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# Synthesis of precursors of iodine-labeled multifunctional ligands containing 2-nitroimidazole for the detection of hypoxic tissues and/or tumors

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**Abstract**—Biocompatible multifunctional ligands with telomeric structure containing 2-nitroimidazole as affinity marker and tosylate as precursor of $^{123}I$ radioactive tracer were prepared. Telomerization of appropriate monomers derived from tris(hydroxymethyl)-acrylamidomethane was performed in the presence of dodecanethiol, and either AIBN or *tert*-butylperoxide. These conjugates are designed to target hypoxic tissues and tumors. © 2001 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Nitroimidazoles belong to a class of compounds known to undergo different intracellular metabolism, depending on the availability of oxygen in tissue. When a nitroimidazole enters a normal cell, the molecule undergoes a single-electron reduction to form a potentially reactive species.[1–3] In the presence of normal oxygen levels the molecule is immediately reoxidized. In hypoxic tissues, the low oxygen concentration is not able to effectively reoxidize the molecule. Further reduction appears to take place, producing reactive intermediates that bind with cell components of hypoxic tissues, such as the myocardium, the brain or tumor.[2–4]

In tumors, the increased cell mass requires additional oxygen supplies to keep the cell alive. Often, however, the increased demand for oxygen outstrips the supply, rendering a portion of the tumor mass hypoxic, in which nitroimidazole will be retained. This unique behavior of nitroimidazoles led to investigate their ability for the visualization of hypoxic tissue in vivo. Furthermore, as hypoxic cells proved to be radioresistant, assessment of tumor hypoxia with specific radiotracer prior to radiation therapy should provide a rational mean of selecting patients for treatment with bioreductive drugs and chemical radiosensitizers.[1–3]

The use of radiolabeled compounds for scintigraphic detection of disease has achieved worldwide recognition in medicine and biology. For single-photon emission tomography (SPET), the radiohalogenation can be performed with $^{77}Br$, yet the radionuclide of choice[2,5–7] is $^{123}I$. However, adding an iodine atom to a molecule may induce modifications of the physicochemical properties and of the in vitro and in vivo pharmacological characteristics of the pharmaceuticals. To minimize these effects, the radioactive iodine should be linked in a position as far as possible from the pharmacophore.[6]

For this reason as well as for many others (including (i) the necessity to decrease the penetration of the drug across the blood–brain barrier in order to minimize peripheral sensory neuropathy associated with the utilization of nitroimidazole derivatives, (ii) the desire to evaluate a possible enhancement of the response that could arise from the administration of a multifunctional agent through a so-called 'cluster effect'), we decided to develop multifunctional agents containing a limited number of both nitroimidazole moieties and the radioelement $^{123}I$, both being grafted on a common hydrocarbon backbone. In this context, we turned our attention towards telomeric/cotelomeric structures that appear to meet most of the requirements mentioned before. In the last 10 years we have developed a new class of low molecular weight carriers named telomers.[7–9] These conjugates were obtained on radical telomerization of a hydrophilic polymerizable monomer such as acryloylaminoacid or tris(hydroxymethyl)acrylamidomethane in the presence of an alkane ($R_HSH$) or fluoroalkanethiol ($R_FSH$) as transfer agent (the so-called telogen). The multifunctional molecules obtained by this method showed physicochemical properties, biodisposition and biocompatibility behavior as well as

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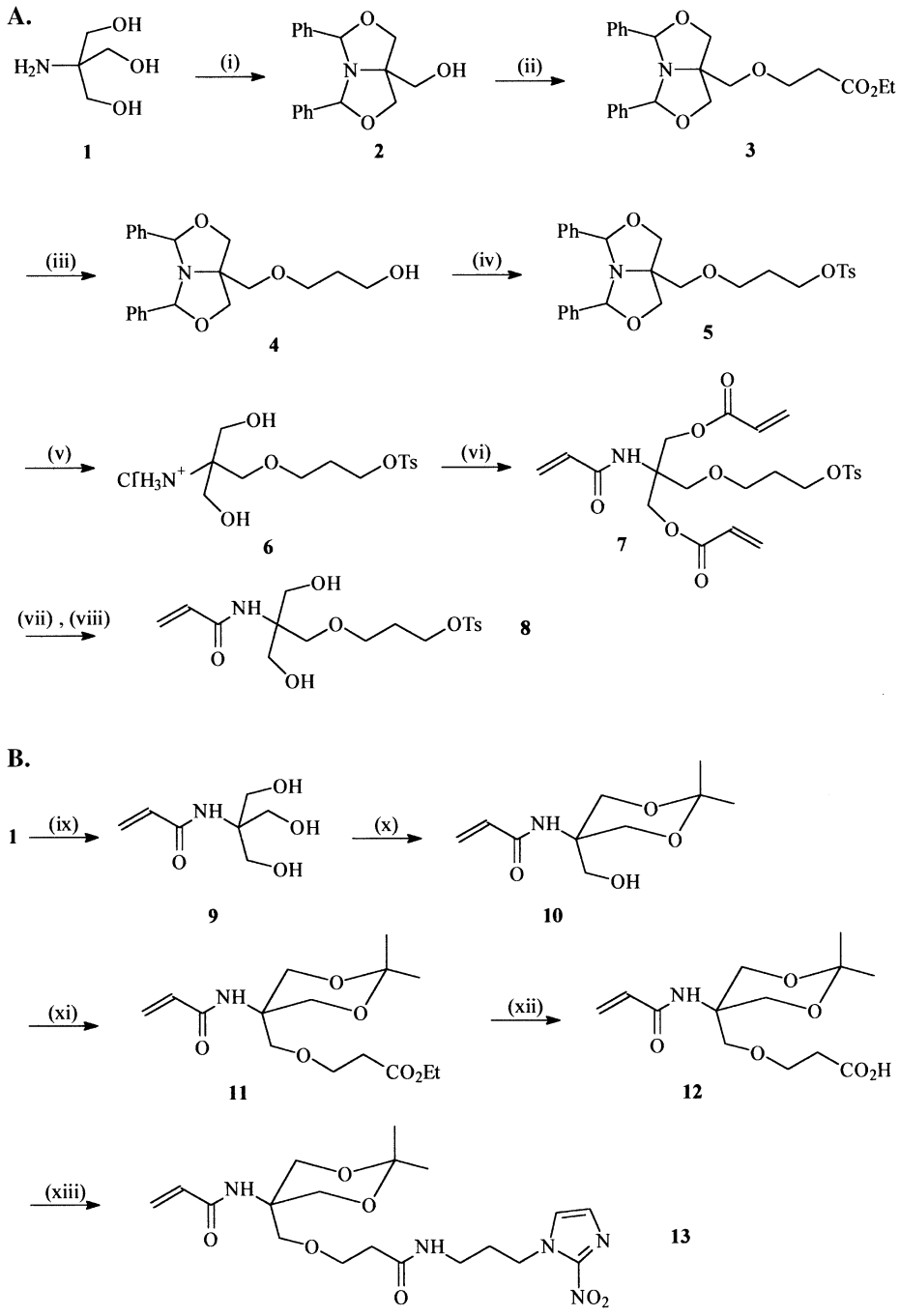
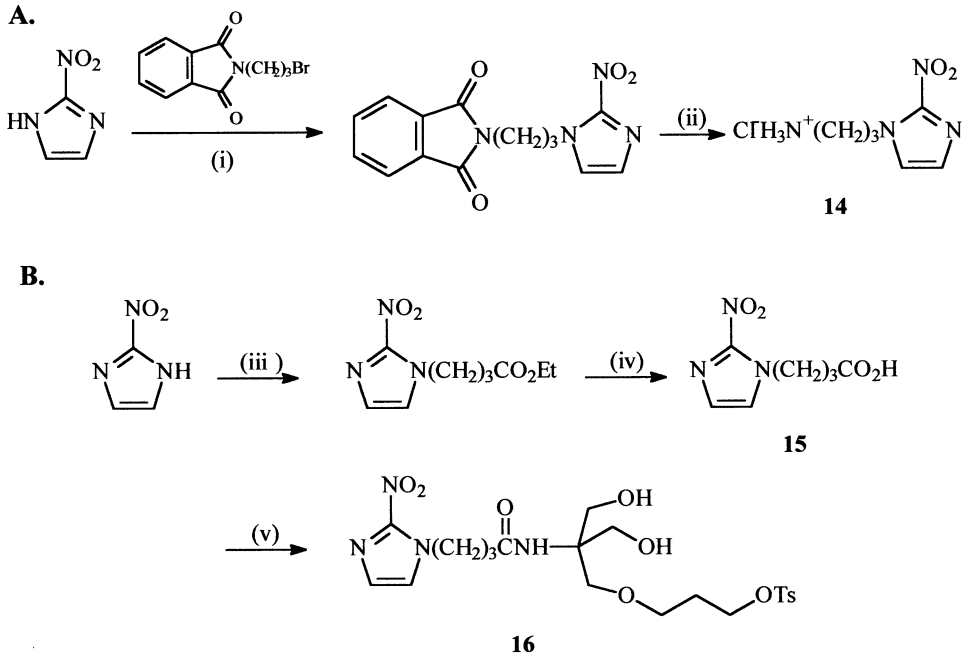



**Scheme 1.** (i) PhCHO, toluene, 65%; (ii) $Br(CH_2)_2CO_2Et$, powdered NaOH, TAH, toluene, 70%; (iii) $LiAlH_4$, THF, 95%; (iv) TsCl, DMAP, TEA, $CH_2Cl_2$, 79%; (v) HCl/MeOH 0.1N, 50°C, 98%; (vi) $H_2C{=}CHCOCl$, TEA, $CH_2Cl_2$, 65%; (vii) MeONa/MeOH; (viii) Amberlite IRC50, 98%; (ix) $H_2C{=}CHCOCl$, KOH/MeOH, 80%; (x) DMP, $CH_3SO_3H$, acetonitrile, 92%; (xi) $Br(CH_2)_2CO_2Et$, powdered NaOH, TAH, $CH_2Cl_2$, 50%; (xii) NaOH 2N then HCl 1N, 89%; (xiii) $Cl^-H_3N^+(CH_2)_3NIM$ (**14**), DMAP, DCC, $CH_2Cl_2$, 45%.

subcellular distribution making them suitable for various purposes involving either oral or intravenous administration.[8,10–12] The following information is particularly interesting in the context of our goal:

1. Pharmacokinetic studies achieved on a $^{14}C$-labeled telomer derived from tris(hydroxymethyl)acrylamidomethane (THAM) have shown that the molecule was widely distributed in rats after both i.v. and p.o. administration. They also displayed a reasonably long half-life time in both plasma and tissues. In contrast, no trace of radioactivity was detected in the brain.[11]
2. Cell uptake and subcellular distribution of a fluorinated telomer derived from THAM was investigated in two cell lines, malignant B16 melanoma and normal rat skin fibroblasts by ion microscopy using mass spectrometry detection.[12] This microanalytical method showed an elective cytoplasmic localization of the molecules with a relatively homogenous distribution. The telomer easily crossed the plasma membrane. However, it had




**Scheme 2.** (i) $K_2CO_3$, DMF, 94%; (ii) $NH_2NH_2$, EtOH, 73%; (iii) $Br(CH_2)_3CO_2Et$, $K_2CO_3$, DMF, 89%; (iv) HCl 1N, 89%; (v) **6**, DMAP, DCC, TEA, $CH_2Cl_2$, 41%.

difficulties in crossing the nuclear membrane.[12] Moreover, results that substantiate the potential of telomers as drug carriers have recently been reported.[13,14]

## 2. Results and discussion

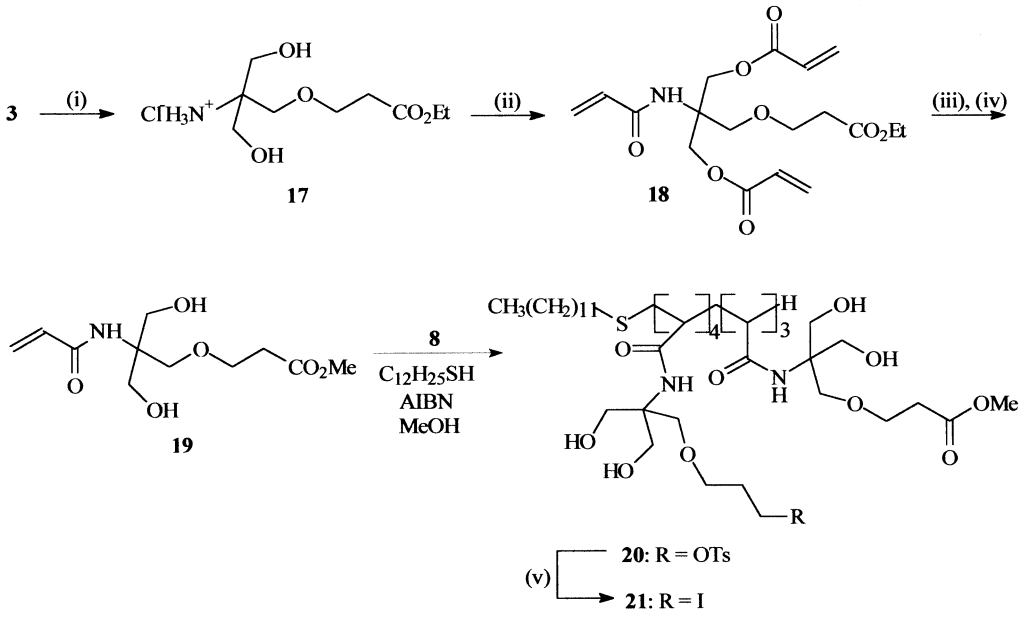
The ultimate goal of our work is the synthesis of a telomeric conjugate **22** (**23**) from polymerizable monomers **8** and **13** and alkanethiol (Scheme 4). Radiohalogen ($^{123}I$) will be introduced in a final step, by substitution of tosyl groups by iodine on treatment with $^{123}INa$ in acetone. The results reported here aim to demonstrate the feasibility of this approach.

The synthetic routes to monomers **8** and **13** are presented in Scheme 1. Although apparently very simple, tris(hydroxymethyl)aminomethane (TRIS, **1**) proved much more difficult to handle than expected. This is due to (i) the presence of three identical hydroxymethyl groups along with that of a primary amino group on the same carbon, (ii) the neopentylic character of the three methylene carbons, making substitution on that position ineffective. Accordingly, we anticipated that the best chemical approach should rely on the nucleophilicity of both the amino and hydroxyl functions, provided the selective protection and deprotection of these groups are possible.

With these constraints in mind, we prepared *cis*-2,8-diphenyl-5-hydroxymethyl-1-aza-3,7-dioxabicyclo[3.3.0.]-octane (**2**)[15–17] which allowed in only one step the simultaneous protection of two hydroxymethyl and amino groups. The stereochemistry of **2** was established based on its proton and $^{13}C$ NMR spectra and on its X-ray crystal structure.[16] The remaining hydroxymethyl group was condensed according to a solid–liquid phase transfer catalysis procedure with ethyl 3-bromopropionate in the presence of powdered sodium hydroxide and tetrabutylammonium sulfate in toluene to afford *cis*-2,8-diphenyl-5-(4′-ethoxycarbonyl-2′-oxabutyl)-1-aza-3,7-dioxabicyclo[3.3.0] octane (**3**) in 70% yield. It should be noted that the dichloromethane initially used as solvent of the reaction was replaced by toluene. This was due to the production of a variable amount of the condensation product of dichloromethane with two moles of compound **2**. This by-product was unambiguously identified based on its elemental analysis, MS, $^{13}C$ and $^{1}H$ NMR spectra. Treatment of **3** with lithium aluminum hydride converted the starting material into *cis*-2,8-diphenyl-5-(5′-hydroxy-2′-oxapentyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane (**4**), in 95% yield.

Compound **4** was reacted with *para*-toluenesulfonyl chloride to afford the key-intermediate **5**, the remote precursor of the polymerizable synthon **8**. Hydrolysis of the functionalized bicyclic intermediate **5** afforded the open-chain derivative **6** as hydrochloride. This was reacted with an excess of acryloyl chloride to produce the fully protected compound **7**. The acryloylester moieties were easily and selectively cleaved by treatment with sodium methoxide in methanol followed by acid resin neutralization to give the fully deprotected monomer **8** in very good yield (Scheme 1A).

Tris(hydroxymethyl)aminomethane (**1**) was converted into the acrylamidomethane derivative (**9**) on reaction with acryloyl chloride. The reaction of **9** with dimethoxypropane afforded 5-acrylamido-5-hydroxymethyl-2,2-dimethyl-1,3-dioxane (**10**) in high yield (92%). The latter was further reacted with ethyl 3-bromopropionate according to a solid phase transfer catalysis procedure to afford 5-acrylamido-5-(4′-(ethoxycarbonyl)-2′-oxabutyl)-2,2-dimethyl-1,3-dioxane (**11**). The acid produced on saponification of **11** with sodium hydroxide was then reacted with the 3′-aminopropyl




**Scheme 3.** (i) HCl/MeOH 0.1N, 95%; (ii) $H_2C{=}CHCOCl$, TEA, $CH_2Cl_2$, 60%; (iii) MeONa/MeOH; (iv) Amberlite IRC50, 98%; (v) NaI, acetone, reflux.

derivative of 2-nitroimidazole **14** to give the monomer **13** (Scheme 1B). The key 3-(2′-nitro-1*H*-imidazolyl)-propylamine hydrochloride (**14**) was prepared by alkylation of 2-nitroimidazole with *N*-(3-bromopropyl)phthalimide followed by treatment of the condensation product with hydrazine monohydrate according to known procedure[4] (Scheme 2A).

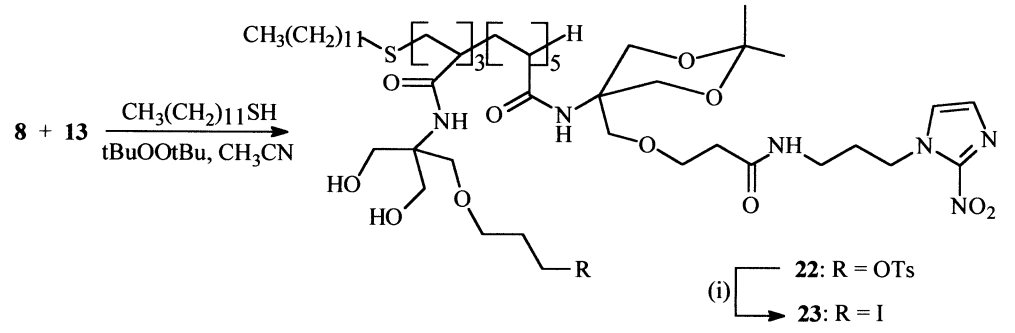
Before proceeding to telomerization, we decided to synthesize a simple ligand **16** derived from tris(hydroxymethyl)-aminomethane carrying only one nitroimidazole marker which will serve subsequently as a probe. The purpose was to assess the enhancement (if any) of the bioactivity of a telomeric multifunctional ligand in comparison to the reference compound **16**. The condensation of 2-nitroimidazole (NIM) with ethyl 4-bromobutanoate at 110°C followed by acid hydrolysis gave 4-(2′-nitro-1*H*-imidazolyl)butanoic acid (**15**) which was further reacted with compound **6** to produce compound **16** (Scheme 2B).

The feasibility of the exchange of the tosyl group by iodine was assessed on compound **20**. Monomer **19** was first prepared as shown in Scheme 3. Hydrolysis of compound **3** followed by peracryloylation of the intermediate **17** led to compound **18**, which in turn was easily converted into the polymerizable monomer **19** on treatment with sodium methoxide in methanol followed by neutralization on an exchange resin to leave the expected methyl ester derivative **19**, in good yield.

Monomers **8** and **19** were allowed to react at 80°C in methanol under a nitrogen atmosphere in the presence of a catalytic amount of α,α′-(azobis)-isobutyronitrile (AIBN), according to known procedures.[7–9] The relative proportion of the telogen agent (dodecanethiol) and monomers was set according to the expected average degree of polymerization ($DP_n$).

The structure of **20** was assigned by $^1H$ NMR spectroscopy (in DMSO-$d_6$). The average degree of polymerization was determined by comparing the area of the signal ascribed to the terminal methyl group (distinct triplet at $\delta$ 0.85) to that ascribed to methine protons (broad singlet at $\delta$ 4.70).

Comparison of terminal methyl peak with that of the aromatic protons (AB pattern at $\delta$ 7.10 and 7.50) of the tosyl group allowed the evaluation of the number of tosyl residues linked to the hydrocarbon backbone to 4. Based on this difference, the number of methyl ester residues was estimated at 3. This was corroborated by the relative

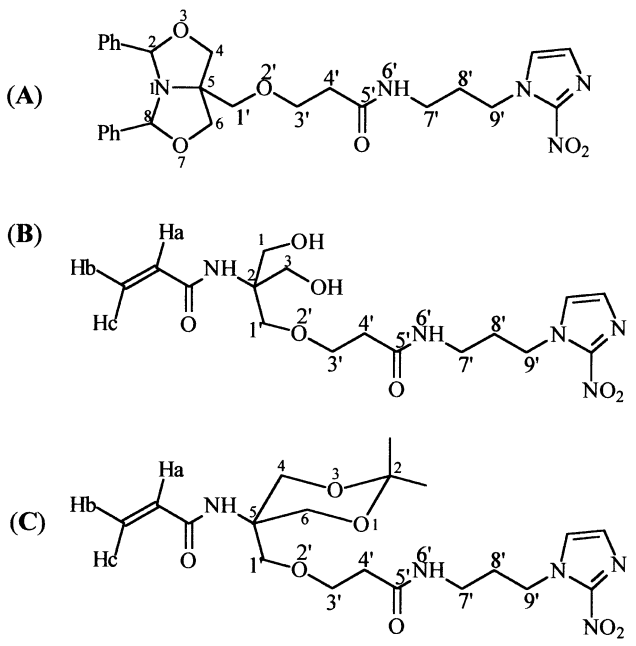



**Scheme 4.** (i) NaI, acetone, reflux.

intensity of the methoxy signal at $\delta$ 3.65. Compound **20** was treated with sodium iodide in refluxing acetone for 5 h. After usual treatment and purification, the $^1$H NMR spectrum of **21** showed the absence of aromatic protons.

However, due to the poor solubility of **13** in methanol, attempts to prepare a cotelomer derived from synthons **8** and **13** was unsuccessful when using experimental conditions applied previously to the synthesis of **20**. We decided to work at 120°C, in a sealed tube, using acetonitrile as solvent. Telomerization of synthons **8** and **13** (Scheme 4) was achieved as mentioned earlier in the presence of a catalytic amount of *tert*-butylperoxide as an initiator and of dodecanethiol to afford telomer **22** in good yield (≥50%). Careful examination of the $^1$H NMR spectrum allowed us to determine the average number of tosyl and NIM moieties to, respectively, 3 and 5. The exchange of the tosyl groups by iodine was achieved on treatment of compound **22** with sodium iodide in refluxing acetone within 5 h. The $^1$H NMR spectrum of **23** showed the absence of the aromatic protons.

Both compounds **16** and **22** will be submitted to biological evaluation after conversion into the $^{123}$I derivatives. This work is currently in progress.




**Scheme 5.**

## 3. Conclusion

In conclusion, we have shown that cotelomers containing both an affinity marker (NIM) and a radioactive tracer ($^{123}$I) can be prepared from monomers derived from biocompatible tris(hydroxymethyl)aminomethane. Telomerization of such monomers in the presence of dodecanethiol and of either AIBN or *tert*-butylperoxide followed by an exchange reaction afforded the desired iodine-labeled conjugates. The latter which were designed with the purpose to target hypoxic tissues and tumors are currently undergoing biological evaluation.

## 4. Experimental

### 4.1. General procedures

The progress of reactions and the homogeneity of compounds were monitored by thin layer chromatography (TLC Merck 254). Detection was achieved by exposure to UV light (254 nm) or by spraying a 1% potassium permanganate aqueous solution or a 5% ninhydrin ethanolic solution followed by heating at 150°C. Purifications were performed on column chromatography over silica gel (Merck 60) or on permeation gel Sephadex® LH 20 (Pharmacia LKB). Melting points were measured on a Büchi 530 apparatus and are reported uncorrected. The $^1$H and $^{13}$C NMR spectra were recorded at 200, 250 or 400 MHz on a Bruker apparatus. Chemical shifts are given in ppm relative to tetramethylsilane using the deuterium signal of the solvent as a heteronuclear reference for $^1$H and $^{13}$C. Coupling constants are given in Hz. Elemental analyses were performed by the Service Central de Microanalyse du CNRS at Vernaison (France). Ultrasound activations were performed by pulse method with a Vibra Cell 75022 (Bioblock Scientific).

Reactions were achieved in anhydrous conditions under dry nitrogen. All solvents were distilled and dried according to standard procedures. For the telomerization, the solutions were carefully deoxygenated by nitrogen bubbling before use. AIBN was purified by recrystallization from absolute ethanol (twice).

### 4.2. Atom numbering

Compounds **2**–**5** are considered as derivatives of *cis*-2,8-diphenyl-1-aza-3,7-dioxa- bicyclo[3.3.0]octane, atoms will be numbered accordingly (see formula A, Scheme 5). Open chain compounds (**6**–**8**, **16**, **17**–**19**) will be treated as derivatives of propane-1,3-diol as exemplified in formula B. Compounds **10**–**13** are considered as 1,3-dioxane derivatives as depicted in formula C.

**4.2.1. *cis*-2,8-Diphenyl-5-hydroxymethyl-1-aza-3,7-dioxa-bicyclo[3.3.0]octane (2).** Tris(hydroxymethyl)aminomethane (10 g, 82.5 mmol) and benzaldehyde (16.8 mL, 165 mmol) were poured into a 500 mL round flask containing 100 mL of hot (80–100°C) xylene, fitted with a Dean and Stark apparatus. The mixture was refluxed until the expected amount of water was recovered in the graduated tube (4–5 h). The xylene was removed under reduced pressure, the oily residue dissolved in hot diethylether followed by filtration to remove the unreacted material (Tris). The filtrate was evaporated to dryness and the solid residue purified by recrystallization from diethylether. Pure **2** was obtained as a white solid (15.9 g, 65%; mp 91–92°C, lit. 93–95°C). The minor *trans* isomer was obtained after silica gel column chromatography (1:1 diethylether–petroleum ether, v/v) of the mother liquors as a white solid (2.0 g, ≈8%, mp: 104–106°C). *cis* Isomer: $^1$H NMR ($CDCl_3$) $\delta$: 1.70 (1H, s, OH); 3.40 (2H, s, 2H-9); 3.90 and 4.00 (4H, AB

system, q, 2H-4 and 2H-6, $J_{gem}$=8.8 Hz); 5.55 (2H, s, H-2, H-8); 7.25–7.45 (10H, m, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$: 66.0, 74.5, 75.5 (C-4, C-5, C-6, C-9); 98.0 (C-2, C-8); 127.0, 128.9, 129.1 and 140.0 (aromatic carbons). *trans* Isomer: $^1$H NMR ($CDCl_3$) $\delta$: 2.40 (1H, t, OH, $J$=5.8 Hz); 3.70 and 3.75 (2H, AB system, q, H-9, $J_{gem}$=11.1 Hz); 3.88 and 3.92 (2H, AB system, q, 2H-4, $J_{gem}$=8.8 Hz); 4.15 and 4.19 (2H, AB system, q, 2H-6, $J_{gem}$=9.7 Hz); 5.30 and 5.50 (2H, 2s, H-2, H-8); 7.20–7.45 (10H, m, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$: 65.0, 72.0, 74.5, 75.0 (C-4, C-5, C-6, C-9); 93.5, 95.0 (C-2, C-8); 127.3, 127.7, 128.3, 129.0, 134.5 and 140.5 (aromatic carbons); FAB$^+$ MS (NOBA) *m/z*: 298 [M+H]$^+$; 320; 266; Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.73; H, 6.40; N, 4.71; Found: C, 72.84; H, 6.41; N, 4.63.

**4.2.2. *cis*-2,8-Diphenyl-5-(4′-ethoxycarbonyl-2′-oxabutyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane (3).** To the mixture of powdered sodium hydroxide (0.34 g, 8.4 mmol) and tetrabutylammonium hydrogenosulfate (TAH) (0.03 g, 0.08 mmol) was added the solution of compound **2** (0.5 g, 1.7 mmol) in hot toluene (5 mL). Ethyl 3-bromopropanoate (0.43 mL, 3.4 mmol) was added dropwise and the reaction mixture subjected to ultrasound for 1 h. After addition of water (5 mL) and magnetic stirring for about 10 min, the organic layer was isolated by decantation and washed with a saturated solution of NaCl (3×5 mL), dried over sodium sulfate and evaporated. Recrystallization from ethyl acetate–petroleum ether gave a white solid material (0.47 g, 70%, mp 68°C). $^1$H NMR ($CDCl_3$) $\delta$: 1.20 (3H, t, 3H-8′, $J$=7.2 Hz); 2.40 (2H, t, 2H-4′, $J$=6.3 Hz); 3.35 (2H, s, 2H-1′); 3.55 (2H, t, 2H-3′, $J$=6.3 Hz); 3.8 and 3.95 (4H, AB system, q, 2H-4 and 2H-6, $J_{gem}$=9.0 Hz); 4.05 (2H, q, 2H-7′, $J$=7.2 Hz); 5.50 (2H, s, H-2, H-8); 7.30–7.50 (10H, m, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$: 15.0 (C-8′); 35.0 (C-4′); 61.0 (C-7′); 68. 7 (C-1′, C-3′); 74.0 (C-4, C-6); 75.5 (C-5); 98.0 (C-2, C-8); 127.6, 128.7, 129.0 and 140.0 (aromatic carbons); 172.0 (C-5′); FAB$^+$ MS (NOBA) *m/z*: 398 |M+H]$^+$; 266; Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.08; H, 6.91; N, 3.36; Found: C, 69.52; H, 6.80; N, 3.53.

**4.2.3. *cis*-2,8-Diphenyl-5-(5′-hydroxy-2′-oxapentyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane (4).** A solution of compound **3** (0.2 g, 0.5 mmol) in anhydrous THF (3 mL) was added dropwise to a suspension of $LiAlH_4$ (0.04 g, 1 mmol) in anhydrous THF (5 mL) under cooling (0°C). Stirring was maintained for 1 h. A solution of 10% aqueous sodium hydroxide (2 mL) and ether (10 mL) were successively added. The phases were separated. The organic phase was washed with a saturated aqueous solution of NaCl. The aqueous phase was extracted with diethylether (3×5 mL). The organic layer obtained was dried over sodium sulfate, the solvent was removed under vacuum to leave a white solid (0.17 g, 95%, mp 66–68°C). $^1$H NMR ($CDCl_3$) $\delta$: 1.70 (2H, m, 2H-4′); 1.90 (1H, s, OH); 3.40 (2H, s, 2H-1′); 3.50 (2H, t, 2H-3′, $J$=5.8 Hz); 3.70 (2H, t, 2H-5′, $J$=5.8 Hz); 3.90 and 4.05 (4H, AB system, q, 2H-4, 2H-6, $J_{gem}$=8.9 Hz); 5.55 (2H, s, H-2, H-8); 7.30–7.55 (10H, m, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$: 32.5 (C-4′); 62.1 and 71.0 (C-1′, C-3′); 74.2 (C-4, C-6); 76.0 (C-5); 97.5 (C-2, C-8); 127.5, 128.5, 129.0 and 140.0 (aromatic carbons); FAB$^+$ MS (NOBA) *m/z*: 356 [M+H]$^+$; 266; Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.98; H, 7.04; N, 3.94; Found: C, 70.27; H, 7.04; N, 3.78.

**4.2.4. *cis*-2,8-Diphenyl-5-(2′-oxa-5′-tosyloxypentyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane (5).** To the solution of compound **4** (0.4 g, 1.1 mmol) in $CH_2Cl_2$ (5 mL) at 20°C were successively added triethylamine (0.2 mL, 1.35 mmol), tosyl chloride (0.26 g, 1.35 mmol) and DMAP (20 mg, 0.13 mmol). The reaction mixture was allowed to react at rt for about 4 h then filtered over celite. After dilution with $CH_2Cl_2$ (10 mL), the organic phase was washed with a saturated sodium chloride solution, dried over sodium sulfate and evaporated to dryness. The residue was purified on a silica gel column (80:20 petroleum ether–AcOEt, v/v). Compound **5** was isolated as an oil (0.5 g, 87%). $^1$H NMR ($CDCl_3$) $\delta$: 1.80 (2H, t, 2H-4′); 2.45 (3H, s, $CH_3$–Ts); 3.30 (2H, s, 2H-1′); 3.35 (2H, t, 2H-3′); 3.82 and 3.95 (4H, AB system, q, 2H-4, 2H-6); 4.05 (2H, t, 2H-5′); 5.55 (2H, s, H-2, H-8); 7.30–7.80 (14H, m, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$: 22 ($CH_3$); 29.0 (C-4′); 67.0 (C-5′); 67.5, 73.5 (C-1′, C-3′); 74.1 (C-4, C-6); 76.0 (C-5); 98.0 (C-2, C-8); 127.5, 128.5, 128.5, 129.5; 130.0, 133.4, 140.0 and 145.0 (aromatic carbons); FAB$^+$ MS (NOBA) *m/z*: 510 [M+H]$^+$; 266; 91; Anal. Calcd for $C_{28}H_{31}NO_6S$: C, 66.01; H, 6.09; N, 2.75; Found: C, 65.50; H, 6.29; N, 2.68.

**4.2.5. 2-Amino-2-(2′-oxa-5′-tosyloxypentyl)propan-1,3-diol hydrochloride (6).** A suspension of compound **5** (0.48 g, 0.9 mmol) in a 1N HCl methanolic solution (10 mL) was heated until homogeneous and heating was prolonged for further 15 min. After cooling, the reaction mixture was concentrated. The aqueous phase was then extracted with $CH_2Cl_2$ (3×5 mL) and subjected to freeze drying. The title compound was obtained as an oily material (0.34 g, 98%). $^1$H NMR ($D_2O$) $\delta$: 1.80 (2H, t, 2H-4′); 2.35 (3H, s, $CH_3$–Ts); 3.45 (6H, m, 2H-1, 2H-3, 2H-1′); 4.05 (2H, t, 2H-3′); 7.35 and 7.50 (4H, AB system, 4H–Ts); $^{13}$C NMR ($D_2O$) $\delta$: 31.0 ($CH_3$); 28.5 (C-4′); 60.0 (C-5′); 61.0 (C-2); 67.5 and 69.5 (C-1′, C-3′); 68.0 (C-1, C-3); 128.5, 130.5, 131.0 and 147.0 (aromatic carbons); FAB$^+$ MS (NOBA) *m/z*: 334 [M+H]$^+$; 302; 155.

**4.2.6. 2-Acrylamido-2-(2′-oxa-5′-tosyloxypentyl)propan-1,3-diol (8).** To a solution of **6** (0.34 g, 0.9 mmol) in anhydrous $CH_2Cl_2$ (10 mL) at 0°C were added successively acryloyl chloride (0.45 mL, 5.5 mmol), catalytic amount of sodium nitrite and triethylamine (1 mL, 7.4 mmol). After stirring 4 h at rt the reaction mixture was washed successively with water (8 mL), 1N HCl (8 mL) and water (8 mL). After drying and evaporation to dryness the oily residue was purified by silica gel column chromatography (20:80 petroleum ether–AcOEt, v/v) to leave 1,3-di-*O*-acryloyl-2-acrylamido-2-(2′-oxa-5′-tosyloxypentyl)propan-1,3-diol (**7**) as an oil (0.3 g, 65%). Compound **7** (0.39 g, 0.8 mmol) dissolved in anhydrous methanol (8 mL) was treated by a catalytic amount of sodium methoxide for 1 h at rt. The reaction mixture was then stirred in the presence of H$^+$ resin Amberlite IRC 50 until pH 6. Subsequent filtration and evaporation afforded the title compound as an oil (0.3 g, 98%). $^1$H NMR (acetone-$d_6$) $\delta$: 1.90 (2H, m, 2H-4′); 2.50 (3H, s, $CH_3$–Ts); 2.90 (2H, s, 2OH); 3.50 (2H, t, 2H-3′), 3.55 (2H, s, 2H-1′); 3.60 and 3.70 (4H, AB system, 2H-1, 2H-3); 4.20 (2H, t, 2H-5′); 5.60 and 5.65 (1H, dd, $J_{cis}$=9.8 Hz, $J_{gem}$=2.4 Hz, $H_b$); 6.18 and 6.25 (1H, dd, $J_{tr}$=16.9 Hz, $H_c$); 6.40 and 6.45 (1H, dd, $H_a$); 7.05 (s, 1H,

NH); 7.50 and 7.80 (4H, AB system, 4H–Ts); $^{13}$C NMR ($CD_3OD$) $\delta$: 21.0 ($CH_3$); 29.0 (C-4′); 61.5 (C-5′); 61.7 (C-2); 66.0 and 69.0 (C-1′, C-3′); 68.0 (C-1, C-3); 126.0 ($CH_2$=); 128.0, 129.0, 133.5 and 145.5 (aromatic carbons); 131.5 (=CH); FAB$^+$ MS (NOBA) *m/z*: 388 $[M+H]^+$; 370; 91; 55; Anal. Calcd for $C_{17}H_{25}NO_7S$: C, 52.71; H, 6.46; N, 3.62; Found: C, 52.41; H, 6.60; N, 3.47.

**4.2.7. Tris(hydroxymethyl)acrylamidomethane (9).** Acryloyl chloride (1.2 mL, 14.8 mmol) was added to tris(hydroxymethyl)aminomethane (Tris) (1 g, 8.2 mmol) in methanol (8 mL) under nitrogen atmosphere. The pH was maintained at 7–8 upon addition of a KOH/MeOH 3N solution. After 3 h, the reaction mixture was filtered and the filtrate evaporated. The oily residue was chromatographed on a silica gel column (80:20, AcOEt–MeOH, v/v) to afford compound (**9**) (1.15 g, 80%, mp 136–137°C) as a white solid. $^1$H NMR (DMSO-$d_6$) $\delta$: 3.60 (6H, d, $2CH_3$); 4.80 (3H, t, 3OH, $J$=6.0 Hz); 5.60 (1H, dd, $J_{cis}$=10.0 Hz, $J_{gem}$=2.3 Hz, $H_b$); 6.00 (1H, dd, $J_{tr}$=16.9 Hz, $H_a$); 6.40 (1H, dd, $H_c$); 7.45 (1H, s, NH); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 61.0 (C-2, C-3, C-4); 63.0 (C-1); 126.0 ($CH_2$=); 133.5 (=CH); 166.0 (C=O); FAB$^+$ MS (NOBA) *m/z*: 176 $[M+H]^+$; 198.

**4.2.8. 5-Acrylamido-5-hydroxymethyl-2,2-dimethyl-1,3-dioxane (10).** 2,2-Dimethoxypropane (4.2 mL, 34.3 mmol) was added at rt to THAM (5 g, 28.6 mmol) in acetonitrile (150 mL) in the presence of catalytic amount of methanesulfonic acid. After 3 h, the reaction mixture was evaporated. The residue was then dissolved in $CH_2Cl_2$. The organic layer was washed with water (2×10 mL) and dried over sodium sulfate. After evaporation, a white solid was obtained (5.7 g, 92%, mp 88°C). $^1$H NMR ($CDCl_3$) $\delta$: 1.45 (6H, s, $2CH_3$); 3.75 (2H, d, 2H-7); 3.85 and 3.95 (4H, AB system, 2H-4, 2H-6); 5.10 (1H, s, OH); 5.75 (1H, dd, $J_{cis}$=10.0 Hz, $J_{gem}$=2.0 Hz, $H_b$); 6.20 (1H, dd, $J_{tr}$=16.0 Hz, $H_a$); 6.35 (1H, dd, $H_c$); $^{13}$C NMR ($CDCl_3$) $\delta$: 19.5 and 28.0 ($CH_3$); 56.5 (C-7); 64.7 and 64.8 (C-4, C-5, C-6); 99.0 (C-2); 128.0 ($CH_2$=); 131.0 (=CH); 167.0 (C=O); FAB$^+$ MS (NOBA) *m/z*: 216 $[M+H]^+$; 238; 158; Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.81; H, 7.90; N, 6.51; Found: C, 55.95; H, 7.90; N, 6.60.

**4.2.9. 5-Acrylamido-5-(4′-(ethoxycarbonyl-2′-oxabutyl)-2,2-dimethyl-1,3-dioxane (11).** To the mixture of powdered sodium hydroxide (0.93 g, 23.2 mmol) and TAH (0.08 g, 0.23 mmol) was added the solution of compound **10** (1 g, 4.6 mmol) in hot $CH_2Cl_2$ (10 mL). Ethyl 3-bromopropanoate (1.2 mL, 9.3 mmol) was added dropwise. After 3 h, 3 mL of water was added. The organic layer was separated by decantation and washed with a saturated solution of NaCl (3×15 mL), dried over sodium sulfate and evaporated. The oily residue was chromatographed on a silica gel column (50:50, ethyl acetate–petroleum ether, v/v) to afford the title compound (0.74 g, 50%). $^1$H NMR ($CDCl_3$) $\delta$: 1.20 (3H, s, 3H-8′); 1.30 (3H, s, $CH_3$); 1.50 (3H, s, $CH_3$); 2.50 (2H, t, 2H-4′); 3.65 and 4.45 (4H, AB system, 2H-4, 2H-6); 3.7 (2H, t, 2H-3′); 3.75 (2H, s, 2H-1′); 4.10 (2H, q, 2H-7′); 5.55 (1H, dd, $J_{cis}$=9.5 Hz, $J_{gem}$=2.0 Hz, $H_b$); 6.10 (1H, dd, $J_{tr}$=16.9 Hz, $H_a$); 6.20 (1H, dd, $H_c$); 6.15 (1H, s, NH); $^{13}$C NMR ($CDCl_3$) $\delta$: 15.0 (C-8′); 22.5 and 26.0 ($CH_3$); 35.5 (C-4′); 54.0 (C-7′); 61.0 (C-5); 62.0 (C-4, C-6); 67.0 and 71.2 (C-1′, C-3′); 99.5 (C-2); 127.0 ($CH_2$=); 132.2 (=CH); 166.5 (C=O); 172.0 (C-5′); FAB$^+$ MS (NOBA) *m/z*: 316 $[M+H]^+$; 338; 258; Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.14; H, 7.94; N, 4.44; Found: C, 57.15; H, 8.03; N, 4.48.

**4.2.10. 5-Acrylamido-5-(4′-carboxy-2′-oxabutyl)-2,2-dimethyl-1,3-dioxane (12).** Aqueous 2N sodium hydroxide (2.5 mL) was added to compound **11** (0.1 g, 0.3 mmol). After vigorous stirring (1 h) the aqueous layer was extracted twice with diethylether (2.5 mL) and adjusted at pH 2 by addition of 2N aqueous HCl followed by extraction with ethyl acetate (4×10 mL). After drying over sodium sulfate and evaporation, compound **12** was obtained as a white solid (0.08 g, 89%, mp: 108–109°C). $^1$H NMR ($CDCl_3$) $\delta$: 1.40 (3H, s, $CH_3$); 1.50 (3H, s, $CH_3$); 2.60 (2H, t, 2H-4′); 3.75 (2H, t, 2H-3′); 3.85 (2H, s, 2H-1′); 3.80 and 4.40 (4H, AB system, 2H-4, 2H-6); 5.60 (1H, dd, $J_{cis}$=9.8 Hz, $J_{gem}$=1.8 Hz, $H_b$); 6.10 (1H, dd, $J_{tr}$=16.9 Hz, $H_a$); 6.20 (1H, s, NH); 6.25 (1H, dd, $H_c$); $^{13}$C NMR ($CDCl_3$) $\delta$: 23.2 and 25.5 ($CH_3$); 35.0 (C-4′); 54.3 (C-5); 63.2 (C-4, C-6); 67.0 and 71.0 (C-1′, C-3′); 99.5 (C-2); 128.0 ($CH_2$=); 131.5 (=CH); 166.5 (C=O); 176.0 ($CO_2H$); FAB$^+$ MS (NOBA) *m/z*: 288 $[M+H]^+$; 310; 230; Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.32; N, 4.87; Found: C, 53.78; H, 7.38; N, 4.84.

**4.2.11. 5-Acrylamido-5-(6′-aza-9′-(2-nitro-1*H*-imidazolyl)-2′-oxa-5′-oxononyl)-2,2-dimethyl-1,3-dioxane (13).** To the suspension of compound **14** (0.13 g, 0.6 mmol) in anhydrous $CH_2Cl_2$ (10 mL) cooled at 0°C were added successively DMAP (70 mg, 0.06 mmol), *N*-ethylmorpholine (0.1 mL, 0.6 mmol), acid **12** (0.15 g, 0.5 mmol) and finally DCC (0.13 g, 0.6 mmol). The reaction mixture was allowed to react 1 h at 0°C then 12 h at rt. After filtration over a bed of celite followed by addition of $CH_2Cl_2$ (10 mL) the organic layer was washed successively with a citric acid aqueous solution (2×5 mL), saturated sodium carbonate solution (2×5 mL) and water (2×5 mL). After drying over sodium sulfate and evaporation, the oily residue was chromatographed on a silica gel column (95:5, AcOEt–MeOH, v/v) to afford the title compound (0.1 g, 45%) as an oil. $^1$H NMR ($CD_3OD$) $\delta$: 1.40 (3H, s, $CH_3$); 1.50 (3H, s, $CH_3$); 2.00 (2H, m, 2H-8′); 2.50 (2H, t, 2H-4′); 3.35 (2H, q, 2H-7′); 3.75 (2H, t, 2H-3′); 3.80 and 4.30 (4H, AB system, 2H-4, 2H-6); 3.85 (2H, s, 2H-1′); 4.45 (2H, t, 2H-9′); 5.60 and 5.65 (1H, dd, $J_{cis}$=8.8 Hz, $J_{gem}$=2.9 Hz, $H_b$); 6.15 and 6.20 (1H, dd, $J_{tr}$=16.9 Hz, $H_a$); 6.25 (1H, s, NH); 6.50 (1H, t, H-6′); 7.15 and 7.30 (2H, d, $J$=1.0 Hz, 2H of NIM); $^{13}$C NMR ($CD_3OD$) $\delta$: 31.0 (C-8′); 34.0 (C-9′); 48.5 (C-7′); 54.0 (C-5); 63.2 (C-4, C-6); 68.0 and 71.5 (C-1′, C-3′); 99.0 (C-2); 127.0 ($CH_2$=); 129.5 (CH of nitroimidazole); 131.5 (=CH); 145.0 (C–$NO_2$); 166.0 (C=O); 172.5 (C-5′); FAB$^+$ MS (NOBA) *m/z*: 440 $[M+H]^+$; 462; 382; 55; Anal. Calcd for $C_{19}H_{29}N_5O_7$: C, 51.94; H, 6.60; N, 15.94; Found: C, 52.37; H, 6.52; N, 15.77.

**4.2.12. 3-(2′-Nitro-1*H*-imidazolyl)-propylamine hydrochloride (14).** To a solution of 2-nitro-imidazole (0.1 g, 0.9 mmol) in DMF (2.5 mL) were added *N*-(3-bromopropyl)phthalimide (0.25 g, 0.9 mmol) and potassium carbonate (0.13 g, 0.9 mmol). The reaction mixture was heated to 110°C for 2 h. After cooling and DMF evaporation, the solid residue was washed with water (6 mL). Filtration left a white solid (0.25 g, 94%, mp 203°C)

which was identified as the *N*-(3-(2′-nitro-1*H*-imidazolyl)-propyl)phthalimide. A stirred suspension of this compound (0.2 g, 0.7 mmol) in ethanol (5 mL) and hydrazine monohydrate (0.06 mL, 1.3 mmol) were heated under reflux for 2 h. The resulting suspension was cooled to 0°C then filtered and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in 1N HCl (3 mL) and filtered, the solvent was removed under reduced pressure to give the title compound (0.1 g, 73%, mp 214°C) after recrystallization from a mixture of methanol–ethyl acetate. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.10 (2H, m, 2H-2′); 2.75 (2H, m, 2H-3′); 4.45 (2H, t, 2H-1′); 7.20 (1H, s, H-4(H-5)); 7.80 (1H, s, H-5(H-4)); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 28.3 (C-2′); 36.7 (C-3′); 47.5 (C-1′); 128.7 and 128.8 (C-4, C-5); 145.5 (C-2); FAB$^+$ MS (NOBA) *m/z*: 171 [M]$^+$; 192; Anal. Calcd for $C_6H_{11}ClN_4O_2$: C, 34.95; H, 5.34; O, 15.53; Found: C, 34.33; H, 5.30; O, 15.22.

**4.2.13. 4-(2-Nitro-1*H*-imidazolyl)butanoic acid (15).** To a solution of NIM (0.5 g, 4.4 mmol) in DMF (8 mL) were added ethyl 4-bromobutanoate (0.8 mL, 5.3 mmol) and potassium carbonate (0.73 g, 5.3 mmol). The reaction mixture was heated to 110°C for 2 h. After cooling and DMF evaporation, the residue was dissolved in ethyl acetate (20 mL). The organic layer was washed with water and dried over sodium sulfate. After evaporation, the residue was chromatographed on a silica gel column (ethyl acetate) to afford ethyl 4-(2-nitro-1*H*-imidazolyl)butanoate (0.9 g, 89%). A stirred suspension of this compound (0.9 g, 4 mmol) was treated with 1N hydrochloric acid (20 mL). After 24 h, the reaction mixture was extracted with ethyl acetate (3×20 mL). The organic layer was dried over sodium sulfate and evaporated to afford the title compound as a white solid (0.7 g, 89%, mp: 114–115°C). $^1$H NMR ($D_2O$) $\delta$: 2.05 (2H, m, 2H-2′); 2.35 (2H, t, 2H-3′); 4.40 (2H, t, 2H-1′); 7.05 (1H, s, H-4(H-5)); 7.35 (1H, s, H-5(H-4)); $^{13}$C NMR ($D_2O$) $\delta$: 27.0 (C-2′); 33.0 (C-3′); 52.5 (C-1′); 130.2 and 130.7 (C-4, C-5); 147.5 (C-2); 180.2 (C-4′); FAB$^+$ MS (NOBA) *m/z*: 200 [M+H]$^+$; 222; Anal. Calcd for $C_7H_9N_3O_4$: C, 42.21; H, 4.52; N, 21.10; Found: C, 41.90; H, 4.62; N, 21.17.

**4.2.14. 2-(*N*-4″-(2-nitro-1*H*-imidazolyl)butanoylamino)-2-(2′-oxa-5′-tosyloxypentyl)propan-1,3-diol (16).** To the suspension of compound **6** (0.4 g, 1.1 mmol) in anhydrous $CH_2Cl_2$ (10 mL) cooled at 0°C were added successively DMAP (0.16 g, 1.3 mmol), triethylamine (0.2 mL, 1.3 mmol), compound **15** (0.22 g, 1.1 mmol) and finally DCC (0.27 g, 1.3 mmol). The reaction mixture was allowed to react 1 h at 0°C then 12 h at rt. After filtration over a bed of celite followed by addition of $CH_2Cl_2$ (10 mL), the organic layer was washed successively with aqueous citric acid solution (2×5 mL), saturated sodium carbonate solution (2×5 mL) and water (2×5 mL). After drying over sodium sulfate and evaporation, the oily residue was chromatographed on a silica gel column (95:10, AcOEt–MeOH, v/v) to afford the title compound (0.23 g, 41%) as an oil. $^1$H NMR ($CD_3OD$) $\delta$: 1.90 (2H, m, 2H-4′); 2.15 (2H, m, 2H-3″); 2.30 (2H, m, 2H-2″); 2.45 (3H, s, $CH_3$–Ts); 3.50 (2H, t, 2H-1′(2H-3′)); 3.55 (2H, t, 2H-3′(2H-1′)); 3.70 (4H, s, 2H-1, 2H-3); 4.15 (2H, t, 2H-5′); 4.50 (2H, t, 2H-4″); 4.65 (1H, s, NH); 7.15 (2H, s, 2H of NIM); 7.50 and 7.80 (4H, AB system, 4H–Ts); $^{13}$C NMR ($CD_3OD$) $\delta$: 22.0 ($CH_3$); 29.0 (C-4′); 33.0 (C-3″); 34.5 (C-2″); 49.5 (C-4″); 63.0 (C-5′); 63.8 (C-2); 64.2 (C-1, C-3); 70.5 and 71.0 (C-1′, C-3′); 127.5 and 129.5 (C–NIM); 128.0, 130.5, 133.0, 145.5 (C–Ts); 145.0 (C–$NO_2$ of NIM); 175.5 (C-1″); FAB$^+$ MS (NOBA) *m/z*: 515 [M+H]$^+$; 537; 497; 402; Anal. Calcd for $C_{21}H_{30}N_4O_9S$: C, 49.03; H, 5.84; N, 10.89; Found: C, 48.70; H, 5.67; N, 11.04.

**4.2.15. 2-Amino-2-(4′-ethoxycarbonyl-2′-oxabutyl)propan-1,3-diol hydrochloride (17).** Compound **3** (0.2 g, 0.6 mmol) was treated as reported for compound **6** to afford the title compound as a white solid (0.12 g, 95%, mp 62°C). $^1$H NMR ($D_2O$) $\delta$: 1.35 (3H, t, 3H-8′); 2.75 (2H, t, 2H-4′); 3.70 (2H, s, 2H-1′); 3.80 (4H, s, 2H-1, 2H-3); 3.90 (2H, t, 2H-3′); 4.30 (2H, q, 2H-7′); FAB$^+$ MS (NOBA) *m/z*: 222 [M+H]$^+$; 244; Anal. Calcd for $C_9H_{20}ClNO_5$: C, 41.94; H, 7.77; N, 5.44; Found: C, 42.30; H, 7.67; N, 5.74.

**4.2.16. 2-Acrylamido-2-(4′-methoxycarbonyl-2′-oxabutyl)propan-1,3-diol (19).** To a solution of **17** (0.65 g, 2.5 mmol) in anhydrous $CH_2Cl_2$ (15 mL) at 0°C were added successively acryloyl chloride (1.2 mL, 5.2 mmol), catalytic amount of sodium nitrite and triethylamine (2.8 mL, 20.3 mmol). After stirring 4 h at rt the reaction mixture was washed successively with water (10 mL), 1N HCl (10 mL) and water (10 mL). After drying and evaporation to dryness the oily residue was purified by silica gel column chromatography (AcOEt) to leave 1,3-di-*O*-acryloyl-2-acrylamido-2-(4′-ethoxycarbonyl-2′-oxabutyl)propan-1,3-diol (**18**) as an oil (0.58 g, 60%). Compound **18** (0.3 g, 0.8 mmol) dissolved in anhydrous methanol (8 mL) was treated by catalytic amount of sodium methoxide for 1 h at rt. The reaction mixture was then stirred in the presence of H$^+$ resin Amberlite IRC 50 until pH 6. Subsequent filtration and evaporation afforded the title compound as an oil (0.2 g, 98%). $^1$H NMR (acetone-$d_6$) $\delta$: 2.60 (2H, t, 2H-4′); 3.30 (3H, s, 3H-7′); 3.60–3.75 (8H, m, 2H-1, 2H-3, 2H-1′, 2H-3′); 5.60 and 5.65 (1H, dd, $J_{cis}$=9.85 Hz, $J_{gem}$=2.3 Hz, $H_b$); 6.18 and 6.25 (1H, dd, $J_{tr}$=16.9 Hz, $H_c$); 6.40 and 6.50 (1H, dd, $H_a$); 7.10 (1H, s, NH); $^{13}$C NMR (acetone-$d_6$) $\delta$: 34.0 (C-4′); 51.0 (C-7′); 62.0 (C-2); 62.8 (C-1, C-3); 67.5 and 70.5 (C-1′, C-3′); 126.0 ($CH_2$=); 132.0 (=CH); 166.5 (C=O amide); 172.1 (C-5′); FAB$^+$ MS (NOBA) *m/z*: 262 [M+H]$^+$; 284; 244; 55; Anal. Calcd for $C_{11}H_{19}NO_6$: C, 50.57; H, 7.28; N, 5.36; Found: C, 50.40; H, 7.47; N, 5.24.

**4.2.17. Telomer 20.** Monomers **8** (0.27 g, 0.7 mmol) and **19** (0.18 g, 0.7 mmol) in methanol (10 mL) were heated under nitrogen at 80°C. Dodecanethiol (41 μL, 0.17 mmol) and AIBN (14 mg, 0.08 mmol) were added. After 8 h at 80°C, the reaction mixture was evaporated. The oily residue was precipitated in diethyl ether (40 mL). The yellow powder obtained was purified on Sephadex® LH-20 to afford the telomer **20** containing three residues **19** and four residues **8** (yield 50%). $^1$H NMR (DMSO-$d_6$) $\delta$: 0.85 (3H, t, $CH_3$ thioalkyl chain); 2.30 (3H, s, $CH_3$–Ts); 3.25–3.55 ($CH_2$); 3.65 ($OCH_3$); 4.70–5.20 (CH); 7.10 and 7.50 (4H, AB, 4H–Ts).

**4.2.18. Telomer 21.** Sodium iodide (0.2 g, 1.4 mmol) in anhydrous acetone (5 mL) was added to the telomer **20** (0.16 g, 0.17 mmol). After 5 h refluxing, the reaction mixture was evaporated. Ethyl acetate (8 mL) was added

to the residue, the organic layer was separated and evaporated to afford telomer **21** (0.12 g). $^1$H NMR (acetone-$d_6$) $\delta$: 0.85 (3H, t, $CH_3$ thioalkyl chain); 3.10–3.25 ($CH_2$); 3.50–3.80 (CH); 4.80 (NH).

**4.2.19. Telomer 22.** Monomers **8** (0.13 g, 0.35 mmol) and **13** (0.15 g, 0.35 mmol), dodecanethiol (16 μL, 0.07 mmol) and *tert*-butyl peroxide (6 μL, 0.08 mmol) in acetonitrile (10 mL) were heated in a sealed tube at 120°C. After 16 h at 120°C, the reaction mixture was evaporated. The oily residue was precipitated in diethylether (20 mL) to afford telomer **22** containing three residues **8** and five residues **13** (yield 50%). $^1$H NMR ($CD_3OD$) $\delta$: 0.95 (3H, t, $CH_3$ thioalkyl chain); 1.31 and 1.36 ($CH_3$ isopropylidene); 2.45 (3H, s, $CH_3$–Ts); 3.35–3.80 ($CH_2$); 4.70–5.52 (CH); 7.15 and 7.55 (2H, s, 2H–NIM); 7.45 and 7.80 (4H, AB system, 4H–Ts).

**4.2.20. Telomer 23.** Sodium iodide (0.05 g, 0.33 mmol) in anhydrous acetone (2.5 mL) was added to compound **22**. After 5 h refluxing, acetone was evaporated and ethyl acetate (5 mL) added to the residue. After decantation, the organic layer was evaporated to dryness to leave a residue, which was examined by NMR spectroscopy without any further purification. $^1$H NMR ($CD_3OD$) $\delta$: 0.95 (3H, t, $CH_3$ thioalkyl chain); 1.33 and 1.37 ($CH_3$ isopropylidene); 3.30–3.80 ($CH_2$); 4.70–5.25 (CH); 7.15 and 7.55 (2H, s, 2H–NIM).

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