The Use of Grignard Reagents in Carbohydrate Synthesis.[1] The Synthesis of Branched-chain Deoxy Sugars and Their Anomerizations

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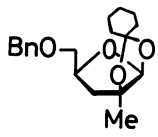
The reactions of methyl 5-*O*-benzyl-2-*O*- and -3-*O*-tosyl-β-D-ribofuranosides with methylmagnesium iodide gave, in one-step, 2-deoxy-3-*C*- and 3-deoxy-2-*C*-methyl branched-chain sugars, respectively. These sugars were anomerized with Grignard reagents; the thermodynamically more stable anomers were converted preferentially into the respective less stable anomers.

Recently, one of the authors has reported that methyl 5,6-*O*-cyclohexylidene-3-*O*-mesyl-α- and -β-D-allofuranosides reacted with Grignard reagents to give 3-deoxy or 3-deoxy-2-*C*-methyl-branched-chain sugars in one-step.[2] These reactions proceeded through 2-keto sugars which were formed *via* eliminations of the mesyloxy groups and 1,2-hydride shifts on the furanose rings. In the course of these studies, it has also been found that methyl glycofuranosides were anomerized by the use of the Grignard reagents.[3] The proposed mechanism consisted of the furanose-ring opening-reclosure by the coordination of sugar oxygens to the magnesium atoms of the reagents.

In this paper we would like to report an extention of these deoxygenation reactions to the tosylates of methyl 5-*O*-benzyl-D-ribofuranosides (**1**), and to report the anomerization of the deoxygenated products obtained therefrom.

The starting materials, methyl 5-*O*-benzyl-2-*O*- and -3-*O*-tosyl-D-ribofuranosides (**2** and **3**), were prepared from **1** by two methods **A** and **B**: the former was the conventional way and the latter involved the activation of hydroxyl groups of **1** with dibutyltin oxide.[4] The results are summarized in Scheme 1. Method **B** was superior to **A** in regioselective tosylation of the hydroxyl group at C-2 and in almost avoiding any production of 2,3-di-*O*-tosylates (**4**).

Treatment of **3**β with 3.4 mol equiv. of MeMgI gave methyl 5-*O*-benzyl-3-deoxy-2-*C*-methyl-β-D-*threo*-pentofuranoside (**5**β) and its C-2 epimer (**6**β) in 81 and 6% yields, respectively (Scheme 2). The structure of **5**β was confirmed by chemical conversion to a known compound, 5-*O*-benzyl-1,2-*O*-cyclohexylidene-3-deoxy-2-*C*-methyl-β-D-*threo*-pentofuranose (**10**).[5] The same reaction on **2**β gave methyl 5-*O*-benzyl-2-deoxy-3-*C*-methyl-β-D-*threo*-pentofuranoside (**7**β) and its C-3 epimer (**8**β) in 57 and 2.5% yields, respectively. In addition, an α-anomer (**8**α, 19%) and a small amount of an open-chain product (**9**, 5%) were isolated; these results suggested that 2-deoxy furanosides were easily anomerized under the Grignard reaction conditions. Debenzylation of **7**β afforded methyl 2-deoxy-3-*C*-methyl-β-D-*threo*-pentofuranoside (**11**), which, without further purifications, was converted into a 3,5-*O*-isopropylidene derivative (**12**), thus indicating the 3,5-*cis* structure of the hydroxyl functions of **7**β.



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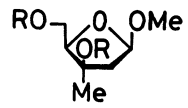
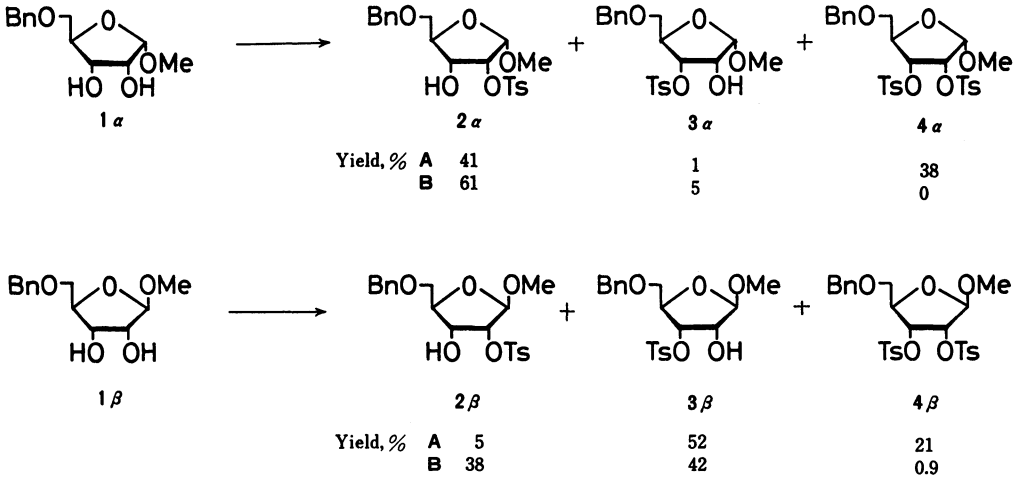
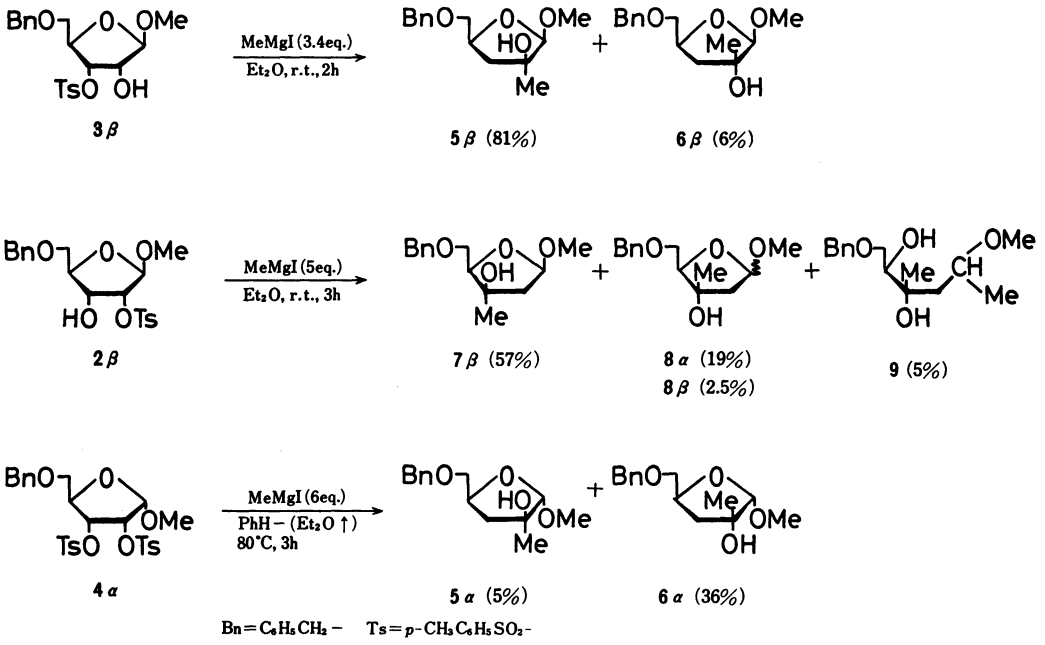


11: R=H
12: R=>C(CH₃)₂

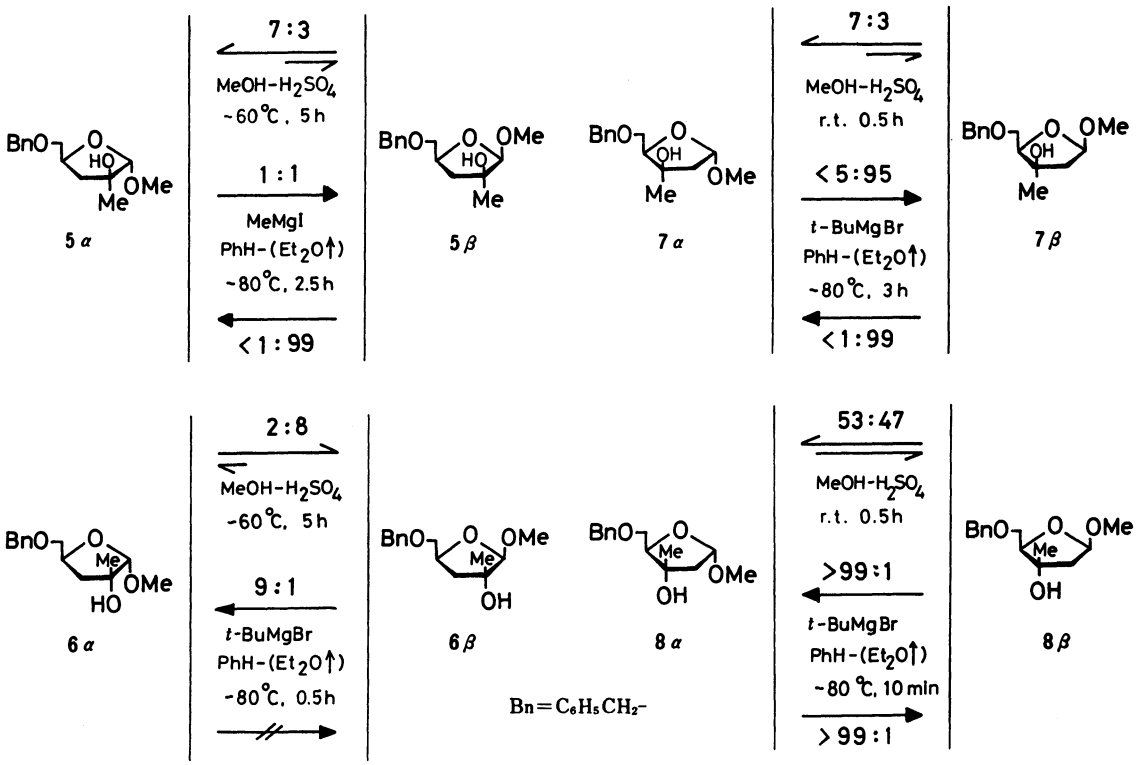


Method **A**: TsCl (1.4 equiv.), Pyr, 0 °C, 24 h.
Method **B**: 1) Bu_2SnO, MeOH; 2) TsCl (1 equiv.), Pyr–DMF–PhH, 0 °C, 50 min.
Bn=$C_6H_5CH_2$–. Ts=*p*-$CH_3C_6H_5SO_2$–.

Scheme 1.



Scheme 2.



Scheme 3.

The reaction of **2***α* with MeMgI did not proceed even under refluxing conditions: An insoluble complex was formed when **2***α* was added to the Grignard reagent.

We attempted to use the ditosylate derivatives, **4***α* and **4***β*, in the present reactions, in the hope that one of the tosyl groups would selectively be cleaved to form a monotosylate derivative, which, in turn would react with the Grignard reagent to give the deoxy compounds *via* a keto sugar. A mixture of **4***α* and MeMgI in benzene–ether was treated at *ca.* 80 °C to produce the expected compound, **6***α*, although in low yield. However, starting from **4***β*, we could not isolate any desired products.

The branched-chain deoxy sugars thus obtained were subjected to the anomerization reaction with an acid as well as with the Grignard reagents (Scheme 3). In the acidic anomerization of the 3-deoxy sugars, the anomers which have 1,2-*trans* oxygen functions always predominated over the 1,2-*cis* counterparts under equilibrating conditions because of the repulsion of the

Table 1. The physical properties and elemental analyses of the sugar derivatives

Compound	Mp θ_m/°C	$[\alpha]_D$/° (c, $CHCl_3$)	Temp/°C	Formula	Found (%) C	H	S
2α	Syrup	+54.0 (1.0)	21	$C_{20}H_{24}O_7S$[a]	58.83	5.72	7.86
2β	Syrup	−11.2 (1.0)	22		58.70	5.93	7.62
3α	Syrup	+77.4 (0.8)	27		58.80	5.97	7.82
3β	Syrup	+5.1 (1.4)	22		58.65	5.76	7.78
4α	87.0—87.5[c]	+44.7 (1.0)	25	$C_{27}H_{30}O_9S_2$[c]	57.48	5.37	11.37
4β	88.5—89.5[b]	+31.9 (1.3)	25		57.69	5.35	11.34
5α	Syrup	+112 (1.0)	21	$C_{14}H_{20}O_4$[e]	66.64	8.17	
5β	40—42[f]	−56.7 (1.0)	20		66.46	7.87	
6α	Syrup	+69.0 (1.1)	25		66.55	7.95	
6β	Syrup	−72.4 (1.0)	20		66.52	7.97	
7α	Syrup[g]	+102 (1.0)	21		66.67	8.21	
7β	Syrup	−50.7 (1.0)	23		66.68	8.02	
8α	Syrup	+108 (0.6)	19		66.70	8.03	
8β	Syrup	−54.8 (0.7)	20		66.58	7.98	
9	Syrup	+11.7 (1.0)	20	$C_{15}H_{24}O_4$[h]	66.98	9.03	
10	49—50[f,i]	−22.4[i] (1.6)	25	$C_{19}H_{26}O_4$	71.75	8.20	
12	Syrup	−110 (0.6)	24	$C_{10}H_{18}O_4$	59.33	9.08	

a) Calcd: C, 58.81; H, 5.92; S, 7.85%. b) Recrystallized from benzene–hexane. c) Calcd: C, 57.64; H, 5.34; S, 11.40%. d) Distilled at *ca.* 143 °C (bath temperature)/2 mmHg. e) Calcd: C, 66.64; H, 7.99%. f) Crystallized on cooling. g) Distilled at 138—144 °C (bath temperature)/2 mmHg. h) Calcd: C, 67.13; H, 9.02%. i) Lit, (Ref. 5): 47—48 °C; $[\alpha]_D^{20}$ −22.6° (*c* 2.6, $CHCl_3$).

1,2-*cis* oxygen functions. On the other hand, in the case of the 2-deoxy sugars, the anomers having 1,3-*trans* oxygen functions were not always favorable; the equilibrated solution of **8** consisted of a mixture of **8α** and **8β** in a ratio of 53 : 47.

The anomerization of each anomer of the deoxy compounds with the Grignard reagents was carried out using a large excess of *t*-BuMgBr (MeMgI for **5**) in a mixture of benzene–ether. The ether was allowed to distill out from the reaction mixture: under these conditions, a lot of precipitates came out as the ether was lost, so that the reaction mixture became heterogeneous. In the case of **5α**, the anomerization with *t*-BuMgBr was very slow under the conditions used. However, when MeMgI was used instead of *t*-BuMgBr, **5α** was anomerized to give a 1 : 1 anomeric mixture. Starting from **5β**, slight anomerization was observed under the same conditions.

On the other hand, the anomerization of **6β** with *t*-BuMgBr was very fast to give a 9 : 1 mixture of the α- and β-anomers. The reverse reaction (from **6α** to **6β**) did not proceed; thus a one-way anomerization[3] was observed in this case.

It is noted that the 3-deoxy sugars, **5** and **6**, were anomerized predominantly with the Grignard reagents from the thermodynamically more stable 1,2-*trans* anomers to the less stable 1,2-*cis* counterparts. In the case of the 2-deoxy sugars, the anomerization of the 1,3-*trans* anomers, **7α** and **8β**, with *t*-BuMgBr also proceeded smoothly to result in the preferred formation of the 1,3-*cis* anomers, **7β** and **8α**, respectively.

The ^1H NMR spectral data of the branched-chain deoxy sugars are summarized in Table 2; these data are consistent with the structures. The methoxyl or methylene (at C-5) protons located next to the branching methyl group in a *cis* manner resonated at higher field than those in a *trans* relation presumably because of the shilding effect of the branching methyl group. These differences in chemical shifts were diagnostic for determining the configuration of the hydroxyl groups at the branching points.

The signs of the specific rotations of the above described deoxy sugars which have the β-D-configuration were negative, whereas the corresponding α-anomers showed positive signs. These phenomena were compatible with those for the methyl pentofuranosides reported earlier.[3,6]

Experimental

The melting points were determined with a Yamato capillary-melting point apparatus and were uncorrected. The ^1H NMR spectra were recorded on a JEOL PS-100 NMR spectrometer, with tetramethylsilane as the internal standard The optical rotations were measured on a Perkin-Elmer Model 241MC polarimeter.

Merck silica gel GF_{254} was used for the TLC, and the compounds were detected by heating after spraying them with a methanol–sulfuric acid–*p*-methoxybenzaldehyde (85 : 10 : 5, v/v) mixture. Merck silica gel 60 (0.063—0.29 mm) was utilized for the column chromatography. The elemental analyses were performed by this Institute.

The Grignard reagents, MeMgI and *t*-BuMgBr, were prepared from magnesium and the corresponding alkyl halide in dry ether, and the Grignard reactions were carried out in dry solvents under an atmosphere of dry nitrogen.

The ^1H NMR spectral data of the compounds are listed in Table 2, while their physical properties and the results of their elemental analyses are summarized in Table 1.

The Tosylation of Methyl 5-O-Benzyl-α- and -β-D-ribofuranosides (1α and 1β). Some of the results and reaction conditions are described in Scheme 1 and Table 1.

Method A: To a cold (0—5 °C) solution of **1α** (4.32 g, 17.6 mmol)[3] or **1β** (8.94 g, 35.2 mmol)[3] in dry pyridine (60 or

TABLE 2. THE ^1H NMR SPECTRA OF THE SUGAR DERIVATIVES

Compound	δ (in $CDCl_3$)
2α	2.40 (3H, s, C-CH_3), 2.8 (1H, br s, OH), 3.33 (3H, s, OMe), 3.50 (2H, d, J=4 Hz, H-5,5'), 3.97 (1H, dd, $J_{2,3}$=5.5 Hz, $J_{3,4}$=2 Hz, H-3), 4.16 (1H, br m, H-4), 4.39 and 4.47 (2H, ABq, J=11 Hz, CH_2Ph), 4.67 (1H, dd, $J_{1,2}$=4 Hz, $J_{2,3}$=5.5 Hz, H-2), 4.85 (1H, d, $J_{1,2}$=4 Hz, H-1), 7.3—7.8 (9H, m, phenyl protons)
2β	2.43 (3H, s, C-CH_3), 2.21 (1H, d, J=8 Hz, OH), 3.24 (3H, s, OMe), 3.59 (2H, m, H-5,5'), 4.0—4.4 (2H, m, H-3 and H-4), 4.54 (2H, s, CH_2Ph), 4.66 (1H, dd, $J_{1,2}$=1 Hz, $J_{2,3}$=5 Hz, H-2), 4.83 (1H, d, $J_{1,2}$=1 Hz, H-1), 7.2—7.8 (9H, m, phenyl protons)
3α	2.44 (3H, s, C-CH_3), 2.70 (1H, d, J=7 Hz, OH), 3.45 (3H, s, OCH_3), 3.5 (2H, m, H-5, 5'), 4.0—4.4 (2H, m, H-3 and H-4), 4. 48 (2H, m, CH_2Ph), 4.71 (1H, dd, J=7 Hz and J=3 Hz, H-3), 4.87 (1H, d, $J_{1,2}$=4 Hz, H-1), 7.2—7.8 (9H, m, phenyl protons)
3β	2.30 (3H, s, C-CH_3), 3.04 (1H, d, J=4 Hz, OH), 3.25 (3H, s, OCH_3), 3.4 (2H, m, H-5,5'), 4.1—4.4 (2H, m, H-2 and H-4), 4.37 (2H, m, CH_2Ph), 4.8 (1H, m, H-3), 4.82 (1H, s, H-1), 7.1—7.8 (9H, m, phenyl protons)
4α	2.40 (6H, s, C-CH_3×2), 3.26 (3H, s, OCH_3), 3.54 (2H, d, J=2 Hz, H-5,5'), 4.33 (1H, m, H-4), 4.46 (2H, d, J=3 Hz, CH_2Ph), 4.60 (1H, dd, $J_{1,2}$=4 Hz, $J_{1,2}$=7 Hz, H-2), 4.8 (1H, m, H-3), 4.76 (1H, d, $J_{1,2}$=4 Hz, H-1), 7.2—7.8 (13H, m, phenyl protons)
4β	2.36 and 2.43 (6H, each s, C-CH_3×2), 3.22 (3H, s, OCH_3), 3.26 (1H, dABq, $J_{5,5'}$ =11 Hz, $J_{4,5'}$=4 Hz, H-5) and 3.48 (1H, dABq, $J_{5,5'}$ =11 Hz, $J_{4,5'}$=3 Hz, H-5'), 4.2 (1H, m, H-4), 4.30 and 4.38 (2H, ABq, J=13 Hz, CH_2Ph), 4.72 (1H, br d, J=4 Hz, H-2), 4.9 (1H, m, H-3), 4.95 (1H, br s, H-1), 7.1—7.8 (13H, m, phenyl protons)
5α	1.34 (3H, s, C-CH_3), 1.89 (1H, dABq, $J_{3,3'}$=14 Hz, $J_{3,4}$=4 Hz, H-3) and 2.23 (1H, dABq, $J_{3,3'}$=14 Hz, $J_{3',4}$=10 Hz, H-3'), 3.36 (3H, s, OCH_3), 3.48 and 3.78 (2H, dABq, J=11 Hz, J=2 Hz, H-5,5'), 4.36 (1H, m, H-4), 4.57 and 4.71 (2H, ABq, J=12 Hz, CH_2Ph), 4.60 (1H, s, H-1), 7.35 (5H, s, phenyl protons)
5β	1.34 (3H, s, C-CH_3), 1.77 (1H, dABq, $J_{3,3'}$=12 Hz, $J_{3,4}$=10 Hz, H-3) and 2.01 (1H, dABq, $J_{3,3'}$=12 Hz, $J_{3',4}$=7 Hz, H-3'), 2.84 (1H, br s, OH), 3.42 (3H, s, OCH_3), 3.48 (2H, m, H-5.5'), 4.2 (1H, m, H-4), 4.57 (2H, s, CH_2Ph), 4.36 (1H, s, H-1), 7.32 (5H, s, phenyl protons)
6α	1.36 (3H, s, C-CH_3), 1.74 and 2.04 (2H, dABq, $J_{3,3'}$=13 Hz, $J_{3,4'}$=8 Hz, H-3,3'), 2.99 (1H, br s, OH), 3.49 (3H, s, OCH_3), 3.4—3.5 (2H, m, H-5,5'), 4.4 (1H, m, H-4), 4.57 (2H, s, CH_2Ph), 4.52 (1H, s, H-1), 7.32 (5H, s, phenyl protons)
6β	1.33 (3H, s, C-CH_3), 1.72 (1H, dABq, $J_{3,3'}$=13 Hz, $J_{3,4}$=9 Hz, H-3) and 1.97 (1H, dABq, $J_{3,3'}$=13 Hz, $J_{3,4}$=7 Hz H-3'), 1.88 (1H, s, OH), 3.30 (3H, s, OCH_3), 3.45 (2H, m, H-5,5'), 4.4 (1H, m, H-4), 4.57 (2H, s, CH_2Ph), 4.51 (1H, s, H-1), 7.29 (5H, s, phenyl protons)
7α	1.40 (3H, s, C-CH_3), 1.91 (1H, dABq, $J_{2,2'}$=14 Hz, $J_{1,2}$=4 Hz, H-2) and 2.29 (1H, dABq, $J_{2,2'}$=14 Hz, $J_{1,2'}$=6 Hz, H-2'), 3.09 (1H, s, OH), 3.39 (3H, s, OCH_3), 3.7—3.9 (3H, m, H-4 and H-5,5'), 4.58 (2H, s, CH_2Ph), 5.11 (1H, dd, $J_{1,2}$=4 Hz, $J_{1,2'}$=6 Hz, H-1), 7.32 (5H, s, phenyl protons)
7β	1.36 (3H, s, C-CH_3), 2.06 (2H, m, H-2,2'), 2.21 (1H, s, OH), 3.37 (3H, s, OCH_3), 3.7 (2H, m, H-5,5'), 3.9 (1H, m, H-4), 4.60 (2H, s, CH_2Ph), 5.00 (1H, psued t, J=3 Hz, H-1), 7.33 (5H, m, phenyl protons)
8α	1.33 (3H, s, C-CH_3), 2.04 (2H, m, H-2,2'), 3.66 (1H, s, OH), 3.43 (3H, s, OCH_3), 3.49 (2H, m, H-5,5'), 4.17 (1H, psued t, J=5 Hz, H-4), 4.52 (2H, s, CH_2Ph), 5.07 (1H, dd, J=6 Hz, J=2 Hz, H-1), 7.32 (5H, s, phenyl protons)
8β	1.38 (3H, s, C-CH_3), 1.93 (1H, dABq, $J_{2,2'}$=14 Hz, $J_{1,2}$=4 Hz, H-2) and 2.29 (1H, dABq, $J_{2,2'}$=14 Hz, $J_{1,2'}$=6 Hz, H-2'), 2.17 (1H, s, OH), 3.38 (3H, s, OCH_3), 3.55 (2H, d, J=6 Hz, H-5,5'), 4.00 (1H, psued t, J=6 Hz, H-4), 4.56 (2H, s, CH_2Ph), 5.04 (1H, dd, $J_{1,2}$=4 Hz, $J_{1,2'}$=6 Hz, H-1), 7.34 (5H, s, phenyl protons)
9	1.12, 1.13, 1.18, and 1.19 (6H, m, C(OH)C$\underline{H}_3$ and CHC$\underline{H}_3$), 1.3—1.9 (2H, m, C$\underline{H}_2$CH), 3.32 and 3.35 (3H, each s, 53 : 47, OCH_3), 3.5—3.9 (4H, m, $BnOCH_2$, C$\underline{H}$OH, and CHOMe), 4.17 (1H, d, J=6 Hz, CHO$\underline{H}$), 4.58 (2H, s, CH_2Ph), 4.34 (5H, s, phenyl protons)
10	1.50 (3H, s, C-CH_3), 2.03 and 2.15 (2H, dABq, $J_{3,3'}$=14 Hz, $J_{3,4}$=8 Hz, H-3,3'), 1.2—1.8 (10H, m, cyclohexane ring protons), 3.58 and 3.66 (2H, dABq, J=10 Hz, J=6 Hz, H-5,5'), 4.24 (1H, m, H-4), 4.59 (2H, s, CH_2Ph), 5.35 (1H, s, H-1), 7.32 (5H, s, phenyl protons)
12	1.44 and 1.48 (6H, each s, isopropyl protons), 2.00 (1H, dABq, $J_{2,2'}$=14 Hz, $J_{1,2}$=6 Hz, H-2) and 2.26 (1H, dABq, $J_{2,2'}$=14 Hz, $J_{1,2'}$=2 Hz, H-2'), 3.38 (3H, s, OCH_3), 3.7—4.1 (3H, m, H-4 and CH_2Ph), 4.98 (1H, dd, $J_{1,2}$=6 Hz, $J_{1,2'}$=2 Hz,H-1)

120 ml), there was added tosyl chloride (4.70 g, 24.6 mmol or 9.20 g, 48.3 mmol), respectively. Each mixture was stirred at 0—5 °C for a few hours, and then allowed to stand in a refrigerator at the same temperature overnight. The usual work-up gave a syrupy mixture, which was purified by silica-gel column chromatography with benzene–ethyl acetate (9 : 1) to afford **4α** (3.77 g, 38%), **3α** (0.05 g, 1%), and **2α** (2.96 g, 41%) from **1α**, or to give **4β** (4.14 g, 21%), **2β** (0.69 g, 5%), and **3β** (7.34 g, 52%) from **1β**.

Method B:[4] A mixture of **1α** or **1β** (508 mg, 2 mmol) and dibutyltin oxide (498 mg, 2 mmol) in methanol (7 ml) was heated at 75—80 °C (bath temperature) for 3 h with stirring.

The methanol was removed by co-evaporation with benzene. The residue was dissolved in hot benzene (5 ml) and *N,N*-dimethylformamide (5 ml), and a solution was cooled to 0—5 °C. Pyridine (180 mg) was added, followed by addition of tosyl chloride (382 mg, 2 mmol), and the mixture was stirred at 0—5 °C for 30 min. Aqueous sodium hydrogencarbonate was added, and the mixture was extracted with ether. The usual work-up gave a syrup, which was chromatographed on a silica-gel column with benzene–ethyl acetate (9 : 1) to provide **3***α* (42 mg, 5%) and **2***α* (502 mg, 61%) from **1***α*, or to afford **4***β* (10 mg, 0.9%), **2***β* (310 mg, 38%), and **3***β* (347 mg, 42%) from **1***β*.

*Methyl 5-O-Benzyl-3-deoxy-2-C-methyl-β-*D-threo-*pentofuranoside (5β) and Methyl 5-O-Benzyl-3-deoxy-2-C-methyl-β-*D-erythro-*pentofuranoside (6β).* To a cold solution of MeMgI (11.6 mmol) in ether (30 ml), there was added **3***β* (1.4 g, 3.43 mmol) in benzene (5 ml) over a period of 5 min. The mixture was stirred at room temperature for 2 h. After cooling, aqueous ammonium chloride was added and the mixture was extracted with ether. The extract was washed with water and dried ($MgSO_4$). Evaporation of the solvent gave a syrup, which was chromatographed on a silica-gel column with benzene–ethyl acetate (9 : 1) to give **5***β* (700 mg, 81%) and **6***β* (50 mg, 6%).

*Methyl 5-O-Benzyl-3-deoxy-2-C-methyl-α-*D-erythro-*pentofuranoside (6α).* A solution of **4***α* (819 mg, 1.45 mmol) in benzene (3 ml) was added to a stirred solution of MeMgI (11.6 mmol) in benzene (15 ml) and ether (15 ml) at room temperature. After the mixture in a flask without a refluxing condenser had been heated at 80—85 °C (bath temperature) to remove the ether for 1 h, the flask was fitted with the refluxing condenser and the heating was continued for 45 min. After cooling, aqueous ammonium chloride was added, and the mixture was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated to give a syrup, which was chromatographed on a silica-gel column with benzene–ethyl acetate (9 : 1) to give the starting material (80 mg, 10%), an unidentified crystalline compound (225 mg), **5***α* (17 mg, 5%), and **6***α* (130 mg, 36%). These compounds (**5***α* and **6***α*) were identical with the samples prepared from the Grignard anomerization of **5***β* and **6***β*, respectively.

*Methyl 5-O-Benzyl-2-deoxy-3-C-methyl-β-*D-threo-*pentofuranoside (7β), Methyl 5-O-Benzyl-2-deoxy-3-C-methyl-α-*D-erythro-*pentofuranoside (8α), and Its β-Anomer (8β), and the Open-chain Product (9).* To a solution of MeMgI (16 mmol) in ether (20 ml), there was added a solution of **2***β* (1.29 g, 3.2 mmol) in benzene (10 ml) at room temperature over a period of 15 min. The mixture was stirred at this temperature for 80 min. The usual work-up gave a syrupy mixture, which was chromatographed on a silica-gel column with benzene–ethyl acetate (9 : 1) to afford **7***β* (455 mg, 57%), **8***α* (150 mg, 19%), **9** (40 mg, 5%), and **8***β* (20 mg, 2.5%).

*5-O-Benzyl-1,2-O-cyclohexylidene-3-deoxy-2-C-methyl-β-*D-threo-*pentofuranose (10).* A mixture of **5***β* (130 mg, 0.52 mmol), cyclohexanone (0.4 ml), and concd sulfuric acid (38 mg) in dry benzene (2 ml) was stirred at room temperature for 30 min. After cooling, aqueous sodium hydrogencarbonate was added under vigorous stirring, and the mixture was extracted with ether. The extract was washed with water and dried ($MgSO_4$). Evaporation of the solvent and an excess of the cyclohexanone by co-evaporation with toluene gave a syrup, which was chromatographed on a silica-gel column with benzene–ethyl acetate (4 : 1) to give **10** (96 mg, 59%). Its physical properties were identical with those of an authentic sample.[5]

*Methyl 2-Deoxy-3,5-O-isopropylidene-3-C-methyl-β-*D-threo-*pentofuranose (12).* A solution of **7***β* (188 mg, 0.75 mmol) in methanol (10 ml) was hydrogenated in the presence of 10% Pd–C (130 mg) under hydrogen atmosphere at ordinary pressure for 3.5 h. The usual work-up gave a syrup, which was chromatographed on a silica-gel column with chloroform–methanol (49 : 1) to afford almost pure methyl 2-deoxy-3-*C*-methyl-*β*-D-*threo*-pentofuranoside (**11**; 119 mg, 98%) as a syrup. This product was used, without further purification, for the isopropylidenation. A mixture of **11** (54 mg, 0.33 mmol), 2,2-dimethoxypropane (0.5 ml), and pyridinium *p*-toluenesulfonate (10 mg)[7] in acetone (1 ml) was stirred at room temperature for 2.5 h. After cooling, aqueous sodium hydrogencarbonate was added, and the mixture was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated to give a syrup, which was purified by silica-gel column chromatography with benzene–ethyl acetate (1 : 1) to provide **12** (46 mg, 69% from **11**).

The Anomerization of the Branched-chain Deoxy Sugars with an Acid. The ratio of *α*- and *β*-anomers in an equilibrium was determined on the basis of the ^1H NMR spectroscopy; these results are summarized in Scheme 3.

From 5β: A mixture of **5***β* (880 mg, 3.5 mmol) and concd sulfuric acid (250 mg) in methanol (40 ml) was heated at 60—65 °C (bath temperature) for 5 h. An equilibrium was reached within 5 h, judging from TLC and ^1H NMR spectroscopic analyses. After cooling, calcium hydroxide (300 mg) was added and the mixture was stirred vigorously. The undissolved materials were filtered through a Celite pad and washed with methanol. The combined filtrate and washing were concentrated, and the residue (**5***α* : **5***β*=7 : 3) was chromatographed on a silica-gel column with benzene–ethyl acetate (9 : 1) to give **5***α* (568 mg, 65%) and **5***β* (248 mg, 28%).

From 6α: A mixture of **6***α* (32 mg, 0.13 mmol), concd sulfuric acid (80 mg) in methanol (13 ml) was treated under the same conditions as described for the acid anomerization of **5***β* to give a 1 : 4 mixture (29 mg) of **6***α* and **6***β*.

From 7β: A mixture of **7***β* (400 mg, 1.59 mmol) and concd sulfuric acid (120 mg) in methanol (35 ml) was stirred at room temperature for 30 min. Within this time an equilibrium was reached. The mixture was treated in a manner similar to that described for the acid anomerization of **5***β* to give a syrupy mixture (**7***α* : **7***β*=7 : 3), which was chromatographed on a silica-gel column with benzene–ethyl acetate (85 : 15) to afford **7***β* (104 mg, 26%) and **7***α* (250 mg, 63%).

From 8α: A mixture of **8***α* (30 mg, 0.12 mmol), concd sulfuric acid (40 mg) in methanol (12 ml) was treated under the same conditions as described for the acid anomerization of **7***β* to afford a 53 : 47 mixture (28 mg) of **8***α* and **8***β*.

The Anomerization of the Branched-chain Deoxy Sugars with the Grignard Reagents. The ratio of the *α*- and *β*-anomers was determined by means of the ^1H NMR spectroscopy; the results are summarized in Scheme 3.

From 5α: To a solution of MeMgI (2.4 mmol) in ether (5 ml) and benzene (10 ml), there was added a solution of **5***α* (120 mg, 0.48 mmol) in benzene (2 ml), and the mixture was heated at 80—85 °C (bath temperature) to remove the ether for 2.5 h. The usual work-up gave a syrupy mixture (**5***α* : **5***β* =1 : 1; 126 mg), the TLC analyses of which indicated that this contained a small amount of degradation products.

From 5β: To a solution of MeMgI (2.4 mmol) in benzene (10 ml) and ether (5 ml), there was added a solution of **5***β* (128 mg, 0.51 mmol) in benzene (2 ml), and the mixture was treated in a manner similar to that described for the Grignard anomerization of **5***α*. The product (**5***α* : **5***β*=<1 : 99; 126 mg) contained a small amount of decomposed materials.

From 6α: A solution of **6***α* (57 mg, 0.23 mmol) in benzene (2 ml) was added to a stirred solution of *t*-BuMgBr (4.8 mmol) in benzene (10 ml) and ether (5 ml) at room temperature, and the mixture was heated at 80—85 °C (bath temperature) for

30 min with stirring to remove the ether. No anomerization was observed by means of TLC analyses. The usual work-up recovered the starting material (50 mg).

From **6**β: A solution of **6**β (130 mg, 0.52 mmol) in benzene (2 ml) was added to a stirred solution of *t*-BuMgBr (4.8 mmol) in benzene (10 ml) and ether (5 ml), and the mixture was treated under the same conditions as those described for the Grignard anomerization of **6**α. The work-up gave a syrup (**6**α : **6**β=9 : 1), which was chromatographed on a silica-gel column with benzene–ethyl acetate (85 : 15) to give **6**α (93 mg, 72%) and **6**β (8 mg, 6%). The former anomer was identical with a sample prepared from **4**α and MeMgI.

From **7**α: To a stirred solution of *t*-BuMgBr (4.8 mmol) in benzene (10 ml) and ether (5 ml), there was added to solution of **7**α (130 mg, 0.52 mmol) in benzene (2 ml) at room temperature; the mixture was heated at 80—85 °C to remove the ether for 3 h with stirring. The usual work-up gave an anomeric mixture (**7**α : **7**β=$<$5 : 95; 131 mg).

From **7**β: The sugar derivative **7**β (130 mg, 0.52 mmol) was treated under the same conditions as described for the Grignard anomerization of **7**α to provide an anomeric mixture (**7**α : **7**β=$<$1 : 99; 112 mg).

From **8**α: The sugar derivative **8**α (43 mg, 0.17 mmol) was treated with *t*-BuMgBr (4.8 mmol) under the same conditions as described for the Grignard anomerization of **7**α, except that the reaction time was 10 min. The work-up recovered the starting material (43 mg), which contained a trace amount of 8β and of unidentified by-products, judging from TLC analyses.

From **8**β: The sugar derivative **8**β (38 mg, 0.15 mmol) was treated with *t*-BuMgBr (4.8 mmol) under the same conditions as described for the Grignard anomerization of **8**α to give **8**α (39 mg), which contained a trace amount of **8**β and of unidentified by-products.

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References

1) Portions of this work have been reported at the 44th National Meeting of the Chemical Society of Japan, Okayama, Oct. 1981.

2) M. Kawana and S. Emoto, *Tetrahedron Lett.*, **1975**, 3395; *Chem. Lett.*, **1977**, 597; *Bull. Chem. Soc. Jpn.*, **53**, 222 (1980).

3) M. Kawana and S. Emoto, *Tetrahedron Lett.*, **1978**, 1561; M. Kawana, H. Kuzuhara, and S. Emoto, *Bull. Chem. Soc. Jpn.*, **54**, 1492 (1981).

4) D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **39**, 24 (1974).

5) H. Ohrui and S. Emoto, *Agric. Biol. Chem.*, **40**, 2267 (1976).

6) S. J. Angyal, *Carbohydr. Res.*, **77**, 37 (1979).

7) M. Miyashita, A. Yoshikoshi, and P. A. Grieco, *J. Org. Chem.*, **42**, 3772 (1977).