Organofluorine compounds and fluorinating agents. Part 11.* Glycosyl fluorides from acetal-protected sugars

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(Received August 28, 1992; accepted April 13, 1993)

Abstract

2-*O*-(2-Acetoxyethyl)-3,4,6-tri-*O*-methyl-α-D-glucosyl fluoride (**5**) was obtained by partial cleavage of the 1,2-*O*-ethanediyl-β-D-glucopyranose derivative **4** at the glycosidic position by means of the HF/nitromethane/acetic anhydride system. The same medium allows the selective cleavage of the 1,2-isopropylidene function in α-D-glucofuranosides (**7**, **11**) and of the 5,6-*O*-isopropylidene group in acetyl 2,3:5,6-di-*O*-isopropylidene-D-mannofuranoside (**15**) with simultaneous conversion into the corresponding acetylated glycosyl fluorides (**8**, **12**, **16**). The second acetal function in **11** and **15** is not cleaved by the weakened HF medium. 2-*O*-Benzyl-protected sugars such as methyl 3,5,6-tri-*O*-methyl-2-*O*-benzyl-D-glucofuranoside (**13**) react intramolecularly in the presence of HF/nitromethane/acetic anhydride to form a cyclic *C*-glycoside (**14**).

Introduction

During the last decade, glycosyl fluorides have become important in glycosylation reactions [2]. The process through which simple glycosyl fluorides are synthesised is well known [3]. More recently, the combination of anhydrous hydrogen fluoride with different bases has become increasingly important [4]. When mixed with bases such as triethylamine, pyridine or nitromethane, anhydrous hydrogen fluoride loses some of its reactivity whilst nevertheless allowing fluorination of monosaccharides at the anomeric position. Under these conditions, acetal-protecting groups are of a temporary nature and allow the synthesis of differently substituted glycosyl fluorides [5].

We have recently described the use of the homogeneous system anhydrous hydrogen fluoride/nitromethane/acetic anhydride for the conversion of acetal-protected monosaccharides into glycosyl fluorides with simultaneous transformation of the acetal protecting groups into ester groups (without contraction or expansion of the corresponding sugar ring) [6].

The utility of this HF-containing three-component system for the selective opening of a 1,2-*O*-ethanediyl-ring in D-glucopyranose derivatives and for the stepwise cleavage of acetal functions to form acetylated glycosyl fluorides is now described.

Results and discussion

In general, the selective introduction of a substituent into the 2-position of glucopyranosides is a complicated process involving a number of synthetic steps. The following example is a model for short syntheses of 2-(2-hydroxyethyl)-D-glucose derivatives with an ethylene spacer in the 2-position. 1,2-*O*-Ethanediyl-linked sugars such as **4** are cleaved at the 1,2-*O*-ethylene unit by HF/nitromethane/acetic anhydride (molar ratio: 1/1–2/0.05–0.15) to form the 2-(2-acetoxyethyl)-3,4,6-tri-*O*-methyl-α-D-glucosyl fluoride **5**. Deacetylation of **5** yields the unprotected D-glucopyranosyl fluoride **6**. The synthesis steps starting at 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl fluoride (**1**) are presented in Scheme 1.

Glycosylation of chloroethanol with 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl fluoride (**1**) catalysed by BF_3 etherate yielded 2-chloroethyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**2**). The formation of the 1,4-dioxan ring with a 1,2-*O*-ethylene bridge under basic conditions [7] followed by methylation results in 1,2-*O*-ethylene-3,4,6-tri-*O*-methyl-β-D-glucopyranose (**4**). To obtain the fluoride **5**, the regioselective cleavage of the intramolecular β-glucoside **4** at the anomeric position was carried out with the reagent system HF/nitromethane/acetic anhydride overnight at 0 °C, during which time compound **4** is completely transformed into the α-D-glucosyl fluoride **5**. The presence of acetic anhydride in the reagent system achieves the esterification of the resulting hydroxy group and causes a shift in the equilibrium between

*For Part 10, see ref. 1.

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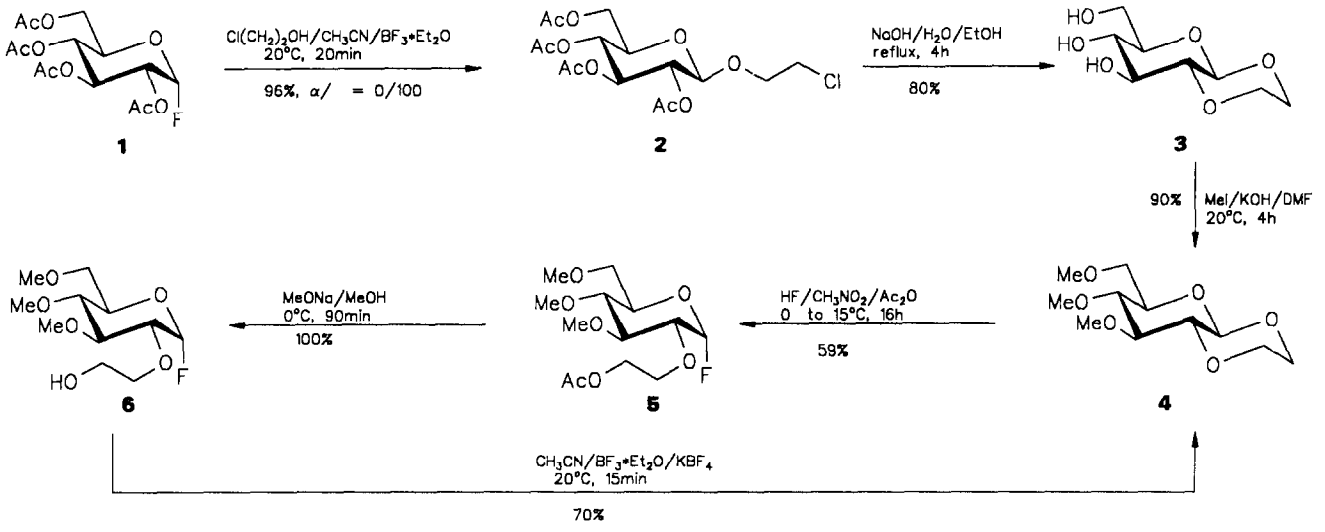
SSDI 0022-1139(93)02938-B

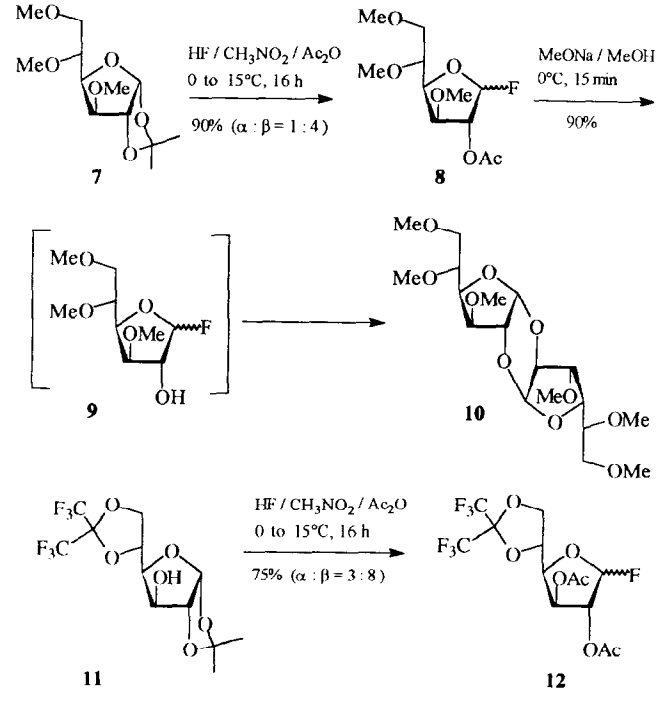


Scheme 1.

4 and the corresponding glycosyl fluoride. If the acetyl group is removed in **5** by means of a solution of sodium methanolate in methanol, the unprotected building block **6** remains behind.

In the first attempts to synthesise analogous crown ether systems starting at **6**, no cyclic oligomers could be obtained; the dioxan ring in the 1,2-position reappeared (α/β ratio = 1:3).

As part of their transformation into glucofuranose-containing cyclic oligosaccharides, the 1,2-isopropylidene protected compounds **7**, **11** were converted into the glycosyl fluorides **8**, **12** in a one step process (Scheme 2).



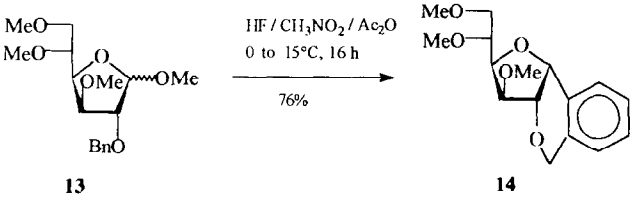
Scheme 2.

In contrast to isopropylidene groups, the 5,6-hexafluoroisopropylidene group in compound **8** [8] is not attacked by the weakened HF medium. This extreme resistance to acidic attack is caused by the strong electron-withdrawing effect of the trifluoromethyl groups in the acetal. The low electron density in the acetal oxygen atoms prevents protolytic cleavage.

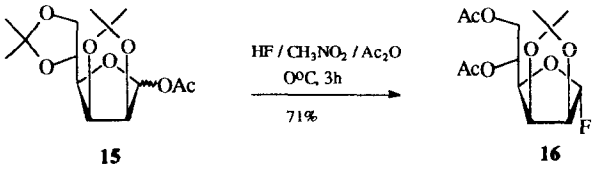
In contrast to pyranosyl fluorides, unprotected furanosyl fluorides are less stable towards nucleophiles. Hence, the deacetylation reaction of compound **8** does not stop at the glycosyl fluoride **9** stage but instead produces only the dimeric 1,2′:2,1′-dianhydro-bis(3,5,6-tri-*O*-methyl-α-D-glucofuranose) (**10**) [9] within 15 min/0 °C (Scheme 2).

When methyl 2-*O*-benzyl-glucofuranoside (**13**) is used as start material, the desired glucofuranosyl fluoride **9** is also unobtainable. Instead of producing the 2-*O*-benzyl-D-glucosyl fluoride, the intramolecular *C*-glucoside **14** was formed in a competition reaction in the system hydrogen fluoride/nitromethane/acetic anhydride (molar ratio = 1:2:0.05; Scheme 3).

Cleavage of the glycosidic linkage leads to the formation of a carbenium–oxonium ion at the anomeric position, which in turn yields the *C*-glucoside **14** by intramolecular arylation.



Scheme 3.



15 16

Scheme 4.

Analogous results starting at benzylated ribo- and arabino-furanose using Lewis acids have been reported by Anastasia *et al.* [10].

Depending on the difference in the reactivity of the acetal groups when treated with the above-mentioned HF system, acetyl 2,3:5,6-di-*O*-isopropylidene-D-mannofuranoside (**15**) allows the stepwise exchange of the acetal groups and the simultaneous introduction of fluorine. The 2,3-*O*-isopropylidene group is not attacked under mild conditions (0 °C, 3 h), and therefore the varied substituted 2,3-*O*-isopropylidene-5,6-di-*O*-acetyl-α-D-mannosyl fluoride (**16**) is accessible (Scheme 4). Complete deacetalisation of **15** forming the known 2,3,5,6-tetra-*O*-acetyl-D-mannofuranosyl fluoride [9] is obtained by treatment for 10–16 h in HF/nitromethane/acetic anhydride (2:4:1 v/v/v) at room temperature.

Experimental

Syntheses of carbohydrate derivatives **1** [11], **3** [7], **7** [12], **11** [8], **13** [13] and **15** [14] were carried out according to literature methods. Fluorination was controlled by TLC using Alufolie Kieselgel $60F_{254}$ (Merck). Melting points were measured with a Leitz Laborlux 12 Pol microscope equipped with a hot stage Mettler FP 90; ^1H and ^{13}C NMR data were recorded on a Bruker AC 250 instrument; see Table 3 below.

2-Chloroethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (2)

A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl fluoride (**1**, 1.14 g, 3.26 mmol) and chloroethanol (0.225 ml, 3.35 mmol) in acetonitrile (12 ml) was stirred with powdered 3 Å molecular sieves for 15 min at 20 °C. $BF_3 \cdot Et_2O$ was then added and the mixture stirred for 20 min. Filtration through Silica Gel was followed by addition of CH_2Cl_2 (60 ml). The solution was neutralised with aqueous hydrogen carbonate, washed and dried ($MgSO_4$). The solvent was evaporated and the crude product recrystallised from water or n-hexane; yield: 1.29 g (96%); m.p. 117 °C (lit. value [15]: 114 °C).

1,2-O-Ethanediyl-3,4,6-tri-O-methyl-β-D-glucopyranose (4)

1,2-*O*-Ethanediyl-β-D-glucopyranose (**3** [7], 0.8 g, 3.88 mmol) was dissolved in dry DMF (40 ml). The solution was cooled to 0 °C, powdered KOH (1.6 g) and methyl iodide (0.5 ml) were added and the mixture stirred for 5 h at room temperature. On cooling (0 °C), MeOH (5 ml) was added. The mixture was stirred for 20 min, neutralised (ion-exchange resin) and the solvent evaporated. The crude product was extracted with $CHCl_3$ (3×20 ml). Recrystallisation (hexane) gave pure **4**; yield: 0.87 g (90%); m.p. 80 °C. Analysis: Calc. for $C_{11}H_{20}O_6$ (248.28): C, 53.21; H, 8.12%. Found: C, 53.0; H, 8.1%.

Glycosyl fluorides 5, 8, 12 and 16, and C-glucoside 14: general procedure

In a Teflon vessel, the corresponding monosaccharide (**4**, **7** [12], **11** [8], **13** [13] or **15** [14], 1 mmol) was dissolved in nitromethane (10 ml) and the solution cooled (0 °C). Acetic anhydride was added followed by anhydrous hydrogen fluoride (for volumes see Table 1). The solution was allowed to stand and to warm up slowly to 15 °C.

TABLE 1. Fluorination reaction

Product	Agent $HF/CH_3NO_2/Ac_2O$ (molar ratio)	Reaction time (h)	Temp. (°C)	Yield (%)	α/β ratio (%)	M.p. (°C) (solvent)	$[\alpha_D]^{25}$ (c)$CHCl_3$	Formula (molar mass)	C/H microanalyses $C_{calc.}$ C_{found}	$H_{calc.}$ H_{found}
5	1:1.5:0.05	16	0–15	59	100:0	syrup	+76.89 (1.29)	$C_{13}H_{23}FO_7$ (310.33)	50.32 50.50	7.47 7.60
8	1:1:0.1	16	0–15	90	20:80	syrup		$C_{11}H_{19}FO_6$ (310.33)	49.62 49.60	7.19 7.20
12	1:1:0.1	16	0–15	75	27:73	syrup		$C_{13}H_{13}F_7O_7$ (414.25)	37.69 37.65	3.16 3.25
14	1:2:0.05	1.5	0	76	100:0	120 (hexane)	−22.58 (0.97)	$C_{16}H_{22}O_5$ (294.35)	65.29 65.35	7.53 7.70
16	1:1.5:0.15	3	0	71	100:0	syrup	+10.57 (0.52)	$C_{13}H_{19}FO_7$ (306.11)	50.98 51.30	6.25 6.25

Work-up procedure

The HF-containing system was slowly added to a cooled solution of triethylamine (3 equiv. of the amount of HF) in CCl_4 (50 ml). The CCl_4 phase was divided off and the upper triethylamine/trishydrogen fluoride layer was extracted twice with CCl_4 (40 ml). The CCl_4 solutions were combined, washed with aqueous $NaHCO_3$ and water, and dried ($MgSO_4$). The solvent was evaporated and the crude product chromatographed (Silica Gel; CH_2Cl_2/ethyl acetate = 4:1, Table 1).

Glycosyl fluoride **6** *and dimeric* D-*glucofuranose derivative* **10***: general deacylation procedure*

To a cooled (0 °C) solution of the glycosyl fluoride (**5**, **8**, 1 mmol) in methanol (3 ml) was added a solution of sodium methanolate (1%, 0.3 ml) with stirring. Neutralisation (ion-exchange resin) and evaporation of the solvent gave pure **6** and **10**, respectively (Table 2).

The ^1H and ^{13}C data relating to the compounds studied are listed in Table 3.

Acknowledgement

Support for our studies by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

TABLE 2. Deacetylation reaction

Product	Reaction time (min)	Yield (%)	M.p. (°C) (solvent)	$[\alpha_D]^{25}$ (c)$CHCl_3$	Formula (molar mass)	C/H microanalyses	
						$C_{calc.}$ C_{found}	$H_{calc.}$ H_{found}
6	90	100	syrup	+84.49 (0.77)	$C_{11}H_{21}FO_6$ (268.13)	49.27 49.40	7.89 7.90
10	15	90	95 (hexane)	−15.31 (1.0)	$C_{18}H_{32}O_{10}$ (408.45)	52.93 53.0	7.90 8.1

TABLE 3. ^1H and ^{13}C NMR data[a]

Product	^1H NMR (250.13 MHz)	^{13}C NMR (62.8 MHz)
4	3.10 (dd, 1H, $J_{2/3}$ ~ 10.0, H-2); 3.26 (m, 2H, H-3,4); 3.42 (ddd, 1H, $J_{4/5}$ ~ 9.5, $J_{5/6'}$ ~ 4.1, H-5); 3.39, 3.54, 3.61 (3s, 3H each, $3OCH_3$); 3.60 (dd, 1H, $J_{6/6'}$ ~ 10.9, H-6'); 3.64 (dd, 1H, $J_{5/6}$ ~ 2.6, H-6); 3.67–3.94 (m, 4H, $2CH_2$); 4.24 (d, 1H, $J_{1/2}$ ~ 7.5, H-1).	59.3, 60.6, 60.6 ($3OCH_3$); 66.0, 66.3 ($2CH_2$); 71.0 (C-6); 76.4 (C-5); 79.4, 79.6 (C-2,4); 83.6 (C-3); 98.2 (C-1).
5	2.05 (s, 3H, CH_3CO); 3.25 (dd, 1H, $J_{4/5}$ ~ 10.0, H-4); 3.30 (ddd, 1H, $J_{2/3}$ ~ 9.7, $J_{2/F}$ ~ 25.5, H-2); 3.38, 3.52, 3.61 (3s, 3H each, $3CH_3$); 3.48 (dd, 1H, $J_{3/4}$ ~ 9.5, H-3); 3.57 (m, 2H, H-6,6'); 3.75 (ddd, $J_{5/6}$ ~ $J_{5/6'}$ ~ 2.6, H-5); 3.84, 4.20 (2m, 2H each, $2CH_2$); 5.60 (dd, 1H, $J_{1/2}$ ~ 2.7, $J_{1/F}$ ~ 53.0, H-1).	20.4 (CH_3CO); 59.2, 60.6, 61.0 ($3OCH_3$); 63.6, 69.6 ($2CH_2$); 70.3 (C-6); 72.4 (d, $J_{5/F}$ ~ 4.1, C-5); 78.3 (C-4); 80.4 (d, $J_{2/F}$ ~ 24.8, C-2); 82.7 (C-3); 105.3 (d, $J_{1/F}$ ~ 227.1, C-1); 170.9 (CH_3CO).
6	3.27 (dd, 1H, $J_{4/5}$ ~ 9, H-4); 3.37 (ddd, 1H, $J_{2/3}$ ~ 9.5, $J_{2/F}$ ~ 24.5, H-2); 3.37, 3.50, 3.63 (3s, 3H each, $3OCH_3$); 3.49 (dd, 1H, $J_{3/4}$ ~ 8, H-3); 3.56 (m, 2H, H-6,6'); 3.68–3.85 (m, 3H, H-5, $2CH_2$); 5.60 (dd, 1H, $J_{1/2}$ ~ 2.6, $J_{1/F}$ ~ 53.2, H-1).	59.2, 60.5, 61.2 ($3OCH_3$); 62.3, 73.3 ($2CH_2$); 70.3 (C-6); 72.5 (d, $J_{5/F}$ ~ 4.01, C-5); 78.7 (C-4); 80.1 (d, $J_{2/F}$ ~ 24.85, C-2); 82.8 (C-3); 105.4 (d, $J_{1/F}$ ~ 226.66, C-1).
β-**8**	2.05 (s, 3H, CH_3CO); 3.40, 3.41, 3.48 (3s, 3H each, $3OCH_3$); 3.54 (dd, 1H, $J_{5/6'}$ ~ 3.24, H-6'); 3.67 (ddd, 1H, $J_{5/6}$ ~ 2.01, H-5); 3.73 (dd, 1H, $J_{6/6'}$ ~ 10.45, H-6); 3.80 (d, 1H, $J_{3/4}$ ~ 4.61, H-3); 4.37 (ddd, 1H, $J_{4/5}$ ~ 9.50, $J_{4/F}$ ~ 6.60, H-4); 5.22 (d, 1H, $J_{2/3}$ ~ 0, $J_{2/F}$ ~ 4.94, H-2); 5.66 (d, 1H, $J_{1/2}$ ~ 0, $J_{1/F}$ ~ 63.59, H-1).	20.6 (CH_3CO); 57.7, 58.3, 59.5 ($3OCH_3$); 71.0 (C-6); 77.0 (C-5); 77.8 (d, $J_{2/F}$ ~ 33, C-2); 81.2 (C-3); 82.5 (d, $J_{4/F}$ ~ 1.9, C-4); 112.3 (d, $J_{1/F}$ ~ 225.6, C-1); 169.5 (CH_3CO).

(*continued*)

TABLE 3. (*continued*)

Product	^{1}H NMR (250.13 MHz)	^{13}C NMR (62.8 MHz)
10	3.33, 3.34, 3.38 (3s, 9H, $3OCH_3$); 3.42 (dd, 1H, $J_{6/6'}\sim10.4$, H-6'); 3.55 (ddd, 1H, $J_{5/6'}\sim5.2$, H-5); 3.64 (dd, 1H, $J_{5/6}\sim2.1$, H-6); 3.79 (d, 1H, $J_{3/4}\sim3.3$, H-3); 3.83 (d, 1H, $J_{2/3}\sim0$, H-2); 4.13 (dd, 1H, $J_{4/5}\sim9.0$, H-4); 5.05 (d, 1H, $J_{1/2}\sim3.9$, H-1).	57.3, 58.3, 59.3 ($3OCH_3$); 72.5 (C-6); 75.4 (C-5); 76.5 (C-2); 79.3 (C-3); 84.7 (C-4); 97.5 (C-1).
β-12	4.28 (dd, $J_{6/6'}\sim8.5$, H-6'); 4.49 (dd, $J_{5/6}\sim6.0$, H-6); 4.64 (ddd, $J_{4/5}\sim7.5$, $J_{4/F}\sim5.0$, H-4); 4.68 (ddd, $J_{5/6'}\sim6.5$, H-5); 5.21 (d, 1H, $J_{2/3}\sim0$, $J_{2/F}\sim4.8$, H-2); 5.48 (d, 1H, $J_{3/4}\sim5.0$, H-3); 5.67 (d, 1H, $J_{1/2}\sim0$, $J_{1/F}\sim60.5$, H-1).	20.4, 20.5 (2s, $2CH_3CO$); 71.0 (C-6); 72.7 (C-5); 77.3 (C-3); 79.3 (d, $J_{2/F}\sim37.01$, C-2); 82.2 (d, $J_{4/F}\sim2.5$, C-4); 111.9 (d, $J_{1/F}\sim228.80$, C-1); 169.0, 169.0 (2s, $2CH_3CO$).
14	3.35, 3.49, 3.52 (3s, 3H each, $3OCH_3$); 3.49 (dd, 1H, $J_{6/6'}\sim10.3$, H-6'); 3.68 (ddd, 1H, $J_{5/6'}\sim5.87$, H-5); 3.75 (dd, 1H, $J_{5/6}\sim2.04$, H-6); 3.95 (d, 1H, $J_{3/4}\sim3.56$, H-3); 4.11 (d, 1H, $J_{4/5}\sim9.14$, H-4); 4.24 (d, 1H, $J_{2/3}\sim0$, H-2); 4.68 (AB, 2H, $J_{A/B}\sim$ 14.7, CH_2); 4.81 (d, 1H, $J_{1/2}\sim3.06$, H-1); 7.03, 7.27, 7.44 (3m, 1, 2, 1H, $H_{arom.}$).	57.8, 58.0, 58.8 ($3OCH_3$); 66.9 (C-6); 73.8, 74.3 (C-5, CH_2); 78.0, 79.0, 79.8 (C-2, 3, 4); 85.9 (C-1); 124.5, 127.4, 128.2, 130.8, 132.5, 135.5 ($6C_{arom.}$).
16	1.29, 1.41 (2s, 3H each, $2CH_3$); 2.04, 2.05 (2s, 3H each, $2CH_3CO$); 4.16 (dd, 1H, $J_{6/6'}\sim12.5$, H-6'); 4.34 (dd, 1H, $J_{4/5}\sim8.1$, $J_{4/F}<1$, H-4); 4.59 (dd, 1H, $J_{5/6}\sim2.5$, H-6); 4.74 (dd, 1H, $J_{2/3}\sim5.9$, $J_{2/F}\sim6.2$, H-2); 4.78 (dd, 1H, $J_{3/4}\sim3.8$, H-3); 5.28 (ddd, 1H, $J_{5/6'}\sim5.1$, H-5); 5.68 (d, 1H, $J_{1/2}\sim0$, $J_{1/F}\sim59.2$, H-1).	20.6, 20.7 ($2CH_3CO$); 24.6, 25.7 ($2CH_3$); 62.7 (C-6); 68.6 (C-5); 78.3, 80.0 (C-3,4); 84.3 (d, $J_{2/F}\sim41.8$, C-2); 113.3 (d, $J_{1/F}\sim222.7$, C-1); 113.4 ($(CH_3)_2C$); 169.4, 170.4 ($2CH_3CO$).

[a]Solvent $CDCl_3$, internal standard TMS, δ (ppm), J (Hz).

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