Notes

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Synthesis of Methyl 2,3-, 2,4- and 3,4-Di-*O*-Methyl-α-D-Fucopyranosides

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Methyl 2,3-(**15**), 2,4-(**11**) and 3,4-di-*O*-methyl-α-D-fucopyranosides (**8**) were prepared from methyl α-D-fucopyranoside *via* methyl 3,4-*O*-isopropylidene-α-D-fucopyranoside. These substances were required in connection with methylation analysis of saponins containing D-fucose residues. Compounds **8** and **11** had not previously been synthesized at the outset of the present work.

Keywords——methyl 3,4-*O*-isopropylidene-α-D-fucopyranoside; methyl 2,3-, 2,4- and 3,4-di-*O*-methyl-α-D-fucopyranosides; selective benzoylation; deacetylation; methylation

Methyl ethers of D-fucose are frequently required as reference substances in studies on the structure of saponins[2,3] and antibiotics.[4]

We report here the synthesis of methyl 2,4-di-*O*-methyl-(**11**) and methyl 3,4-di-*O*-methyl-(**8**) α-D-fucopyranosides from the 3,4-*O*-isopropylidene derivative (**2**), and describe improved routes from the ethyl orthoacetate derivative (**12**) to methyl 2,3-di-*O*-methyl-α-D-fucopyranoside (**15**),[5–7] which has previously been prepared *via* 4,5-isopropylidene-D-fucose dibenzylmercaptal. The procedures are shown in Chart 1. Methyl 3,4-*O*-isopropylidene-α-D-fucopyranoside (**2**) was obtained by the procedure of Schmidt and Wernicke.[8] Methylation of methyl 3,4-*O*-isopropylidene-α-D-fucopyranoside (**2**) with Purdie's reagent[9] gave methyl 3,4-*O*-isopropylidene-2-*O*-methyl-α-D-fucopyranoside (**3**). Methyl 2-*O*-acetyl-3,4-*O*-isopropylidene-α-D-fucopyranoside (**4**) was obtained by the acetylation of compound **2** with acetic anhydride and pyridine. Compounds **3** and **4** were hydrolyzed in 9.8% sulfuric acid for 5 hours at room temperature to give methyl 2-*O*-methyl-(**5**) and methyl 2-*O*-acetyl-(**6**) α-D-fucopyranosides, respectively. Compound **6** was methylated with methyl iodide and silver oxide in N,N-dimethylformamide. The syrupy product (**7**) was deacetylated with triethylamine in methanolic solution to give methyl 3,4-di-*O*-methyl-α-D-fucopyranoside (**8**) ($[\alpha]_D^{25}$ +185°) in 47% yield based on the starting material (**1**).

Compound **5** was benzoylated selectively with equimolar benzoyl chloride in pyridine to give mainly methyl 3-*O*-benzoyl-2-*O*-methyl-α-D-fucopyranoside (**9**), with the 3,4-benzoate compound as a minor product. The low reactivity of the 4-hydroxyl group in α-D-fucopyranoside is understandable in view of its axial disposition.[10] The NMR spectrum of compound **9** showed the H-3 signal as a double doublet at δ 5.34 ($J_{2,3}$ 8 Hz, $J_{3,4}$ 3 Hz). This indicates substitution of the 3-hydroxyl group with a benzoyl group. Compound **9** was

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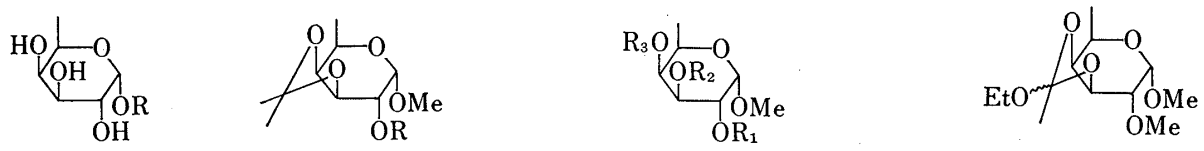
methylated, followed by debenzoylation with methanolic potassium carbonate to afford methyl 2,4-di-*O*-methyl-α-D-fucopyranoside (**11**), ($[\alpha]_D^{25}$ +192°), in 17% yield.

Compound **5** was added to a mixture of dry benzene, triethyl orthoacetate and *p*-toluenesulfonic acid monohydrate. After usual work-up, the reaction syrup, containing methyl 3,4-*O*-(ethyl orthoacetyl)-2-*O*-methyl-α-D-fucopyranoside (**12**), was dissolved in 80% aqueous acetic acid and the solution was kept at room temperature for 10 minutes. Compound **13** was readily prepared in high yield by the controlled acid hydrolysis[11] of **12**. After methylation of **13** followed by deacetylation, compound **15**, methyl 2,3-di-*O*-methyl-α-D-fucopyranoside ($[\alpha]_D^{25}$ +191°), was obtained in 14% yield based on **1**. The syntheses were followed by thin-layer chromatography (TLC) and most of the products were characterized by NMR analyses. Each methyl fucoside was analyzed by gas chromatography (GLC) as shown in Table I.



D-Fucose: R=H
1: R=Me

2: R=H
3: R=Me
4: R=Ac

5: R_1=Me, R_2=R_3=H
6: R_1=Ac, R_2=R_3=H
7: R_1=Ac, R_2=R_3=Me
8: R_1=H, R_2=R_3=Me
9: R_1=Me, R_2=Bz, R_3=H
10: R_1=R_3=Me, R_2=Bz
11: R_1=R_3=Me, R_2=H
13: R_1=Me, R_2=H, R_3=Ac
14: R_1=R_2=Me, R_3=Ac
15: R_1=R_2=Me, R_3=H

12

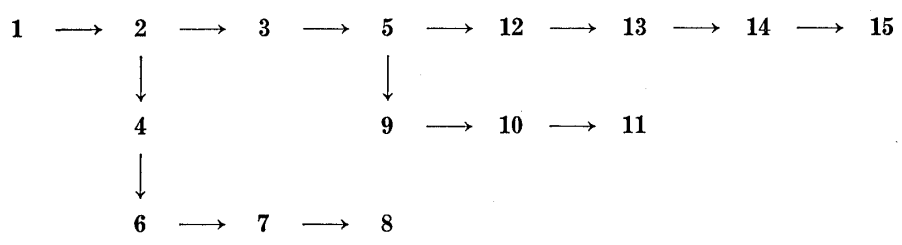


Chart 1

TABLE I. Retention Times of Methyl Fucosides

Compound	8	11	15	5
Retention time (min)	19.01	19.55	19.42	40.30

Separations were carried out at a gas flow rate of 50 ml of nitrogen per min on a column (200×0.3 cm) containing 10% DEGS on Gas Chrom Q at 160°.

Experimental

Melting points were determined with a Yanagimoto micro melting apparatus and are uncorrected. The NMR spectra were recorded on a JNM MH-100 spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. Optical rotations were determined on a JASCO DIP-2 spectrometer. TLC was carried out on glass plates coated with silica gel (Merck GF-254) using solvent A (4: 1 benzene–acetone) or solvent B (4: 1 chloroform-methanol). GLC was performed on a Shimadzu GC-6A gas chromatograph equipped with a hydrogen flame ionization detector.

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Materials——Methyl 3,4-*O*-isopropylidene-α-D-fucopyranoside (**2**) was obtained by the procedure of Schmidt and Wernicke.[8] The synthesis of methyl 2-*O*-methyl-α-D-fucopyranoside (**5**) was performed as described by Springer and Williamson.[6]

Methyl 2-*O*-Acetyl-3,4-*O*-isopropylidene-α-D-fucopyranoside (4)——Compound **2** (300 mg) was acetylated with acetic anhydride (1.5 ml) and pyridine (1.5 ml) at room temperature. After usual work-up, a crystalline product **4** (340 mg, yield 95%) was obtained. NMR δ: 4.74 (d, J=4 Hz, H-1), 3.38 (OMe), 2.13 (OAc), 1.36, 1.52 (isopropylidene Me), 1.38 (d, J=4 Hz, Me). *Anal.* Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.39; H, 7.80.

Methyl 2-*O*-Acetyl-α-D-fucopyranoside (6)——After adding 0.3 ml of 9.8% H_2SO_4 to a methanolic solution (3 ml) of compound **4** (340 mg), the mixture was stirred for 5 hours. The solution was neutralized with Amberlite IR 4B (OH^-) then concentrated to a syrup (219 mg, yield 75%), showing $[\alpha]_D^{24}$ +173° (c=1, methanol). NMR δ: 4.72 (d, J=2 Hz, H-1), 3.40 (OMe), 2.16 (OAc), 1.28 (d, J=6 Hz, Me). *Anal.* Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 49.21; H, 7.36.

Methyl 2-*O*-Acetyl-3,4-di-*O*-methyl-α-D-fucopyranoside (7)——Compound **6** (200 mg) in N,N-dimethylformamide (4 ml) was methylated with silver oxide (500 mg) and methyl iodide (1.5 ml) for 12 hours according to the Kuhn method. The precipitate was filtered off, and the filtrate was diluted with water then extracted with $CHCl_3$. After concentration, a syrupy product was obtained (200 mg, yield 90%). NMR δ: 4.83 (d, J=4 Hz, H-1), 3.40, 3.52 (2×OMe), 2.16 (OAc), 1.22 (d, J=6 Hz, Me).

Methyl 3,4-Di-*O*-methyl-α-D-fucopyranoside (8)——Compound **7** (100 mg) was deacetylated with 4 drops of triethylamine in methanolic solution (1 ml). After standing overnight, the reaction solution was evaporated to a syrup (76 mg, yield 92%). $[\alpha]_D^{25}$ +185° (c=0.5, methanol), NMR δ: 4.82 (d, J=3 Hz, H-1), 3.42, 3.62 (2×OMe), 1.25 (d, J=6 Hz, Me). *Anal.* Calcd for $C_9H_{18}O_5$: C, 52.41; H, 8.80. Found: C, 52.53; H, 8.85.

Methyl 3-*O*-Benzoyl-2-*O*-methyl-α-D-fucopyranoside (9)——Compound **5** (100 mg) was benzoylated with benzoyl chloride (73 mg) in pyridine (10 ml) at −40° for 5 hours. After adding water, the reaction mixture was extracted with chloroform, washed with water and then evaporated to a syrup, which showed two spots (*Rf* 0.82, 0.53 respectively, solvent A) on TLC. Fractionation of the syrup by silica gel column chromatography using benzene: acetone (10: 1) gave **9** (98.7 mg, yield 64%) and 3,4-dibenzoate (24.7 mg, 16%). The product (**9**) was recrystallized from diethyl ether, mp 93°, $[\alpha]_D^{25}$ +132° (c=0.5, chloroform). NMR δ: 4.85 (d, J=4 Hz, H-1), 3.40, 3.44 (OMe), 5.34 (d-d, J=3, 8 Hz, H-3), 8.04 (arom. 2H), 7.40 (arom. 3H), 1.22 (d, J=6 Hz, Me). *Anal.* Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.94; H, 6.88.

Methyl 3-*O*-Benzoyl-2,4-di-*O*-methyl-α-D-fucopyranoside (10)——Methylation of compound **9** (90 mg) by the Kuhn method gave a syrup (85 mg, yield 90%). NMR δ: 4.94 (d, J=2 Hz, H-1), 3.46, 3.48, 3.52 (OMe), 5.44 (d-d, J=3, 10 Hz, H-3), 8.14 (arom. 2H), 7.52 (arom. 3H), 1.20 (d, J=8 Hz, Me).

Methyl 2,4-Di-*O*-methyl-α-D-fucopyranoside (11)——Compound **10** (52 mg) was treated with 3 ml of methanolic potassium carbonate at 40° for 1 hour. The reaction mixture was passed through a column of ion exchange resin (Amberlite IR-120B (H^+)) using methanol as a solvent to yield 48 mg (yield 80%) of syrup. $[\alpha]_D^{25}$ +192° (c=1, methanol), *Anal.* Calcd for $C_9H_{18}O_5$: C, 52.41; H, 8.80. Found: C, 52.26; H, 8.79.

Methyl 4-*O*-Acetyl-2-*O*-methyl-α-D-fucopyranoside (13)——Compound **5** (100 mg) was added to a solution of triethyl orthoacetate (0.7 ml) and *p*-toluenesulfonic acid (0.2 mg) in benzene (0.8 ml). After stirring for 2 hours at room temperature, the reaction appeared to be complete on the basis of TLC using solvent B. Triethylamine (0.04 ml) was added. The resulting solution was washed with water while back extracting the aqueous layer with $CHCl_3$. The organic phases were combined and concentrated *in vacuo* to give a syrupy residue **12**, methyl 3,4-*O*-(ethyl orthoacetyl)-2-*O*-methyl-α-D-fucopyranoside, NMR δ: 4.78 (d, J= 4 Hz, H-1), 3.44, 3.56 (OMe), 1.20 (t, J=8 Hz, $-CH_2-C\underline{H}_3$), 3.58 (q, $-C\underline{H}_2-CH_3$), which was treated with 80% aqueous acetic acid (2 ml) for 10 minutes at room temperature. The reaction was monitored by TLC (solvent B), and stirring was stopped when **12** disappeared on the plate. The solution was then taken to dryness *in vacuo*. A crystalline product **13** was obtained in a yield of 46% based on compound **5**. mp 102°, $[\alpha]_D^{25}$ +163° (c=0.4, methanol), NMR δ: 4.92 (d, J=3 Hz, H-1), 3.46, 3.54 (OMe), 1.16 (d, J=7 Hz, Me), 2.20 (OAc), 5.25 (d-d, J=2, 4 Hz, H-4). *Anal.* Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.34; H, 7.80.

Methyl 4-*O*-Acetyl-2,3-di-*O*-methyl-α-D-fucopyranoside (14)——The procedure for the methylation of **13** (20 mg) was the same as that used for compound **7**. NMR δ: 4.85 (d, J=3 Hz, H-1), 3.41, 3.52 (2×OMe), 2.16 (OAc), 1.12 (d, J=8 Hz, Me).

Methyl 2,3-Di-*O*-methyl-α-D-fucopyranoside (15)——Compound **14** (8.5 mg) was deacetylated with a drop of triethylamine in aqueous methanol. A syrup was obtained in yield 90% (6.35 mg). $[\alpha]_D^{24}$ +191° (c=1, methanol) (lit. +190°[7]), NMR δ: 4.84 (d, J=2 Hz, H-1), 3.43, 3.52 (2×OMe), 1.29 (d, J=6 Hz, Me).

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