Cholesteryl-(L-Lactic Acid)$_{\bar{n}}$ Building Blocks for Self-Assembling Biomaterials

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ABSTRACT: The synthesis and properties of a novel set of building blocks for the preparation of self-assembling biomaterials are described. These molecules consist of a relatively short oligo(L-lactic acid)$_{\bar{n}}$ segment ($\bar{n}$ = 10−40) that is substituted with a cholesterol moiety as an end group and in some cases has a second biofunctional substituent at its other terminus. The cholesterol moiety not only serves to induce liquid crystalline properties and drive the self-assembly of these oligomers, but also is expected to have an effect on the interaction of cells with these materials. The cholesteryl−(L-lactic acid)$_{\bar{n}}$ (CLA$_{\bar{n}}$) oligomers form thermotropic liquid crystals and self-assemble into lamellar structures consisting of interdigitated bilayers. In addition, the CLA$_{\bar{n}}$ oligomers can be homogeneously blended with poly(L-lactic acid), thereby offering the possibility to improve the cell interaction properties of this common surgical biomaterial. Furthermore, the secondary alcohol terminus of the CLA$_{\bar{n}}$ oligomers allows the opportunity to introduce additional bioactive substituents such as cholesterol, indomethacin (an antiinflammatory drug), and pyrene and rhodamine B (which can act as fluorescent labels for bioimaging purposes) and various α-amino acids. These biofunctional CLA$_{\bar{n}}$ oligomers can also be homogeneously mixed with the unsubstituted CLA$_{\bar{n}}$ oligomers and thus could enable a further noncovalent functionalization of self-assembling biomaterials.

Introduction

During the past decade, there has been an increasing interest in bioactive as opposed to bioinert biomaterials for human repair. The initial focus of this field was on nontoxic, biocompatible materials that would be able to replace or repair natural tissues. Current interest has shifted to bioactive materials that can induce a specific biological response. There is also great interest in the preparation of suitable bioactive materials for biosensor design. A number of reviews on these topics can be found in the literature.[1]

Self-assembly is a powerful strategy for the preparation of novel materials with molecularly defined properties.[2] From a biomaterials point of view such noncovalent strategies could allow precise control of the spatial distribution of bioactive ligands, which could in turn impact cell division, cell differentiation as well as the synthesis of extracellular matrix. In this paper, we describe the synthesis and properties of a set of biofunctional building blocks that are designed to self-assemble into layered structures. These molecules consist of a cholesterol moiety, a key component of eukaryotic cell membranes, attached to biodegradable (L-lactic acid)$_{\bar{n}}$ oligomers. The secondary hydroxyl end group of these cholesteryl−(L-lactic acid)$_{\bar{n}}$ (CLA$_{\bar{n}}$) oligomers can be used for further functionalization. The cholesterol moiety was chosen because of its high thermodynamic affinity for the cell membrane and its ability to change the membrane's permeability and fluidity.[3] These characteristics make cholesterol an interesting component of bioactive biomaterials since it could have universal effects regardless of cell type and receptor map on the membrane. There is recent evidence that cholesterol is important in the stability of lipid rafts, important sites for membrane receptors.[4] Thus, cholesterol delivery to cells could be important in signal transduction, cell adhesion with its biological consequences, and cell migration. In addition, the cholesterol moiety was selected because of its mesogenic character known for many derivatives.[5] It was anticipated that the ability of cholesterol to form liquid crystalline phases could provide a driving force for the self-assembly of the molecules discussed here. A layered morphology generated by self-assembly would be an additional interesting feature of biodegradable biomaterials since cells would be exposed to many copies of the same chemistry.

Poly(L-lactic acid) (PLA) is a biocompatible and biodegradable material that is widely used in surgery and tissue engineering research.[6] We study here its chemical modification to generate self-assembling and functionalized materials. The functions considered here include, an antiinflammatory drug, α-amino acids, and fluorescent dyes for bioimaging. First, we discuss the synthesis and characterization of the cholesteryl−(L-lactic acid)$_{\bar{n}}$ (CLA$_{\bar{n}}$) oligomers. Then, we evaluate blends of the CLA$_{\bar{n}}$ oligomers with poly(L-lactic acid). Finally, the synthesis of end functionalized CLA$_{\bar{n}}$ oligomers is discussed and also their blends with nonfunctionalized oligomers.

Results and Discussion

Synthesis. The molecules studied here are schematically described in Figure 1. The synthesis involves the preparation of a CLA$_{\bar{n}}$ oligomer with a desired degree of polymerization, followed by end functionalization of the hydroxyl group.

Cholesteryl—(L-lactic acid)$_{\bar{n}}$ Oligomers. The preparation of the CLA$_{\bar{n}}$ oligomers is outlined in Scheme 1. Depending on the desired length of the oligo(L-lactic acid) segment, the polymerizations were performed either in toluene solution or in bulk. Solution polymer-

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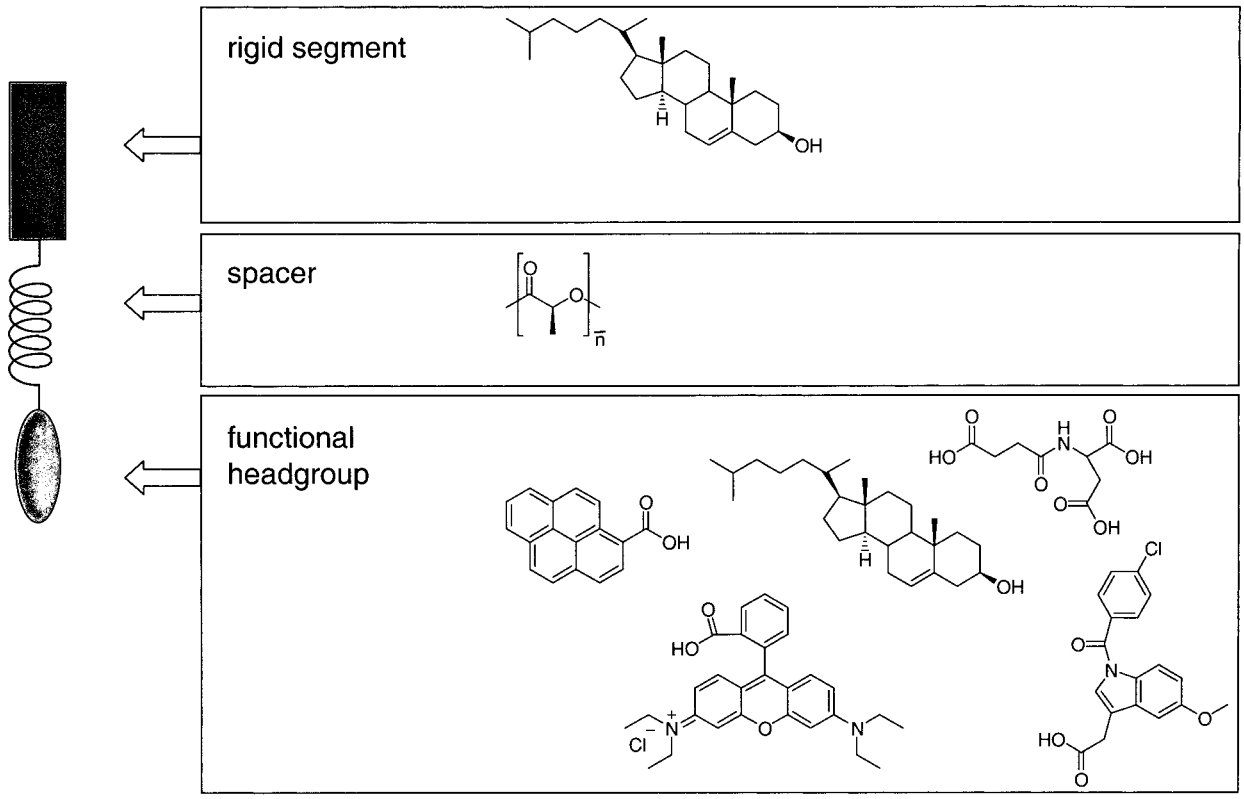
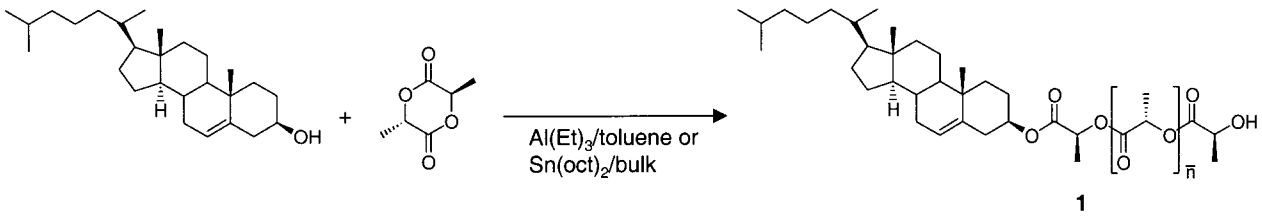


Figure 1. Schematic representation of the cholesteryl−(L-lactic acid)$_{\bar{n}}$ oligomers that have been prepared and studied.

Scheme 1



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izations were initiated by the aluminumalkoxide generated in situ upon addition of 1 equiv of Al(Et)$_3$ to 3 equiv of cholesterol. As expected for a "living" polymerization, the molecular weights could be controlled by the L-lactide/cholesterol ratio, and oligomers were obtained with polydispersities (M_w/M_n) of approximately 1.1.[7] This method is particularly suited for the synthesis of CLA$_{\bar{n}}$ oligomers with $\bar{n} \geq 20$, since products can be easily isolated by precipitation of the reaction mixture in excess methanol. Typically, these longer CLA$_{\bar{n}}$ oligomers were isolated in 85−90% yield. However, yields dropped significantly for lower molecular weight oligomers with $\bar{n} < 20$, due to their increased solubility in methanol. This is in agreement with observations reported by Kricheldorf et al.,[8] who prepared a series of poly(L-lactic acid)s functionalized with a variety of hormones, vitamins, and drugs using a similar procedure.

Lower molecular weight CLA$_{\bar{n}}$ oligomers ($\bar{n} < 20$) were synthesized in bulk at 150 °C using tin(II) bis(2-ethylhexanoate) (Sn(Oct)$_2$) as a catalyst.[9] In the absence of an alcohol as co-initiator, this procedure does not allow accurate control of molecular weight. However, in the presence of cholesterol and a catalytic amount of Sn(Oct)$_2$, narrow distribution oligomers can be prepared with average molecular weights corresponding to the L-lactide/alcohol ratio. Performing the polymerization in bulk makes the workup easier and greatly improves the yields. Although the Sn(Oct)$_2$-catalyzed bulk-polymerization of L-lactide is not strictly a "living" process, the molecular weights can be adjusted by varying the L-lactide/cholesterol ratio, and after workup, oligomers with fairly narrow polydispersities are obtained (∼1.2).

The CLA$_{\bar{n}}$ oligomers were characterized by ^{1}H NMR spectroscopy and MALDI−TOF mass spectrometry. As a representative example, the ^{1}H NMR spectrum and MALDI−TOF mass spectrum of a CLA$_{\bar{n}}$ oligomer that was prepared via the solution method with an initial L-lactide/cholesterol ratio of 10 are shown in Figure 2. From the ^{1}H NMR spectrum, the number-average degree of polymerization of the L-lactid acid block can be determined by comparing the integrals of the signals corresponding to the L-lactid C−H protons (labeled *b* and *c* in Figure 2a) with that of the olefinic proton of the cholesterol moiety (labaelled *a* in Figure 2a). In this way, a number-average degree of polymerization of 21 can be calculated. The MALDI−TOF mass spectrum confirms the chemical composition of the proposed structure. Since the masses of the cholesterol moiety (386 Da) and of a L-lactic acid unit (72 Da) are known, the molecular weight of a CLA$_{\bar{n}}$ oligomer at any given value of *n* can be calculated. For example, an oligomer with a number-average degree of polymerization of 20 has a molar mass of 1826 Da. The difference of 23 Da

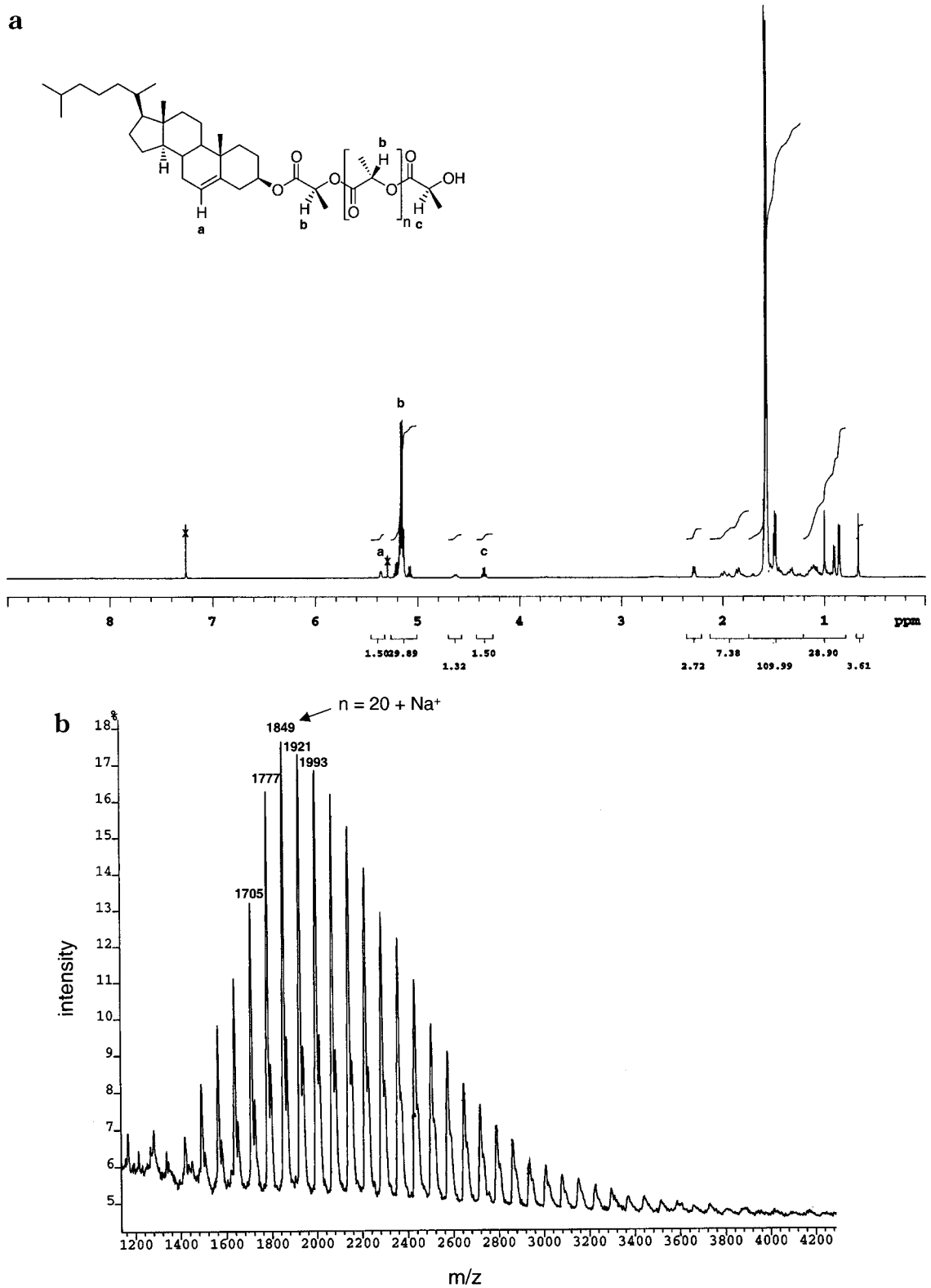


Figure 2. (a) ^{1}H NMR spectrum of a $CLA_{\bar{n}}$ oligomer with a targeted degree of polymerization ($\bar{n}$) of 20. Only peaks that are relevant to the discussion of the spectrum in the text are labeled. The complete assignment of the ^{1}H NMR spectrum can be found in the experimental part. Peaks due to residual solvent in the sample are labeled with "×". (b) MALDI−TOF mass spectrum of a $CLA_{\bar{n}}$ oligomer with a targeted degree of polymerization ($\bar{n}$) of 20. A number of signals are labeled with the corresponding masses.

between this number and the observed mass (1849 Da) is due to Na^+, which acts as a cationizing agent in the MALDI process. Second, using the masses corresponding to the individual peaks and their respective intensities, the number-average (M_n) and weight-average molecular weights (M_w) of the $CLA_{\bar{n}}$ oligomers can be calculated from the MALDI−TOF spectra.[10] From the mass spectrum shown in Figure 2b, values of $\bar{M}_n$ and $\bar{M}_w$ of 2092 and 2147 Da can be determined, respectively. This $\bar{M}_n$ value corresponds to a number-average degree of polymerization of the L-lactic acid units of 24. This number is slightly higher, but close to the number-

average degree of polymerization calculated from ^{1}H NMR (21). Generally, the results from ^{1}H NMR spectroscopy and MALDI mass spectrometry were in good agreement and differed at most by three to four units in the calculated degree of polymerization. Finally, the MALDI−TOF mass spectrum indicate that transesterification reactions occur during the polymerization of L-lactide. The difference in mass between two neighboring peaks is 72 Da, which cannot be explained by a simple ring-opening polymerization of L-lactide without side reactions. In this case, since the monomer L-lactide is composed of two L-lactic acid molecules, only polyester chains containing an even number of repeat units would be obtained and two neighboring peaks in the MALDI−TOF mass spectrum would be spaced at a distance of 144 Da. The observed difference in mass of 72 Da can only be explained by transesterification reactions, which cause chain scrambling and result in the formation of $CLA_{\bar{n}}$ oligomers that can also contain an odd number of L-lactic acid repeat units. The occurrence of such transesterification reactions during the polymerization of L-lactide has been reported before.[11]

Thermal Behavior and Self-Organization. The thermal behavior of the $CLA_{\bar{n}}$ oligomers was investigated by differential scanning calorimetry (DSC) and optical microscopy experiments. As a representative example a DSC trace as well as an optical micrograph of $CLA_{\overline{10}}$ (**1a**) are shown in Figure 3, parts a and b, respectively.

The DSC trace and optical micrograph shown in Figure 3, parts a and b, indicate that **1a** self-assembles into a liquid crystalline phase. The DSC trace reveals a glass transition temperature (T_g) at 32 °C and two phase transitions at 57 and 88 °C. Between crossed polarizers, the material displays a characteristic smectic-like birefringent texture (Figure 2b) until it becomes optically isotropic upon heating to approximately 88 °C. Electron diffraction experiments indicate that under ambient conditions the $CLA_{\bar{n}}$ oligomers can form smectic liquid crystalline phases.[12] Thus, the material exists in a liquid crystalline glassy state below 32 °C, and it is liquid crystalline up to 88 °C when isotropization occurs. The phase transition observed by DSC at 57 °C must involve a phase change between two different types of liquid crystals. Increasing the length of the oligo(L-lactic acid) segment results in an increase of both the glass-transition temperature and the isotropization temperature (T_i) (see Figure 3c). T_g and T_i, however, are still below the T_g and the melting point of high molecular weight poly(L-lactic acid) (PLA), which are 57 °C and 184 °C, respectively.[13] In addition, increasing the length of the (L-lactic acid) segment results in a narrowing of the high-temperature liquid crystalline regime. The observation of liquid crystalline behavior in **1a** is of particular interest since monodisperse $(L\text{-lactic acid})_{\bar{n}}$ oligomers with $\bar{n} < 11$ are known to be completely amorphous.[14] Thus, the results obtained for **1a** clearly demonstrate the ability of the cholesterol segment to induce self-assembly in these oligomers.

To obtain more information about the nature of the liquid crystal to liquid crystal transition, small-angle X-ray scattering (SAXS) experiments were performed at different temperatures (SAXS scans of **1a** at 25 and 65 °C are shown in Figure 4). In both cases the presence of (001) and (002) reflections indicates a lamellar organization of these molecules, and also confirms the formation of a second smectic liquid crystalline phase

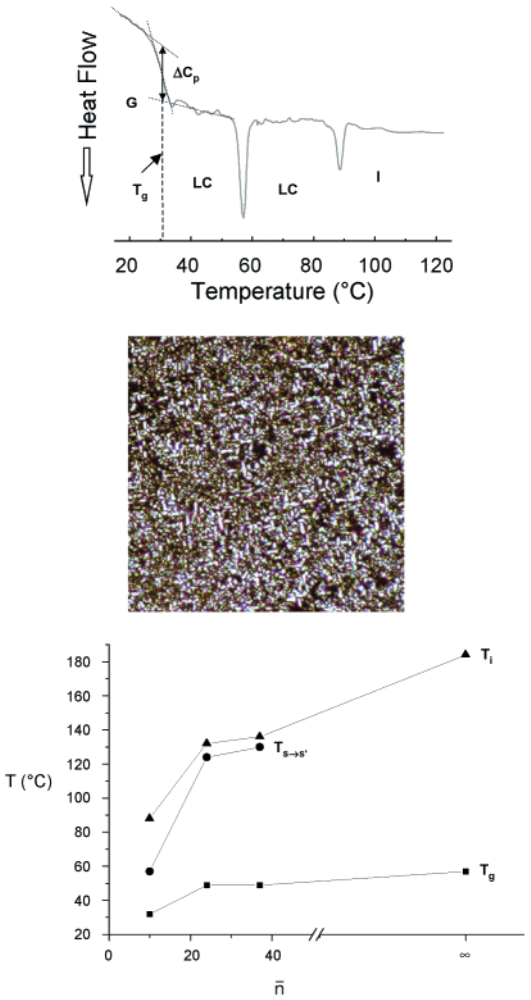


Figure 3. (a) Differential scanning calorimetry scan (2nd heating) of **1a**. As is schematically indicated, the glass transition temperaure (T_g) was taken as the temperature at which half of the change in heat capacity (ΔC_p) has occurred. (b) Optical micrograph between cross-polarizers (taken at room temperature) of **1a**. (c) Phase diagram comparing the thermal behavior of the $CLA_{\bar{n}}$ oligomers (**1a**−**1c**) with that of poly(L-lactic acid).

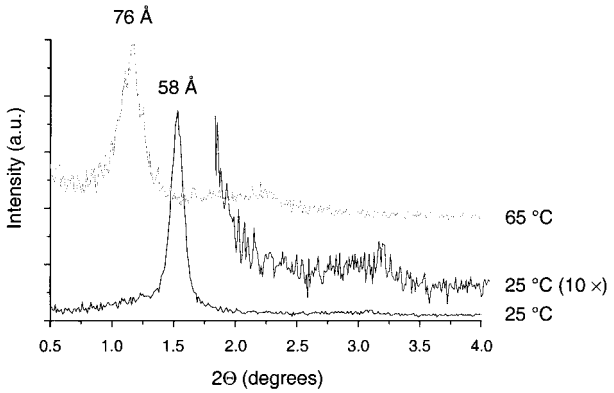


Figure 4. Small-angle X-ray scattering scans of **1a** at 25 and 65 °C.

at elevated temperature. Increasing the temperature results in a increase of the *d* spacing from 58 to 76 Å, most probably due to a more extended conformation of the lactic acid segment. Taking into account an estimated extended length (L) of 43 Å for this oligomer (see also Table 1),[15] these data suggest that the molecules organize into interdigitated bilayers.

Table 1. *d* Spacings and Estimated Molecular Lengths of $CLA_{\bar{n}}$ Oligomers

compound	av no. of repeats ($\bar{n}$)[a]	*d* spacing (Å)[b]	calcd length, *L* (Å)[c]
1a	10	58	43
1b	24	88	84
1c	37	94	121

[a] Average number of L-lactic acid repeat units calculated from the MALDI−TOF mass spectrum. [b] Layer spacing measured by small-angle X-ray scattering. [c] Estimated extended length of average-sized molecules. These numbers were calculated using a length of 14 Å for the cholesterol moiety (obtained from molecular dynamics simulations (SYBYL)) and a length of 2.9 Å per L-lactic acid repeat.[15]

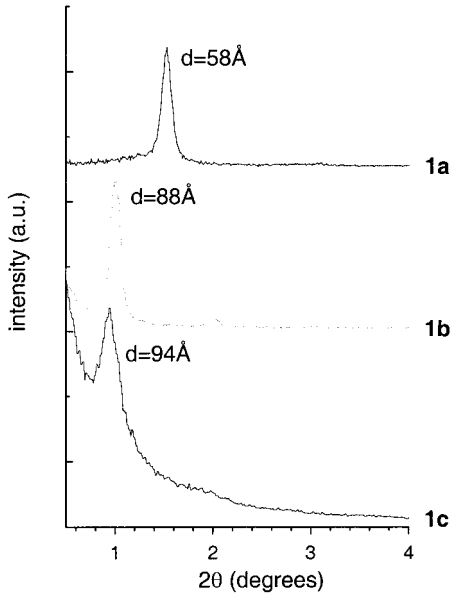


Figure 5. Small-angle X-ray scattering scans recorded at 25 °C of the different $CLA_{\bar{n}}$ oligomers: **1a** ($\bar{n}$ = 10); **1b** ($\bar{n}$ = 24); **1c** ($\bar{n}$ = 37).

In Figure 5, the SAXS scans of **1a** recorded at 25 °C are compared with those of two longer oligomers **1b** and **1c** which contain on average 24 and 37 repeat units of L-lactic acid, respectively. The corresponding *d* spacings together with the estimated extended lengths of an average-sized oligomer are listed in Table 1. Independent of the length of the L-lactic acid segment, both an (001) and an (002) reflection are observed, indicating a lamellar organization of the $CLA_{\bar{n}}$ oligomers. The corresponding layer spacings gradually increase from 58 Å for **1a** to 94 Å for **1c**. Except for **1b**, the observed layer spacings significantly deviate from the estimated extended lengths, suggesting that the molecules organize into interdigitated bilayers.

Blends of Oligomers with Poly(L-lactic acid). Binary blends were prepared by solution mixing of PLA with a certain amount of an $CLA_{\bar{n}}$ oligomer followed by evaporation of the solvent, and were subsequently investigated by means of DSC and small-angle as well as wide-angle X-ray scattering experiments. DSC heating traces and SAXS diffraction scans are shown in Figures 6 and 7, respectively, for several blends of PLA and **1c**.

The DSC traces in Figure 6 clearly show a single T_g for all the investigated **1c**/PLA mixtures, indicating miscibility of both components of the blend.[16] The T_g's of the blends are not significantly broadened in comparison with the pure components, and gradually shift

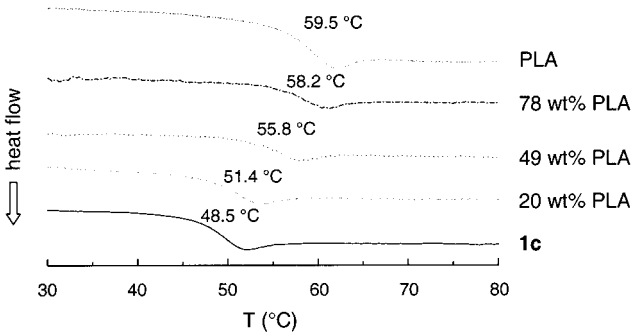


Figure 6. Differential scanning calorimetry heating traces of several blends of **1c** and PLA.

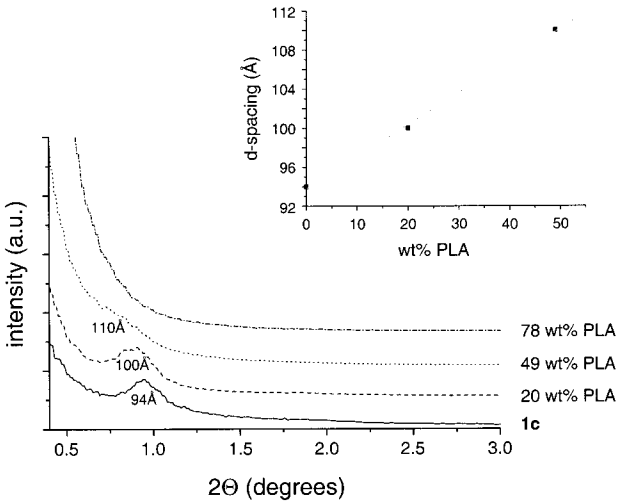


Figure 7. Small-angle X-ray scattering scans recorded at 25 °C of several blends of **1c** and PLA.

from 48.5 °C for pure **1c** to 59.5 °C for the pure PLA. The SAXS data presented in Figure 7 show that the organization of **1c** is not completely disrupted by the addition of up to ∼50 wt % PLA. As was discussed before, SAXS experiments with pure **1c** indicate that the molecules organize into interdigitated bilayers. Upon the addition of 20 wt % PLA, the (001) reflection shifts to a smaller angle, corresponding to a *d* spacing of 100 Å. With 49 wt % PLA in the blend, the (001) reflection is visible as a broad shoulder and indicates a *d* spacing of ∼110 Å. The linear increase in *d* spacing with increasing amounts of PLA in the blend suggests that this material is incorporated in the L-lactic acid domain of the bilayers, resulting in "swelling" of the lamellae. Similar to the pure PLA, no SAXS signal could be observed for blends containing ∼80 wt % or more PLA. The wide-angle X-ray scattering scans (WAXS) shown in Figure 8 indicate a high level of order on a molecular scale for all the investigated **1c**/PLA blends. Throughout the range of investigated compositions, clear WAXS peaks are observed, which do not significantly broaden with increasing amounts of PLA. In particular, the WAXS data show that even blends containing more than 80 wt % PLA (for which no SAXS signals could be observed) are not completely amorphous. This is understandable given the semicrystalline nature of PLA.[13]

The miscibility of $CLA_{\bar{n}}$ oligomers with high molecular weight PLA offers the possibility to modify the properties of biomaterials based on this polymer. Mixing a small amount of a $CLA_{\bar{n}}$ oligomer with PLA prior to the final processing step, or coating a thin layer of these

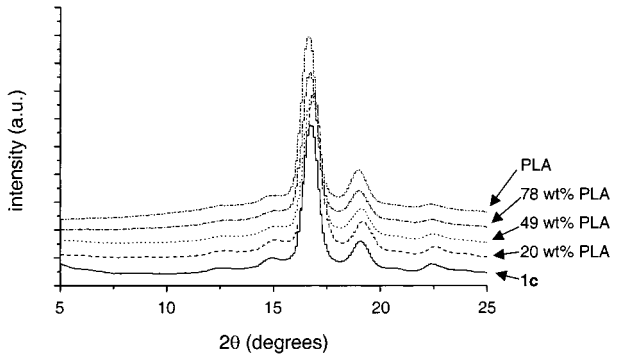


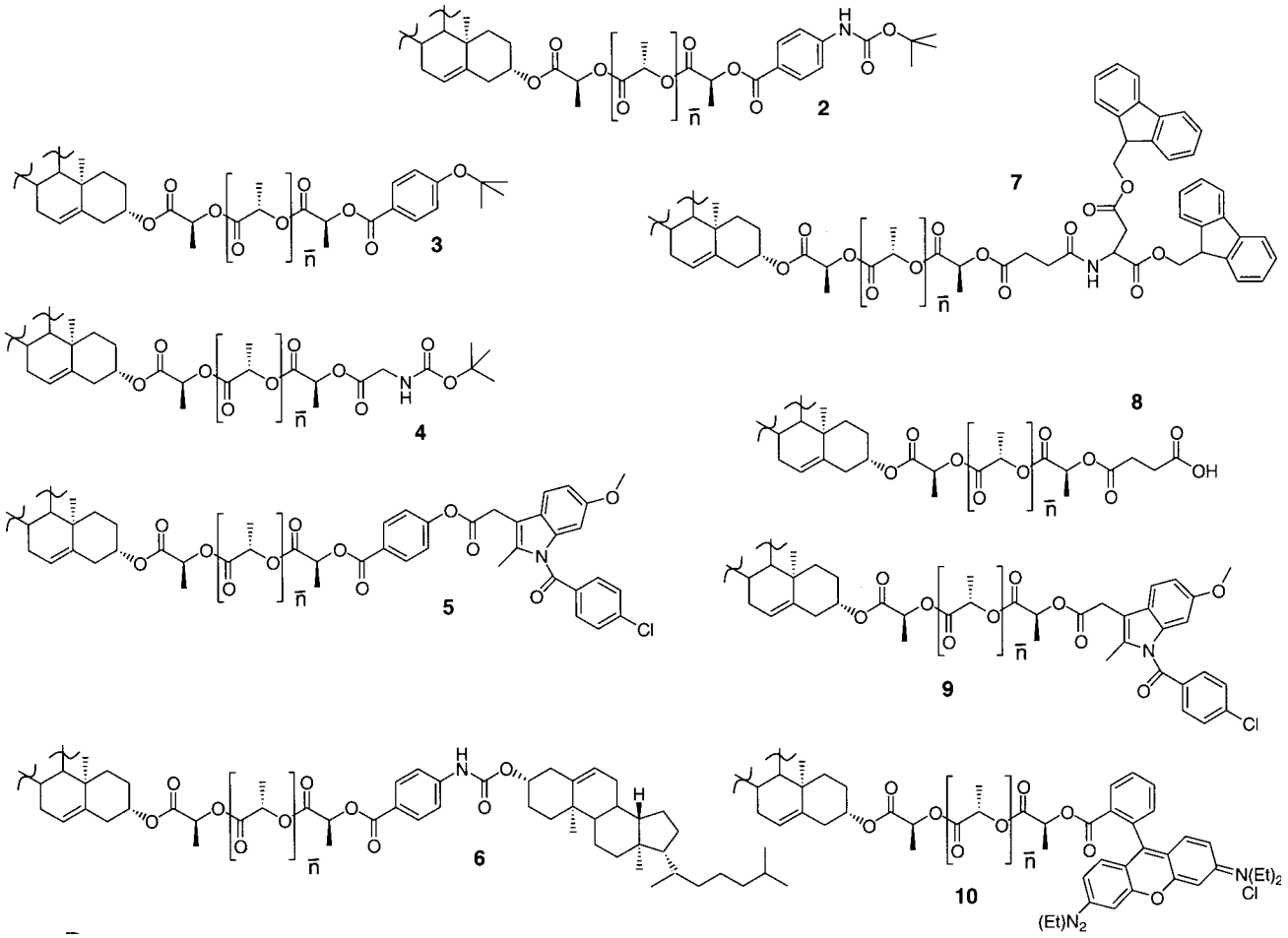
Figure 8. Wide-angle X-ray scattering scans recorded at 25 °C of several blends of **1c** and PLA.

oligomers on the surface of a preformed PLA-based implant could modify cell response.[12]

Biofunctional Cholesteryl−(L-Lactic acid)$_{\bar{n}}$ Oligomers. Synthesis. The secondary alcohol terminus of the CLA$_{\bar{n}}$ oligomers can be used for further functionalization of the molecules. Several of the CLA$_{\bar{n}}$ derivatives that have been prepared are shown in Schemes 2, 6, and 7. The purpose of these functionalizations is 2-fold. First of all, the introduction of new end groups could facilitate further substitution reactions (e.g., by replacement of the secondary alcohol end group by a primary amine). Second, the introduction of new end groups could be useful to control biological response or allow imaging of the oligomers in biological experiments. CLA$_{\bar{n}}$ oligomers with aliphatic and aromatic amino end groups, or phenol or carboxy groups at their chain end are of interest for further functionalization reactions and are obtained upon deprotection of **2**, **3**, **4**, **7**, and **15**. CLA$_{\bar{n}}$ oligomers substituted with a fluorescent dye (e.g., **10** and **13**) could be useful for fluorescent microscopy studies, whereas the attachment of an antiinflammatory drug such as indomethacin (**5**, **9**) results in an oligomeric prodrug.[17] In the latter case, degradation of the L-lactic acid spacer could result in a gradual release of indomethacin.

Most of the CLA$_{\bar{n}}$ derivatives depicted in Scheme 2 were prepared by direct esterification of the secondary alcohol terminus of the oligomer with the corresponding carboxylic acid. Most aromatic acids could be attached under mild conditions using the diisopropylcarbodiimide/(dimethylamino)pyridinium 4-toluenesulfonate (DIPC/DPTS) method.[18] CLA$_{\bar{n}}$ oligomers **2** and **3** were obtained by esterification of 4-*tert*-butoxycarbonylaminobenzoic acid and 4-*tert*-butoxybenzoic acid, respectively, which were prepared as reported previously.[19] The end functionalized CLA$_{\bar{n}}$ oligomers were characterized by means of ^{1}H NMR spectroscopy and MALDI−TOF mass spectrometry. As a representative example, the ^{1}H NMR and mass spectra of **2** are shown in Figure 9. The good agreement between the integrals of the doublets in the aromatic part of the region (indicated with *d* and *e* in Figure 9a) and the complex peak at ∼ 5.35 ppm caused by the olefinic proton of the cholesterol moiety and the C−H proton of the terminal L-lactic acid residue in the ^{1}H NMR spectrum (labeled *a* and *c*) indicates a quantitative end functionalization of the CLA$_{\bar{n}}$ oligomer. From the integrals of the signals at ∼5.15 ppm, which

Scheme 2



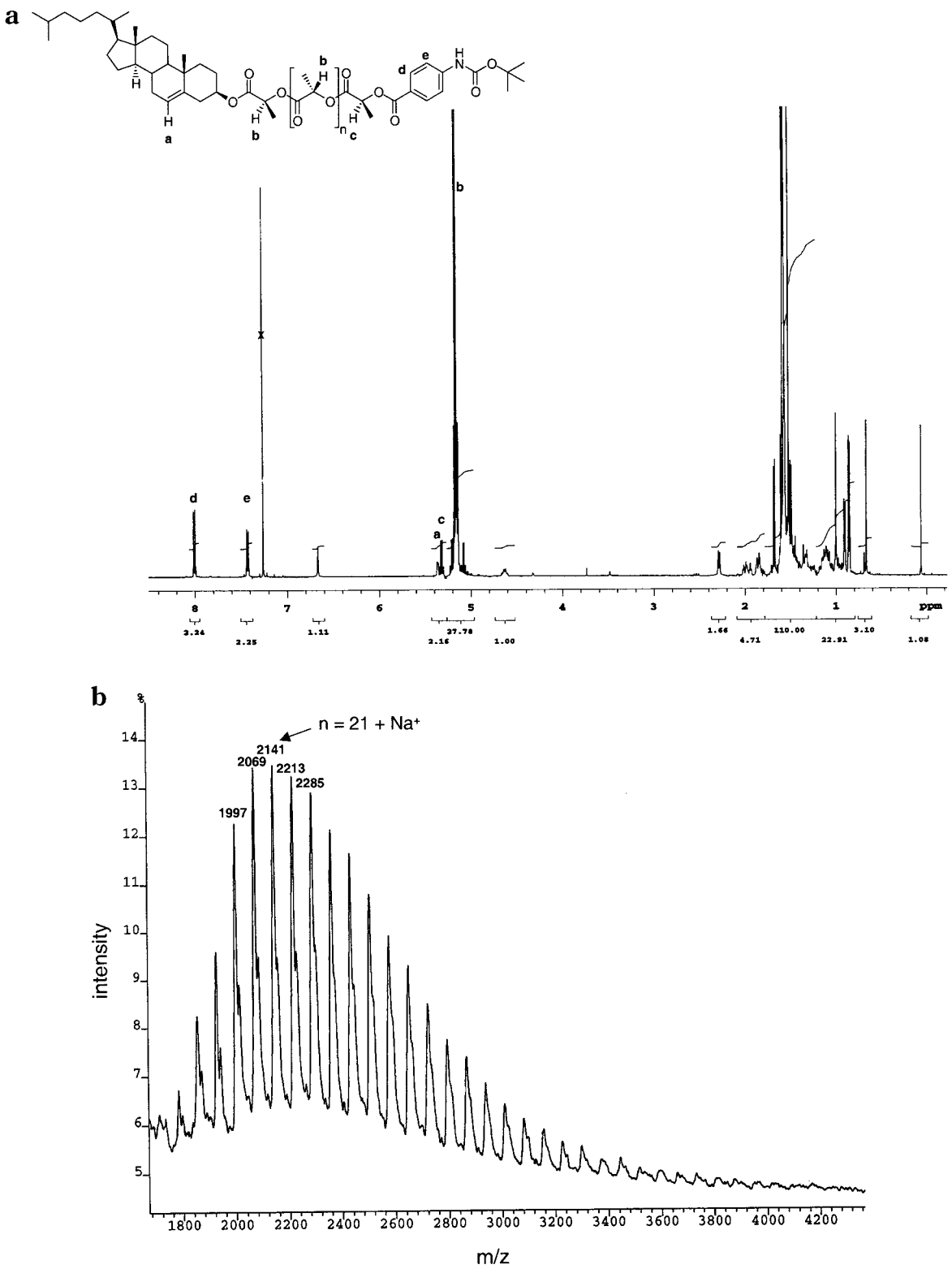
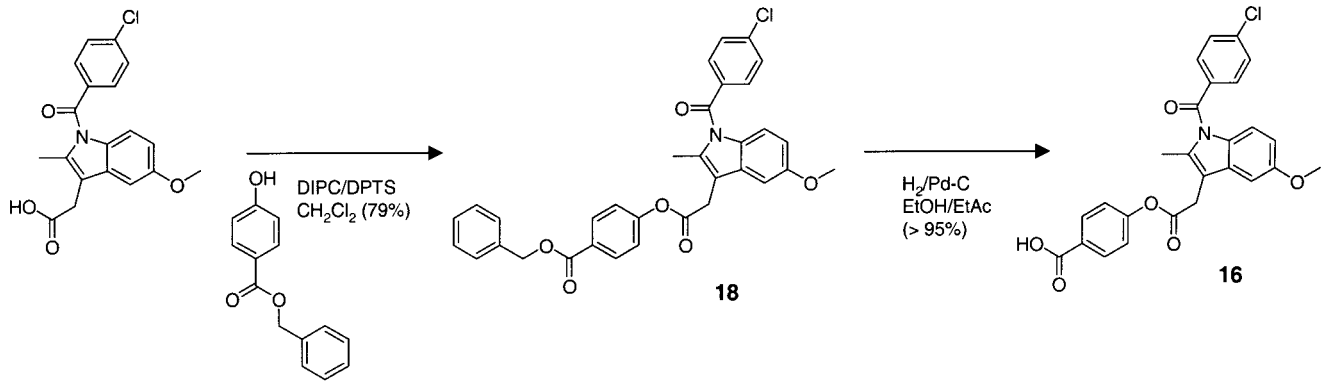


Figure 9. (a) ^{1}H NMR spectrum of the end functionalized $CLA_{\bar{n}}$ derivative **2**. Only peaks that are relevant to the discussion of the spectrum in the text are labeled. The complete assignment of the ^{1}H NMR spectrum can be found in the experimental part. Peaks due to residual solvent in the sample are labeled with "×". (b) MALDI−TOF mass spectrum of the end functionalized $CLA_{\bar{n}}$ derivative **2**. A number of signals are labeled with the corresponding masses.

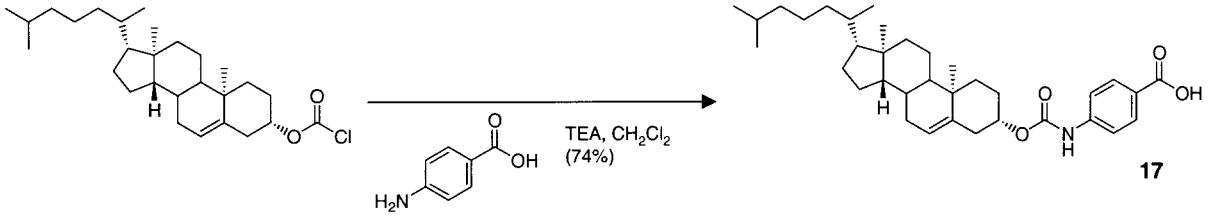
is due to the C−H protons of the L-lactic acid repeats (marked *b* in Figure 9a) and the peak at 5.35 ppm a number-average degree of polymerization of 27 can be calculated. Unambiguous proof for the chemical integrity of **2** was obtained from the MALDI−TOF mass spectrum, which is shown in Figure 9b. In this mass spectrum a series of peaks is labeled with the observed masses. The mass calculated for a Na^+-labeled oligomer **2** with a L-lactic acid segment composed of 21 repeat units (2118 + 23 Da) perfectly matches the measured mass in the mass spectrum, which underlines the success of the end modification. The sodium ions were added during sample preparation and act as cationizing agents to facilitate the MALDI process.

Whereas the synthesis of **5** and **6** could be accomplished using the DIPC/DPTS method, this proce-

Scheme 3



Scheme 4



dure was not found to be effective for the preparation of the Rhodamine B functionalized oligomer **10**. In this case, the coupling of the fluorescent dye could be performed in good yields using using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide−HCl (EDC)[20] as the coupling agent in the presence of 4-(dimethylamino)-pyridine (DMAP) as the acylation catalyst.[21,22] The indomethacin and cholesterol-substituted aromatic acids **16** and **17**, which were used for the preparation of $CLA_{\bar{n}}$ oligomers **5** and **6**, were synthesized as depicted in Schemes 3 and 4. Indomethacin was first esterified with benzyl-4-hydroxybenzoate using the DIPC/DPTS methodology to give intermediate **18**, which was subsequently hydrogenated to afford the final compound (**16**) (Scheme 3). Cholesterol derivative **17** was prepared in a single step by acylation of 4-aminobenzoic acid with cholesterylchloroformate in the presence of triethylamine (Scheme 4).

The esterification of aliphatic carboxylic acids with the $CLA_{\bar{n}}$ oligomers was generally accomplished using the EDC/DMAP methodology described above.[20,21] The carboxylic acid terminated oligomer **8** was obtained by alcoholysis of succinic anhydride in the presence of DMAP. Under EDC/DMAP conditions, indomethacin could be coupled directly to the $CLA_{\bar{n}}$ oligomers, without the need for a 4-hydroxybenzoic acid linker (compound **9**). The protected L-aspartic acid derivative (**21**), which was required for the preparation of oligomers **7** and **15**, was synthesized as shown in Scheme 5. The synthesis first involved the preparation of *N*-(*tert*-butoxycarbonyl)-O^{α},O^{β}-di(9-fluorenylmethyl)-L-asparate (**19**), to protect the carboxylic acid functionalities,[23] followed by removal of the amine protecting group under the action of trifluoroacetic acid (CF_3COOH)[24] and aminolysis of succinic anhydride to afford the desired carboxylic acid (**21**).

Among the structures presented in Scheme 2, the 4-(*tert*-butoxycarbonyl)aminobenzoic acid (**2**), the 4-(*tert*-butoxy)benzoic acid (**3**), the *N*-(*tert*-butoxycarbonyl)-glycine (**4**), and the succinic acid substituted $CLA_{\bar{n}}$ oligomers (**8**) were used for further functionalization. It was anticipated that replacement of the secondary alcohol terminus by a phenolic alcohol, a primary or aromatic amine or a carboxylic acid would facilitate the attachment of functional groups to the $CLA_{\bar{n}}$ oligomers. As an example, the derivatization of the $CLA_{\bar{n}}$−4-(*tert*-butoxy)benzoate (**3**) and the $CLA_{\bar{n}}$−*N*-(*tert*-butoxycarbonyl)glycinate oligomers (**4**) is shown in Schemes 6 and 7, respectively. The 4-hydroxybenzoic acid substituted $CLA_{\bar{n}}$ oligomer **11**, which was obtained after treatment of **3** with a solution of CF_3COOH in CH_2Cl_2, can be easily reacted with various aromatic carboxylic acids under mild DIPC/DPTS conditions.[18] In this way, 1-pyrenecarboxylic acid could be successfully attached to $CLA_{\bar{n}}$ oligomers (compound **13**; Scheme 6).

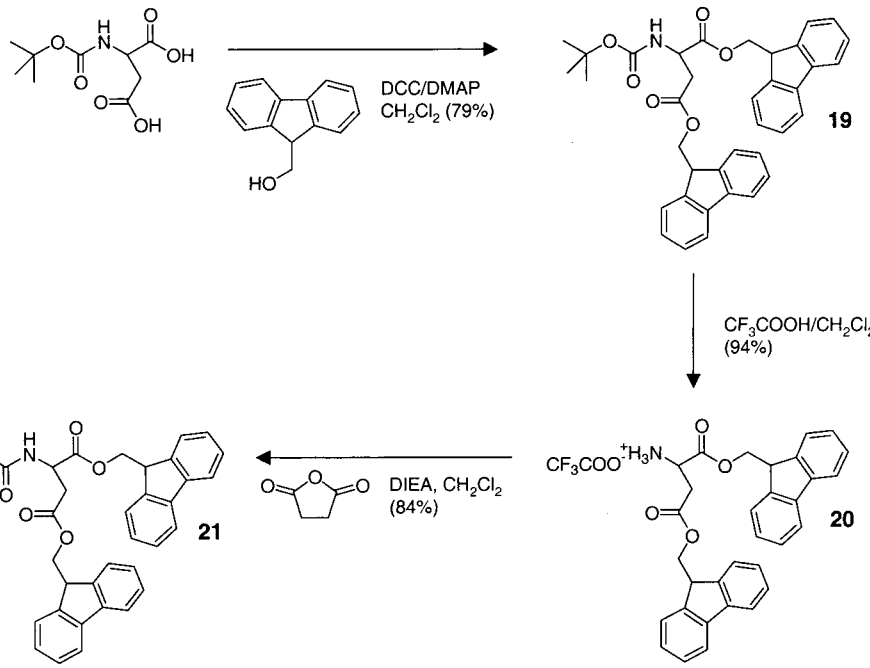
Deprotection of the *tert*-butoxycarbonyl protected oligomer **4** in a 2/1 (v/v) mixture of CH_2Cl_2 and CF_3-COOH afforded the corresponding ammonium trifluoroacetate (**14**), which was acylated with *N*-succinyl-O^{α},O^{β}-di(9-fluorenylmethyl)-L-aspartate (**21**) yielding the L-aspartic acid substituted oligomer **15** (Scheme 7).

Blends with Cholesteryl—(L-Lactic acid)$_{\bar{n}}$. We investigated the miscibility of $CLA_{\bar{n}}$ oligomers with the functionalized derivatives, which could be useful in tailoring biomaterials. The miscibility of $CLA_{\overline{37}}$−4-(indomethacin)benzoate (**5**) and $CLA_{\overline{37}}$−4-(cholesterylcarbamate)benzoate (**6**) with **1c** was investigated with mixtures containing 0−100 wt % of **5** or **6** and **1c** prepared in solution, followed by evaporation of solvent. The homogeneity of the resulting blends was analyzed by DSC, SAXS and WAXS experiments. Representative DSC scans and X-ray diffraction scans for a series of mixtures of **1c** and **6** are shown in Figures 10−12, respectively.

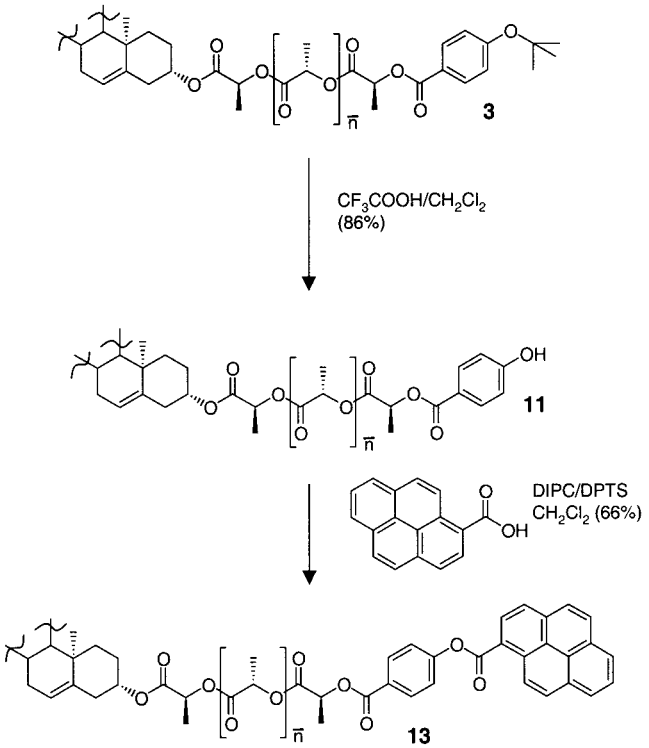
The DSC scans shown in Figure 10 reveal a single T_g for all blend compositions, suggesting miscibility.[16] With increasing amounts of **6**, the T_g gradually shifts from 49 °C for **1c** to 64 °C for pure **6**.

The SAXS scan of pure **6** shows both a (001) and an (002) reflection, suggesting lamellar organization of the oligomers. From these diffraction peaks, a *d* spacing of ∼115 Å can be calculated, which is significantly smaller

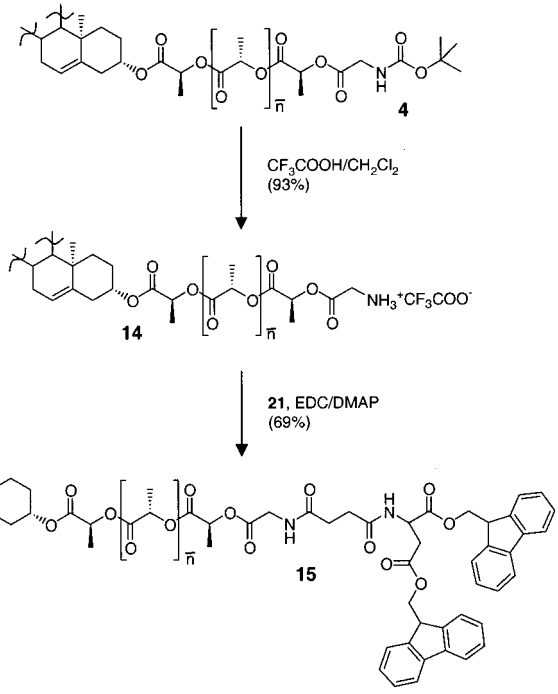
Scheme 5



Scheme 6



Scheme 7



than the estimated extended length of an average-sized molecule in this material (~141 Å).[15] To fulfill these geometric requirements, **6** is probably organized in an interdigitated bilayer structure similar to **1c**. The SAXS scans of blends of **1c** and **6** also show two orders of reflection, demonstrating that they also possess the lamellar order observed in their components with a single periodicity, and also further suggesting molecular miscibility. The corresponding *d* spacings of the blends gradually increase from 94 Å for **1c** to 115 Å for the pure **6**. WAXS scans of the blends also indicated a high degree of order. With the exception of the blend that contained 83 wt % **6**, the wide angle diffraction peak (5 Å, possibly an intermolecular distance) for the blends does not significantly broaden or shift to different scattering angles in comparison with the pure compounds.

A series of blends of **5** and **1c** were prepared and analyzed as described above. The results of DSC, SAXS, and WAXS experiments performed with these blends are presented in Figures 13−15, respectively. Again, a single T_g is observed for all the investigated blends, suggesting that both components are miscible. With increasing amounts of **5**, the T_g of the blends gradually shifts from 49 °C for the pure **1c** to 61 °C for **5**. No signal could be observed in SAXS scans of pure **5**, suggesting very poor ordering in this material. Interestingly, however, the addition of a small amount of **1c** (~11 wt

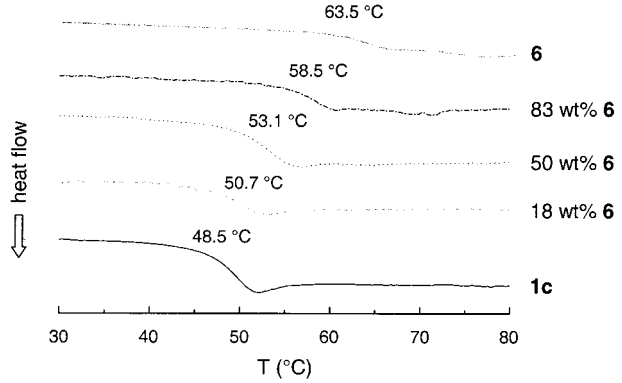


Figure 10. Differential scanning calorimetry scans for a series of mixtures of **1c** and **6**.

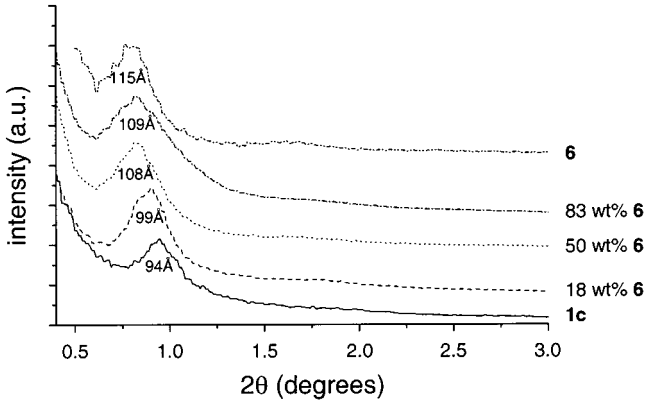


Figure 11. Small-angle X-ray scattering scans recorded at 25 °C for a series of mixtures of **1c** and **6**.

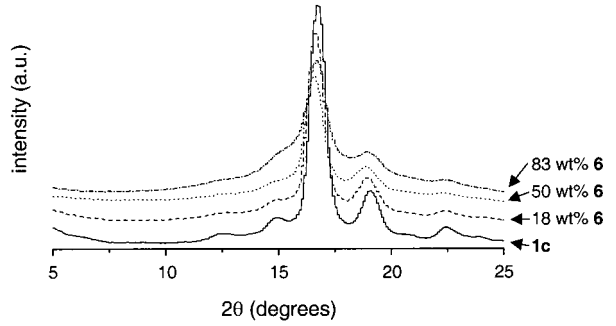


Figure 12. Wide-angle X-ray scattering scans recorded at 25 °C for a series of mixtures of **1c** and **6**.

%) is sufficient to induce order in the blend (see Figure 14). The estimated average extended length of **5** is approximately 138 Å, which is larger than the *d* spacing obtained by SAXS, again indicating that the molecules interdigitate to some extent. The WAXS scans shown in Figure 15 confirm the amorphous nature of **5**, but interestingly local order within the layers is observed even at very low concentrations of **1c**. A possible explanation here is the fact that steric disruption of packing occurs in the indomethacin derivative. However, addition of small amounts of unsubstituted oligomers allows the blend system to order locally.

Conclusions

The covalent attachment of a cholesterol moiety to low molecular weight L-lactic acid oligomers with number-average degrees of polymerization ($\bar{n}$) varying from 10 to 40 results in the formation of thermotropic liquid crystalline materials. The cholesterol moieties not only induce self-assembly, but also make these systems interesting biomaterials since cholesterol is ubiquitous and critically needed in all mammalian cells. In the solid state, the $CLA_{\bar{n}}$ oligomers and their blends with functionalized derivatives self-assemble into interdigitated bilayers of potential interest as temporary resorbable scaffolds in tissue engineering applications. Furthermore, since the $CLA_{\bar{n}}$ oligomers can be homogeneously mixed with PLA, these materials could be used to modify the surfaces of polymeric scaffolds that are already approved for human use. The $CLA_{\bar{n}}$ oligomers can also be easily functionalized with bioactive drugs or fluorescent labels to follow their fate in cells. Such materials could very easily be used as blends with functionalized derivatives given their molecular compatibility.

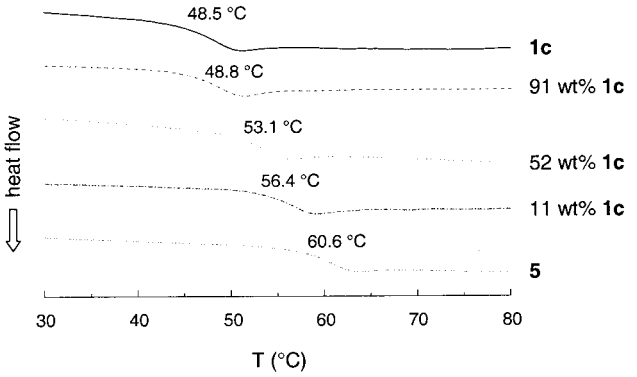


Figure 13. Differential scanning calorimetry scans of a series of mixtures of **1c** and **5**.

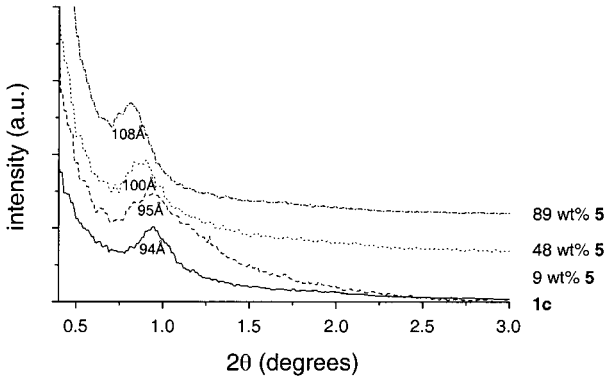


Figure 14. Small-angle X-ray scattering scans recorded at 25 °C of a series of mixtures of **1c** and **5**.

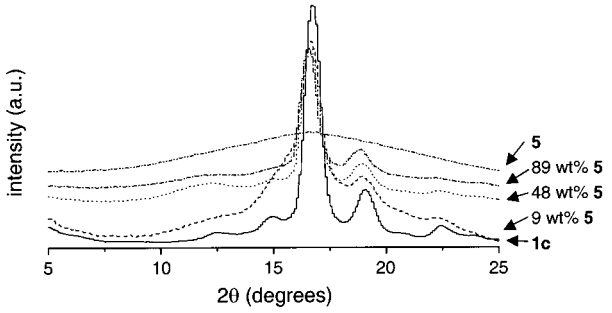


Figure 15. Wide-angle X-ray scattering scans recorded at 25 °C of a series of mixtures of **1c** and **5**.

Experimental Section

General Data. Unless stated otherwise, all reagents and solvents were of commercial grade and were used as received. All reactions were performed under a nitrogen atmosphere.

Methylene chloride (CH_2Cl_2) and toluene were freshly distilled from P_2O_5 and sodium/benzophenone, respectively, prior to use. *N*,*N*′-Dimethylformamide (DMF) was stored over molecular sieves (4 Å). Triethylamine (TEA) was stored over KOH. Cholesterol and L-lactide were recrystallized from ethanol and ethyl acetate, respectively, and vacuum-dried at room temperature to constant weight. 4-(Dimethylamino)pyridinium 4-toluenesulfonate (DPTS) was prepared according to a literature procedure.[18] Reactions were monitored by thin-layer chromatography, using 0.250 mm precoated silicagel 60 F254 glass-plates (Merck). Column chromatography was performed with Merck silica gel 60 (0.040−0.063 mm, 230−400 mesh, 60 Å).

^{1}H and ^{13}C NMR spectra were recorded on Varian U400 or U500 spectrometers at room temperature. Chemical shifts are expressed in parts per million (δ) using residual protons in the indicated solvents as internal standard. Mass spectrometry was performed at the Mass-Spectrometry Laboratory of the School of Chemical Sciences at the University of Illinois at Urbana−Champaign. Low-resolution fast atom bombardment mass-spectra (LR−FAB) were recorded on a Micromass ZAB−SE mass-spectrometer. High-resolution fast atom bombardment mass-spectrometry (HR−FAB) was performed on a Micromass 70-SE−4F instrument. MALDI−TOF mass-spectra were acquired on a PerSeptive Biosystems Voyager-DE STR spectrometer. For the MALDI−TOF experiments, 3-indolylacetic acid (IAA) was used as the matrix and sodium ions were added to facilitate cationization. Elemental analysis was performed in the Microanalysis Laboratory of the School of Chemical Sciences of the University of Illinois at Urbana−Champaign.

Small-angle X-ray scattering (SAXS) experiments were carried out using a Bruker instrument with an Anton Paar high-resolution small angle camera, a Hi-Star area detector, a M18XHF22−SRA rotating anode generator, a camera distance of 630 nm, and Bruker software. Powder diffraction rings were integrated over 360° to yield the diffraction pattern, and the system was calibrated using a silver behenate standard. The samples used for variable temperature studies were placed in sealed 0.7 mm diameter capillary tubes. Differential scanning calorimetry (DSC) experiments were performed using a TA 2920 Modulated DSC instrument with a ramp speed of 10 °C/min.

Synthesis. Cholesteryl−(L-Lactic acid)$_{\bar{n}}$ (1). (i) Solution Polymerization. As a typical example, the synthesis of an oligomer with a targeted length of 20 lactic acid residues will be described: a 1.9 M toluene solution of $Al(Et)_3$ (3 mL, 5.7 mmol $Al(Et)_3$) was added to a mixture of L-lactide (24.65 g, 171 mmol) and cholesterol (6.61 g, 17.1 mmol) in toluene (120 mL). This mixture was stirred for 15 min at room temperature and was then placed in a preheated oil bath at 80 °C. After 5 h, the polymerization was quenched with MeOH (5 mL), and subsequently the warm reaction mixture was precipitated in MeOH (1500 mL). Solids were filtered and vacuum-dried at room temperature. Finally, the crude product was passed over a short column (SiO_2, CH_2Cl_2/MeOH 100/5 (v/v)). Yield: 16.8 g (54%). ^{1}H NMR ($CDCl_3$):[25] δ = 5.35 (d, cholesterol C-6 H, 1H), 5.15 (q, −(O(C=O)C*H*(CH$_3$))$_n$−, *n*H), 5.10 (q, cholesterol−O(C=O)C*H*(CH$_3$)−, 1H), 4.65 (m, cholesterol C-3 H, 1H), 4.35 (q, −O(C=O)C*H*(CH$_3$)OH, 1H), 1.55 (d, −(O(C=O)CH(C*H*$_3$))$_n$−, 3*n*H), 0.65 (s, cholesterol C-18 H, 3H). $\bar{n}$ (^{1}H NMR) = 21. MS (MALDI−TOF): M_w = 2147, M_n = 2092, M_w/M_n = 1.03. $\bar{n}$ (MALDI−TOF MS) = 24.

(ii) Bulk Polymerization. As a typical example the synthesis of an oligomer with a targeted length of 10 lactic acid residues will be described: A mixture of L-lactide (10.19 g, 71 mmol) and cholesterol (5.44 g, 14 mmol) was placed in a preheated oil bath at 150 °C and stirred until everything was molten. Then, a solution of $Sn(oct)_2$ in toluene (1 mL, 0.37 gr $Sn(oct)_2$/mL) was added, and the reaction mixture was stirred at 150 °C. After 5 h, the reaction mixture was allowed to cool to room temperature, and the residual solid was triturated with MeOH (100 mL). Solids were collected by filtration and finally vacuum-dried at room temperature. Yield: 7.82 g (50%). ^{1}H NMR ($CDCl_3$):[25] δ = 5.35 (d, cholesterol C-6 H, 1H), 5.15 (q, −(O(C=O)C*H*(CH$_3$))$_n$−, *n*H), 5.10 (q, cholesterol−O(C=O)C*H*(CH$_3$)−, 1H), 4.65 (m, cholesterol C-3 H, 1H), 4.35 (q, −O(C=O)C*H*(CH$_3$)OH, 1H), 1.55 (d, −(O(C=O)CH(C*H*$_3$))$_n$−, 3*n*H), 0.65 (s, cholesterol C-18 H, 3H). $\bar{n}$ (^{1}H NMR) = 11. MS (MALDI−TOF): M_w = 1938, M_n = 1603, M_w/M_n = 1.21. $\bar{n}$ (MALDI−TOF MS) = 17.

Cholesteryl—(L-lactic acid)$_{\bar{n}}$ 4-(*tert*-butoxycarbonyl)-aminobenzoate (2). As a typical example, the substitution of a cholesteryl-(L-lactic acid)$_{\overline{24}}$ oligomer will be described: DIPC (0.25 mL, 1.60 mmol) was added to a solution of **1** (1.0 g, ∼0.48 mmol), 4-(*N*-*tert*-butoxycarbonyl)aminobenzoic acid (0.28 g, 1.18 mmol), and DPTS (0.41 g, 1.39 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at room-temperature overnight. After that, the reaction mixture was evaporated to dryness. The residue was redissolved in CH_2Cl_2 (20 mL) and precipitated in MeOH (400 mL). Solids were filtered and vacuum-dried. Yield: 1.01 g (91%). ^{1}H NMR ($CDCl_3$):[25] δ = 7.75 (d, Ar*H*, 2H), 6.65 (d, Ar*H*, 2H), 6.70 (s, N*H*, 1H), 5.35 (m, cholesterol C-6 H and −O(C=O)C*H*(CH$_3$)O(C=O)Ar−, 2H), 5.15 (q, −(O(C=O)C*H*(CH$_3$))$_n$−, *n*H), 5.10 (q, cholesterol−O(C=O)C*H*(CH$_3$)−, 1H), 4.65 (m, cholesterol C-3 H, 1H), 1.55 (d, −(O(C=O)CH(C*H*$_3$))$_n$−, 3*n*H), 1.40 (s, (C*H*$_3$)$_3$CO(C=O)−, 9H), 0.65 (s, cholesterol C-18 H, 3H). $\bar{n}$ (^{1}H NMR) = 27. MS (MALDI−TOF): M_w = 2384, M_n = 2345, M_w/M_n = 1.02. $\bar{n}$ (MALDI−TOF MS) = 24.

Cholesteryl—(L-Lactic acid)$_{\bar{n}}$ *N*-(*tert*-butoxycarbonyl)-glycinate (4). As a typical example the end-functionalization of a cholesteryl-(L-lactic acid)$_{\overline{25}}$ oligomer will be described: EDC (0.30 g, 1.56 mmol) was added to an ice-cooled solution of **1** (1.00 g, ∼0.46 mmol), *N*-(*tert*-butoxycarbonyl)glycine (0.26 g, 1.48 mmol) and DMAP (0.10 g, 0.82 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at 0 °C for 4 h. Then, the ice bath was removed, and stirring was continued for another 4 h at room temperature. The reaction mixture was evaporated to dryness, the residue redissolved in CH_2Cl_2 (5 mL) and precipitated in MeOH (100 mL). Solids were filtered and vacuum-dried at room temperature. Yield: 0.90 g (84%). ^{1}H NMR ($CDCl_3$):[25] δ = 5.35 (d, cholesterol C-6 H, 1H), 5.15 (q, −(O(C=O)C*H*(CH$_3$))$_n$−, *n*H), 5.10 (q, cholesterol−O(C=O)C*H*(CH$_3$)−, 1H), 5.00 (b, −C*H*(CH$_3$)O(C=O)CH$_2$−, 1H), 4.65 (m, cholesterol C-3 H, 1H), 4.00 (m, −O(C=O)C*H*$_2$NH−, 2H), 1.55 (d, −(O(C=O)CH(C*H*$_3$))$_n$−, 3*n*H), 1.45 (s, (C*H*$_3$)$_3$CO(C=O)−, 9H), 0.65 (s, cholesterol C-18 H, 3H). $\bar{n}$ (^{1}H NMR) = 27. MS (MALDI−TOF): M_w = 2687, M_n = 2380, M_w/M_n = 1.13. $\bar{n}$ (MALDI−TOF MS) = 25.

Benzyl 4-(Indomethacin)benzoate (18). DIPC (1.0 mL, 6.40 mmol) was added to a solution of indomethacin (1.0 g, 2.80 mmol), DPTS (1.24 g, 4.21 mmol) and benzyl-4-hydroxybenzoate (0.77 g, 3.37 mmol) in DMF (30 mL). The solution was stirred overnight at room temperature. Then, the reaction mixture was poured into water (250 mL). The aqueous mixture was extracted with CH_2Cl_2 (3×), and the combined CH_2Cl_2 extracts were washed with water (1×) and brine (1×). The organic phase was separated, dried over $MgSO_4$, filtered, and evaporated to dryness. The oily residue was triturated with MeOH. Solids were filtered and vacuum-dried. Yield: 1.24 g (79%). ^{1}H NMR ($CDCl_3$): δ = 8.10 (d, Ar*H*(C=O)O−, 2H), 7.68 (d, Ar*H*(C=O)$_n$−, 2H), 7.48 (d, Ar*H*Cl, 2H), 7.40 (m, Ar*H*benzyl, 5H), 7.15 (d, Ar*H*O(C=O)−, 2H), 7.04 (d, Ar*H*, 1H), 6.88 (d, Ar*H*, 1H), 6.70 (dd, Ar*H*, 1H), 5.35 (s, ArC*H*$_2$O−, 2H), 3.95 (s, −C*H*$_2$(C=O)O−, 2H), 3.85 (s, ArOC*H*$_3$, 3H), 2.45 (s, −C*H*$_3$, 3H). MS (LR−FAB) *m*/*z* = 568.2 (MH^+). MS (HR−FAB) *m*/*z* = 567.144800 (calculated 567.144866) for $C_{33}H_{26}NO_6Cl$.

4-(Indomethacin)benzoic acid (16). Pd−C (0.47 g, 50 wt % H_2O) was added to a solution of **18** (1.21 g, 2.13 mmol) in a mixture of EtAc (80 mL) and EtOH (40 mL), and the reaction mixture was stirred overnight at room temperature under a hydrogen atmosphere. Then, the reaction mixture was filtered over a short plug of Celite and evaporated to dryness, affording the free acid in quantitative yield. ^{1}H NMR (DMSO-d_6): δ = 7.98 (d, Ar*H*(C=O)O−, 2H), 7.65 (m, −N(C=O)Ar*H*Cl, 4H), 7.25 (d, Ar*H*O(C=O)−, 2H), 7.15 (d, Ar*H*, 1H), 6.95 (d, Ar*H*, 1H), 6.72 (dd, Ar*H*, 1H), 4.10 (s, −C*H*$_2$(C=O)O−, 2H), 3.75 (s, ArOC*H*$_3$, 3H), 2.25 (s, −C*H*$_3$, 3H). MS (LR−FAB) *m*/*z* = 478.2 (MH^+).

Cholesteryl—(L-Lactic acid)$_{\bar{n}}$ 4-(Indomethacin)benzoate (5). As a typical example, the functionalization of a cholesteryl-(L-lactic acid)$_{\overline{34}}$ oligomer will be described: DIPC (0.11 mL, 0.70 mmol) was added dropwise to a solution of **1** (1.87 g, ~0.66 mmol) **16** (0.38 g, 0.80 mmol) and DPTS (0.20 g, 0.68 mmol) in CH_2Cl_2 (10 mL). After overnight stirring at room temperature, the reaction mixture was evaporated to dryness. The residue was redissolved in a minimal amount CH_2Cl_2 and precipitated in MeOH. Solids were filtered and vacuum-dried. Yield: 1.90 g (88%). ^{1}H NMR (DMSO-d_6):[25] δ = 8.08 (d, Ar*H*(C=O)O−, 2H), 7.70 (m, −N(C=O)Ar*H*Cl, 4H), 7.35 (d, Ar*H*O(C=O)−, 2H), 7.22 (d, Ar*H*, 1H), 6.98 (d, Ar*H*, 1H), 6.78 (dd, Ar*H*, 1H), 5.40 (d, cholesterol C-6 H and −O(C=O)C*H*(CH$_3$)O(C=O)Ar−, 2H), 5.25 (q, −(O(C=O)C*H*(CH$_3$))$_n$−, *n*H), 5.10 (q, cholesterol−O(C=O)C*H*(CH$_3$)−, 1H), 4.55 (m, cholesterol C-3 H, 1H), 4.15 (s, −C*H*$_2$(C=O)O−, 2H), 3.80 (s, ArOC*H*$_3$, 3H), 2.25 (s, −C*H*$_3$, 3H), 1.55 (d, −(O(C=O)CH-(C*H*$_3$))$_n$−, 3*n*H), 0.65 (s, cholesterol C-18 H, 3H). $\bar{n}$ (^{1}H NMR) = 36. MS (MALDI−TOF): M_w = 3598, M_n = 3278, M_w/M_n = 1.10. $\bar{n}$ (MALDI−TOF MS) = 34.

Benzoic Acid−4-cholesterylcarbamate (17). A solution of cholesteryl chloroformate (1.0 g, 2.23 mmol) in CH_2Cl_2 (10 mL) was added to a mixture of 4-aminobenzoic acid (0.306 g, 2.23 mmol) and triethylamine (0.31 mL, 2.23 mmol) in CH_2Cl_2 (20 mL). Then, TEA (0.31 mL, 2.23 mmol) was added dropwise to the reaction mixture, which was subsequently stirred overnight at room temperature. After that, the reaction mixture was washed with an aqueous $KHSO_4$ solution (1×), water (1×), and brine (1×). The organic phase was separated, dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was triturated with MeOH. Solids were filtered and vacuum-dried. Yield: 0.92 g (74%). ^{1}H NMR ($CDCl_3$):[25] δ = 7.85 (d, Ar*H*(C=O)OH, 2H), 6.65 (d, Ar*H*NH(C=O)−, 2H), 5.40 (d, cholesterol C-6 H, 1H), 4.65 (m, cholesterol C-3, 1H), 0.65 (s, cholesterol C-18, 3H). ^{13}C NMR ($CDCl_3$): δ = 161.09, 149.19, 138.91, 132.99, 123.34, 114.16, 79.64, 56.62, 56.08, 49.91, 42.28, 39.66, 39.49, 37.64, 36.77, 36.51, 36.15, 35.77, 31.87, 31.80, 28.21, 28.00, 27.40, 24.26, 23.80, 22.81, 22.55, 21.02, 19.38, 19.26, 18.70, 11.84. MS (LR−FAB) *m*/*z* = 550.4 (MH$^+$).

Cholesteryl—(L-Lactic acid)$_{\bar{n}}$ 4-(Cholesterylcarbamate)benzoate (6). As a typical example, the functionalization of a cholesteryl−(L-lactic acid)$_{\overline{34}}$ oligomer will be described: DIPC (20 μL, 0.13 mmol) was added dropwise to a solution of **1** (0.215 g, ~0.076 mmol) **17** (0.051 g, 0.093 mmol) and DPTS (0.023 g, 0.078 mmol) in CH_2Cl_2 (25 mL). After overnight stirring at room temperature, the reaction mixture was evaporated to dryness. The residue was redissolved in a minimal amount of CH_2Cl_2 and precipitated in MeOH. Solids were filtered and vacuum-dried. Yield: 0.21 g (83%). ^{1}H NMR ($CDCl_3$):[25] δ = 8.00 (d, Ar*H*(C=O)O−, 2H), 7.45 (d, Ar*H*NH-(C=O)−, 2H), 5.40 (d, cholesterol′ C-6 H, 1H), 5.35 (d, cholesterol C-6 H, 1H), 5.30 (q, −O(C=O)C*H*(CH$_3$)O(C=O)Ar, 1H), 5.15 (q, −(OC(=O)C*H*(CH$_3$))$_n$−, *n*H), 5.10 (q, cholesterol−OC(=O)C*H*(CH$_3$)−, 1H), 4.65 (m, cholesterol C-3 H and cholesterol′ C-3 H, 2 × 1H), 1.55 (d, −(OC(=O)CH(C*H*$_3$))$_n$−, 3*n*H), 0.65 (ds, cholesterol C-18 and cholesterol′ C-18 H, 2 × 3H). $\bar{n}$ (^{1}H NMR) = 28. MS (MALDI−TOF): M_w = 3483, M_n = 3119, M_w/M_n = 1.12. $\bar{n}$ (MALDI−TOF MS) = 30.

***N*-(*tert*-Butoxycarbonyl)-*O*$^\alpha$,*O*$^\beta$-di(9-fluorenylmethyl) L-Aspartate (19).** DCC (5.47 g, 26.51 mmol) was added in three portions to an ice-cooled mixture of *N*-*tert*-BOC-L-Asp (2.00 g, 8.58 mmol), 9-fluorenylmethanol (5.00 g, 25.5 mmol) and DMAP (0.17 g, 1.39 mmol) in CH_2Cl_2 (100 mL). After the addition of the DCC was completed, the reaction mixture was stirred at 0 °C for another hour. Then, the ice bath was removed, and the reaction mixture was stirred overnight at room temperature. The precipitated dicyclohexylurea was removed by filtration, and the filtrate was successively washed with 5% $NaHCO_3$ (1×), H_2O (1×), and brine (1×). The organic phase was separated, dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 100/1 (v/v)). Yield: 4.02 g (79%). ^{1}H NMR (DMSO-d_6): δ = 7.85 (m, Ar*H*, 4H), 7.65 (m, Ar*H*, 4H), 7.45 (d, N*H*, 1H), 7.40 (m, Ar*H*, 4H), 7.30 (m, Ar*H*, 4H), 4.55 (m, −C*H*NH(C=O)−, 1H), 4.35 (m, FmC*H*$_2$O−, 4H), 4.20 (m, C*H*^{Fm}CH$_2$O−, 2H), 2.70 (m, −CHC*H*$_2$(C=O)O−, 2H), 1.35 (s, (CH$_3$)$_3$CO(C=O)−, 9H). ^{13}C NMR (DMSO-d_6): δ = 171.19, 170.04, 155.30, 143.51, 140.72, 127.74, 127.15, 125.22, 120.14, 78.56, 66.48, 66.01, 50.03, 46.26, 46.12, 35.53, 28.09. MS (LR−FAB) *m*/*z* = 590.2 (MH$^+$). MS (HR−FAB) *m*/*z* = 590.254300 (calculated 590.254263) for $C_{37}H_{36}NO_6$.

***O*$^\alpha$,*O*$^\beta$-Di(9-fluorenylmethyl)-L-aspartate Trifluoroacetic Acid Salt (20).** TFA (30 mL) was added to an ice-cooled solution of **19** (2.93 g, 4.97 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at 0 °C for 1 h, and at room temperature for another hour. Then, the reaction mixture was evaporated to dryness, and the residue triturated with Et_2O. Solids were filtered and vacuum-dried at room temperature. Yield: 2.82 g (94%). ^{1}H NMR (DMSO-d_6): δ = 8.70 (s, −N*H*$_3$, 3H), 7.85 (m, Ar*H*, 4H), 7.60 (m, Ar*H*, 4H), 7.30 (m, Ar*H*, 8H), 4.35 (m, −C*H*NH(C=O)− and FmC*H*$_2$O− and C*H*^{Fm}CH$_2$O−, 7H), 2.85 (m, −CHC*H*$_2$(C=O)O−, 2H). ^{13}C NMR (DMSO-d_6): δ = 169.19, 168.41, 143.29, 140.75, 127.85, 127.22, 125.12, 120.16, 67.36, 66.49, 48.37, 46.06, 46.00, 33.97. MS (LR−FAB) *m*/*z* = 490.2 (M − CF_3COO^-). MS (HR−FAB) *m*/*z* = 490.201800 (calculated 490.201834) for $C_{32}H_{28}NO_4$.

***N*-succinyl-*O*$^\alpha$,*O*$^\beta$-di(9-fluorenylmethyl)-L-aspartate (21).** *N*,*N*-Diisopropylethylamine (0.60 mL, 3.44 mmol) was added dropwise to a mixture of **20** (1.00 g, 1.66 mmol) and succinic anhydride (0.165 g, 1.65 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at room temperature for 15 h. Then, the reaction mixture was evaporated to dryness, and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 100/10 (v/v)). Yield: 0.82 g (84%). ^{1}H NMR (DMSO-d_6): δ = 8.45 (d, N*H*, 1H), 7.86 (m, Ar*H*, 4H), 7.64 (m, Ar*H*, 4H), 7.40 (m, Ar*H*, 4H), 7.30 (m, Ar*H*, 4H), 4.65 (m, −C*H*NH(C=O)−, 1H), 4.35 (m, FmC*H*$_2$O−, 4H), 4.25 (m, C*H*^{Fm}CH$_2$O−, 2H), 2.65 (m, −CHC*H*$_2$(C=O)O−, 2H), 2.35 (m, −NH(C=O)C*H*$_2$C*H*$_2$(C=O)OH, 4H). ^{13}C NMR (DMSO-d_6): δ = 173.79, 171.27, 170.77, 169.98, 143.57, 140.75, 127.78, 127.19, 125.16, 120.14, 66.45, 66.01, 48.53, 46.17, 46.12, 35.51, 29.82, 29.08. MS (LR−FAB) *m*/*z* = 590.3 (MH$^+$). MS (HR−FAB) *m*/*z* = 590.217900 (calculated 590.217878) for $C_{36}H_{32}NO_7$.

Cholesteryl—(L-Lactic acid)$_{\bar{n}}$ *O*$^\alpha$,*O*$^\beta$-di(9-fluorenylmethyl)-L-aspartate (7). As a typical example, the functionalization of a cholesteryl−(L-lactic acid)$_{\overline{25}}$ oligomer will be described: EDC (0.040 g, 0.21 mmol) was added to an ice-cooled mixture of **1** (0.161 g, ~0.073 mmol), **21** (0.100 g, 0.170 mmol), and DMAP (0.007 g, 0.057 mmol) in CH_2Cl_2 (12 mL) and DMF (2 mL). The reaction mixture was stirred at 0 °C for 3.5 h. Then, the ice bath was removed, and the reaction mixture was stirred at room temperature for another 5 h. After that, the reaction mixture was diluted with CH_2Cl_2 and washed with water (1×) and brine (1×). The organic phase was separated, dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 100/5 (v/v)). Yield: 0.19 g (94%). ^{1}H NMR ($CDCl_3$):[25] δ = 7.75 (m, Ar*H*, 4H), 7.50 (m, Ar*H*, 4H), 7.38 (m, Ar*H*, 4H), 7.25 (m, Ar*H*, 4H), 6.28 (d, N*H*, 1H), 5.35 (d, cholesterol C-6 H, 1H), 5.15 (q, −(O(C=O)C*H*(CH$_3$))$_n$−, *n*H), 5.10 (q, cholesterol−O(C=O)C*H*(CH$_3$)−, 1H), 4.85 (m, −C*H*-(CH$_3$)O(C=O)CH$_2$−, 1H), 4.65 (m, cholesterol C-3 H, 1H), 4.40 (br m, −C*H*NH(C=O)− and FmC*H*$_2$O−, 5H), 4.10 (br m, C*H*^{Fm}CH$_2$O−, 2H), 2.95 (m, −CHC*H*$_2$(C=O)O−, 2H), 2.50 (m, −NH(C=O)C*H*$_2$C*H*$_2$(C=O)NH−, 4H), 1.55 (d, −(O(C=O)CH-(C*H*$_3$))$_n$−, 3*n*H), 0.65 (s, cholesterol C-18 H, 3H). $\bar{n}$ (^{1}H NMR) = 22. MS (MALDI−TOF): M_w = 2767, M_n = 2646, M_w/M_n = 1.05. $\bar{n}$ (MALDI−TOF MS) = 23.

Cholesteryl—(L-Lactic acid)$_{\bar{n}}$ Succinate (8). As a typical example, the modification of a cholesteryl−(L-lactic acid)$_{\overline{25}}$ oligomer will be described: DMAP (0.139 g, 1.14 mmol) was added to a solution of **1** (0.103 g, ~0.047 mmol) and succinic anhydride (0.019 g, 0.19 mmol) in CH_2Cl_2 (10 mL). After overnight stirring at room temperature, the reaction mixture was evaporated to dryness, and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 100/10 (v/v)). Yield: 0.080 g (74%). ^{1}H NMR ($CDCl_3$):[25] δ = 5.35 (d, cholesterol C-6 H, 1H), 5.15 (q, −(O(C=O)C*H*(CH$_3$))$_n$−, *n*H), 5.10 (q, cholesterol−O(C=O)C*H*(CH$_3$)−, 1H), 4.65 (m, choles-

terol C-3 H, 1H), 2.70 (m, −O(C═O)CH_2CH_2(C═O)OH, 4H), 1.55 (d, −(O(C═O)CH(CH_3))$_n$−, 3nH), 0.65 (s, cholesterol C-18 H, 3H). $\bar{n}$ (^{1}H NMR) = 21. MS (MALDI−TOF): M_w = 2030, M_n = 1784, M_w/M_n = 1.14. $\bar{n}$ (MALDI−TOF MS) = 18.

Cholesteryl—(L-Lactic acid)$_{\bar{n}}$—Indomethacin (9). As a typical example, the modification of a cholesteryl−(L-lactic acid)$_{\overline{25}}$ oligomer will be described: EDC (0.096 g, 0.50 mmol) was added to an ice-cooled solution of **1** (0.507 g, ∼0.23 mmol), indomethacin (0.162 g, 0.45 mmol), and DMAP (0.038 g, 0.31 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred overnight in the ice bath, which gradually melted during the course of the reaction. After that, the reaction mixture was evaporated to dryness and the residue redissolved in CH_2Cl_2 (5 mL) and precipitated in MeOH (100 mL). Solids were filtered and vacuum-dried at room temperature. Yield: 0.49 g (84%). ^{1}H NMR ($CDCl_3$):[25] δ = 7.65 (d, −N(C═O)ArH, 2H), 7.45 (d, ArHCl, 2H), 6.96 (d, Ar′H, 1H), 6.88 (d, Ar′H, 1H), 6.65 (dd, Ar′H, 1H), 5.35 (d, cholesterol C-6 H, 1H), 5.15 (q, −(O(C═O)CH(CH$_3$))$_n$− and O(C═O)CH(CH$_3$)O(C═O)CH$_2$−, (n + 1)H), 5.10 (q, cholesterol−O(C═O)CH(CH$_3$)−, 1H), 4.65 (m, cholesterol C-3 H, 1H), 3.85 (s, ArOCH_3, 3H), 3.75 (s, −CH_2-(C═O)−, 2H), 2.35 (s, −CH_3, 3H), 1.55 (d, −(O(C═O)CH-(CH_3))$_n$−, 3nH), 0.65 (s, cholesterol C-18 H, 3H). $\bar{n}$ (^{1}H NMR) = 25. MS (MALDI−TOF): M_w = 2551, M_n = 2429, M_w/M_n = 1.05. $\bar{n}$ (MALDI−TOF MS) = 23.

Cholesteryl—(L-lactic acid)$_{\bar{n}}$—Rhodamine B (10). As a typical example, the modification of a cholesteryl−(L-lactic acid)$_{\overline{25}}$ oligomer will be described: EDC (0.096 g, 0.50 mmol) was added to an ice-cooled solution of **1** (0.52 g, ∼0.24 mmol), Rhodamine B (0.21 g, 0.44 mmol), and DMAP (0.035 g, 0.29 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred overnight in the ice bath, which gradually melted during the course of the reaction. After that, the reaction mixture was evaporated to dryness, redissolved in CH_2Cl_2 (5 mL), and precipitated in MeOH (100 mL). Solids were filtered, vacuum-dried, and purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 100/10 (v/v)). Yield (i): 0.050 g. The MeOH phase was evaporated and subsequently purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 100/10 (v/v)) to provide a second batch of the product. Yield (ii): 0.060 g. Total yield (i + ii): 0.11 g (17%). ^{1}H NMR ($CDCl_3$):[25] δ = 8.35 (d, ArH, 1H), 7.80 (m, ArH, 1H), 7.70 (m, ArH, 1H), 7.30 (d, ArH, 1H), 7.05 (m, ArH, 2H), 6.90 (d, ArH, 1H), 6.80 (m, ArH, 3H), 5.35 (d, cholesterol C-6 H, 1H), 5.15 (q, −(O(C═O)CH(CH$_3$))$_n$− and O(C═O)CH(CH$_3$)O(C═O)Ar−, (n + 1)H), 5.10 (q, cholesterol−O(C═O)CH(CH$_3$)-, 1H), 4.65 (m, cholesterol C-3 H, 1H), 3.60 (q, −NCH_2CH$_3$, 8H), 1.55 (d, −(O(C═O)CH(CH_3))$_n$−, 3nH), 1.30 (t, −NCH$_2$CH_3, 12H), 0.65 (s, cholesterol C-18 H, 3H). $\bar{n}$ (i) (^{1}H NMR) = 24. MS (i) (MALDI−TOF): M_w = 2740, M_n = 2652, M_w/M_n = 1.03. $\bar{n}$ (i) (MALDI−TOF MS) = 25. $\bar{n}$ (ii) (^{1}H NMR) = 22. MS (ii) (MALDI−TOF): M_w = 2185, M_n = 2113, M_w/M_n = 1.03. $\bar{n}$ (ii) (MALDI−TOF MS) = 17.

Cholesteryl—(L-Lactic acid)$_{\bar{n}}$ 4-(1-Pyrenecarboxylate)-benzoate (13). As a typical example, the end-functionalization of a cholesteryl−(L-lactic acid)$_{\overline{25}}$-4-(hydroxy)benzoate oligomer will be described: DIPC (50 μL, 0.32 mmol) was added dropwise to a mixture of **11** (0.103 g, ∼0.045 mmol), 1-pyrenecarboxylic acid (0.025 g, 0.10 mmol), and DPTS (0.047 g, 0.16 mmol) in CH_2Cl_2 (15 mL). After overnight stirring at room temperature, the reaction mixture was evaporated to dryness. The residue was redissolved in CH_2Cl_2 (5 mL) and precipitated in MeOH (100 mL). Solids were filtered and vacuum-dried. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 100/2.5 (v/v)). Yield: 0.075 g (66%). ^{1}H NMR ($CDCl_3$):[25] δ = 9.38 (d, ^{pyrene}ArH, 1H), 8.90 (d, ^{pyrene}ArH, 1H), 8.28 (m, ArH(C═O)O− and ^{pyrene}ArH, 7H), 8.12 (m, ^{pyrene}-ArH, 2H), 7.45 (d, ArHO(C═O)−, 2H), 5.40 (q, −O(C═O)-CH(CH$_3$)O(C═O)Ar−, 1H), 5.35 (d, cholesterol C-6 H, 1H), 5.15 (q, −(O(C═O)CH(CH$_3$))$_n$−, nH), 5.10 (q, cholesterol−O(C═O)-CH(CH$_3$)−, 1H), 4.65 (m, cholesterol C-3 H, 1H), 1.55 (d, −(O(C═O)CH(CH_3))$_n$−, 3nH), 0.65 (s, cholesterol C-18 H, 3H). $\bar{n}$ (^{1}H NMR) = 26. MS (MALDI−TOF): M_w = 2611, M_n = 2519, M_w/M_n = 1.04. $\bar{n}$ (MALDI−TOF MS) = 25.

Cholesteryl—(L-Lactic acid)$_{\bar{n}}$—Glycinate Trifluoroacetic Acid Salt (14). As a typical example the end group modification of an oligomer with an average of 25 repeat units of L-lactic acid will be described: TFA (10 mL) was added to an ice-cooled solution of **4** (0.86 g, ∼0.36 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for another hour. Then, the reaction mixture was evaporated to dryness, and the residue was triturated with n-hexane. Solids were filtered and vacuum-dried at room temperature. Yield: 0.80 g (93%). ^{1}H NMR ($CDCl_3$):[25] δ = 5.35 (d, cholesterol C-6 H, 1H), 5.15 (q, −(O(C═O)CH(CH$_3$))$_n$− and −CH(CH$_3$)O(C═O)CH$_2$−, (n + 1)H), 5.10 (q, cholesterol−O(C═O)CH(CH$_3$)−, 1H), 4.65 (m, cholesterol C-3 H, 1H), 4.00 (br, −O(C═O)CH_2NH−, 2H), 1.55 (d, −(O(C═O)CH(CH_3))$_n$−, 3nH), 0.65 (s, cholesterol C-18 H, 3H). $\bar{n}$ (^{1}H NMR) = 26. MS (MALDI−TOF): M_w = 2313, M_n = 2173, M_w/M_n = 1.06. $\bar{n}$ (MALDI−TOF MS) = 23.

Cholesteryl—(L-lactic acid)$_{\bar{n}}$—Glycine-O^{α},O^{β}-di(9-fluorenylmethyl)-L-aspartate (15). As a typical example the endfunctionalization of a cholesteryl−(L-lactic acid)$_{\overline{23}}$-Gly·TFA oligomer will be described: EDC (0.025 g, 0.130 mmol) was added to an ice-cooled solution of **14** (0.109 g, ∼0.046 mmol), **21** (0.061 g, 0.103 mmol), and DMAP (0.009 g, 0.074 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at 0 °C for 3 h. Then, the reaction mixture was diluted with CH_2Cl_2 and washed with water (1×) and brine (1×). The organic phase was separated, dried over $MgSO_4$, and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 100/5 (v/v)). Yield: 0.09 g (69%). ^{1}H NMR ($CDCl_3$):[25] δ = 7.75 (m, ArH, 4H), 7.50 (m, ArH, 4H), 7.35 (m, ArH, 4H), 7.25 (m, ArH, 4H), 6.48 (d, NH, 1H), 6.38 (t, NH, 1H), 5.35 (d, cholesterol C-6 H, 1H), 5.15 (q, −(O(C═O)CH(CH$_3$))$_n$−, nH), 5.10 (q, cholesterol−O(C═O)-CH(CH$_3$)−, 1H), 4.85 (m, −CH(CH$_3$)O(C═O)CH$_2$−, 1H), 4.65 (m, cholesterol C-3 H, 1H), 4.40 (br m, −CHNH(C═O)− and FmCH_2O−, 5H), 4.10 (br m, CH^{Fm}CH$_2$O− and −O(C═O)CH_2-NH−, 4H), 2.95 (m, −CHCH_2(C═O)O−, 2H), 2.50 (m, −NH-(C═O)CH_2CH_2(C═O)NH−, 4H), 1.55 (d, −(O(C═O)CH(CH_3))$_n$−, 3nH), 0.65 (s, cholesterol C-18 H, 3H). $\bar{n}$ (^{1}H NMR) = 23. MS (MALDI−TOF): M_w = 2806, M_n = 2644, M_w/M_n = 1.06. $\bar{n}$ (MALDI−TOF MS) = 23.

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