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Note

Novel synthesis of carbohydrate fused α-amino γ-lactams and glycopeptides by NIS mediated ring opening of donor–acceptor substituted cyclopropanes

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ABSTRACT

α-Amino γ-lactams have been synthesized from carbohydrate derived cyclopropanecarboxylates using N-iodosuccinimide (NIS) and NaN_3. Cyclopropane ring opening with NIS and NaN_3 in different solvents has been studied. Reductive cyclization of the intermediate di-azides leads to the carbohydrate fused α-amino γ-lactam and γ-lactams. Additionally, the methodology has been successfully extended to the synthesis of a glycopeptide.

γ-Lactam is a key unit in numerous natural products and many synthetic analogues exhibit diverse biological activities.[1–3] Due to the development of antibiotic resistance, γ-lactams are being used as bioisosteres to the most popular β-lactam antibiotics.[4–6] α-Amino γ-lactam (Freidinger–Veber lactam) bridged peptides are more active agonists to lutropin-releasing hormone than parent peptide analogues.[7] D-Cycloserine and (+)-HA-966 are antagonists at the glycine site of *N*-methyl-D-aspartate (NMDA) receptors (Fig. 1).[8] α-Amino γ-lactam bears a close resemblance to D-cycloserine[9] and (+)-1-hydroxy-3-aminopyrrolidine-2-one (HA-966).[10]

The binding ability of striatal dopamine receptor agonists can potentially be enhanced by insertion of the α-amino γ-lactam moiety into peptide mimetics.[11] α-Amino γ-lactam derivatives exhibit antiamensic properties at a low concentration (1 mg/Kg) when studied in mice.[12] α-Amino γ-lactam derivatives also moderately inhibit the *N*-acyl-homoserine mediated bacterial signalling[13] and act as anti-inflammatory agents in vivo.[14] Moreover, carbohydrate fused γ-lactams and lactones have been shown to be good $GABA_A$ receptor ligands in pharmacological studies.[15] Carbohydrate fused α amino γ-lactams are the derivatives of C-linked glyco-amino-acids which are very stable, resistant to enzymatic deglycosylation[16] and have become very crucial synthons in the development of anticancer vaccines.[17] The carbohydrate fused γ-lactams are very similar to polyhydroxylated heterocycles like carbohydrate fused pyrazolidin-3-one, isoxazolidin-5-one and pyrrolidine conjugates which are useful in studying the inhibition of glycosidases.[18,19]

Only a few reports have been published on the synthesis of carbohydrate fused γ-lactams. Calvo-Mateo et al. reported the formation of carbohydrate fused γ-lactam as a side product in very low yield (8%) during the synthesis of sugar amino acids.[20] Pachamuthu et al. utilized Michael addition of dimethyl malonate to tri-*O*-alkyl glycal to achieve the synthesis of carbohydrate fused γ-lactams.[21] Yin and Linker have isolated a carbohydrate fused γ-lactam during a study on the synthesis of the carbohydrate fused lactones.[22]

In continuation of our studies on the synthesis of carbohydrate fused γ-lactones,[23] herein, we disclose a flexible protocol for the synthesis of carbohydrate fused α-amino γ-lactam by ring opening of carbohydrate derived donor–acceptor cyclopropanes.[24–27] The significant advantage of this method is that carbohydrate fused α-amino γ-lactam derivatives are readily converted easily into α-amino γ-lactam-bridged glycopeptide conjugates, subsequently. We commenced our synthetic approach from the cyclopropanation of tri-*O*-(*tert*-butyldimethylsilyl)-D-glucal **1** using methyl diazoacetate and 2 mol% of $Rh_2(OAc)_4$ to give methyl *exo*-α-1,2-cyclopropanecarboxylate **2a** (Scheme 1).[28,29] When cyclopropanecarboxylate **2a** was treated with NIS and NaN_3 in CH_3CN, (rt, 12 h), it gave the corresponding iodo-azide **3a** in very good yield (82%) with high diastereoselectivity.

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0008-6215/

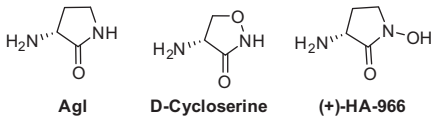
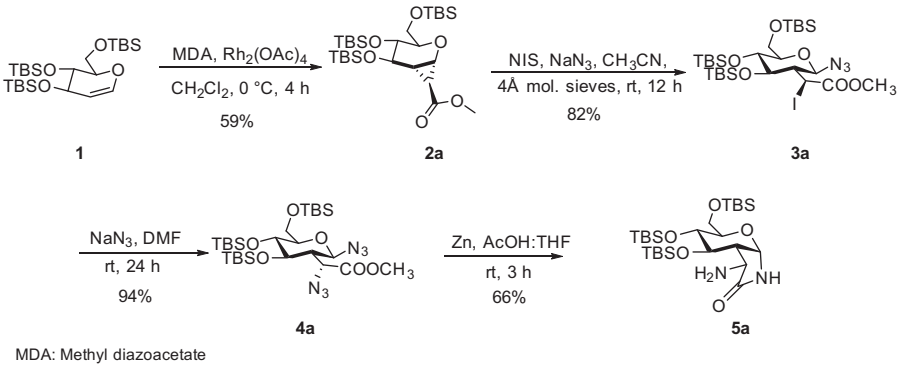


Figure 1. Structure of α-amino γ-lactam and its analogues.

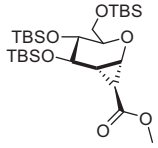
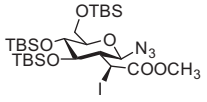
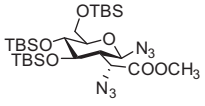
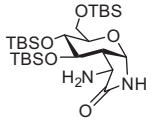
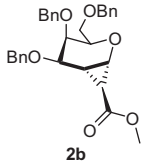
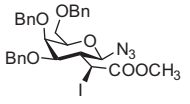
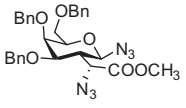
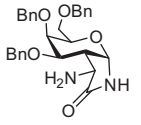
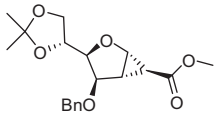
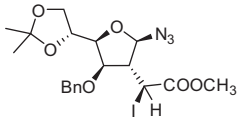
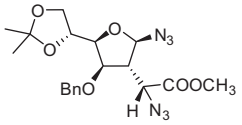
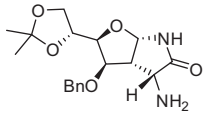
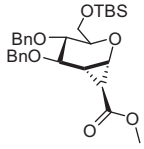
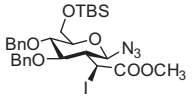
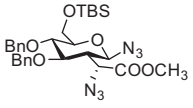
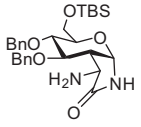
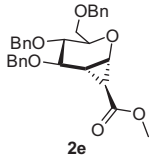
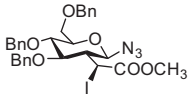
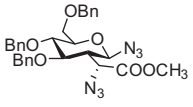
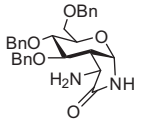
The iodo-azide **3a** was then converted to di-azide **4a** in excellent yield (94%) by treatment with NaN_3 in DMF. The di-azide **4a** on reduction with Zn/AcOH afforded α-amino γ-lactam **5a** (66%) via reductive intramolecular cyclization.[30,31] After standardization of the reaction protocol for glucose fused α-amino γ-lactam **5a**, this general methodology was extended to the synthesis of different carbohydrate fused α-amino γ-lactam derivatives and the results are summarized in Table 1.

Starting from cyclopropanecarboxylates **2b**–**2e**, di-azides **4b**–**4e** were synthesized via iodo-azides **3b**–**3e** in very good yield (70–90%) using NaN_3 in DMF.[32] Further reduction of di-azides **4b**–**4e** with Zn/AcOH provided the corresponding α-amino γ-lactam derivatives **5b**–**5e** respectively in moderate to good yield (40–66%).

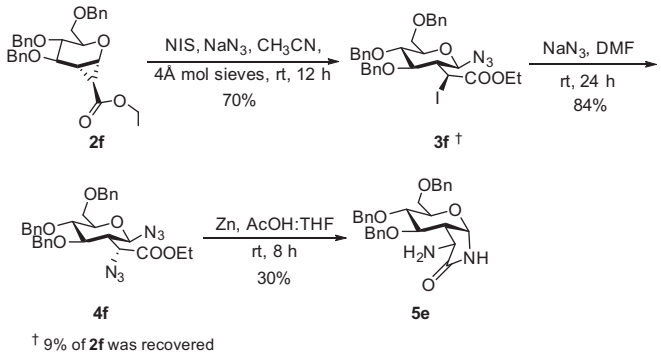


Scheme 1. Synthesis of carbohydrate fused α-amino γ-lactam **5a**.

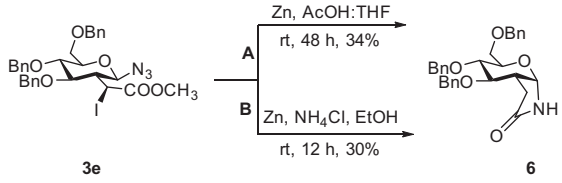
Table 1
Synthesis of carbohydrate fused α-amino γ-lactam derivatives

Entry	Cyclopropane	Iodo-azide	Di-azide	Agl
1	 **2a**	 **3a** (82%)	 **4a** (94%)	
2	 **2b**	 **3b** (70%)	 **4b** (90%)	 **5b** (56%)
3	 **2c**	 **3c** (75%)	 **4c** (70%)	 **5c** (48%)
4	 **2d**	 **3d** (71%)	 **4d** (85%)	 **5d** (59%)
5	 **2e**	 **3e** (78%)*	 **4e** (86%)	 **5e** (40%)

* 10% of **2e** was recovered.



Scheme 2. Synthesis of α-amino γ-lactam **5e** from ethyl cyclopropanecarboxylate **2f**.



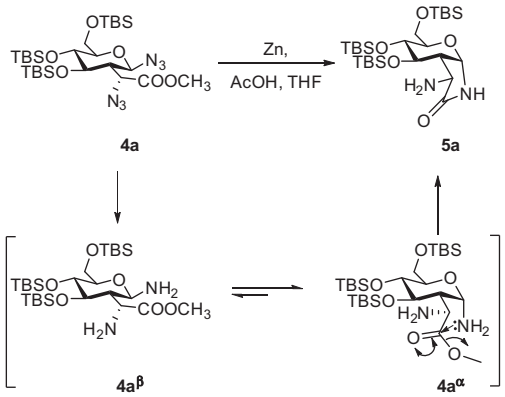
Scheme 3. Synthesis of carbohydrate fused γ-lactam **6**.

When α-amino γ-lactam **5e** was synthesized from cyclopropane ethyl ester **2f**, the yield in the reductive cyclization of **4f** was 30%; this is lower than that obtained in the reduction of the methyl ester of the corresponding glucose derivative **4e** (Scheme 2). The poor yield reflects the lower reactivity of the ethyl ester derivative **4f** compared to the methyl ester **4e** towards lactamization.

In order to improve the yield of glucose fused α-amino γ-lactam **5e**, various conditions of reductive cyclization of di-azide **4e** were studied. Reductive cyclization of **4e** with Lindlar catalyst,[33] Zn activated by trimethylsilyl chloride (TMSCl),[34] Zn(Cu) in AcOH, Mg/MeOH,[35] or In/NH_4Cl[36] failed to furnish α-amino γ-lactam **5e**. Reduction of **4e** with PPh_3/THF/H_2O (Staudinger conditions),[37] Zn/NH_4Cl[38] or Zn/AcOH under ultra-sonication gave a mixture of products, and from which α-amino γ-lactam **5e** was isolated in poor yields (<30%). Nevertheless, after extensive screening, Zn/AcOH was identified to be superior to other reducing systems studied for the reductive cyclization step. We also attempted the one-pot synthesis of di-azide **4e** by treating the cyclopropanecarboxylate **2e** with NIS and NaN_3 in different solvents. When **2e** was reacted with an excess of NaN_3 (4 equiv) and NIS (2.5 equiv) in CH_3CN or CH_2Cl_2, iodo-azide **3e** was obtained in good yield.† When the reaction was performed in DMF, THF or DMSO, only the starting material **2e** was recovered with no observable side reactions. No trace of iodo-azide **3e** or di-azide **4e** was detected in the crude reaction mixture either by ^1H NMR or mass spectrometry.

We also synthesized the carbohydrate fused γ-lactam **6** in a single-step from the iodo-azide **3e** by reductive cyclization (Scheme 3). When iodo-azide **3e** was treated with Zn/AcOH, γ-lactam **6** was isolated in poor yield (34%) even after reaction time was increased to 48 h from 12 h (deiodination occurs under Zn/AcOH conditions).[39] Since reduction of iodo-azide **3e** gave the γ-lactam **6** in poor yield (34%) under Zn/AcOH conditions, reduction of **3e** was carried out with Zn/NH_4Cl (Scheme 3, route **B**).[38] This method also provided γ-lactam **6** in low yield (30%) but in shorter time (12 h). However, neither method **A** nor method **B** furnished the γ-lactam **6** in good yield.

† The yield of **3e** is 75% and 52% in CH_3CN and CH_2Cl_2, respectively. 10% of starting material **2e** was recovered in both the solvents.

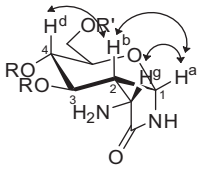


Scheme 4. Plausible mechanism for the synthesis of α-amino γ-lactam **5a**.

The mechanism proposed for the formation of α-amino γ-lactam **5a** from di-azide **4a** is presented in Scheme 4. In the first step, both azide groups are reduced to the corresponding amines in the presence of Zn/AcOH. Due to the anomeric effect[40] the equilibrium shifts from **4a**$^{\beta}$ to **4a**$^{\alpha}$ and lactamization then occurs via internal nucleophilic substitution of the methyl ester by the anomeric amine group to give the carbohydrate fused α-amino γ-lactam **5a** (Scheme 4).

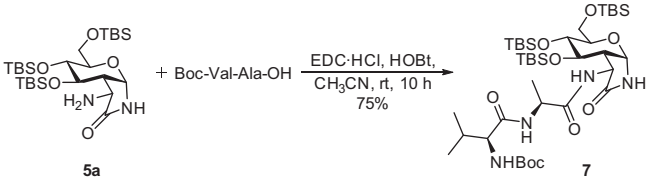
The *cis* geometry of α-amino γ-lactam **5d** was determined by analysis of ^1H NMR and **NOESY** experiments (Supplementary info). The observed coupling constant $^3J_{H^a-H^b}$ for the anomeric proton (**H**$^{\mathbf{a}}$) was found to be 5.5 Hz confirming the presence of a *cis*-bicyclic system. The analysis of NOE cross peaks between **H**$^{\mathbf{a}}$–**H**$^{\mathbf{b}}$, **H**$^{\mathbf{a}}$–**H**$^{\mathbf{g}}$ and **H**$^{\mathbf{b}}$–**H**$^{\mathbf{d}}$ together with the coupling constant ($^3J_{H^a-H^b}$) for the ring junction confirmed that all four protons are *cis* to each other (Fig. 2).

It has been reported that glycopeptide conjugates act as potent δ-opioid receptor agonists after transforming into glycopeptides from glycosylamines.[41] Herein, we have shown the utility of our carbohydrate fused α-amino γ-lactams in the synthesis of α-amino γ-lactam-bridged glycopeptide conjugates in a single-step with high efficiency (Scheme 5).[42,43] When gluco α-amino γ-lactam **5a** was coupled with N-protected dipeptide Boc-Val-Ala-OH in the presence of EDC·HCl and HOBt, it furnished the α-amino γ-lactam-bridged glycopeptide **7** in very good yield (75%). α-Amino γ-lactam derivatives and α-amino γ-lactam-bridged glycopeptides



5d (R= Bn, R'= TBS)

Figure 2. **NOESY** correlation of α-amino-γ-lactam **5d**.



Scheme 5. Synthesis of glycopeptide conjugate **7** of α-amino γ-lactam **5a**.

can be implemented as drugs directed at the central nervous system since the carbohydrate moiety could increase the lipophilicity and render them permeable to the blood–brain barrier.[44]

In summary, a stereoselective synthesis of carbohydrate fused α-amino γ-lactams has been developed involving the ring opening of cyclopropanecarboxylates. After screening, CH_3CN was shown to be a better solvent for the ring opening with NIS and NaN_3 and this methodology has been applied to other benzyl and silyl ether protected carbohydrate derivatives. Carbohydrate fused γ-lactams were also synthesized using this methodology. We also demonstrated the synthesis of an α-amino γ-lactam-bridged glycopeptide conjugate **7** from carbohydrate fused α-amino γ-lactam **5a**.

1. Experimental section

All reactions were carried out in an oven-dried apparatus using dry solvents under anhydrous conditions, unless otherwise noted. All the solvents used for the reaction were dried following the prescribed method over 4 Å molecular sieves or other appropriate drying agents.[45] Chromatography was performed using silica gel (230−400 mesh) with indicated solvents. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualized under UV light and developed using sulphuric acid or vanillin solution. Optical rotation of compounds has been recorded on 'JASCO digital polarimeter: Model DIP-370'. NMR spectra were recorded on a 400 MHz NMR spectrometer 'Bruker Avance 400' and chemical shifts are cited with respect to tetramethylsilane as internal (^1H and ^{13}C). HRMS was recorded on 'MicroMass ESI-TOF' by electron spray ionization method.

1.1. Synthesis of cyclopropanecarboxylate 2a

To a stirred suspension of tri-O-*tert*-butyldimehtylsilyl D-glucal **1** (3 g, 6.0 mmol) and $Rh_2(OAc)_4$ (27 mg, 0.06 mmol) in anhydrous dichloromethane (5 mL), methyl diazoacetate (1.2 g, 12.0 mmol) in dichloromethane (35 mL) was added drop wise over a period of 2 h. After cessation of the nitrogen evolution (5 min), the reaction mixture was concentrated in vacuo and the remaining residue was purified by column chromatography on silica gel (230–400 mesh) using 2% of EtoAc in petroleum ether to obtain the cyclopropanecarboxylate **1a** (1.4 g). Tri-*O*-*tert*-butyldimehtylsilyl D-glucal (0.9 g) was also recovered from the reaction mixture. Yield: 58%; Gummy; $[\alpha]_D^{25}$ 37.0 (*c* 2, $CHCl_3$); R_f = 0.6 (hexanes/EtOAc, 9:1); IR (neat): 2929, 1719, 1443, 1072, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.99–3.94 (m, 2H, H-6, H-6′), 3.81 (dd, 1H, *J* = 1.3, 7.2 Hz), 3.70 (d, 1H, *J* = 3.4 Hz), 3.67 (s, 3H), 3.60–3.57 (m, 2H), 2.27 (dd, 1H, *J* = 1.60, 6.08 Hz, H-2), 1.68 (t, 1H, *J* = 6.68 Hz, H-7), 0.92–0.91 (m, 27H, 3 × $(CH_3)_3C$), 0.12–0.06 (m, 18H, 3 × $(CH_3)_2Si$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7 (C=O), 78.8 (C-1), 71.0, 66.3, 62.3, 55.5 (C-2), 51.6 (C-7), 27.2, 26.2, 25.9, 25.7, 24.8, 18.3, 17.83, 17.79, −4.7, −4.8, −4.9, −5.0, −5.27, −5.34; HRMS (ESI-QTOF) *m*/*z*: Calcd for $C_{27}H_{56}O_6Si_3$ $[M+Na]^+$ 583.3282; Found 583.3290.

1.2. General procedure for the synthesis of iodo-azides

To a solution of cyclopropane carboxylate (1 mmol) and NaN_3 (2.5 mmol) in CH_3CN (7 mL), N-iodosuccinimide (2.5 mmol) and 4 Å molecular sieves were added under argon atmosphere. The reaction mixture was stirred for 12 h at room temperature. After removal of CH_3CN under vacuum, the reaction mixture was diluted with CH_2Cl_2 (20 mL). The reaction mixture was treated with saturated $Na_2S_2O_3$ solution and then the organic layer was separated and dried over anhydrous Na_2SO_4 and the crude product was purified.

1.2.1. 3,4,6-Tri-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-*C*-carbmethoxyiodomethyl-β-D-glucopyranosyl azide (3a)

The iodo-azide **3a** was synthesized using the procedure reported in Section 1.2 and the crude product was purified by column chromatography on silica gel (230–400 mesh) using 10% of ethyl acetate and petroleum ether. Yield: 82%; Gummy; $[\alpha]_D^{25}$ −132.5 (*c* 0.5, $CHCl_3$); R_f = 0.6 (hexanes/EtOAc, 9:1); IR (neat): 1736, 1099,2106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.92 (d, 1H, *J* = 4.56 Hz), 4.66 (d, 1H *J* = 12.16 Hz), 4.25 (s, 1H), 4.03–3.99 (m, 1H), 3.90 (d, 1H, *J* = 2.9 Hz), 3.83–3.78 (m, 5H), 2.28 (dd, 1H, *J* = 4.56, 4.00 Hz), 0.92–0.89 (m, 27H, 3 × $(CH_3)_3C$), 0.22–0.06 (m, 18H, 3 × $(CH_3)_2Si$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1 (C=O), 85.2 (C-1), 81.67, 73.3, 68.9, 63.6, 53.0 (C-2), 47.99 (C-7), 25.9, 25.8, 24.4, 18.3, 17.9, 17.8, −4.0, −4.2, −4.6, −4.9, −5.3, −5.4; HRMS (ESI-QTOF) *m*/*z*: Calcd for $C_{27}H_{56}IN_3O_6Si_3$ $[M+Na]^+$ 752.2419; Found 752.2418.

1.2.2. 3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-carbmethoxyiodomethyl-β-D-galactopyranosyl azide (3b)

The iodo-azide **3b** was synthesized using the procedure reported in Section 1.2 and the crude product was purified by column chromatography on silica gel (230−400 mesh) using 20% of ethyl acetate and petroleum ether. Yield: 70%; Gummy; $[\alpha]_D^{25}$ 7.52 (*c* 0.92, $CHCl_3$); R_f = 0.6 (hexanes/EtOAc, 4:1); IR (neat): 2116, 1744, 1247, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.26 (m, 15H, Ar-H), 4.98–4.95 (m, 1H), 4.82 (d, 1H, *J* = 11.48 Hz, OBn), 4.68–4.63 (m, 2H, OBn), 4.54–4.45 (m, 4H), 3.97 (s, 1H), 3.68–3.61 (m, 4H), 3.42 (s, 3H, COOMe), 2.33–2.27 (m, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3 (C=O), 138.4, 137.7, 136.8, 128.4, 128.2, 128.1, 127.9, 127.8, 127.6, 90.8 (C-1), 81.2, 75.6, 74.4, 73.6, 72.2, 71.1, 68.4, 53.3, 44.5; HRMS (ESI-QTOF) *m*/*z*: Calcd for $C_{30}H_{32}IN_3O_6$ $[M+Na]^+$ 680.1234; Found 680.1273.

1.2.3. 3-*O*-Benzyl-5,6-*O*-isopropylidine-2-deoxy-2-*C*-carbmethoxyiodomethyl-β-D-mannofuranosyl azide (3c)

The iodo-azide **3c** was synthesized using the procedure reported in Section 1.2 and the crude product was purified by column chromatography on silica gel (230−400 mesh) using 15% ethyl acetate and petroleum ether. Yield: 75%; Gummy; R_f = 0.5 (hexanes/EtOAc, 4:1); $[\alpha]_D^{25}$ −5 (*c* 1, $CHCl_3$); IR (neat): 2120, 1723, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.29 (m, 5H, Ar-H), 5.03 (d, 1H, *J* = 2.29 Hz, H-1), 4.71 (d, 1H, *J* = 11.73 Hz, OBn), 4.63 (d, 1H, *J* = 11.73 Hz, OBn), 4.45 (q, 1H, *J* = 6.39 Hz), 4.22 (d, 1H, *J* = 10.25 Hz), 4.18–4.11 (m, 3H), 4.02 (dd, 1H, *J* = 8.6, 6.2 Hz), 3.77 (s, 3H, COOMe), 2.94 (dt, 1H, *J* = 10.24, 1.86 Hz, H-2), 1.43 (s, 3H, $(CH_3)_2C$), 1.37 (s, 3H, $(CH_3)_2C$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (C=O), 137.5, 128. 3, 127.9, 127.8, 109.1 (C-1), 92.5, 83.3, 82.1, 73.1, 71.6, 66.9, 56.1 (C-2), 53.3 (C-7), 26.7, 25.4; HRMS (ESI-QTOF) *m*/*z*: Calcd for $C_{19}H_{24}IN_3O_6$ $[M+Na]^+$ 540.0604; Found 540.0607.

1.2.4. 3,4-Di-*O*-benzyl-6-(*tert*-butyldimethylsilyl)-2-*C*-carbmethoxyiodomethyl-2-deoxy-β-D-glucopyranosyl azide (3d)

The iodo-azide **3d** was synthesized using the procedure reported in Section 1.2 and the crude product was purified by column chromatography on silica gel (230−400 mesh) using 15% of ethyl acetate and petroleum ether. Yield: 71%; Gummy; $[\alpha]_D^{25}$ −10.18 (*c* 4.5, $CHCl_3$); R_f = 0.7 (hexanes/EtOAc, 4:1); IR (neat): 2118, 1749, 1253, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.25 (m, 10H, Ar-H), 4.97 (d, 1H, *J* = 10.44 Hz, OBn), 4.90–4.89 (m, 1H, OBn), 4.78–4.75 (m, 3H), 4.65 (d, 1H, *J* = 8.9 Hz), 3.94–3.87 (m, 3H), 3.82–3.77 (m, 1H), 3.43 (s, 1H), 3.36 (s, 3H, COOMe), 1.78–1.73 (m, 1H, H-2), 0.93 (s, 9H, $(CH_3)_3C$), 0.12–0.07 (m, 6H, $(CH_3)_2Si$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2 (C=O), 137.9,

137.8, 128.5, 128.1, 127.9, 127.7, 89.9 (C-1), 81.4, 79.1, 77.98, 74.98, 74.8, 61.6, 53.6 (C-7), 49.8 (C-2), 28.6, 25.8, 18.3, 0.97, −5.1, −5.4; HRMS (ESI-QTOF) *m/z*: Calcd for $C_{29}H_{40}IN_3O_6Si$ $[M+Na]^+$ 704.1629; Found 704.1629.

1.2.5. 3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-carbmethoxyiodomethyl-β-D-glucopyranosyl azide (3e)[32]

The iodo-azide **3e** was synthesized using the procedure reported in Section 1.2 and the crude product was purified by column chromatography on silica gel (230–400 mesh) using 20% of ethyl acetate and petroleum ether. Yield: 78%; Gummy; $[\alpha]_D^{25}$ −50 (*c* 1, $CHCl_3$); R_f = 0.6 (hexanes/EtOAc, 4:1); IR (neat): 2117, 1747, 1455, 1361, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.10 (m, 15H, Ar-H), 4.97–4.92 (m, 2H), 4.78–4.67 (m, 4H), 4.6 (d, 1H, *J* = 4.3 Hz), 4.57 (d, 1H, *J* = 5.92 Hz), 3.93–3.88 (m, 1H), 3.83–3.75 (m, 3H), 3.58 (d, 1H, *J* = 9.2 Hz), 3.34 (s, 3H), 1.87–1.83 (m, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1 (C=O), 137.9, 137.8, 137.5, 128.4, 128.4, 127.8, 127.7, 127.6, 127.4, 90.4 (C-1), 81.4, 79.3, 77.2, 74.84, 74.80, 73.5, 68.01, 53.5, 49.6 (C-2); HRMS (ESI-QTOF) *m/z*: Calcd for $C_{30}H_{32}IN_3O_6$ $[M+Na]^+$ 680.1233; Found 680.1241.

1.2.6. 3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-carbethoxyiodomethyl-β-D-glucopyranosyl azide (3f)

The iodo-azide **3f** was synthesized using the procedure reported in Section 1.2 and the crude product was purified by column chromatography on silica gel (230–400 mesh) using 20% of ethyl acetate and petroleum ether. Yield: 70%; Gummy; $[\alpha]_D^{25}$ −1.28 (*c* 1, $CHCl_3$); R_f = 0.6 (hexanes/EtOAc, 4:1); IR (neat): 2114, 1740, 1616, 1134, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.07 (m, 15H, Ar-H), 4.95–4.92 (m, 2H), 4.81–4.66 (m, 4H), 4.59 (d, 1H, *J* = 4.28 Hz), 4.56 (d, 1H, *J* = 2.16 Hz), 3.89–3.75 (m, 6H), 3.57 (d, 1H, *J* = 9.60 Hz), 1.86 (t, 1H, *J* = 9.58 Hz, H-2), 1.05 (t, 3H, *J* = 7.14 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6 (C=O), 138.0, 137.7, 137.5, 128.43, 128.42, 128.0, 127.9, 127.7, 127.4, 90.5 (C-1), 81.5, 79.3, 74.8, 74.7, 73.6, 68.0, 62.8, 49.5 (C-2), 29.3, 13.8; HRMS (ESI-QTOF) *m/z*: Calcd for $C_{31}H_{34}IN_3O_6$ $[M+Na]^+$ 694.1390; Found 694.1389.

1.3. General procedure for the synthesis of di-azides

To a stirred solution of iodo-azide (1 mmol) in dry DMF (5 mL) was added NaN_3 (2 mmol) and the reaction mixture was stirred for 24 h at room temperature. DMF was removed under vacuum and the crude product was extracted with CH_2Cl_2 (20 mL). The organic layer was washed with water (10 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the crude product was purified.

1.3.1. 3,4,6-Tri-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-*C*-carbmethoxyazidomethyl-β-D-glucopyranosyl azide (4a)

The di-azide **4a** was synthesized using the procedure reported in Section 1.3 and the crude product was purified by column chromatography on silica gel (230–400 mesh) using 10% of ethyl acetate and petroleum ether. Yield: 94%; Gummy; $[\alpha]_D^{25}$ −2.68 (*c* 1.55, $CHCl_3$); R_f = 0.6 (hexanes/EtOAc, 9:1); IR (neat): 2109, 1750, 1468, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.01 (d, 1H, *J* = 7.2 Hz, H-1), 4.36 (d, 1H, *J* = 6.2 Hz), 3.97 (dd, 1H, *J* = 6.34, 10.26 Hz), 3.86–3.76 (m, 6H), 3.66 (q, 1H, *J* = 4.72 Hz), 2.20 (q, 1H, *J* = 6.2 Hz, H-2), 0.90–0.89 (m, 27H, 3 × $(CH_3)_3C$), 0.14–0.11 (m, 12H, 2 × $(CH_3)_2Si$), 0.07–0.06 (m, 6H, 1 × $(CH_3)_2Si$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7 (C=O), 85.5 (C-1), 80.3, 72.1, 70.6, 63.2, 60.6, 52.7, 48.1 (C-2), 25.8, 18.3, 18.05, 17.99, −3.5, −3.7, −3.9, −4.2, −5.5, −5.4; HRMS (ESI-QTOF) *m/z*: Calcd for $C_{27}H_{56}N_6O_6Si_3$ $[M+Na]^+$ 667.3467; Found 667.3463.

1.3.2. 3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-carbmethoxyazidomethyl-β-D-galactopyranosyl azide (4b)

The di-azide **4b** was synthesized using the procedure reported in Section 1.3 and the crude product was purified by column chromatography on silica gel (230–400 mesh) using 20% of ethyl acetate and petroleum ether. Yield: 90%; Gummy; $[\alpha]_D^{25}$ 77.52 (*c* 0.8, $CHCl_3$); R_f = 0.5 (hexanes/EtOAc, 4:1); IR (neat): 2110, 1747, 1214, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.29 (m, 15H, Ar-H), 4.89 (d, 1H, *J* = 11.6 Hz), 4.71 (d, 1H, *J* = 11.6 Hz), 4.64–4.58 (m, 3H), 4.46 (d, 2H, *J* = 4.40 Hz), 4.39 (d, 1H, *J* = 11.6 Hz, H-2), 3.99 (s, 1H), 3.79 (s, 3H, COOMe), 3.61–3.60 (m, 3H), 3.47 (dd, 1H, *J* = 11.08, 2.12 Hz), 2.71 (t, 1H, *J* = 10.28 Hz, H-7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4 (C=O), 138.2, 137.6, 136.97, 128.74, 128.66, 128.44, 128.37, 128.27, 128.1, 128.0, 127.92, 127.88, 127.7, 86.9, 77.2, 75.4, 74.5, 73.6, 71.4, 70.0, 68.3, 58.4, 52.6, 43.4 (C-2); HRMS (ESI-QTOF) *m/z*: Calcd for $C_{30}H_{32}N_6O_6$ $[M+Na]^+$ 595.2281; Found 595.2288.

1.3.3. 3-*O*-Benzyl-2-*C*-carbmethoxyazidomethyl-2-deoxy-5,6-isopropylidine-β-D-mannofuranosyl azide (4c)

The di-azide **4c** was synthesized using the procedure reported in Section 1.3 and the crude product was purified by column chromatography on silica gel (230–400 mesh) using 15% of ethyl acetate and petroleum ether. Yield: 70%; Gummy; $[\alpha]_D^{25}$ −26.29 (*c* 1.3, $CHCl_3$); R_f = 0.4 (hexanes/EtOAc, 85:15); IR (neat): 2156, 2109, 1754, 1586, 1439, 1244, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.32 (m, 5H, Ar-H), 5.19 (d, 1H, *J* = 3.96 Hz, H-1), 4.67 (d, 1H, *J* = 11.5 Hz, OBn), 4.54 (d, 1H, *J* = 11.5 Hz, OBn), 4.45–4.40 (m, 1H), 4.17–4.11 (m, 2H), 4.05–3.97 (m, 3H), 3.78 (s, 3H, COOMe), 2.66–2.62 (m, 1H, H-7), 1.44 (s, 3H, $(CH_3)_2C$), 1.39 (s, 3H, $(CH_3)_2C$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8 (C=O), 137.4, 128.4, 128.0, 109.3 (C-1), 90.9, 82.1, 79.0, 77.2, 73.2, 72.3, 67.0, 60.3, 53.0, 52.4 (C-2), 26.7, 25.5; HRMS (ESI-QTOF) *m/z*: Calcd for $C_{19}H_{24}N_6O_6$ $[M+Na]^+$ 455.1655; Found 455.1653.

1.3.4. 3,4-Di-*O*-benzyl-6-(*tert*-butyldimethylsilyl)-2-*C*-carbmethoxyazidomethyl-2-deoxy-β-D-glucopyranosyl azide (4d)

The di-azide **4d** was synthesized using the procedure reported in Section 1.3 and the crude product was purified by column chromatography on silica gel (230–400 mesh) using 15% of ethyl acetate and petroleum ether. Yield: 85%; Gummy; $[\alpha]_D^{25}$ 54.31 (*c* 2.15, $CHCl_3$); R_f = 0.6 (hexanes/EtOAc, 85:15); IR (neat): 2112, 1752, 1455, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.30 (m, 10H, Ar-H), 4.97 (d, 1H, *J* = 11.4 Hz, OBn), 4.82 (q, 2H, *J* = 10.6 Hz), 4.64 (d, 1H, *J* = 11.6 Hz), 4.54 (d, 1H, *J* = 9.3 Hz), 4.35 (s, 1H), 3.94–3.87 (m, 2H), 3.81 (s, 3H), 3.77–3.72 (m, 1H), 3.66–3.58 (m, 1H), 3.31 (d, 1H, *J* = 9.44 Hz), 2.21 (t, 1H, *J* = 10.1 Hz, H-7), 0.92 (s, 9H, 1 × $(CH_3)_3C$), 0.09 (s, 6H, 1 × $(CH_3)_2Si$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (C=O), 137.99, 137.7, 128.6, 128.5, 128.2, 127.8, 86.1 (C-1), 78.9, 78.2, 77.9, 75.3, 74.7, 61.6, 58.4, 52. 8, 48.3 (C-2), 25.8, 18.3, −5.1, −5.4; HRMS (ESI-QTOF) *m/z*: Calcd for $C_{29}H_{40}N_6O_6Si$ $[M+Na]^+$ 619.2676; Found 619.2674.

1.3.5. 3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-carbmethoxyazidomethyl-β-D-glucopyranosyl azide (4e)

The di-azide **4e** was synthesized using the procedure reported in Section 1.3 and the crude product was purified by column chromatography on silica gel (230–400 mesh) using 20% of ethyl acetate and petroleum ether. Yield: 86%; Gummy; $[\alpha]_D^{25}$ 65.71 (*c* 2.5, $CHCl_3$,); R_f = 0.55 (hexanes/EtOAc, 4:1); IR (neat): 2112, 1747, 1119, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.20 (m, 15H, Ar-H), 4.96 (d, 1H, *J* = 11.52 Hz, OBn), 4.81 (d, 1H, *J* = 10.84 Hz, OBn), 4.67–4.62 (m, 4H), 4.55 (d, 1H, *J* = 11.98 Hz), 4.34 (s, 1H), 3.79–3.70 (m, 6H), 3.60 (t, 1H, *J* = 9.8 Hz), 3.48 (d,

1H, J = 8.92 Hz), 2.29–2.24 (m, 1H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (C=O), 137.8, 137.65, 137.59, 128.6, 128.5, 128.4, 128.1, 127.8, 126.1, 86.8 (C-1), 79.1, 78.4, 75.1, 74.8, 73.5, 68.1, 58.3, 52.7 (C-7), 48.1 (C-2); HRMS (ESI-QTOF) m/z: Calcd for $C_{30}H_{32}N_6O_6$ $[M+Na]^+$ 595.2281; Found 595.2281.

1.3.6. 3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-carbethoxyazidomethyl-β-D-glucopyranosyl azide (4f)

The di-azide **4f** was synthesized using the procedure reported in Section 1.3 and the crude product was purified by column chromatography on silica gel (230–400 mesh) using 20% of ethyl acetate and petroleum ether. Yield: 84%; Gummy; $[\alpha]_D^{25}$ 73.08 (c 1.8, $CHCl_3$); R_f = 0.5 (hexanes/EtOAc, 4:1); IR (neat): 2109, 1742, 1132, 1118 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.20 (m, 15H Ar-H), 4.96 (d, 1H, J = 11.5 Hz), 4.81 (d, 1H, J = 10.85 Hz), 4.65–4.61 (m, 4H), 4.57–4.54 (m, 1H), 4.32 (s, 1H), 4.26 (q, 2H, J = 7.1 Hz), 3.75–3.71 (m, 3H), 3.63–3.58 (m, 1H), 3.48 (d, 1H, J = 9.6 Hz), 2.30–2.25 (m, 1H, H-2), 1.32 (t, 3H, J = 7.06 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5 (C=O), 137.8, 137.6, 137.6, 128.6, 128.5, 128.4, 128.2, 127.8, 86.8 (C-1), 79.1, 78.4, 77.1, 75.2, 74.8, 73.5, 68.1, 62.2, 58.3, 48.1 (C-2), 13.9; HRMS (ESI-QTOF) m/z: Calcd for $C_{31}H_{34}N_6O_6$ $[M+Na]^+$ 609.2438; Found 609.2438.

1.4. General procedure for the synthesis of carbohydrate fused α-amino γ-lactam

To a stirred solution of di-azide (1 mmol) in 10 mL of AcOH/THF (1:1), Zn dust (1 mmol) was added and the reaction was stirred for 12 h at room temperature (25 °C). After completion of the reaction, Zn was removed by filtration. Then solvent was removed under vacuum followed by dilution with 20 mL of ethyl acetate. The organic layer was thoroughly washed with $NaHCO_3$ solution. It was separated and dried over anhydrous Na_2SO_4. The filtrate was concentrated and the crude product was purified.

1.4.1. (3*S*)-3-Amino-[3,4,6-tri-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-α-D-glucopyranoso][2,3-*b*]-pyrrolidin-2-one (5a)

The α-amino γ-lactam **5a** was synthesized using the procedure reported in Section 1.4 and the crude product was purified by column chromatography on amine-pretreatment silica gel (0.5 mL of Et_3N for 50 g of silica gel) using 1% of $CHCl_3$ and MeOH. Yield: 66%; Gummy; $[\alpha]_D^{25}$ 8.89 (c 1.34, $CHCl_3$); R_f = 0.6 ($CHCl_3$/MeOH, 99:1); IR (neat): 2929, 1715, 1467, 1085 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.19 (s, 1H, NH), 5.44 (d, J = 7.4 Hz, 1H, H-1), 4.21 (s, 1H), 3.77–3.73 (m, 3H), 3.54–3.48 (m, 2H), 2.83–2.78 (m, 1H, H-2), 0.88 (s, 27H, 3 × $(CH_3)_3C$), 0.12–0.05 (m, 18H, 3 × $(CH_3)_2Si$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2 (C=O), 79.2 (C-1), 74.5, 69.3, 68.8, 64.1, 52.5, 41.99, 25.96, 25.89, 25.7, 18.4, 18.0, 17.9, −3.6, −4.3, −4.5, −4.76, −4.79, −5.2, −5.3; HRMS (ESI-QTOF) m/z: Calcd for $C_{26}H_{56}N_2O_5Si_3$ $[M+H]^+$ 561.3575; Found 561.3580.

1.4.2. (3*S*)-3-Amino-(3,4,6-tri-*O*-benzyl-1,2-dideoxy-α-D-galactopyranoso)[2,3-*b*]-pyrrolidin-2-one (5b)

The α-amino γ-lactam **5b** was synthesized using the procedure reported in Section 1.4 and the crude product was purified by column chromatography on amine-pretreatment silica gel (0.5 mL of Et_3N for 50 g of silica gel) using 5% of $CHCl_3$ and MeOH. Yield: 56%; Gummy; $[\alpha]_D^{25}$ 85.04 (c 1, $CHCl_3$); R_f = 0.5 ($CHCl_3$/MeOH, 95:5); IR (neat): 1713, 1519, 1100 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.29 (m, 15H, Ar-H), 5.84 (s, 1H, NH), 5.41 (d, 1H, J = 5.40 Hz, H-1), 4.90 (d, 1H, J = 11.53 Hz, OBn), 4.74 (d, 1H, J = 10.76 Hz, OBn), 4.62–4.57 (m, 2H), 4.52–4.42 (m, 2H), 4.01 (s, 1H), 3.89–3.77 (m, 3H), 3.60–3.50 (m, 2H), 2.97–2.91 (m, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4 (C=O), 138.3, 137.7, 128.5, 128.4, 128.3, 128.0, 127.86, 127.81, 127.74, 127.70, 80.6 (C-1), 76.0, 74.4, 73.5, 71.5, 70.7, 70.6, 68.9, 54.6, 41.8; HRMS (ESI-QTOF) m/z: Calcd for $C_{29}H_{32}N_2O_5$ $[M+Na]^+$ 511.2209; Found 511.2201.

1.4.3. (3*S*)-3-Amino-(3-*O*-benzyl-1,2-dideoxy-5,6-isopropylidine-β-D-mannofuranoso)[2,3-*b*]-pyrrolidin-2-one (5c)

The α-amino γ-lactam **5c** was synthesized using the procedure reported in Section 1.4 and the crude product was purified by column chromatography on amine-pretreatment silica gel (0.5 mL of Et_3N for 50 g of silica gel) using 3% of $CHCl_3$ and MeOH. Yield: 48%; Gummy; $[\alpha]_D^{25}$ −5.16 (c 1, $CHCl_3$); R_f = 0.5 ($CHCl_3$/MeOH, 97:3); IR (neat): 1704, 1655, 1375, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.30 (m, 5H, Ar-H), 6.29 (br s, 1H, NH), 5.63 (d, 1H, J = 6.2 Hz, H-1), 4.61 (s, 2H), 4.49 (d, 1H, J = 4.40 Hz), 4.43 (q, 1H, J = 6.31 Hz), 4.08 (dd, 1H, J = 6.31, 8.47 Hz), 3.97–3.93 (m, J = 5.96, 8.47 Hz, 1H), 3.86 (dd, 1H, J = 3.60, 6.56 Hz), 3.74 (d, 1H, J = 10.24 Hz), 3.15 (dd, 1H, J = 6.26, 10.2 Hz, H-2), 1.43 (s, 3H, $(CH_3)_2C$), 1.37 (s, 3H, $(CH_3)_2C$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6 (C=O), 137.9, 128.6, 128.4, 127.8, 108.9 (C-1), 86.7, 80.8, 78.3, 72.9, 71.9, 66.9, 51.1, 50.5 (C-2), 26.6, 25.3; HRMS (ESI-QTOF) m/z: Calcd for $C_{18}H_{24}N_2O_5$[M+Na]$^+$ 371.1583; Found 371.1584.

1.4.4. (3*S*)-3-Amino-[3,4-di-*O*-benzyl-6-(*tert*-butyldimethylsilyl)-1,2-dideoxy]-α-D-glucopyranoso][2,3-*b*]-pyrrolidin-2-one (5d)

The α-amino γ-lactam **5d** was synthesized using the procedure reported in Section 1.4 and the crude product was purified by column chromatography on amine-pretreatment silica gel (0.5 mL of Et_3N for 50 g of silica gel) using 5% of $CHCl_3$ and MeOH. Yield: 59%; Gummy; $[\alpha]_D^{25}$ 34.32 (c 1.6, $CHCl_3$); R_f = 0.6 ($CHCl_3$/MeOH, 95:5); IR (neat): 1718, 1457, 1257, 1102, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.28 (m, 10H, Ar-H), 5.89 (bs, 1H, NH), 5.42 (d, 1H, J = 5.89 Hz, H-1), 4.86 (s, 2H, OBn), 4.79–4.72 (m, 2H, OBn), 4.01–3.97 (m, 1H, H-3), 3.89 (dd, 1H, J = 3.75, 11.2 Hz, H-6), 3.80–3.74 (m, 3H, H-6′, H-4, H-7), 3.64–3.62 (m, 1H, H-5), 2.82–2.76 (m, 1H, H-2), 0.91 (s, 9H, 1 × $(CH_3)_3C$), 0.07–0.06 (m, 6H, 1 × $(CH_3)_2Si$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5 (C=O), 138.74, 138.1, 128.44, 128.40, 127.8, 127.7, 127.6, 127.5, 80.7 (C-1), 77.2 (C-4), 74.1 (OBn), 73.3 (OBn), 73.1 (C-5), 62.6 (C-6), 54.6 (C-7), 45.7 (C-2), 25.9, 18.3, −5.2, −5.4; HRMS (ESI-QTOF) m/z: Calcd for $C_{28}H_{40}N_2O_5Si$ $[M+Na]^+$ 535.2604; Found 535.2606.

1.4.5. (3*S*)-3-Amino-(3,4,6-tri-*O*-benzyl-1,2-dideoxy-α-D-glucopyranoso)[2,3-*b*]-pyrrolidin-2-one (5e)

The α-amino γ-lactam **5e** was synthesized using the procedure reported in Section 1.4 and the crude product was purified by column chromatography on amine-pretreatment silica gel (0.5 mL of Et_3N for 50 g of silica gel) using 5% of $CHCl_3$ and MeOH. Yield: 40%; Gummy; $[\alpha]_D^{25}$ 33.34 (c 1.15, $CHCl_3$); R_f = 0.5 ($CHCl_3$/MeOH, 95:5); IR (neat): 1719, 1454, 1099, 1070, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.16 (m, 15H, Ar-H), 5.88 (s, 1H, NH), 5.43 (d, J = 5.94 Hz, 1H, H-1), 4.84 (s, 2H), 4.73 (d, 1H, J = 11.16 Hz, OBn), 4.59–4.51 (m, 4H), 3.97–3.94 (m, 1H), 3.76–3.60 (m, 7H), 2.84–2.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4 (C=O), 138.7, 137.7, 128.39, 128.37, 127.8, 127.8, 127.7, 127.5, 127.4, 80.7 (C-1), 77.5, 74.0, 73.5, 73.2, 71.6, 69.1, 54.6, 45.5 (C-1); HRMS (ESI-QTOF) m/z: Calcd for $C_{29}H_{32}N_2O_5$ $[M+Na]^+$ 511.2209; Found 511.2209.

1.5. Procedure for the synthesis of γ-lactam (6)

1.5.1. Method A using Zn/AcOH

To a stirred solution of iodo-azide **3e** (1 mmol) in 10 mL of AcOH/THF (1:1) Zn dust (1 mmol) was added and the reaction

was stirred for 48 h at room temperature (25 °C). After completion of the reaction, Zn was removed by filtration. Then solvent was removed under vacuum followed by dilution with 20 mL of ethyl acetate. The organic layer was thoroughly washed with $NaHCO_3$ solution. It was separated and dried over anhydrous Na_2SO_4. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel using hexanes/EtOAc to furnish the γ-lactam.

1.5.2. Method B using Zn/NH_4Cl

To a stirred solution of iodo-azide **3e** (1 mmol) and NH_4Cl (2 mmol) in 10 mL of EtOH, Zn dust (2 mmol) was added and the reaction was stirred for 12 h at room temperature (25 °C). After completion of the reaction, Zn was removed by filtration. Then the solvent was removed under vacuum followed by dilution with 20 mL of ethyl acetate. The organic layer was thoroughly washed with $NaHCO_3$ solution. It was separated and dried over anhydrous Na_2SO_4. The filtrate was concentrated and the crude product was purified by column chromatography using hexanes/EtOAc to furnish γ-lactam **6**.

1.5.3. 3,4,6-Tri-*O*-benzyl-1,2-dideoxy-α-D-glucopyranoso[2,3-*b*]-pyrrolidin-2-one (6)

The γ-lactam **6** was synthesized using the procedure reported in Section 1.5 and the crude product was purified by column chromatography on silica gel (230–400 mesh) using 50% of ethyl acetate and petroleum ether. Yield: 30%; Gummy; $[\alpha]_D^{25}$ 82.44 (*c* 1, $CHCl_3$); R_f = 0.85 (hexanes/EtOAc, 1:1); IR (neat): 3317, 2922, 2359, 1980, 1709, 1073, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.16 (m, 15H, Ar-H), 5.97 (s, 1H, NH), 5.47 (d, 1H, *J* = 6.76 Hz, H-1), 4.69–4.37 (m, 6H), 3.74–3.68 (m, 1H), 3.67–3.62 (m, 2H), 3.61–3.58 (m, 2H), 2.80–2.77 (m, 1H), 2.54 (dd, 1H, *J* = 6.72, 6.68 Hz), 2.42–2.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.15 (C=O), 137.85, 137.54, 128.50, 128.38, 128.34, 127.80, 127.75, 127.73, 81.88 (C-1), 76.05, 73.35, 72.65, 72.49, 70.77, 69.63, 37.47, 32.84; HRMS (ESI-QTOF) *m*/*z*: Calcd for $C_{29}H_{31}NO_5$ $[M+Na]^+$ 496.2100; Found 496.2101.

1.6. Procedure for the synthesis of glucopeptide (7)

To a stirred solution of α-amino γ-lactam **2a** (25 mg, 0.04 mmol) in CH_3CN (5 mL), diisopropylethylamine (0.03 mL, 0.13 mmol) and Boc-valinylalanine (17 mg, 0.06 mmol) were added at 0 °C. The mixture was stirred for 5 min, followed by the addition of EDC·HCl (13 mg, 0.07 mmol) and HOBt (6 mg, 0.05 mmol). The reaction mixture was warmed to room temperature and stirred for 10 hours. After the completion of the reaction the residue was concentrated in vacuo and extracted with ethyl acetate. The crude product was purified by column chromatography using 5% $CHCl_3$/MeOH to furnish the glucopeptide **7** (28 mg).

1.6.1. Glucopeptide (7)

Yield: 75%; Gummy; $[\alpha]_D^{25}$ −28.30 (*c* 0.8, $CHCl_3$); R_f = 0.5 ($CHCl_3$/MeOH, 95:5); IR (neat): 3313, 1685, 1702, 1709, 1254, 1093, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, 1H, *J* = 6.3 Hz), 6.23 (d, 1H, *J* = 7.7 Hz), 6.03 (s, 1H), 5.62 (d, 1H, *J* = 7.7 Hz), 5.12 (d, 1H, *J* = 7.9 Hz), 4.85 (dd, 1H, *J* = 8.2, 10.1 Hz), 4.57–4.50 (m, 1H), 3.99–3.96 (m, 1H), 3.89–3.70 (m, 6H), 3.04–2.99 (m, 1H), 1.45 (s, 9H), 0.97–0.95 (m, 9H), 0.91–0.89 (m, 27H), 0.19–0.18 (m, 6H), 0.08–0.01 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 171.8, 170.8, 155.7, 78.6, 75.5, 69.2, 67.1, 65.8, 50.7, 48.5, 40.6, 28.3, 26.3, 26.0, 25.7, 19.2, 18.6, 18.4, 17.9, 17.6, −3.8, −4.5, −4.8, −5.0, −5.2, −5.3; HRMS (ESI-QTOF) *m*/*z*: Calcd for $C_{39}H_{78}N_4O_9Si_3$ $[M+Na]^+$ 853.4974; Found 853.5358.

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Supplementary data

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