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An Improved Synthesis of 4-*O*-Benzoyl-2,2-difluorooleandrose from L-Rhamnose. Factors Determining the Synthesis of 2,2-Difluorocarbohydrates from 2-Uloses

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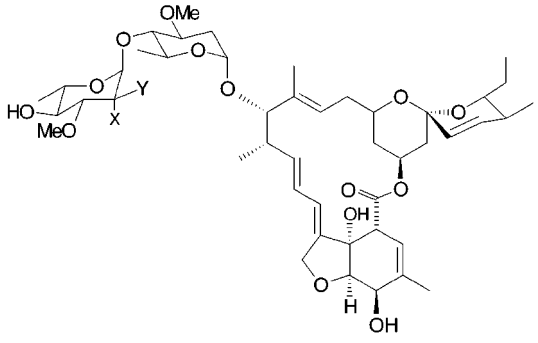
4-*O*-Benzoyl-2,2-difluorooleandrose (**16**) has been synthesized from L-rhamnose. The key steps are the formation of a difluoromethylene group in **12** by reacting ulose **11** with DAST and the chemoselective methylation of diol **13** to give compound **14**. To obtain the 2,2-difluoro compound **12**, the substituents in the neighborhood of the carbonyl group in ulose **11** must be equatorial and the sugar ring must have restricted conformational mobility. This was done using 1,1,2,2-tetramethoxycyclohexane (TMC) to protect the hydroxyls at positions 3 and 4 in the sugar ring.

Avermectines[1] are polycyclic macrolides from the milbemycin family that have a potent antiparasitary activity. Structure−activity relationship studies have shown that the disaccharide di-α-L-oleandrose and especially the terminal oleandrose unit have a crucial role;[2] thus, avermectine B1a monosaccharide has only about 25% of the biological activity of the parent compound **1** (Figure 1).

It is well-known that the glycosidic bond in 2-deoxycarbohydrates is easily hydrolyzed, and this must be avoided if its activity, in biologically active compounds incorporating these units, is to be preserved. One way of modifying organic molecules and improving their biological activity is to introduce fluorine.[3] In particular, introducing fluorine at position 2 of a carbohydrate helps to stabilize the glycosidic bond.[4] To this end, Lukacs et al.[5] synthesized 2-α- and 2-*β*-fluorooleandrose and introduced it as the terminal unit in the disaccharide of avermectine B1a (Figure 1, compounds **2a** and **2b**). Subsequently, with the aim of making the glycosidic bond in these compounds more stable, the same authors published the synthesis of 2,2-difluorooleandrose (as glycosyl fluoride),[6] the key step being the addition of CF_3-OF to a 2-fluoroglycal. One of the drawbacks of this synthesis is the difficulty of activating a glycosyl fluoride with two fluorine atoms in the neighboring position.



1 X=Y= H
2a X= F, Y= H
2b X= H, Y= F

Figure 1.

This report discusses a more efficient procedure of synthesis of 2,2-difluorooleandrose based on the reaction of a 2-ulose with DAST. A key aspect in the synthesis is the use of 1,1,2,2-tetramethoxycyclohexane (TMC) as protecting group.[7]

Results and Discussion

Two different strategies are usually used in the synthesis of *gem*-difluorinated carbohydrates:[8] (1) the carbohydrate is formed from an appropriate *gem*-difluoro synthon, such as (bromodifluoromethyl)acetylene,[9] or ethyl bromodifluoroacetate,[4,10] commonly via a Refortmasky reaction, and (2) by reacting carbonyl groups with (diethylamino)sulfur trifluoride (DAST).[11] We previously studied the reaction of 2-uloses with DAST and found that the axial orientation of the anomeric group gives rise

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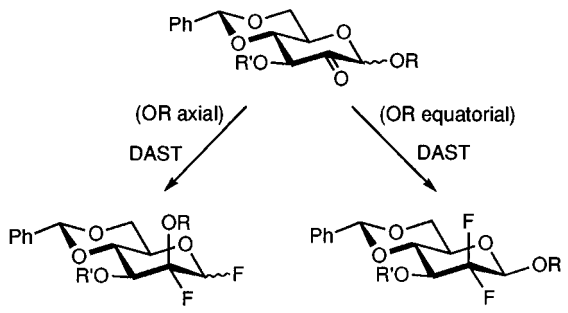
Scheme 1



to 1,2-migrations to afford 1,2-difluoro-2-alkoxy compounds, while *gem*-difluorination is produced in good yield if both neighboring groups are equatorial (Scheme 1).[12]

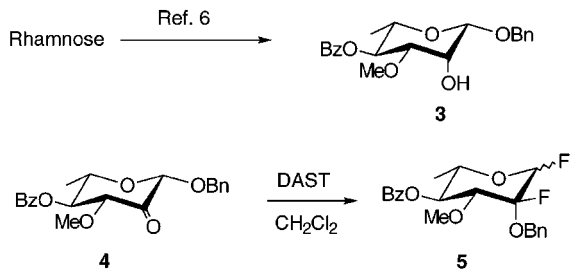
Compound **3** (Scheme 2) was an intermediate in the synthesis of difluorooleandrose.[6] The substituents were all in the equatorial position. Therefore, the oxidation and subsequent reaction with DAST should give the difluoro derivative.

With this aim, compound **3** was oxidized with PCC to give the ulose **4** (ν = 1757 cm^{-1}), which was an inseparable anomeric mixture, according to NMR data, the anomer β being the major one. The use of other oxidation agents such as PDC or CrO_3−Py led to the same results. We thought that the slight traces of HCl present in the $CDCl_3$ could favor the isomerization, but when CD_2Cl_2 was used the behavior was similar. Isomerization may also take place during the purification, so we decided not to isolate the ulose **4** but treated it directly with DAST in methylene chloride at room temperature. Under these conditions, compound **5**, in which a 1,2-transposition has been produced, was isolated in 50% yield. When the reaction took place in benzene or in the presence of Et_3N, the same product was obtained.

The structure of compound **5** was determined by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy on the basis of the following spectroscopic data: (1) the coupling constants for protons H-1 indicate the presence of fluorine at this position;[13,14] (2) two similar groups of signals (double doublets) appear in the ^{13}C NMR spectrum in the 100−110 (J = 223, 44 Hz) region corresponding to C-1 of both isomers (C-2 cannot be seen), and the high value for $^1J_{C,F}$ coupling indicates a fluoroalkoxy substitution for this carbon;[13,15] (3) the presence of four signals in the ^{19}F NMR spectrum, two double doublets (J = 64, 9 and J = 64, 7 Hz, respectively), characteristic of F-1, and two quintuplets (J = 7 Hz), corresponding to F-2 of both isomers; and (4) the coupling constants H-1/F-2 and H-3/F-2, 0 and 14.7, respectively, indicate that F-2 is equatorially oriented.[13,16]

One possible explanation for this is that 1,2-transposition also takes place from the β anomer because the conformational mobility of compound **4** is greater than that of the model compounds (see Scheme 1) in which the oxo group is incorporated in a *trans*-decaline-like ring

Scheme 2



system. The faster reaction of the α-anomer together with the β to α isomerization produced during the long reaction time required for their completion may be another explanation.

We believe that the first reason is more probable, and consequently, the restriction of the conformational mobility in the carbohydrate ring would be a supplementary condition for the *gem*-difluorination of 2-uloses by reaction with DAST.

The presence of an additional *trans*-fused ring at positions 3 and 4 would provide the required rigidity. Recently, Ley has developed different protecting groups, such us 3,3′,4,4′-tetrahydro-6,6′-bi-2H-pyran (bis-DHP)[17] and TMC,[7] able to protect *trans*-diequatorial diols in the presence of *cis* ones.[18]

With this aim, we prepared the benzyl α-L-rhamnopyranoside (**6**)[19] in 69% yield from rhamnose by reacting benzyl alcohol in the presence of AcCl[20] (Scheme 3). This compound was treated with bis-DHP, and a 79% yield of a 3:2 mixture of 3,4- and 2,3-diprotected products was obtained.[21] Despite studying the reaction conditions, we were unable to improve on this result.

On the other hand, when compound **6** was treated with TMC under the reported conditions (trimethyl orthoformate, methanol, CSA, reflux) a 1:1 mixture of methyl and benzyl glycosides **7** and **8**, respectively, was obtained in an overall yield of 80%. That is, a transglycosylation took place in the acid conditions required to form the cyclohexane 1,2-diacetal (CDA) protecting group. It should also be taken into account that the 3,4-diprotected product is the thermodynamic while the 2,3-diprotected product is the result of kinetic control.[18b] This means that heating for a long time will give rise to improve the formation of the 3,4-diprotected compound **8** but these conditions will also favor transglycosylation to give compound **7**.

When the reaction took place in methanol (with no trimethyl orthoformate) and the reaction time was controlled the yield of compound **8** increased to 61%, although under these conditions the product of kinetic control, benzyl 2,3-*O*-(1′,2′-dimethoxycyclohexane-1′,2′-

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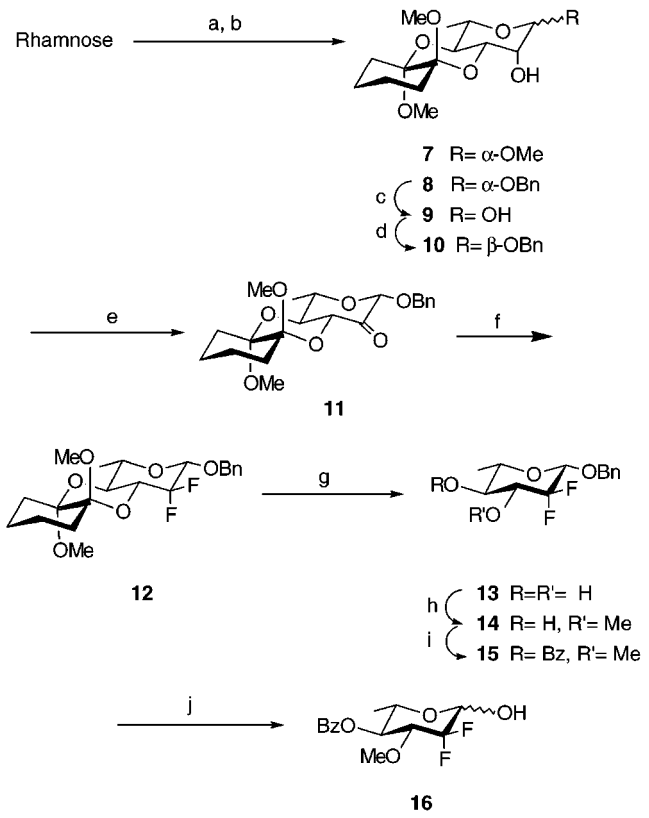
Scheme 3[a]



[a] (a) $PhCH_2OH$/AcCl; (b) CDA, MeOH, H^+; (c) H_2, Pd/C, MeOH/AcOEt; (d) Bu_2SnO, BnBr, benzene; (e) PCC, CH_2Cl_2; (f) DAST, CH_2Cl_2; (g) TFA−H_2O; (h) Bu_2SnO/MeI; (i) BzCl, Py; (j) H_2, Pd/C, MeOH/AcOEt.

diyl)-α-L-rhamnopyranoside (**17**), was also obtained in 16% yield.

The substituents at position 1 and 3 also had to be arranged equatorially, and to do so, the configuration of the anomeric group had to be inverted. This was done by deprotecting the anomeric group by hydrogenolysis to give compound **9** and benzylating the resulting free hydroxyl through the cyclic stannylene intermediate to obtain the β-glycoside **10** with an overall yield of 68% for the two steps.

The ulose **11** was efficiently obtained by oxidizing the alcohol **10** with PCC. This product was stable enough to be purified by chromatography. The reaction of **11** with DAST led to the key *gem*-difluoro compound **12** in a 69% yield. The structure of compound **12** was established by ^1H, ^{13}C, and ^{19}F NMR spectroscopy on the basis of the following facts: (1) In the ^{13}C NMR spectrum there is a triplet (114.7 ppm, J = 252.8 Hz) that is characteristic of a difluoromethylene group, a double doublet (96.9 ppm, J = 26.7, 19.0 Hz) that corresponds to a ketalic carbon coupled with two fluorine atoms, and a triplet (70.3 ppm, J = 18.3 Hz) that were assigned to C-2, C-1, and C-3, respectively. (2) In the ^{19}F NMR spectrum there are two signals at −125.07 ppm and −140.63 ppm showing a J = 241.6 Hz characteristic of fluorine−fluorine geminal coupling.[14] (3) The H-1 appears as a doublet at 4.52 ppm (J = 14.5 Hz), which should correspond to an axial−axial proton−fluorine coupling.[14,17]

Once the 2,2-difluoromethylene group was formed, the diketalic protecting group was easily deprotected by reaction with aqueous trifluoroacetic acid to give the diol **13**. Interestingly, selective methylation of 3-OH in **13** was successfully achieved by reacting with Bu_2SnO to form the stannylene derivative and then treating it with methyl iodide to give compound **14** in an 80% yield. The protection of 4-OH was performed by adding benzoyl chloride to a solution of compound **14** in pyridine. That allowed the indirect confirmation of the methylation position.

The anomeric benzyl group was deprotected by hydrogenolysis, leading to an anomeric mixture of the target product **16** in quantitative yield. The presence of the unprotected anomeric hydroxyl makes it possible to introduce different leaving groups in order to perform the glycosylation reaction.

In conclusion, 4-*O*-benzoyl-2,2-difluorooleandrose (**16**) has been synthesized from L-rhamnose. The key steps are the formation of a difluoromethylene group in **12** by reaction of ulose **11** with DAST and the chemoselective methylation of diol **13** to give compound **14**. To obtain the 2,2-difluorocompound **12** two conditions are required, neighboring substituents to carbonyl group in ulose **11** must be equatorial and the sugar ring must have restricted the conformational mobility. The last condition has been achieved by using 1,1,2,2-tetramethoxycyclohexane (TMC) as the protecting group of hydroxyls at positions 3 and 4 of the sugar ring.

Experimental Section

General Procedures. Melting points were uncorrected. Optical rotations were measured at the indicated temperature in 10 cm cells. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a 300 MHz (300, 75.4, and 282.3 MHz, respectively) apparatus, using $CDCl_3$ as solvent. Elemental analyses were performed at the Servei de Recursos Cientifics (Universitat Rovira i Virgili). Flash column chromatography was performed using silica gel 60 A CC (230−400 mesh). TLC plates were prepared by using Kieselgel 60 PF_{254}. Solvents for chromatography were distilled at atmospheric pressure prior to use. Dichloromethane was distilled from P_2O_5 and stored over molecular sieves. Methanol was distilled from clean dry magnesium turnings and iodine and stored over molecular sieves. Pyridine was distilled from solid KOH and stored over molecular sieves.

4-*O*-Benzoyl-2-*O*-benzyl-2-fluoro-3-*O*-methyl-α,β-L-rhamnopyranosyl Fluoride (5). In a light-protected flask, 138 mg (0.64 mmol) of pyridinium chlorochromate, 210 mg (2.56 mmol) of anhydrous sodium acetate, 732 mg of 4 Å molecular sieves (previously activated), and 4.5 mL of CH_2Cl_2 were introduced and stirred under argon atmosphere. A solution of compound **3** (60 mg, 0.16 mmol) was added to the suspension obtained, and then the resulting reaction mixture was heated to reflux for 2 h. When the reaction finished, it was diluted with ethyl ether and filtered through a Cellite−silica gel pad to separate the chromium salts formed. The remaining solution was evaporated to dryness, and the resulting oil was used in the subsequent reaction without purification. DAST (0.14 mL, 1 mmol) was added dropwise to a solution of this reaction crude (48 mg) in anhydrous CH_2Cl_2 (1 mL). After 24 h, standard workup gave an oil, which was purified by preparative thin-layer chromatography (7/1 hexane/ethyl acetate), yielding the difluoro compound **5** (26 mg, 50% overall yield) as an anomeric mixture. Major isomer (α, F axial in C_1) extracted from the spectrum of the mixture: ^1H NMR ($CDCl_3$) δ 8.00−7.25 (m, 10H), 5.34 (d, 1H, J = 63.7 Hz), 5.24 (m, 1H), 4.95 (d, 1H, J = 11.9 Hz), 4.74 (dd, 1H, J = 11.9, 2.0 Hz), 4.32 (dd, 1H, J = 14.7, 5.3 Hz), 4.23 (m, 1H), 3.46 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.6, 133.5−128.0 (12C), 106.4 (dd, J = 224.3, 43.7 Hz), 83.9 (d, J = 20.6 Hz), 81.7, 80.6, 72.0, 59.4, 20.4; ^{19}F NMR ($CDCl_3$) δ −140.89 (dd, J = 63.7, 9.0 Hz), −119.15 (m). Minor isomer (β, F equatorial in

C_1) extracted from the spectrum of the mixture: ^{1}H NMR ($CDCl_3$) δ 5.33 (d, 1H, J = 64.0 Hz), 3.39 (s, 3H), 1.48 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.6, 133.5−128.0, 106.3 (dd, J = 224.7, 44.2 Hz), 84.2 (d, J = 22.8 Hz), 81.8, 80.7, 71.8, 59.4, 20.3; ^{19}F NMR ($CDCl_3$) δ −144.37 (dd, J = 64.0, 7.3 Hz), −119.00 (m, F_2).

Benzyl α-L-Rhamnopyranoside (6). Rhamnose monohydrated (1.82 g, 10 mmol) was added to a solution of acetyl choride (0.5 mL) in benzyl alcohol (10 mL) and was stirred at 60 °C for 24 h (complete disappearance of starting sugar). Then the reaction was quenched with K_2CO_3 (4.0 g), stirring was continued for 1 h, and ethyl acetate (20 mL) was added. The precipitated salts were filtered and washed with ethyl acetate (2 × 10 mL), and the organic phase was concentrated to half volume and diluted with hexane (80 mL). The resulting emulsion was left to stand for 2 h in the refrigerator and then the solvent was decanted, obtaining a syrup that was purified by flash chromatography eluting first with dichloromethane (600 mL) to separate the remaining benzyl alcohol and then with ethyl acetate (400 mL) to give 1.5 g of compound **6**. A subsequent elution column with ethyl acetate/ethanol 19:1 (500 mL) provided 0.25 g of compound **6** as an α/β anomeric mixture: total yield 69%; ^{1}H NMR ($CDCl_3$) δ 7.35−7.23 (m, 5H), 4.79 (s, 1H), 4.62 (d, 1H, J = 11.8 Hz), 4.42 (d, 1H, J = 11.8 Hz), 3.90 (d, 1H, J = 2.5 Hz), 3.75 (dd, 1H, J = 9.3, 2.5 Hz), 3.63 (m, 1H, J = 9.3, 6.2 Hz), 3.45 (t, 1H, J = 9.3 Hz), 2.19 (s, 2H), 2.12 (s, 1H), 1.25 (d, 3H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 137.0−127.9 (6 C), 99.0, 72.6, 71.7, 70.9, 69.1, 68.2 (2C), 17.5. Anal. Calcd for C_{13} H_{18} O_5: C, 61.41; H, 7.09. Found: C, 61.75; H, 6.95.

Benzyl 3,4-*O*-(1′,2′-Dimethoxycyclohexane-1′,2′-diyl)-α-L-rhamnopyranoside (8). CSA (308 mg, 1.33 mmol) was added to a solution of compound **6** (3.46 g, 13.6 mmol) and 1,1,2,2-tetramethoxycyclohexane (4.60 g, 22.5 mmol) in anhydrous MeOH (8.5 mL), and the mixture was heated to reflux for 75 min. The resulting solution was neutralized with solid $NaHCO_3$ (0.5 g) and evaporated to dryness. The residue obtained was purified by flash chromatography (hexane/ethyl acetate 3:1), and 3.27 g (61%) of compound **8** was obtained together with 850 mg (16%) of product protected at position 2,3 with the α configuration (**17**). **8:** mp 50−52 °C; $[\alpha]^{25}_D$ −146.80° (c = 0.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.26−7.22 (m, 5H), 4.78 (d, 1H, J = 1.5 Hz), 4.63 (d, 1H, J = 11.8 Hz), 4.42 (d, 1H, J = 11.8 Hz), 4.08 (m, 1H), 3.90 (dd, 1H, J = 3.2, 1.5 Hz), 3.84 (m, 2H), 3.14 (s, 3H), 3.12 (s, 3H), 2.69 (s, br, 1H), 1.73−1.60 (m, 4H), 1.50−1.40 (m, 2H), 1.38−1.22 (m, 2H), 1.20 (d, 3H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 137.2, 128.3, 128.1, 127.7, 99.1, 98.9, 98.6, 70.2, 69.0, 69.0, 66.9, 46.9, 46.5, 27.0, 26.9, 21.1, 16.4. Anal. Calcd for C_{21} H_{30} O_7: C, 63.96; H, 7.61. Found: C, 63.55; H, 7.85.

17: ^{1}H NMR ($CDCl_3$) δ 7.28−7.25 (m, 5H), 4.96 (s, 1H), 4.62 (d, 1H, J = 11.6 Hz), 4.43 (d, 1H, J = 11.6 Hz), 4.37 (d, 1H, J = 6.2 Hz), 4.17 (t, 1H, J = 6.3 Hz), 3.66 (m, 1H), 3.35 (t, br, 1H), 3.25 (s, 3H), 3.19 (s, 3H), 2.71 (s, br, 1H), 1.80−1.55 (m, 4H), 1.55−1.30 (m, 4H), 1.21 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 137.0, 128.4−127.4 (5C), 111.0, 101.2, 96.8, 78.5, 77.0, 74.3, 69.2, 66.2, 50.0, 49.0, 35.7, 30.6, 22.8, 21.5, 17.8.

3,4-*O*-(1′,2′-Dimethoxycyclohexane-1′,2′-diyl)-α,β-L-rhamnopyranose (9). Palladium on charcoal was added to a solution of compound **8** (100 mg, 0.254 mmol) in a mixture MeOH/AcOEt (3 mL). This solution was vigorously stirred under hydrogen (1 bar) at room temperature for 7 h. Then the reaction mixture was filtered through a Celite pad and evaporated to dryness. Compound **9** was obtained (quantitative yield) in pure form as a white solid.

Spectroscopic data of **9**α extracted from the spectrum of the mixture: ^{1}H NMR ($CDCl_3$) δ 5.22 (dd, 1H, J = 2.1, 1.2 Hz), 4.19 (ddd, 1H, J =10.4, 3.1, 1.2 Hz), 4.10 (m, 1H), 4.02−3.86 (m, 2H), 3.24 (s, 3H), 3.20 (s, 3H), 3.02 (d, 1H, J = 3.1 Hz), 2.72 (d, 1H, J = 2.1 Hz), 1.80−1.70 (m, 4H), 1.60−1.50 (m, 2H), 1.45−1.33 (m, 2H), 1.27 (d, 3H, J = 6.2 Hz). ^{13}C NMR ($CDCl_3$) δ 99.0 (2C), 94.8, 70.2, 69.0, 68.5, 67.0, 47.0, 46.6, 27.0, 26.9, 21.3 (2C), 16.5.

Spectroscopic data of **9**β extracted from the spectrum of the mixture: ^{1}H NMR ($CDCl_3$) δ 4.80 (dd, 1H, J = 11.3, 1.0 Hz), 4.12−3.50 (m, 5H), 3.22 (s, 3H), 3.21 (s, 3H), 3.00 (d, 1H, J =3.0 Hz), 1.80−1.70 (m, 4H), 1.60−1.50 (m, 2H), 1.45−1.33 (m, 2H), 1.31 (d, 3H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 99.0 (2C), 94.8, 70.8, 70.3, 70.1, 68.4, 47.0, 46.6, 27.0, 26.9, 21.3 (2C), 16.5. Anal. Calcd for $C_{14}H_{24}O_7$: C, 55.26; H, 7.90. Found: C, 55.29; H, 8.04.

Benzyl 3,4-*O*-(1′,2′-Dimethoxycyclohexane-1′,2′-diyl)-β-L-rhamnopyranoside (10). Bu_2SnO (74 mg, 0.30 mmol) was added to a solution of compound **9** (82 mg, 0.27 mmol) in benzene (90 mL) and was then heated to reflux overnight with water exclusion. Then the reaction mixture was concentrated to one-fourth of the initial volume, and Bu_4NBr (87 mg, 0.27 mmol) and BnBr (35 μL) were added. The resulting reaction mixture was again heated to reflux for 24 h and was then evaporated to dryness. The resulting residue was purified by flash chromatography, eluting first with hexane to separate the excess of BnBr and then with hexane/ethyl acetate 2:1. Compound **10** (72 mg, 68%) was obtained as a crystalline solid: mp 140−141 °C; $[\alpha]^{25}_D$ −19.4° (c = 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.25−7.30 (m, 5H), 4.87 (d, 1H, J = 11.8 Hz), 4.58 (d, 1H, J = 11.8 Hz), 4.46 (s, 1H), 3.94 (s, br, 1H), 3.86 (t, 1H, J = 10.1 Hz), 3.70 (dd, 1H, J = 10.1, 2.9 Hz), 3.42 (m, 1H J = 10.1, 6.2 Hz), 3.12 (s, 6H), 2.35 (s, 1H), 1.85−1.53 (m, 4H), 1.50−1.39 (m, 2H), 1.38−1.30 (m, 2H), 1.29 (d, 3H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 136.8, 128.4, 128.4, 128.0, 99.0, 98.5, 98.3, 70.6, 70.6, 70.4, 70.0, 68.6, 46.8, 46.5, 27.0, 26.9, 21.3 (2C), 16.5. Anal. Calcd for C_{21} H_{30} O_7: C, 63.96; H, 7.61. Found: C, 64.05; H, 7.55.

Benzyl 3,4-*O*-(1′,2′-Dimethoxycyclohexane-1′,2′-diyl)-β-L-rhamnopyranosid-2-ulose (11). A mixture of compound **10** (80 mg, 0.20 mmol), PCC (175 mg, 0.81 mmol), sodium acetate (66 mg, 0.80 mmol), and 4 Å activated molecular sieves (230 mg) was placed in a light protected flask under argon, and then anhydrous CH_2Cl_2 (2 mL) was added. After 1 h, the reaction mixture was diluted with CH_2Cl_2, silica gel was added, and the mixture was evaporated to dryness. The resulting residue was purified by flash chromatography (hexane/ethyl acetate 3:2) to obtain 76 mg (97%) of compound **11** as a syrup: $[\alpha]^{26}_D$ −38.0° (c = 0.56, $CHCl_3$); IR (KBr) 1756 cm^{-1} (ν_{CO}); ^{1}H NMR ($CDCl_3$) δ 7.35−7.23 (m, 5H), 4.84 (d, 1H, J = 12.1 Hz), 4.76 (s, 1H), 4.64 (d, 1H, J = 12.1 Hz), 4.53 (d, 1H, J = 10.8 Hz), 3.92−3.73 (m, 2H) 3.13 (s, 3H), 3.10 (s, 3H), 1.82−1.53 (m, 4H), 1.50−1.40 (m, 2H), 1.34 (d, 3H, J = 6.0 Hz), 1.30−1.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 195.1, 136.0, 128.4, 128.2, 128.0, 99.0, 98.2, 97.4, 74.4, 73.0, 71.1, 70.0, 47.2, 46.6, 27.8, 27.4, 21.2 (2C), 17.3. Anal. Calcd for C_{21} H_{28} O_7: C, 64.28; H, 7.14. Found: C, 64.25; H, 7.10.

Benzyl 2,2-Difluoro-3,4-*O*-(1′,2′-dimethoxycyclohexane-1′,2′-diyl)-β-L-rhamnopyranoside (12). A solution of compound **11** (45 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (0.9 mL) was treated with DAST (124 μL, 0.94 mmol) under argon at room temperature. The reaction mixture was stirred for 6 h and was then quenched by adding a saturated solution of $NaHCO_3$ in water. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated to dryness. The resulting syrup was purified by flash chromatography (hexane/ethyl acetate 8:1) to give 33 mg (69%) of the *gem*-difluorinated product **12** as a syrup: $[\alpha]^{25}_D$ −39.6° (c = 0.675, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38−7.36 (m, 5H), 4.98 (d, 1H, J =12.2 Hz), 4.72 (d, 1H, J =12.2 Hz), 4.52 (d, 1H, J =14.5 Hz), 3.96 (ddd, 1H, J = 21.6, 10.4, 5.1 Hz), 3.72 (dt, 1H, J =10.4, 2.0 Hz), 3.58 (m, 1H, J =10.4, 6.0, 0.9 Hz), 3.22 (s, 3H), 3.20 (s, 3H), 1.90−1.50 (m, 8H), 1.36 (d, 3H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 136.3, 128.5, 128.1, 114.7 (t, J = 252.8 Hz), 99.0, 98.5, 96.9 (dd, J = 26.7, 19.0 Hz), 71.0, 70.7, 70.3 (t, J = 18.3 Hz), 70.2 (d, J = 6.2 Hz), 47.0, 46.7, 27.0, 26.7, 21.3 (2C), 16.4; ^{19}F NMR ($CDCl_3$) δ −125.07 (dd, J = 241.6, 5.1 Hz), −140.63 (ddd, J = 241.6, 21.6, 14.5 Hz). Anal. Calcd for C_{21} H_{28} O_6F_2: C, 60.87; H, 6.76. Found: C, 60.90; H, 6.72.

Benzyl 2-Deoxy-2,2-difluoro-β-L-rhamnopyranoside (13). A solution of compound **12** (40 mg, 0.096 mmol) in trifluoroacetic acid−water (95/5) (3 mL) was stirred at room temperature for 20 min. The reaction was monitored by TLC in

hexane/ethyl acetate 1:1. The reaction mixture was evaporated to dryness and immediately purified by flash chromatography (hexane/ethyl acetate 1:1) to obtain 22 mg (82%) of compound **13** as a syrup: $[\alpha]^{26}_D$ +69.56° (c = 0.35, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.37−7.32 (m, 5H), 4.96 (d, 1H, J = 12.2 Hz), 4.69 (d, 1H, J = 12.2 Hz), 4.50 (d, 1H, J = 15.4 Hz), 3.60 (ddd, 1H, J = 19.2, 9.0, 7.2 Hz), 3.37 (m, 2H), 3.20 (s, br, 2H), 1.37 (d, 3H, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 136.0, 128.5, 128.2, 128.1, 115.5 (t, J = 252.4 Hz), 96.2 (dd, J = 26.6, 19.0 Hz), 74.4 (d, J = 6.7 Hz), 74.2 (t, J = 19.4 Hz), 71.8, 71.2, 18.8; ^{19}F NMR ($CDCl_3$) δ −122.76 (dd, J = 244.0, 7.2 Hz), −141.04 (ddd, J = 244.0, 19.2, 15.4 Hz). Anal. Calcd for C_{13} H_{16} O_4F_2: C, 56.93; H, 5.84. Found: C, 56.90; H, 5.88.

Benzyl 2-Deoxy-2,2-difluoro-3-*O*-methyl-*β*-L-rhamnopyranoside (14). Bu_2SnO (31 mg, 0.121 mmol) was added to a solution of compound **13** (30 mg, 0.109 mmol) in benzene (90 mL), and the resulting mixture was heated to reflux for a night with water exclusion. The reaction mixture was evaporated to dryness and coevaporated twice with anhydrous toluene, and the remaining syrup was dissolved in anhydrous toluene (3 mL), treated with Bu_4NBr (37 mg 0.115 mmol) and MeI (70 μL, 1.1 mmol), and heated to reflux. Every 2 h, MeI (50 μL) was added until the starting material disappeared. The reaction was monitored by TLC in hexane/ethyl acetate (3:1). After the reaction mixture was evaporated to dryness, the resulting reaction crude was purified by flash chromatography to yield 25 mg (80%) of compound **14**: $[\alpha]^{26}_D$ +86.38° (c = 0.585, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.40 (m, 5H), 4.99 (d, 1H, J = 12.2 Hz), 4.72 (d, 1H, J = 12.2 Hz), 4.48 (d, 1H, J = 15.1 Hz), 3.66 (s, 3H), 3.40 (m, 2H), 3.17 (ddd, 1H, J = 19.5, 9.1, 5.0 Hz), 2.45 (s, br, 1H, OH), 1.40 (d, 3H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 136.1, 128.5−128.0 (5C), 116.5 (t, J = 255.8 Hz), 96.0 (dd, J = 26.9, 19.1 Hz), 83.1 (t, J = 17.8 Hz). 73.6 (d, J = 7.7 Hz), 71.6, 70.9, 61.4, 17.4; ^{19}F NMR ($CDCl_3$) δ −118.94 (dd, J = 247.3, 5.0 Hz), −139.2 (ddd, J = 247.3, 19.5, 15.1 Hz). Anal. Calcd for C_{14} H_{18} O_4F_2: C, 58.33; H, 6.25. Found: C, 58.30; H, 6.28.

Benzyl 4-*O*-Benzoyl-2-deoxy-2,2-difluoro-3-*O*-methyl-*β*-L-rhamnopyranoside (15). (Dimethylamino)pyridine (0.24 mg) and, dropwise, benzoyl chloride (20 μL, 0.17 mmol) were added to a solution of compound **14** (27 mg, 0.094 mmol) in anhydrous pyridine (1 mL) cooled to 0 °C. The bath was allowed to warm to room temperature, and the reaction was maintained by stirring for 3 h. The reaction mixture was evaporated to dryness and then purified by flash chromatography (hexane/ethyl acetate 5:1) to obtain 31 mg (84%) of compound **15**: $[\alpha]^{25}_D$ = +94.24° (c = 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.04−7.32 (m, 10H), 5.15 (dt, 1H, J = 9.8, 1.5 Hz), 5.01 (d, 1H, J = 12.4 Hz), 4.75 (d, 1H, J = 12.4 Hz), 4.55 (d, 1H, J = 14.8 Hz), 3.64 (m, 2H), 3.54 (s, 3H), 1.32 (d, 3H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 165.0, 136.0−128.1 (12C), 116.2 (t, J = 255.5 Hz), 96.0 (dd, J = 26.7, 19.1 Hz), 81.0 (t, J = 19.2 Hz), 73.9 (d, J = 8.4 Hz), 70.9, 70.5, 61.5, 17.4; ^{19}F NMR ($CDCl_3$) δ −120.12 (dd, J = 248.2, 4.8 Hz), −138.90 (ddd, J = 248.2, 19.5, 14.8 Hz). Anal. Calcd for C_{21} H_{22} O_5 F_2: C, 64.28; H, 5.61. Found: C, 64.39; H, 5.69.

4-*O*-Benzoyl-2-deoxy-2,2-difluoro-3-*O*-methyl-α,*β*-L-rhamnopyranose (16). Palladium on charcoal 10% (18 mg) was added to a solution of compound **15** (27 mg, 0.069 mmol) in a mixture of MeOH/AcOEt (1.5 mL). The reaction mixture was placed under a hydrogen atmosphere (1 bar) and vigorously stirred at room temperature until the starting material completely disappeared. The reaction was monitored by TLC in hexane/ethyl acetate 6:1. The reaction mixture was then filtered through a Celite pad and evaporated to dryness. Compound **16** was obtained in quantitative yield as an anomeric mixture.

Spectroscopic data of **16**α extracted from the spectrum of the mixture: ^1H NMR ($CDCl_3$) δ 8.02−7.40 (m, 5H), 5.14 (d, 1H, J = 6.3 Hz), 5.06 (dt, 1H, J = 9.9, 1.8 Hz), 4.22 (m, 1H, J = 9.9, 6.3 Hz), 4.06 (s, br, 1H), 3.90 (ddd, 1H, J = 21.0, 9.9, 4.2 Hz), 3.60 (s, 3H), 1.15 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 165.4, 133.5−128.6 (6C), 118.0 (t, J = 254.4 Hz), 91.5 (dd, J = 35.2, 27.3 Hz), 78.0 (t, J = 19.4 Hz), 74.3 (d, J = 8.0 Hz), 70.2, 65.7, 17.1; ^{19}F NMR ($CDCl_3$) δ −120.96 (dd, J = 254.4, 4.2 Hz), −124.70 (ddd, J = 254.4, 21.0, 6.3 Hz).

Spectroscopic data of **16***β* extracted from the spectrum of the mixture: ^1H NMR ($CDCl_3$) δ 8.02−7.40 (m, 5H), 4.80 (d, 1H, J = 15.2 Hz); ^{19}F NMR ($CDCl_3$) δ −120.47 (dd, J = 248.4, 4.5 Hz), −142.72 (ddd, J = 248.4, 19.7, 15.2 Hz).

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