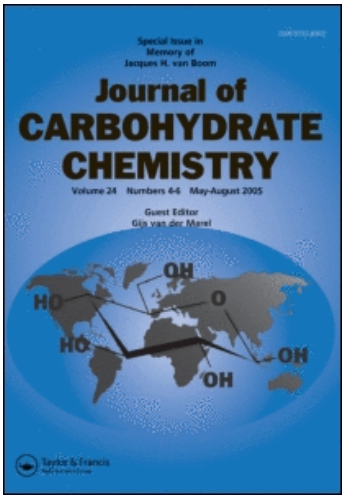

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SYNTHESIS OF NEW UREIDO SUGARS, DERIVATIVES OF 2-AMINO-2-DEOXY-D-GLUCOSE AND AMINO ACIDS

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ABSTRACT

Amino acid methyl, ethyl or benzyl esters have been used as amination agents in reaction with methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(4-nitrophenoxycarbonylamino)-β-**D**-glucopyranoside (**1**). Fourteen new ureido sugars, derivatives of 2-amino-2-deoxy-**D**-glucopyranoside and glycine, **L**-alanine, **L**-valine, **L**-leucine, **L**-phenylalanine, **L**-proline, **L**-aspartic acid and **L**-glutamic acid were obtained.

INTRODUCTION

Ureido sugars are intermediates in the synthesis of nitrosourea sugars, which form an important class of antitumor agents.[1] However, all clinically available agents produce toxic effects that prevent their wider therapeutic application. Thus, the search for new nitrosourea compounds with improved therapeutic indexes is an area of considerable interest.[2]

The most common procedures for the synthesis of ureido sugars and of thioureido sugars involve the reaction of sugar isocyanates and isothiocyanates with ammonia and amines.[3] The isocyanate (isothiocyanate) method has been utilized in the synthesis of a number of glycosyl ureides (glycosyl thioureides). For instance, Haring and Johnson

prepared **D**-glucosylhydantoic acid and **D**-glucosylthiohydantoic acid by treatment of 2,3,4,6-tetra-*O*-acetyl-β-**D**-glucopyranosyl isocyanate with glycine.[4] Micheel and Brunkhorst obtained other derivatives in this series by the same method.[5] Ogura and coworkers improved the method for the reaction of sugar isothiocyanates with some amino acids and obtained glucosyl thioureas in high yield.[6]

Our previous paper reported a new method of the synthesis of ureido sugars.[7] The reaction of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(4-nitrophenoxycarbonylamino)-β-**D**-glucopyranoside (**1**) with an alkylamine gave good yields of alkylureido derivatives which can be further nitrosated.[7] We now report the application of this method in a synthesis of a new class of ureido sugars, derivatives of **D**-glucosamine and amino acids.

RESULTS AND DISCUSSION

Starting from **1** and methyl, ethyl or benzyl esters of amino acids, we obtained fourteen new compounds in good to excellent yields. The yields obtained and some physical data for each compound are summarized in Table 1. The method used is outlined in the Scheme. The structures of **2-8** were confirmed by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR data of these compounds are given in Experimental section. The spectra showed signals corresponding to the glucopyranosyl and amino acid residues. The protons on NH groups attached to C_{α} of amino acid residues were observed in the range 6.03-5.34 ppm. The signals of the NH protons of **2a** and **2b** appeared as triplets ($J_{NH,CH}$ = 5.6 Hz and $J_{NH,CH}$ = 6.0 Hz respectively) due to coupling to the methylene group of the glycine residue. For **3-8** the signals of the NH protons appeared as doublets. The ^{13}C NMR data for **2-8** are given in Table 2. The spectra, as expected, showed signals for all of the carbons corresponding to the glucopyranosyl and amino acid residues. Moreover, signals were observed at 155.7-158.1 ppm for all products in the region where resonances for carbonyl atoms of the ureido groups absorb.[8]

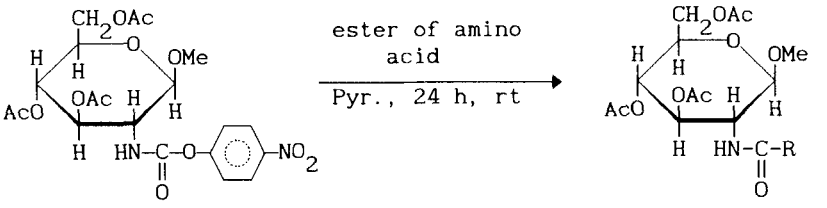
EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. NMR spectra were recorded for solutions in chloroform-*d*

TABLE 1. Physico-chemical and Analytical Data for Compounds 2-9

Compound	Yield (%)	Mp (°C)	$[\alpha]_D$ (degrees *c* 1, $CHCl_3$)	Formula	Analytical data					
					Calcd			Found		
					C	H	N	C	H	N
2a	83	141-143	+9.0	$C_{18}H_{28}O_{11}N_2$	48.21	6.29	6.25	48.22	6.15	6.07
2b	87	190-191	+8.2	$C_{23}H_{30}O_{11}N_2$	54.11	5.92	5.49	54.15	5.67	6.10
3a	75	149-150	+11.6	$C_{19}H_{30}O_{11}N_2$	49.34	6.54	6.06	49.44	6.33	6.09
3b	90	129-130	+4.8	$C_{24}H_{32}O_{11}N_2$	54.94	6.15	5.37	54.78	6.20	5.96
4a	82	174-175	+11.9	$C_{21}H_{34}O_{11}N_2$	51.42	6.99	5.71	51.53	6.87	5.81
4b	70	164-165	+2.2	$C_{26}H_{36}O_{11}N_2$	56.51	6.57	5.07	56.45	6.38	4.96
5a	78	171-172	+6.2	$C_{22}H_{36}O_{11}N_2$	52.37	7.19	5.55	52.41	6.96	5.70
5b	75	174-175	-2.1	$C_{27}H_{38}O_{11}N_2$	57.23	6.76	4.94	57.05	6.75	4.85
6a	80	168-169	+47.0	$C_{24}H_{32}O_{11}N_2$	54.95	6.15	5.34	55.10	6.13	5.24
6b	83	167-168	+15.0	$C_{30}H_{36}O_{11}N_2$	60.00	6.04	4.66	60.01	5.94	4.60
7a	68	184-185	-8.2	$C_{20}H_{30}O_{11}N_2$	50.62	6.37	5.90	50.77	6.32	5.68
7b	80	oil	-19.4	$C_{26}H_{34}O_{11}N_2$	56.71	6.22	5.09	56.61	6.13	4.98
8	91	140-142	+16.5	$C_{32}H_{38}O_{13}N_2$	58.35	5.82	4.25	58.44	5.80	4.15
9	89	190-191	+8.2	$C_{33}H_{40}O_{13}N_2$	58.92	5.99	4.16	59.06	6.01	3.97

SCHEME



1 2 - 9

2a R = NH-CH_2-COOEt

2b R = NH-CH_2-COOBzl

3a R = NH-CH(-CH_3)-COOEt

3b R = NH-CH(-CH_3)-COOBzl

4a R = NH-CH(-$CH(CH_3)_2$)-COOEt

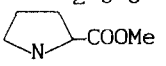
4b R = NH-CH(-$CH(CH_3)_2$)-COOBzl

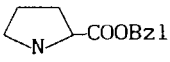
5a R = NH-CH(-$CH_2CH(CH_3)_2$)-COOEt

5b R = NH-CH(-$CH_2CH(CH_3)_2$)-COOBzl

6a R = NH-CH(-$CH_2C_6H_5$)-COOMe

6b R = NH-CH(-$CH_2C_6H_5$)-COOBzl

7a R = 

7b R = 

8 R = NH-CH(-$CH_2COOBzl$)-COOBzl

9 R = NH-CH(-$CH_2CH_2COOBzl$)-COOBzl

(internal Me_4Si) with a Jeol FX 90Q NMR spectrometer. TLC was performed on Silica Gel 60 F_{254} (Merck), using chloroform-acetone (4:1) as eluent and detection by UV light or by charring with sulfuric acid. Column chromatography was conducted on Silica Gel 60 (Merck 230-400 mesh) in chloroform-acetone (4:1). Amino acid esters were synthesized by conventional procedures.[9]

Synthesis of ureido sugars derivatives. To a solution of **1** (2 mmol) in pyridine (30 mL) was added the hydrochloride of a methyl or an ethyl ester of the amino acid

TABLE 2. ^{13}C NMR Data for Compounds 2-9 ($CDCl_3$, internal Me_4Si)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	OMe	CH_3COO	CH_3COO	N-CO-N	COO	C_α	C_β
2a	102.89	55.75	71.73	69.08	73.03	62.36	57.00	170.67, 169.48	20.70	158.04	171.01	42.26	
2b	102.89	55.70	71.68	68.92	72.93	62.25	57.00	170.72, 169.48	20.75	158.10	171.09	42.26	
3a	102.83	55.75	71.76	69.03	73.14	62.36	56.89	170.88, 170.72, 169.48	20.75	157.23	173.86	48.98	18.98
3b	102.83	55.76	71.75	68.86	73.13	62.25	56.89	170.99, 170.72, 169.48	20.75	157.28	173.65	48.98	18.91
4a	102.94	55.86	71.79	69.03	73.14	62.31	56.94	170.88, 170.72, 169.48	20.70	157.61	172.95	58.03	31.53
4b	102.99	55.97	71.79	68.75	73.03	62.14	57.00	170.99, 170.72, 169.42	20.70	157.50	172.73	57.97	31.48
5a	102.94	55.86	71.84	68.97	73.09	62.31	56.89	170.93, 170.61, 169.48	20.70	157.05	173.22	51.80	24.87
5b	102.89	55.82	71.73	68.81	73.05	62.22	56.94	170.95, 170.72, 169.48	20.70	157.39	173.75	51.80	24.81
6a	102.67	55.53	71.73	69.19	73.14	62.47	56.83	170.79, 170.67, 169.53	20.69	157.12	172.83	54.23	38.36
6b	102.67	55.59	71.63	68.92	72.98	62.26	56.83	170.88, 170.72, 169.42	20.70	156.98	172.13	54.07	38.25
7a	102.24	55.59	71.79	69.13	72.76	62.42	56.73	170.83, 170.78, 169.53	20.75	155.16	173.16	59.06	28.85
7b	102.24	55.48	71.79	68.97	72.82	62.36	56.67	170.88, 170.72, 169.48	20.75	155.76	172.51	59.11	29.85
8	102.73	55.64	71.69	68.97	72.98	62.31	56.83	170.72, 169.48	20.64	157.34	171.48 171.05	49.79	37.22
9	102.78	55.75	71.73	68.97	72.98	62.25	56.83	170.93, 170.67, 169.42	20.54	157.23	172.56 172.45	52.50	28.06

Remaining carbon atoms. **2a**: 55.75, 14.19; **2b**: 135.45, 128.62, 128.41, 128.19, 66.91; **3a**: 61.22, 14.14; **3b**: 135.61, 128.67, 128.30, 128.08, 66.97; **4a**: 61.06,.18.91, 17.72, 14.25; **4b**: 135.56, 129.57 ,128.35, 128.24, 66.86, 18.96, 17.50; **5a**: 61.17, 42.10, 22.91, 22.10, 14.14; **5b**: 135.61, 128.87, 128.74, 128.08, 41.88, 22.92, 20.00; **6a**: 136.54, 129.38, 128.41, 126.83, 52.06; **6b**: 136.15, 135.24, 129.38, 128.52, 128.78, 66.97; **7a**: 52.23, 46.00, 24.29; **7b**: 135.83, 128.57, 128.08, 126.94, 66.86, 46.00, 24.22; **8**: 135.50, 135.40, 128.57, 128.35, 128.08, 67.35, 66.64; **9**: 135.89, 135.40, 128.57, 128.35, 128.14, 67.18, 66.43, 30.19.

or the 4-toluenesulphonate of a benzyl ester (2 mmol), and triethylamine (0.28 mL, 2 mmol). The mixture was stirred for 24 h at room temperature. TLC then indicated the absence of **1**. After removal of the solvent under reduced pressure, the residue was dissolved in dichloromethane (40 mL) and washed with ammonia (1M), water, hydrochloric acid (1M), and water, then dried, and concentrated. Column chromatography of the residue and recrystallization from chloroform-hexane gave a ureido sugar. The following compounds were prepared in this manner.

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-glycine ethyl ester (2a)**: ^{1}H NMR δ 5.67 (t, 1H, J = 5.6 Hz, NHGly), 5.31-4.92 (m, 3H, H-3,4, NH), 4.42 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1), 4.28-4.15 (m, 4H, H-6a,6b, OCH_2), 4.08-3.86 (m, 2H, NCH_2), 3.79-3.62 (m, 2H, H-2,5), 3.55 (s, 3H, OMe), 2.09, 2.06, 2.02 (3s, 9H, 3Ac), 1.27 (t, 3H, J = 7.0 Hz, Me).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-glycine benzyl ester (2b)**: ^{1}H NMR δ 7.32 (s, 5H, Ph), 5.74 (t, 1H, J = 6.0 Hz, NHGly), 5.14 (s, 2H, CH_2Ph), 5.39-4.96 (m, 3H, H-3,4, NH), 4.48 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.27-4.15 (m, 2H, H-6a,6b), 4.06-3.78 (m, 2H, NCH_2), 3.73-3.64 (m, 2H, H-2,5), 3.50 (s, 3H, OMe), 2.07, 2.02, 2.00 (3s, 9H, 3Ac).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-L-alanine ethyl ester (3a)**: ^{1}H NMR δ 5.56 (d, 1H, J = 7.0 Hz, NHAla), 5.17 (d, 1H, J = 8.0 Hz, NH), 5.29-4.96 (m, 2H, H-3,4), 4.52-4.35 (m, 1H, NCH), 4.43 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1), 4.29-4.07 (m, 4H, H-6a,6b, OCH_2), 3.79-3.62 (m, 2H, H-2,5), 3.52 (s, 3H, OMe), 2.08, 2.04, 2.01 (3s, 9H, 3Ac), 1.32 (d, 3H, J = 7.0 Hz, Me), 1.27 (t, 3H, J = 7.0 Hz, Me).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-L-alanine benzyl ester (3b)**: ^{1}H NMR δ 7.32 (s, 5H, Ph), 5.62 (d, 1H, J = 6.0 Hz, NHAla), 5.55-5.34 (m, 3H, H-3,4, NH), 5.14 (s, 2H, CH_2Ph), 4.60-4.30 (m, 1H, NCH), 4.45 (s, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.25-4.05 (m, 2H, H-6a,6b), 3.82-3.54 (m, 2H, H-2.5), 3.47 (s, 3H, OMe), 2.06, 2.00 (3s, 9H, 3Ac), 1.35 (d, 3H, J = 8.0 Hz, Me).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-L-valine ethyl ester (4a)**: ^{1}H NMR δ 5.69 (d, 1H, J = 9.0 Hz, NHVal), 5.35-5.01 (m, 3H, H-3,4, NH), 4.52 (d, 1H, $J_{1,2}$ = 8.2 Hz, H-1), 4.57-4.13 (m, 5H, H-6a,6b, OCH_2, NCH), 3.85-3.69 (m, 2H, H-2,5), 3.57 (s, 3H, OMe), 2.55-2.30 (m, 1H, CH),

2.13-2.07 (3s, 9H, 3Ac), 1.33 (t, 3H, J = 7.0 Hz, Me), 1.04, 0.91 (2d, 6H, J = 6.6 Hz, 2Me).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N*'-carbamoyl-L-valine benzyl ester (4b)**: ^{1}H NMR δ 7.35 (s, 5H, Ph), 5.62 (d, 1H, J = 8.8 Hz, NHVal), 5.29-5.09 (m, 3H, H-3,4, NH) 5.15 (s, 2H, CH_2Ph), 4.94-4.38 (m, 1H, NCH), 4.41 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1), 4.23-4.04 (m, 2H, H-6a,6b), 3.78-3.64 (m, 2H, H-2,5), 3.51 (s, 3H, OMe), 2.20-1.70 (m, 1H, CH), 2.09, 2.01 (3s, 9H, 3Ac), 0.84 (2d, 6H, J = 7.0 Hz, 2Me).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N*'-carbamoyl-L-leucine ethyl ester (5a)**: ^{1}H NMR δ 5.34 (d, 1H, J = 8.0 Hz, NHLeu), 5.19-5.05 (m, 2H, H-3,4), 4.86 (d, 1H, J = 8.5 Hz, NH), 4.52-4.38 (m, 1H, NCH), 4.44 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.28-4.07 (m, 4H, H-6a,6b, OCH_2), 3.73-3.62 (m, 2H, H-2,5), 3.52 (s, 3H, OMe), 2.08, 2.04, 2.02 (3s, 9H, 3Ac), 1.60-1.56 (m, 3H, CH_2, CH), 1.27 (t, 3H J = 7.0 Hz, Me), 0.95 (2d, 6H, J = 5.3 Hz, 2Me).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N*'-carbamoyl-L-leucine benzyl ester (5b)**: ^{1}H NMR δ 7.37 (s, 5H, Ph), 5.51 (d, 1H, J = 8.5 Hz, NHLeu), 5.21-5.02 (m, 3H, H-3,4, NH), 5.17 (s, 2H, CH_2Ph), 4.55-4.38 (m, 1H, CH), 4.45 (d, 1H, $J_{1,2}$= 8.5 Hz, H-1), 4.30-4.07 (m, 2H, H-6a,6b), 3.80-3.66 (m, 2H, H-2,5), 3.52 (s, 3H, OMe), 2.11-2.04 (3s, 9H, 3Ac), 1.73-1.41 (m, 3H, CH, CH_2), 0.93 (2d, 6H, J = 4.7 Hz, 2Me).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N*'-carbamoyl-L-phenylalanine methyl ester (6a)**: ^{1}H NMR δ 7.38-7.05 (m, 5H, Ph), 5.94 (d, 1H, J = 7.5 Hz, NHPhe), 5.18-5.03 (m, 3H, H-3,4, NH), 4.94-4.62 (m, 1H, NCH), 4.40 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1), 4.26-4.16 (m, 2H, H-6a,6b), 3.69 (s, 3H, OMe ester), 3.75-3.55 (m, 2H, H-2,5), 3.45 (s, 3H, OMe), 3.07 (d, 2H, J = 5.7 Hz, CH_2Ph), 2.08, 2.02, 2.00 (3s, 9H, 3Ac).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N*'-carbamoyl-L-phenylalanine benzyl ester (6b)**: ^{1}H NMR δ 7.36, 7.30 (2s, 10H, 2Ph), 5.53 (d, 1H, J = 7.6 Hz, NHPhe), 5.20-4.73 (m, 4H, H-3,4, NCH, NH), 5.14 (s, 2H, OCH_2Ph), 4.42 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1), 4.40-4.07 (m, 2H, H-6a,6b), 3.79-3.64 (m, 2H, H-2,5), 3.45 (s, 3H, OMe), 3.08 (d, 2H, J = 5.7 Hz, CH_2Ph) 2.11, 2.05, 2.01 (3s, 9H, 3Ac).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-L-proline methyl ester (7a)**: ^{1}H NMR δ 5.37 (dd, 1H, J = 9.8, 9.4 Hz, H-3), 5.09 (dd, 1H, J = 9.8, 9.4 Hz, H-4), 4.70 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.65 (d, 1H, J = 9.0 Hz, NH), 4.39-4.07 (m, 3H, H-6a,6b, NCH), 3.75 (s, 3H, OMe ester), 3.85-3.68 (m, 2H, H-2,5), 3.52 (s, 3H, OMe), 3.50-3.40 (m, 2H, NCH_2), 2.15-2.03 (m, 4H, $2CH_2$), 2.10, 2.04 (3s, 9H, 3Ac).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-L-proline benzyl ester (7b)**: ^{1}H NMR δ 7.35 (s, 5H, Ph), 5.17 (s, 2H, CH_2Ph), 5.42-5.05 (m, 2H, H-3,4) 4.64 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.50 (d, 1H, J = 9.0 Hz, NH), 4.43-4.30 (m, 1H, NCH), 4.26-4.05 (m, 2H, H-6a,6b), 3.90-3.63 (m, 2H, H-2,5), 3.48 (s, 3H, OMe), 3.50-3.10 (m, 2H, NCH_2), 2.10-1.90 (m, 4H, $2CH_2$), 2.08, 2.01, 2.00 (3s, 9H, 3Ac).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-L-aspartic acid dibenzyl ester (8)**: ^{1}H NMR δ 7.32 (2s, 10H, 2Ph), 6.03 (d, 1H, J = 7.0 Hz, NHAsp), 5.13, 5.06 (2s, 4H, $2CH_2Ph$), 5.30-5.00 (m, 2H, H-3,4), 4.70-4.38 (m, 2H, NCH, NH), 4.63 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.28-4.05 (m, 2H, H-6a,6b), 3.77-3.60 (m, 2H, H-2,5), 3.45 (s, 3H, OMe), 3.04-2.94 (m, 2H, CH_2), 2.09, 2.03, 1.99 (3 s, 9H, 3Ac).

***N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-L-glutamic acid dibenzyl ester (9)**: ^{1}H NMR δ 7.34 (2s, 10H, 2Ph) 5.50 (d, 1H, J = 8.0 Hz, NHGlu), 5.28-4.96 (m, 2H, H-3,4), 5.15, 5.10 (2s, 4H, $2CH_2Ph$), 4.66-4.38 (m, 2H, NCH, NH), 4.43 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1), 4.28-4.05 (m, 2H, H-6a,6b), 3.77-3.60 (m, 2H, H-2,5), 3.47 (s, 3H, OMe), 2.50-1.87 (m, 4H, $2CH_2$), 2.09, 2.02, 1.98 (3s, 9H, 3Ac).

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