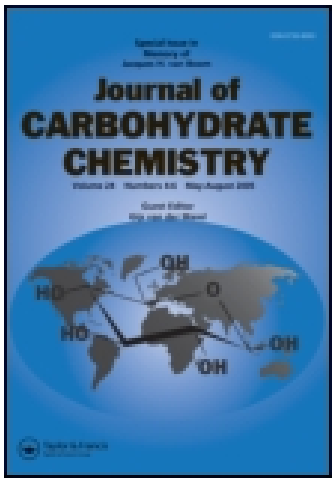


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lcar20

A Common Sugar as Model for Many-Sided Natural Product Modification. From D-Fructose via D-Tagatose to 2-C-Chlorodifluoro-methylated D-Arabinopyranos-5-ulose Derivatives

Ralf Miethchen [a] , Stefan Tews [a] , Arun K. Shaw [b] , Svenja Röttger [a] & Helmut Reinke [a]
[a] Department of Chemistry , University of Rostock , Albert-Einstein-Strasse 3a, D-18059, Rostock, Germany
[b] Medicinal Chemistry Division , Central Drug Research Institute , Lucknow, India
Published online: 18 Aug 2006.

To cite this article: Ralf Miethchen , Stefan Tews , Arun K. Shaw , Svenja Röttger & Helmut Reinke (2004) A Common Sugar as Model for Many-Sided Natural Product Modification. From D-Fructose via D-Tagatose to 2-C-Chlorodifluoro-methylated D-Arabinopyranos-5-ulose Derivatives, Journal of Carbohydrate Chemistry, 23:2-3, 147-161, DOI: 10.1081/CAR-120037572

To link to this article: http://dx.doi.org/10.1081/CAR-120037572

JOURNAL OF CARBOHYDRATE CHEMISTRY
Vol. 23, Nos. 2 & 3, pp. 147–161, 2004

A Common Sugar as Model for Many-Sided Natural Product Modification.[#] From D-Fructose via D-Tagatose to 2-*C*-Chlorodifluoro-methylated D-Arabinopyranos-5-ulose Derivatives

Ralf Miethchen,[1,*] Stefan Tews,[1] Arun K. Shaw,[2] Svenja Röttger,[1] and Helmut Reinke[1]

[1]Department of Chemistry, University of Rostock, Rostock, Germany
[2]Medicinal Chemistry Division, Central Drug Research Institute, Lucknow, India

ABSTRACT

Starting with 3,4-*O*-[(*R*)-2,2,2-trichloroethylidene]-1,2-*O*-isopropylidene-β-D-tagatopyranose **2** obtained from 1,2-*O*-isopropylidene-β-D-fructopyranose **1** by a non-classical one-step acetalization with chloral/DCC, the fluoroalkylated glycosyl donors **15** and **17** were synthesised in 3–4 steps. By this sequence, one stereogenic center was inverted, one new chiral center was introduced, and one stereogenic center, for the time being eliminated, was later re-introduced. The glycals **11** and **12**, key intermediates of the synthesis sequence, were accessible from triflate precursors (e.g., **10**) by treatment with DBU. Corresponding halogeno-(**6**, **7**), tosyl-(**5**, **8**), or mesyl-(**9**) precursors were unsuitable. The stereoselective introduction of a chlorodifluoromethyl group was realised by dithionite-mediated CF_2ClBr-addition to the glycal double bond. Subsequently, either the chlorodifluoromethylated glycosyl bromide (**13**) or the corresponding pyranoses (**14** and **16**) were isolated. The latter were still acetylated to the

[#]Organofluorine Compounds and Fluorinating Agents, Part 30. Part 29: Ref.[1].

*Correspondence: Ralf Miethchen, Department of Chemistry, University of Rostock, Albert-Einstein-Strasse 3a, D-18059 Rostock, Germany; E-mail: ralf.miethchen@chemie.uni-rostock.de.

DOI: 10.1081/CAR-120037572
0732-8303 (Print); 1532-2327 (Online)

1-*O*-acetyl derivatives **15** and **17**, respectively. An x-ray analysis is given for the 5-*O*-tosylate **8**.

Key Words: Epimerization; Esterification; Fluoroalkylation; D-Tagatose.

INTRODUCTION

Regioselectivity and stereochemical control over the chemistry used in the building of molecular frameworks are essential conditions in syntheses of chiral structures. Reasonable common natural products can be used as precursors to synthesise less available analogues of chiral natural substances or of modified chiral building blocks. A second point is that there has been a resurgent interest in recent years in the chemistry of fluorinated compounds, due to their potential pharmaceutical, agrochemical, and material applications.[2] Especially, fluorinated sugars play an important role in the development of potential biological targets as enzyme inhibitors and carbohydrate drug candidates; fluorinated building blocks can also be regarded as very useful tools, e.g., in ^{19}F in vivo NMR spectroscopy. Under consideration of the two aspects mentioned above, 1,2-*O*-isopropylidene-β-D-fructopyranose (**1**) was selected as working model. After conversion of this compound into a D-tagatose derivative (**2**), a fluoroalkyl substituted aldoketose was prepared from that. Simultaneously, one new anomeric center is introduced and a second stereogenic center, firstly removed by a β-elimination reaction, is stereoselectively re-introduced by addition of a fluorinated "building block." Thus, a previously unknown branched sugar is generated, which is used as new fluorinated building block for nucleoside analogues (Sch. 1).

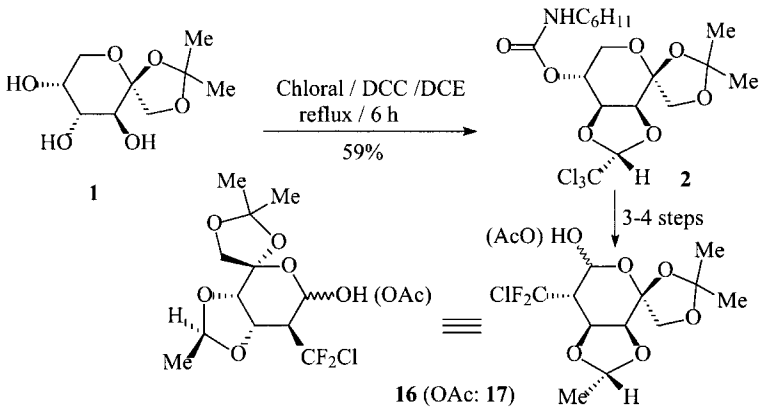
RESULTS AND DISCUSSION

Based on our recent short communication[3] 1,2-*O*-isopropylidene-β-D-fructopyranose (**1**) was converted into 5-*O*-cyclohexylcarbamoyl-3,4-*O*-(2,2,2-trichloroethylidene)-1,2-*O*-isopropyli-dene-β-D-tagatopyranose (**2**) by a non-classical one-pot epimerization reaction (for a review of this reaction type see Ref.[4]).

The D-tagatose derivative was starting material for the final aldoketose derivative **16**. The reaction proceeds via generation of an enolether function in 5,6-position of **2** followed by a selective addition of ClF_2CBr to the enolic double bond; Schs. 4–6. Because the cyclohexylcarbamoyl group of **2** proved to be unsuitable for a direct β-elimination reaction initiated by bases, compound **2** was firstly decarbamoylated by refluxing of **2** in 2% methanolic sodium methoxide yielding hydroxy derivative **3**, or by treatment of **2** with tributyl stannane/AIBN in boiling toluene. The latter procedure caused, simultaneously, a complete hydrodechlorination of the trichloroethylidene group, so that 3,4-*O*-ethylidene-1,2-*O*-isopropylidene-β-D-tagatopyranose (**4**) was obtained. Compound **4** was tosylated generating the ester **5**; Sch. 2.

Cyclic enol ethers are generally important tools for organic syntheses. Especially, molecules with chiral information and an enolic double bond are also suitable precursors for stereoselective fluoroalkylations. In search of the most favorable elimination method to prepare the corresponding enol, different precursors and procedures were studied. Therefore, the halogen derivatives **6**, **7** and the sulfonic acid esters **5**, **8**, **9**, **10** were prepared from

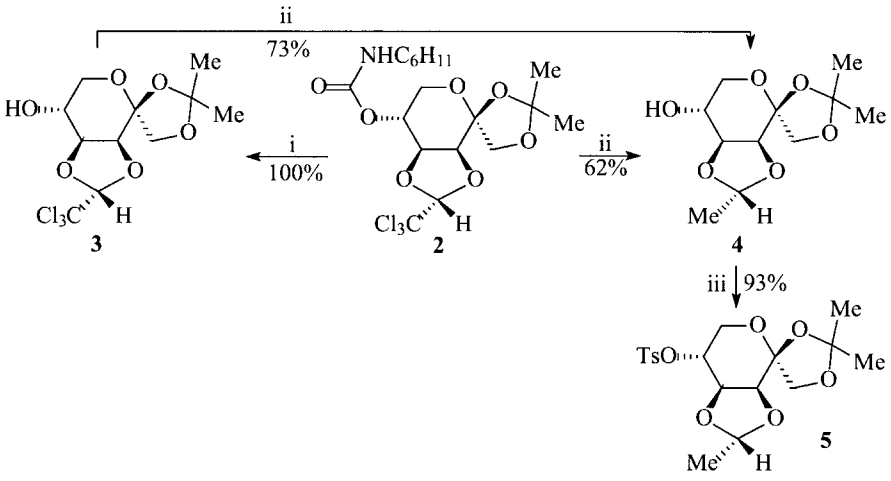
Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016



Scheme 1.

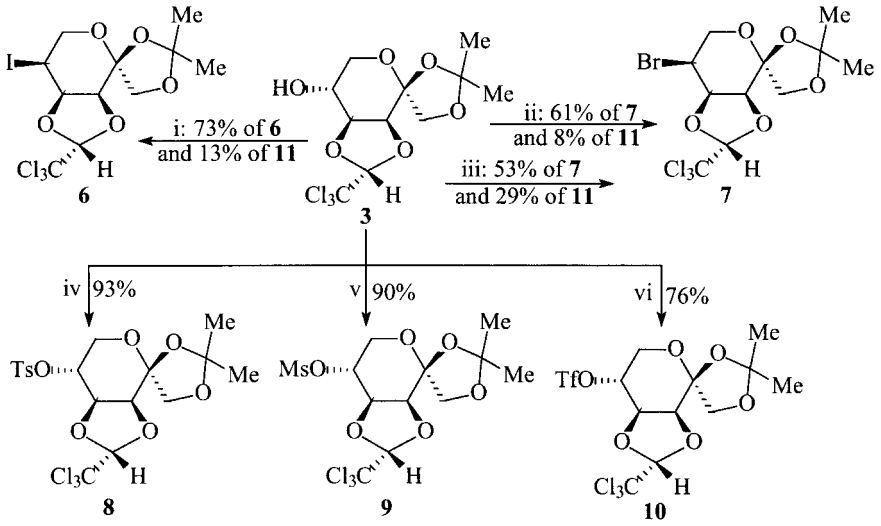
compound **3** and **4**, respectively, as shown in Schs. 2 and 3. However, dehydrohalogenation experiments with **6** and **7** were not successful using DBU. The sulfonic acid esters **5**, **8**, and **9** gave likewise only unsatisfactory yields (20–35%) of the desired 3,4-*O*-(2,2,2-trichloroethylidene)-5,6-dideoxy-1,2-*O*-isopropylidene-β-D-erythro-hexen-5-ulopyranose (**11**) on heating with DBU in different solvents [THF, DMSO, $(CH_2Cl)_2$]. Compared with this, the triflic acid ester **10** turned out to be an excellent precursor for the elimination. After heating of **10** and DBU in toluene, glycal **11** could be isolated in yields of 98%; Sch. 4.

Therefore, the second key intermediate **12** was likewise prepared via a triflic acid ester. The procedure was simplified to the effect that the esterification of **4** with triflyl chloride and the following 5,6-elimination mediated by DBU were carried out without chromatographic purification of the triflic acid ester intermediate. In this way an overall yield of 97% was achieved for enolether **12**; Sch. 5.



Scheme 2. i: MeONa, MeOH, reflux, 8 hr; ii: Bu_3SnH, AIBN, toluene, reflex; iii. TsCl, pyridine, r.t.

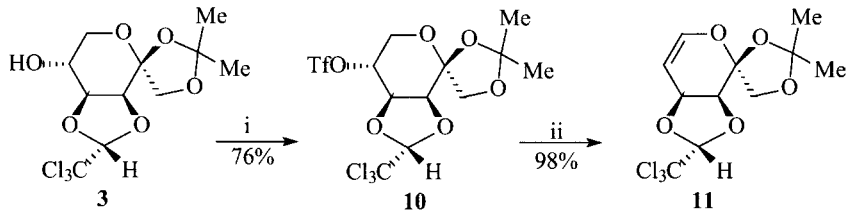
Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016



Scheme 3. i: I_2, PPh_3, toluene; ii: Br_2, PPh_3, toluene; iii: tribromoimidazole, PPh_3, toluene; iv: TsCl, Et_3N, $(CH_2Cl)_2$, reflux, 6 hr; v: MsCl, Et_3N, $(CH_2Cl)_2$, reflux, 3–4 hr; vi: tribromoimidazole, PPh_3, toluene; TfCl, pyridine.

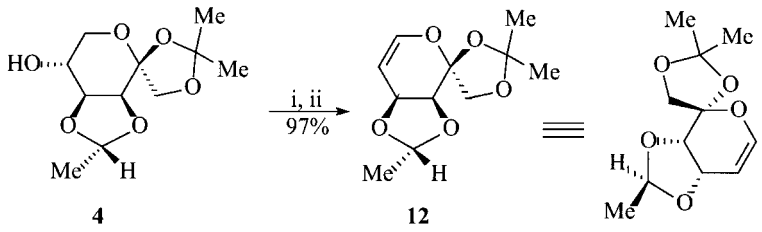
The next step of our strategy was the introduction of the fluorine containing marker group into the enolethers **11** and **12**. Radical additions of halogeno-fluoroalkanes to unsaturated precursors rank among the well suitable methods for the introduction of fluoroalkyl groups into organic compounds. One of the most convenient methods in this field is the dithionite-mediated addition of halogeno-fluoroalkanes to unsaturated precursors;[5–8] first applications of this method in carbohydrate chemistry were already published.[9–11]

Recently, we could show[1] that dithionite-mediated additions of CF_2ClBr to glycals proceed very selectively. In the products, the CF_2Cl-group introduced in 2-position was practically always *trans*-arranged to the neighbouring C-3 substituent. Because the enolethers **11** and **12** are to be conceived as glycals of an aldoketose, the latter method was used to introduce the CF_2Cl-marker group as shown in Sch. 6. The primarily formed glycosyl bromides hydrolyse easily. Therefore, we isolated this intermediate only in the case of 2-deoxy-2-chlorodifluoromethyl-5,6-*O*-isopropylidene-3,4-di-*O*-(2,2,2-trichloro-ethylidene)-β-D-arabinohexopyranos-5-ulosyl bromide (**13**) generated from the glycalic



Scheme 4. i: TfCl, pyridine, r.t.; ii: DBU, toluene, reflux.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

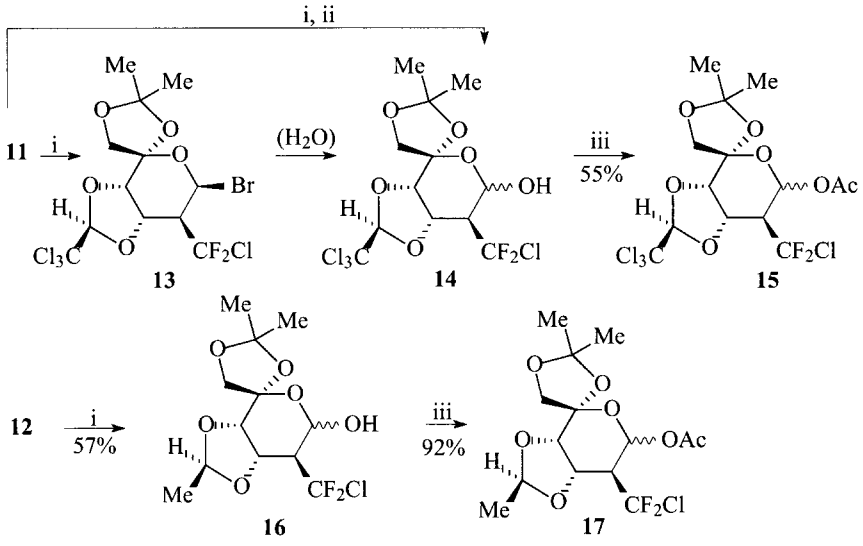


Scheme 5. i: TfCl, pyridine; ii: DBU, toluene, reflux.

precursor **11**. Otherwise, the corresponding 2-chlorodifluoromethyl-2-deoxy-pyranoses **14** and **16** were isolated. These products were subsequently acetylated to the 1-*O*-acetyl derivatives **15** and **17**, respectively; Sch. 6. The target products **15** and **17** contain, related to fructose derivative **1**, one new and one inverted stereogenic center, a *C*-fluoroalkylated marker group, and a favorable protecting group pattern.

The structures of all new compounds are supported by their ^{1}H, ^{13}C, and ^{19}F NMR spectra. The relative small 1-H/2-H-coupling constants of glycosyl bromide **13** (1.6 Hz) indicate an α-configuration. A comparison of the 4-H/5-H-coupling constants of 5-hydroxy-derivative **3** (4.2 Hz), 5-*O*-tosyl-derivative **8** (5.5 Hz), and 5-*O*-mesyl-derivative **9** (4.6 Hz) with those of 5-deoxy-5-iodo-derivative **6** (2.8 Hz) and 5-deoxy-5-bromo-derivative **7** (2.8 Hz) indicates the inversion of configuration at C-atom 5 during the halogenation. The structure of 5-*O*-tosyl-D-tagatose derivative **8** was confirmed by an x-ray analysis (Fig. 1).

The glycals **11** and **12** show characteristic downfield shifts for 1-H (**11**: $\delta = 6.43$; **12**: $\delta = 6.41$) and for the C-atoms 1 and 2 (**11**: $\delta_{C\text{-}1} = 144.9/\delta_{C\text{-}2} = 100.1$; **12**: $\delta_{C\text{-}1} = 145.1/$



Scheme 6. i: CF_2ClBr, $Na_2S_2O_4$, $NaHCO_3$, MeCN, H_2O; ii: Ag_2CO_3, MeOH, H_2O; iii: Ac_2O, pyridine.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

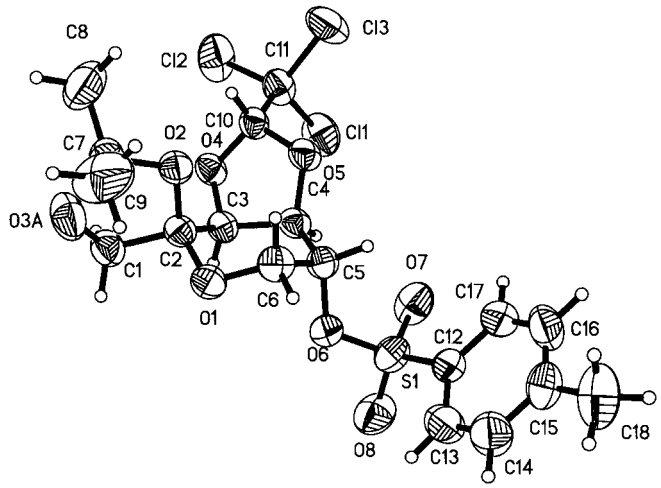


Figure 1. X-ray structure of 3,4-*O*-[(*R*)-2,2,2-trichloroethylidene]-1,2-*O*-isopropylidene-5-*O*-tosyl-β-D-tagatopyranose (**8**) with 30% probability of the thermal ellipsoids. The ring oxygen O3 takes disordered positions (here only one position is shown).

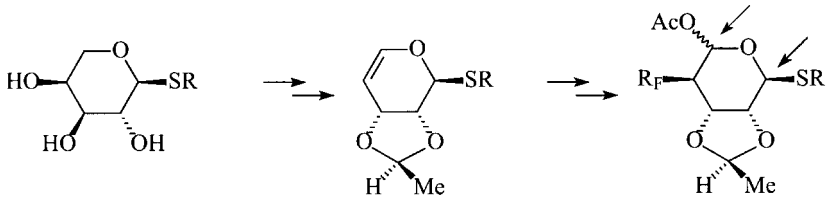
$\delta_{C\text{-}2} = 100.6$). For the CF_2Cl-substituted derivatives **13–17**, the triplet of ring C-atom 2 in the range of $\delta \approx 50.6-53.4$ ($^2J_{C\text{-}2,F} \approx 22-23$ Hz) is characteristic. The CF_2Cl-group itself produces ^{19}F-signals in the range of $\delta \approx -48.6$ to -54.9 with geminal F–F-couplings of 169–174 Hz and $^1J_{F,C}$-couplings of 278–298 Hz. The configuration of the new chiral center (C-2) was assigned on the basis of the 2-H/3-H and 2-H/1-H couplings. The compounds **13**, **14**, **16**, **17** adopt a slightly distorted $^1C_4$ conformation with couplings of $^3J_{2,3} \approx 7.9-9.0$ Hz, $^3J_{1,2} \approx 1.6-2.2$ Hz (β-anomers), and $^3J_{1,2} \approx 8.1-8.5$ Hz (α-anomers). The relative large 2-H/3-H coupling constants of the β-anomers of **13**, **14**, **16**, **17** indicate that these protons come close to a trans-diaxial arrangement. NOE-experiments were carried out to assign the configuration of the chlorodifluoromethylated C-atom in compounds **13–17**. Correlations were found between the acetal-H and the proton located at the chlorodifluoromethylated C-atom. Such correlations are only to expect when the latter has S-configuration.

CONCLUSION

The target compounds **15** and **17** are suitable glycosyl donors, whereas the sequence and individual steps of the demonstrated model reaction are usable for various other synthesis strategies, which use the chiral pool of natural substances. An example using a similar synthesis strategy is sketched in the following illustration; Sch. 7. It stands for conversions of pentopyranoses into fluorinated glycosyl donors with two anomeric positions, which are alternatively usable for subsequent glycosylations.

Key intermediates for *C*-fluoroalkylations are cyclic enol ethers inclusive of glycals. The latter are above all accessible via triflic acid ester precursors. The strategy of combined epimerization–fluoroalkylation, reported in this paper at one selected example, is

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016



Scheme 7. R_F: F, CF_3, CF_2Cl . . .

transferable to various other models in carbohydrate chemistry (for a review about the application of the non-conventional epimerization step see Ref.[4]). Sch. 7 shows such an example for pentoses. The target molecule has, after the reaction sequence, two reactive "anomeric" centers (marked by arrows) which can be alternatively activated for glycosylations.

EXPERIMENTAL

General Remarks

Melting points were obtained using a Leitz polarizing microscope (Laborlux 12 Pol) equipped with a hot stage (Mettler FP 90) and are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker instruments: AC 250 and ARX 300, internal standard TMS for ^{1}H and ^{13}C{^{1}H} NMR spectra, $CFCl_3$ for ^{19}F{^{1}H} NMR spectra. Optical rotations were measured on a polar LμP (IBZ Meßtechnik) instrument. Column chromatography was carried out with Merck Silica Gel 60 (63–200 μm) and TLC on Merck Silica Gel 60 F_{254} sheets. Table 1 summarises in detail the analytical data of the new compounds **3–17**.

X-ray Structure Determination of 8

X-ray diffraction data were collected with a Bruker P4 four circle diffractometer, Mo-K_α radiation ($\lambda = 0.71073$ Å), graphite monochromator, crystal size $0.64 \times 0.62 \times 0.52\,mm^3$, $T = 293(2)$ K, $C_{18}H_{21}Cl_{l3}O_8S$, $M = 503.76$, colourless prism, orthorhombic, space group (H.-M.) $P2_12_12_1$, space group (Hall) $P2ac\ 2ab$, $a = 10.1650(10)$, $b = 11.1790(10)$, $c = 19.847(2)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 2255.3(4)$ Å^3, $Z = 4$, ρ_{calc} $1.484\,Mg\,m^{-3}$, $\mu = 0.540\,mm^{-1}$, $F(0\,0\,0) = 1040$, data collection range: $2.05 \le \Theta \le 21.99°$, $-10 \le h \le 10$, $-11 \le k \le 11$, $-20 \le l \le 20$, 3194 reflections collected, 2755 independent reflections [R(int) = 0.0247], 2576 observed [$I > 2\sigma(I)$], completeness to $\Theta = 21.99°$: 99.6%, $R_1 = 0.0347$(obs.), $wR_2 = 0.0885$(obs.), GOF (F^2) = 1.066, max./min. residual electron density: $+0.142/-0.132\,e\,Å^{-3}$. The weighting scheme was calculated according to $w^{-1} = \sigma^2(F_o^2) + (0.0368P)^2 + 0.4213P$ with $P = (F_o^2 + 2F_c^2)/3$.

The central sugar ring adopts a distorted chair conformation with puckering parameters[12] of $Q = 0.519(3)$ Å (puckering amplitude), $\Theta = 159.0(3)°$, and $\Phi = 177.7(11)°$. In analogy to the literature[12] it could be designated as a $^2C_5$ conformation.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

Table 1. Analytical data of the compounds **3–17**.

Product	Precursor	Yield (%)	Mp (solvent °C)	$[\alpha]_D^{22}$ $CHCl_3$ (*c*)	R_f (eluents, v/v)
3	**2**	83	138 (pentane)	−20.5 (0.52)	0.12 (3 : 1)[a]
4	**3** (**2**)	73	Colourless syrup	−56.2 (0.49)	0.36 (2 : 1)[b]
5	**4**	93	Colourless syrup	$[\alpha]_D^{27}$ −33.9 (0.31)	0.14 (5 : 1)[a]
6	**3**	71	180 subl. (pentane/ether)	−39.6 (1.11)	0.23 (5 : 1)[a]
7	**3**	81	195 (pentane/ether)	−40.0 (1.11)	0.24 (5 : 1)[a]
8	**3**	93	157 (heptane/ether)	−14.7 (1.03)	0.34 (3 : 1)[a]
9	**3**	90	181 (EtOAc)	−34.5 (1.10)	0.35 (5 : 1)[b]
10	**3**	53	113–114 (heptane)	Unstable compound	0.43 (5 : 1)[a]
11	**10**	96	179–181 (heptane)	−66.5 (1.02)	0.28 (10 : 1)[a]
12	**4**	97	101 (heptane/EtOAc)	−24.0 (1.25)	0.27 (5 : 1)[a]
13	**11**	23	Unstable compound		0.31 (3 : 1)[a]
14	**11**	42	Colourless syrup	Anomers	0.22 (3 : 1)[a]
15	**14**	55	Colourless syrup	Anomers	0.17 (6 : 1)[a]
16	**12**	57	180–190 (heptane)	Anomers	0.17 (4 : 1)[a]
17	**16**	92	Colourless syrup	Anomers	0.34 (4 : 1)[a]

[a]Heptane–EtOAc.
[b]Toluene–EtOAc.

The structure was solved by direct methods (Bruker SHELXTL). All non-hydrogen atoms were refined anisotropically, with the hydrogen atoms introduced into theoretical positions and refined according to the riding model. CCDC 207041 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk).

3,4-*O*-[(*R*)-2,2,2-trichloroethylidene]-1,2-*O*-isopropylidene-β-D-tagatopyranose (3). Decarbamoylation of **2** by refluxing for 8 hr in 2% methanolic sodium methoxide solution (TLC-control) yielded **3** in quantitative yield. Purification by column chromatography.

^{1}H NMR (250.1 MHz, $CDCl_3$): 5.55 (s, 1H, acetal-H), 4.61 (m, 1H, $^3J_{3,4} = 5.2$ Hz, 4-H), 4.48 (d, 1H, $^3J_{3,4} = 5.2$ Hz, 3-H), 4.27 (dd, 1H, $^2J_{6a,6b} = 12.8$ Hz, $^3J_{6a,5} = 2.0$ Hz, 6a-H), 4.12 (dd, 1H, $^3J_{4,5} = 4.2$ Hz, $^3J_{6a,5} = 2.0$ Hz, 5-H), 4.09 (s, 2H, 1a-H, 1b-H), 3.62 (dd, 1H, $^2J_{6a,6b} = 12.8$ Hz, $^3J_{6b,5} = 1.7$ Hz, 6b-H), 2.20 (broad s, 1H, OH), 1.53, 1.44 (2s, 6H, 2 × CH_3). $^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$): 113.4 [$C(CH_3)_2$], 108.1 ($CH-CCl_3$), 102.8 (C-2), 99.3 (CCl_3), 76.5 (C-3), 73.2 (C-1), 72.3 (C-4), 65.7 (C-5), 61.1 (C-6), 27.4, 25.1 (2 × CH_3); Anal. calcd for $C_{11}H_{15}Cl_3O_6$ (349.59): C, 37.79; H, 4.32; found C, 37.91, H, 4.35.

3,4-*O*-[(*R*)-Ethylidene]-1,2-*O*-isopropylidene-β-D-tagatopyranose (4). Compound **3** (0.9 g, 2.58 mmol) was dissolved in dry toluene (30 mL). Under argon Bu_3SnH (2.7 mL) and AIBN (20 mg) were added and the mixture was refluxed for 4 hr (TLC-control). When the reaction was finished, an excess of KF-soln. was added and the precipitate was

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

filtered and intensively washed by toluene. The organic layer was separated, washed with brine (30 mL) and water (30 mL), and was dried over Na_2SO_4. Column chromatography gave pure **4**.

^{1}H NMR (250.1 MHz, $CDCl_3$): 5.48 (q, 1H, $^3J_{H,CH3} = 5.0$ Hz, acetal-H), 4.15 (dd, 1H, $^3J_{6,5} = 2.8$ Hz, $^2J_{6a,6b} = 11.6$ Hz, 6a-H), 4.04–4.16 (m, 3H, 3-H, 4-H, 5-H), 4.00 (t, 2H, $^2J_{1a,1b} = 9.0$ Hz, 1a-H, 1b-H), 3.53 (dd, 1H, 6b-H), 2.37 (broad s, 1H, OH), 1.49, 1.38 (2s, 6H, 2 × CH_3), 1.31 (d, 3H, acetal-CH_3). ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$): 112.8 [$C(CH_3)_2$], 103.5 (CH–CH_3), 103.3 (C-2), 75.5 (C-5), 73.1 (C-1), 71.0 (C-3), 66.2 (C-4), 61.8 (C-6), 27.3, 25.4 (2 × CH_3), 21.2 (acetal-CH_3); Anal. calcd for $C_{11}H_{18}O_6$ (246.26): C, 53.65, H, 7.37, found C, 53.31, H, 7.35.

3,4-*O*-[(*R*)-Ethylidene]-1,2-*O*-isopropylidene-5-*O*-(*p*-tosyl)-β-D-tagatopyranose (5). To a solution of **4** (0.55 g, 2.24 mmol) in dry pyridine (10 mL) *p*-toluenesulfonyl chloride (0.53 g, 2.75 mmol) was added and then the mixture was stirred for 26 hr at room temperature. Subsequently, the mixture was diluted with dried toluene and the solvent was evaporated at reduced pressure. After the residue was dissolved in ethyl acetate (20 mL), the further work-up procedure was analogous to that for **8**. Column chromatography [eluent (v/v): heptane/EtOAc = 6/1, $R_F = 0.23$]; giving 0.83 g (93%) of **5** for analytical data of the colourless syrupy product see Table 1.

^{1}H NMR (250.1 MHz, $CDCl_3$): 7.80–7.34 (4d, 4H, $^3J_{H,H} = 8.3$ Hz, phenyl-H), 5.41 (q, 1H, $^3J_{CH3,acetal\text{-}H} = 5.0$ Hz, acetal-H), 4.82 (m, 1H, 5-H), 4.14 (m, 2H, 3-H, 4-H), 4.07 (dd, 1H, $^2J_{6a,6b} = 12.8$ Hz, $^3J_{6a,5} = 2.8$ Hz, 6a-H), 4.01 (d, 1H, $^2J_{1a,1b} = 9.0$ Hz, 1a-H), 3.97 (d, 1H, 1b-H), 3.53 (dd, 1H, 6b-H), 2.44 (s, 3H, tosyl-CH_3), 1.46, 1.41 (2s, 6H, 2 × CH_3), 1.24 (d, 3H, $^3J_{CH3,acetal\text{-}H} = 5.0$ Hz, acetal-CH_3). ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$): 145.0 (tosyl-C–SO_3–), 133.3 (tosyl-C–CH_3), 129.9, 127.9 (tosyl-CH), 113.6 [$C(CH_3)_2$], 103.6 (acetal-C), 103.0 (C-2), 74.9 (C-5), 73.0 (C-1), 72.7 (C-3), 70.8 (C-4), 58.6 (C-6), 27.3, 25.3 (2 × CH_3), 21.7 (tosyl-CH_3), 21.2 (acetal-CH_3); Anal. calcd for $C_{18}H_{24}O_8S$ (400.44): C, 53.99, H, 6.04, S, 8.01, found C, 54.53, H, 6.15, S, 8.12.

3,4-*O*-[(*R*)-2,2,2-Trichloroethylidene]-5-deoxy-5-iodo-1,2-*O*-isopropylidene-β-L-psico-pyranose (6).[13] Compound **3** (0.7 g, 2.0 mmol) was dissolved in dry toluene (50 mL) and triphenylphosphine (1.55 g, 5.8 mmol), imidazole (0.4 g, 5.8 mmol), and iodine (0.89 g, 3.5 mmol) were added under strong stirring and argon atmosphere. The mixture was heated for 5 hr (bath temperature 120°C) then quenched with sat. $NaHCO_3$-soln. (TLC-control). The layers were separated, and the aqueous phase was washed with toluene (2 × 30 mL). The combined organic layers were washed with brine (2 × 50 mL) and water (50 mL), dried over Na_2SO_4, and evaporated under reduced pressure. Column chromatography gave pure **6**. As by-product compound **11** was detected.

^{1}H NMR (250.1 MHz, $CDCl_3$): 5.66 (s, 1H, acetal-H), 4.87 (m, 1H, $^3J_{3,4} = 4.7$ Hz, $^3J_{4,5} = 2.8$ Hz, 4-H), 4.39 (d, 1H, $^3J_{3,4} = 4.7$ Hz, 3-H), 4.14–4.28 (m, 2H, 6a-H, 6b-H), 4.05 (d, 1H, $^2J_{1,1} = 9.1$ Hz, 1a-H), 4.03 (d, 1H, $^2J_{1,1} = 9.1$ Hz, 1b-H), 3.66 (m, 1H, $^3J_{4,5} = 2.8$ Hz, 5-H), 1.53 (s, 3H, CH_3), 1.45 (s, 3H, CH_3). ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$): 113.7 [$C(CH_3)_2$], 107.5 (CH–CCl_3), 102.5 (C-2), 99.2 (CCl_3), 76.2 (C-3), 73.6 (C-4), 73.1 (C-1), 61.2 (C-6), 27.3, 25.0 (2 × CH_3), 16.4 (C-5); MS: chemical ionisation (isobutane): 460.0 (Molpeak 15%), 445.0 ($M^+ - CH_3$, 100%); Anal. calcd for $C_{11}H_{14}Cl_3IO_5$ (459.49): C, 28.75, H, 3.07, found C, 29.13, H, 3.07.

5-Bromo-3,4-*O*-[(*R*)-2,2,2-trichloroethylidene]-5-deoxy-1,2-*O*-isopropylidene-β-L-psico-pyranose (7) (modified Ref.[13]). Compound **3** (0.35 g, 1.0 mmol) was dissolved

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

in dry toluene (30 mL) and triphenylphosphine (0.76 g, 2.9 mmol), imidazole (0.4 g, 5.8 mmol), and bromine (0.1 mL, 3.9 mmol) were added under strong stirring and argon atmosphere. The mixture was heated for 5 hr (bath temperature 120°C) then quenched with sat. $NaHCO_3$-soln. (TLC-control). The layers were separated, and the aqueous phase was washed with toluene (2 × 20 mL). The combined organic layers were washed with brine (2 × 30 mL) and water (30 mL), dried over Na_2SO_4, and evaporated under reduced pressure. Column chromatography gave pure **6**. As by-product compound **11** was detected.

^{1}H NMR (250.1 MHz, $CDCl_3$): 5.67 (s, 1H, acetal-H), 4.91 (m, 1H, $^3J_{3,4} = 4.7$ Hz, $^3J_{4,5} = 2.8$ Hz, 4-H), 4.38 (d, 1H, $^3J_{3,4} = 4.7$ Hz, 3-H), 4.07–4.24 (m, 2H, 6a-H, 6b-H), 4.07 (d, 1H, $^2J_{1,1} = 9.0$ Hz, 1a-H), 4.03 (d, 1H, $^2J_{1,1} = 9.0$ Hz, 1b-H), 3.69 (m, 1H, $^3J_{4,5} = 2.8$ Hz, 5-H), 1.53 (s, 3H, CH_3), 1.45 (s, 3H, CH_3). ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$): 113.8 [$C(CH_3)_2$], 108.1 ($CH{-}CCl_3$), 102.4 (C-2), 99.1 (CCl_3), 75.6 (C-3), 74.4 (C-4), 72.9 (C-1), 59.4 (C-6), 39.8 (C-5), 27.4, 25.1 (2 × CH_3); MS: chemical ionisation (isobutane): 413.0 (Molpeak 21%), 398.0 ($M^+ - CH_3$, 100%); Anal. calcd for $C_{11}H_{14}BrCl_3O_5$ (412.49): C, 32.03, H, 3.42, found C, 32.52, H, 3.64.

3,4-O-[(*R*)-2,2,2-Trichloroethylidene]-1,2-*O*-isopropylidene-5-*O*-(*p*-tosyl)-β-D-tagato-pyranose (8). To a solution of **3** (0.75 g, 2.15 mmol) in dry DCE (15 mL) and Et_3N (5.6 mL, 40 mmol) *p*-toluenesulfonyl chloride (0.76 g, 4.0 mmol) was batchwise added under cooling and then the mixture was refluxed for 6 hr (argon atmosphere). After the mixture was allowed to cool down, water (20 mL) was added and the product was extracted with $CHCl_3$ (50 mL). The chloroform phase was washed with $NaHSO_4$-soln. (3%, 3 × 30 mL) and water (30 mL), then dried over Na_2SO_4, and concentrated under reduced pressure. The brown residue was purified by column chromatography [eluent (v/v): heptane/ethyl acetate = 3/1, $R_F = 0.34$]; for analytical data of the crystalline product **8** see Table 1.

^{1}H NMR (250.1 MHz, $CDCl_3$): 7.64, 7.51, 7.19, 7.11 (4d, 4H, $^3J_{H,H} = 8.2$ Hz, phenyl-H), 5.32 (s, 1H, acetal-H), 4.67 (dd, 1H, $^3J_{3,4} = 3.7$ Hz, $^3J_{5,4} = 5.5$ Hz, 4-H), 4.33 (ddd, 1H, $^3J_{5,4} = 5.5$ Hz, $^3J_{5,6a} = 3.7$ Hz, $^3J_{5,6b} = 1.8$ Hz, 5-H), 4.25 (d, 1H, 3-H), 3.96 (dd, 1H, $^2J_{6a,6b} = 13.7$ Hz, 6a-H), 3.90 (d, 2H, $^2J_{1a,1b} = 9.5$ Hz, 1a-H, 1b-H), 3.42 (dd, 1H, 6b-H), 2.28 (s, 3H, tosyl-CH_3) 1.31, 1.25 (2s, 6H, 2 × CH_3). ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$): 145.5 (tosyl-$C{-}SO_3{-}$), 133.2 (tosyl-$C{-}CH_3$), 129.5, 127.8 (tosyl-CH), 113.5 [$C(CH_3)_2$], 107.9 ($CH{-}CCl_3$), 102.2 (C-2), 98.8 (CCl_3), 74.2, 73.0, 72.0 (C-5, C-3, C-4), 73.7 (C-1), 58.6 (C-6), 27.2, 25.0 (2 × CH_3), 21.7 (tosyl-CH_3); Anal. calcd for $C_{18}H_{21}Cl_3O_8S$ (503.77): C, 42.92, H, 4.20, found C, 43.15, H, 4.17.

3,4-*O*-[(*R*)-2,2,2-Trichloroethylidene]-1,2-*O*-isopropylidene-5-*O*-mesyl-β-D-tagato-pyranose (9). To a solution of **3** (440 mg, 1.78 mmol) in DCE (10 mL) and Et_3N (1.3 mL, 9.0 mmol), methanesulfonyl chloride (0.28 mL, 3.56 mmol) was added under cooling and the mixture was refluxed for 3–4 hr (TLC-control). The work-up procedure was analogous to that for **8**. Column chromatography: [eluent (v/v): heptane/ethyl acetate = 2/1, $R_F = 0.19$]; for analytical data of the crystalline product **9** see Table 1.

^{1}H NMR (250.1 MHz, $CDCl_3$): 5.47 (q, 1H, $^3J_{H,CH3} = 4.9$ Hz, acetal-H), 5.06 (dd, 1H, $^3J_{5,4} = 4.6$ Hz, $^3J_{5,6a} = 8.6$ Hz, $^3J_{5,6b} = 4.6$ Hz, 5-H), 4.31 (dd, 1H, $^3J_{4,3} = 2.1$ Hz, 4-H), 4.21 (d, 1H, 3-H), 4.17 (dd, 1H, $^2J_{6a,6b} = 12.5$ Hz, 6a-H), 4.02 (d, 2H, $^2J_{1a,1b} = 9.2$ Hz, 1a-H, 1b-H), 3.73 (dd, 1H, 6b-H), 3.11 (s, 3H, $-SO_2-CH_3$), 1.50, 1.38 (2s, 6H, 2 × CH_3), 1.32 (d, 3H, acetal-CH_3). ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$): 113.1 [$C(CH_3)_2$], 103.4 ($CH{-}CH_3$), 103.2 (C-2), 74.9, 73.6, 71.3 (C-3, C-4, C-5), 72.9 (C-1),

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

59.9 (C-6), 38.8 ($-SO_2-CH_3$), 27.2, 25.3 ($2 \times CH_3$), 20.8 (acetal-CH_3); Anal. calcd for $C_{12}H_{17}Cl_3O_8S$ (427.68): C, 33.70, H, 4.01, S, 7.50, found C, 34.00, H, 4.02, S, 7.64.

3,4-*O*-[(*R*)-2,2,2-Trichloroethylidene]-5,6-dideoxy-1,2-*O*-isopropylidene-β-D-erythro-hexen-5-ulopyranose (11). 3,4-*O*-[(*R*)-2,2,2-Trichloroethylidene]-5-*O*-trifluoromethanesulfonyl-1,2-*O*-isopropylidene-β-tagatopyranose (10). To a suspension of compound **3** (1.7 g, 4.86 mmol) in pyridine (65 mL) trifluoromethanesulfonyl chloride (2 mL) was added carefully at 0°C (argon atmosphere). After the mixture was allowed to warm up to r.t., it was stirred over night. Then, $CHCl_3$ (100 mL) was added and the mixture was washed with $NaHSO_4$-soln. (5%, 5×100 mL), water (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatographic separation gave compound **10** as a white powder. Traces of **11** were detected. The triflate **10** was used for the following synthetic step without further purification.

^{1}H NMR (250.1 MHz, $CDCl_3$): 5.57 (s, 1H, acetal-H), 5.22 (d, 1H, $^3J_{4,5} = 1.9$ Hz, 5-H), 4.69 (dt, 1H, $^3J_{4,5} = 1.9$ Hz, $^3J_{3,4} = 5.3$ Hz, 4-H), 4.53 (d, 1H, $^3J_{3,4} = 5.3$ Hz, 3-H), 4.34 (dd, 1H, $^3J_{5,6a} = 1.8$ Hz, $^2J_{6a,6b} = 14.2$ Hz, 6a-H), 4.13 (s, 2H, 1a-H, 1b-H), 3.88 (dt, 1H, $^3J_{5,6b} = 1.7$ Hz, $^2J_{6a,6b} = 14.2$ Hz, 6b-H), 1.53 (s, 3H, CH_3), 1.45 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$): 121.3 (CF_3), 113.9 ($C(CH_3)_2$), 108.1 (CH-CCl_3), 102.3 (C-2), 98.5 (CCl_3), 80.3 (C-5), 74.0 (C-3), 73.1 (C-1), 71.9 (C-4), 58.6 (C-6), 27.3, 25.0 ($2 \times CH_3$). $^{19}F\{^1H\}$ NMR (235.4 MHz, $CDCl_3$): −74.62 (s, CF_3).

3,4-*O*-[(*R*)-2,2,2-Trichloroethylidene]-1,2-dideoxy-5(*R*),6-*O*-isopropylidene-β-D-erythro-hexen-5-ulopyranose (11). Triflate **10** (700 mg, 1.45 mmol) was dissolved in dry THF (20 mL). Under stirring DBU (0.35 mL) was added and the mixture was refluxed for 2.5 hr (TLC-control). After cooling the mixture was poured into ice/water (30 mL). It was extracted with chloroform (3×20 mL). The organic layer was washed with water (20 mL), dried over Na_2SO_4, and was evaporated under reduced pressure. Column chromatography gave **11** quantitatively.

^{1}H NMR (250.1 MHz, $CDCl_3$): 6.43 (dd, 1H, $^3J_{1,2} = 6.1$ Hz, $^4J_{1,3} = 0.8$ Hz, 1-H), 5.50 (s, 1 H, acetal-H), 5.30 (dd, 1H, $^3J_{2,3} = 4.3$ Hz, $^3J_{1,2} = 6.1$ Hz, 2-H), 4.91 (m, 1H, $^4J_{1,3} = 0.8$ Hz, $^3J_{2,3} = 4.3$ Hz, $^3J_{3,4} = 6.2$ Hz, 3-H), 4.52 (d, 1H, $^3J_{3,4} = 6.2$ Hz, 4-H), 4.21 (2d, 2H, $^3J_{6a,6b} = 9.2$ Hz, 6a-H, 6b-H), 1.53 (s, 3H, CH_3), 1.46 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$): 144.9 (C-1), 113.8 [$C(CH_3)_2$], 108.1 ($CH-CCl_3$), 102.1 (C-5), 100.1 (C-2), 99.8 (CCl_3), 73.5 (C-4), 71.7 (C-3), 69.6 (C-6), 27.1, 25.4 ($2 \times CH_3$); MS: chemical ionisation (isobutane): 332.0 (Molpeak 100%); Anal. calcd for $C_{11}H_{13}Cl_3O_5$ (331.58): C, 39.85, H, 3.95, found C, 40.04, H, 3.98.

3,4-*O*-[(*R*)-Ethylidene]-1,2-dideoxy-5(*R*),6-*O*-isopropylidene-β-D-erythro-hexen-5-ulo-pyranose (12). To a suspension of compound **4** (1.38 g, 5.61 mmol) in pyridine (40 mL) trifluoromethanesulfonyl chloride (2 mL) was added carefully at 0°C (argon atmosphere). The work-up procedure was analogous to that for **10** (without chromatographic purification). The crude product **4** was dissolved in dry THF (20 mL). DBU (0.35 mL) was added and the mixture was refluxed for 2.5 hr. After cooling the mixture was poured onto ice (40 g) and extracted with chloroform (2×30 mL). The combined organic layers were washed with water (20 mL) and dried over Na_2SO_4. Purification by column chromatography yielded **12** quantitativly.

^{1}H NMR (250.1 MHz, $CDCl_3$): 6.41 (d, 1H, $^3J_{6,5} = 6.1$ Hz, 1-H), 5.44 (q, 1H, $^3J_{H,CH3} = 5.0$ Hz, acetal-H), 5.01 (dd, 1H, $^3J_{5,4} = 3.7$ Hz, 2-H), 4.62 (dd, 1H, $^3J_{4,3} = 5.8$ Hz, 3-H), 4.18 (d, 1H, 4-H), 4.13 (d, 1H, $^2J_{6a,6b} = 9.2$ Hz, 6a-H), 4.02 (d, 1H, $^2J_{6a,6b} = 9.2$ Hz, 6b-H), 1.54, 1.43 (2s, 6H, $2 \times CH_3$), 1.36 (d, 3H, $^3J_{H,CH3} = 5.0$ Hz,

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

acetal-CH_3). $^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$): 145.1 (C-1), 113.4 ($CH-CH_3$), 102.1 (C-5), 100.6 (C-2), 73.9 (C-6), 72.1 (C-3), 68.9 (C-4), 26.9, 25.8 ($2 \times CH_3$), 20.9 (acetal-CH_3); Anal. calcd for $C_{11}H_{16}O_5$ (228.24): C, 57.89, H, 7.07, found C, 57.56, H, 7.12.

2-*C*-Chlorodifluoromethyl-3,4-di-*O*-[(*R*)-2,2,2-trichloroethylidene-2-deoxy-5(*R*),6-*O*-iso-propylidene]-β-D-arabinohexopyranos-5-ulosyl bromide (13). Compound **11** (0.5 g, 1.5 mmol) was dissolved in acetonitrile (20 mL) and water (10 mL). $NaHCO_3$ (1.0 g) was suspended and the mixture cooled to -10°C. Then, CF_2ClBr (approx. 0.2 mL or 25 drops) was condensed via a cooling trap (dry ice/acetone) into the mixture and $Na_2S_2O_4$ (1.0 g) was added. The suspension was allowed to warm up slowly to 20°C within 2 hr. A constant dropwise reflux of the freon is preferable. If the reaction is not finished (TLC-control) a second addition of dithionite should follow. When total turnover was achieved diethylether (30 mL) was added and the layers separated. The organic layer was washed with brine (20 mL) and water (20 mL) and was dried over Na_2SO_4. Compound **13** was separated by column chromatography. Because the product is very sensitive to hydrolyses (formation of **14**), the C, H, N-microanalyses differed significantly.

^1H NMR (250.1 MHz, $CDCl_3$): 5.60 (d, 1H, $^3J_{1,2} = 1.6$ Hz, 1-H), 5.52 (s, 1H, acetal-H), 5.09 (t, 1H, $^3J_{3,4} = 6.8$ Hz, $^3J_{2,3} = 7.9$ Hz, 3-H), 4.86 (d, 1H, 4-H), 4.28 (d, 1H, $^2J_{6a,6b} = 9.1$ Hz, 6a-H), 4.06 (d, 1H, 6b-H), 3.26–3.41 (m, 1H, 2-H), 1.52, 1.43 (2s, 6H, $2 \times CH_3$). $^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$): 132.4 (t, $^1J_{C,F} = 288$ Hz, CF_2Cl), 113.0 [$C(CH_3)_2$], 109.5 ($CH-CCl_3$), 103.0 (CCl_3), 99.4 (C-5), 89.6 (C-1), 74.7 (C-4), 72.6 (C-6), 71.8 (C-3), 52.9 (t, $^2J_{C\text{-}2,F} = 23$ Hz, C-2), 27.1, 25.4 ($2 \times CH_3$). $^{19}F\{^1H\}$ NMR (235.4 MHz, $CDCl_3$): −51.7 (d, $^2J_{Fa,Fb} = 169$ Hz), −54.7 (d, $^2J_{Fa,Fb} = 169$ Hz); MS: chemical ionisation (isobutane): 497.0 (Molpeak 100%).

2-*C*-Chlorodifluoromethyl-3,4-di-*O*-[(*R*)-2,2,2-trichloroethylidene-2-deoxy-5(*S*),6-*O*-isopropylidene]-α/β-D-arabinohexopyranos-5-ulose (14). Compound **11** (0.5 g, 1.5 mmol) were used as for **13**. Hydrolysis of **13** happens in reaction conditions partially but when the mixture was stirred over night $NaHCO_3$ conditions only **14** could be observed. Compound **13** reacts in methanol/water (v/v = 25/1) with silver carbonate more quickly yielding in **14** within 1 hr. Purification by column chromatography yielded the syrupy product **14**.

^1H NMR (250.1 MHz, $CDCl_3$): 5.62 (d, 1H, $^3J_{1,2} = 1.6$ Hz, 1-H), 5.51 (s, 1H, acetal-H), 5.03 (t, 1H, $^3J_{3,4} = 6.8$ Hz, $^3J_{2,3} = 7.9$ Hz, 3-H), 4.92 (d, 1H, $^3J_{3,4} = 6.8$ Hz, 4-H), 4.25 (d, 1H, $^2J_{6a,6b} = 9.1$ Hz, 6a-H), 4.10 (d, 1H, $^2J_{6a,6b} = 9.1$ Hz, 6b-H), 3.16–3.29 (m, 1H, 2-H), 2.97 (broad s, 1H, OH), 1.51, 1.41 (2s, 6H, $2 \times CH_3$). $^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$): 129.7 (t, $^1J_{C,F} = 278$ Hz, CF_2Cl), 114.1 [$C(CH_3)_2$], 108.6 ($CH-CCl_3$), 103.2 (CCl_3), 99.3 (C-5), 90.8 (C-1), 73.9 (C-4), 72.2 (C-6), 71.9 (C-3), 52.8 (t, $^2J_{C\text{-}2,F} = 22$ Hz, C-2), 27.0, 25.1 ($2 \times CH_3$). $^{19}F\{^1H\}$ NMR (235.4 MHz, $CDCl_3$): −48.6 (d, $J_{Fa,Fb} = 169$ Hz), −52.3 (d, $J_{Fa,Fb} = 169$ Hz); MS: chemical ionisation (isobutane): 433.0 (Molpeak 100%). Anal. calcd for $C_{12}H_{14}Cl_4F_2O_6$ (434.04): C, 33.21, H, 3.25, found C, 33.47, H, 3.52.

1-*O*-Acetyl-2-*C*-chlorodifluoromethyl-3,4-di-*O*-[(*R*)-2,2,2-trichloroethylidene-2-deoxy-5(S),6-O-isopropylidene]-D-arabinohexopyranos-5-ulose (15). Compound **14** (100 mg, 0.23 mmol) was dissolved in pyridine (5 mL) and acetic anhydride (5 mL) and was stirred at 20°C over night. Evaporation to dryness and column chromatography gave **15** as anomeric mixture ($\alpha/\beta = 1/2$).

α-Anomer of **15**: ^1H NMR (250.1 MHz, $CDCl_3$): 6.53 (dd, 1H, $^4J_{1,F} = 0.6$ Hz, $^3J_{1,2} = 2.2$ Hz, 1-H), 5.53 (s, 1H, acetal-H), 5.06 (t, 1H, $^3J_{3,4} = 6.9$ Hz, 3-H), 4.72 (d, 1H, $^3J_{3,4} = 6.9$ Hz, 4-H), 4.27 (d, 1H, $^2J_{6a,6b} = 9.2$ Hz, 6a-H), 4.13 (d, 1H, $^2J_{6a,6b} = 9.2$ Hz, 6b-

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

H), 3.45–3.57 (m, 1H, 2-H), 2.06 (s, 3H, C(O)CH_3), 1.53, 1.43 (2s, 6H, 2 × CH_3). $^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$): 168.3 (C═O), 127.2 (t, $^1J_{C,F} = 278$ Hz, CF_2Cl), 113.6 [$C(CH_3)_2$], 109.6 ($CH-CCl_3$), 103.2 (C-5), 99.2 (CCl_3), 87.2 (C-1), 74.7 (C-4), 72.4 (C-6), 71.8 (C-3), 51.5 (t, $^2J_{C\text{-}2,F} = 22.5$ Hz, C-2), 26.8, 25.6 (2 × CH_3), 20.9 [C(O)CH_3]. $^{19}F\{^1H\}$ NMR (235.4 MHz, $CDCl_3$): −52.3 (d, $^2J_{Fa,Fb} = 170$ Hz, Fa), −54.9 (d, $^2J_{Fa,Fb} = 170$ Hz, Fb).

β-Anomer of **15**: ^1H NMR (250.1 MHz, $CDCl_3$): 6.27 (d, 1H, $^3J_{1,2} = 8.1$ Hz, 1-H), 5.52 (s, 1H, acetal-H), 4.91 (t, 1H, $^3J_{3,4} = 7.8$ Hz, 3-H), 4.49 (d, 1H, $^3J_{3,4} = 7.8$ Hz, 4-H), 4.23 (d, 1H, $^2J_{6a,6b} = 8.4$ Hz, 6a-H), 4.08 (d, 1H, $^2J_{6a,6b} = 8.4$ Hz, 6b-H), 3.45–3.57 (m, 1H, 2-H), 2.08 [s, 3H, C(O)CH_3], 1.55, 1.45 (2s, 6H, 2 × CH_3). $^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$): 169.2 (C═O), 129.1 (t, $^1J_{C,F} = 298$ Hz, CF_2Cl), 114.3 [$C(CH_3)_2$], 109.0 ($CH-CCl_3$), 103.3 (C-5), 99.3 (CCl_3), 87.3 (C-1), 74.3 (C-4), 72.4 (C-6), 71.8 (C-3), 53.4 (t, $^2J_{C\text{-}2,F} = 22.5$ Hz, C-2), 26.7, 25.5 (2 × CH_3), 20.9 [C(O)CH_3]. $^{19}F\{^1H\}$ NMR (235.4 MHz, $CDCl_3$): −52.3 (d, $^2J_{Fa,Fb} = 174$ Hz, Fa), −54.9 (d, $^2J_{Fa,Fb} = 174$ Hz, Fb); α/β-**15**: GC-MS (for anomeric mixture): (30 eV): 2 compounds found with closed retention times. Both show same mass spectra: 475.0 (Molpeak, isotopic signal for four chlorine atoms). Anal. calcd for $C_{14}H_{16}Cl_4F_2O_7$ (476.08): C, 35.32, H, 3.39, found C, 35.42, H, 3.60.

2-*C*-Chlorodifluoromethyl-2-deoxy-3,4-di-*O*-[(*R*)-ethylidene-5(*S*),6-*O*-isopropylidene]-α/β-D-arabino-hexopyranos-5-ulose (16). Compound **12** (1.85 g, 8.1 mmol) were used as for **13**. Hydrolysis of the intermediate glycosyl bromide happens in reaction conditions when the mixture is stirred over night in basic conditions. Purification by column chromatography yielded **16**.

^1H NMR (250.1 MHz, $CDCl_3$): 5.56 (m, 1H, 1-H), 5.50 (q, 1H, $^3J_{H,CH3} = 4.9$ Hz, acetal-H), 4.76 (dd, 1H, $^3J_{3,4} = 7.2$ Hz, $^3J_{2,3} = 9.0$ Hz, 3-H), 4.51 (d, 1H, $^3J_{3,4} = 7.2$ Hz, 4-H), 4.18 (d, 1H, $^2J_{6a,6b} = 9.0$ Hz, 6a-H), 4.01 (d, 1H, $^2J_{6a,6b} = 9.0$ Hz, 6b-H), 3.04–3.34 (m, 1H, 2-H), 3.13 (broad s, 1H, OH), 1.48 (s, 3H, CH−CH_3), 1.35, 1.34 (2s, 6H, 2 × CH_3). $^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$): 127.8 (t, $^1J_{C,F} = 295$ Hz, CF_2Cl), 112.8 [$C(CH_3)_2$], 104.0 ($CH-CH_3$), 102.3 (C-5), 89.9 (C-1), 73.1 (C-3), 72.9 (C-4), 69.3 (C-6), 51.9 (t, $^2J_{C\text{-}2,F} = 22$ Hz, C-2), 27.2, 25.4 (2 × CH_3), 20.8 (acetal-CH_3). $^{19}F\{^1H\}$ NMR (235.4 MHz, $CDCl_3$): −50.2 (d, $^2J_{Fa,Fb} = 169$ Hz), −53.4 (d, $^2J_{Fa,Fb} = 169$ Hz). Anal. calcd for $C_{12}H_{14}Cl_4F_2O_6$ (330.71): C, 43.58, H, 5.18, found C, 43.80, H, 5.51.

1-*O*-Acetyl-2-*C*-chlorodifluoromethyl-2-deoxy-3,4-di-*O*-[(*R*)-ethylidene-5(*S*),6-*O*-isopropylidene]-α/β-D-arabinohexopyranos-5-ulose (17). Compound **16** (910 mg, 0.23 mmol) was dissolved in pyridine (20 mL) and acetic anhydride (20 mL) and was stirred at 20°C over night. Evaporation to dryness and column chromatography gave **17** as anomeric mixture ($\alpha/\beta \approx 0.9/1$).

β-Anomer of **17**: ^1H NMR (250.1 MHz, $CDCl_3$): 6.49 (dd, 1H, $^4J_{1,F} = 0.6$ Hz, $^3J_{1,2} = 2.1$ Hz, 1-H), 5.52 (q, 1H, $^3J_{H,CH3} = 4.9$ Hz, acetal-H), 4.75 (dd, 1H, $^3J_{3,4} = 7.2$ Hz, $^3J_{2,3} = 8.9$ Hz, 3-H), 4.42 (d, 1H, $^3J_{3,4} = 7.2$ Hz, 4-H), 4.08–4.23 (m, 2H, 6a-H, 6b-H), 3.39–3.50 (m, 1H, 2-H), 2.05 (d, 3H, $^3J_{H,CH3} \approx 4.9$ Hz, acetal-CH_3), 1.54, 1.40 (2s, 6H, 2 × CH_3). $^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$): 169.3 (C═O), 129.4 (t, $^1J_{C,F} = 297$ Hz, CF_2Cl), 114.1 [$C(CH_3)_2$], 104.3 ($CH-CH_3$), 102.5 (C-5), 87.8 (C-1), 73.0 (C-4), 72.6 (C-6), 71.3 (C-3), 51.2 (t, $^2J_{C\text{-}2,F} = 23$ Hz, C-2), 26.9, 25.5 (2 × CH_3), 20.9 [C(O)CH_3]. $^{19}F\{^1H\}$ NMR (235.4 MHz, $CDCl_3$): −50.8 (d, $^2J_{Fa,Fb} = 172$ Hz, Fa), −53.8 (d, $^2J_{Fa,Fb} = 172$ Hz, Fb).

α-Anomer of **17**: ^1H NMR (250.1 MHz, $CDCl_3$): 6.24 (d, 1H, $^3J_{1,2} = 8.5$ Hz, 1-H), 5.37 (q, 1H, $^3J_{Hac,CH3} = 4.9$ Hz, acetal-H), 4.62 (dd, 1H, $^3J_{3,4} = 8.0$ Hz, $^3J_{2,3} = 9.2$ Hz, 3-H),

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

4.08–4.23 (m, 3H, 4-H, 6a-H, 6b-H), 3.26–3.42 (m, 1H, 2-H), 2.05 (d, 3H, $^{3}J_{H,CH3} = 4.9$ Hz, $CHCH_3$), 1.51, 1.37 (2s, 6 H, 2 × CH_3). $^{13}C\{^{1}H\}$ NMR (62.9 MHz, $CDCl_3$): 168.5 (C═O), 127.6 (t, $^{1}J_{C,F} = 294$ Hz, CF_2Cl), 113.3 [$C(CH_3)_2$], 104.1 ($CH-CH_3$), 102.5 (C-5), 87.8 (C-1), 72.9 (C-4), 72.5 (C-6), 69.3 (C-3), 50.6 (t, $^{2}J_{C\text{-}2,F} = 23$ Hz, C-2), 26.8, 25.3 (2 × CH_3), 20.8 [C(O)CH_3]. $^{19}F\{^{1}H\}$ NMR (235.4 MHz, $CDCl_3$): −50.8 (d, $^{2}J_{Fa,Fb} = 172$ Hz, Fa), −53.8 (d, $^{2}J_{Fa,Fb} = 172$ Hz, Fb). Anal. calcd for $C_{14}H_{19}ClF_2O_7$ (372.75): C, 45.11, H, 5.14, found C, 45.93, H, 5.40.

ACKNOWLEDGMENTS

The authors are grateful to Prof. Dr. Manfred Michalik (Leibniz-Institut fuer Organische Katalyse Rostock) for recording the NMR spectra and helpful discussions and to Claudia Vinke for technical assistance.

REFERENCES

1. Tews, S.; Miethchen, R.; Reinke, H. Stereoselective synthesis and reactivity of 2-chlorodifluoromethyl-substituted monosaccharides. Synthesis **2003**, 707–716.
2. Baasner, B.; Hagemann, H.; Tatlow, J.C., Eds. Organofluorine compounds. In *Houben-Weyl, Methods of Organic Chemistry*; Thieme-Verlag: Stuttgart, 1999/2000; Vol. E 10a-c, and papers cited therein.
3. Frank, M.; Miethchen, R.; Degenring, D. D-Tagatose derivatives from D-fructose by a facile epimerisation procedure. Carbohydr. Res. **1999**, *318*, 167–170.
4. Miethchen, R. Epimerization by non-classical acetalization—a new three component reaction for carbohydrates and inositols. J. Carbohydr. Chem. **2003**, *22*, 801–825.
5. Huang, W.-Y. Perfluoroalkylation initiated with sodium dithionite and related reagent systems. J. Fluorine Chem. **1992**, *58*, 1–8.
6. Wu, F.-H.; Huang, B.N.; Lu, L.; Huang, W.-Y. Addition reactions of dibromodifluoromethane promoted by sulfinatodehalogenation reagents. J. Fluorine Chem. **1996**, *80*, 91–94.
7. Huang, W.-Y.; Wu, F.-H. The sulfinatodehalogenation reaction. Israel J. Chem. **1999**, *39*, 167–170, and papers cited therein.
8. Plenkiewicz, H.; Dmowski, W.; Lipinski, M. Sodium dithionite initiated reactions of Halothane with enol ethers. Facile synthesis of 3-trifluoromethyl substituted vinyl carbonyl compounds. J. Fluorine Chem. **2001**, *111*, 227–232, and papers cited therein.
9. Huang, W.-Y.; Xie, Y. Studies on sulfinatodehalogenation. XIII. Synthesis of 2-perfluoroalkyl-2-deoxy-D-glucose, mono- and poly-*O*-polyfluoroalkylated-D-glucoses. Chinese J. Chem. **1991**, *9*, 351–359; Chem. Abstr. **1992**, *116*, 106596.
10. Zur, C.; Miethchen, R. Organofluorine compounds and fluorinating agents, 19. Dithionite-catalysed addition of perfluoroalkyl iodides to unsaturated carbohydrates. Eur. J. Org. Chem. **1998**, 531–539.
11. Miethchen, R.; Hein, M.; Reinke, H. Organofluorine compounds and fluorinating agents, 22 A new method for the selective introduction of difluoromethyl and trifluoromethyl groups into sugar moieties. Eur. J. Org. Chem. **1998**, 919–923.

12. (a) Cremer, D.; Pople, J.A. A general definition of ring puckering coordinates. J. Am. Chem. Soc. **1975**, *97*, 1354–1358; (b) Cremer, D.; Pople, J.A. Molecular orbital theory of the electronic structure of organic compounds. XXIII. Pseudorotation in saturated five-membered ring compounds. J. Am. Chem. Soc. **1975**, *97*, 1358–1367.
13. Garregg, P.J.; Samuelsson, B. Novel reagent system for converting a hydroxy-group into an iodo-group in carbohydrates with inversion of configuration. J. Chem. Soc. Perkin 1 **1980**, 2866–2869.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016