

Green and Catalyst-free Synthesis of Deoxyrbutin in Continuous-Flow

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Experimental section:

All chemicals were purchased from commercial sources and used without further purification. Melting points were determined on a Buchi B-540 melting point apparatus and uncorrected. Stainless steel 316L tube was purchased from Shanghai Zhaowei Stainless Steel Co., Ltd. High-performance liquid chromatography (HPLC) analysis was carried out on an Agilent 1200 system. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ with tetramethylsilane (TMS, $\delta = 0$) as an internal standard at ambient temperature on a Varian 600 MHz spectrometer.

General Procedure of Etherification in Batch.

A mixture of hydroquinone (33.0 g, 0.3 mol), pyridinium 4-toluenesulfonate (0.8 g, 3.3 mmol) and 2-Me THF (140 mL) was heated by an oil bath with magnetic stirring under protection of N₂. A mixture of 3, 4-dihydro-2*H*-pyran (2.8 g, 33.3 mmol) and 2-Me THF (47 mL) added dropwise into the heated mixture at 60 °C. The reaction mixture kept 60 °C and stirred for additional 4 h to produce deoxyarbutin after dropping finished. Next, NaHCO₃ powder (0.4 g) was added and stirred for 10 min, then removed by vacuum filtration. Ultimately, organic solvent was evaporated to remove, and the product was purified by silica gel column chromatography with EA and *n*-hexane as eluent. 3.98 g product obtained, purity of 98.1%, and yield of 60.4%. m. p. 87 - 88 °C (Literature data¹: 88 - 89 °C). Purity data was obtained by external standard method of HPLC. Figure S1 is standard curve and conditions as follow: Column: sunniest C18 column 250 mm × 4.6 mm, detection wavelength: 290 nm, flow rate: 1.0 mL/ min, flow

condition: 0 – 6 min CH₃CN : H₂O = 50:50, 6 – 20 min CH₃CN : H₂O = 95:5, 20 – 25 min CH₃CN : H₂O = 50:50.

Characterization data of target compound: ¹H NMR (600 MHz, CDCl₃) δ/ ppm: 7.14-6.59 (m, 4H), 5.47-4.77 (m, 1H), 4.07-3.46 (m, 2H), 2.08-1.46 (m, 6H). ¹³C NMR (CDCl₃) δ/ ppm: 151.9, 150.9, 118.0, 117.6, 116.1, 115.9, 97.2, 62.1, 30.5, 25.3, 18.9.

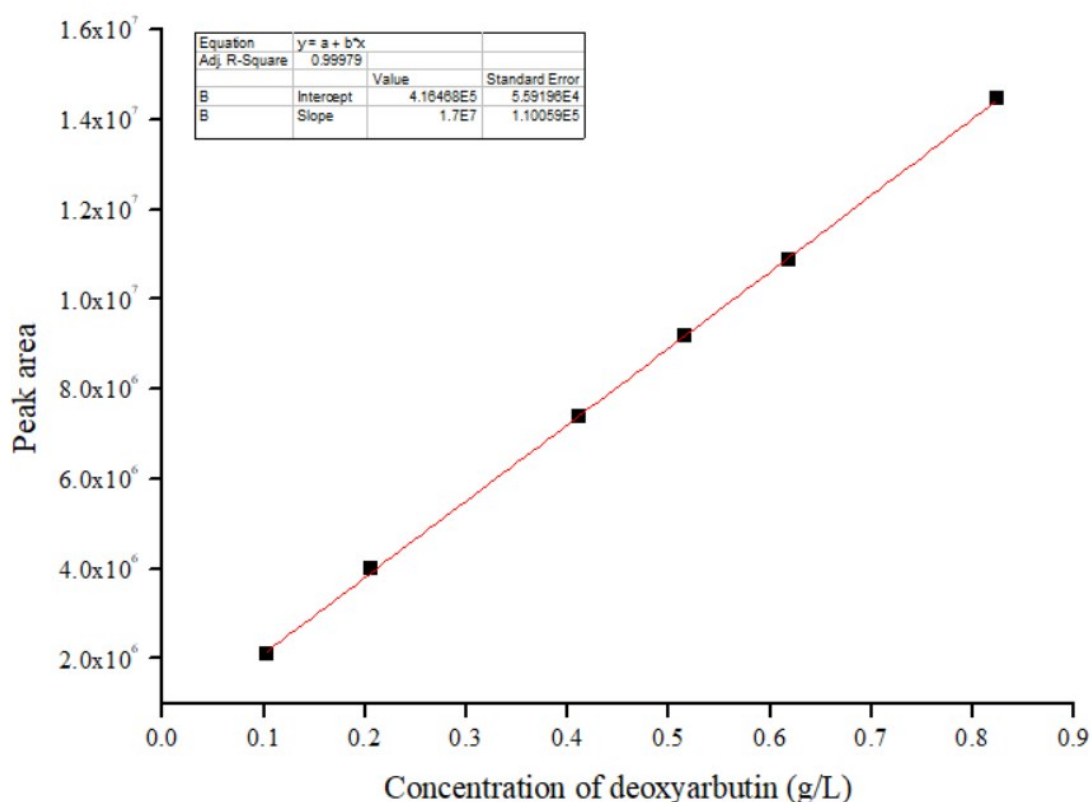


Fig. S1 Standard curve of deoxyarbutin.

Continuous-flow Experimental Procedure of Advanced Design.

As shown in **Scheme 4**, two mixtures, hydroquinone (33.0 g, 0.3 mol) in 125 g of 2-Me THF and DHP (2.8 g, 33.3 mmol) in 42 g of 2-Me THF, were prepared respectively. The two streams were then pumped into etherification tube (SS316L, 1.77 mm i.d., 3.18 mm o.d.), which was immersed in a thermostat-controlled oil bath, *via* a

T-joint by P_1 and P_2 at flow rates of 1.0 mL/ min and 0.3 mL/ min, respectively. After a residence time of 8 min, the reaction mixture was cooled (in a 20 °C thermostat), then flowed through the outlet and accumulated in a collection vessel. The pressure in reactor was controlled under 145 psi by a back pressure regulator. After the reaction, solvent was removed by vacuum rotary evaporation, around 35 g of off-white solid was obtained and then toluene (50 mL) was added at 40 °C. After stirring for 1 h, white hydroquinone solid was separated by filtration in a percent recovery of 99.0%, and m. p. 174 - 175 °C (Literature data²: 175 - 176 °C). The filtrate was then cooled to 10 °C, 4.28 g of white deoxyarbutin powder was obtained by filtration, purity of 98.5%, and yield of 65.3%.

General Procedure of Recycling Experiment.

hydroquinone (33.0 g, 0.3 mol) and DHP (2.8 g, 33.3 mmol) and 167 g 2-Me THF premixed, the mixture was pumped into etherification tube (SS316L, 1.77 mm i.d., 3.18 mm o.d.), flow rate was 1.3 mL/min. After etherification, the mixture was cooled down and collected, solvent 2-Me THF and un reacted DHP was separated and collected from reaction mixture by vacuum rotary evaporation. 35 g of chalky solid was obtained and then toluene (50 mL) was added at 40 °C. After stirring for 1 h, white hydroquinone solid was separated by filtration in a percent recovery of 99.0%, and m. p. 174 - 175 °C (Literature data²: 175 - 176 °C). The filtrate was then cooled to 10 °C, 4.28 g white deoxyarbutin powder was obtained by filtration in a 65.3% yield, and m. p. 86 - 88 °C. Recycled DHP, hydroquinone and 2-Me THF add to premix vessel. Added equimolar DHP and hydroquinone, according to the yield. Repeat procedure several times, and

results shows in Figure S2. According to the results Recovered materials had remarkable compatibility with commercially available raw materials

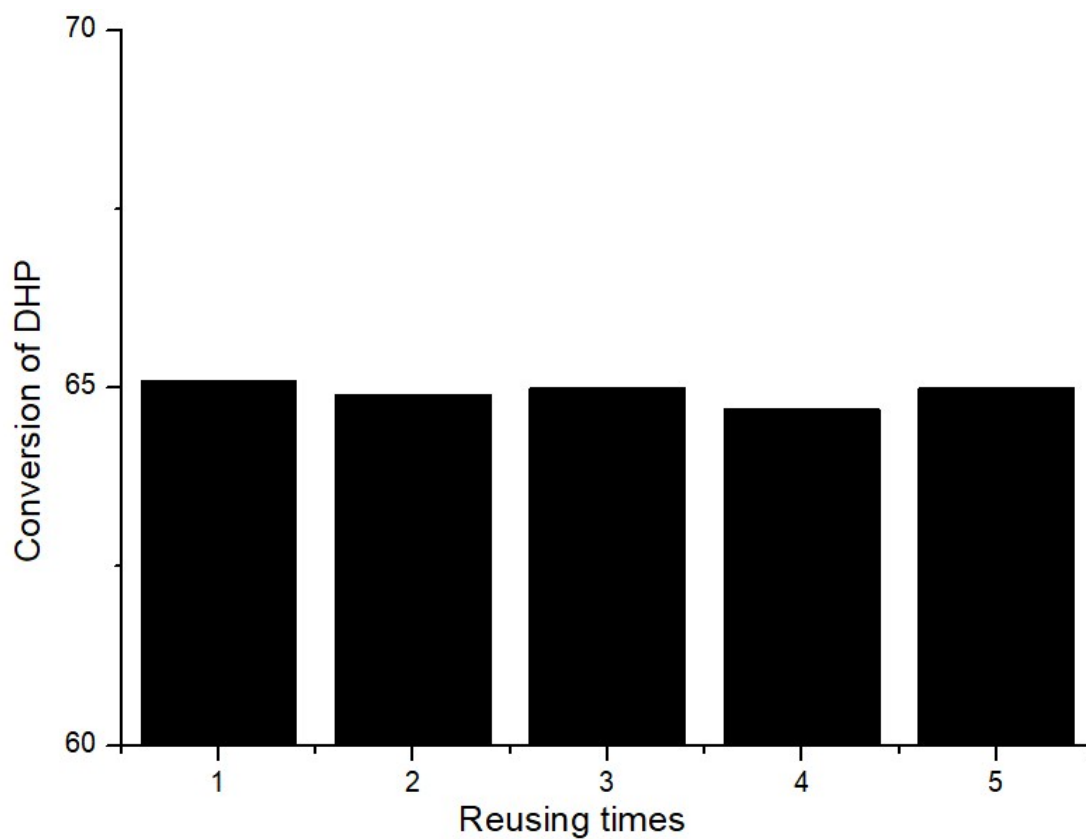


Fig. S2 Recycling and Reusing of materials.

References

1. L. K. T. Lam, C. Yee, R. P. Pai and L. W. Wattenberg, *Org. Prep. Proced. Int.*, 1982, **14**, 241–247.
2. J. R. Hwu and S. C. Tsay, *J. Org. Chem.*, 1990, **55**, 5987–5991.