Reactions of 2-Hydroxy-6,8-dioxabicyclo[3.2.1]oct-3-ene with Diethylaminosulfur Trifluoride and with Halogens. Facile Synthesis of 1,6-Anhydrohalohexopyranoses

Franz Oberdorfer,* Roland Haeckel, Gilbert Lauer

Deutsches Krebsforschungszentrum, Abteilung Radiochemie, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany
Phone +49(6221)422443; Fax +49(6221)422572; E mail: f.oberdorfer@dkfz-heidelberg.de

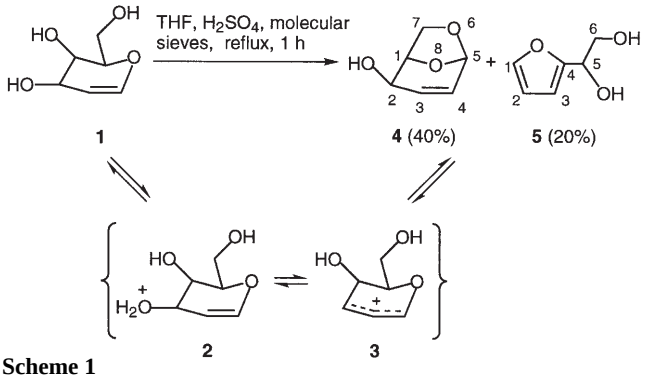
Received 31 July 1997

Abstract: D-Galactal **1** reacts in THF in the presence of catalytic amounts of concentrated sulfuric acid to give (2*R*)-2-hydroxy-6,8-dioxabicyclo[3.2.1]oct-3-ene (**4**) in a Ferrier-type rearrangement in 40% yield. When **4** is treated with diethylaminosulfur trifluoride (DAST) under certain reaction conditions, a novel intramolecular second order allylic rearrangement follows leading to previously unknown diastereomeric monofluoro derivatives **7** and **8**. Direct α-substitution of **4** by DAST affords the 2-monofluoro derivative **6** under kinetic control. When DAST is used with dimethylformamide as solvent an apparent [1,3] sigmatropic migration of the 2-hydroxy group of **4** gives (4*S*)-4-hydroxy-6,8-dioxabicyclo[3.2.1]oct-2-ene (**9**). The corresponding 4-fluoro-substituted product was not obtained from the reaction of **9** with DAST. Oxidation of **4** and repeated treatment with DAST gives a novel 2,2-difluoro compound **11.** Electrophilic addition of bromine to protected **4** afforded the 1,6-anhydromonobromo- and -dibromohexopyranoses **15–17**. Monohalo and monopseudohalo derivatives (-F, -Cl, -Br, -N_3) **22-25** were prepared by nucleophilic oxirane ring opening of the easily available *endo*-epoxides **18–20**.

Key words: diethylaminosulfur trifluoride, glycal rearrangement, dioxabicyclooctenes, 1,6-anhydrohalohexopyranoses, hexose epoxides

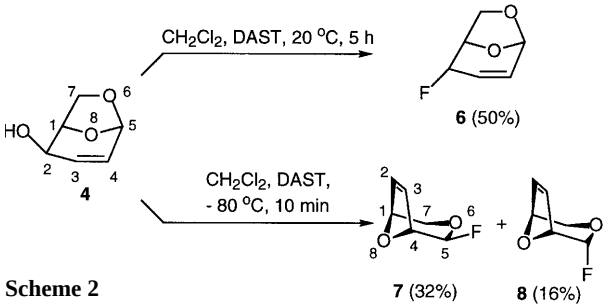
Various methods for preparation of 1,6-anhydrohexopyranoses have been reported[1] including thermal degradation of polysaccharides,[2] cyclization and Lewis acid mediated cyclization of hexopyranoses,[3] and total syntheses by the Diels–Alder reaction of acrolein derivatives[4] following, in principle, the Lewis acid catalyzed diene aldehyde cyclocondensation.[5] The resulting products are generally useful starting materials for a variety of syntheses.[1–7] Locked in the $^1C_4$ conformation, such 1,6-anhydrohexopyranoses are quite rigid structures which offer special advantage for the stereoselective introduction of functional groups at carbohydrate ring positions 2 to 4 while the 1- and 6-hydroxy functions are protected by the anhydro bridge. The 1,6-anhydro bridge is stable in basic media, but is cleaved readily under acidic aqueous conditions. Numerous halogenated dioxabicyclooctanes,[8] as well as dioxabicyclooctanones and -octenones,[9] hiding the carbohydrate configuration have been prepared, mostly by multistep procedures, for their use in stereoselective synthesis and in the chiron approach of assembly of more complex molecules.[10] Among the halohexopyranoses especially attractive are fluoro-substituted sugars,[11] with one or more fluorine atoms at specific molecular sites, as synthetic analogs of natural products with pharmacological activity. In particular, 4-deoxy-4-fluoro-D-glucose is expected to act as a chain terminating agent in glycogen synthesis and has potential in the treatment of glycogen storage diseases. The fluorinated analog of galactose, 2-deoxy-2-fluoro-D-galactose, may be utilized in cancer diagnosis and treatment as a uridylate trapping chemotherapeutic drug.[12] It also impairs *N*-glycosylation of membrane and secretory glycoproteins.[13] We now demonstrate within this work a relatively simple and short preparative route for building chiral centers at hexose carbon positions 2–4, and to a wide variety of 1,6-anhydrohalohexopyranoses, starting from glycals.

A Ferrier-type rearrangement of glycals[14] was applied for the introduction of the 1,6-anhydro bridge into the hexopyranoses. Usually this acid-catalyzed reaction delivers 2,3-unsaturated monocyclic pseudoglycals, but it can be readily diverted to an intramolecular pathway. The strict absence of a nucleophile, including water, and highly diluted conditions are necessary. We previously reported on this novel glycal rearrangement in the case of D-glucal.[15] On treatment of D-galactal **1** in THF in the presence of a small quantity of concentrated sulfuric acid and molecular sieves, compound **4** was formed through the cyclic allylic oxocarbenium ion **3** within 1 hour with 40% yield,[16] together with the expected 2-(D-glycero-1,2-dihydroxyethyl)furan[17] (**5**) (Scheme 1). The presence of copper(II) sulfate, as with D-glucal, or the presence of any other Lewis acid, gave either no reaction at all, or led to the exclusive formation of **5**.



Scheme 1

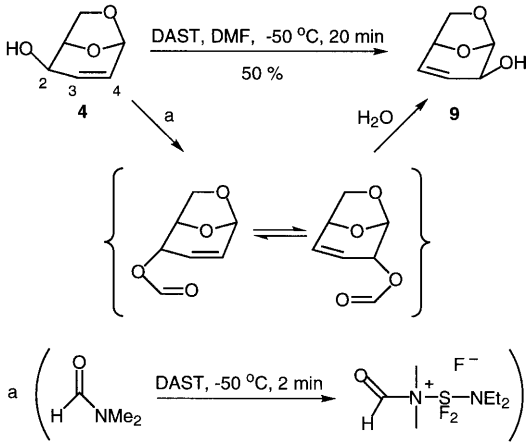
Compound **4** was then reacted with DAST in dichloromethane at low temperature (–80 °C). The expected fluorinated compound **6** was obtained together with the novel diastereomeric fluoro-substituted dioxabicyclooctenes **7** and **8** (Scheme 2). Formation of **7** and **8** could be suppressed successfully at room temperature giving exclusively **6** in 50% yield. Although rearrangements in carbohydrate ring systems in presence of DAST are well known,[18] it was a surprising observation to us that **4** rearranged in the presence of DAST at a low temperature. It seemed that, after an initial attack of DAST at the 2-hydroxy substituent, a second order allylic rearrangement took place where the oxygen atom of the 6-membered ring attacked the 3,4-double bond by the σ-route. Fluoride finally entered the 5-position of **4** from the two possible sides which delivered the diastereomeric compounds **7** with fluorine in the equatorial position and **8** with the fluorine in



Scheme 2

the axial position in a 2:1 ratio. The structures of **7** and **8** were identified by COSY and NOE experiments.

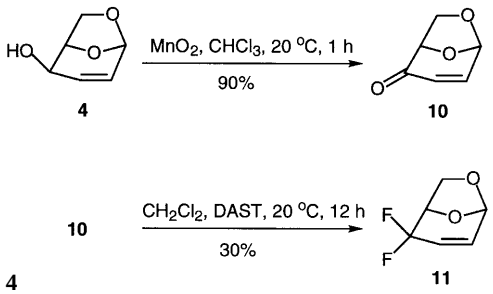
Addition of 2 equivalents of DAST to **4** in DMF as solvent at –50 °C afforded the known compound **9**[19] by a formally suprafacial [1,3] sigmatropic migration of the hydroxy group. This reaction should be a thermally forbidden process and suggested a mechanism by which the solvent was utilized as a support reactant. The reaction probably involved initial quaternization of the amide by DAST. The resulting ion-pair intermediate was then attacked at the carbonyl group by the 2-hydroxy group of **4** yielding the respective formate. A hetero-Cope rearrangement followed and delivered **9** after hydrolysis in 50% yield (Scheme 3). Formate intermediates may be isolated and characterized.[20] It is quite interesting in this case that DAST may be used together with an acid amide as an acylating reagent.



Scheme 3

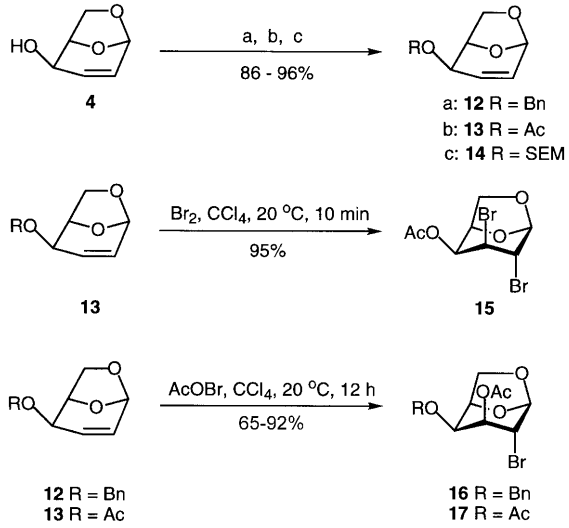
The reaction of an oxo group with DAST was expected to result in difluorination of the carbonyl carbon.[21] We, therefore, readily oxidized **4** to **10** using MnO_2 in $CHCl_3$ following a procedure described by Köll et al.[22] Subsequent treatment of **10** with DAST delivered the novel difluoro derivative **11** (Scheme 4). It was identified by its ^1H, ^{13}C and ^{19}F NMR spectra. The geminal coupling constant for the CF_2 group was 280 Hz.

Protection of **4** with groups of different chemical properties allowed the study of subsequent electrophilic reactions of the dioxabicyclooctene molecule. Following this route we prepared the dibromo compound **15** in a stereoselective reaction of **13** with bromine in only ten minutes and in very good yield (95%). Treatment of compounds



Scheme 4

12 and **13** with acetyl hypobromite in CCl_4 gave monobromo derivatives **16** and **17** (Scheme 5). Compound **14** reacted analogously without significant difference. The formation of a *trans*-diequatorial product was never observed. Fluorine, chlorine and iodine either did not add to the double bond or gave very complex product mixtures which were not analyzed, No reaction occurred with acetyl hypofluorite and acetyl hypochlorite. The brominated derivatives were obtained in 65–92% yield, typically within 12 hours at room temperature.

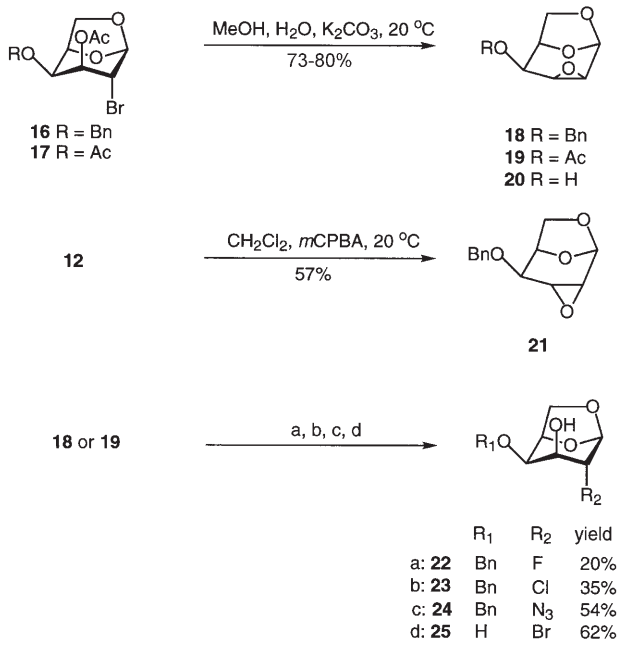


SEM = 2-(trimethylsily)ethoxymethyl
a) BnBr, NaH, DMF, 20 °C, 0.5 h. b) Ac_2-O, pyridine, 20 °C, 12 h. c) SEMCl, *i*-Pr_2NH, 20 °C, 3 h.

Scheme 5

Compounds **16** and **17** were transformed quantitatively into the corresponding bromohydrins and subsequently into the *endo*-epoxides **18**, **19** and **20** in 73–80% yield.[16] The *exo*-epoxide **21** was prepared by a Prilezaev reaction of **12** with almost water-free *m*-chloroperoxybenzoic acid (*m*CPBA) in CH_2Cl_2.[16] Epoxides **18** and **19**, and the respective epimers derived from glucal,[15, 22] were used to prepare 1,6-anhydrohalohexopyranoses (halo = fluoro, chloro, bromo) by nucleophilic opening of the oxirane.[1, 8] Compound **19** lost its acetyl group during the reaction with KBr yielding immediately **25** (Scheme 6).

Acidic cleavage of the 1,6-anhydro bridge of **25** with HCl afforded 2-bromo-2-deoxy-D-galactose which is expected to act as a therapeutic and diagnostic uridylate trapping tool in cancer treatment like its fluoro analog,[12] also prob-



a) KHF_2, ethylene glycol, reflux, 24 h. b) 1,1,2,2-tetrachloroethane, reflux, 12 h. c) NaN_3, EtOH, reflux, 48 h. d) KBr, MeCN, reflux, 3 h

Scheme 6

ably exhibiting radiosensitizing properties. We have presently used this method as a most suitable procedure for the preparation of [$^{80\,m}$Br]-labeled 2-bromo-2-deoxy-D-galactose (half life of $^{80\,m}$Br 4.42 h, γ, ^{80}Br 17.6 min, ≈ 3% β^+) which is applied in tracer kinetic studies of liver galactose metabolism. Pseudohalohexopyranoses may be obtained as well by this procedures, yet only one example is presented in this work by the azido derivative **24**.

Reactions were monitored by TLC with Polygram Sil G/UV 254 (Machery & Nagel). Silica gel (Merck, Kieselgel 60) was used for flash column chromatography. Chemicals were purchased from AIdrich, Sigma or Fluka. Mass spectra (MS) and high resolution mass spectra (HRMS) were measured with a Varian MAT 711 device.

^{1}H, ^{13}C and ^{19}F NMR were measured with Bruker AC-250 and AM-500 spectrometers at the spectroscopy department of the German Cancer Reserch Center; difluorotetrachloroethane and TFA were used as reference for ^{19}F NMR shifts. Spectroscopic data of carbohydrate ring positions are presented in Tables 1 to 4. Chemical shifts of protecting groups are given with the respective preparation procedure (compounds **12–25**). Stereocenters involved in a configuration change were marked by *R* or *S*. Carbohydrate-derived names of products are noted in parentheses.

(2*R*)-2-Hydroxy-6,8-dioxabicyclo[3.2.1]oct-3-ene (1,6-Anhydro-2,3-dideoxy-β-D-*threo*-hex-2-enopyranose, 4):[4]

D-Galactal **1** (0.453 g, 3.1 mmol) was dissolved in THF (45 mL) in the presence of molecular sieves (0.4 nm, 5 g). H_2SO_4(ϱ = 1.84, 0.1 mL) was added and the mixture was refluxed for 1 h, then allowed to reach r.t. It was treated with Et_3N (1 mL) and filtered. The solvent was evaporated and the brown residue purified by flash chromatography (CH_2Cl_2/EtOAc 4:1). Compound **4** eluted first and was obtained as a colorless oil (0.159 g, 40%). The second fraction contained **5** as a colorless oil (0.079 g, 20%).

4: R_f = 0.73 (EtOAc).

Anal. $C_6H_8O_3$ calcd: C 56.25, H 6.29; found: C 56.20, H 6.22.

HRMS: calcd 128.0473 ; found 128.047.

5[17]: R_f = 0.64 (EtOAc).

Anal. $C_6H_8O_3$ calcd: C 56.25, H 6.29; found: C 56.15, H 6.20.

(2*S*)-2-Fluoro-6,8-dioxabicyclo[3.2.1]oct-3-ene (1,6-Anhydro-2,3-dideoxy-4-fluoro-β-D-*erythro*-hex-2-enopyranose, 6):

4 (0.060 g, 0.47 mmol) was dissolved in CH_2Cl_2 (3 mL). KF (0.015 g, 0.26 mmol), K_2CO_3 (0.015 g, 0.11 mmol) and DAST (ϱ = 1.222, 0.125 mL, 0.95 mmol) were added. The solution was stirred for 5 h at 20°C. Sat. Na_2CO_3 (0.5 mL) was added. The organic layer was separated and evaporated. Purification by flash chromatography (hexane/EtOAc 9:1) gave **6** (0.030 g, 50%) as a colorless oil; R_f = 0.27 (hexane/EtOAc 4:1).

Anal. $C_6H_7FO_2$ calcd: C 55.41, H 5.42, F 14.60; found: C 55.50, H 5.40, F 14.50.

HRMS: calcd 130.0430; found 130.044.

(1*R*,2*S*)-2-Fluoro-3,8-dioxabicyclo[3.2.1]oct-6-ene (7) and (1*R*,2*R*)-2-Fluoro-3,8-dioxabicyclo[3.2.1]oct-6-ene (8):

DAST (0.4 mL, 3 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to –80°C. **4** (0.333 g, 2.6 mmol) was dissolved in CH_2Cl_2 (2 mL) and added. After 10 min the solvents were evaporated and the crude products were purified by flash chromatography (hexane/EtOAc 9:1) giving **7** (0.107 g, 32%) and **8** (0.054 g, 16%) as colorless oils.

7: R_f = 0.21 (toluene/CH_2Cl_2/hexane 1:1:1).

Anal. $C_6H_7FO_2$ calcd: C 55.41, H 5.42, F 14.60; found: C 55.75, H 5.50, F 14.55.

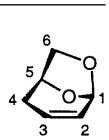
8: R_f = 0.26 (hexane/EtOAc 9:1).

Anal. $C_6H_7FO_2$ calcd: C 55.41, H 5.42, F 14.60; found: C 55.64, H 5.31, F 14.72.

Table 1. ^{1}H NMR Data (250 MHz, $CDCl_3$)[a]

Compound	H-1	H-2	H-3	H-4	H-5	H-6a[b]	H-6b[b]
4[c]	5.51	5.89	5.71	4.82	4.52	3.91	4.19
6	5.53	6.71	5.83	4.40	4.80	3.34	3.88
7	5.83	4.60	6.48	6.78	4.76	3.18	3.89
8	5.41	4.51	6.59	6.78	4.66	3.40	4.35
9[c]	5.52	4.67	6.03	5.85	3.66	3.46	3.95
10	5.78	6.08	7.10	–	4.75	3.63	4.08
11	5.57	6.24	5.78	–	4.65	3.83	3.95
12	5.49	5.88	5.79	4.55	4.55	3.86	4.25
13	5.54	5.97	5.68	5.75	4.66	3.92	4.16
14	5.49	5.87	5.73	4.65	4.75	3.90	4.21
15	5.59	4.52	4.55	4.91	5.17	3.76	4.72
16	5.41	3.87	5.51	4.06	4.38	3.65	4.38
17	5.52	3.95	5.48	5.48	4.50	3.78	4.41
18	5.63	3.53	3.28	3.99	4.36	3.56	4.13
19	5.69	3.58	3.40	5.52	4.49	3.64	4.05
20c	5.67	3.62	3.36	4.26	4.42	3.62	4.01
21	5.56	3.11	3.01	3.96	4.37	3.74	4.17
22c	5.47	4.50	4.13	4.46	3.64	3.87	4.26
23c	5.34	3.64	to 3.75	4.45	3.70	to 3.77	4.07
24c	5.42	3.57	4.07	4.44	3.65	3.81	4.32
25c	5.47	4.03	4.18	4.18	4.42	3.65	4.52

[a] Signal assignments were made according to the original carbohydrate notation. A carbohydrate-derived nomenclature of compounds is given in the experimental part. Chemical shifts are relative to 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propanonic acid (TSP). Only ring protons are considered. Most of the spectra could be analyzed by simple inspection. Compounds which contain protecting groups often show overlapping protons and are strongly second order. These signals were not completely analyzed and the chemical shift values are the midpoints of nearly first order multiplets. For chemical shifts of protecting groups, see experimental part (compounds **12-19**, **21–24**).



[b] Indices a and b denote *exo*- and *endo*-protons at C-6.

[c] δ = OH: **4**: 1.81; **9**: 2.48; **20**: 2.43; **22**: 2.72; **23**: 2.22; **24**: 2.81; **25**: 2.73 (2 H).

Table 2. Coupling Constants J_{HH} (Hz)[a]

Compound	$^3J_{1,2}$	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,6a}$	$^3J_{5,6b}$	$^3J_{6,6}$
4	3.0	9.7	2.0	4.7	6.0	2.0	8.1
6	3.4	9.6	4.5	1.5	6.7	1.8	8.0
7	3.0	5.4	8.2	5.6	0.7	2.7	8.1
8	1.5	5.5	8.1	5.1	1.1	2.2	8.8
9	3.4	3.8	9.6	4.3	6.5	2.1	7.9
10	1.3	9.8	–	–	6.3	1.5	8.2
12	2.9	9.7	1.8	m	≈ 4.5	≈ 1.7	7.7
13	3.1	9.6	4.7	3.4	5.9	2.0	8.0
14	3.0	9.7	3.0	≈ 3.8	5.6	1.3	7.7
15	1.1	2.6	3.4	4.9	5.0	1.0	7.9
16	2.0	1.3	5.0	3.9	5.2	1.1	7.3
17	1.4	1.4	5.1	5.0	5.0	0.7	7.5
18	2.9	4.0	3.0	6.0	6.0	1.6	7.2
19	2.9	4.0	3.0	6.1	6.1	1.6	7.3
21	0.6	4.0	1.0	5.2	6.2	2.0	8.1
22	1.7	1.7	5.2	5.2	3.7	0.5	7.4
23	1.8	m	≈ 3.8	≈ 5.2	5.0	≈ 0.5	7.8
24	1.3	1.5	5.3	5.3	3.8	≈ 0.3	7.7
25	1.5	1.3	2.9	2.3	4.8	≈ 0.4	7.8

[a] Couplings were obtained from the peak frequency listing and rounded to one decimal or were estimated from nearly first order multiplets in each case. Assignments are according to the carbohydrate notation (note a in Table 1). J_{HF} and long range J_{HF} couplings were observed; values are shown in Table 4.

Table 3. ^{13}C NMR Data (62.89 MHz, $CDCl_3$)$_a$

Compound	C-1	C-2	C-3	C-4	C-5	C-6
4	95.80	129.15	128.35	75.25	67.87	62.25
6	95.20	133.55	121.70	83.75	74.15	61.30
7	104.27	64.29	129.44	134.02	66.95	64.66
8	107.48	65.87	131.27	134.49	66.64	65.89
9	95.47	76.81	126.29	130.10	67.17	62.56
10	96.04	127.12	147.33	194.51	79.63	62.72
11	95.60	135.10	122.00	163.00	75.50	75.50
12	95.83	128.33	127.11	74.66	73.47	62.55
13	95.95	130.06	125.51	72.77	70.30	63.05
14	95.93	128.43	127.84	74.47	74.66	62.81
15	101.50	46.68	48.56	64.00	73.08	64.80
16	100.78	46.94	69.31	70.17	73.62	65.21
17	100.91	46.28	70.41	63.82	72.59	65.25
18	97.08	57.35	48.03	69.15	72.56	63.55
19	97.11	57.45	47.72	68.12	68.25	63.74
21	97.05	50.80	48.50	70.46	71.98	63.51
22	98.90	88.30	67.02	71.48	72.13	64.02
23	101.15	79.17	64.01	73.99	73.85	65.26
24	100.34	62.72	68.05	71.99	72.40	64.35
25	100.94	48.38	69.19	64.51	75.19	63.14

[a] For chemical shifts of protecting groups of compounds **12–19** and **21–24** see experimental part.

(4*S*)-4-Hydroxy-6,8-dioxabicyclo[3.2.1]oct-2-ene (1,6-Anhydro-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose, 9):
4 (0.120 g, 0.94 mmol) was dissolved in DMF (5 mL) and cooled to –50 °C. DAST (0.265 mL, 2 mmol) was added and the mixture was stirred for 20 min. H_2O (5 mL) was added. The solvent was evaporated and the residue was purified by flash chromatography (CH_2Cl_2/EtOAc 4:1) to give **9** (0.060 g white solid, 50%); R_f = 0.54 (EtOAc); mp 66 °C (in agreement with Lit.[19, 22]).

Table 4. ^{19}F NMR (235 MHz) Chemical Shift and Coupling Constant Data[a]

Compound	**6**	**7**	**8**	**11**	**22**
δ_F	–92.99	–40.40	–54.48	–16.85 –39.25	–115.62
J (Hz)	^2J = 47.20 ^3J = 2.57 ^3J = 1.61 ^4J = 1.80 ^5J = 0.70	^2J = 69.91 ^3J = 2.23 ^4J = 4.83 ^4J = 0.91 ^4J = 0.32 ^5J = 0.30	^2J = 68.72 ^3J = 1.55 ^4J = 3.31 ^4J = 1.40 ^4J = 0.83 ^5J = 1.10	^2J = 280.0 ^3J = 1.40 ^3J = 0.80	^2J = 44.60 ^3J = 14.22 ^3J = 3.60 ^4J = 0.60 ^5J = 0.54

[a] Chemical shifts are relative to TFA = 0 ppm. Coupling constants were obtained from the peak frequency listing of either ^{1}H or ^{19}F NMR spectra.

6,8-Dioxabicyclo[3.2.1]oct-3-en-2-one (1,6-Anhydro-2,3-dideoxy-4-oxo-β-D-*glycero*-hex-2-enopyranose, 10) and 2,2-Difluoro-6,8-dioxabicyclo[3.2.1]oct-3-ene (1,6-Anhydro-2,3,4-trideoxy-4,4-difluoro-β-D-*glycero*-hex-2-enopyranose, 11):
Compound **10** was prepared according to Lit.[22]; R_f = 0.31 (hexane/acetone 4:1). Analytical data agree. **10** (0.599 g, 4.75 mmol) was dissolved in CH_2Cl_2 (6 mL) and DAST (0.528 mL, 4 mmol) was added. The solution was stirred for 12 h. Water (5 mL) was added. The organic layer was separated and evaporated. Flash chromatography (hexane/acetone 4:1) gave **11** (0.211 g, 30%) as a colorless oil.

11: R_f = 0.45 (hexane/acetone 4:1).
Anal. $C_6H_6F_2O_2$ calcd: C 48.67, H 4.05, F 25.66; found: C 48.50, H 4.00, F 25.50.
HRMS: calcd 148.0336; found 148.058.

Preparation of *O*-Protected Derivatives of 4. Compounds 12–14:

1,6-Anhydro-4-*O*-benzyl-2,3-dideoxy-β-D-*threo*-hex-2-enopyranose (12):
Compound **4** (0.150 g, 1.17 mmol) was dissolved in DMF (5 mL). NaH (0.031 g, 1.3 mmol) was added and the mixture was stirred for 10 min. Benzyl bromide (0.2 mL, 1.68 mmol) was added. After stirring for 30 min at 20°C, H_2O (10 mL) was added. The mixture was extracted with CCl_4 (4 × 25 mL). The combined organic layers were washed, dried and evaporated. The residue was purified by flash chromatography (hexane/ EtOAc 4:1) giving **12** (0.219 g, 86%) as a colorless oil; R_f = 0.47 (hexane/acetone 4:1).

Anal. $C_{13}H_{14}O_3$ calcd: C 71.54, H 6.45; found: C 71.06, H 6.30.
HRMS: calcd 218.0943 ; found 218.238.
^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.55 (m, 3H, H-aCH_2, H-4, H-5), 4.66 (d, 1H, H-bCH_2, $^1J_{a,b}$ = 11.9 Hz), 7.33 (m, 5H, arom.).
^{13}C NMR (62,89 MHz, $CDCl_3$): δ = 71.10 (-CH_2Ph), 127.45, 127.76, 128.10 (arom.), 137.70 (arom.).

4-*O*-Acetyl-1,6-anhydro-2,3-dideoxy-β-D-*threo*-hex-2-enopyranose (13):
Stirring of **4** (0.220 g, 1.72 mmol) in pyridine (3 mL) and Ac_2O (2.8 mL) for 12 h afforded the acetate **13** (0.278 g, 95%) as a colorless oil, following standard workup and flash chromatography (CH_2Cl_2/EtOAc 4:1); R_f = 0.66 (hexane/EtOAc 1:1).

Anal. $C_8H_{10}O_4$ calcd: C 56.44, H 5.87; found: C 56.35, H 5.75.
HRMS: calcd 170.0579; found 170.059.
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.09 (s, 3H, H-CH_3).
^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 20.91 (-CH_3), 170.16 (C=O).

1,6-Anhydro-2,3-dideoxy-4-*O*-[2-(trimethylsilyl)ethoxymethyl]-β-D-*threo*-hex-2-enopyranose (14):
i-Pr_2NH (ϱ = 0.772, 0.525 mL, 4 mmol) and SEMCl (ϱ = 0.942, 4 mL, 22.6 mmol) were added to a solution of **4** (0.210 g, 1.64 mmol) in

CH_2Cl_2 (2 mL). The mixture was stirred for 3 h, then water (20 mL) was added. The organic layer was separated and evaporated. Flash chromatography (hexane/EtOAc 4:1) delivered **14** (0.381 g, 90%) as a colorless oil; R_f = 0.46 (hexane/EtOAc 7:3).

Anal. $C_{12}H_{22}O_4Si$ calcd: C 55.84, H 8.52; found: C 55.80, H 8.50.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.02 (s, 9H, -$SiCH_3$), 0.92 (m, 2H, H-C3′), 3.61 (m, 2H, H-C2′), 4.75 (m, 2H, H-C1′, ^3J = 11.9 Hz, ^3J = 8.0 Hz).
^{13}C NMR (62.89 MHz, $CDCl_3$): δ = –1.46 (-$SiCH_3$), 18.14 (C-3′), 65.47 (C-2′), 94.84 (C-1′).

4-*O*-Acetyl-1,6-anhydro-2,3-dibromo-2,3-dideoxy-β-D-galactopyranose (15):
Derivative **13** (0.187 g, 1.1 mmol) was dissolved in CCl_4 (2 mL). Br_2 (0.176 g, 1.1 mmol) was added at 0 °C. The reaction was complete after 10 min and the solvent was evaporated. Flash chromatography (hexane/EtOAc 9:1) delivered **15** (0.261 g, 95%) as a colorless oil; R_f = 0.70 (hexane/EtOAc 1:1).

Anal. $C_8H_{10}Br_2O_4$ calcd: C 29.10, H 3.03, Br 48.44; found: C 29.00, H 2.95, Br 48.30.
HRMS: calcd 327.8946; found 249.976 (M^+-Br).
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.15 (s, 3H, H-CH_3).
^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 20.65 (-CH_3), 167.20 (C=O).

Reaction with Acetyl Hypobromite. 3-*O*-Acetyl-1,6-anhydro-4-*O*-benzyl-2-bromo-2-deoxy-β-D-galactopyranose (16) and 3,4-Di-*O*-acetyl-1,6-anhydro-2-bromo-2-deoxy-β-D-galactopyranose (17):
Derivative **12** (0.109 g, 0.5 mmol) or **13** (0.357 g, 2.1 mmol) was dissolved in CCl_4 (5 mL). Freshly prepared acetyl hypobromite[23] was added (about 0.5 mmol for **12**; about 2.1 mmol for **13**) and the mixture was stirred for 12 h at 20°C. After addition of H_2O (5 mL), the organic layer was separated, dried and evaporated. Flash chromatography gave **16** (0.164 g, 92%, hexane/acetone 6:1) or **17** (0.422 g, 65%, hexane/EtOAc 4:1) as colorless oils.

16: R_f = 0.35 (hexane/acetone 4:1).
Anal. $C_{15}H_{17}BrO_5$ calcd: C 50.44, H 4.79, Br 22.37; found: C 50.30, H 4.61, Br 22.05.
HRMS: calcd 356.0259; found 356.025 (M^+-H).
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.04 (s, 3H, H-CH_3), 4.38 (m, 3H, H-aCH_2, H-5), 4.54 (d, 1H, H-bCH_2, $^2J_{a,b}$ = 11.9 Hz), 7.25 (m, 5H, arom.).
^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 20.90 (-CH_3), 71.79 (-CH_2PH), 127.71, 128.1, 128.54, 137.27 (arom.), 169.56 (C=O).

17: R_f = 0.18 (hexane/EtOAc 3:1).
Anal. $C_{10}H_{13}BrO_6$ calcd: C 38.86, H 4.20, Br 25.85; found: C 38.70, H 4.10, Br 25.19.
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.04, 2.08 (s, s, 6H, H-CH_3).
^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 20.54 (-CH_3), 20.73 (-CH_3), 169.07 (C=O), 169.50 (C=O).

1,6:2,3-Dianhydro-β-D-*talo*-pyranose (20) and Its *O*-Protected Analogs 18 and 19:
The bromo derivatives **16** (0.997 g, 2.8 mmol) and **17** (0.989 g, 3.2 mmol) were dissolved in MeOH/H_2O (8:1) by volume (80 mL) and K_2CO_3 (0.5 g) was added. The respective solutions were stirred for 3 d at r.t. Evaporation of solvent and chromatography (hexane/EtOAc 4:1) delivered **18** (1,6:2,3-dianhydro-4-*O*-benzyl-β-D-*talo*-pyranose; 0.524 g, 80%, colorless wax) from substrate **16**, and **20** (1,6:2,3-dianhydro-β-D-*talo*-pyranose; 0.364 g, 78%, colorless oil) from substrate **17**. Stirring of crude **20** for 12 h in pyridine (10 mL) and Ac^2O (9 mL) afforded after chromatography (hexane/EtOAc 4:1) **19** (4-*O*-acetyl-1,6:2,3-dianhydro-β-D-*talo*-pyranose; 0.440 g, 73%, colorless oil). Analytical data of **18–20** agree with Lit.[1, 16, 20, 22, 24]

18: R_f = 0.27 (hexane/acetone 4:1).
Anal. $C_{13}H_{14}O_4$ calcd: C 66.66, H 6.01; found: C 65.50, H 5.95.
HRMS : calcd 234.0892; found 234.088.
^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.67 (d, 1H, H-aCH_2, $^2J_{a,b}$ = 11.9 Hz), 4.82 (d, 1H, H-bCH_2), 7.35 (m, 5H, arom.).
^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 71.22 (-CH_2Ph), 127.70, 128.09, 128.57, 137.65 (arom.).

19: R_f = 0.43 (hexane/acetone 3:2).
Anal. $C_8H_{10}O_5$ calcd: C 51.63, H 5.37; found: C 51.40, H 5.20.
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.15 (s, 3H, H-CH_3).
^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 20.79 (-CH_3), 170.15 (C=O).

20: R_f = 0.33 (hexane/acetone 3:2).
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.43 (s, 1H, OH).

1,6:2,3-Dianhydro-4-*O*-benzyl-β-D-*gulo*-pyranose (21):
Derivative **12** (0.523 g, 2.4 mmol) was dissolved in CH_2Cl_2 (5 mL) and stirred at r.t. for 24 h in presence of anhyd *m*CPBA. Then sat. aq Na_2CO_3 was added. The mixture was evaporated nearly to dryness and the residue was extracted several times with portions of hexane/acetone (4:1, 50 mL in total). The combined extracts were concentrated. Flash chromatography (hexane/acetone 5:1) gave **21** (0.320 g, 57%) as a colorless oil; R_f = 0.39 (hexane/acetone 4:1). Analytical data compare well with **18**; $C_{13}H_{14}O_4$ found: C 66.80, H 6.12.

1,6-Anhydro-4-*O*-benzyl-2-deoxy-2-fluoro-β-D-galactopyranose (22):
Compound **18** (0.0492 g, 0.21 mmol) was dissolved in ethylene glycol (2 mL). KHF_2 (0.050 g, 0.64 mmol) was added and the mixture was refluxed for 24 h.[24] Aq 15% K_2CO_3 (15 mL) was added. It was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with water (5 mL), dried and evaporated. Flash chromatography (hexane/EtOAc 5:1) gave **22** (0.011 g, 20%) as a colorless oil; R_f = 0.43 (hexane/acetone 4:1).

Anal. $C_{13}H_{15}FO_4$ calcd: C 61.41, H 5.94, F 7.47; found: C 61.60, H 5.81, F 7.22.
HRMS: calcd 254.0954; found 254.094.
^{1}H NMR (250 MHz, $CDCl_3$): δ =2.72 (dd, 1H, OH), 4.68 (d, 2H, H-CH_2, ^2J = 11.9 Hz), 7.35 (m, 5H, arom.).
^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 72.17 (-CH_2Ph), 127.91, 128.53, 128.80, 136.96 (arom.).

1,6-Anhydro-4-*O*-benzyl-2-chloro-2-deoxy-β-D-galactopyranose (23):
A mixture of **18** (0.300 g, 1.28 mmol) and tetrabutylammonium chloride (2 mg) was refluxed in 1,1,2,2-tetrachloroethane (3 mL) for 12 h. The mixture was cooled and the solvent was evaporated. Product **23** (0.121 g, 35%) was isolated after chromatography (hexane/EtOAc gradient 7:1–4:1) as a waxy white solid; R_f = 0.35 (hexane/EtOAc 4:1).

Anal. $C_{13}H_{15}ClO_4$ calcd: C 57.68, H 5.57, Cl 13.09; found: C 57.77, H 5.41, Cl 13.35.
HRMS: calcd 235.0970; found 235.097 (M^+-Cl).
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.2 (s, 1H, OH), (d, 1H, H-aCH_2, $^2J_{a,b}$ = 11.7 Hz), 4.82 (d, 1H, H-bCH_2), 7.35 (m, 5H, arom.).
^{13}C NMR (62.89 MHz, $CDCl_3$) : δ = 76.35 (-CH_2Ph), 127.95, 128.21, 128.58, 137.42 (arom.).

1,6-Anhydro-2-azido-4-*O*-benzyl-2-deoxy-β-D-galactopyranose (24):
Substrate **18** (0.492 g, 2.1 mmol) was dissolved in EtOH (120 mL), H_2O (30 mL) and NH_4Cl (0.749 g, 14 mmol) and a large excess of NaN_3 (0.748 g, 11.5 mmol) was added. The mixture was refluxed for 48 h. Solvents were evaporated and the product was separated by flash chromatography (hexane/EtOAc 4:1) giving **24** (0.314 g, 54%) as a thick white oil; R_f = 0.20 (hexane/EtOAc 4:1).

Anal. $C_{13}H_{15}N_3O_4$ calcd: C 56.31, H 5.44, N 15.21; found: C 56.17, H 5.31, N 15.28.
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.81 (d, 1H, OH), 4.65 (d, 1H, H-aCH_2, $^2J_{a,b}$ = 11.7 Hz), 4.70 (d, 1H, H-bCH_2), 7.25-7.38 (m, 5H, arom.).
^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 72.19 (-CH_2Ph), 127.89, 128.51, 128.77, 136.92 (arom.).

1,6-Anhydro-2-bromo-2-deoxy-β-D-galactopyranose (25):
Acetate **19** (0.201 g, 1.08 mmol) was dissolved in MeCN (0.5 mL) and KBr (0.357 g, 3 mmol) was added. The mixture was refluxed for 3 h. Evaporation of the solvent followed by chromatography (hexane/

acetone 3:1) gave **25** (0.151 g, 62%) as a colorless oil; R_f = 0.46 (hexane/acetone 3:2).

Anal. $C_6H_9BrO_4$ calcd: C 32.18, H 4.02, Br 35.68; found: C 32.00, H 3.90, Br 35.30.
HRMS: calcd 223.9684; found 223.960 (M^+).
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.73 (s, 2H, OH).

(1) Cerny, M.; Stanek, J. Jr. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23.
Boons, G.-J.; Isles, S.; Setälä, P. *Synlett* **1995**, 755.
(2) Shafizadeh, F.; Furneaux, R. H.; Stevenson, T. T. *Carbohydr. Res.* **1979**, *71*, 169.
Shafizadeh, F. *Adv. Carbohydr. Chem.* **1968**, *23*, 419.
Greenwood, C. T. *Adv. Carbohydr. Chem.* **1967**, *22*, 483.
Knauf, A. E.; Hann, R. M.; Hudson, C. S. *J. Am. Chem. Soc.* **1941**, *63*, 1447.
(3) Michael, F.; Klemmer, A. *Adv. Carbohydr. Chem.* **1961**, *16*, 85.
Yamamoto, K.; Haga, M.; Tijima, S. *Chem. Pharm. Bull.* **1975**, *23*, 233.
Aberg, P.-M.; Ernst, B. *Acta Chem. Scand.* **1994**, *48*, 228.
(4) Ranganayakulu, K.; Singh, U. P.; Murray, T. P.; Brown, R. K. *Can. J. Chem.* **1974**, *52*, 988.
Murray, T. P.; Singh, U. P.; Brown, R. K. *Can. J. Chem.* **1971**, *49*, 2132.
(5) Danishefsky, S. J.; Kerwin, J. F.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.
Danishefsky, S. J.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3183.
Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59.
(6) Schuerch, C. *Acc. Chem. Res.* **1973**, *6*, 184.
(7) Bognar, R.; Farkas, I.; Menyhart, M.; Gross, H.; Paulsen, H. *Carbohydr. Res.* **1968**, *6*, 404.
(8) Podesva, J.; Pacak, J. *Chem. Listy* **1973**, *67*, 785.
(9) Kawai, T.; Isnobe, M.; Peters, S. C. *Aust. J. Chem.* **1995**, *48*, 115.
Matsumoto, M.; Ishikawa, H.; Soya, Y.; Ozawa, T. *Heterocycles* **1994**, *38*, 2377.
(10) Hanessian, S. *Total Synthesis ofNatural Products: The Chiron Approach*; Pergamon: Oxford, 1983.
(11) Tsuchiya, T. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 91.
ACS Symposium Series 374. *Fluorinated Carbohydrates, Chemical and Biochemical Aspects*; Taylor, N. F., Ed.; Am. Chem. Soc.: Washington, DC, 1988.
Card, P. J. *J. Carbohydr. Chem.* **1985**, *4*, 451.
Pacak, J.; Podesva, J.; Tozik, Z.; Cerny, M. *Collect. Czech. Chem. Commun.* **1972**, *37*, 2589.
(12) Grün, B. R.; Berger, U.; Oberdorfer, F.; Hull, W. E.; Ostertag, H.; Keppler, D. *Adv. Enzyme Reg.* **1990**, *30*, 231.
Grün, B. R.; Berger, U.; Oberdorfer, F.; Hull, W. E.; Ostertag, H.; Friedrich, E.; Lehmann, J.; Keppler, D. *Eur. J. Biochem.* **1990**, *190*, 11.
(13) Loch, N.; Geilen, C. C.; Spröndle, I.; Oberdorfer, F.; Tauber, R.; Keppler, D.; Reutter, W. *FEBS Lett.* **1991**, *294*, 217.
Geilen, C. C.; Loch, N.; Reutter, W.; Seppelt, K.; Oberdorfer, F. *Tetrahedron Lett.* **1992**, *33*, 2435.
Korytnyk, W.; Horvath, S. V.; Petri, C. R. *Tetrahedron* **1982**, *38*, 2547.
(14) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443.
Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 199.
(15) Lauer, G.; Oberdorfer, F. *Angew. Chem.* **1993**, *105*, 271; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 272.
(16) Haeckel, R.; Lauer, G.; Oberdorfer, F. *Synlett* **1996**, 21.
(17) Gonzales, F.; Lesage, S.; Perlin, A. S. *Carbohydr. Res.* **1975**, *42*, 267.
(18) Lloyd, A E.; Coe, P. L.; Walker R. T. *J. Fluorine Chem.* **1993**, *60*, 239.
Yamaguchi, T.; Hattori, K.; Ikeda, S.; Tanaka, K. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1683.
Kovac, P.; Yeh, H. J. L.; Jung, G. L.; Claudemans C. P. J. *J. Carbohydr. Chem.* **1986**, *5*, 497.
Baillargeon, D.; Reddi, G. S. *Carbohydr. Res.* **1986**, *154*, 275.
Iyer, V. K.; Horowitz, J. P. *J. Am. Chem. Soc.* **1982**, *47*, 644.
Matsumoto, K.; Ebata, T.; Koseki, K.; Kawakami, H.; Matsushita, H. *Heterocycles* **1991**, *32*, 225.[4]
A racemic mixture of **9** was obtained by Ranganayakulu et al.
(20) Lauer, G. Ph. D. Thesis, University of Heidelberg, 1995.
(21) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(22) Köll, P.; Schultek, T.; Rennecke, R.-W. *Chem. Ber.* **1976**, *109*, 337.
(23) Levine, S. G.; Wall, M. E. *J. Am. Chem. Soc.* **1959**, *81*, 2826.
(24) Cerny, M.; Pacak, J. *Collect. Czech. Chem. Commun.* **1969**, *34*, 3377.