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Synthesis of α-CF_2-mannosides and Their Conversion to Fluorinated Pseudoglycopeptides

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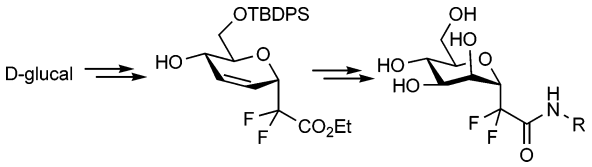
Received November 17, 2007



A methodology allowing the synthesis α-CF_2-mannosides, based on the addition of a difluoroenoxysilane to a glycal followed by a dihydroxylation reaction, is described. The resulting 2,2-difluoro-2-mannosylacetate is converted into two pseudoglycopeptides which may act as E- and P-selectin inhibitors.

The incorporation of fluorine atoms onto biomolecules or synthetic biologically active molecules has become an intense research field in the two or three past decades, especially for drug development purposes.[1] This widespread interest stems from the unique properties of the fluorine atom and of the C−F bond.[1,2] When a fluorine atom is introduced into a biologically active molecule, its small size and its strong electronegativity, along with the strength and short length of the C−F bond, allow induction of alterations of crucial biological properties (such as substrate recognition, metabolic stability, drug transport, etc.) within limited structural modifications.[2b] Due to the implication in many biological events of their natural counterparts, fluorinated carbohydrate derivatives have thus received careful attention whatever the nature of the fluorinated substitution or its position on the sugar backbone.[3] In addition, one major drawback in the use of *O*-glycosides and *O*-glycoconjugates for drug development remains the low metabolic stability of the anomeric bond, highly cleavable in vivo, which erodes the bioavailability of carbohydrate-based drugs. It thus appeared interesting to combine the hydrolytic stability of carbohydrate analogues such as *C*-glycosides with the interesting properties of fluorine to give rise to a new class of glycomimetics.[4,5] The synthesis of these so-called CF_2-glycopyranosides was pioneered by Motherwell and further investigated by others.[6] Our group aimed at providing methodologies which allowed the synthesis of 2,2-difluoro-2-glycosylacetates such as **1** from commercially available and easy-to-handle ethyl bromodifluoroacetate. Compound **1** indeed features a valuable ester function which has already proven useful for further synthetic elaboration.[6g,h] Moreover, we wished to develop different strategies allowing the synthesis of these analogues for many carbohydrate series (glucose, mannose, and galactose) and for any pseudoanomeric center configuration (α or β).

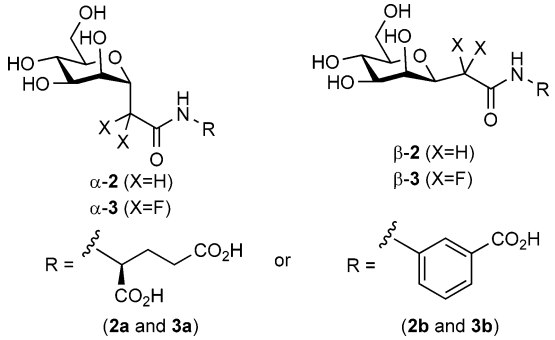


FIGURE 1. α- and β-pseudomannopeptides for E- and P-selectin inhibition.

One of our goals for this project was to synthesize the fluorinated analogues of CH_2-glycopeptides **2** prepared by Wong and Kaila for E- and P-selectin inhibition (Figure 1).[7] The α compounds were designed by Wong on the basis of a study of the host−enzyme interaction, and these small mannose-derived pseudoglycopeptides indeed acted as sialyl Lewis X mimics.[7a] A future evaluation of their fluorinated counterparts for E- and P-selectin inhibition will then be an opportunity to assess the influence of a CF_2 group in pseudoanomeric position. However,

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(3) For reviews on fluorinated carbohydrates and fluorinated sugar mimics, see: (a) Dax, K.; Albert, M.; Ortner, J.; Paul, B. J. *Carbohydr. Res.* **2000**, *327*, 47. (b) Pankiewicz, K. W. *Carbohydr. Res.* **2000**, *327*, 87. (c) Plantier-Royon, R.; Portella, C. *Carbohydr. Res.* **2000**, *327*, 119.

(4) For a review on *C*-glycoside synthesis, see: (a) C-Oligosaccharide synthesis: Skrydstrup, T.; Vauzeilles, B.; Beau, J. M. In *Glycoscience: Chemistry and Chemical Biology*; Fraser Reid, B., Tatstuta, K., Thiem, J., Eds.; Springer: Heidelberg, 2001; Vol. 3, p 2679. For a recent and powerful application of a CH_2-glyconjugate analogue, see: (c) Yang, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Angew. Chem., Int. Ed.* **2004**, *39*, 3818.

(5) For potent nonhydrolyzable CF_2-analogues of bioactive molecules, see: (a) Burke, T. R., Jr.; Lee, K. *Acc. Chem. Res.* **2003**, *36*, 426. (b) Burke, T. R., Jr.; Smyth, M. S.; Otaka, A.; Nomizu, M.; Roller, P. P.; Wolf, G.; Case, R.; Shoelson, S. E. *Biochemistry* **1994**, *33*, 6490. (c) Blackburn, G. M.; Jakeman, D. L.; Ivory, A. J.; Williamson, M. P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2573 and references cited therein.

(6) (a) Houlton, J. S.; Motherwell, W. B.; Ross, B. C.; Tozer, M. J.; Williams, D. J.; Slawin, A. M. Z. *Tetrahedron* **1993**, *49*, 8087. (b) Herpin, T. F.; Motherwell, W. B.; Weibel, J.-M. *Chem. Commun.* **1997**, 923. (c) Brigaud, T.; Lefebvre, O.; Plantier-Royon, R.; Portella, C. *Tetrahedron Lett.* **1996**, *37*, 6115. (d) Berber, H.; Brigaud, T.; Lefebvre, O.; Plantier-Royon, R.; Portella, C. *Chem. Eur. J.* **2001**, *7*, 903. (e) Wegert, A.; Miethchen, R.; Hein, M.; Reinke, H. *Synthesis* **2005**, 1850. (f) Wegert, A.; Hein, M.; Reinke, H.; Hoffmann, N.; Miethchen, R. *Carbohydr. Res.* **2006**, *341*, 2641. (g) Karche, N. P.; Pierry, C.; Poulain, F.; Oulyadi, H.; Leclerc, E.; Pannecoucke, X.; Quirion, J.-C. *Synlett* **2007**, 123. (h) Moreno, B.; Quehen, C.; Rose-Hélène, M.; Leclerc, E.; Quirion, J.-C. *Org. Lett.* **2007**, *9*, 2477. (i) Hirai, G.; Watanabe, T.; Yamaguchi, K.; Miyagi, T.; Sodeoka, M. *J. Am. Chem. Soc.* **2007**, *129*, 15420.

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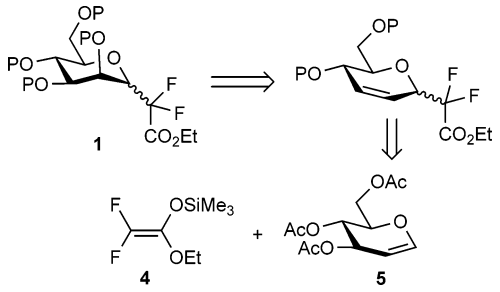
10.1021/jo702466h CCC: $40.75
Published on Web 02/15/2008

SCHEME 1. Retrosynthesis of the α-Mannoside Intermediate



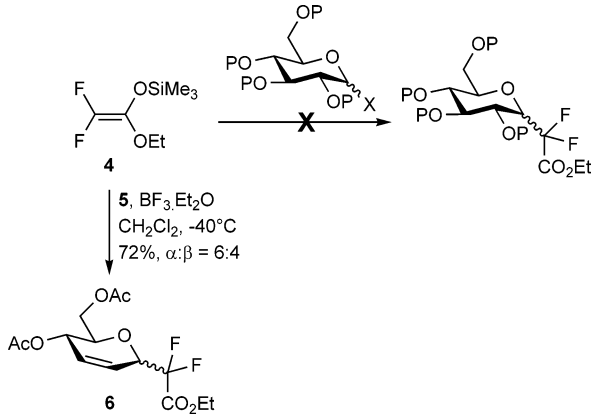
if the synthesis of the β-CF_2-glycopeptides β-**3a** and β-**3b** has already been reported,[6g] no method was available at that time for the synthesis of the required α-CF_2-mannopyranoside intermediates.[8] We wish to report herein the development of such a methodology and the synthesis of the targeted α-glycopeptides α-**3a** and α-**3b**.

The strategy we chose to investigate to achieve this goal relied on the addition of silyl enol ether **4** to a glycosyl donor. If the direct addition of **4** to an activated glycoside appeared as the most straightforward, but also most challenging route, the use of tri-*O*-acetyl-D-glucal **5** as the electrophile was a safe alternative as the subsequent dihydroxylation reaction was expected to lead to a mannose derivative (Scheme 1). An elegant generation of a ketone-derived difluoroenoxysilane and its efficient addition to **5** or to 2-deoxyglycosyl donors has already been reported by Portella.[6c,d] To the best of our knowledge, no double bond functionnalization of the resulting difluoro ketone derivatives has been described by this group.

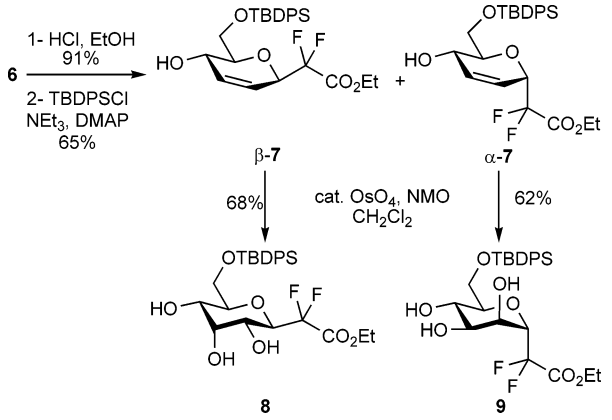
Our first task was to identify an appropriate salt-free source of difluoroketene silyl acetal **4** and determine if it was a suitable nucleophile for glycosylation reactions. Reagent **4** is usually prepared from ethyl bromodifluoroacetate, zinc, and TMSCl in THF, and its isolation has been described by Iseki.[9] This procedure involved repeated precipitations of zinc salts with *n*-pentane and a final distillation of this moisture-sensitive difluoroenoxysilane. However, the unsatisfactory yields we obtained using this method made clear that the isolation of **4** was not suitable for our purposes. The Reformatsky reagent was finally prepared in acetonitrile, solvent in which the amount of homocoupling product is limited, and quenched with TMSCl.[10] Extractions with *n*-pentane eventually provided a salt-free solution of **4** which was used directly for glycosylation reactions.

Despite our efforts and in agreement with Portella's report, this nucleophile failed to react with activated glycosides.[6d] The nature of the protecting group (benzyl, acetates), of the leaving group (acetate, trifluoroacetate, trichloroacetimidate, bromide), and of the Lewis acid (BF_3·Et_2O, $TiCl_4$, TMSOTf, etc.) had little influence on the outcome of the reaction (Scheme 2). A similar approach using glycal **5** as the glycosyl donor proved to be much more attractive since significant amounts of the S_N2' products **6** were isolated in our first attempts. Under optimized

SCHEME 2. Addition of 4 to Glycosyl Donors and D-Glucal



SCHEME 3. Diastereomer Separation and Dihydroxylation Reactions



reaction conditions, the addition of difluoroketene silyl acetal **4** to D-glucal **5** promoted by BF_3·Et_2O in CH_2Cl_2 at −40 °C afforded **6** in 72% yield and in a 6:4 α/β ratio (Scheme 2). Despite our efforts, no improvement in the diastereoselectivity could be obtained without substantial erosion of conversion and yield.

We then decided to submit this unseparable mixture of diastereomers to a dihydroxylation reaction. The use of Upjohn conditions (cat. OsO_4−NMO) using different solvents never led to any conversion of the starting material, suggesting that acetate-protected CF_2-glycosylester **6** was not a good substrate for such a transformation.[11] Protecting group modification, on the other hand, appeared appropriate since complete deacetylation and selective protection of the C-6 alcohol with a TBDPS group allowed the separation of the two diastereomers α-**7** and β-**7** (Scheme 3). Moreover, the presence of a free hydroxy group at C-4 now allowed the dihydroxylation reaction to occur when compounds **7** were subjected to the OsO_4−NMO oxidation system. CF_2-Glycosides **8** and **9** were indeed obtained from β-**7** and α-**7** in 68% and 62% yield, respectively, and only one diastereomer could be detected in each case by ^1H and ^{19}F NMR of the crude mixture (Scheme 3).

The relative configuration of these compounds was determined on the basis of NMR data. An HOESY experiment performed on compound **9** showed a strong F−H_5 correlation, proving that **9**, and thus α-**7**, were indeed α anomers. Moreover,

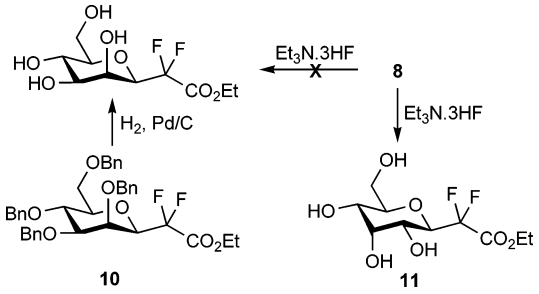
(8) A five-step synthesis of such an analog and its conversion to disaccharide mitetics has been reported during the course of this study: (a) Tony, K. A.; Denton, R. W.; Dilhas, A.; Jiménez-Barbero, J.; Mootoo, D. R. *Org. Lett.* **2007**, *9*, 1441. (b) Denton, R. W.; Tony, K. A.; Hernandez-Gay, J. J.; Canada, F. J.; Jimenez-Barbero, J.; Mootoo, D. R. *Carbohydr. Res.* **2007**, *342*, 1624−1635.

(9) Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *30*, 10271.

(10) Britton, T. C. US Patent 5,618,951, 1997.

(11) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

SCHEME 4. Chemical Correlation Experiments



F−H_3 and F−H_2 correlations observed with the same experiment clearly established the α-mannoside ($^4C_1$ chair conformation) configuration of **9**.[12] This stereoselectivity was predictible since the OH group at C_4 and the CF_2CO_2Et group at C_1 produce a cooperative effect for an *anti* orientation of the OsO_4 addition.[13]

The *β* configuration of *β*-**7** (and therefore of **8**) was confirmed by a NOESY correlation between H_1 and H_5. Unfortunately, an overlap between H_2 and H_3 signals in the NMR spectrum of **8** did not allow us to draw any conclusion concerning C_2 and C_3 configurations from coupling constants or NOESY data. A synthesis of *β*-CF_2-mannopyranoside **10** recently developed by our group prompted us to perform chemical correlation experiments.[6g] Indeed, the *syn*-addition process of the dihydroxylation reaction implied that **8** had to be a *β*-CF_2-mannopyranoside or a *β*-CF_2-allopyranoside. Since the debenzylation of compound **10** and the protodesilylation of **8** afforded two compounds with totally different ^1H and ^{19}F NMR data, the allopyranoside configuration was attributed to **8** (Scheme 4). This result was somehow disappointing as it was hoped that the strong *anti* selectivity generally induced by OH groups for dihydroxylation reactions would afford a *β*-CF_2-mannopyranoside when *β*-**7** was used as the starting material.[13] However, the CF_2 moiety generates apparently greater steric and electrostatic repulsions than the OH group and induces a complete and noteworthy *syn* selectivity to produce **8**.

The synthesis of the targeted fluorinated pseudoglycopeptides α-**3a** and α-**3b** was completed using standard chemistry (Scheme 5). Benzylation of **9** under acidic conditions afforded the common intermediate **12**, which was saponified and coupled to either benzylated l-glutamic acid or ethyl 3-aminobenzoate. Compounds **13** and **14** were then fully deprotected to afford the desired fluorinated analogues of Wong's glycopeptides α-**3a** and α-**3b**.

In summary, we have developed a concise method for the preparation of functionalized CF_2 analogues of α-mannopyranosides. This methodology was applied to the synthesis of fluorinated analogues of pseudoglycopeptides designed by Wong for E- and P-selectin inhibition. A biological evaluation of compounds **3a** and **3b** and other fluorinated glycosides is in preparation.

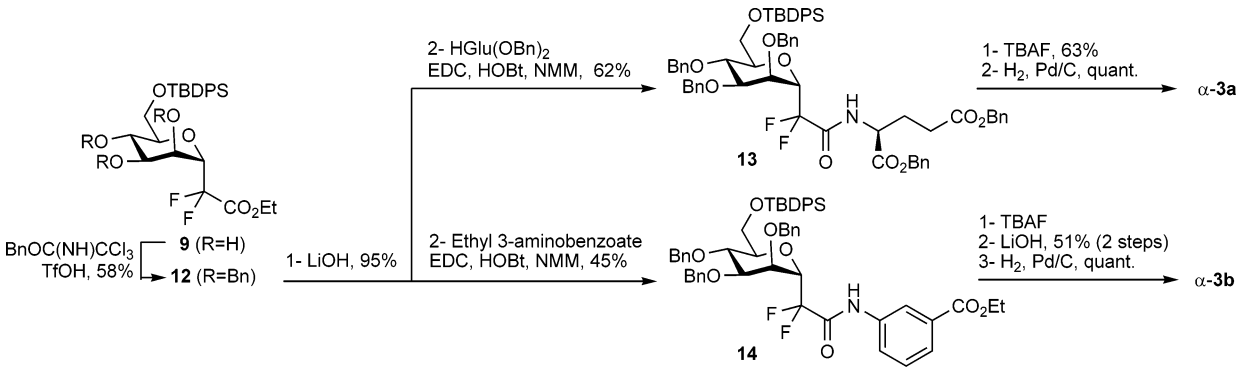
Experimental Section

Ethyl Trimethylsilyl-2,2-difluoroketene Acetal (4). Zinc dust (3 g, 46 mmol) in a Schlenk tube was dried by heating under vacuum and cooled to room temperature under argon atmosphere. Acetonitrile (16 mL) was added, and the zinc was activated under vigorous stirring by adding dibromoethane (3% mol) and TMSCl (5% mol). The mixture was cooled to room temperature, and a solution of ethyl bromodifluoroacetate (3.75 mL, 27 mmol) in acetonitrile (6 mL) was added dropwise over 1 h. The mixture was then stirred for an additional 1 h after the end of the addition, and TMSCl (5 mL, 40mmol) was then added. After 1 h, the reaction mixture was then cooled to 4 °C and extracted with pentane (8 mL + 3 × 4 mL) under argon atmosphere. Care should be taken to avoid moisture contact with **4**, which is used as a pentane solution without further purification.

Ethyl 2-(4,6-Di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-2,2-difluoroacetate (6). To a solution of D-glucal **5** (2 g, 7.35 mmol) in dichloromethane (22 mL) at −40 °C was added a solution of **4** (24 mmol) in pentane and boron trifluoride diethyl etherate (1 mL, 7.9 mmol). The solution was stirred at this temperature for 40 min and neutralized by adding saturated aqueous $NaHCO_3$ (15 mL) and water (15 mL). The organic layer was separated and the aqueous phase extracted with ether (2 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. Purification by column chromatography over silica gel (30% ethyl acetate in hexane) afforded **6** as a colorless oil and as a mixture of anomers (1.78 g, 72%). Fractions of reasonably pure α anomer can, however, be isolated: R_f = 0.23 (30% EtOAc in cyclohexane); ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (dt, J = 10.5 Hz, J = 2.2 Hz, 1H), 6.01−5.94 (m, 1H), 5.24−5.19 (m, 1H), 4.74−4.61 (m, 1H), 4.36 (q, J = 7.2 Hz, 2H), 4.22 (dd, J = 12.1 Hz, J = 5.6 Hz), 4.11 (dd, J = 12.1 Hz, J = 2.7 Hz), 4.05−3.98 (m, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −110.5 (d, J = 260.7 Hz, 1F), −117.7 (dd, J = 260.7 Hz, J = 22.6 Hz, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.8, 170.3, 163.1 (t, J = 30.2 Hz), 114.1 (t, J = 254.7 Hz), 130.0, 122.3, 71.9 (dd, J = 30.5 Hz, J = 24.2 Hz), 71.2, 64.0, 63.3, 62.5, 21.0, 20.8, 14.0. The following analytical data were obtained from the mixture of anomers: IR (neat) ν_{max} 2987, 1764, 1742 cm^{-1}; MS (ESI+) m/z = 359 ($[M + Na]^+$). Anal. Calcd for $C_{14}H_{18}F_2O_7$: C, 50.04; H, 5.40. Found: C, 50.05; H, 5.22.

Ethyl 2-(6-*O*-(*tert*-Butyldiphenylsilyl)-α-D-mannopyranosyl)-2,2-difluoroacetate (9). To a vigorously stirred solution of α-**7** (240 mg, 0.49 mmol) in CH_2Cl_2 (3 mL) was added NMO (250

SCHEME 5. Synthesis of the Fluorinated Pseudoglycopeptides from α-Mannoside 9



mg, 2.1 mmol), a few drops of water, and a solution of osmium tetraoxide (140 μL, 4% in water, 0.02 mmol). The reaction was monitored by TLC (reaction time ~60 h), and after complete consumption of the starting material, the emulsion was dried over magnesium sulfate and directly transferred over a silica gel packed column for purification (0−10% MeOH in CH_2Cl_2) to afford **9** as a colorless oil (159 mg, 62%): $[\alpha]_D$ +0.50 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.63 (m, 4H), 7.48−7.36 (m, 6H), 4.40 (ddd, J = 27.1, 6.7, 1.5 Hz, 1H), 4.31 (bs, 1H), 4.23 (q, J = 6.9 Hz, 2H), 4.00−3.94 (m, 2H), 3.90−3.79 (m, 2H), 3.79−3.74 (m, 1H), 3.20 (bs, 1H), 3.10 (bs, 1H), 2.91 (bs, 1H), 1.21 (t, J = 6.9 Hz, 3H), 1.06 (s, 9H); ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −108.5 (dd, J = 258.6, 6.4 Hz, 1F), −114.2 (dd, J = 258.6, 26.8 Hz, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.8 (dd, J = 32.6, 28.6 Hz), 135.7, 132.6, 130.2, 128.0, 115.2 (t, J = 256.4 Hz), 77.0 (dd, J = 21.6, 29.6 Hz), 75.0, 71.8, 69.9, 66.2, 65.5, 63.4, 26.9, 19.3, 14.0; IR (neat) ν_{max} 3400, 3072, 2932, 2858, 1771 cm^{-1}; MS (ESI+) m/z = 547 ([M + Na]$^+$). Anal. Calcd for $C_{26}H_{34}F_2O_7Si$: C, 59.52; H, 6.53. Found: C, 59.32; H, 6.35.

Di-*O*-benzyl *N*-[2-(2,3,4-Tri-*O*-benzyl-6-*O*-(*tert*-butyldiphenylsilyl)-α-D-mannopyranosyl)-2,2-difluoroacetyl]-L-gluta- mate (13). To a solution of **12** (231 mg, 0.29 mmol, 1 equiv) in THF (2 mL) was added LiOH (14.3 mg, 0.59 mmol, 2 equiv) dissolved in water (1 mL). The reaction was stirred at rt and monitored by TLC, and more LiOH in water was added if necessary. CH_2Cl_2 (10 mL) was added, and the reaction mixture was acidified to pH 1 by addition of HCl (1 N). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the collected organics were washed with water and evaporated under reduced pressure. The crude acid was obtained as a colorless oil (210 mg, 95%) after drying under vacuum and was used for the next step without further purification. This residue was dissolved in CH_2Cl_2 (2 mL), and to this solution were added HGlu(OBn)$_2$·TsOH (170 mg, 0.34 mmol), HOBt (49 mg, 0.29 mmol), NMM (80 μL, 0.72 mmol), and EDC (70 mg, 0.36 mmol). The mixture was stirred for 36 h and then diluted with EtOAc (10 mL). The solution was washed with 10% aq citric acid (10 mL), satd $NaHCO_3$ (10 mL), and brine (10 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (10% EtOAc in cyclohexane) afforded **13** as a colorless oil (183 mg, 62%): $[\alpha]_D$ +3.2 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.61 (m, 4H), 7.42−7.12 (m, 31H), 7.04 (d, J = 7.6 Hz, 1H), 5.04 (s, 2H), 4.99 (d, J = 12.2 Hz, 1H), 4.89 (d, J = 12.2 Hz, 1H), 4.79−4.44 (m, 7H), 4.13−4.06 (m, 2H), 3.95−3.70 (m, 4H), 2.40−2.12 (m, 3H), 2.01−1.89 (m, 1H), 0.99 (s, 9H); ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −110.6 (d, J = 258.6 Hz, 1F), −117.0 (dd, J = 258.6, 20.4 Hz, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.5, 170.5, 162.9 (t, J = 27.0 Hz), 138.5, 138.3, 138.0, 136.0, 135.7, 135.6, 135.0, 133.8, 133.3, 129.7, 129.0, 128.8−127.7 (CH_{Ar}), 116.2 (t, J = 258.2 Hz), 77.7, 77.4, 73.8, 73.7, 72.8 (t, J = 22.0 Hz), 72.6, 72.2, 72.1, 67.6, 66.7, 62.3, 51.8, 29.9, 27.1, 26.9, 19.4; IR (neat) ν_{max} 3351, 3032, 2930, 2857, 1738, 1710 cm^{-1}; MS (ESI+) m/z = 1098 ([M + Na]$^+$). Anal. Calcd for $C_{64}H_{67}F_2NO_{10}Si$: C, 71.42; H, 6.27; N, 1.30. Found: C, 71.34; H, 6.31; N, 1.34.

***N*-(2,2-difluoro-2-(α-D-mannopyranosyl)acetyl)-L-glutamic Acid (α-3a).** To a solution of **13** (92 mg, 0.085 mmol) in THF (3 mL) was added TBAF (1 M solution in THF, 0.1 mL, 0.1 mmol). The mixture was stirred at rt for 3 h and then quenched with satd NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the collected organics were washed with brine (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. Purification by column chromatography (20% EtOAc in cyclohexane) afforded the desired deprotected glycopeptide as a colorless oil (45 mg, 63%). To a solution of this compound (45 mg, 0.054 mmol) in THF (2 mL) were added water (1 mL), a few drops of concd HCl, and Pd/C (tip of spatula). The reaction mixture was purged with H_2 and stirred under an H_2 atmosphere for 24 h. The suspension was then filtered and washed with water, and the filtrate was evaporated under reduced pressure. The residue was dried by successive coevaporations with toluene and then redissolved in water, filtered, and lyophilized to afford **α-3a** (20 mg, quant) as a white solid: mp 118−120 °C; $[\alpha]_D$ +15.55 (*c* 0.6, H_20, λ = 436 nm); ^{1}H NMR (300 MHz, D_2O) δ 4.38 (ddd, J = 21.9, 11.8, 2.4 Hz, 1H), 4.25 (t, J = 2.7 Hz, 1H), 4.16 (dd, J = 4.6, 8.8 Hz, 1H), 3.91−3.86 (m, 1H), 3.79−3.70 (m, 4H), 2.23 (app t, J = 7.7 Hz, 2H), 2.14−2.02 (m, 1H), 1.99−1.86 (m, 1H); ^{19}F NMR (282.5 MHz, D_2O) δ −110.2 (dd, J = 259.1, 11.8 Hz, 1F), −114.53 (dd, J = 259.1, 21.5 Hz, 1F); ^{13}C NMR (75.5 MHz, D_2O) δ 182.5, 177.9, 164.2 (t, J = 27.9 Hz), 116.4 (t, J = 259.3 Hz), 78.2, 76.8 (dd, J = 28.5, 22.2 Hz), 71.3, 66.7, 66.6, 61.2, 56.1, 34.2, 28.0; HRMS (TOF-) calcd for $C_{13}H_{18}F_2NO_{10}$ m/z (M − H)$^-$ 386.0898, found 386.0882.

Acknowledgment. We thank Perigene, Inc., for a PhD grant to F.P., the Association pour la Recherche contre le Cancer for financial support, and Dr. Hassan Oulyadi (LRMN, UMR 6014, Mont Saint-Aignan, France) for the 400 MHz NMR experiments.

Supporting Information Available: Complete experimental details and compound characterization data, as well as copies of ^{1}H, ^{19}F, and ^{13}C spectra. COSY, HMQC, and NOESY or HOESY (400 Mhz) spectra for β-**7** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702466H

(12) This experiment also allowed to establish that the "*exo/anti*" conformation of the C_1-CF_2 bond was the most populated one (see the Supporting Information for details). This terminology was used for O- and CH_2-glycosides: Goekjian, P. G.; Wei, A.; Kishi, Y. In *Carbohydrate-Based Drug Discovery*; Wong, C.-H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1, pp 305−340.

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