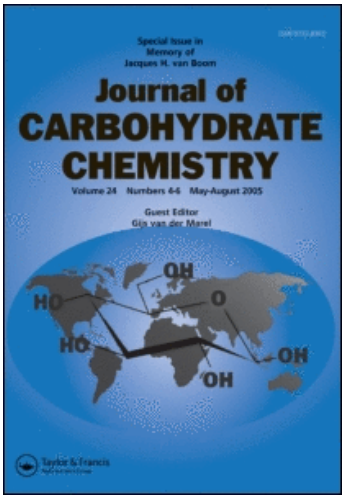

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CONJUGATE ADDITION OF AMINES TO SUGAR DERIVED OLEFINIC ESTERS: SYNTHESIS OF GLYCOSYLATED AMINO ESTERS AS DNA TOPOISOMERASE-II INHIBITORS

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ABSTRACT

Conjugate addition of amines to olefinic esters derived from sugars leading to formation of glycosylated amino esters in a stereoselective manner is described. Some of the synthesized compounds possess DNA topoisomerase-II enzyme inhibitory activities at low concentrations.

Key Words: Conjugate addition; Glycosyl amino ester; DNA topoisomerase-II

INTRODUCTION

The stereoselective introduction of amine functionality at a saturated carbon centre is becoming an important and challenging task for the synthesis of biomolecules. Among them, amino acids and amino sugars as synthetic precursors of β-lactams, peptido-mimetics and many antibiotics are most important.[1] Glycosylated aminoacid

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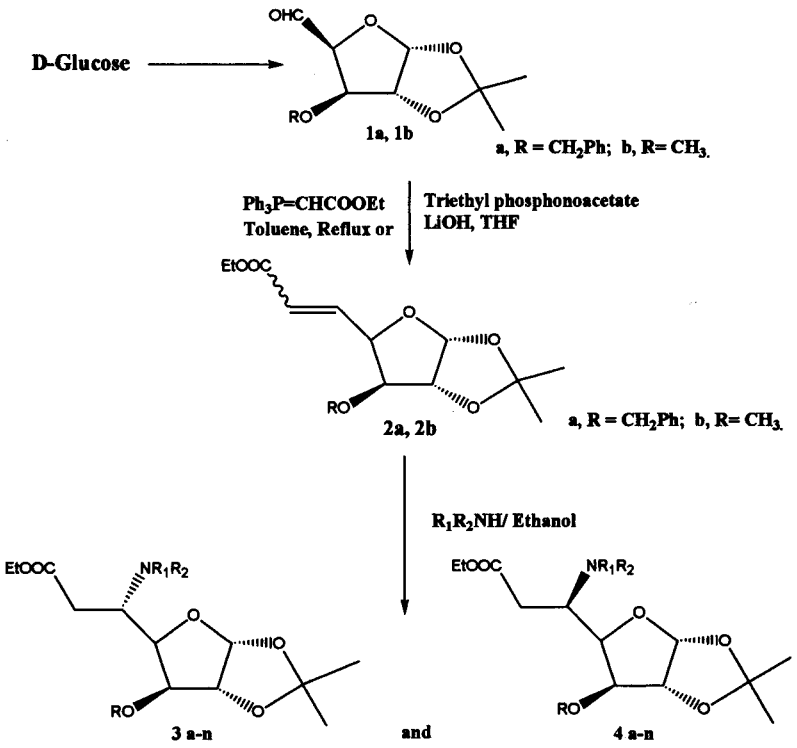
derivatives serve as scaffolds for combinatorial synthesis of glycopeptides and other glycoconjugates.[2,3]

In our ongoing study of glycoconjugates derived from glycosylated β-amino acids, a novel lead molecule has been developed for inhibition of filarial DNA topoisomerase-II, a target in filarial chemotherapy.[3,4] The common methods for stereoselective synthesis of β-amino acids involve either nucleophilic addition[5] of chiral amines to α,β-unsaturated carbonyl or nitrile compounds followed by further chemical manipulation, or nucleophilic addition of amines to chiral olefinic ester derived from chiral molecules.[6] Much information exists for the first approach while only limited information is available for the second one. In the present paper, conjugate addition of amines to the sugar derived olefinic esters and the effect of the resulting compounds on filarial DNA topoisomerase-II (isolated from *Setaria cervi*) are described.

RESULTS AND DISCUSSION

To start with, α,β-unsaturated esters **2a** and **2b** were prepared either by Wittig olefination of D-glucose derived aldehydes **1a** and **1b** or reacting the latter with triethyl phosphonoacetate (Scheme 1). Thus reaction of aldehydes **1a** and **1b** with carbethxymethylene triphenylphosphorane in refluxing toluene gave a mixture of *E* and *Z* isomers in 9:1 ratio, in quantitative yield. However, the reaction of the above aldehydes



Scheme 1. Conjugate addition of amines to sugar derived olefinic esters.

1a and **1b** with triethyl phosphonoacetate in tetrahydrofuran gave exclusively the *E* isomer in quantitative yield. The geometry of the double bond in the olefinic esters was determined on the basis of a ^{1}HNMR spectrum where the $J_{5,6}$ in the major and minor isomers were about 18 Hz and 7 Hz, confirming the *trans* (*E*) and *cis* (*Z*) geometry of the double bond in major and minor isomer respectively.

The attractive feature of stereoselective intermolecular Michael addition of substituted amines to α,β-unsaturated ester derived from D-glucose is that the stereoselectivity at the prochiral β-carbon atom may be controlled either by making use of appropriately protected sugar derived α,β-unsaturated esters or appropriately substituted amines.

Thus, reaction of dimethylamine with compound **2a**, having a 3-*O*-benzyl substituent, in anhydrous ethanol at room temperature gave compounds **3a** and **4a** as a diastereomeric mixture in a 68:32 ratio. Similarly, reaction of **2b**, having a 3-*O*-methyl substituent, with dimethylamine gave a diastereomeric mixture of **3h** and **4h** in almost the same ratio (67:33). Ratios of isomers were determined on the basis of ^{1}H NMR spectra where H-1 and H-2 have different chemical shifts in the major and minor isomers. Conjugate addition of amines with *E* and *Z* isomers were studied separately and it was found that the reaction was sluggish with the *E* isomer in comparison to the *Z* isomer and there was no improvement in stereoselectivity. Addition of amines to olefinic esters in methanol, THF and dichloromethane was also done. In methanol the reaction was fast but the trans esterified amino ester resulted. However, in acetonitrile, THF and dichloromethane the reaction was very slow. The lowering of the temperature of the reactions caused sluggishness in the reaction with no improvement in diastereoselection even with longer reaction times.

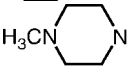
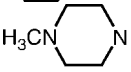
It is clear that 3-*O*-substitution here has only a very marginal effect on diastereoselectivity. Hence, we thought to use some more hindered amines as nucleophiles. The olefinic esters used were either of the *E* or *Z* stereochemistry or a mixture of the two. The effects of the size of amine substituent using *n*-butylamine, benzylamine, pyrrolidine, piperidine, morpholine and *N*-methylpiperazine were studied, both with bulky 3-*O*-benzyl and 3-*O*-methyl substituted olefinic ester derivatives. With *n*-butylamine, the ratio of major and minor isomers in both 3-*O*-benzyl and 3-*O*-methyl cases was almost equal (75:25, 65:35). Improved diastereoselection in the reaction of benzylamine with olefinic esters **2a** and **2b** was observed, as major to minor ratios were 80:20 and 65:35, respectively, indicating that both the amine as well as 3-*O*-substituent in the olefinic ester are important in diastereoselection.

With pyrrolidine, piperidine, morpholine and 1-methylpiperazine, additions to olefinic esters with 3-*O*-benzyl and 3-*O*-methyl substituents proceeded in very good diastereoselection. The best diastereoselection in these cases can be explained by formation of a nucleophilic iminium ion by protonation of amine with solvent to form a chelated transition state. Attack of nucleophile takes place only from the '*si*' face to give the '*S*' isomer.

During the course of this work,[3] a similar study of the conjugate addition of benzylamine to a 3-*O*-benzylated olefinic ester leading to formation of an azasugar was reported by Patil et al.[7] The stereochemistry at C-5 in the major and minor isomers was established as '*S*' and '*R*', respectively.

The stereochemistry at C-5 in compounds **3a–n** and **4a–n** (Table 1) was predicted on the basis of assignments made earlier.[7–9] It is known for a given C-5 epimeric pair, derived from D-glucofuranose, that the $J_{4,5}$, observed in a diastereoisomeric mixture is always higher in the L-*ido*-(C-5 with '*S*' configuration) isomer than in the D-*gluco*-(C-5 with '*R*' configuration) isomer. Further, comparison of the

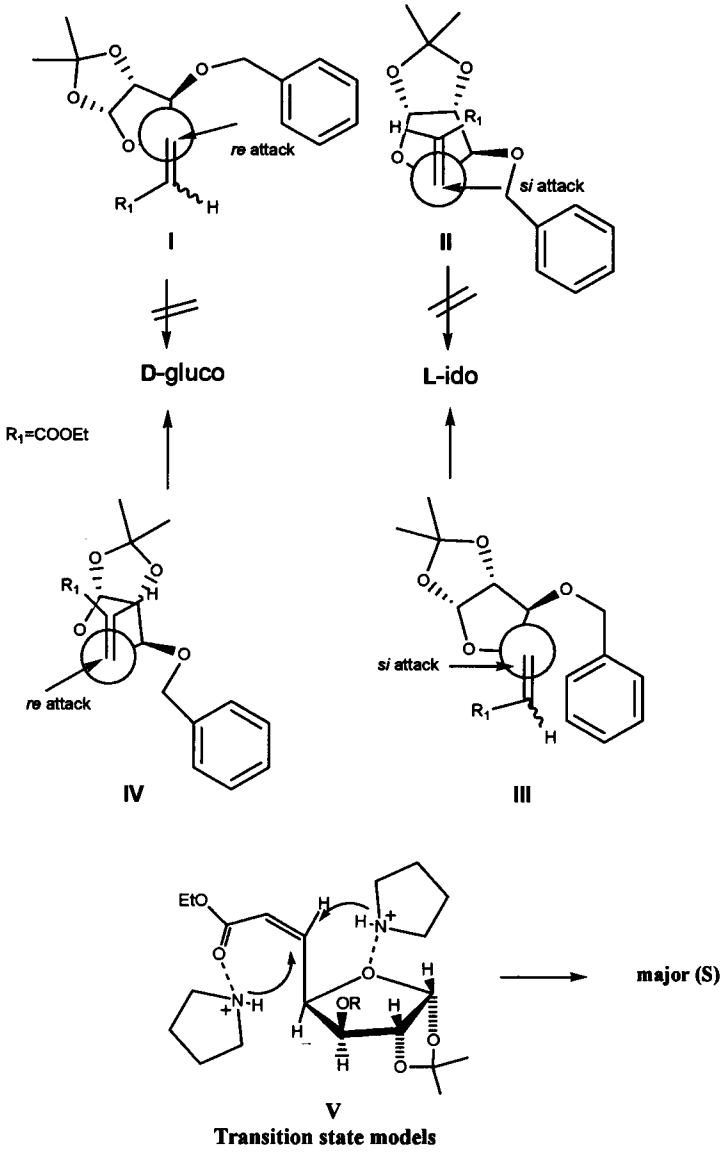
Table 1. Compounds Synthesized

Comp. No.	R	R_1R_2N	Major:Minor
3a and **4a**	CH_2Ph	$(CH_3)_2N$	68:32
3b and **4b**	CH_2Ph	CH_3 $(CH_2)_3NH$	75:25
3c and **4c**	CH_2Ph	$PhCH_2NH$	80:20
3d and **4d**	CH_2Ph		91:9
3e and **4e**	CH_2Ph		90:10
3f and **4f**	CH_2Ph		80:20
3g and **4g**	CH_2Ph		80:20
3h and **4h**	CH_3	$(CH_3)_2N$	67:33
3i and **4i**	CH_3	CH_3 $(CH_2)_3NH$	65:35
3j and **4j**	CH_3	$PhCH_2NH$	65:35
3k and **4k**	CH_3		89:11
3l and **4l**	CH_3		60:40
3m and **4m**	CH_3		80:20
3n and **4n**	CH_3		80:20

chemical shift of H-3 in both isomers is also reported to be diagnostic in deciding the stereochemistry in a given C-5 epimeric pair of D-glucofuranose derivatives, where it is significantly upfield in the L-*ido* isomer as compared to the D-*gluco* isomer. In the ^1H NMR spectra of amino esters **3a–n** and **4a–n**, the signal for H-4 in all the diastereoisomeric mixtures appears as 'dd', and $J_{4,5}$ in the major isomer is around 9 Hz, while in the minor isomer it is around 7 Hz. The chemical shifts for H-3 in the major and minor isomers are about δ 3.94 and δ 4.16, respectively, confirming that the major isomer has the L-*ido* (*S*)- and the minor isomer has the D-*gluco*-(*R*)-configuration at C-5.

The assignment of the '*S*' configuration to the major isomer and '*R*' to the minor isomer could be rationalised by considering the Felkin-Anh transition state models (**I–IV**).[8] In models **I** and **II**, the furanose ring oxygen is placed at a right angle to the C═C, while in **III** and **IV** the 3-*O*-substituent is at a right angle to C═C. Considering the transition states **I** and **II**, '*re*' face attack in **I** and '*si*' face attack in **II** are sterically hindered by the bulky 3-*O*-benzyl substituent. In transition state models **III** and **IV**, conformer **III** (*gauche*) has preference over **IV** due to the π-π interaction of alkene and aromatic system and thus would result in '*si*' face attack, leading to formation of product having the '*S*' stereochemistry at C-5 (Scheme 2).

With pyrrolidine and piperidine as nucleophiles the distereoselection in the 3-*O*-Me derivative is similar to that observed in the 3-*O*-CH_2Ph derivative. This can be rationalised by considering a transition state (**V**) where the pyrrolidinium and piperidinium cation, generated by protonation of amines with alcohol, forms a chelated complex with a



Scheme 2. Transition state models I–V.

furanose ring oxygen and a carbonyl oxygen. In the latter case, the attack of amines is preferred from '*si*' face giving product with the '*S*' configuration at C-5.

DNA Topoisomerase-II Estimation

The reaction catalyzed by DNA topoisomerase-II was measured as reported previously.[3] The standard topoisomerase-II reaction mixture in a final volume of 20

Table 2. Effect of Sugar Derivatives on DNA Topoisomerase-II Inhibitory Activity of Filarial Parasite *Setaria cervi*

Compounds	% Inhibition at (20 μg/Reaction Mixture)	% Inhibition at (5 μg/Reaction Mixture)
3a and **4a**	10	nd
3b and **4b**	46	nd
3c and **4c**	27	nd
3d and **4d**	14	nd
3e and **4e**	Nil	nd
3f and **4f**	27	nd
3g and **4g**	30	nd
3h and **4h**	>90	55
3i and **4i**	>95	60
3j and **4j**	>95	67
3k and **4k**	>80	36
3l and **4l**	>85	Nil
3m and **4m**	>95	20
3n and **4n**	>95	15
Novobiocin (100 nmol)	100	nd
NaldixicAcid (100 nmol)	90	nd

The enzyme was incubated with the compound at 37°C for 10 min and reaction started by addition of pBR322 DNA.
nd = not done.

μL contained 50 mM Tris-HCl (pH 7.5), 50 mM KCl, 10 mM $MgCl_2$, 1 mM ATP, 0.1 mM EDTA, 0.5 mM DDT, 30 μg /mL BSA, 0.25 μg pBR322 and enzyme. The reaction was stopped by adding 5 μL of stop buffer followed by electrophoresis of samples on 1% agarose-gel in Tris-acetate buffer for 18 h at 20 V. Gels were stained with ethidium bromide (0.5 μg/ mL) and visualized on a GDS 7500 UVP (Ultra Violet Products, UK) transilluminator. The effect of inhibitors on the enzyme activity was measured by incubating enzyme with inhibitor (20 μg/ reaction mixture) for 10 min at 37°C and starting the reaction by addition of pBR322. The percent inhibition was determined by measuring the microdensitometry of the gel with a Gel Base/Gel Blot Pro Gel analysis software program (Ultra Violet Products, U.K.). The results obtained for various glycosylated amino esters are summarized in Table 2 and compared with the lead compounds novobiocin and nalidixic acid.

Biological Activity

The percent inhibition of DNA topoisomerase-II of filarial parasite *S. cervi* by glycosylated amino esters is shown in Table 2. Almost all the compounds showed inhibition ranging from more than 10% to 95% at 20 μg/reaction mixture concentration. Compounds possessing more than 80% inhibition at this concentration were tested at 5 μg/reaction mixture concentration. A careful examination of the inhibitory activities associated with the molecules indicates that compounds possessing hydrophobic and

rigid amines at C-5 offer better enzyme inhibitory activity. One compound (**3j**) showing >95% inhibition at 20 μg/reaction mixtures has been selected for further studies, which will be reported in due course.

EXPERIMENTAL

General methods. All melting points were uncorrected. The excess of the reagents or solvents were evaporated under reduced pressure at a bath temperature between the range 45–55°C. The optical rotations were measured in a 0.5 dm tube with Jasco dip-140 polarimeter in chloroform or ethyl acetate. Elemental analyses were performed on a Perkin-Elmer 2400 II elemental analyzer. Column chromatography was performed on silica gel (silica gel 60, 70–230 mesh, Merck). Thin-layer chromatography (silica gel) was used to monitor the reactions. TLC plates were developed in iodine vapors and also by spraying with 5% sulfuric acid in alcohol followed by heating at 100°C.

Ethyl[3-*O*-benzyl-5,6-dideoxy-5-dimethylamino-1,2-*O*-isopropylidene]-α-D-*gluco* and β-L-*ido*-heptofuranuronates (3a, 4a). (*E*) (1*R*, 2*R*, 3*S*, 4*R*) Ethyl-(3-*O*-benzyl-1,2-*O*-isopropylidene-1,4-pentofuranose-4-yl)-hept-5-enoate **2a** (5 g, 14.375 mmol) dissolved in ethanol (50 mL), was magnetically stirred with dimethylamine hydrochloride (2.4 g, 29.425 mmol) and $NaHCO_3$ (0.75 g, 8.925 mmol) at rt for 16-18 h. The reaction mixture was filtered, the filtrate concentrated under reduced pressure, and the syrup thus obtained was dissolved in ethyl acetate (100 mL) and washed with H_2O (2×25 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give crude product, which on column chromatography (SiO_2) using $CHCl_3$: CH_3OH (96:04) as eluent, afforded compounds (**3a** and **4a**) as an inseparable (68:32) diastereomeric mixture. Colourless oil. Rf 0.40 (EtOAc/hexane,1:4), yield 65%: $[\alpha]_D^{20} - 150.00$ (*c*, 0.012, $CHCl_3$); MS (FAB); *m/z* 394 $(M+H)^+$; IR(KBr); ν_{max} cm^{-1} 3055, 2980, 2862, (CH_3 and CH_2 stretching), 1720 (C═O).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (m, 5H, Ar-H), 5.91 (d, $J=3.7$ Hz 1H, H-1, major isomer), 5.86 (d, $J=3.7$ Hz 1H, H-1, minor isomer), 4.66 (d, $J=12$ Hz, 1H, $-OCH_APh$), 4.60 (d, $J=3.7$ Hz, 1H, H-2, major isomer), 4.58(d, $J=3.7$ Hz, 1H, H-2, minor isomer), 4.44 (d, $J=12$ Hz, 1H, $-OCH_BPh$), 4.28 and 4.23 (dd, $J=8.6$ Hz and 3.1 Hz, 1H, H-4), 4.10 (q, $J=7.1$ Hz, 2H, $-OCH_2CH_3$), 4.0 (d, $J=3.1$ Hz, 1H, H-3), 3.72 (m, 1H, H-5), 2.67 and 2.61 (dd, $J=15.5$Hz and 4.7 Hz, 1H, H-6_A), 2.58 and 2.54 (dd, $J=15.5$ Hz and 6.6Hz, 1H, H-6_B), 2.35[s, 6H, $-N(CH_3)_2$], 1.53 and 1.34[each s, each 3H, $C(CH_3)_2$], 1.24 (t, $J=7.1$ Hz, 3H, $-OCH_2CH_3$).

Anal. Calcd for $C_{21}H_{31}O_6N$ (393): C, 64.12; H, 7.88; N, 3.56. Found: C, 64.41; H, 7.68; N, 3.38.

Ethyl[3-*O*-benzyl-5-butylamino-5, 6-dideoxy-1, 2-*O*-isopropylidene]-α-D-*gluco* and β-L-*ido*-heptofuranuronates (3b, 4b). Rf 0.44 and 0.48 (EtOAc/hexane, 3:7), yield: 70%; $[\alpha]^{20}_D - 31.25$ (*c*, 0.012, ethyl acetate); MS (FAB): *m/z* 422 $(M+H)^+$; IR(KBr); ν_{max} cm^{-1} 3350(–NH), 3040, 2990, 2880(CH_3 and CH_2 stretching): 1730 (C═O). ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.35 (m, 5H, Ar-H), 5.95 (d, $J=3.7$Hz, 1H, H-1, major isomer), 5.87 (d, $J=3.7$ Hz 1H, H-1, minor isomer), 4.72 (d, $J=12$ Hz,

1H, $-OCH_APh$), 4.65 (d, $J=3.7$Hz, 1H, H-2, major isomer), 4.60(d, $J=3.7$ Hz, 1H, H-2, minor isomer), 4.45(d, $J=12$ Hz, 1H, $-OCH_BPh$), 4.16–4.08 (m, 3H, H-4 and $-OCH_2CH_3$), 3.90 (d, $J=3.1$ Hz, 1H, H-3), 3.40 (m, 1H, H-5), 2.65 (m, 2H, $-NHCH_2$), 2.38 and 2.32 (dd, $J=15.6$ Hz and 4.7 Hz, 1H, H-6_A), 2.25 and 2.19 (dd, $J=15.6$ Hz and 6.6 Hz, 1H, H-6_B), 1.72[bs, 1H, $-NH(CH_2)_3CH_3$], 1.50[s,3H, $C(CH_3)_2$], 1.42 (m, 2H, $-NHCH_2.CH_2$), 1.32[s, 3H, $C(CH_3)_2$], 1.30 (m, 2H, $-NH.CH_2.CH_2.CH_2$), 1.28 (t, $J=7.1$ Hz, 3H, $-OCH_2CH_3$), 0.88 (t, $J=7.2$ Hz, 3H, $-NH(CH_2)_3CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ 172.20 (C═O), 137.51, 129.10, 128.42 and 128.14 (each Ar–C), 111.90[$C(CH_3)_2$], 105.21(C-1), 82.63 (C-2), 82.26 (C-4), 82.12 (C-3), 71.88 ($-OCH_2Ph$), 60.68 ($-OCH_2CH_3$), 54.44 (C-5), 47.34 ($-NHCH_2$), 36.74 (C-6), 32.90 ($-NHCH_2CH_2$), 27.14 and 26.73[$2\times C(CH_3)_2$], 20.81[$-NH(CH_2)_2CH_2CH_3$], 14.57 ($-OCH_2CH_3$), 14.36[$-NH(CH_2)_3CH_3$].

Anal. Calcd for $C_{23}H_{35}O_6N$ (421): C, 65.56; H, 8.31; N, 3.32. Found: C, 65.12; H, 8.81; N, 3.22.

Ethyl[3-*O*-benzyl-5-benzylamino-5, 6-dideoxy-1, 2-*O*-isopropylidene]-β-L-*ido*-heptofuranuronates (3c, major). Colourless solid mp 74°C, Rf 0.41 (EtOAc/hexane, 1:5), yield 96%. $[\alpha]^{20}_D - 38.94$ (*c*, 0.012, ethyl acetate); MS (FAB): *m/z* 456 $(M+H)^+$; IR (KBr); ν_{max} cm^{-1} 3350(–NH), 3020, 2980, 2920(CH_3 and CH_2 stretching): 1710 (C═O). ^{1}H NMR (200 MHz, $CDCl_3$); δ 7.25 (m, 10H, Ar-H), 5.94 (d, $J=3.89$ Hz, 1H, H-1), 4.69(d, $J=11.82$ Hz, 1H, $-OCH_APh$), 4.64(d, $J=3.93$Hz, 1H, H-2), 4.44 (d, $J=11.8$Hz, 1H, $-OCH_BPh$), 4.25 and 4.19(dd, $J=8.8$ Hz and 3.2 Hz, 1H, H-4), 4.10(q, $J=7.14$ Hz, 2H, $-OCH_2CH_3$), 3.94 (d, $J=3.19$ Hz, 1H, H-3), 3.84 (s, 2H, $-NHCH_2Ph$), 3.52(m, 1H, H-5), 2.46 and 2.40 (dd, $J=15.6$ Hz and 4.7 Hz, 1H, H-6_A), 2.34 and 2.28 (dd, $J=15.6$ Hz and 6.6 Hz, 1H, H-6_B), 1.81 (bs, 1H, $-NHCH_2Ph$), 1.47 and, 1.31[each s, each 3H, C $(CH_3)_2$], 1.24 (t, $J=7.14$Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ 172.80 (C═O), 141.07, 137.97, 128.86,128.69, 128.42, 128.26, 128.12 and 127.27 (each Ar–C), 111.98[$C(CH_3)_2$], 105.20 (C-1), 82.60 (C-2), 82.40 (C-4), 82.22 (C-3), 72.49 ($-OCH_2Ph$), 60.66 ($-OCH_2CH_3$), 53.07 (C-5), 51.67 ($-NHCH_2Ph$), 36.26 (C-6), 27.22 and 26.78[$2\times$ C $(CH_3)_2$], 14.57 ($-OCH_2CH_3$).

Anal. Calcd for $C_{26}H_{33}O_6N$ (455): C, 68.57; H, 7.25; N, 3.07. Found: C, 68.92; H, 7.01; N, 3.41.

Ethyl[3-*O*-benzyl-5-benzylamino-5,6-dideoxy-1,2-*O*-isopropylidene]-α-D-*gluco*-heptofuranuronate (4c, minor). Rf 0.47 (EtOAc/ hexane, 1:5), $[\alpha]^{20}_D - 42.76$ (*c*, 0.012, ethyl acetate); MS (FAB): *m/z* 456 $(M+H)^+$; IR(KBr); ν_{max} cm^{-1} 3350(–NH), 3020, 2980, 2920 (CH_3 and CH_2 stretching): 1710 (C═O). ^{1}H NMR (200 MHz, $CDCl_3$); δ 7.26 (m, 10H, Ar-H), 5.89 (d, $J=3.77$ Hz, 1H, H-1), 4.67 (d, $J=11.72$ Hz, 1H, $-OCH_APh$), 4.59(d, $J=3.7$ Hz, 1H, H-2), 4.53 (d, $J=11.69$ Hz, 1H, $-OCH_BPh$), 4.23 and 4.17 (dd, $J=7.0$ Hz and 2.7 Hz, 1H, H-4), 4.12(q, $J=7.2$ Hz, 2H, $-OCH_2CH_3$), 4.08 (d, $J=2.7$ Hz, 1H, H-3), 3.85 (d, $J=12.8$ Hz, 1H, $-NHCH_APh$), 3.72 (d, $J=12.8$ Hz, 1H, $-NHCH_BPh$), 3.52(m, 1H, H-5), 2.85 and 2.78 (dd, $J=15.6$ Hz and 4.4 Hz, 1H, H-6_A), 2.62 and 2.54 (dd, $J=15.6$ Hz and 6.7 Hz, 1H, H-6_B), 1.68 (s, 1H, $-NHCH_2Ph$), 1.47 and 1.31[each s, each 3H, C $(CH_3)_2$], 1.24 (t, $J=7.14$Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ 172.15 (C═O), 141.07, 137.52, 128.92,128.73, 128.66, 128.47, 128.32 and 127.19 (each Ar–C), 112.01[$C(CH_3)_2$], 105.29 (C-1), 82.76 (C-2), 82.26 (C-4), 82.19

(C-3), 71.91 ($-OCH_2Ph$), 60.80 ($-OCH_2CH_3$), 54.23 (C-5), 52.02 ($-NHCH_2Ph$), 36.91 (C-6), 27.19 and 26.75[$2 \times C(CH_3)_2$], 14.62 ($-OCH_2CH_3$).

Ethyl[3-*O*-benzyl-5, 6-dideoxy-1,2-*O*-isopropylidene-5-(pyrrolidin-1-yl)]-α-D-*gluco* and β-L-*ido*-heptofuranuronates (3d, 4d). Rf 0.5 (EtOAc/hexane, 3:7) yield: 67%; $[\alpha]^{20}_D - 38.00$ (*c*, 0.005, ethyl acetate); MS (FAB): *m*/*z* 420 $(M+H)^+$; IR (KBr); ν_{max} cm^{-1} 2970, 2950, 2900, 2850, 2800 (CH_3 and CH_2 stretching): 1720 (C═O). ^1H NMR (400 MHz, $CDCl_3$); δ 7.35 (m, 5H, Ar-H), 5.95 (d, $J = 3.7$ Hz 1H, H-1, major isomer), 5.90 (d, $J = 3.7$Hz 1H, H-1, minor isomer), 4.71 (d, $J = 12$ Hz, 1H, $-OCH_APh$), 4.60 (d, $J = 3.7$Hz, 1H, H-2, major isomer), 4.58(d, $J = 3.7$Hz, 1H, H-2, minor isomer), 4.42(d, $J = 12$ Hz, 1H, $-OCH_BPh$), 4.22 and 4.17 (dd, $J = 8.6$ Hz and 3.2 Hz, 1H, H-4), 4.12 (q, $J = 7.14$ Hz, 2H, $-OCH_2CH_3$), 3.71 (d, $J = 3.2$ Hz, 1H, H-3), 3.60 (m, 4H, $2 \times -N.CH_2$), 3.50 (dd, $J = 12$ Hz and 4.5 Hz, 1H, H-5), 2.87 (m, 2H, -pyrrolidine proton), 2.62 (m, 2H, -pyrrolidine proton), 2.25 2.19 (dd, $J = 15.6$ Hz and 4.7 Hz, 1H, H-6_A), 2.06 and 2.00 (dd, $J = 15.6$ Hz and 6.7 Hz, 1H, H-6_B), 1.50 and 1.35[each s, each 3H, $C(CH_3)_2$], 1.28 (t, $J = 7.14$ Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ 173.01 (C═O), 137.62, 128.81, 128.33, and 128.17 (each Ar–C), 111.79[$C(CH_3)_2$], 105.38 (C-1), 82.6 (C-2), 81.57 (C-4), 80.92 (C-3), 71.7 ($-OCH_2Ph$), 60.56 ($-OCH_2CH_3$), 55.93 (C-5), 48.95 ($2 \times -NCH_2$), 35.08 (C-6), 27.71 and 23.94[$2 \times C(CH_3)_2$], 23.94 ($2 \times -NCH_2CH_2$), 14.55 (OCH_2CH_3).

Anal. Calcd for $C_{23}H_{33}O_6N$ (419): C, 65.87; H, 7.87; N, 3.34. Found: C, 65.12; H, 7.81; N, 3.42.

Ethyl[3-*O*-benzyl-5, 6-dideoxy-1,2-*O*-isopropylidene-5-(piperidin-1-yl)]-α-D-*gluco* and β-L-*ido*-heptofuranuronates (3e, 4e). Rf 0.52 (EtOAc/hexane, 3:7) yield: 70%; $[\alpha]^{20}_D - 31.49$ (*c*, 0.005, ethyl acetate); MS (FAB): *m*/*z* 434 $(M+H)^+$; IR (KBr); ν_{max} cm^{-1}2980, 2920, 2830,2790, (CH_3 and CH_2 stretching): 1715 (C═O). ^1H NMR (400 MHz, $CDCl_3$); δ 7.25 (m, 5H, Ar-H), 5.95 (d, $J = 3.7$ Hz 1H, H-1, major isomer), 5.90 (d, $J = 3.7$Hz, 1H, H-1, minor isomer), 4.70 (d, $J = 12$ Hz, 1H, $-OCH_APh$), 4.67 (d, $J = 3.7$ Hz, 1H, H-2, major isomer), 4.60(d, $J = 3.7$Hz, 1H, H-2, minor isomer), 4.45 (d, $J = 12$ Hz, 1H, $-OCH_BPh$), 4.25 and 4.20(dd, $J = 8.6$ Hz and 3.2 Hz, 1H, H-4), 4.12 (q, $J = 7.14$ Hz, 2H, $-OCH_2CH_3$), 3.95 (d, $J = 3.2$Hz, 1H, H-3), 3.85 (m, 4H, $2 \times -N.CH_2$), 3.53 (m, 1H, H-5), 2.85 and 2.79 (dd, $J = 15.6$ Hz and 4.6 Hz, 1H, H-6_A), 2.37 and 2.30 (dd, $J = 15.6$Hz and 6.6Hz, 1H, H-6_B), 1.48 and 1.30[each s, each 3H, $C(CH_3)_2$], 1.25 (m, 6H, piperidine proton), 1.20 (t, $J = 7.14$ Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ 172.59 (C═O), 137.46, 128.85, 128.43, and 128.38 (each Ar–C), 111.71[$C(CH_3)_2$], 105.42(C-1), 82.54 (C-2), 81.48 (C-4), 80.26 (C-3), 71.75 ($-OCH_2Ph$), 60.48 (C-5), 60.46 ($-OCH_2CH_3$), 50.59 ($2 \times -NCH_2$), 35.35 (C-6), 27.42 ($2 \times -N.CH_2CH_2$), 27.22 and 26.69[$2 \times C(CH_3)_2$], 25.18 (piperidine carbon), 14.46 ($-OCH_2CH_3$).

Anal. Calcd for $C_{24}H_{35}O_6N$ (433): C, 66.51; H, 8.08; N, 3.23. Found: C, 66.81; H, 8.01; N, 3.48.

Ethyl[3-*O*-benzyl-5, 6-dideoxy1,2-*O*-isopropylidene-5-(morpholin-1-yl)]-α-D-*gluco* and β-L-*ido*-heptofuranuronates (3f, 4f). Rf 0.52 (EtOAc/hexane, 3:7) yield: 59%; $[\alpha]^{20}_D - 31.49$ (*c*, 0.0429, ethyl acetate); MS (FAB): *m*/*z* 436$(M+H)^+$; IR (KBr); ν_{max} cm^{-1} 2960, 2920, 2880, 2840, 2800 (CH_3 and CH_2 stretching): 1740 (C═O). ^1H

NMR (400 MHz, $CDCl_3$); δ 7.32 (m, 5H, Ar-H), 5.95 (d, $J = 3.7$Hz, 1H, H-1, major isomer), 5.91 (d, $J = 3.7$ Hz 1H, H-1, minor isomer), 4.70 (d, $J = 12$ Hz, 1H, $-OCH_APh$), 4.62 (d, $J = 3.7$Hz, 1H, H-2, major isomer), 4.58(d, $J = 3.7$ Hz, 1H, H-2, minor isomer), 4.40(d, $J = 12$ Hz, 1H, $-OCH_BPh$), 4.21 and 4.16 (dd, $J = 8.6$ Hz and 3.2 Hz, 1H, H-4), 4.10 (q, $J = 7.14$ Hz, 2H, $-OCH_2CH_3$), 3.72 (d, $J = 3.2$Hz, 1H, H-3), 3.60 (m, 4H, morpholine proton), 3.45 (m, 1H, H-5), 2.87 and 2.63 (m, 4H, $2 \times -N.CH_2$), 2.26 and 2.20 (dd, $J = 15.6$ Hz and 4.7 Hz, 1H, H-6_A), 2.08 and 2.02 (dd, $J = 15.6$ Hz and 6.6 Hz, 1H, H-6_B), 1.50 and 1.33[each s, each 3H, $C(CH_3)_2$], 1.26 (t, $J = 7.14$ Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ 171.78 (C═O), 137.33, 128.88, 128.52, and 128.46 (each Ar−C), 111.92[$C(CH_3)_2$], 105.44 (C-1), 82.42 (C-2), 81.46 (C-4), 79.99 (C-3), 71.87 ($-OCH_2Ph$), 68.19 (morpholine carbon), 60.59 ($-OCH_2CH_3$), 60.07 (C-5), 49.81 (morpholine carbon), 35.23 (C-6), 27.23 and 26.68[$2 \times C(CH_3)_2$], 14.75 ($-OCH_2CH_3$).

Anal. Calcd for $C_{23}H_{33}O_7N$ (435): C, 63.44; H, 7.58; N, 3.22. Found: C, 63.86; H, 7.56; N, 3.18.

Ethyl[3-*O*-benzyl-5, 6-dideoxy-1,2-*O*-isopropylidene-5-(1-methyl) piperazin-1-yl)] -α-D-*gluco* and β-L-*ido*-heptofuranuronates (3g, 4g). Rf 0.52 (EtOAc/hexane, 3:7) yield: 70%; $[\alpha]^{20}_D - 48.25$ (*c*, 0.011, $CHCl_3$); MS (FAB): *m/z* 449 $(M+H)^+$; IR(KBr); ν_{max} cm^{-1} 3042, 2983, 2941, 2867 (CH_3 and CH_2 stretching): 1721 (C═O). ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.32 (m, 5H, Ar-H), 5.89 (d, $J = 3.7$ Hz 1H, H-1, major isomer), 5.84 (d, $J = 3.7$ Hz 1H, H-1, minor isomer), 4.71 (d, $J = 12$ Hz, 1H, $-OCH_APh$), 4.61 (d, $J = 3.7$ Hz, 1H, H-2, major isomer), 4.58(d, $J = 3.7$ Hz, 1H, H-2, minor isomer), 4.48(d, $J = 12$ Hz, 1H, $-OCH_BPh$), 4.22 and 4.17(dd, $J = 8.6$Hz and 3.2 Hz, 1H, H-4), 4.15 (q, $J = 7.14$ Hz, 2H, $-OCH_2CH_3$), 3.56 (d, $J = 3.7$ Hz, 1H, H-3), 3.48 (m, 1H, H-5), 2.96 (m, 2H, piperazenyl ring proton) 2.81-2.60 (m, 6H, piperazenyl ring proton), 2.48 (s, 3H, $-NCH_3$), 2.60 and 2.54 (dd, $J = 15.6$Hz, and 4.7 Hz, 1H, H-6_A), 2.29 and 2.23 (dd, $J = 15.7$ Hz and 6.6Hz, 1H, H-6_B), 1.48 and 1.31[each s, each 3H, $C(CH_3)_2$], 1.25 (t, $J = 7.14$ Hz, 3H, $-OCH_2CH_3$).

Anal. Calcd for $C_{24}H_{36}O_6N_2$ (448): C, 64.28; H, 8.03; N, 6.25. Found: C, 64.18; H, 8.08; N, 6.28.

Ethyl[3-*O*-methyl-5,6-dideoxy-5-dimethylamino-1,2-*O*-isopropylidene]-α-D-*gluco* and β-L-*ido*-heptofuranuronates (3h, 4h). Rf 0.40 and 0.42 (EtOAc/hexane, 1:4), yield: 60%; $[\alpha]^{20}_D - 35.5$ (*c*, 0.0113, $CHCl_3$); MS (FAB): *m/z* 318 $(M+H)^+$; IR(KBr); ν_{max} cm^{-1} 2986, 2939, 2834, 2787 (CH_3 and CH_2 stretching); 1725 (C═O). ^{1}H NMR (200 MHz, $CDCl_3$); δ 5.91 (d, $J = 3.8$Hz, 1H, H-1, major isomer), 5.84(d, $J = 3.8$Hz 1H, H-1, minor isomer), 4.56 (d, $J = 3.8$ Hz, 1H, H-2, major isomer), 4.52 (d, $J = 3.8$ Hz, 1H, H-2, minor isomer), 4.23 and 4.18(dd, $J = 8.6$ Hz and 3.2 Hz, 1H, H-4), 4.12 (q, $J = 7.1$Hz, 2H, $-OCH_2CH_3$), 3.58 (d, $J = 3.2$ Hz, 1H, H-3), 3.45 (m, 1H, H-5), 3.35 (s, 3H, $-OCH_3$), 2.53 and 2.47 (dd, $J = 15.6$Hz, and 4.7 Hz 1H, H-6_A), 2.38[s, 6H, $-N(CH_3)_2$], 2.18 and 2.11(dd, $J = 15.7$Hz and 6.6 Hz, 1H, H-6_B), 1.49 and 1.30[each s, each 3H, $2 \times C(CH_3)_2$],1.25 (t, $J = 7.10$ Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ 172.20 (C═O), 112.16[$C(CH_3)_2$], 105.39 (C-1), 83.99 (C-2), 82.30 (C-4), 81.79 (C-3), 60.74 ($-OCH_2CH_3$), 54.76 (C-5), 41.39 and 41.09[$2 \times -N(CH_3)$], 33.75 (C-6), 27.15 and 26.62[$2 \times C\ (CH_3)_2$], 14.5 ($-OCH_2CH_3$).

Anal. Calcd for $C_{15}H_{27}O_6N$ (317): C, 56.78; H, 8.52; N, 4.42. Found: C, 56.97; H, 8.48; N, 4.45.

Ethyl[3-*O*-methyl-5-butylamino-5,6-dideoxy-1,2-*O*-isopropylidene]-α-D-*gluco* and β-L-*ido*-heptofuranuronates (3i, 4i). Rf 0.42 and 0.46 (EtOAc/hexane, 3:7), yield: 70%; $[\alpha]^{20}_D - 38.93$ (*c*, 0.0113, $CHCl_3$); MS (FAB): *m/z* 346$(M+H)^+$; IR(KBr); ν_{max} cm^{-1} 2980, 2940, 2860, 2808 (CH_3 and CH_2 stretching): 1720 (C═O). ^{1}H NMR (400 MHz, $CDCl_3$); δ 5.91 (d, *J* = 3.7 Hz 1H, H-1, major isomer), 5.87 (d, *J* = 3.7 Hz 1H, H-1, minor isomer), 4.60 (d, *J* = 3.7 Hz, 1H, H-2, major isomer), 4.57 (d, *J* = 3.7 Hz, 1H, H-2, minor isomer), 4.12–4.05 (m, 3H, $-OCH_2CH_3$ and H-4), 3.80 and 3.71 (d, *J* = 3.1 Hz, 1H, H-3), 3.38 (s, 3H, $-OCH_3$), 3.32 (m, 1H, H-5), 2.67 (m, 2H, $-N.CH_2$), 2.50 and 2.44 (dd, *J* = 15.6Hz and 4.7 Hz, 1H, H-6_A), 2.40 and 2.33 (dd, *J* = 15.6Hz and 6.6 Hz, 1H, H-6_B), 1.77[bs, 1H, $-NH(CH_2)_3CH_3$], 1.49[s, 3H, $C(CH_3)_2$], 1.42[m, 2H, $-NH(CH_2CH_2)$], 1.32[m, 2H, $-NH(CH_2)_2CH_2$)], 1.30[s, 3H, $C(CH_3)_2$],1.27 (t, *J* = 7.14 Hz, 3H, $-OCH_2CH_3$), 0.90[t, 3H, *J* = 7.15Hz, $-NH(CH_2)_3CH_3$]. ^{13}C NMR (proton decoupled, $CDCl_3$); δ 172.20 (C═O), 112.16[$C(CH_3)_2$], 105.39 (C-1), 83.99 (C-2), 82.30 (C-4), 81.79 (C-3), 60.74 ($-OCH_2CH_3$), 54.76 (C-5), 46.60 ($-NHCH_2$), 33.24 (C-6), 31.18 ($-NHCH_2CH_2$), 27.12 and 26.51[2 × $C(CH_3)_2$], 20.22 ($-NHCH_2CH_2CH_2CH_3$), 14.52 ($-OCH_2CH_3$), 13.91[$-NH(CH_2)_3CH_3$].

Anal. Calcd for $C_{17}H_{31}O_6N$ (345): C, 59.13; H, 8.98; N, 4.05. Found: C, 59.42; H, 8.81; N, 4.12.

Ethyl[3-*O*-methyl-5-benzylamino-5,6-dideoxy-1,2-*O*-isopropylidene]-β-L-*ido*-heptofuranuronate (3j, major). Rf 0.38 (EtOAc/hexane, 1:5), yield: $[\alpha]^{20}_D - 41.28$ (*c*, 0.014, ethyl acetate); MS (FAB): *m/z* 380 $(M+H)^+$; IR(KBr); ν_{max} cm^{-1} 3355 (–NH); 3048, 2978, 2923 and 2845 (CH_3 and CH_2 stretching): 1721 (C═O). ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.32 (m, 5H, Ar-H), 5.90(d, *J* = 3.7 Hz 1H, H-1), 4.57 (d, *J* = 3.7 Hz, 1H, H-2.), 4.23 and 2.18 (dd, *J* = 8.6 Hz and 3.1Hz, 1H, H-4), 4.14 (q, *J* = 7.14 Hz, 2H, $-OCH_2CH_3$), 3.90(d, *J* = 12 Hz, 1H, $-NHCH_APh$), 3.85(d, *J* = 12 Hz, 1H, $-NHCH_BPh$), 3.73 (d, *J* = 3.2 Hz, 1H, H-3), 3.39 (m, 1H, H-5), 3.36 (s, 3H, $-OCH_3$), 2.58 and 2.52 (dd, *J* = 15.6Hz and 4.7 Hz, 1H, H-6_A), 2.46 and 2.39(dd, *J* = 15.6Hz and 6.6 Hz, 1H, H-6_B), 2.02(m, 1H, $-NHCH_2Ph$), 1.47 and 1.30[each s, each 3H, $C(CH_3)_2$], 1.25 (t, *J* = 7.14 Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ 172.12 (C═O), 140.96, 128.65, 127.18 (each Ar–C), 111.90[$C(CH_3)_2$], 105.18 (C-1), 84.55 (C-2), 82.83(C-4), 81.59 (C-3), 60.77 ($-OCH_2CH_3$), 57.62 ($-OCH_3$)54.33 (C-5), 51.96 ($-NHCH_2Ph$), 36.89 (C-6), 27.14 and 26.94[2 × $C(CH_3)_2$], 14.62 ($-OCH_2CH_3$).

Ethyl[3-*O*-methyl-5-benzylamino-5,6-dideoxy-1,2-*O*-isopropylidene]-α-D-*gluco*-heptofuranuronate (4j, minor). Rf 0.44 (EtOAc/hexane, 1:5), yield: $[\alpha]^{20}_D - 38.15$ (*c*, 0.013, ethyl acetate); MS (FAB): *m/z* 380 $(M+H)^+$; IR(KBr); ν_{max} cm^{-1} 3351 (–NH); 3051, 2985, 2922 and 2848 (CH_3 and CH_2 stretching): 1721 (C═O). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.35 (m, 5H, Ar-H), 5.90 (d, *J* = 3.7Hz 1H, H-1), 4.60 (d, *J* = 3.7 Hz, 1H, H-2.), 4.28 and 2.23(dd, *J* = 7.0 Hz and 3.2 Hz, 1H, H-4), 4.16 (q, *J* = 7.14 Hz, 2H, $-OCH_2CH_3$), 3.89(d, *J* = 12 Hz, 1H, $-NHCH_APh$), 3.80(d, *J* = 12 Hz, 1H, $-NHCH_BPh$), 3.74 (d, *J* = 3.2 Hz, 1H, H-3), 3.40 (m, 1H, H-5), 3.35 (s, 3H, $-OCH_3$), 2.56 and 2.50 (dd, *J* = 15.6 Hz and 4.7 Hz, 1H, H-6_A), 2.47 and 2.40 (dd, *J* = 15.6 Hz and

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4.7 Hz, 1H, H-6_B), 1.88(m, 1H, $-NHCH_2Ph$), 1.49 and 1.30[each s, each 3H, $C(CH_3)_2$], 1.24 (t, $J = 7.14$ Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ172.76(C═O), 141.15, 128.67, 128.51 and 127.28 (each Ar–C), 111.89[$C(CH_3)_2$], 105.13 (C-1), 84.17 (C-2), 82.36 (C-4), 82.26 (C3), 60.67($-OCH_2CH_3$), 57.98 ($-OCH_3$), 52.75(C-5), 51.94 ($-NHCH_2Ph$), 36.57 (C-6), 27.18 and 26.73[$2 \times C(CH_3)_2$], 14.63 ($-OCH_2CH_3$).

Ethyl[3-*O*-methyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(pyrrolidin-1-yl)]-α-D-*gluco* and β-L-*ido*-heptofuranuronates (3k, 4k). Rf 0.5 (EtOAc/hexane, 3:7), yield: 72%; $[\alpha]^{20}_D - 46.03$ (*c*, 0.030, $CHCl_3$); MS (FAB): *m/z* 344 $(M+H)^+$; IR(KBr); ν_{max} cm^{-1} 3020, 2980, 2940, 2820 (CH_3 and CH_2 stretching): 1725 (C═O). ^1H NMR (400 MHz, $CDCl_3$): δ 5.90 (d, $J = 3.7$Hz, 1H, H-1, major isomer), 5.85 (d, $J = 3.7$ Hz, 1H, H-1, minor isomer), 4.55 (d, $J = 3.7$ Hz, 1H, H-2, major isomer), 4.50(d, $J = 3.7$ Hz, 1H, H-2, minor isomer), 4.25 and 2.20 (dd, $J = 8.6$ Hz and 3.2 Hz, 1H, H-4), 4.12 (q, $J = 7.14$ Hz, 2H, $-OCH_2CH_3$), 3.62 (d, $J = 3.2$ Hz, 1H, H-3), 3.55 (m, 1H, H-5), 3.38 (s, 3H, $-OCH_3$), 2.70 (m, 4H, $2 \times -NCH_2$), 2.47 and 2.41 (dd, 1H, $J = 15.6$ Hz and 4.7 Hz, 1H, H-6_A), 2.33 and 2.26 (dd, $J = 15.6$ Hz and 6.6 Hz, 1H, H-6_B), 1.70 (m, 4H, pyrrolidine H), 1.46 and 1.30[each s, each 3H, $C(CH_3)_2$], 1.21 (t, $J = 7.14$ Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ 173.01(C═O), 111.73[$C(CH_3)_2$], 105.45 (C-1), 83.4 (C-2), 81.87 (C-4), 80.96 (C-3), 60.86 ($-OCH_2CH_3$), 57.93 ($-OCH_3$), 55.49 (C-5), 48.81 ($2 \times -NCH_2$), 35.14 (C-6), 27.70 and 24.7[$2 \times C(CH_3)_2$], 23.98 ($2 \times -NCH_2CH_2$), 14.58 ($-OCH_2CH_3$).

Anal. Calcd for $C_{17}H_{29}O_6N$ (343): C, 59.47; H, 8.45; N, 4.08. Found: C, 59.41; H, 8.38; N, 4.11.

Ethyl[3-*O*-methyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(piperidine-1-yl)]-α-D-*gluco* and β-L-*ido*-heptofuranuronates (3l, 4l). Rf 0.51 (EtOAc/hexane, 3:7), yield: 75%; $[\alpha]^{20}_D - 56.25$ (*c*, 0.028, $CHCl_3$); MS (FAB): *m/z* 358 $(M+H)^+$; IR(KBr); ν_{max} cm^{-1} 3040, 3020, 2960, 2860 (CH_3 and CH_2 stretching): 1720 (C═O). ^1H NMR (400 MHz, $CDCl_3$); δ 5.92 (d, $J = 3.7$Hz 1H, H-1, major isomer), 5.88 (d, $J = 3.7$ Hz, 1H, H-1, minor isomer), 4.67 (d, $J = 3.7$ Hz, 1H, H-2, major isomer), 4.60(d, $J = 3.7$ Hz, 1H, H-2, minor isomer), 4.25 and 2.20(dd, $J = 8.6$ Hz and 3.2 Hz, 1H, H-4), 4.12 (q, $J = 7.14$ Hz, 2H, $-OCH_2CH_3$), 3.95 (d, $J = 3.2$ Hz, 1H, H-3), 3.85 (m, 4H, $2 \times -NCH_2$), 3.53 (m, 1H, H-5), 3.5(s, 3H, $-OCH_3$), 2.80 and 2.74 (dd, $J = 15.6$Hz and 4.7 Hz, 1H, H-6_A), 2.46 and 2.39 (dd, $J = 15.6$Hz and 6.6 Hz, 1H, H-6_B), 1.48 and 1.30[each s, each 3H, $C(CH_3)_2$], 1.25 (m, 6H, piperidine proton), 1.20 (t, $J = 7.14$ Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ 172.59 (C═O), 111.51[$C(CH_3)_2$], 105.20 (C-1), 84.99 (C-2), 82.26 (C-4), 81.87 (C-3), 60.53 (C-5), 60.30 ($-OCH_2CH_3$), 57.46 ($-OCH_3$), 50.44 (($-NCH_2$), 35.61 (C-6), 27.07 ($2 \times -NCH_2CH_2$), 26.52 and 26.42[$2 \times C(CH_3)_2$], 26.34 (piperidine carbon), 14.47 ($-OCH_2CH_3$).

Anal. Calcd for $C_{18}H_{31}O_6N$ (357): C, 60.50; H, 8.68; N, 3.92. Found: C, 60.48; H, 8.71; N, 3.45.

Ethyl[3-*O*-methyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(morpholin-1-yl)]-α-D-*gluco* and β-L-*ido*-heptofuranuronates (3m, 4m). Rf 0.5 (EtOAc/hexane, 3:7), yield: 68%; $[\alpha]^{20}_D - 29.78$ (*c*, 0.014, $CHCl_3$); MS (FAB): *m/z* 360 $(M+H)^+$; IR(KBr); ν_{max} cm^{-1} 3000, 2980, 2860 (CH_3 and CH_2 stretching): 1735 (C═O): ^1H NMR (400 MHz,

$CDCl_3$); δ 5.98 (d, $J = 3.7$ Hz, 1H, H-1, major isomer), 5.91 (d, $J = 3.7$Hz, 1H, H-1, minor isomer), 4.64 (d, $J = 3.7$ Hz, 1H, H-2, major isomer), 4.57(d, $J = 3.7$Hz, 1H, H-2, minor isomer), 4.12-4.00 (m, 3H, H-4 and $-OCH_2CH_3$), 3.62 (m, 5H, H-5 and morpholine protons), 3.48 (d, $J = 3.2$Hz, 1H, H-3), 3.40(s, 3H, $-OCH_3$), 2.85 (m, 2H, morpholine protons), 2.61 (m, 2H, morpholine protons), 2.46 and 2.40 (dd, $J = 15.6$Hz and 4.7 Hz, 1H, H-6_A), 2.30 and 2.24 (dd, $J = 15.6$Hz and 6.5 Hz, 1H, H-6_B), 1.48 and 1.32[each s, each 3H, $C(CH_3)_2$], 1.25 (t, $J = 7.5$ Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ 171.78 (C═O), 111.62[$C(CH_3)_2$], 105.17 (C-1), 84.86 (C-2), 81.58 (C-4), 80.64 (C-3), 68.32(CH_2O−morpholine), 60.52 ($-OCH_2CH_3$), 60.13 (C-5), 57.57 ($-OCH_3$), 49.67 (($-NCH_2CH_2O$−morpholine), 35.26 (C-6), 27.11 and 26.53[$2 \times C(CH_3)_2$], 14.55 ($-OCH_2\ CH_3$).

Anal. Calcd for $C_{17}H_{29}O_7N$ (359): C, 56.82; H, 8.07; N, 3.89. Found: C, 56.76; H, 8.12; N, 3.78.

Ethyl[3-*O*-methyl-5, 6-dideoxy-1,2-*O*-isopropylidene-5-(1-methyl) piperazin-1-yl)]-α-D-*gluco* and β-L-*ido*-heptofuranuronates (3n, 4n). Rf 0.51 (EtOAc/hexane, 3:7), yield: 65%; $[\alpha]^{20}_D - 31.66$ (*c*, 0.038, $CHCl_3$); MS (FAB): *m/z* 373 $(M+H)^+$; IR(KBr); ν_{max} cm^{-1} 3020, 2980, 2960 and 2840 (CH_3 and CH_2 stretching): 1720 (C═O). ^{1}H NMR (400 MHz, $CDCl_3$); δ 5.90 (d, $J = 3.7$Hz 1H, H-1, major isomer), 5.84 (d, $J = 3.7$ Hz 1H, H-1, minor isomer), 4.50 (d, $J = 3.7$ Hz, 1H, H-2, major isomer), 4.52(d, $J = 3.7$ Hz, 1H, H-2, minor isomer), 4.20−4.09 (m, 3H, H-4 and $-OCH_2CH_3$), 3.54 (d, $J = 3.2$Hz, 1H, H-3), 3.45 (m, 1H, H-5), 3.37(s, 3H, $-OCH_3$), 2.95 (m, 2H, piperazine protons), 2.48 (s, 3H,$-NCH_3$), 2.44 and 2.38(dd, $J = 15.6$H and 4.7Hz, 1H, H-6_A), 2.29 and 2.23 (dd, $J = 15.5$Hz and 6.5Hz, 1H, H-6_B), 1.49 and 1.30[each s, each 3H, $C(CH_3)_2$], 1.28 (t, $J = 7.5$ Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (proton decoupled, $CDCl_3$); δ 171.95 (C═O), 111.67[$C(CH_3)_2$], 105.16 (C-1), 84.49 (C-2), 80.99 (C-3), 80.70 (C-4), 60.49 ($-OCH_2CH_3$), 59.75 (C-5), 58.46 ($-OCH_3$), 56.48 and 51.47(piperazine carbon), 46.22($-NCH_3$), 35.68(C-6), 27.53 and 27.13[$2 \times C(CH_3)_2$], 14.47 ($-OCH_2CH_3$).

Anal. Calcd for $C_{18}H_{32}O_6N$ (372): C, 58.08; H, 8.60; N, 7.52. Found: C, 58.14; H, 8.48; N, 7.58.

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