PERKIN 1

A new method for the polymer-supported synthesis of cyclic oligoesters for potential applications in macrocyclic lactone synthesis and combinatorial chemistry

Clare L. Ruddick,† Philip Hodge,* Anthony Cook and Andrew J. McRiner

Chemistry Department, University of Manchester, Oxford Road, Manchester, UK M13 9PL

Received (in Cambridge, UK) 16th November 2001, Accepted 7th January 2002
First published as an Advance Article on the web 4th February 2002

Attachment of ω-hydroxyalkanecarboxylic acids to Merrifield beads followed by treatment with a catalytic amount of di-*n*-butyltin oxide in chlorobenzene at 133 °C for 4–18 h brought about the formation of the corresponding cyclic oligomers (COs) as the main (>92%) soluble products in yields of 56–83%. Similar results were obtained with polymer-supported (PS) ricinoleic acid, which has a secondary hydroxy group, but attempts to carry out analogous reactions with PS lithocholic acid failed. PS 20-hydroxyicos-10-enoic acid and *N*-(11-hydroxyundecanoyl)-11-aminoundecanoic acid reacted well to give COs, the cyclic monomers being the major products. Samples of these cyclic monomers were isolated. The latter two hydroxy acids were also successfully assembled on the beads (the former using olefin metathesis) and then cyclo-oligomerised. There are several possible applications for this PS synthetic method. Thus, the COs might be used, *via* transesterifications, for the preparation of soluble combinatorial libraries of macrocycles, or used as starting materials for the small-scale combinatorial synthesis of copolyesters. For both of these applications the fact that the PS syntheses afford families of COs is not a problem because the applications involve the establishment of equilibria into which all of the COs can feed. Finally, these PS reactions may provide a useful approach to the small-scale synthesis of macrocyclic lactones with 15 or more ring atoms, since with these ring sizes the cyclised monomers are formed in >67% yield.

Introduction

There is considerable interest in the synthesis of macrocyclic lactones,[1,2] not least because there are many important naturally occurring compounds of this general type. For example, erythromycin A, whose structure includes a 14-membered lactone, has significant antibacterial activity,[3] and valinomycin, whose structure includes a 36-membered ring incorporating six ester and six amide linkages, is important in the transport of K^+ across biological membranes.[4] The classical approach to the synthesis of such macrocycles is to cyclise an appropriate α,ω-bifunctional compound at high dilution so that first order *intra*molecular reactions are heavily favoured over second order *inter*molecular reactions, *i.e.* to carry out the cyclisation at a concentration significantly below the "effective molarity".[5] Polymer-supported (PS) reactions have been considered as an alternative to high dilution syntheses[6] because, under appropriate conditions, they can provide some "site isolation".[7–10] Consequently several PS syntheses of macrocyclic lactones have been reported where the aim was to obtain the cyclised *monomer* in high yield with the help of site isolation.[11–18] In most of these cases, however, either the loadings on the beads were low, the yields of the cyclised monomers were modest, and/or chromatography was needed to isolate the desired products. In only a few of these reaction systems was any site isolation actually demonstrated.[12,14–17]

This paper presents a further method for the PS synthesis of macrocyclic lactones. The aim in this case was simply to obtain in solution, by an experimentally convenient procedure, good yields of cyclic oligomers (COs) essentially free of linear oligomers or other species. It was not specifically intended to achieve site isolation. There are three potential applications for such PS syntheses. Firstly, in appropriate cases the COs may be used, *via* transesterifications (TEs) at high dilution, for the preparation of soluble combinatorial libraries of macrocycles.[19] Secondly, the COs may be used as starting materials for a novel type of entropically driven ring-opening polymerisation that simply involves heating the neat COs with a TE catalyst.[20] Such polymerisations offer the opportunity to synthesise combinatorial libraries of copolyesters.[21] Note that for both of these applications the fact that a family of COs is produced is not a problem because the applications involve the establishment of equilibria into which all the COs can feed. Finally, in certain cases the reactions may provide a useful approach to the synthesis of macrocyclic lactones.

To carry out this new type of PS macrocycle synthesis, an unprotected ω-hydroxy acid is bound, at loadings as high as conveniently possible, to Merrifield beads **1** *via* ester linkages (see Scheme 1). TE is then brought about by heating the beads in the presence of a suitable catalyst. Both chain growth (for example, "a" in Scheme 1) and cyclisation reactions (for example, "b" in Scheme 1) occur, *but only the cyclic products are released into solution*. The linear products remain bound to the beads *via* their end groups. It was initially anticipated that the cyclic products in solution would then equilibrate, again *via* TEs, so that eventually, whatever COs were formed initially, a family of COs would eventually be present in their equilibrium proportions. However, the results presented below indicate that, with the most successful TE catalyst used, little or no equilibration occurs, *i.e.* the composition of the CO products is largely kinetically controlled.

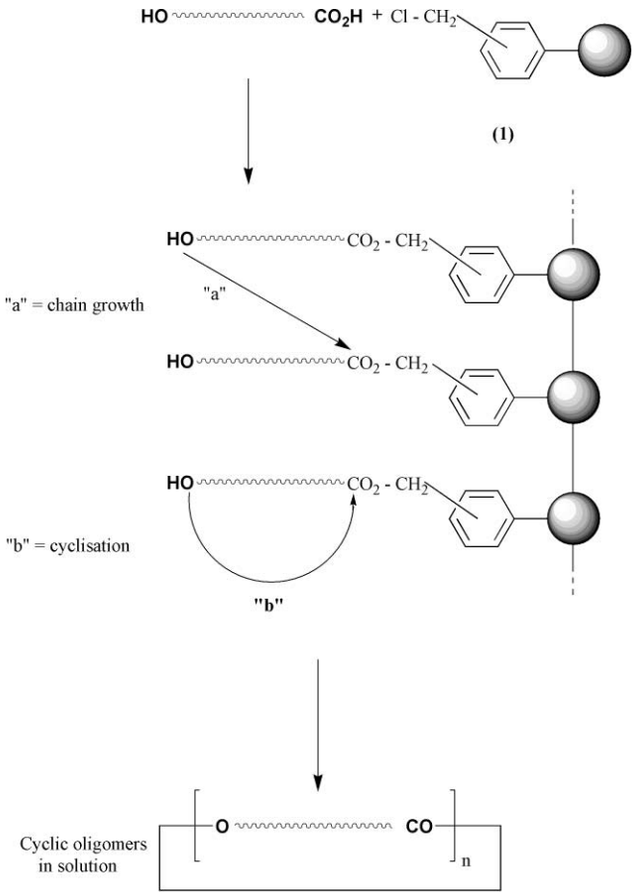
† *Current address*: Mettler-Toledo Myriad Ltd., 2, Saxon Way, Melbourn, Hertfordshire, UK.

DOI: 10.1039/b110528k

Table 1 Cyclo-oligomerisation of various polymer-supported hydroxyacids

Entry	Hydroxyacid starting material	Ring atoms per repeat unit	Loading/ mmol g^{-1} [a]	Reaction time/h	Yield of solubles (%)	Percentage cyclic (%) [b]	Percentage composition of cyclic *n*-mers by weight [c]							MALDI-TOF MS [e]
							n = 1	*n* = 2	*n* = 3	*n* = 4	*n* = 5	*n* = 6	*n* = 7 [d]	
1	11-Hydroxyundecanoic acid (**2**)	12	1.15	4	66	98	1.0	67	22	6.4	2.2	1.2	0.2	11
2	11-Hydroxyundecanoic acid (**2**)	12	0.39	4	25 (74) [g]	96	14	75	9.1	1.5	0.2	0	0	—
3	11-Hydroxyundecanoic acid (**2**)	12	0.10 [f]	4	3 (34) [g]	99	36	60	3.6	0.4	0	0	0	—
4	12-Hydroxydodecanoic acid (**3**)	13	0.44	4	55	96	4.1	77	10	6.3	1.5	0.5	0.6	6
5	12-Hydroxydodecanoic acid (**3**)	13	0.25 [f]	4	22 (46) [g]	98	12	72	12	2.8	0.3	0.2	0.7	—
6	8-Hydroxyoctanoic acid (**4**)	9	0.47	18	67	100	0	76	17	4.9	1.3	0.5	0.2	8
7	10-Hydroxydecanoic acid (**5**)	11	0.65	18	56	98	0	83	13	3.0	0.7	0.2	0.1	13
8	Ricinoleic acid (**13**)	13	0.37	18	69	90	30	58	9.9	1.7	0.3	0.1	0	—
9	Lithocholic acid (**15**)	14	0.63	18	14	—[h]	—	—	—	—	—	—	—	—
10	15-Hydroxypentadecanoic acid (**17**)	16	0.96	18	81	98	60 [i]	31	6.7	1.8	0.5	0	0	—
11	16-Hydroxyhexadecanoic acid (**9**)	17	0.42	18	83	96	51 [i]	35	8.4	2.9	1.1	0.6	1.0	—
12	20-Hydroxyicos-10-enoic acid (**19**)	21	0.46	18	70	97	87 [i]	7	3.2	1.8	1.0	0	0	—
13	20-Hydroxyicos-10-enoic acid (**19**)	21	0.14 [f]	18	61	99	92	5	2.5	0.4	0.1	0	0	—
14	Undec-10-enoic acid (**23**) [j]	21	0.61	18	61	92	82	14	2.8	0.6	0.4	0.2	0	—
15	Hydroxyacid (**25**)	24	0.46	18	97 [f]	100	74	18	2.3	0.5	0	0	5.2 [k]	7
16	Hydroxyacid (**30**) [l]	24	1.17	18	58	100	83 [i]	15	2.0	0	0	0	0	—

[a] See Experimental section for loading procedure. [b] Calculated from the average degree of polymerisation of the soluble product as estimated from the SEC analysis, and the number of end groups per repeat unit as estimated from the ^{1}H NMR spectrum. [c] By SEC-analysis. [d] Except where indicated otherwise, these were higher linear and/or cyclic oligomers. [e] Samples of selected products were studied by MALDI-TOF mass spectrometry. Peaks due to cyclics were clearly seen for cyclic *n*-mers from *n* = 3 up to the values given. [f] Sample used was the polymer beads recovered from the experiment summarised in the preceding entry. [g] First yield is that based on the original starting material. Yield in parentheses is yield based on the starting material for the experiment summarised in that particular entry. [h] SEC trace showed many peaks. No assignment possible. [i] A sample of the cyclic monomer was isolated by column chromatography. [j] Subsequently converted on the beads into PS hydroxyacid (**19**) at a loading of 0.21 mmol g^{-1}. [k] A portion of this product (5.2%) consisted of the products with *n* ester groups *n* + 1 amide groups. Yields were 4.0, 1.1, 0.2 and 0.1% for *n* = 2 to 5 respectively. [l] Subsequently converted on the beads into PS hydroxyacid (**25**) at a loading of 0.82 mmol g^{-1}.



Scheme 1

We have previously prepared some simple cyclic oligoesters by cyclo-depolymerising appropriate polyesters,[20,22,23] but this approach first requires the synthesis of the corresponding polymers and is clearly less convenient especially if, for example, a natural product is to be synthesised.

Results and discussion

A range of ω-hydroxy acids, or other ω-substituted acids which might subsequently be elaborated on the beads into ω-hydroxy acids, were attached to chloromethylated (1.60 mmol of Cl per gram) 1% cross-linked polystyrene beads **1** (see Scheme 1 and Table 1). Except where indicated otherwise this was achieved by treating the beads with the caesium salt of the hydroxy acid in *N,N*-dimethylformamide (DMF) at 50 °C for 3 days.[24] The loadings obtained, assessed by weight gains and the losses of chlorine from the beads, were generally in the range 0.4–1.0 mmol g^{-1} (see Table 1). Thus, assuming the beads swelled in the reaction solvent by a factor of 5, the concentrations of the PS hydroxy acids in the beads *at the start* of the reactions were greater than 8×10^{-2} M. This is above the "effective molarity" of the various hydroxy acids,[5] so it was not expected that under these initial reaction conditions there would be any evidence of site isolation. To bring about cyclo-oligomerisation, the PS ω-hydroxy acids were treated with a TE catalyst in a suitable solvent (*ca.* 40 ml of solvent per gram of beads). At the end of the reaction period the beads were filtered off and the soluble products recovered and analysed by size exclusion chromatography (SEC), by ^{1}H NMR spectroscopy (mainly for seeking evidence for the lack of end groups) and, in some cases, by MALDI-TOF mass spectrometry. The results are summarised in Table 1: note that the SEC traces give the percentage compositions *by weight*.

The proportions of the various COs produced were essentially as expected.[25] Thus, when the rings are strainless, the smaller a given ring is the more of it is present. Consistent with this, when strained medium-sized rings could be formed, very little of those cyclic products are present in the mixtures of COs. When the cyclic monomer has 15 or more ring atoms it is the major product, and, as there is a significant jump in ring size on going from the monomer to the dimer to the trimer *etc.*, it is relatively easy to separate the cyclic monomer from the higher oligomers.

Cyclo-oligomerisations of PS 11-hydroxyundecanoic acid (2), PS 12-hydroxydodecanoic acid (3), PS 8-hydroxyoctanoic acid (4) and PS 10-hydroxydecanoic acid (5)

In view of the ready availability of 11-hydroxyundecanoic acid **2** and the corresponding COs **6** and linear oligomers,[22] the PS cyclo-oligomerisation of this acid was selected for detailed study. Three possible catalyst–solvent systems for TE were investigated. Treatment of the PS acid (0.64 mmol g^{-1}) with 0.3 equivalents of potassium methoxide in toluene at 110 °C for 4 h gave a 33% yield of soluble material. SEC and ^{1}H NMR spectroscopic analysis, in comparison with authentic samples, indicated[22] that it consisted of 80% cyclic oligoundecanoates **6** and 20% linear oligoundecanoates. Lithium bis(trimethylsilyl)amide (5 mol%) in chlorobenzene at 133 °C for 4 h gave a better yield of soluble product (59%), but again it consisted of both cyclic products **6** (74%) and linear oligomers (26%). Finally, treatment with di-*n*-butyltin oxide (3 mol %) in chlorobenzene at 133 °C for 4 h gave a 66% yield of soluble product that was 98% COs (**6**). Clearly di-*n*-butyltin oxide in chlorobenzene was the most successful catalyst–solvent combination and unless indicated otherwise this combination was used as standard in all the subsequent experiments.

$HO - (CH_2)_m - CO_2H$	$[(CH_2)_m - CO_2]_n$
(2) : m = 10	**(6) : m = 10**
(3) : m = 11	**(7) : m = 11**
(4) : m = 7	**(10) : m = 15**
(5) : m = 9	**(11) : m = 7**
(9) : m = 15	**(12) : m = 9**
(17) : m = 14	**(18) : m = 14**

The composition of the soluble product obtained from 11-hydroxyundecanoic acid **2** under the standard conditions is summarised in Table 1, entry 1. A typical SEC trace and MALDI-TOF mass spectrum are shown in Fig. 1. As noted above the yield was only 66% so, in an attempt to increase the yield, the beads were retreated using the original conditions. This produced COs equivalent to a further 25% yield. Repeating the process a third time gave a further 3% yield, so that overall the yield was 94%. The compositions of the second and third products are summarised in entries 2 and 3 of Table 1. It will be noted that the compositions of the soluble products differed considerably. This also proved to be the case in similar experiments with 12-hydroxydodecanoic acid **3** (see Table 1, entries 4 and 5).

Two important conclusions can be drawn from the results with PS acids **2** and **3**. First, it is evident that in each system the COs **6** and **7** released into solution undergo little or no equilibration, otherwise for the experiments with each hydroxy acid the CO fractions would all have the same composition. The failure to equilibrate seems surprising given that various polyesters *in solution* undergo cyclodepolymerisation readily with di-*n*-butyltin oxide as the catalyst.[22,23] It can, however, be rationalised on the basis of some other results we have obtained with polymers.[26] These strongly suggest that di-*n*-butyltin oxide functions as a TE catalyst by first reacting with hydroxy end groups to give species of the type **8** [see eqn. (1)].

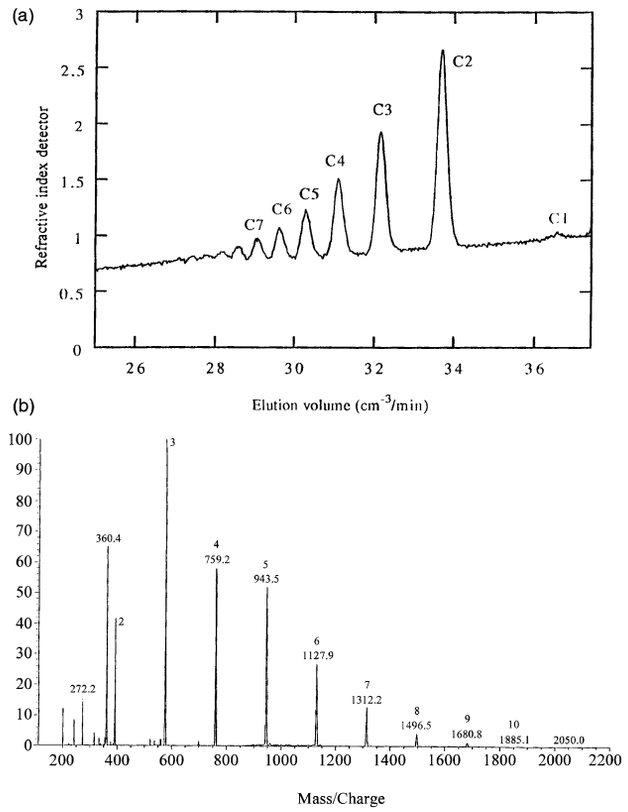
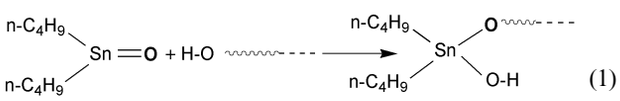


Fig. 1 (a) SEC trace of cyclic undecanoates (**6**), and (b) MALDI-TOF MS of the soluble product from the cyclo-oligomerisation of polymer-supported 11-hydroxyundecanoic acid (**2**).



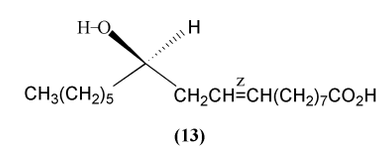
(8)

If there are no hydroxy end groups TE is extemely slow. Species of the type **8** must then react further to achieve TE. Translated to the present system, it suggests that TE is initiated by the di-*n*-butyltin oxide reacting with the hydroxy groups of the bound hydroxy acids. As the COs have no end groups, once liberated into the solution surrounding the beads, they can effectively only take part in further TEs if they re-enter the beads. Apparently they do not do so to any great extent and so equilibration of the COs is very slow. Consistent with this, cyclo-oligomerisations of PS acids **2** and **9** in the same vessel gave a soluble product whose MALDI-TOF mass spectrum showed peaks due to both cyclic oligoundecanoates **6** and cyclic oligohexadecanoates **10** but very little evidence for cyclic products containing both types of repeat unit. The second important conclusion to be drawn is that as the loadings prior to the cyclo-oligomerisations decrease, the compositions of the CO products indicate that cyclisation becomes more important relative to oligomerisation, *i.e.* there is some degree of site isolation at the lower loadings. This trend is not unexpected.[7–10]

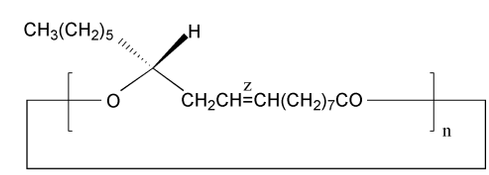
Cyclo-oligomerisations of PS 8-hydroxyoctanoic acid **4** and PS 10-hydroxydecanoic acid **5** were carried out similarly to those of PS acids **2** and **3** except that the reactions were carried out once for 18 h rather than being carried out more than once for 4 h. These reactions gave COs **11** and **12** in yields of 67 and 56%, respectively. The compositions of the CO fractions (see Table 1, entries 6 and 7), like those from PS hydroxyundecanoic acid **2** and PS 12-hydroxydodecanoic acid **3** at the higher loadings (*i.e.* entries 1 and 6, respectively), are very similar to the compositions obtained by the cyclo-depolymerisation of the corresponding polyesters.[22] The latter reactions almost certainly gave COs that were equilibrated because the reaction mixtures were homogeneous and the reaction times and temperature sufficient for the composition of the mixtures of COs to stabilise.[22] Thus, it appears that the compositions of the kinetically and thermodynamically generated mixtures of COs are very similar. This is not surprising.[5] Finally, it will be noted that with all the four hydroxyalkanoic acids considered in this section, the proportion of cyclised monomer in the soluble products from the initial cyclisations is <4%. It is low because the cyclic monomers are medium-sized rings. The main products (67–83% by weight) are the relatively strainless cyclic dimers.

Cyclo-oligomerisations of PS hydroxy acids with secondary hydroxy groups

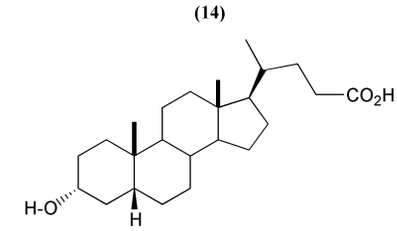
All the hydroxy acids considered above had primary hydroxy groups. Two with secondary hydroxy groups were also investigated. The first was ricinoleic acid [(*Z*,*R*)-12-hydroxyoctadec-9-enoic acid] **13**. When the PS acid **13** was treated for 18 h with di-*n*-butyltin oxide under the standard conditions cyclo-oligomerisation occurred to afford COs **14** in 69% yield (see Table 1, entry 8). Presumably the configuration of the carbon atom bearing the hydroxy group is retained in these COs. Although the cyclic dimer was the major product (58%), the cyclic monomer, which has a 13-membered ring, was formed in 30% yield. The latter compares with yields from PS 12-hydroxydodecanoic acid **3** of <4% of dodecanolactone (**7**; n = 1), which also has a 13-membered ring. The difference arises because the *cis*-olefinic linkage in the COs from ricinoleic acid result in the ring in cyclic monomer **14** being less strained than that in dodecanolactone **7** (n = 1).



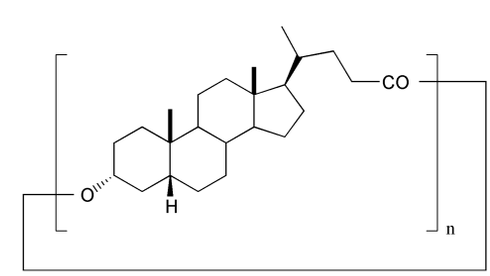
(13)



(14)

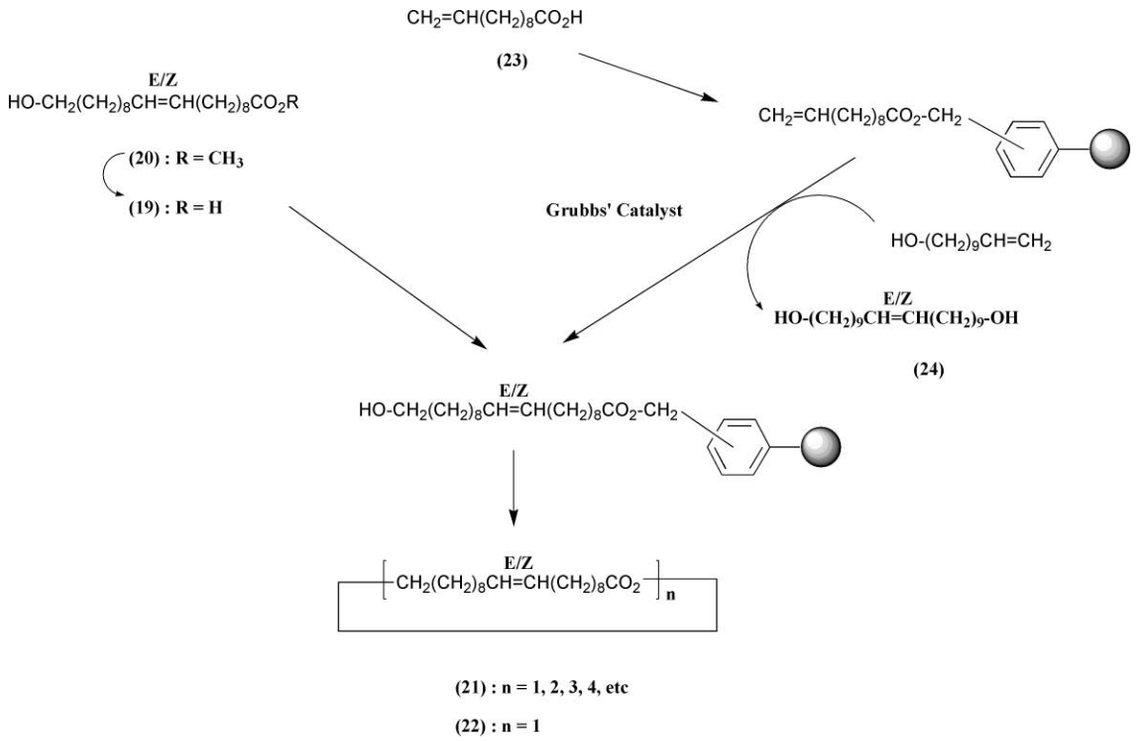


(15)

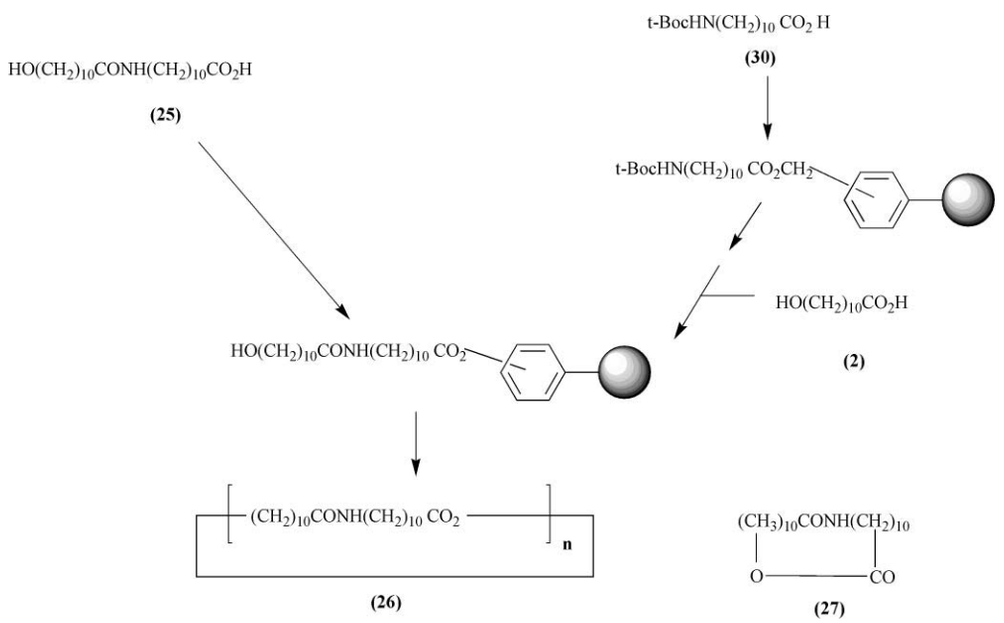


(16)

The second hydroxy acid studied, which contains a secondary hydroxy group, was lithocholic acid **15**. The loading achieved with this acid was only 0.63 mmol g^{-1}, but even at this loading



Scheme 2



Scheme 3

ca. 22% by weight of the beads is due to the steroid. We have studied other reactions of this PS acid before.[27] Surprisingly in view of the results obtained with ricinoleic acid **13**, treatment of the PS acid for 18 h with di-*n*-butyltin oxide under the standard conditions gave only a small soluble fraction which, by SEC, was a complex mixture which did not show the pattern expected for a mixture of COs. Use of the other catalyst systems tried initially with 11-hydroxyundecanoic acid **2** produced no soluble products other than, in the case of sodium methoxide, some methyl lithocholate. It had been hoped the reactions would have given some of the lithocholic acid COs **16** studied by Sanders' group.[28] These failures may well be due to steric congestion.[27]

Cyclo-oligomerisations of larger PS hydroxy acids: synthesis of hydroxy acids on the polymer beads

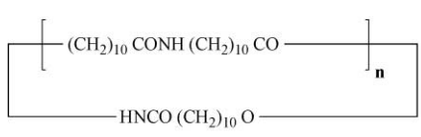
15-Hydroxypentadecanoic acid **17** and 16-hydroxyhexadecanoic acid **9** were studied next. PS acid **17** and PS acid **9** were cyclo-oligomerised for 18 h under the standard reaction conditions to give high yields of COs **18** and **10**, respectively (see Table 1, entries 10 and 11). The cyclic monomers from these acids, which contain 16 and 17 ring atoms, respectively, are essentially strainless. Accordingly the cyclic monomers were the main products: 60% and 51% by weight, respectively (corresponding to 76 mol% and 71 mol%, and 59% and 57% overall yields respectively) of the soluble products. Samples of the cyclic monomers were isolated by chromatography. Clearly these are satisfactory methods for the small-scale synthesis of these macrocyclic lactones.

Attention was next turned to hydroxy acids which could form even larger rings and which, additionally, might be assembled on the beads. The first to be studied were the mixed geometrical isomers of 20-hydroxyicos-10-enoic acid **19** (see Scheme 2). These were prepared by a cross-metathesis reaction between

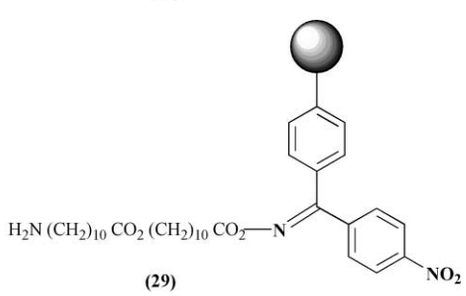
undec-10-enol and methyl undec-10-enoate using Grubbs' catalyst,[29] followed by hydrolysis of the hydroxy ester product **20**. The PS hydroxy acid **19** was subjected to cyclo-oligomerisation for 18 h under the standard conditions to give COs **21**, then the recovered beads were retreated using the original cyclo-oligomerisation conditions (see Table 1, entries 12 and 13). The total yield of soluble product was 88%, the cyclic monomer was the major product in each case (87% and 92% by weight, respectively, corresponding to 92 mol% and 96 mol%). As in the other cases discussed above, relative to the first reaction, the second reaction showed some evidence for site isolation.[7–10] A sample of the mixed geometrical isomers of cyclic monomer **22** was isolated using column chromatography.

In order to assemble the hydroxy acid **19** on the beads, undec-10-enoic acid **23** was bound to the beads using the usual procedure (see Table 1, entry 14, and Scheme 2). The PS acid was then reacted with a large excess of undec-10-enol in the presence of Grubbs' olefin metathesis catalyst.[29] Any "dimeric" product **24** formed by reaction between two undec-10-enol molecules would be washed from the beads after the metathesis reaction. The PS products were subjected to cyclo-oligomerisation for 18 h using the standard conditions. Any PS acid **23** residues that reacted but only with each other or did not react at all would remain attached to the beads during the TE reaction. Thus, the only molecules to be produced in solution during the cyclo-oligomerisation would be the desired COs **21**. Analysis of the soluble product from the cyclo-oligomerisation confirmed this. The yield of COs **21** was 61% and the composition of the product (entry 14) was very similar to that summarised in entry 12 of Table 1.

A second hydroxy acid that could be assembled on the beads is acid **25** (see Scheme 3). This acid was first prepared using a literature procedure,[30] and was attached to the beads using the procedure first reported by Merrifield,[31] *i.e.* treating the chloromethylated resin beads with the acid and triethylamine in ethyl acetate. The PS acid **25** was subjected to cyclo-oligomerisation for 18 h using the usual procedures (see Table 1 entry 15). The reaction took place cleanly to give a very high yield of soluble product **26**, 74% of which was the cyclised monomer **27**. A sample of the cyclic monomer **27** was isolated. Approximately 5% of the soluble product was a series of COs **28** formed by an ester-amide exchange reaction. The COs **26** have been prepared before by a related PS system where the PS amino acid **29** was cyclo-oligomerised through reactions of ester linkages with amines.[18]



(28)



(29)

Finally, hydroxy acid **25** was synthesised on the beads (see Scheme 3) by first attaching the 11-(*tert*-butyloxycarbonylamino)undecanoic acid **30** to the beads using the Merrifield procedure[31] (see Table 1, entry 16). The tBoc group was removed by treatment with trifluoroacetic acid and the product coupled with 11-hydroxyundecanoic acid **2** using dicyclohexylcarbodiimide.[31] When this product was subjected to cyclo-oligomerisation, using the standard procedure, COs **26** were formed in similar proportions to previously but in a somewhat lower yield than before (see entry 16 of Table 1).

Conclusions

Attachment of ω-hydroxy acids **2**–**5**, **9**, and **17**, all bearing primary hydroxy groups, to Merrifield beads followed by treatment with a catalytic amount of di-*n*-butyltin oxide in chlorobenzene at 133 °C for between 4 and 18 h brought about the formation of the corresponding COs as the main (>92%) soluble products in yields of 56–83%. Similar results were obtained with ricinoleic acid **13**, which has a secondary hydroxy group, but attempts to carry out analogous reactions with lithocholic acid **15** failed. The hydroxy acids **19** and **25** also reacted well to give COs and samples of the cyclic monomers **22** and **27** were isolated. The hydroxy acids **19** and **25** were also successfully assembled on the beads.

There are several possible applications for COs synthesised by the above approach. Thus, they might be used for the preparation of soluble combinatorial libraries of macrocycles,[19] or as starting materials for the small-scale combinatorial synthesis of a range of copolyesters.[21] For both of these applications the fact that the PS syntheses affords families of COs is not a problem because these applications involve the establishment of equilibria into which all the COs can feed. Thirdly, the reactions may provide a useful approach to the small-scale synthesis of macrocyclic lactones with 15 or more ring atoms, since with these ring sizes the cyclised monomer will be the main soluble product.

Experimental

Unless indicated otherwise chemicals were purchased from Aldrich, Sigma or Lancaster and were used without further purification. Organic extracts were dried with magnesium sulfate. Solid samples were dried in a vacuum oven at 1.0 mmHg and the temperatures indicated. Melting points were determined using an Electrothermal apparatus and are uncorrected. Infrared spectra were recorded using a Perkin Elmer 1720 instrument; unless indicated otherwise solid samples were prepared as potassium bromide discs and liquid samples as thin films between sodium chloride plates. ^{1}H NMR spectra were recorded for solutions in deuteriated chloroform on a Varian Gemini 200 MHz NMR instrument using TMS as an internal standard. Chemical shifts (δ) are quoted in ppm. relative to tetramethylsilane. ^{13}C NMR spectra were recorded for solutions in deuteriated chloroform on a Bruker AC 300e (300 MHz) instrument. MALDI mass spectrometry was carried out on a Kratos Kompact 3 using dihydroxybenzoic acid as matrix and applying the samples to the plate as a solution in chloroform. Elemental analyses were carried out by Butterworth Laboratories, Teddington, Middlesex. SEC analyses were carried out for solutions in chloroform using an instrument equipped with a Gilson 307 pump operating at a flow rate of 0.3 ml min^{-1} through four Polymer Labs 3μ Mixed E columns in tandem with a GBC LC 1240 differential refractometer for detection.

Source of various hydroxy acids

Hydroxy acids **3**, **4**, **9**, **13** and **15** were commercial samples. 10-Hydroxydecanoic acid **5** was available in the laboratory from earlier studies.[22] 15-Hydroxypentadecanoic acid **17** was prepared by the hydrolysis of a commercial sample of pentadecanolactone, and *N*-(11-hydroxyundecanoyl)-11-aminoundecanoic acid **25** was prepared according to a literature procedure.[30]

Synthesis of 11-hydroxyundecanoic acid (2)

11-Bromoundecanoic acid (50.0 g) was dissolved in chloroform (50 ml). Tetra-*n*-butylammonium hydroxide (40 wt% aqueous solution) was added to achieve neutrality (phenolphthalein as indicator). The two-phase mixture was stirred rapidly and heated under reflux for 36 h. The mixture was then cooled and poured into acidified methanol (50 ml concentrated sulfuric acid in 500 ml methanol). The polyundecanoate precipitated out, was collected, dissolved in the minimum amount of chloroform and re-precipitated from methanol (1 l). The white powder was filtered off and dried at 40 °C under vacuum (32.5 g). The polymer was hydrolysed by being stirred with aqueous potassium hydroxide (20 g in 500 ml) for 18 h at reflux temperature. The clear solution was cooled and acidified carefully with concentrated sulfuric acid. The white flakes that formed were filtered off and dried at 40 °C under vacuum. Recrystallisation from ethyl acetate–petroleum ether gave colourless needles (28.0 g, 73%), m.p. 63–65 °C (lit.,[32] 68 °C); ν_{max}(film) 3500–3300 (br, OH), 1714 cm^{-1} (C=O, acid); δ_H($CDCl_3$): 5.0–4.2 (br s, 2H, OH), 3.62 (t, J = 6.5 Hz, 2H, CH_2OH), 2.33 (t, J = 6.5 Hz, 2H, CH_2CO_2), 1.55 (quint, J = 6.5 Hz, 2H, CH_2CH_2OH), 1.34 ppm (br m, 14H, 7 CH_2); *m*/*z* (CI) 220 [M + $(NH_4)^+$], 203 [$(M+1)^+$], 185 [$(M - OH)^+$].

Synthesis of 20-hydroxyicos-10-enoic acid 19

(a) Synthesis of methyl 20-hydroxyicos-10-enoate 20. A mixture of Grubbs' catalyst [bis(tricyclohexylphosphine)benzylideneruthenium dichloride purchased from Strem Chemicals] (46 mg, 0.057 mmol), methyl undec-10-enoate (1.01 g, 5.43 mmol), undec-10-enol (0.95 g, 5.59 mmol) and dichloromethane (50 ml) was stirred at 20 °C under argon for 18 h. The solvent was then evaporated off and the residue subjected to column chromatography over silica gel with petroleum ether–ethyl acetate (7 : 13 v/v) as the eluant. This gave methyl 20-hydroxyicos-10-enoate (443 mg, 24%) as an oil with ν_{max}(KBr) 3600–3200 (br, OH), 1738 cm^{-1} (ester carbonyl); ^{1}H NMR δ($CDCl_3$) 5.35 (m, 2H, –CH=CH–), 3.61 (t, J = 6.5 Hz, 2H, CH_2OH), 3.65 (s, 3H, OCH_3), 2.28 (t, J = 6.5 Hz, 2H, CH_2COO), 1.95 (m, 4H, CH_2–CH=CH–CH_2) 1.57 (m, 6H, 3 CH_2) and 1.31 ppm (br s, 20H, 10 CH_2); ^{13}C NMR δ($CDCl_3$) 173.7 (C=O), 130.6 (*trans* CH=CH), 129.6 (*cis* CH=CH) (ratio of *trans* and *cis* signals 0.80 : 0.20), 63.5 (CH_3OCO), 51.9 (CH_2OH), 34.6, 33.3, 33.2, 33.0, 30.1, 29.9, 29.8, 29.7, 29.6, 29.5, 26.2, 25.4 and 25.4 ppm; *m*/*z* (CI) 341 [$(M + 1)^+$].

(b) Hydrolysis of the geometrical isomers of methyl 20-hydroxyicos-10-enoate (20). The above ester (274 mg, 0.81 mmol) was suspended in 2 M aqueous sodium hydroxide (20 ml) and the mixture was heated under reflux for 4 h. The mixture, which was then homogeneous, was acidified with 2 M hydrochloric acid and extracted with ethyl acetate. The solvent was evaporated from the dried extract. The residue (244 mg, 93%) was a pale yellow solid, mp 65–70 °C, which had ν_{max}(KBr) 1702 cm^{-1} (acid carbonyl); δ_H($CDCl_3$) 5.45 (m, 2H –CH=CH–), 3.65 (t, J = 6.5 Hz, 2H, CH_2OH), 2.30 (t, J = 6.5 Hz, 2H, CH_2COO), 2.00 (m, 4H, CH_2–CH=CH–CH_2) 1.57 (m, 6H, 3 CH_2) and 1.31 ppm (br s, 20H, 10 CH_2); *m*/*z* (CI) 344 [$(M + NH_4)^+$] and 327 [$(M + 1)^+$].

General procedures for loading hydroxy acids onto Merrifield resin

(a) Table 1, entry 1. The following procedure[24] is typical of that used in the experiments summarised in Table 1, entries 1, 4, 6–8, 10–12, 14 and 16.

11-Hydroxyundecanoic acid **2** (3.02 g, 14.95 mmol) was dissolved in 95% ethanol (20 ml) and water (5 ml) was added. The solution was titrated to neutral (pH meter) using aqueous cesium carbonate solution. The solution was then evaporated to dryness and the residual water removed azeotropically with toluene. The solid was partially dissolved in DMF (30 ml) and Merrifield resin (7.52 g, 1.6 mmol of chloromethyl groups per gram, 1% cross-linked) was added. The suspension was heated at 50 °C for 3 days with stirring. The resin was then collected by filtration and washed successively with DMF, DMF–water (1 : 1), ethanol and acetone before being dried at 40 °C *in vacuo*. The product (9.30 g, a weight gain of 1.78 g, corresponding to 10.76 mmol of acid, equal to 1.16 mmol of acid per gram) had ν_{max}(KBr) 1734 cm^{-1} (C=O, ester). Elemental analysis for chlorine gave 0.48%, which corresponds to a loading of 1.13 mmol of acid per gram of resin.

(b) Table 1, entry 9. The following procedure[27] is typical of that used for the experiments summarised in Table 1, entries 9 and 15.

Lithocholic acid **15** (752 mg, 2.00 mmol), triethylamine (200 mg, 2.00 mmol) and ethyl acetate (120 ml) were stirred together at 20 °C for 30 min. Merrifield resin (1.25 g, 1.6 mmol g^{-1}, 1% cross-linked) was added and the mixture heated under reflux for 90 h. The beads were filtered off and thoroughly washed successively with ethyl acetate, ethanol and dichloromethane. The dried product (1.59 g) had ν_{max}(KBr) 1726 cm^{-1} (C=O, ester). The increase in weight of the beads corresponds to a loading of 0.63 mmol g^{-1} of steroid.

General procedure for cyclo-oligomerisation of PS hydroxy acids

The following are typical of the procedures used to achieve cyclo-oligomerisation. The results summarised in Table 1 were achieved using procedure (iii) with the reaction times indicated in the table.

(i) Using potassium methoxide. PS 11-hydroxyundecanoic acid **2** (0.97 g, 1.12 mmol) was suspended in toluene (40 ml) under a nitrogen atmosphere. Potassium methoxide (2.28 mg, 0.33 mmol) was added and the suspension heated under reflux for 4 h. The beads were then filtered off and washed with chloroform. The combined filtrate and washings were evaporated to dryness. This left a colourless solid (67.0 mg, 33%) which had ν_{max}(KBr) 1734 cm^{-1}. SEC analysis, using authentic samples of cyclic and linear oligomers from previous studies,[22] indicated the presence of methyl 11-hydroxyundecanoate (19%) and both cyclic (65%) and linear oligomers (16%).

(ii) Using lithium bis(trimethylsilyl)amide. PS 11-hydroxyundecanoic acid **2** (1.50 g, 1.74 mmol) was suspended in chlorobenzene (50 ml) under a nitrogen atmosphere. Lithium bis(trimethylsilyl)amide (15 mg, 0.09 mmol) was added and the suspension heated under reflux for 4 h. The beads were then filtered off and washed with chloroform. The combined filtrate and washings were evaporated to dryness. This left a colourless solid (183 mg, 57%), which had ν_{max}(KBr) 1734 cm^{-1}; SEC analysis indicated the presence of both cyclic (74%) and linear oligomers (26%).

(iii) Using dibutyltin oxide. (a) PS 11-hydroxyundecanoic acid (1.23 g, 1.41 mmol g^{-1}) was suspended in chlorobenzene (50 ml). Dibutyltin oxide (11.0 mg, 0.042 mmol) was added and the mixture was heated under reflux for 4 h. The resin was recovered and washed with chloroform. The combined filtrate and washings were evaporated to give a white solid (171 mg, 0.93 mmol, 66%). The recovered resin had ν_{max}(KBr) 1734 cm^{-1} (ester carbonyl). The white solid had ν_{max}(KBr) 1730 cm^{-1} (ester carbonyl); δ_H($CDCl_3$) 4.08 (t, J = 6.5 Hz, 2H, CH_2OCO), 2.31 (t, J = 6.5 Hz, 2H, CH_2CO_2), 1.65 (br m, 2H, CH_2) and 1.34 ppm (s, 14 H, 7 × CH_2); MALDI-TOF MS showed peaks due to COs from the cyclic dimer upto the cyclic undecamer, see Fig. 1; SEC showed cyclic products from the monomer upto the nonamer.

(b) The recovered resin from experiment (a) was resuspended in chlorobenzene (50 ml) and dibutyltin oxide (5.0 mg) was added. The reaction was heated again under reflux for 4 h and the work-up procedure conducted as before yielding a further batch of colourless solid (65 mg, 0.35 mmol, 25%) which was analysed as above.

(c) The recovered resin from experiment (b) was resuspended in chlorobenzene (50 ml) and dibutyltin oxide (3.0 mg) was added. The reaction was again heated under reflux for 4 h and the work-up procedure conducted as before yielding a further batch of colourless solid (8 mg, 0.042 mmol, 3%) which was analysed as above.

On-bead synthesis of PS 20-hydroxyicos-10-enoic acid (19)

(a) Loading of undec-10-enoic acid (25) onto Merrifield beads. Undec-10-enoic acid **25** was attached to the Merrifield beads using the procedure described above for attaching hydroxy acid **2**. The loading achieved was 0.61 mmol g^{-1}.

(b) Synthesis of PS hydroxy acid 19. A mixture of the above PS undec-10-enoic acid (7.80 g, 4.75 mmol), undec-10-enol (5.65 g, 33 mmol), Grubb's catalyst (40 mg) and dichloromethane (100 ml) was stirred at 20 °C under nitrogen for 48 h. The beads were then filtered off, thoroughly washed with dichloromethane, and dried at 40 °C under vacuum. The beads (7.85 g) of PS hydroxy acid **19** had ν_{max}(KBr) 1736 cm^{-1}. A small sample of the acid was cleaved from the beads using sodium methoxide in methanol. The amount of acid **19** recovered, identified by ^{1}H NMR spectroscopy, corresponded to a loading of 0.21 mmol g^{-1}.

On-bead synthesis of PS *N*-(11-hydroxyundecanoyl)-11-aminoundecanoic acid (25)

(a) Attachment of acid 30. 11-(*tert*-Butyloxycarbonylamino)-undecanoic acid **30** was synthesised as described previously[33] and attached to the Merrifield beads using the procedure described above for attaching 11-hydroxyundecanoic acid **2**. The loading achieved was 1.17 mmol g^{-1}.

(b) Deprotection of PS acid 30. The PS acid **30** (3.97 g, 4.66 mmol), prepared in (a) above, was stirred in a mixture of dichloromethane and trifluoroacetic acid (1 : 1 v/v, 40 ml) at 20 °C for 4 h. The beads were then collected by filtration and washed thoroughly with dichloromethane. The beads were stirred with a mixture of diisopropylethylamine and dichloromethane (1 : 3 v/v, 40 ml) at 20 °C for 1 h. The beads were collected by filtration and washed with dichloromethane. The treatment with base was then repeated. Finally the beads were filtered off and washed successively with dichloromethane, methanol and ether. The dried beads (4.12 g) had ν_{max} (KBr) 1730 cm^{-1} and, by elemental analysis, N = 1.50%. The latter corresponds to a loading of 1.07 mmol g^{-1} of 11-aminoundecanoic acid.

(c) Coupling of 11-hydroxyundecanoic acid (2) to PS 11-aminoundecanoic acid. The total product from the experiment described in (b) above was swollen in dichloromethane (30 ml). Dicyclohexylcarbodiimide (0.40 g, 3.20 mmol) was added and the mixture cooled to 0 °C. A solution of 11-hydroxyundecanoic acid **2** (0.62 g, 3.05 mmol) in dichloromethane (10 ml) was added dropwise to the stirred mixture over 30 min, then the mixture was stirred for 48 h. The beads were collected by filtration, washed successively and extensively with dichloromethane, methanol, ether, and ether. The dried beads (2.58 g) had ν_{max}(KBr) 1734 and 1655 cm^{-1}, no bands due to amine groups, and, by elemental analysis, N = 1.15%. The latter corresponds to PS hydroxy acid **26** with a loading of 0.82 mmol g^{-1}.

Isolation of cyclic monomers 18, 10, 22 and 27

The experiments were carried out as indicated in Table 1. In each case the crude soluble product was subjected to column chromatography over silica gel with hexane–ether (first two and final entries) or petroleum ether–ethyl acetate (third entry) as the eluant. This afforded samples of the pure cyclic oligomers.

Cyclic monomer **18** (n = 1) had mp 33–34 °C (lit.,[34] 35–37 °C); ν_{max}(KBr) 1734 cm^{-1} (C=O, ester); δ_H($CDCl_3$) 4.10 (t, J = 6.5 Hz, 2H, CH_2OCO), 2.33 (t, J = 6.5 Hz, 2H, CH_2OCO), 1.67 (br m, 2H, CH_2) and 1.32 ppm (s, 22H, CH_2).

Cyclic monomer **10** (n = 1) had mp 30–33 °C (lit.,[35] 33–34 °C); ν_{max}(KBr) 1735 cm^{-1} (C=O, ester); δ_H($CDCl_3$) 4.05 (t, J = 6.5 Hz, 2H, CH_2OCO), 2.30 (t, J = 6.5 Hz, 2H, CH_2OCO), 1.67 (br m, 2H, CH_2) and 1.36 ppm (s, 24H, CH_2).

Cyclic monomer **22** was obtained as a clear oil, ν_{max}(KBr) 1737 cm^{-1} (C=O, ester); ^{1}H NMR δ($CDCl_3$) 5.35 (m, 2H, –CH=CH–), 4.16 (t, J = 6.5 Hz, 2H, CH_2OCO), 2.30 (t, J = 6.5 Hz, 2H, CH_2COO), 2.00 (br m, 4H, CH_2–CH=CH–CH_2), 1.63 (m, 6H, 3 CH_2) and 1.31 ppm (s, 20H, 10 × CH_2); ^{13}C NMR δ($CDCl_3$) 176.3 (C=O), 131.4 and 131.1 (*trans* CH=CH), 130.6 (*cis* CH=CH) (ratio of *trans* and *cis* signals 0.80 : 0.20), 64.5 (CH_2OCO), 35.0 (CH_2CO), 32.5, 32.2 (CH_2CH=CHCH_2), 29.9, 29.8, 29.7, 29.6, 29.5, 29.5, 29.3, 29.2, 29.1, 28.9, 28.8, 28.5, 26.3 and 25.7 ppm; *m*/*z* (CI) 326 [$(M + NH_4)^+$] and 309 [$(M + 1)^+$]; one peak on SEC; accurate MS found 308.2720, calculated for $C_{20}H_{36}O_2$ 308.2715.

Cyclic monomer **27** was obtained as crystals, mp 98–100 °C, ν_{max}(KBr) 1729 and 1644 cm^{-1} (ester and amide carbonyls); δ_H($CDCl_3$) 5.35 (br s, 1H, NH), 4.03 (t, J = 6.5 Hz, 2H, CH_2OCO), 3.20 (m, 2H, CH_2NHCO), 2.25 (t, J = 6.5 Hz, 2H, CH_2COO), 2.10 (t, J = 6.5 Hz, 2H, CH_2CONH) and 1.40 ppm (m, 32H, 16 CH_2); *m*/*z* (CI) 368 [$(M + 1)^+$]; $C_{22}H_{41}O_3N$ requires C, 71.93, H, 11.17 and N, 3.81%, found C, 71.55, H, 11.05 and N, 3.20%.

Acknowledgements

We thank the EPSRC for financial support (Grant GR/K/73305) and James Logan, Robert Thomas and Michael Doward for experimental assistance.

References

1 C. J. Roxburgh, *Tetrahedron*, 1995, **51**, 9767.
2 W. H. Kruizinga and R. M. Kellogg, *J. Am. Chem. Soc.*, 1981, **103**, 5183 and references cited therein.
3 H. A. Kirst, *Prog. Med. Chem.*, 1993, **30**, 57.
4 M. Dobler, in *Comprehensive Supramolecular Chemistry*, eds. J. L. Atwood, J. E. D. Davies, D. D. MacNicol and F. Vögtle, Pergamon, Oxford, 1992, vol. 1, ch. 5, pp. 267–313.
5 G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, 1981, **14**, 95.
6 J. I. Crowley and H. Rapoport, *Acc. Chem. Res.*, 1976, **9**, 135.
7 P. Hodge and E. Khoshdel, *React. Polym.*, 1985, **3**, 143.
8 P. Hodge and J. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2319.
9 *Polymeric Reagents and Catalysts*, ed. W. T. Ford, ACS Symposium Series 308, Washington DC, 1986.
10 P. Hodge, *Chem. Soc. Rev.*, 1997, **26**, 417.
11 L. T. Scott and J. O. Naples, *Synthesis*, 1976, 738.
12 S. L. Regen and Y. Kimura, *J. Am. Chem. Soc.*, 1982, **104**, 2064.
13 R. A. Amos, R. W. Emblidge and N. Havens, *J. Org. Chem.*, 1983, **48**, 3598.
14 B. M. Trost and R. W. Warner, *J. Am. Chem. Soc.*, 1983, **105**, 6940.
15 S. Mohanraj and W. T. Ford, *J. Org. Chem.*, 1985, **50**, 1616.
16 M. Tomoi, T. Watanabe, T. Suzuki and H. Kakiuchi, *Makromol. Chem.*, 1985, **186**, 2473.
17 (*a*) P. Hodge, J.-L. Jiang, G. J. Owen and M. P. Houghton, *Polymer*, 1996, **37**, 5059; (*b*) P. Hodge, M. P. Houghton and M. S. K. Lee, *J. Chem. Soc., Chem. Commun.*, 1993, 581.
18 P. Hodge and P. Peng, *Polymer*, 1999, **40**, 1871.
19 P. Monvisade, P. Hodge and C. L. Ruddick, *Chem. Commun.*, 1999, 1987.
20 P. Hodge, *React. Funct. Polym.*, 2001, **48**, 15.

21 P. Hodge and S. D. Kamau, unpublished results.
22 C. L. Ruddick, P. Hodge, Z. Yang, R. L. Beddoes and M. Helliwell, *J. Mater. Chem.*, 1999, **9**, 2399.
23 P. Hodge, Z. Yang, A. Ben-Haida and C. S. McGrail, *J. Mater. Chem.*, 2000, **10**, 1533.
24 B. F. Gisin, *Helv. Chim. Acta*, 1973, **56**, 1476.
25 H. Jacobson and W. H. Stockmayer, *J. Chem. Phys.*, 1950, **18**, 1600.
26 S. Dad, A. J. Hall, P. Hodge, R. J. Kell and C. L. Ruddick, unpublished results.
27 P. Hodge, J. Kemp, E. Khoshdel and G. M. Perry, *React. Polym.*, 1985, **3**, 299.
28 P. A. Brady, R. P. Bonar-Law, S. J. Rowan, C. J. Suckling and J. K. M. Sanders, *Chem. Commun.*, 1996, 319.
29 R. H. Grubbs, S. J. Miller and G. C. Fu, *Acc. Chem. Res.*, 1995, **28**, 446.
30 B. Jasse, *Bull. Chim. Soc. Fr.*, 1969, **3**, 953.
31 R. B. Merrifield, *J. Am. Chem. Soc.*, 1963, **85**, 2149.
32 K. B. Wiberg and R. F. Waldron, *J. Am. Chem. Soc.*, 1991, **113**, 7697.
33 C. Galli and L. Mandolini, *Org. Synth.*, 1978, **58**, 98.
34 H. H. Mathur and S. C. Bhattacharyya, *J. Chem. Soc.*, 1963, 3505.
35 P. Peng and P. Hodge, *Polymer*, 1998, **39**, 981.