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Cross Metathesis Assisted Solid-Phase Synthesis of Glycopeptoids

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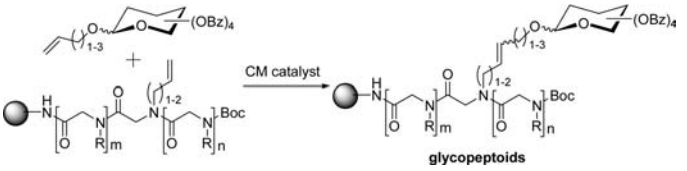
ABSTRACT



A solid-phase synthesis of glycopeptoids was explored through olefin cross metathesis (CM). Peptoids and sugar derivatives with appropriate olefin moieties were coupled in the presence of an olefin metathesis catalyst to afford glycopeptoids in good yields. This systematic solid-phase CM study can provide facile access to the molecular sources of glycopeptidomimetics and postchemical modifications on various molecular scaffolds.

Glycosylation, a complex post-translational modification, involves the attachment of glycans to proteins and lipids through a series of enzymatic reactions. It plays vital roles in cell−cell recognition, protein folding, stabilization, cell growth regulation, cell differentiation, immunological response, metastasis, and bacterial and viral infections.[1] Unlike transcription or translation, it is a nontemplate driven process and abberant glycosylation can lead to numerous genetic disorders.[2] Glycoconjugates have been separated from natural sources to explore glycosylation, but they are very difficult to obtain in adequate purity and quantity.

Therefore, a main goal is to manipulate the syntheses of glycoconjugates and glycopeptides as biological probes and lead compounds for glycobiology and drug discovery. Peptides are promising units for the synthesis of glycoconjugates and glycopeptides, though their disadvantages include sensitivity to proteases, limited cell permeability, and poor bioavailability. Much work has been focused toward modifying peptides to generate new peptidomimetics with improved pharmacokinetic characteristics, including peptoids, *N*-substituted glycine oligomers with side chains directly attached to the nitrogen atoms of amide bonds.[3] They possess advantages such as broad chemical diversity, proteolytic stability, and improved cell permeability over peptides.[4]

The solid-phase synthesis of peptoids is straightforward and can be supported by a large number of amine monomers.[5] Moreover, peptoids can act as inhibitors of protein−protein interactions, molecular carriers, and potent antimicrobial agents.[6] Their advantages and characteristics make them suitable for the development of glycopeptoids as glycopeptide mimetics which can be useful chemical tools in glycobiology and chemical glycomics. So far, a few syntheses of *N*-, *O*-, *C*-, and *S*-linked

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glycopeptoids have been reported.[7] Usually modification of glycoconjugates could be achieved by olefin cross metathesis (CM),[8] bioorthogonal ligation,[9] the use of transistion metal complexes,[10] cross-coupling reactions,[11] and azide–alkyne cycloadditions.[12]

CM has emerged as one of the most powerful tools in the preparation of carbon–carbon bonds over the past decade and has provided a convenient synthetic route to simple alkenes and substituted precursors. The well-defined olefin metathesis catalysts prepared by Grubbs et al. may tolerate a variety of functional groups and have facilitated metathesis chemistry.[13] Since the reactants and products of olefin metathesis are alkenes, great care must be taken to design reactions so as to avoid unnecessary side products. CM has been intensively studied in solution, with few examples reported in the solid phase.[14] The versatility of CM has also been extended to the aqueous phase where site-selective modification of proteins bearing allyl sulfides has been accomplished.[8]

The synthesis of glycopeptoids reported here involved attaching sugar derivatives to alkenyl moiety-containing peptoids through solid-phase CM (Figure 1). Peptoids with various side chains were prepared on beads with strategically positioned alkenyl components in different chain lengths. *O*-Linked sugar-alkenyl derivatives (**16**–**30**) were prepared from mannose, galactose, and glucose precursors (Scheme 1). Free sugars were peracetylated or perbenzoylated and underwent selective anomeric deprotection by methylamine in THF.[15] The obtained lactols (**8**–**11**) were treated with trichloroacetonitrile in DBU to produce glycosyl trichloroacetimidates (**12**–**15**). Glycosyl imidate donors were activated by trimethylsilyltriflate, followed by nucleophilic attack of primary alcohols such as allyl alcohol, 3-buten-1-ol, 4-penten-1-ol, and 3-methyl-3-buten-1-ol to furnish four sugar derivatives from each monosaccharide in high yields.

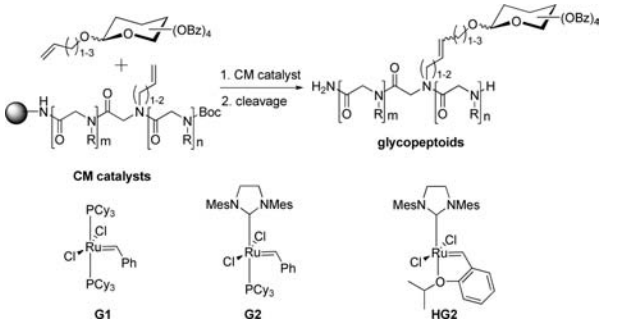
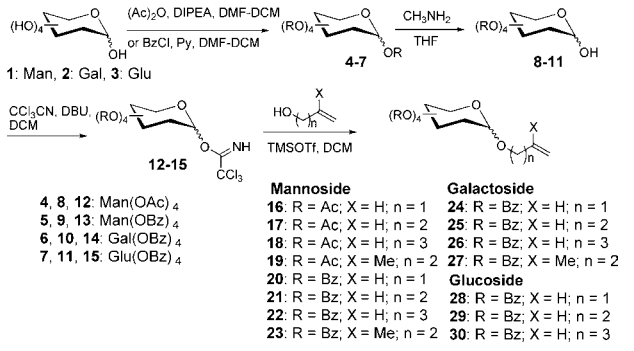


Figure 1. General schematic representation for the solid-phase synthesis of glycopeptoids via CM.

Scheme 1. Synthesis of Alkene-Containing Sugar Derivatives



To study solid-phase CM, 4-mer peptoids (**31**–**32**) were first prepared with terminal units of allylamine or butenylamine (3-buten-1-amine) on Rink Amide LL resin (100–200 mesh, 0.4 mmol/g) (Scheme 2). The terminal amine of the peptoids was capped by di-*tert*-butyl dicarbonate. The three most commonly used olefin metathesis catalysts G1, G2, and HG2 were tested (Figure 1).[16] Peptoids (**31**–**32**) with terminal allyl or butenyl groups were reacted with mannosides (**20**–**21**) with allyl or butenyl groups in the presence of the catalysts under microwave or reflux conditions (for details, see Supporting Information). The catalyst was used at 2–5 mol %, and 5 mol % was suitable for the catalysis of solid-phase CM. Increasing the catalyst loading to 10 mol % increased the homodimerization of the sugars in solution. G1 and G2 provided much lower yields; HG2 gave a higher yield. In addition, allyl–allyl (with allyl units each from the peptoids and the sugar derivatives) combinations were

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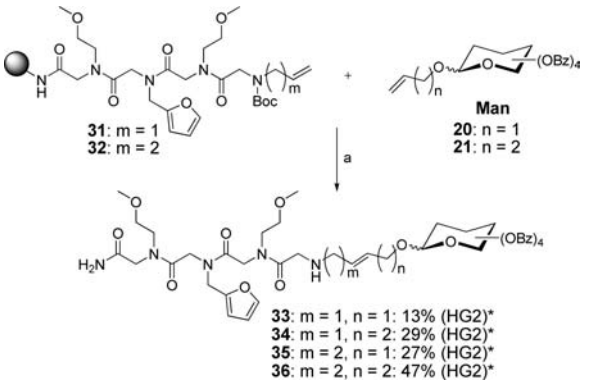
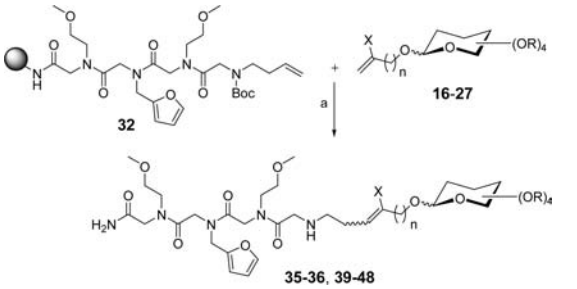
Scheme 2. Optimization of Solid-Phase CM



[a] Reagents and conditions: (i) sugar derivative (20 equiv, 25 mM), catalyst (5 mol %), DCM, 40 °C, 8 h; (ii) 92% TFA. *CM conversion efficiency was determined by HPLC analysis. For details, see Supporting Information.

Table 1. Effects of Various Alkene-Containing Sugar Derivatives on Solid-Phase CM[a]



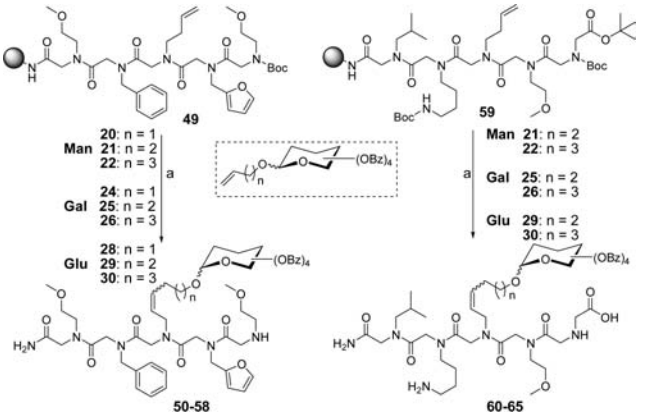
entry[b]	sugar derivative	glycopeptoid	conv (%)[c]
1	**16**	**39**	12
2	**17**	**40**	15
3	**18**	**41**	30
4	**19**	**42**	<5
5	**20**	**35**	27
6	**21**	**36**	47
7	**22**	**43**	39
8	**23**	**44**	<5
9	**24**	**45**	29
10	**25**	**46**	40
11	**26**	**47**	46
12	**27**	**48**	<5

[a] Reagents and conditions: (i) sugar derivative (20 equiv, 25 mM), HG2 (5 mol %), DCM, 40 °C, 8 h; (ii) 92% TFA. [b] Rink Amide AM resin (0.4 mmol/g). [c] Conversion efficiency was determined by HPLC analysis.

not suitable for the synthesis of glycopeptoids; allyl–butenyl combinations resulted in improved yields to some extent. Surprisingly, butenyl–butenyl combinations gave much higher yields (up to 47%).

With this information in hand, butenyl–butenyl combinations were then used to study the relationship between reaction time and yield. Peptoid **37** and sugar derivative **21** were reacted together with HG2. The CM yield of **38** gradually increased to 76% from 2 to 8 h before slowly decreasing to 70% at 12 h (see Supporting Information). This behavior might be due to the product of the first CM reaction also participating in CM reactions with either the peptoid or the sugar; this was confirmed by MALDI-TOF. Therefore, 8 h was considered optimal for the CM reactions.

Table 2. Solid-Phase CM of Peptoids Containing Arbitrary Sequences on Different Resins[a]



entry[b]	peptoid	sugar derivative	glycopeptoid	conv (%)[c]
1	**49**	**20**	**50**	21
2	**49**	**21**	**51**	46
3	**49**	**22**	**52**	44
4	**49**	**24**	**53**	27
5	**49**	**25**	**54**	47
6	**49**	**26**	**55**	49
7	**49**	**28**	**56**	28
8	**49**	**29**	**57**	49
9	**49**	**30**	**58**	32
10	**49**	**20**	**50**	16
11	**49**	**21**	**51**	37
12	**49**	**22**	**52**	40
13	**49**	**21**	**51**	50
14	**49**	**21**	**51**	49
15	**49**	**21**	**51**	51
16	**59**	**21**	**60**	52
17	**59**	**22**	**61**	63
18	**59**	**25**	**62**	35
19	**59**	**26**	**63**	51
20	**59**	**29**	**64**	46
21	**59**	**30**	**65**	53

[a] Reagents and conditions: (i) sugar derivative (20 equiv, 25 mM), HG2 (5 mol %), DCM, 40 °C, 8 h; (ii) 92% TFA. [b] Entries 1–9: Rink Amide AM resin (0.4 mmol/g), sugar derivative (20 equiv, 25 mM); entries 10–12: Rink Amide AM resin (0.2 mmol/g), sugar derivative (20 equiv, 25 mM); entries 13–15: Rink Amide AM resin (0.2 mmol/g), sugar derivative (50, 75, and 100 mM, respectively); entries 16–21: TentaGel MB RAM resin (0.4 mmol/g), sugar derivative (20 equiv, 25 mM). [c] Conversion efficiency was determined by HPLC analysis.

The versatility of solid-phase CM methodology was demonstrated by conducting reactions between peptoid **32** and sugar derivatives (**16**–**27**) (Table 1). The CM of butenyl–butenyl/pentenyl fragments generally proceeded

well and gave higher yields than allyl−allyl combinations. CM reactions with sugar derivatives protected by acetyl groups gave lower yields than those protected by benzoyl groups. These results corroborate previous observations that acetyl groups could chelate with metal alkylidene complexes, hampering the reaction pathway and giving nonmetathetic products.[17] Sugar derivatives (**19**, **23**, and **27**) with disubstituted alkenyl moieties were almost spectators to CM even though this type of alkene participated in solution-phase CM to give trisubstituted products.[18] In most cases, homodimerized peptoids were produced as byproducts in moderate yields.

Furthermore, alkenyl moieties placed in the middle of the peptoid sequences were tested to assess the steric effects on the CM reaction under various reaction conditions (Table 2). The best results were also achieved using butenyl−butenyl/pentenyl combinations, showing that there was no strong steric hindrance. However, the homodimerizaton of peptoids on the resin was inevitable.

Thus, we tried to change reaction conditions such as the loading capacity of the resin and the concentration of sugar derivatives to reduce the homodimerization of peptoids. However, there was no dramatic improvement for the production of CM products with a reduced loading capacity of the resin and an increased concentration of sugar derivatives (Table 2, entries 10−15).

The effects of the resin on solid-phase CM were next tested. Peptoid **59** was prepared on TentaGel MB RAM resin (0.4 mmol/g), a commonly used resin in on-bead assays. The CM reactions were carried out with sugar derivatives containing butenyl or pentenyl fragments (Table 2, entries 16−21) and were successful on both hydrophobic Rink Amide resin and hydrophilic TentaGel resin. Actually, TentaGel resin gave slightly better results than Rink Amide resin because TentaGel resin contains long polyethylene glycol linkers. Especially, it is very desirable for protected amino or acid moieties such as *N*-Boc-1,4-butanediamine (Nlys) and glycine *tert*-butyl ester (Nasp) to be compatible with solid-phase CM, so as to provide highly diverse glycopeptoids. Finally, for the preparaton of debenzoylated glycopeptoids, the benzoyl protecting groups of the sugar moiety were easily deprotected by using sodium methoxide in CH_3OH/THF at reflux to give almost quantitatively a free sugar-containing glycopeptoid (see Supporting Information).

In conclusion, the solid-phase synthesis of glycopeptoids by cross-metathesis resulted in good yields. The CM of butenyl−butenyl/pentenyl combinations was superior to that of other allyl pairings. The stereochemistry of the sugar did not affect the CM, and phosphine-free HG2 was found to be the better catalyst in our study. The type of resin was shown to have no significant effect on solid-phase CM, and any side chains, including protected charged moieties, could be employed. Such solid-phase CM reactions can provide facile access to useful molecular sources of glycopeptidomimetics and postchemical modification on various molecular scaffolds.

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Supporting Information Available. Experimental details for the syntheses of sugar derivatives and peptoids and solid-phase CM, ^{1}H NMR, ^{13}C NMR, and MALDI-TOF spectral data, and RP-HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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