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Designing nanotubes

Changing the dimensions of a nanotube by a change in design.

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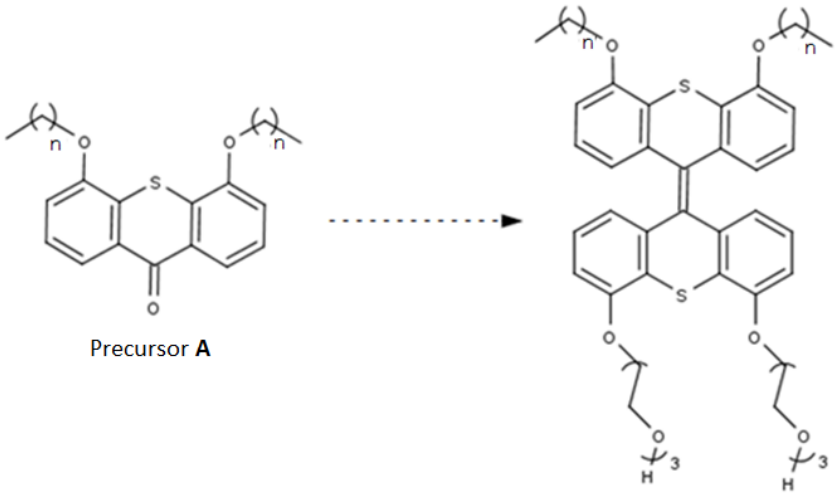
Abstract

Amphiphile molecule **B** (n=11), designed to be a light-induced switch, was found to form self-assembled, stable, uniform nanotubes. In this report an attempt to change the dimensions of the nanotube wall is described. The approach is based on a systematic change in the molecular design of the molecule i.e. on changing the length of the alkyl chains (n in scheme). A hydrophobic precursor **A** (n=17) for a new nanotube amphiphile **B** (n=17) is synthesized, in attempt to control the morphology of the nanotubes.



Precursor **A**

Amphiphile **B**

Introduction

Molecular self-assembly is a scientifically and technologically important field to explore.[1] Self-assembling systems are at the foundation of life and are key to complex systems like a living cell, which makes self-assembling systems so interesting from conceptual point of view. Also from synthetic point of view self-assembling systems are a hot issue, considering the ability we have to synthesize various molecules that self-assemble into a wide range of nanostructures.[1,2] Examples of these structures are micelles, nanotubes, vesicles, rods and bilayers, formed using DNA[3], peptides[4] or synthetic amphiphiles[5]. These nanostructures can be of huge importance for development in electronics, biomedicine and new improved materials.[3] Despite the large number of nanostructures that are created these days, it still remains a great challenge to control the morphology of these nanostructures. Another challenge is to design self-assembling structures that show dynamic behaviour.[1,2]

Recently, an amphiphilic molecule designed to be a light-induced switch was found to have the ability to form self-assembled nanotubes (Figure 1).[6] Special features of these nanotubes are their uniformity, high stability and the unique ability to form end-capped systems using DOPC, which can be assembled and disassembled without affecting the nanotube itself. Most special is the photo activity of the monomers, which allows controlled disassembly of the nanotubes; in other words: this self-assembled system shows dynamic behavior.

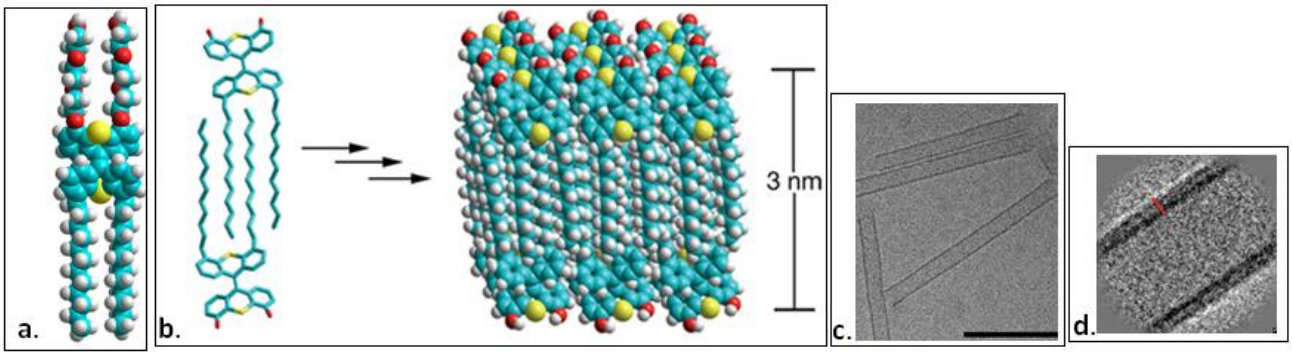


Figure 1. a) Structure of 'original' nanotube amphiphile. b) calculated molecular model of the bilayer structure of the 'original' nanotube amphiphile. C is turquoise; O is red; H is white and S is yellow. Interdigitated alkyl chains suggest an outer S – outer S distance of approximately 3 nm. The oligoethylene glycol chains were omitted. c) Cryo-TEM image of self-assembled nanotubes under aqueous conditions. Scale bar represents 100 nm. d) Cryo-TEM image of self-assembled nanotube, red bar indicates an approximately 3 nm thick wall.[6]

Here we present the synthesis of a new hydrophobic precursor for a new nanotube-forming amphiphile in an attempt to make a controlled change in the dimensions of the nanotube wall. Figure 2 shows the end-capped nanotube with the diameter of the end-cap being larger that the diameter of the nanotube. We found it to be a challenge to try to increase the diameter of the nanotube in an attempt to approach the diameter of the end-cap and so make the end-capped system better fitted. The 'original' nanotube amphiphile contains hydrophobic dodecyl(-$C_{12}H_{25}$) chains (Figure 1a), the 'new' nanotube amphiphile will

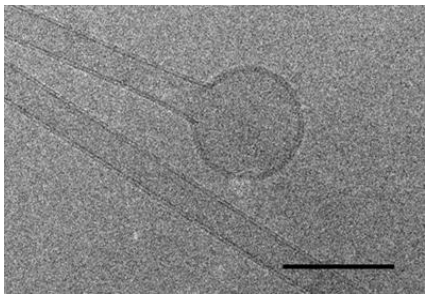
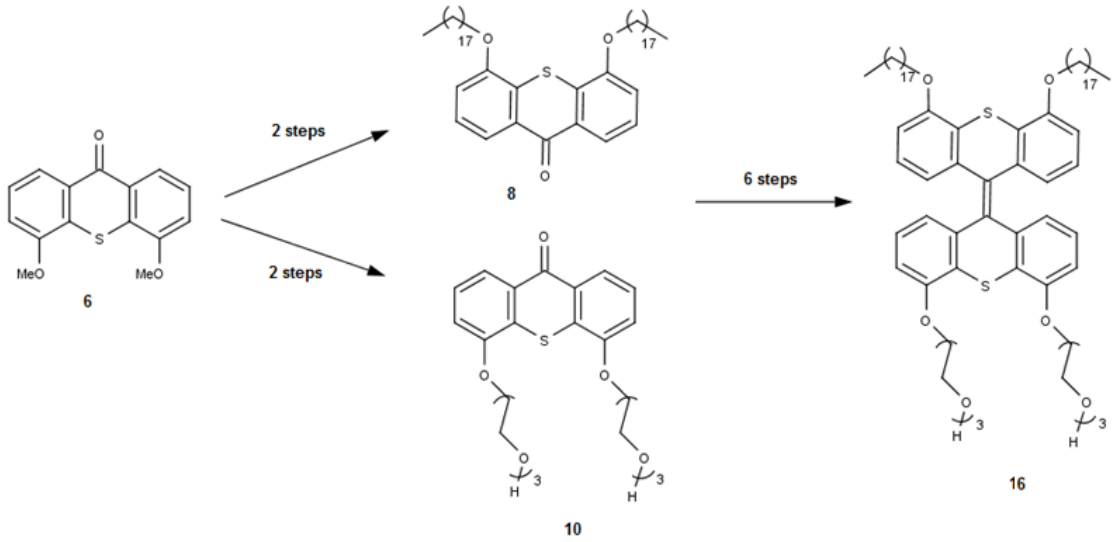


Figure 2. CRYO-TEM image of a DOPC end-capped nanotube. Scale bar represents 100 nm.[7]

contain hydrophobic octadecyl (-$C_{18}H_{37}$) chains (Scheme 1, amphiphile **16**). So far we only had time to synthesize the new hydrophobic precursor **8**, but in this report we also present the future plans, which contains schemes for the complete synthesis of amphiphile **16**.
We also highlight the mechanisms of two interesting reactions used in the synthesis; the Snieckus anionic Friedel-crafts cyclisation reaction and the Barton-Kellogg reaction.

Scheme 1 contains an overview of the synthesis of nanotube amphiphile **16**. Firstly 'key building block' **6** was synthesized, which was used in synthesis for hydrophobic precursor **8**, proceeding in two steps. For future plans, 'key building block' **6** will also be used for synthesis of hydrophilic precursor **10**. After another six steps, coupling precursors **8** and **10**, nanotube amphiphile **16** should be synthesized.

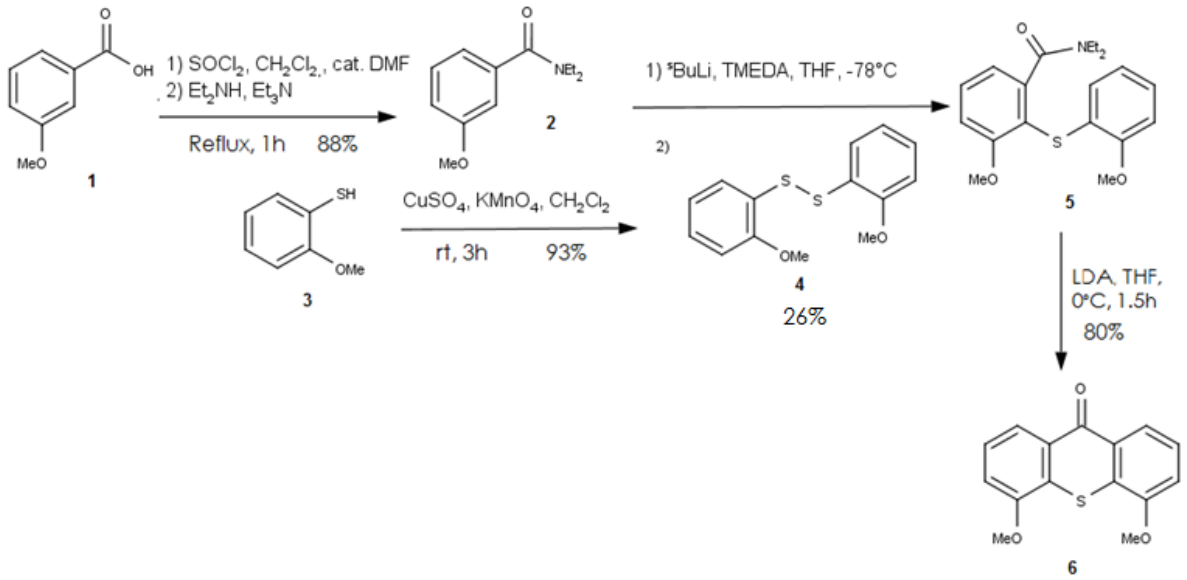


*Scheme 1. General overview of the synthesis of nanotube amphiphile **16**.*

Results and discussion

Synthesis of 'key building block' 6

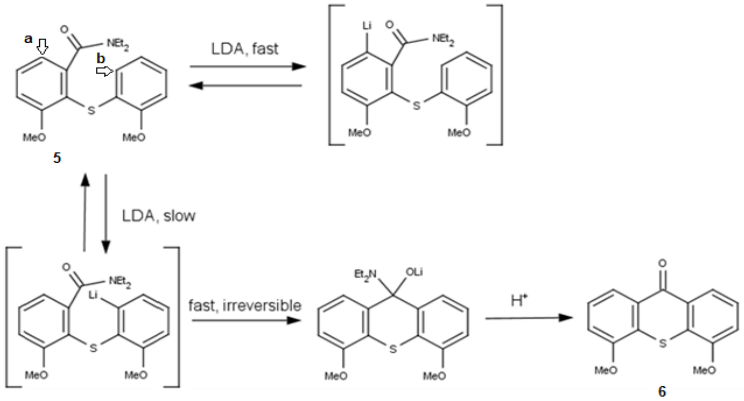
Using a previously published procedure[7], we were able to synthesize 'key building block'**6**. (Scheme 2). In the first step acid **1** was converted into amide **2** via an acyl chloride. The yield of this reaction was 70%, containing 23% starting material. In parallel, disulfide **4** was synthesized via an oxidative dimerization of thiol **3** with 88% yield. The third step contained the ortho-lithiation of amide **2** followed by treatment with disulfide **4**. The first attempt yielded 2.5% (still impure), probably because there was still 3-methoxybenzoic acid present. It was however possible to recover more than 70% of starting material, this time pure, so the reaction could be repeated. The second attempt the reaction yielded thioether **5**, but by use of column chromatography (SiO_2, pentane:EtOAc=95:5; also SiO_2, DCM) purification of the product was not possible, only separation of disulfide **4** from both amide **2** and the product succeeded. Recrystallization (EtOAc) was found to be a good purification method and yielded 1.12 g (3.87 mmol, 26%) of pure thioether **5**. Synthesis was continued and a Snieckus anionic Friedel-crafts cyclisation reaction of thioether **5** using LDA formed 'key building block' **6** in a 80% yield.



*Scheme 2. Synthesis of 'key building block' **6** based on a procedure published by Pollard, M.M. et al* [7]

Snieckus anionic Friedel-crafts cyclisation reaction.[8]

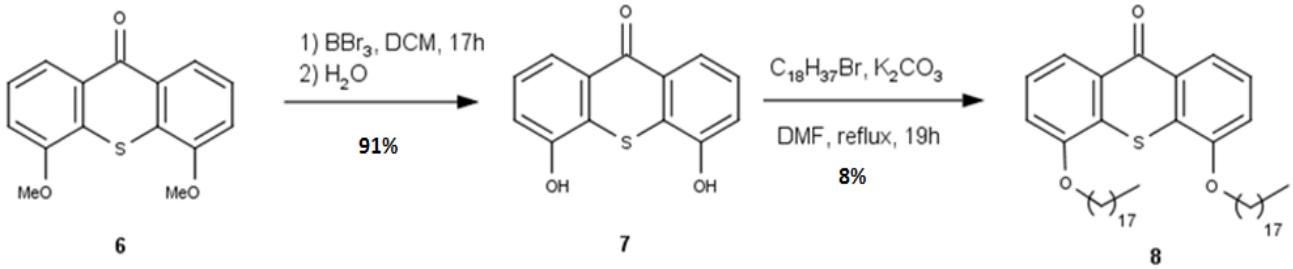
The mechanism of the ring-closing reaction of thioether **5** towards ketone **6** is shown in Scheme 3.[7] The reaction proceeds through an ortho-lithiation; this ortho-lithiation can take place in two places, indicated with **a** and **b.** Position **a** is kinetically favoured, so first the thioether lithiates at this ortho position. However, when there is no electrophile present, this intermediate will not react and equilibrates with the kinetically less favoured intermediate lithiated at position **b**. Since the amide-group is electrophilic and in right position to attack at the **b** lithiated place, a ring-closing reaction occurs. This reaction is irreversible, so the equilibrium will shift towards the **b** lithiated compound. After acidic work-up, ketone **6** is formed.[8]



*Scheme 3. Snieckus anionic Friedel-crafts cyclisation reaction: formation of ketone **6**.*[8]

Synthesis of 4,5-Bis(octadecyloxy)-9H-thioxanthene-9-one (8)

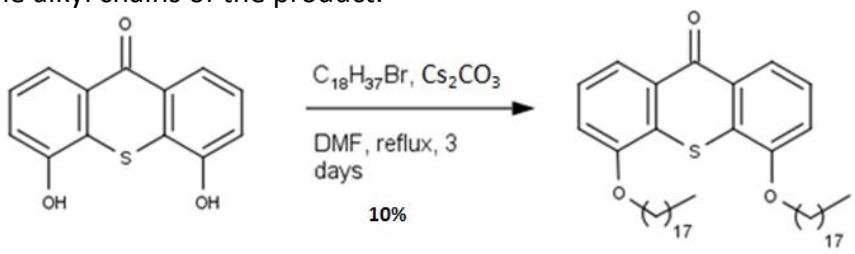
The synthesis of ketone **8** contained a deprotection followed by a Williamson ether synthesis (Scheme 4). The deprotection was performed using boron tribromide in dichloromethane and



*Scheme 4. Synthesis of ketone **8** (method a).*

yielded 91% of diol **7**. A Williamson ether synthesis of diol **7** with stearyl bromide was performed to synthesize ketone **8** (method a) in 8% yield, much lower than expected for a Williamson ether synthesis reaction. The structure and purity of ketone **8** were confirmed by ^{1}H-NMR, ^{13}C-NMR, HRMS and elemental analysis.

In an attempt to increase the yield of ketone **8**, the Williamson ether synthesis was done according to Scheme 5, using Cs_2CO_3 and increasing the reaction time (method b). However, method b did not show significant increase in yield (yield: 10%). Most of the material is lost in the purification which was done using flash column chromatography (SiO_2, EtOAc:pentane, 1:9). Using heptane, octane or even nonane as a solvent in the flash column chromatography might be a solution to this problem, due to stronger interactions of the solvent with the alkyl chains of the product.

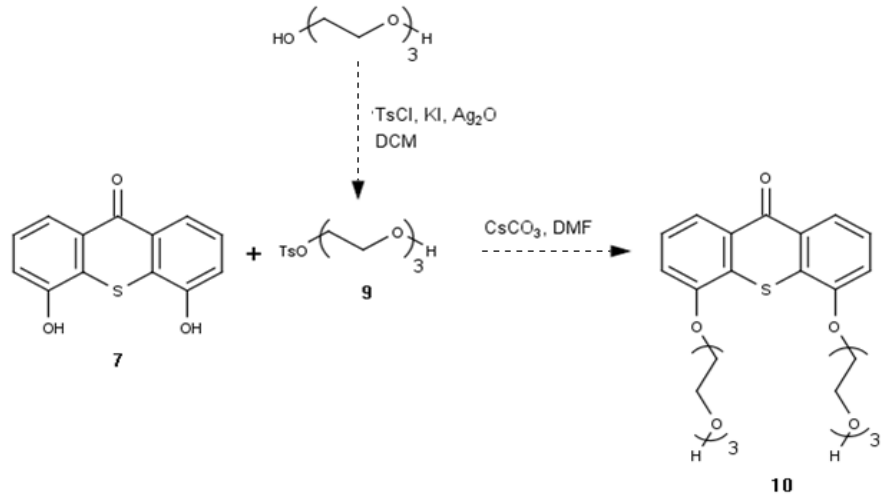


*Scheme 5. Alternative conditions for the synthesis of ketone **8** (method b).*

Future plans

Synthesis of the hydrophilic precursor (10).

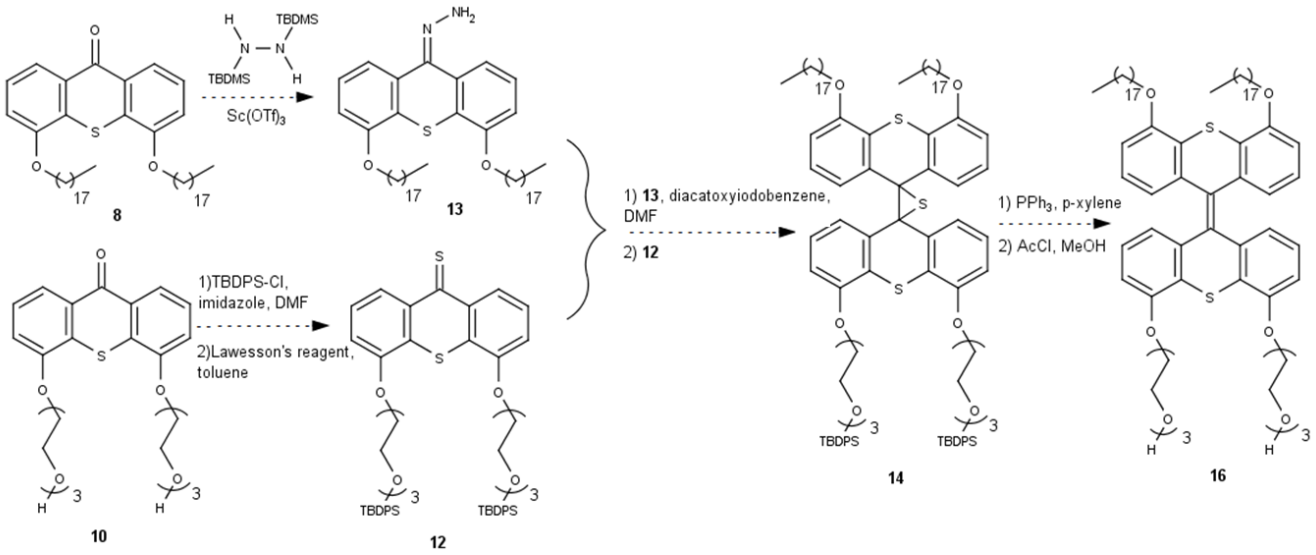
Tolysation of triethylene glycol will form molecule **9**, which is a PEG-derived alkylating agent. Then diol **7** will be PEGylated with this tosyl-triethylene glycol **9** in presence of Cs_2CO_3 to form ketone **10** (Scheme 6).



*Scheme 6. Synthesis of hydrophilic precursor **10**.*

Synthesis of nanotube amphiphile 16

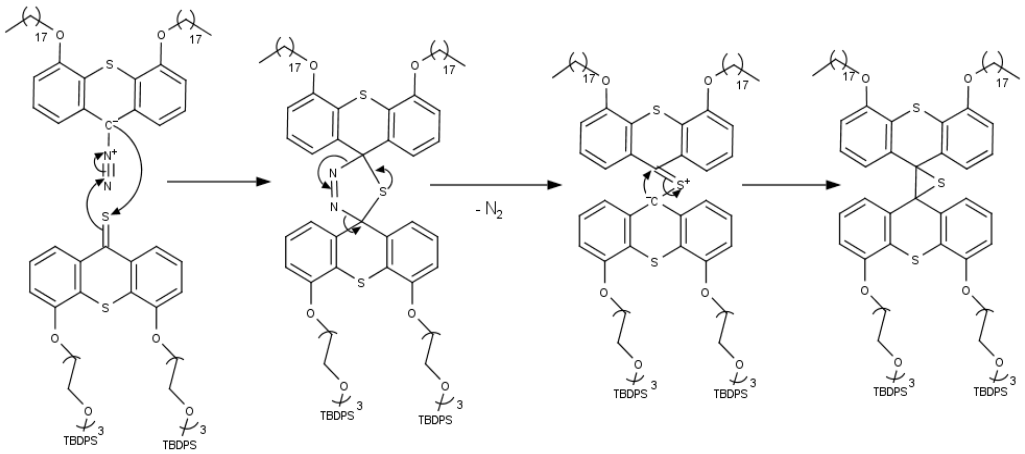
In order to couple precursors **8** and **10**, ketone **8** is transformed into hydrazone **13** and molecule **10** is transformed into thioketone **12** after protecting the alcohol groups (Scheme 7). The hydrazone then is activated, thioketone **12** is added and episulfide **14** should be formed. After a reaction analogous to the Wittig reaction, the alkene should be formed and after deprotection the desired nanotube amphiphile **16** should be synthesized.



*Scheme 7. Synthesis of nanotube amphiphile **16.***

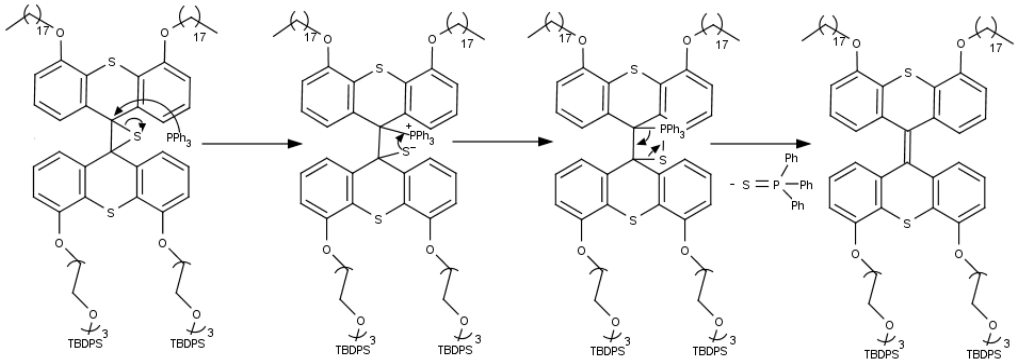
Barton-Kellogg reaction[9]

The reaction in which molecules **13** and **12** react with each other and form nanotube amphiphile **16** is called the Barton-Kellogg reaction. Scheme 8 shows the mechanism towards the formation of the episulfide. The activated hydrazone reacts with the thioketone in a 1,3-dipolar cycloaddition reaction to form a thiadiazoline. The thiadiazoline is an unstable compound what results in formation of the episulfide.[9]



Scheme 8. Barton-Kellogg reaction (I): formation of the episulfide.

In the second part of the Barton-Kellogg reaction (Scheme 9), triphenylphosphine is added to open the three-membered ring of the episulfide. Now a reaction analogous to a Wittig reaction occurs and after release of triphenylphosphinesulfide the alkene is formed.[9]



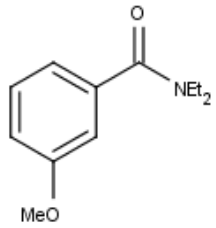
Scheme 9. Barton-Kellogg reaction (II): formation of the alkene.

Conclusions

Recrystallization was found to be a good method to separate amide **2** from thioether **5**. Compared to the purification method used in the previous procedure, recrystallization provides an improved way to obtain thioether **5**, used in synthesis towards key building block **6**. Both synthesis and deprotection of 'key building block' **6** were successful. Improving the yield of ketone **8** is necessary and requires more research, since both method a and b did not give good yields.

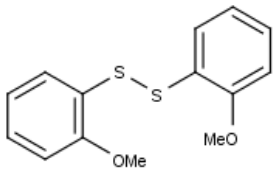
Experimental Section

Preparation of N,N-Diethyl-3-methoxy-benzamide (2)



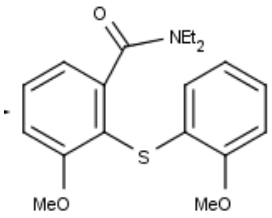
This amide was synthesized using the procedure published by Pollard, M.M. et al.[7] To a solution of 3-methoxybenzoic acid (19.0g, 0.125 mol) in CH_2Cl_2 (100 ml) was added $SOCl_2$ (22 ml, 36 g, 0.3 mol) and a drop of DMF. The mixture was refluxed for 1 h and then cooled in an ice bath to 0°C. Using a dropping funnel, diethylamine (13.6 ml, 9.5 g, 0.130 mol) and triethylamine (18.0 ml, 13.0 g, 0.130 mol) were slowly added. While stirring, the mixture was allowed to warm up to room temperature and was left for 2 h. The mixture was quenched with 300 ml water and 100 ml of CH_2Cl_2 was added. The organic layer was extracted twice with 100 ml aqueous solution of 10% HCl and washed twice with an aqueous solution of 1 N NaOH. After drying over $MgSO_4$ and concentrating *in vacuo* the crude product was obtained as a dark brown oil (22.6 g; NMR showed 23% of starting material present, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$), δ=7.29 (t, 7.8 Hz, 1H), 6.95-6.87 (m, 3H), 3.81 (s, 3H), 3.53 (bs, 2H), 3.26 (bs, 2H), 1.19 (bs, 4H), 1.11 (bs, 2H).

Preparation of Di(2-metoxyphenyl)disulfide (4)



This disulfide was synthesized using the procedure published by Pollard, M.M. et al.[7] To 400 ml CH_2Cl_2 were added $CuSO_4.5H_2O$ (74.9 g, 0.30 mol), $KMnO_4$ (63.3 g, 0.30 mol) and 2-methoxybenzenethiol (32.3 g, 0.115 mol). The reaction mixture was placed on ice and was left to stir for 4 hours. Filtration over celite removed the solids and after flash column chromatography (SiO_2, heptane:ethyl acetate) the product was obtained as a slightly purple solid (30.20 g, 0.108 mol, 88%); ^{1}H NMR (400 MHz, $CDCl_3$), δ= 7.54 (dd, J=7.8, 1.5 Hz, 2H), 7.19 (ddd, J=7.9, 7.7, 1.6 Hz, 2H), 6.91 (ddd, J=7.6, 7.5, 0.9 Hz, 2H), 6.86 (d, J=8.1 Hz, 2H), 3.90 (s, 6H).

Preparation of N,N-Diethyl-3-methoxy-2-(2-methoxy-phenylsulfanyl)-benzamide (5)

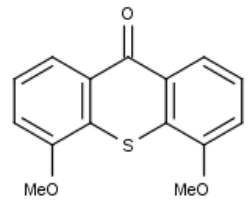


This benzamide was synthesized using a modified procedure published by Pollard, M.M. et al[7]. Where they purified the product using column chromatography (SiO_2, heptane:ethyl acetate=4:1), we found that recrystallization (ethyl acetate) was an easier way of obtaining very pure product.

Dry THF (250 ml) was cooled down to -80°C under N_2-atmosphere, then s-BuLi (12.5 ml, 16.5 mmol) and TMEDA (2.4 ml, 16.5 mmol)

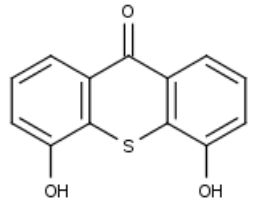
were added. The mixture was stirred for 30 min at -80°C and a solution of amide **2** (3.1 g, 15 mmol) in dry THF (50 ml) was added slowly. After 1.5 h of stirring at -80°C, disulfide **4** (7.6 g, 26.4 mmol) was added and the mixture was left to stir for 16 hours. To the mixture then ether (200 ml) was added and the mixture was washed twice with 200 ml of an aqueous solution of 1 N NaOH and then dried over Na_2SO_4. After concentrating *in vacuo* the product was obtained as a red solid. Column chromatography (SiO_2, pentane:ethyl acetate=19:1) gave the product as slightly yellow crystals, still containing amide. (4.18 g, 0.013 mol). After recrystallization (EtOAc) 1.12 g (3.87 mmol, 26%) of pure thioether **5** was obtained. ^{1}H NMR (200 MHz, $CDCl_3$), δ=7.34 (t, J=8 Hz, 1H), 7.03 (dd, J=10.4, 4.4 Hz, 1H), 6.94 (d, J=7.9 Hz, 2H), 6.79 (d, J=8.0 Hz, 1H), 6.75-6.63 (m, 2H), 3.87 (s, 3H), 3.75 (s, 3H), 3.45-3.25 (m, 2H), 3.20-2.9 (m, 2H), 1.16 (t, 7.1 Hz, 3H), 0.98 (t, 7.1, 3H).

Preparation of 4,5-dimethoxy-9H-thioxanthene-9-one (6)



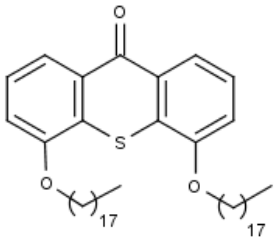
This ketone was synthesized using procedure B published by Pollard, M.M. et al.[7] Under N_2-atmosphere 50 ml dry THF was cooled down to 0°C in an ice bath and LDA (20 mmol, 10 ml, 2M) was slowly added. A solution of thioether **5** (1.12 g, 3.25 mmol) in 50 ml dry THF was also cooled down to 0°C and then dropwise added to the flask containing the LDA. The ice bath was removed and the yellow mixture was left to stir for 1.5 h. An aqueous solution of NH_4Cl (1M, 100ml) was added and after extraction with ether (3X100 ml) the organic layer was dried over Na_2SO_4. The solvents were removed *in vacuo* and after flash column chromatography (SiO_2, pentane:EtOAc=80:20), the product was obtained as yellow crystals (0.719 g, 2.6 mmol, 80%); ^{1}H NMR (201 MHz, $CDCl_3$), δ=8.25 (d, J=8.2 Hz, 2H), 7.(t, J=8.1 H, 2H), 7.14 (d, J=8.3 Hz, 2H), 4.05 (s, 6H).

Preparation of 4,5-Dihydroxy-9H-thioxanthene-9-one (7)



This diol species was synthesized using the procedure published by Pollard, M.M. et al.[7] A solution of diether **6** (1.07 g, 3.92 mmol) in 100 ml dry DCM was cooled down to 0°C under N_2-atmosphere. To the mixture then BBr_3 (18 ml, 18 mmol, 1M) was slowly added and the mixture was left to stir overnight, turned from a yellow solution to a dark red solution. Then the mixture was cooled down again to 0°C and 60 ml water was slowly added. Yellow precipitate formed while doing this. After the mixture was poured into 500 ml EtOAc, it was filtered and washed with EtOAc (100 ml, 5 times). The organic phase was washed with water (300 ml) and brine (300 ml). After washing the organic phase was dried over Na_2SO_4 and the organic solvent was removed *in vacuo* to give a brown solid. After column chromatography (EtOAc:Pentane, 20:80) a yellow solid was afforded (0.613 g, 2.51 mmol, 91% yield). ^{1}H NMR (200 MHz, DMSO-d6), δ=7.29 (d, J=8.1 Hz, 2H), 7.38 (t, J=7.9 Hz, 2H), 7.20 (d, J=6.6 Hz, 2H).

Preparation of 4,5-Bis(octadecyloxy)-9H-thioxanthene-9-one (8)



Method a)To a solution of diol **7** (0.569 g, 2.3 mmol) in 100 ml dry DMF under nitrogen atmosphere was added K_2CO_3 (1.61 g, 11.6 mmol) and after it had dissolved 1-octadecylbromide was added. The mixture was then refluxed for 19 h and then cooled down to rt. After it was poured into 1 L water, it was extracted with 400 ml EtOAc. The

organic phase was then washed with water (200 ml) and brine (200 ml) and then it was dried over Na_2SO_4. After column chromatography (EtOAc:pentane, 10:90) a yellow solid (148 mg, 0.20 mmol, 8%) was afforded.

Method b) A solution of diol **7** (0.613 g, 2.51 mmol) in 100 ml dry DMF under nitrogen atmosphere was prepared. After adding Cs_2CO_3 (4.13 g, 12.7 mmol) and stirring for 10 minutes, stearyl bromide (2.63, 7.9 mmol) was added. The mixture was left to reflux for 3 days. The reaction mixture was then left to cool down to rt and a yellow precipitate formed. The suspension was poured into 400 ml water and more yellow precipitate was formed. After extraction with EtOAc (2X 150 ml, 2X300 ml) the organic layers were combined and washed with brine (300 ml) and dried over Na_2SO_4. After removing the solvents *in vacuo* a brownish oil was obtained. Flash column chromatography (EtOAc:pentane, 10:90) gave a yellow solid (185 mg, 0.25 mmol, 10%). m.p. 80.4-80.8°C ; ^{1}H NMR (400 MHz, $CDCl_3$), δ=8.24 (d, J=7.7 Hz, 2H), 7.41 (t, J=8.0 Hz, 2H), 7.12 (d, J=8.0 Hz, 2H), 4.19 (t, J=6.5 Hz, 4H), 1.99-1.88 (m, 4H), 1.65-1.55 (m, 4H), 1.45-1.20 (m, 46 H), 0.88 (t, J=6.9 Hz, 6H); HRMS (ESI, $[M+H]^+$) m/z: calcd for $C_{49}H_{82}O_3S$: 749.5906, found 749.5873; elemental analysis calcd (%) for $C_{49}H_{80}O_3S$: C, 78.55; H, 10.76; S, 4.28; found: C, 78.48; H, 11.10; S, 3.09.

Also 40 mg of the single-substituted compound was obtained after method a; ^{1}H NMR (400 MHz, $CDCl_3$), δ=8.24 (t, J=7.8 Hz, 2H), 7.41 (q, J=8.0 Hz, 2H), 7.17-7.08 (m, 2H), 4.19 (t, J=6.5, 2H), 1.98-1.8 (m, 2H), 1.61-1.47 (m, 8H), 1.47-1.2 (m, 24H), 0.88 (t, J=6.8 Hz, 3H).

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