CHEMISTRY LETTERS, pp. 935-938, 1983.

STEREOSELECTIVE SYNTHESIS OF 1,2-*CIS*-GLYCOFURANOSIDES USING GLYCOFURANOSYL FLUORIDES

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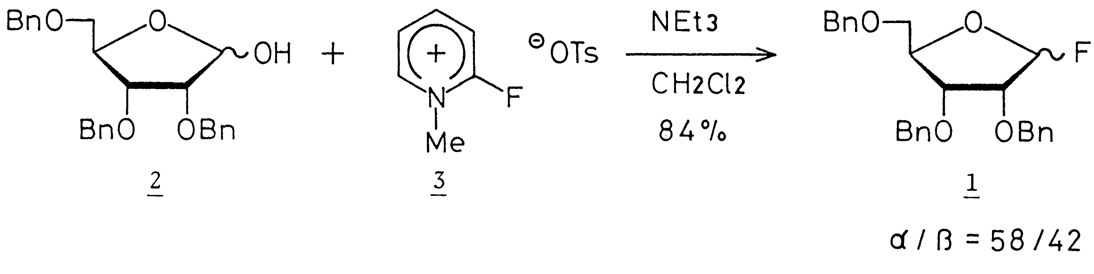
1,2-*cis*-Ribofuranosides are stereoselectively synthesized in high yields by the reaction of β-ribofuranosyl fluoride and alcohols in the presence of stannous chloride and trityl perchlorate. Under similar condition, α-arabinofuranosyl fluoride reacts with cholestanol to give 1,2-*cis*-arabinofuranoside predominatly.

Stereoselective formation of O-glycosidic bond is one of the most important problems in carbohydrate chemistry. Recently much effort has been devoted to the stereoselective synthesis of glycopyranosides and several efficient methods have been developed by the appropriate combination of sugar derivatives and activators.[1] However, stereoselective synthesis of glycofuranosides, especially 1,2-*cis*-glycofuranosides, is known to be a more difficult problem compared with glycopyranosides synthesis. Therefore, up to date, no general and efficient method for 1,2-*cis*-glycofuranosides synthesis has been reported,[2] and exploration of a convenient method for the synthesis of 1,2-*cis*-glycofuranosides is strongly desired.

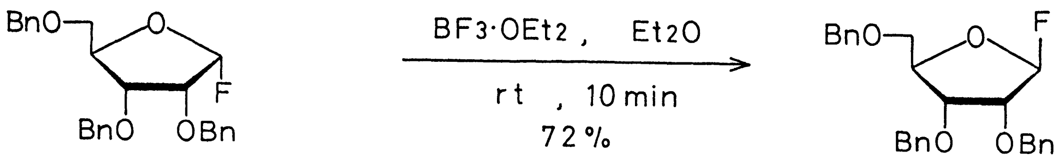
Concerning a stereoselective synthesis of α-glucosides, we have already reported a useful method of treating β-glucopyranosyl fluoride with alcohols using stannous chloride and silver perchlorate as activators.[3] In this communication, we wish to describe an efficient method for the preparation of 1,2-*cis*-glycofuranosides in high yields from glycofuranosyl fluorides with alcohols.

First, the preparation of 2,3,5-tri-O-benzyl-β-D-ribofuranosyl fluoride (1β) was studied. In the presence of triethyl amine, 2,3,5-tri-O-benzyl-D-ribofuranose[4] (2) smoothly reacted with 2-fluoro-1-methylpyridinium tosylate[5] (3) at room temperature to give an anomeric mixture of the corresponding ribofuranosyl fluorides[6] in 84% yield (Scheme 1).



(1)

These two fluorides could be easily separated by silica gel chromatography, and we found that the corresponding β-anomer was obtained in 72% yield (Scheme 2, recovered α-anomer 14%) by treating α-anomer with boron trifluoride etherate in ether at room temperature for 10 min, followed by quenching the reaction with triethyl amine.



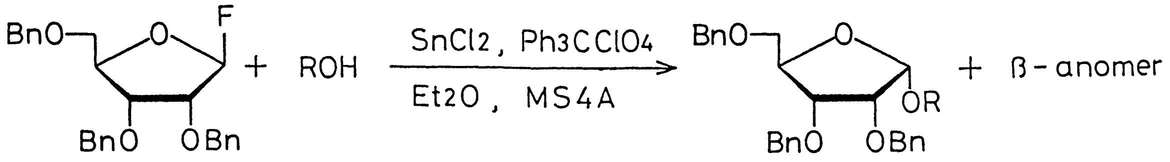
1α 1β

(2)

Next, we tried the reaction of β-ribofuranosyl fluoride (1β) with 3β-cholestanol as an alcohol. When the reaction was carried out in the presence of stannous chloride and 4A molecular sieve in ether at 0°C, the glycoside was obtained in good yield (93%, α/β = 72/28).

As described previously,[3] addition of silver perchlorate generally improved yield and selectivity in the α-glucosides synthesis. However, in this case, when silver perchlorate was used as additive, the reaction was extremely accelerated and gave 1,2-*trans*-ribofuranoside as a major product.

Various activators and solvents were examined in order to achieve higher selectivity in the present procedure. After screening the combination of Lewis acids [such as SnF_2, $SnBr_2$, $Sn(OAc)_2$, $Sn(OSO_2CF_3)_2$] and solvents, we found that the combined use of stannous chloride and trityl perchlorate[7] in ether solution gave the best result. Various ribofuranosides were synthesized under these conditions (see Table).



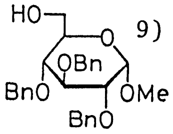
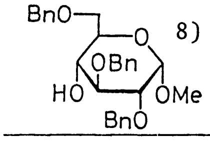
1β

(3)

According to the present procedure, even a sterically hindered alcohol such as methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside[8] could smoothly react with 1β under mild conditions and the corresponding disaccharide was obtained in high yield.

The following is a typical procedure for the preparation of 3β-cholestanyl 2,3,5-tri-O-benzyl-α-D-ribofuranoside: To a stirred suspension of stannous chloride (2.0 mmol), trityl perchlorate (2.0 mmol), and 4A molecular sieve in ether (1 ml) was added an ether solution (4 ml) of 3β-cholestanol (1.7 mmol) and 1β (2.0 mmol) at -15°C. After the reaction was completed, aqueous sodium hydrogen carbonate solution was added to the reaction mixture. This mixture was filtered using celite and extracted with ether. After the organic layer was dried over

Table 1. Synthesis of Ribofuranosides a)

Alcohol	Yield(%)	α/β	α-Anomer δ_H (J_{12})	α-Anomer δ_C	β-Anomer δ_H (J_{12})	β-Anomer δ_C
Cholestanol	88	81/19	5.13(3.5)	99.8	5.15(<0.8)	103.3
MeOH	89	88/12	4.8 (3∼4) b)	102.4	4.9 (0)	106.3 c,d)
t-BuOH	90	85/15	5.30(3.8)	96.4	5.26(2.1)	100.5 c)
 9)	95	88/12	5.14(3∼5) b)	102.0	5.07(0.8)	105.9
 8)	96	85/15	5.61(3.8)	101.8	5.38(2.8)	106.5

a) Chemical shifts (ppm) and coupling constant (Hz) are values of anomeric proton and carbon.

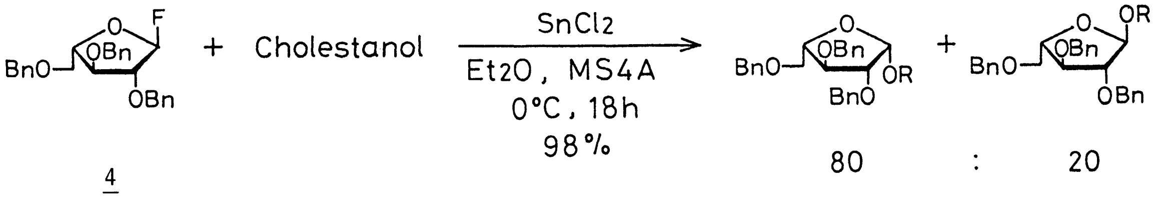
b) Accurate coupling constant could not be measured because the anomeric proton resonance showed complex pattern.

c) Reaction was carried out in the absence of trityl perchlorate at rt (MeOH) or 0°C (t-BuOH) and excess amount of alcohol was used (yield based on 1β).

d) Lit, 10) α-anomer: δ_H 4.86 (J_{12}= 4 Hz), β-anomer: δ_H 4.89 (J_{12}= 0 Hz).

sodium sulfate, solvent was removed under reduced pressure, and the residue was purified by TLC to give 3β-cholestanyl 2,3,5-tri-O-benzyl-α-D-ribofuranoside (71%) and the corresponding β-anomer (17%).

In addition, a similar result was observed in the reaction of 2,3,5-tri-O-benzyl-α-L-arabinofuranosyl fluoride 11) (4) with 3β-cholestanol (Scheme 4).



(4)

R = 3β-Cholestanyl

These results demonstrate that the glycosyl fluoride method is indeed generally applicable to the synthesis of 1,2-*cis*-glycofuranosides having various aglycons.

We thank Dr. N. Yonezawa of the Faculty of Engineering on our campus for taking 400 MHz NMR spectra.

The present work was supported by a Grant-in-Aid for Scientific Research No. 57118002 from the Ministry of Education, Science and Culture.

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1) For example, to synthesize 1,2-*cis*-glycopyranosides, see: K. Igarashi, J. Irisawa, and T. Honma, Carbohydr. Res., 39, 341 (1975); R. U. Lemieux, K. B. Hendriks, R. V. Stick, and K. James, J. Am. Chem. Soc., 97, 4056 (1975); J.-R. Pougny, J.-C. Jacquinet, M. Nassr, D. Duchet, M.-L. Milat, and P. Sinaÿ, J. Am. Chem. Soc., 99, 6762 (1977). See also: H. Paulsen, Angew. Chem., Int. Ed. Engl., 21, 155 (1982).
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3) T. Mukaiyama, Y. Murai, and S. Shoda, Chem. Lett., 1981, 431.
4) R. Barker and H. G. Fletcher, Jr., J. Org. Chem., 26, 4605 (1961).
5) T. Mukaiyama, Angew. Chem., Int. Ed. Engl., 18, 707 (1979).
6) The physical constants of these fluorides are as follows: α-anomer (1α): colorless oil, $[\alpha]_D^{19}$ +32°(c = 1.1, $CHCl_3$), ^1H-NMR ($CDCl_3$) δ 5.64 (H-1, dd, J_{1F} = 66 Hz, J_{12} = 3.1 Hz), ^{13}C-NMR ($CDCl_3$) δ 108.5 (C-1, d, J_{1F} = 232.5 Hz), ^{19}F-NMR ($CDCl_3$, C_6F_6) ϕ 133 (dd, J_{1F} = 66 Hz, J_{2F} = 24 Hz).

   Elemental analysis, Found: C, 73.80; H, 6.42%. Calcd for $C_{26}H_{27}O_4F$: C, 73.91; H, 6.44%.

   β-Anomer (1β): white fine needle, mp 45.0 - 45.5°C, $[\alpha]_D^{21}$ +52° (c = 1.0, $CHCl_3$), ^1H-NMR ($CDCl_3$) δ 5.63 (H-1, d, J_{1F} = 63.5 Hz), ^{13}C-NMR ($CDCl_3$) δ 112.4 (C-1, d, J_{1F} = 224.0 Hz), ^{19}F-NMR ($CDCl_3$, C_6F_6) ϕ 116 (d of m, J_{1F} = 63.5 Hz).

   Elemental analysis, Found: C, 74.21; H, 6.55%. Calcd for $C_{26}H_{27}O_4F$: C, 73.91; H, 6.44%.

   Both fluorides are much stable compared with other perbenzylated glycosyl chloride or bromide, which are generally used in glycosylation reaction, and these fluorides can be stored in refrigerator for several months without any change. The desired β-anomer (1β) can be easily free from the α-anomer (1α) by recrystallization from ether-petroleum ether.
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8) J.-M. Petit, J.-C. Jacquinet, and P. Sinaÿ, Carbohydr. Res., 82, 130 (1980).
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10) M. Kawana, H. Kuzuhara, and S. Emoto, Bull. Chem. Soc. Jpn., 54, 1492 (1981).
11) Colorless oil, $[\alpha]_D^{18}$ -22.3° (c = 1.5, $CHCl_3$), ^1H-NMR ($CDCl_3$) δ 5.72 (H-1, d, J_{1F} = 61.5 Hz), ^{13}C-NMR ($CDCl_3$) δ 113.5 (C-1, d, J_{1F} = 224.6 Hz), ^{19}F-NMR ($CDCl_3$, C_6F_6) ϕ 121 (dd, J_{1F} = 61.5 Hz, J_{2F} = 9 Hz).

(Received April 25, 1983)