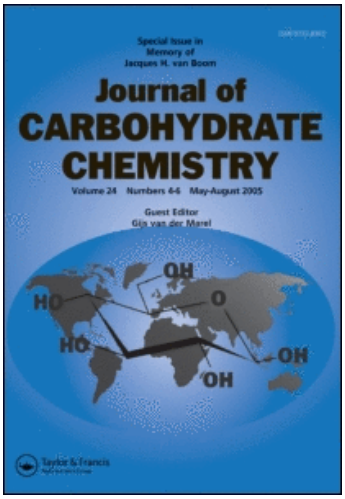

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CRYSTALLINE METHYL β-L-RHAMNOFURANOSIDE FROM FISCHER GLYCOSIDATION OF L-RHAMNOSE

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ABSTRACT

Flash chromatography of the mixture obtained by reaction of L-rhamnose with methanol in the presence of cation-exchange resin, in addition to methyl α-L-rhamnofuranoside (3) and methyl rhamnopyranosides 1 and 2 gave methyl β-L-rhamnofuranoside (4) in 8% yield. ^{13}C and ^{1}H NMR spectra of 3 and 4 as well as their calculated conformation in solution are discussed.

INTRODUCTION

From the acid catalyzed reaction of L-rhamnose with methanol three methyl glycosides are known: methyl α-L-rhamnopyranoside (1), obtained[1-6] from the equilibrium mixture in 50-78% yield by simple crystallization; methyl β-L-rhamnopyranoside (2), isolated[2,7,8] from the mother liquor in ca. 3% yield (usually via its crystalline tri-O-acetyl derivative); and methyl α-L-rhamnofuranoside (3), chromatographically separated in 30% yield from an early stage of the glycosidation reaction.[9-11] Regarding the low yield of 2 as compared to its maximum ratio in this reaction (ca. 17%)[12] on the one hand, and the markedly more complicated

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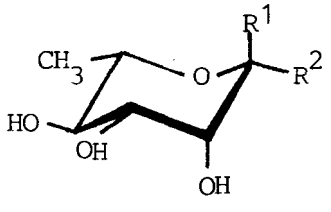
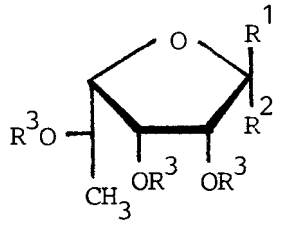
procedures for its synthesis by alternative routes[13-15] on the other, we decided to reinvestigate its isolation by chromatographic means.

RESULTS AND DISCUSSION

When repeating the chromatographic separations[9,10,16] of the glycosidation mixture we were surprised to find that the boiling of a mixture of L-rhamnose, strong cation-exchange resin and methanol for 90 min, i.e. under the conditions described by Anisuzzaman and Whistler,[10] yielded not only the previously described compounds 1, 2, 3, and unreacted L-rhamnose, but also an unknown compound 4, which all could be easily isolated by flash liquid chromatography. System chloroform/methanol[10] separated the pair 1 and 2 from compound 3 and compound 4, while system benzene/ethanol separated compounds 1, 3, and the pair 2 and 4; a combination of both chromatographic treatments gave all four compounds 1 - 4 in pure state.





1 $R^1 = OCH_3$, $R^2 = H$
2 $R^1 = H$, $R^2 = OCH_3$
3 $R^1 = OCH_3$, $R^2 = R^3 = H$
4 $R^1 = R^3 = H$, $R^2 = OCH_3$
7 $R^1 = H$, $R^2 = OCH_3$, $R^3 = COCH_3$
8 $R^1 = OCH_3$, $R^2 = H$, $R^3 = COCH_3$

The unknown 4, isolated after 30 min reaction period in 8% yield, mp 65 - 67° C, $[\alpha]_D$ +129° (water), turned out to be the remaining possible glycoside, methyl β-L-rhamnofuranoside (4),

having all four substituents oriented to one side of the tetrahydrofurane ring.[17,18]

As expected, no marked differences were observed for the ^{13}C chemical shifts of C-1, C-2, and C-3 signals of methyl β-L--rhamnofuranoside (4) and methyl β-D-mannofuranoside[19] (5), the replacement of CH_2OH at C-5 with CH_3 affected only the C-4 and C-5 resonances (Table 1). The latter was shielded by 4 p.p.m. due to this replacement, which corresponded to the results found by simple alcohols or hexopyranosides, respectively.[19,20] The downfield shift of C-4 (+4.5 p.p.m.) has also an analogy to hexopyranosides,[20] the analogy being the strong dependence upon axial or equatorial orientation of OH-4 (configuration D-manno +5 p.p.m., D-galacto +2.5 p.p.m.). According to the ^1H NMR data (Tables 2 and 3), both furanosides 4 and 5 have the side-chain in zigzag conformation, with anti-periplanar orientation of hydrogen atoms H-4 and H-5 ($J_{4,5}$ = 8.5 Hz). In other words, the spatial orientation of C-4 and C-5 substituents in the furanoside 4 should be the same as, for example, in methyl α-L-rhamnopyranoside (1) in $^1C_4$(L) conformation. The downfield shift observed is almost identical with that found with mannopyranosides but not with galactopyranosides.

The chemical shift difference of position 4 between rhamnofuranoside 4 and mannofuranoside 5 became evident also in ^1H NMR spectra (Table 2), replacement of CH_2OH by CH_3 caused an upfield shift of 0.21 p.p.m. At the same time, the conformity of vicinal coupling constants (Table 3) indicated that such a replacement did not markedly affect the conformation of the five membered ring, and thus both compounds will adopt the same segment of pseudorotational itinerary. To assign this segment, we used the recent empirical generalization[23] of the Karplus equation which takes into account not only the dependency of coupling constants on the electronegativities of substituents but also the spatial orientation of these substituents relative to the

TABLE 1

Carbon-13 Chemical-Shift Data for Methyl Glycofuranosides in Deuterium Oxide

Methyl furanoside	Chemical shifts (δ, p.p.m.)						
	C-1	C-2	C-3	C-4	C-5	C-6	CH_3O
α-L-rhamnoside[a] (3)	109.7	77.8	72.3	84.7	66.4	20.4	57.2
α-D-mannoside[19] (6)	109.7	77.9	72.5	80.5	70.6	64.5	57.2
β-L-rhamnoside (4)	103.5	73.2	70.9	85.1	66.9	20.3	56.6
β-D-mannoside[19] (5)	103.6	73.1	71.2[b]	80.7	71.0[b]	64.4	56.8

a. See also, Ref. 30. b. Assignments may be interchanged.

TABLE 2

Proton Chemical-Shift Data for Methyl Glycofuranosides in Deuterium Oxide

Methyl furanoside	Chemical shifts (δ, p.p.m.)						
	H-1	H-2	H-3	H-4	H-5	H-6	CH_3O
α-L-rhamnoside (3)	4.94	4.12	4.31	3.85	4.03	1.28	3.45
α-D-mannoside[21] (6)	4.93	4.12	4.31	3.97	--	--	3.43
β-L-rhamnoside (4)	4.88	4.19	4.28	3.77	4.03	1.30	3.38
β-D-mannoside[21] (5)	4.87	4.20	4.28	3.98	--	3.68	3.37

TABLE 3

Proton-Proton, Spin-Coupling Data for Methyl Glycofuranosides in Deuterium Oxide

Methyl furanoside	Coupling constants (Hz)				
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
α-L-rhamnoside (3)	4.5	4.5	2.6	7.9	6.0
α-D-mannoside[21,22] (6)	4.25	4.5	2.7	8.5	2.8 5.7
β-L-rhamnoside (4)	4.5	5.0	3.5	8.5	6.0
β-D-mannoside[21,22] (5)	4.5	5.0	3.6	8.5	--- 5.5

coupled protons. We have calculated coupling constants $J_{2,3}$ and $J_{3,4}$ for all conformations of the pseudorotational circuit, i.e. for all values of phase angle P (refs. 24 and 25), with puckering amplitude ϕ_m ranging from 32° to 45°. Assuming that methyl β-L-rhamnofuranoside (4) adopted only one segment of the pseudorotational itinerary in solution, the best fit values[26] were obtained for the segment with predominant $^2T_3$(L) conformation having the ϕ_m value of 35°. The calculated slopes of $J_{2,3}$ and $J_{3,4}$ are shown in Figure 1; for the conformation mentioned above, the theoretical values obtained are 4.98 Hz and 3.54 Hz. The same conformation, with quasi-axial anomeric methoxyl group and quasi-equatorial bulky side-chain, was proposed by Angyal[21] for L-enantiomer of glycoside 5, whereas Cyr and Perlin[22] prefered the conformation ^{4}E(L). For the last mentioned possibility, our calculations gave $J_{2,3}$ = 6.77 Hz and $J_{3,4}$ = 2.78 Hz, quite different from the experimental data (Table 3).

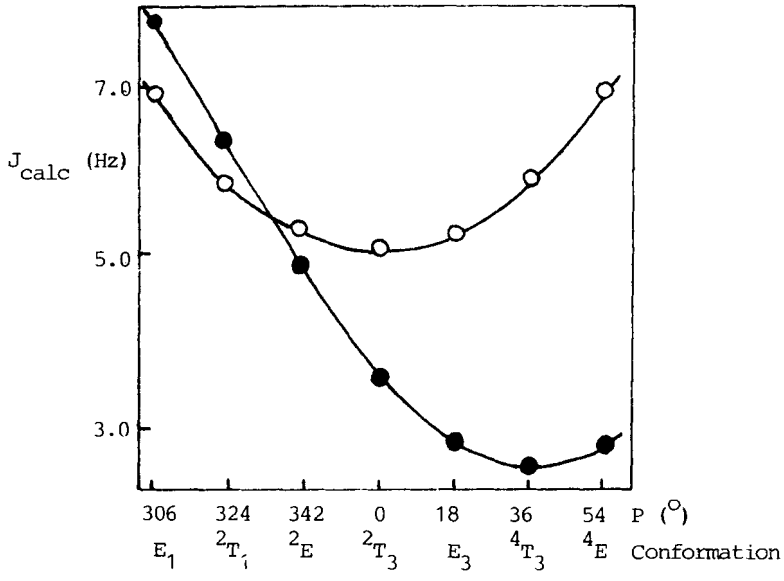


Fig. 1. Calculated coupling constants $J_{2,3}$ (o) and $J_{3,4}$ (●) in methyl β-L-rhamnofuranoside (4) as a function of conformation defined by the pseudorotation phase angle P (puckering amplitude ϕ_m 35°).

Principally, the same difference in ^{13}C and ^1H chemical shifts as found for the pair 4 and 5 can also be traced for the pair methyl α-L-rhamnofuranoside (3) and methyl α-D-mannofuranoside (6). The coupling constant values $J_{2,3}$ and $J_{3,4}$ indicate that 3 adopts the segment defined by $^2T_3$(L) conformation (P 0°), or partly by E_3(L) (P 18°) with puckering amplitude ϕ_m 39°. Other conformations from the calculated set (ϕ_m 32° - 45°, P 0° - - 360°) give a worse coincidence with experimental data. Angyal proposed[21] the conformation E_3(L) for L-enantiomer of 5, Cyr and Perlin[22] conformation ^4E(L). For the last mentioned conformation the calculated values ($J_{2,3}$ = 6.52 Hz, $J_{3,4}$ = 2.20 Hz) differ significantly from the experimental ones (Table 3).

As expected, methyl β-L-rhamnofuranoside (4) yielded a mixture of pyranosides 1 and 2 when heated with methanol in the

presence of cation-exchange resin. Acetylation of 4 gave syrupy tri-O-acetyl derivative 7, acetylation shifts of protons in ^{1}H NMR confirmed the furanoid structure of glycoside 4. Similarly, ^{1}H NMR spectrum of methyl 2,3,5-tri-O-acetyl-α-L-rhamnofuranoside (8) confirmed the furanoid structure of anomer 3.

Fischer glycosidation of L-rhamnose may thus give all four possible methyl rhamnosides including the uncommon methyl β-L--rhamnofuranoside (4) in reasonable yields; in the case of our target methyl β-L-rhamnopyranoside (2) the yield as high as 11% was obtained by simple chromatographic separation. As compounds of this type possess antiallergic activity,[28,29] our further attention will be paid to investigating the optimum conditions of the formation of each 1 - 4.

EXPERIMENTAL

General Procedures. Melting points were obtained with a Kofler hot stage apparatus and are uncorrected. Optical rotations were measured on an Opton Photoelectric Precision Polarimeter 0.005 at 20°C. ^{1}H NMR spectra were recorded with a Varian XL-100-15 at 100 MHz, ^{13}C NMR spectra with a Tesla BS-567 at 25.14 MHz, the spectra were recorded at 25°C. Tetramethylsilane (in deuterochloroform) and sodium 4,4-dimethyl-4-silapentane-1-sulfonate or 1,4-dioxane (in deuterium oxide) were the internal standards. Column chromatography was performed on silica gel Lachema (Brno) 100 - 160 μm and TLC on silica gel according to Stahl, 10 - 40 μm (Merck, Darmstadt), with solvent systems as follows: A, chloroform - methanol 15 : 1; B, benzene -ethanol 7 : 1; C, benzene - ethanol 20 : 1. Components on TLC plates were visualized by spraying with 1% cerium(IV) sulfate in 10% sulfuric acid and subsequent mineralization. Solutions were concentrated under reduced pressure.

Methyl β-L-rhamnofuranoside (4). A solution of L-rhamnose (1.88 g) in methanol (40 ml) was boiled for 30 min under reflux

with 6 ml of Amberlite IR 120 (H^+) resin. The mixture was then cooled, filtered, the resin washed thoroughly with methanol, and combined filtrates were evaporated to give a syrup. Three spots could be detected (TLC), in addition to unreacted L-rhamnose, in both solvent A [Rf values: 0.19 (3), 0.17 (4, tailing), 0.09 (1 + 2)] and solvent B [Rf values: 0.19 (3), 0.11 (1), 0.07 (2 + 4)]. The mixture was separated by column chromatography on silica gel (100 g, solvent A) to give a fraction of furanosides 3, 4 (950 mg) and a fraction of pyranosides 1, 2 (891 mg). Column chromatography of the furanoside fraction on silica gel (100 g) using solvent B afforded first the major compound, methyl α-L-rhamnofuranoside (3), 765 mg (37.5%), mp 56-58°C (ether, repeated recrystallization from benzene gave a sample with the same melting point), $[\alpha]_D$ -98° (c 1.2, water), -94° (c 1.0, chloroform), [ref.[10,30] mp 58°C (ether), ref.[9] mp 62°C (benzene), $[\alpha]_D$ -92° (chloroform),[10] -98.6° (water),[9] -97° (chloroform)[30]], followed by methyl β-L-rhamnofuranoside (4), 176 mg (8.6%). Compound 4 crystallized from ethereal solution after a charcoal treatment; recrystallization from the same solvent gave an analytical sample, mp 65 - 67°C, $[\alpha]_D$ +129° (c 1.3, water). Anal. Calcd for $C_7H_{14}O_5$ (178.2): C, 47.18; H, 7.92. Found: C, 47.32; H, 7.81. Pyranoside fraction was chromatographed on silica gel (100 g, solvent B) to give methyl α-L-rhamnopyranoside (1), (630 mg, 30.8%), mp 108 - 109°C (ethanol), $[\alpha]_D$ -63° (c 1.1, water), identical to an independently synthesized sample[3] [ref.[1] mp 108 - 109°C, $[\alpha]_D$ -62.5° (water), see also refs. 2 - 6, 16], followed by methyl β-L-rhamnopyranoside (2), 233 mg (11.4%) having the same physical constants as described in refs. 7 - 9, 13, 15, 16, mp 138 - 139°C, $[\alpha]_D$ +95° (c 1.1, water).

Reaction of Methyl β-L-rhamnofuranoside (4) with Methanol Catalyzed by Cation-exchange Resin. A solution of 4 (100 mg) in methanol (4 ml) was stirred for 30 h at 60°C with 0.5 ml of Amberlite IR 120 (H^+). The mixture was cooled, filtered, and

resin washed with methanol. The filtrate was evaporated to dryness and products were separated by column chromatography on silica gel (40 g). Elution with solvent B gave 93 mg of methyl α-L-rhamnopyranoside (1), followed by 5 mg of methyl β-L-rhamnopyranoside (2), identical to samples obtained above.

Methyl 2,3,5-tri-O-acetyl-β-L-rhamnofuranoside (7). Acetic anhydride (1.5 ml) was added to a solution of 4 (60 mg) in pyridine (2 ml) and the mixture was allowed to stand at room temperature overnight. After addition of water, the mixture was evaporated and the residue purified by chromatography on silica gel (20 g) using solvent C. Triacetate 7 was obtained as a colorless oil, 91 mg (89%), $[\alpha]_D$ +87° (c 0.9, chloroform). ^{1}H NMR ($CDCl_3$): 1.35 (3H, d, $J_{5,6}$ = 6.1 Hz, H-6), 1.98 (3H, s, CH_3COO), 2.08 (3H, s, CH_3COO), 2.10 (3H, s, CH_3COO), 3.40 (3H, s, CH_3O), 4.08 (1H, dd, $J_{3,4}$ = 4.8 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 5.0 (2H, m, H-1, H-2), 5.10 (1H, dq, $J_{4,5}$ = 9.0 Hz, $J_{5,6}$ = 6.1 Hz, H-5), 5.65 (1H, dt, $J_{2,3} = J_{3,4}$ = 4.8 Hz, $J_{1,3}$ = 1.0 Hz, H-3).

Anal. Calcd for $C_{13}H_{20}O_8$ (304.3): C, 51.31; H, 6.62. Found: C, 51.48; H, 6,58.

Methyl 2,3,5-tri-O-acetyl-α-L-rhamnofuranoside (8). A mixture of furanosides 3 and 4 (275 mg, 1 : 1) was acetylated with acetic anhydride (8 ml) in pyridine (13 ml). After the excess of reagent was decomposed with water, the mixture was evaporated to dryness and chromatographed on silica gel column (100 g) using benzene-ethanol 100 : 1. Triacetate 8 (162 mg) was eluted first, followed by β-anomer 7 (142 mg); mixed fractions were rechromatographed analogously. Methyl 2,3,5-tri-O-acetyl-α-L--rhamnofuranoside (8) did not crystallize, $[\alpha]_D$ -94° (c 1.0, chloroform). ^{1}H NMR ($CDCl_3$): 1.33 (3H, d, $J_{5,6}$ = 6.2 Hz, H-6), 1.98 (3H, s, CH_3COO), 2.05 (6H,, s, 2 x CH_3COO), 3.41 (3H, s, CH_3O), 4.15 (1H, dd, $J_{3,4}$ = 4.1 Hz, $J_{4,5}$ = 8.6 Hz, H-4), 5.00 (1H, d, $J_{1,2}$ = 3.3 Hz, H-1), 5.09 (1H, dq, $J_{4,5}$ = 8.6 Hz, $J_{5,6}$ =

= 6.2 Hz, H-5), 5.16 (1H, dd, $J_{1,2}$ = 3.3 Hz, $J_{2,3}$ = 5.0 Hz, H-2), 5.55 (1H, dd, $J_{2,3}$ = 5.0 Hz, $J_{3,4}$ = 4.1 Hz, H-3).

Anal. Calcd for $C_{13}H_{20}O_8$ (304.3): C, 51.31; H, 6.62. Found: C, 51.16; H, 6.43.

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26. We did not take into account the calculated $J_{1,2}$ values which are slightly higher ($^2T_3$(L) 5.73 Hz, ^2E(L) 5.35 Hz) than the experimental ones (Table 3). The same is true in the case of glycoside 3; the existence of two oxygen atoms at C-1 is not exactly reflected even by this method.

27. Optimum puckering amplitude ϕ_m 39° is lower than the amplitude of methyl α-L-lyxopyranoside (ϕ_m 43.1°, calculated from crystallographic data[33]). Coupling constants corresponding to the value 43.1° would be quite different from those for glycoside 3.

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