Simple and efficient synthesis of arbutin

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Abstract
An efficient synthesis of arbutin, 4-hydroxyphenyl-D-glucopyranoside (**1**), in both α- and β-anomeric form, starting from penta-*O*-acetyl-α(β)-D-glucopyranoside (**2**) and 4-hydroxyphenylacetate (**3**) was developed. The BF_3•Et_2O-catalysed glycosylation reaction of **2** with **3** proceeds with complete retention of anomeric configuration.

Keywords: Arbutin, glycosides, transesterification, Lewis acids, natural products

Introduction

β-Arbutin is a naturally occuring glycoside found in several common medical plants.[1-5] Among them, the bearberry leaves (*Arctostaphylos uvae ursi*) is a widely used source of this important pharmaceutical active substance.[6] The arbutin-containing plant-drugs have been used for the treatment of urinary infections and as depigmenting agent.[7-9] The first synthesis of arbutin starting from tetra-*O*-acetyl-α-bromo-D-glucopyranoside and hydroquinone was described in early 20th centaury.[10] However, the first practical synthesis of arbutin from penta-*O*-acetyl-β-D-glucopyranoside and hydroquinone monobenzylether is based on the $POCl_3$-mediated glycosylation.[11] More recently developed syntheses of β-arbutin by Lewis acid-catalysed glycosylation of 2,3,4,6-tetra-*O*-acetyl-1-*O*-trifluoroacetyl-α-D-glucopyranose with hydroquinone,[12] or by employing tributyltin phenoxides[13] suffer from several disadvantages: the use of expensive 1-trifluroacetyl-sugars, very toxic organotin reagents, or partial isomerisation at the anomeric position takes place.

Finally an alternative synthesis of β-arbutin based on enzymatic glycosylation (α-amylase from *Bacillus macerance*) of hydroquinone with glucose was reported.[14] The synthesis was conducted in an aqueous buffered media furnishing both anomeric arbutins in reasonable yields but with tedious work-up. Nowadays, an efficient, inexpensive and scalable route to pure arbutin is still a great challenging area for both academic and industrial chemists.

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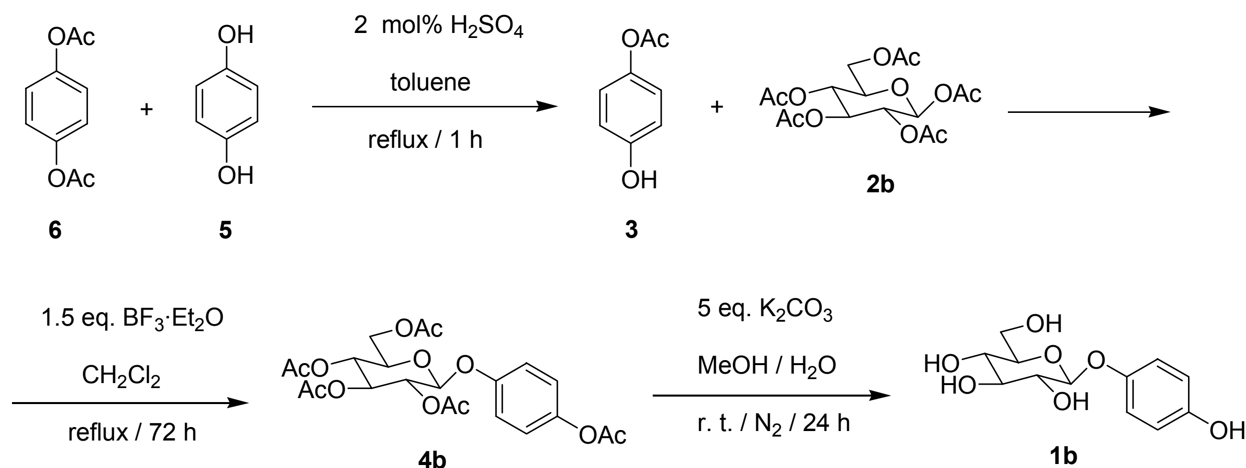
Results and Discussion

We decided to employ Helferich glycosylation reaction of readily available penta-*O*-acetyl-β-D-glucopyranoside (**2b**) and 4-hydroxyphenylacetate (**3**) as the most reasonable aglycone donor for the arbutin synthesis. This glycosylation reaction catalysed by boron trifluoride etherate ($BF_3{\cdot}Et_2O$)[15] has given expected peracetylated-β-arbutin (**4b**) in 55-62% yield. The latter was converted to β-arbutin (**1b**) in 83-92% yield either by saponification with potassium carbonate in aqueous methanol or by aminolysis with methanolic ammonia. According to our knowledge, there are no reports about the use of 4-hydroxyphenylacetate (**3**) as the aglycone donor in any glycosylation reactions. Various difficulties connected with the preparation of 4-hydroxyphenylacetate (**3**), either by mono-acetylation of hydroquinone (**5**),[16] or other multy-step approaches[17-19] based on the preparative chromatographic purifications make its use rather unatractive. Surprisingly, 4-hydroxyphenylacetate (**3**) is not a commercially available substance, indeed. However, we have found that the transesterification of readily available hydroquinone diacetate (**6**) with hydroquinone (**5**) proceeds smoothly in refluxing toluene in the presence of catalytic amount of sulfuric acid giving 4-hydroxyphenylacetate (**3**) as the sole product in essentially quantitative yield. The crude product was successfully employed in the glycosylation reaction (Scheme 1).



Scheme 1

Boron trifluoride etherate was proved to be the most efficient glycosylation catalyst as it provided clean reaction and high conversions within reasonable reaction times.[20] In addition to dichloromethane, other chlorinated solvents such as chloroform, tetrachloromethane or 1,2-dichloroethane have been tested in order to achieve higher reaction temperatures and thus higher conversions within shorter reaction times. Although the reaction times were significantly reduced in refluxing chloroform (65°C, 24 h) or 1,2-dichloroethane (80°C, 8 h), the glycosylation reactions were apparently less clean. Alternative Lewis acid catalysts including $SnCl_4$,[21,22]

$ZnCl_2$,[23] $FeCl_3$[24] as well as *p*-TsOH as protic acid were probed. Whereas the glycosylation reaction catalysed with $SnCl_4$, $ZnCl_2$ (refluxing chloroform), or *p*-TsOH (refluxing toluene) gave very low conversions, $FeCl_3$ caused oxidation of 4-hydroxyphenylacetate affording an unatractive tar, presumably due to oxidative phenolic coupling reaction and polymerization. Moreover BF_3-anisole complex[25] was also less effective catalyst. Finally $BF_3{\cdot}Et_2O$ in dry dichloromethane at molar ratio **2** : **3** : $BF_3{\cdot}Et_2O$ = 1 : 1.5 : 1 have given the highest yields.

Unnatural α-arbutin (**1a**) was prepared by the same route employing penta-*O*-acetyl-α-D-glucopyranoside (**2a**) with similar success. Complete retention of the anomeric configuration occurs under our reaction conditions – no opposite anomeric product was detected by HPLC in both glycosylation reactions.

Experimental Section

General Procedures. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-GEM 300 instrument, shifts are given in ppm downfield from TMS as an internal standard. HPLC analyses were performed with a Thermo Separation Products (San Jose, CA) instrument equipped with vacuum degasser SCM 1000, quaternary gradient pump P4000, autosampler AS 3000, scanning UV/VIS detector UV 3000 HR and ChromQuest 251 software. TLC analyses were performed on Merck's (Darmstadt, Germany) DC-alufolien with Kieselgel 60_{254}. Elemental analyses were done in Central Analytical Service (CAS) at Ruđer Bošković Institute. The optical rotations were measured on a A. Kruss Polarimeter with sodium lamp (589 nm, 20°C). Melting points (mp) were determined on a Büchi B-540 instrument.

Preparation of 4-hydroxyphenylacetate (3). To a mixture of hydroquinone diacetate (**6**, 19.41 g, 0.1 mol) and hydroquinone (**5**, 11.01 g, 0.1 mol) in toluene (60 ml), sulfuric acid (0.1 ml, 184 mg, 1.9 mmol, 2 mol%) was added. The reaction mixture was refluxed with stirring under nitrogen for 1 h. The reaction mixture was cooled, diluted with toluene (60 ml), washed with water (3x50 ml), dried (Na_2SO_4), filtered, and evaporated to dryness. The crude 4-hydroxyphenylacetate (30.18 g, 99.2%) was obtained as colourless waxy crystals, mp 57.5-60°C, single spot on TLC, and used in the further synthesis without an additional purification. An analytical sample was prepared by preparative chromatography of crude product (2.00 g), R_f= 0.43, on a silica gel (200 g) column by using CH_2Cl_2/2-PrOH (9.5:0.5) as an eluent followed by recrystallization from *n*-hexane to give 1.87 g (94%) of pure 4-hydroxyphenylacetate (**3**) as colourless needles; mp 62-63°C, lit.[17] mp 60-70°C, lit.[19] mp 60-63°C; IR (KBr, cm^{-1}) ν 3390, 3045, 3010, 2950, 1730, 1590, 1493, 1433, 1357, 1217, 1177, 1083; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (3H, s, CH_3COO), 6.72 (2H, d, J = 9.0 Hz), 6.86 (2H, d, J = 8.7 Hz), 7.68 (1H, s, O*H*); ^{13}C NMR (300 MHz, $CDCl_3$) δ 24.4, 115.8, 122.0, 143.3, 153.8, 171.0.

General procedure for penta-*O*-acetyl-α,β-arbutin (4a,b)
To a solution of penta-*O*-acetyl-β-D-glucopyranoside (**2b**, 3.90 g, 10 mmol) and 4-hydroxyphenylacetate (**3**, 2.28 g, 15 mmol) in 50 ml of anhydrous (CaH_2) dichloromethane, a solution of $BF_3 \cdot Et_2O$ (50%, 2.5 ml, 10 mmol) was added. The resulting reaction mixture was refluxed for 72 h. After being cooled, the reaction mixture was vigorously stirred with saturated aqueous $NaHCO_3$ solution (50 mL) for 1 h. The organic layer was separated, whereas the aqueous layer was extracted with dichloromethane (2x25 ml). The combined extracts were dried (Na_2SO_4), filtered and evaporated. From the residual viscous yellowish oil, 3.01 g (62%) of pure penta-*O*-acetyl-β-arbutine (**4b**), R_f= 0.64, was isolated by preparative chromatography over silica gel with CH_2Cl_2/2-PrOH (9.5:0.5) as an eluent; mp 142.8-143.5°C, lit.[10] mp 143-144°C; $[\alpha]_D^{20}$ = -27±2° (c=1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3483, 3002, 2973, 2966, 1749, 1647, 1606, 1596, 1504, 1432, 1372, 1227, 1182, 1131, 1100, 1075, 1042, 1013; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04-2.08 (12H, m, $COCH_3$), 2.29 (3H, s, $PhOCOCH_3$), 3.82-3.88 (1H, m), 4.14-4.19 (1H, m), 4.26-4.32 (1H, m), 5.03-5.05 (1H, m), 5.13-5.23 (1H, m), 5.26-5.33 (1H, m), 7.01 (4H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.3, 20.8, 61.7, 68.0, 70.9, 71.9, 72.5, 99.3, 117.9, 122.5, 146.2, 154.4, 169.3, 169.4, 169.7, 170.2, 170.5.

Penta-*O*-acetyl-α-arbutin (**4a**, 2.89 g, 60%) was prepared by the same procedure as described above, but employing penta-*O*-acetyl-α-D-glucopyranoside (**2a**). Slightly yellow viscous oil; R_f= 0.50 with CH_2Cl_2/2-PrOH (9.5:0.5) as an eluent; $[\alpha]_D^{20}$ = +125±2° (c=2, $CHCl_3$); IR (KBr, cm^{-1}) ν 3055, 2963, 1749, 1647, 1599, 1504, 1435, 1369, 1220, 1129, 1039; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01-2.09 (12H, m, $COCH_3$), 2.29 (3H, s, $PhOCOCH_3$), 4.09-4.13 (2H, m), 4.23-4.28 (1H, m), 5.01-5.06 (1H, m), 5.12-5.18 (1H, m), 5.65-5.72 (1H, m), 7.00-7.03 (2H, m), 7.08-7.11 (2H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.3, 20.4, 20.4, 20.6, 20.8, 61.4, 67.9, 68.1, 69.8, 70.2, 117.2, 122.6, 145.9, 153.2, 169.6, 169.7, 169.9, 170.2, 170.6.

General procedure for preparation of α,β-arbutin (1a,b). To a solution of penta-*O*-acetyl-β-D-arbutin (**4b**, 485 mg, 1 mmol) in methanol (50 ml) and water (10 ml), potassium carbonate (2.07 g, 15 mmol) was added. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 24 h. Then a methanolic solution of concentrated sulfuric acid (0.4 ml, 0.74 g, 7.5 mmol) was added dropwise during 15 minutes. The reaction mixture was evaporated to dryness. Thus obtained solid residue was extracted with boiling ethylacetate (3x50 ml). Collected organic extracts were evaporated under reduced pressure. The crude product (270 mg) was recrystallized from ethylacetate affording 230 mg (85%) of pure β-arbutin (**1b**) as colourless needles; mp 199-200°C, lit.[3] mp 199.5-200°C; single spot on TLC, R_f= 0.47 with EtOAc/MeOH/H_2O (100:17:3) as an eluent; HPLC (>99% chemical and anomeric purity), Supelcosil LC-NH_2, UV 230 nm, MeCN/MeOH (75:25), temp. 22°C, flow 1.5 ml / min, r. t. 6.79 min.; $[\alpha]_D^{25}$ = -65±2° (c= 2 in water); IR (KBr, cm^{-1}) ν 3378, 2913, 2856, 1648, 1513, 1459, 1411, 1371, 1218, 1109, 1080, 1050, 1013; ^{1}H NMR (300 MHz, D_2O) δ 3.32-3.48 (4H, m), 3.58-3.64 (1H, m), 3.75-3.79 (1H, m), 4.80 (1H, d, *J* = 7.2 Hz, β-anomeric config.), 6.72 (2H, d, *J* =

8.7 Hz), 6.90 (2H, d, J = 8.9 Hz); ^{13}C NMR (300 MHz, D_2O) δ 61.4, 67.4, 70.3, 73.9, 76.5, 76.9, 102.3, 117.2, 119.4, 151.5, 152.3; Anal. Calcd for $C_{12}H_{16}O_7$: C, 52.94; H, 5.92; Found: C, 52.81; H, 5.78.

α-Arbutin (**1a**, 246 mg, 90%) was prepared by the method described above. Colourless crystals, mp 204-206°C; R_f= 0.45 with EtOAc/MeOH/H_2O (100:17:3); HPLC (>99% chemical and anomeric purity), Supelcosil LC-NH_2, UV 230 nm, MeCN/MeOH (75:25), temp. 22°C, flow 1.5 ml / min, r. t. 7.64 min.; $[\alpha]_D^{20}$ +162±2° (c= 2 in water); IR (KBr) ν 3419, 3246, 2971, 2945, 2924, 2896, 1637, 1607, 1515, 1457, 1414, 1371, 1231, 1198, 1148, 1106, 1084, 1059, 1035, 1012; ^{1}H NMR (300 MHz, CD_3OD) δ 3.38-3.44 (1H, m), 3.50-3.55 (1H, m), 3.66-3.86 (4H, m), 5.29 (1H, d, J = 3.7, α-anomeric config.), 6.85 (2H, d), 7.00 (2H, d); ^{13}C NMR (300 MHz, CD_3OD) δ 62.8, 71.9, 73.8, 74.5, 75.3, 100.9, 117.1, 120.3, 152.4, 154.3; Anal. Calcd for $C_{12}H_{16}O_7$: C, 52.94; H, 5.92; Found: C, 52.79; H, 5.83.

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