

HETEROCYCLES, Vol. 99, No. 1, 2019, pp. 200 - 212. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 26th May, 2018, Accepted, 26th June, 2018, Published online, 2nd July, 2018
DOI: 10.3987/COM-18-S(F)9

EFFICIENT SYNTHESIS OF *O*-LINKED GLYCOCONJUGATES OF AMINO ACIDS FROM CARBOHYDRATE-DERIVED DONOR-ACCEPTOR CYCLOPROPANES

Gade Kishore, Vibha Gautam, Shrutisagar Dattatraya Haveli, and Srinivasan Chandrasekaran*

Department of Organic Chemistry, Indian Institute of Science, Bangalore-560012, Karnataka, India. Corresponding author. Tel: + 91 80 2293 2404; Fax: + 91 80 2360 0529; E-mail: scn@iisc.ac.in, scn45@yahoo.com

Abstract – *N*-Iodosuccinimide (NIS) mediated ring opening of carbohydrate-derived donor-acceptor cyclopropanes with free “CO₂H” group of *N*-protected L-amino acids at ambient conditions afforded iodo derivatives of glycosyl ester of L-amino acids. The iodides were subsequently converted easily into corresponding azides using NaN₃ in DMF followed by reduction with Zn/AcOH to produce ester linked glycosyl amino acids. A similar strategy was adopted to synthesize *C*-linked glycoamino acid derivatives from different *N*-protected L-amino alcohols. By using an orthogonal strategy *C*- and *O*-linked glycopeptides were also synthesized.

INTRODUCTION

For the last four decades, compounds containing cyclopropane ring have proved to be valuable synthons for diverse types of transformations in organic synthesis.¹ Cyclopropane derivatives are also used in preclinical or clinical drug candidates for cancer therapy, infectious diseases, anti-HIV, antibacterial and cardiovascular drugs.² Cyclopropanes substituted with both electron withdrawing and donating groups which are called as donor-acceptor cyclopropanes (DA-cyclopropanes) have been found to be excellent building blocks for the synthesis of natural products and heterocyclic drugs.³ In particular, carbohydrate-derived DA-cyclopropane derivatives have also been used as key intermediates in the synthesis of natural products, and numerous biologically active heterocyclic derivatives.⁴

Due to the presence of a number of chiral centers and high functionalization, carbohydrate derivatives are used as alternatives to natural amino acids to study conformational stabilities of peptide and peptidomimetics.⁵ Glycoconjugates of amino acids especially *O*-linked glycosyl amino acids (via an ether

linkage) like T_N antigen, Thomsen-Friedenreich (TF or T) antigen, or sialyl-Tn antigen (STn antigen) are available in human cells as a complex *O*-glycans and in cancerous cells (**Figure 1**).⁶

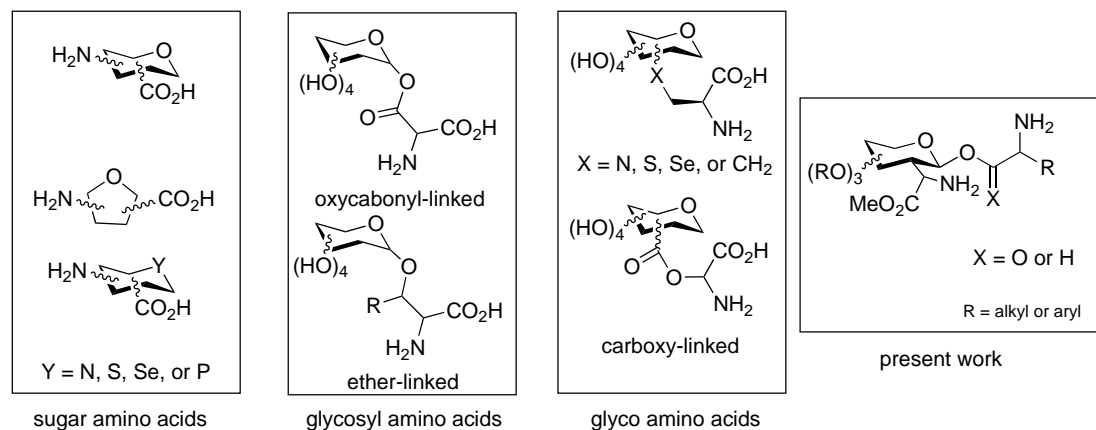


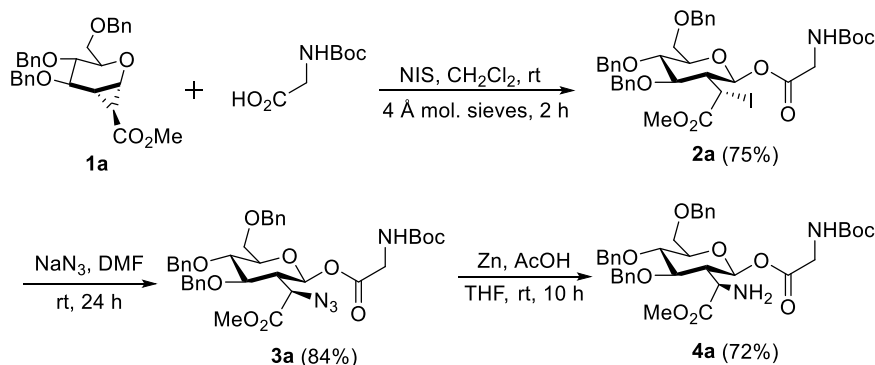
Figure 1

O-Linked glycoconjugates of amino acids are used as tumour-markers that could specifically deliver anti-cancer drugs to tumour cell surfaces.⁷ Another type of *O*-linked glycoconjugates of amino acids is ester linked glycoconjugates (via oxycarbonyl, $-\text{OCO}$ group) which are less common in nature and can be found in crown gall tumours of plant roots and some muscle tissues of animals.⁸ The ester linked glycosides exhibit anti-inflammatory effects and antiviral properties.⁹ Among different types of linkages between amino acids and carbohydrates like *O*-linked,¹⁰ *N*-linked, *S*-linked,¹¹ or phosphate-linked glycoconjugates of amino acids, the *C*-linked derivatives are chemically and metabolically resistant to enzymatic degradation (**Figure 1**).¹² *C*- and *O*-Linked carbohydrate-derived peptide mimetics have become very useful tools to study the inter- and intra-cell signalling processes and are key building blocks for the synthesis of natural glycopeptides, antibiotics, and anti-cancer drugs.¹³ In continuation of our interest in the development of new synthetic methodologies on carbohydrate-derived DA-cyclopropanes¹⁴ we report here our work on the synthesis of both *O*-linked and *C*-linked glycoconjugates of amino acids.¹⁵

RESULTS AND DISCUSSION

In order to synthesize glycoconjugates of amino acids, carbohydrate-derived donor-acceptor cyclopropane **2a** was obtained by stereoselective cyclopropanation of 3,4,6-tri-*O*-benzyl-D-glucal **1a** using methyl diazoacetate and a catalytic amount of $\text{Rh}_2(\text{OAc})_2$ (2 mol%).¹⁶ Glucose derived cyclopropanecarboxylate **1a** was reacted with *N*-Boc protected glycine in the presence of electrophilic activator *N*-iodosuccinimide (NIS) at room temperature (25 °C) to produce iodo derivative of glycosyl ester of glycine **2a** in good yield (75%).¹⁷ When iodide **2a** was treated with NaN_3 in DMF, azide derivative **3a** was obtained in high

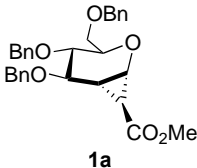
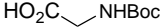
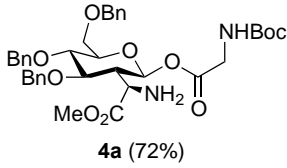
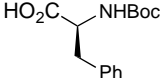
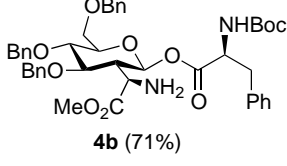
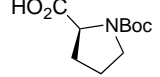
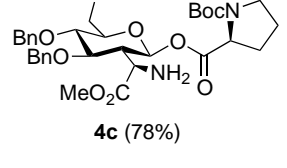
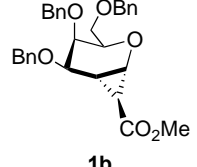

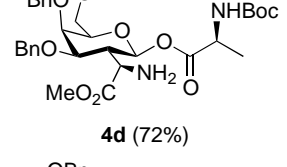
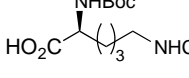
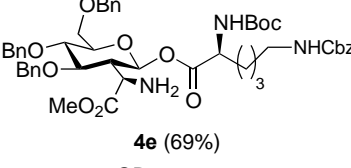
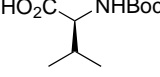
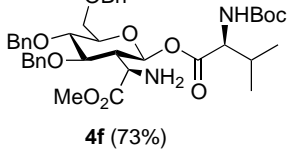
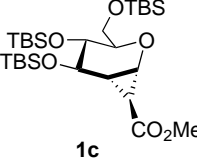

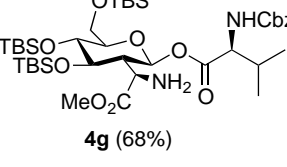
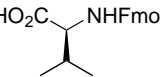
yield (84%) that would serve as a masked amine for the preparation of glycopeptides discussed later. The reduction of azide **3a** with zinc and acetic acid (Zn/AcOH) furnished the glycosyl ester **4a** in good yield (72%) (Scheme 1).



Scheme 1

This strategy has been extended to the synthesis of different glycoconjugates of amino acid derivatives by treating carbohydrate-derived DA-cyclopropanes (**1a**, **1b**, and **1c**) with various *N*-protected amino acids separately, under similar reaction conditions (Table 1). In all the cases, the iodides **2b–2h** were formed in moderate to good yields (61%–85%). The iodo derivative of glycosyl ester of proline, **2c** was identified as a mixture of two diastereomers (3:2 ratio) based on ^1H and ^{13}C NMR spectroscopy.¹⁸ Compound **2c** was obtained in moderate yield (52%) compared to the formation of other iodo derivatives (**2a–2b** & **2d–2g**). The iodides **2b–2g** (except **2h**) were converted to the corresponding azides **3b–3g** respectively using NaN_3 in DMF (24 h) with excellent diastereoselectivity. The iodide derivative **2h** of glycosyl ester of Fmoc-protected L-valine did not get converted into azide **3h** even after increasing the reaction time (24 h to 72 h) and also increasing reaction temperature from room temperature (25 °C) to 50 °C. Among the three *N*-protected L-valine derivatives (–Fmoc, –Boc, and –Cbz) of glycosyl esters, Boc and Cbz protected iodide derivatives (**2f** & **2g**) were completely converted into the corresponding azide derivatives (**3f** & **3g**) respectively without any difficulty. It is evident that Fmoc group causes the steric hindrance and hence resulted in an incomplete conversion of iodide **2h** to azide **3h**. Reduction of other azides **3b–3g** using Zn/AcOH afforded the corresponding glycosyl esters of amino acid derivatives **4b–4g** in good yields (Table 1).

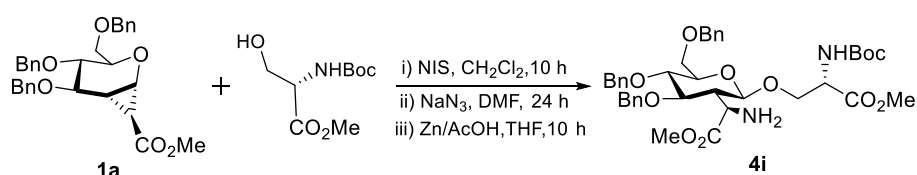
Table 1

Entry	Cyclopropane derivative	Amino acid	Iodide	Azide	Glycosyl amino acid
1)			2a (75%)	3a (84%)	
2)	1a		2b (68%)	3b (76%)	
3)	1a		2c (52%)	3c (82%)	
4)			2d (85%)	3d (73%)	
5)	1a		2e (61%)	3e (70%)	
6)	1a		2f (74%)	3f (84%)	
7)			2g (67%)	3g (74%)	
8)	1a		2h (62%)	Iodide 2h & azide 3h ^a	---

^aStarting material **2h** not fully consumed and azide **3h** was not isolated.

After achieving the synthesis of divergent glycosyl esters of amino acids, we decided to further extend this methodology for the synthesis of *O*-linked glycopeptides which are very important tools in biological studies.¹⁹ In this direction, deprotection of the *t*-butyl carbamate (NHBoc) of glycosyl ester of glycine **4a** was attempted and it was not successful probably due to acid-sensitive and highly reactive anomeric

acyloxy group attached to pyranose ring.²⁰ Therefore, we turned our attention towards the preparation of glycoconjugate derivatives linked via an ether linkage from the hydroxy group of amino alcohols and amino acids. Accordingly, *O*-glycosylation was achieved by ring opening of glucose derived DA-cyclopropane **1a** with free hydroxy group of *N*-Boc protected methyl ester of L-serine using electrophilic activator *N*-iodosuccinimide (NIS). As expected, the iodo derivative of glycosyl serine **2i** was obtained in good yield (**Scheme 2**). Reaction of the iodide with NaN₃ followed by reduction with Zn/AcOH yielded the glycopyranosyl serine **4i**.



Scheme 2

To further explore this strategy for the synthesis of *C*-linked glyco amino acids, cyclopropanecarboxylate **1a** was treated with *N*-Boc protected L-phenylglycinol and L-phenylalaninol in presence of NIS. The iodo derivatives **2j** & **3j** thus formed were transformed into azides **3j** & **3k** followed by reduction with Zn/AcOH to provide the corresponding *C*-linked glyco amino acids **4j** & **4k** respectively (**Table 2**).

Table 2

Entry	Carbohydrate derivative	Amino alcohols	Iodide	Azide	Glyco amino acid
1)			2i (75%)	3i (84%)	 4i (74%)
2)	1a		2j (68%)	3j (76%)	 4j (72%)
3)	1a		2k (52%)	3k (82%)	 4k (69%)

The crystal structure of iodide **2d** (CCDC number: 995269) clearly confirmed the *trans* stereochemistry at the anomeric carbon and C-2 of pyranose framework (**Figure 2**). This was congruent with the assigned stereochemistry of iodides **2a–2k** at C-7 and the corresponding glycosyl amino acid derivatives **4a–4k**.

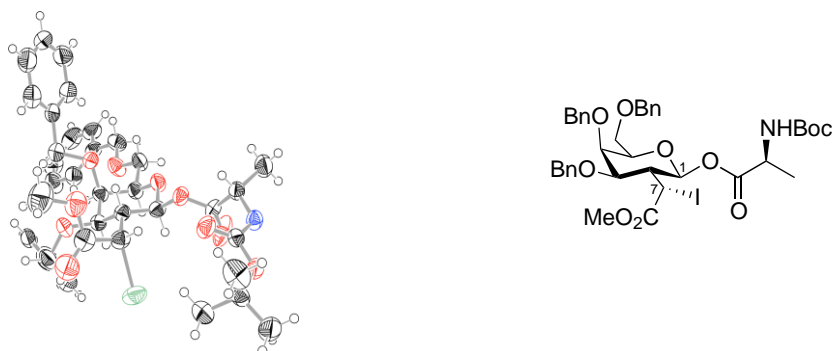
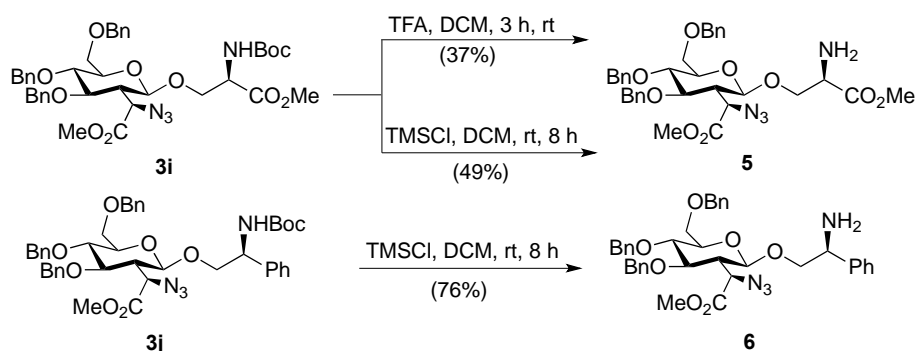


Figure 2

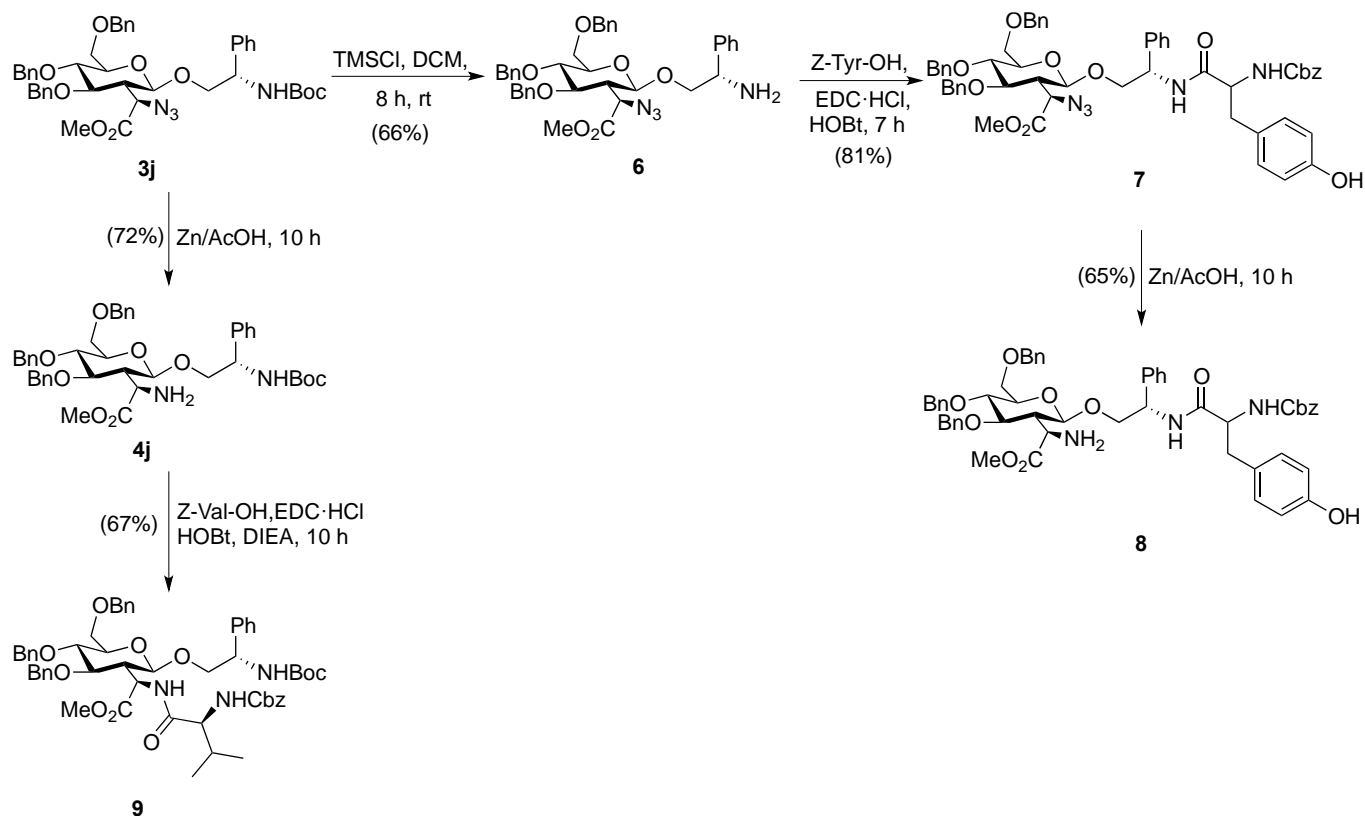
To synthesize both *O*- and *C*-linked glycopeptides orthogonally from one starting material, we took advantage of the fact that one azide group ($-N_3$) and one NHBoc group are tethered in the carbohydrate framework via two different linkages. Additionally, the N_3 group was used as a masked amine ($-NH_2$) which circumvents the protection and deprotection steps for the synthesis of *O*- and *C*-linked glycopeptides in the orthogonal strategy. In this approach, deprotection of glycosyl serine **3i** was done using 10% TFA in CH_2Cl_2 which gave the free amine **5** in low yield (37%, **Scheme 3**).²¹ In order to improve the yield, deprotection was performed under very mild conditions using trimethylsilyl chloride (TMSCl).²² When glycosyl serine **3i** was treated with TMSCl in CH_2Cl_2 , it gave the free amine **5** in moderate yield (49%). As the deprotection of NHBoc of serine derivatives was achieved only in moderate yield, we switched to *L*-phenylglycinol derivative. Deprotection of NHBoc in azide derivative **3j** was performed using TMSCl which gave free amine **6** in good yield (76%, **Scheme 3**).



Scheme 3

The glyco amino acid **6** was coupled with *Z*-Tyr-OH using EDC·HCl and HOBT to furnish the *O*-linked glycopeptide **7** in excellent yield (81%, **Scheme 4**). The azide group present in *O*-linked glycopeptide **7** was then reduced with Zn/AcOH to produce the glycopeptide **8** in moderate yield (65%). The amine **8** can

be used for the synthesis of *O*-linked glycopeptides. From the same molecule of glyco amino acid **3j**, *C*-linked glycopeptide **9** was synthesized from azide derivative **3j** by reducing N_3 group to NH_2 and further coupling with an amino acid. The azide present in **3j** was first converted to free amine **4j** with $Zn/AcOH$ in good yield (72%) and the amine **4j** was then coupled with *Z*-Val-OH to synthesize the *C*-linked glycopeptide **9** (67%) (Scheme 4).



Scheme 4

In conclusion, stereoselective synthesis of *O*- and *C*-linked glycoconjugates of amino acids was achieved by NIS-mediated ring-opening of carbohydrate-derived cyclopropanecarboxylates with carboxylic 'CO₂H' and hydroxy group of amino acid derivatives. Among three *N*-protected amino acids (–Fmoc, –Boc, and –Cbz) of amines, the reaction of glycosyl ester of *N*-Fmoc protected amino acid was not successful due to the steric hindrance of the bulky Fmoc group. During our studies on the deprotection of $NHBoc$ we found that trimethylsilyl chloride is a better reagent than trifluoroacetic acid. Finally, we have been able to demonstrate the development of an excellent method for the synthesis of both *O*- and *C*-linked glycopeptides using the orthogonal deprotection strategy.

EXPERIMENTAL

All reactions were carried out in oven-dried apparatus using dry solvents under argon atmosphere unless otherwise noted. All solvents for routine isolation of products and chromatography were reagent grade

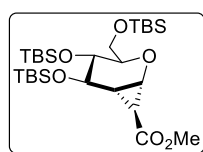
and redistilled. All the solvents used for the reaction were dried following the prescribed method over 4 Å molecular sieves or other appropriate drying agents.²³ All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualizing under UV light and developed using H₂SO₄ or vanillin solution. ¹H, ¹³C NMR spectra were recorded on a 300, 400 or 500 MHz NMR spectrometer and chemical shifts are cited with respect to SiMe₄ as internal (¹H and ¹³C). Chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd doublet of doublet), coupling constant in Hertz (Hz), and a number of protons are presented in standard format. Infrared (IR) spectra were measured on a Jasco FTIR 410 spectrophotometer as a thin film on NaCl pellet by dissolving compounds in CHCl₃. HRMS were recorded “MicroMass ESI-TOF” with electrospray ionization (ESI) and quadrupolar mass analyzer with time-of-flight (TOF) detector. Optical rotation of compounds was recorded on “JASCO digital polarimeter DIP-370” or Jasco P-2000. Single crystal X-ray data collection was recorded on a BRUKER-SMART APEX CCD-single crystal diffractometer.

General procedure for the cyclopropanation of D-glycals to form (1a–1c)²⁴

To a stirred suspension of D-glycal (10 mmol) and Rh₂(OAc)₄ (0.1 mmol) in anhydrous DCM (10 mL), methyl diazoacetate (20.0 mmol) in DCM (75 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 EtOAc and petroleum ether of appropriate composition to obtain the cyclopropanecarboxylate. Spectral data of compounds **1a** and **1b** can be found in the supporting information.

1,5-Anhydro-2-deoxy-1,2-C-(*exo*-carbmethoxymethylene)-3,4,6-tri-*O*-*tert*-butyldimethylsilyl- α -D-glucitol (**1c**).

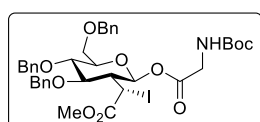
Yield 58%; Gummy; $[\alpha]_D^{25} +37.0$ (*c* 2, CHCl₃); $R_f = 0.6$ (hexanes/EtOAc, 9:1); IR (neat): 2929, 1719, 1443, 1072, 834 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.99–3.94 (m, 2H, H-6, H-6'), 3.81 (dd, 1H, *J* = 1.3, 7.2 Hz), 3.70 (d, 1H, *J* = 3.4 Hz), 3.67 (s, 3H), 3.60–3.57 (m, 2H), 2.27 (dd, 1H, *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 × (CH₃)₃C), 0.12–0.06 (m, 18H, 3 × (CH₃)₂Si); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₇H₅₆O₆Si₃ [M+Na]⁺ 583.3282; Found 583.3290.



General procedure for the synthesis of iodides (2a–2k). To a solution of cyclopropanecarboxylate (1 mmol) and *N*-protected amino acid (1.2 mmol) in CH₂Cl₂ (7 mL) under argon atmosphere was added *N*-iodosuccinimide (1.3 mmol) and 4 Å molecular sieves (250 mg). The reaction mixture was stirred for certain time (2 h for **2a–2h** and 12 h for **2i–2k**) at room temperature (25 °C). After complete disappearance of the starting material, the reaction mixture was diluted with CH₂Cl₂ (20 mL). The

reaction mixture was treated with a saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution and then the organic layer was separated and dried over anhydrous Na_2SO_4 . The crude product obtained after removal of solvent was purified by column chromatography on silica gel (230–400 mesh) using EtOAc and petroleum ether of appropriate composition to obtain the corresponding iodide derivatives. Physical, spectral data of compounds **2b–2k** and crystal data of compound **2d** can be found in the supporting information.

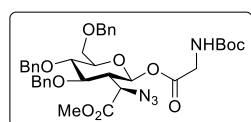
3,4,6-Tri-*O*-benzyl-2-(1-iodo-2-methoxy-2-oxoethyl)-1,2-dideoxy- β -D-glucopyranos-1-yl *N*-{[(2-methyl-2-propanyl)oxy]carbonyl}glycinate (2a**).** Yield 52%; $R_f = 0.5$ (hexanes/EtOAc, 8:2); White



solid; mp 52–54 °C; $[\alpha]_D^{25} +1.7$ (c 1, CHCl_3); IR (KBr): 3390, 2923, 1745, 1722, 1366, 1155, 1089, 736, 698 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): 7.32–7.07 (m, 15H), 5.69 (d, 1H, $J = 8.4$ Hz), 5.21 (bs, 1H), 4.97–4.45 (m, 7H), 3.95–3.59 (m, 7H), 3.35 (s, 3H), 2.21 (t, 1H, $J = 8.4$ Hz), 1.44 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3): 168.4, 167.2, 155.5, 137.8, 137.5, 137.4, 128.9, 128.2, 127.8, 127.6, 127.5, 127.5, 127.3, 94.6, 81.0, 79.9, 78.9, 75.4, 74.6, 74.5, 73.3, 67.9, 53.2, 48.7, 42.3, 28.1; HRMS (ESI-QTOF) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{37}\text{H}_{44}\text{INO}_{10}\text{Na}$ 812.1903; Found 812.1880.

General procedure for the synthesis of azides (3a–3g & 3i–3k). To a stirred solution of iodo derivative of glycosyl ester of amino acid (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 (25 °C). 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 by column chromatography on silica gel (230–400 mesh) using EtOAc and petroleum ether of appropriate composition to furnish the pure azide derivatives. Physical and spectral data of compounds **3b–3g**, **3i–3k** can be found in the supporting information.

3,4,6-Tri-*O*-benzyl-2-(1-azido-2-methoxy-2-oxoethyl)-1,2-dideoxy- β -D-glucopyranos-1-yl *N*-{[(2-methyl-2-propanyl)oxy]carbonyl}glycinate (3a**).** Yield 74%; Gummy; $R_f = 0.5$ (hexanes/EtOAc, 8:2);



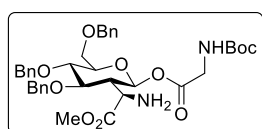
$[\alpha]_D^{25} +88.5$ (c 1, CHCl_3); IR (neat): 3421, 2929, 2871, 2113, 1778, 1747, 1719, 1498, 1366, 1215, 1158, 1075, 737 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): 7.37–7.16 (m, 15H), 5.61 (d, $J = 8.7$ Hz, 1H), 4.95 (d, $J = 11.4$ Hz, 2H), 4.79 (d, $J = 7.5$ Hz,

1H), 4.67–4.57 (m, 3H), 4.47 (d, $J = 11.2$ Hz, 1H), 4.318 (d, $J = 1.5$ Hz, 1H), 3.842–3.492 (m, 10H), 2.454 (t, $J = 9$ Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3): 170.4, 168.1, 135.3, 137.8, 137.6, 128.6, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 91.8, 79.9, 79.1, 78.1, 75.6, 75.1, 74.7, 73.6, 67.9, 57.8, 52.6, 47.3, 42.3, 42.0, 28.2; HRMS (ESI-QTOF) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{37}\text{H}_{44}\text{N}_4\text{O}_{10}\text{Na}$ 727. 2955; Found 727. 2940.

General procedure for the synthesis of glycosyl esters of amino acids (4a–4g & 4i–4k). To a stirred solution of azide (1 mmol) in 10 mL of AcOH:THF (1:1), Zn dust (2 mmol) was added and the reaction

mixture was stirred for 12 h at room temperature (25 °C). After disappearance of starting material, Zn was removed by filtration. The solvent was then removed under vacuum followed by dilution with 20 mL of EtOAc. The organic layer was thoroughly washed with water. To the organic layer, 20 mL of saturated aq. NaHCO₃ solution was added left for stirring for 3 h. The organic layer was then separated and dried over anhydrous Na₂SO₄. The filtrate was concentrated and the crude product was purified by column chromatography on amine pre-treated silica gel (0.5 mL of Et₃N for 50 g of silica gel) using EtOAc and petroleum ether of appropriate composition to furnish glycosyl esters. Physical and spectral data of compounds **4b–4g**, **4i–4k** can be found in the supporting information.

3,4,6-Tri-*O*-benzyl-2-(1-amino-2-methoxy-2-oxoethyl)-1,2-dideoxy-β-D-glucopyranos-1-yl N-[(2-methyl-2-propanyl)oxy]carbonyl}glycinate (4a**).** Yield 72%; Gummy; *R*_f = 0.5 (hexanes/EtOAc, 5:5);



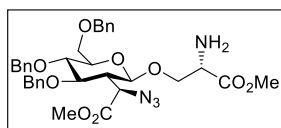
$[\alpha]^{25}_{\text{D}} +65.4$ (*c* 1, CHCl₃); IR (neat): 3421, 3363, 2928, 1724, 1682, 1284, 739, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 7.25–7.11 (m, 15H), 5.11 (d, *J* = 2.8 Hz, 1H), 4.86–4.65 (m, 2H), 4.56–4.34 (m, 3H), 3.96–3.76 (m, 2H), 3.60 (s, 3H),

3.51–3.48 (m, 1H), 2.92 (d, *J* = 6.6 Hz, 1H), 2.40 (dt, *J* = 11.3, 3.4 Hz, 1H), 1.36 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): 172.4, 169.9, 167.7, 155.9, 138.2, 137.7, 132.5, 130.9, 128.79, 128.8, 128.4, 128.4, 128.4, 127.9, 127.8, 127.6, 127.4, 92.7, 75.6, 74.6, 73.4, 68.7, 68.2, 52.6, 45.8, 38.7, 30.4, 28.9, 28.3, 23.8, 23.0, 14.0, 11.0; HRMS (ESI-QTOF) *m/z*: [M+Na]⁺ Calcd for C₃₇H₄₆N₂O₁₀Na 701.3050; Found 701.3038.

Synthesis of glycosyl amino acids (5** & **6**) by deprotection of NHBoc. Method A: Use of trifluoroacetic acid.** To a cold solution of *N*-Boc protected amine, **3a** (0.1 mmol) in 3 mL of 10% trifluoroacetic acid (TFA) in CH₂Cl₂ was added at ice-cold temperature and the reaction mixture was stirred for 3 h. After the disappearance of starting material, the solvent was removed under vacuum followed by dilution with 20 mL of EtOAc. The organic layer was thoroughly washed with water. To the organic layer, 20 mL of saturated aq. NaHCO₃ solution was added and left for stirring for 3 h. The organic layer was then separated and dried over anhydrous Na₂SO₄. The filtrate was concentrated and the crude product was purified by column chromatography on amine pre-treated silica gel (0.5 mL of Et₃N for 50 g of silica gel) using EtOAc and petroleum ether of appropriate composition to furnish free amine derivative of glycosyl amino acids.

Method B: Use of trimethylsilyl chloride. To an ice-cold solution of *N*-Boc protected amine, **3a**, (0.2 mmol) in 3 mL of in CH₂Cl₂, trimethylsilyl chloride (1 mmol) was added at ice-cold temperature and the reaction mixture was stirred for 8–12 h. After disappearance of starting material, the reaction mixture was diluted with 20 mL of EtOAc. The organic layer was thoroughly washed with water. To the organic layer, 20 mL of saturated aq. NaHCO₃ solution was added and stirred for 3 h. The organic layer was then separated and dried over anhydrous Na₂SO₄. The filtrate was concentrated and the crude product was purified by column chromatography on amine pre-treated silica gel (0.5 mL of Et₃N for 50 gr of silica

gel) using EtOAc and petroleum ether of appropriate composition to furnish free amine derivative of glycosyl amino acid. Physical and spectral data of compound **6** can be found in the supporting information.

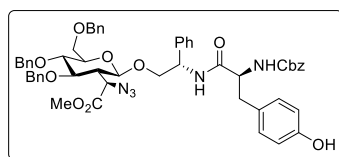


(S)-2-Carbomethoxy-2-(amino)ethyl 3,4,6-tri-O-benzyl-2-(1-azido-2-methoxy-2-oxoethyl)-1,2-dideoxy- β -D-glucopyranoside (5). Yield: 66%; Gummy; R_f =

0.4 (hexanes/EtOAc, 5:5); $[\alpha]^{25}_D +42.7$ (c 3.3, CHCl_3); IR (neat): 3392, 2921, 2111, 1745, 1217, 1063, 737, 698 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): 7.38–7.20 (m, 15H), 4.94 (d, J = 11.6 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H), 4.64–4.53 (m, 4H), 4.38 (d, J = 8.4 Hz, 1H), 4.29 (d, J = 1.72 Hz, 1H), 4.11–4.07 (m, 1H), 3.76–3.57 (m, 13H), 3.40–3.35 (m, 1H), 2.34–2.17 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): 173.4, 170.8, 138.0, 137.8, 137.8, 128.6, 128.4, 128.3, 128.2, 128.1, 127.8, 127.6, 100.2, 79.6, 78.5, 75.0, 74.7, 73.5, 71.8, 68.3, 58.1, 54.5, 52.5, 52.1, 48.7; HRMS (ESI-QTOF) m/z : $[\text{M}+\text{Na}]$ Calcd for $\text{C}_{34}\text{H}_{40}\text{N}_4\text{O}_9\text{Na}$ 671.2693; Found 671.2690.

Synthesis of glycopeptides. EDC·HCl (1.2 mmol) was added to an ice-cold solution of glycosyl amino acid derivative (0.1 mmol), amino acid (0.13 equiv.), *N,N*-diisopropylethylamine (2.5 mmol) and HOBT (1.2 mmol) in 2 mL of DMF. The reaction mixture was stirred for 10 h. After the disappearance of starting material, the solvent was removed under vacuum followed by dilution with 20 mL of EtOAc. The organic layer was thoroughly washed with 2N HCl solution, followed by water and then with a saturated aq. 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 (230–400 mesh) using EtOAc and petroleum ether of appropriate composition to furnish glycopeptides. Physical and spectral data of compounds **8** and **9** can be found in the supporting information.

Glycopeptide 7. Yield: 81%; R_f = 0.5 (EtOAc); Gummy; $[\alpha]^{25}_D +64.1$ (c 1.5, CHCl_3); IR (Neat): 3342,



2112, 1745, 1722, 1713, 1515, 1217, 1054, 753, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): 7.38–7.16 (m, 27H), 7.04 (d, J = 7.9 Hz, 2H), 6.69 (d, J = 7.8 Hz, 2H), 5.59 (d, J = 8.1 Hz, 1H), 5.09 (s, 2H), 5.01–4.99 (m, 1H), 4.93 (d, J = 11.5 Hz, 1H), 4.78 (d, J = 10.9 Hz, 1H), 4.68–4.60 (m, 2H), 4.54–4.50 (m, 2H), 4.44–4.41 (m, 1H), 4.23 (d, J = 1.5 Hz, 1H), 4.16–4.11 (m, 1H), 3.74–3.61 (m, 5H), 3.53–3.48 (m, 1H), 3.35 (s, 3H), 3.23–3.21 (m, 1H), 3.10–2.95 (m, 2H), 2.25–2.20 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): 170.7, 170.6, 155.2, 138.8, 137.7, 137.6, 137.1, 136.3, 130.4, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.97, 127.93, 127.8, 127.2, 126.7, 115.7, 100.1, 79.3, 78.4, 74.9, 74.8, 74.4, 73.5, 68.4, 66.8, 58.0, 56.8, 52.7, 52.6, 52.3, 48.4; HRMS (ESI-QTOF) m/z : $[\text{M}+\text{Na}]$ Calcd for $\text{C}_{55}\text{H}_{57}\text{N}_5\text{O}_{11}$ $[\text{M}+\text{Na}^+]$ 986.3952; Found 986.3953.

ACKNOWLEDGEMENTS

G.K. and S.D.H. thank UGC, New Delhi for a Senior Research Fellowship. V.G. thanks DST, New Delhi for a fellowship under the Women Scientists Programme and S.C.N. thanks Indian National Science Academy, New Delhi for the Senior Scientist position. We thank the Department of Science and Technology, India, for use of the CCD facility setup under the IRHPA-DST program at IISc.

SUPPLEMENTARY MATERIAL

Preparation, ^1H and ^{13}C NMR data of glyconjugates of amino acids **2a–2k**, **3a–3g**, **3i–3k**, **4a–4g**, **4i–4k** and **5–9** can be found in the supporting information. Complete crystallographic data of compound **2d** was deposited at the Cambridge Crystallographic Data Centre, **CCDC 995269** and this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (fax: +44 1223 336033, email: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

REFERENCES

1. C. A. Carson and M. A. Kerr, *Chem. Soc. Rev.*, 2009, **38**, 3051; P. Tang and Y. Qin, *Synthesis*, 2012, **44**, 2969.
2. S. F. Martin, G. O. Dorsey, T. Gane, M. C. Hillier, H. Kessler, M. Baur, B. Mathä, J. W. Erickson, T. N. Bhat, S. Munshi, S. V. Gulnik, and I. A. Topol, *J. Med. Chem.*, 1998, **41**, 1581; T. T. Talele, *J. Med. Chem.*, 2016, **59**, 8712.
3. H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151; M. Yu and B. L. Pagenkopf, *Tetrahedron*, 2005, **61**, 321; H. M. L. Davies and J. R. Denton, *Chem. Soc. Rev.*, 2009, **38**, 3061; T. F. Schneider, J. Kaschel, and D. B. Werz, *Angew. Chem. Int. Ed.*, 2014, **53**, 5504.
4. P. Sears and C.-H. Wong, *Angew. Chem. Int. Ed.*, 1999, **38**, 2300; B. L. Pagenkopf and N. Vemula, *Eur. J. Org. Chem.*, 2017, 2561.
5. F. Schweizer, *Angew. Chem. Int. Ed.*, 2002, **41**, 230.
6. T. Ju, V. I. Otto, and R. D. Cummings, *Angew. Chem. Int. Ed.*, 2011, **50**, 1770; S. D. Kuduk, J. B. Schwarz, X.-T. Chen, P. W. Glunz, D. Sames, G. Ragupathi, P. O. Livingston, and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1998, **120**, 12474.
7. R. D. Egleton, S. A. Mitchell, J. D. Huber, J. Janders, D. Stropova, R. Polt, H. I. Yamamura, V. J. Hruby, and T. P. Davis, *Brain Res.*, 2000, **881**, 37.
8. Š. Horvat, L. Varga, and J. Horvat, *Synthesis*, 1986, 209; R. J. Tennant-Eyles and A. J. Fairbanks, *Tetrahedron: Asymmetry*, 1999, **10**, 391.
9. H. Chen, S.-Q. Huang, and J.-Y. Xie, *J. Chem. Res.*, 2008, **2008**, 486; R. Haddoub, N. Laurent, M.

- Meloni, and S. Flitsch, *Synlett*, 2009, 3328.
10. R. J. Payne and C.-H. Wong, *Chem. Commun.*, 2010, **46**, 21.
 11. L. Käsbeck and H. Kessler, *Liebigs Ann. Chem.*, 1997, 165.
 12. A. Dondoni and A. Massi, *Acc. Chem. Res.*, 2006, **39**, 451.
 13. S. J. Danishefsky and J. R. Allen, *Angew. Chem. Int. Ed.*, 2000, **39**, 836.
 14. G. Kishore, V. Gautam, and S. Chandrasekaran, *Carbohydr. Res.*, 2014, **390**, 1.
 15. V. Ganesh, P. R. Sridhar, and S. Chandrasekaran, *Isr. J. Chem.*, 2016, **56**, 417.
 16. C. M. Timmers, M. A. Leeuwenburgh, J. C. Verheijen, G. A. van der Marel, and J. H. van Boom, *Tetrahedron: Asymmetry*, 1996, **7**, 49.
 17. S. D. Haveli, P. R. Sridhar, P. Suguna, and S. Chandrasekaran, *Org. Lett.*, 2007, **9**, 1331.
 18. D. Pal and P. Chakrabarti, *J. Mol. Biol.*, 1999, **294**, 271.
 19. T. Buskas, S. Ingale, and G.-J. Boons, *Glycobiology*, 2006, **16**, 113.
 20. B. Capon, *Chem. Rev.*, 1969, **69**, 407.
 21. A. S. Ripka, R. S. Bohacek, and D. H. Rich, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 357.
 22. R. S. Lott, V. S. Chauhan, and C. H. Stammer, *J. Chem. Soc., Chem. Commun.*, 1979, **0**, 495.
 23. W. L. F. Armarego and C. L. L. Chai, in *Purification of Laboratory Chemicals*, 6th edn., Butterworth-Heinemann, Oxford, 2009.
 24. P. R. Sridhar, K. C. Ashalu, and S. Chandrasekaran, *Org. Lett.*, 2004, **6**, 1777.