Synthesis of Functional Poly(1,4-ketone)s Bearing Bioactive Moieties by Pd-Catalyzed Insertion Polymerization

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Received July 2, 2006; Revised Manuscript Received September 18, 2006

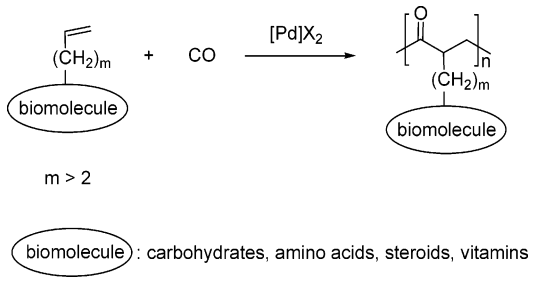
The synthesis of novel alternating polyketones bearing pendent bioactive moieties is presented. These materials were prepared by palladium catalyzed coordination polymerization of carbon monoxide and α-olefins substituted with protected tyrosine or with dipeptide sequences such as tyrosine-glycine, tyrosine-alanine, and tyrosine-valine. Copolymerization experiments of CO with monomers containing vitamin E or testosterone were also successfully performed under mild reaction conditions. The dicationic Pd (II) bis(phoshine) complex [Pd(dppp)-$(NCCH_3)_2$]$(BF_4)_2$ was used as catalyst precursor giving rise to macromolecules with well-defined structures.

Introduction

Synthetic polymers bearing pendent bioactive molecules are highly attractive materials due to their outstanding potential applications in pharmacological and biological fields.[1] Among different polymerization techniques, the late transition metal-catalyzed polymerizations appeared to be the most promising methods for preparation of functional polymers with precisely controlled structures. Metathesis (ROMP and ADMET)[2,3] and atom transfer radical (ATRP)[4] polymerizations, for instance, are extensively used to produce biofunctionalized macromolecules. A unique control of molecular weight, polydispersity, and stereoregularity is offered, however, by metal catalyzed insertion polymerization. For that reason, the use of the latter for polymerization of monomers with polar functional groups is attracting much interest.[5]

Poly(1,4-ketone)s are a class of polymers accessible via Pd^{II} catalyzed insertion polymerization of α-olefins and carbon monoxide. A remarkable advantage of these materials is the possibility to easily tune their mechanical and surface properties. Hence, polymers ranging from highly crystalline to thermoplastic soft elastomers are available.[6] The hydrophilicity of the surface is adjustable from nonpolar to highly polar by a proper selection of the α-olefin component.[7] Chiral polyketones with high enantiomeric excess can also be prepared.[8] In addition, the carbonyl groups offer an opportunity for further functionalization through chemical derivatization.[9] Besides these valuable properties, we have demonstrated that defined polyketone structures possess a promising biocompatibility.[10] Depending on the monomer composition, the polymer surface supported a selective growth of adult human bone marrow cells.[11] These findings together with the fact that polyketones add a new type of polymer backbone to the family of biologically active polymers motivated us to focus research on the synthesis of polyketones functionalized with bioactive molecules. One way to design such materials is to copolymerize CO with α-olefins bearing bioactive moieties (Scheme 1). Since there are only a limited number of examples of functional polyketones reported,[12] these copolymerizations are challenging experiments. The first successful attempt was the synthesis of polyketones containing pendent monosaccharides.[13] The surprising tolerance shown by the catalytic system toward the glycosylated monomers prompted us to perform copolymerization experiments with CO and alkenes substituted with amino acids. Functional polymers based on amino acids are ideal candidates for a variety of applications, owing to their inherent biological compatibility, multifunctionality, and chirality.[14] Due to the perfect alternation of the two monomers (CO and α-olefin), the Pd catalyzed insertion polymerization would afford highly functionalized materials with amino acids in the side chains. The present communication describes the synthesis of such macromolecules. Additionally, the polymerization catalysis of other biologically relevant monomers like those containing representatives of vitamins and steroids is discussed.

Scheme 1. Synthesis of Functional Polyketones Bearing Pendent Bioactive Molecules



Results and Discussion

New vinyl monomers bearing tyrosine or dipeptides with tyrosine-glycine, tyrosine-alanine and tyrosine-valine sequences were prepared (Scheme 2, a). Since the carboxyl or amino groups of the amino acids might interfere with the Pd-catalyst, they were reversibly protected. Esters of glycine, alanine, or valine respectively were attached to precursor **1**−**1** by means of routine peptide coupling agents EDAC and HOBT (see the Experimental Section). Furthermore, monomers containing lipophilic groups such as vitamin E and testosterone were also synthesized. Monomer **5** resulted from an etherification of α-D,L-tocopherol and 6-bromo-1-hexene in presence of K_2CO_3 (Scheme 2, b), whereas monomer **6** was synthesized through DCC/DMAP

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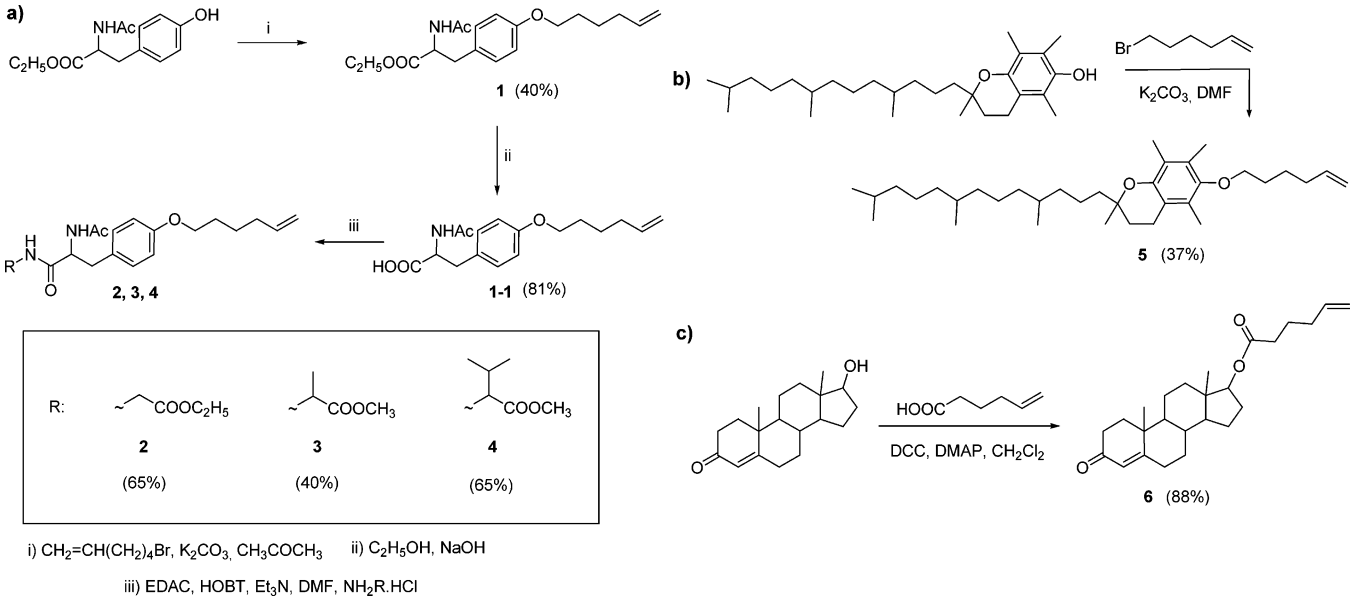
10.1021/bm0606364 CCC: $33.50
Published on Web 10/07/2006

Scheme 2. Synthesis of Monomers **1**−**4** (a), **5** (b), and **6** (c)



mediated esterification between 17-β-hydroxy-androst-4-en-3-one and 5-hexenoic acid (Scheme 2, c). It is apparent from the literature that a longer spacer between the double bond and the polar group reduces the tendency for chelation of the latter to the metal center.[5] Several authors showed that for successful polymerization of functional monomers with CO the functionality has to be separated from the double bond by at least two methylene groups.[15] Therefore, to disfavor backbiting of any of the nucleophilic heteroatoms (OR and NHR) of the monomers to Pd-center,[16] we used C4-alkenyl spacers. An additional role of the spacers was to provide materials with less sterically congested functional groups, which would be advantageous for interaction with other molecules (e.g., proteins and drugs). Intentionally, in monomer **6**, the polymerizable spacer was attached to the testosterone molecule via an ester linkage. Since the ester bond is labile and might rapidly hydrolyze to liberate a pharmacologically active steroid (Ringsdorf's model), the corresponding oligomer could serve as a drug-delivery agent.[17]

The newly synthesized functional olefins were copolymerized with carbon monoxide according to Scheme 3. The catalyst precursor was activated by addition of a defined amount of diethylene glycol (DEG).[18] The results of the copolymerization experiments are listed in Table 1.

The narrow polydispersities revealed a formation of homogeneous products under the conditions applied. As seen from the degrees of polymerization, the standard catalyst used for these first investigations afforded well-defined structures ranging from oligomers to macromolecules of low molecular weight. However, the degrees of polymerization might be a question of catalyst and process design.[18,19] In addition, one should consider that the optimal degrees of polymerization are application-specific. The molecular weights reported can be ascribed to backbiting of the monomer's nucleophilic atoms to the coordination site of the catalyst and/or steric hindrance of the bulky monomer structures. In fact, the olefin insertion is the rate determining step in the polymerization cycle,[20] and the coordination of the olefinic double bond is likely to depend on the steric characteristics of the alkene and on the geometry of the catalytically active complex.[7,21]

The high steric hindrance (more than for monomer **1)** of the olefins substituted with dipeptides (**2**−**4**) influenced significantly their reactivity. Accordingly, oligomers with diminished degrees

Scheme 3. Copolymerization of CO with Monomers **1**−**6**

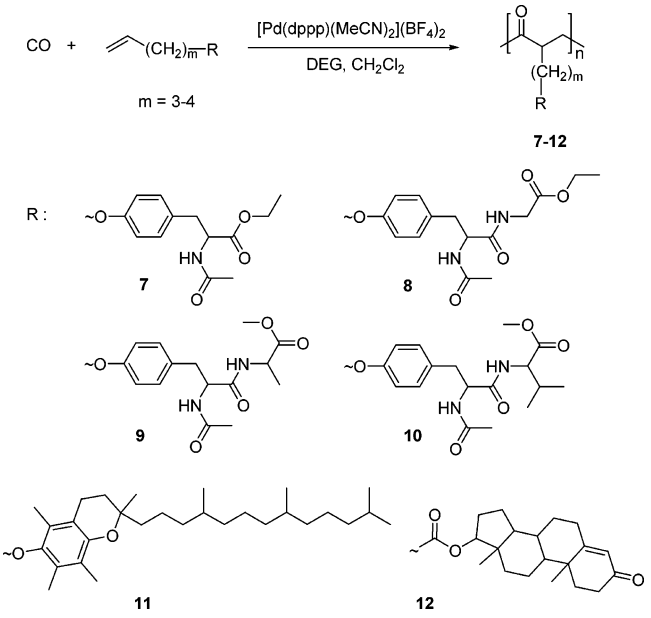


Table 1. Copolymerization Results

monomer	oligomer	$P_{(CO)}$, bar	M_w,[a] g mol^{-1}	M_n,[a] g mol^{-1}	PDI[a]	DP[b]	yield,[c] %	T_g, °C
1	**7**	30	11800	8900	1.33	25	55	29.0
2		30						
2	**8**	60	3200	2500	1.28	6	10	40.7
3		30						
3	**9**	60	3200	2500	1.28	6	15	60.5
4	**10**	60	5000	3800	1.32	8	21	82.5
5	**11**	30	18000	12500	1.44	23	70	−25.0
6	**12**	30	7600	4700	1.62	12	58	110.5

[a] Average values measured by GPC (relative to polystyrene standards). [b] Average degree of polymerization calculated from GPC data ($CHCl_3$ solvent). [c] Based on the isolated mass after purification.

of polymerization and yields were obtained. We believe that the backbiting effect was additionally contributed by the second amide group (peptide linkage) present in those monomers. Most probably the peptide oxygen coordinated to the Pd center, which slowed down the propagation rate. Hence, termination reactions became more competitive with propagation, and products with short chain lengths were obtained. Oligomers with slightly

higher yields were formed from the copolymerization of CO with monomer **4**. Presumably the coordination of the carbonyl oxygen of the peptide linkage to the Pd center was partially disfavored by the isopropyl branch from the valine residue, which led to an improved polymerization performance of this monomer.

The pressure of carbon monoxide played a crucial role for the copolymerization of the monomers bearing dipeptides. Thus, when **2** and **3** were copolymerized under 30 bar initial CO pressure, no products were formed. This is consistent with the assumption that the oxygen electron donors coordinate to the metal center. The Pd−O interaction could not be disrupted by an incoming carbon monoxide molecule when the applied pressure was low. An increased CO pressure led, however, to product formation.

Direct evidence that multiple insertions of monomers **2**−**4** occurred was provided by MALDI-TOF spectra of the corresponding oligomers (Figure 1). The mass of each peak consists of a certain number of repeating units, plus one saturated and one unsaturated chain end group and a sodium atom.[22]

The best polymerization results were found for the copolymerization of CO with monomer **5**, most likely due to the fewer number of heteroatoms present in the α-tocopherol molecule.

The chemical structures of the obtained products were confirmed by ^{13}C and ^{1}H NMR and IR spectroscopies. The three signals attributable to the carbonyl groups of the main chain (head−head, head−tail, and tail−tail enchainment) in ^{13}C NMR spectrum proved the regioirregularity of the oligomers.

DSC measurements revealed the oligomers to be amorphous. The lack of crystallinity was attributed to the bulky pendent groups and the stereoirregularity of the backbone. The T_g values of the products were dependent on the nature of the side chain substituents. Oligomer **7** bearing tyrosine moieties had a glass transition temperature of 29 °C. The presence of a second amino acid in the structure of oligomer **8** caused a decrease in the chain mobility. Higher T_g was measured for those oligomers, respectively. Further rising of the glass transition temperature was observed for oligomers **9** (60.5 °C) and **10** (82.5 °C) in proportion to the increasing bulkiness of the pendent dipeptide sequence. Oligomer **12** showed the highest T_g (110.5 °C) due to the rigid testosterone moieties, whereas oligomer **11** possessed a very low T_g value (−25 °C) as a result of the more flexible structure of the vitamin E molecule (C12-alkyl chain).

Conclusion

The presented approach is one of the rare instances of introducing bioactive molecules into a polar backbone using insertion polymerization catalysis, which offers, in principle, a unique control of the polymer microstructure. Since these were initial experiments, we applied a cheap and readily available catalyst. However, the results clearly demonstrated that for the copolymerization of such highly functionalized monomers a new catalyst design is needed. A catalyst with reduced electrophilicity of the metal center would be presumably more favorable toward the applied monomers. Recently, we reported on a new neutral, single site Pd-catalyst that produces nonalternating ethylene−CO copolymers.[23] Further research will be focused on the synthesis of ligands suitable for polymerization of bulky polar monomers.

Since chiral systems are of high interest for bio-applications, a real challenge would also be the use of catalytic systems able to produce chiral biofunctionalized polyketones.

Studies concerning the biocompatibility of the described oligomers are in progress. Initial in vivo experiments with poly(propylene-CO) polymers functionalized with tyrosine moieties showed a good biocompatibility of the this polymer to urothelial cells. The results of these studies will be reported elsewhere.

Experimental Section

Materials. All chemicals were of commercial grade and used as received unless otherwise stated. $[Pd(dppp)(NCCH_3)_2](BF_4)_2$ was prepared as described previously.[24] CH_2Cl_2 (Fluka) was dried by refluxing over CaH_2 and distilled prior to use. Diethylene glycol (DEG-Fluka) was passed as 1:1 mixture with dried CH_2Cl_2 through a column of aluminum oxide, and then the solvent was removed under vacuum and DEG was stored over 4 Å molecular sieves. Carbon monoxide gas was provided by BASF AG and used without further purification.

General Methods. Polymer molecular weights were measured in $CHCl_3$ by gel permeation chromatography (GPC), using a Styragel column and calibrated relative to polystyrene standards. ^{1}H and ^{13}C NMR[25] spectra were recorded on a Bruker AMX 500 spectrometer. Chemical shifts (δ), referred to internal standards, are given in ppm. Infrared spectra were recorded on a Bruker FT-IR IFS 113v spectrometer. MALDI-TOF measurements were performed on a Bruker Daltonics Reflex III (Section Mass Spectrometry-University of Ulm). 2,5-Dihydroxybenzoic acid (DHB) was used as matrix material. Ions, formed by a pulsed UV laser beam (nitrogen laser, 337 nm), were accelerated at 20 kV. A Perkin-Elmer DSC 7 instrument was used for differential scanning calorimetry measurements. Glass transitions were determined from the second heating scan. Elemental analyses were performed at the Microanalytical Section of the University of Ulm.

Monomer Synthesis. *N*-Acetyl-*O*′-(hex-5-enyl)-L-tyrosine Ethyl Ester (1). To a solution of *N*-acetyl-L-tyrosine ethyl ester (10 g, 37.1 mmol) in acetone (100 mL) was added K_2CO_3 (7.4 g, 53.8 mmol), followed by 6-bromo-1-hexene (5 mL, 37.1 mmol). The mixture was stirred at reflux for 3 days. After this time, the solvent was removed on a rotary evaporator, and the remaining white solid was dissolved in a mixture of aqueous 5% NaOH/Et_2O (1/1 v/v; 450 mL). The aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The resulting viscous oil was washed with hexane to provide a white solid product (40% yield). ^{1}H NMR ($CDCl_3$): δ = 6.95 (d, 2H, 2 *H*C═), 6.76 (d, 2H, 2 *H*C═), 5.97 (d, 1H, N*H*), 5.80 (m, 1H, *H*C═CH_2), 4.98 (m, 2H, HC═CH_2), 4.79 (q, 1H, C$^*H$), 4.13 (q, 2H, CH_2), 3.89 (t, 2H, CH_2), 3.10 (dd, 1H, CH_a-H_b), 2.96 (dd, 1H, CH_a-H_b), 2.10 (m, 2H, CH_2), 1.95 (s, 3H, NHCOCH_3), 1.75 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 1.22 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ = 171.7 (HN*C*O), 169.4 (*C*OOCH$_2$), 158.1 (>*C*═), 138.4 (H*C*═CH_2), 130.2 (>*C*═), 127.6 (2 HC═), 114.7 (HC═*C*H$_2$), 114.4 (2 H*C*═), 67.6 (*C*H$_2$), 61.4 (*C*H$_2$), 53.20 (*C**H), 36.9 (*C*H$_2$), 33.4 (*C*H$_2$), 28.6 (*C*H$_2$), 25.2 (*C*H$_2$), 23.1 (*C*H$_3$), 14.1 (*C*H$_3$). IR (cm^{-1}, KBr): 3300 (N−H), 1740 (C═O), 1656 (C−N), 1550 (N−H). Anal. Calcd for $C_{19}H_{27}NO_4$ (333.42 g mol^{-1}): C 68.47; H 8.11; N 4.20. Found: C 68.39; H 8.09; N 4.18.

***N*-Acetyl-*O*′-(hex-5-enyl)-L-tyrosine (1−1).** A solution of *N*-acetyl-*O*′-(hex-5-enyl)-L-tyrosine ethyl ester (**1**; 5 g, 15 mmol) in ethanol (15 mL) was cooled in an ice bath for 10 min. Next 1.2 M NaOH (25 mL) was added. The mixture was allowed to warm to room temperature and stirred overnight. After that, the solution volume was reduced in vacuum to 25 mL and washed with $CHCl_3$. The aqueous layer was acidified with $NaHSO_4$ (pH 2−3) and extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$), and then the solvent was removed on a rotary evaporator to yield the product (81% yield). ^{1}H NMR (THF-d_8): δ = 6.83 (d, 1H, N*H*), 6.72 (d, 2H, 2 *H*C═), 6.45 (d, 2H, 2 *H*C═), 5.50 (m, 1H, *H*C═CH_2), 4.68 (m, 2H, HC═CH_2), 4.35 (q, 1H, C$^*H$), 3.58 (t, 2H, CH_2), 2.77 (dd, 1H, CH_a-H$_b$), 2.57 (dd, 1H, CH_a-H_b), 1.79 (m, 2H, CH_2), 1.49 (s, 3H, CH_3), 1.42 (m, 2H, CH_2), 1.23 (m, 2H, CH_2). ^{13}C NMR (THF-d_8): δ = 173.7 (COOH), 169.7 (HNCO), 159.3 (>*C*═), 139.7 (H*C*═CH_2), 131.3 (2 HC═), 130.4

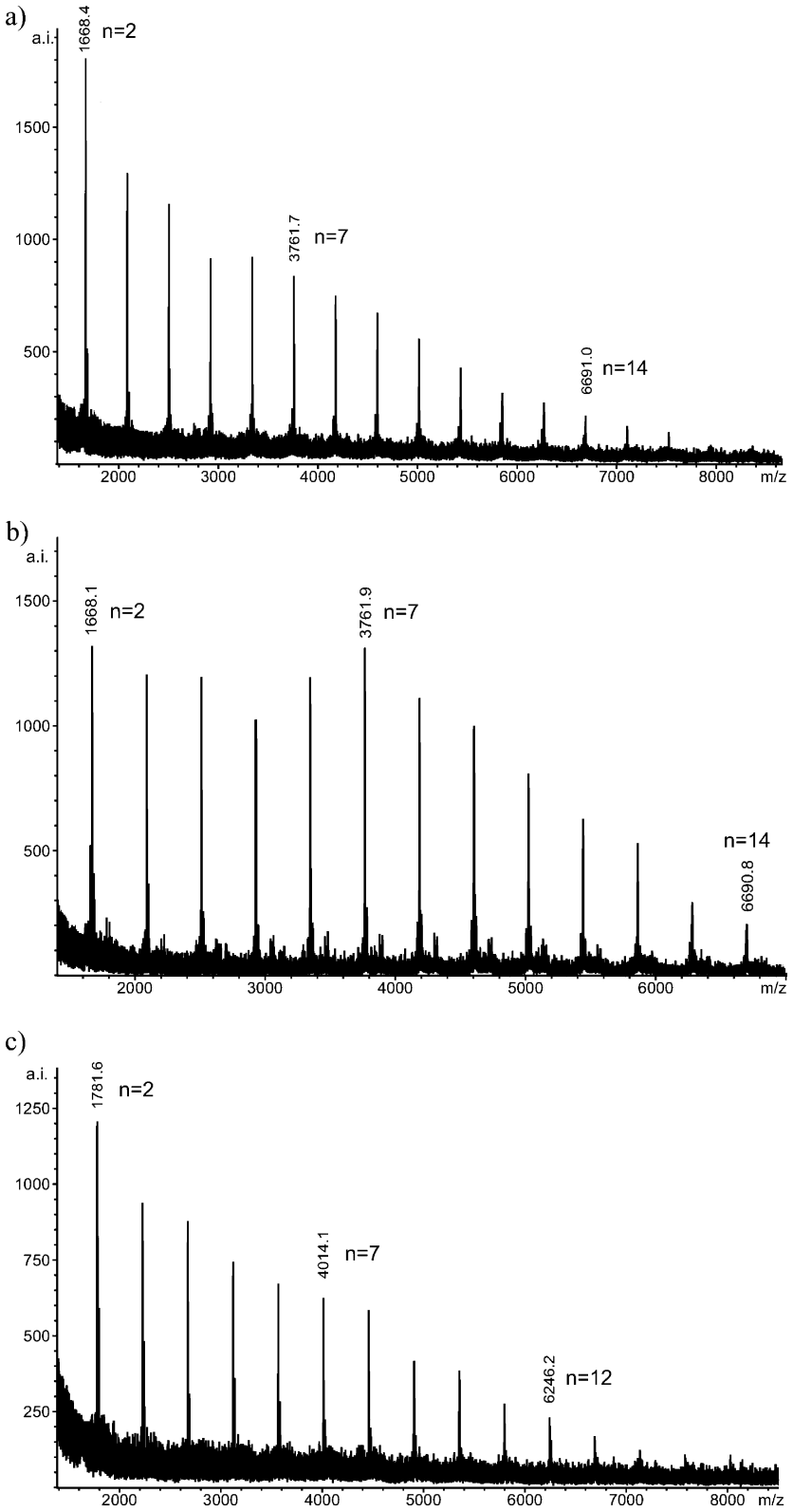


Figure 1. MALDI-TOF spectra of the oligomers bearing dipeptide sequences: (a) **8**, (b) **9**, and (c) **10**.

(>*C*═), 115.2 (HC═*C*H_2), 115.1 (2 H*C*═), 68.5 (*C*H_2), 54.4 (*C**H), 37.8 (*C*H_2), 34.6 (*C*H_2), 30.05 (*C*H_2), 26.6 (*C*H_2), 22.7 (*C*H_3). IR (cm^{-1}, KBr): 3300 (N−H), 3000−2480 (O−H overlapped with C−H), 1710 (C═O), 1625 (C−N), 1556 (N−H), 1248 (C−O−C). Anal. Calcd for $C_{17}H_{23}NO_4$ (305.37 g mol^{-1}): C 66.89; H 7.54; N 4.59. Found: C 66.50; H 7.45; N 4.35.

***N*-Acetyl-*O*′-(hex-5-enyl)-L-tyrosylglycine Ethyl Ester (2).** A solution of *N*-acetyl-*O*′-(hex-5-enyl)-L-tyrosine (**1**−**1**; 2.2 g, 7.1 mmol) in dry DMF (15 mL) was added to a mixture of glycine ethyl ester hydrochloride (1.5 g, 10.7 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDAC; 1.6 g, 8.5 mmol), and 1-hydroxybenzotriazole (HOBT; 0.96 g, 7.1 mmol). Next, triethylamine (Et_3N; 2 mL, 14.2 mmol) was added, and the mixture was stirred at room temperature for 24 h. After that, the solvent was removed under vacuum, and the obtained yellow oil was partitioned between H_2O and ethyl acetate (70 mL of each). The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed on silica gel ($CHCl_3/C_2H_5OH$ −

98/2) to yield a white solid product (65% yield). ^{1}H NMR ($CDCl_3$): δ = 7.06 (d, 2H, 2 *H*C═), 6.78 (d, 2H, 2 *H*C═), 6.63 (d, 1H, N*H*), 6.38 (d, 1H, N*H*), 5.80 (m, 1H, *H*C═CH_2), 4.98 (m, 2H, HC═CH_2), 4.65 (q, 1H, C$^*H$), 4.13 (q, 2H, CH_2), 3.94 (t, 2H, CH_2), 3.89 (s, 2H, CH_2), 3.10 (dd, 1H, CH_a-H$_b$), 2.92 (dd, 1H, CH$_a$-H_b), 2.08 (m, 2H, CH_2), 1.92 (s, 3H, NHCOCH_3), 1.75 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 1.23 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ = 171.4 (HN*C*OCH$_3$), 170.1 (HN*C*O), 169.2 (*C*OO), 158.0 (>*C*═), 138.4 (H*C*═CH_2), 130.2 (>*C*═), 128.2 (2 H*C*═), 114.7 (HC═*C*H$_2$), 114.5 (2 H*C*═), 67.6 (*C*H$_2$), 61.4 (*C*H$_2$), 54.3 (*C**H), 41.2 (*C*H$_2$), 37.3 (*C*H$_2$), 33.4 (*C*H$_2$), 28.6 (*C*H$_2$), 25.2 (*C*H$_2$), 23.1 (NHCO*C*H$_3$), 14.1 (CH$_2$*C*H$_3$). IR (cm^{-1}, KBr): 3300 (N−H), 1753 (C═O), 1645 (C−N), 1546 (N−H). Anal. Calcd for $C_{21}H_{30}N_2O_5$ (390.47 g mol^{-1}): C 64.62; H 7.69; N 7.18. Found: C 64.61; H 7.69; N 6.95.

***N*-Acetyl-*O*′-(hex-5-enyl)-L-tyrosylalanine Methyl Ester (3) and *N*-Acetyl-*O*′-(hex-5-enyl)-L-tyrosylvaline Methyl Ester (4).** Monomers **3** and **4** were prepared following the same procedure as described for **4**. However, **1**−**1** was reacted with L-alanine methyl ester hydrochloride for the synthesis of **5** (40% yield) or with L-valine methyl ester hydrochloride for the synthesis of **4** (65% yield), respectively. (**3**): ^{1}H NMR ($CDCl_3$): δ = 7.07 (d, 2H, 2 *H*C═), 6.78 (d, 2H, 2 *H*C═), 6.42 (d, 1H, N*H*), 6.24 (d, 1H, N*H*), 5.79 (m, 1H, *H*C═CH_2), 4.98 (m, 2H, HC═CH_2), 4.62 (q, 1H, C$^*H$), 4.44 (m, 1H, C$^*H$CH$_3$), 3.89 (t, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.08 (dd, 1H, CH_a-H$_b$), 2.92 (dd, 1H, CH$_a$-H_b), 2.08 (m, 2H, CH_2), 1.94 (s, 3H, NHCOCH_3), 1.75 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 1.33−1.31 (d, 3H, CH$_2$CH_3). ^{13}C NMR ($CDCl_3$): δ = 172.6 (HN*C*OCH$_3$), 170.6 (HN*C*O), 169.9 (*C*OOCH$_3$), 158.1 (>*C*═), 138.4 (H*C*═CH_2), 130.3 (>*C*═), 128.1 (2 H*C*═), 114.7 (HC═*C*H$_2$), 114.5 (2 H*C*═), 67.7 (*C*H$_2$), 54.4 (*C**H), 52.3 (O*C*H$_3$), 48.2 (*C**-HCH$_3$), 37.6 (*C*H$_2$), 33.4 (*C*H$_2$), 28.7 (*C*H$_2$), 25.3 (*C*H$_2$), 23.1 (NHCO*C*H$_3$), 18.1 (C*H*C*H$_3$). IR (cm^{-1}, KBr): 3290 (N−H), 1753 (C═O), 1641 (C−N), 1551 (N−H). Anal. Calcd for $C_{21}H_{30}N_2O_5$ (390.47 g mol^{-1}): C 64.62; H 7.69; N 7.18. Found: C 64.78; H 7.67; N 7.24. **(4)** ^{1}H NMR ($CDCl_3$): δ = 7.07 (d, 2H, 2 *H*C═), 6.78 (d, 2H, 2 *H*C═), 6.52 (d, 1H, N*H*), 6.44 (d, 1H, N*H*), 5.77 (m, 1H, *H*C═CH_2), 4.98 (m, 2H, HC═CH_2), 4.75 (q, 1H, C$^*H$), 4.37 (m, 1H, C$^*H$CH(CH$_3$)$_2$), 3.88 (t, 2H, CH_2), 3.66 (s, 3H, OCH_3), 3.10 (dd, 1H, CH_a-H$_b$), 2.92 (dd, 1H, CH$_a$-H_b), 2.07 (m, 3H, C*HC*H*(CH$_3$)$_2$; CH_2), 1.93 (s, 3H, NHCOCH_3), 1.74 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 0.81−0.75 (m, 6H, CHCH(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): δ = 171.6 (HN*C*OCH$_3$), 171.1 (HN*C*O), 170.0 (*C*OOCH$_3$), 158.0 (>*C*═), 138.4 (H*C*═CH_2), 130.2 (>*C*═), 128.1 (2 H*C*═), 114.7 (HC═*C*H$_2$), 114.5 (2 H*C*═), 67.6 (*C*H$_2$), 57.4 (*C**HCH(CH$_3$)$_2$), 54.6 (*C**H), 52.0 (O*C*H$_3$), 37.4 (*C*H$_2$), 33.4 (*C*H$_2$), 31.0 (CH*C*H(CH$_3$)$_2$), 28.7 (*C*H$_2$), 25.3 (*C*H$_2$), 23.0 (NHCO*C*H$_3$), 18.8−18.1 (2C, CHCH(*C*H$_3$)$_2$). IR (cm^{-1}, KBr): 3292 (N−H), 1740 (C═O), 1641 (C−N), 1544 (N−H). Anal. Calcd for $C_{23}H_{34}N_2O_5$ (418.53 g mol^{-1}): C 66.02; H 8.13; N 6.69. Found: C 65.76; H 8.05; N 6.49.

5-Hexen-1-yl-(α-Tocopheryl)-ether (5). To a solution of α-D,L-tocopherol (8 g, 18.5 mmol) in DMF (60 mL) was added K_2CO_3 (5.1 g, 37 mmol), followed by 6-bromo-1-hexene (4.5 mL, 33.4 mmol). The mixture was stirred at 110 °C for 3 days. Then the K_2CO_3 solid was filtered off, and the solvent was removed under reduced pressure. The remaining brown oily product was dissolved in 5% NaOH/Et_2O (1/1 v/v; 400 mL). The aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The obtained viscous oil was flash chromatographed on silica gel (hexane/ethyl acetate, 14 > 3/0.3) to yield a light orange honey-like product (37% yield). ^{1}H NMR ($CDCl_3$): δ = 5.84 (m, 1H, *H*C═CH_2), 5.00 (m, 2H, HC═CH_2), 3.63 (m, 2H, CH$_2$CH_2O), 2.56(t, 2H, CH_2), 2.15 (s, 3H, Ar−CH_3), 2.11 (s, 3H, Ar−CH_3), 2.07 (s, 3H, Ar−CH_3), 1.79 (m, 4H, 2 CH_2), 1.64−1.02 (broad m, 25 aliph. protons), 1.22 (s, 3H, CCH_3), 0.87 (d, 6H, 2 CH_3), 0.85 (d, 3H, CH_3), 0.84 (d, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ = 148.4 (>*C*═), 147.6 (>*C*═), 138.7 (H*C*═CH_2), 127.8 (>*C*═), 125.8 (>*C*═), 122.8 (>*C*═), 117.4 (>*C*═), 114.6 (HC═*C*H$_2$), 74.7(>*C*═), 72.8 (*C*H$_2$), 40.1 (*C*H$_2$), 39.4 (*C*H$_2$), 37.6−37.4 (4 *C*H$_2$), 33.7 (*C*HCH$_3$), 32.8 (*C*HCH$_3$), 32.7 (*C*H$_2$), 31.3 (*C*H$_2$), 29.8 (*C*H$_2$), 27.9 (*C*H(CH$_3$)$_2$), 25.5 (*C*H$_2$), 24.8 (*C*H$_2$), 24.4 (*C*H$_2$), 23.8 (C*C*H$_3$), 22.7 (CH*C*H$_3$), 22.6 (CH*C*H$_3$), 21.0 (*C*H$_2$), 20.6 (*C*H$_2$), 19.8−19.6 (2 *C*H$_3$), 12.7 (C*C*H$_3$), 11.8 (C*C*H$_3$), 11.7 (C*C*H$_3$). IR (cm^{-1}, KBr): 2926−2865 (CH$_3$, CH$_2$, CH), 1460, 1385 (C═C), 1255 (C−O−C). Anal. Calcd for $C_{35}H_{60}O_2$ (512.85 g mol^{-1}): C 81.96; H 11.81. Found: C 81.72; H 11.72.

17-β-5-hexenoyloxy-androst-4-en-3-one (6). 17-β-hydroxy-androst-4-en-3-one (4 g, 14 mmol), 5-hexenoic acid (2 mL, 16.8 mmol), and 4-(dimethylamino)pyridine (DMAP; 0.34 g, 2.8 mmol) were dissolved in CH_2Cl_2 (70 mL). *N*,*N*′-Dicyclohexylcarbodiimide (DCC; 3.5 g, 16.8 mmol) was dissolved in another portion of CH_2Cl_2 (40 mL). The two solutions were combined and stirred at 0 °C for 1 h. The start of the reaction was indicated by formation of dicyclohexylurea precipitate. The mixture was stirred at room temperature for another 24 h. After this time, the white precipitate was filtered off and the residual mixture was diluted with CH_2Cl_2. Next the solution was washed successively with 0.5 M HCl, saturated $NaHCO_3$ and distilled water. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The product was flash chromatographed on silica gel (hexane/ethyl acetate, 6 > 2.5/1) to give a white solid (88% yield). ^{1}H NMR ($CDCl_3$): δ = 5.74 (m, 1H, *H*C═CH_2), 5.69 (s, 1H, C*H*═C<), 4.97 (m, 2H; HC═CH_2), 4.57 (t, 1H, C*H*OCO), 2.39−2.26 (m, 6H, 3 CH_2), 2.13−1.98 (m, 4H, 2 CH_2), 1.69−1.32 (br., m, 12H, 5 CH_2, 2 C*H*), 1.15 (s, 3H, CH_3), 1.02−0.91 (br., m, 3H, CH_2, C*H*), 0.80 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ = 199.4 (*C*═O), 173.5 (O*C*═O), 170.9 (>*C*═), 137.6 (H*C*═CH_2), 123.8 (H*C*═), 115.2 (HC═*C*H$_2$), 81.2 (*C*H), 53.6 (*C*H), 50.1 (*C*H), 42.4 (*C*CH), 38.5 (*C*CH), 36.5 (*C*H$_2$), 35.6 (*C*H$_2$), 35.3 (*C*H), 33.8 (*C*H$_2$), 33.7 (*C*H$_2$), 33.0 (*C*H$_2$), 32.6 (*C*H$_2$), 31.4 (*C*H$_2$), 27.4 (*C*H$_2$), 24.1 (*C*H$_2$), 23.4 (*C*H$_2$), 20.4 (*C*H$_2$), 17.3 (*C*H$_3$), 12.0 (*C*H$_3$). IR (cm^{-1}, KBr): 2940−2850 (CH$_3$, CH$_2$, CH), 1731 (C═O, ester), 1675 (C═O), 1230 (C−O−C). Anal. Calcd for $C_{25}H_{36}O_3$ (384.52 g mol^{-1}): C 78.08; H 9.44. Found: C 77.85; H 9.37.

Oligomer Synthesis. *N*-Acetyl-*O*′-(hex-5-enyl)-l-tyrosine ethyl ester/CO (7). [Pd(dppp)(NCCH$_3$)$_2$](BF$_4$)$_2$ catalyst (70 mg, 90.3 μmol) and diethylene glycol (0.52 mL, 5.5 mmol) as activator were placed under argon into a 50 mL stainless steel autoclave equipped with a glass inlay and a stirring bar. Then a solution of **1** (2.5 g, 7.5 mmol) in dry CH_2Cl_2 (20 mL) was added. Next the autoclave was pressurized under vigorous stirring with 30 bar of carbon monoxide. The reaction was running for 72 h at room temperature. After this time, the remaining gases were vented off, and the polymerization mixture was extracted with the same amount of water. The organic phase was filtered, concentrated, and added dropwise into cold Et_2O (500 mL) with stirring. The resulting precipitate was dissolved in CH_2Cl_2, the solution was passed through a short silica column (Merck silica 60 (63−200 μm)) to remove the catalyst, concentrated, and poured in the same manner into cold Et_2O. The solid precipitate was dried under vacuum for 24 h at room temperature. ^{1}H NMR ($CDCl_3$): δ = 6.92 (2H, 2 *H*C═), 6.69 (2H, 2 *H*C═), 6.34 (1H, N*H*), 4.70 (1H, C$^*H$NH), 4.06 (2H, CH_2CH$_3$), 3.79 (2H, CH$_2$CH_2OAr), 2.93 (2H, CHCH_2Ar) 2.65−2.26 (br., C*H* and CH_2 oligomer backbone), 1.87 (3H, NHCOCH_3), 1.64−1.31 (6H, 3 CH_2), 1.15 (3H, CH$_2$CH_3). ^{13}C NMR ($CDCl_3$): δ = 214.3, 211.9, 208.5 (*C*═O oligomer backbone); 171.7 (NH*C*OCH$_3$), 169.5 (*C*OOC$_2$H$_5$), 157.8, 130.1, 127.9, 114.3 (6C$_{aromat}$), 67.3 (CH$_2$CH_2OAr), 61.1 (*C*H$_2$-CH$_3$), 53.2 (*C**HNH), 45.2−42.1 (br., *C*H and *C*H$_2$ oligomer backbone); 36.9 (CH*C*H$_2$Ar), 30.8, 29.1, 23.4 (3 *C*H$_2$), 22.7 (NHCO*C*H$_3$), 13.9 (CH$_2$*C*H$_3$). IR (cm^{-1}, KBr): 3400 (br., N−H), 3000−2867 (CH$_3$, CH$_2$, CH), 1743 (C═O), 1707 (C═O oligomer backbone), 1660 (C−N), 1556 (N−H).

***N*-Acetyl-*O*′-(hex-5-enyl)-l-tyrosylglycine Ethyl Ester/CO (8).** Monomer **2** (4.6 mmol, 1.80 g) was copolymerized with CO in the same manner as described for monomer **1**; however, 60 bar CO pressure was applied. The catalyst was separated from the product by the use of preparative GPC. ^{1}H NMR ($CDCl_3$): δ = 7.04 (2H, 2 *H*C═), 6.69 (2H, 2 *H*C═), 4.73 (1H, C$^*H$), 4.12 (2H, CH_2CH$_3$), 3.89 (2H, CH$_2$CH_2-OAr), 3.78 (2H, CONHCH_2), 2.98−2.85 (br., 2H, CHCH_2Ar), 2.49−2.28 (br., C*H* and CH_2 oligomer backbone), 1.87 (3H, NHCOCH_3), 1.66−1.33 (br., 6H, 3 CH_2), 1.18 (3H, CH$_2$CH_3). ^{13}C NMR ($CDCl_3$):

δ = 212.1−208.6 (*C*═O oligomer backbone), 172.0 (NH*C*OCH$_3$), 170.4 (*C*ONH), 169.4 (*C*OOC$_2$H$_5$), 157.7, 130.1, 128.6, 114.2 (6C$_{aromat}$), 67.3 (CH$_2$*C*H$_2$OAr), 61.2 (*C*H$_2$CH$_3$), 54.3 (*C**H), 45.5−42.5 (br., *C*H and *C*H$_2$ oligomer backbone), 41.2 (*C*H$_2$COOC$_2$H$_5$), 37.2 (C*H*C*H$_2$), 29.2, 28.7, 25.7 (3 *C*H$_2$), 22.8 (NHCO*C*H$_3$), 14.0 (CH$_2$*C*H$_3$). IR (cm^{-1}, KBr): 3400 (br., N−H), 3000−2860 (CH$_3$, CH$_2$, CH), 1751 (br., C═O ester and Ac groups) with shoulder at 1707 (C═O oligomer backbone), 1652 (C−N), 1540 (N−H), 1240 (C−O−C).

***N*-Acetyl-*O*′-(hex-5-enyl)-l-tyrosylalanine Methyl Ester/CO (9).** Monomer **3** (2.0 mmol, 0.80 g) was copolymerized with CO in the same manner as described for monomer **2**. ^{1}H NMR (CDCl$_3$): δ = 7.04 (2H, 2 *H*C═), 6.71 (2H, 2 *H*C═), 4.74 (1H, C**H*CH$_2$), 4.43 (1H, C**H*CH$_3$), 3.83 (2H, CH$_2$C*H*$_2$OAr), 3.67 (3H, COOC*H*$_3$), 2.98−2.83 (br., 2H, C*HC*H*$_2$), 2.69−2.20 (br., C*H* and C*H*$_2$ oligomer backbone), 1.90 (3H, NHCOC*H*$_3$), 1.69−1.40 (br., 6H, 3 C*H*$_2$), 1.29−1.21 (3H, C*HC*H*$_3$). ^{13}C NMR (CDCl$_3$): δ = 211.9−209.3 (*C*═O oligomer backbone), 172.7 (NH*C*OCH$_3$), 171.4 (*C*ONH), 170.2 (*C*OOCH$_3$), 157.8, 130.2, 128.6, 114.4 (6C$_{aromat}$), 67.6 (CH$_2$*C*H$_2$OAr), 54.4 (*C**HCH$_2$), 52.2 (COO*C*H$_3$), 48.1 (*C**HCH$_3$), 45.4−42.5 (br., *C*H and *C*H$_2$ oligomer backbone), 37.5 (C*H*C*H$_2$), 29.2, 28.6, 25.7 (3 *C*H$_2$), 22.9 (NHCO*C*H$_3$), 17.7 (C*H*C*H$_3$). IR (cm^{-1}, KBr): 3400 (br., N−H), 3060−2860 (CH$_3$, CH$_2$, CH), 1749 (br., C═O ester and Ac groups) with shoulder at 1706 (C═O oligomer backbone), 1645 (C−N), 1549 (N−H), 1244 (C−O−C).

***N*-Acetyl-*O*′-(hex-5-enyl)-l-tyrosylvaline Methyl Ester/CO (10).** Monomer **4** (6.7 mmol, 2.8 g) was copolymerized with CO in the same manner as described for monomer **2**. ^{1}H NMR (CDCl$_3$): δ = 7.00 (2H, 2 *H*C═), 6.67 (2H, 2 *H*C═), 4.86 (1H, C**H*CH$_2$), 4.37 (1H, C**H*CH(CH$_3$)$_2$), 3.79 (2H, CH$_2$C*H*$_2$OAr), 3.65 (3H, COOC*H*$_3$), 2.93 (br., 2H, C*HC*H*$_2$), 2.79−2.34 (br., C*H* and C*H*$_2$ oligomer backbone), 2.05 (1H, C*H*(CH$_3$)$_2$), 1.88 (3H, NHCOC*H*$_3$), 1.65−1.31 (br., 6H, 3 C*H*$_2$), 0.82−0.77 (br., 6H, 2 C*H*$_3$). ^{13}C NMR (CDCl$_3$): δ = 214.0, 212.2, 208.8 (*C*═O oligomer backbone); 171.7 (br., overlapped *C*ONH and NHCOCH$_3$), 170.2 (*C*OOCH$_3$), 157.7, 130.3, 128.7, 114.3 (6C$_{aromat}$), 67.3 (CH$_2$*C*H$_2$OAr), 57.5 (*C**HCH(CH$_3$)$_2$), 54.5 (*C**HCH$_2$), 51.9 (COO*C*H$_3$), 45.3−42.4 (br., *C*H and *C*H$_2$ oligomer backbone), 37.6 (C*H*C*H$_2$), 30.8 (C*H*C*H(CH$_3$)$_2$), 29.2, 28.8, 23.5 (3 *C*H$_2$), 22.9 (NHCO*C*H$_3$), 18.8−17.9 (2C, 2 *C*H$_3$). IR (cm^{-1}, KBr): 3400 (br., N−H), 3000−2870 (CH$_3$, CH$_2$, CH), 1747 (br., C═O ester and Ac groups) with shoulder at 1707 (C═O oligomer backbone), 1648 (C−N.), 1548 (N−H), 1244 (C−O−C).

5-Hexen-1-yl-(α-Tocopheryl)-ether/CO (11). The copolymerization of monomer **5** (6.8 mmol, 3.5 g) was performed in the same manner as described for monomer **1**. The product was isolated by precipitation of concentrated oligomer's solution in cold acetone. ^{1}H NMR (CDCl$_3$): δ = 3.59 (2H, CH$_2$C*H*$_2$OAr), 3.16−2.96 (br., 2H, C*H*$_2$ oligomer backbone), 2.52−2.40 (br., 3H, C*H* oligomer backbone overlapped with C*H*$_2$ tocopheryl moiety), 2.20−2.05 (br., 9H, 3 C*H*$_3$), 1.73−1.07 (br., m, 32H), 0.87−0.84 (br., 12H, 4 C*H*$_3$). ^{13}C NMR (CDCl$_3$): δ = 212.4, 212.1, 208.7 (*C*═O oligomer backbone), 148.2, 147.6, 127.6, 125.6, 122.6, 117.3 (6C$_{aromat}$), 74.6 (*C*CH$_3$), 72.4 (CH$_2$*C*H$_2$-OAr), 45.6−42.2 (br., *C*H and *C*H$_2$ oligomer backbone), 40.3, 39.3, 37.6−37.4, 32.7, 31.2, 27.9, 25.5, 24.7, 24.4, 23.6, 22.7, 22.6, 21.0, 20.6, 19.6, 12.7, 11.8, 11.7 (25 C, *C*H$_2$ and *C*H). IR (cm^{-1}, KBr): 2925−2864 (CH$_3$, CH$_2$, CH), 1708 (C═O oligomer backbone), 1458, 1377 (C═C arene), 1255 (C−O−C), 1088.

17-β-5-hexenoyloxy-androst-4-en-3-one/CO (12). The copolymerization of monomer **6** (9.1 mmol, 3.5 g) was performed in the same manner as described for monomer **1**. The product was isolated by precipitation of concentrated oligomer's solution in cold methanol. ^{1}H NMR (CDCl$_3$): δ = 5.65 (s, 1H, C*H*═C<), 4.52 (br., 1H, C*H*OCO), 3.04−2.83 (br., 1H, C*H* oligomer backbone), 2.35−2.09 (br., m, 8H, C*H*$_2$ oligomer backbone, 3 C*H*$_2$), 1.96−1.30 (br., m, 16H, 7 C*H*$_2$, 2 C*H*), 1.12 (s, C*H*$_3$), 0.98−0.88 (br., m, 3H, C*H*$_2$, C*H*), 0.77 (s, 3H, C*H*$_3$). ^{13}C NMR (CDCl$_3$): δ = 212.2−208.1 (*C*═O oligomer backbone), 198.9 (*C*═O testosterone), 172.7 (*C*═O ester linkage), 170.4 (CH═*C*<), 123.8 (*C*H═C<), 82.2 (>*C*HOC), 53.6 (*C*H), 50.1 (*C*H), 45.1−42.3 (br., 3C, *C*H$_2$, *C*H oligomer backbone, overlapped with >*C*CH$_3$), 38.4 (>*C*CH$_3$), 36.5 (*C*H$_2$), 35.6 (*C*H$_2$), 35.2 (*C*H), 33.7 (2C, OCO*C*H$_2$ overlapped with O═C*C*H$_2$), 32.5 (*C*H$_2$), 31.3 (2C, 2 *C*H$_2$), 27.4 (*C*H$_2$), 23.3 (*C*H$_2$), 22.2 (*C*H$_2$), 20.4 (*C*H$_2$), 17.2 (*C*H$_3$), 12.0 (*C*H$_3$). IR (cm^{-1}, KBr): 2940−2855 (CH$_3$, CH$_2$, CH), 1731 (br., C═O ester linkage) with shoulder at 1706 (C═O oligomer backbone), 1674 (C═O testosterone), 1230 (C−O−C).

Acknowledgment. The research was supported by the European Commission (Contract No. HPRN-CT- 2000-0004).

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BM0606364