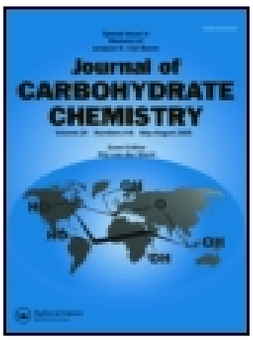

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Synthesis of aryl α-*O*-L-rhamnopyranoside by two-step reaction in one pot

Nianping Liu[a], Xiangguang Tian[a], Zekun Ding[a], Yongda Zhou[a], Wan Zhang[a], Qingbing Wang[a], Yi Zhang[a], Yijun Gu[b,§], and Jianbo Zhang[a]

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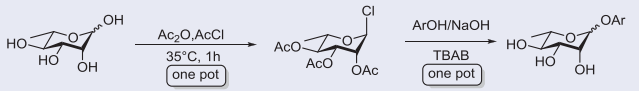
ABSTRACT

The title compounds were conveniently synthesized by a phase transfer catalyzed approach in two steps and one pot using the rhamnopyranosyl chloride as key intermediate. The two-step one-pot procedure is more convenient and environmentally friendly, compared to the published synthetic routes. Besides, the structure-reactivity relationship and the plausible mechanism for this base-catalyzed glycosylation were discussed by means of the Hammett equation.

GRAPHICAL ABSTRACT



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Rhamnoside; rhamnopyranosyl chloride; phase transfer catalysis; α-O-aryl rhamnoside

Introduction

Aryl α-L-rhamnosides are important functional biomolecule in glycobiological researches.[1–7] For instance, *para*-nitrophenyl α-L-rhamnopyranoside, which releases *para*-nitrophenol in the presence of α-L-rhamnosidase, is featured with its chromogenic properties.[7–9] It can also serve as a synthetic intermediate in enzymatic glycosylation for the preparation of other rhamnosides and bioactive compounds.[10–12]

Several preparation methods for the aryl α-L-rhamnoside have been reported in the literature.[13] As a classic synthetic method towards glycosides, Köenigs-Knorr reaction was first applied to the target compounds by Shintaro Kamiya et al.[14] However, highly poisonous mercuric cyanide and mercuric bromide were used as catalysts in this synthesis, and furthermore the overall yield was rather low. The

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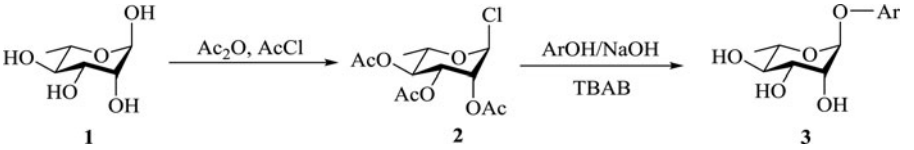
§Present address: Room 328, Building 41, Yueyang Road 320, Shanghai Institute of Biochemistry and Cell Biology/National Center of Protein Sciences Shanghai, Chinese Academy of Sciences, Shanghai 200032, China.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lcar.



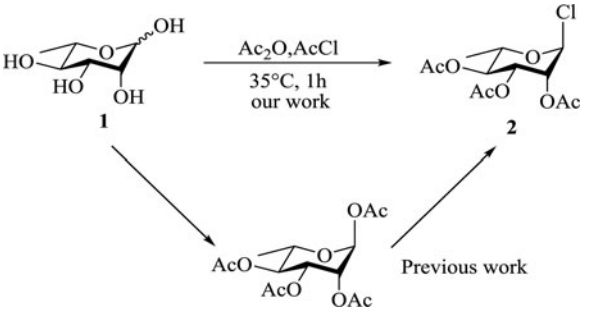
Scheme 1. Synthesis of α-*O*-aryl L-rhamnopyranoside.

same authors also reported the use of Helferich glycosylation for the synthesis as a modification. As a result, this shortened the synthesis to three steps, where the glycosylation reaction was successfully catalyzed by *p*-toluenesulfonic acid, antimonyl trichloride or other Lewis acids. The glycosylation yields ranged from 40 to 60%. The same type of reaction was also reported by Westphal, Garegg and Nishio,[7, 15, 16] with $ZnCl_2$, $SnCl_4$ and $BF_3{\cdot}OEt_2$ as catalysts, and the glycosylation yields were 38%, 53% and 36.4%, respectively. Apparently, in these synthetic methods either the involved reagents were highly toxic or the reactions were not easy to handle as strictly anhydrous condition was required.

With the purpose of developing an eco-friendly synthetic strategy, a series of methods were explored by our group.[17] A convenient and effective method was finally found, in which the title compounds were synthesized in only two steps (Scheme 1). Initially, L-rhamnose (**1**) was acetylated and chlorinated in the presence of acetyl chloride to prepare 2,3,4-tri-*O*-acetyl-α-L-rhamnosyl chloride (**2**); then **2** was directly converted into the target molecule **3** under phase transfer catalytic condition.

Results and discussion

A single-step synthesis of aromatic α-D-glucoside was reported.[18–20] We wanted to applied it to the direct synthesis of aromatic α-L-rhamnoside, but the attempt failed. Thus, we came up with a two-step method using the glycosyl halide as the key intermediate. As far as we are concerned, glycosyl chloride and bromide are one of the most commonly applied glycosylation reactions. Compared with rhamnosyl chloride, rhamnosyl bromide is more easily decomposed under most glycosylation conditions, so we tried to applied rhamnosyl chloride as glycosyl donor in the synthesis of aromatic α-L-rhamnosides in consideration of its stability and convenient preparation method.[21–24] The previous strategies to obtain rhamnosyl chloride



Scheme 2. Synthetic strategies towards rhamnosyl chloride.

were usually focused on indirect methods (Scheme 2), which are time consuming synthetic procedures.[23, 25–27]

In order to circumvent this problem, we carried out the acetylation step with acetic anhydride and acetic chloride under acidic conditions using H_2SO_4/SiO_2 as catalyst, which allowed for chlorination as well, to establish a one-pot synthetic route (Scheme 2)with a good yield (67.5%). This method has advantages including short route, simple operation, and non-use of toxic reagent, and solvent-free condition. Here, acetyl chloride was employed as both an acetylating and a chlorinating reagent for L-rhamnose. Modest heating condition (room temperature to 35 °C) was required to initiate the reaction, and then the reaction was spontaneously accelerated by the catalyst. The rhamnosyl chloride **2** was characterized with ^{1}H NMR.[26]

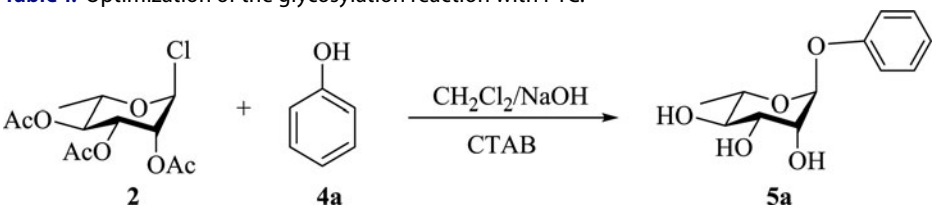
Inspired by the alkaline condition for deacetylation and the glycosylation method we have developed in alkaline systems,[9] we explored to achieve glycosylation and deacetylation steps in the same vessel. Different alkaline systems, such as CH_3ONa/CH_3OH, $NaOH/H_2O$, pyridine/H_2O, *etc*, were examined.[28] The CH_3ONa/CH_3OH and pyridine/H_2O systems could rarely offer the target product. The $NaOH/H_2O$ system only resulted in a little amount of the product with too many by-products. In order to improve the yield, we tried phase transfer catalyst (PTC) condition,[28] which gave good results. Thus, the CTAB/$NaOH/H_2O$ system was further optimized using a model reaction (Table 1).

Initially, we tried the reaction of **2** with phenol (**4a**) (Table 1) in the presence of 0.3 equiv. of cetyltrimethyl ammonium bromide (CTAB) as the phase transfer catalyst and 10% NaOH as the promoter in CH_2Cl_2 at 20 °C, which gave a 25.6% yield. Next, we examined the influence of the amount of phenol on the glycosylation. As is demonstrated in Table 1, with the equivalency of phenol ranging from 1.1 to 2.0, the reaction proceeded rather slowly and the yields were low. In addition, the formation of by-products increased when the reaction time was lengthened (entries 2–3). We also found that with 2.5 equiv. of phenol, the reaction proceeded well and the product was obtained in acceptable yield (entry 4). However, the yield of the desired compound **5a** did not increased dramatically when 3.0 equiv. of phenol was utilized (entry 5).

Subsequently, we explored the influence of different phase transfer catalysts, such as tetrabutyl ammonium bromide (TBAB), cetyltrimethyl ammonium bromide (CTAB), benzyltriethyl aminium chloride (TEBA) and tetrabutyl ammonium hydrogen sulfate (TBAHS), and further optimized the conditions (entry 4 and 6–12).[21] It was indicated that 0.2 equiv. of TBAB (entry 10) greatly promoted the reaction, considering the yield and time-efficiency.

In addition, the type and equivalency of the base used in the system were also explored (entry 10 and entries 13–18). We tried different bases such as NaOH, $NaCO_3$, Bu_4NOH and KOH in 7.5 equiv., and the results showed NaOH was the best. Next, we tested different equivalencies of NaOH (entry 10 and entries 16–18). Apparently, 7.5 equiv. of 10% NaOH was superior. It is noteworthy that the yield improved dramatically when 10% NaOH was added into the system in batches instead of addition at once (entries 10 and 19–23), and the 1:1:1 volume ratio of batches gave the optimal results.

Table 1. Optimization of the glycosylation reaction with PTC.



Entry	Eq. (phenol)	PTC	Eq. (PTC)	Base	Eq. (base)	Batch addition method of base (v/v)	T (°C)	Time (h)	Yield (%)[a]
1	1.1	CTAB	0.3	NaOH	7.5	1:0 [c]	20	24	25.6
2	1.5	CTAB	0.3	NaOH	7.5	1:0	20	24	27.2
3	2.0	CTAB	0.3	NaOH	7.5	1:0	20	24	35.5
4	2.5	CTAB	0.3	NaOH	7.5	1:0	20	12	48.2
5	3.0	CTAB	0.3	NaOH	7.5	1:0	20	12	49.1
6	2.5	TBAB	0.3	NaOH	7.5	1:0	20	10	59.0
7	2.5	TEBA	0.3	NaOH	7.5	1:0	20	16	52.1
8	2.5	TBAHS	0.3	NaOH	7.5	1:0	20	12	53.6
9	2.5	TBAB	0.1	NaOH	7.5	1:0	20	15	51.2
10	2.5	TBAB	0.2	NaOH	7.5	1:0	20	10	59.8
11	2.5	TBAB	0.5	NaOH	7.5	1:0	20	10	58.2
12	2.5	TBAB	1.0	NaOH	7.5	1:0	20	9	55.7
13	2.5	TBAB	0.2	Na_2CO_3	7.5	1:0	20	24	n.d[b]
14	2.5	TBAB	0.2	Bu_4NOH	7.5	1:0	20	10	n.d
15	2.5	TBAB	0.2	KOH	7.5	1:0	20	10	58.6
16	2.5	TBAB	0.2	NaOH	2.5	1:0	20	24	42.1
17	2.5	TBAB	0.2	NaOH	5.0	1:0	20	16	45.2
18	2.5	TBAB	0.2	NaOH	10.0	1:0	20	10	43.8
19	2.5	TBAB	0.2	NaOH	7.5	2:1	20	12	66.8
20	2.5	TBAB	0.2	NaOH	7.5	1:1	20	10	68.9
21	2.5	TBAB	0.2	NaOH	7.5	1:2	20	10	72.5
22	2.5	TBAB	0.2	NaOH	7.5	1:4	20	10	69.4
23	2.5	TBAB	0.2	NaOH	7.5	1:1:1	20	10	74.7
24	2.5	TBAB	0.2	NaOH	7.5	1:1:1	0	24	—
25	2.5	TBAB	0.2	NaOH	7.5	1:1:1	30	5	90.0
26	2.5	TBAB	0.2	NaOH	7.5	1:1:1	40	3	—

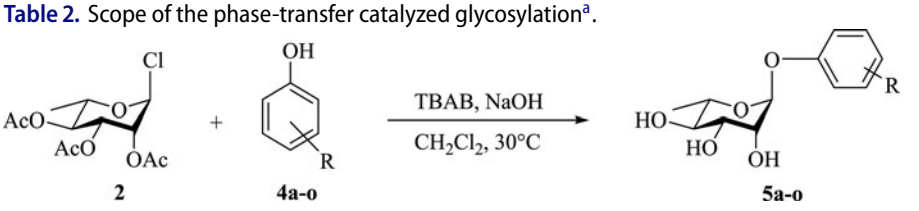
[a]Isolated yield [b]Not detected [c]Adding base into the reaction system at one-time or in batches, for example, 2:1 means batch adding at volume ratio of 2:1

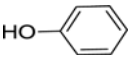
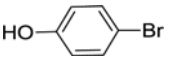
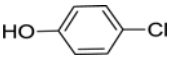
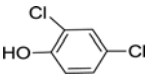
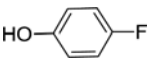
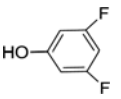
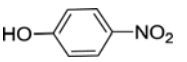
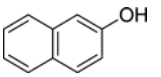
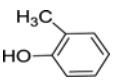
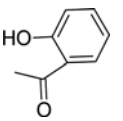
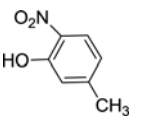
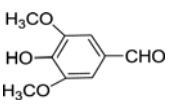
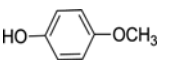
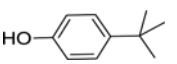
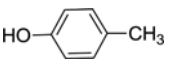
Finally, we explored the influence of temperature on the reaction ranged from 0 to 40°C (entries 23–26). The best result was achieved when the glycosylation was treated at room temperature (entry 25). Satisfactorily, with TBAB (0.2 equiv) as the phase transfer catalyst, 10% NaOH (7.5 equiv.) as the promoter that was added into the reaction system in batches and CH_2Cl_2 as solvent, the reaction at 30 °C could afford **5a** in a 90% overall yield (Table 1, entry 25).

Encouraged by these results, we further extended the scope of this reaction to a series of phenols **4a-4o** as glycosyl acceptors, as illustrated in Table 2 (entries 1–15). The reactions proceeded completely in 4.5–6 hours in good to excellent yields (63.6%–98.2%) for both the phenols with electron-withdrawing substituents (entries 2–8) and the phenols with electron-donating substituents (entries 13–15), as well as those with hindered substituents (entries 9–12). All the structures of products were confirmed by NMR and HR-MS data.

Besides, we further ascertained the stereochemical property and bioactivity of *para*-nitrophenyl α-L-rhamnopyranoside **5g** as a representative glycosylation

Table 2. Scope of the phase-transfer catalyzed glycosylation[a].

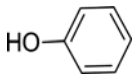
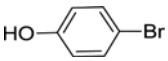
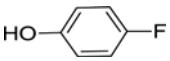
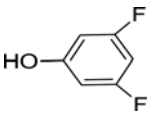
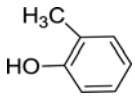
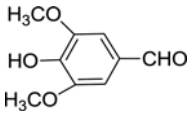
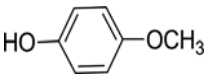
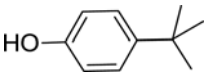
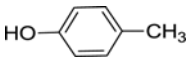


Entry	Acceptor	Product	Time (h)	Yield (%)[b]
1		**5a**	5	90.0
2		**5b**	5	84.0
3		**5c**	5	86.1
4		**5d**	4.5	81.0
5		**5e**	5	86.0
6		**5f**	5	81.5
7		**5g**	4.5	63.6
8		**5h**	5.5	89.4
9		**5i**	6	94.7
10		**5j**	5	83.0
11		**5k**	5	62.0
12		**5l**	5	75.0
13		**5m**	5.5	98.2
14		**5n**	5.5	93.8
15		**5o**	5	92.8

[a]Reaction conditions: TBAB (0.2 equiv.), rhamnosyl chloride (1.0 equiv.) phenols (2.5 equiv.), batch adding 10%NaOH, CH_2Cl_2, 30°C [b]Isolated yield.

product. The compound was recrystallized from 95% ethanol *via* solvent evaporation at room temperature as colorless bulk crystals. The crystal structures were determined to find out their stereochemistry and solid-state conformations. Crystal data and structural refinement are specified in elsewhere,[7, 9] which confirmed the α-configuration of the product. Additionally, the enzymatic hydrolysis assay was also tested to confirm its bioactivity and stereochemistry.[4, 29] The enzymatic hydrolysis of **5a** was carried out in 0.05 M acidic acid/sodium acetate buffer (pH 4.0, 4.5 and 5.0) with incubation at 40 °C. In the reaction procedure, the hydrolytic rate of the rhamnoside kept constant with the authentic compound. One unit of enzymatic activity was defined as the amount, which released 1 mol of *para*-nitrophenol per minute in the buffer (pH 4.0), which is consistent with the reported activity of the commercial naringinase (EC 3.2.1.40). Therefore, all the results showed that the product we obtained is alpha-configuration anomer.

Table 3. Reaction of rhamnosyl chloride with phenols on large scales.

Entry	Accept	Product	Time(h)	Yield(%)[a]
1		**5a**	8	89.9
2		**5b**	7	81.5
3		**5e**	7	81.5
4		**5f**	7	79.2
5		**5i**	9	91.2
6		**5l**	8	70.7
7		**5m**	9	94.5
8		**5n**	9	89.8
9		**5o**	8	87.8

[a]Isolated yield.

Furthermore, it is crucial for the reactions to achieve on large scales. As described in Table 3, it was shown that **2** was glycosylated with different phenols on three-grams scales to afford satisfactory yields, which provided the evidence for the industrial application of the synthetic method.

Notably, as shown in Table 2, it was evident that substituents exerted a significant influence on the reaction yields. The results indicated that electro-withdrawing substituents reduced the yields, while electron-donating substituents gave excellent results. However, influential factors on the reaction yield are rather complex. Herein, we reported our studies about the impact of *para*-substituents in the phenols on the final yields (Table 4).

Because the k/k_H is proportional to the yield/yield$_H$, we chose yield/yield$_H$ as the substitution plugging into Hammett equation and drew the corresponding Hammett curve.[30–32] However, when we chose classical constant σ_p to plug into the Hammett equation, we obtained an unsatisfactory linear correlation coefficient ($R^2 = 0.9571$). Based on this result, we suspected that the nucleophiles of this reaction was not the phenol molecules (ArOH) but the phenolic anions (ArO^-), which was formed as an extremely strong nucleophile when phenol contained strong electron-withdrawing functional group such as nitro, as the acceptors during glycosylation progress. Thus, we needed to introduce another constant σ_p^- to fit the Hammett equation.[30–32] Under this condition, we found that the *para*-substituent constants could fit the Hammett equation with superb linear relationship ($R^2 = 0.9977$), as depicted in Figure 1.[30–34]

Therefore, we proposed a plausible mechanism for the new PTC synthesis of aryl α-L-rhamnoside as depicted in Scheme 3.[27] First, the reaction proceeded quickly *via* the formation of a glycosyl cation that could be stabilized by the neighboring acetyl group at O-2 via the formation of an oxacarbenium ion intermediate. As a

Table 4. The reaction rates of *para*-substituent phenols and substituent constants[a].

Entry	Substituent	Yield, %	Yield/Yield $_H$	lg(Yield/Yield$_H$)	σ_p
1	p-OCH_3	98.2	1.091	0.038	−0.27
2	p-CMe_3	93.8	1.042	0.018	−0.15
3	p-CH_3	92.8	1.031	0.013	−0.14
4	p-C_6H_5	89.4	0.993	−0.003	0.005
5	p-H	90.0	1	0	0
6	p-F	86.0	0.956	−0.02	−0.15
7	p-Cl	86.1	0.957	−0.019	0.24
8	p-Br	84.0	0.933	−0.03	0.26
9[c]	p-NO_2	63.6	0.707	−0.151	1.27

[a]Phenols and anilinium ions where a lone pair of electrons on the O- or NH_2- group could be delocalized into substituents. This problem was solved by defining a new constant σ_p^- obtained from the phenol or aniline data distinguished from classic constant σ_p.

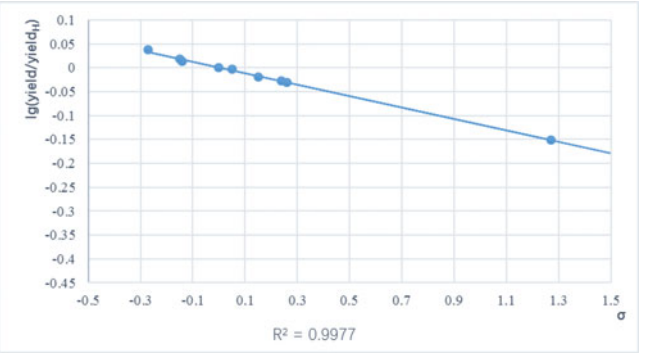
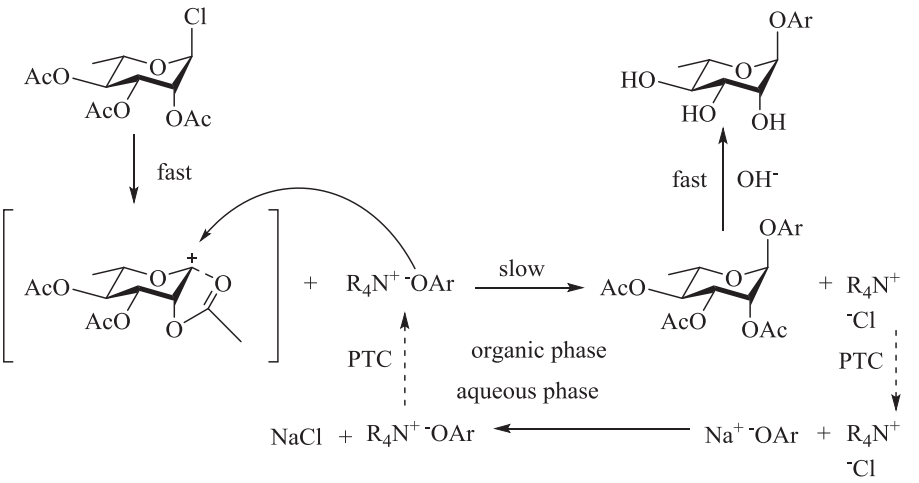


Figure 1. Hammett curve of the reaction of 2,3,4-tri-*O*-acetyl-α-L-rhamnosyl chloride with phenols[a]. [a] linear correlation coefficient $R^2 = 0.9977$.



Scheme 3. A plausible mechanism for PTC synthesis of aryl α-L-rhamnoside involving the neighboring group participation.

result, this reactive intermediate could only be glycosidated by the attack of phenolic anion formed under the phase transfer catalyst condition from the backside, which is the rate-determining step. This can explain the unique α-selectivity and high yield of glycosides, as well as the influence of substituents in the phenol on the reaction yields. At last, the deacetylation reaction was completed to obtain the desirable products. Therefore, the nucleophilicity of nucleophilic reagent is of great significance in this one-pot glycosylation.

Conclusion

In brief, we have successfully developed an efficient and green method for the synthesis of aromatic rhamnosides under PTC conditions with TBAB as the catalyst and 10% NaOH as the promoter, which was achieved in CH_2Cl_2 at 30 °C. This synthetic method has the features, such as easy accessibility of all regents used, avoiding the utilization of heavy metallic salt or other toxic reagents, short reaction steps, simple

workup procedures and high yield, as compared with previous approaches. It is a novel synthetic method that may have industrial scale applications.

Experimental

General Methods

^{1}H NMR spectra were recorded on a Bruker DRX-500 (500 MHz) spectrometer with Me_4Si as internal standard. Mass spectra were detected on Agilent 5973N and Agilent 6120 EI mass spectrometer. Elemental analyses were taken on a Vario El III instrument. All the reagents were purchased with purity of AR. All the reactions were monitored using TLC on silica gel HF_{254} [10–40 μm, Yantai, China (0.2 mm)]. Reaction products were purified by flash chromatography using Silica gel 60 (300–400 mesh or 100–200 mesh, Yantai, China). Authentic *para*-nitrophenyl-α-L-rhamnoside for enzymatic assay was from SIGMA (St. Louis, Missouri). α-L-rhamnosidase was *Penicillum decumbens* naringinase from SIGMA (St. Louis, Missouri), which specific activity is 300 U/g.

2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl chloride (2)

1.00 g rhamnose·H_2O (**1**) (5.49 mmol) and 4.7 ml CH_3COCl (65.9 mmol) were stirred for 15hr with an oil bath heated at 35 °C at the beginning stage for 1h. Nitrogen atmosphere was needed to protect the reaction. Then the mixture was diluted by dichloromethane and washed by saturated sodium bicarbonate, dried over anhydrous Na_2SO_4 and evaporated to a brown yellow syrupy, which was purified by column chromatography. After chromatography, a yellowish syrupy 1.32 g was obtained. Yield: 67.5%. Colorless crystalloid could be obtained after recrystallized from petroleum ether: ethyl acetate = 1:1 (1.27 g, 65%).

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 5.94(d, 1H, $J = 2$ Hz), 5.57(dd, 1H, $J = 4$, 10 Hz), 5.39(s, 1H), 5.14(t, 1H, $J = 9.5$ Hz), 4.18(m, 1H), 2.16, 2.08, 2.00(3s, 9H), 1.27(d, 3H, $J = 6.2$ Hz).

p-nitrophenyl-α-L-rhamnoside (3)

0.78 mL10%NaOH aqueous was dropped slowly into a mixture of 251 mg 2,3,4-tri-O-acetyl-α-L-rhamnosyl chloride (0.81 mmol), 282 mg *para*-nitrophenol (2.03 mmol), 89 mg cetyl alkyl trimethyl ammonium bromide (0.24 mmol) and 5 mL CH_2Cl_2. Two hours later, 1.10 mL 10% NaOH aqueous was added slowly into reaction system in batches in the next 6 hours.

The reaction was detected by thin layer chromatography until the glycosyl chloride disappeared. Then the reaction mixture was directly separated by flash chromatography and 74.4 mg white powder was obtained in yield of 32%. It can be recrystallized from absolute methanol to give the title compound in yield of 36% (72.5 mg). Mp: 179–180°C.

^{1}H-NMR (CD_3OD, 500M Hz): δ 8.22(m, 2H), 7.25(m, 2H), 5.60(d, 1H, J = 2.0 Hz), 4.03(q, 1H, J = 2, 4 Hz), 3.84(q, J = 3.3 Hz, 1H), 3.55 (m, 1H), 3.48 (t, 1H, J = 9.5 Hz), 1.22(d, 3H, J = 6.0 Hz);

^{13}C-NMR (CD_3OD, 125M Hz): δ 150.83, 141.85, 124.75, 115.62, 98.01, 71.62, 70.15, 69.75, 69.34, 16.07.

Elemental Analysis: Calcd. for $C_{12}H_{15}NO_7 \cdot CH_3OH$: C, 49.21; H, 6.04; N, 4.42. Found: C, 49.27; H, 5.82; N, 4.82 (Crystal from methanol). Calcd. for $C_{12}H_{15}NO_7 \cdot H_2O$: C, 47.53; H, 5.65; N, 4.62. Found: C, 47.77; H, 5.52; N, 4.62 (Crystal from PE/EA).

Hydrolysis of para-nitrophenyl-α-L-rhamnoside by α-rhamnosidase

A reaction mixture consisting of 0.2 ml of 10 mM *para*-nitrophenyl-α-rhamnoside (**3**), 0.1 ml sodium acetate buffer (pH 4.0, 4.5 and 5.0) and 0.2 ml of enzyme solution was incubated at 40°C. The reaction was terminated by the addition of 2 ml of 1.0 M Na_2CO_3. The absorbance of *para*-nitrophenol was measured at 400 nm. One unit of enzymatic activity was defined as the amount, which liberated 1 µmol of *para*-nitrophenol per minute under pH 4.0.

phenyl-α-L-rhamnoside (5a)

^{1}H-NMR (CD_3OD, 500M Hz): δ 7.27(m, 2H); 7.06(m, 2H); 6.99(t,1H, J = 7.4 Hz), 5.42(s,1H);4.00(q,1H, J = 1.8 Hz); 3.85(q,1H, J = 3.4 Hz); 3.65(m,1H), 3.47(t,1H, J = 9.5 Hz); 1.23(d,3H, J = 6.2 Hz);

ESI-LRMS: Calcd for $C_{12}H_{16}O_5Na$ ($M+Na^+$) 263.07, found 263.00

p-bromophenyl-α-L-rhamnoside (5b)

^{1}H-NMR (CD_3OD,500M Hz): δ 7.42 (d, 2H, J = 8.0 Hz), 7.01(d, 2H, J = 9.0 Hz), 5.40(s, 1H), 3.99(s, 1H), 3.82(q, 1H, J = 3.3 Hz), 3.60(m, 1H), 3.45(t, 1H, J = 9.5 Hz), 1.22(d, 3H, J = 6.0 Hz)

^{13}C-NMR (CD_3OD, 125 MHz): δ155.9, 133.4, 119.4, 115.3, 99.9, 73.7, 72.1, 71.9, 70.8, 18.0;

ESI-LRMS: Calcd for $C_{12}H_{15}BrO_5$ ($M+H^+$) 318.01, found 318.25

p-chlorophenyl-α-L-rhamnoside (5c)

^{1}H-NMR (CD_3OD, 500 MHz): δ 7.28 (m, 2H), 7.05(m,2H), 5.40(s,1H), 3.98(dd,1H, J = 3.3 Hz), 3.81(q,1H, J = 3.3 Hz), 3.60(m,1H), 3.43(t,1H, J = 9.5 Hz), 1.22(d,3H, J = 6.2 Hz);

^{13}C-NMR (CD_3OD,125 MHz): δ 156.5, 130.4, 128.0, 118.9, 99.9, 73.7, 72.1, 71.9, 70.7, 18.0;

ESI-LRMS: Calcd for $C_{12}H_{15}ClO_5Na$ ($M+Na^+$) 297.05, found 296.90

2,4-di-chlorophenyl-α-L-rhamnoside (5d)

^{1}H-NMR (CD_3OD,500 MHz): δ7.43(d,1H, J = 8.0 Hz), 7.24(m,2H), 5.48(s,1H), 4.06(d,1H, J = 1.25 Hz), 3.89(q, 1H, J = 3.3 Hz), 3.60(m,1H), 3.46(t, 1H, J = 9.5 Hz), 1.22(d,3H, J = 7.0 Hz);

^{13}C-NMR (CD_3OD, 125 MHz): δ152.0, 130.8, 128.9, 128.3, 125.5, 118.7, 100.4, 73.5, 72.1, 71.8, 71.2, 17.9;

ESI-LRMS: Calcd for $C_{12}H_{15}Cl_2O_5$ ($M+H^+$) 309.0, found 309.2

p-flurophenyl-α-L-rhamnoside (5e)

^{1}H-NMR (CD_3OD, 500 MHz): δ 7.00(d, 2H, J = 9.0 Hz), 6.94(t, 2H, J = 17.4 Hz), 5.38(s, 1H), 4.05(d,1H, J = 1.25 Hz), 3.88(q, 1H, J = 3.3 Hz), 3.67(m, 1H), 3.49(t, 1H, J = 9.5 Hz), 1.23(d, 3H, J = 6.2 Hz)

ESI-LRMS: Calcd for $C_{12}H_{15}FO_5Na$ ($M+Na^+$) 281.08, found 280.98

3,5-diflurophenyl-α-L-rhamnoside (5f)

^{1}H-NMR(CD_3OD, 500 MHz): δ 6.65 (m, 2H),6.51(m, 1H), 5.44(s, 1H), 4.02(s, 1H), 3.82(q, 1H, J = 3.4 Hz), 3.58(m, 1H), 3.35(t, 1H, J = 9.5 Hz),1.23(d, 3H, J = 6.2 Hz)

ESI-LRMS: Calcd for $C_{12}H_{14}F_2O_5Na$ ($M+Na^+$) 299.07, found 299.14

p-nitrophenyl-α-L-rhamnoside (5g)

^{1}H-NMR (CD_3OD, 500 MHz): δ 8.22(m, 2H), 7.25(m, 2H), 5.60(d, 1H, J = 2.0 Hz), 4.03(dd, 1H, J = 2.0, 4.0 Hz), 3.84(q, 1H, J = 3.4 Hz), 3.55 (m, 1H), 3.48 (t, 1H, J = 9.5 Hz), 1.22(d, 3H, J = 6.2 Hz)

ESI-LRMS: Calcd for $C_{12}H_{15}ClO_5Na$ ($M+Na^+$) 297.05, found 296.90

2- naphthyl-α-L-rhamnoside (5h)

^{1}H-NMR (CD_3OD, 500 MHz): δ7.78 (d, 2H, J = 8.8 Hz), 7.73(d, 1H, J = 8.2 Hz),7.47(d, 1H, J = 1.8 Hz),7.42(t, 1H, J = 1.5 Hz),7.33(t, 1H, J = 15.0 Hz),7.20(q, 1H, J = 8.9 Hz), 5.59(s, 1H), 4.08(t, 1H, J = 2.7 Hz),3.93(q, 1H, J = 3.4 Hz), 3.71(m, 1H), 3.49(t, 1H, J = 9.5 Hz),1.25(d, 3H, J = 6.2 Hz);

ESI-LRMS: Calcd for $C_{16}H_{18}O_5Na$ ($M+Na^+$) 313.10, found 313.08

o-methylphenyl-α-L-rhamnoside (5i)

^{1}H-NMR (CD_3OD, 500 MHz): δ 7.12(m,3H); 6.89(t, 1H, J = 6.9 Hz); 5.43(s, 1H); 4.04(s, 1H); 3.90(q, 1H, J = 3.4 Hz); 3.63(m, 1H); 3.47(t, 1H, J = 9.5 Hz); 2.22(s, 3H), 1.24(d, 3H, J = 6.2 Hz).

ESI-LRMS: Calcd for $C_{13}H_{19}O_5Na$ ($M+H^+$) 255.1, found 255.6

o-acetylphenyl-α-L-rhamnoside (5j)

^{1}H-NMR (CD_3OD, 500 MHz): δ7.63(m, 1H), 7.46(m, 1H), 7.33(d, 1H, $J = 8.0$ Hz), 7.06(dd, 1H, $J = 11.0$ Hz), 5.56(d, 1H, $J = 1.5$ Hz), 4.10(t, 1H, $J = 2.7$ Hz), 3.88(q, 1H, $J = 3.5$ Hz), 3.62(q, 1H, $J = 6.5$ Hz), 3.50(t, 1H, $J = 9.5$ Hz), 2.59(s, 3H), 1.25(d, 3H, $J = 6.5$ Hz)

ESI-LRMS: Calcd for $C_{14}H_{18}O_6Na$ ($M+Na^+$) 305.10, found 305.17

5-methyl-2-nitrophenyl-α-L-rhamnoside (5k)

^{1}H-NMR (CD_3OD, 500 MHz): δ7.75(d, 1H, $J = 8.5$ Hz), 7.26(s, 1H), 6.97(d, 1H, $J = 8.0$ Hz), 5.59(d, 1H, $J = 1.5$ Hz), 4.04(q, 1H, $J = 2.0$ Hz), 3.87(q, 1H, $J = 3.5$ Hz), 3.64(d, 1H, $J = 6.0$ Hz), 3.47(t, 1H, $J = 9.5$ Hz), 2.42(s, 3H), 1.24(d, 3H, $J = 6.5$ Hz)

ESI-LRMS: Calcd for $C_{13}H_{17}NO_7Na$ ($M+Na^+$)322.09, found 322.17

2,6-dimethoxyl-4-aldehydephenyl-α-L-rhamnoside (5l)

^{1}H-NMR(CD_3OD,500 MHz): δ9.86(s, 1H), 7.22(s, 1H), 5.39(d, 1H, $J = 1.5$ Hz), 4.23(d, 1H, $J = 3.5$ Hz), 4.14(q, 1H, $J = 3.3$ Hz), 3.89(d, 6H, $J = 3.5$ Hz), 3.83(s, 1H), 1.21(d, 3H, $J = 6.5$ Hz)

ESI-LRMS: Calcd for $C_{15}H_{20}O_8Na$ ($M+Na^+$) 351.11, found 351.17

p-methoxylphenyl-α-L-rhamnoside (5m)

^{1}H-NMR (CD_3OD, 500 MHz): δ6.98(d, 2H, $J = 6.9$ Hz), 6.86(d, 2H, $J = 6.8$ Hz), 5.29(s,1H), 3.98(s, 1H), 3.82(s, 1H), 3.75(s, 3H), 3.68(q, 1H, $J = 6.5$ Hz), 3.45(t, 1H, $J = 9.5$ Hz), 1.23(d, 3H, $J = 6.5$ Hz);

ESI-LRMS: Calcd for $C_{13}H_{18}O_6Na$ ($M+Na^+$) 293.10, found 293.08

p-tert-butylphenyl-α-L-rhamnoside (5n)

^{1}H-NMR (CD_3OD, 500 MHz): δ7.31(d, 2H, $J = 8.8$ Hz), 6.97(d, 2H, $J = 8.8$ Hz), 5.37(d, 1H, $J = 1.5$ Hz), 3.98(q, 1H, $J = 9.7$ Hz), 3.84(q, 1H, $J = 3.5$ Hz), 3.66(q, 1H, $J = 1.4$ Hz), 3.45(t, 1H, $J = 9.5$ Hz), 1.29(s, 10H), 1.23(d, 3H, $J = 6.2$ Hz).

ESI-LRMS: Calcd for $C_{16}H_{24}O_5Na$ ($M+Na^+$) 319.15, found 319.09

p-methylphenyl-α-L-rhamnoside (5o)

^{1}H-NMR (CD_3OD, 500 MHz): δ7.07(d, 2H, $J = 8.3$ Hz), 6.92(d, 2H, $J = 8.5$ Hz), 5.35(d, 1H, $J = 1.5$ Hz), 3.98(q, 1H, $J = 3.1$ Hz), 3.82(dd, 1H, $J = 9.5$ Hz), 3.64(m, 1H), 3.43(t, 1H, $J = 19.0$ Hz), 2.27(s, 3H), 1.21(d, 3H, $J = 6.2$ Hz)

ESI-LRMS: Calcd for $C_{13}H_{18}O_5Na$ ($M+Na^+$) 277.10, found 277.11

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