Synthesis of Reversed *C*-glycopeptide Mimics Monomer from Galactose *via* Passerini Reaction

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(Received on 23rd April 2018, accepted in revised form 30th May 2018)

Summary: *C*-glycopeptidomimetics are formed by the condensation of sugar unit and analogues of amino acid residue which generates a new carbon-carbon sigma bond. In glycopeptides, this condensation occurs in side chain of amino acid but introduction of isonitrile moiety on *N*-terminal of amino acid mimic unit can also be a route to produce such compounds. It is observed that *C*-glycopeptidomimetics are more stable than their *N*- and *O*-analogues under physiological conditions but their synthesis is a challenging task due to relatively less reactive *C*-6 position of hexose. In present work, synthesis of reversed *C*-glycopeptidomimetics (pseudoglycopeptides) was done by Passerini reaction protocol which is famous for peptide synthesis due to its mild conditions and easy workup. This paper discusses the use of α-D-galactose, a cheap and easily available monosaccharide to prepare reversed *C*-glycopeptidomimetics. The term reversed *C*-glycopeptidomimetics is derived for its analogy with reversed *C*-nucleosides, as in these reactions, instead of anomeric carbon i.e. more reactive site, *C*-6 undergoes to produce desired products.

Key words: Reversed *C*-glycopeptidomimetics, Mimics monomer of *C*-Glycopeptides, α-D-galactose, Passerini reaction.

Introduction

Sugar molecules (glycans) attached with amino acid side chains of peptides through covalent bonds to produce a special class of compounds known as glycopeptides. Vancomycin, teicoplanin and telavancin are few examples of such compounds [1].

Since the last decade, glycan part of glycopeptides is found to be interesting for chemists due to its key role in various biological processes. It is found to be involved in protein modification [2], adhesion of cells [3], inflammation, tumour metastasis [4] and correct receptor identification [5]. It is also noted that glycopeptides and glycoproteins play important role during fertilization, development of neurons, hormone functions, immunity responses and inflammatory responses [6,7]. Attachment of glycans also increases stability of tertiary protein structures [8,9]. For example, RNase-B, which contains a high-mannose oligosaccharide unit at Asn-34, is more stable than RNase-A, which is unglycosylated pancreatic ribonuclease [10].

Due to their significant applications in biological systems, synthetic strategies are being made to produce various useful glycopeptides similar to naturally occurring glycopeptides Various retrosynthetic approaches were introduced to carry out synthesis of glycopeptides and to produce new and more effective mimetics using chemical, enzymatic or biological means. Some remarkable efforts for the preparation of short length glycopeptides are also documented in literature [11, 12]. Meanwhile attachment of oligosaccharides [13,14] and attempts to prepare pure proteins [15,16] are also sub-topics of the same subject as their correlation and combined form shows the formation of glycoprotein too.

Glycopeptidomimetics are synthetic analogues of glycopeptides to overcome their limited bioavailability. In glycopeptidomimetics, N-substituted chains attached with carbohydrate units result in formation of amide linkage which results in their improved proteolytic stability than available glycopeptides. Longer hydrophobic chains present in these molecules enhance their cell permeability [17, 18]. It is considered that the first *C*-linked glycopeptoid analogue to Ser-*O*-GlcNAc residue has been synthesis by the Kessler group [19]. Although, Thomas Szekely and Olivier Roy synthesised are also reported as the one who synthesized *C*-linked glycopeptidomimetics analogue to Ser-*O*-GlcNAc residue. Like glycopeptidomimetics are also

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classified as *N*-linked glycopeptidomimetics, *O*-linked glycopeptidomimetics and *C*-linked glycopeptidomimetics and well documented by Roy and his team [20].

Furthermore, Zuckermann and co-workers synthesized 6-amino-6-deoxy-1,2:5,6-di-*O*-isopropylidene-*α*-D-galactopyranose (**1a**) and used it as sub monomer for the synthesis of *C*-linked glycopeptoid oligomers [21].

Molecules that contain sugar units linked to amino acids or amino acid residues through carbon carbon sigma bond termed as *C*-glycopeptoid. In such glycopeptoid, usually sugar is attached to amino acid side chain. The main aim is to produce a stable covalent bond which can sustain under physiological conditions and may have good stability against enzymatic action than their parent compounds. The term glycopeptidomimetics could refer to attachment of any amino acid residue with any carbon of monosaccharide but if such connection particularly occurring at the *C*-6 position of sugar i.e. reverse position of sugar, it may be referred as reversed *C*-glycopeptidomimetics since it is an analogue of reversed *C*-nucleosides already reported in literature [30].

Passerini protocol, a multi component reaction, MCR) is a well-known method for peptide synthesis. It is employed for the formation of ester amide linkage by reacting isonitrile, aldehyde, and carboxylic acid units to produce new carbon-carbon connectivity [22]. Resulting molecules, if contain sugar residue along with a moiety that mimic amino acid, by means of chain elongation, are glycopeptoid monomer. Here it is obvious that, isonitrile play a vital role in synthesis of glycopeptoid assemblies [23,24].

Experimental

Reagents and chemicals

α-D-galactose, 4-aminobenzoic acid and all fatty acids were purchased from Sigma-Aldrich and used as purchased without further purification. Methyl 4-isocyanobenzoate was synthesised in lab by a three steps route which is described here. All solvents were of analytical grade and used as purchased without further purification.

Instrumentation

TLC (Thin Layer Chromatography)-visualisation was conducted on UV-lamp at wavelength = 254 nm. Infrared spectra were recorded on JASCO FT/IR-4200. AVANCE-III, 300 MHz spectrometer was used to record NMR spectra taking $CDCl_3$ as solvent. For mass spectra Agilent Technologies 6890 N instrument was used.

Synthesis of 1,2:3,4-di-O-isopropylidene-α-D-galactose **1a**

Following the protocol provided by Kratha. K.P.R., compound **1a** was prepared [25]. In a round bottom flask of 1000 ml, 5 g of *α*-D-galactose was dissolved in 250 ml acetone and 0.5 g iodine was added in it. The reaction was stirred at room temperature for 18 hours and formation of product was observed on TLC. After completion of reaction, iodine was quenched by saturated aqueous solution of $Na_2S_2O_3$ and acetone was recovered through rotavapor. In a separating funnel, product was collected in organic layer by solvent extraction with ethyl acetate (3x10 ml). organic layer was dried over Na_2SO_4 and after evaporation of solvent, a thick brown syrup was obtained.

(Rf = 0.6 in 9:1 toluene: ethyl acetate, Product yield = 70 %).

Synthesis of 1,2:3,4-di-O-isopropylidene-6-oxo-α-D-galactopyranose **1b**

Compound **1b** was prepared as reported by Corey, E. J., *et.al.* [26]. In a round bottom flask of 100 ml fitted with reflux condenser, 1.24 g (5.76 mmol) of PCC (Pyridinium Chlorochromate) was dissolved in 50 ml anhydrous dichloromethane and 1 g (3.84 mmol) of 1,2:3,4-di-*O*-isopropylidene-*α*-D-galactose was added in it. About 1 g of 4Å molecular sieves was also added. The reaction was refluxed for 4 hours and formation of product was observed on TLC. After completion of reaction, product was filtered from black gummy mass and was washed with dichloromethane. Further purification was done by column chromatography. A pale-yellow oil was obtained as **1b**. Obtained data was compared with reported literature available [31].

(Rf = 0.7 in 9:1 toluene: ethyl acetate, Product yield = 60 %)

Esterification of 4-aminobenzoic acid **3**

Esterification of p-aminobenzoic acid was done by Fischer esterification method [27]. 5 g (36.47 mmol) of 4-aminobenzoic acid was dissolved in 50 ml methanol and 4 ml sulfuric acid was added in it. The reaction was refluxed for four hours and the

product was obtained as beige crystals. (Product yield = 50 %)

N-Formylation of Methyl 4-aminobenzoate **3a**

A mixture of 0.30 g (2 mmol) **3a**, 151 ml (4 mmol) methanoic acid and 12.7 mg (5 mmol%) iodine was stirred at 70 °C for 3 hours [28]. After completion of reaction, as monitored on TLC, mixture was diluted with dichloromethane and iodine was quenched by saturated solution of $Na_2S_2O_3$. Organic layer was further washed with brine and saturated solution of sodium bicarbonate and was dried over $MgSO_4$. Further purification of product was done by column chromatography. (Product yield = 60 %)

*Conversion of **3b** into Methyl 4-isocyanobenzoate* **3c**

0.358 g (2 mmol) of **3b** and 762 mg (3 mmol) iodine were dissolved in about 5ml of dichloromethane and 788 mg (3 mmol) triphenylphosphine was added in it. Then, 602 mg (830 µl, 6 mmol) triethylamine was added in mixture dropwise over a period of five minutes. The mixture was stirred at room temperature for five hours and product formation was monitored by TLC [29]. Organic layer was diluted with dichloromethane and was washed with distilled water. Later it was dried over sodium sulphate to obtain white amorphous product.

(Product yield =45 %)

Synthesis of Reversed C-glycopeptidomimetics **4a-4f**

In a general experiment, 0.258 g (1 mmol) of compound **1b** was dissolved in dichloromethane and mixed with 1 mmol of compound **2a-f** in a round bottom flask. After five minutes, a solution of 0.161 g (1 mmol) **3c**, dissolved in 1 ml of dichloromethane was introduced in it by a pipette. The reaction was stirred at room temperature for next eight hours to overnight period. Formation of product **4a-4f** was monitored by TLC and further purification of product was done by preparative thick layer chromatography with a solvent system Hexane: Ethyl acetate (8:2).

Rf values for compounds **4a-4f** were observed as 0.4, 0.5, 0.5, 0.6, 0.6 and 0.7 respectively in 8:2 Hexane: Ethyl acetate. Product yield for compounds **4a-4f** was 50 %, 70 %, 65 %, 78 %, 87 % and 90 % respectively.

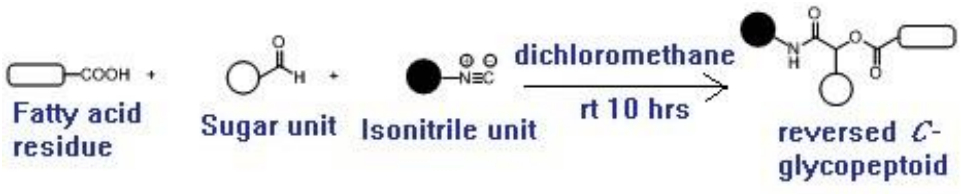
Results and discussion

Carbohydrate chemistry is an interesting field of research. Sugars play vital role in biochemical reactions. Their connection with other biomolecules to produce significant structures like Deoxyribonucleic acid (DNA), Ribonucleic acid (RNA), Glycoproteins, Glycolipids, and Glycopeptides offers them special place in natural products chemistry. We used *α*-D-galactose for synthesis of reversed *C*-glycopeptidomimetics since it is cheap and easily available monosaccharide, furthermore it offers an easy strategy to produce reversed *C*-glycopeptoid. *C*-glycopeptoid are thermally more stable than other types of glycopeptidomimetics. The term 'reversed *C*-glycopeptidomimetics has been introduced due to analogy with reversed *C*-Nucleosides [30] i.e. amino acid moiety is linked through *C*-6 instead of anomeric position *C*-1 of *α*-D-galactose.

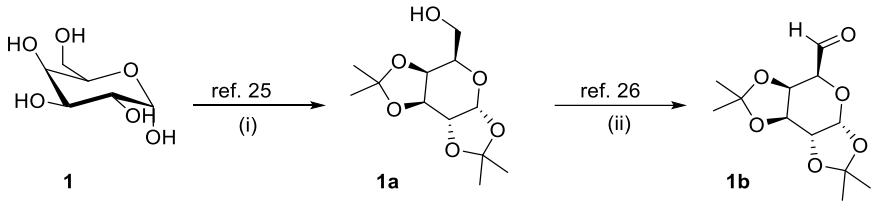
Six reversed *C*-glycopeptidomimetics were prepared using Passerini reaction; a three components reaction of aldehyde, carboxylic acid and isonitrile to furnish amide ester linkage Scheme-1.

The aldehyde component **1b** was obtained from *α*-D-galactopyranose (**1**). *α* -D-galactopyranose (**1**) was reacted with acetone in the presence of iodine to obtain 1,2:3,4-di-*O*-isopropylidene-*α*-D-galactopyranose **1a** [25]. Unprotected primary hydroxyl group of isopropylidene derivative**1a** was oxidized into aldehyde using PCC [26] to furnish 1,2:3,4-di-*O*-isopropylidene-6-oxo-*α*-D-galactopyranose **1b** (Scheme-2). It was observed the oxidation reaction using PCC requires 4 Å molecular sieves and no reaction occurred when 3 Å molecular sieves were used. Furthermore, activation of 4Å molecular sieves at 300 °C was also done to get satisfactory results. Similarly, ethyl acetate can be considered as best solvent for extraction of **1a** from water as with halogenated solvents ($CHCl_3$ and CH_2Cl_2) poor yields of **1a** were obtained.

We have used freshly prepared isonitrile **3c**. Preparation of isonitrile was carried out in three steps. 4-amino benzoic acid (**3**) was subjected to Fischer esterification followed by N-formylation using iodine and formic acid at 70 °C under solvent free conditions to obtain 4-methylcarboxyl-*N*-formyl benzoate **3b** in moderate yield. **3b** was converted into isonitrile **3c** by treating with triphenylphosphine and iodine in the presence of catalytic amount of triethylamine. Infrared spectra of **3c** showed peak at 2153cm^{-1} (Scheme-3).

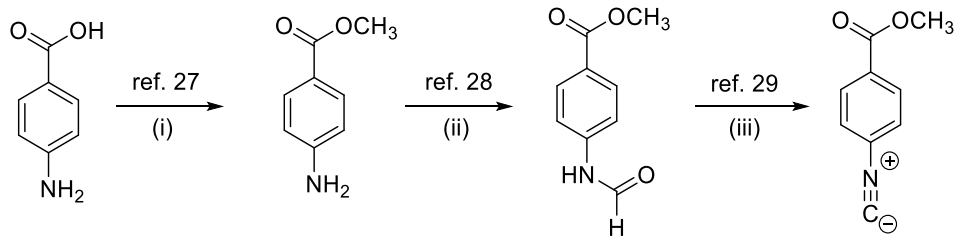


Scheme-1: A schematic presentation of Passerini reaction.



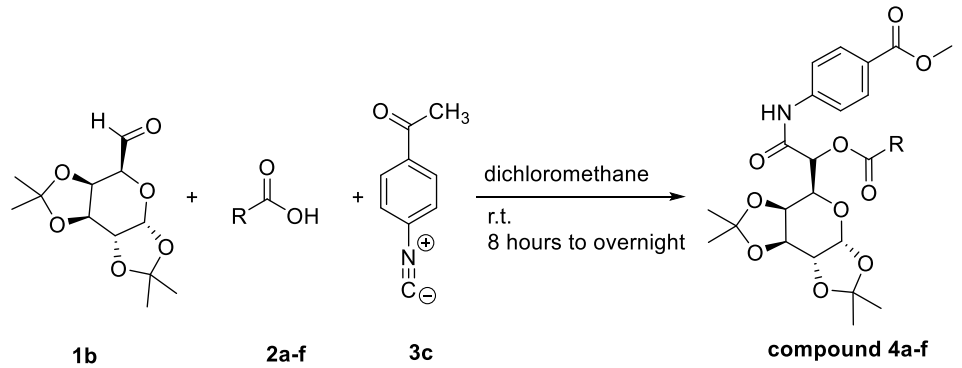
(i) acetone/ I_2 , rt. 18 hrs. (ii) pyridinium chlorochromate (PCC) in dichloromethane, reflux. 4 hrs.

Scheme-2: Synthesis of 1,2:3,4-di-O-isopropylidene-6-oxo-α-D-galactopyranose **1b.**



(i) methanol, H_2SO_4 cocn., reflux, 4 hrs. (ii) HCOOH, I_2, 70 °C, neat, 3 hrs.
(iii) I_2, Ph_3P, Et_3N, dichloromethane, rt, 5 hrs.

Scheme-3: Synthesis of Methyl 4-isocyanobenzoate **3c.**



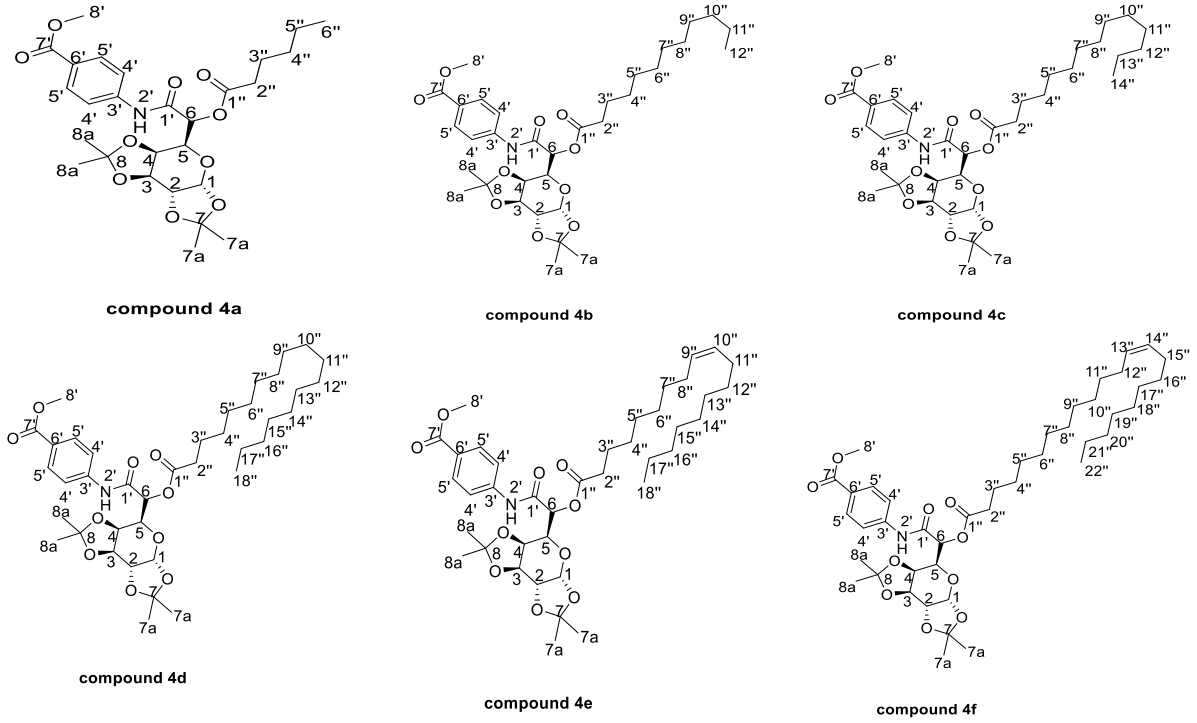
R	2a/4a caproic acid	2b/4b lauric acid	2c/4c myristic acid	2d/4d stearic acid	2e/4e oleic acid	2f/4f erucic acid

Scheme-4: Reversed *C*-glycopeptidomimetics via Passerini reaction.

For the carboxylic component, different aliphatic acids were used i.e. caproic acid **2a**, three saturated fatty acids including lauric acid **2b**, myristic acid **2c**, and stearic acid **2d** and two unsaturated fatty acids; oleic acid **2e** and erucic acid **2f**.

Passerini reaction was carried out at room temperature using sugar aldehyde **1b**, different aliphatic acids (**2a-2f**) and isonitrile **3c** in dichloromethane and stirred for 8 hours to overnight (*vide experimental*). Progress of reaction was monitored through TLC. It was observed that unsaturated fatty acids require longer reaction times (**Scheme-4**).

All compounds, except **4c,** were obtained as yellow liquids, i.e. **4a, 4b, 4d, 4e** and **4f**. However, **4c** was a white amorphous solid. The reactions duration was recorded as 8 hours for **4a**, 10 hours for **4b, 4c** and **4d** and an overnight period for compounds **4e** and **4f**. The confirmation of the formation of compounds **4a-4f** was done by Infrared, EIMS and ^{1}H-NMR spectroscopy (*vide* Table-1). ^{1}H-NMR spectra showing downfield anomeric proton around δ 5.6 as doublet with a coupling constant of 4.8 Hz confirming α stereochemistry of H-1 and in accordance with the reported literature [31]. Another downfield methine suggested formation of amide ester bond connecting newly formed amino acid moiety with monosaccharide through sugar's *C*-6 position. The IR spectra of all six compounds **4a-4f** showed signal of carbonyl of amide group around 1710-1693 cm^{-1} due to delocalization of lone pair of nitrogen atom in amide group and a signal of NH stretch of amide at 3342-3265 cm^{-1}. The EIMS spectra of compounds **4a-4f** showed molecular ion peaks (M^+) at *m/z* 535.3 (**4a**), 619.2 (**4b**), 647.3 (**4c**), 703.3 (**4d**), 701.3 (**4e**), and 757.2 (**4f**), corresponding to molecular formula, $C_{27}H_{37}NO_{10}$, $C_{33}H_{49}NO_{10}$, $C_{35}H_{53}NO_{10}$, $C_{39}H_{61}NO_{10}$, $C_{39}H_{59}NO_{10}$ and $C_{43}H_{67}NO_{10}$ respectively. The ^{1}H-NMR spectra of **4a-4f** displayed some common signals in all compounds i.e. one proton doublet around δ 5.6 ascribed to -CH of anomeric carbon of sugar, two double doublets each for two protons around δ 4.64 and 4.37 attributed to methine groups of C-2, C-3, C-4 and C-5 of sugar, another double doublet of one proton around δ 5.20 due to *C*-6 of sugar. Two singlets, each for six protons were also found at δ 1.42 and 1.46 due to methyl groups of isopropylidene moiety. Every spectrum has a singlet of one proton at δ 8.52 due to NH group. Aromatic protons were found in each spectrum around δ 7.57 and 7.96 as double doublets that refer to four protons and their *J*-values also confirmed the structural features. In each spectrum due to presence of methoxy protons at position marked as 8' a singlet of three protons was found at δ 3.86 beside respective signals of each compound (detailed data shown in table 1).



Scheme-5: Reversed C-glycopeptidomimetics (**4a-4f**).

Table-1: ^{1}H-NMR shifts for compounds **4a-f**; ($CDCl_3$, 300 MHz); δ_H (ppm), (m, J in Hz)**.**

H-No.	4a	4b	4c	4d	4e	4f
H-1	5.60 (d, 4.8)	5.60 (d, 4.8)	5.61 (d, 4.8)	5.58 (d, 4.8)	5.60 (d, 4.8)	5.61 (d, 4.8)
H-2	4.64 (dd, 7.5, 2.4)	4.64 (dd, 7.5, 2.4)	4.64 (dd, 7.5, 2.4)	4.64 (dd, 7.5, 2.4)	4.64 (dd, 7.5, 2.4)	4.64 (dd, 7.5, 2.4)
H-3	4.65 (dd, 7.5, 2.4)	4.65 (dd, 7.5, 2.4)	4.65 (dd, 7.5, 2.4)	4.65 (dd, 7.5, 2.4)	4.65 (dd, 7.5, 2.4)	4.65 (dd, 7.5, 2.4)
H-4	4.37 (dd, 4.8, 2.4)	4.36 (dd, 4.8, 2.4)	4.38 (dd, 4.8, 2.4)	4.38 (dd, 4.8, 2.4)	4.36 (dd, 4.8, 2.4)	4.37 (dd, 4.8, 2.4)
H -5	4.38 (dd, 4.8, 2.4)	4.37 (dd, 4.8, 2.4)	4.389 (dd, 4.8, 2.4)	4.39 (dd, 4.8, 2.4)	4.37 (dd, 4.8, 2.4)	4.39 (dd, 4.8, 2.4)
H-6	5.20 (d, 9.3)	5.20 (d, 9.3)	5.20 (d, 9.3)	5.20 (d, 9.3)	5.20 (d, 9.3)	5.20 (d, 9.3)
7_a-CH_3	1.42 (s)	1.43 (s)	1.43 (s)	1.41 (s)	1.43 (s)	1.43 (s)
8_a-CH_3	1.46 (s)	1.46 (s)	1.46 (s)	1.45 (s)	1.47 (s)	1.46 (s)
NH (2')	8.52 (s)	8.53 (s)	8.53 (s)	8.54 (s)	8.52 (s)	8.52 (s)
CH (4')	7.57 (dd, 8.7,)	7.58 (dd, 8.7,)	7.58 (dd, 8.7,)	7.58 (dd, 8.7,)	7.59 (dd, 8.7,)	7.58 (dd, 8.7,)
CH (5')	7.96 (dd, 8.7, 2.0)	7.98 (dd, 8.7, 2.0)	7.98 (dd, 8.7, 2.0)	7.97 (dd, 8.7, 2.0)	7.96 (dd, 8.7, 2.0)	7.95 (dd, 8.7, 2.0)
OCH_3	3.87 (s)	3.87 (s)	3.87 (s)	3.86 (s)	3.87 (s)	3.87 (s)
H-2''	1.65 (t)	1.63 (t)	1.61 (t)	1.66 (t)	1.67 (t)	1.66 (t)
H-3''	1.31 (m)	1.23 (m)	1.30 (m)	1.27 (m)	1.28 (m)	1.24 (m)
H-4''	1.31 (m)	1.23 (m)	1.30 (m)	1.22 (m)	1.28 (m)	1.24 (m)
H-5''	1.31 (m)	1.23 (m)	1.30 (m)	1.22 (m)	1.28 (m)	1.24 (m)
H-6''	0.87 (t)	1.23 (m)	1.30 (m)	1.22 (m)	1.28 (m)	1.24 (m)
H-7''	---	1.23 (m)	1.30 (m)	1.22 (m)	1.28 (m)	1.24 (m)
H-8''	---	1.23 (m)	1.30 (m)	1.22 (m)	1.77 (m)	1.24 (m)
H-9''	---	1.23 (m)	1.30 (m)	1.22 (m)	5.32 (dd)	1.24 (m)
H-10''	---	1.23 (m)	1.30 (m)	1.22 (m)	5.32 (dd)	1.32 (m)
H-11''	---	1.23 (m)	1.30 (m)	1.22 (m)	1.77 (m)	1.32 (m)
H-12''	---	0.86 (t)	1.30 (m)	1.22 (m)	1.28 (m)	1.98 (m)
H-13''	---	---	1.30 (m)	1.22 (m)	1.28 (m)	5.35 (dd)
H-14''	---	---	0.87 (t)	1.22 (m)	1.28 (m)	5.35 (dd)
H-15''	---	---	---	1.22 (m)	1.28 (m)	1.98 (m)
H-16''	---	---	---	1.22 (m)	1.28 (m)	1.32 (m)
H-17''	---	---	---	1.22 (m)	1.28 (m)	1.32 (m)
H-18''	---	---	---	0.85 (t)	0.83 (t)	1.24 (m)
H-19''	---	---	---	---	---	1.24 (m)
H-20''	---	---	---	---	---	1.24 (m)
H-21''	---	---	---	---	---	1.24 (m)
H-22''	---	---	---	---	---	0.85 (t)

Conclusion

To summarize, Passerini reaction was used as synthetic route to produce a series of six reversed *C*-glycopeptidomimetics which is a challenging task due to less reactive nature of reverse position of sugar. This series of six novel compounds offers a dimension to synthesize new compounds with characteristics to mimic *C*-glycopeptides and their use as monomers to elongate peptide chains and thus, can be considered as simple and convenient monomers. The resultant reversed C-glycopeptidomimetics are expected to show more diversity in their structure and physiochemical action than their naturally occurring analogues due to the resemblance in structure. However further studies for their applications in biological and industrial grounds are under consideration.

Conflict of interest

No hidden conflict of interest was found among the authors of this paper.

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