SHORT PAPER

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First total synthesis of Kuhistanol D†

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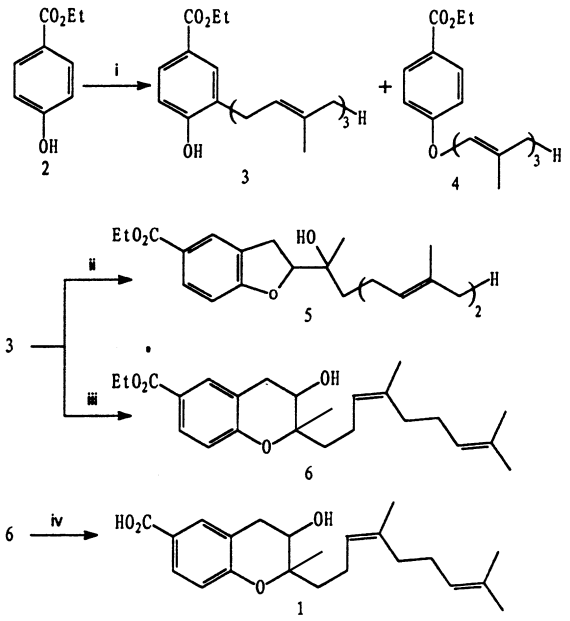
First total synthesis of Kuhistanol D, starting from readily available ethyl 4-hydroxybenzoate, is described.

Keywords: Kuhistanol D, synthesis, phenol by the Sharpless epoxidation

Kuhistanol D **1**, first isolated by Yoshihisa Takaishi and co-workers in 2000 from the roots of the Uzbekistan medicinal plant *Ferula kuhistanica*,[1] (3μg/ml) has been shown to exhibit significant inhibitory effect (%) on cytokine production [IL-4; 70.3%, IL-2: 77.3%, IFN-γ: 61.8%] in lipopoly saccharide stimulated human peripheral mono-nuclear cells, when compared with the reference compound, prednisolone (0.3μg/ml) [IL-4; 55.3% IL-2: 65.6%. IFN-γ: 60.2%].

Kuhistanol D **1** has a novel structure containing a prenylated unit and 2, 3-dihydro-3-hydroxybenzo-pyran. The chemical structure and relative stereo-chemistry were determined by spectral methods. Herein we report a facile first total synthesis of **1** from ethyl 4-hydroxybenzoate **2** and farnesyl bromide.

The synthetic route of **1** is outlined in Scheme 1.



Scheme 1 Reagents and conditions: (i) NaH, Benzene, Farnesyl bromide, 50°C, 24h, 34%. (ii) $Ti(O^iPr)_4$, D-(-)-DET, TBHP, CaH_2, Silica gel, Molecular sieves 4 Å, CH_2Cl_2 72h, 78%. (iii) 1) $Ti(O^iPr)_4$, D-(-)-DET, TBHP, CaH_2, Silica gel, Molecular sieves 4 Å, CH_2Cl_2, 72h; 2) $HClO_4$, EtOH, H_2O, reflux 12h, 74%. (iv) 4N NaOH, EtOH, H_2O, r. t., 16h, 91%.

Ethyl 4-hydroxybenzoate **2** was alkylated with farnesyl bromide mediated by NaH in benzene to give the aromatic alkylation product **3** in 34% yield and unexpected product **4**.[2] The farnesylated phenol **3** then was subjected to epoxidation under Sharpless conditions. Sharpless epoxidation of prenylated phenols worked quite well,[3] but the epoxide was not stable on column chromatography on silica gel. We obtained benzofuran **5** by purifying the crude epoxide product on flash column chromatography on silica gel. The crude epoxide product without further purification, was treated with $HClO_4$ in EtOH and H_2O to give benzopyran 6 in 74% yield.[4] Unfortunately, this epoxidation reaction showed no stereoselectivity, giving a racemic mixture.[3] Deprotection of benzopyran **6** by normal basic hydrolysis gave **1** in 91% yield and in 23% overall yield from ethyl 4-hydroxybenzoate **2**. The synthesis described here is short and efficient.

Experimental

^1H NMR spectra were recorded on a Avance DRX200 or a Bruker AM-400 spectrometer in $CDCl_3$ Solution using TMS as the internal reference. IR spectra were obtained on a Nicolet AVATAR 360 FT-IR (film) spectrometer. Mass spectra were measured on a VG ZAB-HS spectrometer by direct inlet at 70eV. TLC monitored all reactions. Purification of products was conducted by flash column chromatography on silica gel (200-300mesh) purchased from Yan Tai Yuan Bo silica Gel Co.

Ethyl 3-(3,7,11-trimethyl-2,6,10-dodecatriene)- 4-hydroxybenzoate **3**: A mixture of ethyl 4-hydroxy-benzoate **2** (498mg, 3mmol), 25ml of anhydrous benzene and NaH (60%) (120mg, 3mmol) was heated to 50°C with stirring for two hours. The mixture was cooled to room temperature and farnesyl bromide (0.81ml, 3mmol) was added. After 1h in r. t. the mixture was heated to 50°C for 21 hours, then cooled to room temperature. The reaction mixture was treated with water (20ml) and extracted thoroughly with ethyl acetate (3×40ml). The organic phases was washed with water and brine, then dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (pet. ether:ethyl acetate v/v 15:1) afforded the C-alkylated phenol **3** (388mg, 34%) as a colourless oil, along with the O-alkylated product **4** (500mg, 45%).

The phenol **3:** IR (film): ν_{max}/cm^{-1} 3408, 2971, 2923, 1714, 1606, 1271, 1168, 1106, 1014, 847, 770; ^1H-NMR ($CDCl_3$ 200MHz) δ (ppm): 7.82 (br. 2H), 6.82 (d, *J*=8.2Hz, 1H), 5.32 (br. t. *J*=7.2Hz, 1H), 5.09 (br. 2H), 4.35 (q, *J*=6.9Hz, 2H), 3.39 (d, *J*=7.8Hz, 1H), 1.9-2.2 (br. 8H), 1.79 (s, 3H), 1.65 (s, 3H), 1.55 (s, 6H), 1.39 (t, *J*=7.6Hz, 3H); EIMS (*m/z*): 370 (M^+. 16), 355 (3), 327 (15), 288 (14), 257 (16), 234 (35), 219 (59), 205 (61), 191 (10), 179 (32), 136 (19), 109 (14), 81 (51), 69 (100), 41 (49).

The O-alkylated product **4:** IR (film): ν_{max}/cm^{-1}: 3384, 2977, 2923, 1682, 1604, 1280, 1117, 1024, 772; ^1H-NMR ($CDCl_3$, 400MHz) δ (ppm): 7.98 (d, *J*=8.9 Hz, 2H), 6.91 (d, *J*=8.9Hz, 2H), 5.48 (t, *J*=6.5Hz, 1H), 5.10 (br, t, *J*=6.5Hz, 2H), 4.58 (d, *J*=6.5Hz, 2H), 4.33 (q, *J*=7.2Hz, 2H), 1.95-2.15 (m, 8H), 1.75 (s, 3H), 1.68 (s, 3H), 1.61 (s, 6H), 1.35 (t, *J*=7.3Hz, 3H); EIMS (*m/z*): 370 (M+, 4), 325 (7), 204 (65), 189 (1), 167 (7), 137 (12), 121 (42), 109 (9), 81 (82), 69 (100), 41 (48).

Ethyl 2-(-1-hydroxyl-1,5,9-trimethyl-4,8-decandiene)-2,3-dihydro-1-benzofuran-6-carboxylate **5.** To a suspension of $Ti(O^iPr)_4$ (77mg, 0.27mmol) CaH_2 (20mg), powdered and freshly activated 4 Å molecular sieves (30mg) and silica gel (20mg) in anhydrous CH_2Cl_2 (10ml) was added dropwise a solution of D-(-)-DET (56mg, 0.27mmol) in anhydrous CH_2Cl_2 (2ml) at –20°C with stirring. After being stirred for an additional 10 min at –20°C, the solution of the phenol **3** (99mg, 0.27mmol) in anhydrous CH_2Cl_2 (2ml) was added dropwise to the above reaction mixture. The mixture was further stirred for 15 min at that temperature and then cooled to –40°C. A solution of *tert*-BuOOH in toluene (3.2M, 0.17ml, 0.54mmol) was added. The resulting mixture was stirred for a further 72h at that tem-

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perature before being allowed to warm to –30°C. The reaction was then quenched by the addition of 10% aqueous tartaric acid (10ml). The mixture was allowed to warm to room temperature gradually and was stirred for a further 1h prior to extraction with ethyl ether (3 × 30ml). The combined organic phase was washed with water and brine, and then dried over $MgSO_4$. Evaporation of the solvent gave the crude product (139mg). Flash column chromatography on silica gel using pet. ether:ethyl acetate (v/v 15:1) as an eluent afforded the benzofuran **5** (79mg, 76%) as a colourless oil. IR (film): ν_{max}/cm^{-1}: 3422, 2925, 2380, 1705, 1620, 1443, 1278, 1167, 1112, 773; ^{1}H-NMR ($CDCl_3$, 400MHz) δ (ppm): 7.87 (m, 2H), 6.78 (d, *J*=7.8Hz, 1H), 5.12 (m, 2H), 4.72 (dd, *J*=9.1, 3.1Hz, 1H), 4.34 (q, *J*=7.2Hz, 2H), 3.23 (dd, *J*=8.6,4.3Hz, 1H), 3.14 (m, 1H), 2.10 (m, 4H), 1.70 (s, 3H), 1.38 (t, *J*=7.2Hz, 3H), 1.32 (s, 6H); HRMS. Calcd for $C_{24}H_{34}O_3$+H =387.2530; found: 387.2525.

Ethyl 2-methyl-2-(4,8-dimethyl-3,7-mondiene)-3-hydroxy-3,4-dihydro-benzopyran-6-carboxylate **6.** According to the procedure described for preparation of compound **5**, phenol **3** (240mg, 0.65mmol) was treated with $Ti(O^iPr)_4$ (185mg, 0.65mmol), CaH_2 (30mg), M.S. 4 Å (40mg), silica gel (30mg) and *t*-BuOOH (3.2M, 0.4ml, 1.3mmol) at –30°C. Evaporation of the solvent gave a yellow oil (271mg). The yellow oil (39mg) was taken up in the mixture of EtOH (3ml), H_2O (2ml). To the above mixture was added the aqueous $HClO_4$ (70%, 0.3mmol). The mixture was then refluxed for 16h, and diluted with water (5ml) after being cooled to room temperature. The mixture was extracted with ethyl ether (3 × 20ml) and the combined organic phases were dried, evaporated and purified by column chromatography with pet. ether:ethyl acetate (v/v 15:1) give benzopyran **6** (26mg, 74%) as a colourless oil. IR (film) ν_{max}/cm^{-1}: 3208, 2922, 1612, 1514, 1476, 1416, 1161, 1078, 798; ^{1}H-NMR ($CDCl_3$, 400MHz) δ (ppm): 7.82 (m, 2H), 6.86 (d, *J*=8.9Hz, 1H), 5.10 (br. t. *J*=7.3Hz, 2H), 4.35 (q, *J*=7.3Hz, 2H), 3.92 (br., d, *J*=4.4Hz, 1H), 3.10 (dd, *J*=16.7, 4.8Hz, 1H), 2.84 (dd, *J*=16.7, 5.8Hz, 1H), 1.96–2.18 (m, 8H), 1.67 (s, 3H), 1.59 (s, 3H), 1.38 (t, *J*=7.3Hz, 3H), 1.35 (s, 6H); EIMS (*m*/*z*): 386 (M^+, 1), 325 (4), 297 (2), 243 (12), 179 (9), 153 (3), 91 (69), 84 (10), 69 (33), 41 (24).

Kuhistanol D **1:** A solution of benzopyran **6** (8mg, 0.02mmol) in EtOH:H_2O (v/v: 1:2) 5ml was added 4N sodium hydroxide 1ml. The mixture was stirred for 4h in room temperature. The solution was acidified with dilute hydrochloric acid (10%) and extractive with ether (3 × 20ml). The combined ether extracts were washed with water and brine, dried over $MgSO_4$. Evaporation of the solvent followed by flash column chromatography on silica gel eluting with pet. ether:ethyl acetate (v/v: 4:1) to afford **1** (7mg, 91%). IR(film) ν_{max}/cm^{-1}: 3421, 2381, 1642, 1411, 1268, 1108, 773, 618; ^{1}H-NMR (CDCl3, 400MHz) δ (ppm): 7.82 (m, 2H), 6.86 (d, *J*=8.9Hz, 1H), 5.10 (br. t. *J*=7.3Hz, 2H), 3.90 (m, 1H), 3.06 (br., d, *J*=16.7Hz, 1H), 2.81 (br., d, *J*=16.7Hz, 1H), 1.96-2.18 (m, 8H), 1.67 (s, 3H), 1.59 (s, 3H), 1.35 (s, 6H); HRMS: calcd for $C_{22}H_{30}O_3$+H =359.2217; found: 359.2217.

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