SYNTHESIS OF METHYL ETHERS OF METHYL (METHYL α-D-GLUCOPYRANOSID)URONATE

E. V. Evtushenko, and Yu. S. Ovodov

UDC 547.917+543.544.45

Methyl (methyl α-D-glucopyranosid)uronate (I) has been obtained by the catalytic oxidation of methyl α-D-glucopyranoside with oxygen in the presence of platinum on carbon with a yield of 31%. The partial methylation of (I) followed by preparative liquid column chromatography on silica gel has provided a convenient method of obtaining all the methyl ethers of (I) in the individual state.

Methyl ethers of uronic acids are necessary for structural investigations of acidic oligo- and polysaccharides. The most convenient method of obtaining methyl ethers of uronic acids is based on the oxidation of the primary hydroxy groups in methyl O-benzyl-O-methylhexopyranosides with chromium trioxide in acetone in the presence of dilute sulfuric acid [1, 2]. However, to obtain all the methyl ethers of, in particular, D-glucuronic acid requires a large number of synthetic stages [1].

In the present paper we propose a convenient method for obtaining all the methyl ethers of methyl (methyl α-D-glucopyranosid)uronate by its partial methylation followed by the preparative liquid chromatography of the methyl ethers and their acetates. Below we give the R_f and R_T* values of methyl ethers of methyl (methyl α-D-glucopyranosid)uronate:

	Positions of the methyl groups							
	0	*2*	*3*	*4*	*2,3*	*2,4*	*3,4*	*2,3,4*
R_f†	0,21	0,33	0,36	0,33	0.55	0,51	0,55	7,78
R_f	0,44	0,33	0,45	0,53	0,38	0,40	0,59	0,42
R_T	3,43	1,70	1,00	1,14	0,51	0,57	0,38	0,19
R_T†	1,57	1,27	1,05	0,92	0,59	0,78	0,35	—

As we see, the differences in the chromatographic mobilities of the methyl ethers of (I) in a thin layer permit their separation into fractions with equal degrees of substitution and, to some extent, within the fractions, i.e., the 3-O-methyl and 2,3-di-O-methyl ethers of (I) are obtained directly with good yields. The great differences in the mobilities of the acetates of the 3,4- and 2,4-di-O-methyl and the 2-, 3-, and 4-mono-O-methyl ethers, respectively, ensure the quantitative separation of these two mixtures at loads on the column of up to several grams. The overall yield of the individual acetate of the methyl ethers was 95%. This operation was monitored with the aid of TLC and GLC. The methyl ethers of (I) were identified by ^{13}C NMR spectroscopy (Table 1) using figures published previously [3].

EXPERIMENTAL

Melting points were measured on a Boëtius instrument and specific rotations on a Perkin-Elmer M 141 automatic polarimeter using chloroform solutions. ^{13}C NMR spectra were obtained on a Bruker HX-90E spectrometer, the chemical shifts (ppm) being measured relative to CH_3OH as standard, taking $\delta_{CH_3} = 49.6$ ppm. The solvent was D_2O. TLC was performed on silica gel L (5-40 μm, Chemapol). The chloroform–methanol (95:5) system was used for the methyl ethers of (I). Acetates of the methyl ethers of (I) were chromatographed in the ethyl acetate–hexane (1:1) system. GLC was performed on a Tsvet-106 instrument fitted with a flame-ionization de-

*In relation to the 3-O-methyl ether of (I) and (II, 1 min).
†Values given for the acetates.

Pacific Ocean Institute of Bioorganic Chemistry, Eastern Scientific Center, Academy of Sciences of the USSR, Vladivostok. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 35-37, January-February, 1987. Original article submitted May 28, 1986.

 0009-3130/87/2301-0026$12.50

TABLE 1. ^{13}C Chemical Shifts for Methyl (Methyl α-D-glucopyranosid)uronate and Its Methyl Ethers

Positions of the methyl groups	^{13}C chemical shifts										
	C-1	C-2	C-3	C-4	C-5	C 6	MeO-1	MeO-2	MeO-3	MeO-4	MeO-6
0	100,4	71.4	73,3	72,0	71,4	172,3	56.2				53.8
2	97,8	80,5	72,5	72,0	71.1	172,3	56.0	58,8			53,8
3	100.4	71,1	83,1	71,5	71,5	172,2	56,2		60.9		53.7
4	100.3	71,5	72,9	81,8	69,9	172,4	56,2			60,6	53,9
2,3	97,7	80,1	82,3	71.6	71.6	172,1	56,1	53,6	60,8		53,7
2,4	97,8	80,5	72,3	81,9	69,7	172,2	56.1	58,8		60,7	54,0
3,4	100,3	71,1	82,9	81,4	70.0	172,1	56,3		60,9	60,5	54.0
2,3,4	97,9	80,2	82,4	81,5	69,9	172.1	56,1	8,8	61.0	60,6	54,0

tector and double columns (0.3 × 200 cm). The packing used was 1.5% of NPGS on Chromaton N-AW-HMDS (0.125-0.160 mm, Chemapol). The rate of flow of argon was 60 ml/min. The thermostat temperature was 190°C. Column chromatography was performed on silica gel L (100-160 μm, Chemapol). The acetates of the methyl ethers of (I) were de-acetylated by treatment with a 0.1 N solution of sodium methanolate in absolute methanol at room temperature, with monitoring by TLC. The products obtained contained up to 20-30% of impurities (TLC) and were used for NMR spectroscopy.

Methyl (methyl α-D-glucopyranosid)uronate (I). The initial (I) was obtained by the catalytic oxidation of methyl α-D-glucopyranoside. With vigorous stirring, oxygen was passed through a solution of methyl α-D-glucopyranoside (10.0 g) in 150 ml of water in the presence of platinum on carbon (2.0 g) at 90°C for 5 h. Sodium bicarbonate (4.2 g) was added in four portions to maintain a weakly alkaline medium. The solution was filtered, de-ionized with KU-2 cation exchange resin (H^+), and evaporated. The resulting syrup was dissolved in absolute methanol and the solution was boiled under reflux for 1 h and was evaporated. The reaction product obtained was purified by chromatography on a silica gel column, using a gradient of methanol in chloroform. Chromatographically pure (I) was obtained with a yield of 3.5 g (31%) in the form of a syrup, $[\alpha]_D^{20}$ +123.2° (c 0.9).

Partial Methylation of (I). A solution of 6.0 g of compound (I) in 50 ml of methanol was treated with 6 ml of methyl iodide and 6.0 g of silver oxide, and the mixture was stirred with a magnetic stirrer in the dark at room temperature for 1 h. Then it was filtered and the filtrate was evaporated. This gave 6.3 g of a syrupy mixture of methylated derivatives of (I).

Separation of the Methyl Ethers of (I). The mixture of methylethers of (I) (6.0 g) was deposited on a column (3 × 45 cm). Elution with a gradient of methanol in chloroform gave: the 2,3,4-tri-O-methyl ether of (I) (0.4 g), syrup $[\alpha]_D^{20}$ +111.3° (c 1.2); the 2,4-di-O-methyl ether of (I) (1.0 g), syrup, $[\alpha]_D^{20}$ +130.7° (c 1.4); a mixture of the 2,3- and 3,4-di-O-methyl ethers of (I) (1.3 g); the 3-O-methyl ether of (I) (0.6 g), mp. 84-85°C, $[\alpha]_D^{20}$ + 133.1° (c 0.9); and a mixture of mono-O-methyl ethers of (I) (2.4 g). The mixtures of mono- and di-O-methyl ethers obtained were acetylated with acetic anhydride in pyridine and the products were chromatographed on a column of silica gel in a gradient of ethyl acetate in hexane. The load on the column (2 × 35 cm) of the mixture of acetates of 2,3- and 3,4-di-O-methyl ethers was 1.4 g. The yield of the acetate of the 3,4-di-O-methyl ether of (I) was 0.4 g, syrup, $[\alpha]_D^{20}$ +139.9° (c 1.3), and that of the acetate of the 2,3-di-O-methyl ether of (I) was 0.9 g, syrup, $[\alpha]_D^{20}$ +102.3° (c 0.9). The load on the column (3 × 45 cm) of the mixture of acetates of mono-O-methyl ethers was 2.8 g. The yield of the acetate of the 4-O-methyl ether of (I) was 0.5 g, mp 89-90°C, $[\alpha]_D^{20}$ +123.3° (c 0.9); that of the acetate of the 3-O-methyl ether of (I) was 0.5 g, syrup, $[\alpha]_D^{20}$ + 112.9° (c 2 3); and that of the acetate of the 2-O-methyl ether of (I) was 1.7 g, mp 67-68°C, $[\alpha]_D^{20}$ + 139.3° (c 1.3).

SUMMARY

A convenient method is proposed for the synthesis of all the methyl ethers of methyl (methyl α-D-glucopyranosid)uronate.

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SYNTHESIS OF METHYL ETHERS OF METHYL (METHYL β-D-GALACTOPYRANOSID)URONATE

E. V. Evtushenko and Yu. S. Ovodov

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The oxidation of methyl β-D-galactopyranoside with oxygen in the presence of platinum and carbon gave methyl (methyl β-D-galactopyranosid)uronate (I) with a yield of 20%. The partial methylation of (I) with methyl iodide in the presence of silver oxide followed by preparative liquid chromatography on silica gel provided a convenient method for obtaining all the methyl ethers in the individual state.

Syntheses of the methyl ethers of methyl (methyl α-D-galactopyranosid)uronate have been described previously (1) in which the key stage is the oxidation of the primary hydroxy group in partially methylated, partially benzylated, methyl α-D-galactopyranosides. To obtain methyl ethers of D-galacturonic acid, in the present work we have used the simpler approach proposed previously for obtaining methyl ethers of methyl (methyl α-D-glucopyranosid)uronate [2]. It is based on the catalytic oxidation of methyl β-D-galactopyranoside with oxygen in the presence of platinum on carbon, which takes place with the participation of the primary hydroxyl. The resulting uronic acid methyl glycoside is converted under the action of methanol into methyl (methyl β-D-galactopyranosid)uronate (I), by the partial methylation of which, followed by preparative liquid chromatography, the individual methyl ethers of (I) have been obtained.

The differences in the chromatographic mobilities of the methyl ethers of (I) enabled all the methyl ethers of (I) with the exception of the 2,3- and 2,4-di-O-methyl ethers to be obtained by liquid column chromatography. These ethers are readily crystallized from the usual solvents. The total yield of methyl ethers on chromatotraphy was 95%. The separation was monitored by TLC and GLC. Below we give the R_f and R_T values of the methyl ethers of (I) (* — retention times of the acetates of the methyl ethers):

	Positions of the methyl groups							
	2	3	4	2,3	2,4	3,4	2,3,4	—
R_f	0,31	0,25	0,28	0,45	0,46	0,42	0,63	0,08
R_T, NPGS, 210°	1,23	1,09	1,00 (13,2 min)	0,35	0,33	0,50	0,16	—
R_T^*, NPGS, 190°	0,68	1,00 (23,1 min)	1,08	0,30	0,44	0,74	0,19	1,40
R_T, QF-1, 175°	0,90	1,24	1,00 (12,3 min)	0,71	0,61	0,85	0,46	—
R_T^*, QF-1, 155°	1,00 (10,2 min)	1,38	2,00	0,35	0,70	1,24	0,26	2,29

^{13}C NMR spectroscopy was used for the identification of the methyl ethers of (I). The assignment of the signals in (I) was made by comparison with the spectrum of methyl β-D-galactopyranoside [3]. The assignment of the signals in the methyl ethers of (I) was made in the light of known laws [4]. The signals of the carbon atoms in the ^{13}C NMR spectra of the methyl ethers of (I) are given at the top of the next page.

EXPERIMENTAL

Melting points were measured on a Boëtius instrument. Specific rotations were determined on a Perkin-Elmer M 141 automatic polarimeter using methanol as the solvent. ^{13}C NMR spectra were obtained on a Bruker HX-90E spectrometer. Chemical shifts are given in parts per million

Pacific Ocean Institute of Bioorganic Chemistry. Far Eastern Scientific Center, Academy of Sciences of the USSR, Vladivostok. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 37-39, January-February, 1987. Original article submitted August 20, 1986.

 0009-3130/87/2301-0028$12.50