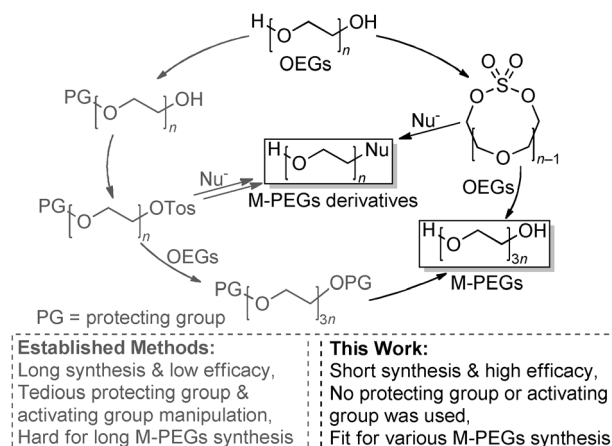


Highly Efficient Synthesis of Monodisperse Poly(ethylene glycols) and Derivatives through Macrocyclization of Oligo(ethylene glycols)**

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Abstract: A macrocyclic sulfate (MCS)-based approach to monodisperse poly(ethylene glycols) (M-PEGs) and their monofunctionalized derivatives has been developed. Macrocyclization of oligo(ethylene glycols) (OEGs) provides MCS (up to a 62-membered macrocycle) as versatile precursors for a range of monofunctionalized M-PEGs. Through iterative nucleophilic ring-opening reactions of MCS without performing group protection and activation, a series of M-PEGs, including the unprecedented 64-mer (2850 Da), can be readily prepared. Synthetic simplicity coupled with versatility of this new strategy may pave the way for broader applications of M-PEGs.

PEGs are biocompatible polymers with diverse applications. Regular PEGs even with an excellent polydispersity index (PDI) are still complex mixtures of different length oligomers^[1] (Figure 3, PEG1500), which brings a range of problems in their applications.^[2] Therefore, M-PEGs are much more desirable than regular PEGs.^[3] However, efficient synthesis of M-PEGs remains a long-standing challenge even after decades of efforts^[1,4] owing to the following issues (Scheme 1, chain tripling method was illustrated as an example): 1) Long synthesis, low yield, and tedious purification dramatically deteriorate the synthetic efficacy. 2) No synthesis on M-PEGs above 2500 Da has ever been reported. The longest M-PEGs reported so far is a 56-mer (2484 Da) which was recently synthesized by Livingston's group.^[4j] It is noteworthy that 4000 Da is regarded as a minimum requirement for PEGs to achieve the so-called stealth effect in biopharmaceuticals.^[5] 3) PEG monofunctionalization is a difficult task because it requires large excess amount of PEGs (up to 10 equiv), expensive reagents, and tedious manipulation of protecting and activating group(s).^[4g,6] Therefore, new synthetic strategies to address these issues are of great importance.



Scheme 1. Strategies for M-PEGs and synthesis of derivatives.

Transforming 1,2- or 1,3-diols into the corresponding cyclic sulfates, where the sulfate group acts as both a protecting group and an activating group during nucleophilic ring-opening reaction, has been widely used in the monofunctionalization of these diols.^[7,8] We envisioned that this strategy could be applied in the synthesis of M-PEGs and derivatives to improve the synthetic efficacy by avoiding hydroxy group protection and activation as well as undesired difunctionalization (Scheme 1).

To our knowledge, there is no report on MCS, but three reports of formation of macrocyclic sulfites (17-membered and below).^[9] After unsuccessful attempts on the macrocyclization of commercially available tetra(ethylene glycol) **1a** through transesterification^[10] with diisopropyl sulfite, macrocyclization of **1a** with SOCl_2 in the presence of Et_3N was carried out (Supporting Information, Table S1). Fortunately, the 14-membered macrocyclic sulfite **3a** was obtained in a 51% yield (Table S1, entry 1). It was found that excess amount of reagents is required to promote the reaction (Table S1, entries 2–5). Elevated temperature and high concentration of **1a** both lowered the yield of **3a** (Table S1, entries 4, 6, 7) while the latter is a common phenomenon in macrocyclization. It was also found that slow addition of SOCl_2 over 1 hour and stirring at 0°C for an additional hour provided a high yield of **3a** (Table S1, entries 8–10). Monitoring the reaction with ^1H NMR indicated that slow addition of SOCl_2 is crucial for the macrocyclization process (Supporting Information, Figure S1). As for the base, DIPEA, DMAP or their combination gave much better yields of **3a** than K_2CO_3 or pyridine (Table S1, entries 11–14). Solvent screening

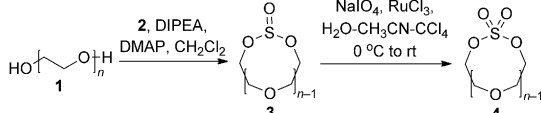
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[**] The research was financially supported by the National Natural Science Foundation of China (No. 21372181). We thank Dr. Yihua Bruce Yu, Dr. Wei Zhang, Dr. Xingang Zhang, and Dr. Xiuhua Xu for their help with the manuscript preparation.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201410309>.

Table 1: Macrocyclization of oligo(ethylene glycols).^[a]



Entry	1	n	Conc. [mol L ⁻¹]	T [°C]	t ^[b] [h]	Yield [%] 3	Yield [%] 4
1	1a	4	0.041	0	1	84(3a)	87(4a)
2	1b	2	0.041	0	1	76(3b)	96(4b)
3	1c	3	0.041	0	1	71(3c)	98(4c)
4	1d	5	0.041	0	1	81(3d)	86(4d)
5	1e	6	0.041	0	1	79(3e)	94(4e)
6	1f	7	0.041	10	1	72(3f)	96(4f)
7	1g	8	0.021	10	1	82 ^[c] (3g)	75(4g)
8	1h	9	0.021	10	12	71(3h)	89(4h)
9	1i	10	0.021	10	12	57(3i)	84(4i)
10	1j	12	0.005	10	72	63 ^[d] (3j)	83(4j)
11	1k	16	0.005	10	40	51(3k)	69(4k)
12	1l	20	0.003	25	24	49(3l)	62(4l)

[a] Reactions were performed on 1–5 g scales. [b] Reaction time after dropwise addition of SOCl₂. [c] A yield of 53% was obtained at 0.041 mol L⁻¹ of **1g**. [d] A yield of 59% was obtained at 0.010 mol L⁻¹ of **1j**.

indicated that CH₂Cl₂ is the solvent of choice (Table S1, entries 15–18).

Under the optimal macrocyclization conditions (Table S1, entry 14), the scope of this reaction on OEGs was then investigated (Table 1). Reactions with commercially available di(ethylene glycol) **1b** and tri(ethylene glycol) **1c** gave the corresponding medium-sized cyclic sulfites **3b** and **3c** in good yields (Table 1, entries 2,3). Macrocyclization of OEGs **1d–1l**, which were synthesized from **1a–1c** and their MCS **4a–4c** (see Supporting Information), also provided the corresponding macrocyclic sulfites **3d–3l** with good yields (Table 1, entries 4–12). Increased reaction time and/or elevated reaction temperature for OEGs above 7-mer are necessary to drive the reaction to completion (Table 1, entries 6–12). To avoid the formation of polymers and catenane-like side products, the reaction was further diluted which resulted in improved macrocyclization yields (Table 1, entries 7–12). It is noteworthy that the macrocyclization concentrations are much higher than conventional concentrations for similar-sized lactonization (usually < 0.001 mol L⁻¹), which facilitates large-scale preparation of MCS. It is interesting to point out that a 62-membered macrocyclic sulfite **3l** was obtained with a 49% yield (Table 1, entry 12 and Figure 1). From a synthetic chemistry point of view, formation of macrocycles such as **3l** in high yield without template is very rare. Oxidation of the macrocyclic sulfites **3a–3l** with ruthenium tetroxide gener-

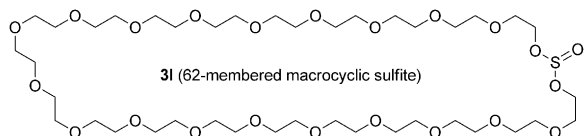
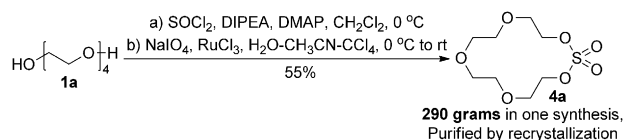


Figure 1. Structure of macrocyclic sulfite **3l**.

ated in situ afforded the corresponding MCS **4a–4l** in good to excellent yields. It was also found that direct oxidation of the crude macrocyclic sulfite **3a** without chromatographic purification conveniently provided MCS **4a** with comparable yields.

It is noteworthy that these macrocyclic sulfites are prone to decompose, but corresponding MCS are much more stable. For example, no change was detected by ¹H NMR after MCS **4a** had been placed in open air at room temperature for 2 months. For the convenience of downstream M-PEG synthesis, 290 g of MCS **4a** were prepared in a 55% yield (Scheme 2). It is notable that **4a** was conveniently purified by



Scheme 2. Large-scale preparation of macrocyclic sulfate **4a**.

recrystallization instead of flash chromatography, and CH₂Cl₂ was recovered during large-scale preparation.

The structures of MCS were confirmed by NMR and MS (see the Supporting Information). Furthermore, a single crystal of the 26-membered MCS **4g** was obtained.^[13] X-ray structure indicates that **4g** adopts a twisted conformation like a partially folded Arabic number 8 (Figure 2). It is interesting

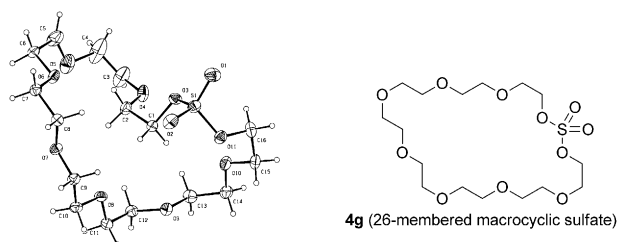
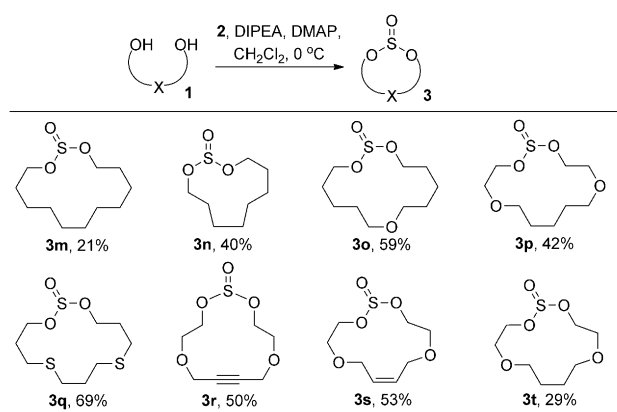


Figure 2. Single-crystal X-ray structure of macrocyclic sulfate **4g**.^[13]

to observe that the bond length and bond angle between the wrapped part and the exposed part are very different (Figure 2 and Supporting Information). Such structural feature indicates that the exposed part of the sulfate is less sterically hindered and would be more reactive toward nucleophiles.

Successful macrocyclization of OEGs encouraged us to expand the reaction scope to non-OEG diols. Results shown in Scheme 3 indicate that non-OEG diols can form macrocyclized products in decent yields under the same conditions for OEGs. Interestingly, it was found that incorporation of heteroatom(s) into diols could dramatically improve the yield of macrocyclic sulfites. For example, macrocyclic sulfite **3m** was obtained in a poor yield, but equally sized macrocyclic sulfites **3a**, **3o**, **3p**, and **3q**, each with O or S in the backbone, were obtained with good yields. Among them, OEG-derived **3a** (Table 1, entry 1) gave the highest yield. The conformation changes resulted from the heteroatom(s) may account for the



Scheme 3. Macrocyclization of non-OEG diols.

improved yields. It was also found that formation of 11-membered macrocyclic sulfite **3n** is much easier than 14-membered **3m** and 13-membered **3t**. Introducing double or triple bond may facilitate the macrocyclization as well (**3r–3s**). Our results indicate that OEGs are actually ideal substrates for this macrocyclization.

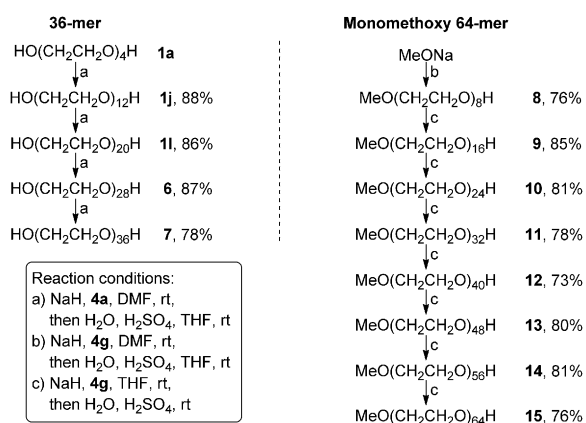
Monofunctionalization of OEGs through one-pot nucleophilic ring-opening reaction of MCS was then explored (Table 2). Readily available **4a** was used for the treatment with a range of O-, S-, C-, N- and F-containing nucleophiles and a variety of monofunctionalized tetra(ethylene glycols) **5a–5s** were conveniently prepared. From O-containing nucleophiles, including alcohols, phenols, and sodium carboxylates, many useful ether and ester derivatives of tetra(ethylene glycols) **5a–5m** were obtained in good yields (Table 2, entries 1–13). Monobenzylated tetra(ethylene glycol) **5a** and octa(ethylene glycol) **5b**, which were widely used in M-PEG synthesis,^[41] were obtained through sequential reactions of benzyl alcohol with **4a**. Two useful surfactants **5c** and **5d** in material sciences were conveniently prepared in one step.^[11] A clickable OEG **5e** was also prepared in a 94% yield. MeONa is also a good nucleophile for this reaction to afford methoxy-OEG **5f**. Even KO^tBu, which is a preferred base in M-PEG synthesis,^[44f] is able to nucleophilic attack **4a** to give *tert*-butyl-OEG **5g** as a result of the high reactivity of MCS. It is notable that *tert*-butyl-OEGs such as **5g** are important building blocks that are very difficult to prepare through other means.^[44] A precursor of ¹⁹F magnetic resonance imaging agents **5h** was also conveniently prepared in a quantitative yield.^[12] 7-Hydroxy-4-methylcoumarin, which is a bioactive probe with good fluorescence properties, reacted with **4a** to afford a fluorescent OEG **5k**. Besides OEG ethers, OEG esters **5l** and **5m** were obtained with quantitative yields. From S-containing nucleophiles, such as potassium thioacetate and triphenylmethanethiol, sulfur can be efficiently introduced into OEGs (Table 2, entries 14, 15). The reaction with potassium thioacetate was carried out in water and **4a** was consumed in several minutes. The result indicates that MCS may be promising aqueous PEGylation agents for cysteine-containing peptides and proteins. With C-containing nucleophile diethyl malonate, a carbon–carbon single bond was constructed in **5p** (Table 2, entry 16). When

Table 2: Nucleophilic ring-opening of macrocyclic sulfate **4a**.^[a]

Entry	NuH/Base	Product	5, Yield
1	BnOH/NaH	BnO(CH ₂) ₄ H	5a , 93%
2	BnO(CH ₂) ₄ H/NaH	BnO(CH ₂) ₈ H	5b , 88%
3	ⁿ C ₈ F ₁₇ (CH ₂) ₃ OH/NaH	ⁿ C ₈ F ₁₇ (CH ₂) ₃ O(CH ₂) ₄ H	5c , 76%
4	ⁿ C ₈ H ₁₇ OH/NaH	ⁿ C ₈ H ₁₇ O(CH ₂) ₄ H	5d , 80%
5	≡C–OH/NaH	≡C–O(CH ₂) ₄ H	5e , 94%
6 ^[b]	MeONa	MeO(CH ₂) ₄ H	5f , 70%
7	KO ^t Bu	^t BuO(CH ₂) ₄ H	5g , 48%
8	$\text{F}_3\text{C}-\text{C}(\text{CF}_3)_2-\text{ONa}$	$\text{F}_3\text{C}-\text{C}(\text{CF}_3)_2-\text{O}(\text{CH}_2)_4\text{H}$	5h , 99%
9	$\text{C}_6\text{H}_4\text{OH}/\text{NaH}$	$\text{C}_6\text{H}_4\text{O}(\text{CH}_2)_4\text{H}$	5i , 92%
10	$\text{MeO}_2\text{C}-\text{C}_6\text{H}_4\text{OH}/\text{NaH}$	$\text{MeO}_2\text{C}-\text{C}_6\text{H}_4\text{O}(\text{CH}_2)_4\text{H}$	5j , 83%
11	$\text{7-Hydroxy-4-methylcoumarin}/\text{K}_2\text{CO}_3$	$\text{7-Hydroxy-4-methylcoumarin-O}(\text{CH}_2)_4\text{H}$	5k , 72%
12	AcONa	AcO(CH ₂) ₄ H	5l , 99%
13	BzONa	BzO(CH ₂) ₄ H	5m , 99%
14	AcSK	AcS(CH ₂) ₄ H	5n , 88%
15	TrtSH/NaH	TrtS(CH ₂) ₄ H	5o , 84%
16	$\text{EtO}_2\text{C}-\text{CH}_2-\text{CO}_2\text{Et}/\text{K}_2\text{CO}_3$	$\text{EtO}_2\text{C}-\text{CH}_2-\text{C}(\text{CH}_2)_4\text{H}$	5p , 34%
17	BnNH ₂ /NaH	$\text{H}(\text{OCH}_2)_4\text{N}(\text{Bn})(\text{OCH}_2)_4\text{H}$	5q , 80%
18	NaN ₃	$\text{N}_3(\text{CH}_2)_4\text{H}$	5r , 97%
19 ^[b, c]	NaF	$\text{F}(\text{CH}_2)_4\text{H}$	5s , 88%

[a] All reactions were performed on 1 g scales. [b] DMF was used as solvent. [c] The reaction was run at 120 °C.

amine or azide was used as the nucleophile, nitrogen could be conveniently incorporated into OEGs (Table 2, entries 17, 18). In the case of benzylamine, an one-pot dual nucleophilic ring-opening reaction afforded a tertiary amine **5q** in an 80% yield. Another clickable OEG **5r** was obtained in an excellent yield when NaN₃ was employed. Finally, the weak nucleophilic reagent NaF successfully attacked **4a** to give a monofluorinated OEG **5s** in an 88% yield (Table 2, entry 19). Since the ring-opening reaction is completed at 120 °C in a few minutes, it may provide a useful way for the radiochemical synthesis of ¹⁸F labelled PEGs. These ring-opening reactions indicate that MCS are highly reactive toward a broad range of nucleophiles. Therefore, this MCS-based OEG monofunctionalization provides an efficient and alternative method for many important OEG derivatives, especially for those hard to synthesize with other methods.



Scheme 4. Synthesis of M-PEGs **7** and monomethoxy M-PEGs **15**.

The nucleophilic ring-opening reaction of MCS was then employed to the synthesis of M-PEGs and derivatives (Scheme 1). To illustrate the generality and efficacy of this strategy, 36-mer **7** and monomethoxy 64-mer **15** were chosen as the target molecules (Scheme 4). Firstly, from tetra(ethylene glycol) **1a** and its MCS **4a**, 36-mer **7** was successfully prepared in four steps with an overall yield of 51%. During the four cycles of one-pot dual chain extension reaction, the bis(sodium sulfate) intermediates are insoluble in THF and DMF was used instead. After the ring-opening reaction, DMF was removed and the intermediate was directly hydrolyzed in THF. Secondly, from MeONa and MCS **4g**, a series of monomethoxy M-PEGs **8–15**, which are the most used forms in PEGylation, were conveniently prepared. The longest monomethoxy M-PEG **15**, a 64-mer, was prepared in eight steps with an overall yield of 15%. Monomethoxy M-PEG **15** is eight units more than the longest M-PEG reported so far.^[4j] Apart from monomethoxy M-PEGs, other monofunctionalized M-PEGs such as N₃-, F-, TrtS-, and Bn-substituted M-PEGs (Table 2) can also be prepared with this MCS-based strategy.

Comparing to known M-PEG synthesis, our method reduces half of the synthetic steps by omitting the hydroxy group protection and activation. Furthermore, one-pot dual chain extension reaction further minimized the synthetic steps by introducing two OEG fragments at a time. As for the purification, all the intermediates were purified by flash chromatography on silica gel with methanol and CH₂Cl₂ as eluents. It was found that most impurities can be removed by selectively extracting sodium sulfate intermediates into water and leaving most impurities in the organic phase. The rest impurities can be easily removed by flash chromatography after hydrolysis of the intermediates. In this way, excess MCS in this reaction were also recovered. With this strategy, many biopharmaceutically useful M-PEGs and derivatives which are difficult to synthesize with established methods can be conveniently prepared within minimal synthetic steps from the corresponding OEGs and MCS. Finally, we want to point out that the selection of OEG and MCS is very flexible which depends on the target M-PEG and the availability of starting materials.

The monodispersity of M-PEGs was measured by MALDI-TOF-MS (Figure 3).^[4f,i] It was found that M-PEGs

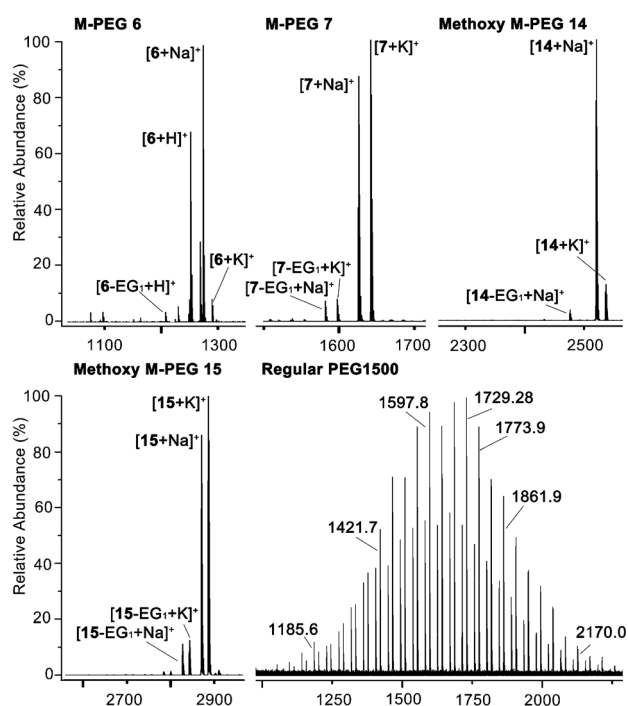


Figure 3. MALDI-TOF-MS of M-PEGs **6** and **7**, monomethoxy M-PEGs **14** and **15**, and regular PEG1500.

28-mer **6** and 36-mer **7** together with monomethoxy M-PEGs 56-mer **14** and 64-mer **15** synthesized through this method exhibit high monodispersity. Based on the MALDI-TOF-MS, PDIs of these M-PEGs were calculated as 1.00057 (**6**), 1.00007 (**7**), 1.00005 (**14**), and 1.00003 (**15**). Negligible impurities, derived from starting materials^[4j] and depolymerization, can be detected by MALDI-TOF-MS. As a comparison, MALDI-TOF-MS of the commercially available regular PEG1500 contains more than 26 pairs of peaks corresponding to different length oligomers (each pair containing a $[M+Na]^+$ peak and a $[M+K]^+$ peak).

In conclusion, we have prepared a class of novel MCS and successfully applied them into OEG monofunctionalization, M-PEGs and derivatives synthesis. Although the chemistry 5- and 6-membered small cyclic sulfates have been well-established, it is the first report on synthesis and application of MCS up to a 62-membered macrocycle. From these stable and easily available MCS, various highly valuable M-PEGs and related compounds in a broad range of applications can be conveniently prepared with high efficacy and purity. Moreover, such MCS are promising in the branched M-PEG synthesis, ¹⁸F radiolabeling of PEGs, and aqueous PEGylation of therapeutic peptides and proteins. Those works are currently in progress and will be reported in due course.

Received: October 21, 2014

Revised: December 8, 2014

Published online: January 29, 2015

Keywords: cyclization · macrocycles · macrocyclic sulfates · poly(ethylene glycol) · synthetic methods

- [1] D. Niclescu-Duvaz, J. Getaz, C. J. Springer, *Bioconjugate Chem.* **2008**, *19*, 973–981.
- [2] a) M. J. Vicent, L. Dieudonné, R. J. Carbajo, A. Pineda-Lucena, *Expert Opin. Drug Delivery* **2008**, *5*, 593–614; b) V. Gaberc-Porekar, I. Zore, B. Podobnik, V. Menart, *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 242–250.
- [3] a) M. Berna, D. Dalzoppo, G. Pasut, M. Manunta, L. Izzo, A. T. Jones, R. Duncan, F. M. Veronese, *Biomacromolecules* **2006**, *7*, 146–153; b) A. Bach, C. N. Chi, G.-F. Pang, L. Olsen, A. S. Kristensen, P. Jemth, K. Strømgaard, *Angew. Chem. Int. Ed.* **2009**, *48*, 9685–9689; *Angew. Chem.* **2009**, *121*, 9865–9869; c) T. Muraoka, K. Adachi, M. Ui, S. Kawasaki, N. Sadhukhan, H. Obara, H. Tochio, M. Shirakawa, K. Kinbara, *Angew. Chem. Int. Ed.* **2013**, *52*, 2430–2434; *Angew. Chem.* **2013**, *125*, 2490–2494.
- [4] a) R. Fordyce, E. L. Lovell, H. Hibbert, *J. Am. Chem. Soc.* **1939**, *61*, 1905–1910; b) E. M. D. Keegstra, J. W. Zwikker, M. R. Roest, L. W. Jenneskens, *J. Org. Chem.* **1992**, *57*, 6678–6680; c) A. Harada, J. Li, M. Kamachi, *J. Am. Chem. Soc.* **1994**, *116*, 3192–3196; d) F. A. Loiseau, K. K. Hii, A. M. Hill, *J. Org. Chem.* **2004**, *69*, 639–647; e) S. A. Ahmed, M. Tanaka, *J. Org. Chem.* **2006**, *71*, 9884–9886; f) A. C. French, A. L. Thompson, B. G. Davis, *Angew. Chem. Int. Ed.* **2009**, *48*, 1248–1252; *Angew. Chem.* **2009**, *121*, 1274–1278; g) G. Székely, M. Schaepertoens, P. R. J. Gaffney, A. G. Livingston, *Polym. Chem.* **2014**, *5*, 694–697; h) Y. Li, Q. Guo, X. Li, H. Zhang, F. Yu, W. Yu, G. Xia, M. Fu, Z. Yang, Z.-X. Jiang, *Tetrahedron Lett.* **2014**, *55*, 2110–2113; i) K. Maranski, Y. G. Andreev, P. G. Bruce, *Angew. Chem. Int. Ed.* **2014**, *53*, 6411–6413; *Angew. Chem.* **2014**, *126*, 6529–6531; j) G. Székely, M. Schaepertoens, P. R. J. Gaffney, A. G. Livingston, *Chem. Eur. J.* **2014**, *20*, 10038–10051.
- [5] K. Knop, R. Hoogenboom, D. Fischer, U. S. Schubert, *Angew. Chem. Int. Ed.* **2010**, *49*, 6288–6308; *Angew. Chem.* **2010**, *122*, 6430–6452.
- [6] a) T. Gibson, *J. Org. Chem.* **1980**, *45*, 1095–1098; b) N. N. Reed, K. D. Janda, *J. Org. Chem.* **2000**, *65*, 5843–5845.
- [7] a) Z.-X. Jiang, Y.-Y. Qin, F.-L. Qing, *J. Org. Chem.* **2003**, *68*, 7544–7547; b) Z.-X. Jiang, Y. B. Yu, *J. Org. Chem.* **2007**, *72*, 1464–1467.
- [8] For reviews, see: a) B. B. Lohray, *Synthesis* **1992**, 1035–1052; b) H.-S. Byun, L. He, R. Bittman, *Tetrahedron* **2000**, *56*, 7051–7091.
- [9] a) H. W. Roesky, H. G. Schmidt, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 695; *Angew. Chem.* **1985**, *97*, 711; b) Z. Florjańczyk, D. Raducha, A. Kozera-Szalkowska, *Macromolecules* **1996**, *29*, 826–834; c) M. J. Wingstrand, C. M. Madsen, M. H. Clausen, *Tetrahedron Lett.* **2009**, *50*, 693–695.
- [10] S. A. King, B. Pipik, D. A. Conlon, M. Bhupathy, *Synth. Commun.* **1997**, *27*, 701–707.
- [11] a) J. Boekhoven, P. van Rijn, A. M. Brizard, M. C. A. Stuart, J. H. van Esch, *Chem. Commun.* **2010**, *46*, 3490–3492; b) J. Lai, V. Molinier, M. Sauthier, L. Moity, Y. Castanet, A. Mortreux, J.-M. Aubry, *Langmuir* **2012**, *28*, 242–250.
- [12] a) Z.-X. Jiang, Y. Feng, Y. B. Yu, *Chem. Commun.* **2011**, *47*, 7223–7235; b) X. Yue, Y. Feng, Y. B. Yu, *J. Fluorine Chem.* **2013**, *152*, 173–181.
- [13] CCDC 1027571 (**4g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.