Available online at www.sciencedirect.com
SCIENCE DIRECT
Carbohydrate Research 341 (2006) 1758–1763
Carbohydrate RESEARCH

Note

Fluorinated acyclo-*C*-nucleoside analogues from glycals in two steps☆

Constantin Mamat, Martin Hein and Ralf Miethchen*

Institut für Chemie, Universität Rostock, Albert-Einstein-Straße 3a, D-18059 Rostock, Germany

Received 3 December 2005; received in revised form 31 December 2005; accepted 10 January 2006
Available online 26 January 2006

Dedicated to Professor Dr. Reint Eujen on the occasion of his 60th birthday

Abstract—A convenient two-step strategy is reported for the synthesis of fluorinated optically pure acyclo-*C*-nucleoside analogues starting from simple glycals. In the first step, benzyl- or *p*-methoxybenzyl-protected glycals are treated with trifluoroacetic anhydride, bromodifluoroacetyl chloride, trichloroacetyl chloride, and perfluorooctanoyl chloride, respectively, in the presence of Et_3N. This one-pot procedure yields 1,2-unsaturated sugars (1,5-anhydro-3,4,6-tri-*O*-benzyl (or *p*-methoxybenzyl) 2-deoxy-2-perhalogenoacyl-D-*arabino* / *lyxo*-hex-1-enitols **4**–**9**) acylated at C-2. In the second step, a selective ring transformation is induced by treatment of the C-acylated glycals with bis-nucleophiles (hydrazine, phenylhydrazine, *o*-phenylenediamine, hydroxylamine). In particular, 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-trifluoroacetyl-D-*arabino*-hex-1-enitol (**4**) and 1,5-anhydro-2-deoxy-2-trifluoroacetyl-3,4,6-tri-*O*-(*p*-methoxybenzyl)-D-*arabino*-hex-1-enitol (**8**) were reacted with these nucleophiles generating the final *C*-nucleoside analogues of pyrazole (**10**, **11**, and **12**), diazepine (**13**), and isoxazole (**15**), respectively, containing a carbohydrate side chain linked to the heterocyclic ring.

Keywords: Carbohydrates; Heterocycles; Ring transformation; Trifluoromethylated *C*-nucleosides

Fluorinated analogues of natural substances are mainly of interest in bioorganic chemistry,[2–7] since single fluorine atoms or trifluoromethyl groups introduced in place of hydrogen atoms often increase the biological activity of parent compounds. However, reviews on synthetic strategies of trifluoromethyl substituted natural substance analogues[3] and of trifluoromethyl substituted heterocycles[8] show that the pool of suitable fluorinated building blocks, as well as of methods for their preparation, are quite limited, especially when trifluoromethyl substituted heteroaromatics linked to a chiral moiety are the target molecules. Due to the interest in trifluoromethyl-substituted heteroaromatics with a hydrophilic lateral chain, we focused our efforts on a two-step strategy for the synthesis of such compounds starting from 1,2-unsaturated monosaccharide derivatives.

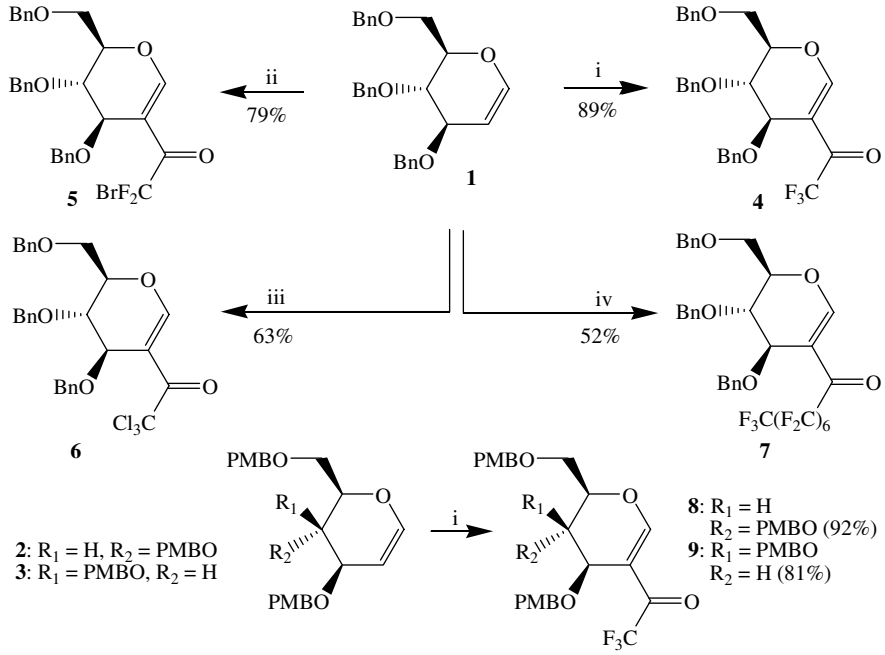
It is well known that the enol ether unit of glycals allows electrophilic addition reactions[9–12] including C-acylations. Generally, acylations of enol ethers require the use of carboxylic acid reagents with high electrophilic potential.[13–16] Activation of the reagents can be made by Friedel–Crafts-type catalysts, however, polymerization often results even when mild Lewis acid catalysts are used.[13,15] In carbohydrate chemistry, 2-C-formylations have been described by Ramesh and Balasubramanian[17] under Vilsmeier–Haack conditions and 2-C-acetylations were realized by Priebe et al.[12] using acetic anhydride in the presence of Lewis acids.

When the reaction was carried out in the presence of triethylamine, we found that, after the addition of highly electrophilic carbonyl compounds (perhalogenocarboxylic acid anhydrides or chlorides), a selective 1,2-elimination to glycals follows. Thus (Scheme 1), 1,5-anhydro-3,4,6-tri-*O*-benzyl-D-*arabino*-hex-1-enitol (**1**) and trifluoroacetic anhydride, bromodifluoroacetyl chloride, trichloroacetyl chloride, or pentadecafluorooctanoyl chloride gave under these reaction conditions

☆ Organofluorine Compounds and Fluorinating Agents, Part 34; for Part 33, see Ref. 1.

* Corresponding author. Fax: +49 381 498 6412; e-mail: ralf.miethchen@uni-rostock.de

0008-6215/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2006.01.011



Scheme 1. Reagents and conditions: (i) $(CF_3CO)_2O$, Et_3N, DMF, rt; (ii) BrF_2C–C(O)Cl, Et_3N, DMF, rt; (iii) Cl_3C–C(O)Cl, Et_3N, DMF, rt; (iv) $F_3C(CF_2)_6C(O)Cl$, pyridine, DMF, rt, PMB = *p*-methoxybenzyl.

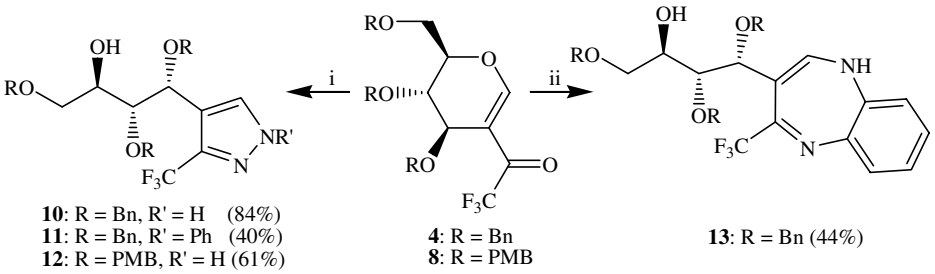
the corresponding β-keto vinyl ether derivatives **4**–**7** in yields of 52–89%. Moreover, the *p*-methoxybenzyl protected starting materials **2** and **3** were reacted with trifluoroacetic anhydride in the presence of triethylamine generating the C-trifluoroacetylated glycals **8** and **9**, respectively (yields 81% and 92%).

The addition–elimination sequence of such acylation reactions was already investigated as two-step procedure. At first, the 1:1 adduct from 3,4-dihydro-2*H*-pyran and trichloroacetyl chloride was isolated at room temperature. Subsequent thermal treatment of the compound resulted in HCl elimination with re-formation of the double bond[18] (see also Refs. 15 and 19). C-Acylations of the glycals **1**–**3** in the presence of triethylamine proceeded readily at room temperature with subsequent elimination. However, reaction times of 2–5 days were required for a completion of the reaction.

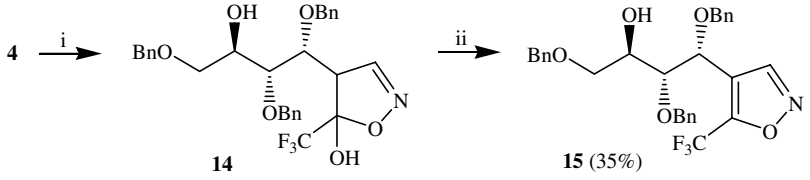
α,β-Unsaturated carbonyl compounds are suitable bis-electrophiles in syntheses of five- and six-membered heterocycles.[14,20–24] In particular, the 2-C-trihaloacetylated glycals **4**–**9** are potential precursors for syntheses of halomethyl substituted heteroaromatics. Optically pure acyclo-*C*-nucleoside analogues should be likewise accessible from those using a method of ring transformation based on a strategy reported by Peseke and co-workers.[25,26] and Yadav et al.[27] The authors synthesized optically pure acyclo-*C*-nucleoside analogues by treatment of 2-*C*-formyl glycals with different bis-nucleophiles. The reaction starts by attack of the corresponding bis-nucleophile on the formyl group and proceeds through intramolecular cyclization with simultaneous opening of the pyranose ring set off by the second nucleophilic group. The heterocyclic ring so generated is linked to a chiral side chain consisting of C4–C6 of the former pyranose unit. This type of reaction was only applied to formyl derivatives of unsaturated sugars so far. Because of the interest in trifluoromethyl-substituted heteroaromatics, the applicability of the method on the carbonyl active β-keto vinyl ethers **4** and **8** was studied (Schemes 2 and 3).

It is known that *N*-nucleophiles such as aliphatic amines, aniline, and hydrazine react with fluorine containing α,β-unsaturated carbonyl compounds.[22] The condensation of 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-trifluoroacetyl-2-deoxy-D-*arabino*-hex-1-enitol (**4**) with hydrazine and phenylhydrazine yields pyrazole derivatives **10** and **11**, respectively (Scheme 2). In the same manner, the *p*-methoxybenzyl protected glucal **8** reacts with hydrazine to give compound **12**.

Because some benzodiazepines show biological activity, for example, chlorodiazepine oxide is used as tranquilizer[28] and fluoroazepine as a soporific,[29] the strategy of ring transformation was also used to synthesize a trifluoromethyl substituted benzodiazepine derivative. 5-Trifluoromethyl-2,3-dihydro-1,4-diazepine has previously been synthesized by Chu et al.[21] from 4-ethoxy-1,1,1-trifluoro-3-buten-2-one and ethylene diamine in good yield. However, the reaction with *o*-phenylenediamine only produced benzimidazole derivatives as elimination products. In our case no elimination was observed when *o*-phenylenediamine reacts with the



Scheme 2. Reagents and conditions: (i) H_2NNHR', EtOH, 24 h, reflux; (ii) *o*-phenylenediamine, EtOH, 24 h, reflux.



Scheme 3. Reagents and conditions: (i) Hydroxylamine, EtOH, 24 h, rt; (ii) $(CF_3CO)_2O$, pyridine, rt.

glucal **4** as shown in Scheme 2. Diazepine derivative **13** was isolated as a yellowish oil in 44% yield.

The reaction of **4** with hydroxylamine proceeds in pyridine to give the hydroxyisoxazoline derivative **14**, which was not isolated in pure form but instead the crude product was dehydrated to isoxazole **15** by treatment with trifluoroacetic anhydride in pyridine (Scheme 3).

The structures of the new compounds are supported by NMR spectra, micro- and GC–MS analyses. The 1,2-unsaturated monosaccharide derivatives **4**–**9** show characteristic H-1 (7.70 to 8.38 ppm) and C-1 signals (161.1–162.2 ppm). The ^{19}F NMR-spectra of compounds **4**, **8**, and **9** show singlets for the trifluoromethyl group at about −70 ppm; the singlet of the difluoromethyl group of **5** is found at −55.1 ppm. The downfield shift of the CF_3-signal of compounds **10**, **11**, and **12** (−50 to −60 ppm) indicates that this group is linked to an aromatic system.[22] The corresponding signals for diazepine derivative **13** (−66.9 ppm) and isoxazole **15** (−68.8 ppm) indicate that these CF_3-groups are located on an activated double bond.

1. Experimental

1.1. General

Melting points were obtained using a Leitz polarizing microscope (Laborlux 12 Pol) equipped with a hot stage (Mettler FP 90) and are uncorrected. Microanalyses were carried out with a C/H/N/S-analyser Thermoquest Flash EA 1112. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker instruments: AC 250, ARX 300 and AVANCE 500, internal standard TMS for ^1H and ^{13}C NMR spectra, $CFCl_3$ for ^{19}F NMR spectra. MS: Intecta AMD 402 (EI with 70 eV or chemical ionization with isobutane). Optical rotations were measured on a polar LμP (IBZ Meßtechnik) instrument. Chromatographic separations and TLC detections were carried out with Merck Silica Gel 60 (63–200 μm) and Merck Silica Gel 60 F_{254} sheets, respectively. TLCs were developed by 5% methanolic sulfuric acid and heating.

1.2. 1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-trifluoroacetyl-D-*arabino*-hex-1-enitol (4)

To a solution of 1.0 g (2.4 mmol) of 1,5-anhydro-3,4,6-tri-*O*-benzyl-D-*arabino*-hex-1-enitol (**1**)[30] in dry DMF (5 mL) and dry Et_3N (0.5 mL) trifluoroacetic anhydride (0.9 mL, 4.8 mmol) was added (argon atmosphere) and the solution was stirred for 4 days at rt (TLC control). Then, an ice/ethyl acetate/Et_3N-mixture (20/20/1 mL) was added and the aqueous phase was extracted three times with ethyl acetate. The organic layer was washed with water and dried with $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel; heptane/ethyl acetate 10:1). Yield of **4**: 1.1 g (89%). R_f 0.55 (heptane/EtOAc 10:1); $[\alpha]_D^{23}$ +1.1 (*c* 2.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 3.63 (dd, 1H, $^2J = 10.7$, $^3J_{5,6a} = 4.9$ Hz, H-6a,), 3.79 (dd, 1H, $^2J = 10.7$, $^3J_{5,6b} = 7.6$ Hz, H-6b), 3.84 (t, 1H, $^3J_{3,4} = 2.2$ Hz, H-3), 4.42 (dd, 1H, $^3J_{4,5} = 2.4$, $^3J_{3,4} = 2.2$ Hz, H-4), 4.47–4.65 (m, 6H, $3 \times CH_2Ph$), 4.70–4.77 (ddd, 1H, $^3J_{4,5} = 2.4$, $^3J_{5,6a} = 4.9$, $^3J_{5,6b} = 7.6$ Hz, H-5), 7.20–7.36 (m, 15H, Ph), 7.86 (d, 1H, $J = 1.5$ Hz, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 66.3 (C-4), 68.3 (C-6), 70.9 (C-3), 71.8, 73.1, 73.5 ($3 \times CH_2Ph$), 78.7 (C-5), 110.7 (C-2), 116.8 (q, $J_{C,F} = 291.1$ Hz, CF_3), 127.9, 128.0, 128.1, 128.3, 128.6, 128.7 (Ph), 137.2, 137.7, 137.9 (Ph,

3 × quart. C) 161.7 (C-1), 179.4 (q, $J_{C,F} = 34.6$ Hz, C=O); ^{19}F NMR (235 MHz, $CDCl_3$): δ −69.9 (CF_3); MS (FAB pos. NBA/NaCl): m/z (%) = 535 (33) [M^++Na]; 405 (34) [M^+−OBn]. Anal. Calcd for $C_{29}H_{27}F_3O_5$ (512.52): C, 67.96; H, 5.31. Found: C, 67.83; H, 5.46.

1.3. 1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-bromodifluoroacetyl-2-deoxy-D-*arabino*-hex-1-enitol (5)

Glucal **1** (0.56 g, 1.3 mmol) was acylated with bromodifluoroacetyl chloride (0.9 mL, 2.6 mmol) as described for compound **4**. 0.61 g (79%) of product **5** was isolated. R_f 0.70 (heptane/EtOAc 1:1); $[\alpha]_D^{21}$ −19.3 (*c* 1.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.63 (dd, 1H, $^2J = 10.7$, $^3J_{5,6a} = 4.9$ Hz, H-6a), 3.80 (dd, 1H, $^2J = 10.7$, $^3J_{5,6b} = 7.9$ Hz, H-6b), 3.84 (m, 1H, H-3), 4.42–4.46 (m, 1H, H-4), 4.47–4.66 (m, 6H, 3 × CH_2Ph), 4.69–4.77 (m, 1H, H-5), 7.20–7.36 (m, 15H, Ph), 8.02 (s, 1H, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 66.4 (C-4), 68.1 (C-6), 70.9 (C-3), 71.6, 72.8, 73.3 (*C*H_2Ph), 78.4 (C-5), 108.7 (C-2), 114.0 (t, $J = 317.5$ Hz, CF_2Br), 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.6 (Ph), 137.1, 137.4, 137.7 (Ph, quart. C) 161.4 (C-1), 181.4 (t, $J = 25.8$ Hz, C=O); ^{19}F NMR (235 MHz, $CDCl_3$): δ −55.1 (CF_2); MS (EI, 70 eV): m/z (%) = 572 (0.1) [M^+]; 465 (20) [M^+−OBn]; 359 (15) [M^+−2OBn]. Anal. Calcd for $C_{29}H_{27}BrF_2O_5$ (573.43): C, 60.74; H, 4.75. Found: C, 60.40; H, 4.71.

1.4. 1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-trichloroacetyl-D-*arabino*-hex-1-enitol (6)

Glucal **1** (1.0 g, 2.4 mmol) was acylated with trichloroacetyl chloride (0.5 mL, 4.8 mmol) as described for compound **4**. 0.85 g (63%) of product **6** was isolated; R_f 0.70 (heptane/EtOAc 1:1); $[\alpha]_D^{22}$ +4.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.63 (dd, 1H, $^2J = 10.7$, $^3J_{5,6a} = 4.9$ Hz, H-6a), 3.81 (dd, 1H, $^2J = 10.7$, $^3J_{5,6b} = 7.9$ Hz, H-6b), 3.83 (m, 1H, H-3), 4.42–4.46 (m, 1H, H-4), 4.47–4.66 (m, 6H, CH_2Ph), 4.69–4.77 (m, 1H, H-5), 7.20–7.36 (m, 15H, Ph), 8.38 (s, 1H, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 67.8 (C-4), 68.3 (C-6), 71.4 (C-3), 71.7, 73.0, 73.4 (*C*H_2Ph), 78.1 (C-5), 106.3 (C-2), 127.8, 127.9, 128.0, 128.2, 128.5, 128.6, 128.7 (Ph), 137.4, 137.7, 138.1 (Ph, quart. C) 161.1 (C-1), 180.8 (C=O), MS (EI, 70 eV): m/z (%) = 453 (5) [M^+−$PhCH_2O$]; 347 (14) [M^+−2$PhCH_2O$]. Anal. Calcd for $C_{29}H_{27}Cl_3O_5$ (561.88): C, 61.99; H, 4.84. Found: C, 62.15; H, 5.04.

1.5. 1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-perfluorooctanoyl-D-*arabino*-hex-1-enitol (7)

Glucal **1** (250 mg, 0.6 mmol) was acylated with pentadecafluoro-octanoyl chloride[31] (519 mg, 1.2 mmol) as described for compound **4**. 254 mg (52%) of product **7** was isolated; R_f 0.60 (heptane/EtOAc 2:1); $[\alpha]_D^{22}$ −11.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.65 (dd, 1H, $^2J = 10.7$, $^3J_{5,6} = 5.2$ Hz, H-6a), 3.79 (dd, 1H, $^2J = 10.7$, $^3J_{5,6} = 7.6$ Hz, H-6b), 3.84 (t, 1H, $^3J = 2.4$ Hz, H-3), 4.42–4.54 (m, 6H, CH_2Ph, H-4), 4.65 (d, 1H, CH_2Ph), 4.68–4.76 (dd, 1H, $^3J_{5,6a} = 5.2$, $^3J_{5,6b} = 7.6$ Hz, H-5), 7.19–7.39 (m, 15H, Ph), 7.94 (s, 1H, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 66.4 (C-4); 68.1 (C-6); 70.8 (C-3); 71.6, 73.0, 73.3 (*C*H_2Ph); 78.5 (C-5); 113.1 (C-2); 127.7, 127.8, 128.0, 128.1, 128.4, 128.7 (Ph), 137.1, 137.5, 137.8 (Ph, quart. C) 162.2 (C-1), 181.2 (C=O, $J_{C,F} = 25$ Hz); ^{19}F NMR (235 MHz, $CDCl_3$): δ −80.5 (CF_3); −112.0, −112.2 (CF_2C=O); −120.8, −121.0, −121.7, −122.4 (4 × CF_2); −125.9 (CF_2CF_3); MS (FAB pos. NBA): m/z (%) = 705 (20) [M^+−OBn]. Anal. Calcd for $C_{35}H_{27}F_{15}O_5$ (526.21): C, 51.74; H, 3.35. Found: C, 51.53; H, 3.19.

1.6. 1,5-Anhydro-2-deoxy-2-trifluoroacetyl-3,4,6-tri-*O*-(*p*-methoxybenzyl)-D-*arabino*-hex-1-enitol (8)

1,5-Anhydro-3,4,6-tri-*O*-(*p*-methoxybenzyl)-D-*arabino*-hex-1-enitol (**2**)[32] (1.15 g, 2.33 mmol) was acylated with trifluoroacetic anhydride (2.3 mL, 4.66 mmol) as described for compound **4**. 1.3 g (92%) of the syrupy product **8** was isolated; R_f 0.66 (heptane/EtOAc 1:2); $[\alpha]_D^{21}$ −6.9 (*c* 1.8, $CHCl_3$); ^{1}H NMR (250 MHz, C_6D_6): δ 3.28, 3.29, 3.30 (3s, 9H, OMe), 3.61 (dd, 1H, $^2J = 10.7$, $^3J_{5,6a} = 5.7$ Hz, H-6a), 3.70 (dd, 1H, $^2J = 10.4$ Hz, $^3J_{5,6b} = 7.3$ Hz, H-6b), 3.81 (t, 1H, $^3J_{3,4} = 2.1$ Hz, H-3), 4.17 (dd, 2H, $^2J = 11.9$ Hz, CH_2Ph), 4.21 (s, 2H, CH_2Ph), 4.55 (dd, 2H, $^2J = 10.9$ Hz, CH_2Ph), 4.63 (t, 1H, $^3J_{4,5} = 2.1$ Hz, H-4), 4.74 (ddd, 1H, $^3J_{4,5} = 2.1$, $^3J_{5,6a} = 5.7$, $^3J_{5,6b} = 7.3$ Hz, H-5), 6.70–6.83 (m, 6H, Ph), 6.98–7.16 (m, 6H, Ph), 7.78 (d, 1H, $J = 1.2$ Hz, H-1); ^{13}C NMR (75.5 MHz, C_6D_6): δ 54.8 (OMe), 66.6 (C-4), 68.1 (C-6), 70.7 (C-3), 71.2, 72.9, 73.1 (*C*H_2Ph), 79.1 (C-5), 111.4 (C-2), 114.1, 114.3 (Ph), 121.4 (q, $J_{C,F} = 292.3$ Hz, CF_3), 129.6, 129.8, 130.1, 130.3, 130.5 (Ph), 159.9, 160.0 (Ph, quart. C), 161.8 (C-1), 179.4 (q, $J_{C,F} = 34.6$ Hz, C=O); ^{19}F NMR (235 MHz, C_6D_6): δ −68.6 (CF_3). MS (EI, 70 eV): m/z (%) = 602 (1) [M^+], 482 (12) [M^+−PMB], 362 (2) [M^+−2PMB]. Anal. Calcd for $C_{32}H_{33}F_3O_8$ (602.60): C, 63.78; H, 5.52. Found: C, 63.77; H, 5.55.

1.7. 1,5-Anhydro-2-deoxy-2-trifluoroacetyl-3,4,6-tri-*O*-(*p*-methoxybenzyl)-D-*lyxo*-hex-1-enitol (9)

1,5-Anhydro-3,4,6-tri-*O*-(*p*-methoxybenzyl)-D-*lyxo*-hex-1-enitol (**3**)[32] (1 g, 2.4 mmol) was acylated with trifluoroacetic anhydride (0.9 mL, 4.8 mmol) as described for compound **4**. 0.82 g (81%) of the syrupy product **9** was isolated. R_f 0.64 (heptane/EtOAc 1:1); $[\alpha]_D^{23}$ −43.1 (*c* 0.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.78–3.95

(m, 12H, H-4, H-6a, H-6b, 3 × MeO), 4.45 (dd, 2H, $^2J = 11.6$ Hz, CH_2Ph), 4.52 (d, 1H, $^2J = 11.6$ Hz, CH_2Ph), 4.59–4.71 (m, 4H, H-3, CH_2Ph), 4.74 (d, 1H, $^2J = 10.4$ Hz, CH_2Ph), 6.82–6.92 (m, 6H, Ph), 7.19–7.26 (m, 6H, Ph), 7.70 (d, 1H, $J_{H,F} = 1.2$ Hz, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.4 (MeO), 66.2 (C-3), 68.1 (C-6), 71.6 (*C*H_2Ph), 73.0 (C-4), 73.1, 74.5 (2 × *C*H_2Ph), 78.5 (C-5), 112.2 (C-2), 113.7, 113.9, 114.1 (Ph), 116.7 (q, $J_{C,F} = 294.0$ Hz, CF_3), 129.3, 129.4, 129.7, 130.0, 130.8 (Ph), 161.5 ($J_{C,F} = 5.3$ Hz, C-1), 178.6 (q, $J_{C,F} = 35.2$ Hz, C=O); ^{19}F NMR (235 MHz, $CDCl_3$): δ −70.1 (CF_3); MS (CI-isobutane): *m*/*z* (%) = 602 (1) [M^+]; 482 (3) [M^+−PMB−H]; 360 (1) [M^+−2PMB]. Anal. Calcd for $C_{32}H_{33}F_3O_8$ (602.60): C, 63.78; H, 5.52. Found: C, 63.21; H, 5.37.

1.8. 4-(1,2,4-Tri-*O*-benzyl-D-*arabino*-1,2,3,4-tetrahydroxybutyl)-3-trifluoromethyl-1*H*-pyrazole (10)

Glucal **4** (324 mg, 0.63 mmol) was dissolved in 15 mL ethanol, and 1 mL of hydrazine hydrate (98%) was added. The solution was heated for 24 h under reflux. After removal of the solvent, the residue was purified by column chromatography (heptane/EtOAc 2:1). Yield 280 mg (84%). R_f 0.42 (heptane/EtOAc 1:1); $[\alpha]_D^{21}$ −12.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (250 MHz, C_6D_6): δ 3.07 (s, 1H, OH), 3.05–3.68 (m, 2H, H-4′a, H-4′b), 3.84 (dd, 1H, $^3J_{2',1'} = 2.7$ Hz, H-2′), 4.11–4.49 (m, 7H, $^2J =$ 11.3 Hz, H-3′, CH_2Ph), 5.35 (d, 1H, $^3J_{1',2'} = 2.7$ Hz, H-1′), 7.05–7.35 (m, 15H, Ph), 7.50 (s, 1H, H-5 pyrazole); ^{13}C NMR (125 MHz, C_6D_6): δ 70.2 (C-3′), 71.3 (C-4′), 71.6 (*C*H_2Ph), 72.6 (C-1′), 73.3, 74.4 (*C*H_2Ph), 81.9 (C-2′), 118.4 (C-4 pyrazole), 122.6 (q, $J_{C,F} = 268.9$ Hz, CF_3), 127.4, 127.6, 127.7, 127.8, 127.9, 128.1, 128.3 (Ph), 131.1 (C-5 pyrazole), 138.0, 138.1, 138.2 (Ph, quart. C), 139.8 (q, $J_{C,F} = 36.2$ Hz, C-3 pyrazole); ^{19}F NMR (235 MHz, C_6D_6): δ −57.7 (CF_3); MS (FAB pos. NBA/NaCl): *m*/*z* (%) = 549 (55) [M^++Na^+], 509 (10) [M^+−OH], 457 (5) [M^+−CF_3], 419 (62) [M^+−OBn]. Anal. Calcd for $C_{29}H_{29}F_3O_4$ (526.21): C, 66.15; H, 5.55; N, 5.52. Found: C, 66.14; H, 5.80; N, 5.05.

1.9. 4-(1,2,4-Tri-*O*-benzyl-D-*arabino*-1,2,3,4-tetrahydroxybutyl)-1-phenyl-3-trifluoromethyl-1*H*-pyrazole (11)

Glucal **4** (150 mg, 0.29 mmol) was dissolved in 15 mL ethanol, and 0.3 mL of freshly distilled phenylhydrazine was added. The solution was heated for 24 h under reflux. After removal of the solvent, the remaining phenylhydrazine was distilled off by bulb tube distillation at 70 °C/10^{-1} Torr and the residue was purified by column chromatography (heptane/EtOAc 10:1). Yield 70 mg (40%); R_f 0.52 (heptane/EtOAc 1:1); $[\alpha]_D^{22}$ −44.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.61–3.68 (m, 3H, H-4′a, H-4′b, H-2′), 4.09 (dt, 1H, H-3′), 4.28 (d, 1H, $^2J = 11.0$ Hz, CH_2Ph), 4.41 (dd, 2H, $^2J = 11.6$ Hz, CH_2Ph), 4.52 (dd, 2H, $^2J = 12.2$ Hz, CH_2Ph), 4.64 (d, 1H, $^2J = 11.0$ Hz, CH_2Ph), 5.10 (d, 1H, $^3J_{H,F} = 1.8$ Hz, H-1′), 7.10–7.53 (m, 20H, Ph), 7.97 (s, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$): δ 70.2 (C-3′), 71.1 (C-4′), 71.9 (*C*H_2Ph), 72.1 (C-1′), 73.6, 74.6 (*C*H_2Ph), 81.0 (C-2′), 120.5 (q, $J_{C,F} = 269.4$ Hz, CF_3), 123.0 (C-4), 126.1, 127.9, 128.0, 128.1, 128.4, 128.6, 128.7, 129.1, 129.5 (Ph), 137.4, 137.9, 138.5 (Ph, quart. C), 137.9 (q, $J_{C,F} = 34.0$ Hz, C-3), 141.5 (C-5), ^{19}F NMR (235 MHz, $CDCl_3$): δ −54.4 (CF_3); MS (CI-isobutane): *m*/*z* (%) = 603 (14) [M^++H], 495 (29) [M^+−OBn]. Anal. Calcd for $C_{35}H_{33}F_3N_2O_4$ (602.65): C, 69.76; H, 5.52; N, 4.65. Found: C, 69.39; H, 5.91; N, 4.41.

1.10. 4-[1,2,4-Tri-*O*-(*p*-methoxybenzyl)-D-*arabino*-1,2,3,4-tetrahydroxybutyl]-1-phenyl-3-trifluoromethyl-1*H*-pyrazole (12)

Glucal **8** (251 mg, 0.4 mmol) was dissolved in 15 mL ethanol, and 1 mL of hydrazine hydrate (98%) was added. The solution was heated for 24 h under reflux. After removal of the solvent, the residue was purified by column chromatography (heptane/EtOAc 2:1). Yield 156 mg (61%). R_f 0.29 (heptane/EtOAc 1:2); $[\alpha]_D^{22}$ −31.8 (*c* 0.9, $CHCl_3$); mp 84.5–87.5 °C (heptane); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.84 (br s, 1H, OH), 3.52–3.59 (m, 3H, H2′, H-4′a, H4′b), 3.70, 3.77, 3.78 (s, 9H, OMe), 4.96–4.06 (m, 1H, H-3′), 4.10 (d, 1H, $^2J =$ 11.0 Hz, CH_2Ph), 4.25 (dd, 2H, $^2J = 11.6$ Hz, CH_2Ph), 4.44 (dd, 2H, $^2J = 11.6$ Hz, CH_2Ph), 4.48 (d, 1H, $^2J = 11.0$ Hz, CH_2Ph), 5.00 (d, 1H, $^3J_{1',2'} = 2.4$ Hz, H-1′), 6.68–7.28 (m, 12H, Ph), 7.79 (s, 1H, H-5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 70.2 (C-3′), 70.8 (C-4′), 71.1 (CHPh), 71.4 (C-1′), 73.1, 74.0 (CHPh), 81.7 (C-2′), 113.6, 113.9 (Ph), 118.3 (C-4), 121.9 (q, $J_{C,F} = 268.8$ Hz, CF_3), 129.5, 129.6, 129.7, 129.9, 130.0 (Ph), 131.5 (C-5), 139.6 (q, $J_{C,F} = 36.4$ Hz, C-3), 159.3, 159.4, 159.5 (Ph, quart. C), ^{19}F NMR (235 MHz, $CDCl_3$): δ −59.4 (CF_3). MS (CI–isobutane): *m*/*z* (%) = 616 (2) [M^+], 494 (1) [M^+−PMB]. Anal. Calcd for $C_{32}H_{35}F_3N_2O_7$ (616.63): C, 62.33; H, 5.72; N, 4.54. Found: C, 62.11; H, 5.80; N, 4.71.

1.11. 3-(1,2,4-Tri-*O*-benzyl-D-*arabino*-1,2,3,4-tetrahydroxybutyl)-4-trifluoromethyl-1*H*-benzo[*b*] [1,4]-diazepine (13)

Glucal **4** (204 mg, 0.4 mmol) was dissolved in 15 mL ethanol, and 43 mg (0.4 mmol) of *o*-phenylenediamine were added. The solution was stirred 24 h at rt. After removal of the solvent, the residue was purified by column chromatography (heptane/EtOAc 5:1). Yield 104 mg (44%). R_f 0.51 (heptane/EtOAc 1:1); $[\alpha]_D^{22}$ +192.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.70 (dd, 2H, $^3J_{3',4'} = 4.0$ Hz, H-4′a, H-4′b), 3.75 (dd, 1H, $^3J_{2',3'} =$ 7.6, $^3J_{1',2'} = 2.1$ Hz, H-2′), 4.17 (m, 1H, $^3J_{2',3'} = 7.6$,

$^3J_{3',4'} = 4.0$ Hz, H-3′), 4.34–4.58 (m, 2H, $^2J = 11{,}3$ Hz, CH_2Ph), 5.26 (d, 1H, $^3J_{1',2'} = 2.1$ Hz, H-1′), 6.90–7.35 (m, 19H, Ph, H-6 to H-9), 8.03 (d, 1H, $^3J_{N,2} = 13.4$ Hz, H-2), 9.05 (d, 1H, $^3J_{N,2} = 13.4$ Hz, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 70.1 (C-3′), 71.0 (C-4′), 72.3, 73.7, 75.3 (*C*H_2Ph), 76.8 (C-1′), 82.2 (C-2′), 104.4 (C-3), 121.8 (q, $J = 292.9$ Hz, CF_3), 117.5, 120.0, 126.0 (C6–C9), 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7 (Ph), 137.0, 137.4, 137.9 (Ph, quart. C), 149.0 (C-2), 176.5 (q, $J_{C,F} = 31.7$ Hz, C-4); ^{19}F NMR (235 MHz, $CDCl_3$): δ −66.9 (s, CF_3); MS (ESI, +*c*): *m*/*z* (%) = 603 (100) [M^++H], 585 (48) [M^+−OH], 495 (50) [M^+−OBn].

1.12. 4-(1,2,4-Tri-*O*-benzyl-D-*arabino*-1,2,3,4-tetrahydroxybutyl)-5-trifluoromethyl-isoxazole (15)

Glucal **4** (313 mg, 0.61 mmol) was dissolved in 5 mL of pyridine, and 0.5 mL of saturated hydroxylamine hydrochloride solution was added. The solution was stirred for 2 days. After removal of the solvent the residue was dissolved in 0.5 mL of pyridine and 0.5 mL of trifluoroacetic anhydride. The solution was stirred overnight. Then, a satd $NaHCO_3$-solution was added and the aqueous phase was extracted three times with ethyl acetate. The organic layer was dried with $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel; heptane/ethyl acetate 10:1). Yield 108 mg (34%). R_f 0.52 (heptane/EtOAc 1:1); $[\alpha]_D^{22}$ +11.3 (*c* 1.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.70 (dd, $^2J =$ 11.0, $^3J_{3',4'b} = 4.6$ Hz, H-4′b), 3.78 (dd, 1H, $^2J = 11.0$, $^3J_{3',4'a} = 5.5$ Hz, H-4′a), 3.94 (t, 1H, $^3J = 4.9$ Hz, H-2′), 4.19–4.24 (m, 1H, $^3J_{1',2'} = 4.9$ Hz, H-1′), 4.51 (s, 2H, CH_2Ph), 4.53–4.60 (m, 1H, $^3J_{3',4'a} = 5.5$, $^3J_{3',4'b} =$ 4.6 Hz, H-3′), 4.61, 4.62 (2s, 2H, CH_2Ph), 4.65 (d, 1H, $^2J = 11.2$ Hz, CH_2Ph), 4.81 (d, 1H, $^2J = 11.2$ Hz, CH_2Ph), 7.20–7.40 (m, 16H, Ph, H-5); ^{13}C NMR (62 MHz, $CDCl_3$): δ 66.8 (C-4′), 71.1 (C-2′), 72.9 (C-1′), 73.1, 73.6, 73.7 (*C*H_2Ph), 79.3 (C-3′), 114.2 (C-4), 122.6 (q, $J_{C,F} = 276.6$ Hz, CF_3), 127.8, 128.0, 128.1, 128.4, 128.5, 128.6, 128.8 (Ph), 136.6, 137.0, 137.5 (Ph, quart. C); ^{19}F NMR (235 MHz, $CDCl_3$): δ −68.8 (CF_3). MS (CI–isobutane): *m*/*z* (%) = 510 (29) [M^+−OH], 418 (15) [M^+−BnOH]. Anal. Calcd for $C_{29}H_{28}F_3NO_5$ (527.54): C, 66.03; H, 5.35; N, 2.66. Found: C, 66.22; H, 4.60; N, 2.89.

References

1. Wegert, A.; Reinke, H.; Miethchen, R. *Synthesis* **2005**, 1850–1858.
2. Tsuchiya, T. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 91–277.
3. Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, 1991.
4. Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993.
5. Resnati, G.; Soloshonok, V. A. *Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards*; Pergamon Press: Oxford, 1996.
6. Yamamoto, H. *Organofluorine Compounds—Chemistry and Applications*; Springer: Berlin, 2000.
7. Special Issue: *Fluoro Sugars*, Miethchen, R.; Defaye, J. (Eds.), *Carbohydr. Res.* **2000**, *327*, 1–218.
8. Burger, K.; Wucherpfennig, U.; Brunner, E. *Adv. Heterocycl. Chem.* **1994**, *60*, 1–64.
9. Collins, P.; Ferrier, R. *Monosaccharides: Their Chemistry and their Roles in Natural Products*; Wiley: Chichester, 1995; p 319.
10. Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1380–1419.
11. Seeberger, P. H.; Haase, W. C. *Chem. Rev.* **2000**, *100*, 4349–4393.
12. Priebe, W.; Grynkiewicz, G.; Nemati, N. *Tetrahedron Lett.* **1992**, *33*, 7681–7684.
13. Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, 499–502.
14. Colla, A.; Martins, M. A. P.; Clar, G.; Krimmer, S.; Fischer, P. *Synthesis* **1991**, 483–486.
15. Effenberger, F.; Maier, R.; Schönwälder, K.-H.; Ziegler, T. *Chem. Ber.* **1982**, *115*, 2766–2782.
16. Hojo, M.; Masuda, R.; Sakaguchi, S.; Takagawa, M. *Synthesis* **1986**, 1016–1917.
17. Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron Lett.* **1991**, *32*, 3875–3878.
18. Trost, B. M.; Balkovec, J. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1983**, *105*, 6755–6757.
19. Bailey, D. H.; Johnson, R. E.; Albertson, N. F. *Org. Synth.* **1971**, *51*, 100–103.
20. Zanatta, N.; de Cortelini, M. F. M.; Carpes, M. J. S.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1997**, *34*, 509–513.
21. Chu, Q.-L.; Wang, Y.; Zhu, S.-Z. *Synth. Commun.* **2000**, *30*, 677–687.
22. Song, L.-P.; Chu, Q.-L.; Zhu, S.-Z. *J. Fluorine Chem.* **2001**, *107*, 107–112.
23. Abdel-Fattah, A. A. A. *Synthesis* **2005**, 245–249.
24. Jones, B. G.; Branch, S. K.; Thompson, A. S.; Threadgill, M. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2685–2691.
25. Montero, A.; Feist, H.; Michalik, M.; Quincoces, J.; Peseke, K. *Synthesis* **2002**, 664–668.
26. Bari, A.; Feist, H.; Michalik, D.; Michalik, M.; Peseke, K. *Synthesis* **2004**, 2863–2868.
27. Yadav, J. S.; Reddy, B. V. S.; Satheesh, G.; Naga Lakshmi, P.; Kiran Kumar, S.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 8587–8590.
28. Cash, D. J.; Serfözö, P.; Allan, A. M. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 704–711.
29. Hunter, A. W. *Pharm. J.* **1974**, *212*, 88–90.
30. Blackburne, I. D.; Fredericks, P. M.; Guthrie, R. D. *Aust. J. Chem.* **1976**, *29*, 381–391.
31. Malik, A. A.; Sharts, C. M. *J. Fluorine Chem.* **1987**, *34*, 395–408.
32. Dransfield, P. J.; Gore, P. M.; Prokeš, I.; Shipman, M.; Slawin, A. M. Z. *Org. Biomol. Chem.* **2003**, *1*, 2723–2733.