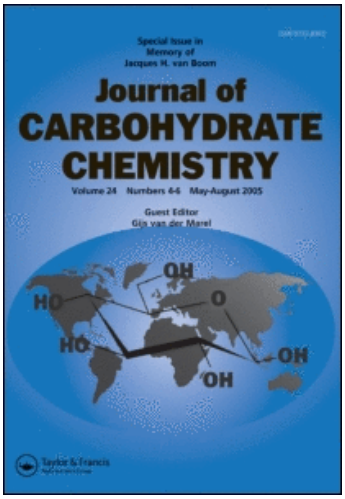

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Synthesis of Derivatives of 2,6-Dideoxy-2,2-Difluoro-3-*O*-Methyl-l-Arabinopyranose (2,2-Difluorooleandrose)

Christophe Bliard[a]; Pal Herczegh[a]; Alain Olesker[a]; Gabor Lukacs[a]
[a] Institut de Chimie des Substances Naturelles du C.N.R.S., Gif-sur-Yvette Cedex, France

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SYNTHESIS OF DERIVATIVES OF 2,6-DIDEOXY-2,2-DIFLUORO-3-O-METHYL-L-ARABINOPYRANOSE (2,2-DIFLUOROOLEANDROSE)

Christophe Bliard, Pal Herczegh, Alain Olesker and Gabor Lukacs*

Institut de Chimie des Substances Naturelles du C.N.R.S.,
91198 Gif-sur-Yvette Cedex, France.

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ABSTRACT

L-Oleandrose is the carbohydrate constituent of the potent anthelmintic agents the avermectins. Diethylaminosulfur trifluoride treatment of appropriate uloses did not give gem-difluoro sugars. Trifluorofluoroxymethane or xenon difluoride addition to the double bond of 4-O-benzoyl-6-deoxy-2-fluoro-3-O-methyl-L-glucal produced protected 2,2-difluorooleandrose derivatives activated at their anomeric center and ready for glycosidation.

INTRODUCTION

In view of the considerable interest in the avermectins[1] and the importance for biological activity of their carbohydrate constituent oleandrose, the synthesis of analogues of this monosaccharide became a major target in our laboratory. In a recent paper, we have reported the stereospecific synthesis of C-2β- and C-2α-fluorooleandrose[2] from which C-2"β- 1 and C-2"α-fluoro-

avermectin-B_{1a} 2 were prepared. At this time we report the synthesis of protected oleandrose derivatives in which both C-2 hydrogen atoms have been replaced by fluorine.

RESULTS AND DISCUSSION

Diethylaminosulfur trifluoride (DAST) treatment of a variety of uloses has been reported to afford the corresponding gem-difluoro sugars.[3] Such reactions were also investigated in our laboratory. Results seem to depend on the particular structure of the carbohydrate ketone. In the reaction mixture produced from DAST treatment of oleandrose derivatives 3 and 4 no C-2 gem-difluoro sugar was detected.

Therefore, another obvious approach to the synthesis of protected 2,2-difluorooleandrose appeared to be by way of the addition of either trifluorofluoroxymethane or xenon difluoride to 4-O-benzoyl-6-deoxy-2-fluoro-3-O-methyl-L-glucal 13. The latter was prepared from the known[2] benzyl 4-O-benzoyl-6-deoxy-3-O-methyl-α-L-mannopyranoside 5 in seven steps. Hydrogenolysis of the benzyl group of 5 gave the free sugar 6. Dibutyltin oxide treatment of 6 was followed by regiospecific 1-O-β-benzylation of the stannylene complex 7 by benzyl bromide furnishing the equatorially 1-O-substituted sugar 8. The hydroxyl group of 8, being in a favourable environment,[4] underwent S_N2 reaction in the presence of DAST furnishing the fluorocarbohydrate 9. Hydrogenolysis of the benzyl group of 9 afforded the free sugar 10. Acetylation of 10 was followed by anomeric bromination and then dehydrobromination giving 13 in an overall yield of 48% from 5.

Trifluorofluoroxymethane addition to the double bond of L-glucal derivative 13 afforded a mixture from which careful chromatography allowed the isolation of four different protected 2,2-difluorooleandrose derivatives 14, 15, 16 and 17 in an overall

yield of 72.5%. Specific yield of each constituent of the mixture was respectively 16%, 42%, 9,5% and 5%. Trifluorofluoroxymethane could be advantageously replaced by xenon difluoride since the latter reagent gave only 15 (58%) and 16 (29%) ready for glycosidation in view of their fluorine activated anomeric centers. The preparation and biological activity of C-2"-gem difluoro avermectin-B_{1a} 18 will be reported elsewhere.

EXPERIMENTAL

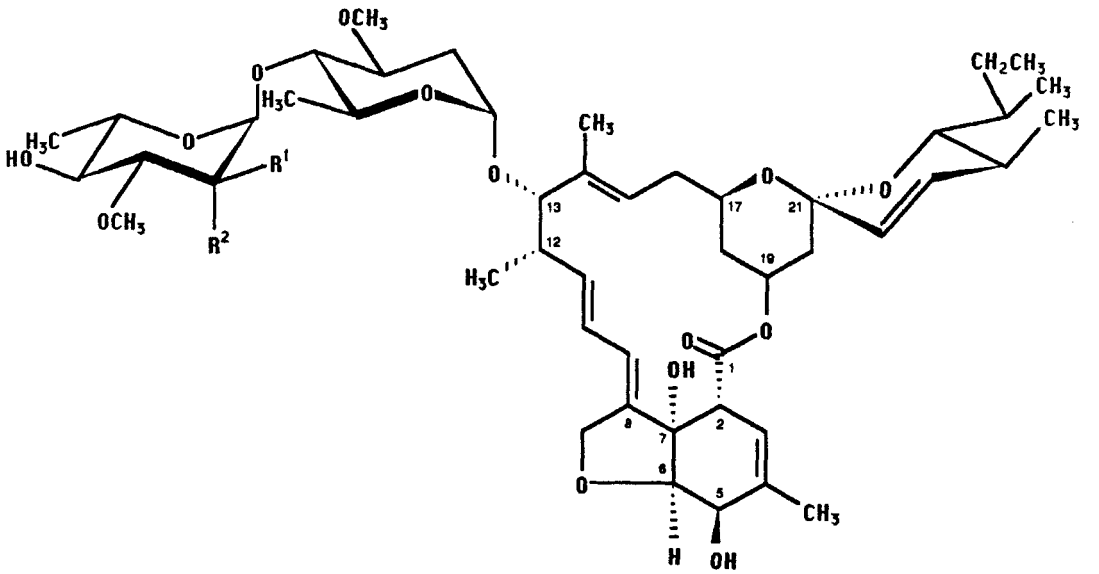
General Procedures. The melting point were determined with a Buchi apparatus and are uncorrected. A Perkin-Elmer Model 141 MC polarimeter and 1-dm tubes were used for measurement of specific rotations. ^{1}H NMR spectra were recorded in chloroform-d solution at 400 MHz. The ^{13}C NMR spectrum was measured in chloroform-d solution at 50.31 MHz with a Bruker WP-200 spectrometer. Chemical shifts are given in parts per million, and tetramethylsilane was the internal standard (δ 0.000). Carbon-13 chemical shifts for aromatic carbons are not given. Microanalyses were performed by the Service Central de Microanalyse du CNRS. Silica gel 60 PF_{254} (Merck) activated at 120°C was the support for TLC and for column chromatography. The term "standard workup" means that the organic layer was washed with water, dried over Na_2SO_4, and filtered and the solvent was removed at reduced pressure.

4-O-Benzoyl-6-deoxy-3-O-methyl-L-mannopyranose (6). To a solution of 5 (1.86 g, 5 mmol) in ethanol (100 mL) was added 10% Pd/C (2.25 g) and the mixture was stirred overnight in a hydrogen atmosphere at normal pressure. After filtration of the catalyst and evaporation of the solvent, crude homogeneous 6 was obtained quantitatively.

Benzyl 4-O-benzoyl-6-deoxy-3-O-methyl-β-L-mannopyranoside (8). Compound 6 (1.40 g, 5 mmol) in toluene (3 x 30 mL) was carefully dried by three successive evaporations of the solvent at reduced pressure at 45°C. The residue was dissolved in benzene (150 mL) and dibutyltin oxide (1.37 g, 5.5 mmol) and tetrabutylammonium sulfate (352 mg, 1 mmol) were added to the solution. The mixture was refluxed in a nitrogen atmosphere for 16 h in a Dean-Stark apparatus. After evaporation of the solvent the residue was dissolved in dry benzene (50 mL), benzyl bromide (1.0 g, 6 mmol) was added and the mixture was refluxed in a nitrogen atmosphere for 24 h. The reaction was monitored by thin layer chromatography. The solvent was evaporated and the residue in ethyl acetate solution filtered on kieselguhr. After evaporating the solvent the residue was chromatographed on silica gel giving 8 (980 mg, 70%), mp 73°C, $[\alpha]_D^{22}$ + 112° (c 1.0, chloroform); mass spectrum m/z 372 (M^+); ^1H NMR δ: 8.04-7.35 (m, 10H, 2 Ph); 5.33 (t, 1H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4); 4.98 and 4.72 (2d, 2H, J_{gem} = 12 Hz, CH_2Ph); 4.54 (s, 1H, H-1); 4.22 (d, 1H, $J_{2,3}$ = 3 Hz, H-2); 3.56 (m, 1H, H-5); 3.41 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{3,4}$ = 10 Hz, H-3); 3.38 (s, 3H, OMe); 2.55 (bs, 1H, OH); 1.34 (d, 3H, $J_{5,6}$ = 7 Hz, Me).

Anal. Calcd for $C_{21}H_{24}O_6$: C, 67.74; H, 6.45. Found: C, 67.81; H, 6.33.

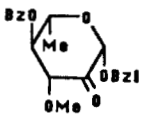
Benzyl 4-O-benzoyl-2,6-dideoxy-2-fluoro-3-O-methyl-β-L-glucopyranoside (9). To a solution of 8 (744 mg, 2 mmol) in dry dichloromethane (5 mL) was added diethylaminosulfur trifluoride (0.35 mL, 2.65 mmol) drop by drop in an argon atmosphere with stirring. The mixture was refluxed for 1 h, then poured into a cold solution of sodium hydrogenocarbonate (5%, 20 mL) and extracted with dichloromethane. The organic layer was washed with a 0.1% aqueous solution of potassium permanganate, water and the solvent was evaporated giving a residue which was chromatographed. Pure 9 (595 mg, 80%), was obtained as fine needles, mp 86°C;



1 $R^1 = H$; $R^2 = F$

2 $R^1 = F$; $R^2 = H$

18 $R^1 = R^2 = F$



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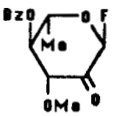

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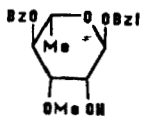

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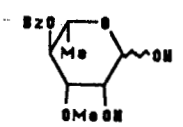

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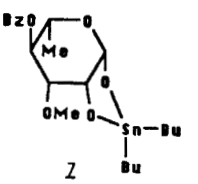

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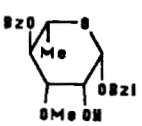

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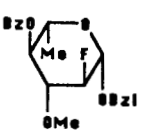

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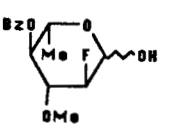

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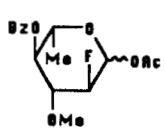

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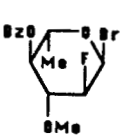

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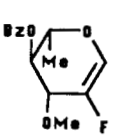

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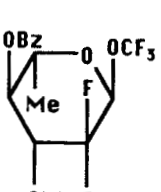

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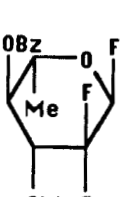

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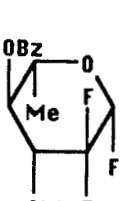

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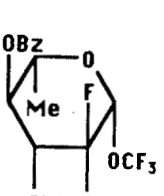

17

$[\alpha]_D^{22}$ + 71°, (c 1.0, chloroform); mass spectrum m/z 374 ($M^{+\cdot}$); ^{1}H NMR δ: 8.06-7.40 (m, 10H, 2 Ph); 5.05 (t, 1H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4); 4.97 and 4.72 (2d, 2H, J_{gem} = 12 Hz, CH_2Ph); 4.62 (dd, 1H, $J_{1,2}$ = 7.5 Hz, $J_{1,F}$ = 3 Hz, H-1); 4.43 (dt, 1H, $J_{1,2} = J_{2,3}$ = 7.5 Hz, $J_{2,F}$ = 51 Hz H-2); 3.61 (m, 1H, H-5); 3,60 (ddd, 1H, $J_{2,3}$ = 7.5 Hz, $J_{3,4}$ = 10 Hz, $J_{3,F}$ = 15 Hz, H-3); 3.49 (s, 3H, OMe); 1.29 (d, 3H, $J_{5,6}$ = 7 Hz, Me). ^{13}C NMR δ: 165.5 (C=O); 99.3 (d, $J_{1,F}$ = 23.1 Hz, C-1); 92.9 (d, $J_{2,F}$ = 187.4 Hz, C-2); 82.5 (d, $J_{3,F}$ = 18.3 Hz, C-3); 74.9 (d, $J_{4,F}$ = 8.8 Hz, C-4); 70.9 and 70.5 (C-5 and CH_2Ph); 60.2 (OMe); 17.5 (C-6).

Anal. Calcd for $C_{21}H_{23}FO_5$: C, 67.29; H, 6.19; F, 5.08. Found: C, 66.99; H, 6.17; F, 4.79.

4-O-Benzyl-2,6-dideoxy-2-fluoro-3-O-methyl-L-glucopyranose (10). To a solution of 9 (374 mg, 1 mmol) in ethanol (20 mL) was added 10% Pd/C (0.5 g) and the mixture was stirred overnight in a hydrogen atmosphere at normal pressure. After filtration of the catalyst and evaporation of the solvent, crude homogenous 10 was obtained quantitatively as a syrup.

1-O-Acetyl 4-O-benzyl-2,6-dideoxy-2-fluro-3-O-methyl-α- and β-L-glucopyranose (11). To a solution of 10 (282 mg, 1 mmol) in pyridine (10 mL) was added at 0°C acetic anhydride (1 mL) and 4-dimethylaminopyridine (30 mg) and the mixture was stirred for 3 h at room temperature. Dilution with water was followed by dichloromethane extraction. Evaportion of the solvent gave 11 (310 mg, 99%) as a syrup.

4-O-benzyl-2,6-dideoxy-2-fluoro-3-O-methyl-α-L-glucopyranosyl bromide (12). To a solution of 11 (163 mg, 0.5 mmol) in acetic acid (10 mL) was added hydrobromic acid (2 mL in 30% acetic acid) and the mixture was stirred for 2 h at room temperature in a nitrogen atmosphere. The solution was poured into 5% cold aqueous hydrogenocarbonate and extracted with dichloromethane. After evaporation of the solvent, the residue was chromatographed

to give 12 (135 mg, 80%) as a homogeneous syrup); $[\alpha]_D^{22}$ -155°, (c 1.5, chloroform); mass spectrum m/z 362-364 ($M^{+\cdot}$); ^{1}H NMR δ: 8.00-7.50 (m, 5H, Ph); 6.50 (d, 1H, $J_{1,2}$ = 4 Hz, H-1); 5.04 (t, 1H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4); 4.50 (ddd, 1H, $J_{1,2}$ = 4 Hz, $J_{2,3}$ = 10 Hz, $J_{2,F}$ = 50 Hz, H-2); 4.12 (m, 1H, H-5); 3.92 (dt, 1H, $J_{2,3} = J_{3,4}$ = 10 Hz, $J_{3,F}$ = 30 Hz, H-3); 3.50 (s, 3H, OMe); 1.27 (d, 3H, $J_{5,6}$ = 7 Hz, Me).

4-O-Benzoyl-6-deoxy-2-fluoro-3-O-methyl-L-glucal (13). To a solution of 12 (347 mg, 1 mmol) in acetonitrile (10 mL) were added at -20°C diethylamine (2 mL, 3 mmol) and tetra-n-butylammonium bromide (320 mg, 1 mmol) and the mixture was refluxed for 3 h in a nitrogen atmosphere. After neutralization with cold 0.1N hydrochloric acid and dichloromethane extraction, the residue was chromatographed on silica gel to afford pure syrupy 13 (210 mg, 80%); $[\alpha]_D^{22}$ + 14° (c 3.4, chloroform); mass spectrum m/z 266 ($M^{+\cdot}$); ^{1}H NMR δ: 8.07-7.48 (m, 5H, Ph); 6.73 (d, 1H, $J_{1,F}$ = 6 Hz, H-1), 5.33 (t, 1H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4); 4.34 (m, 1H, H-5); 4.10 (bd, 1H, $J_{3,4}$ = 10 Hz, H-3); 3.55 (s, 3H, OMe); 1.40 (d, 3H, $J_{5,6}$ = 6 Hz, Me); ^{13}C NMR δ: 165.5 (CO); 145.4 (d, $J_{2,F}$ = 240 Hz, C-2); 130.8 (d, $J_{1,F}$ = 40.2 Hz, C-1); 73.9 (d, $J_{3,F}$ = 21.7 Hz, C-3); 72.5 (C-4); 71.6 (d, $J_{5,F}$ = 9 Hz, C-5); 57.6 (OMe); 15.6 (Me).

Anal. Calcd for $C_{14}H_{15}FO_4$: C, 63.16; H, 5.64; F, 7.14. Found: C, 63.41; H, 5.50; F, 7.02.

Trifluoromethyl 4-O-benzoyl-2,6-dideoxy-2,2-difluoro-3-O-methyl-α-L-arabinopyranoside (14); 4-O-benzoyl-2,6-dideoxy-2,2-difluoro-3-O-methyl-α-L-arabinopyranosyl fluoride (15); 4-O-benzoyl-2,6-dideoxy-2,2-difluoro-3-O-methyl-β-L-arabinopyranosyl fluoride (16); Trifluoromethyl 4-O-benzoyl-2,6-dideoxy-2,2-difluoro-3-O-methyl-β-L-arabinopyranoside (17). To a solution of 13 (280 mg, 0.8 mmol) in dry trichlorofluoromethane (30 mL) containing calcium oxide (15 mg) in an argon atmosphere at -60°C was

added trifluorofluoroxymethane gas (50 mmol) in argon (mixture ratio: trifluorofluoroxymethane/argon = 1:9) in about 10 min. The course of the reaction was monitored until test samples no longer reacted with alkaline potassium permanganate. After filtration and concentration to dryness, the residue was chromatographed (9:1 hexane-ethyl acetate), giving pure syrupy 14 (R_f 0.38), (62 mg, 16%), $[\alpha]_D^{22}$ - 26° (c 0.64, chloroform); mass spectrum m/z 370 ($M^{+\cdot}$); ^{1}H NMR δ: 8.08-7.48 (m, 5H, Ph); 5.50 (d, 1H, $J_{1,Fa}$ = 5 Hz, H-1); 5.21 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 10 Hz, H-4); 4.20 (m, 1H, H-5); 3,82 (ddd, 1H, $J_{3,4}$ = 9 Hz, $J_{3,Fa}$ = 20 Hz, $J_{3,Fe}$ = 5 Hz, H-3); 3.58 (s, 3H, OMe); 1,30 (d, 3H, $J_{5,6}$ = 7 Hz, Me); ^{13}C NMR δ 165.1 (C=O); 121.0 (q, $J_{C,F}$ = 260 Hz, OCF_3); 115.8 (dd, $J_{2,F}$ = 246 Hz, $J_{2,F'}$ = 260 Hz, C-2); 94.2 (dd, $J_{1,F}$ = 30.8 Hz, $J_{1,F'}$ = 39.5 Hz, C-1); 78.0 (t, $J_{3,F}$ = $J_{3,F'}$ = 18.8 Hz, C-3); 73.1 (d, $J_{4,F}$ = 7.8 Hz, C-4); 69.1 (C-5); 61.7 (OMe); 17.1 (Me).

Anal. Calcd for $C_{15}H_{15}F_5O_5$: C, 48.65; H, 4.05; F, 25.67. Found: C, 48.81; H, 3.91; F, 25.62.

Following the elution pure syrupy 15 was obtained (R_f 0.35), (132 mg, 42%), $[\alpha]_D^{22}$-0.2° (c 0.53, chloroform); mass spectrum m/z 304 ($M^{+\cdot}$); ^{1}H NMR δ: 8.05-7.50 (m, 5H, Ph); 5.50 (dd, 1H, $J_{1,F1}$ = 51 Hz, $J_{1,Fe}$ = 3 Hz, H-1); 5,25 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 10 Hz, H-4); 4.20 (m, 1H, H-5); 3.90 (m, 1H, H-3); 3.58 (s, 3H, OMe); 1.30 (d, 3H, $J_{5,6}$ = 7 Hz, Me); ^{13}C NMR δ: 166.1 (C=O); 115.7 (ddd, $J_{2,F2}$ = 247 Hz, $J_{2,F2'}$ = 265 Hz, $J_{2,F1}$ = 36 Hz, C-2); 103.6 (ddd, $J_{1,F1}$ = 228 Hz, $J_{1,F2}$ = 40 Hz, $J_{1,F2'}$ = 32 Hz, C-1); 78.1 (t, $J_{3,F2}$ = $J_{3,F2'}$ = 19 Hz, C-3); 73.2 (d, $J_{4,F2}$ = 9 Hz, C-4); 69.1 (d, $J_{5,F1}$ = 3 Hz, C-5); 61.7 (OMe); 17.1 (Me).

Anal. Calcd for $C_{14}H_{15}F_3O_4$: C, 55.26; H, 4.93; F, 18.75. Found: C, 55.40; H, 4.85; F, 18.81.

Following the elution pure syrupy 16 was obtained (R_f 0.17), (30 mg, 9.5%), $[\alpha]_D^{22}$ + 33° (c 0.9, chloroform); mass spectrum m/z 304 ($M^{+\cdot}$); ^{1}H NMR δ: 8.06-7.50 (m, 5H, Ph); 5.43 (dd, 1H,

$J_{1,F1}$ = 50 Hz, $J_{1,F2a}$ = 8 Hz, H-1); 5.26 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 10 Hz, H-4); 3.98 (m, 1H, H-5); 3.72 (m, 1H, H-3); 3.60 (s, 3H, OMe); 1.44 (d, 3H, $J_{5,6}$ = 7 Hz, Me); ^{13}C NMR δ: 165.2 (C=O); 104.0 (ddd, $J_{1,F1}$ = 226 Hz, C-1); 79.7 (t, $J_{3,F2}$ = $J_{3,F2'}$ = 20 Hz, C-3); 72.6 (d, $J_{4,F2}$ = 5 Hz, C-4); 71.5 (d, $J_{5,F1}$ = 3 Hz, C-5); 61.4 (OMe); 18.3 (Me).

Anal. Calcd for $C_{14}H_{15}F_3O_4$: C, 55.26; H, 4.93; F, 18.75. Found: C, 55.44; H, 4.81; F, 18.90.

Following the elution pure syrupy 17 was obtained (R_f 0.15), (15 mg, 5%), $[\alpha]_D^{22}$ + 28° (c 1.2, chloroform); mass spectrum m/z 370 ($M^{+\cdot}$); ^{1}H NMR δ: 8.04-7.48 (m, 5H, Ph); 5.19 (d, 1H, $J_{1,Fa}$ = 16 Hz, H-1); 5.17 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 10 Hz, H-4); 3.83 (m, 1H, H-5); 3.72 (ddd, 1H, $J_{3,Fa}$ = 22 Hz, $J_{3,4}$ = 10 Hz, $J_{3,Fe}$ = 5 Hz, H-3); 3.57 (s, 3H, OMe); 1.46 (d, $J_{5,6}$ = 7 Hz, Me); ^{13}C NMR δ 165.0 (C=O), 126.7 (q, $J_{C,F}$ = 260 Hz, OCF_3); 115.0 (t, $J_{2,F}$ = $J_{2,F'}$ = 255 Hz, C-2); 93.2 (t, $J_{1,F}$ = $J_{1,F'}$ = 25 Hz, C-1); 80.6 (t, $J_{3,F}$ = $J_{3,F'}$ = 19 Hz, C-3); 73.1 (d, $J_{4,F}$ = 8 Hz, C-4); 72.4 (C-5); 61.7 (OMe); 17.7 (Me).

Anal. Calcd for $C_{15}H_{15}F_5O_5$: C, 48.65; H, 4.05; F, 25.67. Found: C, 48.81; H, 3.99; F, 25.55.

Compounds 15 and 16 by another method. To a solution of 13 (12 mg, 0.05 mmol) in dichloromethane (1 mL) was added xenon fluoride under stirring (14 mg, 0.07 mmol). The solution was cooled to 0° C and to it was added slowly boron trifluoride etherate (45 µL, 0.05 mol) in 1M toluene solution. Stirring was maintained for 30 min. at room temperature. Dilution with water and extraction with dichloromethane was followed by chromatography on silica gel. Syrupy 15 (8 mg, 58%) and 16 (4 mg, 29%) were thus obtained.

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