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DIRECT KETALISATION OF *vic.*- DIOLS WITH HEXAFLUOROACETONE. CONVERSION OF D-GLUCOSE AND L-RHAMNOSE DERIVATIVES TO HEXAFLUOROACETONE KETALS

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Abstract: The cyclic hexafluoroacetone ketals **3** and **6** of the title compounds **1** and **5** were prepared with hexafluoroacetone (HFA) in the presence of dicyclohexylcarbodiimide (DCC). The reaction of 1,2-O-isopropylidene-α-D-glucofuranose **1** with HFA leads without DCC addition only to a mixture of unstable hemiketals. This mixture of hemiketals was methylated with diazomethane and the corresponding methylketals **2** were separated.
Acetic acid 80% selectively cleaves the mixed diketal **3** at the 1,2-position to form 5,6-O-hexafluoroisopropylidene-α/β-D-glucofuranose **4**. The ^{1}H-, ^{13}C-, ^{19}F n.m.r. data of the hexafluoroacetone ketals are discussed, and the mass spectrometric fragmentation of compound **3** is presented.

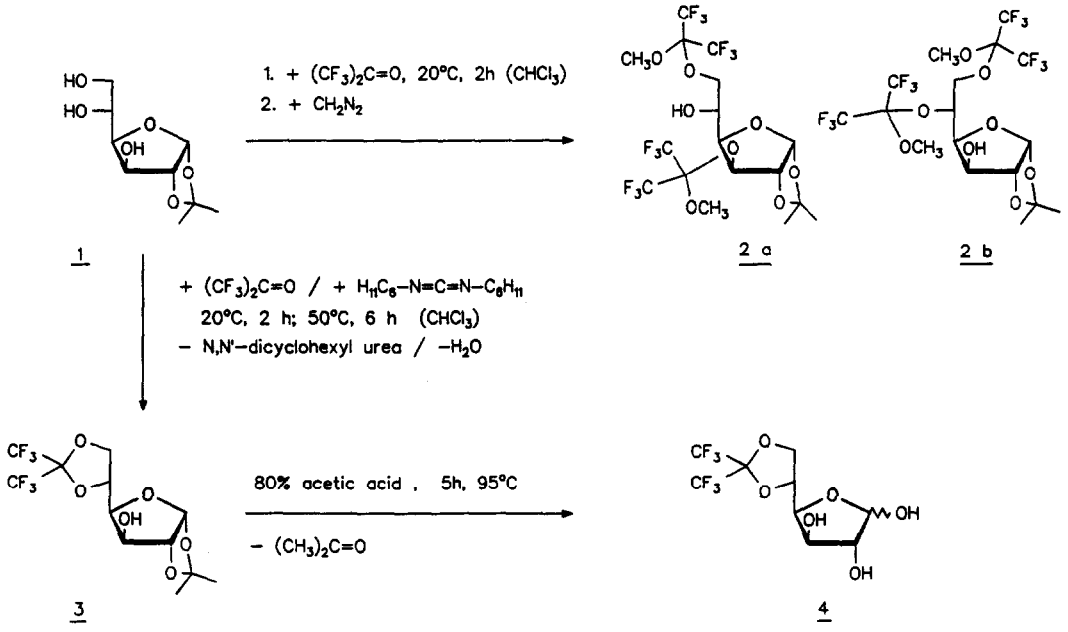
INTRODUCTION

All previous attempts to convert *vic.*-diols by reaction with hexafluoroacetone (HFA) in the corresponding cyclic ketals were unsuccessful,[1] since the reaction stops at the hemiketal. Therefore, the cyclic ketals were only prepared by condensation of ß-chlorohydrins[2] or bromohydrins[3] with HFA, by heating cyclic carbonates of polyols[4] with HFA, or by heating epoxides[5] with HFA in the presence of small amounts of $n\text{-}Bu_4NBr/H_2O$. In contrast, α-hydroxy carboxylic acids smoothly react with hexafluoroacetone to form 2,2-bis-trifluoromethyl-1,3-dioxolaneones-(4).[6]
Hexafluoroacetone ketals of sugars have not been described in the literature. These cyclic ketal functions could be very useful in synthetic

applications, because they are probably more stable than the conventional cyclic acetals or ketals as protecting groups. Mixed sugar ketals could be cleaved stepwise. Therefore, a procedure was attempted for a direct ketalisation of partial unprotected monosaccharides with hexafluoroacetone.

DISCUSSION AND RESULTS

1,2-O-Isopropylidene-α-D-glucofuranose (**1**) and methyl-α-L-rhamnopyranoside (**5**) were selected as models for our investigations with hexafluoroacetone. Treatment of these sugar derivatives in chloroform at r.t. with HFA yielded, as expected, mixtures of unstable hemiketals.

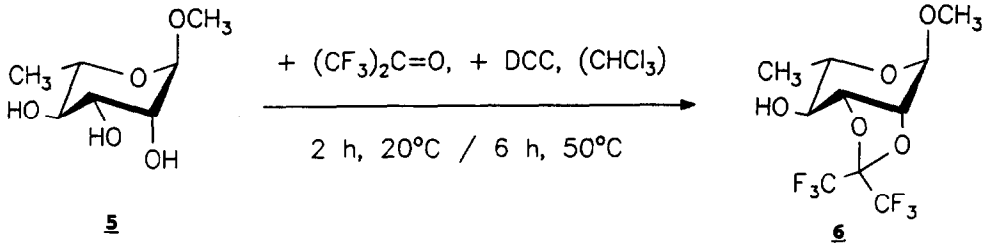


Scheme 1. Ketalisation of 1,2-O-isopropylidene-α-D-glucofuranose (**1**) with hexafluoroacetone; selective cleavage of the mixed diketal **3** to 5,6-O-hexafluoroisopropylidene-α/β-D-glucofuranose (**4**).

Methylation of the hemiketal mixture of the D-glucofuranose derivative with diazomethane yielded at least four products (t.l.c.). The major product **2a** and a by-product **2b** were separated by chromatography as crystalline compounds. These both compounds contain two hexafluoroacetone moieties (scheme 1). The further by-products were not yet identified. All components of the methylketal mixture **2** contain one of the

hexafluoroacetone moieties at the oxygen in 6-position, showing the predominant attack by HFA on this position.

Hexafluoroacetone ketalisation of **1** and **5** to form the bis-trifluoromethyl-1,3-dioxolane derivatives **3** and **6**, respectively, is possible in the presence of dicyclohexylcarbodiimide (DCC). Thus, treatment of 1,2-O-isopropylidene-α-D-glucofuranose (**1**) suspended in chloroform, with HFA in the presence of DCC at r.t. (2 h) and 50°C (6 h) leads to the expected hexafluoroacetone ketal **3** in 35% yield (scheme 1, table 1 and 2). It should be noted that the formation of dicyclohexyl urea is the key for the success of the reaction. When the reaction temperature was increased three by-products were observed in small amounts, that increased significantly during the first part of the reaction.[7] These by-products were separated by column chromatography[7] and will be reported in a further publication.
To prove whether the different ketal functions in **3** can be cleaved separately, the compound was heated in 80% aqueous acetic acid. It is known that 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose is cleaved predominantly by aqueous acids at the 5,6-position.[8] We found the opposite for the mixed diketal **3** since the 1,2-ketal cleaved first (scheme 1). Thus the 5,6-protected cyclic D-glucofuranose ketal **4** is readily accessible giving in addition to the α- and β-anomers of **4** also a by-product in small amounts if few drops of sulfuric acid are added to the acetic acid solution. The reaction time to cleave the ketal is shorter in this case (2h in comparison to 5h); the by-product was not yet identified exactly.



5 **6**

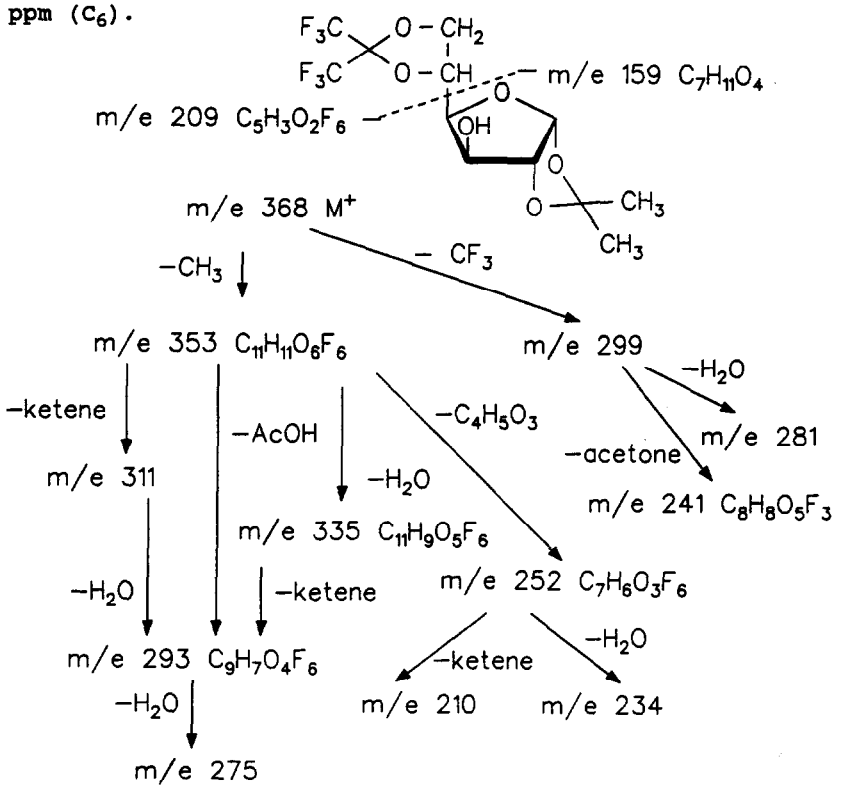
Scheme 2. Ketalisation of methyl-α-L-rhamnoside **5** with hexafluoroacetone in presence of dicyclohexylcarbodiimide.

A chloroform solution of methyl-α-L-rhamnopyranoside (**5**) containing HFA in the presence of DCC is almost quantitatively converted into methyl-2,3-O-hexafluoroisopropylidene-α-L-rhamnopyranoside (**6**) (scheme 2, table 1) after 2 h at 20°C and 6 h at 50°C. Few by-products were detectable by t.l.c..

Unprotected L-rhamnose did not react selectively with hexafluoroacetone/dicyclohexylcarbodiimide.[7]

The proposed structures for compounds **2a-b**, **3**, **4** and **6** are supported by mass spectrometric and n.m.r. spectroscopic (^1H, ^{13}C, ^{19}F) data; scheme 3, table 2. Two trifluoromethyl groups in the ^{19}F spectra are found for the compounds **3**, **4**, **6** and four trifluoromethyl groups for **2a** and **2b**, respectively.

The significant down field shift of the C_5- and C_6-atoms (δ = 75.15 and δ = 71.00 ppm) in the ^{13}C n.m.r. spectrum of **3** suggests that these positions are part of a bis-trifluoromethyl-dioxolane ring. The relative values of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose are δ = 72.33 ppm (C_5) and δ = 66.13 ppm (C_6).



Scheme 3. Mass spectrometric fragmentation of 1,2-O-isopropylidene-5,6-O-hexafluoroisopropylidene-α-D-glucofuranose (**3**).

The down field shift of the protons in 5- and 6-position of **3** also confirms the location of the fluorinated functional group (table 2).

Similar effects are found in 2- and 3-position of **6** as well as in 3-,5- or 6-position of the methylketals **2a-b** (table 2).

Mass spectrometric investigations were carried out for compound **3** on a double focussing reversed geometry mass spectrometer. The isobutane CI mass spectrum was used to get further information about the molecular weight of **3**. The prominent MH^+-peak and the resulting adduct ion $(M+C_3H_7)^+$ suggest a molecular mass of 368. The 70 eV-electron ionisation mass spectrum shows a (M - 15)-signal at m/e = 353 as base peak. We analyzed its elemental composition by peak matching (used resolution R = 10.000), including also all significant (M-X)-peaks in the upper mass range. The intensity of the molecular ion is very small (< 1%).

The ion-statistical main fragmentation pathway is characterized by a primary methyl radical loss from the 1,2-O-isopropylidene group. The following neutral losses of acetic acid or water and ketene from the demethylated molecule have been established by means of Linked Scan measurements with collision activation in the first field free region (Constant Neutral Losses).[9]

Another important fragmentation is a CF_3 removal (m/e = 299) and a following acetone neutral loss. Further Linked Scan experiments (Parent and Daughter Scans) were used for securing the fragmentation pattern in scheme 3.

The fragments m/e = 159 and m/e = 209 are also necessary for structure elucidation. Their elemental compositions were found by high resolution mass determination; they result from a cleavage of the C_4- and C_5-bond of compound **3**. Existence and location of the free OH-group in 3-position was confirmed by a H/D-exchange experiment with CH_3OD.

EXPERIMENTAL

Column chromatography and t.l.c. were carried out by use of t.l.c. aluminium foil Silicagel 60 F_{254} and Silicagel 60 (63-200 μm) (Merck), respectively. Spectroscopic data were determinated with Bruker AC-250 and WM-500 n.m.r. instruments as well as a AMD 402 mass spectrometer (AMD intectra); a Polamat A (Carl-Zeiss-Jena) was used for optical rotations The melting points were determined with a micro heating stage of Boetius.

Hemiketalisation of 1,2-O-isopropylidene-α-D-glucofuranose with hexafluoroacetone following methylation to form the methylketals 2

An excess of dry hexafluoroacetone, prepared by dropping of 2.0 g (9 mmol) hexafluoroacetone-trihydrate in conc.sulfuric acid at 135°C, was introduced continuously above a suspension of 1.0 g (4.5 mmol) 1,2-isopropylidene-α-D-glucofuranose (**1**)[10] in 10 ml absolute chloroform (vigorous stirring at r.t.). Non-absorbed HFA condensed in a methanol/solid CO_2 condenser and

returned to the solution. 1,2-O-Isopropylidene-α-D-glucofuranose (**1**) dissolves during the reaction slowly. An excess of diazomethane dissolved in ether was subsequently added, the solvents evaporated and the residue (2.8 g) analyzed by t.l.c. (eluent: ethyl acetate / toluene 1:6 v/v). The five components (R_F = 0.31 (**2b**), R_F = 0.53 (major product **2a**), R_F = 0.58, R_F = 0.63, R_F = 0.65) were separated in three fractions by column chromatography. **2a** (1.5 g) and **2b** (24 mg) could be isolated from fraction 2 and 3 respectively, as crystalline compounds (scheme 1; table 1 and 2).

Table 1. Yields, Melting points, elementary analysis and optical rotations of the compounds **2**-**4** and **6**.

Educt	Product	Formula (mol wt)[a]	Yield (%)	m.p. (°C)	C/H/N-Analysis calculated/found	$[\alpha]_D$ $CHCl_3$[b]
1	**2**	$C_{17}H_{20}F_{12}O_8$ (580.37)	57.5(**2a**)	60-62	C = 35.18 / 35.50 H = 3.48 / 3.70	-8.29
			0.9(**2b**)	82.5		-1.83
1	**3**	$C_{12}H_{14}F_6O_6$ (368.24)	35.0	140.5	C = 39.14 / 39.60 H = 3.84 / 3.90	+2.73
3	**4**α/β	$C_9H_{10}F_6O_6$ (328.15)	90.0	syrup	C = 32.94 / 33.20 H = 3.08 / 3.50	
5	**6**	$C_{10}H_{12}F_6O_5$ (326.15)	88.3	syrup	C = 36.83 / 37.10 H = 3.72 / 3.85	-52.35

a) molecular weight was confirmed by mass spectrometry (mol peak, CI); b) c = 1.0.

1,2-O-Isopropylidene-5,6-O-hexafluoroisopropylidene-α-D-glucofuranose (4)

22.7 mmol dry hexafluoroacetone, prepared as above described, were introduced continuously above a suspension of 5.0 g (22.7 mmol) 1,2-O-isopropylidene-α-D-glucofuranose (**1**)[10] in 50 ml absolute chloroform containing 4.68 g (22.7 mmol) dicyclohexylcarbodiimide (DCC) were vigorously stirred at r.t.. Non-absorbed HFA condensed in a methanol/solid CO_2 condenser and returned to the solution. The 1,2-O-isopropylidene-α-D-glucofuranose (**1**) dissolves during the reaction slowly. After 2 h the homogeneous solution was heated at 50°C for 6 h, cooled down and filtered from N,N´-dicyclohexyl urea. Treatment of the organic phase with water leads to hydrolysis of unreacted DCC and formed hemiketals. After drying of the organic phase with $CaCl_2$ and evaporation of the solvent a residue with four compounds was obtained: the main product **3** (R_f = 0.53) and the by-products (R_f values: 0.62, 0.81, 0.89); t.l.c. eluent: ethyl acetate/chloroform = 1 : 5 v/v. The mixture was separated by column chromatography with the same eluent in two fractions. The HFA ketal **3** was collected together with the by-product (R_f = 0.62) as first fraction; after evaporation of the solvents compound **3** was sublimated at 70°C / 0.001 torr; yield: 2.9 g (35%). The residue of sublimation was recrystalized with n-hexane, yielding 1,2-O-isopropylidene-5,6-O-(N-cyclohexylcarbimido)-α-D-glucofuranose; m.p. 84-87°C ($[\alpha]_D$ = + 30.43, $CHCl_3$).[7]

Table 2 ^{1}H-, ^{13}C- and ^{19}F n.m.r. data of the hexafluoroacetone hemiketal **2** and the ketals **3**, **4**, **6**.

Comp.	^{1}H n.m.r. ($CDCl_3$/TMS) δ, J (Hz)	^{13}C n.m.r. ($CDCl_3$/TMS) δ, J (Hz)	^{19}F n.m.r. $CDCl_3/CFCl_3$ δ, J (Hz)
2a	1.31 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), -2.68 (broad, 1H, 5-OH) 3.61 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3) 3.96 (d, 2H, H-6,6') 4.12 (dt, 1H, $J_{5,6/6'}$ = 4.5, H-5), 4.27 (dd, 1H, $J_{4,5}$ = 9, H-4), 4.70 (d, 1H, $J_{2,3}$ = 0, H-2), 4.72 (d, 1H, $J_{3,4}$ = 3, H-3), 5.88 (d, 1H, $J_{1,2}$ = 4, H-1)	26.10 (CH_3), 26.27 (CH_3), 52.33 (OCH_3), 54.49 (OCH_3) 65.84, 66.07, 76.78, 78.19 (C-3 - C-6), 82.35 (C-2), 95.57 (m, $J_{Cq,F}$ = 41.1, $2C_q^b$), 104.34 (C-1), 112.06 (Cq^c) 120.17 (q, $J_{\underline{C}F3,F}$ = 294.0, $4CF_3$)	-75.58 (q, 3F, $J_{CF3,CF3}$ = 7.9, CF_3), -75.82 (q, 3F, $J_{CF3,CF3}$ = 9.2, CF_3), -76.12 (q, 6F, $J_{CF3,CF3}$ = 10.0, CF_3)
2b	1.29 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), -2.55 (broad, 1H, 3-OH), 3.60 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.01 (dd, 1H, H-6), 4.11 (dd, 1H, $J_{6,6'}$ = 11.0, H-6'), 4.32 (d, 1H, $J_{3,4}$ = 2.5, H-3), 4.42 (dd, 1H, $J_{4,5}$ = 7, H-4), 4.52 (d, 1H, $J_{2,3}$ = 0, H-2), 4.62 (ddd, 1H, $J_{5,6}$ = 1.5, $J_{5,6'}$ = 3.5, H-5), 5.90 (d, 1H, $J_{1,2}$ = 3.5, H-1)	26.16 (CH_3), 26.38 (CH_3), 52.63 (OCH_3), 54.37 (OCH_3) 63.31, 72.19, 74.52, 77.69 (C-3 - C-6), 84.74 (C-2), 96.5 (m, $J_{Cq,F}$ - 40.0, $2C_q^b$), 104.55 (C-1), 112.04 (Cq^c) 120.20 (q, $J_{\underline{C}F3,F}$ = 290.5, $4CF_3$)	-75.49 (q, 3F, $J_{CF3,CF3}$ = 8.2, CF_3), -75.63 (q, 3F, $J_{CF3,CF3}$ = 10.9, CF_3), -75.77 (q, 3F, $J_{CF3,CF3}$ = 7.8, CF_3), -77.19 (q, 3F, $J_{CF3,CF3}$ = 10.3, CF_3)
3[a]	1.32 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.97 (d, 1H, $J_{3,OH}$ = 5, OH), 4.22 (dd, 1H, $J_{4,5}$ = 7, H-4), 4.28 (dd, 1H, $J_{6,6'}$ = 7, H-6), 4.38 (dd, 1H, $J_{3,4}$ = 3, H-3), 4.48 (dd, 1H, H-6'), 4.54 (d, 1H, H-2), 4.71 (ddd, 1H, $J_{5,6}$ = 7, $J_{5,6'}$ = 7, H-5), 5.92 (d, 1H, $J_{1,2}$ = 4, H-1)	26.52 (CH_3), 27.15 (CH_3), 71.00 (C-6), 75.15 (C-5), 78.11 (C-3), 80.34 (C-4), 85.92 (C-2), 100.52 (spt, $J_{Cq,F}$ = 39.2, C_q^b), 106.01 (C-1), 112.90 (Cq^c), 120.91 (q, $J_{\underline{C}F3,F}$ = 293.9, CF_3), 121.40 (q, $J_{\underline{C}F3,F}$ = 290.0, CF_3)	-78.82 (q, 3F, $J_{CF3,CF3}$ = 6.7, CF_3), -80.05 (q, 3F, CF_3)
4[d]	6.19 (H-1/α, $J_{1,2}$ = 6) 6.18 (H-1/β)	66.29, 69.29, 69.69, 74.74, 74.93, 75.96, 76.56, 79.86, 79.97, 80.71 (C-1 - C-6 of the α/β-anomers), 97.48 (C-1/α), 103.20 (C-1/β), 98.98 (spt, $J_{Cq,F}$ = 33.1, C_q^b), 120.12 (q, $J_{\underline{C}F3,F}$ = 289.6, CF_3), 120.61 (q, $J_{\underline{C}F3,F}$ = 291.2, CF_3)	-79.95 (q, 3F, $J_{CF3,CF3}$ = 8.2, CF_3), -80.24 (q, 3F, CF_3)
6	1.31 (d, 3H, CH_3), 3.38 (s, 3H, OCH_3), -4.0 (broad, 1H, OH), 3.82 (dq, 1H, $J_{5,6}$ = 5.5, H-5), 3.90 (dd, 1H, $J_{2,3}$ = 9, H-2), 4.30 (dd, 1H, $J_{4,5}$ = 9, H-4), 4.40 (d, 1H, $J_{1,2}$ = 6, H-1), 4.52 (dd, 1H, $J_{3,4}$ = 9, H-3)	18.97 (C-6), 55.52 (OCH_3), 66.43 (C-4), 72.38 (C-5), 82.02 (C-3), 82.09 (C-2), 101.61 (C-1), 101.91 (spt, $J_{Cq,F}$ = 34.1, C_q^b), 119.61 (q, $J_{\underline{C}F3,F}$ = 287.2, CF_3), 120.72 (q, $J_{\underline{C}F3,F}$ = 291.2, CF_3)	-81.25 (q, 3F, $J_{CF3,CF3}$ = 7.5, CF_3), -81.49 (q, 3F, $J_{CF3,CF3}$ = 7.7, CF_3)

a) in CD_2Cl_2; b) quart. C atom of the hexafluoroisopropylidene group; c) quart. C atom of the isopropylidene group; d) in DMSO-D6.

The both by-products of the second fraction are also crystalline compounds melting at 96-98°C ($[\alpha]_D$ = +1.74, $CHCl_3$) and 105-109°C ($[\alpha]_D$ = + 41.15, $CHCl_3$), respectively.

5,6-O-Hexafluoroisopropylidene-α/β-D-glucofuranose (4)

1.0 g (2.7 mmol) **3**, dissolved in 5 ml 80% acetic acid was heated 5 h at 95°C (t.l.c. control; eluent: ethyl acetate) and after this the solution was neutralized with sodium hydrogencarbonate and then extracted with ether or ethyl acetate. After evaporation of the organic phase remained a syrup, which was purified by column chromatography (eluent: ethyl acetate). 0.8 g (90%) of a mixture of 5,6-O-hexafluoroisopropylidene-α/β-D-glucofuranose (**4**) was obtained as a syrup.

Methyl-2,3-O-hexafluoroisopropylidene-α-L-rhamnopyranoside (6)

2.1 g (11.8 mmol) methyl-L-rhamnopyranoside (**5**)[11] and 2.44 g (11.8 mmol) DCC, both dissolved in 50 ml chloroform were treated with one equivalent HFA and worked up as described for 1,2-O-isopropylidene-5,6-O-hexafluoroisopropylidene-α-D-glucofuranose (**3**). The crude product (3.85 g) contained only very small amounts of sugar by-products, which were separated by column chromatography (ethyl acetate/chloroform 1:5 v/v).Yield: 3.4 g syrup **6** (88%).

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