ELSEVIER

Journal of Fluorine Chemistry 115 (2002) 149–154

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

Synthesis of homochiral 2-C-perfluoroalkyl substituted D- and L-riboses

Uwe Eilitz[a], Christoph Böttcher[a], Lothar Hennig[a], Alois Haas[b], Cecile Boyer[b], Klaus Burger[a,*]

[a]*Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, D-04103 Leipzig, Germany*
[b]*Ruhr-Universität, Bochum FNO 034, D-44780 Bochum, Germany*

Received 26 November 2001; received in revised form 29 January 2002; accepted 6 February 2002

Dedicated to Professor H. Bürger on the occasion of his 65th birthday.

Abstract

Homochiral 2-C-perfluoroalkyl substituted D- and L-riboses were synthesized via Barbier, Grignard and Ruppert type reactions. The influence of the size of the perfluoroalkyl groups, attached to C-2, on the furanose/pyranose as well as on the α-furanose/β-furanose and α-pyranose/β-pyranose ratio in solution was studied.

Keywords: Stereoselective fluoroalkylation reactions; 2-C-heptafluoropropyl D-ribose; 2-C-nonafluorobutyl L-ribose

1. Introduction

Modification of bioactive compounds by introduction of fluorine and fluoroalkyl groups is an area of current interest [1–3]. Fluorine and/or fluoroalkyl groups placed in strategic positions of a molecule may profoundly modify chemical properties, biological activity and selectivity [4–6]. Furthermore, fluorine as well as difluoromethyl and trifluoromethyl groups are suitable NMR probes for monitoring transport and metabolism of drugs by ^{19}F NMR spectroscopy in vitro and in vivo [7]. The usefulness of ^{18}F-labelled carbohydrates, especially 2-deoxy-2-[^{18}F]fluoro-D-glucose to study pathophysiological processes in man non-invasively using positron-emission-tomography (PET), led to a widespread investigation of differently ^{18}F-labelled sugar derivatives [8].

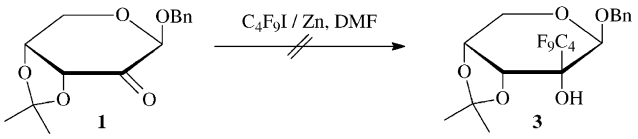
Chemically modified carbohydrates are substructures of nucleosides exhibiting anti-viral, anti-cancer and anti-HIV activity [9]. Among the possible modifications of the carbohydrate ring, the C-2 position is of special interest, since it has been shown that a methyl group placed at C-2 of a sugar moiety induces severe conformational changes. The rotation about the *N*-glycosidic bond becomes restricted, resulting in an increased nuclease resistance and consequently in an enhanced biological activity [10,11]. Reactions at C-1 of carbohydrates via cationic intermediates are much more difficult to achieve when a trifluoromethyl group is attached to C-2 [12]. Consequently, glycosides derived from thus modified carbohydrates should exhibit improved chemical and enzymatic stability. A review on fluoro sugars [13] prompts us to disclose a preparatively simple access to homochiral D- and L-ribose derivatives bearing perfluoroalkyl substituents of different chain length (C_3F_7 and C_4F_9) at C-2 [14]. Incorporation of long perfluoroalkyl chains into carbohydrates provides access to compounds with mesogenic and tenside properties. Surface active compounds of this type are of interest to pharmacy and biochemistry [15,16].

2. Results and discussion

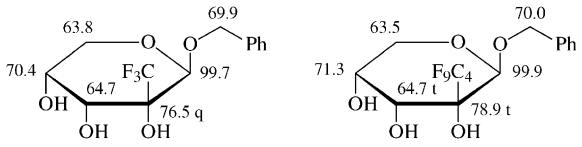
Recently we reported on the synthesis of 2-C-trifluoromethyl D-L-ribose and D-L-arabinose [17] and of 2-C-trifluoromethyl D-ribose [18] starting from the readily available trifluoromethyl containing building block methyl trifluoropyruvate. We now describe methodology for stereoselective introduction of perfluoroalkyl groups in a late step of the synthetic sequence. We tested three methods for introduction of perfluoroalkyl groups into D- and L-ribose, namely the Barbier, the Grignard and the Ruppert reaction. As substrate we applied benzyl D-3,4-*O*-isopropylidene-β-erythro-pentopyranosid-2-ulose and benzyl L-3,4-*O*-isopropylidene-β-erythro-pentopyranosid-2-ulose (**1** and **2**), respectively [19] (Scheme 1).

* Corresponding author. Tel.: +49-341-9736529; fax: +49-341-9736599.
E-mail address: burger@organik.chemie.uni-leipzig.de (K. Burger).

0022-1139/02/$ – see front matter
PII: S0022-1139(02)00042-8



Scheme 1.



Scheme 3.

First, we reacted **1** with perfluorobutyl iodide and Zn in DMF with sonification according to the standard protocol [20] and under modified conditions without success. This was not unexpected, since only aldehydes are reported to give good yields in Barbier type reactions [21], while in the case of ketones the yields are notoriously low, due mainly to steric reasons [20,22] (Scheme 2).

When in a Ruppert type reaction, **1** was treated with heptafluoropropyl trimethylsilane [23] in the presence of tetrabutylammonium fluoride (TBAF) as a catalyst, an oil was obtained after column chromatography in low yield (9%). A slight improvement of the yield (25%) was accomplished when TBAF was substituted by tetrabutylammonium difluorophenylstannate as a catalyst. ^{19}F NMR spectroscopy of the crude product revealed that only one diastereomer was formed. Because of the concave geometry of **1** the carbonyl group should be attacked preferentially from the Si-site to give the benzyl 2-C-heptafluoropropyl-3,4-*O*-isopropylidene-β-D-erythro-ribopyranoside (**4**).

Deblocking of the acetonide protecting group can be achieved on treatment with diluted acetic acid (60%). Comparison of the ^{13}C NMR spectra of benzyl 2-C-heptafluoropropyl-β-D-ribopyranoside (**5**) formed in 83% yield with its 2-C-trifluoromethyl analogue [13] reveals that the size of the fluoroalkyl side chain does not affect conformational equilibria profoundly as long as the anomeric OH-function remains protected (Scheme 3).

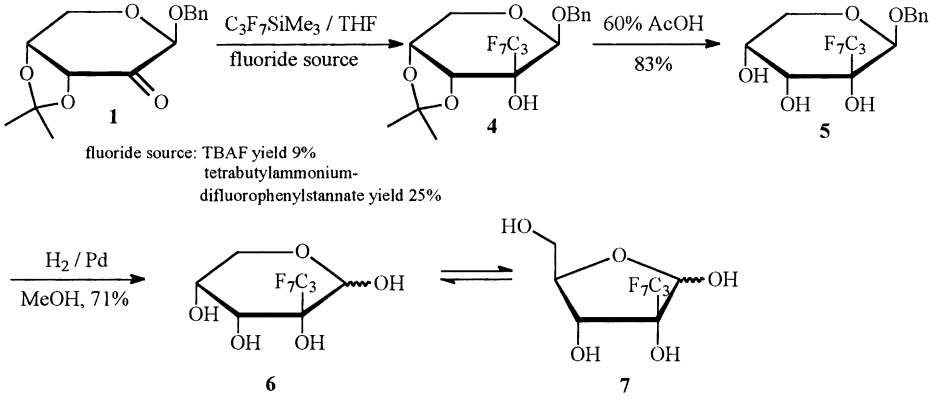
Deblocking of the benzyl group by catalytic hydrogenation at room temperature is a surprisingly slow process (4 weeks) and affords the unprotected 2-C-heptafluoropropyl D-ribose **7** in 73% yield as a colorless compound, readily recrystallized from water. NMR spectra of a freshly prepared solution in D_6-acetone reveals that only a single compound is present. Based on the ^1H and ^{13}C NMR data we ascribe this compound the structure of an α-furanose. After a few days a stable equilibrium mixture consisting of α-furanose (69%), β-furanose (17%), α-pyranose (<1%) and β-pyranose (14%) was formed (Scheme 2).

In water solution mutarotation can be observed. For a freshly prepared solution of **7** in water ($c = 1$) an optical rotation was measured $[\alpha]_D = +16.7$ which changed during one day to $[\alpha]_D = -13.3$.

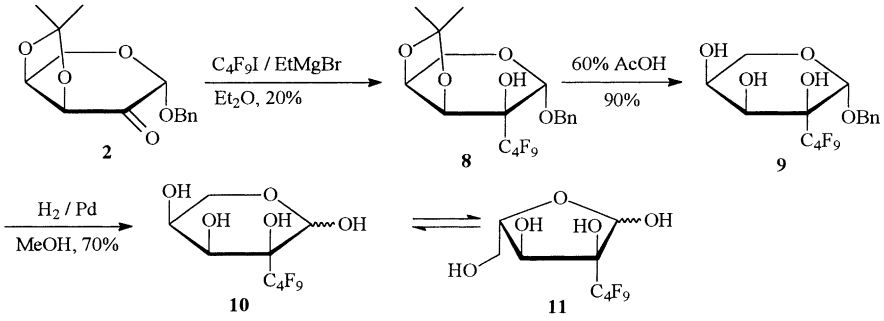
To introduce the perfluorobutyl group into benzyl-3,4-*O*-isopropylidene-β-L-erythro-pento-pyranosid-2-ulose (**2**) we choose perfluorobutyl magnesium bromide, readily prepared from perfluorobutyl iodide and ethyl magnesium bromide [24,25]. Because of the concave shape of the acetone protected sugar moiety, nucleophilic attack from the Si-site is unfavorable and CC-bond formation occurs exclusively from the Re-site to give the C-2 perfluoroalkyl-substituted L-ribose derivative **8**. Again the yield is low (20%) (Scheme 4).

The acetonide was cleaved on treatment with diluted acetic acid (60%) to give the corresponding benzyl 2-C-perfluoroalkyl-β-L-ribopyranoside **9**. The unprotected 2-C-perfluorobutyl L-ribose was obtained on hydrogenolysis (**9** → **10** → **11**) as an oil of only poor water solubility. Therefore, mutarotation could not be recorded and the optical rotation was measured in methanol.

The relative amounts of tautomeric forms for 2-C-nonafluorobutyl-L-ribose at equilibrium in D_6-acetone at room temperature are: 80% α-furanose, 11% β-furanose, <1% α-pyranose and 9% β-pyranose. With increasing size of the substituents at C-2 the ratio of furanose increases, while the ratio of pyranose decreases (see Table 1). In the furanose series α-furanose dominates, where the anomeric OH group is placed *trans* in respect to the bulky perfluoroalkyl group, while in the pyranose series β-pyranose dominates, where the anomeric OH function is *cis* positioned with respect to



Scheme 2.



Scheme 4.

Table 1
Relative amounts of tautomeric forms of differently substituted riboses at equilibrium in D_6-acetone and D_2O

Ribose	α-Furanose	β-Furanose	α-Pyranose	β-Pyranose	References
Ribose*	7	14	21	58	[26]
2-Desoxy-2-*C*-fluor-	2	11	21	66	[27]
2-C-CH_3	35	22	28	15	[14]
2-C-CH_2OH*	42	29	13	16	[28]
2-C-CF_3	65, 74*	21, 18*	2, 1*	12, 7*	[18]
2-C-C_3F_7	69	17	<1	14	
2-C-C_4F_9[a]	80	11	<1	9	

[a] L-Configured.
* Data recorded in D_2O.

the bulky, equatorially placed perfluoroalkyl group occupying the favorable axial position (anomeric effect).

3. Experimental

3.1. General

Microanalyses were carried out with a Heraeus CNH-O Rapid apparatus. Melting points were determined on a Boetius apparatus and are corrected. Mass spectra were obtained with a MASSLAB VG 12-250 instrument (EI, 70 eV). IR spectra were measured with a Genesis Series FTIR ATI Mattson spectrometer. NMR spectra were recorded on Varian Gemini 200 (^{1}H 199.96; ^{13}C 50.29 MHz), Gemini 2000 (^{1}H 200.04; ^{13}C 50.31 MHz) and Gemini 300 (^{1}H 300.8; ^{13}C 75.46 MHz) instruments. Chemical shifts are reported in parts per million relative to tetramethylsilane. For ^{19}F NMR spectra, external trifluoroacetic acid was used as reference. Optical rotations were measured with a Schmidt and Haensch Polartronic polarimeter. All solvents were dried by standard methods. Reactions were carried out under dry argon.

3.1.1. (−) Benzyl-2-C-heptafluoropropyl-3,4-O-isopropylidene-β-D-ribopyranoside (4)

Method A: Heptafluoropropyl trimethylsilane (0.67 g, 2.75 mmol) was added via syringe to a solution of benzyl-3,4-*O*-isopropylidene-β-D-pentopyranosid-2-ulose (**1**) [28] (0.69 g, 2.5 mmol) in THF at 0 °C under inert gas. Then a 1 M TBAF solution (0.5 ml) in THF was added dropwise. After 1 h at 0 °C, the reaction mixture was warmed up to room temperature. The progress of the reaction was monitored by TLC. When the starting material was consumed (ca. 4 h), THF was evaporated and the remaining residue extracted with CH_2Cl_2. The organic phase was stirred with water (20 ml). The CH_2Cl_2 phase was separated and the water phase extracted with CH_2Cl_2 (3×). The organic phase was dried with $MgSO_4$ and evaporated to dryness. The remaining oil was purified by column chromatography (eluent: EtOAc, $R_F = 0.87$) to give 0.1 g (9%) of **4** as a colorless oil.

Method B: The reaction was performed in CH_2Cl_2, tetra-*n*-butylammonium difluoro-phenylstannate instead of TBAF was applied as a catalyst. After the reaction was complete the solvent was evaporated and the residue extracted with MeOH and treated with TBAF (2.5 mmol). After stirring the mixture for 12 h, MeOH was distilled off and the residue was purified by chromatography (see earlier paragraph) to give 0.28 g (25%) of **4**.

$[\alpha]_D = -69.7$ ($c = 1.4$, $CHCl_3$); IR (Nujol) ν 1778, 1734, 1457, 1381, 1190, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.40 [s, 3H, $C(CH_3)_2$], 1.61 [s, 3H, $CH(CH_3)_2$], 3.51 (s, 1H, OH-2), 4.01 (d br., 1H, $^2J_{5a/5b} = 12.8$ Hz, H-5a), 4.10 (d br, 1H, $^2J_{5a/5b} = 12.8$ Hz, H-5b), 4.33 (dd, 1H, $^3J_{4/3} = 6.8$ Hz, $^3J_{4/5} = 2$ Hz, H-4), 4.52 (d, 1H, $^2J = 11.8$ Hz, CH_{2a}), 4.64 (d, 1H, $^3J_{4/3} = 6.8$ Hz, H-3), 4.73 (d, 1H, $^2J = 11.8$ Hz, CH_{2b}), 5.19 (s, 1H, H-1), 7.26–7.38 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 25.1 (CH_3), 26.4 (CH_3), 58.4 (C-5), 68.8 (d, $^3J_{CF} = 1.2$ Hz, C-3), 70.0 (d, $^3J_{CF} = 1.5$ Hz, C-3), 70.9 (CH_2), 71.2 (C-4),

72.3 (t, $^2J_{CF} = 26.4$ Hz, C-2), 97.4 (t, $^3J_{CF} = 1.9$ Hz, C-1), 109.8 [$C(CH_3)_2$], 110.0 (tq, $^1J_{CF} = 270.0$ Hz, $^2J_{CF} = 33$ Hz, CF_2), 118.6 (qt, $^1J_{CF} = 261$ Hz, $^2J_{CF} = 31.6$ Hz, CF_3), 121.2 (tt, $^1J_{CF} = 278.9$, $^2J_{CF} = 33.9$ Hz, CF_2), 128.3 (C-4, Ph), 128.6 (C-2, 6, Ph), 128.9 (C-3, 5, Ph), 136.7 (C-1, Ph); ^{19}F NMR ($CDCl_3$): δ −47.57 (dd, 1F, $^2J = 289.1$ Hz, $J = 6.1$ Hz, CF_2), −45.85 (dd, 1F, $^2J = 288.4$ Hz, $J = 6.1$ Hz, CF_2), −40.63 (ddq, $^2J = 291.5$ Hz, $J = 18.4$ Hz, $J = 10.7$ Hz, CF_2), −37.79 (ddq, 1F, $^2J = 293$ Hz, $J = 15.2$ Hz, $J = 10.7$ Hz, CF_2), −2.85 (m, CF_3); MS, EI (*m/z*): 433 ($M^+ - CH_3$), 390 (M^+ − acetone), 357 (M^+ − Bn), 299 (M^+ − acetone − Bn), 253 $(C_7H_4F_7O_2)^+$, 169 $(C_3F_7)^+$, 91 $(C_7H_7)^+$, 59 $(C_3H_7O)^+$, 43 $(C_2H_3O)^+$. Anal. Found: C, 48.11; H 4.20%. Calcd. for $C_{18}H_{19}F_7O_5$ (448.35): C, 48.22; H, 4.27%.

3.1.2. (−) Benzyl-2-C-heptafluoropropyl-β-D-ribopyranoside (5)

A solution of benzyl-2-C-heptafluoropropyl-3,4-*O*-isopropylidene-β-D-ribopyranoside (**4**) (0.054 g, 0.12 mmol) in 60% AcOH (5 ml) was stirred at 40–50 °C for 24 h. The crude product obtained after evaporation to dryness was recrystallized from THF/hexanes to give **5** as colorless crystals 0.041 g (83%), mp: 165–166 °C.

$[\alpha]_D = -87.5$ ($c = 0.48$, acetone); IR (KBr): ν 1474, 1458, 1384, 1310, 1267, 1206, 1185, 1141 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.84 (dd, 1H, $^2J_{5a/5b} = 12.6$ Hz, $^3J_{5a/4} = 1.8$ Hz, H-5a), 4.06 (dd, 1H, $^2J_{5a/5b} = 12.6$ Hz, $^3J_{5b/4} = 1.3$ Hz, H-5b), 4.14 (m, 1H, H-4), 4.22–4.24 (m, 2H, H-3, OH-3), 4.58 (d, 1H, $^2J = 11.7$ Hz, CH_2), 4.77 (d, 1H, $^2J = 11.7$ Hz, CH_2), 5.11 (s, 1H, H-1), 5.25 (d, 1H, $^3J_{H-4/OH-4} = 4.5$ Hz, OH-4), 5.54 (s, 1H, OH-2), 7.36–7.42 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 63.5 (C-5), 64.7 (t, $^3J_{CF} = 1.9$ Hz, C-3), 70.0 (CH_2), 71.3 (C-4), 78.9 (t, $^2J_{CF} = 22.1$ Hz, C-2), 99.9 (C-1), 110–122 (m, $CF_2CF_2CF_3$), 128.1 (C-4, Ph), 128.2 (C-2, 6, Ph), 128.8 (C-3, 5, Ph), 137.8 (C-1, Ph); ^{19}F NMR ($CDCl_3$): δ −46.72 (dd, 1F, $^2J = 286.1$ Hz, $J = 12.5$ Hz, CF_2), −44.20 (ddd, 1F, $^2J = 286.3$ Hz, $J = 11.8$ Hz, $J = 7$ Hz, CF_2), −38.27 (ddq, 1F, $^2J = 293.8$ Hz, $J = 29.3$ Hz, $J = 10.0$ Hz, CF_2), −35.03 (ddq, 1F, $^2J = 293$ Hz, $J = 25.5$ Hz, $J = 12.8$ Hz, CF_2), −2.55 (m, CF_3); MS, EI (*m/z*): 317 (M^+ − Bn), 299 (M^+ − Bn − H_2O), 283 (M^+ − OBn − H_2O), 271 (M^+ − BnO − CH_2O), 241 $(C_6H_4F_7O_2)^+$, 169 $(C_3F_7)^+$, 91 $(C_7H_7)^+$, 43 $(C_2H_3O)^+$. Anal. Found: C, 44.13; H 3.68%. Calcd. for $C_{15}H_{15}F_7O_5$ (408.29): C, 44.54; H, 3.75%.

3.1.3. (−) 2-C-Heptafluoropropyl-D-ribose (7)

A mixture of benzyl-2-C-heptafluoropropyl ribopyranoside (**5**) (0.012 g, 0.03 mmol) and a catalyst (10% Pd/C) in dry MeOH was stirred in an atmosphere of hydrogen until the starting material was completely consumed (ca. 4 weeks, ^{19}F NMR analysis). After filtration, the organic phase was evaporated to give an oil, which crystallized slowly. Crystallization from H_2O gave **7**, 0.007 g (73%), mp: 70–81 °C.

$[\alpha]_D = +16.7$ ($c = 1$, H_2O), after 1 day −13.3; IR (Nujol) ν 1460, 1378, 1347, 1258, 1147, 1042 cm^{-1}; MS, EI (*m/z*): 301 (M^+ − OH), 282 ($M^+ - 2H_2O$), 254 (M^+ − OH− CH_2OH), 241 (M^+ − HCOOH − CH_2OH), 169 $(C_3F_7)^+$, 97 $(C_5H_7O_2)^+$, 55 $(C_3H_3O)^+$, 41 $(C_2HO)^+$.

3.2. Relative amounts of tautomeric forms at equilibrium in D_6-acetone

3.2.1. α-Furanose (69%)

^{1}H NMR: δ 3.59 (dd, 1H, $^2J_{5a/5b} = 12.6$ Hz, $^3J_{5a/4} = 4.5$ Hz, H-5a), 3.70 (m, 1H, H-4), 3.78 (d, 1H, $^2J_{5a/5b} = 12.6$ Hz, H-5b), 4.25 (d, 1H, $^3J_{4/3} = 8.1$ Hz, H-3), 5.43 (s, 1H, H-1); ^{13}C NMR: δ 60.6 (C-5), 69.8 (C-3), 81.0 (C-4), 95.4 (C-1), signal of C-2 could not be extracted because of low intensity; ^{19}F NMR: δ −47.63 (dd, 1F, $^2J = 291.3$, $J = 4.7$ Hz, CF_2), −45.10 (dd, 1F, $^2J = 292.9$ Hz, $J = 6.2$ Hz, CF_2), −43.80 (m, 2F, CF_2), −3.0 (m, 3F, CF_3).

3.2.2. β-Furanose (17%)

^{1}H NMR: δ 3.66 (dd, 1H, $^2J_{5a/5b} = 12.5$ Hz, $^3J_{4/5} = 4.2$ Hz, H-5a), 3.89 (d, 1H, $^2J_{5a/5b} = 12.5$ Hz, H-5b), 3.95 (m, 1H, H-4), 4.01 s, 1H, H-3), 4.78 (s, 1H, H-1); ^{13}C NMR: δ 63.2 (C-5), 71.3 (C-3), 83.9 (C-4), 100.9 (C-1), signal of C2 could not be extracted because of low intensity; ^{19}F NMR: δ −47.00 (dd, 1F, $^2J = 286.3$ Hz, $J = 10.7$ Hz, CF_2), −44.20 (ddd, 1F, $^2J = 286.8$ Hz, $J = 10.7$ Hz, $J = 6$ Hz, CF_2), −38.50 (dm, 1F, $^2J = 293.0$ Hz, CF_2), −36.30 (ddt, 1F, $^2J = 288.3$ Hz, $J = 21.3$ Hz, $J = 10.7$ Hz, CF_2), −2.55 (m, 3F, CF_3).

3.2.3. α-Pyranose (<1%), β-Pyranose (14%)

^{1}H NMR: δ 3.13 (dd, 1H, $^2J_{5a/5b} = 8.9$ Hz, $J_{5a/4} = 6.2$ Hz, H-5a), 3.48 (dd, 1H, $^2J = 8.9$ Hz, $^3J_{5b/4} = 6.1$ Hz, H-5b), 4.10 (s, 1H, H-3), 5.22 (s, 1H, H-1), H-4 could not be extracted; ^{13}C NMR: δ 73.6 (C-5), 64.8 (C-3), 99.9 (C-1), C-2 and C-4 could not be extracted because of low intensity; ^{19}F NMR: δ −46.34 (dd, 1F, $^2J = 289.8$ Hz, $J = 10.7$ Hz, CF_2), −42.98 (dd, 1F, $^2J = 289$ Hz, $J = 9.2$ Hz, CF_2), −39.05 (ddq, 1F, $^2J = 288.5$ Hz, $J = 10.7$ Hz, CF_2), −35.03 (ddq, 1F, $^2J = 293.0$ Hz, $J = 25.8$ Hz, $J = 13.5$ Hz, CF_2), −3.20 (m, 3F, CF_3).

3.2.4. (+) Benzyl-3,4-O-isopropylidene-2-C-perfluorobutyl-β-L-ribopyranoside (8)

A solution of perfluorobutyl iodide (1.02 g, 2.95 mmol) in dry ether (10 ml), under inert gas and exclusion of light, was cooled to −45 °C and treated with ethylmagnesium bromide (2.97 ml, 1 M in THF). After stirring the reaction mixture at −45 °C for 0.5 h benzyl-3,4-*O*-isopropylidene-erythro-L-pentopyranosid-2-ulose (**2**) [29] (0.68 g, 0.15 mmol) in ether (5 ml) was added. The reaction mixture was warmed up to room temperature within 3 h and afterwards treated with a saturated solution of NH_4Cl. Then the mixture was extracted with ether, the organic phase was dried with $MgSO_4$ and evaporated to dryness. The crude reaction product was purified by column chromatography (eluent: CH_2Cl_2, $R_F = 0.53$) to give 0.25 g (20%) **8** as colorless crystals, mp: 68–70 °C.

$[\alpha]_D = +70$ ($c = 4$, $CHCl_3$); IR (KBr) ν 2987, 2878, 1786, 1711, 1455, 1383, 1367, 1257, 1215, 1190 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 [s, 3H, $C(CH_3)_2$], 1.61 [s, 3H, $C(CH_3)_2$], 3.50 (s, 1H, OH-2), 4.00 (dd, 1H, $^2J_{5a/5b} = 12.9$ Hz, $^3J_{5a/4} = 3.2$ Hz, H-5a), 4.09 (dd, 1H, $^2J_{5a/5b} = 12.9$ Hz, $^3J_{5b/4} = 1.6$ Hz, H-5b), 4.33 (ddd, 1H, $^3J_{4/3} = 6.8$ Hz, $^3J_{4/5a} = 3.2$ Hz, $J = 1.6$ Hz, H-4), 4.52 (d, 1H, $^2J = 11.6$ Hz, CH_{2a}), 4.64 (d, 1H, $^3J_{3/4} = 6.8$ Hz, H-3), 4.72 (d, $^2J = 11.6$ Hz, CH_{2b}), 5.19 (s, 1H, H-1), 7.26–7.36 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 25.0 (CH_3), 26.4 (CH_3), 58.3 (C-5), 69.0 (d, $^3J_{CF} = 1.8$ Hz, C-3), 69.1 (d, $^3J_{CF} = 1.8$ Hz, C-3), 70.9 (CH_2), 71.2 (C-4), 72.3 (td, $^2J = 22.1$ Hz, $^3J_{CF} = 2.0$ Hz, C-2), 97.4 (t, $^3J_{CF} = 1.6$ Hz, C-1), 109.8 (CMe_2), 111.2–126.4 (C_4F_9), 128.4 (C-4, Ph), 128.6 (C-2, 6, h), 129.0 (C-3, 5, Ph), 136.7 (C-1, Ph). ^{19}F NMR ($CDCl_3$): δ −48.74, −48.18, −44.01, −43.25, −41.61 (m, 4F, CF_2CF_2), −40.17 (dm, 1F, $^2J = 295.5$ Hz, CF_2), −37.13 (dm, 1F, $^2J = 297.6$ Hz, CF_2), −3.05 (m, 3F, CF_3); MS, EI (m/z): 483 ($M^+ - Me$), 407 ($M^+ - Bn$), 349 ($M^+ - Bn - acetone$), 319 ($M^+ - Bn - acetone - CH_2O$), 303 ($M^+ - OBn - acetone - CH_2O$), 219 $(C_4F_9)^+$, 91 $(C_7H_7)^+$, 59 $(C_3H_7O)^+$, 43 $(C_2H_3O)^+$. Anal. Found: C, 45.69; H, 3.76%. Calcd. for $C_{19}H_{19}F_9O_5$ (498.36): C, 45.79; H, 3.84%.

3.2.5. (+)-Benzyl-2-C-perfluorobutyl-β-L-ribopyranoside (9)

Benzyl-3,4-*O*-isopropylidene-2-C-perfluorobutyl-β-L-ribopyranoside (**8**) (0.145 g, 0.3 mmol) and 60% AcOH (5 ml) were stirred at 40–50 °C for 24 h. After evaporation of the solvent, the remaining residue was purified by crystallization from THF/hexanes to give 0.12 g (90%) **9**, mp: 147–149 °C (colorless crystals).

$[\alpha]_D = +67.4$ ($c = 0.46$, acetone); IR (KBr) ν 3343, 1343, 1267, 1201, 1183, 1145, 1099, 1061 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.83 (dd, 1H, $^2J_{5a/5b} = 12.6$ Hz, $^3J_{5a/4} = 1.4$ Hz, H-5a), 4.05 (d, 1H, $^2J_{5a/5b} = 12.6$ Hz, H-5b), 4.13 (m, 1H, H-4), 4.24 (d, 1H, $^3J_{3/4} = 3$ Hz, H-3), 4.58 (d, 1H, $^2J = 11.6$ Hz, CH_{2a}), 4.81 (d, 1H, $^2J = 11.6$ Hz, CH_{2b}), 5.11 (s, 1H, H-1), 7.36–7.42 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 63.5 (C-5), 64.7 (C-3), 70.0 (CH_2), 71.3 (C-4), 79.5 (t, $^2J_{CF} = 22.1$ Hz, C-2), 99.9 (C-1), 110–126 (C_4F_9), 128.2 (C-2, 4, 6, Ph), 128.8 (C-3, 5, Ph), 137.8 (C-1, Ph); ^{19}F NMR ($CDCl_3$): δ −48.58 (dm, 1F, $^2J = 291.3$ Hz, CF_2), −46.21 (dm, 1F, $^2J = 294.6$ Hz, CF_2), −42.99 (dm, 1F, $^2J = 288.3$ Hz, CF_2), −40.96 (dm, 1F, $^2J = 288.5$ Hz, CF_2), −37.23 (d, 1F, $^2J = 291.8$ Hz), −34.82 (ddt, 1F, $^2J = 294.6$ Hz, $J = 21.5$ Hz, $J = 14$ Hz, CF_2), −3.0 (m, 3F, CF_3); MS, EI (m/e) = 351 ($M^+ - Bn$), 321 ($M^+ - Bn - CH_2O$), 219 $(C_4F_9)^+$, 91 (C_7H_7), 43 $(C_2H_3O)^+$.

3.2.6. (+)-2-C-Perfluorobutyl-L-ribose (11)

A solution of benzyl-2-C-perfluorobutyl-β-L-ribopyranoside (**9**) (0.07 g, 0.15 mmol) in dry MeOH (5 ml) was stirred in the presence of a Pd/C catalyst in an atmosphere of hydrogen until the starting material was completely consumed (4 weeks, ^{19}F NMR analysis). After filtration and evaporation of the solvent 0.036 g (70%) of **11** were obtained as a colorless oil.

$[\alpha]_D = +2.1$ ($c = 0.42$, MeOH). IR (Nujol) ν 1451, 1413, 1340, 1247, 1149, 1084, 1041 cm^{-1}; MS, EI (m/z) = 332 ($M^+ - 2H_2O$), 303 ($M^+ - OH - CH_2OH$), 291 ($M^+ - HCOOH - CH_2OH$), 97 $(C_5H_7O_2)^+$, 55 $(C_3H_3O)^+$, 41 $(C_2HO)^+$.

3.3. Relative amounts of tautomeric forms at equilibrium in D_6-acetone

3.3.1. α-Furanose (80%)

^1H NMR: δ 3.68 (dd, 1H, $^2J = 12.7$ Hz, $^3J_{4/5} = 4.5$ Hz, H-5) 3.86 (m*, H-4), 3.87 (d*, $^2J = 12.7$ Hz, H-5), 4.34 (d, 1H, $^3J_{3/4} = 8.0$ Hz, H-3), 5.52 (s, 1H, H-1); ^{13}C NMR: δ 60.6 (C-5), 69.9 (C-3), 80.9 (C-4), 95.5 (C-1), C-2 could not be extracted because of low intensity; ^{19}F NMR: δ −49.33 (dm, 1F, $^2J = 292$ Hz, CF_2), −47.37 (dm, 1F, $^2J = 293$ Hz, CF_2), −43.51 (m, 2F, CF_2), −44.30 (dm, 1F, $^2J = 298$ Hz, CF_2), −41.98 (dm, $^2J = 298$ Hz, CF_2), −3.25 (m, 3F, CF_3).

3.3.2. β-Furanose (11%)

^1H NMR: δ 3.77 (dd*, 1H, $^2J_{5a/5b} = 12.6$ Hz, $^3J_{5a/4} = 1.7$ Hz, H-5a), 3.98 (dd*, 1H, $^2J_{5a/b} = 12.6$ Hz, $^3J_{5b/4} = 1.2$ Hz, H-5b), 4.00 (m*, 1H, H-4), 4.10 (s*, 1H, H-3), 4.89 (s, 1H, H-1); ^{19}F NMR: δ −49.05 (dm, 1F, $^2J = 292$ Hz, CF_2), −46.35 (dm, 1F, ^2J =292 Hz, CF_2), −42.97 (dm, 1F, $^2J = 296$ Hz, CF_2), −40.04 (dm, 1F, $^2J = 299$ Hz, CF_2), −38.68 (dm, 1F, ^2J =292 Hz, CF_2), −36.38 (dm, 1F, $^2J = 293$ Hz, CF_2), −3.25 (m*, 3F, CF_3).

3.3.3. α-Pyranose (<1%), β-Pyranose (9%)

^1H NMR: δ 3.23 (dd, 1H, $^2J_{5a/5b} = 8.6$ Hz, $^3J_{5a/4} = 6.1$ Hz, H-5a), 3.57 (dd, 1H, $^2J_{5a/5b} = 8.6$ Hz, $^3J_{5b/4} = 6.1$ Hz, H-5b), 4.35 (s*, 1H, H-3), 5.33 (s*, 1H, H-1), H-4 could not be extracted; ^{19}F NMR: δ − 49.5 (dm*, 1F, CF_2), −46.35 (dm*, 1F, CF_2), −41.93 (dm, 1F, $^2J = 291$ Hz, CF_2), −41.18 (dm, 1F, $^2J = 294$ Hz, CF_2), −37.80 (dm, 1F, $^2J = 291$ Hz, CF_2), −35.08 (dm, 1F, ^2J =295 Hz, CF_2), −3.25 (m*, 3F, CF_3); (* Resonance signals are overlapping).

Acknowledgements

The authors are grateful to the European Community (TMR: Contract no. ERBFMRXCT 970 120: "Fluorine: A Unique Tool for Engineering Molecular Properties"), the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.

References

[1] I. Ojima, J.R. Mc Carthy, J.R. Welch, Biomedical frontiers of fluorine chemistry, ACS Symposium Series 639 (1996) and literature cited therein.

[2] R. Filler, Y. Kobayashi, L.M. Yagupolskii, Studies in Organic Chemistry 48, Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications, Elsevier, Amsterdam, 1993, and literature cited therein.
[3] J.T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, Wiley, 1990 and literature cited therein.
[4] J.F. Liebman, A. Greenberg, W.R. Dolbier (Eds.), Fluorine-Containing Molecules, Structure, Reactivity, Synthesis and Applications, VCH, Weinheim, 1988.
[5] M. Hudlicky (Ed.), Chemistry of Organic Fluorine Compounds, Vol. 2, Ellis Horwood, Chichester, 1976.
[6] N.F. Taylor, Fluorinated carbohydrates, chemical and biological aspects, ACS Symposium Series 374, 1988.
[7] (a) J.T. Gerig, in: L.S. Berliner, J. Reuben (Eds.), Biological Magnetic Resonance, Vol. 1, Plenum Press, New York, 1978, pp. 139–203.;
(b) J.T. Gerig, Methods Enzymol. 177 (1989) 3;
(c) D.H. Gregory, J.T. Gerig, Biopolymers 31 (1991) 845;
(d) M. Cushmann, H.H. Patel, J. Scheuring, A. Bacher, J. Org. Chem. 57 (1992) 5630.
[8] B. Beuthien-Baumann, K. Hamacher, F. Oberdorfer, J. Steinbach, Carbohydr. Res. 327 (2000) 107. and literature cited therein.
[9] C.B. Reese, C.N.V.S. Varaprasad, J. Chem. Soc., Perkin Trans. I (1994) 189.
[10] Y. Murai, H. Shiroto, T. Ishizaki, T. Iimori, Y. Kodama, Y. Ohtsuka, T. Oishi, Heterocycles 33 (1992) 391.
[11] T. Iimori, Y. Murai, S. Ohuchi, Y. Kodama, Y. Ohtsuka, T. Oishi, Tetrahedron Lett. 32 (1991) 7273.
[12] (a) R.D. Chambers, Fluorine in Organic Chemistry, New York, Wiley, 1973.;
(b) J.T. Welch, Tetrahedron 43 (1987) 3123;
(c) C. Schmidt, Synletters (1994) 241 and 238.
[13] R. Plantier-Royon, C. Portella, Carbohydr. Res. 327 (2000) 119. and literature cited therein.
[14] U. Eilitz, Ph.D. Thesis, University of Leipzig, 1998.
[15] J.G. Riess, J. Greiner, Carbohydr. Res. 327 (2000) 147. and literature cited therein.
[16] R. Miethchen, M. Hein, Carbohydr. Res. 237 (2000) 169. and literature cited therein.
[17] T.A. Logothetis, U. Eilitz, W. Hiller, K. Burger, Tetrahedron 54 (1998) 14023.
[18] U. Eilitz, C. Böttcher, J. Sieler, S. Gockel, A. Haas, Tetrahedron 57 (2001) 3921.
[19] R.E. Ireland, L. Courtney, B.J. Fitzsimmons, J. Org. Chem. 48 (1983) 5186.
[20] A. Solladie-Cavallo, D. Farkharic, S. Fritz, T. Lazrak, J. Suffert, Tetrahedron Lett. 25 (1984) 4117.
[21] D. Peters, C. Zur, R. Miethchen, Synthesis (1998) 1033.
[22] T. Kitazume, N. Ishikawa, J. Am. Chem. Soc. 107 (1985) 5186.
[23] G.K.S. Prakash, A.K. Judin, Chem. Rev. 97 (1997) 757.
[24] R.D. Chambers, W.K.R. Musgrave, J. Savory, J. Chem. Soc. (1962) 1993.
[25] S. Lavaire, R. Plantier-Royon, C. Portella, Tetrahedron Assym. 9 (1998) 213.
[26] (a) J. Lehmann, Kohlenhydrate, Georg Thieme Verlag, Stuttgart, 1996.;
(b) S.J. Angyal, Adv. Carbohydr. Chem. Biochem. 42 (1984) 15;
(c) G. Schilling, A. Keller, Liebigs Ann. Chem. 1977, 1475.
[27] P.N. Sanderson, B.C. Sweatman, R.D. Farrant, J.C. Lindon, Carbohydrat. Res. 119 (1997) 11746.
[28] T. Kitazume, N. Ishikawa, Chem. Lett. (1981) 1337.
[29] R.C. Petter, D.G. Powers, Tetrahedron Lett. 30 (1989) 659.