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PERFLUOROALKYLATED MONOESTERS OF 1,4-D-SORBITAN, ISOSORBIDE AND ISOMANNIDE : NEW SURFACTANTS FOR BIOMEDICAL APPLICATIONS

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SUMMARY

A one step selective synthesis of pure 1,4-D-Sorbitan monoesters **4** was achieved by treating 1,4-D-Sorbitan **1** with $R_F(CH_2)_nCOCl$ ($R_F = C_4F_9$, C_5F_{11}, C_8F_{17}; n = 2, 10) in pyridine at room temperature. ^{13}C NMR establishes that esterification occurred on carbon 6 only. While isomannide, **3**, gives only one monoester, **8**, the less symmetrical isosorbide **2** leads to two monoesters displaying significantly different physical properties. These compounds display moderate surface activities and do not perturb the growth and viability of Namalva lymphoblastoïd cell cultures.

INTRODUCTION

Esters of the low-cost intramolecular mono and dianhydrides of hexitols have been employed, usually as mixtures, as nonionic surface-active agents, since the beginning of this century [1-3]. The cyclic inner ethers **1-3** (Scheme 1) formed by loss of one or two molecules of water from sorbitol and mannitol, and commonly called sorbitan, isosorbide and isomannide, are usually obtained in situ during the industrial esterification process [4, 5]. The esterification of sorbitan has been achieved with a wide range of saturated and unsaturated fatty acids, leading to a range of emulsifiers commonly known as Spans. These are essentially water-insoluble substances in which the hydrophobic character predominates (low hydrophilic-lipophilic balance, HLB) ; they are generally used as emulsifiers for

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preparing water-in-oil-type emulsions. These emulsifying agents become water-soluble, and reach high HLB values when polyoxyethylene chains are introduced, as in the products commonly known as Tweens or Polysorbates [6]. The literature describes emulsifying systems in which these two families of surfactants are used together; the combination of two agents with significantly different HLB values often gives better results than each one taken separately. Thus, for example, stable oil-in-water emulsions can be prepared by using polysorbate 20 as the primary emulsifying agent and sorbitan monolaurate, which is much less hydrophilic, as a stabilizer [7].

Some of the surfactants belonging to these two sorbitan-derived families are among the least toxic ones presently known and have therefore found numerous applications in medicine and pharmacy as in vehicles for drug administration and targetting, creams, ointments, suppository bases, as vasodilatators, intraocular pressure releasers, stabilizers for antibiotics, etc..; they are also used in cosmetic preparations, in the food industry, as detergents, in pesticides, as coating agents etc..[8].

Our search for more fluorophilic, hence more amphiphilic, but still biocompatible surfactants [9], in view of stabilizing fluorocarbon emulsions destined to serve as injectable oxygen-carriers (the so-called blood substitutes) [10-12] incited us to synthesize a family of esters of sorbitan, isosorbide and isomannide having a perfluoroalkylated chain, and to compare their performance with those of their hydrocarbon chain analogs. The perfluoroalkyl group was to be linked to the ester function by a hydrocarbon segment consisting of a variable number of methylene groups. Both the length of the F-alkyl chain itself and the total length of the hydrophobic chain are indeed expected to influence the surfactant's characteristics, its emulsion stabilisation capability, and the biological response it may provoke [13].

Industrially, the preparation of hexitol esters generally proceeds by heating D-sorbitol or D-mannitol directly with the fatty acid in the presence of acid or alkaline, or successively acid and alkaline, catalysts [14]. This approach is not selective and the commercially available products indeed all consist of complex mixtures containing unreacted material, mono and dianhydrides, several sorbitan monoesters in different positions, and variable amounts of polyesters [15, 16]. Figure 1 illustrates this situation.

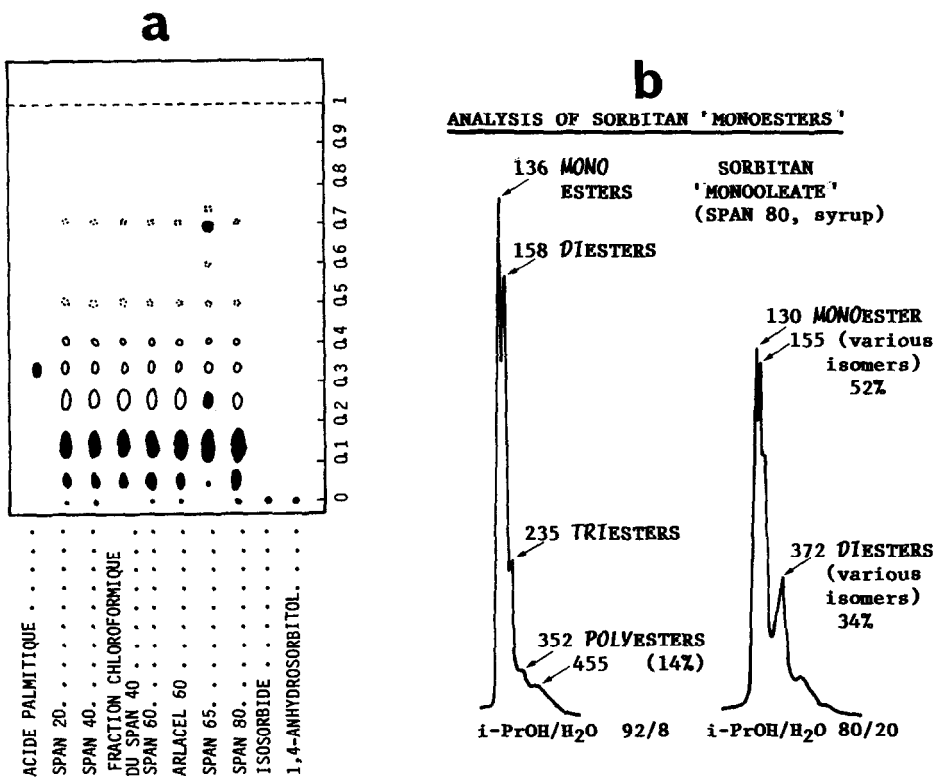
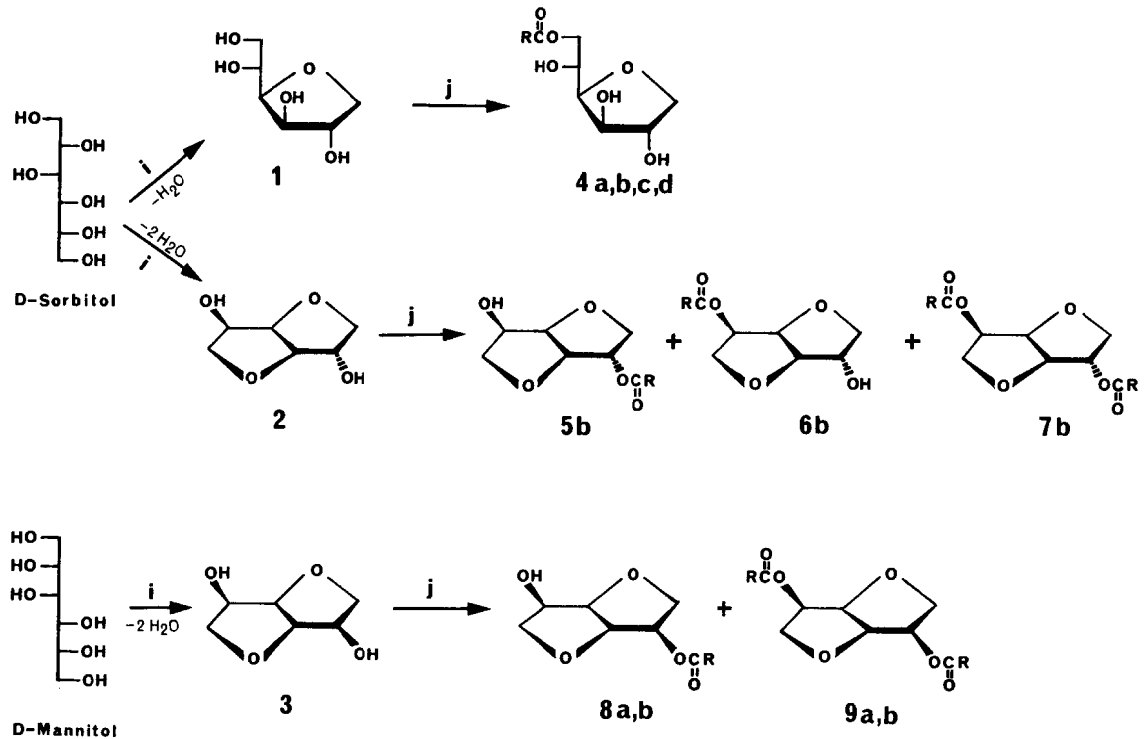


Fig. 1 . Purity of commercial surfactants as analyzed by TLC (fig. a : ref 15) and HPLC (fig. b : ref 16).

The use of such complex and poorly defined mixtures can hardly be envisaged in preparations destined to be administered intravenously in large amounts, as will be the case with fluorocarbon emulsions. Our objective was therefore to produce pure, well defined amphiphiles, which obliged us to investigate a more selective two-step approach (scheme 1) in which the mono and dianhydrosorbitol and mannitol **1** [17], **2** [18] and **3** [19] were prepared first, isolated and purified, and only then esterified. The esterification of 1,4-D-sorbitan (50% excess) using the acyl chlorides, $R_F(CH_2)_nCOCl$, (n = 2 or 10, R_F being a linear perfluoroalkylated chain of 4, 5



i : Δ, H^+ ; j : $R_F(CH_2)_nCOCl/Py$, $CHCl_3$

R : $R_F(CH_2)_n$; a : $C_5F_{11}(CH_2)_2$, b : $C_8F_{17}(CH_2)_2$, c : $C_4F_9(CH_2)_{10}$, d : $C_8F_{17}(CH_2)_{10}$

Scheme 1 . Synthesis route of perfluoroalkylated 1,4-D-sorbitan, isosorbide and isomannide esters.

or 8 carbon atoms), occurred essentially on the primary hydroxy group [20]; the formation of a minute amount of an unidentified less polar compound was detected by TLC, but it was eliminated completely during the purification process. The monoesters were obtained in yields ranging from 43 to 74% after purification by recrystallization or column chromatography. Their purity was checked by TLC and HPLC (fig. 2).

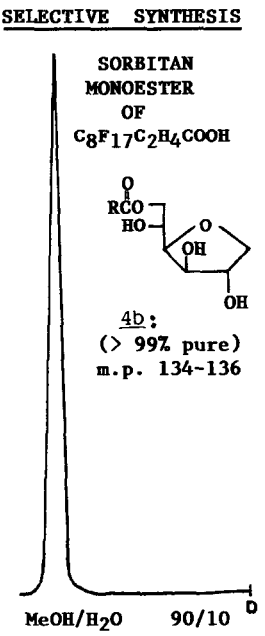


Fig. 2 : Purity of **4b** by HPLC (compare to fig. 1b)

The structure of the sorbitan esters **4a-d** and the position at which the esterification took place were determined by ^{13}C NMR. A carbon-proton coupled spectrum (Off-Resonance technique), allowed the assignment of the primary hydroxyl group; comparing the $^{13}C\{^1H\}$ decoupled spectrum with that of free 1,4-D-sorbitan [21] then showed that the C-6 carbon, α to the carbonyl function, had shifted downfield, while C-5, β to C(O), had shifted upfield. The methylene groups α and β to the F-alkyl chain have very characteristic signals both for the 1,4-D-sorbitan esters and for the isomannide and isosorbide esters. Thus in the $^{13}C\{^1H\}$ decoupled spectrum, the CH_2 α to the R_F group gives a triplet with $^2J_{CF}$ = 22 Hz, and the CH_2 β to R_F a triplet with $^3J_{CF}$ = 6 Hz. If one compares **4a,b** with **4c,d** one notices that in the latter case the CH_2 α to the carbonyl group is deshielded by about 9 ppm because the ten methylene groups act as a screen, and therefore the α and β effect induced by the R_F and C(O) become independent.

The esterification of **2** and **3** led to variable amounts of mono and diester; the amount of diester present can be reduced by use of an excess of isosorbide or isomannide ; thus for example 7% of **9a** was formed when the **3**/R_F ratio was of 2.6/1, instead of 24% of **9b**, when there was only a 15% excess of **3** with respect to the acyl chloride.

Both the exo and the endo hydroxyl groups of **2** are known to undergo esterification in proportions depending on the medium and the acylating agent [22]. In the case of the perfluoroalkylated acid chlorides, when the reaction was conducted in pyridine, the exo-monoester **5b** was formed predominantly (53%) along with some endo-monoester **6b** (20%) and a relatively small amount of diester **7b** (4.5%).

The structures of the isomannide and isosorbide esters were determined as above. The ^{13}C signals assigned to the bridgehead carbon atoms (C-3,4) in the isomannide monoesters **8a,b** are shifted further downfield, as they are adjacent to two tertiary carbon atoms, whereas one neighbouring atom of the C-2,5 is a secondary carbon. The comparison between the isomannide **3** and its monoesters **8a,b** shows an increase of the number of signals from 3 into 6; the C-2 carbon α to the carbonyl group are shifted downfield by 2.9 ppm while C-1 and C-3, β to C(O), are shifted upfield by 4.1 and 1.5 ppm respectively. The assignment of C-1,6 was made on the basis of the carbon-proton coupled spectrum (triplet by Off-Resonance technique). In the symmetrical diesters **9a,b** the carbons C-1,2,3 are equivalent to C-4,5,6.

^{13}C NMR was also efficacious for confirming the structure assignment : **5b** displays a downfield shift of C-2 by 2.6 ppm compared to isosorbide [23, 24]; similarly, C-5 in **6b** is shifted downfield by 2.8 ppm. In the spectrum of the diester **7b** one notices a downfield shift of both C-2 and C-5 by 2.3 and 2.4 ppm respectively.

The isosorbide monoesters **5b, 6b** display quite distinct physical properties. The endo-ester **6b** was found to be significantly more soluble in polar organic solvents than the exo-ester **5b**. For example, **6b** and **5b** were soluble at 42 and 23 g/l, respectively, in MeOH, while **5b** was more soluble than **6b** in CCl_4. This reflects the reduced polar character of the latter, which can be assigned to the fact that the V shape of the molecule makes intramolecular hydrogen bonding possible. This difference in polarity is further evidenced by TLC, where **5b** is eluted more readily (r_f = 0.38) than **6b** (r_f = 0.15, $CHCl_3$-MeOH 10:0.5).

As expected the perfluoroalkylated monoesters have very low solubilities in water, lower than those of their hydrocarbonated analogs. The most soluble ones are the F-pentyl esters of 1,4-D-sorbitan **4a** and isomannide **8a** (ca. 0.1 g/l). These products are however dispersible in aqueous Pluronic F-68 solutions.

Their surface activity is illustrated by the lowering of the surface tension, γ_S, and F-decalin/water interfacial tension, γ_i, they induce when they are dispersed at a 1% concentration in a 1 g/l Pluronic F-68 solution in water : **4a** : γ_S = 37.5, γ_i = 21.0; **8a** : γ_S = 39.5, γ_i = 28.5 ±0.3 mNm^{-1}. It should however be noted that this lowering of the surface or interfacial tensions is not very considerable, compared to those obtained with perfluoroalkylated derivatives of pentitols or hexitols [25].

The esters **4a** and **8a** were stable when heated in aqueous solutions under nitrogen or oxygen at 121°C for 15 min (FDA sterilization norm); HPLC analysis (Eluant : MeOH-H_2O 90 :10) showed no detectable modification.

Preliminary indications of the biological inertness of these compounds are given by the absence of influence of a 0.1 g/l solution of **4a** and **8a** on the cell's growth rate and viability of a lymphoblastoïd cell culture of the Namalva strain when compared to controls.

EXPERIMENTAL

Physical methods

Melting points were measured on a Reichert apparatus. Infrared spectra were realized with a Bruker IFS 45 spectrometer (ν cm^{-1}), ^1H NMR (δ ppm, internal reference Me_4Si), ^{19}F NMR (δ ppm, internal reference CCl_3F) and ^{13}C NMR (δ ppm, internal reference Me_4Si) spectra with a Bruker WP 80 or WH 90 spectrometer, mass spectra with a Ribermag R10-10 spectrometer. TLC were effected on silica gel plates (Merck 60 F_{254}) ; two revelators were used for detection (A : H_2SO_4-MeOH 1/1 and B : $KMnO_4$-NaOH 0,5g/100ml 1N). Column chromatography was performed with Kieselgel 60, 70-230 mesh ASTM (Merck). HPLC was realized with a Waters analytical model 510 with a differential refractometer detector R401 equipped with a column Si resolve 5µ 15cm x 3.9mm for the isomannide and isosorbide derivatives and a column C_{18} Bondapak 9µ 30cm x 3.9mm for the sorbitan derivatives. Optical rotations were measured with a Perkin Elmer 141 polarimeter (1dm cell, at 589nm).

Starting materials

Solvents (chloroform, acetone, pyridine) were distilled in the usual ways, and stored under dried argon. All reactants were dried under reduced pressure (10^{-2}mm Hg) before use when the reaction was conducted in dry conditions (esterification).

n-$C_8F_{17}(CH_2)_2CO_2H$ was a gift from Atochem. The acids $C_5F_{11}(CH_2)_2CO_2H$ and $R_F(CH_2)_{10}CO_2H$ (R_F = n-C_4F_9, n-C_8F_{17}) were synthesized as formerly described [25]. The F-alkyl acyl chlorides $R_F(CH_2)_nCOCl$ were obtained by refluxing the corresponding acid with an excess of thionyl chloride and distilled off (n = 2, R_F = n-C_5F_{11}, b.p. = 55°C/20 mm Hg, 82%; n = 2, R_F = n-C_8F_{17}, b.p. = 98°C/20 mm Hg, 90%; n = 10, R_F = n-C_4F_9, b.p. = 104°C/0,06 mm Hg, 98%; n = 10, R_F = n-C_8F_{17}, b.p. = 130°C/0,07 mm Hg, 92%).

Pure 1,4-monoanhydro-D-sorbitan **1** was obtained in 38% yield according to the literature [17] : TLC ($CHCl_3$-EtOH 1 :1, rev.A) r_f = 0,26; m.p. = 108-112°C

(lit. 115-116°C) [17]; $|\alpha|_D^{25}$ = -21.4° (c 1.1, H_2O) (lit. : -21.9°, c 2.5, H_2O) [17]. The structure was confirmed by ^{13}C NMR (D_2O) [21].

1,4 :3,6-dianhydro-D-sorbitol **2** was synthesized as described by Hockett [18] : typically 100g of D-sorbitol yielded, after distillation and recrystallization from AcOEt, 49g of **2** (61%), m.p. = 61-63°C (lit. : 61.9-64°C [18], $|\alpha|_D^{26}$ = +44.7° (c 1, H_2O) (lit : 44.8°, H_2O [18]). **2** showed one spot by TLC ($CHCl_3$-EtOH 5 :1, rev. A, r_f = 0.31) and the structure was confirmed by ^1H NMR [26].

1,4 :3,6-dianhydro-D-mannitol [19] **3** was obtained similarly : TLC ($CHCl_3$-EtOH 5 :1, rev. B) r_f = 0.43; m.p. = 95-98°C (lit. : 87°C [19]); $|\alpha|_D^{24}$ = +96.4° (c 1, MeOH) (lit : +90.9°, H_2O [19]).

A- 1,4-Sorbitan derivatives

*6-O-|3'-(F-pentyl)-propanoyl|-1,4-D-sorbitan, **4a***

A solution of 6.21g (17.2 mmol) of 3-(F-pentyl)-propanoyl chloride in 80ml of anhydrous chloroform was added dropwise (7h) to 7g (42.6 mmol) of 1,4-D-sorbitan in 30ml of anhydrous pyridine. After 24h at room temperature with vigorous stirring, the mixture was concentrated under reduced pressure. 200ml of water and 100ml of ether were added, the water layer was extracted twice with 100ml of ether, the organic phases were washed with water to neutrality, dried (Na_2SO_4), and evaporated, yielding a white solid which was purified by column chromatography (CH_2Cl_2-EtOH 5 :1 then 5 :2), giving 6.22g (74%) of pure **4a**, which can be recrystallized from a $CHCl_3$-MeOH mixture to give white needles.

TLC (CH_2Cl_2-EtOH 5 :1, rev. B) r_f = 0.72; HPLC (MeOH-H_2O 90 :10) t_r = 3.65 mn; m.p. = 127-129°C; $|\alpha|_D^{22}$ = -0.9 (c 1.1, MeOH); Anal. found : C 34.70, H 3.28, F 43.31%; calcd for $C_{14}H_{15}O_6F_{11}$: C 34.44, H 3.09, F 42.80%; IR (KBr) : 3490, 3330 (OH), 1715 (C=O), 1140-1350 (C-F); ^1H NMR (DMSO-d_6) : 2.29-2.85 (m, 4H, $C_2H_4R_F$), 3.39-5.08 (m, 11H, sorbitan protons); ^{19}F NMR (CD_3OD) : -80.5 (3F, CF_3), -113.9, (2F, $CF_{2\alpha}$), -122.5 (2F), -123.3 (2F), -126.0 (2F, $CF_{2\omega}$); ^{13}C NMR (DMSO-d_6) : 24.9 (t, $^3J(CF)$ = 4.8 Hz, C-2'), 25.6 (t, $^2J(CF)$ = 22 Hz, C-3'), 66.0 (C-5), 67.8 (C-6), 73.6 (C-1), 75.5 (C-3), 76.5 (C-2), 80.6 (C-4), 171.0 (C=O); MS (CI : NH_3) : m/e 507 100% $M+1+18|^+$, m/e 506 98% $M+18|^+$, m/e 489 99% $M+1|^+$, m/e 471 66% $M+1-18|^+$.

*6-O-|3'-(F-octyl)-propanoyl|-1,4-D-sorbitan, **4b***

A similar process to that used for product **4a** was applied to 9.22g (18 mmol) of 3-(F-octyl)-propanoyl chloride and 5.89g (35.9 mmol) of 1,4-D-sorbitan. After 24h at room temperature, the precipitate was filtered, washed with water then

with chloroform, yielding, after crystallization from MeOH 6.85g (60%) of **4b**.
TLC (CH_2Cl_2-EtOH 5 :2, rev. A) r_f = 0.43; HPLC (MeOH-H_2O 90 :10) t_r = 4.4 mn; m.p. = 134-136°C; $|\alpha|_D^{18}$ = -2° (c 1, DMSO); Anal. found : C 32.04 , H 2.39 , F 50.62%; calcd for $C_{17}H_{15}O_6F_{17}$: C 31.99 , H 2.37 , F 50.60%; IR (KBr) : 3440 (OH), 1720 (C=O), 1115-1345 (C-F); ^{19}F NMR (CD_3OD) : -80.8 (3F, CF_3), -114.0 (2F, $CF_2\alpha$), -121.8 (6F), -122.7 (2F), -123.1 (2F), -126.1 (2F, $CF_2\omega$); ^{13}C NMR (DMSO-d_6): 26.2 (C-2'), 26.9 (t, $^2J(CF)$ = 22 Hz, C-3'), 66.0 (C-5), 67.8 (C-6), 73.7 (C-1), 75.6 (C-3), 76.5 (C-2), 80.6 (C-4), 171.0 (C=O); MS (CI : NH_3) = m/e 657 27% M+1 + 18|$^+$, m/e 656 100% M+18|$^+$, m/e 639 49% M+1|$^+$, m/e 638 34% M$^+$.

*6-O-|11'-(F-butyl)-undecanoyl|-1,4-D-sorbitan, **4c***

The same procedure as for **4a**, when applied to 8.28g (19.59 mmol) of 11-(F-butyl)-undecanoyl chloride in 90ml of anhydrous chloroform and 6.54g (39.8 mmol) of 1,4-D-sorbitan gave, after treatment as for **4b**, and purification by column chromatography (CH_2Cl_2-EtOH 5 :1 then 5 :2), 7.6 g (71%) of **4c** as a white solid.
TLC (CH_2Cl_2-EtOH 5 :1, rev. B) r_f = 0.75; HPLC (MeOH-H_2O 90 :10) t_r = 5.8 mn; $|\alpha|_D^{23}$ = -1.2 (c 1.1, MeOH); Anal. found : C 45.84, H 5.56, F 31.14%; calcd for $C_{21}H_{31}O_6F_9$: C 45.82, H 5.67, F 31.06%; IR (KBr) : 3385, 3280 (OH), 1730 (C=O), 1130-1280 (C-F); ^{19}F NMR (DMSO-d_6) : -80.7 (3F, CF_3), -113.8 (2F, $CF_2\alpha$), -124.1 (2F, $CF_2\beta$), -125.8 (2F, $CF_2\omega$); ^{13}C NMR (DMSO-d_6) : 19.9 (C-10'), 24.7 (C-3'), 29.1 (C-4' to C-9'), 29.9 (t, $^2J(CF)$ = 23 Hz, C-11'), 33.8 (C-2'), 66.3 (C-5), 67.2 (C-6), 73.8 (C-1), 75.7 (C-3), 76.6 (C-2), 80.7 (C-4), 173.3 (C=O).

*6-O-|11'-(F-octyl)-undecanoyl|-1,4-D-sorbitan, **4d***

Likewise, 2.6g (15.8 mmol) of 1,4-anhydro-D-sorbitol **1** when allowed to react with 3.3g (5.3 mmol) of 11-(F-octyl)-undecanoyl chloride gave, after treatment as for **4b**, and recrystallization from methanol, 2.5g (67%) of **4d**.
TLC (CH_2Cl_2-MeOH 10 :1, rev. B) r_f = 0.56; HPLC (MeOH-H_2O 90 :10) t_r = 11.6 mn; m.p. = 126°C; $|\alpha|_D^{26}$ = -1° (c 1.1, DMSO); Anal. found : C 40.71, H 4.22 , F 42.86%; calcd for $C_{25}H_{31}O_6F_{17}$: C 40.01 , H 4.16 , F 43.03%; IR (KBr) : 3395 (OH), 1730 (C=O), 1150-1245 (C-F); ^{19}F NMR (CD_3OD) : -81.5 (3F, CF_3), -114.3 (2F, $CF_2\alpha$), -122.2 (6F), -123.1 (2F), -123.5 (2F), -126.7 (2F, $CF_2\omega$); ^{13}C NMR (CD_3OD) : 21.3 (C-10'), 26.1 (C-3'), 30.4 (C-4' to C-9'), 32.0 (t, $^2J(CF)$ = 23 Hz, C-11'), 35.2 (C-2'), 68.0 (C-5), 70.0 (C-6), 74.9 (C-1), 78.1 (C-3), 78.6 (C-2), 81.6 (C-4), 175.8 (C=O); MS (CI : NH_3) : m/e 769 6% M+1 + 18|$^+$, m/e 768 15% M+18|$^+$, m/e 751 100% M+1|$^+$, m/e 750 74% M$^+$.

B- Isosorbide and isomannide derivatives

2-O-[3'-(F-octyl)-propanoyl]-1,4:3,6-dianhydro-D-sorbitol, ***5b,*** *5-O-[3'-(F-octyl)-propanoyl]-1,4:3,6-dianhydro-D-sorbitol,* ***6b,*** *and 2,5di-O-[3'-(F-octyl)-propanoyl]-1,4:3,6-dianhydro-D-sorbitol,* ***7b***

To a large excess of **2** (9g, 61.6 mmol, 2.5 eq.), dissolved in 340ml of anhydrous chloroform and 2.60ml (32.2 mmol) of anhydrous pyridine, were added dropwise 12.32g (24.1 mmol) of 3-(F-octyl)-propanoyl chloride in chloroform. After stirring overnight at room temperature the chloroform was evaporated; addition of water and of a minimum of ether precipitated **5b.** Filtration and washing gave 4.23g of **5b,** which was purified by recrystallization from a hexane-methanol mixture. The filtrate was washed to neutrality, dried on Na_2SO_4 and evaporated, yielding 9.46g of a white solid, analyzed by TLC ($CHCl_3$-MeOH 10 :0.5, rev. A) as a mixture of **5b, 6b** and **7b.** Recrystallization from ether gave 2.8g of **5b** with traces of **6b,** which were separated by column chromatography ($CHCl_3$-MeOH 10 : 0.5). The filtrate from the last recrystallization, which contains mainly **6b** and **7b,** was also chromatographed. The overall procedure yielded :

- the monoester **5b:** 7.94g, 53%.

TLC ($CHCl_3$-MeOH 10 :0.5, rev. A) r_f = 0.38; m.p. = 113-118°C; $[\alpha]_D^{21}$ = +20.6° (c 1, acetone); Anal. found : C 33.18, H 2.10, F 51.78 %; calcd for $C_{17}H_{13}O_5F_{17}$: C 32.92, H 2.11, F 52.07%; IR (KBr) : 3430 (OH), 1745 (C=O), 1180-1280 (C-F); ^{1}H NMR (acetone d_6) : 2.1-2.37 (m, $C_2H_4R_F$), 2.76-3.3 (m, H-1, H-1', H-6, H-6', OH), 3.36-3.56 (m, H-5), 3.58-3.80 (m, H-3, H-4), 5.15 (m, H-2); ^{19}F NMR (acetone-d_6) : -80.9 (3F, CF_3), -114.1 (2F, $CF_2\alpha$), -121.6 (6F), -122.4 (2F), -123.2 (2F), -125.9 (2F, $CF_2\omega$); ^{13}C NMR (acetone-d_6) : 26.0 (C-2'), 27.0 (t, ^{2}J(CF) = 23.5 Hz, C-3'), 72.9 (C-5), 73.4 (C-6), 73.8 (C-1), 80.2 (C-2), 83.0 (C-4), 86.4 (C-3), 171.0 (C=O); MS (EI) : m/e 620 5% M^+, m/e 475 19% $C_8F_{17}C_2H_4C{\equiv}O^+$, m/e 128 65% loss of $R_FC_2H_4CO_2H$ --> $C_6H_8O_3$, m/e 85 61% loss of $CH_2CHO\cdot$ by 128 ---> $C_4H_5O_2$, m/e 69 100%.

- the monoester **6b** : 2.96g, 20%.

TLC ($CHCl_3$-MeOH 10 :0.5, rev : A) r_f = 0.15; m.p. = 107-111°C $[\alpha]_D^{21}$ = +34.6° (c 1, acetone); Anal found : C 33.03, H 2.25, F 51.80 %; calcd for $C_{17}H_{13}O_5F_{17}$: C 32.92, H 2.11, F 52.07 %; IR (KBr) : 3410 (OH), 1740 (C=O), 1180-1280 (C-F); ^{1}H NMR (acetone-d_6) : 2.25-2.90 (m, $C_2H_4R_F$), 3.61-3.97 (m, H-1, H-1', H-6, H-6'), 4.06-4.42 (m, H-2, H-3, OH), 4.77 (triplet, H-4), 5.16 (quartet, H-5); ^{19}F NMR (acetone-d_6) : -80.9 (3F, CF_3), -114.3 (2F, CF_2), -121.5 (6F), -122.4 (2F), -123.2 (2F), -125.9 (2F, $CF_2\omega$); ^{13}C NMR (acetone-d_6) : 25.8 (C-2'), 27.1 (t,

$^2J(CF)$ = 23.5 Hz, C-3'), 71.0 (C-6), 76.1 (C-5),76.4 (C-1), 76.8 (C-2), 81.5 (C-4), 89.7 (C-3), 171.2 (C=O); MS (EI) : m/e 620 12% M^+, m/e 475 23% $C_8F_{17}C_2H_4C{\equiv}O^+$, m/e 128 99% loss of $R_FC_2H_4CO_2H$ —> $C_6H_8O_3$, m/e 85 63% loss of CH_2CHO by 128 ——> $C_4H_5O_2$, m/e 69 100%.

- the diester **7b** : 1.2g, 4.5%.
TLC ($CHCl_3$-MeOH 10 :0.5, rev. A) r_f = 0.9; m.p. = 115-118°C; IR (KBr) : 1735 (C=O), 1100-1270 (C-F); ^{19}F NMR ($CDCl_3$) : -81.5 (3F, CF_3), -114.8 (2F, $CF_2\alpha$), -121.1 (6F) -122.9 (2F), -123.7 (2F), -126.4 (2F, $CF_2\omega$); ^{13}C NMR ($CDCl_3$) : 25.5, 25.7 (2t, $^3J(CF)$ = 4.8 Hz, C-2'), 26.8, 26.9 (2t, $^2J(CF)$ = 22 Hz, C-3'), 70.5 (C-6), 73.3 (C-1), 74.7 (C-5), 78.9 (C-2), 80.8 (C-4), 86.1 (C-3), 170.2, 170.5 (2C=O).

2(5)-O-|3'-(F-pentyl)-propanoyl|-1,4 :3,6dianhydro-D-mannitol, ***8a,*** *and 2,5-di-O-|3'-(F-pentyl)-propanoyl|-1,4 :3,6-dianhydro-D-mannitol,* ***9a***

4.26g (11.81 mmol) of 3-(F-pentyl)-propanoyl chloride in 50ml of chloroform were added dropwise in 2 h to a solution of 1,4 :3,6-dianhydro-D-mannitol (4.51g, 30.89 mmol) in 150ml of anhydrous chloroform and 3ml of pyridine. Stirring was maintained for 24h at room temperature , the reaction being monitored by TLC (CH_2Cl_2-CH_3CN 5 :1, rev. A). Chloroform was then evaporated, and water (150ml) and ether (150ml) were added. The aqueous phase was extracted 4 times with 100ml of ether. The organic phases were combined, washed to neutrality, dried over Na_2SO_4 and evaporated. Purification on column chromatography (CH_2Cl_2-EtOH 10 :0.5) afforded 3.99g (72%) of monoester **8a** and 0.67g (7%) of diester **9a** as white solids.

8a : TLC (CH_2Cl_2-CH_3CN 5 :1, rev. A) r_f = 0.41; m.p. = 41-42°C, $|\alpha|_D^{25}$ = +63.3° (c 1, $CHCl_3$); Anal. found : C 35.54 , H 2.56 , F 44.41%; calcd for $C_{14}H_{13}O_5F_{11}$: C 35.76 , H 2.78 , F 44.44%; IR (KBr) : 3465 (OH), 1745 (C=O), 1100-1345 (C-F); ^1H NMR ($CDCl_3$) : 2.12-2.85 (m, $C_2H_4R_F$), 3.26-4.34 (m, H-1, H-1', H-6, H-6', OH), 4.45 (triplet, H-3), 4.7 (t, H-4), 5.18 (quartet, H-2); ^{19}F NMR ($CDCl_3$) : -81.4 (3F, CF_3), -115.3 (2F, $CF_2\alpha$), -123.2 (2F), -124.3 (2F), -126.9 (2F, $CF_2\omega$); ^{13}C NMR ($CDCl_3$) : 25.4 (t, $^3J(CF) < 6$ Hz, C-2'), 26.5 (t, $^2J(CF)$ = 24 Hz, C-3'), 71.0 (C-1), 72.3 (C-5), 73.9 (C-6), 74.8 (C-2), 80.5 (C-3), 81.8 (C-4), 170.9 (C=O); MS (EI) : m/e 325 77% $C_5F_{11}C_2H_4C{\equiv}O^+$, m/e 128 3% $C_6H_8O_3$, m/e 110 100% $C_6H_6O_2$, m/e 85 17% $C_4H_5O_2$, m/e 69 33%.

9a : TLC (CH_2Cl_2-CH_3CN 5 :1, rev. A) r_f = 0.83; m.p. = 29-30°C; $|\alpha|_D^{25}$ = +67.1° (c 1.2, $CHCl_3$). Anal. found : C 33.17, H 2.02, F 52.56%; calcd for $C_{22}H_{16}O_6F_{22}$: C 33.26, H 2.03, F 52.62%; IR (KBr) : 1740 (C=O), 1110-1340 (C-F); ^1H NMR ($CDCl_3$) : 2.15-2.85 (m, $C_2H_4R_F$), 3.71-4.15 (m, H-1, H-1'), 4.68-4.77 (m, H-3,

H-4), 5.02-5.23 (m, H-2, H-5); ^{19}F NMR ($CDCl_3$) : -81.5 (3F, CF_3), -115.3 (2F, $CF_2\omega$), -123.2 (2F), -124.3 (2F), -126.9 (2F, $CF_2\omega$); ^{13}C NMR ($CDCl_3$) : 25.5 (t, $^3J(CF) < 6$ Hz, C-2'), 26.8 (t, $^2J(CF) = 24$ Hz, C-3'), 70.7 (C-1, C-6), 74.5 (C-2, C-5), 80.6 (C-3, C-4), 170.9 (C=O) ; MS (EI) : m/e 325 100% $C_5F_{11}C_2H_4C{\equiv}O|^+$, m/e 85 80% $C_4H_5O_2$, m/e 69 85% .

2(5)-O-|3'-(F-octyl)-propanoyl|-1,4 :3,6-dianhydro-D-mannitol, ***8b****, and 2,5-di-O-|3'-(F-octyl)-propanoyl|-1,4 :3,6 dianhydro-D-mannitol,* ***9b***

The same procedure as for **8a** and **9a** applied to 15.39g (30.1 mmol) of 3-(F-octyl)-propanoyl chloride in chloroform and 5.28g (36.2 mmol) of isomannide in 200ml of anhydrous chloroform and 4ml of pyridine, led after stirring and treatment, to a mixture of **8b** and **9b** (TLC $CHCl_3$-CH_3CN 5 :1). Preparative HPLC ($CHCl_3$-CH_3CN 5 :1 , column Waters prepak 500, silice support) led to 8.12g (43%) of monoester **8b** and 7.83g (24%) of diester **9b**.

8b : White flakes , recrystallized from hexane; TLC ($CHCl_3$-CH_3CN 5 :1, rev. A) $r_f = 0.51$; m.p. = 93°C; $|\alpha|_D^{24} = +48.4°$ (c 1, $CHCl_3$); Anal. found : C 33.00, H 1.95, F 51.84%; calcd for $C_{17}H_{13}O_5F_{17}$: C 32.91, H 2.11, F 52.07%; IR (KBr) : 3490 (OH), 1745 (C=O), 1100-1300 (C-F); ^1H NMR ($CDCl_3$) : 2.16-2.89 (m, $C_2H_4R_F$), 3.42-4.3 (m, H-1, H-1', H-6, H-6', OH), 4.46 (triplet, H-3), 4.65 (triplet, H-4), 5.16 (quartet, H-2); ^{19}F NMR ($CDCl_3$) : -81.4 (3F, CF_3), -115.0 (2F, $CF_2\alpha$), -122.4 (6F), -123.3 (2F), -123.9 (2F), -126.7 (2F, $CF_2\omega$); ^{13}C NMR ($CDCl_3$) : 25.3 (t, $^3J(CF) < 6$ Hz, C-2'), 26.6 (t, $^2J(CF) = 24$ Hz, C-3'), 71.0 (C-1), 72.4 (C-5), 74.0 (C-6), 74.9 (C-2), 80.6 (C-2), 81.9 (C-4), 170.9 (C=O); MS (CI) : m/e 638 100% $M+18|^+$, m/e 621 55% $M+1|^+$, m/e 620 1% M^+, m/e 475 2% $C_8F_{17}C_2H_4C{\equiv}O^+$, m/e 128 34% $C_6H_8O_3$, m/e 110 22% $C_6H_6O_2$.

9b : Recrystallized from hexane, white flakes, TLC ($CHCl_3$-CH_3CN 5 :1, rev. A) $r_f = 0.97$; m.p. = 108°C; $|\alpha|_D^{20} = +52°$ (c 1, $CHCl_3$); Anal. found : C 30.74, H 1.31, F 59.60%; calcd for $C_{28}H_{16}F_{34}O_6$: C 30.73, H 1.47, F 59.02%; IR (KBr) : 1745 (C=O), 1100-1300 (C-F); ^1H NMR ($CDCl_3$) : 2.15-2.85 (m, $C_2H_4R_F$), 3.72-4.15 (m, H-1, H-1'), 4.68-4.77 (m, H-3, H-4), 5.02-5.23 (m, H-2, H-5); ^{19}F NMR ($CDCl_3$) : -81.4 (3F, CF_3), -115.0 (2F, $CF_2\alpha$), -122.4 (6F), -123.2 (2F), -123.9 (2F), -126.7 (2F, $CF_2\omega$); ^{13}C NMR ($CDCl_3$) : 25.4 (t, $^3J(CF) < 6$ Hz, C-2'), 26.7 (t, $^2J(CF) = 24$ Hz, C-3'), 70.7 (C-1, C-6), 74.5 (C-2, C-5), 80.7 (C-3, C-4), 170.9 (C=O); MS (EI) : m/e 475 12% $C_8F_{17}C_2H_4C{\equiv}O^+$, m/e 110 100% $C_6H_6O_2$, m/e 69 30%.

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