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Preliminary communication

A novel procedure for *C*-glycosylation involving Lewis acid-catalyzed coupling-reactions of glycosyl fluorides with enol trimethylsilyl ethers†

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Only a few glycosyl fluorides had been used as glycosylating agents* before Mukaiyama *et al.* demonstrated the excellent utility of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride[5] and of 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl fluoride[6] in the Lewis acid-catalyzed reaction with alcohols, which gives the corresponding 1,2-*cis*-glycosides with high stereoselectivity in high yields.

On the other hand, we have recently established a novel approach to the preparation of glycosyl fluorides by the reaction of aldose derivatives having OH-1 free with the equimolar adduct of hexafluoropropene with a secondary amine[7], an adduct that had been proved by Ishikawa *et al.*[8] to be useful for the conversion of alcohols into the corresponding alkyl fluorides. We now report a novel procedure for *C*-glycosylation involving the Lewis acid-catalyzed coupling-reaction of glycosyl fluorides with isopropenyl trimethylsilyl ether, which was used herein as a model trimethylsilyl derivative of a protic nucleophile**.

Treatment of 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl fluoride*** (**1β**; 630 mg, 1.5 mmol) with isopropenyl trimethylsilyl ether[12] (2; 0.5 mL, 3.1 mmol) in diethyl ether (2 mL), in the presence of boron trifluoride–diethyl etherate as the catalyst, followed by chromatographic separation on a column of silica gel with 1:19 ethyl acetate–benzene as the eluant, afforded a mixture of 4,7-anhydro-5,6,8-tri-*O*-benzyl-1,3-dideoxy-D-*altro*-(**3α**) and -D-*allo*-2-octulose (**3β**); see Scheme 1.

†Synthetic Studies by the Use of Fluorinated Intermediates, Part I.

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*Treatment of glycosyl fluorides with MeONa/MeOH[1] or with HCl/MeOH[2] was known to give the corresponding methyl glycosides, and, in a particular case, glycosyl glycosides[3]; these investigations were undertaken in order to determine the structure of glycosyl fluorides or to clarify the reaction mechanism for the formation of methyl glycosides, or both. Glycosyl fluorides have never been used as normal substrates for glycoside synthesis[4].

***C*-Glycosylation reactions have recently been performed by the use of trimethylsilyl derivatives of protic nucleophiles[9,10]. For general aspects of the reaction, see ref. 11.

***The reaction of **4** with diethyl 1,1,2,3,3,3-hexafluoropropylamine (2.5 equiv.) for 96 h at room temperature, followed by chromatographic separation on a column of silica gel, gave **1β** in 56.3% yield plus **1α** in 19.1% yield[7].

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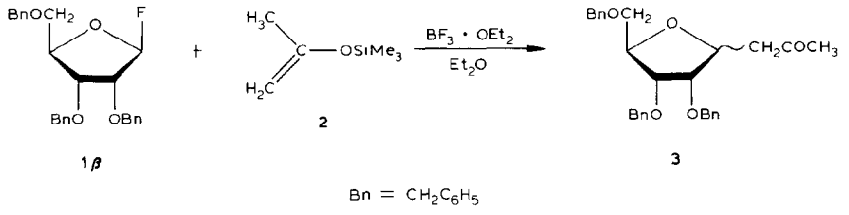


Scheme 1

Compound 3α was a syrup, and had $[\alpha]_D^{20}$ + 27° ($CHCl_3$); $\nu_{C=O}$ 1705 cm^{-1}; ^{1}H-n.m.r. (200 MHz, $CDCl_3$–Me_4Si): δ 2.07 (s, 3 H, H-1), 2.81 (q, 1 H, H-3, $J_{3,3'}$ 17.3, $J_{3,4}$ 6.4 Hz), 2.95 (q, 1 H, H-3′, $J_{3',4}$ 7.2 Hz), 3.48 (q, 1 H, H-8, $J_{8,8'}$ 10.8, $J_{7,8}$ 4.2 Hz), 3.58 (q, 1 H, H-8′. $J_{7,8'}$ 3.5 Hz), 4.05 (q, 1 H, H-6, $J_{5,6}$ 4.4, $J_{6,7}$ 6.5 Hz), ~4.14 and ~4.17 (overlapping 1-proton t and 1-proton m, H-5 and H-7, respectively, $J_{4,5}$ ~4.4 Hz), 4.44 and 4.76 [2 d, 2 H, -CH_2Ph (AB type), J 11.3 Hz], 4.47 and 4.56 [2 d, 2 H, -CH_2Ph (AB type), J ~11.8 Hz], 4.52 and 4.63 [2 d, 2 H, -CH_2Ph (AB type), J ~11.6 Hz], ~4.52 [H-4, irradiation here resulted in the conversion of all H-3 (q), H-3′ (q), and H-5 (t) into doublets, although this proton signal was difficult to discriminate from other proton signals that appeared together], and 7.31 (s, 15 H, 3 C_6H_5); ^{13}C-n.m.r. (50.4 MHz, $CDCl_3$–Me_4Si): δ 30.59 (C-1), 43.92 (C-3), 70.05 (C-8), 72.61, 73.34, 73.46, (-CH_2Ph), 76.04 (C-4), 77.74 (C-5), 79.44 (C-7), 79.74 (C-6), 127.5, 127.6, 127.8, 127.9, 128.0, 128.3, 128.4, 137.8, 138.1, 138.2 (C_6H_5), and 207.5 (C-2).

Anal. Calc. for $C_{29}H_{32}O_5$: C, 75.63; H, 7.00. Found: C, 75.59; H, 7.09.

Compound 3β was a syrup, and had $[\alpha]_D^{20}$ −1° ($CHCl_3$); ^{1}H-n.m.r. (200 MHz, $CDCl_3$–Me_4Si): δ 2.13 (s, 3 H, H-1), 2.55 (q, 1 H, H-3, $J_{3,3'}$ 15.5, $J_{3,4}$ 7.2 Hz), 2.63 (q, 1 H, H-3′, $J_{3',4}$ 5.5 Hz), 3.49 (d, 2 H, H_2-8, $J_{7,8}$ 4.1 Hz), 3.65 (q, 1 H, H-5, $J_{4,5}$ 6.3, $J_{5,6}$ 5.2 Hz), 3.92 (q, 1 H, H-6, $J_{6,7}$ 4.2 Hz), 4.21 (q, 1 H, H-7), 4.43 (bq, 1 H,

TABLE I

BORON TRIFLUORIDE-CATALYZED REACTION OF 2,3,5-TRI-*O*-BENZYL-β-D-RIBOFURANOSYL FLUORIDE (1β) WITH ISOPROPENYL TRIMETHYLSILYL ETHER (2) [a]

Entry No.	*$BF_3 \cdot OEt_2$ (mol.equiv.)*	*Reaction temperature*	*Reaction time*	*Yield of 3 (%)*	*Ratio of 3α to 3β* [b]
1	2	room temp.	20 min	69	7:1
2	1	room temp.	1 h	76	10:1
3	0.2	room temp.	1 h	85	16:1
4	0.1	room temp.	1 h	90.8	17:1
5	0.1	room temp.	20 min	91.5	17:1
6	0.1	−19°C	20 min	92	17:1
7	0.05	room temp.	5 min	94.6	>20:1
8	0.01	room temp.	16 h	7 [c]	100:0

[a] All of the reactions were performed by the use of 1β (1.5 mmol) and 2 (2 mol. equiv.) in Et_2O (2 mL). [b] These ratios were calculated in terms of the ratio of the area of the proton signals of the 1-methyl and 3-methylene groups in the n.m.r. spectrum of each of the resulting mixtures. [c] Compound 1β was recovered in 89% yield.

H-4), 4.49 and 4.61 [2 d, each 1 H, -CH_2Ph (AB type), J 11.8 Hz], 4.50, 4.51, and 4.54 (3 s, 1 H, 1 H, and 2 H, respectively, 2 CH_2Ph), 7.32 and 7.34 (2 s, 15 H, 3 C_6H_5); ^{13}C-n.m.r. (50.4 MHz, $CDCl_3$–Me_4Si); δ 30.54 (C-1), 47.53 (C-3), 70.16 (C-8), 71.76, 72.00, and 73.36 (-CH_2Ph), 76.84 (C-4 and C-6), 80.56 (C-5), 81.61 (C-7), 127.5, 127.6, 127.8, 128.0, 128.3, 137.8, 138.1 (C_6H_5), and 206.7 (C-2).

The results thus obtained are summarized in Table I. As may be seen from Entries 1–7, the yields and stereoselectivity in the *C*-glycosylation were lowered on increasing the proportion of the catalyst and on extending the reaction time; these aspects suggest the occurrence of isomerization or degradation of the resulting glycosyl compounds. The reaction performed with the catalyst (0.05 equiv.) for 5 min at room temperature gave the best yield and stereoselectivity, and it may be assumed that the reaction was induced effectively, or that the reactivity of 1β is remarkably high (beyond our expectations). In contrast, the reaction induced by only 0.01 equiv. of the catalyst gave only a small amount of the products, in addition to the recovery of 1β (89% yield; Entry 8).

Table II shows the results obtained for the reactions performed in dichloromethane and in acetonitrile, respectively. Comparison of the yields and stereoselectivity with those obtained in diethyl ether (Entries 4 and 6) proved the superiority of the last-mentioned as the solvent.

As already mentioned, it was assumed that, once formed, 3α might be isomerized into 3β during the course of the reaction. Therefore, 3α was subjected to treatment with various Lewis acids, *i.e.*, BF_3•OEt_2, $SnCl_4$, Al_2Cl_6, and $ZnBr_2$ in such solvents as Et_2O, CH_2Cl_2, C_6H_6, and *N*,*N*-dimethylformamide; the ratio of 3α to 3β at equilibrium was found to be ~2:5. The mixture obtained by treating 3α (350 mg) with BF_3•OEt_2 (1 equiv.) in Et_2O for 24 h at room temperature was chromatographed, to give 3β (90 mg) containing only a trace of 3α.

In ^{1}H-n.m.r. spectroscopy, the benzyl methylene proton signals of 3α appeared with conspicuously different chemical shifts (δ 4.44–4.76) from those of 3β, which appeared in a narrower range of chemical shifts (δ 4.49–4.61)*, although it was impossible to determine the configuration of C-4 on the basis of the H-4 chemical shift and

TABLE II

REACTIONS PERFORMED IN DICHLOROMETHANE AND IN ACETONITRILE [a]

Entry No.	*Solvent*	*BF_3•OEt_2 (mol.equiv.)*	*Reaction temperature*	*Reaction time (min)*	*Yield of 3 (%)*	*Ratio of 3α to 3β*
1	CH_2Cl_2	0.1	room temp.	60	84	8:1
2	CH_2Cl_2	0.1	−19°C	20	87	8:1
3	CH_3CN	0.1	room temp.	60	79	5:1
4	CH_3CN	0.1	−19°C	20	81	5:1

[a] AU reactions were performed by use of the amounts of reagents 1β, 2, and solvent, given in footnote *a* of Table I.

*The acetonyl group of 3α should sterically hinder the free rotation of its CH_2Ph-5 group, in contrast to that of 3β, bringing about such nonequivalence in chemical shift of the methylene proton signals with the large difference seen. A similar type of splitting of benzyl methylene proton signals had also been found[10] in the 100-MHz, ^{1}H-n.m.r. spectrum of 2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl cyanide.

TABLE III

THE REACTION OF 2,3,5-TRI-*O*-BENZYL-α-D-RIBOFURANOSYL FLUORIDE (1α) WITH ISOPROPENYL TRIMETHYLSILYL ETHER (2) [a]

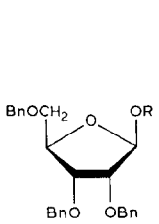
Entry No.	$BF_3 \cdot OEt_2$ *(mol.equiv)*	*Yield of 3 (%)*	*Ratio of 3α to 3β*
1	0.1	82	20:1
2	0.05	89	20:1

[a] Both of the reactions were performed for 20 min at room temperature, just as described in Table I, other than the use of 1α instead of 1β.

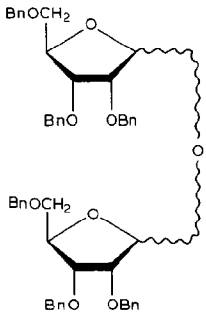
$J_{4,5}$. In ^{13}C-n.m.r. spectroscopy, on the other hand, the C-3 and C-4 signals of 3α (δ 43.92 and 76.04, respectively) appeared at higher magnetic field[10,13] than those of 3β (δ 47.53 and 76.84, respectively). Moreover, the specific rotations of 3α and 3β in chloroform were +27 and −1°, respectively. The structures of 3α and 3β were thus assigned as already mentioned, involving the α- and β-D-ribofuranosyl moiety, respectively.

For comparison, the reaction of the anomer (1α)*** of 1β was similarly performed, and the results thus obtained are summarized in Table III. The stereoselectivity in these reactions was substantially the same as that of the β anomer, although 1α seems to be less reactive. Incidentally, Mukaiyama *et al.*[6] obtained a 14:72 mixture of 1α and 1β by treating a 100:1 mixture with $BF_3 \cdot OEt_2$ in Et_2O. Treatment of 1α with $BF_3 \cdot OEt_2$ (0.05 equiv.) in Et_2O for 20 min at room temperature, followed by chromatographic separation, gave 1α (33.5% yield) and 1β (51.9% yield), respectively. In this case, 2,3,5-tri-*O*-benzyl-D-ribofuranose (14.6% yield) was obtained as the hydrolysis product; it was proved that 1α is more susceptible to hydrolysis than 1β on chromatography through silica gel. Therefore, it may be presumed that *C*-glycosylation precedes the anomerization in the reaction of 1α, and that the stereoselectivity in the *C*-glycosylation is substantially the same in reactions with both 1α and 1β. Moreover, it may be presumed that the reactions described proceed *via* the 2,3,5-tri-*O*-benzyl-D-ribofuranosyl carbenium ion, *i.e.*, *via* the SN1 mechanism, giving 3α as the kinetically controlled product, and 3β as the thermodynamically controlled product.

As an additional aspect of this reaction, it is of remarkable interest to describe the formation of a trehalose type of disaccharide observed in the reactions of 1β induced by $SnCl_4$ and $ZnBr_2$, *etc.*, during 24–48 h at room temperature, giving 3 in poor yield, but 1,1′-di-D-ribosyl derivatives as major products; the latter might be formed by the coupling reaction of 1β with 2,3,5-tri-*O*-benzyl-D-ribofuranose (4) produced by hydrolysis of 1β by moisture in the air. Therefore, reaction of 1β with an equimolar proportion of 4 (ref. 14) in the presence of $BF_3 \cdot OEt_2$ (0.1 equiv.) was performed, and was found to give 2,3,5,2′,3′,5′-hexa-*O*-benzyl-(β-D-ribofuranosyl β-D-ribofuranoside) (7) in 71% yield. Similar treatment of 1β with trimethylsilyl 2,3,5-tri-*O*-benzyl-β-D-ribofuranoside (5) gave 7 in 54% yield. Moreover, treatment of 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl acetate (6) with $ZnBr_2$ (1 equiv.) in Et_2O for 24 h at room temperature gave 2,3,5,2′,3′,5′-hexa-*O*-benzyl-(α-D-ribofuranosyl α-D-ribofuranoside) (8) in 79% yield. Elementary analyses and mass-spectral data [*m/z* 823 (M^+)] of 7 and 8 supported the structures assigned. In the



4 R = H
5 R = $SiMe_3$
6 R = $COCH_3$



7 β,β
8 α,α

^{1}H-n.m.r. spectra, 7 displayed a sharp singlet at δ 5.39, and 8, a broad singlet at δ 5.6. The specific rotations of 7 and 8 are +25 and +147°, respectively.

Such a system involving the Lewis acid-catalyzed reaction of glycosyl fluorides with trimethylsilyl derivatives of protic nucleophiles may be expected to be applicable to the synthesis of a wide variety of glycosyl compounds, in addition to those of *C*-glycosyl compounds and trehalose-type disaccharides.

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