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Efficient Synthesis of Glycosylated Matijin-Su Derivatives via Ultrasonic Irradiation

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Matijin-Su (**1**) is a phenylalanine dipeptide compound with anti-hepatitis B virus (HBV) activity. Previous reports suggest that the synthesis of glycosylated Matijin-Su derivatives needs at least 10 steps. To simplify the synthetic procedure, we have developed a shorter and more efficient method for the preparation via ultrasound irradiation. Two galactopyranosylated (**2**) and two glucopyranosylated (**3**) derivatives were synthesized in 6 or 7 steps. The overall yields for the total synthesis of galactopyranosylated derivatives were markedly increased to 39% (**2a**) or 22% (**2b**). And the yields for glucopyranosylated derivatives also reached 29% (**3a**) or 16% (**3b**).

Keywords Matijin-Su, dipeptide, glycosylation, ultrasonic irradiation

Introduction

Matijin-Su (*N*-(*N*-benzoyl-*L*-phenylalanyl)-*O*-acetyl-*L*-phenylalanol, Figure 1), a dipeptide derivative with anti-HBV activity, was isolated from *Dichondra repens* Forst.[1] The anti-HBV activity of Matijin-Su and its dipeptide derivatives had been reported in our previous studies.[2] In addition, one compound was also developed into a new drug for treatment of Hepatitis B and entered phase II clinical trial in China.[3]

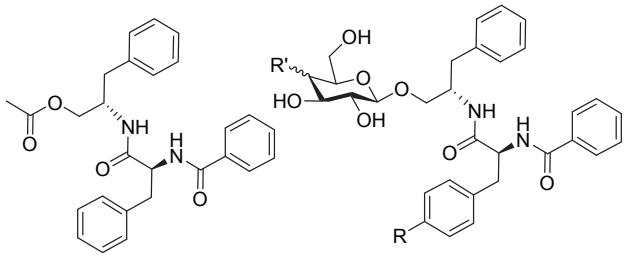

Figure 1 The structures of Matijin-Su and its glycosylated derivatives **2** and **3**.

To date, Matijin-Su derivatives, including heterocyclic derivatives,[4] isosteres,[5] nitric oxide-releasing derivatives[6] and general derivatives[7] have been obtained. For glycosylated Matijin-Su derivatives, only several galactopyranosylated derivatives have been described in the literature.[8] And it was difficult to be synthesized via the traditional classical methods, such as Koenigs-Knorr-Methode or thioglycosides as glycosyl donors, by using desacetyl Matijin-Su as the starting material. These glycosylated derivatives could only be prepared by using *L*-phenylalanol (**4**) as the starting material (Scheme 1). The synthesis needs 10—11 steps and involves several protection and deprotection steps which increase the cost and the time to synthesize them. And the overall yields of synthesis of target compounds **2a**—**2b** and **13a**—**13c** were only 5.4%—7.3%, which affect the study of activities for glycosylated Matijin-Su derivatives.

Herein, we report a more effective method for synthesis of glycosylated derivatives **2** and **3**. Scheme 2 shows the synthetic route for compounds **2** and **3**. This approach was based on the ultrasound-promoted glycosylation reaction as a key step. All target compounds could be prepared using *L*-phenylalanine (**14a**) or *L*-tyrosine (**14b**) as starting material. After the amino group was benzoylated with benzoyl chloride in 2 mol/L KOH to give compounds **11a**—**11b**, the hydroxyl group of compound **11b** was protected with Ac_2O in pyridine to afford **15**. Then, compound **11a** or **15** reacted with *L*-phenylalanol in the presence of isobutyl chloroformate (IBCF) and *N*-methylmorpholine (NMM) to give intermediates **16a** and **16b**. Glycosylation of intermediates **16** with tetra-*O*-acetyl-*D*-galactopyranosyl bromide (**19a**) or tetra-*O*-acetyl-*D*-glucopyranosyl bromide (**19b**) was achieved in the presence of silver trifluoromethane sulfonate (AgOTf) under ultrasonic irradiation in dark

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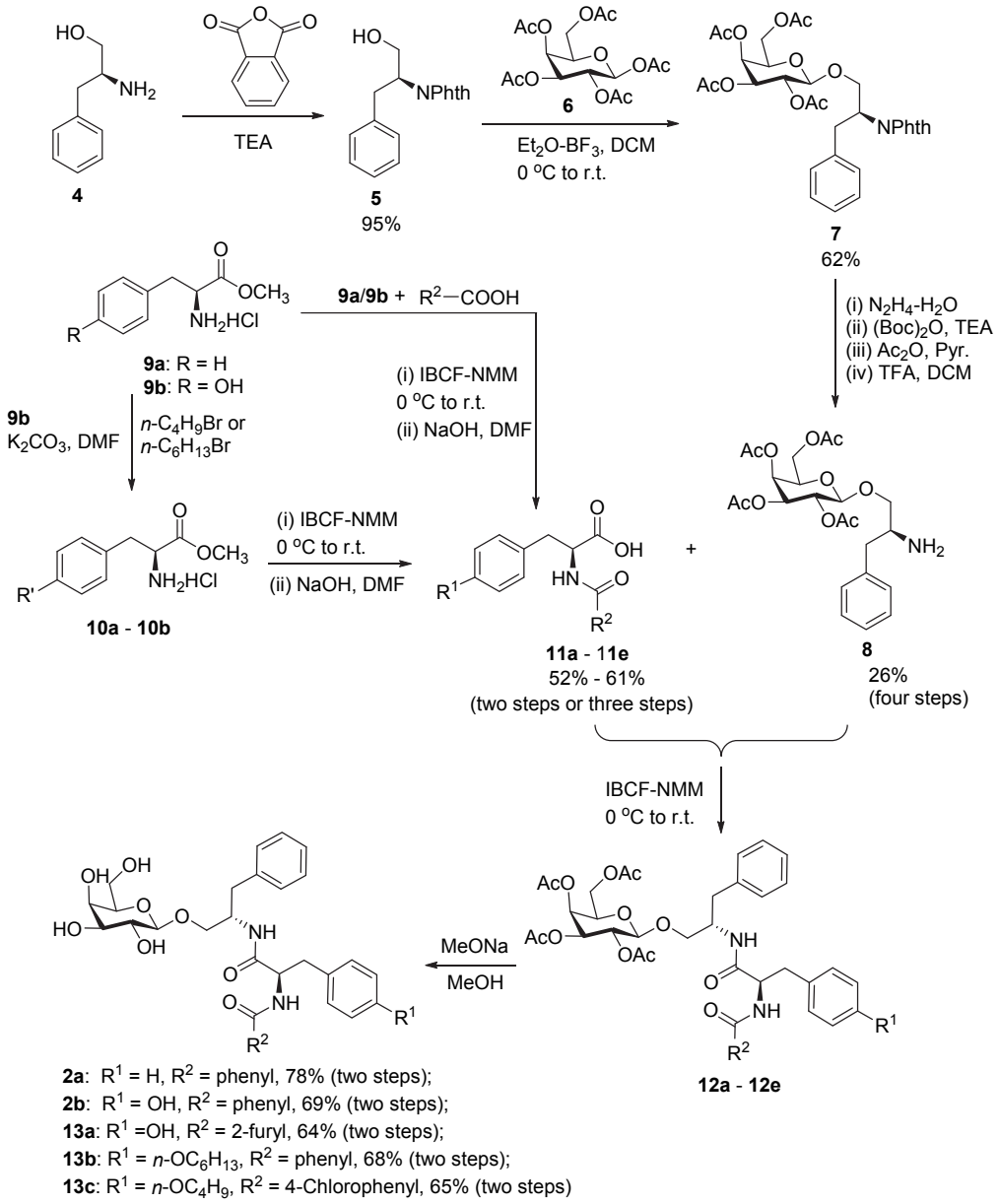
Scheme 1 Synthetic procedure for galactopyranosylated Matijin-Su derivatives reported by literature



room to provide the key intermediates **20** and **21**. After that, the acetyl groups were deprotected with MeONa in MeOH to provide glycosylated target derivatives **2** and **3**.

Results and Discussion

As shown in Scheme 2, compared with the previous synthetic route, four glycosylated Matijin-Su derivatives **2** and **3** were synthesized in higher yields and fewer steps. Subsequently, the potential factors affecting the ultrasound-promoted glycosylation reaction of **16a** and **19a**, such as ultrasonic frequency and promoters, were discussed.

We found that the glycosylation reaction was performed under ultrasonic irradiation (Table 1). With the frequency increasing, the reaction time was shortened. But, the yield also decreased when the frequency reached 4.0×10^4 Hz by using different promoters (Table 1, Entries 3, 7 and 11). And the yield of some reactions was decreased by more than 15%, such as the glycosylation by using Ag_2CO_3 as promoter at 2.5×10^4 Hz and 4.0×10^4 Hz (Table 1, Entries 2 and 3). It means that a higher frequency might reduce the stability of the sugar donor. In addition, compared with the use of Ag_2CO_3 or Ag_2O as promoter in other equal conditions, AgOTf has better yield and shorter reaction time.

After that, the relation between yield and acceptor/donor ratio under the frequency 2.5×10^4 Hz and using AgOTf as promoter was also studied (Table 2). The reaction time for glycosylation of **16a** and **19a** was shortened by increase of acceptor/donor ratio. In the initial experiment, acceptor **16a** was allowed to react with donor **19a** (1.0 equiv.) in CH_2Cl_2 for 15 min lead-

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Scheme 2 Synthetic route for glycosylated Matijin-Su derivatives via ultrasonic irradiation

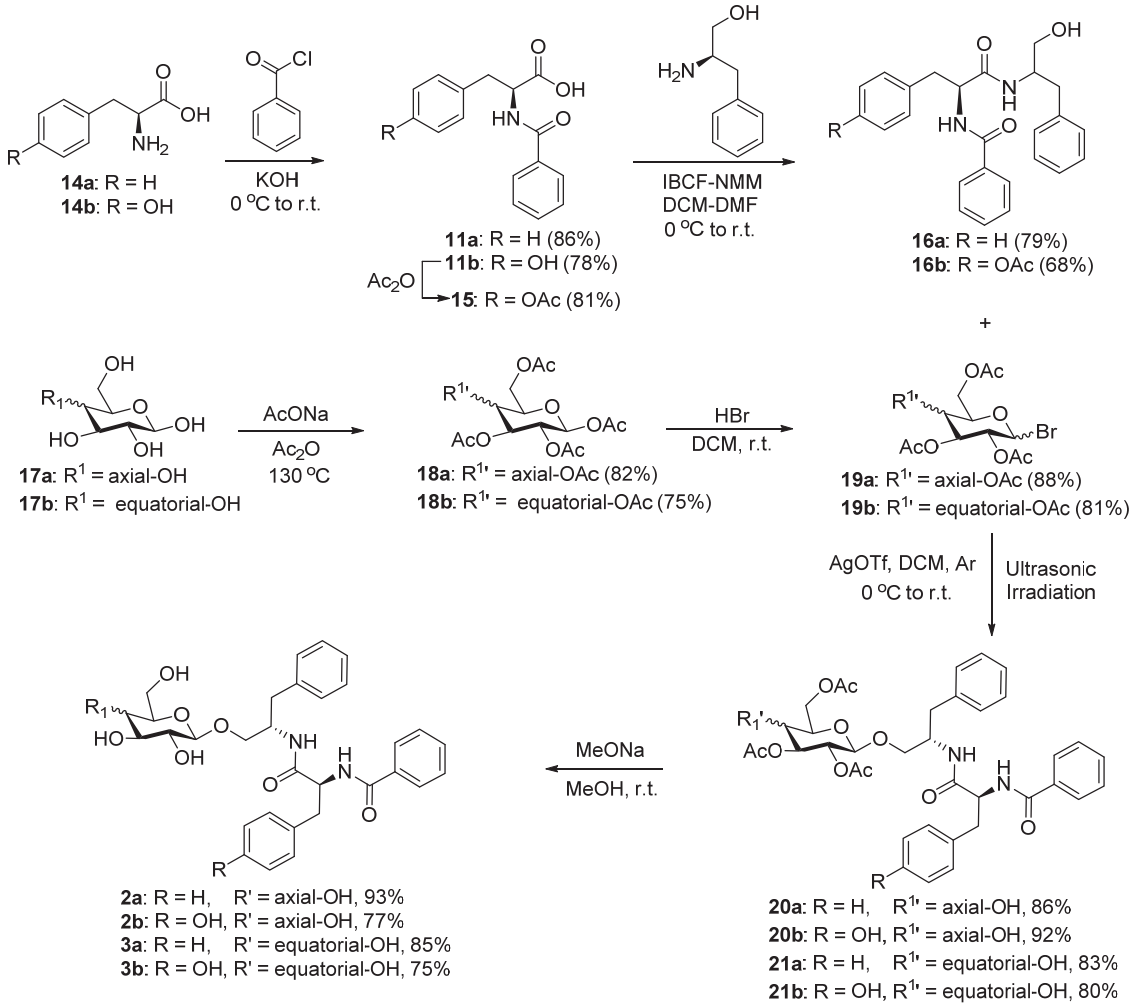
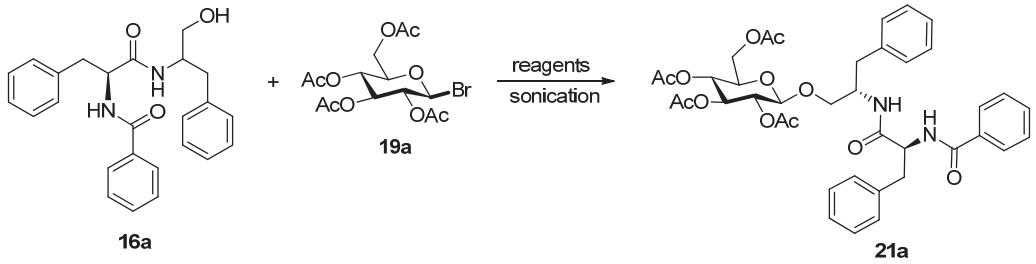


Table 1 The influence of different ultrasonic wave and promoters for glycosylation of **16a** and **19a**[a]



Entry	Frequency[b]/Hz	Time[d]	Promoter	Yield/%	Entry	Frequency[b]/Hz	Time[d]	Promoter	Yield/%
1	1.6×10^4	17 min	Ag_2CO_3	74[e]	7	4.0×10^4	7 min	AgOTf	58
2	2.5×10^4	13 min	Ag_2CO_3	81	8	—	45 h	AgOTf	—
3	4.0×10^4	9 min	Ag_2CO_3	62	9	1.6×10^4	15 min	Ag_2O	71
4	—[c]	48 h	Ag_2CO_3	—[f]	10	2.5×10^4	11 min	Ag_2O	79%
5	1.6×10^4	14 min	AgOTf	77	11	4.0×10^4	10 min	Ag_2O	64
6	2.5×10^4	10 min	AgOTf	86	12	—	46 h	Ag_2O	—

[a] Reagents and conditions: acceptor (20 mg), donor (31 mg, 1.5 equiv.), anhydrous CH_2Cl_2, 4 Å molecular sieves (50 mg), promoter (Table 1, 1.2 equiv. for donor), argon atmosphere, room temperature. [b] The frequency of ultrasonic wave in the chemical reaction. [c] General chemical reaction without ultrasonic wave. [d] Time for acceptor to be completely consumed by TLC. [e] Purification by silica gel column chromatography. [f] Traces observed by TLC.

ing to poor yield of **21a** (54% yield) (Table 2, Entry 1). Gratifyingly, the use of 2 equiv. **19a** as the donor led to the best yield of **21a** (88% yield) (Table 2, Entries 4). However, when the reaction was carried out with three times **19a**, the yield of target compound was lower than that of 2 equiv. (Table 2, Entries 4 and 5). This result may have been caused by instantaneous excess bromine ion from the process of formation of carbocation and the donor **19a** was degraded by ultrasonic in the reaction system with AgOTf (1.2 equiv. for acceptor).

Table 2 The influence of acceptor/donor molar ratio for glycosylation of **16a** and **19a**[a]

Entry	Acceptor/donormol ratio	Time[b]/min	Yield/%
1	1∶1.0	15	54
2	1∶1.2	16	66
3	1∶1.5	11	85
4	1∶2.0	9	88
5	1∶3.0	8	81

[a] Reagents and conditions: acceptor (10 mg), donor (Table 2), anhydrous CH_2Cl_2, 4 Å molecular sieves (30 mg), AgOTf (8 mg, 1.2 equiv. for acceptor), argon atmosphere, room temperature and 2.5×10^4 Hz. [b] Time for acceptor to be completely consumed by TLC.

According to the results, we also envisaged that the quantity of promoter can also affect the rate and amount of the formation process of carbocation. A preliminary set of experiments employing different equivalent of AgOTf as promoter with **16a** and **19a** at 2.5×10^4 Hz confirmed the validity of our hypothesis, as the corresponding **21a** derived from **19a** was obtained in variable yields depending on the amount of promoter (Table 3). Acceptor **16a** was allowed to react with donor **19a** in CH_2Cl_2 and promoter AgOTf (0.5 equiv.) for 21 min leading to poor yield of **21a** (57% yield) (Table 3, Entry 1). Fortunately, the use of AgOTf (1.2 equiv. for acceptor) led to the best yield of **21a** (83% yield) (Table 3, Entry 3). Moreover, when the reaction was carried out with the promoter of 1.5 or 2.0 equiv., the yield of target compound **21a** was lower than that of 1.2 equiv. (Table 3, Entry 3—5).

Table 3 The influence of acceptor/promoter molratio for glycosylation of **16a** and **19a**[a]

Entry	Acceptor/promotermolratio	Time[b]/min	Yield/%
1	1∶0.5	21	57
2	1∶1.0	14	78
3	1∶1.2	12	83
4	1∶1.5	12	74
5	1∶2.0	9	70

[a] Reagents and conditions: acceptor (10 mg), donor (31 mg, 1.5 equiv.), anhydrous CH_2Cl_2, 4 Å molecular sieves (30 mg), AgOTf (Table 3), argon atmosphere, room temperature and 2.5×10^4 Hz. [b] Time for acceptor was completely consumed by TLC.

From the results shown in Tables 1—3, the optimal conditions for ultrasound-promoted glycosylation reaction could be defined as acceptor **16a**, glycosyl donor **19a** (1.5 equiv.), anhydrous CH_2Cl_2, 4 Å molecular sieves (twice the mass of the acceptor), AgOTf (1.2 equiv.), argon atmosphere, room temperature and ultrasonic frequency (2.5×10^4 Hz). Then, target compounds **2b**, **3a** and **3b** were also synthesized under the optimal conditions. In comparison with the reported method (Scheme 1), the new synthetic route of galactopyranosylated compounds can be reduced to six steps (**2a**) or seven steps (**2b**) by using ultrasound irradiation to perform glycosylation introduced in this paper and the overall yields were also increased to 39% (**2a**) or 22% (**2b**). Furthermore, the total yields of glucopyranosylated target compounds **3** also reached 29% (**3a**) or 16% (**3b**).

In addition, as described in Scheme 3, the glycosylation of **16a** with **22** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and *N*-iodosuccinimide (NIS) under ultrasonic irradiationor using **18** as adonor in the presence of BF_3•Et_2O under ultrasonic irradiation according to the equivalent of substrates from references[9] was also explored. Using thioglycosides **22** as glycosyl donor, the target intermediates **20a** and **21a** could be obtained except that the yield (30% for **20a**, 35% for **21a**) was lower than those using compound **19** as a donor (86% for **20a**, 83% for **21a**) in CH_2Cl_2. But, the target compound was not formed by using the same donor in the presence of TMSOTf-NIS without ultrasonic. As for **18a** or **18b** employed as adonor, the reactions did not proceed in the presence of BF_3•Et_2O under ultrasonic irradiation for 40 min, and the acceptor **16a** was untouched (TLC analysis). We firstly guessed that this result may have been caused by BF_3•Et_2O volatilization (room temperature) in ultrasonic and its too few equivalent according to the literature. Therefore, excess BF_3•Et_2O has been used for this reaction in subsequent experiments. But, the target compounds were still not formed. And they were not achieved under BF_3•Et_2O in the presence of CH_2Cl_2 without ultrasonic, either. Thus, we thought that BF_3•Et_2O did not make the donor **18a** or **18b** form carbocation, it just formed a coordination bond with this donor. These results could be attributed to the type of glycosyl donor and the rate of molecular motion.

Conclusions

In summary, an efficient procedure for synthesis of glycosylated Matijin-Su derivatives with substituted *L*-phenylalanine and *D*-glucose or *D*-galactose under ultrasonic irradiation is presented in detail. And the condition of ultrasonic reaction was also optimized. The present work is superior to the previously reported methods[8] as follows: (i) mild reaction conditions, (ii) higher yields, (iii) simpler experimental procedure. Additionally, the glycosylation can be scaled up to 100 mg

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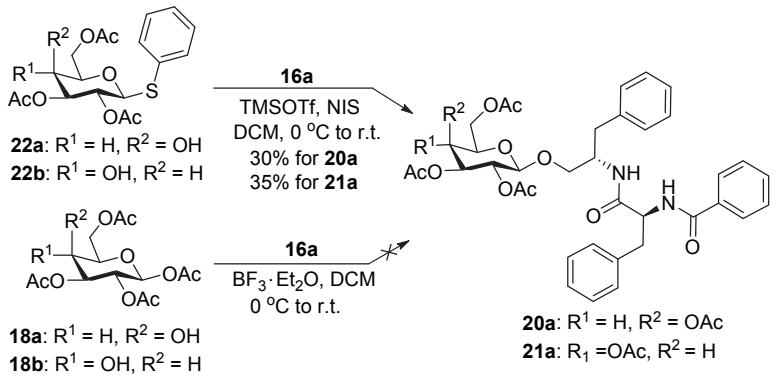
Scheme 3 Synthetic procedure for glycosylation reaction by using **22** or **18** as a donor



scale in good yields. Now, more glycosylated Matijin-Su derivatives can be synthesized via the developed chemical approaches in this paper. And the studies of synthesis for other glycosylated Matijin-Su derivatives will be reported elsewhere.

Experimental

General methods

All NMR data were collected on a Varian INOVA 400-MHz spectrometer in $CDCl_3$ or DMSO-d_6. Chemical shifts are given using TMS as internal reference and coupling constants (*J*) are given in Hz. High-resolution mass spectrometry (HRMS) data were recorded on an Agilent 1100 LC/MS and an STAR Pulsar I system spectrometer, and LRMS data were acquired on a Micromass Quatro-LC Electrospray spectrometer using electrospray ionization (ESI). Optical rotations were measured using a JASCO P-2000 polarimeter at 22 to 24 ℃ in the specified solvents. The 200－300 and 300－400 mesh silica gel (Qingdao Ocean Chemical Factory, P. R. China) was used for TLC and column chromatography, respectively. All air- or moisture-sensitive reactions were operated using dry solvents under argon atmosphere. Chemicals were purchased from Acros, Fluka, or Aladdin and used without further purification.

All compounds were prepared as described in Scheme 2. Benzoyl chloride was treated with substituted *L*-phenylalanine or *L*-tyrosine in 2 mol/L KOH solution to give compound **11a** (86%) and **11b** (78%) according to the standard procedure.[10] Then, the hydroxyl group of compound **11b** was protected by esterification with Ac_2O in pyridine to prepare **15**. Finally, compounds **11a** and **15** reacted with *L*-phenylalanol in the presence of IBCF and NMM to afford intermediates **16a** (79%) and **16b** (68%) based on the reference.[11] All spectral data of intermediates **11** and **16** were consistent with those of a previous study.[12]

***N*-Benzoyl-*O*-acetyl-*L*-tyrosine (15)** Acetic anhydride (0.41 g, 4.0 mmol) was added dropwise to a stirred solution of **11b** (0.57 g, 2.0 mmol) in pyridine (5 mL) at 0 ℃. After stirring at room temperature overnight, the reaction solution was poured into cold water, and the mixture was adjusted to pH 5 to 6 before being extracted with ethyl acetate, washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated *in vacuo* to afford **15**. White solid, yield 81%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.51 (s, 1H), 8.76 (d, J=8.1 Hz, 1H), 7.80 (d, J=7.3 Hz, 2H), 7.52 (t, J=7.2 Hz, 1H), 7.43 (t, J=7.4 Hz, 2H), 7.40 (d, J=8.4 Hz, 2H), 7.18 (d, J=8.3 Hz, 2H), 4.69 (m, 1H), 3.22 (dd, J=13.9, 4.2 Hz, 1H), 3.10 (dd, J=13.5, 11.0 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 173.2, 169.8, 166.5, 149.2, 136.0, 133.9, 131.5, 130.2 (C×2), 128.4 (C×2), 127.1 (C×2), 120.8 (C×2), 54.3, 35.7, 19.9. ESI-MS *m/z*: 350.2 [M＋Na]$^+$. Anal. calcd for $C_{18}H_{17}NO_5$: C 66.05, H 5.23, N, 4.28; found C 66.07, H 5.22, N 4.29.

Compounds **18a－18b**, **19a－19b** and **22a－22b** were synthesized according to literature.[9,13] And the all spectral data were in agreement with literature.

General synthetic protocol for glycosylation with 16 and 19 in the presence of AgOTf under ultrasonic irradiation

A solution of compound **16** (50 mg, 1.0 equiv.) and **19** (1.5 equiv.) in anhydrous CH_2Cl_2 (5 mL) and activated 4 Å molecular sieves (100 mg) was stirred for 0.5 h under argon atmosphere and dark at ambient temperature. Then, AgOTf (1.2 equiv.) was added. The mixture was sonicated at ambient temperature until intermediate **16** was completely consumed by TLC monitor. The reaction mixture was diluted with CH_2Cl_2 and filtered with Celite. The resulted filtrate was concentrated and purified to afford compounds **20** and **21**. (Caution: Because too long ultrasound reaction (⩾10 min) may raise the temperature inside the reaction vessel, the system should be cooled after 10 min before the next run if the reaction needs to continue.)

***N*-(*N*-Benzoyl-*L*-phenylalanyl)-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-*D*-galactopyranosyl)-*L*-phenylalanol (20a)** Colorless oil, 78.3 mg, yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75－7.72 (m, 2H), 7.52－7.50 (m, 1H), 7.45－7.42 (m, 2H), 7.33－7.28 (m, 5H), 7.21－7.16 (m, 3H), 7.11－7.09 (m, 2H), 6.87 (d, J=7.8 Hz, 1H), 6.19 (d, J=8.4 Hz, 1H), 5.40 (dd, J=3.4, 1.2 Hz, 1H),

5.22 (dd, *J*=10.6, 8.0 Hz, 1H), 5.05 (dd, *J*=10.4, 3.6 Hz, 1H), 4.80−4.75 (m, 1H), 4.33 (d, *J*=8.0 Hz, 1H), 4.20−4.11 (m, 3H), 3.83−3.78 (m, 1H), 3.63 (dd, *J*=10.2, 4.1 Hz, 1H), 3.44 (dd, *J*=10.2, 3.2 Hz, 1H), 3.20 (dd, *J*=13.7, 5.8 Hz, 1H), 3.14 (dd, *J*=13.6, 7.9 Hz, 1H), 2.81−2.74 (m, 2H), 2.15 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 170.4, 170.2, 170.1, 169.5 (C×2), 166.9, 137.2, 136.6, 133.7, 131.8, 129.4 (C×2), 129.1 (C×2), 128.7 (C×2), 128.5 (C×4), 127.1, 127.0 (C×2), 126.6, 101.1, 70.6 (C×2), 69.0, 68.8, 66.9, 61.3, 54.8, 50.2, 38.6, 36.6, 20.9, 20.7, 20.6 (C×2). ESI-MS *m/z*: 733.6 $[M+H]^+$. Anal. calcd for $C_{39}H_{44}N_2O_{12}$: C 63.92, H 6.05, N 3.82; found C 63.91, H 6.06, N 3.83.

***N*-[*N*-Benzoyl-*O*-acetyl)-*L*-tyrosyl]-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-*D*-galactopyranosyl)-*L*-phenylalanol (20b)** Colorless oil, 79.0 mg, yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.76 (d, *J*=7.2 Hz, 2H), 7.52 (t, *J*=7.4 Hz, 1H), 7.44 (t, *J*=7.6 Hz, 2H), 7.24−7.10 (m, 7H), 6.79 (d, *J*=8.4 Hz, 2H), 6.56 (d, *J*=10.2 Hz, 1H), 6.22 (d, *J*=8.8 Hz, 1H), 5.38 (dd, *J*=3.6, 0.8 Hz, 1H), 5.23 (dd, *J*=10.6, 8.0 Hz, 1H), 5.03 (dd, *J*=10.4, 3.6 Hz, 1H), 4.74−4.67 (m, 1H), 4.29−4.20 (m, 2H), 4.19 (d, *J*=8.0 Hz, 1H), 4.04 (dd, *J*=11.4, 6.0 Hz, 1H), 3.75 (t, *J*=6.4 Hz, 1H), 3.59 (dd, *J*=10.2, 3.6 Hz, 1H), 3.42 (dd, *J*=10.4, 2.8 Hz, 1H), 3.10 (dd, *J*=13.5, 4.8 Hz, 1H), 3.01 (dd, *J*=13.5, 4.8 Hz, 1H), 2.82−2.70 (m, 2H), 2.21 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 170.9, 170.4, 170.3 (C×2), 169.6, 167.3, 166.8, 155.3, 137.2, 133.7, 131.8, 130.6 (C×2), 129.1 (C×2), 128.6 (C×2), 128.5 (C×2), 128.1, 127.0 (C×2), 126.6, 115.8 (C×2), 101.2, 70.7, 70.5, 69.6, 68.9, 67.0, 61.6, 55.4, 50.2, 38.3, 36.5, 20.8, 20.7, 20.6 (C×2), 20.5. ESI-LRMS *m/z*: 791.7 $[M+H]^+$. Anal. calcd for $C_{41}H_{46}N_2O_{14}$: C 62.27, H 5.86, N 3.54; found C 62.27, H 5.85, N 3.55.

***N*-(*N*-Benzoyl-*L*-phenylalanyl)-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-*D*-glucopyranosyl)-*L*-phenylalanol (21a)** Colorless oil, 75.6 mg, yield 83%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.80−7.75 (m, 2H), 7.54−7.48 (m, 1H), 7.46−7.42 (m, 2H), 7.36−7.28 (m, 5H), 7.22−7.14 (m, 3H), 7.11−7.07 (m, 2H), 6.56 (d, *J*=7.2 Hz, 1H), 6.15 (d, *J*=8.0 Hz, 1H), 5.39 (dd, *J*=3.6, 1.2 Hz, 1H), 5.18 (dd, *J*=10.0, 7.6 Hz, 1H), 5.02 (dd, *J*=8.4, 3.6 Hz, 1H), 4.84−4.77 (m, 1H), 4.30 (d, *J*=7.6 Hz, 1H), 4.22−4.09 (m, 3H), 3.85−3.77 (m, 1H), 3.62 (dd, *J*=9.9, 3.2 Hz, 1H), 3.43 (dd, *J*=10.0, 3.2 Hz, 1H), 3.18 (dd, *J*=13.6, 5.6 Hz, 1H), 3.07 (dd, *J*=11.0, 7.6 Hz, 1H), 2.78−2.71 (m, 2H), 2.13 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 171.2, 170.4, 170.2, 170.1, 169.7, 167.0, 137.5, 136.8, 133.6, 131.5, 129.5 (C×2), 128.9 (C×2), 128.6 (C×2), 128.5 (C×2), 128.4 (C×2), 127.0, 126.8 (C×2), 126.5, 102.4, 70.7 (C×2), 69.1, 68.9, 66.7, 61.2, 55.0, 50.1, 38.5, 36.7, 21.1, 20.8, 20.6 (C×2). ESI-MS *m/z*: 733.3 $[M+H]^+$. Anal. calcd for $C_{39}H_{44}N_2O_{12}$: C 63.92, H 6.05, N 3.82; found C 63.90, H 6.08, N 3.81.

***N*-[*N*-Benzoyl-*O*-acetyl)-*L*-tyrosyl]-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-*D*-glucopyranosyl)-*L*-phenylalanol (21b)** Colorless oil, 68.7 mg, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.77 (d, *J*=6.8 Hz, 2H), 7.51 (t, *J*=5.6 Hz, 1H), 7.43 (t, *J*=8.0 Hz, 2H), 7.24−7.10 (m, 7H), 6.94 (d, *J*=7.6 Hz, 2H), 6.80 (d, *J*=8.4 Hz, 1H), 6.22 (d, *J*=8.8 Hz, 1H), 5.41 (dd, *J*=4.4, 1.6 Hz, 1H), 5.22 (dd, *J*=10.4, 8.0 Hz, 1H), 5.02 (dd, *J*=10.4, 3.6 Hz, 1H), 4.72−4.66 (m, 1H), 4.28−4.21 (m, 2H), 4.19 (d, *J*=8.0 Hz, 1H), 4.05 (dd, *J*=10.4, 6.4 Hz, 1H), 3.77 (t, *J*=6.4 Hz, 1H), 3.58 (dd, *J*=10.2, 3.6 Hz, 1H), 3.39 (dd, *J*=10.4, 3.6 Hz, 1H), 3.10 (dd, *J*=10.8, 4.8 Hz, 1H), 3.04−2.96 (m, 1H), 2.80−2.75 (m, 2H), 2.19 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 171.3, 170.5, 170.2 (C×2), 169.8, 167.1, 166.5, 155.6, 137.1, 133.6, 131.9, 130.7 (C×2), 129.0 (C×2), 128.5 (C×2), 128.4 (C×2), 127.9, 127.1 (C×2), 126.5, 116.0 (C×2), 102.3, 71.1, 70.7, 69.5, 69.1, 66.8, 61.7, 55.6, 50.3, 38.2, 36.4, 21.1, 20.8, 20.5 (C×2), 19.9. ESI-LRMS *m/z*: 791.5 $[M+H]^+$. Anal. calcd for $C_{41}H_{46}N_2O_{14}$: C, 62.27, H 5.86, N 3.54; found C 62.29, H 5.83, N 3.56.

General procedure for target compounds 2 and 3

The methanol solution of MeONa (4.0 equiv.) was dropwise added to a methanol solution of glycoside **20** or **21** (30 mg, 1.0 equiv.) at room temperature. After being stirred for 1.0 h, the reaction mixture was diluted with MeOH and neutralized with dowex H^+ resin to pH 5 to 6. The resin was filtered off and washed with MeOH. The resulted filtrate was concentrated and purified to give compounds **2** or **3**.

***N*-(*N*-Benzoyl-*L*-phenylalanyl)-*O*-(*β*-*D*-galactopyranosyl)-*L*-phenylalanol (2a)** White powder, 21.5 mg, yield 93%. m.p. 229−231 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 7.70−7.68 (m, 2H), 7.52−7.49 (m, 1H), 7.42 (t, *J*=8.0 Hz, 2H), 7.29−7.14 (m, 9H), 7.12−7.08 (m, 1H), 4.84 (dd, *J*=9.0, 6.4 Hz, 1H), 4.25−4.19 (m, 1H), 4.07 (d, *J*=8.0 Hz, 1H), 3.81−3.76 (m, 2H), 3.71−3.65 (m, 2H), 3.62−3.54 (m, 2H), 3.44 (dd, *J*=9.6, 3.6 Hz, 1H), 3.38−3.32 (m, 1H), 3.15 (dd, *J*=13.8, 6.4 Hz, 1H), 3.01−2.94 (m, 2H), 2.82 (dd, *J*=13.6, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ*: 173.3, 169.9, 139.7, 138.7, 135.3, 132.9, 130.5 (C×2), 130.4 (C×2), 129.5 (C×4), 129.3 (C×2), 128.5 (C×2), 127.8, 127.3, 105.5, 76.6, 74.8, 72.5, 71.9, 70.2, 62.6, 56.7, 52.6, 39.0, 38.0; HRMS-ESI *m/z*: 587.2368 $[M+Na]^+$; calcd for $C_{31}H_{36}N_2O_8Na$ 587.2364.

***N*-(*N*-Benzoyl-*L*-tyrosyl)-*O*-(*β*-*D*-galactopyranosyl)-*L*-phenylalanol (2b)** White powder, 17.0 mg, yield 77%. m.p. 227−229 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 9.11 (s, 1H), 8.40 (d, *J*=8.4 Hz, 1H), 7.89 (d, *J*=8.4 Hz, 1H), 7.80−7.76 (m, 2H), 7.52−7.48 (m, 1H), 7.45−7.41 (m, 2H), 7.24−7.11 (m, 5H), 7.07 (d, *J*=8.4 Hz, 2H), 6.60 (d, *J*=8.4 Hz, 2H), 4.85 (d, *J*=4.6 Hz, 1H), 4.72 (d, *J*=5.5 Hz, 1H), 4.63 (t, *J*=5.5 Hz, 1H), 4.59−4.52 (m, 1H), 4.36 (d, *J*=4.5 Hz, 1H), 4.09−4.04 (m, 2H), 3.61−3.41 (m, 5H), 3.36−3.27 (m, 3H), 2.95 (dd, *J*=13.7, 5.2 Hz, 1H), 2.91−2.77 (m,

2H), 2.69 (dd, J=13.5, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 171.2, 166.1, 155.6, 138.7, 134.1, 131.2, 130.1 (C×2), 129.3 (C×2), 128.4, 128.2 (C×2), 128.0 (C×2), 127.4 (C×2), 125.9, 114.8 (C×2), 103.7, 75.2, 73.4, 70.6, 69.6, 68.1, 60.5, 55.2, 50.3, 36.4, 36.3. HRMS-ESI m/z: 603.2315 $[M+Na]^+$; calcd for $C_{31}H_{36}N_2O_9Na$ 603.2313.

***N*-(*N*-Benzoyl-*L*-phenylalanyl)-*O*-(*β*-*D*-glucopyranosyl)-*L*-phenylalanol (3a)** White powder, 19.7 mg, yield 85%. m.p. 213—216 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.77—7.72 (m, 2H), 7.55—7.50 (m, 1H), 7.45—7.41 (m, 2H), 7.31—7.15 (m, 9H), 7.12—7.08 (m, 1H), 4.64 (dd, J=8.4, 6.0 Hz, 1H), 4.24—4.18 (m, 1H), 4.08 (d, J=8.0 Hz, 1H), 3.79—3.72 (m, 2H), 3.68—3.54 (m, 4H), 3.42 (dd, J=9.6, 3.6 Hz, 1H), 3.36 (dd, J=6.8, 5.6 Hz, 1H), 3.16 (dd, J=13.2, 6.0 Hz, 1H), 2.99—2.93 (m, 2H), 2.81 (dd, J=13.6, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.9, 168.7, 140.1, 139.3, 135.5, 133.0, 130.7 (C×2), 130.5 (C×2), 129.6 (C×2), 129.4 (C×2), 129.3 (C×2), 128.5 (C×2), 127.9, 127.3, 106.5, 76.7, 75.8, 72.4, 71.8, 69.8, 62.5, 56.5, 52.6, 39.1, 37.9; HRMS-ESI m/z: 587.2353 $[M+Na]^+$; calcd for $C_{31}H_{36}N_2O_8Na$ 587.2364.

***N*-(*N*-Benzoyl-*L*-tyrosyl)-*O*-(*β*-*D*-glucopyranosyl)-*L*-phenylalanol (3b)** White powder, 16.5 mg, yield 75%. m.p. 211—214 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.92 (s, 1H), 8.41 (d, J=7.6 Hz, 1H), 7.90 (d, J=6.4 Hz, 1H), 7.82—7.76 (m, 2H), 7.56—7.51 (m, 1H), 7.49—7.41 (m, 2H), 7.24—7.21 (m, 2H), 7.20—7.06 (5H, m), 6.61 (d, J=8.4 Hz, 2H), 4.80 (d, J=4.5 Hz, 1H), 4.71 (d, J=5.6 Hz, 1H), 4.62 (t, J=5.4 Hz, 1H), 4.60—4.54 (m, 1H), 4.37 (d, J=4.5 Hz, 1H), 4.09—4.04 (2H, m), 3.61—3.41 (m, 5H), 3.35—3.27 (m, 3H), 2.94—2.79 (m, 3H), 2.71 (dd, J=13.6, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.1, 166.5, 155.3, 139.0, 134.2, 131.4, 129.8 (C×2), 129.2 (C×2), 128.3, 128.2 (C×2), 127.9 (C×2), 127.5 (C×2), 126.0, 115.1 (C×2), 104.2, 75.3, 73.5, 70.8, 70.2, 68.5, 61.1, 55.6, 50.2, 36.5, 36.4. HRMS-ESI m/z: 603.2318 $[M+Na]^+$; calcd for $C_{31}H_{36}N_2O_9Na$ 603.2313.

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