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Communications

A Shortcut to the Preparation of Naturally Occurring Arbutin

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Naturally occurring arbutin (4-hydroxyphenyl β-D-glucopyranoside) was initially isolated from medical plants such as bearberry leaves (*Arctostaphylos uvae ursi*), *etc*.[1] Besides the multiple pharmaceutical applications it owns, arbutin is also well-known as a green, reliable and highly efficient skin-whitening agent, which effectively inhibits human tyrosinase.[2] The preparation of arbutin mainly falls into two pathways: organic synthesis and enzymatic glycosylation. Indeed, since the first chemical approach to arbutin was realized from tetra-*O*-acetyl-α-bromo-D-glucopyranoside with hydroquinone in the last century,[3] various other strategies have been successively developed. Among which, penta-*O*-acetyl-β-D-glucopyranoside seems to be the most utilized glyco-donor.[4] More recently, Cepanec *et al*. reported a simple and efficient synthesis starting from penta-*O*-acetyl-β-D-glucopyranoside and 4-hydroxyphenylacetate catalyzed *via* $BF_3{\cdot}Et_2O$ in a total yield of around 50%.[5] Nevertheless, although these glycosylations proceeded smoothly and afforded effectively the final product, there still remain several drawbacks such as incomplete anomeric retention, relatively low total yield and especially, long reaction time (commonly more than 24 h for 2 - 3 steps).

Microwave irradiation is known as a powerful tool for both enhancing the reaction efficacy and economizing the reaction time. To our surprise, though this methodology has been massively introduced into carbohydrate chemistry,[6] its elongation to the preparation of arbutin is still unreported. Consequently, with a continuing interest on arbutin and its derivatives,[7] we describe here a shortcut to the synthesis of arbutin *via* microwave irradiation.

Experimental Section

Solvents were purified by standard procedures. ^{1}H NMR spectra were recorded on a Bruker DRX500 spectrometer in $CDCl_3$ or D_2O solutions. Microwave-assisted syntheses were performed in a Whirlpool VIP273F system. Optical rotations were measured using a SG WZZ-2A polarimeter at room temperature and a 10 cm 1 mL cell. Column chromatography was performed on E. Merck Silica Gel 60 (230 - 400 mesh). Analytical thin-layer chromatography was performed on E. Merck aluminum percolated plates of Silica Gel 60F-254 with detection by UV and by spraying with 6 N H_2SO_4 and heating at 300 ^oC. High resolution mass spectra (HRMS) were recorded on a KE465 LCT Premier/XE instrument using standard conditions (ESI, 70 eV).

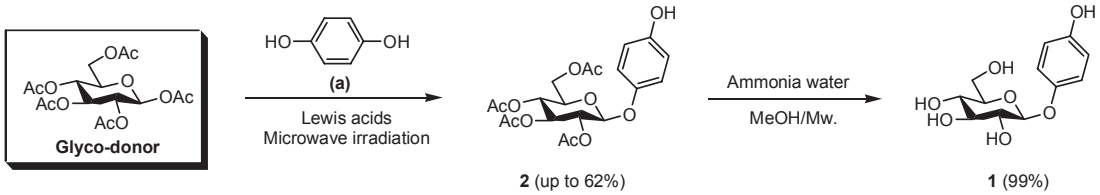
Preparation of tetra-*O*-acetyl-arbutin (2). To a soln. of penta-*O*-acetyl-β-D-glucopyranoside (200 mg, 0.5 mmol) and hydroquinone (112.4 mg, 1.0 mmol) in MeOH (10 mL), was added dry $BF_3{\cdot}Et_2O$ (40.8 μL, 0.2 mmol). This was then transferred to the microwave oven (240 W) for 10 min. After completion of the reaction monitored by TLC, the mixture was evaporated, washed with brine, extracted with CH_2Cl_2 and dried over $MgSO_4$. The dried organic layer was concentrated, then purified by column chromatography (petroleum ether/EtOAc; 3:1) to give the known **2**[8] as a white solid (140.2 mg, 62.1%). TLC R_f = 0.57 (petroleum ether/EtOAc; 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (dd, 2H, J = 2.2, 6.7 Hz), 6.75 (dd, 2H, J = 2.2, 6.7 Hz), 5.28-5.22 (m, 2H), 5.16 (t, 1H, J = 9.2, 9.8 Hz), 4.94 (d, 1H, J = 7.6 Hz), 4.30 (dd, 1H, J = 5.2, 12.3 Hz), 4.20 (dd, 1H, J = 2.4, 12.2 Hz), 3.82-3.78 (m, 1H), 2.10, 2.08, 2.04, 2.02 (4s, 12H).

Preparation of arbutin (1). To a soln. of **2** (140.2 mg, 0.3 mmol) in MeOH (10 mL), was added 28% ammonia water (0.17 mL, 4.5 mmol) which was then transferred to the microwave oven (240 W) for 10 min. The mixture was evaporated to directly afford the desired **1** as sole product (white powder, 86.6 mg, 99%). TLC R_f = 0.48 (AcOH/H_2O/*n*-BuOH; 1:5:3); $[\alpha]_D^{20}$ = −33.7 (c = 0.5, MeOH); ^{1}H NMR (500 MHz, D_2O) δ 6.81 (d, 2H, J = 9.0 Hz), 6.62 (d, 2H, J = 9.0 Hz), 4.82 (d, 1H, J = 7.4 Hz), 3.80-3.21 (m, 6H); HRMS: calcd for $C_{12}H_{16}O_7$+Na: 295.0794, found: 295.0788.

Result and Discussion

As shown in Table 1, we initially performed the Helferish glycosylation by employing penta-*O*-acetyl-β-D-glucopyranoside and hydroquinone as starting materials promoted *via* four different Lewis acids. Surprisingly, under microwave irradiation, $SnCl_4$ and $BF_3{\cdot}Et_2O$ catalyzed reactions favorably afforded the desired product (**2**) with complete retention of β-configuration within only ten minutes (entry 1, 2). However, two solid

Table 1. Preparation of arbutin *via* microwave irradiation (240 W, 10 min)



entry	**a** (equiv.)	Lewis acid	solvent	α:β (yield %)
1	2	$SnCl_4$ (0.5 equiv.)	CH_2Cl_2	0:1 (41.1)
2	2	$BF_3{\cdot}Et_2O$ (0.5 equiv.)	CH_2Cl_2	0:1 (52.7)
3	2	4 Å ms (900 mg)	CH_2Cl_2	-
4	2	Mont. K-10 (900 mg)	CH_2Cl_2	-
5	2	$BF_3{\cdot}Et_2O$ (0.5 equiv.)	$CHCl_3$	0:1 (47.8)
6	2	$BF_3{\cdot}Et_2O$ (0.5 equiv.)	DMF	-
7	2	$BF_3{\cdot}Et_2O$ (0.5 equiv.)	MeCN	-
8	1.5	$BF_3{\cdot}Et_2O$ (0.5 equiv.)	CH_2Cl_2	0:1 (45.2)
9	2	$BF_3{\cdot}Et_2O$ (0.3 equiv.)	CH_2Cl_2	0:1 (**62.1**)

acids (4 Å molecular sieve and montmorillonite K-10) failed to promote the reaction (entry 3, 4) under same condition. In addition, $BF_3{\cdot}Et_2O$ catalyzed reaction more effectively afforded **2** with a yield of 52.7% (entry 2). Such result completely accords with the former report which indicated $BF_3{\cdot}Et_2O$ as the most efficient glycosylation catalyst, providing clean reactions as well as high conversions.[9] Prompted by such exciting outcome, optimization of the reaction condition was further actualized. Clearly, the yield decreased (47.8%) when using $CHCl_3$ as the solvent (entry 5) whereas aprotic solvents such as DMF and MeCN provided deleterious impact as no apparent reacting trace could be monitored (entry 6, 7). As shown in entry 8, lowering the loading of hydroquinone from 2 equiv. to 1.5 equiv. rendered yield decrease. Finally, the best yield (62.1%, entry 9) was obtained *via* a catalyst loading reduction from 0.5 equiv. to 0.3 equiv. within 10 min. The desired final product (**1**) was then satisfactorily obtained by deprotection of **2** *via* ammonia water under microwave irradiation in almost quantitive yield (99%) within another 10 min.

In summary, we have efficiently and rapidly synthesized the naturally occurring arbutin *via* microwave irradiation. Using commercially available and inexpensive penta-*O*-acetyl-β-D-glucopyranoside and hydroquinone, such natural product was obtained through a simple expeditious 2-step workup including $BF_3{\cdot}Et_2O$ catalyzed glycosylation and deprotection with considerable total yield of > 60% and complete retention of anomeric configuration. Most notably, thanks to the introduction of microwave irradiation, only 20 min were consumed for the reaction process from raw materials to the final product **1**. To the best of our knowledge, such result represents the fastest access to the achievement of arbutin with comparable and retainable reaction efficiency among current relevant reports.

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