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Stereoselective synthesis of *C*-glycosyl analogues of phenylalanine

Xin Xu, Ghada Fakha and Denis Sinou*

Laboratoire de Synthèse Asymétrique, Associé au CNRS, ESCPE Lyon, Université Claude Bernard Lyon I, 43, Boulevard du 11 Novembre 1918, 69622 Villeurbanne Cédex, France

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Abstract—Condensation of 1-[4,6-di-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl]-4-bromobenzene (**2**) with methyl 2-acetamidoacrylate in the presence of $Pd(OAc)_2$, $P(C_6H_4\text{-}O\text{-}CH_3)_3$, and $AgNO_3$, afforded the unsaturated *C*-glycosyl enamido ester **3d** in 80% yield. Reduction of compound **3d** in the presence of [Rh(COD)(*R*,*R*)-(Et-DuPHOS)]OTf gave the corresponding unsaturated *C*-glycosyl (*R*)-phenylalanine derivative, when the [Rh(COD)(*S*,*S*)-(Et-DuPHOS)]OTf catalyst gave the *C*-glycosyl (*S*)-phenylalanine derivative, in 67 and 79% yield, respectively. Bis-hydroxylation of compound **4**, followed by acetylation afforded the *C*-mannopyranosyl phenylalanine derivative **5** in overall 30% yield.

1. Introduction

O-Linked glycopeptides are involved in various cellular and biological processes.[1,2] However, glycopeptides are chemically and enzymatically unstable, since they contain the natural *O*- or *N*-glycosidic linkage. This is a problem which limits their uses in many cases. One way to circumvent this drawback is the use of C-analogues of O-glycosylated aminoacids, in order to increase their stability towards hydrolysis. Another benefit relative to these compounds is their uses as probe and understanding of the mechanisms of a number of key cellular processes. This simple transformation of a *O*-glycosidic bond to a *C*-glycosidic bond could effectively provide very useful informations on the specific role of the carbohydrate moiety of glycopeptides. These C-glycosylated amino acids can also be readily incorporated into larger and biological more relevant molecular frameworks, in order to modify these glycopeptides. In this context, much effort has been devoted to the development of new technologies for the construction of some *C*-glycosyl amino acids.[3] Different approaches to the synthesis of *C*-glycosyl glycine,[4–9] *C*-glycosyl alanine,[10–13] *C*-glycosyl serine,[14–29] *C*-glycosyl asparagine,[22,29–31] *C*-glycosyl tyrosine,[32] as well as more complex *C*-glycosyl amino acids,[30,33–35] have been described in the literature. We have previously described a new access to *C*-glycosyl glycine via a palladium(0)-catalyzed alkylation of 2,3-unsaturated aryl glycoside with ethyl nitroacetate or with *N*-(diphenylmethylene)glycine ethyl ester.[36] According to our continuous interest in the synthesis of *C*-glycosyl analogues of amino acids, we describe in this paper a palladium(0)-catalyzed access to *C*-glycosyl analogues of phenylalanine.

2. Results and discussion

We described previously the stereospecific access to various unsaturated α- and β-*C*-arylglycosides via the condensation of an aryl Grignard reagent with *p*-*tert*-butylphenyl 4,6-di-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**1**); a palladium catalyst complex, obtained by mixing $PdCl_2(CH_3CN)_2$ and dppf, allowed the formation of the corresponding α-configurated *C*-glycoside, whereas the β-anomer was obtained in the presence of the catalyst $NiCl_2$(dppe).[37] Among the functionalized *C*-aryl glycosides obtained, *C*-*p*-bromophenyl Δ^2-glycopyranosides are of particular interest, since the presence of the bromide on the aromatic ring allows a lot of transformation, for instance in the presence of a palladium or a nickel complex. Condensation of carbohydrate **1** with the Grignard reagent $BrMgC_6H_4$-*p*-Br in the presence of $PdCl_2(CH_3CN)_2$+ dppf as the catalyst afforded the unsaturated α-*C*-aryl glycoside **2** in 30% yield. One of the most useful transformation of compound **2** would be the Heck reaction of this derivative in the presence of various esters, unsaturated ketones, or nitriles.

In order to test the feasibility of this Heck reaction using α-*C*-*p*-bromophenyl glycoside **2**, we performed the condensation first in the presence of methyl acrylate as the unsaturated substrate (Scheme 1). Condensation occurred readily in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3 in dimethylformamide as the solvent at 100°C to give the corresponding coupling product **3a** in 60% yield after purification by column chromatography (Table 1, entry 1). It is to be noticed that only the *E*-isomer was

Keywords: *C*-aryl glycoside; *C*-glycosyl phenylalanine; Heck reaction.

* Corresponding author. Tel.: +33-4-72-448183; fax: +33-4-78898914; e-mail: sinou@univ-lyon1.fr

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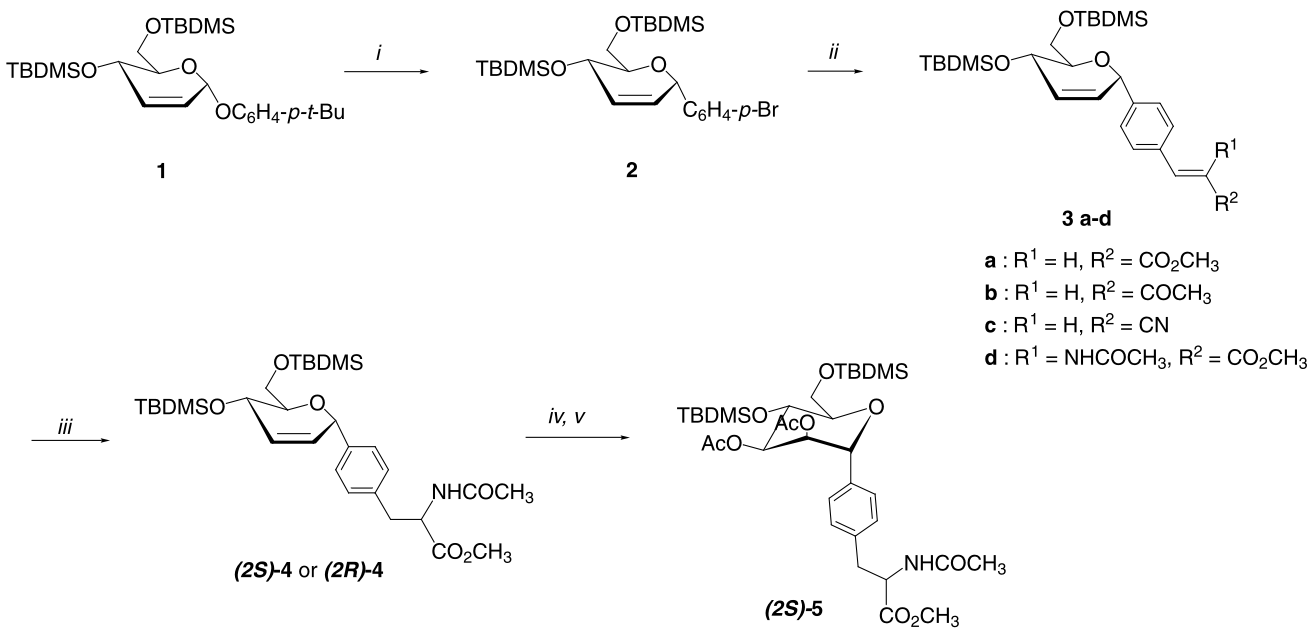

Scheme 1. Synthesis of *C*-glycosyl phenylalanine analogues *Reagents*: (i) BrMg-C_6H_4-4-Br, $PdCl_2(CH_3CN)_2$, dppf, THF, 25°C. (ii) $CH_2{=}CHR^1R^2$, $Pd(OAc)_2$, PAr_3, NEt_3, DMF, Δ. (iii) H_2, [Rh(COD)(Et-DuPHOS]OTf. (iv) OsO_4, CH_3COCH_3, H_2O. (v) Ac_2O, C_5H_5N.

Table 1. Heck-coupling reaction of *C*-bromophenyl carbohydrate **2** with various alkenes

Entry	Alkene	Phosphine	Additive	Yield **3** (%)
1	R^1=H, R^2=CO_2Me	PPh_3	No	**3a** (60)
2	R^1=H, R^2=COMe	PPh_3	No	**3b** (82)
3	R^1=H, R^2=CN	PPh_3	No	**3c** (63)
4	R^1=NHCOMe, R^2=CO_2Me	PPh_3[a]	No	**3d** (0)
5	R^1=NHCOMe, R^2=CO_2Me	PPh_3	$AgNO_3$	**3d** (14)
6	R^1=NHCOMe, R^2=CO_2Me	P(*o*-tolyl)$_3$[b]	No	**3d** (33)
7	R^1=NHCOMe, R^2=CO_2Me	P(*o*-tolyl)$_3$[b]	$AgNO_3$	**3d** (80)

[**2**]/[alkene]/[$Pd(OAc)_2$]/[NEt_3]/[additive]=10:20:1:2:80:20; T=100°C; 12 h.
[a] 19 h.
[b] [Pd]/[P(*o*-tolyl)$_3$]=1:3.

detected, characterized by a coupling constant J=16.2 Hz for the ethylenic proton.

This Heck reaction was then extended to methyl vinyl ketone and acrylonitrile under exactly the same conditions (Table 1, entries 2, 3). The unsaturated functionalized *C*-aryl glycosides **3b** and **3c** were obtained in 82 and 63% yield after column chromatography, respectively. Only the stereoisomer *E* was obtained as shown by the coupling constant J=16.2 and 16.7 Hz for the ethylenic proton of **3b** and **3c**, respectively.

We then turned our attention to the condensation of bromophenyl glycoside **2** with methyl 2-acetamido acrylate, in order to obtain *C*-glycosidic dehydrophenylalanine methyl ester derivatives. Although several methods appeared recently in the literature concerning the preparation of dehydroaminoacids using a palladium-catalyzed vinylation, this condensation seemed more difficult under the usual Heck reaction conditions.[38–43]

Effectively when the condensation was performed at 100°C for 12 h in the presence of 0.1 equiv. of $Pd(OAc)_2$ and 0.2 equiv. of PPh_3, no formation of the desired product was detected (Table 1, entry 4); addition of silver carbonate (2 equiv.) allowed the formation of compound **3d** in 14% yield (Table 1, entry 5). However, when P(C_6H_4-*o*-CH_3)$_3$ (0.4 equiv.) was used as the ligand, instead of PPh_3, the desired product **3d** was obtained in 33% yield after column chromatography (Table 1, entry 6). When this ligand was combined with silver carbonate (2 equiv.), the yield in **3d** increased to 80% (Table 1, entry 7). Since a single stereoisomer was obtained in this condensation as shown from the NMR spectra, the *Z* configuration was attributed to **3d**, according to the previous results in this field.[38–43]

In order to reduce the *C*-glycosyl enamide ester **3d** to the *C*-glycosyl amino acid **4**, we used [Rh(COD)(Et-DuPHOS)]-OTf as the hydrogenation catalyst. The DuPHOS-Rh^+ catalyst seems effectively to be the appropriate candidate for this reduction, since it has been shown that it reduced a variety of enamides with excellent chiral inductions.[44] Moreover, this catalyst has been successfully applied in the reduction of some *C*-glycosyl enamide precursors.[19] The reduction was performed in MeOH as the solvent and under 10 bar H_2. When the reduction was performed using (*R*,*R*)-Et-DuPHOS or (*S*,*S*)-Et-DuPHOS as the chiral ligand under 10 bar H_2, two different compounds, resulting from the reduction of the double bond of the enamido moiety only, were produced in 67 and 64% yield, respectively. These two diastereoisomers show small differences in the ^{1}H NMR spectra, and particularly the signal corresponding to the ester group; according to these spectra, we postulated that this *C*-glycosyl amino acid was produced in >95% de in the two cases. The reaction was also performed under 5 bar H_2 to give the expected product in 79% yield, and more than 95% de. According to the results of Burk et al.[44] we postulated that reduction of compound **3d** using the two enantiomeric catalysts [Rh(COD)(*R*,*R*)-(Et-DuPHOS)]OTf and [Rh(COD)(*S*,*S*)-(Et-DuPHOS)]OTf gave the (*R*)- and (*S*)-glycosyl amino acid **4**, respectively.

Then we try to bis-hydroxylated the unsaturated carbohydrate moiety of compound **4**. Bis-hydroxylation of compound **4** in a mixture of acetone/water using a catalytic amount of OsO_4 in the presence of *N*-methyl-morpholine gave a diol, which was directly acetylated. Purification by column chromatography gave the *C*-mannopyranosyl amino acid derivative **5** in 30% yield. The attribution of the manno configuration to this compound was mainly based on the coupling constants observed for H-1 ($J_{1,2}$=2.2 Hz) and H-4 ($J_{4,3}$=8.8 Hz), characteristics of an equatorial–equatorial and an axial–axial disposition for the hydrogens, and so a manno configuration. This configuration is also in agreement with a bis-hydroxylation on the less hindered side of the double bond of the unsaturated carbohydrate.

3. Conclusion

In conclusion, a Heck-coupling reaction of an appropriate *C*-*p*-bromophenyl unsaturated glycoside led with good yields to the corresponding *C*-glycosyl enamide ester. Hydrogenation of this unsaturated substrate using [Rh(COD)(Et-DuPHOS]OTf as the catalyst produced the corresponding unsaturated *C*-glycosylphenylalanine with a high ed, and having the D- or the L-stereochemistry at the α-amino acid center, depending on the catalyst precursor. Bis-hydroxylation of this compound, followed by acetylation of the resulting diol, gave the *C*-manno pyranosyl phenylalanine derivative. Experiments to explore the potentiality of this new methodology and his extension to the β-anomer are under way and will be reported in due course.

4. Experimental

4.1. General methods

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (60 F-254, Merck). Compounds were visualized under UV light (254 nm) or by spraying with an H_2SO_4 solution and heating. Column chromatography was performed on silica gel 60 (40–63 mesh, Merck). NMR spectra were recorded on Bruker AC 200 and AM 300 spectrometers, and chemical shifts are given in ppm on the δ scale from internal tetramethylsilane. Reactions involving palladium complexes were carried out in a Schlenk tube under a nitrogen atmosphere. THF was distilled from sodium/benzophenone and stored under a nitrogen atmosphere. $Pd(OAc)_2$, triphenylphosphine, tri(*o*-tolyl) phosphine, methyl acrylate, methyl vinyl ketone, acrylo-nitrile, methyl 2-acetamidoacrylate, [Rh(COD)(*R*,*R*)-(Et-DuPHOS)]OTf, and [Rh(COD)(*S*,*S*)-(Et-DuPHOS)]-OTf are from commercial source. *p*-*tert*-Butylphenyl 4,6-di-*O*-(*tert*-butyldimethylsilyl)-2,3-dide-oxy-α-D-*erythro*-hex-2-enopyranoside (**1**) was prepared as already described.[37]

4.1.1. 1-[4,6-Di-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl]-4-bromophenyl (2). To a solution of the unsaturated carbohydrate **1** (447 mg, 0.88 mmol) and $PdCl_2(CH_3CN)_2$ (22.8 mg, 0.088 mmol) and dppf (48.8 mg, 0.088 mol) in 4 mL of THF was added at room temperature a solution of the Grignard reagent prepared from magnesium (128 mg, 5.2 mmol) and 1,4-dibromobenzene (1028.6 mg, 4.36 mmol) in 10 mL of THF. The reaction was followed by TLC. After disappearance of the starting material, diethyl ether (100 mL) was added, the ethereal solution was washed with water (2×20 mL), and dried. Concentration and column chromatography on silica gel, using petroleum ether/dichloromethane as the eluent, furnished 135.6 mg of compound **2** (yield 30%). Oil; R_f 0.33 (petroleum ether/dichloromethane 2/1); $[\alpha]_D^{25}=-12.8$ (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.04 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.89 (s, 9H, $SiMe_3$), 0.91 (s, 9H, $SiMe_3$), 3.37 (ddd, *J*=8.0, 6.3, 2.4 Hz, 1H, H-5), 3.68 (dd, *J*=11.1, 6.3 Hz, 1H, H-6), 3.87 (dd, *J*=11.1, 2.4 Hz, 1H, H-6), 4.18 (dd, *J*=8.4, 1.7 Hz, 1H, H-4), 5.10 (bs, 1H, H-1), 5.85 (d, *J*=10.4 Hz, 1H, H-2), 6.05 (d, *J*=10.4 Hz, 1H, H-3), 7.32 (d, *J*=8.6 Hz, 2H, H_{arom}), 7.42 (d, *J*=8.6 Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.1 (SiMe), −5.0 (SiMe), −4.6 (SiMe), −4.1 (SiMe), 18.1 (Si*C*Me$_3$), 18.5 (Si*C*Me$_3$), 25.9 (SiC*Me*$_3$), 26.1 (SiC*Me*$_3$), 63.4 (C-6), 64.3 (C-4), 73.1 (C-5), 74.8 (C-1), 121.6 (C-Br), 127.9, 129.6, 130.9, 132.9, and 139.5 (C-2, C-3, C_{arom}).

Anal. Calcd for $C_{24}H_{41}O_3BrSi_2$ (513.67): C, 56.12; H, 8.05. Found: C, 56.26; H, 7.99.

4.2. General procedure

A solution of *C*-*p*-bromophenyl glycoside **2** (309 mg, 0.6 mmol) and the unsaturated substrate (1.2 mmol) in DMF (4 mL) was heated at 100°C in the presence of $Pd(OAc)_2$ (13.5 mg, 1.2 mmol), monophosphine (0.2 mmol), NEt_3 (0.67 mL, 4.8 mmol), and eventually $AgNO_3$ (204.8 mg, 1.2 mmol) for the indicated time. After being cooled to room temperature, water (10 mL) was added, and the solution was treated by Et_2O (3×15 mL). Evaporation of the solvent under reduced pressure gave an oil that was purified by column chromatography on silica gel using the indicated solvent to give the coupled product **3**.

4.2.1. Methyl 3-[4{4,6-di-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl}phenyl]propenoate (3a). Oil; R_f 0.24 (petroleum ether/dichloro methane 1/2); $[\alpha]_D^{25}=-31.4$ (*c* 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.03 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.88 (s, 18H, $SiCMe_3$), 3.39 (ddd, *J*=8.1, 6.3, 2.2 Hz, 1H, H-5), 3.69 (dd, *J*=11.0, 6.3 Hz, 1H, H-6), 3.81 (s, 3H, OCH_3), 3.86 (dd, *J*=11.0, 2.2 Hz, 1H, H-6), 4.16 (ddd, *J*=8.1, 1.8, 1.8 Hz, 1H, H-4), 5.27 (bs, 1H, H-1), 5.89 (ddd, *J*=10.3, 1.8, 1.8 Hz, 1H, H-3), 6.06 (ddd, *J*=10.3, 3.3, 1.8 Hz, 1H, H-2), 6.43 (d, *J*=16.2 Hz, 1H, =CH–), 7.50 (bs, 4H, C_6H_4), 7.68 (d, *J*=16.2 Hz, 1H, C_6H_4–C*H*=); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.3 (SiMe), −5.2 (SiMe), −4.7 (SiMe), −4.2 (SiMe), 18.0 (Si*C*Me$_3$), 18.4 (Si*C*Me$_3$), 25.8 (SiC*Me*$_3$), 25.9 (SiC*Me*$_3$), 51.7 (OCH_3), 63.3 (C-6), 64.2 (C-4), 73.2 (C-1), 74.9 (C-5), 117.7 (=CH–CO_2), 127.8, 127.9, 128.1, 131.2, 133.5, 142.9, and 144.6 (C_6H_4–CH=, C-2, C-3), 165.0 (CO).

Anal. Calcd for $C_{28}H_{46}O_5Si_2$ (518.84): C, 64.82; H, 8.94. Found: C, 64.88; H, 8.86.

4.2.2. 4-[4{4,6-Di-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl}phenyl]-2-oxobut-3-ene (3b). Oil; R_f 0.29 (petroleum ether/ethyl acetate 10/1); $[\alpha]_D^{25}=+12.9$ (*c* 0.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.89 (s, 18H, $SiCMe_3$), 2.39 (s, 3H, $COCH_3$), 3.40 (ddd, *J*=8.1, 6.6, 2.2 Hz, 1H, H-5), 3.71 (dd, *J*=11.0, 6.6 Hz, 1H, H-6), 3.87 (dd, *J*=11.0, 2.2 Hz, 1H, H-6), 4.16 (bd, *J*=8.1 Hz, 1H, H-4), 5.28 (bs, 1H, H-1), 5.90 (ddd, *J*=10.5, 1.8, 1.8 Hz, 1H, H-3), 6.07 (ddd, *J*=10.5, 3.1, 1.8 Hz, 1H, H-2), 6.72 (d, *J*=16.2 Hz, 1H, =CH–), 7.51 (bs, 4H, C_6H_4), 7.52 (d, *J*=16.2 Hz, 1H, C_6H_4–C*H*=); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.3 (SiMe), −5.2 (SiMe), −4.7 (SiMe), −4.2 (SiMe), 18.0 (Si*C*Me_3), 18.4 (Si*C*Me_3), 25.8 (SiC*Me*$_3$), 26.0 (SiC*Me*$_3$), 27.8 (CO*C*H_3), 63.3 (C-6), 64.2 (C-4), 73.2 (C-1), 75.0 (C-5), 127.0 (=*C*HCO), 127.1, 127.9, 128.2, 129.2, 130.3, 141.6, and 143.2 (C_6H_4–CH=, C-2, C-3), 198.0 (CO).

HRMS *m*/*z* (FAB) calcd for $[M-H]^+$ ($C_{28}H_{45}O_4Si_2$) 501.2856, found 501.2855.

4.2.3. 3-[4{4,6-Di-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl}phenyl]propenenitrile (3c). Oil; R_f 0.44 (petroleum ether/ethyl acetate 10/1); $[\alpha]_D^{25}=-52.2$ (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.88 (s, 9H, $SiCMe_3$), 0.89 (s, 9H, $SiCMe_3$), 3.38 (ddd, *J*=14.7, 6.6, 2.3 Hz, 1H, H-5), 3.70 (dd, *J*=11.0, 6.6 Hz, 1H, H-6), 3.86 (dd, *J*=11.0, 2.3 Hz, 1H, H-6), 4.16 (ddd, *J*=14.7, 3.7, 1.8 Hz, 1H, H-4), 5.28 (bs, 1H, H-1), 5.87 (d, *J*=16.7 Hz, =CHCN), 5.91 (dd, *J*=10.3, 3.7, 1.8 Hz, 1H, H-3), 6.05 (ddd, *J*=10.3, 2.9, 1.8 Hz, 1H, H-2), 7.40 (d, *J*=16.7 Hz, 1H, C_6H_4–C*H*=), 7.43 (d, *J*=8.2 Hz, 2H, C_6H_4), 7.52 (d, *J*=8.2 Hz, 2H, C_6H_4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.3 (SiMe), −5.1 (SiMe), −4.7 (SiMe), −4.2 (SiMe), 18.0 (Si*C*Me_3), 18.4 (Si*C*Me_3), 25.8 (SiC*Me*$_3$), 26.0 (SiC*Me*$_3$), 63.3 (C-6), 64.1 (C-4), 73.1 (C-1), 75.0 (C-5), 96.2 (=*C*H–CN), 118.2 (CN), 127.4, 128.0, 131.3, 132.7, 144.0, 148.3, and 150.3 (C_6H_4–CH=, C-2, C-3).

Anal. Calcd for $C_{27}H_{43}NO_3Si_2$ (485.82): C, 66.75; H, 8.92. Found: C, 66.84; H, 8.88.

4.2.4. Methyl 2-acetamido-3-[4{4,6-di-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl}phenyl]propenoate (3d). Oil; R_f 0.24 (petroleum ether/ethyl acetate 2/1); $[\alpha]_D^{25}=-17.1$ (*c* 0.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.90 (s, 18H, $SiCMe_3$), 2.10 (s, 3H, $COCH_3$), 3.40 (ddd, *J*=8.1, 6.2, 2.6 Hz, 1H, H-5), 3.70 (dd, *J*=11.0, 6.2 Hz, 1H, H-6), 3.80 (s, 3H, NHCOC*H*$_3$), 3.86 (dd, *J*=11.0, 2.6 Hz, 1H, H-6), 4.16 (ddd, *J*=8.1, 1.8, 1.5 Hz, 1H, H-4), 5.30 (bs, 1H, H-1), 5.85 (ddd, *J*=10.5, 1.5, 1.5 Hz, 1H, H-3), 6.07 (ddd, *J*=10.5, 3.0, 1.8 Hz, 1H, H-2), 6.90 (bs, 1H, NH), 7.36–7.45 (m, 5H, C_6H_4–CH=); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.3 (SiMe), −5.1 (SiMe), −4.7 (SiMe), −4.2 (SiMe), 18.0 (Si*C*Me_3), 18.4 (Si*C*Me_3), 22.0 (CO*C*H_3), 25.8 (SiC*Me*$_3$), 26.0 (SiC*Me*$_3$), 52.7 (COO*C*H_3), 63.3 (C-6), 64.1 (C-4), 73.2 (C-1), 74.9 (C-5), 125.4, 125.6, 127.5, 127.9, 131.1, 131.8, 132.1, 132.8, 133.0, and 143.6 (C_6H_4–*C*H=, C-2, C-3), 165.8 (CO_2), 169.3 (*C*OCH_3).

HRMS *m*/*z* (FAB) calcd for $[M-H]^+$ ($C_{30}H_{48}NO_6Si_2$) 574.3020, found 574.3024.

4.3. Hydrogenation of unsaturated compound 3d

An autoclave was charged with compound **3d** (90 mg, 0.16 mmol), and catalyst [Rh(COD)(Et-DuPHOS]OTf (2.5 mg, 3.5×10^{-3} mmol). After five vacuum/H_2 cycles, ethanol (7 mL) was added, and the reactor was pressurized to an initial pressure of 5–10 bar hydrogen. The reaction was allowed to stir at room temperature for 24 h. Evaporation of the solvent followed by column chromatography on silica using a mixture of petroleum ether/ethyl acetate as the eluent gave the *C*-glycosyl phenylalanine methyl ester **4**.

4.3.1. Methyl (2*R*)-2-acetamido-3-[4{4,6-di-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl}phenyl]propanoate (4). Oil; R_f 0.44 (petroleum ether/ethyl acetate 1/1); $[\alpha]_D^{25}=-14.1$ (*c* 1.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.06 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiCMe_3$), 0.92 (s, 9H, $SiCMe_3$), 2.02 (s, 3H, $COCH_3$), 3.14 (dd, *J*=14.0, 6.7 Hz, 1H, CH_2), 3.16 (dd, *J*=14.0, 6.7 Hz, 1H, CH_2), 3.43 (ddd, *J*=8.2, 6.5, 2.5 Hz, 1H, H-5), 3.70 (dd, *J*=11.1, 6.5 Hz, 1H, H-6), 3.76 (s, 3H, NHCOC*H*$_3$), 3.88 (dd, *J*=11.1, 2.5 Hz, 1H, H-6), 4.18 (ddd, *J*=8.2, 3.9, 1.9 Hz, 1H, H-4), 4.91 (m, 1H, C*H*NH), 5.27 (bs, 1H, H-1), 5.89 (ddd, *J*=10.3, 3.9, 1.9 Hz, 1H, H-3), 5.93 (m, 1H, NH), 6.06 (ddd, *J*=10.3, 3.2, 1.9 Hz, 1H, H-2), 7.08–7.41 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.3 (SiMe), −5.1 (SiMe), −4.7 (SiMe), −4.2 (SiMe), 18.0 (Si*C*Me_3), 18.4 (Si*C*Me_3), 23.2 (CO*C*H_3), 25.8 (SiC*Me*$_3$), 26.0 (SiC*Me*$_3$), 37.4 ($C_6H_4C$$H_2$), 52.3 ($CO_2C$$H_3$), 53.1 (CHNH), 63.3 (C-6), 64.2 (C-4), 73.2 (C-1), 74.7 (C-5), 127.6, 128.4, 129.2, 130.0, 134.9, and 139.3 (C_6H_4, C-2, C-3), 169.7 (CO_2), 172.1 (*C*OCH_3); *m*/*z* (EI) 579 $[M+H]^+$, 577 $[M-H]^+$, 463 $[M-SiMe_2CMe_3]^+$.

4.3.2. Methyl (2*S*)-2-acetamido-3-[4{4,6-di-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl}phenyl]propanoate (4). Oil; R_f 0.44 (petroleum ether/ethyl acetate 1/1); $[\alpha]_D^{25}=+31.7$ (*c* 2.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiCMe_3$), 0.92 (s, 9H, $SiCMe_3$), 2.02 (s, 3H, $COCH_3$), 3.12 (dd, *J*=14.0, 5.4 Hz, 1H, CH_2), 3.16 (dd, *J*=14.0, 5.8 Hz, 1H, CH_2), 3.43 (ddd, *J*=8.4, 6.3, 2.2 Hz, 1H, H-5), 3.73 (dd, *J*=11.1, 6.3 Hz, 1H, H-6), 3.78 (s, 3H, NHCOC*H*$_3$), 3.88 (dd, *J*=11.1, 2.2 Hz, 1H, H-6), 4.17 (ddd, *J*=8.4, 1.9, 1.9 Hz, 1H, H-4), 4.91 (m, 1H, C*H*NH), 5.27 (bs, 1H, H-1), 5.89 (ddd, *J*=10.4, 1.9, 1.9 Hz, 1H, H-3), 5.92 (m, 1H, NH), 6.06 (ddd, *J*=10.4, 1.9, 1.9 Hz, 1H, H-2), 7.07 (d, *J*=8.0 Hz, 2H, C_6H_4), 7.39 (d, *J*=8.0 Hz, 2H, C_6H_4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.3 (SiMe), −5.1 (SiMe), −4.7 (SiMe), −4.2 (SiMe), 18.0 (Si*C*Me_3), 18.4 (Si*C*Me_3), 23.1 (CO*C*H_3), 25.8 (SiC*Me*$_3$), 26.0 (SiC*Me*$_3$), 37.4 ($C_6H_4C$$H_2$), 52.3 ($CO_2C$$H_3$), 53.1 (CHNH), 63.3 (C-6), 64.2 (C-4), 73.2 (C-1), 74.7 (C-5), 127.6, 128.3, 129.2, 130.7, 134.9, and 139.3 (C_6H_4, C-2, C-3), 169.6 (CO_2), 172.0 (*C*OCH_3).

Anal. Calcd for $C_{30}H_{51}NO_6Si_2$ (577.91): C, 62.35; H, 8.90. Found: C, 63.32; H, 8.97.

4.3.3. Methyl (2*S*)-2-acetamido-3-[4{4,6-di-*O*-(*tert*-butyldimethylsilyl)-2,3-di-*O*-acetyl-α-D-mannopyranosyl}phenyl] propanoate (5). To a solution of unsaturated compound (2*S*)-**4** (220 mg, 0.4 mmol) in a mixture of acetone/water (5 mL/1 mL) was added *N*-methyl morpholine oxide (178 mg, 1.6 mmol), and then OsO_4 (4.4 mg, 0.017 mmol). After being stirred at room temperature until all the starting material disappeared, an aqueous solution of sodium bisulfite (5 mL) was added. After 30 min, an aqueous solution of sodium chloride was added (40 mL), and the organic product was extracted with dichloromethane (2×50 mL). Evaporation of the solvent gave the crude diol. This diol was stirred in the presence of C_5H_5N (2 mL) and acetic anhydride (2 mL) for 24 h; addition of a saturated aqueous solution of cuprous sulfate (5 mL), followed by extraction with CH_2Cl_2 (4×50 mL), evaporation of the solvent, and purification by column chromatography on silica using a mixture petroleum ether/ethyl acetate as the eluent gave 83 mg of compound **5** as an oil (yield 30%). Oil; R_f 0.51 (petroleum ether/ethyl acetate 1/2); $[\alpha]_D^{25}=+73.0$ (*c* 1.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.02 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.80 (s, 9H, $SiCMe_3$), 0.95 (s, 9H, $SiCMe_3$), 1.98 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 3.07 (dd, *J*=13.9, 5.9 Hz, 1H, CH_2), 3.13 (dd, *J*=13.9, 5.5 Hz, 1H, CH_2), 3.34 (ddd, *J*=8.8, 4.8, 2.9 Hz, 1H, H-5), 3.67–3.70 (m, 1H, H-3), 3.72 (s, 3H, $NHCOCH_3$), 3.80 (dd, *J*=11.0, 2.9 Hz, 1H, H-6), 3.86 (dd, *J*=11.0, 4.8 Hz, 1H, H-6), 4.13 (dd, *J*=8.8, 8.8 Hz, 1H, H-4), 4.81–4.94 (m, 2H, C*H*NH, H-2), 4.95 (d, *J*=2.2 Hz, 1H, H-1), 5.96 (m, 1H, NH), 7.10 (d, *J*=8.1 Hz, 2H, C_6H_4), 7.45 (d, *J*=8.1 Hz, 2H, C_6H_4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.3 (SiMe), −5.0 (SiMe), −4.9 (SiMe), −4.5 (SiMe), 18.1 ($SiCMe_3$), 18.4 ($SiCMe_3$), 20.9 ($COCH_3$), 21.2 ($COCH_3$), 23.2 ($NHCOCH_3$), 25.7 ($SiCMe_3$), 25.9 ($SiCMe_3$), 37.5 ($C_6H_4CH_2$), 52.4 (CO_2CH_3), 53.0 (CHNH), 62.3 (C-6), 66.3, 69.5, 73.3, 75.5, and 76.3 (C-1, C-2, C-3, C-4, C-5), 126.9, 129.7, 130.0, and 130.4 (C_6H_4), 169.7 (CO_2), 170.4 ($COCH_3$), 170.5 ($COCH_3$), 172.0 ($COCH_3$).

HRMS *m*/*z* (FAB) calcd for $[M+H]^+$ ($C_{34}H_{58}NO_{10}Si_2$) 696.3599, found 696.3607.

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