First total synthesis of two resveratrol derivatives

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The total synthesis of two resveratrol derivatives with an isobutyryl substituent is reported for the first time.

Keywords: synthesis, resveratrol, derivative

Resveratrol is a low molecular weight plant phenols. Analogues have been reported to possess various biological and pharmacological activities such as anti-carcinogenic,[1] anti-inflammatory,[2] and estrogenic activity,[3] and to act as an antioxidants, modulating lipid and lipoprotein metabolism, and inhibiting platelet aggregation.[3] Compound **1** and **2** were isolated[4] from the root bark of *Ekebergia benguelensis* collected in Zimbabwe and were shown to be resveratrol derivatives with an isobutyryl substituent. The total synthesis of these two compounds has not been reported previously. We describe their synthesis for the first time as shown in Scheme 1.

Reagents and conditions: (i) $(EtO)_3PO$, reflux; (ii) NBS, $CHCl_3$; (iii) PCC, CH_2Cl_2; (iv) NaH, **4**, DMF; (v) n-BuLi, isobutyryl chloride, Et_2O; (vi) BBr_3, CH_2Cl_2; (vii) 3N HCl, MeOH.

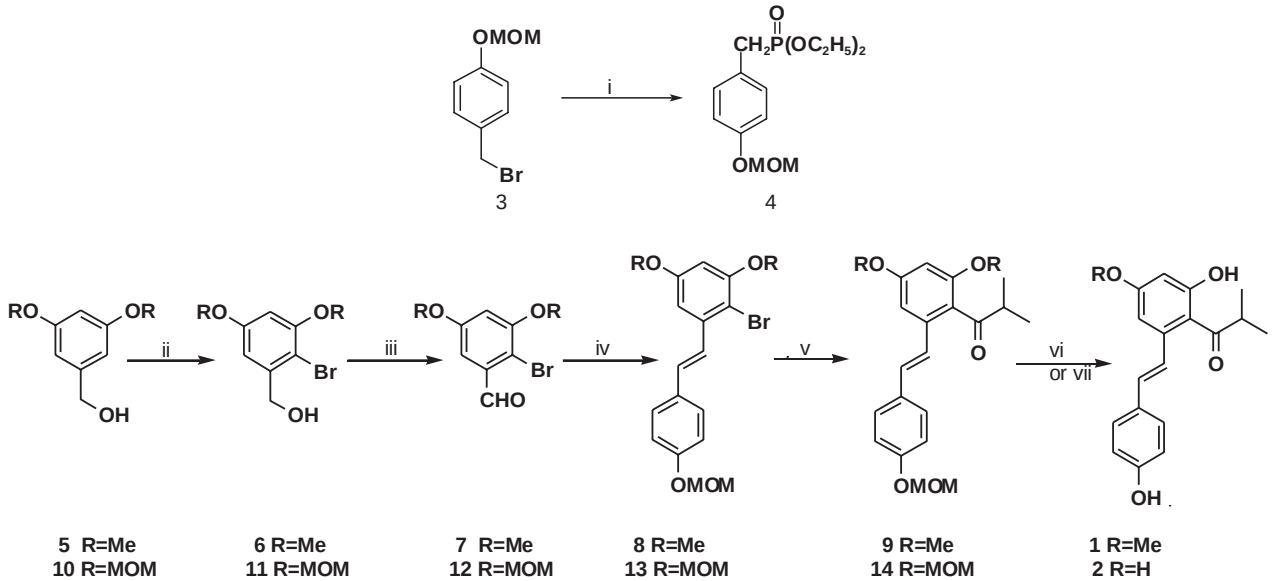
The reaction of **3**[5] with $(EtO)_3PO$ under refluxing gave **4**. Compound **5** was brominated by NBS to give compound **6**,[6] which in turn was oxidized by PCC to afford aldehyde **7**.[7] The condensation of **7** with **4** in the presence of NaH/DMF afforded **8**. Compound **8** was converted to a lithium reagent, and then added to a solution of isobutyryl chloride to afford compound **9**.[8] Demethylation of **9** with BBr_3 in CH_2Cl_2 gave the target compound **1** in high yield. Although many demethylation methods and reaction conditions were tried it was not possible to obtain product **2** from **1** or **9** directly. However, by using MOM instead of Me to protect the phenolic hydroxy group, compound **10** reacted under the same conditions as **5** to give **14**. The target compound **2** was then easily obtained by deprotection of **14** in MeOH with 3N HCl. All spectroscopic data of **1** and **2** were in agreement with those found in the literature.[4]

Experimental

Melting points were measured on a Kofler apparatus and were uncorrected. The ^1H NMR and ^{13}C NMR data were recorded with Avance-200 MHz or Avance-300 MHz spectrometer. The chemical shifts are reported in ppm relative to TMS. Mass spectra were recorded on a ZAB-HS spectrometer. IR spectra were recorded on a Nicolet FT-170SX spectrometer. Flash column chromatography was generally performed on silica gel (200–300 mesh) eluting with petroleum ether/ethyl acetate and TLC inspections on silica gel GF_{254} plates with petroleum ether/ethyl acetate.

1-{2,4-Bis-methoxymethoxy-6-[2-(4-methoxymethoxy-phenyl) –vinyl]–phenyl}-2-methyl-propan-1-one **9**: Butyllithium (0.37 ml, 2.5 M, 0.94 mmol) was added slowly to a solution of **8** (322 mg, 0.85 mmol) in ethyl ether at –80˚C under nitrogen. After 30 min at this temperature, the reaction mixture was added slowly to a solution of isobutyryl chloride (0.17 ml, 1.62 mmol) in ethyl ether at room temperature under nitrogen. After 1 h, the reaction was quenched with water and extracted three times with diethyl ether. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was flash chromatographed using petroleum ether and ethyl acetate (15: 1, v/v) as eluent. A bright yellow oil **9** (205 mg, 65 %) was obtained. MS (EI): 370 (M^+), 327, 297, 231, 149, 101. ^1H NMR (300 MHz, $CDCl_3$): δ 1.13 (d, 6H, *J*=6.9 Hz), 3.10 (sept, 1H, *J*=6.9, 6.9 Hz), 3.48 (s, 3H), 3.79 (s, 3H), 3.87 (s, 3H), 5.180 (s, 2H), 6.39 (s, 1H), 6.77 (s, 1H), 6.84 (d, 1H, *J*=16.2 Hz), 6.94 (m, 1H), 7.02(d, 2H, *J*=8.7 Hz), 7.36 (d, 2H, *J*=8.7 Hz).

1-{2-hydroxy-6-[(1E)-2-(4-hydroxyphenyl)ethenyl]-4-mehoxyphenyl}-2-methyl-1-propanone **1**: To a solution of **9** (152 mg, 0.41 mmol) in dry CH_2Cl_2 was added one drop of BBr_3 at 0 ˚C, 5 min later brine was added to the reaction, and it was extracted with CH_2Cl_2 The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was flash chromatographed using petroleum ether and ethyl acetate (6: 1, v/v) as eluent. The bright yellow amorphous powder **1** (105 mg, 82 %) was obtained. M.p. 171–173 ˚C. MS (EI): 312 (M^+), 297, 269,



Scheme 1

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241. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (d, 6H, *J*=6.6 Hz), 3.57 (sept, 1H, *J*=6.6 Hz), 3.84 (s, 3H), 6.39 (d, 1H, *J*=2.4 Hz), 6.54 (d, 1H, *J*=2.4 Hz), 6.80 (d, 1H, *J*=15.9 Hz), 6.87 (d, 2H, *J*=8.4 Hz), 7.12 (d, 1H, *J*=15.9 Hz), 7.35 (d, 2H, *J*=8.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7, 39.3, 55.5, 100.0, 108.3, 113.9, 115.9, 126.1, 128.2, 129.5, 132.2, 142.3, 156.1, 164.1, 164.6, 212.5. IR (KBr/cm^{-1}) 3378, 2967, 2932, 1604, 1512, 1462, 1379, 1353, 1210, 1155. HRFABMS *m/z* 311.1289 (calcd for $C_{19}H_{19}O_4$, 311.1289).

1-{2,4-dihydroxy-6-[(1E)-2-(4-hydroxyphenyl)ethenyl]-phenyl}-2-methyl-1-propanone **2**: 3N HCl (1 ml) was added to a solution of **14** (91 mg, 0.21mmol) in MeOH at room temperature, then this reaction was refluxed overnight. The MeOH was evaporated and the residue was extracted with ethyl acetate. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was flash chromatographed using petroleum ether and ethyl acetate (3: 1, v/v) as eluent. The bright yellow amorphous powder **2** (60 mg, 95 %) was obtained. MS (EI): 298 (M^+), 255, 227. ^{1}H NMR (300 MHz, acetone-d_6): δ 1.11 (d, 6H, *J*=6.6 Hz), 3.47 (sept, 1H, *J*=6.6 Hz), 6.33 (d, 1H, *J*=2.4 Hz), 6.66 (d, 1H, *J*=2.4 Hz), 6.85 (d, 2H, *J*=8.4 Hz), 6.91 (d, 1H, *J*=16.0 Hz), 7.12 (d, 1H, *J*=16.0 Hz), 7.41 (d, 2H, *J*=8.4 Hz). ^{13}C NMR (75 MHz, acetone-d_6) δ 19.3, 41.0, 102.5 107.0, 116.6, 117.1, 125.4, 129.0, 129.6, 132.3, 141.6, 158.6, 161.9, 212.0. IR (KBr/cm^{-1}) 3356, 2971, 2933, 1606, 1513, 1480, 1350, 1353, 1200, 1171. HRFABMS *m/z* 297.1138 (calcd for $C_{18}H_{17}O_4$, 297.1132).

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