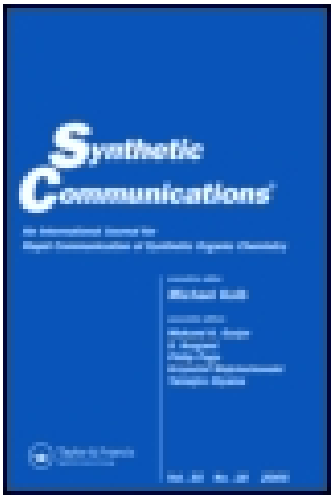

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Cross-metathesis of C-Glycosides and Peptides

Peter Brüchner [a] , David Koch [a] , Ulrike Voigtmann [b] & Siegfried Blechert [a]
[a] Institut für Organische Chemie, Technische Universitaet Berlin , Berlin, Germany
[b] Schering AG , Berlin, Germany
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Cross-metathesis of *C*-Glycosides and Peptides

Peter Brüchner and David Koch
Institut für Organische Chemie, Technische Universitaet Berlin, Berlin, Germany

Ulrike Voigtmann
Schering AG, Berlin, Germany

Siegfried Blechert
Institut für Organische Chemie, Technische Universitaet Berlin, Berlin, Germany

Abstract: Peptides bearing an acryloyl residue at their *N*-terminus were coupled with various *C*-glycosides in an equimolar ratio via cross-metathesis. The newly formed olefin was obtained with high E/Z selectivity in satisfying to high yields with low homodimerization of the starting materials. The posttranslational cross-metathesis approach was shown to be suitable for the combinatorial synthesis of a small library of *C*-glycopeptides.

Keywords: *C*-glycopeptides, cross-metathesis, posttranslational synthesis

Carbohydrates play a pivotal role in a variety of diseases, such as cancer, inflammation, and autoimmune diseases, as well as microbial infections and graft rejection.[1] Inhibition of carbohydrate-processing enzymes involved in the synthesis, transport, and cleavage of oligosacharides is of great interest,

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Address correspondence to Siegfried Blechert, Institut für Organische Chemie, Sekr. C3, Technische Universitaet Berlin, Strasse des 17. Juni 135, 10623 Berlin, Germany. E-mail: blechert@chem.tu-berlin.de

highlighting the importance of carbohydrate-based inhibitors. These may find applications as novel therapeutic agents or as tools for studying their biological targets. Hence, there is a rising need for rapid and broadly applicable synthetic routes to stable, well-defined glycopeptide analogues.

A large number of synthetic investigations have been made into the synthesis of *C*-glycoside amino acids and peptides because of their particular stability against hydrolysis.[2] The synthesis of glycoamino acids by cross-metathesis[3] has been achieved by a number of research groups.[4–7] Most of these approaches can be classified as cotranslational, that is, the cross-metathesis linkage between the sugar and an amino acid is installed first, while the actual peptide assembly is carried out at a later stage. Normally, derivatized vinyl-and allylglycine have been employed, together with vinyl- and allyl-*C*-glycosides as coupling partners, using $(PPh_3)_2Cl_2Ru = Ph$ **1** as the (pre)catalyst. Common drawbacks in these examples are the formation of *E*/*Z*-isomeric mixtures of the newly formed olefin, the use of high catalyst loadings (20 mol%), and the occasional use of harsh conditions. In addition, homodimerization of both coupling partners is generally observed.[8]

The more convergent posttranslational route (i.e., the cross-metathesis of peptides bearing an olefin moiety with vinyl- or allyl-*C*-glycosides) has notable advantages, mainly better suitability for solid-phase synthesis.[5] However, the challenge of this approach lies in the unpredictable behavior of peptides caused by conformational features, solubility issues, as well as the array of different functional groups that might affect the metathesis catalyst. As far as we know, there are only two reports on a cross-metathesis between sugar and peptide. The first gives account of an glycylglycine ester that became alkenylated at the *N*-terminus and coupled with protected *O*- and *C*-allyl glycosides of *N*-acetylglucosamine, galactose, and mannose, yielding four glycopeptoides in the range of 40 to 52%, besides homodimer side products.[7] The second account showed the cross-metathesis of alanyl-allylglycinyl-phenylalanyl methylester with three *C*-glycosides, one of them being a disaccharide, giving yields between 39 and 68%.[5]

With the advent of the second-generation Grubbs catalyst **2** in the late 1990s,[9] new variations in cross-metathesis became available for synthetic chemistry (i.e., the coupling of electron-poor olefins with electron-rich olefins). These problems in cross-metathesis are minimal in the cases of α,β-unsaturated carbonyl compounds, which react efficiently with alkylated nonconjugated olefins.[10,11] We were interested in combining the advantages of this CM-variation with the posttranslational approach to *C*-glycopeptide synthesis and to explore the limits of this route. In general, the strategy involves acylation at the *N*-terminus of various peptides with acryloyl chloride, followed by cross-metathesis with several sugar derivatives (Fig. 1).

(Pre)catalysts **2** and **3**[12] are known to promote the cross-metathesis of acrylamide derivatives unlike **1** or several molybdenum catalysts. Hence, these two were compared to each other in a series of reactions (Fig. 2). Thus *N*-acryloyl-glycinyl-prolinyl methylester **7** was coupled with *C*-glycosides

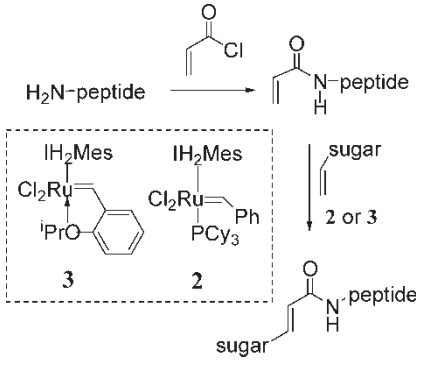


Figure 1. Acylation and cross-metathesis of a peptide ester.

4, **5**, and **6** to give *C*-glycopeptides **8**, **9**, and **10**. The results (Fig. 2) show that (pre)catalyst **3** clearly performed better[13] than **2** and was therefore used in all further cross-metathesis reactions. It is noteworthy that for the more challenging substrates such as the completely unprotected **5** or the sterically encumbered vinyl-glycoside **6**, (pre)catalyst **3** gave a yield increase of more than 25% of the products **9** and **10** when compared to reaction with (pre)catalyst **2**.

In a further step, stoichiometry of the two cross partners was optimized. Known *C*-allyl glycoside **11**[14] and peptide **11** were reacted with each other in varying ratios (Table 1).

Reaction of sugar **11** with 1 equivalent of peptide **12**, using 5 mol% of **3**, gave the heterocoupled product **13** in 65% yield (Table 1), and ^{1}H NMR analysis of the crude mixture showed the presence of 15% of the sugar dimer **14** (entry 1). Raising the amount of **12** to 1.5 equivalents (entry 2)

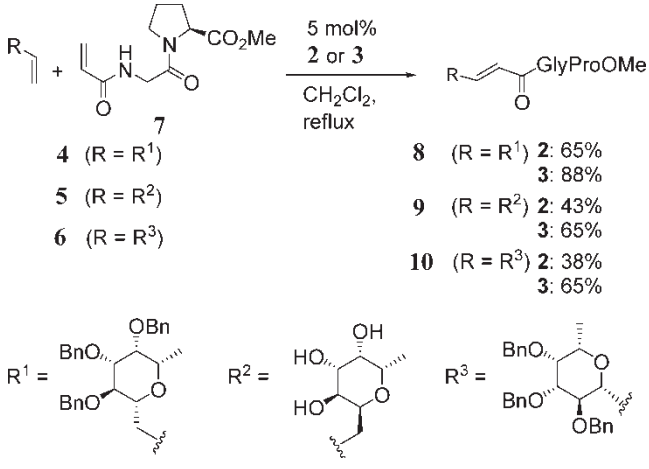
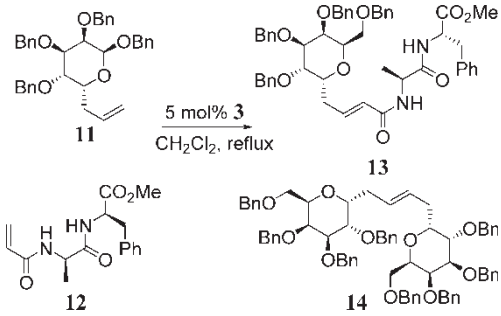


Figure 2. Comparison between (pre)catalysts **2** and **3**.

Table 1. Cross-metathesis of sugar **11** with peptide **12**



Entry	**11**:**12**	**14** (%)[a]	**13** (%)[b]
1	1:1	15	65
2	1:1.5	7	69
3	1:2	9	76

[a]Determined by NMR.
[b]Isolated yield.

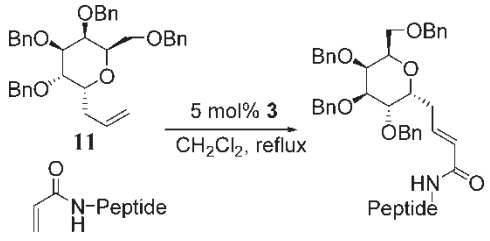
and finally to 2 equivalents (entry 3) gave at best only an 11% yield increase of **13**. Therefore, the chemoselectivity of the reaction was considered to be sufficient with an equimolar ratio of sugar and peptide. We proceeded to test the general applicability of the reaction and the tolerance of the catalyst toward functional groups. Thus, cross-metathesis with sugar **11** was attempted using peptides with a broad range of functionality, in the presence of (pre)catalyst **3** (Table 2).

Good to satisfying yields were obtained with a wide range of functional groups. Even in the presence of a thioether (entry 8), cross-metathesis resulted in a satisfying yield of 58%. Basic and/or coordinating functionality can deactivate metathesis catalysts.[15] Hence, the results with the peptides containing histidine (entry 2), where no desired product was obtained, and tryptophan[16] (entry 10), which gave a 17% yield, are consistent with this observation. In addition, utilization of 5 mol% precatalyst **3** gives comparable yields to the previously-mentioned cross-metathesis examples where up to 20 mol% (pre)catalyst **1** or **2** have been used.[4,6]

With these encouraging results in hand, we investigated the synthesis of a small library of glycopeptides. Cross-metathesis was attempted using five fucose derivatives and eight acylated peptides (Table 3).

The use of peptides with an unprotected *C*-terminus failed either because of chelation to the catalyst by the carboxylic acid or insolubility of the peptide in DCM (entry 1). In contrast, esterified peptides gave good yields (entries 2–8). Benzyl- and acetyl-protected allyl-sugars **4** and **32** were consistently good coupling partners and gave yields of 60–90%. In all cases except for **33**,

Table 2. Scope of (pre)catalyst **3** in cross-metathesis



Entry	Peptide	Product[a]
1	AlaPheOMe **12**	65% **13**
2	AlaHisOMe **14**	nc[b]
3	AlaTyrOMe **16**	3% **17**
4	PheSerOMe **18**	43% **19**
5	Lys(N-Cbz)PheOMe **20**	62% **21**
6	AlaGlnOMe **22**	46% **23**
7	AlaGlu(β-OMe)OMe **24**	62% **25**
8	GlyMetGlyOMe **26**	58% **27**
9	PheGlyGlyOMe **28**	62% **29**
10	GlyGlyTrpOMe **30**	17% **31**

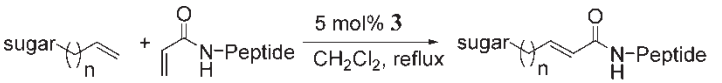
[a]Isolated yields.
[b]No conversion observed.

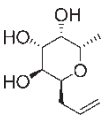
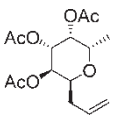
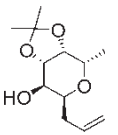
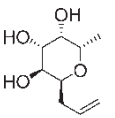
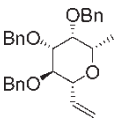
the E/Z ratios of the crossed products were higher throughout than 19:1. The completely unprotected glycoside **5** gave variable yields but with consistently high E/Z ratios. Considering that **5** provides numerous potential chelates for catalyst deactivation, the good yields obtained (entries 2, 3, 5, and 7) are delightful. The acetal protected **33** gave consistently good yields. In contrast to the completely protected glycosides **4** and **32**, the E/Z ratios with **33** as cross-partner were distinctively lower. Engelhardt et al. reported that E/Z ratios are affected by chelation of the catalyst.[17] Therefore, it seems logical to suggest that chelation by the free hydroxyl group in **33** would account for the observed lower ratios. The low yields obtained with vinylic **6** are likely due to the steric bulk of the α,β-branched olefin. A remarkable exception is in entry 2 with the proline-containing peptide. It is possible that rotamers may be playing a role here, but more evidence would be needed to support this.

In summary, a small library of glycopeptides has been built, employing cross-metathesis in a posttranslational manner as a synthetic method for connecting sugar and peptide moieties.

(Pre)catalyst **3** was shown to outperform catalyst **2** for our substrates. In contrast to most reported examples, synthesis of *C*-glycoside peptides was performed under very mild conditions, employing peptide and sugar in an

Table 3. Synthesis of a glycopeptide library



Entry[a]	Peptide	 **4**	 **32**	 **33**	 **5**	 **6**
1	GlyGlyOH **34**	15% **35**	—	—	—	—
2	GlyProOMe **7**	88% **8**	77% **36**	88% (8:1) **37**	65% **9**	65% **10**
3	GlyGlyOMe **38**	85% **39**	65% **40**	71% (5:1) **41**	72% **42**	30% **43**
4	AlaAlaOMe **44**	79% **45**	66% **46**	66% **47**	15%[b,c] **48**	35% **49**
5	Asp(β-OMe)PheOMe **50**	68% **51**	74% **52**	75% (3:1) **53**	60%[d] **54**	29% **55**
6	GlyGlyAlaOMe **56**	70% **57**	58% **58**	72% (4:1) **59**	36% **60**	33% **61**
7	AlaGlyGlyOMe **62**	65% **63**	49% **64**	88% (4:1) **65**	72% **66**	nc[e]
8	LeuAlaProOMe **67**	53% **68**	62% **69**	72% (4:1) **70**	40% **71**	17% **72**

[a]In all cases, E/Z ratio was >19:1. For glycopeptideseries **33,** E/Z ratios are given in brackets.
[b]The product was not isolated.
[c]Yield was estimated from isolated starting material and the NMR.
[d]Yield estimated by NMR.
[e]No conversion observed.

equimolar ratio with low homodimerization. Furthermore, the reaction was shown to have a remarkable scope with (pre)catalyst **3** tolerating a wide range of functionality and therefore allowing access to structurally diverse molecules with an array of different functional groups. The simple preparation of the metathesis precursors and the satisfying to high yields obtained provide scope for transposition to solid-phase synthesis with rapid construction of large glycopeptide libraries. Further results from these studies will be presented in due course.

EXPERIMENTAL

Data for selected samples only. For complete spectra and characterization data, please contact the authors. All reagents were obtained commercially and were used without further purification. All reactions were carried out under an inert atmosphere (N_2) unless otherwise indicated. ^{1}H and ^{13}C spectra were recorded at 500.0 and 125.8 MHz or 400.0 and 100.6 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) upfield relative to the internal solvent peak. Mass spectra were obtained at an ionizing potential of 70 eV. Melting points are uncorrected. (Pre)catalysts **2** and **3** were prepared according to literature procedures.[9,12] *C*-glycosides **4**, **5**, **6**, **32**, and **33** were provided by Schering AG.

General Procedure for Esterification and Acylation of the Peptides

Aqueous HCl (3 ml, 36%) was added to a suspension of the peptide (4.3 mmol) in 43 ml of freshly distilled dimethoxypropane and left stirring at ambient temperature for 24 to 48 h. The resulting blackened mixture was concentrated in vacuo, and the residue was taken up in 14 ml of MeOH. After addition of 93 ml of diethylether, the precipitate was filtrated and dissolved in 6 ml of DMF and 1.3 g of triethylamine (12.8 mmol, 3 equiv.). The solution was cooled in a $-10^{\circ}C$ (NaCl-saturated) ice bath. Acryloyl chloride (7.7 mmol, 1.8 equiv.) was added dropwise over 30 min. After the addition was complete, the reaction was warmed to room temperature and stirred for 5 h. Water (20 ml) was added. Extraction with ethylacetate failed. Therefore, the mixture was lyophilized, and the residue was purified by chromatography and recrystallization (MeOH/EtOAc/pentane) to yield a colorless solid. Spectral details, yields, and solvents for chromatography are given for each compound separately.

General Procedure for Cross-metathesis

(Pre)catalyst **2** or **3** (0.0023 mmol, 5 mol%) was added to a solution of 0.047 mmol of *C*-glycoside (1 equiv.) and 0.047 mmol of acylated peptide

(1 equiv.) in 1 ml of dry DCM at 40°C. After 18 h, the mixture was concentrated in vacuo, and the residue was purified by chromatography (SiO_2, solvents given separately). Yields are given in Tables 2 and 3.

Data

***N*-Acryloyl-glycinyl-prolinyl methylester 7.** Yield 49% (SiO_2, EtOH/DCM 1/4) ^{1}H NMR (200.0 MHz, MeOD): δ 6.34–6.20 (m, 2H), 5.66 (dd, $J = 1.4$, 10.3 Hz, 1H), 4.45–4.43 (m, 1H), 4.20–4.02 (m, 2H), 3.82–3.53 (m, 2H), 3.68 (s, 3H), 2.34–1.82 (m, 4H). ^{13}C NMR (50.0 MHz, MeOD): δ 176.6 (C_q), 171.7, 170.6 (C_q), 134.1 (CH), 129.6 (CH_2), 62.9 (CH), 55.2 (CH_3), 49.8 (CH_2), 45.0 (CH_2), 32.4 (CH_2), 28.1 (CH_2); MS (EI, 110°C): m/z (%) 241 (2) [M^+], 240 (4), 128 (70), 84 (16), 70 (100), 55 (34); HRMS ($C_{11}H_{16}N_2O_4$): calcd. 240.1110; found 240.1115; mp 97–98°C.

Glycopeptide 13. (SiO_2, hexanes/EtOAc 1/1) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15–7.40 (m, 20H), 7.07 (d $J = 7.0$ Hz, 2H), 6.80 (m, 1H), 6.68 (br d, $J = 8.0$ Hz), 5.91 (br d, $J = 8.0$ Hz, 1H), 5.78 (d, $J = 16.0$ Hz, 1H), 4.40–4.59 (m, 10H), 3.95–4.15 (m, 3H), 3.85 (m, 1H), 3.74 (m, 5H), 3.65 (m, 1H), 3.12 (dd, $J = 14.0$, 6.0 Hz, 1H), 3.02 (dd, $J = 14.0$, 6.0 Hz, 1H) 2.53 (m, H), 2.44 (m, 1H), 1.30 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.8 (C_q), 171.7 (C_q), 166.5 (C_q), 141.8 (CH), 138.5 (2 C_q), 138.3 (C_q), 138.2 (C_q), 135.8 (C_q), 129.3 (CH), 128.7 (CH), 128.5 (2CH), 128.4 (2 CH), 128.1 (CH), 128.0 (CH), 127.9 (2 CH), 127.7 (3 CH), 127.6 (CH), 127.2 (CH), 125.0 (CH), 76.3 (CH), 74.1 (CH), 73.3 (2 CH_2), 73.1 (CH), 67.1 (CH_2), 53.4 (CH_2), 52.4 (CH), 48.6 (CH), 37.9 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 29.8 (CH_2), 18.0 (CH_3); MS (EI): m/z (%) = 840 (M^+, <1), 270 (4), 264 (8), 201 (36), 181 (12), 130 (24), 91 (100). HRMS ($C_{51}H_{56}N_2O_9$): calcd. 840.3986; found 840.3989.

Glycopeptide 17. (SiO_2, hexanes/EtOAc 1/2) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15–7.40 (m, 20H), 6.80 (d, $J = 7.0$ Hz, 2H), 6.70 (d, $J = 7.0$ Hz, 1H) 5.74 (m, 2H), 4.40–4.85 (m, 10H), 3.90–4.25 (m, 4H), 3.74 (m, 4H), 3.66 (m, 2H), 3.09 (dd, $J = 14.0$, 5.0 Hz, 1H), 2.81 (dd, $J = 14.0$, 8.0 Hz, 1H), 2.60 (m, 1H), 2.32 (m, 1H), 1.25 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.0 (C_q), 171.6 (C_q), 165.3 (C_q), 155.6 (C_q), 142.2 (CH), 138.4 (CH), 138.2 (CH), 137.9 (2 CH), 130.5 (CH), 130.4 (CH), 128.6 (CH), 128.5 (2 CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (2 CH) 127.7 (CH), 127.6 (2 CH), 126.6 (C_q), 125.2 (CH), 115.8 (CH), 76.7 (CH), 74.1 (CH), 73.3 (3 CH_2), 66.8 (CH_2), 53.3 (CH_3), 52.5 (CH), 48.3 (CH), 36.9 (CH_2), 29.8 (CH_2), 17.3 (CH_3); MS (EI): m/z (%) = 856 (M+, <1), 181 (6), 107 (10), 91 (100), 77 (5); HRMS ($C_{51}H_{56}N_2O_{10}$): calcd. 856.3935; found 856.3954.

Glycopeptide 19. (SiO_2, hexanes/EtOAc 1/3) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15–7.40 (m, 20H), 7.02 (br d, $J = 8.0$ Hz, 1H), 6.74 (m, 1H), 6.21 (br d, $J = 8.0$ Hz, 1H), 5.79 (d, $J = 15.0$ Hz, 1H), 4.40–4.75 (m, 10H), 3.95–4.15 (m, 3H), 3.85 (m, 3H), 3.71 (m, 5H), 3.63 (m, 1H), 3.15 (dd, $J = 13.0$, 7.0 Hz, 1H), 3.03 (dd, $J = 14.0$, 7.0 1H), 2.49 (m, 1H), 2.39 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 71.1 (C_q), 170.5 (C_q), 166.1 (C_q), 142.5 (CH), 138.5 (C_q), 138.4 (C_q), 138.3 (C_q), 138.1 (C_q), 136.4 (C_q), 129.4 (CH), 128.9 (CH), 128.7 (CH), 128.5 (3 CH), 128.4 (CH), 128.1 (CH), 127.9 (2 CH), 127.7 (2 CH), 127.6 (CH), 127.1 (CH), 124.7 (CH), 76.5 (CH), 74.1 (CH), 73.2 (CH_2), 73.1 (CH_2), 67.0 (CH_2), 62.6 (CH_2), 55.0 (CH_3), 54.8 (CH), 52.7 (CH), 38.0 (CH_2), 29.8 (CH_2); MS (EI): m/z (%) = 856 (M+, <1), 210 (4), 181 (11), 97 (7), 91 (100), 57 (9); HRMS ($C_{51}H_{56}N_2O_{10}$): calcd. 856.3935; found 856.3949.

Glycopeptide 21. (SiO_2, hexanes/EtOAc 2/3) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15–7.40 (m, 20H), 7.07 (d $J = 7.0$ Hz, 1H), 6.80 (m, 1H), 6.61 (br d, $J = 8.0$ Hz, 1H), 6.09 (br d, $J = 8.0$ Hz, 1H), 5.83 (d, $J = 15.0$ Hz), 5.06 (m, 2H), 4.99 (m, 1H), 4.35–4.85 (m, 10H), 3.95–4.15 (m, 3H), 3.85 (m, 1H), 3.73 (m, 2H), 3.66 (m, 4H), 2.95–3.20 (m, 4H), 2.54 (m, 1H), 2.42 (m, 1H), 1.79 (m, 1H), 1.25–1.63 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.9 (C_q), 171.3 (C_q), 165.7 (C_q), 156.7 (C_q), 141.9 (CH), 138.5 (2 C_q), 138.4 (C_q), 138.2 (C_q), 136.7 (C_q), 135.7 (C_q), 129.3 (CH), 128.7 (CH), 128.6 (CH), 128.5 (2 CH), 128.4 (CH), 128.1 (2 CH), 127.9 (2 CH), 127.7 (2 CH), 127.6 (CH), 127.2 (CH), 125.0 (CH), 76.5 (CH), 74.2 (CH), 73.3 (CH_2), 73.2 (CH_2), 73.1 (CH_2), 67.2 (CH_2), 66.7 (CH_2), 53.3 (CH_3), 52.8 (CH), 52.5 (CH), 40.4 (CH_2), 37.8 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 22.2 (CH_2); MS (EI): m/z (%) = 1031 (M+, <1), 368 (6), 201 (4), 181 (7), 156 (13), 122 (7), 91 (100), 68 (20).

Glycopeptide 23. (SiO_2, EtOAc) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15–7.40 (m, 20H), 6.79 (m, 1H), 6.33 (m, 1H), 5.89 (d, $J = 15.0$ Hz, 1H), 5.69 (m, 1H), 4.40–4.70 (m, 10H), 4.05 (m, 2H), 3.98 (br s, 1H), 3.89 (m, 1H), 3.55–3.70 (m, 6H), 2.54 (m, 1H), 2.34 (m, 1H), 2.05–2.30 (m, 5H), 1.93 (m, 1H), 1.34 (d, $J = 7$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.7 (C_q), 172.6 (C_q), 172.1 (C_q), 165.8 (C_q), 142.1 (CH), 38.4 (C_q), 138.3 (C_q), 138.2 (C_q), 138.0 (C_q), 128.5 (2 CH), 128.4 (CH), 128.1 (CH), 128.0 (2 CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 125.2 (CH), 76.6 (CH), 74.1 (CH), 73.2 (CH_2), 73.0 (CH_2), 67.0 (CH_2), 52.5 (CH_3), 52.0 (CH), 49.0 (CH), 31.3 (CH_2), 27.2 (CH_2), 17.8 (CH_3); MS (EI): m/z (%) = 789 (M+, <1), 181 (8), 91 (100), 84 (2); HRMS ($C_{46}H_{51}N_3O_9$): calcd. 789.3625; found 789.3633.

Glycopeptide 25. (SiO_2, hexanes/EtOAc 1/2) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15–7.40 (m, 20H), 6.97 (br d, $J = 8.0$ Hz, 1H), 6.79 (m, 1H), 6.06 (br d, $J = 8.0$ Hz, 1H), 5.82 (d, $J = 15.0$ Hz, 1H), 4.40–4.75 (m, 10H), 4.06

(m, 2H), 4.01 (br s, 1H), 3.85 (m, 1H), 3.73 (m, 5H), 3.64 (m, 4H), 2.52 (m, 1H), 2.25–2.45 (m, 3H), 2.20 (m, 1H), 2.01 (m, 1H), 1.36 (d, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2 (C_q), 172.2 (C_q), 171.9 (C_q), 165.4 (C_q), 141.6 (CH), 138.4 (C_q), 138.3 (C_q), 138.1 (C_q), 128.4 (2 CH), 128.3 (CH), 128.0 (CH), 127.8 (2 CH), 127.6 (CH), 127.5 (CH), 125.0 (CH), 76.4 (CH), 74.1 (CH), 73.2 (CH_2), 73.0 (CH_2), 52.5 (CH_3), 51.8 (2 CH), 48.7 (CH), 29.9 (CH_2), 27.0 (CH_2), 18.2 (CH_3); MS (EI): m/z (%) = 836 (M+, <1), 181 (10), 105 (4), 91 (100), 84 (8), 57 (4). HRMS ($C_{48}H_{56}N_2O_{11}$): calcd. 836.3884; found 836.3881.

Glycopeptide 27. (SiO_2, hexanes/EtOAc 1/10) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15–7.40 (m, 20H), 7.16 (m, 2H), 6.79 (m, 1H), 6.09 (br s, 1H), 5.95 (d, $J = 15.0$ Hz, 1H), 4.40–4.75 (m, 10H), 4.08 (m, 2H), 3.90–4.05 (m, 4H), 3.81 (m, 2H), 3.55–3.75 (m, 6H), 2.56 (m, 3H), 2.35 (m, 1H), 1.94–2.15 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4 (C_q), 170.2 (C_q), 169.3 (C_q), 166.8 (C_q), 142.2 (CH), 138.4 (2 CH), 138.1 (CH), 128.6 (CH), 128.5 (2 CH), 128.4 (CH), 128.1 (CH), 127.9 (2 CH), 127.8 (2 CH), 127.1 (CH), 124.6 (CH), 76.7 (CH), 74.2 (CH), 73.2 (CH_2), 67.5 (CH_2), 52.4 (CH_3), 52.3 (CH), 43.7 (CH_2), 41.2 (CH_2), 30.7 (CH_2), 30.1 (CH_2), 29.8 (CH_2), 15.3 (CH_3); MS (EI): m/z (%) = 867 (M+, <1), 181 (8), 105 (4), 91 (100), 61 (5); HRMS ($C_{48}H_{57}N_3O_{10}S$): calcd. 867.3765; found 867.3741.

Glycopeptide 29. (SiO_2, hexanes/EtOAc 1/9) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10–7.40 (m, 23H), 6.96 (m, 2H), 6.78 (m, 1H), 6.29 (br d, $J = 8.0$ Hz, 1H), 5.85 (d, $J = 15.0$ Hz, 1H), 4.40–4.70 (m, 10H), 3.55–4.15 (m, 16H), 3.09 (dd, $J = 15.0$, 7.0 Hz, 1H), 3.02 (dd, $J = 14.0$, 7.0 Hz, 1H), 2.52 (m, 1H), 2.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6 (C_q), 170.3 (C_q), 169.1 (C_q), 166.2 (C_q), 142.4 (CH), 138.4 (2 C_q), 138.3 (C_q), 138.1 (C_q), 136.5 (C_q), 129.3 (CH), 128.8 (CH), 128.5 (3 CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (2 CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.1 (CH), 124.8 (CH), 76.6 (CH), 74.1 (CH), 73.2 (CH_2), 63.1 (CH_2), 67.1 (CH_2), 55.1 (CH_3), 52.4 (CH), 43.0 (CH_2), 41.1 (CH_2), 37.8 (CH_2); MS (EI): m/z (%) = 883 (M+, <1), 368 (6), 317 (4), 256 (4), 213 (3), 181 (9), 130 (9), 98 (22), 91 (100), 55 (12).

Glycopeptide 31. (SiO_2, EtOAc/MeOH 20/1) ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.82 (s, 1H), 7.46 (d $J = 8.0$ Hz, 1H), 7.20–7.40 (m, 22H), 7.09 (m, 2H), 6.93 (br s, 1H), 6.74–6.88 (m, 3H), 5.88 (m, 2H), 4.84 (m, 1H), 4.44–4.73 (m, 8H), 4.10 (m, 1H), 4.00 (m, 2H), 3.59–3.83 (m, 10H), 3.28 (m, 1H), 2.54 (m, 1H), 2.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3 (C_q), 169.7 (C_q), 168.7 (C_q), 166.7 (C_q), 142.3 (CH), 138.4 (C_q), 138.3 (C_q), 138.2 (C_q), 138.0 (C_q), 136.2 (C_q), 128.6 (CH), 128.5 (2 CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.9 (2 CH), 127.8 (2 CH), 127.6 (CH), 127.5 (CH), 124.5 (CH), 123.6 (CH), 122.0 (CH), 119.5 (CH), 118.4 (CH), 111.6

(C_q), 109.3 (CH), 74.2 (CH), 73.2 (CH), 73.1 (CH_2), 67.4 (CH_2), 52.6 (CH_3), 52.5 (CH), 43.3 (CH_2), 43.0 (CH_2), 27.3 (CH_2); MS (EI): m/z (%) = 922 (M+, <1), 368 (2), 328 (2), 284 (4), 256 (7), 201 (11), 181 (15), 162 (8), 130 (23), 91 (100), 77 (6).

Glycopeptide 8. (SiO_2, EtOAc) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.25 (m, 15H, Ar-H), 6.89–6.84 (m, 1H), 6.42 (s, 1H, NH), 5.86 (d, J = 15.6 Hz, 1H), 4.98–4.95 (m, 2H), 4.77–4.62 (m, 4H), 4.53–4.51 (m, 1H), 4.16–4.03 (m, 2H), 3.76–3.48 (m, 5H), 3.74 (s, 3H), 3.42–3.40 (m, 1H), 3.30–3.26 (m, 1H), 2.70–2.65, 2.38–2.31 (m, 2H), 2.27–2.00 (m, 4H), 1.13 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.1 (C_q), 167.0 (C_q), 165.6 (C_q), 141.5 (CH), 138.5, 138.2, 138.2 (C_q), 128.3, 128.3, 128.2, 128.0, 127.9, 127.6, 127.5, 127.4 (CH), 124.7 (CH), 85.1 (CH), 78.4 (CH), 78.3 (CH), 76.7 (CH), 75.2 (CH_2), 74.4 (CH_2), 74.1 (CH), 72.2 (CH_2), 58.8 (CH), 52.2 (CH_3), 45.8 CH_2), 41.9 (CH_2), 34.3 (CH_2), 28.9 (C-16), 24.5 (CH_2), 17.1 CH_3); MS (EI, 250°C): m/z (%) = 670 (<1) [M], 517 (1), 181 (6), 154 (7), 130 (15), 111 (7), 91 (100), 70 (10); HRMS ($C_{39}H_{46}N_2O_8$): calcd. 670.3254; found 670.3250.

Glycopeptide 36. (SiO_2, EtOAc) ^{1}H NMR (500 MHz, $CDCl_3$/MeOD): δ 6.78–6.73 (m, 1H), 5.97 (d, J = 15.4 Hz, 1H), 5.29–5.25 (m, 1H), 5.21 (br s, 1H), 5.17–5.13 (m), 4.48–4.45 (m, 1H), 4.28–4.25 (m, 1H), 4.17–4.02 (m, 2H), 3.97–3.92 (m, 1H), 3.73–3.69 (m, 1H), 3.70 (s, 3H), 2.64–2.57, 2.40–2.35 (m, 2H), 2.26–1.85 (m, 4H), 2.11, 2.02, 1.97 (s, each 3H), 1.10 (d, J = 6.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 72.2 (C_q, 170.5, 170.1, 169.8 (C_q), 167.0 (C_q, 165.1 (C_q), 139.9 (CH), 125.5 (CH), 71.4 (CH), 70.4 (CH), 68.4 (CH), 68.1 (CH), 66.0 (CH), 58.9 (CH), 52.4 (CH_3), 46.0 (CH_2), 42.0 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 24.6 (CH_2), 20.7, 20.7, 20.6 (CH_3) 15.9 (CH_3); MS (EI, 270°C): m/z (%) = 526 (16) [M], 398 (15), 341 (10), 273 (22), 171 (10), 153 (38), 128 (90), 111 (37), 83 (11), 70 (100); HRMS ($C_{24}H_{34}N_2O_{11}$): calcd. 526.2163; found 526.2163.

Glycopeptide 37. (SiO_2, EtOAc/MeOH 10/1) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (s, 1H, NH), 6.81–6.75 (m, 1H), 5.98 (d, J = 15.4 Hz, 1H), 4.54–4.52 (m, 1H), 4.32–4.27, 3.95–3.91 (m, 2H), 4.29–4.27 (m, 1H), 4.12–4.05 (m, 3H), 3.78–3.56 (m, 3H), 3.73 (s, 3H), 3.08 (d, J = 4.1 Hz, 1H, OH), 2.56–2.52, 2.47–2.43 (m, 2H), 2.27–2.00 (m, 4H), 1.48 (s, 3H), 1.32 (s, 3H), 1.24 (d, J = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.4 (C_q, 167.7 (C_q), 166.3 (C_q), 140.6 (CH), 125.6 (CH), 109.3 (C_q), 75.4 (CH), 74.9 (CH), 70.2 (CH), 68.0 (CH), 65.6 (CH), 59.1 (CH), 52.5 (CH_3), 46.3 (CH_2), 41.9 (CH_2), 33.8 (CH_2), 29.1 (CH_2), 27.0 (CH_2), 24.7 (CH_3), 24.6 (CH_3), 17.7 (CH_3); MS (EI, 200°C): m/z (%) = 440 [M], 364 (6), 312 (5), 254 (9), 228 (16), 187 (19), 130 (100), 70 (68), 59 (7). HRMS ($C_{21}H_{32}N_2O_8$): calcd. 440.2159; found 440.2161.

Glycopeptide 9. (SiO_2, EtOAc/MeOH 10/1) ^{1}H NMR (500 MHz, $CDCl_3$/MeOD): δ 7.39–7.25 (m, 15H), 6.83–6.78 (m, 1H), 6.03 (d, $J = 15.4$ Hz, 1H), 4.47–4.45 (m, 1H), 4.21–3.99 (m, 3H), 3.90–3.87 (m, 1H), 3.78–3.55 (m, 5H), 3.7 (s, 3H), 2.60–2.51 (m, 2H), 2.23–2.00 (m, 4H), 1.19 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$/MeOD): δ 172.4 (C_q), 167.3 (C_q, 166.4 (C_q), 141.8 (CH), 124.2 (CH), 73.8 (CH), 70.8 (CH), 70.4 (CH), 67.9 (CH), 67.0 (CH), 58.7 (CH), 51.7 (CH_3), 45.8 (CH_2), 41.2 (CH_2), 28.5 (CH_2), 27.5 (CH_2), 24.1 (CH_2), 17.3 (CH_3); MS (EI, 280°C): m/z (%) = 400 (6) [M], 228 (20), 187 (14), 154 (30), 130 (52), 111 (38), 83 (46), 69 (100). HRMS ($C_{18}H_{28}N_2O_8$): calcd. 400.1845; found 400.1852.

Glycopeptide 10. (SiO_2, EtOAc) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.25 (m, 15H), 7.04 (dd, $J = 4.3$, 15.4 Hz, 1H), 6.51 (s, 1H, NH), 6.24 (d, $J = 15.4$ Hz, 1H), 4.99, 4.85, 4.76, 4.71, 4.62 (m, 6H), 4.55–4.53 (m, 1H), 4.17–4.07 (m, 2H), 3.88–3.85 (m, 1H), 3.76–3.70 (m, 1H), 3.74 (s, 3H), 3.64–3.62 (m, 3H), 3.53–3.48 (m, 2H), 2.27–2.00 (m, 4H), 1.19 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3 (C_q, 167.0 (C_q), 165.4 (C_q), 140.6 (CH), 138.7, 138.5, 138.1 (C_q), 128.5, 128.5, 128.4, 128.3, 128.3, 127.8, 127.6, 127.8, 127.6 (CH), 124.1 (CH), 84.9 (CH), 78.8 (CH), 78.8 (CH), 76.6 (CH), 75.6 (CH_2), 74.6 (CH_2), 74.3 (CH), 72.8 (CH_2), 59.0 (CH), 52.5 (CH_3), 46.0 (CH_2), 42.2 (CH_2), 29.1 (CH), 24.7 (CH_2), 17.3 (CH_3); MS (EI, 250°C): m/z (%) = 656 (2) [M], 565 (6), 436 (5), 251 (12), 181 (7), 130 (5), 91 (100), 70 (7). HRMS ($C_{38}H_{44}N_2O_8$): calcd. 656.3098; found 656.3079.

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