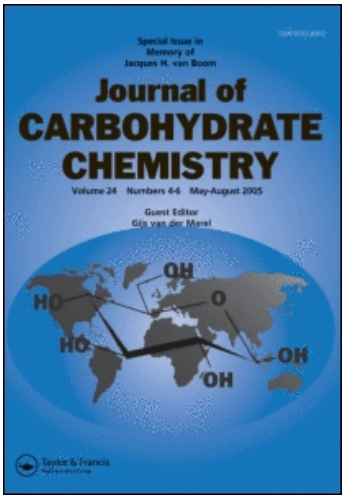

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AN UNUSUAL CYCLIC SYSTEM: DERIVATIVES OF *N*-ACETYL [2-DEOXY-β-D-MANNOPYRANOSID]URONO-6,2-LACTAM

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ABSTRACT

Syntheses are described of a new ring system, namely derivatives of *N*-acetyl [2-deoxy-β-D-mannopyranosid]urono-6,2-lactam. These were formed by participation of a 2-acetamido-2-deoxy group in the oxidation using pyridinium dichromate of a 6-hydroxyl group in a mannopyranosidic system The structures of the new compounds were determined mainly by NMR experiments *inter alia* by HMBC techniques.

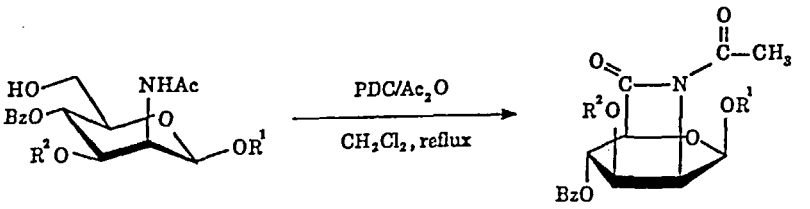
INTRODUCTION

We have previously reported the synthesis of a disaccharide derivative corresponding to the repeating unit of the capsular polysaccharide of *Haemophilus influenzae* type d, namely *p*-nitrophenyl 2-acetamido-3-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-β-D-mannopyranosiduronic acid.[1] In the course of that work, a ring closure to a novel cyclic imide system was observed. The reactions leading to this system and its identification are now described for the first time. The ring closure was not desired for the synthesis of the target compound, and was eventually circumvented by choosing an alternative reaction scheme already described.[1]

RESULTS AND DISCUSSION

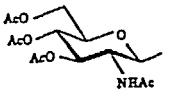
The ring closure was observed with both monosaccharide and disaccharide derivatives. Thus, upon oxidation with pyridinium dichromate (PDC) and acetic anhydride in dichloromethane[2] of methyl 2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-mannopyranoside

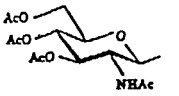
(6), the desired uronic acid was not formed. Instead, imidation by ring closure occurred, leading to compound 8 (50%). Similarly, the same oxidative treatment of *p*-nitrophenyl 2-acetamido-3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-4-*O*-benzoyl-2-deoxy-β-D-mannopyranoside (7) yielded the imido compound 9 (87%).



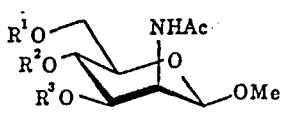
6 R^1=Me, R^2=Bz

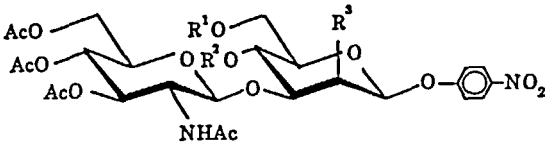
8 R^1=Me, R^2=Bz

7 R^1=  R^2= 

9 R^1=  R^2= 

The routes leading to the two imides were as follows: Methyl 2-acetamido-2-deoxy-β-D-mannopyranoside (1) was tritylated in the 6-position and then benzoylated to give 2. Detritylation of 2 then gave 6. *p*-Nitrophenyl 3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2–azido-4,6-*O*-benzylidene-2-deoxy–β-D-mannopyranoside (3)[1] was first reduced to the corresponding 2-amino compound which immediately was *N*-acetylated. The product 4 was then subjected to mild hydrolysis to remove the benzylidene group, giving the diol 5. This was selectively converted into the 6-*O*-*tert*-butyldimethylsilyl ether, monobenzoylation at the 4-position, followed by desilylation at the 6-position then gave 7.





1 R^1=R^2=R^3=H

2 R^1=CPh_3, R^2=R^3=Bz

3 R^1, R^2=PhCH, R^3=N_3

4 R^1, R^2=PhCH, R^3=NHAc

5 R^1=R^2=H, R^3=NHAc

Oxidation, as described above, of the 6-OH compounds 6 and 7 did not give the desired uronic acid derivatives. The ^{13}C NMR of the two products showed that an oxidation at C-6 had taken place, since the CH_2OH signal at ~62 ppm had been replaced by a carbonyl signal at ~165 ppm, but other changes that were not in accordance with the uronic acid structure were found in the spectra. Thus, the N-CO-CH_3 signals of the mannose unit had moved 3 ppm downfield and the C-2 signals 2 ppm downfield compared to the precursors (6 and 7), indicating that some change had taken place that involved the acetamido function at

TABLE I

Selected ^{1}H- and ^{13}C-NMR data for 8 (δ in ppm, J in Hz)

	1	2	3	4	5	6		NAc
^{13}C δ	97.4	52.6	71.7	74.4	75.2	166.5	C=O	170.5
^{1}H δ	5.18	5.51	5.53	5.38	4.66	—	CH_3	26.2
$^3J_{H,H}$	1.7	2.5	2.3	1.7	—	—		

TABLE II

Selected ^{1}H- and ^{13}C-NMR data for 9 (δ in ppm, J in Hz)

	1	2	3	4	5	6		NAc
^{13}C δ	94.7	51.9	74.7	75.0	75.8	165.5	C=O	170.5[a]
^{1}H δ	5.83	5.56	4.38	5.32	4.72	—	CH_3	26.4
$^3J_{H,H}$	1.7	2.3	2.3	1.6	—	—		
	1′	2′	3′	4′	5′	6′		NAc′
^{13}C δ	99.0	54.5	72.1	68.3	72.2	61.6	C=O	170.4[a]
^{1}H δ	5.00	3.86	5.28	5.07	3.60	4.12 4.03	CH_3	23.2
$^3J_{H,H}$	8.3	10.7	9.4	10.0	4.2/2.7	— —		

[a]May be interchanged.

C-2. The ^{1}H NMR spectra showed that all $^3J_{H,H}$ coupling constants of the mannose unit had changed dramatically, and all protons appeared almost as singlets with very small coupling constants (TABLES I and II) suggesting a considerable change of conformation. Furthermore, the ^{1}H NMR, did not show any carboxylic acid proton nor any amide proton.

Taking all these observations into consideration, we assumed the structures 8 and 9 for the two oxidation products. To verify these structures, ^{1}H-detected heteronuclear multiple bond connectivity by 2D multiple quantum NMR (HMBC) spectra were run, and it was found that for both compounds, H-2 was coupled to the C-6 carbonyl (FIG. 1 for compound 9), thereby proving the 2,6-bridge. Unambiguous assignments of ^{1}H and ^{13}C NMR spectra were made by phase-sensitive double quantum filtered COSY and HMQC spectra. Selected NMR data for compounds 8 and 9 are listed in TABLES I and II. Other NMR data and also elemental analyses were in agreement with the structures postulated. 2,6-Bridges in hexopyranoses have been reported,[3,4] but to the best of our knowledge, the present ring system has not been demonstrated before.

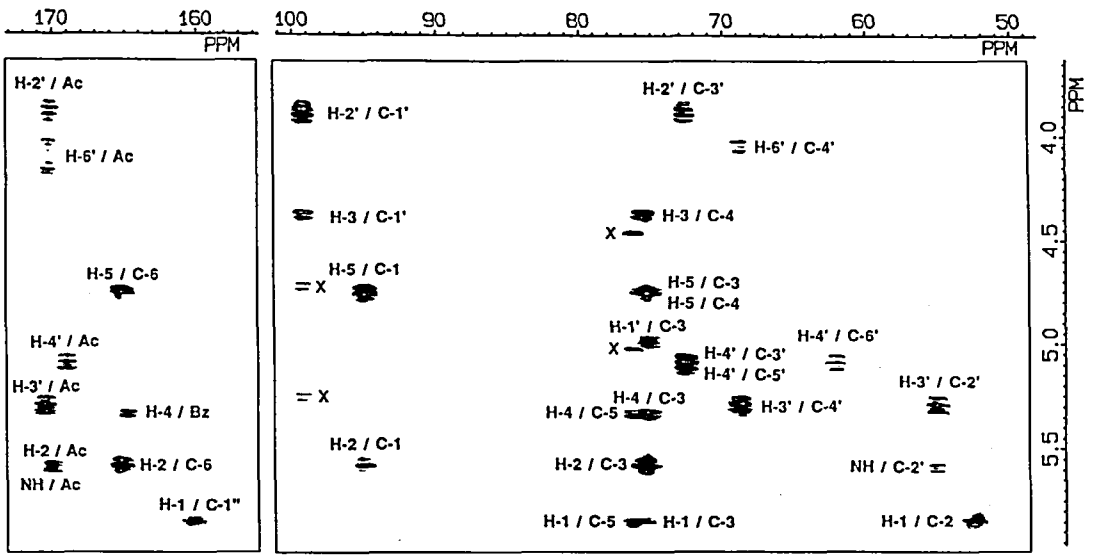


Fig. 1 *^{1}H-detected ^{1}H- and ^{13}C-multiple bond shift correlation (HMBC) spectrum of* **9**. *Incompletely supressed one bond correlations are indicated by X.*

EXPERIMENTAL

General methods. These were the same as those previously reported.[1] The NMR spectra of compounds **8** and **9** were recorded at ambient temperature in $CDCl_3$ (δ_C 77.02, δ_H 7.24) on a Varian XL300 spectrometer. ^{1}H observed one-bond and multiple-bond heteronuclear shift correlation (HMQC[5] and HMBC[6]) spectra of compounds **8** and **9** with sample spinning were acquired in phase-sensitive mode on a Varian XL300 spectrometer which had been modified to perform the experiments using a double difference method.[7] A bilinear rotation operator pulses (BIRD) followed by a delay (0.5 sec), or a low-pass *J*-filter was added at the beginning of the pulse sequence[7] to enhance the supression of signals arising from ^{12}C in the HMQC spectrum, or one-bond correlation peaks in the HMBC spectrum, respectively. Typically, the spectrum (SW 2114.6 Hz and SW2 11778.6 Hz) consisted of 2x192 increments of t_1, and each t_2 data set (2048 data points) was composed of 192 transients. A delay time of 3.45 msec was set for HMQC and 50 msec for HMBC. The second delay was set to zero in HMBC. Slight broadening in both dimensions were applied on FIDs prior to Fourier transformation (2048x512 points). ^{13}C decoupling was not applied during acquisitions.

Methyl 2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-6-*O*-trityl-β-D-manno-pyranoside (2). Trityl chloride (118 mg, 0.4 mmol) was added at room temperature to a solution of methyl 2-acetamido-2-deoxy-β-D-mannopyranoside[1] (**1**, 50 mg, 0.2 mmol)

and 4-dimethylaminopyridine (catalytic amount) in pyridine (1 mL) and the solution was heated at 40 °C for two days (TLC., chloroform-methanol, 9:1). The reaction mixture was diluted with dichloromethane and washed with water once, the organic layer was separated and concentrated and put onto a column and eluted with chloroform-methanol, 9:1. The crude monotritylated compound was dissolved in pyridine (3 ml) and benzoyl chloride (45 µL, 0.4 mmol) was added at 0.°C After 2 h (TLC, toluene-ethyl acetate, 1:1) the reaction mixture was concentrated and toluene was evaporated twice from the residue, whereafter column chromatography (toluene-ethyl acetate, 1:1) gave **2** (90 mg, 62%). $[\alpha]_D$ -79° (*c* 1.2, chloroform). ^{13}C-NMR data ($CDCl_3$): δ 23.3 (CH_3CON), 50.6, 56.9, 62.4, 67.0, 72.7, 74.3 (OCH_3, C-2, C-3, C-4, C-5, and C-6), 86.8 (CPh_3), 100.1 (C-1), 127.0-143.7 (aromatic C), 165.1, 165.8 (2xPhCO), 170.4 (CH_3CON).

Anal. Calcd. for $C_{42}H_{39}NO_8$: C, 73.6; H, 5.7; N, 2.0. Found: C, 73.2 ; H, 5.7; N, 2.0.

Methyl *N*-acetyl-3,4-di-*O*-benzoyl-2-deoxy-β-D-mannopyranosid-urono-6,2-lactam (8). A solution of **2** (90 mg, 0.13 mmol) in aqueous acetic acid (70%, 2mL) was stirred for 5 h at room temperature whereafter the reaction mixture was concentrated, toluene was evaporated twice from the residue, which then was purified by column chromatography (chloroform-methanol 9:1) to give methyl 2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-mannopyranoside (**6**, 49 mg, 83%). ^{13}C-NMR data ($CDCl_3$): δ 22.9 (CH_3CON), 50.8, 57.1, 61.0, 67.2, 72.2, 75,0 (OCH_3, C-2, C-3, C-4, C-5, and C-6), 100.6 (C-1), 128.2-133.7 (aromatic C), 165.9, 166.6 (2xPhCO), 171.4 (CH_3CON).

Acetic anhydride (84 µL, 0.88 mmol) was added at room temperature to a stirred suspension of pyridinium dichromate (65 mg, 0.22 mmol) and **6** (49 mg, 0.11 mmol) in dichloromethane (5 mL). The mixture was refluxed for 1 h (TLC., toluene-ethyl acetate, 6:1). The reaction mixture was cooled to room temperature, a few drops of methanol was added, and the mixture stirred for an additional 15 min. The reaction mixture was then placed on a silica gel column and eluted with ethyl acetate, concentrated and put on another column (toluene-ethyl acetate, 9:1) to yield **8** (20 mg, 50 %). $[\alpha]_D$ -216° (*c* 0.61, chloroform). ^{13}C-NMR data ($CDCl_3$): δ 55.6 (OCH_3), 128.6-133.8 (aromatic C), 165.3, 165.8 (2xPhCO), 170.5 (CH_3CON). For ^{1}H-NMR data ($CDCl_3$) and further ^{13}C-NMR data, see TABLE 1.

Anal. Calcd. for $C_{23}H_{21}NO_8$: C, 62.9; H, 4.8; N, 3.2. Found: C, 62.9; H, 5.0; N, 2.9.

***p*-Nitrophenyl 3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-2-deoxy-β-D-mannopyranoside (5).** Triphenylphosphine (58 mg, 0.22 mmol) was added at room temperature to a stirred solution of *p*-nitrophenyl 3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-mannopyranoside[1] (**3**, 150 mg, 0.20 mmol) in dichloromethane (10 mL) which was stirred overnight. Water (10 mL) was added and the

two-phase system was refluxed overnight. The organic layer was separated and toluene was evaporated twice from the residue. Acetyl chloride (23 μL, 0.32 mmol) was added at 0 °C to a stirred solution of the crude amine in dichloromethane/pyridine (1:1, 12 mL). After 1 h the reaction mixture was concentrated and toluene was evaporated twice from the residue which then was purified on a silica gel column (chloroform-methanol, 15:1) to give *p*-nitrophenyl 3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-mannopyranoside (**4**, 137 mg, 90 %). ^{13}C-NMR data (C_5D_5N): δ 20.4, 20.5 (*C*H$_3$CO), 23.1, 23.4 (*C*H$_3$CON), 50.4, 55.3, 62.9, 67.8, 68.9, 70.0, 72.6, 74.4, 75.9, 78.0 (C-2, 3, 4, 5, 6, C-2′, 3′, 4′, 5′ ,6′), 98.0, 100.1, 102.1 (C-1, C-1′, PhCH), 117.3-162.0 (aromatic C), 169.6, 170.5, 171.7 (carbonyl C).

4 (232 mg, 0.31 mmol) was suspended in aqueous acetic acid (5 mL, 70%) and heated at 70 °C for 1 h until TLC. indicated complete reaction (chloroform-methanol, 15:1). The reaction mixture was concentrated and toluene was evaporated twice from the residue, which then was purified on a silica gel column (chloroform-methanol, 15:1) to yield **5** (154 mg, 73 %), $[\alpha]_D$ -98° (*c* 1.1, pyridine). ^{13}C-NMR data (C_5D_5N): δ 20.4, 20.5, 20.6 (*C*H$_3$CO), 23.2, 23.4 (*C*H$_3$CON), 50.4, 55.0, 62.3, 62.8, 66.4, 70.0, 72.6, 74.6, 79.7, 80.6 (C-2, 3, 4, 5, 6, C-2′, 3′, 4′, 5′ ,6′), 97.7, 99.5 (C-1, C-1′), 117.1-162.3 (aromatic C), 169.7, 170.5, 171.9 (carbonyl C).

Anal. Calcd. for $C_{28}H_{37}N_3O_{16}$: C, 48.9; H, 5.4; N, 6.1. Found: C, 48.4; H, 5.2; N, 5.8.

***p*-Nitrophenyl 3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-4-*O*-benzoyl-2-deoxy-β-D-mannopyranoside** (**7**). *tert*-Butyldimethylsilyl chloride (89 mg, 0.6 mmol) was added at room temperature to a stirred solution of **5** (101 mg, 0.15 mmol) in pyridine (10 mL), which was stirred overnight. The solution was cooled to 0 °C and benzoyl chloride (35 μL, 0.3 mmol) was added. Stirring was continued for 2 h and the temperature allowed to attain room temperature. The reaction mixture was concentrated and toluene was evaporated twice from the residue. The residue was dissolved in a solution of triethylammonium fluoride in THF (5mL, 1M) and the solution was stirred at room temperature overnight. The reaction mixture was concentrated, dissolved in dichloromethane and washed with water, dried with magnesium sulphate, concentrated and put on a silica gel column (not flash chromatography, chloroform-methanol, 15:1) to yield **7** (98 mg, 86 %). $[\alpha]_D$ -115° (*c* 0.51, chloroform). ^{13}C-NMR data (C_5D_5N): δ 20.4, 20.5, 20.5 (*C*H$_3$CO), 23.1, 23.4 (*C*H$_3$CON), 50.1, 55.6, 62.0, 63.0, 69.0, 70.0, 72.5, 74.1, 77.2, 77.6, (C-2, 3, 4, 5, 6, C-2′, 3′, 4′, 5′ ,6′), 97.4, 100.2 (C-1, C-1′), 117.2-162.4 (aromatic C), 165.9, 169.6, 170.3, 170.7, 171.7 (carbonyl C).

Anal. Calcd. for $C_{35}H_{41}N_3O_{17}$: C, 54.2; H, 5.3; N, 5.4. Found: C, 54.2; H, 5.2; N, 5.1.

***p*-Nitrophenyl 3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*-acetyl-4-*O*-benzoyl-2-deoxy-β-D-mannopyranosiduro-no-6,2-lactam (9).** **7** (40 mg, 0.05 mmol) was treated in the same way as **6**, but the time of reaction was 30 min (TLC., chloroform-methanol, 9:1), and the second silica gel column was eluted with ethyl acetate, to yield **9** (34 mg, 87 %). $[\alpha]_D$ -136° (*c* 0.61, chloroform).^{13}C-NMR data ($CDCl_3$): δ 20.5, 20.6, 20.6 (CH_3CO), 116.7-143.2 (aromatic C), 160.4 (C-1′′), 165.0 (PhCO), 169.2 (CH_3CO-C-4′), 170.4, 170.5 (CH_3CONH, CH_3CON), 170.8, 171.1 (CH_3CO-C-3′, CH_3CO-C-6′). ^{1}H-NMR data ($CDCl_3$): δ 5.57 (NH, d, $J_{2',NH}$ 8.3 Hz). For further NMR data, see TABLE 2.

Anal. Calcd. for $C_{35}H_{37}N_3O_{17}$: C, 54.5; H, 4.8; N, 5.5. Found: C, 54.6; H, 5.1; N, 5.2.

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