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Note

Novel synthesis of methyl 4,6-*O*-benzylidenespiro[2-deoxy-α-D-*arabino*-hexopyranoside-2,2′-imidazolidine] and its homologue and sugar-γ-butyrolactam derivatives from methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose

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ABSTRACT

Novel methyl 4,6-*O*-benzylidenespiro[2-deoxy-α-D-*arabino*-hexopyranoside-2,2′-imidazolidine] and its homologue methyl 4,6-*O*-benzylidene-3′,4′,5′,6′-tetrahydro-1′*H*-spiro[2-deoxy-α-D-*arabino*-hexopyranoside-2,2′-pyrimidine] have been synthesized in good yields by reaction of methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose with 1,2-diaminoethane and 1,3-diaminopropane. The results are completely different from the reaction with arylamines or alkylamines. One-pot synthesis of novel (*E*)-methyl 4-[hydroxy (methoxy)methylene]-5-oxo-1-alkyl-(4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranosido)[3,2-*b*]pyrrolidines has been achieved by the reaction of alkylamines with the butenolide-containing sugar, derived from the aldol condensation of methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose with diethyl malonate. These sugar-γ-butyrolactam derivatives are potential GABA receptor ligands.

Amino sugars and sugar–heterocyclic hybrids are of significant importance for use as tools in glycobiology and the treatment of many human diseases.[1] Among them, sugar lactams are not only important biological substances,[2] but also are synthetic precursors of imino sugars[3] and structural components of natural products.[4] Owing to their various biological properties and potential use, there has been significant interest in the synthesis of these types of compounds.[5] We developed a convenient one-pot method for the synthesis of new types of indole derivatives **2** and **3** by reaction of methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose **1** (Scheme 1) with arylamines.[6] In order to synthesize *N*-alkyl derivatives of allosamidin (a chitinase inhibitor), we developed another method for the selective synthesis of *N*-alkyl-D-allosamines **7** by reaction of **1** with alkylamines followed by reduction.[7] This method offers attractive and important features: (1) the easily available **1** undergoes a 'carbonyl group transfer' reaction to form **6** via the possible pathway shown in Scheme 1. The nucleophilic addition of alkylamine to **1** generates intermediate **4**. Dehydration of **4** in weakly acidic medium produces enol intermediate **5**, which undergoes isomerization to give keto **6**; (2) both steps for the synthesis of *N*-alkyl-D-allosamines show very high stereoselectivity.

In continuation of our studies on the application of methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose, herein we report the novel synthesis of sugar-containing spiro-imidazolidine and its homologue as well as sugar-γ-butyrolactam derivatives. In previous work, a compound containing a 2-substituted imidazolidine moiety showed prostate antagonist activity.[8] 2-Disubstituted imidazolidine was used as a catalyst for the conversion of an epoxide into the corresponding vicinal halohydrin with elemental halogen[9] and for efficient conversion of an epoxide into a β-hydroxy thiocyanate with ammonium thiocyanate in high yields under mild reaction conditions.[10] Chiral imidazolidines were shown to be efficient organocatalysts in the enantioselective addition reaction of nitroalkanes with α,β-unsaturated enones to prepare functionalized precursors of different complex organic molecules.[11] Sugar-containing imidazolidine and its homologue should be used as new water-soluble chiral catalysts for these reactions, and these compounds are expected to possess biological activities. 1,2-Diaminoethane was therefore employed to react with **1** (Scheme 2) in the presence of NH_4Cl at 60 °C. Sugar-containing spiro-imidazolidine **9** was obtained in 66% yield. The reactants obviously undergo a condensation reaction to form intermediate **8**, followed by an intramolecular nucleophilic addition reaction. This reaction was performed at different temperatures in various solvents such as THF, DMF, CH_2Cl_2 and cyclohexane. No 'carbonyl group transfer' product was formed. When 1,3-diaminopropane was used to react with **1**, the desired homologue **10** was produced

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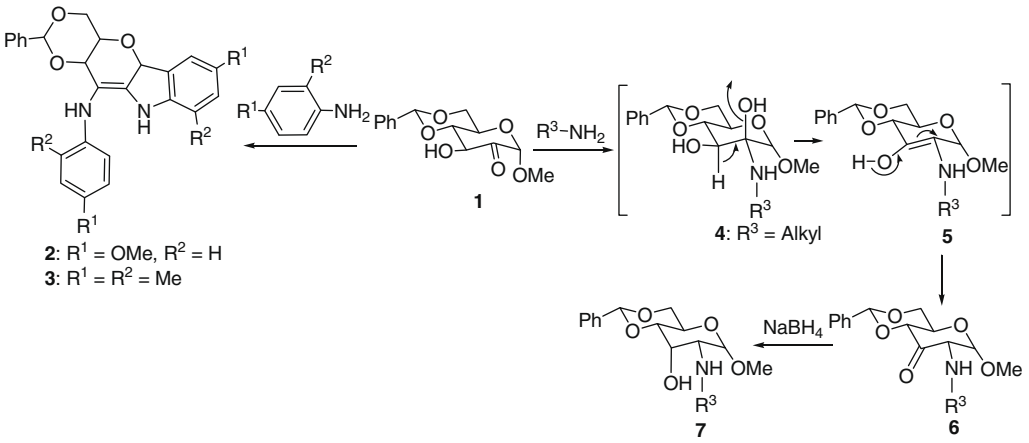
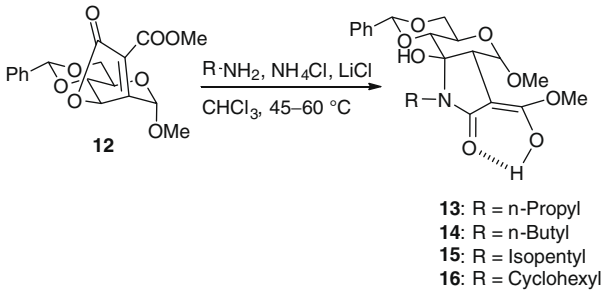


Scheme 1. Synthesis of indole derivatives and *N*-alkyl-D-allosamines.

in 63% yield. However, under the same conditions, thiosemicarbazide gave the condensation product **11** in 72% yield. No analogue of spiro-imidazolidine or 'carbonyl group transfer' product was formed. The new compounds were characterized by spectroscopic data. The high-resolution mass spectrum of compound **9** displayed an [M+1] peak at *m/z* 323.1624, together with elemental analysis indicating the formula to be $C_{16}H_{23}N_2O_5$. In the ^{1}H NMR spectrum, the proton that appeared as a singlet at δ 4.44 was assigned to H-1. The proton at δ 4.21 (d, *J* 10.0 Hz) was coupled with that at δ 3.73 (t, *J* 10.0 Hz). They were ascribed to H-3 and H-4. The four protons at δ 2.99–3.33, which appear as three multiplets, were assigned to the protons of the imidazolidinyl group. This was also confirmed by a DEPT spectrum showing two secondary carbons besides C-6. The ^{13}C NMR peak at δ 101.2 was assigned to C-1. The signal at δ 82.1 was ascribed to C-2. The two signals at δ 71.1 and 80.7 were assigned to C-3 and C-4. All the assignments were made on the basis of 2D NMR spectra.

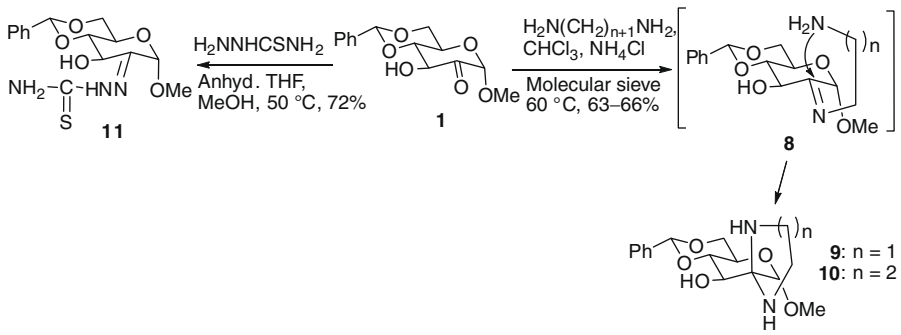
The different reaction patterns of methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose attracted our attempts to use it for the synthesis of sugar-γ-butyrolactam derivatives. γ-Butyrolactams are of biological relevance as GABA receptor ligands.[12] They have also been shown to possess anticonvulsant and antioxidant activity.[13] Besides, γ-butyrolactams can be used as biosynthetic precursors of GABA analogues and as key intermediates for the synthesis of pyrrolidines.[14] Consequently, fructose-fused γ-butyrolactams have been synthesized, and their preliminary biological evaluation as GABA receptor ligands has been performed.[2a] However, glucopyranoside-γ-butyrolactam and its derivatives remain unknown. Our synthesis began with the preparation of compound **12** (Scheme 3) by reaction of **1** with diethyl malonate in the presence of NaOMe as we formerly reported.[15] Propylamine



Scheme 3. Synthesis of sugar-γ-butyrolactam derivatives.

was then employed to react with **12** under various conditions to generate sugar-γ-butyrolactam derivative **13**. The temperature, catalyst and solvent have an influence on the reaction (Table 1, entries 1–6). The optimum temperature is 45 °C. Above 60 °C, TLC indicates that the reaction is complicated and the yield decreases, perhaps due to the cleavage of the benzylidene acetal in the weakly acidic medium. The solvent $CHCl_3$ is better than THF and MeCN, and a 65% yield of **13** is attained by the use of $CHCl_3$ in the presence of NH_4Cl and LiCl. The experiments were then performed with other alkylamines such as *n*-butylamine, isopentylamine and cyclohexylamine. The results are identical with that of propylamine, and the optimized results are depicted in Table 1, entries 7–9.

The new compounds were all characterized by spectroscopic data. The high-resolution mass spectrum of compound **13** showed an [M−Me] peak at *m/z* 406.1500, together with elemental analysis, indicating its formula to be $C_{21}H_{27}NO_8$. In the ^{1}H NMR



Scheme 2. Synthesis of sugar-containing spiro-imidazolidine and its homologue.

Table 1
Synthesis of sugar-γ-butyrolactam derivatives under various conditions

Entry	Temperature (°C)	Time (min)	Catalyst	Solvent	Product	Yield (%)
1	55	60	—	$CHCl_3$	**13**	38
2	55	30	NH_4Cl	$CHCl_3$	**13**	46
3	60	50	LiCl	$CHCl_3$	**13**	45
4	45	35	NH_4Cl, LiCl	$CHCl_3$	**13**	65
5	45	40	NH_4Cl, LiCl	THF	**13**	53
6	45	45	NH_4Cl, LiCl	MeCN	**13**	50
7	50	50	NH_4Cl, LiCl	$CHCl_3$	**14**	62
8	50	50	NH_4Cl, LiCl	$CHCl_3$	**15**	63
9	60	55	NH_4Cl, LiCl	$CHCl_3$	**16**	60

spectrum, the proton at δ 5.32 (d, *J* 4.4 Hz) was coupled with that at δ 4.09 (d, *J* 4.4 Hz). They are ascribed to H-1 and H-2, respectively. The proton at δ 4.64 (d, *J* 8.4 Hz) is assigned to H-4. These coupling patterns indicate that no H-3 exists. The DEPT spectrum showed three secondary carbon signals at δ 69.5, 42.0 and 23.0, corresponding to C-6 and those of propyl group. In the ^{13}C NMR spectrum, the two signals at δ 102.0 and 57.8 are ascribed to C-1 and C-2. The peak at δ 78.2 is ascribed to C-3. The three peaks displayed at δ 197.1, 170.7 and 168.1 as quaternary carbons were assigned to C=O, β- and α-unsaturated carbons, respectively. All the assignments are based on 2D spectra.

The reactants for the formation of the product **13**–**16** undergo a aminolysis, with subsequent rearrangement, followed by intramolecular nucleophilic addition as the main steps in one pot, as described in Scheme 4. The reaction sequence starts with a NH_4Cl–LiCl-catalyzed regioselective aminolysis of lactone **12** to form intermediate **17**, in which case, the five-membered ring is opened and the amide is formed. Subsequent double-bond migration produces dienol intermediate **18.** This is caused by the electron-withdrawing ester and amide groups. In **18**, an intramolecular hydrogen bond is easily formed as a stable six-membered ring between the enolic hydroxy and carbonyl group. The isomerization of the enolic group in the sugar ring generates keto intermediate **19**. This is followed by an intramolecular nucleophilic addition reaction to give the final products **13**–**16**.

In summary, several novel transformations of methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose to different amino-substituted derivatives have been conveniently achieved in good yields under mild conditions. Novel sugar-containing spiro-imidazolidine and its homologue spiro-tetrahydropyrimidine have been easily synthesized. The one-pot synthesis of novel sugar-γ-butyrolactam derivatives, which are potential GABA receptor ligands, has also been accomplished, and the possible pathway for their formation has been elucidated.

1. Experimental

1.1. General methods

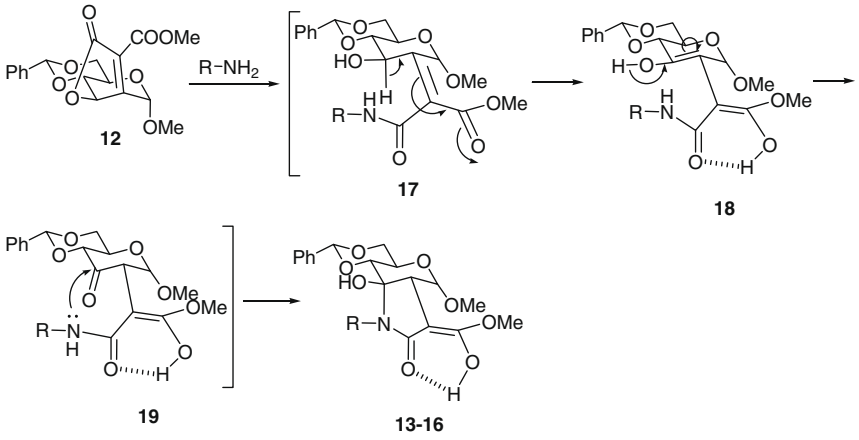
Melting points were measured in open capillary tubes or on a WC-1 melting point apparatus and are uncorrected. Elemental analyses were carried out on a MOD 1106 analyzer. Infrared spectra were recorded on a Shimadzu IR-435 instrument using KBr disks in the 400–4000 cm^{-1} region. NMR spectra were recorded with a Bruker DPX-400 spectrometer, and chemical shifts are given as δ values and are referenced to Me_4Si as the internal reference or to the residual solvent signal. Liquid secondary-ion mass spectrometry spectra were taken with a ZAB-2SE double-focusing mass spectrometer. Thin-layer chromatography (TLC) was carried out on glass plates coated with Silica Gel $60F_{254}$. The zones were detected with UV light when possible, or by charring with 1:9 concd H_2SO_4–EtOH followed by heating.

1.2. General procedure for the synthesis of compounds 9 and 10

A mixture of methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose (**1**, 0.50 g, 1.78 mmol), 4 Å molecular sieves (1.0 g), NH_4Cl (0.0090 g, 0.18 mmol) and dry $CHCl_3$ (15 mL) was stirred at 60 °C. 1,2-Diaminoethane or 1,3-diaminopropane (1.10 equiv) in 5 mL of dry $CHCl_3$ was added dropwise for 10 min. The reaction was monitored by TLC. Then the molecular sieves were filtered off. The filtrate was diluted with 15 mL of $CHCl_3$, washed with H_2O (1 × 5 mL) and brine (1 × 5 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was recrystallized from EtOH to give **9** or **10** as a crystalline solid.

1.2.1. Methyl 4,6-*O*-benzylidenespiro[2-deoxy-*a*-D-*arabino*-hexopyranoside-2,2′-imidazolidine] (9)

Yield: 66%; mp 155–156 °C; R_f 0.55 (2:1 cyclohexane–EtOAc); IR (KBr; cm^{-1}): 3324, 3300, 3096, 2960, 2921, 2868, 1458, 1405, 1153, 1095, 1068, 1042, 992, 981, 763, 704; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51–7.49 (m, 2H, Ph), 7.38–7.35 (m, 3H, Ph), 5.55 (s, 1H, PhC*H*), 4.44 (s, 1H, H-1), 4.28 (dd, 1H, $J_{6a,5}$ 3.2 Hz, $J_{6a,6b}$



Scheme 4. A possible pathway for the formation of **13**–**16**.

8.8 Hz, H-6a), 4.21 (d, 1H, $J_{3,4}$ 10.0 Hz, H-3), 3.87–3.84 (m, 2H, H-5, H-6b), 3.73 (t, 1H, $J_{4,3} = J_{4,5}$ 10.0 Hz, H-4), 3.44 (s, 3H, OMe), 3.33–3.14 (m, 2H, NCHCHN), 3.04–2.99 (m, 2H, NCHCHN); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.2, 129.2, 128.3, 126.4 (Ph), 102.0 (PhCH), 101.2 (C-1), 82.1 (C-2), 80.7 (C-4), 71.1 (C-3), 68.9 (C-6), 62.8 (C-5), 55.5 (OMe), 46.3, 45.3 (NCH_2CH_2N); HRFABMS (*m/z*): $[M+1]^+$ calcd for $C_{16}H_{23}N_2O_5^+$, 323.1607; found, 323.1624. Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.60; H, 6.86; N, 8.70.

1.2.2. Methyl 4,6-*O*-benzylidene-3′,4′,5′,6′-tetrahydro-1′*H*-spiro[2-deoxy-*a*-D-*arabino*-hexopyranoside-2,2′-pyrimidine] (10)

Yield: 63%; mp 142 °C (dec); R_f 0.65 (2:1 cyclohexane–EtOAc); IR (KBr; cm^{-1}): 3338, 3292, 2923, 2889, 1459, 1118, 1096, 1064, 999, 748, 700; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50–7.48 (m, 2H, Ph), 7.35–7.33 (m, 3H, Ph), 5.54 (s, 1H, PhC*H*), 5.12 (s, 1H, H-1), 4.25 (dd, 1H, $J_{6a,5}$ 4.4 Hz, $J_{6a,6b}$ 10.0 Hz, H-6a), 3.94–3.87 (m, 2H, H-4, H-6b), 3.82 (dt, 1H, $J_{5,6a}$ 4.4 Hz, $J_{5,6b} = J_{5,4}$ 10.0 Hz, H-5), 3.67 (d, 1H, $J_{3,4}$ 10.0 Hz, H-3), 3.48 (s, 3H, OMe), 3.07–2.87 (m, 4H, $NCH_2CH_2CH_2N$), 1.63–1.47 (m, 2H, $NCH_2CH_2CH_2N$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.3, 129.0, 128.2, 126.3 (Ph), 101.8 (PhCH), 96.7 (C-1), 78.2 (C-4), 72.0 (C-3), 71.1 (C-2), 68.8 (C-6), 62.7 (C-5), 55.6 (OMe), 40.1, 40.0 ($NCH_2CH_2CH_2N$), 25.8 ($NCH_2CH_2CH_2N$); HRFABMS (*m/z*): $[M+1]^+$ calcd for $C_{17}H_{25}N_2O_5^+$, 337.1763; found, 337.1748. Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.68; H, 7.18; N, 8.35.

1.3. (*E*/*Z*)-Methyl 4,6-*O*-benzylidene-2-deoxy-2-(2-carbamothioylhydrazono)-*a*-D-*arabino*-hexopyranoside (11)

A mixture of methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose (**1**, 0.40 g, 1.42 mmol), NH_4Cl (0.0070 g, 0.13 mmol) and dry THF (15 mL) was heated to 50 °C with stirring. Thiosemicarbazide (0.13 g, 1.42 mmol) in anhyd MeOH (5 mL) was added dropwise for 10 min. The reaction was monitored by TLC. Then the mixture was evaporated to dryness. The residue was dissolved in EtOAc (25 mL), washed with H_2O (1 × 5 mL) and brine (1 × 5 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was recrystallized from MeOH to give 0.36 g of **11** (72%) as white solid. Mp 169–171 °C; R_f 0.60 (1:1 cyclohexane–EtOAc); IR (KBr; cm^{-1}): 3434, 3313, 2937, 2882, 1600, 1499, 1452, 1404, 1089, 1055, 1030, 995, 947, 749, 696; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51–7.49 (m, 2H, Ph), 7.41–7.39 (m, 3H, Ph), 5.56 (s, 1H, PhC*H*), 5.08 (d, 1H, $J_{3,4}$ 10.0 Hz, H-3), 4.90 (s, 1H, H-1), 4.34 (dd, 1H, $J_{6a,5}$ 4.8 Hz, $J_{6a,6b}$ 10.0 Hz, H-6a), 4.01 (dt, 1H, $J_{5,6a}$ 4.8 Hz, $J_{5,6b} = J_{5,4}$ 10.0 Hz, H-5), 3.81–3.73 (m, 2H, H-4, H-6b), 3.43 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.1 (C=S), 141.6 (C-2), 136.4, 129.5, 128.4, 126.2 (Ph), 102.2 (PhCH), 102.0 (C-1), 82.3 (C-4), 74.1 (C-3), 68.7 (C-6), 62.7 (C-5), 55.1 (OMe); HRFABMS (*m/z*): $[M+1]^+$ calcd for $C_{15}H_{20}N_3O_5S^+$, 354.1124; found, 354.1120. Anal. Calcd for $C_{15}H_{19}N_3O_5S$: C, 50.98; H, 5.42; N, 11.89. Found: C, 50.97; H, 5.40; N, 11.88.

1.4. General procedure for the synthesis of compounds 13–16

A mixture of **12** (0.30 g, 0.83 mmol), LiCl (0.0017 g, 0.041 mmol), NH_4Cl (0.0022 g, 0.041 mmol) and dry $CHCl_3$ (20 mL) was heated to 45–60 °C (Table 1, entries 4, and 7–9) with stirring, to which 1.0 equiv of alkylamine in dry $CHCl_3$ (5 mL) was added dropwise for 15 min with stirring. The reaction was monitored by TLC. Then the solution was washed with H_2O (1 × 5 mL) and brine (1 × 5 mL), dried over Na_2SO_4 and evaporated to dryness. The residues crystallized from EtOH to give **13–16** as white solids.

1.4.1. (*E*)-Methyl 4-[hydroxy(methoxy)methylene]-5-oxo-1-propyl-(4,6-*O*-benzylidene-2-deoxy-*a*-D-glucopyranosido)[3,2-*b*]pyrrolidine (13)

Yield: 65%; mp 146–147 °C; R_f 0.45 (1:1 cyclohexane–EtOAc); IR (KBr; cm^{-1}): 3409, 2963, 2918, 1741, 1674, 1522, 1130, 1020, 752, 699; ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.51–7.48 (m, 2H, Ph), 7.38–7.36 (m, 3H, Ph), 5.73 (s, 1H, PhC*H*), 5.32 (d, 1H, $J_{1,2}$ 4.4 Hz, H-1), 4.64 (d, 1H, $J_{4,5}$ 8.4 Hz, H-4), 4.36 (dd, 1H, $J_{6a,5}$ 2.8 Hz, $J_{6a,6b}$ 8.4 Hz, H-6a), 4.09 (d, 1H, $J_{2,1}$ 4.4 Hz, H-2), 4.04–4.00 (m, 2H, H-5, H-6b), 3.74 (s, 3H, OMe), 3.40 (s, 3H, C(1)-OMe), 3.23–3.16 (m, 2H, NCH_2), 1.55–1.49 (m, 2H, $CH_3CH_2CH_2N$), 0.89 (t, 3H, *J* 7.2 Hz, $CH_3CH_2CH_2N$); ^{13}C NMR (acetone-d_6, 100 MHz): δ 197.1 (C=O), 170.7 (C=C(OH)OMe), 168.1 (C=C(OH)OMe), 138.4, 129.6, 128.7, 127.1 (Ph), 103.0 (PhCH), 102.0 (C-1), 82.9 (C-4), 78.2 (C-3), 69.5 (C-6), 66.6 (C-5), 57.8 (C-2), 55.6 ($C(1)OCH_3$), 53.2 (OCH_3), 42.0 ($NCH_2CH_2CH_3$), 23.0 ($NCH_2CH_2CH_3$), 11.4 ($NCH_2CH_2CH_3$); HRFABMS (*m/z*): $[M-Me]^+$ calcd for $C_{20}H_{24}NO_8^+$, 406.1502; found, 406.1500; $[M+H_2O-1]^+$ calcd for $C_{21}H_{28}NO_9^+$, 438.1764; found, 438.1748. Anal. Calcd for $C_{21}H_{27}NO_8$: C, 59.85; H, 6.46; N, 3.32. Found: C, 59.86; H, 6.44; N, 3.33.

1.4.2. (*E*)-Methyl 4-[hydroxy(methoxy)methylene]-5-oxo-1-butyl-(4,6-*O*-benzylidene-2-deoxy-*a*-D-glucopyranosido)[3,2-*b*]pyrrolidine (14)

Yield: 62%; mp 148–150 °C; R_f 0.50 (1:1 cyclohexane–EtOAc); IR (KBr; cm^{-1}): 3464, 2958, 2923, 1743, 1679, 1520, 770, 704; ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.37–7.35 (m, 2H, Ph), 7.34–7.23 (m, 3H, Ph), 5.60 (s, 1H, PhC*H*), 5.18 (d, 1H, $J_{1,2}$ 4.4 Hz, H-1), 4.51 (d, 1H, $J_{4,5}$ 8.8 Hz, H-4), 4.23 (dd, 1H, $J_{6a,5}$ 2.8 Hz, $J_{6a,6b}$ 8.0 Hz, H-6a), 3.95 (d, 1H, $J_{2,1}$ 4.4 Hz, H-2), 3.91–3.87 (m, 2H, H-5, H-6b), 3.60 (s, 3H, OMe), 3.27 (s, 3H, C(1)-OMe), 3.14–3.03 (m, 2H, CH_2N), 1.40–1.33 (m, 2H, $CH_3CH_2CH_2CH_2N$), 1.26–1.19 (m, 2H, $CH_3CH_2CH_2CH_2N$), 0.77 (t, 3H, *J* 7.2 Hz, $CH_3CH_2CH_2CH_2N$); ^{13}C NMR (acetone-d_6, 100 MHz): δ 197.2 (C=O), 170.7 (C=C(OH)OMe), 168.0 (C=C(OH)OMe), 138.4, 129.7, 128.7, 127.1 (Ph), 102.9 (PhCH), 102.1 (C-1), 82.9 (C-4), 78.2 (C-3), 69.6 (C-6), 66.6 (C-5), 57.8 (C-2), 55.7 ($C(1)OCH_3$), 53.2 (OCH_3), 39.9 ($NCH_2CH_2CH_2CH_3$), 31.9 ($NCH_2CH_2CH_2CH_3$), 20.4 ($NCH_2CH_2CH_2CH_3$), 13.9 ($NCH_2CH_2CH_2CH_3$); HRFABMS (*m/z*): $[M-Me]^+$ calcd for $C_{21}H_{26}NO_8^+$, 420.1658; found, 420.1700; $[M+H_2O-1]^+$ calcd for $C_{22}H_{30}NO_9^+$, 452.1921; found, 452.1937. Anal. Calcd for $C_{22}H_{29}NO_8$: C, 60.68; H, 6.71; N, 3.22. Found: C, 60.66; H, 6.70; N, 3.21.

1.4.3. (*E*)-Methyl 4-[hydroxy(methoxy)methylene]-5-oxo-1-(3-methylbutyl)-(4,6-*O*-benzylidene-2-deoxy-*a*-D-glucopyranosido)[3,2-*b*]pyrrolidine (15)

Yield: 63%; mp 134–135 °C; R_f 0.65 (1:1 cyclohexane–EtOAc); IR (KBr; cm^{-1}): 3467, 3417, 2965, 2930, 1744, 1675, 1522, 1128, 1092, 700; ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.51–7.48 (m, 2H, Ph), 7.39–7.36 (m, 3H, Ph), 5.73 (s, 1H, PhC*H*), 5.32 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 4.65 (d, 1H, $J_{4,5}$ 9.2 Hz, H-4), 4.36 (dd, 1H, $J_{6a,5}$ 2.4 Hz, $J_{6a,6b}$ 8.0 Hz, H-6a), 4.08 (d, 1H, $J_{2,1}$ 4.0 Hz, H-2), 4.04–4.01 (m, 2H, H-5, H-6b), 3.74 (s, 3H, OMe), 3.39 (s, 3H, C(1)-OMe), 3.23–3.15, 3.04–2.97 (m, each 1H, NCH_2), 1.64–1.59, 1.45–1.37 (m, each 1H, $CH_2CH(CH_3)_2$), 1.19–1.11 (m, 1H, $CH_2CH(CH_3)_2$), 0.90–0.87 (6H, m, $CH_2CH(CH_3)_2$); ^{13}C NMR (acetone-d_6, 100 MHz): δ 197.3 (C=O), 170.7 (C=C(OH)OMe), 168.1 (C=C(OH)OMe), 138.4, 129.7, 128.7, 127.1 (Ph), 102.9 (PhCH), 102.1 (C-1), 82.9 (C-4), 78.2 (C-3), 69.5 (C-6), 66.6 (C-5), 57.8 (C-2), 55.7 ($C(1)OCH_3$), 53.2 (OCH_3), 45.8 (NCH_2), 35.4 ($CH_2CH(CH_3)_2$), 27.5 ($CH_2CH(CH_3)_2$), 17.3, 11.4 ($CH_2CH(CH_3)_2$); HRFABMS (*m/z*): $[M+H_2O-1]^+$ calcd for $C_{23}H_{32}NO_9^+$, 466.2077; found, 466.2076. Anal. Calcd for $C_{23}H_{31}NO_8$: C, 61.46; H, 6.95; N, 3.12. Found: C, 61.45; H, 6.93; N, 3.13.

1.4.4. (*E*)-Methyl 4-[hydroxy(methoxy)methylene]-5-oxo-1-cyclohexyl-(4,6-*O*-benzylidene-2-deoxy-*a*-D-glucopyranosido)[3,2-*b*]pyrrolidine (16)

Yield: 60%; mp 132–134 °C; R_f 0.60 (1:1 cyclohexane–EtOAc); IR (KBr; cm^{-1}): 3383, 3298, 2926, 2852, 1744, 1670, 1124, 1084, 616, 637; ^1H NMR (acetone-d_6, 400 MHz): δ 7.50–7.49 (m, 2H, Ph), 7.38–7.36 (m, 3H, Ph), 5.73 (s, 1H, PhC*H*), 5.32 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.66 (d, 1H, $J_{4,5}$ 9.4 Hz, H-4), 4.36–4.34 (m, 1H, H-6a), 4.06 (d, 1H, $J_{2,1}$ 3.6 Hz, H-2), 4.03–4.00 (m, 2H, H-5, H-6b), 3.72 (s, 3H, OMe), 3.38 (s, 3H, C(1)-OMe), 1.92–1.85, 1.78–1.66, 1.58–1.55, 1.35–1.18 (m, 11H, cyclohexyl-H); ^{13}C NMR (acetone-d_6, 100 MHz): δ 197.7 (C=O), 170.6 (C=*C*(OH)OMe), 167.2 (*C*=C(OH)OMe), 138.3, 129.6, 128.7, 127.1 (Ph), 102.9 (Ph*C*H), 102.0 (C-1), 82.9 (C-4), 77.8 (C-3), 69.6 (C-6), 66.7 (C-5), 58.1 (C-2), 55.6 (C(1)O*C*H$_3$), 53.2 (O*C*H$_3$), 49.2, 32.8, 26.1, 25.2 (cyclohexyl-C); HRFABMS (*m*/*z*): $[M+H_2O-1]^+$ calcd for $C_{24}H_{32}NO_9^+$, 478.2077; found, 478.2032.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2010.01.004.

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