COMMUNICATION

Synthesis of a conformationally rigid *scyllo*-inositol polymer as a novel chelating ligand †

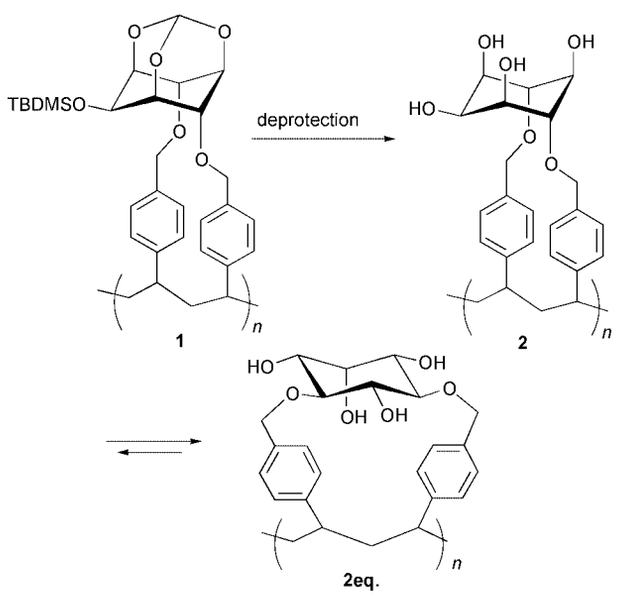
Tae-Hyun Kim [a,b] **and Andrew B. Holmes** *[a,b]

[a] *University Chemical Laboratory, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW*
[b] *Melville Laboratory for Polymer Synthesis, Department of Chemistry, University of Cambridge, Pembroke Street, Cambridge, UK CB2 3RA. E-mail: abh1@cam.ac.uk*

Received (in Cambridge, UK) 11th June 2001, Accepted 10th September 2001
First published as an Advance Article on the web 27th September 2001

A poly(pentyl methacrylate) carrying a conformationally rigid *scyllo*-inositol substituent (with all axial hydroxy groups) in the 5-position of the pentyl ester chain has been synthesised.

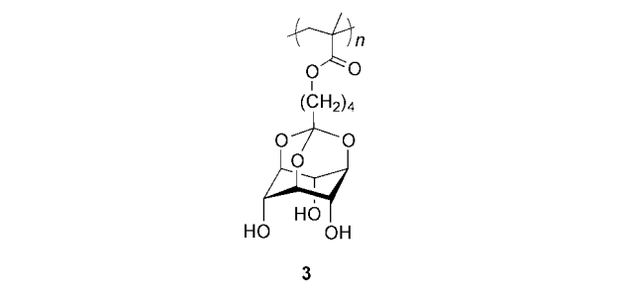
The search for new polymeric ligands capable of binding certain metal ions has continued over the last decade.[1,2] We were interested in developing a novel polymer with an organised backbone and oriented functional groups. Inositol (cyclohexane-1,2,3,4,5,6-hexaol) scaffolds were ideally suited to deliver such features.[3–5] We have recently shown that a cyclopolymer **2** based on *myo*-inositol, designed to deliver axial hydroxy groups by virtue of its rigid bridging backbone, actually prefers the equatorial conformation **2eq.** when prepared by deprotection of the precursor **1** (Scheme 1).[6,7]



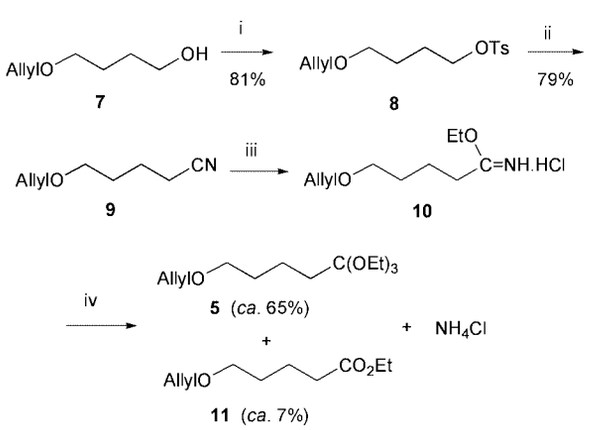
Scheme 1

We now report the synthesis of the poly(pentyl methacrylate) **3** carrying the conformationally rigid *scyllo*-inositol side chain substituent in which all hydroxy groups are oriented axially.

The synthesis of **3** requires the *myo*-inositol derivative **6**, which was obtained by transorthoesterification of the orthoester **5** with *myo*-inositol **4** (Scheme 2).[8] Removal of the allyl ether protecting group in **6** would allow introduction of a polymerisable group. The alkyl chain in **6** was expected to serve as a spacer keeping the polymerisable group distant from the bulky inositol unit.



Scheme 2



Scheme 3 *Reagents and conditions*: i. TsCl, Et_3N, DMAP, CH_2Cl_2, 25 °C, 4 h; ii. NaCN, 4 Å sieves, DMSO, 50 °C, 24 h; iii. EtOH, dry HCl, 0 °C, 6 days; iv. EtOH, ether, reflux, 20 h.

The synthesis of the orthoester **5** is outlined in Scheme 3. Cyanide displacement of the tosylate **8** (prepared from the known alcohol **7**[9]) afforded the nitrile **9**. This was treated with saturated ethanolic hydrogen chloride to give the inseparable mixture of the orthoester **5** (65%) and the ethyl ester **11** (7%).[10] The *myo*-inositol orthoester derivative **6**‡ was obtained in 70% by exchange of the orthoester **5** in DMF (Scheme 2).[11]

Using a modification of Kishi's procedure,[8] we prepared the *scyllo*-inositol orthoester **16**‡ in 36% yield from **6** over 6 steps (Scheme 4).

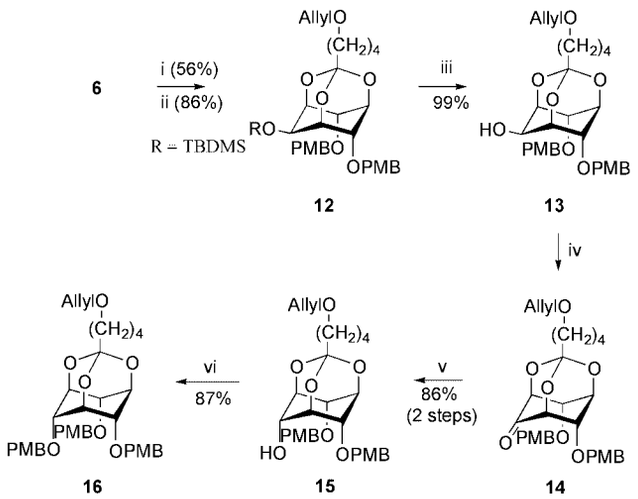
Deprotection of the allyl group in **16** was carried out in a two step sequence, namely, isomerisation of the allyl group to the enol ether **17** using Wilkinson's catalyst,[12] followed by hydrolysis to the alcohol **18**.‡[13] Esterification with methacryloyl chloride in pyridine yielded the monomer **19**‡ (Scheme 5).

† Electronic supplementary information (ESI) available: experimental procedures for preparation of compounds **3**, **5**, **6** and **20**. See http://www.rsc.org/suppdata/p1/b1/b105105a/

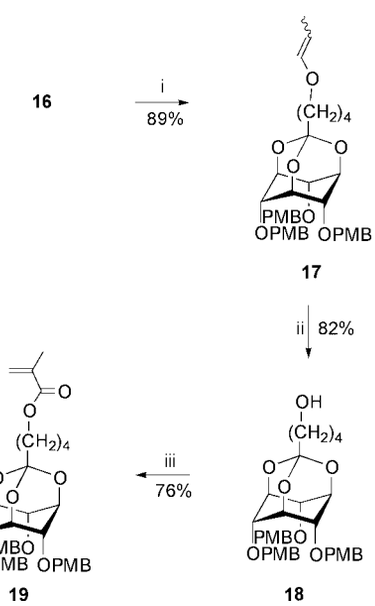
 DOI: 10.1039/b105105a

Table 1 Effect of varying polymerisation conditions on the yield and molecular weight (determined by GPC) of the polymer **20**

Experiment	Concentration of **19**/M	Polymerisation time/h	Amount of initiator (wt% of **19**)	Yield (%)	M_n ($\times 10^3$)
1	0.06	24	1.6	22	6.7
2	0.04	48	1.6	62	5.6
3	0.1	48	1.6	62	6.2
4	0.1	48	2.4	62	3.7



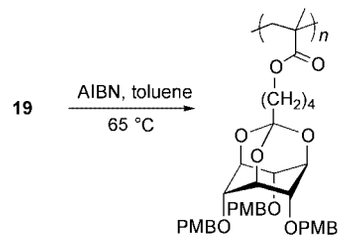
Scheme 4 *Reagents and conditions*: i. TBDMSCl, 2,6-dimethylpyridine, DMF, 25 °C, 24 h; ii. NaH, *p*-methoxybenzyl chloride, DMF, 25 °C, 12 h; iii. TBAF, THF, 25 °C, 1 h; iv. DMSO, oxalyl chloride, THF, Et_3N, −78 °C to 25 °C, 18 h; v. $NaBH_4$, methanol–THF, 25 °C, 18 h; vi. NaH, DMF, *p*-methoxybenzyl chloride, 25 °C, 12 h.



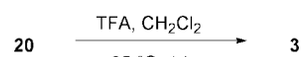
Scheme 5 *Reagents*: i. $Rh(I)Cl(PPh_3)_3$, DABCO, ethanol–toluene–H_2O; ii. Hg(II)O, $HgCl_2$, acetone–H_2O; iii. methacryloyl chloride, DMAP, pyridine.

Polymerisation of the *scyllo*-inositol monomer **19** was carried out at 65 °C in toluene with AIBN as a radical initiator under various conditions (Scheme 6 and Table 1).

Although the molecular weight of the polymer **20** depends on the concentration of the monomer and the amount of initiator, the polymerisation yield is only dependent on the reaction time. This indicates that the polymer grows slowly, requiring longer reaction time and was not consistent with our original assumption that the alkyl spacer should circumvent the slow propagation step of the polymerisable group due to the bulky inositol scaffold. It is now thought that the entanglement



Scheme 6



Scheme 7

of the alkyl chain brings the polymerisable moiety close to the inositol unit, causing slow propagation. The polymerisation and the molecular weight have yet to be optimised. Removal of the PMB groups in polymer **20** was carried out in the presence of TFA in 89% yield (Scheme 7).

In conclusion, we have successfully synthesised the poly(pentyl methacrylate) carrying a conformationally rigid *scyllo*-inositol substituent as a possible metal-chelating ligand, which will be investigated in future.

Acknowledgements

We thank EPSRC for financial support and provision of the Swansea MS service, the Cambridge Overseas Trust, Robinson College, and the CVCP (UUK) for scholarships (to T.-H. Kim).

References

‡ All new compounds exhibited satisfactory analytical data, which included combustion microanalysis, IR, ^1H and ^{13}C NMR spectra, and mass spectra. Experimental procedures for the preparation of compounds **3**, **5**, **6** and **20** have been deposited as Electronic Supplementary Information.

1 G. Wulff, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 21.
2 T. Kaliyappan and P. Kannan, *Prog. Polym. Sci.*, 2000, **25**, 343.
3 S. J. Angyal, *Tetrahedron*, 1974, **30**, 1695.
4 K. Hegetschweiler, M. Ghisletta, T. F. Fässler, R. Nesper, H. W. Schmalle and G. Rihs, *Inorg. Chem.*, 1993, **32**, 2032.
5 J. Tae, R. D. Rogers and L. A. Paquette, *Org. Lett.*, 2000, **2**, 139; L. A. Paquette and J. Tae, *J. Am. Chem. Soc.*, 2001, **123**, 4974.
6 T.-H. Kim, P. Dokolas, N. Feeder, M. Giles, A. B. Holmes and M. Walther, *Chem. Commun.*, 2000, 2419.
7 T.-H. Kim, M. Giles and A. B. Holmes, *Chem. Commun.*, 2000, 2421.
8 H. W. Lee and Y. Kishi, *J. Org. Chem.*, 1985, **50**, 4402.
9 I. Kadota, M. Kawada, V. Gevorgyan and Y. Yamamoto, *J. Org. Chem.*, 1997, **62**, 7439.
10 S. M. McElvain and J. W. Nelson, *J. Am. Chem. Soc.*, 1942, **64**, 1825.
11 D. C. Billington, R. Baker, J. J. Kulagowski, I. M. Mawer, J. P. Vacca, S. J. deSolms and J. R. Huff, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1423.
12 E. J. Corey and J. W. Suggs, *J. Org. Chem.*, 1973, **38**, 3224.
13 R. Gigg and C. D. Warren, *J. Chem. Soc. (C)*, 1968, 1903.