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A Post-Modification Strategy for the Synthesis of Uniform, Hydrophilic/Hydrophobic Patterned α-Hydroxy Acid Oligomers

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Hydrophilic/hydrophobic patterning is a well-established design strategy to guide secondary structure formation of both natural as well as non-natural oligomers and polymers. This contribution explores the feasibility of a new approach for the synthesis of uniform, sequence-defined, hydrophilic/hydrophobic patterned oligo(α-hydroxy acid)s. The proposed strategy is based on post-modification of a reactive oligoester scaffold composed of an alternating sequence of hydrophobic [(2*S*)-2-hydroxy-4-methylpentanoic acid] and masked hydrophilic [(2*S*)-2-hydroxypent-4-enoic acid] α-hydroxy acids. The use of (2*S*)-2-hydroxypent-4-enoic acid instead of a complex side-chain-protected hydrophilic building block obviates the need for additional protective group chemistry during chain extension. In a subsequent post-modification step, the allyl side chains can be quantitatively modified via free-radical addition of different ω-functional thiols to afford hydrophilic/hydrophobic patterned oligoesters. The proposed synthetic strategy provides an interesting alternative to rapidly generate libraries of foldamers with identical chain length and monomer sequence but different side-chain functionalities.

Introduction

Foldamers are synthetic oligomers that can fold into conformationally ordered states akin to those of peptides, nucleic acids or polysaccharides.[1–3] Foldamers represent an attractive tool to probe and understand the basic sequence-structure-function relationships that govern protein folding. In addition, many foldamers have been reported with interesting properties that could be useful for a variety of applications. Amongst others, foldamers have been prepared that possess host-guest properties,[4–6] display antimicrobial[7–10] or enzymatic activities,[11] act as antagonists to inhibit the anticoagulant function of heparin[12] or as HIV fusion inhibitor,[13] modify the growth of calcite crystals[14] or can be used as thermal sensors.[15]

The foldamers that have been reported so far are extremely diverse with regards to the nature of the building blocks from which they have been constructed.[1–3] A class of building blocks that has received only limited attention are α-hydroxy acids. Oligo(α-hydroxy acid) foldamers, however, are of potential interest for a number of reasons. First of all, oligo(α-hydroxy acid)s are structurally related to peptides, but lack amide bonds in their main chain. As a result, a comparison of the folding properties of oligo(α-hydroxy acid)s to those of the corresponding peptide analogues could provide insight into the role of hydrogen bonding in the formation of peptide/protein secondary structures. Furthermore, in contrast to many of the other foldamers reported so far, oligo(α-hydroxy acid)s are potentially hydrolytically degradable, which could be advantageous for future medical or biological applications.

In the literature, two strategies for the synthesis of uniform, sequence-defined oligo(α-hydroxy acid)s have been reported.[16] Huang and Hermes described a convergent/divergent solution approach for the preparation of perfectly alternating L-lactic acid-co-glycolic acid oligomers containing up to 16 structural units.[17] These oligomers were prepared from an orthogonally protected L-lactic acid-co-glycolic acid dimer containing a methoxyethoxymethyl ether (MEM) and a benzyl ester group to selectively block the hydroxy and the carboxylic acid functional groups, respectively, and were generated using 1,3-dicyclohexylcarbodiimide (DCC)/4-(dimethylamino)pyridine (DMAP) coupling chemistry for chain extension. Kuisle et al. have developed a solid phase strategy for the preparation of uniform, sequence-specific oligo(α-hydroxy acid)s based on tetrahydropyranyl (THP) ether-protected building blocks.[18,19] Synthesis was carried out on a Wang resin and oligomers containing up to eight α-hydroxy acid units were obtained

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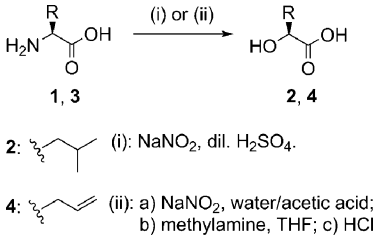
via repetitive sequences of *N*,*N*′-diisopropylcarbodiimide (DIC)/DMAP mediated coupling reactions and deprotection steps. As the work by Huang and Hermes and Kuisle et al. was not aimed at the preparation of oligomers with defined monomer sequences that can induce folding into specific secondary structures, the conformational properties of the oligo(α-hydroxy acid)s were not investigated. Related work by Seebach and co-workers has focused on the synthesis and structure of oligo(3-hydroxyalkanoate)s, i.e. oligo(β-hydroxy acid)s.[20–22] Following a convergent/divergent solution phase strategy that involved the use of (*tert*-butyl)diphenylsilyl (TBDPS) and benzyl ester protecting group chemistry and acid chloride/pyridine mediated chain extension, Lengweiler et al. were able to prepare uniform oligomers containing up to 128 repeat units. Circular dichroism and NMR spectroscopy studies on oligo(3-hydroxyalkanoate) analogues of helix forming β-peptides, however, did not provide evidence for the formation of conformationally ordered solution states.[23–25]

In this contribution, we report a novel synthetic strategy for the preparation of uniform, sequence-defined α-hydroxy acid oligomers that are designed to fold into regular β-sheet secondary structures. To guide secondary structure formation, the α-hydroxy acid oligomers are patterned with an alternating sequence of hydrophilic and hydrophobic substituents. This concept of hydrophilic/hydrophobic patterning has already been successfully applied to direct folding of de novo designed peptides as well as non-natural oligomers and polymers and it has been shown that alternating sequences of hydrophilic (P) and hydrophobic (NP) residues can promote the formation of β-sheet structures.[8,9,26–44] The synthesis of uniform hydrophilic/hydrophobic patterned oligomers typically involves a repetitive sequence of coupling and deprotection reactions using a hydrophobic and an appropriate side-chain-protected hydrophilic building block followed by a deprotection step to remove the side-chain protective groups from the hydrophilic repeat units. This contribution explores the feasibility of an alternative synthetic strategy, which is based on post-modification of a reactive oligoester scaffold. The hydrophilic/hydrophobic patterned oligomers that will be discussed here are based on an oligoester scaffold composed of (2*S*)-2-hydroxy-4-methylpentanoic acid (a leucine analogue) as the hydrophobic (NP) and (2*S*)-2-hydroxypent-4-enoic acid as a masked hydrophilic (P) building block. The use of (2*S*)-2-hydroxypent-4-enoic acid obviates the need for additional protective group chemistry to block side chain functional groups that could interfere with the chain extension. It also facilitates the access to libraries of hydrophilic/hydrophobic patterned oligomers with diverse hydrophilic functional groups since the allyl side chains can be smoothly converted into a variety of functional groups via radical addition of appropriate ω-functional thiols.[45–47] The focus of the present contribution is on establishing the feasibility of the proposed post-modification strategy and the structural characterization of the resulting oligomers. The conformational properties and self-assembling behavior of these materials will be subject of forthcoming publications.

Results and Discussion

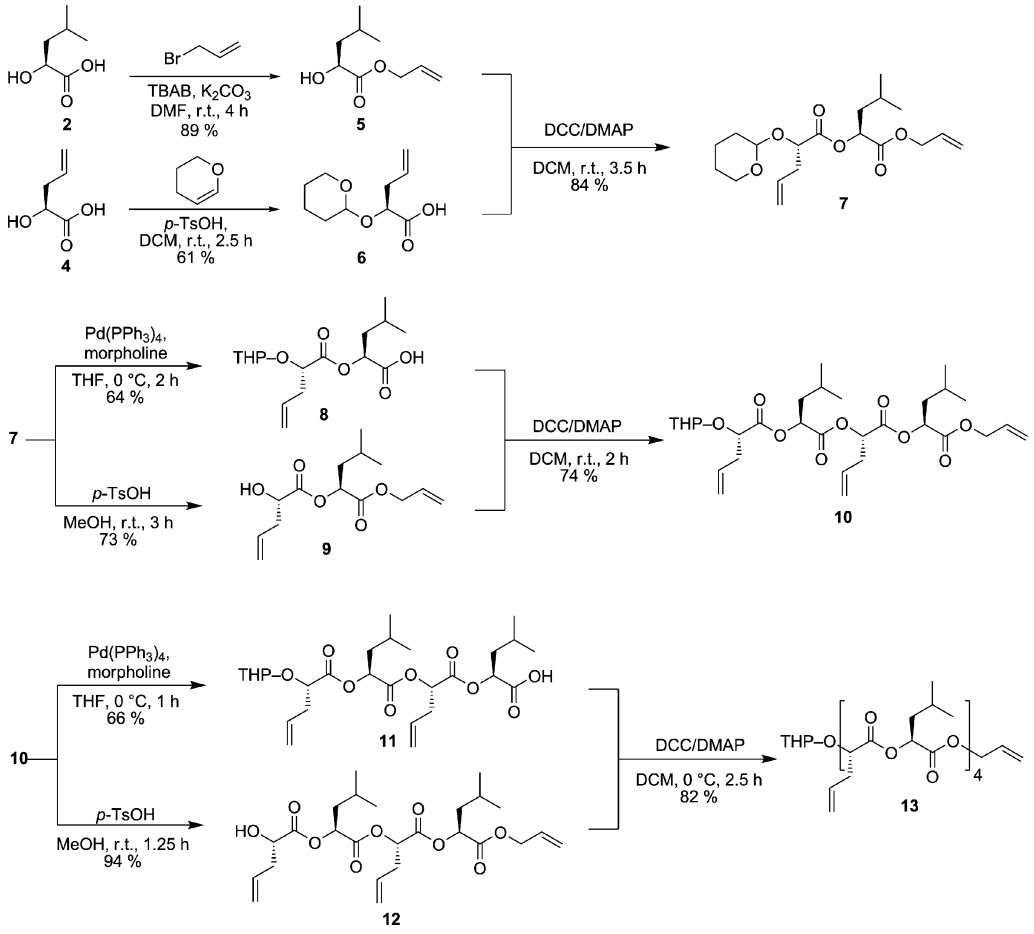
Synthesis of the Oligoester Scaffold

Starting compounds for the synthesis of the targeted oligoester scaffolds were L-leucine and L-allylglycine. L-Allylglycine was prepared in three steps from (*R*,*R*)-(–)-pseudoephedrine and glycine methyl ester according to a procedure published by Myers et al.[48] Subsequently, via a one step diazotization reaction, L-leucine and L-allylglycine were converted into the corresponding α-hydroxy acids (Scheme 1). (2*S*)-2-Hydroxy-4-methylpentanoic acid (**2**) was readily obtained in 88% yield following a literature procedure, by diazotization of L-leucine using $NaNO_2$ in an aqueous solution of H_2SO_4.[49] Application of this procedure to the synthesis of (2*S*)-2-hydroxypent-4-enoic acid (**4**), however, did not yield satisfactory results. Compound **4** was obtained in 69% yield according to another literature procedure that involved reaction of L-allylglycine with $NaNO_2$ in a 8:2 (v/v) mixture of water and acetic acid, followed by quenching the reaction with methylamine.[50]



Scheme 1. Synthesis of α-hydroxy acids **2** and **4**.

The synthesis of oligoester scaffolds consisting of 2, 4 or 8 alternating repeat units of **2** and **4** is shown in Scheme 2. The oligomers were prepared via a convergent/divergent growth process, which required orthogonal protection of both chain ends. The synthetic route outlined in Scheme 2 is based on a protective group strategy that uses tetrahydropyran (THP) ether and allyl ester groups to mask the hydroxy and carboxylic terminal groups, respectively. The hydroxy group of **4** was protected by reacting the hydroxy acid with an excess of dihydropyran (1.4 equiv.) in the presence of a catalytic amount of *p*TosOH (0.02 equiv.) to give **6** as a mixture of diastereoisomers.[51] The carboxylic acid group of **2** was masked as an allyl ester and was prepared using allyl bromide in the presence of tetrabutyl ammonium bromide and potassium carbonate to afford **5** in 89% yield. According to ^{1}H NMR spectroscopy, **5** was obtained in ca. 90% purity (see Supporting Information, Figure S3). The ESI-TOF mass spectrum of **5** revealed the presence of allyl ester-protected (2*S*)-2-hydroxy-4-methylpentanoic acid oligomers byproducts (Supporting Information, Figure S4). These side products, which are probably the result of transesterification reactions that accompany the protection reaction, could not be separated with column chromatography. It was found, however, that the coupling products of these



Scheme 2. Synthetic route for the preparation of oligo(α-hydroxy acid)s **7**, **10** and **13**.

dimeric and trimeric (2*S*)-2-hydroxy-4-methylpentanoic acid impurities could be easily removed after the esterification/chain extension step so that the desired oligomers could be isolated as the pure tetra- or octamers (vide infra).

Chain extension was carried out by reacting 1.1 equiv. of the monoprotected carboxylic acid building block and 1 equiv. of the monoprotected hydroxy building block in CH_2Cl_2 in the presence of 1.1 equiv. DCC as a coupling agent and a catalytic amount of DMAP (0.1 equiv.). In this way, the double-protected dimer **7** was obtained in 84% yield after column chromatography. Compound **7** was characterized by ^1H and ^{13}C NMR spectroscopy, as well as ESI-TOF mass spectrometry. ^1H NMR and ^{13}C NMR spectra of **7** are included in the Supporting Information (Figure S5 and S6). Within the experimental accuracy (ca. 5%), the experimentally determined integrals in the ^1H NMR spectrum agreed with the expected values, indicating that compound **7** was isolated with a purity of ≥ 95%. The ESI-TOF mass spectrum of **7** is shown in Figure 1 (A). The signals at *m*/*z* 355.2130, 377.1741 and 393.1598 represent the $[M + H]^+$, $[M + Na]^+$ and $[M + K]^+$ ions of the desired compound **7**, respectively. In addition, Figure 1 (A) reveals signals at *m*/*z* 491.2036 and 605.2910, which were assigned to sodium adducts of side-products due to coupling of the allyl ester-protected (2*S*)-2-hydroxy-4-methylpentanoic acid dimers and trimers with **6**. As the integrals of the ^1H NMR spectrum of **7** were in good agreement with the expected values, the level of these trace impurities is thought not to exceed ca. 5%. The carboxylic acid function of **7** could be deprotected via Pd^0-catalyzed allyl transfer to morpholine (1.05 equiv.) using tetrakis(triphenylphosphane)palladium(0) [$Pd(PPh_3)_4$] (0.1 equiv.) to give building block **8** in 64% yield after purification. Selective removal of the THP protecting group could be achieved by treating **7** with a catalytic amount of *p*TosOH (1 mg mL^{-1}) in dry methanol yielding intermediate **9** in good yield. The acid **8** and the alcohol **9** were subsequently coupled using 0.1 equiv. DMAP and a slightly higher excess of DCC (1.4 equiv.) to favor the formation of the *O*-acylisourea intermediate. Column chromatography using a mixture of diethyl ether and pentane as the eluent allowed to successfully remove by-products that were generated due to reaction of the impurities present in **7** and afforded tetramer **10** in 74% yield. The ESI-TOF mass spectrum of **10** in Figure 1 (B) shows signals at *m*/*z* 589.3011 and 605.3306 corresponding to $[M + Na]^+$ and $[M + K]^+$ ions, respectively. The ^1H and ^{13}C NMR spectra of **10** are included in the Supporting Information (Figure S7 and S8). Selective deprotection of **10** using the

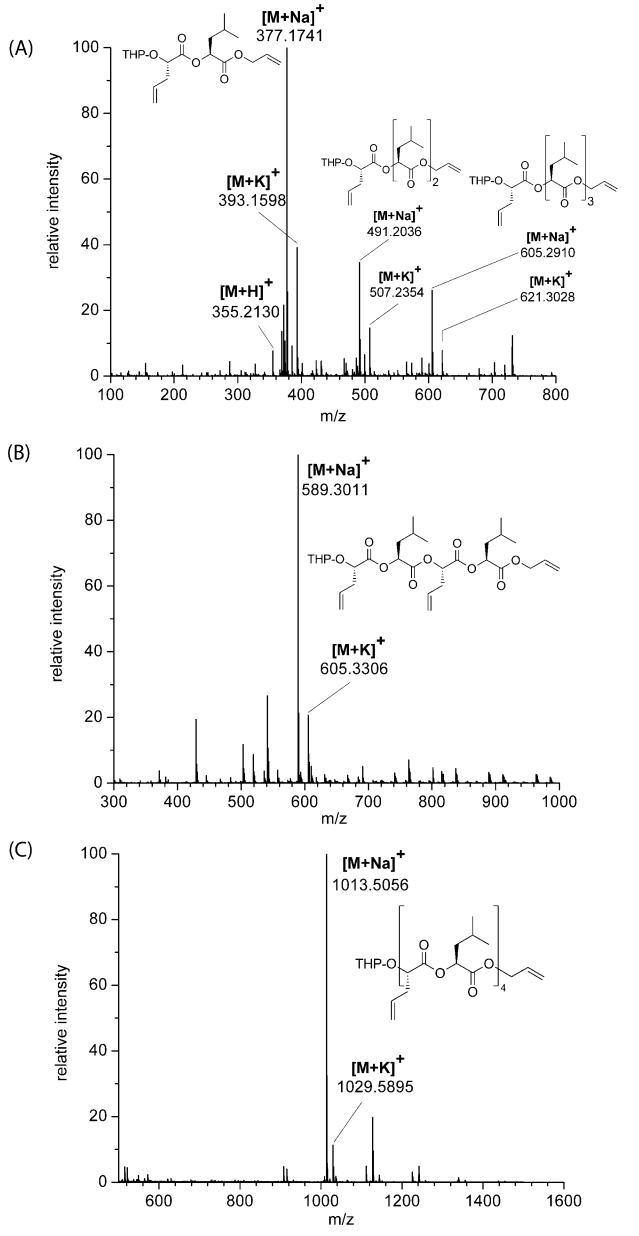


Figure 1. ESI-TOF mass spectra of (A) dimer **7**; (B) tetramer **10**; (C) octamer **13**.

same reaction conditions that were also used for dimer **7** afforded carboxylic acid **11** and alcohol **12** in 66% and 94% yield, respectively. Subsequent coupling of **11** and **12** at 0 °C, finally gave the octamer **13** in 82% isolated yield after column chromatography. ^{1}H and ^{13}C NMR spectra of **13** are included in the Supporting Information (Figure S9 and S10). The ESI-TOF mass spectrum shown in Figure 1 (C) reveals two major peaks at *m*/*z* 1013.5056 and 1029.5895, which can be assigned to the sodium ($[M + Na]^+$) and potassium ($[M + K]^+$) adducts of **13**.

While an accurate mass (< 5 ppm) could be obtained by ESI-TOF-MS for each of the compounds **7**, **10** and **13** (see Table 1), mass measurements alone do not provide information about the primary structure, i.e. hydroxy acid sequence, of these oligomers. To verify the alternating primary structure, oligomers **10** and **13** were analyzed by ESI tandem mass spectrometry. Collision-induced dissociation (CID) relies on the dissociation of a precursor ion upon collision with neutral gas molecules to induce fragmentation of the molecule along the most labile bonds. Following the nomenclature that is used to describe peptide fragmentation patterns, the fragment ions generated after dissociation of the ester bonds are named *b*- or *y*-ions if they originate from the *O*-terminal or *C*-terminal part of the oligomer, respectively.[52,53] Figure 2 shows the fragmentation patterns observed for the sodium adducts of tetramer **10** and octamer **13**. The losses of 98 and 114 Da correspond to the fragmentation of $C_5H_6O_2$ [(2*S*)-2-hydroxypent-4-enoic acid residue] and $C_6H_{10}O_2$ [(2*S*)-2-hydroxy-4-methylpentanoic acid residue], respectively. The dominant peaks in the MS/MS spectra, located at *m*/*z* 505.3624 and 929.5825 for tetramer **10** and octamer **13** respectively, are due to the loss of the *O*-terminal THP group. Signals at *m*/*z* 463.3110 and 887.5460 for tetramer **10** and octamer **13**, respectively, correspond to subsequent loss of the allyl ester protecting group. The fragment ions of the $[M + Na]^+$ adduct of the tetramer **10** and octamer **13** have been assigned to c_n/z_n that are formed after loss of the protecting groups (series are annotated in the full spectrum). These MS/MS data confirm the strictly alternating structure of (2*S*)-2-hydroxy-4-methylpentanoic acid and (2*S*)-2-hydroxypent-4-enoic acid residues.

Table 1. Summary of theoretical and experimental masses of H^+/Na^+ adducts of the different oligo(α-hydroxy acid)s as measured by ESI-TOF-MS.

Product	Composition	$M_{theor.}$ [Da]	$M_{exp.}$ [Da]	Mass accuracy [ppm]
7	$C_{19}H_{30}O_6 + H^+$	355.2121	355.2130	2.53
10	$C_{30}H_{46}O_{10} + Na^+$	589.2989	589.3011	3.73
13	$C_{52}H_{78}O_{18} + Na^+$	1013.5086	1013.5056	2.96
14	$C_{18}H_{30}O_9S_2 + H^+$	455.1410	455.1394	3.52
15	$C_{23}H_{42}O_8S_2 + H^+$	511.2399	511.2414	2.93
16	$C_{18}H_{36}N_2O_5S_2 + H^+$	425.2144	425.2122	5.17
17	$C_{31}H_{50}O_{15}S_3 + H^+$	759.2390	759.2385	0.66
18	$C_{31}H_{59}N_3O_9S_3 + H^+$	714.3492	714.3477	2.10
19	$C_{57}H_{90}O_{27}S_5 + H^+$	1367.4352	1367.4371	1.39
20	$[C_{57}H_{105}N_5O_{17}S_5 + 2H]^{2+}$	646.8133	646.8143	1.55

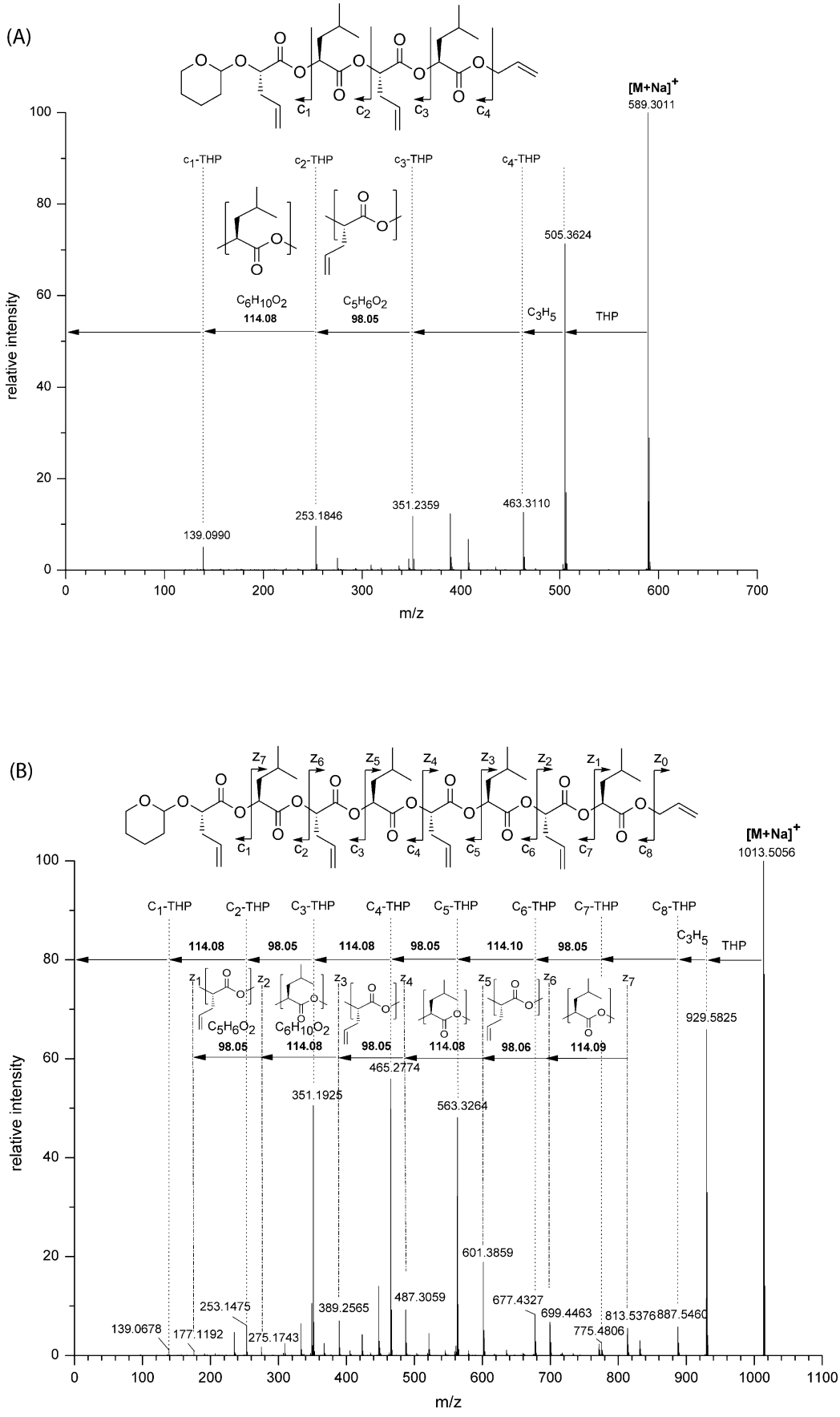
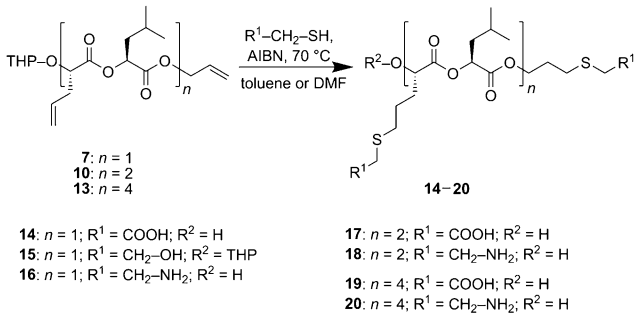


Figure 2. ESI-MS/MS spectra of (A) tetramer **10** and (B) octamer **13**.

Post-Modification

The allyl side group of the (2*S*)-2-hydroxypent-4-enoic acid repeat units in oligomers **7**, **10** and **13** provides a unique chemical handle that can be converted into a wide variety of polar functional groups via radical addition of appropriate ω-functional thiols. In this contribution, the modification of the allyl side groups of the (2*S*)-2-hydroxypent-4-enoic acid repeat units with thioglycolic acid, mercaptoethanol and cysteamine hydrochloride was explored in order to convert these masked hydrophilic repeat units into carboxylic acid, hydroxy and amine groups and generate oligo(α-hydroxy acid)s with an alternating hydrophilic/hydrophobic monomer sequence (Scheme 3).



Scheme 3. Post-modification of dimer **7**, tetramer **10** and octamer **13**.

In a first series of experiments, the conditions for the free-radical addition of the different thiols were optimized using dimer **7** as the substrate. These reactions were carried out at 70 °C for 18 h in toluene or DMF, under nitrogen atmosphere and using different amounts of thiol and AIBN. The progress of the reaction was monitored with ^{1}H NMR spectroscopy and mass spectrometry and the results of these experiments are summarized in Table 2.

Figure 3 compares the ^{1}H NMR spectrum of **7** with ^{1}H NMR spectra of the crude reaction mixtures obtained after modification of **7** with thioglycolic acid under different conditions. To obtain a quantitative conversion of the allyl groups, a 2.5-fold excess of thioglycolic acid with respect to allyl groups was necessary. The quantitative post-modification is apparent by comparison of the ^{1}H NMR spectra in Figure 3 (A, C). The appearance of the methylene proton peaks adjacent to the sulfur atom (**c′**, **f′**, **g′**, **h′**), the disappearance of the olefin protons (**b**, **e**, **c**, **f**) and the shift of proton **d** to **d′** from 4.7–4.5 ppm to 4.4–4.2 ppm indicate a complete conversion of the allyl groups. ^{1}H NMR analysis of the crude reaction mixture of entry #1 in Table 2, which was carried out with an excess of allyl groups relative to thioglycolic acid, reveals that the post-modification reaction is not regioselective. Comparison of the spectra in Figure 3 (A, B) suggests that half of the (2*S*)-2-hydroxypent-4-enoic acid repeat units (intensity of the signal **a**) and half of the allyl protecting groups (intensity of the signal **d**) have been modified.

Whereas a 2.5-fold molar excess of thiol relative to double bonds was sufficient to allow a quantitative post-modification of **7** with thioglycolic acid, these reaction conditions resulted only in the modification of 75% of the allyl groups when mercaptoethanol was used (entry #9 in Table 2). By using a 10-fold excess of mercaptoethanol, however, 90% of the allyl groups of **7** could be modified (entry #10 in Table 2). In contrast to thioglycolic acid and mercaptoethanol, cysteamine hydrochloride is only poorly soluble in toluene. Post-modification of **7** with cysteamine hydrochloride in toluene was carried out under heterogeneous conditions and resulted in incomplete double bond conversion (entry #11 in Table 2). When DMF instead of toluene was used as the solvent, a homogeneous reaction mixture was obtained and the allyl group conversion was quantitative under the same reaction conditions (entry #12 in Table 2). ^{1}H NMR spectra and ESI-TOF mass spectra of the post-modified analogues of **7** (**14**, **15** and **16**) are shown in Figures 4 and 5, respectively. The ^{1}H NMR spectra illustrate the quantitative allyl group conversion upon post-modification of **7** with thioglycolic acid and cysteamine hydrochloride and reveal the presence of residual unreacted allyl groups (ca. 10%) in the mercaptoethanol-modified dimer **15**. Further analysis of the ^{1}H NMR spectra also reveals that the thiol radical addition in some cases is accompanied by partial or complete loss of the THP pro-

Table 2. Summary of reaction conditions that were evaluated to optimize the radical addition of various thiols to **7**.

Entry	Thiol	Solvent	$[C=C]_0/[RSH]_0/[AIBN]_0$	Product	Conversion [% of modified C=C[a]]
1	Thioglycolic acid	toluene	1:0.5:0.02	14	50
2	Thioglycolic acid	toluene	1:1.5:0.02	14	90
3	Thioglycolic acid	toluene	1:1.5:0.2	14	98
4	Thioglycolic acid	toluene	1:2.5:0.2	14	100
5	Thioglycolic acid	toluene	1:10:0.33	14	100
6	Mercaptoethanol	toluene	1:0.5:0.02	15	35–37
7	Mercaptoethanol	toluene	1:1.5:0.02	15	60–70
8	Mercaptoethanol	toluene	1:1.5:0.2	15	50
9	Mercaptoethanol	toluene	1:2.5:0.2	15	75
10	Mercaptoethanol	toluene	1:10:0.33	15	90
11	Cysteamine hydrochloride	toluene	1:10:0.33	16	50
12	Cysteamine hydrochloride	DMF	1:10:0.33	16	100

[a] Based on ^{1}H NMR analysis of the crude reaction mixture.

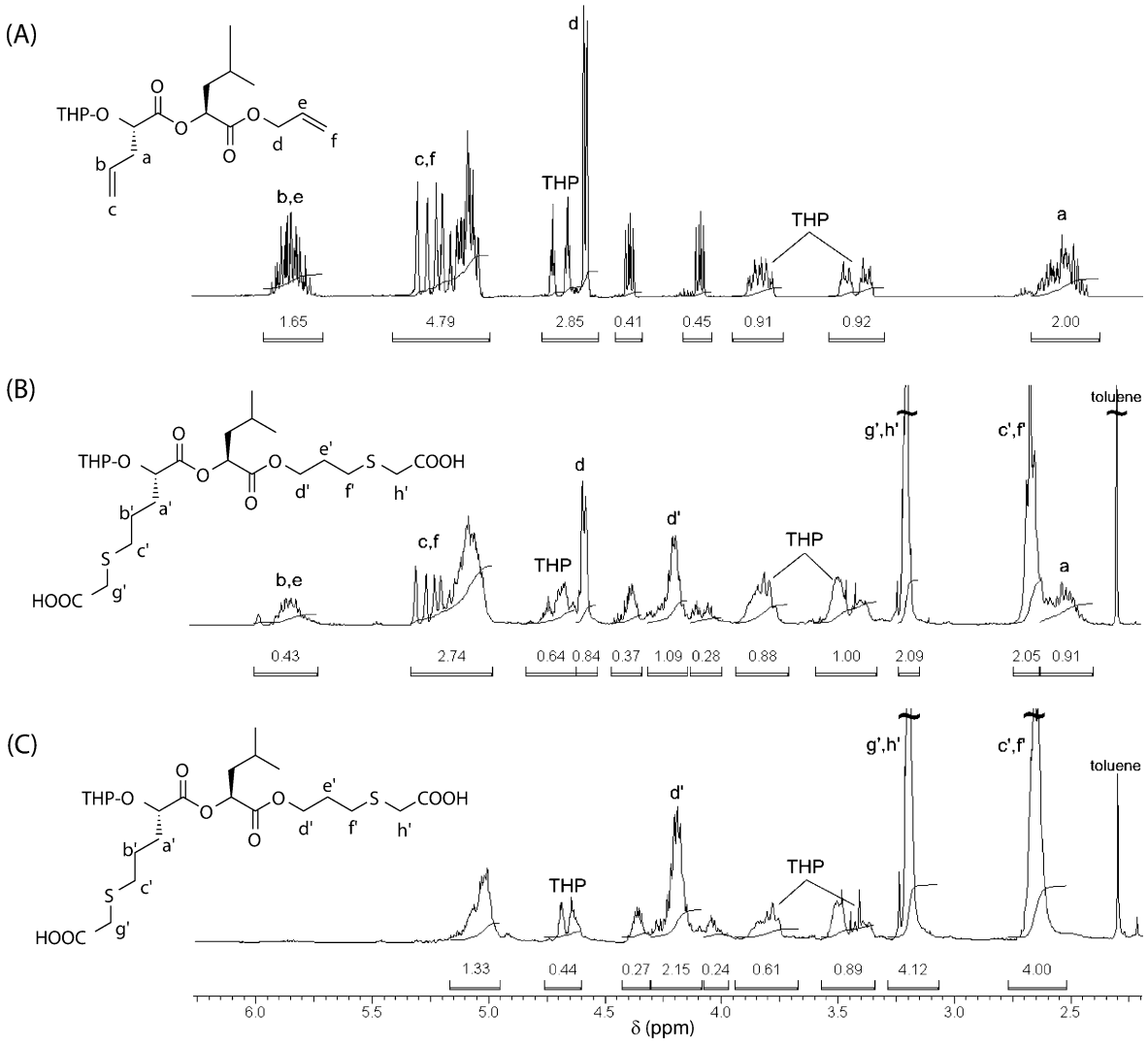


Figure 3. ^{1}H NMR spectra ($CDCl_3$) of (A) dimer **7**; (B) the crude reaction mixture obtained after modification of **7** using $[C=C]_0/[RSH]_0/[AIBN]_0$ = 1:0.5:0.02 (≈ 50% conversion) (entry #1, Table 2); (C) the crude reaction mixture obtained after modification of **7** using $[C=C]_0/[RSH]_0/[AIBN]_0$ = 1:2.5:0.2 (quantitative) (entry #4, Table 2).

tecting group. According to the ^{1}H NMR spectra of the crude reaction mixtures of entries #5, #10 and #12 from Table 2, THP cleavage was quantitative for dimer **14**, partial for **16** and absent for the radical addition of mercaptoethanol (compound **15**). The ^{1}H NMR spectra further indicate that the radical addition of the different thiols to **7** proceeded in the expected *anti*-Markovnikov fashion.[46,54–59] Markovnikov addition products should have produced a multiplet at 1.2–1.3 ppm due to the additional methyl groups and one or two quartets between 2.7–3.0 ppm due to additional methylene groups adjacent to the sulfur atoms, which are absent in the spectra in Figure 4. The ESI-TOF mass spectra of the post-modified dimers **14**, **15** and **16** are shown in Figure 5. The major peaks in the mass spectra at $[M + H]^+$ 455.1394, 511.2414 and 425.2122 correspond to the quantitatively post-modified dimers. The mass spectra further confirm that the thiol radical addition is accompanied by complete or partial loss of the THP protecting groups in case of thioglycolic acid and cysteamine hydrochloride and that post-modification with mercaptoethanol does not affect the THP group. The peak at *m*/*z* 509.2753 in the mass spectrum of **16** represents the $[M + H]^+$ signal of the THP-protected, post-modified dimer.

The results summarized in Table 2 provided the starting point for the post-modification of the longer oligomers **10** and **13**. A first attempt to post-modify tetramer **10** with a 2.5-fold excess of thioglycolic acid only resulted in partial conversion of the double bonds (ca. 70%). When the reaction was carried out with a 10-fold excess of thioglycolic acid, however, i.e. $[C=C]_0/[RSH]_0/[AIBN]_0$ = 1:10:0.3, quantitative allyl group conversion was obtained. These reaction conditions were subsequently also successfully used for the post-modification of **10** with cysteamine hydrochloride as well as for the post-modification of **13** with thioglycolic acid and cysteamine hydrochloride. In all cases, the ^{1}H NMR spectra of the crude reaction mixtures indicated

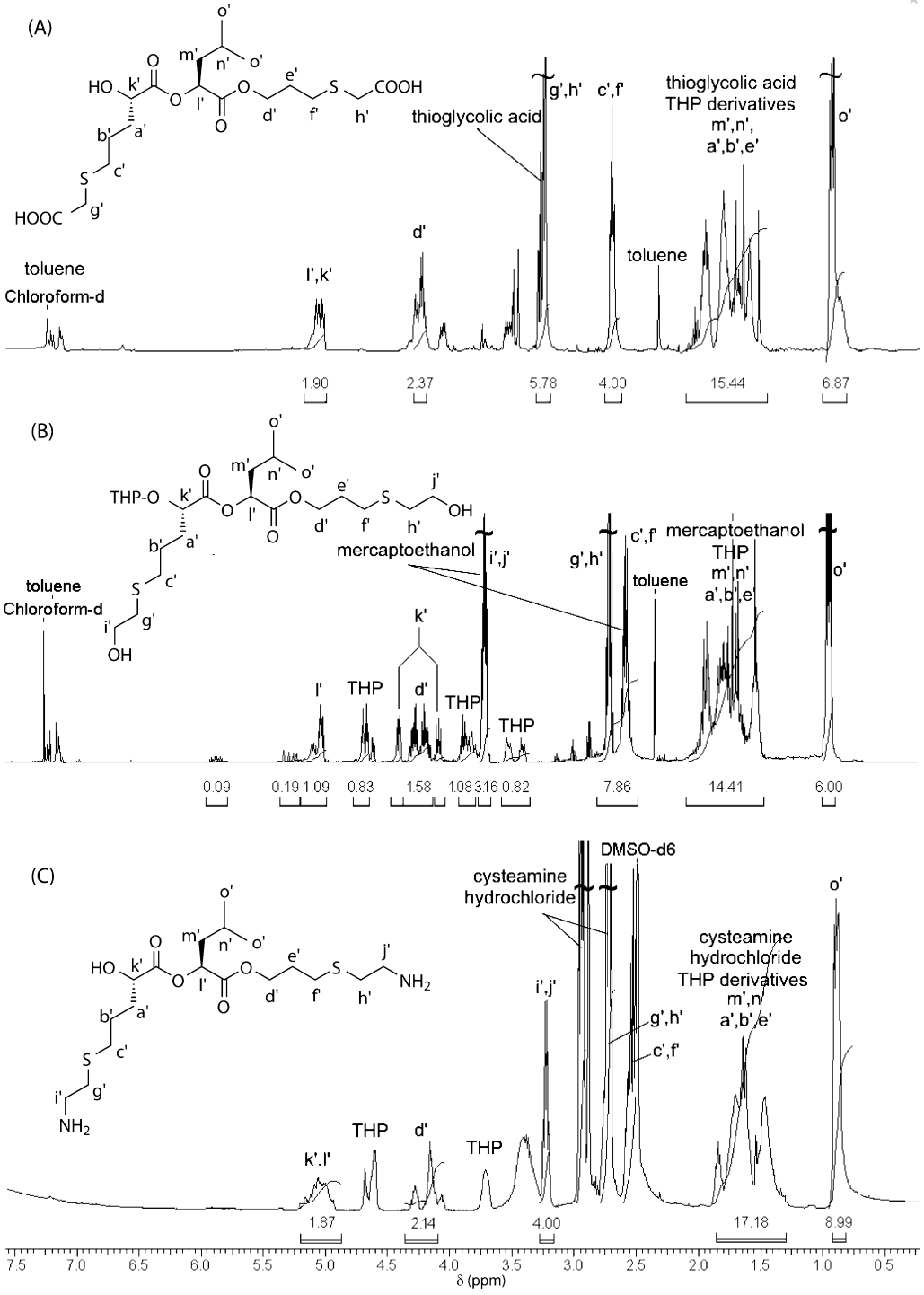


Figure 4. ^{1}H NMR spectra of crude mixtures after radical additions of various thiols to **7** using $[C{=}C]_0/[RSH]_0/[AIBN]_0$ = 1:10:0.33. (A) thioglycolic acid-modified dimer (**14**) (entry #5, Table 2); (B) mercaptoethanol-modified dimer (**15**) (entry #10, Table 2); (C) cysteamine hydrochloride-modified dimer (**16**) (entry #12, Table 2).

quantitative allyl group conversion. To remove the excess of thiol, the crude products were purified with RP-HPLC to afford the pure post-modified oligomers **17**, **18**, **19** and **20**.

As a representative example, Figure 6 shows the ^{1}H NMR spectra of the purified post-modified oligomers **19** and **20** (^{1}H NMR spectra of **17** and **18** are included in the Supporting Information Figure S11). The absence of any signals due to the allyl side chains confirms the quantitative post-modification. Furthermore, the absence of any resonances due to the THP protecting group that is present in the starting oligomers **10** and **13** indicates that also for these longer oligomers, post-modification is accompanied by loss of the THP protective group. The ^{1}H NMR spectra are supported by the results of ESI-TOF mass spectrometry experi-

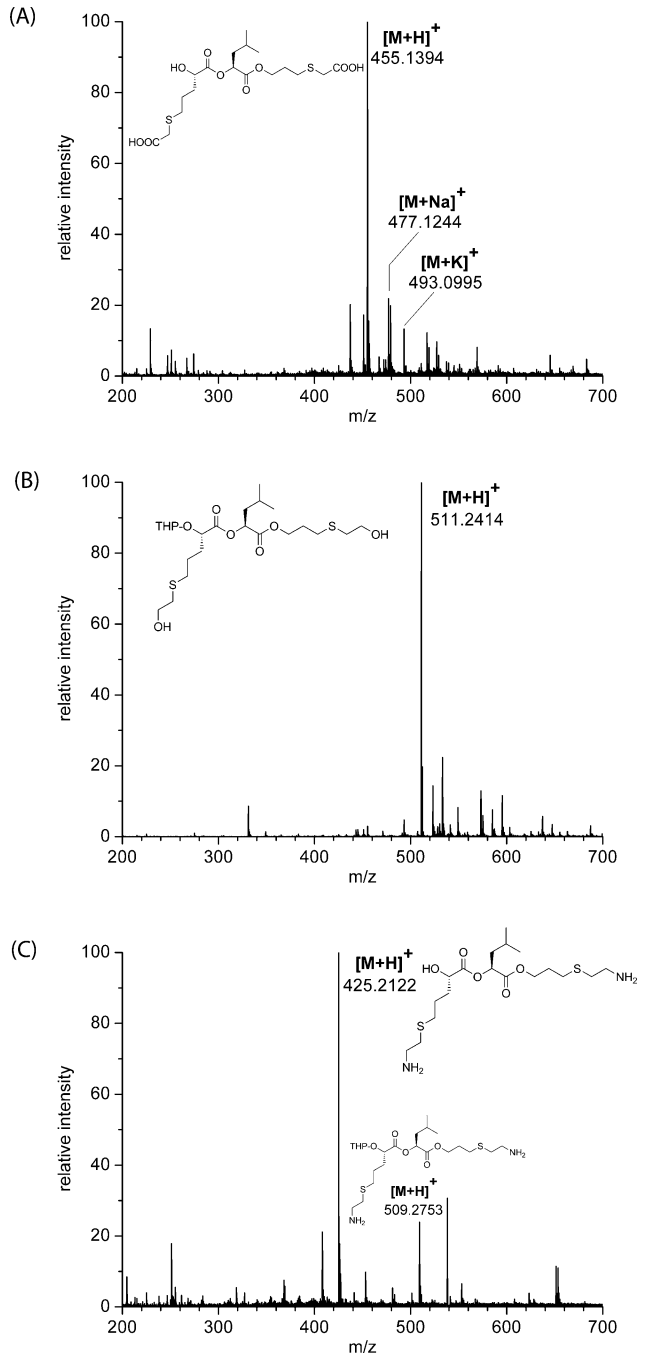


Figure 5. ESI-TOF mass spectra of (A) thioglycolic acid-modified dimer (**14**); (B) mercaptoethanol-modified dimer (**15**); (C) cysteamine hydrochloride-modified dimer (**16**).

ments, which are shown in Figure 7 for **19** and **20** (and in Figure S12 for **17** and **18**). In the ESI mass spectra of oligomers **17**, **18** and **19** protonated molecular ions $[M + H]^+$ could be detected at *m*/*z* 759.2385, 714.3477 and 1367.4371 with a mass accuracy better than 5 ppm (Table 1). The corresponding doubly $[M + 2H]^{2+}$ and triply $[M + 3H]^{3+}$ protonated species were also detected for **18** at *m*/*z* 357.6840 and 238.8021, and for **20** at *m*/*z* 646.8143 and 431.5513, respectively. The ESI-TOF mass spectrum of **20** reveals the presence of both the unprotected **20** as well as the THP-protected cysteamine hydrochloride-modified octamer. Since the ^{1}H NMR spectrum in Figure 7 (C) does not reveal any resonances that can be attributed to the THP group, the THP-protected derivative of **20** is assumed to be present only in trace amounts (< 5%).

To confirm the alternating, hydrophilic/hydrophobic patterned monomer sequence, the post-modified oligomers were analyzed by tandem mass spectrometry. As a representative example, Figure 8 shows ESI-MS/MS spectra of oligomers **17** and **19**. Fragmentation of the protonated oligoesters **17** and **19** (*m*/*z* 759.2390 and 1367.4351, respectively) generally occurred through reactions that involved cleavage of the ester bonds along the oligoester backbone and produced b_n and z_n series of ions. The losses of 114 and 190 Da correspond to the fragmentation of (2*S*)-2-hydroxy-4-methylpentanoic acid and (2*S*)-5-[(carboxymethyl)-thio]-2-hydroxypentanoic acid residues, respectively. Strictly alternating sequences of (2*S*)-2-hydroxy-4-methylpentanoic acid and (2*S*)-5-[(carboxymethyl)thio]-2-hydroxypentanoic acid residues could be observed for both oligoesters. The peak located at *m*/*z* 741.2367 for **17** corresponds to the loss of a water molecule from the parent ion. Water loss was observed on most of the *a* and *b*-ions. The peak at *m*/*z* 695.2334 corresponds to the loss of a carboxylic acid HCOOH (CH_2O_2) group. This loss of ca. 46 Da is also observed for b_1, b_3, z_1, z_2 and z_3 ions, giving the peaks at *m*/*z* 145.0431, 449.1481, 201.1094, 391.1441 and 505.2131, respectively. In the same manner for the octamer **19**, the main peaks at *m*/*z* 1349.4305 and 1303.4187 correspond to the loss of a water molecule from the parent ion and the additional loss of a carboxylic acid CH_2O_2 group, respectively. The additional signal at *m*/*z* 1257.4177 corresponds to the subsequent loss of ca. 46 Da. The product ion at *m*/*z* 133.0543 observed for both oligomers correspond to the $C_5H_9O_2S$ group and could be either the z_0 ion, or the *O*-terminal or the lateral $C_5H_9O_2S$ chains.

Conclusion

In this contribution, we have explored the feasibility of a novel strategy for the preparation of uniform, hydrophilic/hydrophobic patterned α-hydroxy acid oligomers. To avoid complex protective group strategies and side-chain-protected building blocks, the synthetic strategy presented in this report involves post-modification of a reactive oligoester scaffold with a precisely defined length and a strictly alternating sequence of hydrophobic [(2*S*)-2-hydroxy-4-methylpentanoic acid] and masked hydrophilic [(2*S*)-2-hydroxypent-4-enoic acid] α-hydroxy acids. Oligomers containing up to 8 α-hydroxy acid repeat units could be prepared via a straightforward convergent/divergent growth process without the need for protective group chemistry to block the allyl groups of the (2*S*)-2-hydroxypent-4-enoic acid residues during the chain growth process. In a subsequent post-modification step, the allyl side chain functional groups of these oligoesters could be quantitatively modified

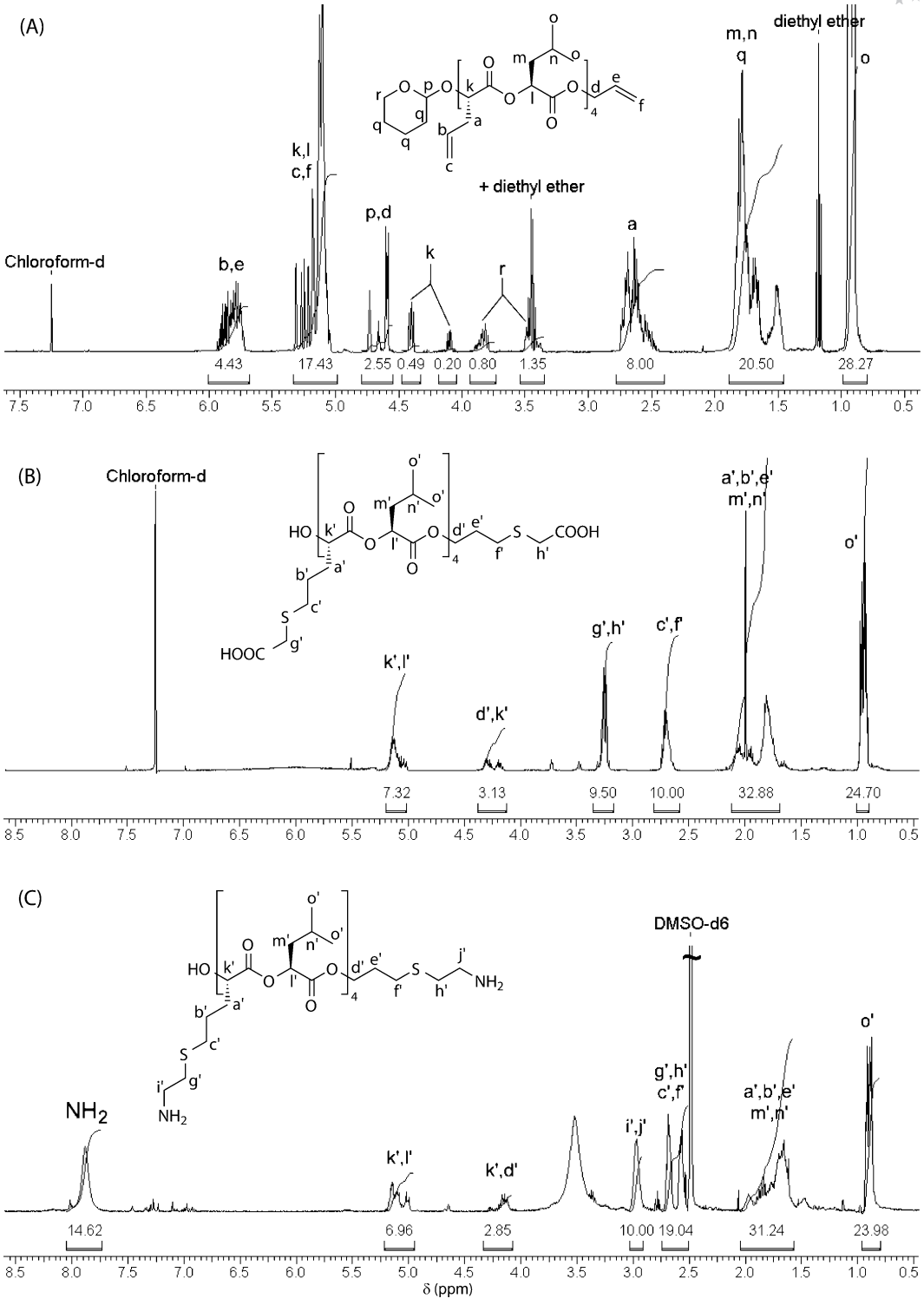


Figure 6. ^{1}H NMR spectra of (A) octamer (**13**); (B) thioglycolic acid-modified octamer (**19**); (C) cysteamine hydrochloride-modified octamer (**20**).

via free-radical addition of various ω-functional thiols to afford hydrophilic/hydrophobic patterned oligoesters. The chemical composition of these oligomers was confirmed by ^{1}H NMR spectroscopy and ESI-TOF mass spectrometry and the alternating hydrophilic/hydrophobic monomer sequence could be confirmed using ESI tandem mass spectrometry experiments. The proposed synthetic strategy may be an interesting alternative approach to generate libraries of foldamers and study the effect of side-chain functionality on folding properties.

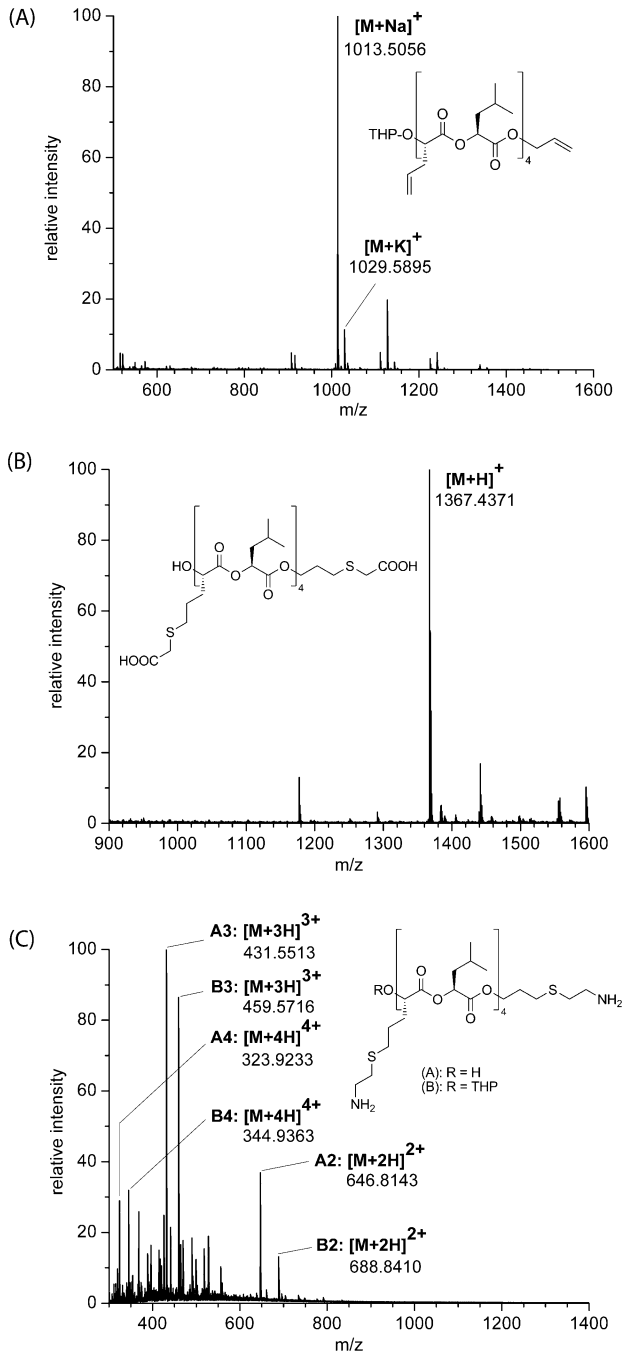


Figure 7. ESI-TOF mass spectra of (A) octamer (**13**); (B) thioglycolic acid-modified octamer (**19**); (C) cysteamine hydrochloride-modified octamer (**20**).

Experimental Section

Materials: All reagents were purchased from Fluka or Sigma–Aldrich and used as received. All reactions were carried out under nitrogen atmosphere in oven-dried glassware (150 °C, for 12 h). Solvents were purified through a PureSolv® System from Innovative Technology under nitrogen prior to use. Column chromatography was performed by using silica gel 60. Thin layer chromatography (TLC) was performed on precoated aluminum sheets (TLC Silica gel 60 F254). Thin layer chromatograms were visualized either under a 254 nm UV light or with iodine, bromocresol, ninhydrin or $KMnO_4$ solutions. Allylglycine was prepared in three steps from (*R*,*R*)-(–)-pseudoephedrine and glycine methyl ester according to a procedure published by Myers et al.[48]

Analytical Methods: ^1H and ^{13}C NMR spectra were recorded using an AVANCE-400 spectrometer (Bruker). Chemical shift values (δ) are reported in ppm and $CDCl_3$ (solvent) (^1H, δ = 7.25 ppm; ^{13}C, δ = 77.0 ppm) or [D_6]DMSO (solvent) (^1H, δ = 2.49 ppm; ^{13}C, δ = 39.50 ppm) was used as internal standard.

Semi-preparative reverse-phase high-pressure liquid chromatography (RP-HPLC) was performed using a Waters Delta 600 instrument equipped with a Waters Atlantis® dC_{18} column (OBD™ 5 μm, 30 × 150 mm). Modified oligomers obtained after radical addition of thioglycolic acid or cysteamine hydrochloride were dissolved in acetonitrile/water (1:1) and DMSO, respectively. The solutions were injected onto the HPLC column and subsequently eluted with linear gradients from 100% ammonium acetate buffer (pH = 7) to 100% acetonitrile, over 30 min. For samples injected in DMSO, an isocratic flow of ammonium acetate (6 min) preceded the gradient elution with ammonium acetate and acetonitrile. The flow rate was 20 mL min^{-1}. Elution was monitored with a UV-detector with dual wavelength detection at 214 nm and 220 nm.

Electrospray ionization mass spectrometry experiments (ESI-MS and ESI-MS/MS) were performed on a quadrupole time-of-flight mass spectrometer (Q-TOF) Ultima API (Waters) fitted with a standard Z-spray source and operated in the positive ionization mode. The lockSpray™ interface was employed for more accurate mass analysis (< 5 ppm). Single MS analyses were followed by MS/MS experiments on the selected precursor ions. The collision energy was manually adjusted for the most efficient and informative fragmentation. The samples were first dissolved in an appropriate solvent and acidified (0.1% HCOOH). Then, 5 μL of the sample solution was introduced into the mass spectrometer by infusion at a flow rate of 10 μL min^{-1} with a solution of MeOH/H_2O/HCOOH, 50:49.9:0.1 (v/v/v). Data analysis was performed using MassLynx™ 4.1 software. External calibration was carried out with 0.05% phosphoric acid.

Procedures

General Procedure for the Ester Coupling Reaction (GP1): A mixture of carboxylic acid (1.1 equiv.), alcohol (1 equiv.) and DMAP (0.1 or 0.05 equiv.) was dissolved in CH_2Cl_2 (0.3 M solution) and cooled to 0 °C. DCC (1.1 equiv. or 1.4 equiv.) was added to the reaction mixture, which was stirred 5 min at 0 °C and then at room temperature. The reaction was followed by TLC and stopped when no more alcohol could be detected. Precipitated urea was filtered off over Celite, the filtrate evaporated to half of its volume and, if necessary, filtered again to remove any residual urea. The CH_2Cl_2 solution was washed twice with 0.5 N HCl, once with a saturated aqueous solution of $NaHCO_3$, dried with $MgSO_4$, concentrated under reduced pressure and dried under high vacuum. The crude product was purified by silica gel column chromatography (CH_2Cl_2 or diethyl ether/pentane, 1:4).

General Procedure for the Allyl Ester Cleavage (GP2): To a solution of allyl ester (1 equiv.) in THF at 0 °C were added $Pd(PPh_3)_4$ (0.1 equiv.) and dropwise morpholine (1.05 equiv.). The reaction mixture was stirred at this temperature until it was judged to be complete as monitored by TLC. The solvent was removed under reduced pressure (30 °C), the remaining residue dissolved in CH_2Cl_2, washed three times with 1 N HCl, dried with $MgSO_4$ and concentrated. The resulting oil was dissolved in diethyl ether, filtered through Celite, concentrated and dried under high vacuum. The crude product was purified by silica gel column chromatography (diethyl ether/pentane, 4:1).

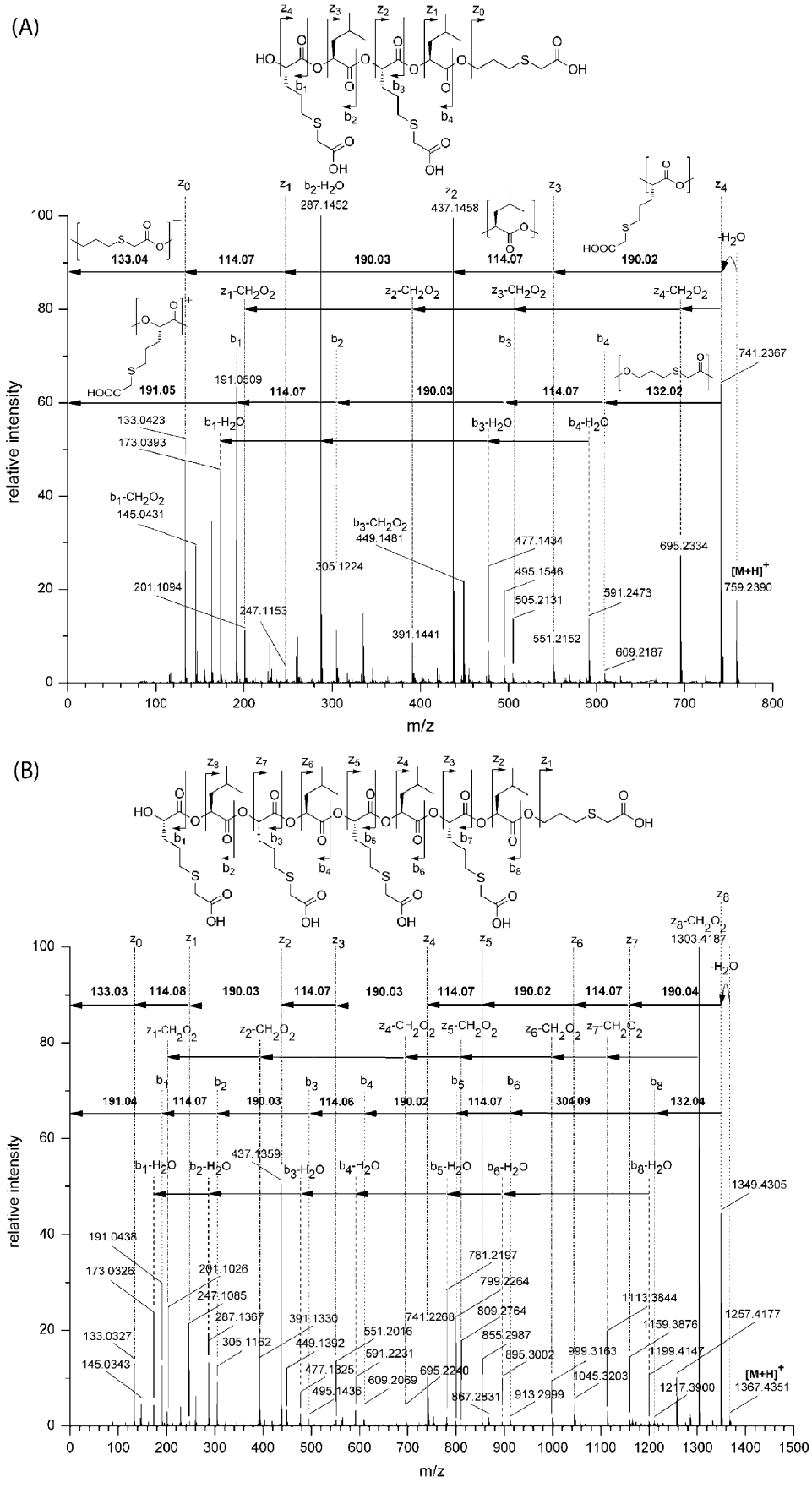


Figure 8. ESI-MS/MS spectra of (A) thioglycolic acid-modified tetramer (**17**) and (B) thioglycolic acid-modified octamer (**19**).

General Procedure for the THP Ether Cleavage (GP3): The THP-protected oligomer (1 equiv.) was treated with a solution of *p*-toluenesulfonic acid (*p*TosOH) (0.07 or 0.4 equiv.) in methanol and the reaction was followed by TLC. After completion of the reaction, the mixture was concentrated under vacuum. The residue was taken up in diethyl ether, washed with a saturated aqueous solution of $NaHCO_3$ and NaCl, dried with $MgSO_4$, concentrated under reduced pressure and dried under high vacuum. Purification by silica gel column chromatography (diethyl ether/pentane, 1:4) afforded the deprotected compound.

General Procedure for the Radical Addition of Thiols (GP4): A carefully dried 5 mL round-bottomed flask was charged with oligomer **7**, **10** or **13** (1 equiv. of allyl groups), AIBN (0.02 to 0.33 equiv.) and thiol (0.5 to 10 equiv.). The flask was evacuated and flushed with nitrogen three times. A minimal amount of nitrogen-saturated solvent (toluene or DMF) was added to the mixture which was then allowed to react 18 h at 70 °C. The reaction product was then evaporated to dryness.

(2*S*)-2-Hydroxy-4-methylpentanoic Acid (2): To a stirred solution of L-leucine **1** (7.87 g, 60 mmol) in an aqueous solution of 0.5 M H_2SO_4 (240 mL, 120 mmol) was added dropwise a solution of $NaNO_2$ (24.84 g, 360 mmol) in water (90 mL) at 0 °C over 3 h. The reaction was warmed to room temperature and stirred for additional 24 h. Once the reaction was finished as shown by TLC, the reaction mixture was extracted three times with diethyl ether (1 × 150 and 2 × 100 mL). The combined organic layers were washed twice with saturated brine (2 × 30 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The sticky yellow oil was recrystallized from diethyl ether to give **2** (6.95 g, 52.6 mmol, 88%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30–4.26 (m, 1 H, C*H*-OH), 1.93–1.86 (m, 1 H, CH_2-C*H*), 1.64–1.60 (m, 2 H, CH_2), 0.96–0.95 (m, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.53, 68.89, 43.19, 24.45, 23.18, 21.41 ppm. EI-MS: *m*/*z* (%) = 150 (49) $[M + NH_3]^+$, 133 (16) $[M + H]^+$, 99 (100), 81 (15), 71 (93) for $C_6H_{12}O_3$.

(2*S*)-2-Hydroxypent-4-enoic Acid (4): To a stirred solution of L-allylglycine **3** (14.97 g, 130 mmol) in water/acetic acid 8:2 (v/v) (1300 mL) was added dropwise a solution of $NaNO_2$ (17.94 g, 260 mmol) in water (260 mL) at 0 °C over 3 h. Once the reaction was finished as shown by TLC, the reaction was quenched with 2 M methylamine solution in THF (130 mL, 260 mmol). The solvent was removed under reduced pressure. The residual aqueous solution was acidified to pH = 2 with 6 N HCl and extracted with ethyl acetate (2 × 2000 and 1 × 1000 mL). The solvent was evaporated and the residue purified by silica gel column chromatography ($CHCl_3$/MeOH/acetic acid, 90:9:1) to give **4** (10.31 g, 88.8 mmol, 69%) as a light yellow oil. R_f = 0.58 ($CHCl_3$/MeOH/acetic acid 90:9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83–5.73 (m, 1 H, C*H*=CH_2), 5.17–5.12 (m, 2 H, CH=CH_2), 4.34–4.32 (m, 1 H, C*H*-OH), 2.62–2.56 and 2.49–2.42 (m, 2 H, CH-CH_2-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.37, 131.95, 119.15, 69.77, 38.16 ppm. ESI-MS: *m*/*z*: calcd. for $C_5H_8O_3 + Na^+$: 139.0371; found 139.0346.

Allyl (2*S*)-2-Hydroxy-4-methylpentanoate (5): Tetrabutyl ammonium bromide (6.45 g, 20.0 mmol) and K_2CO_3 (33.12 g, 240 mmol) were suspended in DMF (400 mL). Then, allyl bromide (20.3 mL, 240 mmol) and **2** (26.43 g, 200 mmol) were added and the reaction was followed by TLC. After 4 h stirring at room temperature, the reaction mixture was concentrated to a quarter of its initial volume and diethyl ether (620 mL), 5% aq. citric acid solution (400 mL) and water (100 mL) were added. The aqueous phase was separated and extracted three times with diethyl ether (3 × 200 mL). The combined organic phases were washed twice with 5% $NaHCO_3$ (2 × 100 mL) and saturated NaCl (2 × 100 mL) solutions, dried with $MgSO_4$, concentrated under reduced pressure and dried under high vacuum. Purification by silica gel column chromatography (diethyl ether/pentane, 1:4) afforded **5** (30.67 g, 177.1 mmol, 89%) as a light yellow, oily liquid. R_f = 0.43 (diethyl ether/pentane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93–5.87 (m, 1 H, C*H*=CH_2), 5.34–5.24 (m, 2 H, CH=CH_2), 4.65–4.59 (m, 2 H, O-CH_2), 4.22–4.19 (m, 1 H, C*H*-OH), 1.93–1.82 (m, 1 H, CH_2-C*H*), 1.57–1.53 (m, 2 H, CH-CH_2-CH), 0.96–0.91 (m, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.51, 131.47, 118.92, 69.05, 66.02, 43.46, 24.38, 23.21, 21.50 ppm. EI-MS: *m*/*z* (%) = 190 (7) $[M + NH_3]^+$, 173 (100) $[M + H]^+$, 145 (11), 127 (11), 113 (14), 98 (14), 87 (62), 85 (30), 71 (16). ESI-MS: *m*/*z*: calcd. for $C_9H_{16}O_3 + H^+$: 173.1178; found 173.1170.

(2*S*)-2-(Tetrahydro-2*H*-pyran-2-yloxy)pent-4-enoic Acid (6): **4** (14.55 g, 125.4 mmol) and *p*TosOH (479.2 mg, 2.52 mmol) were dissolved in CH_2Cl_2 (260 mL) and cooled to 4 °C. Dihydropyran (16.3 mL, 179.8 mmol) was added dropwise. After 5 min, the ice bath was removed and the mixture warmed to room temperature. The reaction was followed by TLC. After 2.5 h, the reaction mixture was extracted twice with 0.2 N KOH (2 × 300 mL). The combined KOH layers were acidified to pH 3–4 with 6 N HCl and extracted three times with CH_2Cl_2 (3 × 300 mL). The pH of the aqueous layer was controlled between extractions and adjusted with more HCl if necessary. The combined CH_2Cl_2 extracts were washed with water, dried with $MgSO_4$, concentrated under reduced pressure and dried under high vacuum. The crude product was purified by silica gel column chromatography using a gradient mixture of 100% CH_2Cl_2 to 100% CH_3CN to give **6** as a mixture of diastereoisomers as a sticky oil (15.35 g, 76.8 mmol, 61%). R_f = 0.61 (CH_2Cl_2/CH_3CN, 2:0.75). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85–5.66 (m, 1 H, C*H*=CH_2), 5.09–5.00 (m, 2 H, CH=CH_2), 4.69–4.68 and 4.60–4.58 [m, 1 H, O-C*H*(CH_2)-O], 4.31–4.28 and 4.09–4.06 (m, 1 H, C*H*-CO), 3.91–3.74 and 3.46–3.39 (m, 2 H, O-CH_2-CH_2), 2.55–2.38 (m, 2 H, CH-CH_2-CH), 1.82–1.42 [m, 6 H, (CH_2)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.41, 175.38, 132.94, 132.38, 118.21, 117.82, 99.94, 96.94, 76.57, 73.02, 63.11, 61.83, 36.94, 36.40, 30.05, 29.91, 25.03, 24.77, 19.25, 18.47 ppm. EI-MS: *m*/*z* (%) = 218 (29) $[M + NH_3]^+$, 201 (62) $[M + H]^+$, 155 (36), 102 (28), 85 (100); 71 (10). ESI-MS: *m*/*z*: calcd. for $C_{10}H_{16}O_4 + H^+$: 201.1127; found 201.1144.

Double-Protected Dimer 7: According to GP1, **6** (11.23 g, 56.1 mmol) and **5** (8.78 g, 51 mmol) were reacted in the presence of DMAP (0.62 g, 5.1 mmol) and DCC (11.57 g, 56.1 mmol) in CH_2Cl_2 (170 mL) for 3.5 h. Purification by silica gel column chromatography (CH_2Cl_2) yielded **7** (mixture of diastereoisomers; 15.44 g, 43.6 mmol, 84%) as a colorless oil. R_f = 0.44 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91–5.74 (m, 2 H, C*H*=CH_2), 5.30–5.03 (m, 5 H, CH=CH_2, CO-O-C*H*), 4.72–4.56 [m, 3 H, O-CH_2-CH, O-C*H*(CH_2)-O], 4.40–4.37 and 4.10–4.06 [m, 1 H, O-C*H*(CH_2)-CO], 3.88–3.77 and 3.49–3.34 (m, 2 H, CH_2-CH_2-O), 2.66–2.42 (m, 2 H, CH_2=CH-CH_2), 1.84–1.44 [m, 9 H, CH-(CH_2)$_3$-CH_2, (CH_3)$_2$-C*H*-CH_2], 0.91–0.87 (m, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.86, 169.81, 133.29, 131.42, 118.80, 117.85, 96.89, 73.16, 70.85, 65.74, 61.93, 39.66, 36.83, 30.10, 25.28, 24.47, 21.36, 18.72 ppm. ESI-MS: *m*/*z*: calcd. for $C_{19}H_{30}O_6 + H^+$: 355.2121; found 355.2130.

THP-Protected Dimer 8: According to GP2, **7** (3.59 g, 10.1 mmol) was treated with $Pd(PPh_3)_4$ (1.155 g, 1.00 mmol) and morpholine (916.3 mg, 10.52 mmol) at 0 °C in 40 mL of THF for 2 h. The crude product was purified by silica gel column chromatography (diethyl

ether/pentane, 4:1) to yield **8** (mixture of diastereoisomers; 2.04 g, 6.50 mmol, 64%) as a colorless oil. R_f = 0.78 (diethyl ether/pentane, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.94–5.75 (m, 1 H, C*H*=CH_2), 5.19–5.08 (m, 3 H, CH=CH_2, C*H*-COOH), 4.75–4.58 [m, 1 H, O-C*H*(CH_2)-O], 4.44–4.41 and 4.12–4.09 [m, 1 H, O-C*H*(CH_2)-CO], 3.96–3.81 and 3.52–3.40 (m, 2 H, CH_2-CH_2-O), 2.66–2.50 (m, 2 H, CH-CH_2-CH), 1.86–1.49 [m, 9 H, (CH_2)$_3$, CH_2-C*H*-(CH_3)$_2$]; 0.96–0.91 (m, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.58, 171.93, 133.23, 118.07, 97.11, 73.33, 70.67, 62.15, 39.51, 37.10, 30.15, 25.35, 24.59, 22.94, 21.40, 18.83 ppm. ESI-MS: *m*/*z*: calcd. for $C_{16}H_{26}O_6$ + Na^+: 337.1627; found 337.1631.

Allyl Ester-Protected Dimer 9: According to GP3, **7** (3.55 g, 10 mmol) was treated with 133 mL of a solution of *p*TosOH in methanol (1 mg mL^{-1}) and the reaction mixture was stirred at room temperature for 3 h. The crude product was purified by silica gel column chromatography (diethyl ether/pentane, 1:4) to give **9** (1.98 g, 7.32 mmol, 73%) as a colorless oil. R_f = 0.37 (diethyl ether/pentane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.98–5.82 (m, 2 H, C*H*=CH_2), 5.37–5.16 [m, 5 H, CH=CH_2, O-C*H*(CH_2)-CO], 4.66–4.63 (m, 2 H, O-CH_2-CH), 4.35–4.32 (m, 1 H, OH-C*H*), 2.69–2.53 (m, 2 H, CH-CH_2-CH), 1.86–1.69 [m, 3 H, CH_2-C*H*-(CH_3)$_2$], 0.98–0.94 (m, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.98, 169.69, 132.36, 131.31, 119.07, 118.99, 71.74, 69.64, 65.96, 39.63, 38.72, 24.55, 22.92, 21.42 ppm. ESI-MS: *m*/*z*: calcd. for $C_{14}H_{22}O_5$ + H^+: 271.1545; found 271.1575.

Double-Protected Tetramer 10: According to GP1, **8** (2.66 g, 8.45 mmol) and **9** (2.08 g, 7.68 mmol) were reacted in the presence of DMAP (95.7 mg, 0.78 mmol) and DCC (2.23 g, 10.83 mmol) in CH_2Cl_2 (25 mL) for 2 h. Purification by silica gel column chromatography (diethyl ether/pentane, 1:4) yielded **10** (mixture of diastereoisomers; 3.22 g, 5.68 mmol, 74%) as a colorless oil. R_f = 0.71 (diethyl ether/pentane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.94–5.75 (m, 3 H, C*H*=CH_2), 5.32–5.06 (m, 9 H, CH=CH_2, CO-O-C*H*), 4.75–4.59 [m, 3 H, O-CH_2-CH, O-C*H*(CH_2)-O], 4.42–4.39 and 4.12–4.09 [m, 1 H, O-C*H*(CH_2)-CO], 3.90–3.80 and 3.49–3.38 (m, 2 H, CH_2-CH_2-O), 2.75–2.45 (m, 4 H, CH_2=CH-CH_2), 1.87–1.48 [m, 12 H, CH-(CH_2)$_3$-CH_2, (CH_3)$_2$-C*H*-CH_2], 0.95–0.90 (m, 12 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.98, 169.79, 169.62, 168.71, 133.37, 133.07, 131.46, 118.91, 118.04, 117.94, 96.99, 73.24, 71.65, 70.80, 70.56, 65.90, 62.02, 39.59, 39.37, 37.16, 35.09, 30.10, 25.37, 24.51, 22.90, 21.46, 18.81 ppm. ESI-MS: *m*/*z*: calcd. for $C_{30}H_{46}O_{10}$ + Na^+: 589.2989; found 589.3011.

THP-Protected Tetramer 11: According to GP2, **10** (504.7 mg, 0.89 mmol) was treated with $Pd(PPh_3)_4$ (102.8 mg, 0.09 mmol) and morpholine (79.7 mg, 0.91 mmol) at 0 °C in 15 mL of THF for 1 h. The crude product was purified by silica gel column chromatography (diethyl ether/pentane, 4:1) to yield **11** (mixture of diastereoisomers; 311.4 mg, 0.59 mmol, 66%) as a colorless oil. R_f = 0.54 (diethyl ether/pentane, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95–5.76 (m, 2 H, C*H*=CH_2), 5.19–5.09 (m, 7 H, CH=CH_2, CO-O-C*H*), 4.75–4.68 [m, 1 H, O-C*H*(CH_2)-O], 4.43–4.40 and 4.14–4.12 [m, 1 H, O-C*H*(CH_2)-CO], 3.86–3.84 and 3.51–3.39 (m, 2 H, CH_2-CH_2-O), 2.73–2.52 (m, 4 H, CH-CH_2-CH), 1.82–1.52 [m, 12 H, (CH_2)$_3$, CH_2-C*H*-(CH_3)$_2$], 0.96–0.91 (m, 12 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.86, 172.08, 169.72, 168.70, 133.35, 131.33, 119.11, 118.03, 97.05, 73.30, 71.78, 71.18, 70.89, 62.08, 39.47, 39.40, 37.18, 35.06, 30.19, 25.37, 24.56, 22.90, 21.43, 18.80 ppm. ESI-MS: *m*/*z*: calcd. for $C_{27}H_{42}O_{10}$ + Na^+: 549.2676; found 549.2651.

Allyl Ester-Protected Tetramer 12: According to GP3, **10** (504.3 mg, 0.89 mmol) was treated with 9 mL of a solution of *p*TosOH in methanol (1 mg mL^{-1}) and the reaction mixture was stirred at room temperature for 1.25 h. The crude product was purified by silica gel column chromatography (diethyl ether/pentane, 1:4) to give **12** (405.5 mg, 0.84 mmol, 94%) as a colorless oil. R_f = 0.29 (diethyl ether/pentane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95–5.81 (m, 3 H, C*H*=CH_2), 5.37–5.13 [m, 9 H, CH=CH_2, O-C*H*(CH_2)-CO], 4.65–4.64 (m, 2 H, O-CH_2-CH), 4.36–4.32 (m, 1 H, OH-C*H*), 2.80–2.54 (m, 4 H, CH-CH_2-CH), 1.91–1.64 [m, 6 H, CH_2-C*H*-(CH_3)$_2$], 0.99–0.94 (m, 12 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.95, 169.62, 169.44, 168.66, 132.38, 131.42, 131.35, 119.15, 119.06, 118.97, 71.93, 71.72, 71.46, 69.66, 65.96, 39.59, 39.39, 38.75, 35.10, 24.54, 24.52, 22.96, 22.92, 21.47, 21.39 ppm. ESI-MS: *m*/*z*: calcd. for $C_{25}H_{38}O_9$ + Na^+: 505.2414; found 505.2428.

Double-Protected Octamer 13: According to GP1, **11** (232.4 mg, 0.44 mmol) and **12** (205.9 mg, 0.43 mmol) were reacted in the presence of DMAP (2.9 mg, 0.024 mmol) and DCC (123 mg, 0.6 mmol) in CH_2Cl_2 (5 mL) for 2.5 h at 0 °C. Purification by silica gel column chromatography (diethyl ether/pentane, 1:4) yielded **13** (mixture of diastereoisomers; 345.6 mg, 0.35 mmol, 82%) as a colorless oil. R_f = 0.61 (diethyl ether/pentane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93–5.76 (m, 5 H, C*H*=CH_2), 5.32–5.08 (m, 17 H, CH=CH_2, CO-O-C*H*), 4.74–4.61 [m, 3 H, O-CH_2-CH, O-C*H*(CH_2)-O], 4.43–4.39 and 4.12–4.09 [m, 1 H, O-C*H*(CH_2)-CO], 3.90–3.80 and 3.50–3.38 (m, 2 H, CH_2-CH_2-O), 2.73–2.49 (m, 8 H, CH_2=CH-CH_2), 1.84–1.49 [m, 18 H, CH-(CH_2)$_3$-CH_2, (CH_3)$_2$-C*H*-CH_2], 0.95–0.90 (m, 24 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.95, 169.78, 169.59, 169.56, 169.34, 169.31, 168.67, 168.59, 133.34, 133.05, 131.45, 131.37, 131.33, 118.99, 118.95, 118.90, 118.03, 117.93, 96.97, 76.20, 73.22, 71.87, 71.74, 71.64, 71.30, 70.77, 70.53, 65.89, 61.99, 39.55, 39.42, 39.34, 39.31, 37.13, 36.87, 35.03, 34.85, 30.15, 25.39, 24.50, 24.48, 24.46, 24.43, 22.95, 22.93, 22.92, 22.88, 21.42, 21.34, 21.35, 21.28, 18.79 ppm. ESI-MS: *m*/*z*: calcd. for $C_{52}H_{78}O_{18}$ + Na^+: 1013.5086; found 1013.5056.

(9*S*,12*S*)-12-Hydroxy-9-isobutyl-8,11-dioxo-7,10-dioxa-3,16-dithiaoctadecane-1,18-dioic Acid (14): The synthesis of this compound was optimized in a number of reactions, which are summarized in Table 2. The following protocol describes the optimal conditions (Entry 5 in Table 2). According to GP4, **7** (35.4 mg, 0.1 mmol, 0.2 mmol allyl groups) was treated with AIBN (10.8 mg, 0.066 mmol) and thioglycolic acid (138.9 μL, 2 mmol) in 4 mL of toluene at 70 °C for 18 h. The reaction product was then evaporated to dryness, dissolved in CH_2Cl_2 and washed twice with a saturated solution of NaCl. The organic phase was dried with $MgSO_4$, concentrated under reduced pressure and dried under high vacuum to give **14** (42.1 mg, 0.093 mmol, 92.7%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.10–4.97 (m, 2 H, C*H*-CO), 4.23–4.15 (m, 2 H, O-CH_2), 3.20 (s, 4 H, CH_2-COOH), 2.67–2.64 (m, 4 H, CH_2-S), 1.95–1.49 [m, 9 H, CH_2-C*H*-(CH_3)$_2$, O-CH_2-CH_2, CH-(CH_2)$_2$], 0.91–0.79 (m, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.19, 175.80, 174.62, 170.01, 71.97, 69.90, 63.83, 39.48, 33.37, 33.12, 33.00, 31.85, 30.48, 28.86, 25.26, 24.52, 22.86, 21.45 ppm. ESI-MS: *m*/*z*: calcd. for $C_{18}H_{30}O_9S_2$ + H^+: 455.1410; found 455.1394.

3-[(2-Hydroxyethyl)thio]propyl (2*S*)-2-{[(2*S*)-5-[(2-Hydroxyethyl)thio]-2-(tetrahydro-2*H*-pyran-2-yloxy)pentanoyl]oxy}-4-methylpentanoate (15): The synthesis of this compound was optimized in a number of reactions, which are summarized in Table 2. The following protocol corresponds to the optimized conditions (Entry 10 in Table 2). According to GP4, 7 (35.2 mg, 0.1 mmol, 0.2 mmol allyl groups) was treated with AIBN (10.8 mg, 0.066 mmol) and mercaptoethanol (140.6 μL, 2 mmol) in 4 mL of toluene at 70 °C for 18 h.

The reaction product was then evaporated to dryness, dissolved in CH_2Cl_2 and washed twice with a saturated solution of NaCl. The organic phase was dried with $MgSO_4$, concentrated under reduced pressure and dried under high vacuum to give 15 (mixture of diastereoisomers; 45.7 mg, 0.090 mmol, 89.5%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.28–4.96 (m, 1 H, CO-O-C*H*), 4.65–4.55 [m, 1 H, O-C*H*(CH_2)-O], 4.36–4.33 and 4.06–4.01 (m, 1 H, C*H*-CO), 4.22–4.14 (m, 2 H, O-CH_2-CH_2), 3.83–3.74 and 3.48–3.33 (m, 2 H, CH-O-CH_2), 3.67–3.64 (m, 4 H, CH_2-OH), 2.67–2.47 (m, 8 H, CH_2-S-CH_2), 1.96–1.47 [m, 15 H, CH_2-C*H*-(CH_3)$_2$, O-CH_2-CH_2, CH-(CH_2)$_2$, (CH_2)$_3$], 0.90–0.86 (m, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.50, 170.29, 97.28, 72.94, 71.34, 63.68, 62.39, 60.59, 60.39, 39.54, 35.07, 34.84, 31.73, 31.49, 31.20, 30.20, 27.89, 25.31, 25.11, 24.57, 22.90, 21.53, 18.97 ppm. ESI-MS: *m*/*z*: calcd. for $C_{23}H_{42}O_8S_2 + H^+$: 511.2399; found 511.2414.

3-[(2-Aminoethyl)thio]propyl (2*S*)-2-({(2*S*)-5-[(2-Aminoethyl)thio]-2-hydroxypentanoyl}oxy)-4-methylpentanoate (16): The synthesis of this compound was optimized in two reactions, which are summarized in Table 2. The following protocol corresponds to the optimized conditions (Entry 12 in Table 2). According to GP4, **7** (35.8 mg, 0.1 mmol, 0.2 mmol allyl groups) was treated with AIBN (10.8 mg, 0.066 mmol) and cysteamine hydrochloride (227.2 mg, 2 mmol) in 4 mL of DMF at 70 °C for 18 h. The reaction product was then evaporated to dryness, dissolved in CH_2Cl_2 and washed twice with a saturated solution of NaCl. The organic phase was dried with $MgSO_4$, concentrated under reduced pressure and dried under high vacuum to give **16** (33.1 mg, 0.078 mmol, 78.1%) as a light yellow oil. ^{1}H NMR (400 MHz, DMSO): δ = 5.16–4.91 (m, 2 H, C*H*-CO), 4.31–4.10 (m, 2 H, O-CH_2), 3.25–3.20 (m, 4 H, CH_2-NH_2), 2.74–2.70 (m, 4 H, S-CH_2), 2.59–2.49 (m, 4 H, CH_2-S), 1.87–1.40 [m, 9 H, CH_2-C*H*-(CH_3)$_2$, O-CH_2-CH_2, CH-(CH_2)$_2$], 0.95–0.84 (m, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 162.32, 161.13, 72.72, 70.82, 69.78, 41.88, 40.70, 35.82, 33.98, 33.88, 30.78, 27.82, 25.43, 23.44, 22.68, 21.28 ppm. ESI-MS: *m*/*z*: calcd. for $C_{18}H_{36}N_2O_5S_2 + H^+$: 425.2144; found 425.2122.

17: According to GP4, **10** (16.5 mg, 0.029 mmol, 0.087 mmol allyl groups) was treated with AIBN (4.73 mg, 0.029 mmol) and thioglycolic acid (60.65 μL, 0.873 mmol) in 3.3 mL of toluene at 70 °C for 18 h. The reaction product was then evaporated to dryness and purified by RP-HPLC (t_R = 24.34 min) to give **17** (21.2 mg, 0.028 mmol, 96.3%) as a light yellow oil. ^{1}H NMR (400 MHz, DMSO): δ = 5.14–5.11 (m, 1 H, C*H*-CO), 5.05–4.99 (m, 2 H, C*H*-CO), 4.20–4.09 (m, 3 H, C*H*-OH, O-CH_2), 3.22–3.19 (d, *J* = 13.74 Hz, 6 H, CH_2-COOH), 2.64–2.54 (m, 6 H, CH_2-S), 2.02–1.56 [m, 16 H, CH_2-C*H*-(CH_3)$_2$, O-CH_2-CH_2, CH-(CH_2)$_2$], 0.92–0.86 (m, 12 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 173.65, 171.50, 171.47, 171.45, 169.45, 169.37, 168.81, 71.83, 71.40, 69.98, 69.01, 63.66, 33.05, 32.96, 32.92, 32.88, 32.84, 31.36, 30.97, 29.35, 27.98, 27.48, 24.12, 24.05, 24.01, 23.56, 23.56, 22.78, 22.63, 21.37, 21.35 ppm. ESI-MS: *m*/*z*: calcd. for $C_{31}H_{50}O_{15}S_3 + H^+$: 759.2390; found 759.2385.

18: According to GP4, **10** (32.2 mg, 0.057 mmol, 0.170 mmol allyl groups) was treated with AIBN (9.23 mg, 0.056 mmol) and cysteamine hydrochloride (193.6 mg, 1.70 mmol) in 6.4 mL of DMF at 70 °C for 18 h. The reaction product was then evaporated to dryness and purified by RP-HPLC (t_R = 20.20 min) to give **18** (37.9 mg, 0.053 mmol, 93.5%) as a light yellow oil. ^{1}H NMR (400 MHz, DMSO): δ = 7.95 (s, 6 H, NH_2), 5.14–5.12 (m, 1 H, C*H*-CO), 5.04–5.02 (m, 2 H, C*H*-CO), 4.18–4.13 (m, 3 H, C*H*-CO, O-CH_2), 2.98 (s, 6 H, CH_2-NH_2), 2.71–2.68 (m, 6 H, S-CH_2), 2.59–2.53 (m, 6 H, CH_2-S), 2.07–1.62 [m, 16 H, CH_2-C*H*-(CH_3)$_2$, O-CH_2-CH_2, CH-(CH_2)$_2$], 0.93–0.87 (m, 12 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 173.72, 169.39, 168.83, 158.12, 71.82, 71.37, 70.02, 68.99, 63.70, 38.42, 38.37, 38.32, 32.78, 32.78, 30.35, 29.93, 29.44, 27.95, 27.95, 27.80, 27.74, 26.76, 24.56, 24.13, 24.01, 22.79, 22.79, 22.63, 22.63, 21.38, 21.38 ppm. ESI-MS: *m*/*z*: calcd. for $C_{31}H_{59}N_3O_9S_3 + H^+$: 714.3492; found 714.3477.

19: According to GP4, **13** (10.3 mg, 0.0104 mmol, 0.052 mmol allyl groups) was treated with AIBN (2.82 mg, 0.017 mmol) and thioglycolic acid (36.13 μL, 0.52 mmol) in 2 mL of toluene at 70 °C for 18 h. The reaction product was then evaporated to dryness and purified by RP-HPLC (t_R = 24.30 min) to give **19** (11.2 mg, 0.008 mmol, 78.8%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.19–5.01 (m, 7 H, C*H*-CO), 4.32–4.15 (m, 3 H, C*H*-OH, O-CH_2), 3.31–3.21 (m, 10 H, CH_2-COOH), 2.73–2.64 (m, 10 H, CH_2-S), 2.09–1.71 [m, 30 H, CH_2-C*H*-(CH_3)$_2$, O-CH_2-CH_2, CH-(CH_2)$_2$], 0.97–0.91 (m, 24 H, CH_3) ppm. ESI-MS: *m*/*z*: calcd. for $C_{57}H_{90}O_{27}S_5 + H^+$: 1367.4352; found 1367.4371.

20: According to GP4, **13** (19.8 mg, 0.02 mmol, 0.1 mmol allyl groups) was treated with AIBN (5.42 mg, 0.033 mmol) and cysteamine hydrochloride (113.6 mg, 1.0 mmol) in 4 mL of DMF at 70 °C for 18 h. The reaction product was then evaporated to dryness and purified by RP-HPLC (t_R = 18.80 min) to give **20** (17.3 mg, 0.013 mmol, 67.0%) as a light yellow oil. ^{1}H NMR (400 MHz, DMSO): δ = 7.88 (s, 10 H, NH_2), 5.17–4.99 (m, 7 H, C*H*-CO), 4.29–4.10 (m, 3 H, C*H*-CO, O-CH_2), 3.03–2.91 (m, 10 H, CH_2-NH_2), 2.70–2.66 (m, 10 H, S-CH_2), 2.58–2.53 (m, 10 H, CH_2-S), 2.03–1.62 [m, 30 H, CH_2-C*H*-(CH_3)$_2$, O-CH_2-CH_2, CH-(CH_2)$_2$], 0.93–0.87 (m, 24 H, CH_3) ppm. ESI-MS: *m*/*z*: calcd. for $[C_{57}H_{105}N_5O_{17}S_5 + 2H]^{2+}$: 646.8133; found 646.8143.

Supporting Information (see also the footnote on the first page of this article): Additional NMR and mass spectra of compounds **2**, **4**–**7**, **10**, **13**.

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