hydrophilic molecules. Since conjugate **7** is still too unpolar to be water-soluble, other hydrophilic compounds will be tested in the near future to create polyfluorinated probes that are even more suitable for ^{19}F MRI.

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