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MACROCYCLIC ETHERS BY FREE RADICAL CYCLIZATIONS

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Abstract : Tin hydride reduction of ω-iodo-polyoxaalkyl acrylates **1** using syringe pump addition of both reactants to a solution of AIBN in benzene at 80°C afforded the corresponding cyclic polyethers in excellent yields.

Since their discovery by PEDERSEN,[1] macrocyclic ethers have been extensively used as complexing agents for metallic cations.[1,2] The various routes developed for their synthesis involve ionic processes.[3] Apart from free radical functionalizations of commercially available crown ethers,[4] we were unaware of any report of the formation of a macrocyclic polyether by a free radical process until 1996. The synthesis of macrolactones by free radical reduction of ω-iodoalkyl unsaturated esters by tributyltin hydride, first undertaken by PORTER et al,[5] prompted us to investigate the possible synthesis of macrocyclic ethers by the cyclization of analogous compounds having a polyethylene oxide chain in

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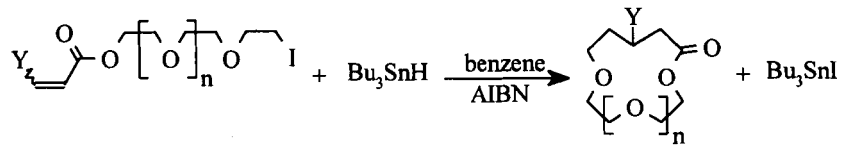
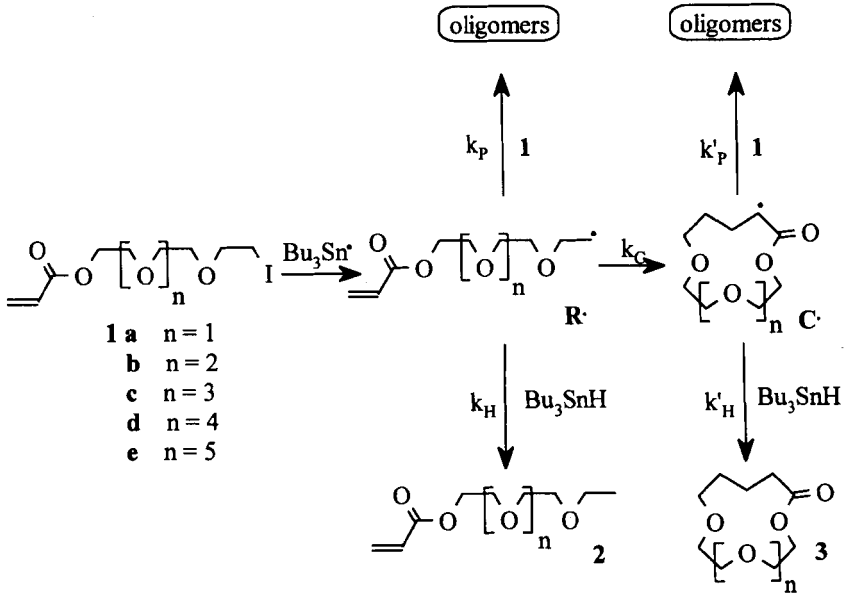
place of the alkyl one. In a preliminary communication in association with the Beckwith group, we identified the viability of such an approach (Y = H or CO_2Et, n = 2-5) (scheme 1).[6]



Scheme 1

The scheme 2, presented in the case of acrylic derivatives shows the different reactions in competition as well as the secondary compounds which could be produced besides the expected macrocycles.



Scheme 2

In order to produce essentially the cyclic ether **3** we have to consider the rates of the competing reactions :

$v_2 = k_H.[Bu_3SnH].[R^\cdot]$ production of **2**,

$v_P = k_P.[\mathbf{1}].[R^\cdot]$ addition of $\mathbf{R}^\cdot$ to the double bond of **1**,

$v_C^\cdot = k_C.[R^\cdot]$ generation of $\mathbf{C}^\cdot$,

$v'_P = k'_P.[\mathbf{1}].[C^\cdot]$ addition of $\mathbf{C}^\cdot$ to the double bond of **1**,

$v_3 = k'_H.[Bu_3SnH].[C^\cdot]$ formation of **3**.

For a successful access to the macrocyclic ether **3** the following conditions must be fullfilled :

$v_C^\cdot >> v_2 \Rightarrow k_C >> k_H.[Bu_3SnH]$ (1)

$v_C^\cdot >> v_P \Rightarrow k_C >> k_P.[\mathbf{1}]$ (2)

$v_3 >> v'_P \Rightarrow k'_H.[Bu_3SnH] >> k'_P.[\mathbf{1}]$ (3)

From the literature it was possible to estimate the various rate constants at 80°C :

$k_H \approx 6.1.10^6$ l.mol^{-1}.s^{-1},[7] $k'_H \approx 6.9.10^5$ l.mol^{-1}.s^{-1},[8] $k_C \approx 3\text{-}15.10^4$ s^{-1},[6]

$k_P \approx 8.3.10^5$ l.mol^{-1}.s^{-1},[9] $k'_P \approx 3.6.10^3$ l.mol^{-1}.s^{-1}.[10]

According to these values one can see that if the tin hydride concentration is lower than 5.10^{-3} l.mol^{-1}, inequation (1) is fullfilled. For a reaction performed with stoechiometric amounts of tin hydride and **1** this is also the case for inequations (2) and (3). In order to avoid the use of high volumes of solvents we decided to use the simultaneous additions of the two reactants with syringe pumps (fig. 1) with a slow rate.

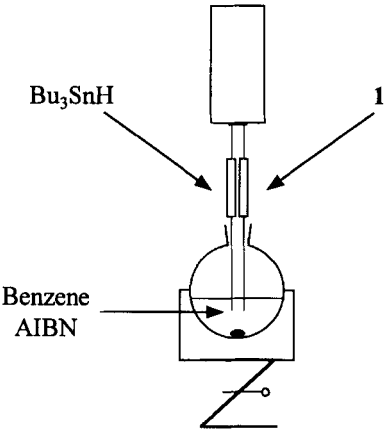


Figure 1

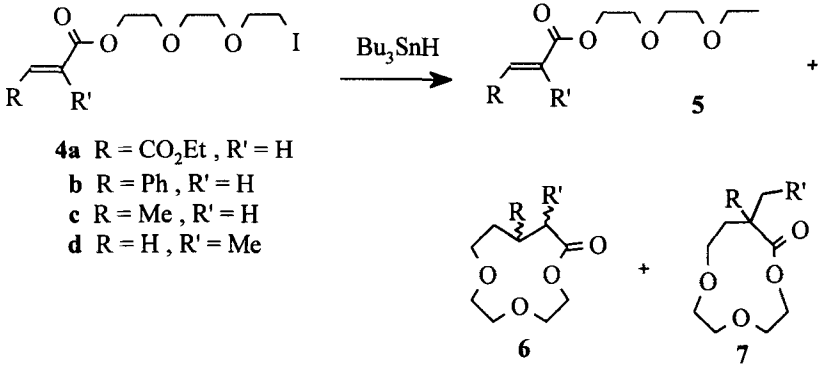
The reaction performed with various ω–iodopolyoxaalkyl acrylates **1** afforded the macrocyclic ethers **3** corresponding to the endo mode of cyclization, with good yields (**3a-3d**)[11], if we except the case of **3e** (table 1). No exo adduct was obtained. The compounds **2a-2d** were also produced but in small amounts (yield < 10%), conversely to **2e** (**3e/2e** ≈ 2) which made the purification of **3e** difficult leading to a low yield of the isolated macrocyclic ether. The other expected compounds according to scheme 2 were also observed but in much smaller quantities.

Other unsaturated esters of 8-iodo-3,6-dioxaoctyle were used to produce macrocyclic ethers (scheme 3 and table 2).

When the subsituent R is ethoxycarbonyl (**4a**) or phenyl (**4b**) the expected endo (**6a** or **6b**) and exo cyclization products (**7a** or **7b**) were observed (table 2). The separation of these isomeric macrocycles obtained from the fumaric derivative was possible but, unfortunately not for the ones coming from the cinnamic one.

Table1 : Yields of isolated macrocyclic ethers

Cyclic ether	Cycle size	Addition rate (mmole / hour)	Yield (%)
3a	12	3.2	76
3b	15	2.8	72
3c	18	2.5	70
3d	21	2.2	63
3e	24	1.1	30



4a R = CO_2Et , R' = H
b R = Ph , R' = H
c R = Me , R' = H
d R = H , R' = Me

Scheme 3

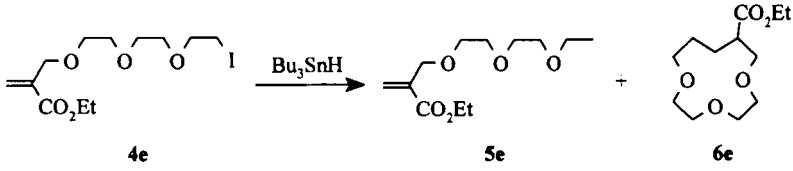
Table 2 : Yield of the isolated macroheterocycles.

	Addition rate (mmole / hour)	Yield (%) 6	7
4a	2.6	37	21
4b	2.6	50*	
4c	0.1	40	
4d	3.1	60	
4e	2.6	64	

* mixture of **6b** and **7b** (10 / 90)

With a methyl as substituent R, the cyclization reaction was much slower than when it was an hydrogen[12] and even with a much lower rate of addition of the reactants (about 0.1 mmole/hour),[13] the uncyclized reduction product (**5c**) was obtained besides the cyclic ether **6c** since the single endo adduct was obtained. Their difficult separation was the main reason of the relatively low yield of this last one.

One of the inconveniences of the macrocyclic ethers described in this paper for applications could be the presence of the ester function in the ring. Thus we decided to perform the reduction of compound **4e** by tributyltin hydride. The expected cyclic compound **6e** was isolated with a fair yield (table 2) from the reaction mixture containing small amounts of the uncyclized reduction product **5e** (scheme 4).



4e **5e** **6e**

Scheme 4

In conclusion, macrocyclic ethers could be produced efficiently by the free radical reduction of ω-iodopolyoxalkyl alkenoates by tin hydride provided the two reactants were added very slowly with syringe pumps.

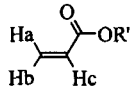
Experimental part

NMR spectra were recorded in $CDCl_3$ with $Si(CH_3)_4$ as an internal standard using

a BRUCKER AC 200 or 250 spectrometers. They are reported by δ-values (ppm) and coupling constants (*J*, Hz). Microanalysis of the iodine and macrocyclic compounds were performed by CNRS at Vernaison.

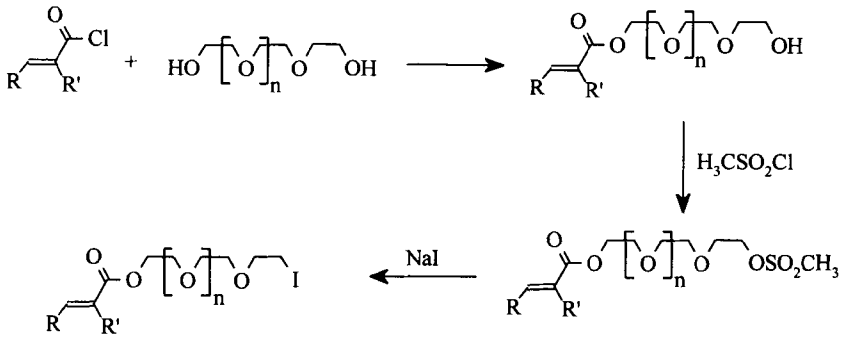
All solvents were distilled over drying reagents before use. Acryloyl, cinnamoyl, methacryloyl, crotonoyl, oxalyl and methanesulfonyl chloride, tri- and tetra-ethylene glycol, sodium iodide, pyridine, triethylamine, diethyl fumarate, 2,3-dihydropyran, ethyl acrylate, formaldehyde, 1,4-diazabicyclo[2,2,2]octane (DABCO), para-toluenesulfonic acid (PTSA), bis-(tributyltin)oxide and poly methylhydrogenosiloxane were commercially available compounds. Tributyltin hydride was prepared according to,[14] penta-, hexa-ethylene glycol and 1,8-dichloro-3,6-dioxaoctane according to,[1] ethyl 2-bromomethylpropenoate according to.[15]

The following notation was adopted for the hydrogen atoms in the double bond of the ester compounds :



The iodide **1a**, **b**, **c**, **d**, **4a**, **b**, **c, d** and **e** were obtained as described in the scheme 5.

8-Hydroxy-3,6-dioxaoctyl acrylate. Acryloyl chloride (13.6g, 0.15mol) was added to a stirred solution of triethylene glycol (45g, 0.3mol) and triethylamine (16.2g, 0.16mol) in dry THF (100ml). The mixture was stirred for 16 h. The



Scheme 5

solution was filtered and concentrated. The residue was dissolved in chloroform (100ml). The organic phase was successively washed with hydrochloric acid (2×20ml, 5% aqueous solution), sodium hydrogenocarbonate (2×10ml, 5% aqueous solution) and brine, and then dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by chromatography over silica gel [ether/methanol : 90/10] to afford 8-hydroxy-3,6-dioxaoctyl acrylate (14.7g, 48%) as a pale yellow oil. **^{1}H NMR** (250 MHz) : 2.92 (1H, s, OH), 3.44 - 3.62 (10H, m, O-CH_2), 4.19 (2H, t, J = 4.8 Hz, COO-CH_2), 5.73 (1H, dd, J = 10.3, 1.5 Hz, Hb), 6.02 (1H, dd, J = 17.3, 10.3 Hz, Hc), 6.30 (1H, dd, J = 17.3, 1.5 Hz, Ha). **^{13}C NMR** (62.9 MHz,) : 61.2 (CH_2-OH), 63.1 (COO-CH_2), 68.8, 69.9, 70.3 (O-CH_2), 72.4 (CH_2-CH_2-OH), 127.9 (CH_2=CH), 131.0 (CH_2=CH), 165.9 (C=O).

11-Hydroxy-3,6,9-trioxaundecyl acrylate, similarly prepared from tetraethylene glycol and purified [with ether/methanol : 95/5 as eluent] as 8-hydroxy-3,6-dioxaoctyl acrylate, was obtained as a pale yellow oil (16.4g, 44%). **^{1}H NMR** (200 MHz) : 3.21 (1H, s, OH), 3.44 - 3.72 (14H, m, O-CH_2), 4.23 (2H, t, J = 4.8 Hz, COO-CH_2), 5.76 (1H, dd, J =10.3, 1.2 Hz, Hb), 6.06 (1H, dd, J = 17.2, 10.3 Hz, Hc), 6.34 (1H, dd, J = 17.2, 1.2 Hz, Ha). **^{13}C NMR** (50.3 MHz) : 61.4 (CH_2-OH), 63.5 (COO-CH_2), 68.9, 70.0, 70.2, 70.3, 70.4 (O-CH_2), 72.5 (CH_2-CH_2-OH), 128.0 (CH_2=CH), 131.0 (CH_2=CH), 166.0 (C=O).

14-Hydroxy-3,6,9,12-tetraoxatetradecyl acrylate, similarly prepared from pentaethylene glycol and purified [with ether/methanol : 95/5 as eluent] as 8-hydroxy-3,6-dioxaoctyl acrylate, was obtained as a pale yellow oil (15.3g, 35%). **^{1}H NMR** (250 MHz) : 3.05 (1H, s, OH), 3.49 - 3.69 (18H, m, O-CH_2), 4.23 (2H, t, J = 4.8 Hz, COO-CH_2), 5.76 (1H, dd, J = 10.3, 1.5 Hz, Hb), 6.07 (1H, dd, J = 17.2, 10.3 Hz, Hc), 6.35 (1H, dd, J = 17.2, 1.5 Hz, Ha). **^{13}C NMR** (62.9 MHz) : 61.1 (CH_2-OH), 63.3 (COO-CH_2), 68.7, 69.9, 70.1, 70.2 (O-CH_2), 72.3 (CH_2-CH_2-OH), 127.9 (CH_2=CH), 130.7 (CH_2=CH), 165.7 (C=O).

17-Hydroxy-3,6,9,12,15-pentaoxaheptadecyl acrylate, similarly prepared from hexaethylene glycol and purified [with ether/methanol : 90/10 as eluent] as 8-hydroxy-3,6-dioxaoctyl acrylate, was obtained as a pale yellow oil (25.2g, 50%).

^{1}H NMR (250 MHz) : 3.21 (1H, s, OH), 3.41 - 3.63 (22H, m, O-CH_2), 4.16 (2H, t, J = 4.7 Hz, COO-CH_2), 5.70 (1H, dd, J = 10.3, 1.5 Hz, Hb), 6.00 (1H, dd, J = 17.3, 10.3 Hz, Hc), 6.27 (1H, dd, J = 17.3, 1.5 Hz, Ha). **^{13}C NMR** (62.9 MHz) : 61.0 (CH_2-OH), 63.2 (COO-CH_2), 68.5, 69.7, 69.97, 70.02 (O-CH_2), 72.1 (CH_2-CH_2-OH), 127.8 (CH_2=CH), 130.5 (CH_2=CH), 165.6 (C=O).

E 8-Hydroxy-3,6-dioxaoctyl 3-ethoxycarbonylpropenoate was prepared by reaction between triethylene glycol and E 3-ethoxycarbonylpropenoyl chloride which was obtained from E 3-ethoxycarbonylpropenoic acid. This acid was prepared by the saponification of diethyl fumarate in a ethanol-potassium hydroxide medium.

E 3-Ethoxycarbonylpropenoic acid. A solution of potassium hydroxide (7.3g, 0.13mol) in ethanol (50ml) was added to a stirred mixture of diethyl fumarate (44.7g, 0.26 mol) in ethanol (100ml) at room temperature. The mixture was stirred for 8 h. The solvent was removed under reduced pressure. The residue was dissolved in an aqueous solution of sodium hydrogenocarbonate (5%) until pH ≈ 10. The unreacted diethyl fumarate was extracted with chloroform (3×50ml). The aqueous phase was then acidified (pH ≈ 1) with hydrochloric acid (5% aqueous solution). The E 3-ethoxycarbonylpropenoic acid was extracted with chloroform (3×100ml). The combined organic phases were dried and concentrated. The acid (33.3g, 89%) was used without any further purification. **^{1}H NMR** (250 MHz) :

1.33 (3H, t, J = 7.1 Hz, C$\underline{H}_3$), 4.28 (2H, q, J = 7.1 Hz, COO-C$\underline{H}_2$), 6.85 and 6.93 (2H, AB system, J_{AB} = 15.7 Hz, C$\underline{H}$=C$\underline{H}$), 11.2 (1H, s, COO$\underline{H}$).

E 3-Ethoxycarbonylpropenoyl chloride. A mixture of E 3-ethoxycarbonyl propenoic acid (15.8g, 0.11mol) and pyridine (13.4g, 0.17mol) in dichloromethane (75ml) was stirred. A few drops of oxalyl chloride and DMF were added until the color turned orange and a precipitate appeared. Oxalyl chloride (27.9g, 0.22mol) was then added. The mixture was stirred for 4 h at room temperature. The solvent was removed under reduced pressure and THF (150ml) was added to be used for the next step of the synthesis. **^{1}H NMR** (250 MHz) : 1.31 (3H, t, J = 7.0 Hz, C$\underline{H}_3$), 4.25 (2H, q, J = 7.0 Hz, COO-C$\underline{H}_2$), 6.87 and 6.95 (2H, AB system, J_{AB} = 15.7 Hz, C$\underline{H}$=C$\underline{H}$).

E 8-Hydroxy-3,6-dioxaoctyl 3-ethoxycarbonylpropenoate. A solution of E 3-ethoxycarbonylpropenoyl chloride (0.11mol) in THF (150ml) was added to a stirred mixture of triethylene glycol (33.0g, 0.22mol) and pyridine (9.5g, 0.12mol) in THF (100ml) under nitrogen. The solution was stirred for 16 h, filtered, rinced with ether and concentrated. The residue was dissolved in chloroform (100ml), treated and purified as for 8-hydroxy-3,6-dioxaoctyl acrylate [with ether as eluent] to afford E 8-hydroxy-3,6-dioxaoctyl 3-ethoxycarbonylpropenoate (19.7g, 65%) as an oil. **^{1}H NMR** (250 MHz) : 1.21 (3H, t, J = 7.1 Hz, C$\underline{H}_3$), 2.92 (1H, s, O$\underline{H}$), 3.48 - 3.68 (10H, m, O-C$\underline{H}_2$), 4.15

(2H, q, J = 7.1 Hz, COO-C$\underline{H}_2$-CH$_3$), 4.26 (2H, t, J = 4.8 Hz, COO-C$\underline{H}_2$), 6.77 (2H, s, C$\underline{H}$=C$\underline{H}$). **^{13}C NMR** (62.9 MHz) : 13.9 (C$\underline{H}_3$), 61.2 (COO-C$\underline{H}_2$-CH$_3$), 61.4 (C$\underline{H}_2$-OH), 64.1 (COO-C$\underline{H}_2$-CH$_2$), 68.6, 70.1, 70.4 (O-C$\underline{H}_2$), 72.3 (C$\underline{H}_2$-CH$_2$-OH), 133.0, 133.9 (C$\underline{H}$=C$\underline{H}$), 164.68, 164.73 (C$\underline{=}$O).

E 8-Hydroxy-3,6-dioxaoctyl 3-phenylpropenoate, similarly prepared from cinnamoyl chloride and purified [with ether as eluent] as 8-hydroxy-3,6-dioxaoctyl acrylate but with cinnamoyl chloride (25.0g, 0.15mol) instead of acryloyl chloride, was obtained as an oil (22.7g, 54%). **^{1}H NMR** (200 MHz) : 3.03 (1H, s, O$\underline{H}$), 3.48 - 3.64 (8H, m, O-C$\underline{H}_2$), 3.70 (2H, t, J = 4.8 Hz, COO-CH$_2$-C$\underline{H}_2$), 4.28 (2H, t, J = 4.8 Hz, COO-C$\underline{H}_2$), 7.26 - 7.45 (5H, m, Ph), 6.39 and 7.62 (2H, AB system, J_{AB} = 16.0 Hz, C$\underline{H}$=C$\underline{H}$). **^{13}C NMR** (50.3 MHz) : 61.5 (C$\underline{H}_2$-OH), 63.4 (COO-C$\underline{H}_2$), 69.0, 70.1, 70.4 (O-C$\underline{H}_2$), 72.4 (C$\underline{H}_2$-CH$_2$-OH), 117.6 (=C$\underline{H}$-COO), 127.9, 128.7 (aromatic o and m C), 130.2 (aromatic p C), 134.1 (aromatic C), 145.0 (=C$\underline{H}$-Ph), 166.7 (C$\underline{=}$O).

E 8-Hydroxy-3,6-dioxaoctyl but-2-enoate, similarly prepared and purified [with ether as eluent] as 8-hydroxy-3,6-dioxaoctyl acrylate but with crotonoyl chloride (15.7g, 0.15mol) and potassium carbonate (11.0g, 0.08mol) instead of acryloyl chloride and triethylamine respectively, was obtained as an oil (17.3g, 53%). **^{1}H NMR** (250 MHz) : 1.69 (3H, dd, J = 6.9, 1.7 Hz, C$\underline{H}_3$), 2.86 (1H, s, O$\underline{H}$), 3.38 - 3.56 (10H, m, O-C$\underline{H}_2$), 4.09 (2H, t, J = 4.8 Hz, COO-C$\underline{H}_2$), 5.68 (1H, qd, J =

15.5, 1.7 Hz, Hc), 6.81 (1H, qd, J = 15.5, 6.9 Hz, Ha). **^{13}C NMR** (62.9 MHz) : 17.6 ($\underline{C}H_3$), 61.0 ($\underline{C}H_2$-OH), 62.8 (COO-$\underline{C}H_2$), 68.7, 69.8, 70.1 (O-$\underline{C}H_2$), 72.2 ($\underline{C}H_2$-CH_2-OH), 122.0 (=$\underline{C}$H-COO), 144.8 (=$\underline{C}$H-CH_3), 166.0 ($\underline{C}$=O).

8-Hydroxy-3,6-dioxaoctyl 2-methylpropenoate, similarly prepared and purified [with ether as eluent] as 8-hydroxy-3,6-dioxaoctyl acrylate but with methacryloyl chloride (15.7g, 0.15mol) instead of acryloyl chloride, was obtained as an oil (15.0g, 46%). **^{1}H NMR** (200 MHz) : 1.92 (3H, dd, J = 1.5, 1.0 Hz, CH_3), 2.77 (1H, s, OH), 3.55 - 3.75 (10H, m, O-CH_2), 4.28 (2H, t, J = 4.8 Hz, COO-CH_2), 5.55 (1H, qu, J = 1.5 Hz, Hc), 6.11 (1H, qd, J = 1.5, 1.0 Hz, Ha). **^{13}C NMR** (50.3 MHz) : 18.3 ($\underline{C}H_3$), 61.7 ($\underline{C}H_2$-OH), 63.7 (COO-$\underline{C}H_2$), 69.1, 70.3, 70.6 (O-$\underline{C}H_2$), 72.5 ($\underline{C}H_2$-CH_2-OH), 125.9 (=$\underline{C}H_2$), 136.1 (H_2C=$\underline{C}$), 167.4 ($\underline{C}$=O).

Ethyl 2-(10-hydroxy-2,5,8-trioxadecyl)propenoate. A solution of ethyl 2-bromomethylpropenoate[15] (4.9g, 25mmol) and triethylene glycol (15g, 100mmol) in dichloromethane (50ml) was cooled to 0°C. The triethylamine (5.1g, 50mmol) was so added. When the medium reached room temperature, it was stirred for 30 minutes, heated to reflux for 24h. This organic phase was washed with hydrochloric acid (4×10ml, 5% aqueous solution) until acid pH and brine (2×10ml), dried over $MgSO_4$ and then concentrated. The ethyl 2-(10-hydroxy-2,5,8-trioxadecyl)propenoate was purified (3.9g, 60%) by liquid solid chromatography over silica [ether/pentane : 80/20]. **^{1}H NMR** (250 MHz) : 1.18

(3H, t, J = 7.2 Hz, CH_3), 3.15 (1H, s, OH), 3.59 - 3.68 (12H, m, O-CH_2), 4.14 (2H, q, J = 7.2 Hz, COO-CH_2), 4.16 (2H, t, J = 1.5 Hz, H_2C=C-CH_2-O), 5.77 (1H, q, J = 1.5 Hz, Hb), 6.17 (1H, q, J = 1.5 Hz, Ha). **^{13}C NMR** (62.9 MHz) : 13.9 (CH_3), 60.4 (COO-CH_2), 61.3 (CH_2-OH), 69.0, 69.9, 70.0, 70.1, 70.4 (O-CH_2), 72.4 (CH_2-CH_2-OH), 125.4 (=CH_2), 137.0 (H_2C=C), 165.6 (C=O).

8-Mesyloxy-3,6-dioxaoctyl acrylate. Pyridine (9.5g, 0.12mol) was added to a stirred mixture of 8-hydroxy-3,6-dioxaoctyl acrylate (20.4g, 0.10mol) and methanesulfonyl chloride (12.6g, 0.11mol) under nitrogen at 0°C. The mixture was stirred for 4 h, acidified with hydrochloric acid (5% aqueous solution) until pH ≈ 1. The aqueous phase was extracted twice with chloroform (2×70ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated. The mesylate was used without any further purification. **^{1}H NMR** (250 MHz) : 2.98 (3H, s, CH_3), 3.53 - 3.68 (8H, m, O-CH_2), 4.19 (2H, t, J = 4.8 Hz, COO-CH_2), 4.26 (2H, t, J = 4.5 Hz, CH_2-OSO_2), 5.75 (1H, dd, J = 10.4, 1.6 Hz, Hb), 6.05 (1H, dd, J = 17.4, 10.4 Hz, Hc), 6.32 (1H, dd, J = 17.4, 1.6 Hz, Ha).

11-Mesyloxy-3,6,9-trioxaundecyl acrylate was prepared as 8-mesyloxy-3,6-dioxaoctyl acrylate. **^{1}H NMR** (250 MHz) : 2.97 (3H, s, CH_3), 3.51 - 3.66 (12H, m, O-CH_2), 4.18 (2H, t, J = 4.9 Hz, COO-CH_2), 4.25 (2H, t, J = 4.5 Hz, CH_2-OSO_2), 5.74 (1H, dd, J = 10.3, 1.5 Hz, Hb), 6.04 (1H, dd, J = 17.4, 10.3 Hz, Hc), 6.30 (1H, dd, J = 17.4, 1.5 Hz, Ha).

14-Mesyloxy-3,6,9,12-tetraoxatetradecyl acrylate was prepared as 8-mesyloxy-3,6-dioxaoctyl acrylate. **^{1}H NMR** (250 MHz) : 2.97 (3H, s, CH_3), 3.51 - 3.66 (16H, m, O-CH_2), 4.18 (2H, t, J = 4.7 Hz, COO-CH_2), 4.25 (2H, t, J = 4.4 Hz, CH_2-OSO_2), 5.73 (1H, dd, J = 10.3, 1.5 Hz, Hb), 6.03 (1H, dd, J = 17.4, 10.3 Hz, Hc), 6.30 (1H, dd, J = 17.4, 1.5 Hz, Ha).

17-Mesyloxy-3,6,9,12,15-pentaoxaheptadecyl acrylate was prepared as 8-mesyloxy-3,6-dioxaoctyl acrylate. **^{1}H NMR** (200 MHz) : 2.98 (3H, s, CH_3), 3.52 - 3.67 (20H, m, O-CH_2), 4.19 (2H, t, J = 4.8 Hz, COO-CH_2), 4.26 (2H, t, J = 4.5 Hz, CH_2-OSO_2), 5.73 (1H, dd, J = 10.3, 1.5 Hz, Hb), 6.03 (1H, dd, J = 17.4, 10.3 Hz, Hc), 6.30 (1H, dd, J = 17.4, 1.5 Hz, Ha).

E 8-Mesyloxy-3,6-dioxaoctyl 3-ethoxycarbonylpropenoate was prepared as 8-mesyloxy-3,6-dioxaoctyl acrylate. **^{1}H NMR** (250 MHz) : 1.24 (3H, t, J = 7.2 Hz, CH_2-CH_3), 3.00 (3H, s, SO_2-CH_3), 3.62 - 3.74 (8H, m, O-CH_2), 4.19 (2H, q, J = 7.2 Hz, COO-CH_2-CH_3), 4.24 - 4.35 (4H, m, COO-CH_2-CH_2 and CH_2-OSO_2), 6.80 (2H, s, CH=CH).

E 8-Mesyloxy-3,6-dioxaoctyl 3-phenylpropenoate was prepared as 8-mesyloxy-3,6-dioxaoctyl acrylate. **^{1}H NMR** (200 MHz) : 3.04 (3H, s, CH_3), 3.64 - 3.68 (6H, m, O-CH_2), 3.74 (2H, t, J = 4.6 Hz, COO-CH_2-CH_2), 4.30 - 4.37 (4H, m, COO-CH_2 and CH_2-OSO_2), 7.34 - 7.53 (5H, m, Ph), 6.46 and 7.68 (2H, AB system, J_{AB} = 16.0 Hz, CH=CH).

E 8-Mesyloxy-3,6-dioxaoctyl but-2-enoate was prepared as 8-mesyloxy-3,6-dioxaoctyl acrylate. **^{1}H NMR** (250 MHz) : 1.83 (3H, dd, J = 7.0, 1.6 Hz, HC=C$\underline{H}_3$), 3.01 (3H, s, SO_2-C$\underline{H}_3$), 3.61 - 3.72 (8H, m, O-C$\underline{H}_2$), 4.20 (2H, t, J = 4.7 Hz, COO-C$\underline{H}_2$), 4.28 (2H, t, J = 4.5 Hz, C$\underline{H}_2$-OSO_2), 5.82 (1H, qd, J = 15.5, 1.6 Hz, $\underline{Hc}$), 6.94 (1H, qd, J = 15.5, 7.0 Hz, $\underline{Ha}$).

E 8-Mesyloxy-3,6-dioxaoctyl 2-methylpropenoate was prepared as 8-mesyloxy-3,6-dioxaoctyl acrylate. **^{1}H NMR** (250 MHz) : 1.83 (3H, dq, J = 1.0, 1.5 Hz, C=C$\underline{H}_3$), 3.02 (3H, s, SO_2-C$\underline{H}_3$), 3.53 - 3.67 (8H, m, O-C$\underline{H}_2$), 4.18 (2H, t, J = 4.9 Hz, COO-C$\underline{H}_2$), 4.25 (2H, t, J = 4.5 Hz C$\underline{H}_2$-OSO_2), 5.47 (1H, qu, J = 1.5 Hz, $\underline{Hb}$), 6.01 (1H, qd, J = 1.5, 1.0 Hz, $\underline{Ha}$).

Ethyl 2-(10-mesyloxy-2,5,8-trioxadecyl)propenoate was prepared as 8-mesyloxy -3,6-dioxaoctyl acrylate. **^{1}H NMR** (250 MHz) : 1.18 (3H, t, J = 7.2 Hz, CH_2-C$\underline{H}_3$), 2.97 (3H, s, SO_2-C$\underline{H}_3$), 3.59 - 3.68 (10H, m, O-C$\underline{H}_2$), 4.14 (2H, q, J = 7.2 Hz, COO-C$\underline{H}_2$-CH_3), 4.16 (2H, t, J = 1.5 Hz, C=C-C$\underline{H}_2$-O), 4.25 (2H, t, J = 4.5 Hz, C$\underline{H}_2$-OSO_2), 5.77 (1H, q, J = 1.5 Hz, $\underline{Hb}$), 6.17 (1H, q, J = 1.5 Hz, $\underline{Ha}$).

8-Iodo-3,6-dioxaoctyl acrylate 1a. A stirred solution of 8-mesyloxy-3,6-dioxaoctyl acrylate (28.2g, 0.10mol) and sodium iodide (18g, 0.12mol) dissolved in dry acetone (150ml) was heated to reflux for 14 h. The solvent was removed under reduced pressure. The residue was dissolved in minimum water. The iodide was then extracted with chloroform (5×50ml). The organic phases were then

dried over $MgSO_4$ and concentrated. Chromatographic purification [ether/pentane : 60/40] of the residue gave 8-iodo-3,6-dioxaoctyl acrylate **1a** as an oil (17.6g, 56%). **Microanalysis** : $C_9H_{15}IO_4$ requires C, 34.41 ; H, 4.81 ; I, 40.40 %. Found : C, 34.21 ; H, 4.84 ; I, 39.57 %. **^{1}H NMR** (250 MHz) : 3.19 (2H, t, J = 6.8 Hz, CH_2-I), 3.60 (4H, s, O-CH_2), 3.69 (4H, 2t, J = 4.9, 6.8 Hz, COO-CH_2-CH_2 and CH_2-CH_2-I), 4.25 (2H, t, J = 4.9 Hz, COO-CH_2), 5.80 (1H, dd, J = 10.3, 1.5 Hz, Hb), 6.09 (1H, dd, J = 17.3, 10.3 Hz, Hc), 6.40 (1H, dd, J = 17.3, 1.5 Hz, Ha). **^{13}C NMR** (62.9 MHz) : 2.9 (CH_2-I), 63.5 (COO-CH_2), 69.1, 70.1, 70.5 (O-CH_2), 71.8 (CH_2-CH_2-I), 128.2 (CH_2=CH), 131.0 (CH_2=CH), 166.0 (C=O).

11-Iodo-3,6,9-trioxaundecyl acrylate 1b was prepared as described above for **1a** [with ether/pentane : 80/20 as eluent] (18.3g, 51%). **Microanalysis** : $C_{11}H_{19}IO_5$ requires C, 36.89 ; H, 5.35 ; I, 35.43 %. Found : C, 36.63 ; H, 5.46 ; I, 35.46 %. **^{1}H NMR** (250 MHz) : 3.16 (2H, t, J = 6.8 Hz, CH_2-I), 3.68 - 3.55 (12H, m, O-CH_2), 4.21 (2H, t, J =4.8 Hz, COO-CH_2), 5.74 (1H, dd, J = 10.3, 1.6 Hz, Hb), 6.05 (1H, dd, J = 17.3, 10.3 Hz, Hc), 6.32 (1H, dd, J = 17.3, 1.6 Hz, Ha). **^{13}C NMR** (62.9 MHz) : 2.9 (CH_2-I), 63.5 (COO-CH_2), 68.9, 70.0, 70.4$_1$, 70.4$_3$ (O-CH_2), 71.7 (CH_2-CH_2-I), 128.1 (CH_2=CH), 130.8 (CH_2=CH), 165.8 (C=O). The spectroscopic data recorded for this compound agree closely with those obtained from a sample independently prepared elsewhere.[11]

14-Iodo-3,6,9,12-tetraoxatetradecyl acrylate 1c was prepared as described above for **1a** [with ether/methanol : 98/2 as eluent] (30.2g, 75%). **Microanalysis** :

$C_{13}H_{23}IO_6$ requires C, 38.82 ; H, 5.76 ; I, 31.55 %. Found : C, 38.38 ; H, 5.63 ; I, 31.40 %. **^{1}H NMR** (250 MHz) : 3.17 (2H, t, J = 6.8 Hz, C$\underline{H}_2$-I), 3.57 - 3.69 (16H, m, O-C$\underline{H}_2$), 4.22 (2H, t, J = 4.7 Hz, COO-C$\underline{H}_2$), 5.75 (1H, dd, J = 10.4, 1.5 Hz, Hb), 6.05 (1H, dd, J = 17.5, 10.4 Hz, Hc), 6.33 (1H, dd, J = 17.5, 1.5 Hz, Ha). **^{13}C NMR** (62.9 MHz) : 2.9 ($\underline{C}H_2$-I), 63.5 (COO-$\underline{C}H_2$), 68.9, 70.0, 70.3$_5$, 70.4$_0$, 70.4$_3$ (O-$\underline{C}H_2$), 71.7 ($\underline{C}H_2$-CH_2-I), 128.1 (CH_2=$\underline{C}$H), 130.8 ($\underline{C}H_2$=CH), 165.8 ($\underline{C}$=O). The spectroscopic data recorded for this compound agree closely with those obtained from a sample independently prepared elsewhere.[11]

17-Iodo-3,6,9,12,15-pentaoxaheptadecyl acrylate 1d was prepared as described above for **1a** [with ether as eluent] (27.7g, 62%). **Microanalysis** : $C_{15}H_{27}IO_7$ requires C, 40.37 ; H, 6.10 ; I, 28.44 %. Found : C, 40.40 ; H, 6.23 ; I, 28.30 %. **^{1}H NMR** (250 MHz) : 3.17 (2H, t, J = 6.8 Hz, C$\underline{H}_2$-I), 3.57 - 3.69 (20H, m, O-C$\underline{H}_2$), 4.22 (2H, t, J = 4.7 Hz, COO-C$\underline{H}_2$), 5.75 (1H, dd, J = 10.4, 1.5 Hz, Hb), 6.06 (1H, dd, J = 17.5, 10.4 Hz, Hc), 6.33 (1H, dd, J = 17.5, 1.5 Hz, Ha). **^{13}C NMR** (62.9 MHz) : 2.9 ($\underline{C}H_2$-I), 63.5 (COO-$\underline{C}H_2$), 68.9, 70.0, 70.3$_5$, 70.3$_8$, 70.4$_3$ (O-$\underline{C}H_2$), 71.7 ($\underline{C}H_2$-CH_2-I), 128.1 (CH_2=$\underline{C}$H), 130.8 ($\underline{C}H_2$=CH), 165.8 ($\underline{C}$=O). The spectroscopic data recorded for this compound agree closely with those obtained from a sample independently prepared elsewhere.[11]

E 8-Iodo-3,6-dioxaoctyl 3-ethoxycarbonylpropenoate 4a was prepared as described above for **1a** [with ether/pentane : 80/20 as eluent] (19.3g, 50%).

Microanalysis : $C_{12}H_{19}IO_6$ requires C, 37.32 ; H, 4.96 ; I, 32.86 %. Found : C, 37.14 ; H, 5.10 ; I, 32.62 %. **^{1}H NMR** (250 MHz) : 1.23 (3H, t, J = 7.1 Hz, C$\underline{H}_3$), 3.17 (2H, t, J = 6.9 Hz, C$\underline{H}_2$-I), 3.58 - 3.70 (8H, m, O-C$\underline{H}_2$), 4.17 (2H, q, J = 7.1 Hz, COO-C$\underline{H}_2$-CH$_3$), 4.27 (2H, t, J = 4.9 Hz, COO-C$\underline{H}_2$), 6.78 (2H, s, C$\underline{H}$=C$\underline{H}$). **^{13}C NMR** (62.9 MHz) : 2.8 ($\underline{C}H_2$-I), 14.0 ($\underline{C}H_3$), 61.2 ($\underline{C}H_2$-CH$_3$), 64.2 (COO-$\underline{C}H_2$), 68.8, 70.0, 70.4 (O-$\underline{C}H_2$), 71.8 ($\underline{C}H_2$-CH$_2$-I), 133.0, 133.8 ($\underline{C}H$=$\underline{C}H$), 164.6, 164.7($\underline{C}$=O).

E 8-Iodo-3,6-dioxaoctyl cinnamate 4b was prepared as described above for **1a** [with ether/pentane : 80/20 as eluent] (21.5g, 55%). **Microanalysis** : $C_{15}H_{19}IO_4$ requires C, 46.17 ; H, 4.91 ; I, 32.52 %. Found : C, 45.92 ; H, 4.82 ; I, 32.41 %. **^{1}H NMR** (250 MHz) : 3.15 (2H, t, J = 6.8 Hz, C$\underline{H}_2$-I), 3.58 - 3.71 (8H, m, O-C$\underline{H}_2$), 4.28 (2H, t, J = 4.8 Hz, COO-C$\underline{H}_2$), 7.26 - 7.45 (5H, m, Ph), 6.39 and 7.61 (2H, AB system, J_{AB} = 16.0 Hz, C$\underline{H}$=C$\underline{H}$). **^{13}C NMR** (62.9 MHz) : 2.8 ($\underline{C}H_2$-I), 63.4 (COO-$\underline{C}H_2$), 69.0, 69.9, 70.3 (O-$\underline{C}H_2$), 71.7 ($\underline{C}H_2$-CH$_2$-I), 117.6 (=$\underline{C}$H-COO), 127.9, 128.6 (aromatic o and m $\underline{C}$), 130.1 (aromatic p $\underline{C}$), 134.1 (aromatic $\underline{C}$), 144.7 (=$\underline{C}$H-Ph), 166.5 ($\underline{C}$=O).

E 8-Iodo-3,6-dioxaoctyl crotonate 4c was prepared as described above for **1a** [with ether/pentane : 70/30 as eluent] (19.4g, 59%). **Microanalysis** : $C_{10}H_{17}IO_4$ requires C, 36.59 ; H, 5.22 ; I, 38.69 %. Found : C, 36.21 ; H, 5.01 ; I, 38.98 %. **^{1}H NMR** (250 MHz) : 1.83 (3H, dd, J = 7.0, 1.6 Hz, C$\underline{H}_3$), 3.20 (2H, t, J = 7.0

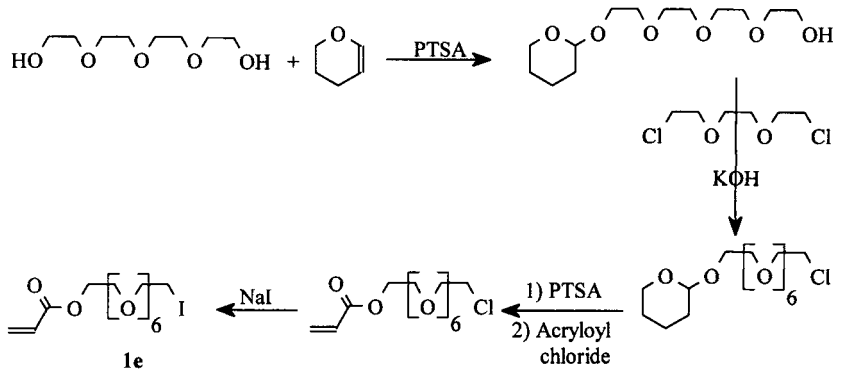
Hz, C$\underline{H}_2$-I), 3.61 - 3.72 (8H, m, O-C$\underline{H}_2$), 4.22 (2H, t, J = 4.7 Hz, COO-C$\underline{H}_2$), 5.82 (1H, qd, J = 15.5, 1.6 Hz, =C$\underline{H}$-COO), 6.94 (1H, qd, J = 15.5, 7.0 Hz, =C$\underline{H}$-CH_3). **^{13}C NMR** (62.9 MHz) : 2.9 ($\underline{C}H_2$-I), 17.9 ($\underline{C}H_3$), 63.2 (COO-$\underline{C}H_2$), 69.2, 70.1, 70.4 (O-$\underline{C}H_2$), 71.9 ($\underline{C}H_2$-CH_2-I), 122.4 (=$\underline{C}$H-COO), 144.9 (=$\underline{C}$H-CH_3), 166.2 ($\underline{C}$=O).

8-Iodo-3,6-dioxaoctyl methacrylate 4d was prepared as described above for **1a** [with ether/pentane : 70/30 as eluent] (9.9g, 30%). **Microanalysis** : $C_{10}H_{17}IO_4$ requires C, 36.59 ; H, 5.22 ; I, 38.69 %. Found : C, 36.30 ; H, 5.13 ; I, 38.96 %. **^{1}H NMR** (250 MHz) : 1.83 (3H, dd, J = 1.5, 1.0 Hz, C$\underline{H}_3$), 3.14 (2H, t, J = 6.9 Hz, C$\underline{H}_2$-I), 3.53 - 3.67 (8H, m, O-C$\underline{H}_2$), 4.18 (2H, t, J = 4.9 Hz, COO-C$\underline{H}_2$), 5.47 (1H, qu, J = 1.5 Hz, Hb), 6.01 (1H, qd, J = 1.5, 1.0 Hz, Ha). **^{13}C NMR** (62.9 MHz) : 2.8 ($\underline{C}H_2$-I), 18.1 ($\underline{C}H_3$), 63.5 (COO-$\underline{C}H_2$), 68.9, 69.9, 70.3 (O-$\underline{C}H_2$), 71.7 ($\underline{C}H_2$-CH_2-I), 125.5 (C=$\underline{C}H_2$), 135.8 ($\underline{C}$=CH_2), 166.9 ($\underline{C}$=O).

Ethyl 2-(10-iodo-2,5,8-trioxadecyl) propenoate 4e was prepared as described above for **1a** [with ether/pentane : 90/10 as eluent] (30.5g, 82%). **Microanalysis** : $C_{12}H_{21}IO_5$ requires C, 38.71 ; H, 5.65 ; I, 34.14 %. Found : C, 38.51 ; H, 5.52 ; I, 34.24 %. **^{1}H NMR** (250 MHz) : 1.22 (3H, t, J = 7.2 Hz, C$\underline{H}_3$), 3.18 (2H, t, J = 7.0 Hz, C$\underline{H}_2$-I), 3.68 (2H, t, J = 7.0 Hz, C$\underline{H}_2$-CH_2-I), 3.59 - 3.71 (8H, m, O-C$\underline{H}_2$), 4.14 (2H, q, J = 7.2 Hz, COO-C$\underline{H}_2$), 4.16 (2H, t, J = 1.5 Hz, C=C-C$\underline{H}_2$-O), 5.82 (1H, q, J = 1.5 Hz, Hb), 6.22 (1H, q, J = 1.5 Hz, Ha). **^{13}C NMR** (62.9 MHz) : 2.9

($\underline{C}H_2$-I), 14.1 ($\underline{C}H_3$), 60.5 (COO-$\underline{C}H_2$), 69.1, 70.0, 70.1, 70.4, 70.5 (O-$\underline{C}H_2$), 71.8 ($\underline{C}H_2$-CH_2-I), 125.4 (C=$\underline{C}H_2$), 137.1 ($\underline{C}$=CH_2), 165.6 ($\underline{C}$=O).

20-Iodo-3,6,9,12,15,18-hexaoxaicosanyl acrylate 1e was prepared as described in scheme 6.



Scheme 6

3,6,9,12-Tetraoxa-12-(2-tetrahydropyranyl)dodecan-1-ol. A solution of tetraethylene glycol (29.1g, 150mmol), 2,3-dihydropyran (6.3g, 75mmol) and PTSA (2.5g, 10mmol) in dry THF (50ml) was stirred for 3 h at room temperature. After neutralization with pyridine, the solvent was removed under reduced pressure. The residue was dissolved in chloroform (100ml). This organic phase was washed with water (30ml), dried over $MgSO_4$ and concentrated. The alcohol was purified (14.0g, 67%) by column chromatography over silica gel [ether/ ethanol : 90/10]. **^{1}H NMR** (250 MHz) : 1.38 - 1.75 (6H, m, $\underline{C}H_2$), 3.24 (1H, s, O$\underline{H}$), 3.45 - 3.58 (16H, m, O-$\underline{C}H_2$), 3.69 - 3.76 (2H, m, $(CH_2)_3$-$\underline{C}H_2$-O-CH), 4.51

(1H, t, J = 3.4 Hz, C<u>H</u>). **^{13}C NMR** (62.9 MHz) : 19.1 (<u>C</u>H$_2$-CH$_2$-CH), 25.1 (<u>C</u>H$_2$-(CH$_2$)$_2$-CH), 30.2 (<u>C</u>H$_2$-CH), 61.3 (<u>C</u>H$_2$-OH), 61.9 (CH-O-<u>C</u>H$_2$-CH$_2$-O), 66.3 ((CH$_2$)$_3$-<u>C</u>H$_2$-O), 70.1, 70.2, 70.2$_8$, 70.3$_4$ (O-<u>C</u>H$_2$), 72.4 (<u>C</u>H$_2$-CH$_2$-OH), 98.6 (<u>C</u>H).

1-Chloro-3,6,9,12,15,18,21-heptaoxa-21-(2-tetrahydropyranyl) henicosane. A mixture of the previous prepared alcohol (11.1g, 40mmol) and 1,8-dichloro-3,6-dioxaoctane[1] (15g, 80mmol) was heated at 90°C. Finely ground potassium hydroxide (2.5g, 44mmol) was then added, and after 72 h a new portion (2g, 36mmol). Once the alcohol has reacted (verified by GPC), acetone (100ml) was added. The precipitate was filtered and the solvent was removed under reduced pressure. The chlorinated compound was isolated (7.2g, 42%) by column chromatography over silica gel [ether/ethanol : 90/10]. **^{1}H NMR** (250 MHz) : 1.24 - 1.65 (6H, m, C<u>H</u>$_2$), 3.21 - 3.53 (28H, m, OC<u>H</u>$_2$ and C<u>H</u>$_2$-Cl), 3.57 - 3.67 (2H, m, (CH$_2$)$_3$-C<u>H</u>$_2$-O-CH), 4.39 (1H, t, J = 3.4 Hz, C<u>H</u>). **^{13}C NMR** (62.9 MHz) : 18.9 (<u>C</u>H$_2$-CH$_2$-CH), 24.9 (<u>C</u>H$_2$-(CH$_2$)$_2$-CH), 29.9 (<u>C</u>H$_2$-CH), 42.2 (<u>C</u>H$_2$-Cl), 61.4 (CH-O-<u>C</u>H$_2$-CH$_2$-O), 66.0 ((CH$_2$)$_3$-<u>C</u>H$_2$-O), 69.9, 70.0 (O-<u>C</u>H$_2$), 70.7 (<u>C</u>H$_2$-CH$_2$-Cl), 98.1 (<u>C</u>H).

20-Chloro-3,6,9,12,15,18-hexaoxaicosan-1-ol. A solution of the above described chloro compound (6.4g, 15mmol) and PTSA (0.05g, 0.2mmol) in methanol (100ml) was heated at 70°C for 12 h. The solvent was removed under reduced

pressure. 20-chloro-3,6,9,12,15,18-hexaoxaicosan-1-ol (5.2g) was obtained quantitatively. **^{1}H NMR** (250 MHz) : 3.51 - 3.70 (all the protons). **^{13}C NMR** (62.9 MHz) : 42.6 ($\underline{C}H_2$-Cl), 61.5 ($\underline{C}H_2$-OH), 70.0, 70.1, 70.2, 70.3$_7$, 70.4$_0$, 70.4$_4$, (O-$\underline{C}H_2$), 71.2 ($\underline{C}H_2$-CH_2-Cl), 72.3 ($\underline{C}H_2$-CH_2-OH).

20-Chloro-3,6,9,12,15,18-hexaoxaicosanyl acrylate. Acryloyl chloride (1.8g, 20mmol) was added to a stirred solution of the above compound (5.2g, 15mmol) and triethylamine (1.5g, 15mmol) in THF (30ml). The mixture was stirred for 16 h at room temperature, filtered and concentrated. The residue was dissolved in chloroform (80ml). The organic phase washed with once sodium hydrogenocarbonate (10ml, satureted solution) and twice with brine, was then dried and concentrated. The residue was purified by chromatography [ether/ ethanol : 90/10] to afford the chlorinated acrylate (2.9g, 48%).**^{1}H NMR** (250 MHz) : 3.42 - 3.56 (26H, m, O-$\underline{C}H_2$ and $\underline{C}H_2$-Cl), 4.08 (2H, t, J =4.8 Hz, COO-$\underline{C}H_2$), 5.64 (1H, dd, J = 10.3, 1.6 Hz, Hb), 5.93 (1H, dd, J = 10.3, 17.2 Hz, Hc), 6.20 (1H, dd, J = 17.2, 1.6 Hz, Ha). **^{13}C NMR** (62.9 MHz) : 42.3 ($\underline{C}H_2$-Cl), 63.1 (COO-$\underline{C}H_2$), 68.5, 69.9, 70.0 (O-$\underline{C}H_2$), 70.7 ($\underline{C}H_2$-CH_2-Cl), 127.8 (CH_2=$\underline{C}H$), 130.5 ($\underline{C}H_2$=CH), 165.5 ($\underline{C}$=O).

20-Iodo-3,6,9,12,15,18-hexaoxaicosanyl acrylate 1e. A solution of the above chloro compound (2.4g, 6mmol) and sodium iodide (1.4g, 9mmol) in dry acetone (20ml) was heated under reflux for 12 h. The precipitate was filtered, washed

with acetone and the solvent was removed under reduced pressure. **1e** was isolated (2.4g, 81%) after column chromatography of the residue over silica gel [ether/methanol : 88/12]. **Microanalysis** : $C_{17}H_{31}IO_8$ requires C, 44.64 ; H, 6.37 ; I, 25.88 %. Found : C, 41.12 ; H, 6.21 ; I, 26.02 %. **^{1}H NMR** (250 MHz) : 3.06 (2H, t, J = 7.0 Hz, C$\underline{H}_2$-I), 3.45 - 3.58 (24H, m, O-C$\underline{H}_2$), 4.10 (2H, t, J = 4.8 Hz, COO-C$\underline{H}_2$), 5.65 (1H, dd, J = 10.4, 1.6 Hz, $\underline{Hb}$), 5.95 (1H, dd, J = 10.4, 17.4 Hz, $\underline{Hc}$), 6.22 (1H, dd, J = 17.4, 1.6 Hz, $\underline{Ha}$). **^{13}C NMR** (62.9 MHz) : 2.8 ($\underline{C}H_2$-I), 63.1 (COO-$\underline{C}H_2$), 68.5, 69.6, 69.9$_9$, 70.0$_2$, 70.0$_5$ (O-$\underline{C}H_2$), 71.3 ($\underline{C}H_2$-CH_2-I), 127.8 (CH_2=$\underline{C}$H), 130.5 ($\underline{C}H_2$=CH), 165.4 ($\underline{C}$=O).

2,5,8-Trioxa-1-oxocyclododecane 3a. Under argon, a stirred solution of AIBN (49mg, 0.3mmol) in fresh distilled benzene (30ml) was heated under reflux. Two 1ml syringes (Terumo) respectively filled with tin hydride[14] (0.87g, 3mmol) and iodide **1a** (0.94g, 3mmol) respectively, were completed to 1ml with dry benzene and placed on a syringe pump (Razel model A-99). The flow rate during the addition was about 3.2 mmol/h. At the end of the addition, refluxing was continued for 15 min. The reaction mixture was then cooled and the solvent removed under reduced pressure. Upon dissolution of the residue in acetonitrile, the tin compounds were extracted with pentane. After elimination of the solvent, 2,5,8-trioxa-1-oxocyclo dodecane **3a** was isolated (0.43g, 76%) by column chromatography over silica gel [ether/pentane : 60/40]. **Microanalysis** : $C_9H_{16}O_4$ requires C, 57.43 ; H, 8.57 %. Found : C, 57.20 ; H, 8.48 %. **^{1}H NMR** (250 MHz)

: 1.49 -1.59 (2H, m, $C\underline{H}_2$-CH_2-CH_2-CO_2), 1.70 - 1,88 (2H, m, $C\underline{H}_2$-CH_2-CO_2), 2.25 - 2.30 (2H, m, $C\underline{H}_2$-CO_2), 3.38 - 3.43 and 3.49 - 3.53 (4H and 2H, m, O-$C\underline{H}_2$), 3.60 (2H, t, J = 4.6 Hz, CO_2-CH_2-$C\underline{H}_2$), 4.21 (2H, t, J = 4.6 Hz, CO_2-$C\underline{H}_2$). **^{13}C NMR** (62.9 MHz) : 21.7 ($\underline{C}H_2$-CH_2-CO_2), 27.9 ($\underline{C}H_2$-CH_2-CH_2-CO_2), 34.3 ($\underline{C}H_2$-CO_2), 62.3 (CO_2-$\underline{C}H_2$), 68.6 (CO_2-CH_2-$\underline{C}H_2$), 69.1, 70.3, 71.0 (O-$\underline{C}H_2$), 173.6 ($\underline{C}$=O).

2,5,8,11-Tetraoxa-1-oxocyclopentadecane 3b prepared from **1b** as described above for **3a** [with an addition rate of 2.8 mmol/h and ether/pentane : 60/40 as eluent], was obtained as a pale oil (0.50g, 72%). **Microanalysis** : $C_{11}H_{20}O_5$ requires C, 56.88 ; H, 8.68 %. Found : C, 57.06 ; H, 8.79 %. **^{1}H NMR** (250 MHz) : 1.61 (2H, qu, J = 6.4 Hz, $C\underline{H}_2$-CH_2-CH_2-CO_2), 1.73 (2H, qu, J = 6.4 Hz, $C\underline{H}_2$-CH_2-CO_2), 2.35 (2H, t, J = 6.4 Hz, $C\underline{H}_2$-CO_2), 3.48 (2H, t, J = 6.4 Hz, O-$C\underline{H}_2$-CH_2-CH_2-CH_2-CO_2), 3.60 - 3.52 (8H, m, O-$C\underline{H}_2$), 3.64 (2H, t, J = 4.3 Hz, CO_2-CH_2-$C\underline{H}_2$), 4.21 (2H, t, J = 4.3 Hz, CO_2-$C\underline{H}_2$). **^{13}C NMR** (62.9 MHz) : 21.9 ($\underline{C}H_2$-CH_2-CO_2), 28.3 ($\underline{C}H_2$-CH_2-CH_2-CO_2), 33.7 ($\underline{C}H_2$-CO_2), 62.9 (CO_2-$\underline{C}H_2$), 68.7 (CO_2-CH_2-$\underline{C}H_2$), 69.8, 70.1, 70.4, 70.5, 70.9 (O-$\underline{C}H_2$), 173.5 ($\underline{C}$=O). The spectroscopic data recorded for this compound agree closely with those obtained from a sample independently prepared elsewhere.[11]

2,5,8,11,14-Pentaoxa-1-oxocyclooctadecane 3c prepared from **1c** as described above for **3a** [with an addition rate of 2.5 mmol/h and ether/pentane : 90/10 as

eluent], was obtained as a pale oil (0.58g, 70%). **Microanalysis** : $C_{13}H_{24}O_6$ requires C, 56.51 ; H, 8.75 %. Found : C, 56.35 ; H, 8.97 %. **^{1}H NMR** (250 MHz) : 1.47 - 1.58 (2H, m, $C\underline{H}_2$-CH_2-CH_2-CO_2), 1.58 - 1.72 (2H, m, $C\underline{H}_2$-CH_2-CO_2), 2.26 (2H, t, J = 6.5 Hz, $C\underline{H}_2$-CO_2), 3.36 (2H, t, J = 6.5 Hz, O-$C\underline{H}_2$-CH_2-CH_2-CH_2-CO_2), 3.42 - 3.56 (14H, m, O-$C\underline{H}_2$), 4.09 (2H, t, J = 4.5 Hz, CO_2-$C\underline{H}_2$). **^{13}C NMR** (62.9 MHz) : 22.2 ($\underline{C}H_2$-CH_2-CO_2), 28.4 ($\underline{C}H_2$-CH_2-CH_2-CO_2), 34.1 ($\underline{C}H_2$-CO_2), 62.9 (CO_2-$\underline{C}H_2$), 68.5 (CO_2-CH_2-$\underline{C}H_2$), 69.7, 69.9, 70.1, 70.3, 70.4 (O-$\underline{C}H_2$), 173.4 ($\underline{C}$=O). The spectroscopic data recorded for this compound agree closely with those obtained from a sample independently prepared elsewhere.[11]

2,5,8,11,14,17-Hexaoxa-1-oxocyclounicosane 3d prepared from **1d** as described above for **3a** [with an addition rate of 2.2 mmol/h and ether/methanol : 99/1 as eluent], was obtained as a pale oil (0.61g, 63%). **Microanalysis** : $C_{15}H_{28}O_7$ requires C, 56.23 ; H, 8.81 %. Found : C, 55.95 ; H, 8.70 %. **^{1}H NMR** (250 MHz) : 1.53 - 1.62 (2H, m, $C\underline{H}_2$-CH_2-CH_2-CO_2), 1.64 - 1.78 (2H, m, $C\underline{H}_2$-CH_2-CO_2), 2.34 (2H, t, J = 6.6 Hz, $C\underline{H}_2$-CO_2), 3.46 (2H, t, J = 6.6 Hz, O-$C\underline{H}_2$-CH_2-CH_2-CH_2-CO_2), 3.51 - 3.67 (18H, m, O-$C\underline{H}_2$), 4.19 (2H, t, J = 4.3 Hz, CO_2-$C\underline{H}_2$). **^{13}C NMR** (62.9 MHz) : 22.2 ($\underline{C}H_2$-CH_2-CO_2), 28.9 ($\underline{C}H_2$-CH_2-CH_2-CO_2), 34.2 ($\underline{C}H_2$-CO_2), 63.6 (CO_2-$\underline{C}H_2$), 69.0 (CO_2-CH_2-$\underline{C}H_2$), 70.3, 70.5, 70.6, 70.7, 70.8, 70.9, 71.0, 71.1 (O-$\underline{C}H_2$), 173.6 ($\underline{C}$=O). The spectroscopic data recorded for this compound agree closely with those obtained from a sample independently prepared elsewhere.[11]

2,5,8,11,14,17,20-Heptaoxa-1-oxocyclotetracosane 3e prepared from **1e** as described above for **3a** [with an addition rate of 1.1 mmol/h and ether/ethanol : 92/8 as eluent], was obtained as a pale oil (0.33g, 30%). **Microanalysis** : $C_{17}H_{32}O_8$ requires C, 56.03 ; H, 8.85 %. Found : C, 55.81 ; H, 8.82 %. **^{1}H NMR** (250 MHz) : 1.46 - 1.74 (4H, m, $C\underline{H}_2$-$C\underline{H}_2$-CH_2-CO_2), 2.31 (2H, t, J = 7.1 Hz, $C\underline{H}_2$-CO_2), 3.42 (2H, t, J = 6.1 Hz, O-$C\underline{H}_2$-CH_2-CH_2-CH_2-CO_2), 3.48 - 3.64 (22H, m, O-$C\underline{H}_2$), 4.55 (2H, t, J = 4.5 Hz, CO_2-$C\underline{H}_2$). **^{13}C NMR** (62.9 MHz) : 21.9 ($\underline{C}H_2$-CH_2-CO_2), 28.7 ($\underline{C}H_2$-CH_2-CH_2-CO_2), 34.0 ($\underline{C}H_2$-CO_2), 63.4 (CO_2-$\underline{C}H_2$), 69.1, 70.2, 70.5, 70.6$_0$, 70.6$_4$, 70.6$_8$, 70.7$_1$, 70.7$_4$ (O-$\underline{C}H_2$), 173.6 ($\underline{C}$=O).

11-Ethoxycarbonyl-2,5,8-trioxa-1-oxocyclododecane 6a and **11-ethoxy carbonylmethyl-2,5,8-trioxa-1-oxocycloundecane 7a** were prepared from **4a** as described above for **3a** [with an addition rate of 2.6 mmol/h]. Chromatography on silica [ether/pentane : 60/40] allowed their separation (0.29g, 37% for **6a** and 0.16g, 21% for **7a**).

6a. Microanalysis : $C_{12}H_{20}O_6$ requires C, 55.37 ; H, 7.74 %. Found : C, 55.12 ; H, 7.48 %. **^{1}H NMR** (250 MHz) : 1.22 (3H, t, J = 7.1 Hz, $C\underline{H}_3$), 1.72 - 1.86 (1H, m, O-CH_2-$C\underline{H}_2$-CH), 1.88 - 1.98 (1H, m, O-CH_2-$C\underline{H}_2$-CH), 2.46 (1H, dd, J = 10.8, -15.4 Hz, $C\underline{H}_2$-CO_2), 2.82 (1H, dd, J = 2.5, -15.4 Hz, $C\underline{H}_2$-CO_2), 3.02 - 3.15 (1H, m, C$\underline{H}$), 3.42 - 3.69 (8H, m, O-$C\underline{H}_2$), 4.11 (2H, q, J = 7.1 Hz, CO_2-$C\underline{H}_2$-CH_3), 4.21 (1H, ddd, J = 2.8, 6.3, -11.8 Hz, CO_2-$C\underline{H}_2$-CH_2-O), 4.37 (1H, ddd, J = 2.7, 6.7, -11.8 Hz, CO_2-$C\underline{H}_2$-CH_2-O). **^{13}C NMR** (62.9 MHz) : 14.6 ($\underline{C}H_3$), 31.0

($\underline{C}H_2$-CH-CH_2-CO_2), 37.1 ($\underline{C}H_2$-CO_2), 39.3 ($\underline{C}H$), 61.2 (CO_2-$\underline{C}H_2$-CH_3), 63.3 (CO_2-$\underline{C}H_2$-CH_2-O), 69.2 (O-$\underline{C}H_2$-CH_2-CH), 69.3 (CO_2-CH_2-$\underline{C}H_2$-O), 70.1, 71.4 (O-$\underline{C}H_2$), 172.3 (cyclic $\underline{C}$=O), 175.1 ($\underline{C}O_2$-CH_2-CH_3).

7a. Microanalysis : $C_{12}H_{20}O_6$ requires C, 55.37 ; H, 7.74 %. Found : C, 55.05 ; H, 7.68 %. **^{1}H NMR** (250 MHz) : 1.18 (3H, t, J = 7.1 Hz, $\underline{C}H_3$), 1.72 - 1.82 (2H, m, O-CH_2-$\underline{C}H_2$-CH), 2.34 (1H, dd, J = 5.9, -16.4 Hz, CH-$\underline{C}H_2$-CO_2), 2.75 (1H, dd, J = 8.9, -16.4 Hz, CH-$\underline{C}H_2$-CO_2), 2.80 - 2.89 (1H, m, $\underline{C}H$), 3.48 - 3.82 (8H, m, O-$\underline{C}H_2$), 3.95 (1H, ddd, J = 1.5, 5.4, -12.0 Hz, CO_2-$\underline{C}H_2$-CH_2-O), 4.06 (2H, q, J = 7.1 Hz, CO_2-$\underline{C}H_2$-CH_3), 4.47 (1H, ddd, J = 1.4, 8.8, -12.0 Hz, CO_2-$\underline{C}H_2$-CH_2-O). **^{13}C NMR** (62.9 MHz) : 14.6 ($\underline{C}H_3$), 33.3 ($\underline{C}H_2$-CH-CH_2-CO_2), 37.0 ($\underline{C}H_2$-CO_2), 41.2 ($\underline{C}H$), 61.1 (CO_2-$\underline{C}H_2$-CH_3), 65.8 (CO_2-$\underline{C}H_2$-CH_2-O), 70.0 (O-$\underline{C}H_2$-CH_2-CH), 70.3 (CO_2-CH_2-$\underline{C}H_2$-O), 71.3, 73.1 (O-$\underline{C}H_2$), 172.1 ($\underline{C}O_2$-CH_2-CH_3), 175.8 (cyclic $\underline{C}$=O).

2,5,8-Trioxa-1-oxo-11-phenylcyclododecane 6b and **11-benzyl-2,5,8-trioxa-1-oxocycloundecane 7b** prepared from **4b** as described above for **3a** [with an addition rate of 1.3 mmol/h and ether/pentane : 50/50 as eluent], were obtained as a pale oil (0.40g, 50%, mixture of **6b/7b** : 10/90). **Microanalysis** : $C_{15}H_{20}O_4$ requires C, 68.16 ; H, 7.63 %. Found : C, 68.502 ; H, 7.58 %. **^{1}H NMR** (250 MHz) : 1.55 - 1.69 (1H(**7a**), m, O-CH_2-$\underline{C}H_2$-CH and 1H(**7b**), m, O-CH_2-$\underline{C}H_2$-CH), 1.85 - 2.08 (1H(**7a**), m, O-CH_2-$\underline{C}H_2$-CH and 1H(**7b**), m, O-CH_2-$\underline{C}H_2$-CH), 2.53 - 2.68 (3H(**7a**), m, $\underline{C}H$-$\underline{C}H_2$-CO_2 and 2H(**7b**), m, $\underline{C}H$-$\underline{C}H_2$-Ph), 2.88 - 3.01

(1H(**7b**), m, $C\underline{H}_2$-Ph), 3.20 - 3.89 (8H(**7a**), m, O-$C\underline{H}_2$ and 9H(**7b**), m, O-$C\underline{H}_2$ and CO_2-$C\underline{H}_2$), 4.01 - 4.11 (1H(**7a**), m, CO_2-$C\underline{H}_2$), 4.29 - 4.38 ((1H(**7b**), m, CO_2-$C\underline{H}_2$), 4.50 - 4.61 (1H(**7a**), m, CO_2-$C\underline{H}_2$), 7.07 - 7.22 (5H(**7a**), m, Ph and 5H(**7b**), m, Ph). **^{13}C NMR** (62.9 MHz) : 32.7 (O-CH_2-$\underline{C}H_2$-CH(**7b**)), 35.4 (O-CH_2-$\underline{C}H_2$-CH(**7b**)), 38.5 ($\underline{C}H_2$-Ph(**7b**)), 39.1 ($\underline{C}$H(**7a**)), 42.3 ($\underline{C}H_2$-COO(**7a**)), 47.2 ($\underline{C}$H(**7b**)), 62.5 (COO-$\underline{C}H_2$(**7a**)), 64.9 (COO-$\underline{C}H_2$(**7b**)), 68.5, 68.6, 69.4, 71.0 (O-$\underline{C}H_2$(**7a**)), 70.3, 70.4, 70.9, 72.6 (O-$\underline{C}H_2$(**7b**)), 126.3 (aromatic p $\underline{C}$(**7b**)), 126.4 (aromatic p $\underline{C}$(**7a**)), 127.3, 128.5 (aromatic o and m $\underline{C}$(**7a**)), 128.3, 128.9 (aromatic o and m $\underline{C}$(**7b**)), 139.0 (aromatic $\underline{C}$(**7b**)), 145.2 (aromatic $\underline{C}$(**7a**)), 172.6 (C=O(**7a**)), 176.0 (C=O(**7b**)).

11-Methyl-2,5,8-trioxa-1-oxocyclododecane 6c prepared from **4c** as described above for **3a** [with an addition rate of 0.1 mmol/h and ether/pentane : 50/50 as eluent], was obtained as a pale oil (0.24g, 40%). **Microanalysis** : $C_{10}H_{18}O_4$ requires C, 59.39 ; H, 8.97 %. Found : C, 59.70 ; H, 8.72 %. **^{1}H NMR** (250 MHz) : 1.00 (3H, d, J = 6.7 Hz, $C\underline{H}_3$), 1.38 -1.50 (1H, m, O-CH_2-$C\underline{H}_2$-CH), 1.58- 1,75 (1H, m, O-CH_2-$C\underline{H}_2$-CH), 2.23 - 2.38 (1H, m, $C\underline{H}$), 2.11 (1H, dd, J = 2.7, -13.5 Hz, $C\underline{H}_2$-CO_2), 2.42 (1H, dd, J = 2.5, -13.5 Hz, $C\underline{H}_2$-CO_2), 3.45 - 3.64 (6H, m, O-$C\underline{H}_2$), 3.70 (2H, t, J = 5.1 Hz, CO_2-CH_2-$C\underline{H}_2$), 4.16 (1H, ddd, J = 3.9, 4.9, -11.9 Hz, CO_2-$C\underline{H}_2$), 4.45 (1H, ddd, J = 3.9, 5.4, -11.9 Hz, CO_2-$C\underline{H}_2$). **^{13}C NMR** (62.9 MHz) : 22.1 ($\underline{C}H_3$), 27.9 ($\underline{C}$H), 35.8 (O-CH_2-$\underline{C}H_2$-CH), 42.6 ($\underline{C}H_2$-CO_2), 62.6 (CO_2-$\underline{C}H_2$), 68.7 (CO_2-CH_2-$\underline{C}H_2$), 68.9, 69.3, 71.0 (O-$\underline{C}H_2$), 173.2 ($\underline{C}$=O).

12-Methyl-2,5,8-trioxa-1-oxocyclododecane 6d prepared from **4d** as described above for **3a** [with an addition rate of 3.1 mmol/h and ether/pentane : 50/50 as eluent], was obtained as a pale oil (0.36g, 60%). **Microanalysis** : $C_{10}H_{18}O_4$ requires C, 59.39 ; H, 8.97 %. Found : C, 59.50 ; H, 8.78 %. **^{1}H NMR** (250 MHz) : 1.10 (3H, d, J = 7.1 Hz, $C\underline{H}_3$), 1.48 -1.58 (2H, m, $C\underline{H}_2$-CH_2-CH), 1.80- 1,67 (2H, m, $C\underline{H}_2$-CH), 2.50 (1H, qd, J = 4.9, 7.1 Hz, C<u>H</u>), 3.42 - 3.56 (6H, m, O-$C\underline{H}_2$), 3.62 (2H, ddd, J = 3.1, 6.2, -11.9 Hz, CO_2-CH_2-$C\underline{H}_2$), 4.09 (1H, ddd, J = 3.1, 6.1, -11.9 Hz, CO_2-$C\underline{H}_2$), 4.48 (1H, ddd, J = 3.1, 6.4, -11.9 Hz, CO_2-$C\underline{H}_2$). **^{13}C NMR** (62.9 MHz) : 16.9 ($\underline{C}H_3$), 25.7 ($\underline{C}H_2$-CH_2-CH), 30.4 ($\underline{C}H_2$-CH), 39.6 (<u>C</u>H), 62.3 (CO_2-$\underline{C}H_2$), 68.7 (CO_2-CH_2-$\underline{C}H_2$), 70.3 (O-$C\underline{H}_2$-$(CH_2)_2$-CH), 69.0, 71.0 (O-$\underline{C}H_2$), 176.4 (<u>C</u>=O).

1-Ethoxycarbonyl-3,6,9-trioxacyclododecane 6e prepared from **4e** as described above for **3a** [with an addition rate of 2.6 mmol/h and ether/pentane : 70/30 as eluent], was obtained as a pale oil (0.47g, 64%). **Microanalysis** : $C_{12}H_{22}O_5$ requires C, 58.52 ; H, 9.00 %. Found : C, 58.23 ; H, 8.78 %. **^{1}H NMR** (250 MHz) : 1.18 (3H, t, J = 7.1 Hz, $C\underline{H}_3$), 1.38 -1.80 (2H, m, O-CH_2-$C\underline{H}_2$-CH_2-CH), 1.70-2.08 (2H, m, O-CH_2-CH_2-$C\underline{H}_2$-CH), 2.76 - 2.86 (1H, m, C<u>H</u>), 3.68 - 3.50 (12H, m, O-$C\underline{H}_2$), 4.09 (2H, q, J = 7.1 Hz, CO_2-$C\underline{H}_2$). **^{13}C NMR** (62.9 MHz) : 14.2 ($\underline{C}H_3$), 23.9 (O-CH_2-CH_2-$\underline{C}H_2$-CH), 26.1 (O-CH_2-$\underline{C}H_2$-CH_2-CH), 43.8 (<u>C</u>H), 60.2 (CO_2-$\underline{C}H_2$), 60.2, 69.6, 69.9, 70.0, 70.7, 71.2 (O-$\underline{C}H_2$), 173.9 (<u>C</u>=O).

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[13] Indeed, the rate of addition of the reactants cannot be decreased too much since the degradation of the reactants in the needle of the syringe, and then in the syringe, would become the major process (e.g. oligomerization or polymerization of the unsaturated ester).

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