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Switchable polymer-grafted mesoporous silica's: from polyesters to polyamides biosilica hybrid materials

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ABSTRACT

We report in this piece of work the synthesis of biosilica hybrid materials able to develop from hydrophobic polyesters to intermediate hydrophilic polyesters and then to polyamides through an O–N acyl transfer shift. After demonstration of the O–N acyl shift on a model depsipeptide anchored in the pores of ordered mesoporous silica (OMS), the preparation of three bio oligomer–silica hybrid materials is described. The oligomerisation of protected serine lactones was initiated in the pores of carboxylate functionalized OMS. Hybrid protected serine polyester–OMS were obtained and could be converted (i) into cationic polyesters, which could be switched (ii) into neutral polyamide–OMS in basic conditions through a multi O–N acyl shift.

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1. Introduction

Silica hybrid based materials obtained by the sol–gel process have attracted considerable attention since a quarter of a century. They constitute a fascinating class of materials combining the properties of organic moieties and inorganic matrices.[1–4] Since the discovery of ordered mesoporous silicas,[5] their surface modification of inner pores with organic functional groups has been extensively investigated to render them suitable for a wide number of applications,[6] such as catalysis,[7] separation,[8] chemical sensors,[9,10] etc. Incorporation of several types of functional organic units into the channels of mesoporous silica has attracted many efforts for the design and organization of multi-functionalized mesoporous materials.[11]

Generally, organic functionalities can be incorporated into mesoporous materials, either by post synthesis[12] (grafting) or by direct synthesis (one-pot) method.[13] It was demonstrated that the direct synthesis method produces hybrid material with high content of organic groups (up to 25% molar) and more homogeneous surface coverage of the silica inner pores.[14] This approach consists in the co-hydrolysis and polymerization of tetraethylorthosilicate (TEOS: silica precursor) with an organotrialkoxysilane $RSi(OR')_3$ in the presence of a surfactant as a structure-directing agent. After elimination of the surfactant, ordered mesoporous silica (OMS) with high porosity, surface area, and tuneable pores of 2–30 nm diameter can be obtained.

Compared to other materials of undefined porosity, such as silica gels, the use of OMS greatly rationalizes the inclusion of organic compounds in a non-covalent or covalent way. Large protein, such as enzymes[15,16] and heme proteins[17] were covalently immobilized on hexagonal[18] and cubic[19] phases of OMS. Recently, hybrid peptide oligomer–silica OMS were prepared by amino acid *N*-carboxyanhydride (NCA)[20] polymerization, initiated by amino groups present in the pores of OMS.[21,22]

On the other hand, serine lactone has already been used to obtain polyesters.[23,24] In a general manner, esters formed on the side chain of serine, are known to easily undergo an O–N acyl shift.[25,26] This reaction is extensively used in the field of peptide science for the synthesis of difficult sequences,[27] cyclic peptides,[28] C-terminal peptide alcohols.[29] More recently, we take profit of this acyl transfer reaction to the synthesis of serine polyester oligomers in solution able to shift to serine polyamide oligomers.[30]

In this paper, we applied the same methodology to the preparation of bioorganic hybrid OMS whose pores contain switchable serine oligomers. Three different hybrid materials can be obtained sequentially (i.e., protected serine polyester, cationic polyester, and

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neutral polyamide silica hybrids) using a multi O–N acyl transfer that takes place within the pores of OMS. Such materials could find potential applications as controllable nanocontainers.

2. Results and discussion

2.1. Model depsipeptide grafted in OMS pores

As a proof of concept, we first studied the O–N acyl shift on a model depsipeptide Boc-Ser(Fmoc-Phe)-Lys-NH_2 **1** grafted on nonfunctionalized OMS. For that purpose, we used the methodology we recently set up[31] consisting in the synthesis of hybrid trialkoxysilyl protected peptides that were directly involved in hydrolysis and condensation on the surface of the OMS pores (Scheme 1, step f). The OMS used here was SBA-15 type, which was obtained by hydrolysis and polycondensation of TEOS in the presence of Pluronic P123 as surfactant.[32] The depsipeptide **1** reacted with trialkoxysilyl propyl isocyanate to yield the hybrid pseudo peptide **2**, which was isolated and characterized (Supplementary data S5–S6). Compound **2** was grafted into the pores of OMS by reaction between alkoxy groups and silanol (SiOH) of the surface. It is worth noting this new type of biomolecule grafting did not require any ligation chemistry between inorganic and bioorganic moieties. Briefly, SBA-15 suspended in a DMF solution containing the hybrid peptide blocks was stirred for 1 h at rt, then 24 h at 80 °C. This two-step procedure allowed the hybrid peptide block to penetrate into the pores. Hybrid material **3** was characterized by X-ray diffraction, elemental analysis, BET, and FTIR. N_2 adsorption–desorption measurements at 77 K showed type IV isotherms with a clear H1-type hysteresis loop at high relative pressure (Supplementary data S1), characteristic of mesoporous materials. XRD patterns exhibited three low-angle reflections, d_{100}, d_{110}, and d_{200}, characteristic of well-ordered SBA-15 type materials (Supplementary data S2). Transmission Electron Microscopy (TEM) provided further evidence of an ordered hexagonal structure (Supplementary data S2). Taken together, these results indicated that properties of OMS were conserved after chemical modification with depsipeptide units. The efficiency of depsipeptide loading of hybrid OMS **3** was determined by elemental analysis (0.11 mmol g^{-1}) (Table 1). Boc protecting groups were removed by neat TFA treatment yielding cationic material **4**. Boc removal and N–O acyl shift were monitored by the Kaiser test. It has to be underlined that the O–N acyl transfer could not take place till the amino group was free. This was achieved by treatment of hybrid silica **3** with 10% Et_3N in DCM. After 12 h, the hybrid silica **5** was obtained.

Table 1
Properties of OMS determined by N2 adsorption and elemental analysis

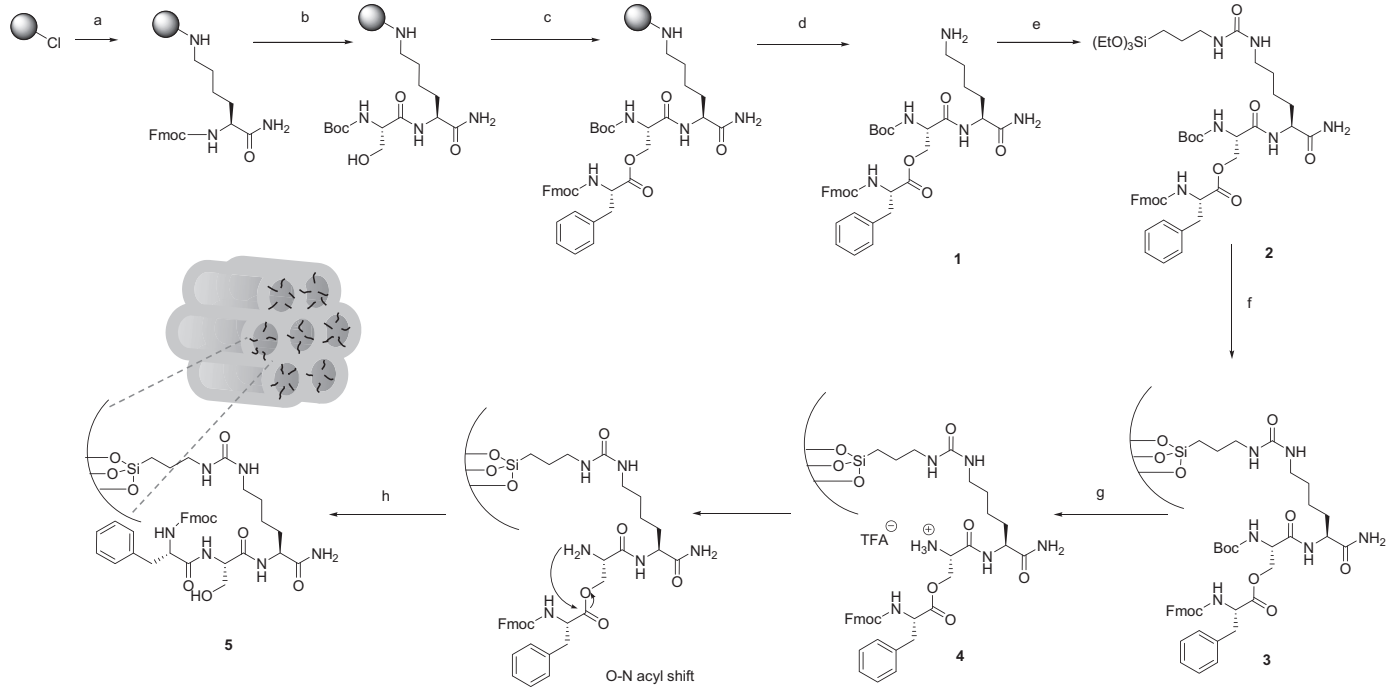
	Area surface[a] (m^2 g^{-1})	Pore volume[a] (cm^3 g^{-1})	%N[b]
SBA	674	1.18	—
3	337	0.63	0.85
4	520	0.91	/
5	457	0.86	/
6	643	1.22	1.02
7	540	0.83	—
9a–b	271–133	0.81–0.35	3.0–4.7
10a–b	389–323	0.89–0.65	/
11a–b	281–157	0.74–0.44	/

[a] Calculated by BET.
[b] Calculated by elemental analyses.

2.2. Hybrid biopolymer–silica material

The next step of the study was the use of the O–N acyl shift for the synthesis of a hybrid biopolymer–silica material. To obtain the starting polyester–silica hybrid material, we set up the polymerization of protected serine lactone. This ring opening polymerization (ROP)[33] could be initiated by the carboxylate salt prepared from cyano OMS **6**. Thus, a mesoporous material functionalized with CN groups with controlled loading (0.7 mmol g^{-1}) was prepared in one-pot by hydrolysis and co-condensation of tetraethylorthosilicate (TEOS) with the desired amount of cyanopropyltriethoxysilane in the presence of P123 as surfactant under acidic conditions. The obtained OMS **6** was well organized in a 2D-hexagonal structure as shown by the XRD pattern diffraction (Supplementary data S3).

Carboxylic functionalized mesoporous silicas (0.7 mmol g^{-1} loading) were prepared by oxidation of the nitrile **6** OMS following



Scheme 1. Synthesis of a hybrid trialkoxysylyl depsipeptide and preparation of switchable hybrid peptide-OMS. (a) Fmoc-Lys-NH_2, DIEA; (b) Fmoc deprotection: DMF/pip; coupling: Boc-Ser-OH, BOP, DIEA; (c) esterification: Fmoc-Phe-OH, DIC/DMAP; (d) TFE/DCM 3/7 v/v; (e) $Et_3OSi(CH_2)_3NCO$, DMF; (f) grafting on SBA-15 OMS in DMF; (g) Boc removal, TFA; (h) 10% Et_3N in DCM for 24 h, O–N acyl shift.

the method already described.[34] Carboxylate potassium salt was prepared by treatment of the carboxylic acid OMS **7** with potassium pentadionate in anhydrous ethanol. OMS **7** was characterized by ^{13}C CP-MAS NMR, porosimetry measurements, and elemental analysis. The spectrum revealed three signal resonances at 13.5, 18.6, and 37.0 ppm attributed to the propyl chain and an additional signal at 180.4 ppm for the carbonyl (Supplementary data S4).

N_2 adsorption–desorption measurements of OMS **7** (Supplementary data S1) showed an isotherm type IV with H_1-type hysteresis loop at relative high pressure, characteristic of a mesoporous material with large pores and regular pore size distribution with high surface area (540 $m^2\ g^{-1}$) and pore volume (0.83 cc g^{-1}).

Carboxylate functionalized OMS reacted overnight with different concentrations of Boc serine lactone (0.1 and 0.2 M, corresponding to 5 or 10 equiv) in dry dichloromethane solution (Table 2). Resulting samples of hybrid mesoporous silicas **9** were filtered and thoroughly washed with DCM and DMF. Aliquots were dried, weighted, and analyzed by various methods. Firstly, transmission FTIR was used to check the appearance of the characteristic carbonyl vibration band at 1720 cm^{-1}. As described before, Boc protecting groups were removed from hybrid material **9** by neat TFA treatment to yield cationic polyester **10**. After treatment of polyester **10** by DCM/Et_3N (9/1 v/v), two characteristic carbonyl vibration bands at 1658 and 1549 cm^{-1} appeared indicating formation of peptide bonds on the silica due to the multi O–N acyl transfer, yielding polyamide **11** (Scheme 2). As expected, in hybrid materials **6**–**11** a strong silyl ether band at 1061 cm^{-1} was observed. It is worth noting that Kaiser test did not reveal the presence of free amino groups (Fig. 1).

Table 2
Hybrid polyesters OMS **9** prepared from Boc-serine lactone

Exp.	OMS loading (mmol of free COOK/g)	Equiv of lactone	[Lactone]	Exp. average oligomer length[a]
a	0.7	5	0.1	~4.1
b	0.7	10	0.2	~8.1

[a] Determined by weight increase/elemental analysis.

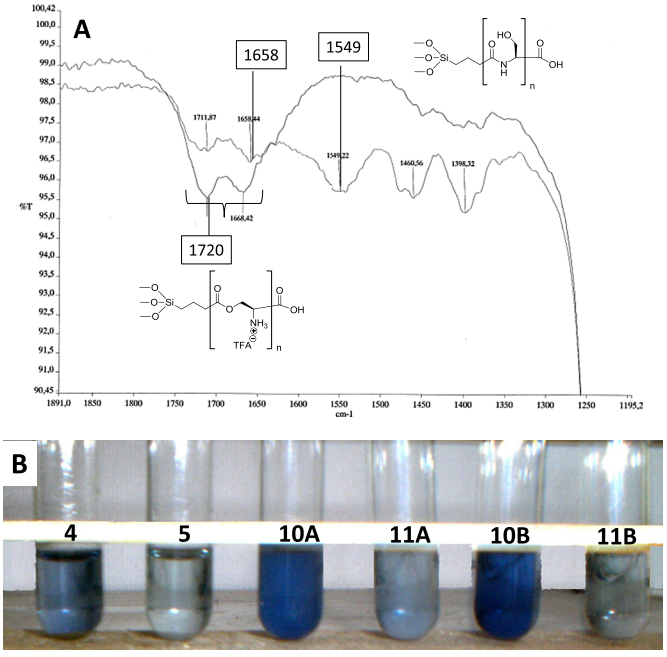
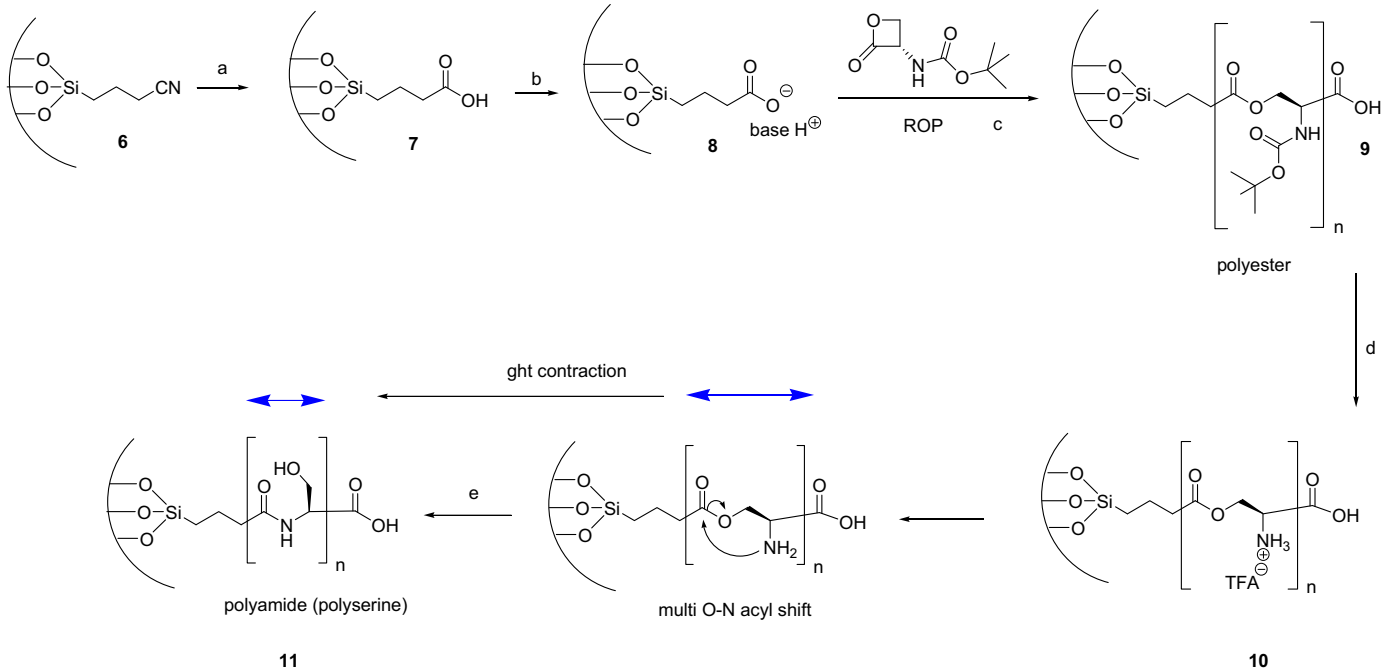


Fig. 1. (A) FT-IR, (B) Kaiser test for OMS, before and after O–N acyl shift.

The nitrogen adsorption–desorption isotherm of functionalized material **9** after lactone oligomerisation is shown in the Supplementary data section (SD Fig. S1). It showed a very similar isotherm to that of the starting material with 271 and 133 $m^2\ g^{-1}$ of surface area, 0.81 and 0.35 cc g^{-1} of pore volume, respectively for OMS **9a** (n=4) and **9b** (n=8). This surface area and pore volume diminution demonstrated that oligomers developed within the pores of mesoporous materials. In addition, elemental analysis of nitrogen contents (Table 1) for OMS **9** clearly showed an increase of oligomer size from 4 (**9a**) to 8 units (**9b**). After TFA treatment, an increase of both the surface area and the pore volume, 389 and 323 $m^2\ g^{-1}$, and



Scheme 2. Synthesis of switchable hybrid polymer-OMS. (a) Hydrolysis of CN into COOH by H_2SO_4 (50%), 100 °C; (b) Potassium pentadionate; (c) Polymerization initiated by complexed carboxylate salts; (d) Boc removal by TFA; (e) 10% Et_3N in DCM, 24 h, O–N acyl shift.

0.89 and 0.65 cc g^{-1} was observed, respectively for OMS **10a** and **10b**, indicating the removal of Boc protecting groups, confirmed by a positive Kaiser test.[35] After treatment of cationic polyester **10** by DCM/Et_3N (9/1 v/v), a decrease of specific area and pore volume (281 and 157 m^2 g^{-1}; 0.74 and 0.44 cc g^{-1}) was observed despite chain length contraction, due to the increase of volume oligomer and decrease of hydrophilicity, a negative Kaiser test confirming the disappearance of free amino groups.

In conclusion, we showed that OMS hybrid materials of SBA-15 type, functionalized with COOH groups could be used as nanoreactors for controlled Ring Opening oligopolymerization of lactone units. The obtained switchable oligomers confined in the pores were fully accessible and the polyester to polyamide transformation was quantitative. These tailored oligomers could be used as switchable nanovalves in multifunctionalized nanobiomaterials for drug delivery control for instance.

3. Experimental section

3.1. Synthesis of depsipeptide 1

Fmoc-Lys-NH_2 (4 equiv) was anchored on a trityl chloride resin using DIEA (8 equiv) and anhydrous DMF. The reaction mixture was stirred at room temperature for 2 h, and then washed with DMF/MeOH/DIEA (17/2/1) (3×), DCM (3×), MeOH (1×), DCM (1×). Quantitative Fmoc tests were performed as spot checks. The Nα-Fmoc deprotection step was performed by treatment with a solution of piperidine (20% v/v in DMF) for 20 min.

Boc-Ser-OH elongation was performed using the Fmoc/^{t}Bu strategy using BOP as coupling reagent. The coupling step was carried out on the resin using Boc-Ser-OH (3 equiv) in DMF in the presence of BOP (3 equiv) and DIEA (6 equiv) for 2 h at room temperature. After the coupling step, the resin was washed with DMF (3×), DCM (3×), MeOH (1×), and DCM (1×).

DIC (3 equiv) and DMAP (0.3 equiv) were added to a solution of Fmoc-Phe-OH (6 equiv relative to the resin substitution) in a mixture of anhydrous DCM and DMF (50/50) at 0 °C (3 mL $mmol^{-1}$). The resulting mixture was stirred with the previously functionalized resin for 6 h at room temperature. This procedure was repeated twice, and resin was washed with DMF (3×), DCM (3×), MeOH (1×), and DCM (1×).

Solid-supported depsipeptides were cleaved by stirring the resin with a TFE/AcOH/DCM (2/1/7 v/v/v) solution for 1 h. After filtration, the resin was submitted to a second cleavage step for an additional 1 h and filtered. The combined filtrates were concentrated under reduced pressure. The depsipeptide **1** was precipitated with diethylether, filtered, and dried under high vacuum. Crude compounds were analyzed by analytical HPLC and LC/MS and used without further purification. LC/MS *m*/*z* 702.3 $[M+H]^+$; HPLC tr, 1.55 min. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{48}O_8N_5$ $[M+H]^+$ 702.3503, found 702.3497.

3.2. Synthesis of hybrid of triethoxysilyl depsipeptide 2

To a solution of depsipeptide (**1**) (0.1 mmol) in 100 μL of DMF was added DIEA (2.1 equiv) and 3-isocyanatopropyltriethoxysilane (1.2 equiv). The reaction mixture was stirred for 2 h at room temperature. Reaction was monitored by HPLC. Ether (30 mL) was poured into the reaction mixture. The precipitate was suspended in ether and collected by filtration. This procedure was repeated three times to remove TICPS and DIEA. All crude compounds were analyzed by analytical HPLC, LC/MS, and NMR and used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): 0.47 (m, 2H), 1.14 (t, 9H, *J*=7.2 Hz), 1.23 (m, 2H), 1.37 (m, 6H), 2.88–2.97 (m, 6H), 3.69–3.76 (q, 6H, *J*=7.2 Hz, *J*=14), 4.06–4.40 (m, 8H), 5.68–5.78 (m, 2H), 7.06 (s, 2H), 7.10 (s, 2H), 7.15–7.64 (m, 13H), 7.88 (br s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 173.7, 171.9, 168.9, 158.5, 156.4, 155.8, 144.1, 141.1, 138.0, 129.5, 128.7, 128.1, 127.5, 126.9, 125.7, 120.6, 79.2, 66.2, 64.9, 58.1, 55.9, 53.9, 52.7, 46.9, 42.5, 36.8, 32.5, 30.3, 28.6, 24.0, 22.9, 18.7, 7.7. ^{29}Si NMR (75 MHz, DMSO-d_6): −45.1. LC/MS *m*/*z* 949.4 $[M+H]^+$; HPLC tr, 2.04 min; *m*/*z* 847.3 Siliconium ions [depsipeptide-Si$(OH)_2]^+$; HPLC rt, 1.64 min. HRMS (ESI) *m*/*z* calcd for $C_{42}H_{55}O_{11}N_6Si$ $[M]^+$ 847.3698, found 847.3704.

3.3. Preparation of hybrid depsipeptide–OMS by grafting 3

To a solution of SBA-15 (500 mg) in 20 mL of dry DMF was added hybrid depsipeptide block **2** (50 mg). The reaction mixture was stirred for 1 h at room temperature and 24 h at 80 °C. The functionalized SBA-15 (SBA-Pep) was filtered off and washed with DMF (3×10 mL), 1DCM (3×10 mL), diethylether (3×10 mL), and dried in vacuo.

The deprotection step was realized by treatment of the hybrid silica with 5 mL TFA/DCM (2/1 v/v) for 1 h. The functionalized deprotected SBA-15 (SBA-Pep) was filtered off and washed with DMF (3×10 mL), DCM (3×10 mL), diethylether (3×10 mL), and dried in vacuo.

3.4. Synthesis of carboxylic functionalized mesoporous silica 7 at 0.7 mmol g^{-1}

4.0 g of triblock copolymer $[EO_{20}PO_{70}EO_{20}$ with PEO [poly(-ethylene oxide)] and PPO [poly(propylene oxide)], and Pluronic P123 as surfactant were dissolved in an aqueous HCl solution (160 mL, pH=1.5). This solution was poured into a mixture of TEOS (8.86 g, 42.6 mmol) and 0.5 g (2.2 mmol) of cyanopropyltriethoxysilane at room temperature. The mixture was stirred for 2 h giving rise to a microemulsion. After heating this perfectly transparent solution at 60 °C, a small amount of NaF (80 mg) was added under stirring to induce polycondensation. The mixture was left at 60 °C under stirring for 48 h. The resulting solid was filtered and washed with ethanol and ether. The surfactant was removed by hot ethanol extraction in a Soxhlet apparatus for 24 h. After filtration and drying at 60 °C in vacuo, 3.10 g (95%) of the nitrile functionalized OMS **6** were obtained as a white solid. 500 mg of nitrile functionalized OMS was converted into carboxylic acid OMS **7** by treatment with 5 mL of H_2O/H_2SO_4 solution (1/1 v/v), stirred at 150 °C for 5 h, filtered, and washed with water and acetone, and dried in vacuo.

3.5. Preparation of serine lactone

To a stirred solution of dried Ph_3P (4.9 mmol) in 100 mL of anhydrous THF at −80 °C was added DEAD (4.9 mmol) dropwise over 10 min. After 15 min, a solution of Boc-L-Serine (4.88 mmol) in THF was added dropwise over 15 min to the stirred solution at −80 °C. The solution was stirred at −80 °C for 20 min and overnight at room temperature. Solvent was removed in vacuo, and the resulting product was purified by chromatography on silica gel using EtOAc/Hexane (30/70 v/v) as eluent.

3.6. Lactone oligomerisation (exp 1, 2)

500 mg of carboxylic acid mesoporous silica **7** was poured into a solution of potassium pentadionate (1.2 equiv) in 5 mL of anhydrous ethanol. The suspension was refluxed for 24 h, filtered, washed with ethanol, and dried to give the respective potassium carboxylate salt. 200 mg of this material were poured into a solution of dibenzo-18-crown-6 ether in dichloromethane placed in a 12 mL plastic syringe equipped with frit. A solution of serine lactone was added to the syringe, placed overnight under gentle stirring. Syringe was percolated and functionalized OMS was

washed with DCM (3×10 mL), DMF (3×10 mL), diethylether (3×10 mL), and dried in vacuo.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.090.

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