Polyanion Inhibitors of Human Immunodeficiency Virus and Other Viruses. 5. Telomerized Anionic Surfactants Derived from Amino Acids†

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ω-Acryloyl anionic surfactants, whose polar heads are derived from amino acids, have been telomerized to prepare polyanions of a predetermined molecular weight. The main goal of this study was to verify whether the antiviral activity is influenced by the degree of polymerization of the polyanions. The oligomeric polyanions were evaluated for their activity against human immunodeficiency virus (HIV-1 or HIV-2) and various other RNA and DNA viruses. With regard to their anti-HIV activity, a minimum number of anionic groups was necessary to achieve an inhibitory effect. Moreover, to be active the overall conformation of the polyanion must be such that the anionic groups are located on the external site of the molecule. With some of the polyanions, a 50% inhibition concentration (IC_{50}) as low as 1 μg/mL, or even 0.1 μg/mL, was noted against HIV-1 in CEM-4 and MT-4 cells, respectively. The most potent polyanions also proved active against human cytomegalovirus and herpex simplex virus at concentrations of 5−10 and 20−40 μg/mL, respectively. No activity was observed against any of the other viruses tested (i.e., vesicular stomatitis, Sindbis, Semliki forest, parainfluenza, Junin, Tacaribe, Coxsackie, polio, reo, and vaccinia). No toxicity for the host cells was observed at concentrations up to 200 μg/mL.

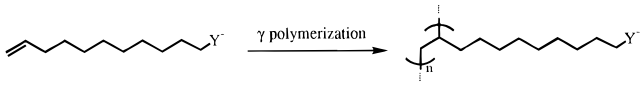
Introduction

The inhibition of the binding of the human immunodeficiency virus (HIV) envelope glycoprotein to the CD4 receptor by polyanionic substances is now well established.[1] These compounds may offer an alternative treatment strategy as their mode of action differs from that of the nucleoside analogues which are used for the treatment of prevention of AIDS. Polyanions can be useful as vaginal microbicides[2] and for topical applications against respiratory tract virus infection.[3] Clinical trials are under way with some of the polyanionic compounds.[4]

In a previous article,[5] we have shown that polyanions, obtained by γ-polymerization in micellar solution of ω-unsaturated anionic surfactants derived from the 11-undecenoic acid (Scheme 1), are inhibitory to HIV, without toxicity to the host cells (CEM-4 or MT-4). Anti-HIV activities of these polyanions have been demonstrated *in vitro* based on a reduction of the reverse transcriptase activity in the culture supernatant or inhibition of the virus-induced cytopathic effect, the 50% inhibition concentration (IC_{50}) being in the range of 0.1−3.5 μg/mL.

Despite the interesting inhibitory effects observed *in vitro*, the *in vivo* use of these compounds seems to be compromised because of their poor bioavailability due to their high molecular weight. Indeed, polymers have the tendency to accumulate in tissues or organs, particularly when they have a high molecular weight.[6,7] To have access to a better bioavailability, we thought to synthesize smaller similar polyanions of a molecular weight lower than 5000 Da, a value more prone to transfer through biological barriers. Indeed there is evidence that polyanions of limited molecular weight, such as the modified cyclodextrin sulfates, can cross biological barriers and are orally available.[8,9]

Scheme 1



For this purpose we decided to use various 11-(*N*-acryloyl-*N*-alkylamino)undecanoic acid derivatives as starting monomeric units. Indeed those monomers can be submitted to a telomerization process. A telomerization reaction differs from a polymerization reaction by the presence in the reaction medium of a chain transfer agent (telogen) whose role is to limit the length of the macromolecular chain and to permit to obtain polymers with low degrees of polymerization (DP_n). These oligomers are called telomers.[10,11]

We present here the synthesis and the telomerization of several methyl esters derived from various 11-(*N*-acryloyl-*N*-alkylamino)undecanoic acids, used as monomers. The saponification of the obtained telomers led to small polyanions whose antiviral activities are also reported.

Monomer Synthesis

Only the methyl 11-(*N*-acryloylamino)undecanoate (**1**) has been described in the literature and used for an IR study of the amide bands.[12] We have prepared this compound from the commercially available 11-aminoundecanoic acid (Scheme 2).

N-Alkyl analogues of **1** were prepared from the 11-bromoundecanoic acid on which the bromine has been substituted by a methylamino or an ethylamino group,

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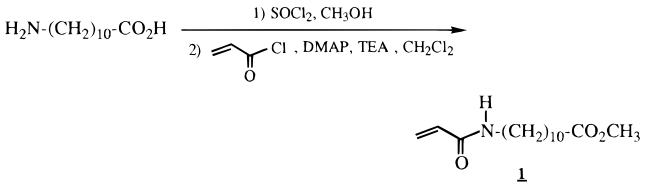
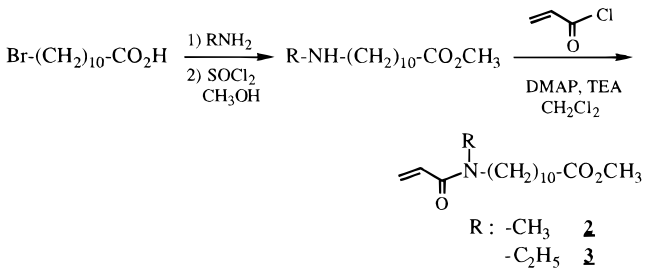
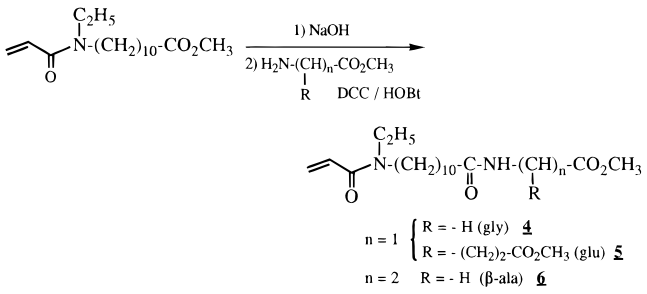
Scheme 2



Scheme 3



Scheme 4



by refluxing it with an aqueous solution of the corresponding amine (Scheme 3). The amino acids obtained after recrystallization in water are consistent with those described in the literature.[13] The carboxylic function of the preceding acids was then protected by a methyl ester function. The esterification has been realized by reacting methanol in the presence of thionyl chloride.[14,15] Methyl esters are amorphous white solids, isolated in quantitative yields.

Monomers **2** and **3** were obtained by condensing at 0 °C the acryloyl chloride with methyl 11-(*N*-alkylamino)-undecanoate in methylene chloride in the presence of 4-(dimethylamino)pyridine (DMAP) and triethylamine used as catalyst.[16,17] After purification by chromatography on silica gel, the structure of the obtained acrylic monomers was characterized by the usual methods. As the anionic head, we decided to graft an amino acid unit. We used glycine, β-alanine, and glutamic acid, as these amino acids gave the best results in the case of the polyanions obtained by γ-polymerization.[18]

Two synthesis strategies have been involved according to the starting monomer. We used method A (Scheme 4) to prepare the *N*-ethylamino derivatives. Amino acids were condensed as their methyl esters with methyl 11-(*N*-acryloyl-*N*-ethylamino)undecanoate by the dicyclohexylcarbodiimide/hydroxybenzotriazole couple.[19,20]

As direct coupling led to medium yields for the previous *N*-ethyl derivatives, we tried to improve them by using method B to prepare monomers derived from the 11-aminoundecanoic acid. This method required protection of the amine function of the 11-aminoundecanoic acid by a *tert*-butyloxycarbonyl (Boc) group.[21−24] The N-protected acid[25] was coupled to the amino acid esters with the DCC/HOBt couple; then the acrylamide function was introduced after deprotection by trifluoroacetic acid (Scheme 5). Actually obtained yields were roughly in the same range as those with method A.

The structures of the monomers having an amino acid residue as a polar head were determined without ambiguity by the usual spectrometric methods. ^{1}H NMR spectroscopy (Scheme 6) revealed that the resonance of the protons H_a, H_b, and H_c of the acrylamide group appears as an ABC system.[26] The proton H_a shifted to the weak field because of the proximity of the carbonyl group. Due to the rigidity of the acrylamide group, protons H_b and H_c are nonequivalent and differently coupled from the proton H_a, and the observed signals are split doublets.

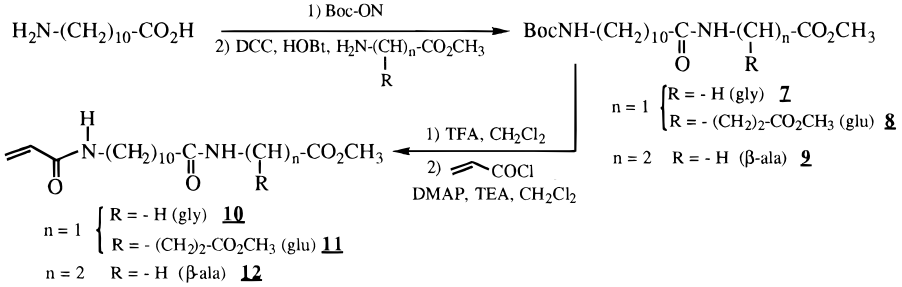
Monomer Telomerization

Former monomers were telomerized so as to obtain compounds with a controlled molecular weight and with a maximum value near 5000 Da. The telomerization reaction required a polymerizable monomer called a taxogen and a transfer agent, most often a thiol, called a telogen in the presence of a radical initiator.

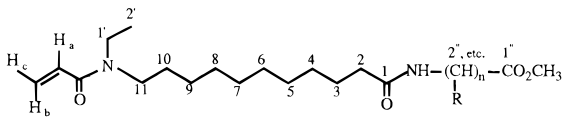
All telomerizations were done with dodecanethiol as the telogen agent. The radical initiator used, azobis(isobutyronitrile) (AIBN), has a first-order decomposition reaction,[27] so it is progressively added to maintain the radical concentration. Moreover, a weak amount of AIBN is sufficient to initiate the reaction[28] when the telogen is an alkanethiol. The DP_n of the telomers can be adjusted to a desired value, depending upon the thiol/monomer initial concentration ratio (R_o). Theoretically, if the transfer constant is equal to unity, the DP_n should be equal to R_o.

Telomerization reactions were performed under nitrogen by refluxing in acetonitrile, used as solvent (80 °C), a mixture of monomer and dodecanethiol in fixed concentrations. When the temperature was stabilized, half of the AIBN was added at time $t = 0$, the other half being added 1 h after. At the end of the reaction, the solvent was eliminated under reduced pressure and

Scheme 5



Scheme 6



Scheme 7

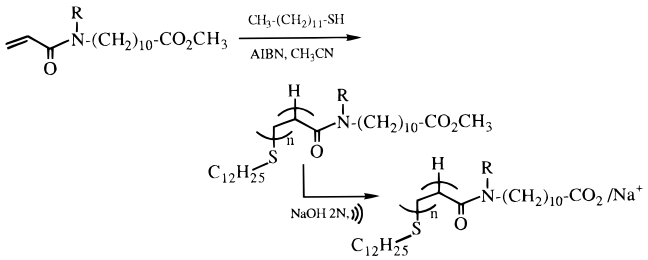
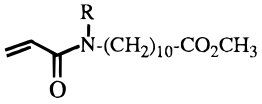


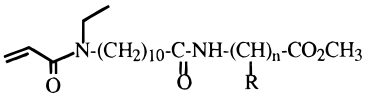
Table 1. Telomerization of Monomers **1**−**3**[a]



monomers	telomers	$10^2[M]_o$ (M)	$10^3[T]_o$ (M)	R_o	DP_n found
1, R = H	**1**T_4	2.48	4.93	5	4.3
	1T_6	2.48	3.09	8	6
	1T_{11}	2.48	2.06	12	11.2
	1T_{20}	2.48	1.21	20	20
2, R = Me	**2**T_5	0.470	0.470	10	5.3
	2T_9	0.410	0.273	15	9.5
	2T_{13}	1.77	0.707	25	12.7
	2T_{20}	1.30	0.367	35	20.3
3, R = Et	**3**T_4	4.0	8.0	5	4
	3T_{11}	4.0	2.0	20	10.8
	3T_{16}	4.0	0.80	50	16
	3T_{40}	4.0	0.33	120	40

[a] $[M]_o$ and $[T]_o$: initial monomer and dodecanethiol concentrations, respectively. $R_o = [M]_o/[T]_o$.

Table 2. Telomerization of Monomers **4**−**6**[a]



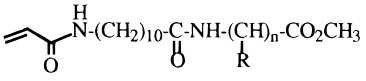
monomers	telomers	$10^4[M]_o$ (M)	$10^5[T]_o$ (M)	R_o	DP_n found
4, $n = 1$	**4**T_3	1.41	2.82	5	2.7
R = H	**4**T_5	1.41	1.41	10	5.4
(glycine)	**4**T_{15}	1.73	0.69	25	15.3
5, $n = 2$	**5**T_5	1.22	1.74	7	5.5
R = H	**5**T_8	1.45	0.97	15	8.3
(β-alanine)	**5**T_{30}	1.90	0.50	38	29.7
	5T_{50}	6.79	0.57	120	>50
6, $n = 1$	**6**T_3	1.82	3.63	5	3
R = $(CH_2)_2CO_2Me$	**6**T_{10}	1.82	1.50	12	10
(glutamic acid)	**6**T_{17}	1.82	0.91	20	17
	6T_{25}	11.3	1.03	110	>25

[a] $[M]_o$ and $[T]_o$: initial monomer and dodecanethiol concentrations, respectively. $R_o = [M]_o/[T]_o$.

the reaction medium was purified by gel permeation chromatography on a Sephadex LH20 column (CH_2Cl_2/CH_3OH, 1/1).

The DP_n value was determined by ^1H NMR, comparing the integration of the methyl ester protons (H_x) with that of the terminal methyl group of the dodecanethiol (H_y): $DP_n = H_x/H_y$. For each telomer, reagent concentrations as well as R_o and observed DP_n values are reported in Tables 1−3. It appears that the DP_n values observed are close to the corresponding R_o values only

Table 3. Telomerization of monomers **10**−**12**[a]



monomers	telomers	$10^4[M]_o$ (M)	$10^5[T]_o$ (M)	R_o	DP_n found
10, $n = 1$	**10**T_3	1.53	5.11	3	2.8
R = H	**10**T_7	1.53	2.19	7	7.4
(glycine)	**10**T_{14}	1.53	1.04	15	14
11, $n = 2$	**11**T_2	2.35	7.84	3	2.3
R = H	**11**T_3	1.47	2.10	7	3.5
(β-alanine)	**11**T_6	1.47	0.98	15	6.5
	11T_8	1.47	0.74	20	8
12, $n = 1$	**12**T_2	2.47	8.09	3	2.2
R = $(CH_2)_2CO_2Me$	**12**T_3	1.46	2.08	7	3.2
(glutamic acid)	**12**T_5	1.14	0.76	15	5.5
	12T_{15}	1.94	0.55	35	15

[a] $[M]_o$ and $[T]_o$: initial monomer and dodecanethiol concentrations, respectively. $R_o = [M]_o/[T]_o$.

in the case of the non-N-alkylated monomers. For the *N*-methyl or *N*-ethyl monomers, the DP_n values are systematically lower than the R_o ones. This is obviously the result of a steric effect.

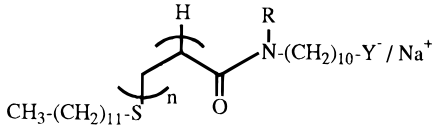
Telomers as ester forms were saponified by 2 N aqueous sodium hydroxide in excess under sonication; the pH was then adjusted to 8.5−9 by an ion exchange resin. Telomers as sodium salts were isolated by lyophilization.

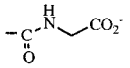
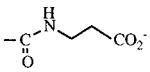
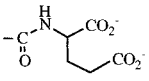
Biological Results

The tests performed in CEM-4 cells (Table 4) show that about one-third of the telomeric polyanions exhibit an inhibitory effect against HIV-1. At first glance, this result is surprising since previous polyanions obtained by polymerization of ω-unsaturated anionic surfactants have systematically proven to be active against HIV.[5,18] We think that this different behavior results from structural differences between the two types of polyanions (Scheme 8). Two factors differentiate the two compound families, namely: (i) the presence of amide groups close to the polymeric chain in the case of telomers (Scheme 8a) and (ii) the number of lateral chains bearing anionic groups.

Concerning the former factor, it is well known that a small structural modification (i.e., changing a methyl versus an ethyl[29] or an N-H group versus an *N*-ethyl group[30]) can drastically alter the self-assembling properties of a surfactant. In a similar way the introduction of a single perfluorinated residue at the end of the polymeric chain of a telomerized tenside modifies its micellar properties by changing the hydrophilic/lipophilic balance (HLB) of the compound.[31] So it seems possible that the introduction of amide groups, by decreasing the hydrophobic character near the polymeric chain, disturbs the conformation of some acrylic polyanions: the globular structure of micellar type could not be achieved if the HLB value is inadequate. It is noteworthy that among the three first series of polyanions (**1**T, **2**T, and **3**T), in which the substituent of the nitrogen corresponds respectively to a hydrogen, a methyl, or an ethyl group, only the polyanions of the third series are active. In this last case, the presence of ethyl groups may confer a sufficient hydrophobic character in the vicinity of the polymeric chain, to restore a conformation close to that in a micellar aggregate.

Table 4. Anti-HIV Activity of the Telomers in CEM-4 Cells[a]



Y	R	telomers	n	CC_{50}[b] µg/mL	IC_{50}[c] µg/mL
$-CO_2^-$	H	**1**T_4	4.3	29	NA
		1T_6	6.0	37	NA
		1T_{11}	11.2	99	NA
		1T_{20}	20.0	>50	NA
	Me	**2**T_5	5.3	>200	NA
		2T_9	9.5	>200	NA
		2T_{13}	12.7	>200	NA
		2T_{20}	20.3	>200	NA
	Et	**3**T_4	4.0	100	25
		3T_{11}	10.8	50	4
		3T_{16}	16.0	27	>11
		3T_{40}	40.0	30	5
	H	**10**T_3	2.8	118	NA
		10T_7	7.4	>300	15
		10T_{14}	14.0	>300	194
	Et	**4**T_3	2.7	50	NA
		4T_5	5.4	>100	120
		4T_{15}	15.3	80	4
	H	**11**T_2	2.3	>300	NA
		11T_3	3.5	>300	NA
		11T_6	6.5	42	NA
		11T_8	8.0	>100	NA
	Et	**5**T_5	5.5	50	NA
		5T_8	8.3	>100	NA
		5T_{30}	29.7	>100	NA
	H	**12**T_2	2.2	>100	NA
		12T_5	5.0	>100	11
		12T_7	7.0	>100	12
		12T_{15}	15.0	>100	15
	Et	**6**T_3	3.0	>100	21
		6T_{10}	10.0	>300	46
		6T_{17}	17.0	>300	25
		6T_{25}	25.0	>300	1

[a] All data represent the average value of at least two separate experiments. [b] 50% cytotoxic concentration, or compound concentration required to reduce the viability of uninfected cells by 50% after 5 days of incubation in the presence of the compound. [c] 50% inhibitory concentration, or compound concentration required to inhibit HIV-induced cytopathicity by 50% (based on the MTT assay). NA = not active.

The second parameter to take into account is the polymerization degree (DP_n) of the telomers. This term governs the number of anionic groups. In the case of vinylic polyanions (Scheme 8b), the DP_n ranked between 30 and 60.[32] With telomer type polyanions, the DP_n value has been modulated between 3 and 40. From Table 4, we note that small polyanions ($DP_n < 10$) are generally inactive or weakly active. However, with DP_n values higher than 10, it is difficult to obtain a correlation between activity and the number of anionic groups. Indeed, the three most active compounds (**6**T_{25}, **4**T_{15}, and **3**T_{11}) possess respectively 50, 15, and 11 anionic groups.

Table 5. Anti-HIV Activity of the Telomers in MT-4 Cells

compd	CC_{50}[a] (µg/mL)	IC_{50}[b] (µg/mL) cytopathicity HIV-1	IC_{50}[b] (µg/mL) cytopathicity HIV-2	IC_{50}[c] (µg/mL) syncitium formation HIV-1	IC_{50}[c] (µg/mL) syncitium formation HIV-2
1T_6	136	20	47	50	150
1T_{11}	>250	55	69	150	150
1T_{20}	>250	5	1.3	30	50
2T_5	128	28	70	150	150
3T_{16}	30	>16	>29	30	50
5T_5	>250	13	30	30	30
6T_{25}	>250	0.1	7	6	30
11T_2	>250	6	27	30	6
11T_6	>250	3	12	10	10

[a] 50% cytotoxic concentration, or compound concentration required to reduce the viability of mock-infected MT-4 cells by 50%. [b] 50% inhibitory concentration, or compound concentration required to inhibit HIV-induced cytopathicity in MT-4 cells by 50%. [c] 50% inhibitory concentration, or concentration required to inhibit by 50% syncitium formation between MOLT-4 cells and HIV-1 (III_B) or HIV-2 (ROD)-infected HUT-78 cells. All data represent mean values of two separate experiments.

Some telomer polyanions were evaluated against HIV-1 and HIV-2 in MT-4 cells (Table 5). They were all found to be active against the virus-induced cytopathic effect and syncitium formation, albeit at rather high IC_{50} values. The best activities were seen with compound **6**T_{25}, which inhibited the cytopathic effect of HIV-1 at an IC_{50} of 0.1 µg/mL, and compound **1**T_{20}, which inhibited the cytopathic effect of HIV-2 at an IC_{50} of 1.3 µg/mL. These two polyanions were nontoxic (CC_{50} > 250 µg/mL).

The activity of this last group of polyanions was also determined against several other RNA or DNA viruses. Their 50% inhibitory concentrations (IC_{50}) and the cytotoxicities as measured in different cell lines are reported in Tables 6 and 7, respectively. Marked antiviral effects were noted with some of the compounds (i.e., **3**T_{16} and **6**T_{25}) against HCMV (IC_{50} in the range of 5−10 µg/mL) and with these and two other compounds (i.e., **11**T_2 and **11**T_6) against HSV (IC_{50} in the range of 20−40 µg/mL). No appreciable activity was noted with any of the compounds against various other viruses such as vaccinia, vesicular stomatitis, parainfluenza-3, reo-1, Sindbis, Semliki forest, Junin, Tacaribe, Coxsackie B4, and polio-1 (Table 6).

Conclusion

The telomerization reaction intended to prepare a new series of polyanions derived from amphiphilic monomers permitted access to low molecular weight polymers, with the possibility to vary their degree of polymerization. To achieve activity against HIV-1 and HIV-2, the number of anionic groups carried by the polyanion must be higher than 10. However a suitable HLB of the

Scheme 8

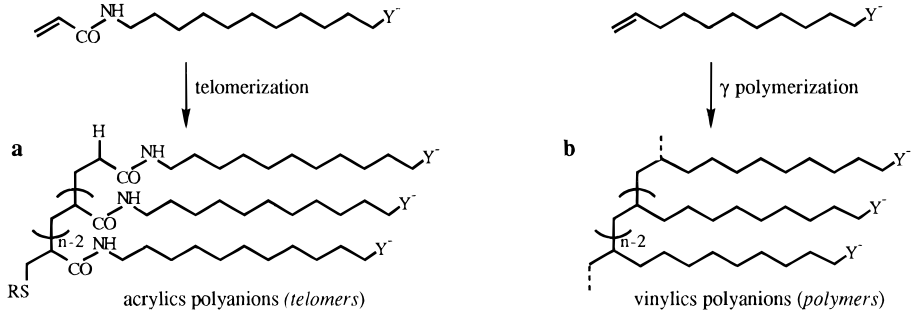


Table 6. Inhibitory Effect of Several Telomers on the Replication of DNA and RNA Viruses

		IC_{50}[a] (μg/mL)								
virus	cell line	dextran sulfate	**1**T_6	**1**T_{11}	**1**T_{20}	**2**T_5	**3**T_{16}	**5**T_5	**6**T_{25}	**11**T_2	**11**T_6
HSV-1 (KOS)	E_6SM	2	>200	>100	>100	>200	>40	70	20	40	20
HSV-2 (G)	E_6SM	2	>200	>100	20	70	20	20	>40	20	20
HSV-1 TK$^-$ (B2006)	E_6SM	2	>200	>100	>100	>200	>200	150	40	70	20
HCMV (AD169)	HEL	0.6	>50	>50	40	>50	9	50	10	30	25
HCMV (Davis)	HEL	0.4	35	>50	15	>50	9	20	5	23	20
vaccinia	E_6SM	100	>200	>100	>100	>200	>40	>200	>40	>200	>200
vesicular stomatitis	E_6SM	2	>200	>100	>100	>200	>40	>200	>40	>200	>200
parainfluenza-3	Vero	>400	>200	>100	>200	>200	>200	>200	>10	>200	>200
reovirus-1	Vero	>400	>200	>100	>200	>200	>200	>200	>10	>200	>200
Sindbis	Vero	40	>200	>100	>200	>200	>200	>200	>10	>200	>200
Semliki forest	Vero	>400	>200	>100	>200	>200	>200	>200	>10	>200	>200
Junin	Vero	8	>50	>50	>50	>50	20	>50	>50	50	43
Tacaribe	Vero	7	>50	>50	>50	>50	>20	>50	>50	43	50
Coxsackie B4	HeLa	>400	>200	>200	>200	>200	>200	>200	>200	>200	>200
polio-1	HeLa	>400	>200	>200	>200	>200	>200	>200	>200	>200	>200

[a] 50% inhibitory concentration, or compound concentration required to reduce virus-induced cytopathicity by 50%. Virus was added in the presence of the compounds, and the cells were further incubated until the cytopathic effect (CPE) was scored.

Table 7. Cytotoxicity of the Telomers for Different Cell Lines

	MMC[a] (μg/mL)									
cell line	dextran sulfate	**1**T_6	**1**T_{11}	**1**T_{20}	**2**T_5	**3**T_{16}	**5**T_5	**6**T_{25}	**11**T_2	**11**T_6
E_6SM	>400	>200	>200	200	>400	100	>400	100	400	>200
HEL	>200	>50	>50	>50	>50	>50	>50	>50	>50	>50
HeLa	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
Vero	>200	>200	>100	>200	>200	>200	>200	>40	>200	>200

[a] Minimum cytotoxic concentration, or compound concentration required to cause a microscopically detectable alteration of normal cell morphology. For HEL cells, the MCC corresponds to the 50% inhibitory concentration required to inhibit cell growth by 50%.

compound seems indispensable to lead to an overall conformation that makes of the anionic groups exposed at the external part of the molecule, as is the case in a micellar structure.

Experimental Protocols

Merck silica gel 60 F254 (0.25 mm) plates were employed for analytical TLC. Compounds were revealed by UV (254 nm), iodine, 20% (in water) sulfuric acid, or 10% (in methanol) ninhydrin sprayings.

Merck silica gel 60H was used for fast silica gel column chromatography. Melting points were determined using a Bucchi 530 apparatus. Sonication reactions were performed with a 72434 Bioblock Scientific Vibra cell apparatus. Infrared spectra were obtained on a IR-FT Bonem MB-100 spectrometer. ^{1}H and ^{13}C NMR were recorded on Bruker AC200 and WP200SY spectrometers, respectively. For ^{1}H and ^{13}C NMR we have used numbers reported in Scheme 6. Chemical shifts are expressed in ppm (δ). Mass spectra were recorded on a Jeol DX 100 spectrometer. Used matrix was *m*-nitrobenzylic alcohol (NOBA) or thioglycerol (GT). Microanalyses were performed in the analytical department of the CNRS (ENSCM-Montpellier). C, H, and N elemental analysis was done for most of the monomers; the observed deviations to the indicated formula were always less than 0.4%.

Methyl 11-(*N*-Acryloylamino)undecanoate (1). To a suspension of 11-aminoundecanoic acid (5.0 g, 24.9 mM, 1 equiv) in 50 mL of methanol was added thionyl chloride (2.9 mL, 40 mM, 1.6 equiv). The mixture was magnetically stirred at room temperature for 2 h and then refluxed for 2 h. The solvent (methanol) was evaporated under reduced pressure, and the white residue obtained was dissolved in anhydrous ether. After filtration and drying, the ester (4.8 g) was isolated as a white powder (yield 89%, mp 155−156 °C, R_f 0.45 ($CHCl_3$/EtOH, 8/2, v/v)).

To a solution of methyl 11-aminoundecanoate ester (3 g, 12 mM, 1 equiv) of 50 mL of anhydrous CH_2Cl_2 at 0 °C were successively added 4-(*N*,*N*-dimethylamino)pyridine (DMAP; 90 mg) and triethylamine (3.6 mL, 26.4 mM, 2.2 equiv). The freshly distilled acryloyl chloride (1.25 mL, 15.6 mM, 1.3 equiv) dissolved in 5 mL of CH_2Cl_2 was added dropwise. Stirring was maintained for 3 h at 0 °C; then 100 mL of CH_2Cl_2 was added, and the organic phase was successively washed twice with 50 mL of aqueous 1 N HCl, twice with 50 mL of aqueous 5% $NaHCO_3$, and finally with H_2O. After usual workup of the organic phase and recrystallization (ether/hexane, 1/1, v/v), 6.5 g of white powder was isolated for ester **1**: yield 97%; mp 55 °C; R_f 0.73 (AcOEt/EtOH, 8/2, v/v); IR (KBr, ν, cm^{-1}) 3282 (N−H), 2926 (Csp^2−H), 1731 (C═O), 1550 (N−H, δ), 1230−1173 (C−O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.1−1.3 (m, 12H, H_4−H_9), 1.4−1.6 (m, 4H, H_3, H_{10}), 2.25 (t, 2H, H_2), 3.25 (q, 2H, H_{11}), 3.6 (s, 3H, CO_2Me), 5.55 (dd, 1H, H_b), 5.65 (m, 1H exch, NH), 6.0 (dd, 1H, H_c), 6.2 (dd, 1H, H_a); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 25 (C_3, C_{10}), 27 (C_4, C_9), 30 (C_5−C_8), 34 (C_2), 40 (C_{11}), 51 (CH_3, ester), 126 (C_b), 131 (C_a), 165 (C═O, acrylate), 174 (C═O, ester); MS (FAB$^+$, NOBA) *m*/*z* 270 [M + H]$^+$, 539 [2M + H]$^+$, 238 [M + H − MeOH]$^+$. Anal. ($C_{15}H_{27}NO_3$) C, H, N.

Methyl 11-(*N*-Acryloyl-*N*-methylamino)undecanoate (2). To an aqueous solution of 40% methylamine (66 mL, 740 mM, 20 equiv) was added 11-bromoundecanoic acid (10 g, 37 mM, 1 equiv). The mixture was magnetically stirred for 7 h at room temperature. The methylamine excess was eliminated under reduced pressure. The obtained residue was recrystallized in H_2O; 4.37 g of white powder was isolated (yield 55%, mp 136−137 °C, R_f 0.58 ($CHCl_3$/EtOH, 1/1, v/v).

Esterification in CH_3OH by thionyl chloride led to the corresponding methyl ester (yield 96%, mp 136 °C, R_f 0.55 ($CHCl_3$/EtOH, 8/2, v/v).

Following the procedure described for the ester **1**, methyl 11-(*N*-methylamino)undecanoate (4 g, 17.2 mM, 1 equiv), DMAP (100 mg), and acryloyl chloride (1.95 mL, 22.7 mM, 1.3 equiv) were used. After a short silica gel column (CH_2Cl_2/EtOH, 95/5), 4.05 g of yellow oil was isolated for **2**: yield 82%; R_f 0.64 ($CHCl_3$/EtOH, 95/5, v/v); IR ($CHCl_3$, ν, cm^{-1}) 2928−2851 (C−H), 1735 (C═O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.1−1.3 (m, 12H, H_4−H_9), 1.4−1.6 (m, 4H, H_3, H_{10}), 2.2 (t, 2H, H_2), 3.0 (2s, 3H, N-CH_3), 3.3 (dt, 2H, H_{11}), 3.6 (s, 3H, CO_2Me), 5.6 (dd, 1H, H_b), 6.3 (m, 1H, H_c), 6.6 (dd, 1H, H_a); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 25 (C_3, C_{10}), 27 (C_4, C_9), 30 (C_5−C_8), 34 (C_2), 36 ($C_{1'}$), 47 (C_{11}), 51 (CH_3, ester), 127 (C_b), 128 (C_a), 166 (C═O,

acrylate), 175 (C═O, ester); MS (FAB$^+$, NOBA) m/z 284 [M + H]$^+$, 252 [M − MeOH]$^+$, 228. Anal. ($C_{16}H_{29}NO_3$) C, H, N.

Methyl 11-(*N*-Acryloyl-*N*-ethylamino)undecanoate (3). According to the procedure described for the synthesis of **2**, methyl 11-(*N*-ethylamino)undecanoate (5.5 g, 22.6 mM, 1 equiv), DMAP (70 mg), 100 mL of CH_2Cl_2, and acryloyl chloride (6 mL, 29.3 mM, 2.2 equiv) were used; 5.8 g of a yellow oil was isolated for the ester **3**: yield 89%; R_f 0.69 ($CHCl_3$/EtOH, 95/5, v/v); IR ($CHCl_3$, ν, cm^{-1}) 2931−2856 (C−H), 1729 (C═O, ester), 1644 (C═O, amide), 1250−1170 (C−O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.1 (m, 3H, $H_{2'}$), 1.2−1.4 (m, 12H, H_4−H_9), 1.5−1.6 (m, 4H, H_3, H_{10}), 2.3 (t, 2H, H_2), 3.4 (m, 4H, H_{11}, $H_{1'}$), 3.7 (s, 3H, CO_2Me), 5.7 (dd, 1H, H_b), 6.3 (dd, 1H, H_c), 6.6 (dd, 1H, H_a) (J_{ac} = 16.7 Hz, J_{ab} = 8 Hz, J_{bc} = 2.3 Hz); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 13.5 and 15 ($C_{2'}$), 25 (C_3, C_{10}), 27 (C_4, C_9), 30 (C_5−C_8), 34 (C_2), 41 and 42.5 ($C_{1'}$), 46 and 47.5 (C_{11}), 51 (CH_3, ester), 126 (C_b), 131 (C_a), 166 (C═O, acrylate), 175 (C═O, ester); MS (FAB$^+$, GT) m/z 298 [M + H]$^+$, 406 [M + H + GT]$^+$, 595 [2M + H]$^+$, 242. Anal. ($C_{17}H_{31}NO_3$) C, H, N.

Methyl*N*-(11-(*N*′-Acryloyl-*N*′-ethylamino)undecanoyl)-amino Acid Ester. General Method. To a suspension of methyl amino ester hydrochloride (10 mM) in 50 mL of CH_2Cl_2 at 0 °C were successively added *N*-ethylmorpholine (1.27 mL, 10 mM, 1 equiv), hydroxybenzotriazole (1.35 g, 10 mM, 1 equiv), and 11-(*N*-acryloyl-*N*-ethylamino)undecanoic acid (2.84 g, 10 mM, 1 equiv) obtained by saponification under sonication of the monomer **3**. Then dicyclohexylcarbodiimide (2.06 g, 10 mM, 1 equiv) was fractionally added with a catalytic amount of DMAP (100 mg). Magnetic stirring was maintained for 2 h at 0 °C and then for 6 h at room temperature. The DCU precipitate was eliminated by filtration on Celite, and the volume of the reaction medium was diluted with 50 mL of CH_2Cl_2. The organic phase was successively washed twice with 50 mL of aqueous 1 N HCl, twice with 50 mL of saturated aqueous $NaHCO_3$, and finally twice with 50 mL of H_2O. After elimination of CH_2Cl_2 under reduced pressure, the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 95/5, v/v).

Methyl *N*-(11-(*N*′-acryloyl-*N*′-ethylamino)undecanoyl)-glycinate (4): yield 57%; mp 29−30 °C; R_f 0.88 ($CHCl_3$/EtOH, 8/2, v/v); IR (KBr, ν, cm^{-1}) 3300 (N−H), 2922−2848 (Csp^3−H), 1742 (C═O), 1648 (C═C), 1557 (N−H); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.1 (m, 3H, $H_{2'}$), 1.15−1.3 (m, 12H, H_4−H_9), 1.5−1.7 (m, 4H, H_3, H_{10}), 2.2 (t, 2H, H_2), 3.1−3.4 (m, 4H, H_{11}, $H_{1'}$), 3.65 (s, 3H, CO_2Me), 3.9 (d, 2H, $H_{2''}$), 5.6 (dd, 1H, H_b) 6.3 (dd, 1H, H_c), 6.45 (m, 1H, NH), 6.5 (dd, 1H, H_a); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 13 and 14.5 ($C_{2'}$), 25 (C_3, C_{10}), 27 (C_4, C_9), 30 (C_5−C_8), 34.5 (C_2), 36 ($C_{2''}$), 42 and 43 ($C_{1'}$), 46 and 47 (C_{11}), 51.5 (CH_3, ester), 128 (C_a and C_b), 166 (C═O, acrylate), 170 (C═O, ester), 174 (C═O, amino acid); MS (FAB$^+$, GT) m/z 355 [M + H]$^+$, 463 [M + GT + H]$^+$, 210, 112. Anal. ($C_{19}H_{34}N_2O_4$) C, H, N.

Methyl *N*-(11-(*N*′-acryloyl-*N*′-ethylamino)undecanoyl)-*β*-alaninate (5): yield 52%; R_f 0.85 ($CHCl_3$/EtOH, 8/2, v/v); IR ($CHCl_3$, ν, cm^{-1}) 3303 (N−H), 2925−2851 (C−H), 1741 (C═O), 1641 (C═C), 1544 (N−H); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.1 (m, 3H, $H_{2'}$), 1.15−1.3 (m, 12H, H_4−H_9), 1.4−1.65 (m, 4H, H_3, H_{10}), 2.1 (t, 2H, H_2), 2.6 (t, 2H, $H_{2''}$), 3.2−3.4 (m, 4H, $H_{1'}$, H_{11}), 3.45 (m, 2H, $H_{3''}$), 3.6 (s, 3H, CO_2Me), 5.6 (dd, 1H, H_c), 6.1 (dd, 1H, NH), 6.2 (dd, 1H, H_b), 6.4 (dd, 1H, H_a); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 12.5−14.5 ($C_{2'}$), 25 (C_3, C_{10}), 26 (C_4, C_9), 30 (C_5−C_8), 34 ($C_{3''}$), 35 (C_2), 36.5 ($C_{2''}$), 41 and 42 ($C_{1'}$), 46 and 47 (C_{11}), 51 (CO_2Me), 126 and 127 (C_a, C_b), 166 (C═O, acrylate), 170 (C═O, amino acid), 174 (C═O, ester); MS (FAB$^+$, GT) m/z 369 [M + H]$^+$, 477 [M + H + GT]$^+$, 845 [2M + H + GT]$^+$. Anal. ($C_{20}H_{36}N_2O_4$) C, H, N.

Methyl *N*-(11-(*N*′-acryloyl-*N*′-ethylamino)undecanoyl)-L-glutamate (6): yield 49%; R_f 0.80 ($CHCl_3$/EtOH, 8/2, v/v); IR (CH_3Cl, ν, cm^{-1}) 3428 (N−H), 2931−2856 (C−H), 1736 (C═O, ester), 1663−1630 (C═O, amide); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.1 (m, 3H, $H_{2'}$), 1.15−1.3 (m, 12H, H_4−H_9), 1.4−1.6 (m, 4H, H_3, H_{10}), 2.0 (m, 2H, $H_{3''}$), 2.2 (t, 2H, H_2), 2.4 (m, 2H, $H_{2''}$), 3.2−3.5 (m, 4H, $H_{1'}$, H_{11}), 3.7 and 3.75 (2s, 6H, 2CO_2Me), 4.6 (m, 1H, $H_{4''}$), 5.6 (dd, 1H, H_b), 6.4 (m, 1H, NH), 6.45 (dd, 1H, H_c), 6.5 (dd, 1H, H_a) (J_{ac} = 16.7 Hz, J_{ab} = 12.5 Hz, J_{bc} = 2.28 Hz); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 12.5−14.5 ($C_{2'}$), 26 (C_3, C_{10}), 27.5 (C_4, C_9), 29 (C_5−C_8), 30 ($C_{2''}$, $C_{3''}$), 36 (C_2), 41 and 42 ($C_{1'}$), 46 and 47 (C_{11}), 52 (2 CH_3, esters), 126 and 127 (C_a, C_b), 166 (C═O, acrylate), 170 (C═O, amino acid), 173 and 174 (C═O, esters); MS (FAB$^+$, NOBA) m/z 441 [M + H]$^+$, 266, 225, 176, 112. Anal. ($C_{23}H_{40}N_2O_6$), C, H, N.

Methyl *N*-(11-(*N*′-(*tert*-Butyloxycarbonyl)amino)undecanoyl)amino Acid Esters 7−9. 11-(*N*-(*tert*-Butyloxycarbonyl)amino)undecanoic Acid. To a solution of triethylamine (0.9 mL, 6.55 mM, 1.5 equiv) of Boc-ON (1.18 g, 4.8 mM, 1.1 equiv) in 16 mL of a H_2O/dioxane (50/50) mixture was added 11-aminoundecanoic acid (1 g, 4.37 mM, 1 equiv). Magnetic stirring was maintained for 3 h at room temperature; then 20 mL of H_2O and 25 mL of AcOEt were added. The aqueous phase was acidified by adding aqueous 5% citric acid till precipitation. After extraction with ethyl acetate, the organic phase was concentrated under reduced pressure. After recrystallization (hexane), 1.04 g of acid was obtained as a white powder (yield 80%, mp 77−78 °C (lit.[19] mp 79 °C), R_f 0.68 (AcOEt)).

General Method. To a solution of methyl amino ester hydrochloride (10 mM) in 40 mL of anhydrous THF at 0 °C was successively added *N*-ethylmorpholine (10 mM) followed by 11-(*N*-(*tert*-butyloxycarbonyl)amino)undecanoic acid (10 mM), HOBt (10 mM), and dicyclohexylcarbodiimide (10 mM). The mixture was magnetically stirred for 1 h at 0 °C and then for 18 h at room temperature. The solvent was eliminated under reduced pressure and substituted by 50 mL of AcOEt. The DCU was eliminated by filtration on Celite, and the organic phase was successively washed twice with 25 mL of saturated aqueous $NaHCO_3$, twice with 25 mL of aqueous 10% citric acid solution, and finally twice with 25 mL of H_2O. The compound was purified by chromatography under reduced pressure (CH_2Cl_2).

Methyl *N*-(11-(*N*′-(*tert*-butyloxycarbonyl)amino)undecanoyl)glycinate (7): yield 55%; mp 74−75 °C; R_f 0.56 ($CHCl_3$/EtOH, 95/5, v/v); IR (KBr, ν, cm^{-1}) 3264 (N−H), 2922−2848 (C−H), 1761−1679 (C═O), 1521 (N−H, δ), 1415−1370 (C−H, tBu); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.2 (m, 12H, H_4−H_9), 1.4 (m, 9H, tBu), 1.5 (m, 4H, H_{10}, H_3), 2.15 (t, 2H, H_2), 3.0 (m, 2H, H_{11}), 3.5 (s, 3H, CO_2Me), 4.0 (d, 2H, $H_{2''}$), 4.4 (m, 1H, NH′), 5.9 (m, 1H, NH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 25 and 25.5 (C_3, C_{10}), 26.5 (C_4, C_9), 28.5−30.5 (C_5−C_8), 30 (tBu), 34.5 (C_2), 36 ($C_{2''}$), 41 (C_{11}), 52.5 (CH_3, ester), 80 ($C_{2'}$), 171 (C═O, ester), 174 (C═O, amino acid); MS (FAB$^+$, NOBA) m/z 373 [M + H]$^+$, 273, 90, 57 [tBu]$^+$. Anal. ($C_{19}H_{36}N_2O_5$) C, H, N.

Methyl *N*-(11-(*N*′-(*tert*-butyloxycarbonyl)amino)undecanoyl)-*β*-alaninate (8): yield 50%; mp 62−63 °C; R_f 0.58 ($CHCl_3$/EtOH, 95/5, v/v); IR (KBr, ν, cm^{-1}) 3333 (N−H), 2921−2855 (C−H), 1741−1678−1645 (C═O), 1420−1365 (C−H, tBu); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.2 (m, 12H, H_4−H_9), 1.4 (m, 9H, tBu), 1.5−1.6 (m, 4H, H_{10}, H_3), 2.1 (t, 2H, H_2), 2.4 (t, 2H, $H_{2''}$), 3.0 (m, 2H, H_{11}), 3.6 (s, 3H, CO_2Me), 3.45 (m, 2H, $H_{3''}$), 4.6 (m, 1H, NH′), 6.1 (m, 1H, NH); MS (FAB$^+$, NOBA) m/z 387 [M + H]$^+$, 410 [M + Na + H]$^+$, 287, 57 [tBu]$^+$. Anal. ($C_{20}H_{38}N_2O_5$), C, H, N.

Methyl *N*-(11-(*N*′-(*tert*-butyloxycarbonyl)amino)undecanoyl)-L-glutamate (9): yield 54.5%; mp 64−65 °C; R_f 0.61 ($CHCl_3$/EtOH, 95/5, v/v); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.1 (m, 12H, H_4−H_9), 1.4 (m, 9H, tBu), 1.6 (m, 4H, H_{10}, H_3), 1.9 (m, 2H, $H_{3''}$), 2.1 (t, 2H, H_2), 2.4 (m, 2H, $H_{2''}$), 3.0 (m, 2H, H_{11}), 3.6 and 3.7 (2s, 6H, 2CO_2Me), 4.5 (m, 1H, $H_{4''}$), 4.6 (m, 1H, NH), 6.1 (m, 1H, NH); MS (FAB$^+$, NOBA) m/z 459 [M + H]$^+$, 449, 302, 202. Anal. ($C_{23}H_{42}N_2O_7$) C, H, N.

Methyl *N*-(11-(*N*′-Acryloylamino)undecanoyl)amino Acid Esters 10−12. General Method. The preceding Boc-amino esters (5 mM) were dissolved in 15 mL of a mixture composed of trifluoroacetic acid and CH_2Cl_2 (1/1, v/v). After stirring for 1 h at room temperature, the reaction mixture was evaporated under reduced pressure. The residue was triturated several times with anhydrous ether; the trifluoroacetate salts of the corresponding methyl *N*-(11-(*N*′-acryloylamino)-undecanoyl)amino esters were isolated as a white powder in a roughly quantitative yield.

In 50 mL of CH_2Cl_2 at 0 °C were added the trifluoroacetate of methyl *N*-(11-aminoundecanoyl)amino ester (2 mM, 1 equiv), triethylamine (0.61 mL, 4.4 mM, 2.2 equiv), and a catalytic

amount of DMAP; then acryloyl chloride (0.21 mL, 2.6 mM, 1.3 equiv) dissolved in 5 mL of CH_2Cl_2 was added dropwise. The reaction mixture was maintained under magnetic stirring for 3 h at 0 °C. After addition of 50 mL of CH_2Cl_2, the organic phase was successively washed twice with 50 mL of CH_2Cl_2. The organic phase was successively washed twice with 50 mL of aqueous 1 N HCl, twice with 50 mL of H_2O, twice with 50 mL of aqueous 5% $NaHCO_3$, and finally with H_2O. After evaporation under reduced pressure, the obtained residue was recrystallized (ether).

Methyl *N*-(11-(*N′*-acryloylamino)undecanoyl)glycinate (10): yield 47%; mp 61−62 °C; R_f 0.73 (AcOEt); IR ($CHCl_3$, ν, cm^{-1}) 3298 (N−H), 2923−2848 (Csp^3−H), 1742 (C═O, ester), 1640 (C═O, amide); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15−1.35 (m, 12H, H_4−H_9), 1.4−1.65 (m, 4H, H_3, H_{10}), 2.15 (t, 2H, H_2), 3.2 (q, 2H, H_{11}), 3.65 (s, 3H, CO_2Me), 4.0 (d, 2H, $H_{2''}$), 5.5 (dd, 1H, H_b), 5.55 (m, 1H, NH), 6.0 (m, 1H, NH), 6.05 (dd, 1H, H_c), 6.2 (dd, 1H, H_a); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 25.5 (C_3, C_{10}), 27 (C_4, C_9), 29 (C_5−C_8), 36 (C_2), 39 ($C_{2''}$), 41 (C_{11}), 52 (CH_3, ester), 126 (C_b), 131 (C_a), 166 (C═O, acrylate), 171 ($C_{1''}$), 175 (C_1); MS (FAB$^+$, NOBA) *m*/*z* 327 $[M + H]^+$, 238, 184, 90. Anal. ($C_{17}H_{30}N_2O_4$) C, H, N.

Methyl *N*-(11-(*N′*-acryloylamino)undecanoyl)-*β*-alaninate (11): yield 48% mp 103 °C; R_f 0.59 ($CHCl_3$/EtOH, 95/5, v/v); IR ($CHCl_3$, ν, cm^{-1}) 3032−3018 (C−H), 1724−1709 (C═O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.1−1.3 (m, 12H, H_4−H_9), 1.4−1.6 (2t, 4H, H_{10}, H_3), 2.1 (t, 2H, H_2), 2.5 (t, 2H, $H_{2''}$), 3.3 (q, 2H, H_{11}), 3.45 (q, 2H, $H_{3''}$), 3.6 (s, 3H, CO_2Me), 5.5 (dd, 1H, H_b), 6.0 (m, 1H, NH), 6.1 (m, 1H, H_c), 6.2 (dd, 1H, H_a); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 25 (C_3, C_{10}), 26 (C_4, C_9), 29.5 (C_5−C_8), 34 ($C_{2''}$), 36 ($C_{3''}$), 39 (C_{11}), 51 (CH_3), 126 (C_b), 130 (C_b), 165 (C═O, acrylate), 174 (C═O, ester); MS (FAB$^+$, GT) *m*/*z* 341 $[M + H]^+$, 449 $[M + H + GT]^+$, 287. Anal. ($C_{18}H_{32}N_2O_4$) C, H, N.

Methyl *N*-(11-(*N′*-acryloylamino)undecanoyl)-L-glutamate (12): yield 47%; mp 70 °C; R_f 0.64 ($CHCl_3$/EtOH, 90/10, v/v); IR ($CHCl_3$, ν, cm^{-1}) 3511−3410 (N−H), 2931−2855 (C−H), 1734−1724−1716 (C═O), 1624 (C═C); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.1−1.3 (m, 12H, H_4−H_9), 1.45 (t, 2H, H_3), 1.55 (t, 2H, H_{10}), 1.9 (sx, 2H, $H_{3''}$), 2.15 (t, 2H, H_2), 2.4 (m, 2H, $H_{2''}$), 3.2 (t, 2H, H_{11}), 3.6 and 3.7 (2s, 6H, $2CO_2Me$), 4.55 (m, 1H, $H_{4''}$), 5.5 (dd, 1H, H_b), 6.0 (m, 1H, NH), 6.1 (m, 1H, H_c), 6.2 (dd, 1H, H_a), 6.3 (m, 1H, NH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 26 (C_3, C_{10}), 27 (C_4, C_9), 28 ($C_{3''}$), 29 (C_5−C_8), 30 ($C_{2''}$), 36 (C_2), 39.5 (C_{11}), 51 ($C_{4''}$), 52 ($2CH_3$), 125 (C_b), 131 (C_a), 166 (C═O, amide), 174 (C═O, esters); MS (IE) *m*/*z* 412 $[M]^+$, 352 $[M - CO_2Me]^+$, 238. Anal. ($C_{21}H_{36}N_2O_6$) C, H, N.

Telomerization Reaction. General Procedure. The reaction was realized in acetonitrile as solvent under nitrogen. AIBN (Aldrich) was recrystallized twice from ethanol. The monomer was dissolved in acetonitrile (dried and distilled from CaH_2); then the telogen (dodecanethiol, previously distilled from CaO) was added, and the reaction mixture was heated to 80 °C before adding half of the amount of AIBN. The AIBN remaining was added 1 h later. The reaction medium was maintained at 80 °C under magnetic stirring and under nitrogen for 20 h.

The solvent was eliminated under reduced pressure, and the compound was purified by gel permeation chromatography on a Sephadex LH20 column using CH_2Cl_2/CH_3OH (1/1, v/v) as eluent. The DP_n and the structure were determined by ^{1}H NMR spectroscopy.

Pure fractions of telomers were dissolved in an excess of aqueous 2 N NaOH solution under magnetic stirring for several hours. The aqueous phase was recovered and washed with ethyl acetate, and the pH value was adjusted to 8.5−9.0 with an acidic resin (Dowex 50 W-2X). After filtration, the aqueous phase containing sodium salts was lyophilized. Telomers were recovered as a white powder with a melting point generally superior to 200 °C. Yields were of the order of 60%.

Biological Methods. The different compounds were examined for their antiviral activity according to well-established procedures.[5,33,34] The origin of the viruses, human immunodeficiency virus type 1 (HIV-1, strain HTLV-III$_B$/LAI) and type 2 (HIV-2, strain LAV-2$_{ROD}$), herpex simplex virus type 1 (HSV-1, strain KOS), thymidine kinase deficient (TK^-) HSV-1 (strain B2006), herpes simplex virus type 2 (HSV-2, strain G), human cytomegalovirus (HCMV, strains AD169 and Davis), vaccina virus, vesicular stomatitis virus, parainfluenza virus type 3, reovirus type 1, Junin virus, Tacaribe virus, Sindbis virus, Semliki forest virus, Coxsackie B4 virus, and poliovirus type 1, has been described previously.[33,34]

Cytotoxicity measurements were based on either microscopic examination of alteration of normal cell morphology or inhibition of cell growth. The cell lines used for both the antiviral activity and cytotoxicity assays were CEM-4, MT-4, Vero, HeLa, human embryonic lung (HEL), and human embryonic skin-muscle (E_6SM) fibroblasts.

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