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An Improved C-Deglycosylation of Mangiferin to Norathyriol

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Norathyriol (**1**, Figure 1), also known as 1,3,6,7-tetrahydroxyxanthone, is a bioactive metabolite of mangiferin (**2**), a polyhydroxyxanthone C-glycoside isolated from the leaves of *Mangifera indica*.[1] Due to its diverse therapeutic properties, including anticancer,[2] antidiabetic,[3] and antihyperuricemia activities,[4] norathyriol has attracted the attention of biologists as well as synthetic and medicinal chemists.

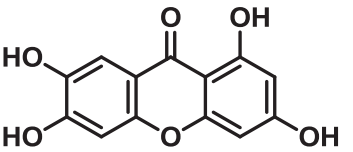

Figure 1 Structure of norathyriol (**1**).

To date, several concise synthetic routes to norathyriol have been reported.[5–7] However, *C*-deglycosylation of mangiferin is considered more convenient and economical than the total synthesis *via* Friedel-Crafts acylation. Although specific intestinal bacteria are able to produce norathyriol from mangiferin,[8,9] production *via* chemical reactions would be more practical and effective for obtaining a large amount of pure norathyriol than biological *C*-deglycosylation. Although acid-labile *O*-glycosides are readily hydrolyzed to the corresponding aglycones under mild acidic conditions,[10] cleavage of the *C*-glycosidic bond of mangiferin requires the use of hydriodic acid (HI), the strongest hydrohalic acid. Moreover, an excess of phenol is used in the *C*-deglycosylation of mangiferin as well as other *C*-glycosides (*Scheme 1*).[11–13] For example, Ding *et al.* used 60 mL of phenol (28.8 equiv.) in HI solution to obtain 4.2 g of crude norathyriol (68% yield) by *C*-deglycosylation of mangiferin (10 g).[13] We sought to find alternative conditions for the *C*-deglycosylation of mangiferin that lead to equivalent outcomes without the use of an excess of phenol.[14] In this article, we describe a practical and mild method for the *C*-deglycosylation of mangiferin for the preparation of norathyriol.

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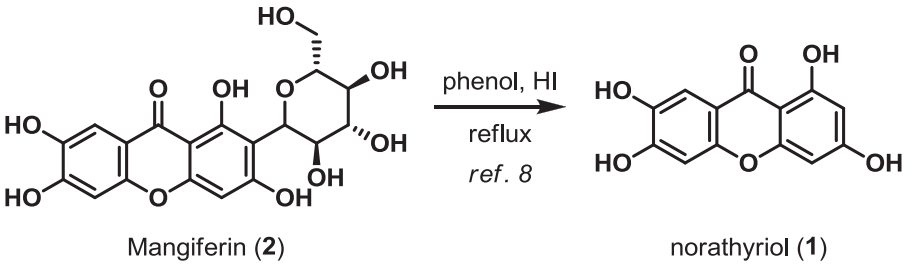
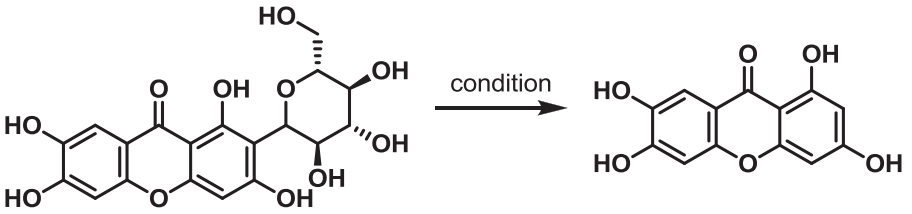
This article is dedicated to the memory of Prof. J.-P. Anselme.



Scheme 1 *C*-Deglycosylation of mangiferin to norathyriol.

Initially the *C*-deglycosylation of mangiferin to norathyriol was performed according to the literature procedure.[11] A mixture of mangiferin (300 mg per test) was heated at 150°C with 1.1 g of phenol (16.5 equiv.) and HI (>57%, 1.5 mL) for 6 h and 130 mg (70%) of crude norathyriol was obtained as a brown solid (entry 1, *Table 1*) as previously reported. To determine the reaction conditions that can provide norathyriol without the use of phenol, we attempted to cleave the *C*-glycosidic bond of mangiferin in the same way as *O*-deglycosylation using only strong acids such as HI (entry 2), H_2SO_4 (entries 3 and 4), HBr (entry 5), and *c*-HCl (entry 6). However, the desired norathyriol could not be

Table 1
Optimization of *C*-deglycosylation of mangiferin to norathyriol using resorcinol.



entry[a]	additive (equiv.)	acid (mL)	results (%)[b]
1	phenol (16.5)	*c*-HI (1.5)	**1** (70%)
2	—	*c*-HI (10)	No reaction
3	—	*c*-H_2SO_4 (10)	No reaction
4	—	50% H_2SO_4 (10)	No reaction
5	—	*c*-HBr (10)	No reaction
6	—	*c*-HCl (10)	No reaction
7	resorcinol (1.5)	*c*-HI (1.5)	**1** (68%)
8	resorcinol (1.5)	*c*-HCl (10)	**1** (70%)
9	resorcinol (1.5)	6N HCl (10)	**1** (71%)
10	resorcinol (1.5)	3N HCl (10)	**1** (71%)
11	phenol (16.5)	*c*-HCl (10)	No reaction

[a]Mixture of mangiferin (300 mg per test), additive, and acid was refluxed for 6 h. [b]Yield of crude norathyriol.

obtained when mangiferin was refluxed without phenol in the acidic aqueous solution. The proposed mechanism for aryl *C*-glycosylation involves nucleophilic attack on the anomeric carbon of the activated sugar by an activated aromatic ring.[15] Considering that glycosylation and deglycosylation are mutually reversible *via* nucleophilic displacement at the anomeric center,[16] we supposed that water is not sufficiently nucleophilic to attack the anomeric carbon of mangiferin, and an aryl nucleophile is essential for *C*-deglycosylation.

Resorcinol can undergo diverse substitution reactions as a nucleophile similar to phenol. However, resorcinol exhibits greater nucleophilicity[17] and may be more biocompatible than phenol.[18] We hypothesized that resorcinol would be a more reactive substitute for phenol in the *C*-deglycosylation of mangiferin. According to our expectation, heating mangiferin in HI with 1.5 equivalents of resorcinol produced norathyriol (entry 7). Moreover, with the use of resorcinol, mangiferin could be readily deglycosylated to norathyriol under relatively mild acidic conditions, such as refluxing in concentrated (entry 8) or even moderately dilute (entries 9 and 10) hydrochloric acid. After purification by column chromatography and recrystallization from ethanol, pure norathyriol was obtained as a yellowish solid, as previously reported.[11–13] In addition, no problems were encountered in this reaction using 1.5 equivalents of resorcinol and 3N hydrochloric acid when the reaction was scaled up to 10 g. On the other hand, norathyriol was not obtained when mangiferin was refluxed with phenol and concentrated hydrochloric acid (entry 11). These results seem to imply that resorcinol is a more reactive additive for *C*-deglycosylation than phenol, and the former enables the efficient generation of norathyriol from mangiferin under milder reaction conditions.

In summary, this article describes an improved mild method for the preparation of norathyriol by *C*-deglycosylation of mangiferin using resorcinol as an additive. This method may have applications in the *C*-deglycosylation of other *C*-glycosides, as well.

Experimental Section

Mangiferin (95%; Xian Lyphar Biotech Co.) and other reagents were obtained commercially and were used without further purification. Flash column chromatography was performed using silica gel 60 (230−400 mesh, Merck) with the indicated solvents. Thin-layer chromatography (TLC) was performed using 0.25-mm silica gel plates (Merck). Mass spectra were obtained using a VG Trio-2GC-MS instrument, and high-resolution mass spectra were obtained using a JEOL JMS-AX 505 WA unit. ^{1}H and ^{13}C spectra were recorded on a Bruker Advance III 800 (800 MHz) instrument in deuteriodimethylsulfoxide (DMSO-d_6). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent. ^{1}H NMR data are reported in the order of chemical shift, multiplicity (s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and/or multiple resonances), number of protons, and coupling constant in hertz (Hz).

Norathyriol (1). To a solution of mangiferin (300 mg, 0.710 mmol) in 3 N HCl (10 mL) was added resorcinol (117 mg, 1.06 mmol) at ambient temperature. The reaction mixture was refluxed for 6 h and then cooled to ambient temperature. The reaction mixture was slowly quenched with saturated $NaHCO_3$ solution and stirred for 30 min. The brown precipitate was collected by filtration, washed with H_2O, and then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (gradient 50% EtOAc in *n*-hexane to only EtOAc) to afford 131 mg (71%) of the crude norathyriol. After recrystallization with ethanol, pure norathyriol was obtained as a yellowish solid,

mp. >320°C (decomp.). The NMR spectral data were identical with those reported[8]: ^{1}H NMR (800 MHz, DMSO-d_6) δ 13.16 (s, 1 H), 10.76 (bs, 1H), 7.37 (s, 1H), 6.85 (s, 1H), 6.31 (d, 1H, $J = 2.1$ Hz), 6.14 (d, 1H, $J = 2.1$ Hz); ^{13}C NMR (800 MHz, DMSO-d_6) δ 178.9, 164.7, 162.6, 157.3, 154.0, 150.9, 143.7, 111.8, 108.0, 102.6, 101.6, 97.7, 93.6; LR-MS (FAB+) *m/z* 261 ($M+H^+$); HR-MS (FAB+) calcd for $C_{13}H_9O_6$ ($M+H^+$) 261.0394; found: 261.0399.

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