Synthesis of Isoeuparin and Isotubaic Acid

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Received October 19, 2005

Key Words : Natural product, Isoeuparin, Isotubaic acid

The compounds containing the benzofuran moiety are widely distributed in nature.[1] They are used as versatile intermediates in organic and natural product synthesis.[2] They have also shown a range of biologically activities.[3] Among these, isoeuparin (**1**) was isolated from the roots of *Tagetes patula*[4] and isotubaic acid (**2**) (rotenic acid) was obtained from the natural insecticide rotenone as a degradation product[5] (Figure 1). The synthetic approaches to isoeuparin[6] and isotubaic acid[5] had been reported. We have used these known reactions in the synthesis of isoeuparin derivatives, but these reactions produce the expected products in low yield.[6] The necessity for overcoming this problem has prompted a search for new routes for the synthesis of isoeuparin (**1**) and isotubaic acid (**2**).

We have interest in the rhodium(II)-catalyzed reaction of iodonium ylides with several substrates.[7] Recently, we have tried rhodium(II)-catalyzed reactions of iodonium ylides with electron-deficient and conjugated alkynes.[8] These reactions provided tetrahydrobenzofuran derivatives **3**-**6** in moderate yields (Scheme 1). As an application of these methodologies, we describe herein an efficient total synthesis of isoeuparin (**1**) and isotubaic acid (**2**) starting from **6**.

Our synthetic strategy of isoeuparin (**1**) and isotubaic acid (**2**) is depicted in Scheme 2. The crucial starting material **6** was readily prepared in 53% yield from the iodonium ylide and 2-methyl-1-buten-3-yne in the presence of 1 mol % of $Rh_2(Opiv)_4$.[8] The reaction of **6** with methyl carbonate using excess NaH in the presence of a catalytic amount of KH in THF gave **7** in 96% yield.[9] Oxidation of **7** with DDQ in refluxing 1,4-dioxane afforded aromatic compound **8** in 46% yield.[10] Support for the structural assignment of **8** comes from spectroscopic analysis. The ^{1}H NMR spectrum of **8** shows the expected two aromatic protons at δ 7.73 (d, J = 8.8 Hz) and δ 6.96 (d, J = 8.8 Hz). Conversion of **8** to isoeuparin (**1**) was accomplished by hydrolysis and the subsequent addition of MeLi. Reaction of **8** with 2.5 M NaOH in refluxing methanol gave acid **9** in 97% yield, which was treated with excess MeLi (4 eq) in toluene at 50 °C for 4 h to afford **1** in 65% yield.[11] The spectroscopic properties of our synthetic material **1** agreed well with those reported in the literature.[6a]

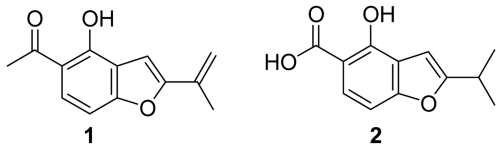
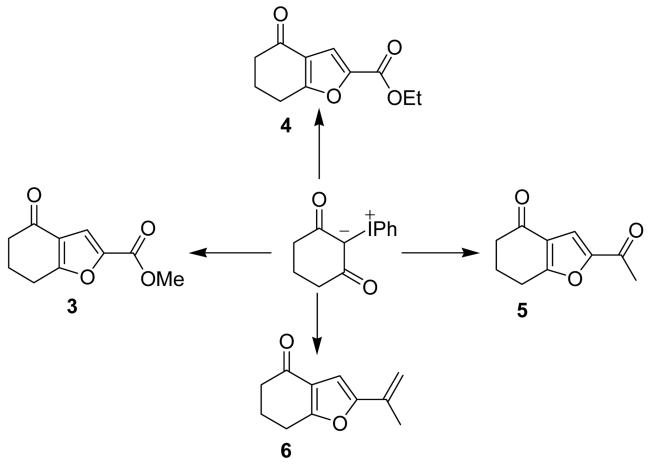


Figure 1



Scheme 1

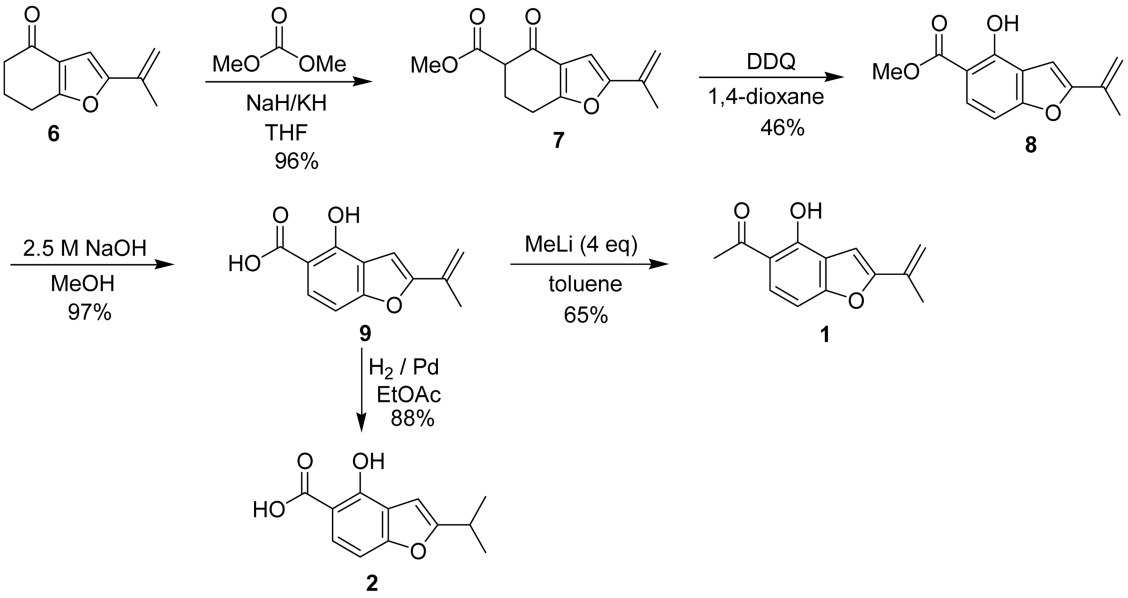
Conversion of **9** to isotubaic acid (**2**) was carried out by catalytic hydrogenation. Hydrogenation of **9** at 20 psi H_2 for 10 min in ethyl acetate afforded **2** in 88% yield. The spectral data of our synthetic material **2** agreed well with those reported in the literature.[5]

In conclusion, we have described here the synthesis of isoeuparin (**1**) and isotubaic acid (**2**) starting from tetrahydrobenzofuran **6**. These synthetic approaches are expected to be widely used in the total synthesis of other natural products containing the benzofuran moiety.

Experimental Section

All experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). Melting points were determined in capillary tubes on a Fisher-Johns apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Model ARX (300 MHz) spectrometer in $CDCl_3$ using 7.26 ppm as the solvent chemical shift. ^{13}C NMR spectra were recorded on a Bruker Model ARX (75 MHz) spectrometer in $CDCl_3$ using 77.0 ppm as the solvent chemical shift. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS mass spectra were carried out on JEOL JMS-700 spectrometer by Korea Basic Science Institute.

2-Isopropenyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-5-carboxylic acid methyl ester (7). To a stirred suspension of



Scheme 2

sodium hydride (0.681 g, 28.40 mmol) and potassium hydride (50 mg, 35 wt % dispersion in mineral oil) in dry THF (40 mL) under a N_2 atmosphere was added a solution of **6** (1.0 g, 5.68 mmol) in dry THF (5 mL) at 0 °C. The mixture was stirred for 30 mim and dimethyl carbonate (2.568 g, 28.40 mmol) was added slowly over 10 min. The ice bath was removed and the reaction mixture was heated slowly to reflux over 30 min and maintained at reflux for 30 min. After cooling the reaction mixture, water (10 mL) and saturated NH_4Cl solution (30 mL) were dropwiseadded carefully. The aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel to give **7** (1.276 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (1H, s), 5.51 (1H, s), 5.02 (1H, s), 3.73 (3H, s), 3.49 (1H, dd, J = 8.1, 4.8 Hz), 3.13-3.10 (1H, m), 2.93-2.80 (1H, m), 2.65-2.51 (1H, m), 2.41-2.27 (1H, m), 1.98 (3H, s); IR (neat) 3113, 1736, 1680, 1595, 1437, 1350, 1308, 1202, 1157, 982, 947, 883 cm^{-1}; HRMS: m/z (M^+) Calcd for $C_{13}H_{14}O_4$: 234.0892. Found: 234.0894.

4-Hydroxy-2-isopropenylbenzofuran-5-carboxylic acid methyl ester (8). A mixture of **7** (1.10 g, 4.70 mmol) and DDQ (2.134 g, 9.40 mmol) in dioxane (30 mL) was heated under reflux for 3 h. The resulting mixture was cooled in an ice bath and solid was removed by filtration through a short pad of Celite. The filtrate was evaporated under reduced pressure and purified by flash column chromatography on silica gel to give **8** (0.502 g, 46%). mp 90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.4 (1H, s), 7.73 (1H, d, J = 8.8 Hz), 6.96 (1H, d, J = 8.8 Hz), 6.80 (1H, s), 5.73 (1H, s), 5.16 (1H, s), 3.95 (3H, s), 2.10 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 160.0, 157.5, 157.0, 132.8, 126.7, 119.0, 113.8, 106.4, 104.0, 101.1, 52.6, 19.7; IR (KBr) 3129, 3096, 2959, 1672, 1626, 1472, 1437, 1350, 1323, 1275, 1254, 1192, 1167, 1138, 995, 876 cm^{-1}; HRMS: m/z (M^+) Calcd for $C_{13}H_{12}O_4$: 232.0736. Found: 232.0734.

4-Hydroxy-2-isopropenylbenzofuran-5-carboxylic acid (9). To a solution of the ester **8** (0.25 g, 1.08 mmol) in methanol (5 mL) was added an aqueous solution of sodium hydroxide (2.5 M, 4.4 mL, 10.8 mmol) at room temperature. The reaction mixture was then heated at reflux for 12 h. After cooling, methanol was evaporated under reduced pressure and water (10 mL) was added. The resultant solution was acidified with 2 N-HCl to pH ~2 and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The dark brown crude product was purified by flash column chromatography to afford **9** (0.228 g, 97%). mp 214-215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (1H, s), 7.80 (1H, d, J = 8.8 Hz), 7.1 (1H, d, J = 8.8 Hz), 6.82 (1H, s), 5.75 (1H, s), 5.18 (1H, s), 2.11 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 159.6, 157.8, 156.7, 132.9, 127.6, 118.8, 113.4, 103.4, 101.1, 19.6; IR (KBr) 3424 (br OH), 3138, 2854, 1667, 1628, 1474, 1445, 1402, 1318, 1258, 1173, 1109, 1067, 955, 883 cm^{-1}; HRMS: m/z (M^+) Calcd for $C_{12}H_{10}O_4$: 218.0579. Found: 218.0581.

Isoeuparin (1). To a solution of the ester **9** (0.10 g, 0.46 mmol) in toluene (5 mL) was added MeLi (1.6 M, 1.2 mL, 1.92 mmol) at room temperature. The reaction mixture was then heated at 50 °C for 4 h. After cooling, water (10 mL) was added. The solution was acidified with 2 N-HCl and was stirred for 30 min. The resultant was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford **1** (0.064 g, 65%). mp 106-107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.16 (1H, s), 7.62 (1H, d, J = 8.8 Hz), 6.97 (1H, d, J = 8.8 Hz), 6.82 (1H, s), 5.74 (1H, s), 5.17 (1H, s), 2.64 (3H, s), 2.10 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 159.5, 158.5, 156.8, 132.4,

127.4, 119.0, 114.4, 113.5, 103.4, 108.9, 26.9, 19.2; IR (neat) 2925, 2854, 1631, 1466, 1369, 1326, 1276, 1248, 1161, 1115, 1064, 833 cm^{-1}.

Isotubaic acid (2). A solution of **9** (0.09 g, 0.41 mmol) in ethyl acetate (10 mL) was stirred palladium-carbon (10%, 60 mg) under 20 psi hydrogen for 10 min. Removal of the catalyst and solvent gave the residue, which was purified by column chromatography to give **2** (0.08 g, 88%). m.p 184-185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.03 (1H, s), 7.75 (1H, d, J = 8.8 Hz), 6.98 (1H, d, J = 8.8 Hz), 6.56 (1H, s), 3.08-3.01 (1H, m), 1.33 (6H, d, J = 6.9 Hz); IR (neat) 3424 (br OH), 2957, 2926, 2855, 1669, 1628, 1460, 1318, 1258, 1173, 1053, 881 cm^{-1}.

Acknowledgement. This work was supported by the Korea Research Foundation Grant (R05-2004-000-10224-0) funded by the Korean government. Dr Ronald Tepper in discussion of this work is greatly appreciated.

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