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Polymer-supported syntheses of cyclic oligodepsipeptides

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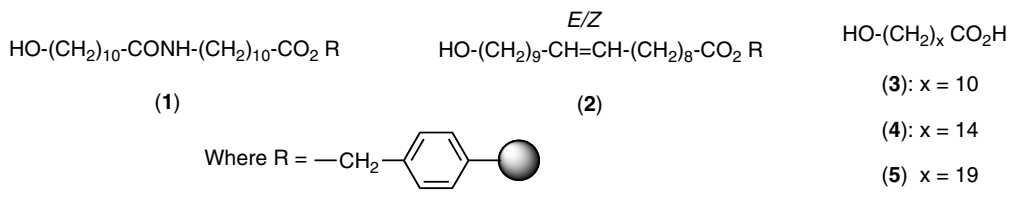
Abstract—A simple PS cyclization-cleavage method is described for the small-scale synthesis of cyclic oligodepsipeptides with 15 to 27 ring atoms per repeat unit. In selected cases, the cyclic monomers were isolated and characterized. If the cyclic oligomers are needed for the preparation of static or dynamic combinatorial libraries of macrocycles or for entropically-driven ring-opening polymerizations, *all members* of the family of macrocyclic oligomers are of interest as they all react through equilibration to give the same products.

Macrocycles are of interest for their potential recognition properties[1] and as monomers for entropically-driven ring-opening polymerizations.[2,3] In the former context combinatorial libraries of macrocycles, both static[4,5] and dynamic,[6] are also of interest. The preparation of combinatorial libraries generally requires relatively small amounts (<100 mg) of the contributing macrocycles. Ring-opening polymerizations of macrocycles are unusual in that they are driven by entropy and are potentially useful because being macrocyclic they can contain major functional units in the ring,[2] for example, macrocycles containing steroid (lithocholic acid) units in the rings have been polymerized successfully.[7]

In an earlier paper we described a simple polymer-supported (PS) synthesis of cyclic esters.[8] This involves attaching a hydroxy acid to chloromethylated polystyrene beads (Merrifield beads) via an ester linkage by using a nucleophilic substitution reaction: see Scheme 1. Cyclization is then achieved by treating the supported hydroxyester with a catalytic amount of di-*n*-butyltin oxide. As any linear species formed are bound to the beads via an ester link, *only cyclic species are released into solution*.

Whilst several macrocycles have been prepared previously using a similar cyclization-cleavage approach,[9–17] attractive features of our method are that the hydroxyl groups do not need protecting and it uses readily available Merrifield beads. Thus, in the related syntheses the ω-hydroxyl or amino groups generally need protecting during attachment and specially reactive ester linkages are required, for example, *p*-sulfonylphenyl esters,[9,11,12] *O*-acyl benzophenone oximes,[9,13,14] thioesters,[15] or acyl diazenes.[16,17] In some cases the activated esters are generated immediately prior to the cyclization step.[10–12,16]

Another attractive feature of our PS approach is that it lends itself to the synthesis of the required hydroxyester on the beads. Thus, in our earlier work hydroxyesters **1** and **2** were prepared on the beads.[8] We now report the synthesis and cyclization of several PS peptide-containing hydroxy acids to afford cyclic oligodepsipeptides: see Scheme 2 and Table 1.



Keywords: Macrocycles; Cyclization-cleavage; Cyclic depsipeptides; Macrocyclic libraries.
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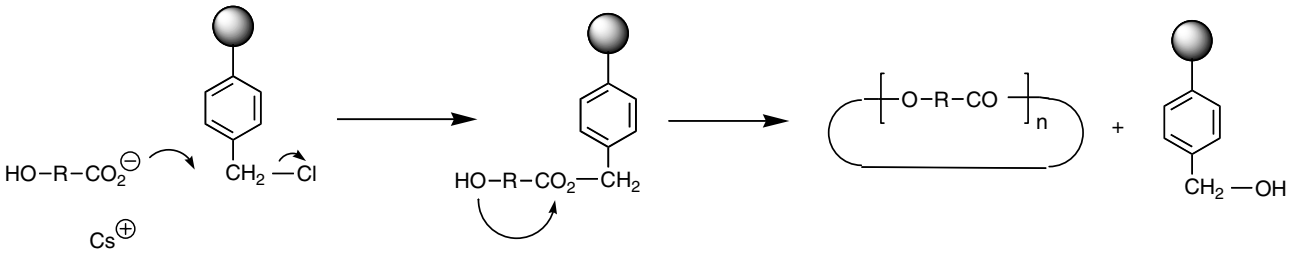
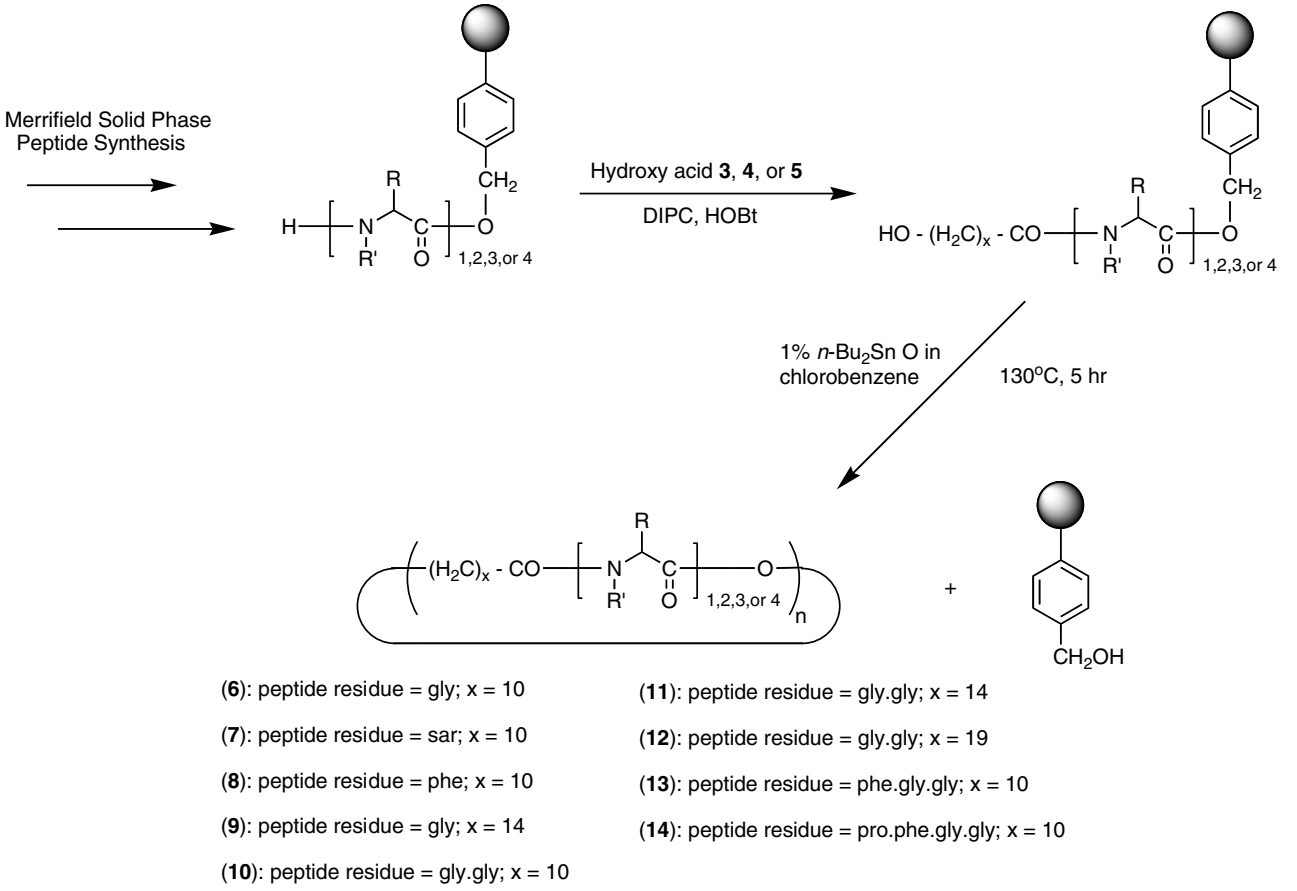


Scheme 1. General scheme for the polymer-supported cyclo-oligomerization of ω-hydroxy acids.



(**6**): peptide residue = gly; x = 10

(**7**): peptide residue = sar; x = 10

(**8**): peptide residue = phe; x = 10

(**9**): peptide residue = gly; x = 14

(**10**): peptide residue = gly.gly; x = 10

(**11**): peptide residue = gly.gly; x = 14

(**12**): peptide residue = gly.gly; x = 19

(**13**): peptide residue = phe.gly.gly; x = 10

(**14**): peptide residue = pro.phe.gly.gly; x = 10

Scheme 2. Reaction scheme used in the present work to give cyclic compounds **6**–**14**.

The polymer beads used were 1% crosslinked polystyrene of 200–400 mesh with a loading of 1.0–3.0 mmol/g of chloromethyl groups. Solid phase peptide syntheses were carried out using the standard Merrifield-type of protocol:[18] (i) attach N-*t*-Boc protected amino acid using cesium carbonate in DMF at 60 °C for 6 days (see Table 1 footnotes for the loadings achieved), followed by capping with cesium acetate; (ii) deprotect with trifluoroacetic acid in dichloromethane (1.0 vol:1.0 vol) at 23 °C for 1 h; (iii) neutralize with triethylamine in DMF at 23 °C for 2 h; (iv) couple using diisopropylcarbodiimide (DIPC) and 1-hydroxy-7-benzotriazole (HOBt). After the final terminal amino groups had been deprotected either 11-hydroxyundecanoic acid (**3**), 15-hydroxypentadecanoic acid (**4**) or 20-hydroxyeicosanoic acid (**5**) were attached using DIPC and HOBt. The hydroxyl groups did not need protecting as amino groups are significantly more reactive than hydroxyl groups and only 0.90 equiv of the hydroxy acid was used. The supported hydroxy acids were treated with 2.0 mol % of di-*n*-butyltin oxide in chlorobenzene at 132 °C for 24 h. This brought about cyclo-oligomerization to give homologous families of cyclic oligomers. The beads were filtered off and the solvent evaporated to give the crude macrocycles **6**–**14**. The mixtures were analyzed by size exclusion chromatography (SEC) using a stationary phase capable of resolving oligomers and MALDI TOF mass spectra. The results are summarized in Table 1. The cyclics had from 15 to 27 ring atoms per repeat unit. The procedure for a typical addition of a hydroxy

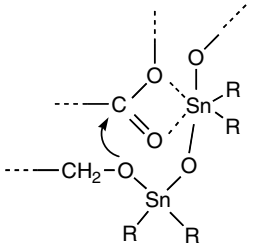
Table 1. Summary of polymer-supported syntheses of macrocyclic products

Entry	Carbon atoms in hydroxy acid and amino acids used[a]	Product	Yield[b] (%)	RA/RU[c]	Composition of cyclic product[d]					Compound isolated[e]
					C1	C2	C3	C4	C5	
1	11 + gly[f]	**6**	63	15	65	19	10	4	2	**15**
2	11 + sar[g]	**7**	60	15	79	17	3	1	—	**16**
3	11 + phe[h]	**8**	90	15	58	39	1	—	—	**17**
4	11 + phe[i]	**8**	64	15	45	47	5	3	—	**17**
5	15 + gly[i]	**9**	64	19	95	3	2	—	—	**18**
6	11 + gly.gly[i]	**10**	56	18	87	12	1	—	—	**19**
7	15 + gly.gly[i]	**11**	35	22	95	2	2	1	—	**20**
8	20 + gly.gly[i]	**12**	30	27	90	5	3	2	—	**21**
9	11 + phe.gly.gly[i]	**13**	48	21	74	17	6	2	1	—
10	11 + pro.phe.gly.gly[i]	**14**	38	24	90	7	3	—	—	—

[a] Amino acids are shown with the N-atoms to the left and the carboxyl groups to the right. Hence the first amino acid attached to the beads is the one on the right. Loadings of the first amino acids are given in the footnotes.
[b] The yield of cyclic products after removing the polymer beads relative to the amount of the first amino acid residue.
[c] RA/RU = ring atoms per repeat unit.
[d] By SEC: calibrated with cyclic oligoundecanoates.[23]
[e] By preparative HPLC. See Scheme 3.
[f] Loading of amino acid 0.98 mmol/g based on elemental analyses for N and Cl.
[g] Loading of amino acid 1.70 mmol/g based on elemental analyses for N and Cl.
[h] Loading of L-amino acid 0.70 mmol/g based on elemental analyses for N and Cl.
[i] Loading of L-amino acid 2.76 mmol/g based on elemental analyses for N and Cl.

acid and cyclo-oligomerization is given below.[19] Our previous work[8] indicates that there was a degree of site isolation in the cyclo-oligomerizations of supported 11-hydroxyundecanoic acid (**3**) and 12-hydroxydodecanoic acid at loadings of <1.0 mmol/g. Consistent with this, in the present work, where there are more ring atoms present in the cyclized hydroxy acids, the major products were the smallest strainless rings, that is, the cyclic monomers, and the larger rings were then present in progressively decreasing amounts as the rings become larger.[20] When a substantially higher loading was used, as in the reaction summarized in entry 4 (compare entry 3), oligomerization was more important and there were higher proportions of the cyclic dimer and higher oligomers.

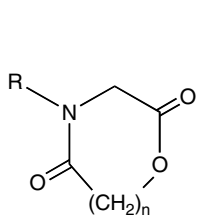
The means by which di-*n*-butyltin oxide catalyses transesterifications is unclear.[21] Tin(IV) species may interact with the O-atom of the carbonyl group and so activate it to nucleophilic attack. Tin(IV) alkoxides may also be involved, as may the tendency to form $-SnR_2-O-SnR_2-$ linkages. The latter may actually organize the reactive species. A scheme which includes all these features is shown in Scheme 3. In practice the di-*n*-butyltin oxide almost certainly first binds to the hydroxyl end groups. Accordingly at the end of the cyclization reaction, the tin species may be bound to the supported hydroxyl groups. However, elemental analyses on the recovered polymer and the products from selected cyclizations indicate that only about 75% of the tin is polymer bound with about 25% being soluble. The tin residues were removed easily by passing a solution of the macrocycles in chloroform down a short column of alumina.



Scheme 3. Suggested mechanism of catalysis of transesterification by di-*n*-butyltin oxide. In the present reactions R = *n*-butyl.

In several cases (see Table 1) the cyclic monomers were isolated by preparative HPLC and characterized by FTIR and ^{1}H NMR spectroscopies and elemental analyses. The structures of these, **15**–**21**, are shown in Scheme 4. To check whether the chiral center in product **17** was racemised by the reaction conditions, a portion was resubjected to the cyclo-oligomerization conditions and the cyclic monomer was then reisolated. The optical rotation was, within the experimental error, unchanged.

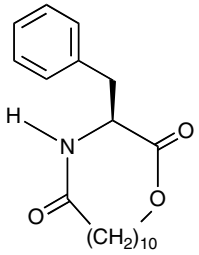
In conclusion, a simple PS cyclization-cleavage method is described for the small-scale synthesis of cyclic oligodepsipeptides with 15 to 27 ring atoms per repeat unit. In selected cases the cyclic monomers were isolated and characterized. It should, however, be noted that if cyclic oligomers are needed for the preparation of static[4,5] or dynamic[6] combinatorial libraries of macrocycles or for ring-opening polymerizations,[2] *all members* of the family of macrocyclic oligomers are of interest as they all react through equilibration to give the same products. Studies to prepare libraries using the above products are underway. It should also be noted that macrocycles of the above general type may also serve as mimics of β-turns in peptides and proteins.[22]



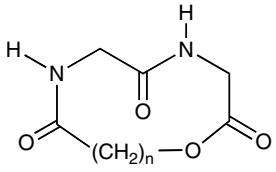
(**15**): R = H; n = 10; mp 101 - 102 °C

(**16**): R = CH_3; n = 10; mp 76 - 77 °C

(**18**): R = H; n = 14; mp 73 - 74 °C



(**17**): mp 127 - 129 °C



(**19**): n = 10; mp 120 - 121 °C

(**20**): n = 14; mp 134 - 135 °C dec.

(**21**): n =19; mp 142 - 143 °C dec.

Scheme 4. Cyclic monomers that were isolated. Products were recrystallized from ether-ethyl acetate.

Acknowledgements

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19. The following, see Table 1 entry 4, is typical of the procedures used. *(i) Synthesis of PS Phe-11-hydroxyundecanoate:* A DMF (25 mL) suspension of PS Phe (1.00 g, 2.76 mmol), containing 11-hydroxyundecanoic acid (0.500 g, 2.48 mmol), DIPC (0.46 mL, $d = 0.815$ g/mL, 2.98 mmol), and HOBt anhydrous (0.40 g, 2.98 mmol) was stirred for 30 h at 20 °C. The resin was collected by filtration and washed successively with DMF, dichloromethane, ethanol, and acetone before being dried at 45 °C in vaccuo to give the desired product (1.360 g). The weight gain corresponds to 1.44 mmol of acid per gram. FTIR (KBr disc) ν_{max} 1736 and 1652 cm^{-1}. By elemental analysis nitrogen = 2.79%. Calcd N = 2.84%. IR (KBr):
(ii) Cyclo-oligomerisation of PS Phe-11-hydroxyundecanoate: PS Phe-11-hydroxyundecanoate (1.23 g, 1.77 mmol) was suspended in chlorobenzene (55 mL). Di-*n*-butyltin oxide (2 mol %, 0.010 g, 0.042 mmol) was added and the mixture was heated under reflux for 24 h. The resin was recovered and washed with chloroform. The combined filtrate and washings were evaporated to give the cyclic oligomers **8** as a pale yellow solid (0.374 g, 64% yield). The percentage composition of cyclic *n*-mers by weight, as estimated by SEC analysis, is summarized in Table 1, entry 1. The MALDI-ToF mass spectrum showed peaks, $[M+Na]^+$, due to cyclic monomer up to the cyclic hexamer.
(iii) Isolation of the cyclic monomer (**17**): A portion (90 mg) of the crude soluble product described above was fractionated by preparative HPLC (eluent: 50/50 v/v ethyl acetate–hexane, direct phase, flow rate: 15 mL/min). This gave, after recrystallization from ethyl acetate–hexane, the pure cyclic monomer **17** (40 mg) as a white solid. It had mp 128–129 °C and $[\alpha]_D^{22}$ −11.4 (*c*, 1.2 in $CHCl_3$); FTIR (KBr): ν_{max} 3330 (m, =C–H), 2922–2852 (m, –C–H), 1735 (s, C=O, ester), 1647 (s, C=O, amide), 1533 (m, N–H bend), 1244 (m, C–O) cm^{-1}; ^{1}H NMR (500 MHz): δ 7.32–7.25 (m, 3H, Ar–C*H*), 7.17–7.14 (m, 2H, Ar–C*H*), 5.75 (d, 1H, N*H*, $J = 8.5$ Hz), 5.00–4.96 (m, 1H, H(α)), 4.13 (m, 2H, O–CH_2), 3.17–3.09 (m, 2H, CH_2Ph), 2.31–2.26 (m, 1H), 2.12–2.06 (m, 1H), 1.87–1.81 (m, 1H), 1.70–1.18 (m, 15H) ppm. ^{13}C NMR (125.82 MHz): δ 172.4, 171.3, 136.1, 129.3, 128.6, 127.0, 65.5, 53.2, 38.1, 35.4, 27.5, 27.4, 26.61, 26.59, 26.4, 25.9, 24.9, 24.1 ppm. EI calcd 331.21. Found: 331.
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