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Note

Microwave-assisted efficient synthesis of aryl ketone β-C-glycosides from unprotected aldoses

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ABSTRACT

Condensation between unprotected aldoses and dibenzoylmethane catalyzed by $NaHCO_3$ in the cosolvents EtOH and H_2O (4:1) under microwave irradiation gave aryl ketone β-C-glycosides **6b–i** in higher yields (from 50% with *C*-riboside **6g** up to 99% with C-glucoside **6b**) and better anomeric selectivities (β-configuration >95%) in a shorter reaction time (90 min), compared with previous conventional methodologies. This method provides an attractive alternative to the existing means for the preparation of high value ketone β-C-glycosides.

C-Glycosides are used as building blocks for the synthesis of a variety of biologically important natural products[1,2] and synthetic compounds.[3–5] Kidamycin,[6] flavone C-glycoside,[7] β-C-glycoside analogs of KRN7000,[8] fagomine C-glycoside[9], and C-glycoside SGLT2 inhibitors[10] have been reported to exhibit antitumor, antibacterial, antiviral, antidiabetic, and glycosidase inhibitory activities. The interest in C-glycosides lies on the stability of the C-glycosidic linkage, which is resistant to both enzymatic and chemical hydrolysis. Therefore, stereoselective synthesis of C-glycosides has been a challenging task for organic chemists.

Alkyl ketone β-C-glycosides have been synthesized conveniently in alkaline aqueous media for many years.[11–16] This methodology is based on Knoevenagel condensation between the carbanion of the β-diketone **2a** and the aldehyde group of an unprotected aldose **1** (Scheme 1). β-Elimination of water, followed by intramolecular Michael cyclization gives the intermediate C-glycoside **5a**, which undergoes a retro-Claisen aldolization under the basic conditions with concomitant sodium carboxylate elimination to afford alkyl ketone β-C-glycoside **6a**. Pro-Xylane™, a *C*-xyloside alcohol preparing from the reduction of an alkyl ketone β-C-glycoside obtained by this method is found to stimulate sulfated glycosaminoglycan (GAG) synthesis and has recently been an example of 'Green' chemical used in cosmetics.[15] However, this method for the synthesis of aryl ketone β-C-glycosides is less reported, and involves long reaction time (12 h) and low yields (6% with *C*-xyloside,[15] 38% with *C*-galactoside and 64% with C-glucoside[16]). As a result, we need faster and more efficient methodologies for the synthesis of aryl ketone β-C-glycosides.

Compared to conventional heating techniques, such as use of an oil bath, microwave irradiation is a clean, cheap, and convenient method. This method of heating usually shows noticeable improvements such as shorter reaction times, higher yields, and better selectivities, so the use of microwave irradiation has become popular in recent years among chemists both to improve classical organic reactions and to promote new reactions. Nevertheless, the application of microwave heating in carbohydrate chemistry is less well investigated.[17–19] A microwave-assisted conversion of carbohydrates has been recently explored in our laboratory.[20]

In this paper, we describe a rapid and stereospecific synthesis of several aryl ketone β-C-glycoside derivatives catalyzed by inorganic base in EtOH–H_2O (4:1, v/v) via the microwave-assisted Knoevenagel condensation between unprotected aldoses and dibenzoylmethane, which gives moderate to excellent yields and almost exclusively (>95%) the thermodynamic β-configuration as shown by ^1H and ^{13}C NMR spectroscopy. To the best of our knowledge, this methodology has not been previously reported.

In order to optimize the reaction conditions, we chose D-glucose as a model substrate for this condensation. First, the effect of various solvents and inorganic bases was investigated (Table 1). Surprisingly, the solvent had a tremendous effect on the reaction yield. When the reaction was performed in pure water (entry 1), only trace amounts of aryl ketone β-C-glucoside **6b** were obtained. This low yield (7%) can be explained by the poor solubility of dibenzoylmethane in pure water. However, we were pleased to observe that the combined use of ethanol with water made

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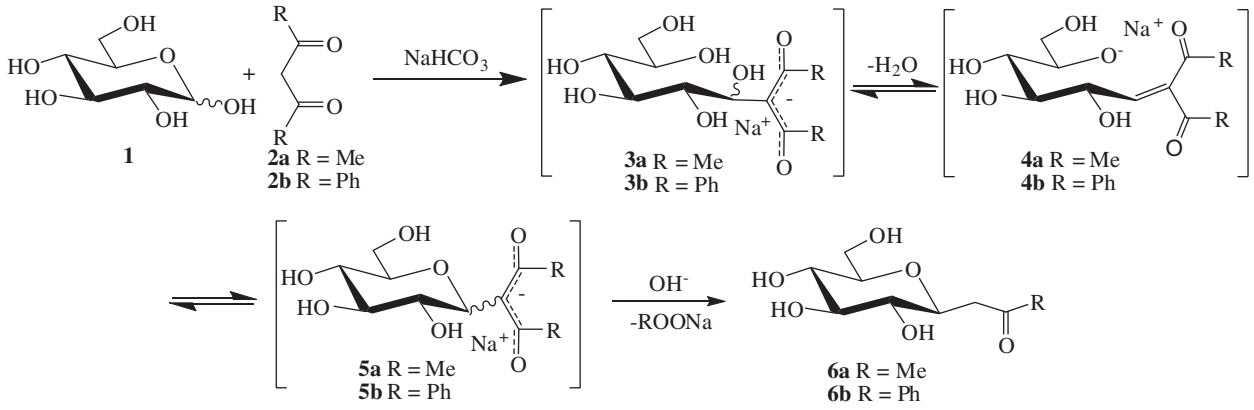


Scheme 1. Condensation of D-glucose with a β-diketone.

dibenzoylmethane more soluble and led to great improvements in the yields (entries 2–4), the increase in the volume ratio of ethanol to water raised the yield of C-glucoside **6b**, and the best yield (97%) was achieved at the ratio of 4:1 (entry 4). Then, after the maximum, the yield dropped rapidly and was only 12% when pure ethanol was used as solvent (entry 5), because of the poor solubility of D-glucose in pure ethanol. Other co-solvents were also tested (entries 6–9), such as THF–H_2O (4:1), CH_3CN–H_2O (4:1), DMF–H_2O (4:1), DMSO–H_2O (4:1), which all gave low yields. The lowest yield (4%) in THF–H_2O (4:1) may probably be correlated to the low boiling point (66 °C) and low microwave-absorbing (loss tangent, tan δ = 0.047) of the solvent THF.[21]

Besides the difference of solvents, dissimilarities were observed when changing the species of inorganic bases. D-Glucose was condensed with dibenzoylmethane in co-solvents EtOH–H_2O (4:1) using either sodium bicarbonate, sodium carbonate, potassium carbonate, potassium hydroxide, or sodium hydroxide as catalyst. The yield of C-glucoside **6b** decreased accordingly with increasing the catalyst basicity (entries 3 and 10–13). Thus, sodium bicarbonate proved to be the best choice of catalyst.

Following the initially promising result, we then turned our attention to the optimization of the reaction conditions with respect to microwave irradiation power, irradiation time, and dibenzoylmethane (or sodium bicarbonate)–glucose molar ratio.

Two different reaction conditions were studied by varying the microwave irradiation power from 200 to 800 W (Fig. 1). It appeared that irradiation power had no significant impact on the reaction outcome. The yield of C-glucoside **6b** reached 97% at 400 W in condition A.

Table 1
Effects of various solvents and inorganic bases on the yield of C-glucoside **6b**[a]

Entry	Solvent	Base	Time (min)	Yield[b] (%)
1	H_2O	$NaHCO_3$	90	7
2	EtOH–H_2O (1:1)	$NaHCO_3$	90	59
3	EtOH–H_2O (2:1)	$NaHCO_3$	60	78
4	EtOH–H_2O (4:1)	$NaHCO_3$	60	97
5	EtOH	$NaHCO_3$	90	12
6	THF–H_2O (4:1)	$NaHCO_3$	60	4
7	CH_3CN–H_2O (4:1)	$NaHCO_3$	60	58
8	DMF–H_2O (4:1)	$NaHCO_3$	60	69
9	DMSO–H_2O (4:1)	$NaHCO_3$	60	59
10	EtOH–H_2O (2:1)	K_2CO_3	60	68
11	EtOH–H_2O (2:1)	Na_2CO_3	60	64
12	EtOH–H_2O (2:1)	KOH	60	49
13	EtOH–H_2O (2:1)	NaOH	60	39

[a] Reactions were performed with D-glucose (1 mmol), dibenzoylmethane (2 mmol), base (2 mmol, except 1 mmol for K_2CO_3 or Na_2CO_3), and 5 mL solvent under microwave irradiation with a power of 400 W, refluxing for the given time.
[b] Determined by HPLC.

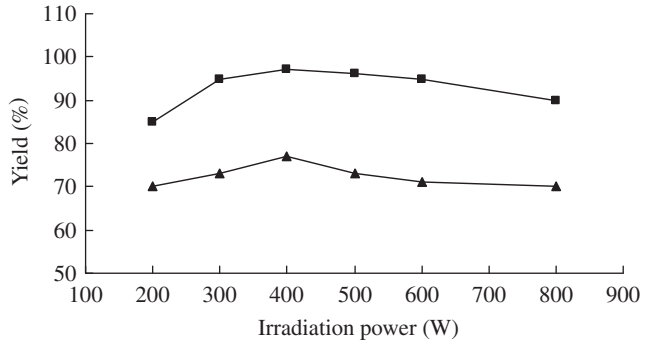


Figure 1. Effect of microwave irradiation power on the yield of C-glucoside **6b**. Condition A (■): D-glucose (1 mmol), dibenzoylmethane (2 mmol), $NaHCO_3$ (2 mmol), and 5 mL EtOH–H_2O (4:1) under microwave irradiation with the given power, reflux, 60 min; condition B (▲): D-glucose (1 mmol), dibenzoylmethane (1.5 mmol), $NaHCO_3$ (1.5 mmol), and 5 mL EtOH–H_2O (4:1) under microwave irradiation with the given power, reflux, 90 min. The yield was determined by HPLC.

Figure 2 shows the influence of irradiation time on the yield of C-glucoside **6b** at an irradiation power of 400 W. For the condensation of glucose with dibenzoylmethane, the yield reached the maximum (almost 100%) after 90 min, and decreased remarkably at longer irradiation times as side reactions increased. The by-product 2,5-disubstituted furan was formed from a reversible ring closure between the carbonyl group of ketone β-C-glycoside and the C-2′ hydroxyl group to give a hemiacetal, followed by dehydration.[12]

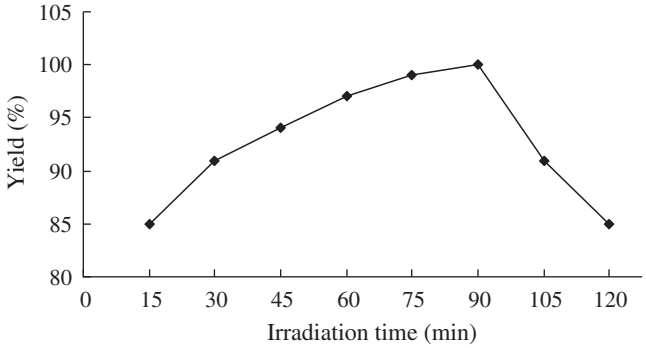


Figure 2. Influence of microwave irradiation time on the yield of C-glucoside **6b**. Reactions were performed with D-glucose (1 mmol), dibenzoylmethane (2 mmol), $NaHCO_3$ (2 mmol), and 5 mL EtOH–H_2O (4:1) under microwave irradiation with a power of 400 W, refluxing for the given time. The yield was determined by HPLC.

By changing the dibenzoylmethane (or sodium bicarbonate)–glucose molar ratio, a comparison between microwave irradiation and classical oil bath heating has been performed to analyze the different effects between the two heating systems (Fig. 3). Experiments under classical oil bath heating have been conducted using conditions similar to those under microwave irradiation: same quantity of reactants, heating in a thermostatic oil bath at the refluxing temperature. The yield of C-glucoside **6b** under microwave irradiation appeared to be strongly dependent on the dibenzoylmethane (or sodium bicarbonate)–glucose molar ratio. The highest yield (almost 100%) was provided at a dibenzoylmethane (or sodium bicarbonate)–glucose molar ratio of 2:1 and an irradiation power of 400 W. Higher molar ratio (>2:1) did not lead to better results. Oil bath heating had no significant impact on the reaction outcome, and gave lower yields (80–91%) with longer reaction time (15 h). A possible reason for the higher yields under microwave irradiation is that 'specific' or 'nonthermal' microwave effects cause a decrease in activation energy or an increase in the pre-exponential factor. Furthermore, the condensation performed in the co-solvents EtOH–H_2O (4:1) by oil bath heating gave higher yields than previous reports.[12,15,16,22]

Based on these results, we next explored the synthetic generality of this microwave-assisted condensation protocol. Thus, a series of unprotected aldose substrates, including D-glucose, D-mannose, D-galactose, D-xylose, D-arabinose, D-ribose, D-maltose monohydrate, and D-lactose monohydrate, all of which exist as common glycosidic components in many C-glycosides, were used for the condensation with dibenzoylmethane into aryl ketone β-C-glycosides **6b**–**i** (Table 2). The nature of the aldoses had an impact on the reaction yields (from 50% with *C*-riboside **6g** up to 99% with C-glucoside **6b**).

C-Glucoside **6b** (entry 1) was separated by silica gel column chromatography and the structure was established by ^{1}H NMR, ^{13}C NMR, and ESI-LCMS spectra. In the ^{1}H NMR (300 MHz) spectrum, the H-1′ signal was a characteristic doublet of doublet doublets with a large coupling constant ($J_{1',2'}$ 9.3 Hz), indicating a trans-diaxial orientation of the C-1′ and C-2′ hydrogen atoms as expected for β-D configured pyranose moiety adopting a $^4C_1$ conformation. Analogously, the ^{1}H and ^{13}C NMR spectral data were consistent with a β anomeric configuration and a $^4C_1$ (D) conformation for other products as well as compared with previous literature reports.[15,16,22,23] *C*-Mannoside **6c** was also prepared with an excellent yield (entry 2). *C*-Galactoside **6d** afforded a good yield (entry 3), and was found to further dehydrate to give 2,5-disubstituted furan by TLC analysis.[12] It is worth pointing out that in the ^{1}H NMR (300 MHz, DMSO-d_6) spectra of *C*-pentoside (entries 4–6), the hydrogen atoms of the hydroxyl groups were all doublet peaks, indicating the carbon which –OH connected to only had one hydrogen atom, namely there was no $HOCH_2$– group. Therefore, all the three *C*-pentosides (**6e**–**g**) were pyranose rather than furanose isomers. In the case of *C*-arabinoside **6f**, the anomeric configuration was determined through NOESY spectra (500 MHz, D_2O). The significant Nuclear Overhauser Effect between H-1′ with H-5′a indicated that compound **6f** was β-configuration, not α-configuration (Fig. 4). Indeed, we noticed that the disaccharyl C-glycosides were obtained along with the monosaccharyl C-glycosides as monitored by TLC analysis, which could be attributed to the degradation of either disaccharide or disaccharyl C-glycosides or both in the conditions of the reaction. Consequently, disaccharide only afforded moderate yields (55% with *C*-maltoside **6h**, 60% with *C*-lactoside **6i**, entries 7 and 8). In conclusion, this approach gave higher yields and better anomeric selectivities (β-configuration >95%) in a shorter reaction time (90 min), compared with previously reported methods.[12,15,16,22]

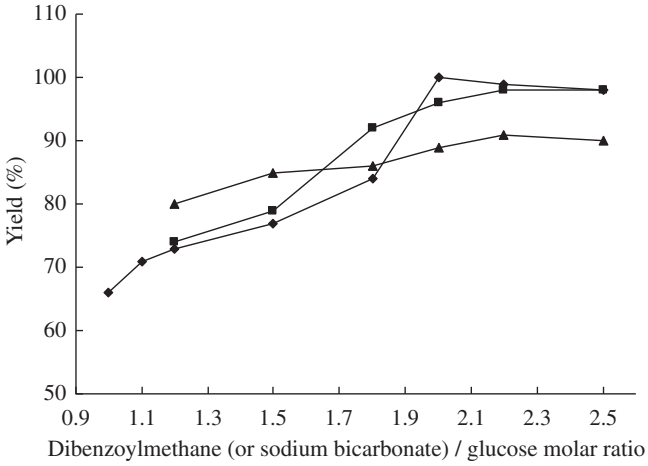


Figure 3. Comparison between microwave irradiation and oil bath heating at different dibenzoylmethane (or sodium bicarbonate)/glucose molar ratio. Reaction conditions: D-glucose (1 mmol), dibenzoylmethane, $NaHCO_3$ (the amount given in this figure), and 5 mL EtOH–H_2O (4:1) under microwave irradiation with a power of 300 W (■) or 400 W (♦), refluxing for 90 min, or under oil bath heating (▲), refluxing for 15 h. The yield of C-glucoside **6b** was determined by HPLC.

In summary, we have described a detailed optimization procedure for the microwave-assisted synthesis of aryl ketone β-C-glycoside in D-glucose case and investigated the scope of this methodology for the preparation of several C-glycoside derivatives. This one-step protocol involves direct condensation between unprotected aldoses and dibenzoylmethane catalyzed by inorganic base in EtOH–H_2O (4:1). Faced with environmental concerns, this methodology offers attractive features, including high yields, excellent anomeric selectivities, and short reaction times. In our opinion, the present method of the microwave-assisted Knoevenagel condensation provides an efficient alternative to the existing means to synthesize ketone β-C-glycosides, and could open new vistas for the preparation of high value ketone β-C-glycosides that could be expanded to large scale production.

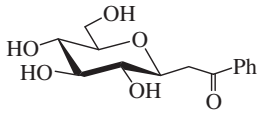
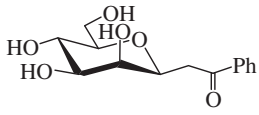
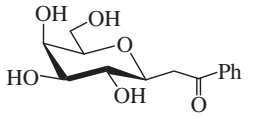
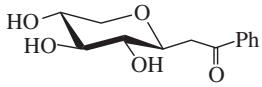
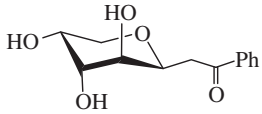
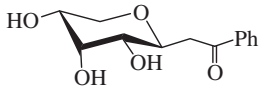
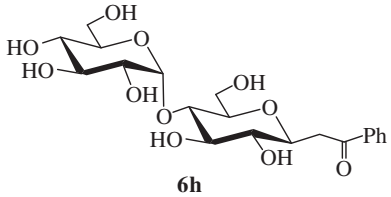
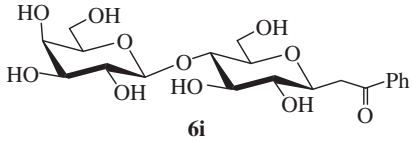
1. Experimental

Microwave irradiation was performed in a MAS-1 microwave reactor apparatus (Shanghai Sineo Microwave Chemistry Technology Co., Ltd). Melting points (mp) were determined on a WRS-1B digital melting-point apparatus (Shanghai Shenguang Instrument Co., Ltd). Optical rotations were measured on a WZZ-2B automatic polarimeter (Shanghai Precision & Scientific Instrument Co., Ltd). ^{1}H, ^{13}C, and NOESY NMR spectra were recorded on a Bruker DRX-300 (DRX-400 or AVANCE III 500) spectrometer. ESI-LCMS spectra were obtained on a Shimadzu LCMS-2010EV mass spectrometer. HRESIMS were recorded on a Thermo Finnigan TSQ Quantum-LC/MS/MS spectrometer. Samples were analyzed on a Shimadzu LC-20A High Performance Liquid Chromatography with internal standard peracetylated C-glucoside **6b** derivative (purity >99%), using a SPD-20A prominence UV/vis detector which was set at 254 nm and a Shimadzu Shim-pack VP-ODS (5 μm, 4.6 × 250 mm) LC Column with the eluent MeOH–H_2O (7:3, v/v) at a flow rate of 1 mL min^{-1}. All chemicals were analytical pure and used without further purification, except internal standard peracetylated C-glucoside **6b** derivative was prepared in our own laboratory.

1.1. General procedure for condensation under microwave irradiation

Unprotected aldose (1 mmol), dibenzoylmethane (449 mg, 2 mmol), sodium bicarbonate (168 mg, 2 mmol), and 5 mL (or 10 mL for disaccharide) EtOH–H_2O (4:1) were introduced and

Table 2
Microwave-assisted Knoevenagel condensation of unprotected aldoses with dibenzoylmethane catalyzed by $NaHCO_3$ in the co-solvents EtOH–H_2O (4:1)[a]

Entry	Substrate	Product **6b–i**[b]	δ (H-1′), ($J_{1',2'}$/Hz) δ (C-1′)	Yield[d] (%)	Ref.[e]
1	D-Glucose	 **6b**	3.77 (9.3) 79.6	99	12,15,22,23
2	D-Mannose	 **6c**	4.02 (—[c]) 80.0	98	22,23
3	D-Galactose	 **6d**	3.73 (9.0) 76.2	71	16
4	D-Xylose	 **6e**	3.57 (—[c]) 77.2	89	15,22,23
5	D-Arabinose	 **6f**	3.60 (—[c]) 77.3	53	—
6	D-Ribose	 **6g**	3.91 (9.6) 71.8	50	22,23
7	D-Maltose monohydrate	 **6h**	3.78 (9.2) 78.1	55	—
8	D-Lactose monohydrate	 **6i**	3.82 (9.2) 78.5	60	—

[a] Reaction conditions: unprotected aldose (1 mmol), dibenzoylmethane (2 mmol), $NaHCO_3$ (2 mmol), and 5 mL (or 10 mL for disaccharide) EtOH–H_2O (4:1) under microwave irradiation with a power of 400 W, reflux, 90 min.
[b] All the products were characterized by ^1H NMR, ^{13}C NMR, and MS spectra.
[c] Anomeric proton peaks overlapped with sugar skeletal proton peaks.
[d] Isolated yields after purification by column chromatography on silica gel.
[e] ^1H NMR, ^{13}C NMR, MS spectra data, and yields were compared with these references.

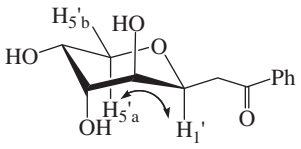

6f

Figure 4. Nuclear Overhauser effect observed between H-1′ with H-5′a in *C*-arabinoside **6f**.

mixed in a 50 mL single-necked flask equipped with a reflux condenser. The microwave irradiation power and irradiation time were set at the experimental conditions given above. When microwave irradiation started, the EtOH–H_2O (4:1) began to reflux within 1 minute. After the microwave reactor was turned off, the solutions were allowed to cool to rt and treated with cation exchange resin (sodium form) to reach pH 5. The resin was filtered and EtOH was evaporated. The aq soln was washed with CH_2Cl_2 and concentrated. The products were analyzed by HPLC or purified by column chromatography on silica gel (step gradient from 20:1 to 4:1 EtOAc–EtOH) with the yields given in Table 2.

1.1.1. 1-Phenyl-2-*C*-(β-D-arabinopyranosyl)ethanone (6f)

Yield: 53% as a white solid; mp 145–147 °C; $[\alpha]_D^{20}$ −10.0 (*c* 1.0, MeOH); ^1H NMR (500 MHz, D_2O): δ 3.13–3.18 (dd, 1H, J = 9.4,

16.7 Hz, H-2a), 3.41–3.45 (dd, 1H, J = 2.3, 16.7 Hz, H-2b), 3.47–3.49 (m, 1H, H-4′), 3.50 (s, 1H, H-2′), 3.53–3.55 (dd, 1H, J = 3.3, 9.5 Hz, H-3′), 3.66–3.72 (m, 2H, H-5′), 3.87 (s, 1H, H-1′), 7.41–7.44 (t, 2H, J = 7.8 Hz, Ph),7.55–7.58 (t, 1H, J = 7.4 Hz, Ph), 7.84–7.86 (d, 2H, J = 7.7 Hz, Ph); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.06–3.15 (dd, 1H, J = 9.0, 15.9 Hz, H-2a), 3.22–3.33 (m, 4H, H-2b, H-4′, H-2′, H-3′), 3.50–3.62 (m, 3H, H-5′, H-1′), 4.46–4.47 (d, 1H, J = 3.6 Hz, OH), 4.67–4.69 (d, 1H, J = 5.4 Hz, OH), 4.94–4.96 (d, 1H, J = 5.1 Hz, OH), 7.48–7.53 (t, 2H, J = 7.5 Hz, Ph), 7.59–7.64 (m, 1H, Ph), 7.91–7.94 (dd, 2H, J = 1.5, 8.0 Hz, Ph); ^{13}C NMR (75 MHz, DMSO-d_6): δ 41.1, 68.9, 69.9, 70.5, 73.9, 77.3, 128.0, 128.6, 133.0, 137.1, 198.7; ESI-MS: m/z = 275.1 $[M+Na]^+$; HRESIMS: m/z = 253.1059 $[M+H]^+$ (calcd for $C_{13}H_{17}O_5$ 253.1071).

1.1.2. 1-Phenyl-2-*C*-(β-D-maltosyl) ethanone (6h)

Yield: 55% as a white solid; mp 230–232 °C (dec.); $[\alpha]_D^{20}$ +74.9 (c 1.0, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 3.10–3.16 (m, 1H), 3.21–3.28 (m, 2H), 3.30–3.72 (m, 11H), 3.75–3.81 (ddd, 1H, J = 3.2, 9.2 Hz, H-1′), 5.26–5.27 (d, 1H, J = 3.6 Hz, H-1″), 7.40–7.44 (t, 2H, J = 8.0 Hz, Ph), 7.54–7.58 (t, 1H, J = 7.6 Hz, Ph), 7.84–7.86 (d, 2H, J = 7.2 Hz, Ph); ^{13}C NMR (100 MHz, D_2O): δ 41.2, 60.5, 60.7, 69.4, 71.8, 72.7, 72.9, 73.2, 75.7, 77.1, 77.8, 78.1, 99.7, 128.4, 128.9, 134.2, 136.4, 202.6; ESI-MS: m/z = 467.1 $[M+Na]^+$; HRESIMS: m/z = 467.1517 $[M+Na]^+$ (calcd for $C_{20}H_{28}O_{11}Na$ 467.1524).

1.1.3. 1-Phenyl-2-*C*-(β-D-lactosyl) ethanone (6i)

Yield: 60% as a white solid; mp 170–172 °C; $[\alpha]_D^{20}$ +26.9 (c 1.0, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 3.12–3.19 (m, 1H), 3.23–3.30 (m, 1H), 3.36–3.47 (m, 3H), 3.50–3.57 (m, 3H), 3.58–3.69 (m, 4H), 3.71–3.79 (m, 2H), 3.79–3.85 (ddd, 1H, J = 3.2, 9.2 Hz, H-1′), 4.32–4.33 (d, 1H, J = 7.6 Hz, H-1″), 7.42–7.46 (t, 2H, J = 8.0 Hz, Ph), 7.56–7.60 (t, 1H, J = 7.6 Hz, Ph), 7.87–7.89 (d, 2H, J = 7.8 Hz, Ph); ^{13}C NMR (100 MHz, D_2O): δ 41.2, 60.1, 61.1, 68.6, 71.0, 72.6, 73.0, 75.4, 75.7, 75.9, 78.4, 78.5, 102.9, 128.4, 128.9, 134.2, 136.4, 202.7; ESI-MS: m/z = 466.8 $[M+Na]^+$; HRESIMS: m/z = 467.1538 $[M+Na]^+$ (calcd for $C_{20}H_{28}O_{11}Na$ 467.1524).

1.2. General procedure for condensation under oil bath heating

D-Glucose (180 mg, 1 mmol), dibenzoylmethane, sodium bicarbonate (the amount given in Fig. 3), and 5 mL EtOH–H_2O (4:1) were introduced and mixed in a 25 mL single-necked flask equipped with a reflux condenser. The reaction mixture was stirred at the boiling point of the co-solvents for 15 h. After the reactions were complete, the mixture was treated as described above.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2010.11.027.

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