Communications to the Editor

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NEW SYNTHESIS OF 2-DEOXY-2-FLUORO-D-GALACTOSE

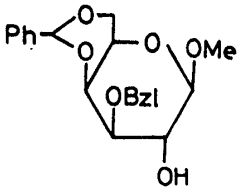
Terushi Haradahira, Minoru Maeda, Yuji Yano, and Masaharu Kojima*
Faculty of Pharmaceutical Sciences, Kyushu University,
Maidashi 3-1-1, Higashi-ku, Fukuoka 812, Japan

A nucleophilic displacement reaction of methyl 3,4-O-isopropylidene-2-O-(trifluoromethanesulfonyl)-6-O-trityl-β-D-talopyranoside (10) with tetraalkylammonium fluorides in acetonitrile gave methyl 2-deoxy-2-fluoro-3,4-O-isopropylidene-6-O-trityl-β-D-galactopyranoside (11). Excellent conversion of 11 into 2-deoxy-2-fluoro-D-galactose (1) was achieved by hydrolysis with 5 N hydrochloric acid.

KEYWORDS ———— fluorination; nucleophilic displacement; tetraalkylammonium fluoride; methyl 3,4-O-isopropylidene-2-O-(trifluoromethanesulfonyl)-6-O-trityl-β-D-talopyranoside; 2-deoxy-2-fluoro-D-galactose

Fluorinated deoxy-carbohydrates have been widely used in the study of various aspects of carbohydrate transport and metabolism. Recently the ^{18}F-labeled analog of 2-deoxy-2-fluoro-D-galactose (1) has been investigated *in vivo* by positron emission tomography as a new radiopharmaceutical for liver function.[1] The previously reported synthesis of 1 includes the electrophilic addition of either CF_3OF[2] or CH_3COOF[3] to 3,4,6-tri-O-acetyl-D-galactal and the current preparation of 1 with ^{18}F includes in the initial step a similar addition of ^{18}F-F_2.[4] This radiosynthetic method, however, entails the inherent loss of 50% of the fluorine activity, because only one of the two fluorine atoms in the reagent is utilized in the product. The successful fluoride displacements at C_2 of suitably protected β-D-manno- and gluco-pyranosides have recently been achieved by the use of the trifluoromethanesulfonyloxy group with remarkable leaving ability.[5,6,7] We have developed an alternative synthesis of 1 using the nucleophilic displacement of the C_2-triflate function of a talopyranoside with fluoride ion, which, in the radiopharmaceutical synthesis with ^{18}F, has in principle the advantage of utilizing all the available fluorine.

Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-(trifluoromethanesulfonyl)- and methyl 3,4-O-isopropylidene-2-O-(trifluoromethanesulfonyl)-6-O-trityl-β-D-talopyranosides (8) and (10), precursors needed for the synthesis of 1, were prepared by the following sequence of reactions. Oxidation of the known β-D-galactopyranosides (2) and (5) with dimethyl sulfoxide in acetic anhydride gave the 2-uloses (3) and (6), which were reduced to 4 and 7, respectively, with lithium aluminum hydride. Conventional sulfonylation of 4 and 7 with trifluoromethanesulfonic anhydride in pyridine gave the required 8 and 10, respectively, the ^1H-NMR spectra of which



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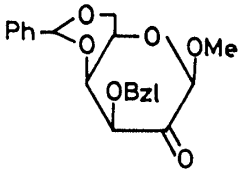

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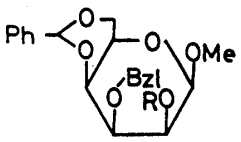
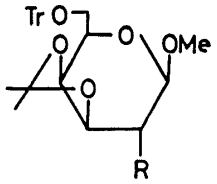
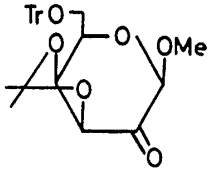


4: R=H
8: R=SO_2CF_3



5: R=OH
11: R=F



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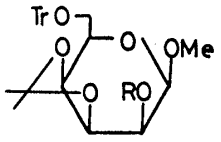
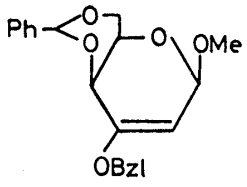


7: R=H
10: R=SO_2CF_3



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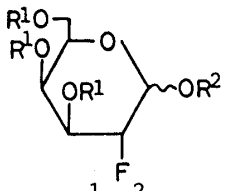

1: R^1=R^2=H
12: R^1=H R^2=CH_3 (β-anomer)
13: R^1=R^2=$COCH_3$

Bzl=$C_6H_5CH_2$
Tr=$(C_6H_5)_3C$

confirmed the talo configuration.[8]

When 8 was allowed to react with tetraethylammonium fluoride in acetonitrile at 50°C for 30 min, no fluorination was observed; instead, 8 underwent elimination to give the hex-2-enopyranoside (9) in 74% yield. On the other hand, treatment of 10 with the same fluorinating agent in acetonitrile at 50°C for 50 min resulted in displacement of the sulfonyloxy group to give methyl 2-deoxy-2-fluoro-3,4-O-isopropylidene-6-O-trityl-β-D-galactopyranoside (11) (mp 152°C, $[\alpha]_D$ -38.6°) in 50% yield. Similar treatment with tetramethylammonium fluoride in acetonitrile under reflux for 30 min or with tetra-n-butylammonium fluoride in acetonitrile at room temperature for 90 min also afforded 11 in 45 and 38% yield, respectively. In these reactions, thin layer chromatography separated the two major products. The one with the lower R_f value gave analyses consistent with 11, but the product with the higher R_f value could not be isolated by column chromatography on silica gel using n-hexane-ethyl acetate (20:1), probably because of decomposition. The structure of 11 was determined by elemental analysis and by mass and ^{1}H-NMR spectra.[9] Further proof of 11 was provided by partial hydrolysis with acetic acid to methyl 2-deoxy-2-fluoro-β-D-galactopyranoside (12), which showed the same ^{13}C-NMR spectral data as that reported by Kováč et al.[10]

The failure of 8 toward fluoride displacement, in comparison with the corresponding mannopyranoside,[7] can be attributed to the destabilizing interaction between the outgoing leaving group in the S_N2 transition state and the permanent dipole associated with the axial C_4-O bond in 8, like that in the 6-sulfonates of the

galactopyranosides;[11] therefore 8 underwent preferentially to antiperiplanar elimination involving the C_3-hydrogen and the C_2-sulfonyloxy group. In contrast, it is of interest that the use of 10 protected as its 3,4-O-isopropylidene acetal facilitated the displacement reaction with fluoride ion as described above. Inspection of a Newman projection of 10 indicates that the C_4-O bond of the 3,4-acetal ring is inclined at ca. 40° to the C_5-C_6 bond and the C_4-oxygen atom becomes get somewhat more apart from the C_2-sulfonyloxy group than it is in 8, owing to steric constraints imposed by the five-membered acetal ring. Such a stereochemical change might result in reduced dipolar repulsion in the S_N2 transition state, relative to that in 8.

Hydrolysis of 11 with 50% methanesulfonic acid under reflux for 20 min gave crystalline 1 (mp 133-136°C, $[\alpha]_D$ +60.3°) in 64% yield. Furthermore, excellent conversion into 1 was achieved by refluxing with 5 N hydrochloric acid for 30 min in 86% yield. The obtained 1 showed mp, optical rotation and ^{1}H-NMR spectral properties as reported[2] and was further characterized by conversion into the tetraacetate (13).

In the present work, 1 was obtained in 40% overall yield from 10 and this synthetic method could be reasonably adapted to the radiopharmaceutical synthesis of 1 with ^{18}F.

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8) 8 ^{1}H-NMR ($CDCl_3$) δ: 3.26-3.62 (2H, m, H-3,5), 3.59 (3H, s, OCH_3), 4.0-4.45 (3H, m, H-4,6), 4.43 (1H, s, H-1), 4.68 and 4.73 (2H, 2d, J_{gem}=12.8Hz, $PhCH_2O$), 5.10 (1H, d, $J_{2,3}$=3.2Hz, H-2), 5.50 (1H, s, PhCH), 7.20-7.60 (10H, m, aromatic).
10 ^{1}H-NMR ($CDCl_3$) δ: 1.34, 1.54 (3H, s, CH_3), 3.50-3.84 (3H, m, H-3,4,5), 3.53 (3H, s, OCH_3), 4.20-4.43 (2H, m, H-6), 4.33 (1H, d, $J_{1,2}$=1.2Hz, H-1), 4.81 (1H, br d, $J_{2,3}$=5.1Hz, H-2), 7.21-7.52 (15H, m, aromatic).
9) 11 ^{1}H-NMR ($CDCl_3$) δ: 1.36, 1.48 (3H, s, CH_3), 3.41-4.33 (5H, m, H-3,4,5,6), 3.56 (3H, s, OCH_3), 4.24 (1H, dt, $J_{1,2}$=$J_{2,3}$=7.4Hz, $J_{2,F}$=47.6Hz, H-2), 4.30 (1H, dd, $J_{1,F}$=2.0Hz, H-1), 7.20-7.52 (15H, m, aromatic).
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