SYNTHESIS OF METHYL ETHERS OF METHYL 2-ACETAMIDO-2-DEOXY-α-D-GLUCOPYRANOSIDE

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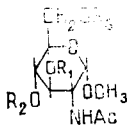
UDC 547.917+543.544.45

A convenient method is proposed for the synthesis of all the individual methyl ethers of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside based on the partial methylation of 2-acetamido-2-deoxy-α-D-glucopyranoside with dimethyl sulfate in an alkaline medium followed by preparative liquid column chromatography on silica gel of the resulting mixture of methyl ethers.

The directed syntheses of methyl ethers of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside (I) described previously [1] have a fairly large number of stages. We propose a convenient method for obtaining all the methyl ethers of (I) by the partial methylation of (I) followed by liquid chromatography of the methyl ethers and their acetates.

The initial (I) was obtained as described in [2] using a cation exchange resin. Preparative liquid chromatography of the acetylated methyl glycosides was used to eliminate the contaminating β-anomer.

Table 1 gives the chromatographic properties of the methyl ethers of (I) and their acetates. To separate the methyl ethers of (I) in accordance with their degrees of substitution we used liquid chromatography on silica gel. The mono- and di-O-methyl ethers were acetylated and the products were rechromatographed on a column of silica gel. Under these conditions complete separation of the acetates of the methyl ethers was achieved. The positions of the methyl groups were determined with the aid of the results of ^{13}C NMR spectroscopy published previously [3]



	R_1	R_2	R_3		R_1	R_2	R_3
I	H	H	H	IX	CH_3	Ac	Ac
II	CH_3	H	H	X	Ac	CH_3	Ac
III	H	CH_3	H	XI	Ac	Ac	CH_3
IV	H	H	CH_3	XII	CH_3	CH_3	Ac
V	CH_3	CH_3	H	XIII	CH_3	Ac	CH_3
VI	CH_3	H	CH_3	XIV	Ac	CH_3	CH_3
VII	H	CH_3	CH_3	XV	Ac	Ac	Ac
VIII	CH_3	CH_3	CH_3				

EXPERIMENTAL

Melting points were measured on Boëtius instrument. Specific rotations were determined on a Perkin-Elmer M-141 automatic polarimeter. NMR spectra were taken on Bruker WM-250 spectrometer. The solvent used was $CDCl_3$, with TMS as internal standard. TLC was performed on silica gel L 5-40 μ (Chemapol). The methanol–chloroform (1:9) system (1) was used for the methyl ethers of (I), the dioxane–chloroform (1:3) system (2) with glass columns for methyl ether acetates of (I), and the ethyl acetate–hexane (1:4) system (3) for the acetates of the methyl glucosaminides. Column chromatography was carried out on silica gel 63-100 μ (Chemapol). GLC was performed on a Tsvet-106 instrument with glass columns (0.3 × 200 cm). The liquid phases chosen were 1.5% of NPGS and 2% of QF-1 on Chromaton N-AW HMDS (0.125-0.160 mm) and 3% of ECNSS-M on Gas-Chrom Q (0.125-0.150 mm). The rate of flow of argon was 60 ml/min. The column thermostat temperature for the QF-1 and NPGS columns was 200°C, and for the ECNSS-M column 190°C.

Acetylation was carried out with acetic anhydride in pyridine.

Deacetylation. A solution of an acetate in absolute methanol (10 ml per 1 g) was treated with a 0.4 N solution of sodium methanolate in an amount of 0.003 equivalent of

Pacific Ocean Institute of Bioorganic Chemistry, Far Eastern Scientific Center, USSR Academy of Sciences, Vladivostok. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 787-790, November-December, 1987. Original article submitted March 11, 1987; revision submitted July 10, 1987.

0009-3130/87/2306-0651$12.50

TABLE 1. Chromatographic Properties of Methyl 2-Acetamido-2-deoxy-α-D-glucopyranoside and Its Methyl Ethers

Positions of the methyl groups	R_f	R_f^*	R_T^{**}		
			QF-1	NPGS	ECNSS-M
—	0,13	0,65	1,45	1,73	1,83
3	0,28	0,45	1,31	1,86	2,12
4	0,31	0,65	1,00	1,00	1,00
6	0,32	0,55	0,66	0,70	0,69
3,4	0,52	0,47	0,70	0,87	0,89
3,6	0,51	0,39	0,57	0,75	0,78
4,6	0,52	0,58	0,38	0,36	0,32
3,4,6	0,65	0,50	0,25	0,31	0,28

*Values given for the acetates.
**Retention times of the acetates of the methyl ethers of (I) relative to the acetate of the 4-O-methyl ether (X): for columns with QF-1, NPGS, and ECNSS-M, 15.3, 35.4, and 16.5 min, respectively.

sodium methanolate per one equivalent of the acetate. The mixture was kept at 60°C for 5 min. The process was monitored by TLC. The solution was cooled, deionized with KU-2 ion exchange resin (H^+), and filtered, and the filtrate was evaporated.

Methyl 2-Acetamido-2-deoxy-α-D-glucopyranoside (I). 2-Acetamido-2-deoxy-D-glucopyranose (10 g) was dissolved in absolute methanol (200 ml), and the solution was boiled in the presence of anhydrous KU-2 resin (H^+) (30 g) for 6 h. The resin was separated off by filtration and was washed with methanol, the filtrate was evaporated, and the residue was acetylated. The yield of the mixture of acetates of methyl glucosaminides was 13.8 g (85%). This mixture was deposited on a column of silica gel (3 × 40 cm) and elution was performed with a gradient of ethyl acetate in hexane. The yield of methyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranoside (XV) was 10.2 g; mp 112-113°C, $[\alpha]_D^{20}$ +86.0° (c 1.7; chloroform); R_f in system 3 — 0.53. For literature figures, see [10, 11]. PMR (δ, ppm): 1.96, 2.03, 2.04, 2.11, (4s, 12 H, 4 OAc); 3.42 (s, 3 H, OCH_3); 3.94 (m, 1 H, H-5); 4.11 (dd, 1 H, H-6); 4.25 (dd, 1 H, H-6); 4.36 (m, 1 H, H-2); 4.75 (d, 1 H, H-1); 5.17 (m, 2 H, H-3, H-4); 5.71 (d, 1 H, NH). The yield of methyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside was 2.0 g, mp 159-160°C, $[\alpha]_D^{20}$ −22.0 (c 1.0; methanol); R_f in system 3 — 0.47. For literature figures, see [4]. The deacetylation of 10 g of (XV) gave 6.0 g of (I), with mp 190-191°C, $[\alpha]_D^{20}$ +133.0 (c 1.5; water). For literature figurs, see [5].

Partial Methylation of (I). A solution of 5.8 g of (I) in the minimum amount of water was treated dropwise with dimethyl sulfate (9 ml) and a 30% solution of caustic soda (16 ml) with stirring by a magnetic stirrer at room temperature for 2 h. The solution was deionized with ion exchange resins and was evaporated. The yield of the mixture of methyl ethers in the form of a syrup was 6.1 g.

Liquid Chromatography of the Methyl Ethers of (I). The mixture of methyl ethers of (I) obtained (6.1 g) was deposited on a column (3 × 40 cm) of silica gel and was eluted with a gradient of methanol, in chloroform. This gave 0.2 g of 2-acetamido-3,4,6-tri-O-methyl-2-deoxy-α-D-glucopyranoside (VIII), mp 151°C, $[\alpha]_D^{20}$ +119.0° (c 1.6; chloroform). For literature figures, see [4]. PMR (δ, ppm): 2.03 (s, 3 H, OAc); 3.37, 3.43, 3.53, and 3.55 (4 s, 12 H, 4 OCH_3); 3.43 (m, 5 H, H-3, H-4, H-5, H-6, H-6'); 4.20 (m, 1 H, H-2); 4.66 (d, 1 H, H-1); 5.60 (d, 1 H, NH). The amount of the mixture of mono-O-methyl ethers of (I) obtained was 1.96 g, that of the mixture of di-O-methyl ethers of (I) was 0.92 g, and the amount of initial (I) recovered was 2.2 g.

A mixture of the acetates of the mono-O-methyl ethers of (I) (2.4 g) was deposited on a column (2 × 30 cm) of silica gel and was eluted with a gradient of dioxane in hexane. This gave 0.69 g of methyl 2-acetamido-3,6-di-O-acetyl-4-O-methyl-2-deoxy-δ-glucopyranoside (X), with mp 42-44°C, $[\alpha]_D^{20}$ +78.3° (c 1.6; chloroform). For literature figures, see [6]. PMR (δ, ppm): 2.04, 2.09, and 2.10 (3 s, 9 H, OAc); 3.37 and 3.40 (2 s, 6 H, 2 OCH_3); 3.58 (t, 1 H, H-4); 3.97 (m, 1 H, H-5); 4.10 (dd, 1 H, H-6); 4.21 (dd, 1 H, H-6'); 4.35 (m, 1 H, H-2); 4.74 (d, 1 H, H-1); 5.10 (t, 1 H, H-3); 5.65 (d, 1 H, NH). The deacetylation of (X) gave methyl 2-acetamido-4-O-methyl-2-deoxy-α-D-glucopyranoside (III), with mp 231°C, $[\alpha]_D^{20}$

+156.3° (c 1.1; methanol). For literature figures, see [6]. The yield of methyl 2-acetamido-3,4-di-O-acetyl-6-O-methyl-2-deoxy-α-D-glucopyranoside (XI) was 0.80 g, mp 120-122°C, $[\alpha]_D^{20}$ +93.2° (c 1.7; chloroform). For literature figures, see [7]. PMR (δ, ppm): 1.96. 2.04, and 2.06 (3 s, 9 H, 3 OAc); 3.38 and 3.43 (2 s, 6 H, 2 OCH_3); 3.45 (m, 2 H, H-6, H-6'); 3.87 (m, 1 H, H-5); 4.32 (m, 1 H, H-2); 4.73 (d, 1 H, H-1); 5.15 (m, 2 H, H-3, H-4); 5.70 (d, 1 H, NH). The deacetylation of (XI) gave 2-acetamido-6-O-methyl-2-deoxy-α-D-glucopyranoside (IV), mp 189-190°C, $[\alpha]_D^{20}$ +135.8° (c 1.5; methanol). For literature figures, see [7]. The yield of methyl 2-acetamido-4,6-di-O-acetyl-3-O-methyl-2-deoxy-α-D-glucoypranoside (IX) was 0.57 g, mp 171-172°C, $[\alpha]_D^{20}$ + 94.7° (c 1.3; chloroform). For literature figures, see [1]. PMR (δ, ppm): 1.96, 2.10, and 2.13 (3 s, 9 H, 3 OAc); 3.38 and 3.45 (2 s, 6 H, 2 OCH_3); 3.37 (t, 1 H, H-3); 3.78 (m, 1 H, H-5); 4.30 (m, 3 H, H-2, H-6, H-6'); 4.48 (d, 1 H, H-1); 5.19 (dd, 1 H, H-4); 5.73 (d, 1 H, NH). The deacetylation of (IX) gave methyl 2-acetamido-3-O-methyl-2-deoxy-α-D-glucopyranoside (II), with mp 211-212°C, $[\alpha]_D^{20}$ +119.2° (c 1.3; methanol). For literature figures, see [5].

The mixture of acetates of di-O-methyl ethers of (I) (0.9 g) was separated similarly. This gave 0.38 g of methyl 2-acetamido-3-O-acetyl-4,6-di-O-methyl-2-deoxy-α-D-glucopyranoside (XIV), mp 108-109°C, $[\alpha]_D^{20}$ +83.1° (c 1.2; chloroform). For literature figures, see [9]. PMR (δ, ppm): 1.95 and 2.10 (2 s, 6 H, 2 OAc); 3.38, 3.45, and 3.47 (3 s, 9 H, 3 OCH_3), 3.55 (m, 4 H, H-4, H-5, H-6, H-6'); 4.24 (m, 1 H, H-2); 4.70 (d, 1 H, H-1); 5.16 (dd, 1 H, H-3); 5.72 (d, 1 H, NH). After deacetylation, methyl 2-acetamideo-4,6-di-O-methyl-2-deoxy-α-D-glucopyranoside (VII) was obtained with mp 202-203°C, $[\alpha]_D^{20}$ + 142.3° (c 1.0; methanol). For literature figures, see [9]. The yield of methyl 2-acetamido-3,4-di-O-methyl-2-deoxy-α-D-glucopyranoside (XII) was 0.23 g; mp 171-172°C, $[\alpha]_D^{20}$ +114.0° (c 1.4; chloroform). For literature figures, see [8]. PMR (δ, ppm): 2.05 and 2.12 (2 s, 6 H, 2 OAc); 3.38, 3.55, and 3.56 (3 s, 9 H, 3 OCH_3); 3.29 (m, 2 H, H-3, H-4); 3.69 (m, 1 H, H-5); 4.27 (m, 3 H, H-2, H-6, H-6'); 4.63 (d, 1 H, H-1); 5.65 (d, 1 H, NH). The deacetylation of (XII) gave methyl 2-acetamido-3,4-di-O-methyl-2-deoxy-α-D-glucopyranoside (V) with mp 191-192°C, $[\alpha]_D^{20}$ + 142.5° (c 1.3; ethanol). For literature figures, see [8]. The yield of methyl 2-acetamido-4-O-acetyl-3,6-di-O-methyl-2-deoxy-α-D-glucopyranoside (XIII) was 0.12 g mp 163-165°C, $[\alpha]_D^{20}$ +98.3°(c 1.2; chloroform). For literature figures, see [1]. PMR (δ, ppm): 2.05 and 2.12 (2 s, 6 H, 2 OAc); 3.37, 3.39, and 3.42 (3 s, 9 H, 3 OCH_3); 3.53 (m, 3 H, H-3, H-6, H-6'); 3.81 (m, 1 H, H-5); 4.34 (m, 1 H, H-2); 4.74 (d, 1 H, H-1); 5.04 (t, 1 H, H-4); 5.62 (d, 1 H, NH). The deacetylation of (XIII) yielded methyl 2-acetamido-3,6-di-O-methyl-2-deoxy-α-D-glucopyranoside (VI), with mp 162-163°C, $[\alpha]_D^{20}$ +124.4° (c 1.3; methanol). For literature figures, see [1].

SUMMARY

A convenient method for obtaining all the individual methyl ethers of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside has been described.

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