A Novel Route to Stereoselective Synthesis of (4*R*,5*S*)-*O*-Acetylosmundalactone and (4*S*,5*R*)-*O*-Acetylosmundalactone†

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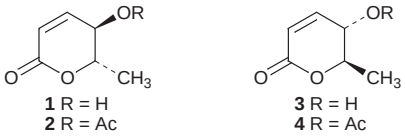
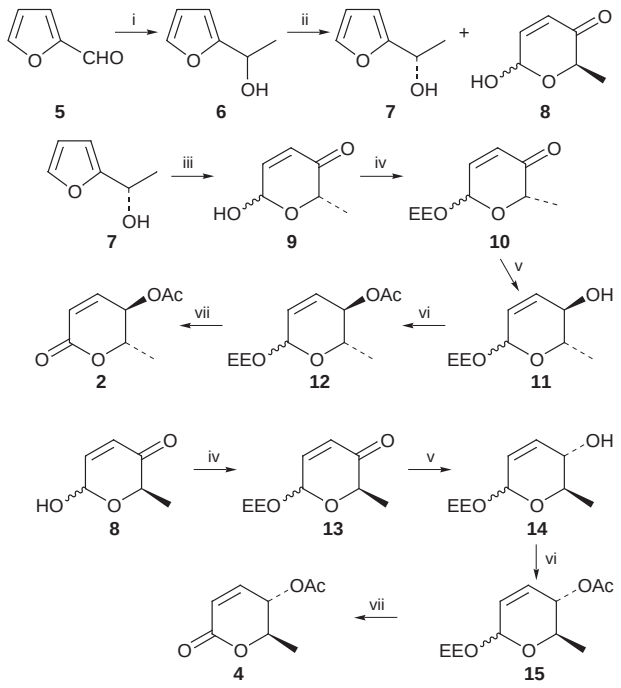
A route has been developed for the enantioselective synthesis of (4*R*,5*S*)-*O*-acetylosmundalactone **1** and (4*S*,5*R*)-O-acetylosmundalactone **2** by using Sharpless kinetic resolution of the racemic 1-(2-furyl)ethanol **6** as a key step.

(4*R*,5*S*)-*O*-Osmundalactone (**1**), isolated from *Osmunda japonica Thunb*,[1] has antifeeding activities against the larve of the yellow butterfly *Eurema hercabe mandaarina De L'Orza*. (4*S*,5*R*)-*O*-Osmundalactone (**4**), the enantiomer of **1**, was isolated from *Paxillus atromentosus* by Buchanan.[2] To our knowledge, no synthetic work on the compound **3** has been reported and only the isomer **1** can be obtained by the routes developed by Hollenbeak[3] and Steven.[4] In this paper, we present a simple and effective synthetic route to both **2** and **4**.



As shown in Scheme 1, the readily available furfural (**5**) reacted with methylmagnesium iodide to afford the furyl methyl alcohol **6**, which was resolved by Sharpless's method. The unreactive **7** and the oxidative product **8** were obtained in yields of 42 and 45% respectively. The alcohol **8** was protected by ethyl vinyl ether to yield **13**, which was selectively reduced by $NaBH_4/CeCl_3 \cdot 7H_2O$ to give the *trans* compound **14**. The alcohol **14** was protected by acetic anhydride and then was oxidized by CrO_3/HOAc to yield (4*S*,5*R*)–osmundalactone **4** in 70% yield and no *cis* compound was detected by ^{1}H NMR. The absolute configuration of C-5 was unambiguously assigned as *R* according to the rule of Sharpless kinetic resolution of furfuryl methanol developed by Kusakabe.[5] To determine the absolute configuration of C-4, we compared the $J_{4,5}$ valve with that of a similar structure reported in literature.[6] For the *cis* compound it was found that $J_{4,5} = 2-3$ Hz, while the $J_{4,5}$ of the *trans* compound was 6–9 Hz. In compound **4** we found that $J_{4,5}$ was 6.6 Hz, so we confirm that the absolute configuration of C-4 was *S*, and that compound **4** is (4*S*,5*R*)-*O*-acetylosmundalactone. The synthetic procedure and characterization of the isomer **2** were carried out in a similar way. By comparing with the data listed in the literature,[2] we knew that the optical purity of **2** is 93.6% and the optical purity of **4** is 93%



Scheme 1 *Reagents and conditions*: i, CH_3MgI, diethyl ether; ii, $Ti(OPr^i)_4$, D-(−)-DIPT, TBHP, CH_2Cl_2; iii, NBS, THF:H_2O(4:1); iv, ethyl vinyl ether, PPTS, CH_2Cl_2; v, $NaBH_4/CeCl_3 \cdot 7H_2O$, CH_3OH; vi, acetic anhydride, DMAP; vii, CrO_3/HOAc.

Experimental

IR spectra (KBr) were recorded on a Nicolet 170 SXFT-IR spectrometer and ^{1}H NMR spectra were obtained on a Bruker AM-400 spectrometer using Me_4Si as internal standard. Mass spectra were recorded on a ZAB-HS mass spectrometer (EI). Microanalyses were performed on a MOD-1106 elemental analyser. Both $Ti(OPr^i)_4$ and D-(−)-DIPT were purchased from Aldrich and used without further purification. Light petroleum was used for chromatography (bp 60–90 °C).

1-(2-*Furyl*)*ethanol* **6**.—To a N_2 flushed three-neck flask containing methylmagnesium iodide [0.123 mol in 50 ml of anhydrous ethyl ether, prepared from Mg (3.0 g, 0.1223 mol) and methyl iodide (17.5 g, 0.123 mol)] was slowly added a solution of freshly distilled furfural in 30 ml of anhydrous ethyl ether at 0 °C. The mixture was then stirred for another 3 h at room temperature. After the reaction was complete, it was quenched by saturated NH_4Cl, extracted with diethyl ether and dried over Na_2SO_4. After removal of the solvent, the residue was purified through column chromatography using light petroleum–ethyl acetate as eluant (10:1, v/v) to give the pure alcohol **6** as a yellowish oil (10.4 g, 84%). ν_{max}/cm^{-1} (KBr) 3354, 2982, 1671, 1010; *m/z* (EI) 112 (M^+), 97 (base); δ_H ([$^2H_6$] acetone) 1.46 (3 H, d, $J = 6.5$ Hz), 4.79 (1 H, q, $J = 6.5$ Hz), 6.17 (1 H, d, $J = 3.1$ Hz), 6.28 (1 H, dd, $J = 3.1$, 1.6 Hz), 7.32 (1 H, d, $J = 1.6$ Hz). (Found: C, 64.30; H, 7.15. $C_6H_8O_2$ requires C, 64.27; H, 7.19%.)

Kinetic Resolution of Alcohol **6**.—To a flame dried, N_2 flushed 100 ml three-neck flask containing anhydrous CH_2Cl_2 (30 ml) was added $Ti(OPr^i)_4$ (2.01 ml, 6.96 mmol). The solution was then cooled to −20 °C D-(−)-DIPT (1.77 ml, 8.35 mmol) was added through a syringe, the mixture was stirred for 10 min at this temperature, then cooled to −40 °C, a solution of **6** in anhydrous CH_2Cl_2 (10 ml) was added, and the solution was stirred at this temperature for another 30 min. To this solution was added TBHP (4.18 mmol). The mixture was stirred for 3 h at −3 °C, then stored in a refrigerator for 24 h. The reaction was quenched by $FeSO_4$ (0.387 g 1.39 mmol) followed by 10% tartaric acid (20 ml), the solution was stirred until the water layer was transparent then extracted with CH_2Cl_2 and dried over

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Na_2SO_4. After removal of the solvent at reduced pressure, the residue was chromatographed on silica gel (light petroleum–ethyl acetate; 8:1 v/v) to give a low melting point compound **8** (0.374 g, 42%), and (*S*)-**7** (0.351 g, 45%). (*S*)-**7** $[\alpha]_D^{20}$ − 19.1° (*c*, 0.86, $CHCl_3$); (lit.[8] $[\alpha]_D^{20}$ − 20.8° (*c*. 1.27 $CHCl_3$); other spectra data was same as **6**. Compound **8** (two isomers were obtained in ratio of 3:1, the data of the major product is reported here): ν_{max}/cm^{-1} (KBr) 3388, 2982, 1696, 1629; *m/z* (EI) 128 (M^+), 111, 84 (base); δ_H ([$^2H_6$] acetone) 1.23 (3 H, d, *J* = 6.7 Hz), 3.46 (s, OH), 4.63 (1 H, q, *J* = 6.7 Hz), 5.23 (1 H, d, *J* = 3.2 Hz), 5.98 (1 H, d, *J* = 10.2 Hz), 6.99 (1 H, dd, *J* = 10.2, 3.2 Hz). (Found: C, 56.32; H, 6.31. $C_6H_8O_3$ requires C, 56.25; H, 6.29%.)

(*S*)-6-*Hydroxy*-2-*methyl*-2,6-*dihydropyran*-3-*one* **9**.—The alcohol **6** (0.323 g, 2.88 mmol) was dissolved in 10 ml THF:H_2O (4:1, v/v), NBS (0.513 g, 2.88 mmol) was added portionwise. The reaction was monitored by TLC, then quenched with 10% KI (1.0 ml) followed by 15% $Na_2S_2O_4$ (0.2 ml); the mixture was then stirred until the color turned yellowish, then neutralized by saturated $NaHCO_3$, extracted with diethyl ether and dried over Na_2SO_4. Evaporation and chromatography of the residue using light petroleum–acetate (8:1, v/v) as eluant gave the ketone **9** (two isomers were obtained in ratio of 3:1) (0.310 g, 84%). Other spectral data were same as these compound for **8**.

(2R)-6-(1-*Ethoxyethyl*)-2-*methyl*-2,6-*dihydropyran*-3-*one* **13** *and its Isomer* **10**.—To a solution of **8** (0.387 g, 2.87 mmol) in CH_2Cl_2 (15 ml) was added ethyl vinyl ether (2.064 g, 2.74 ml, 28.7 mmol) and cat. PPTS. The mixture was stirred for 1.5 h, then H_2O (5 ml) was added, extracted by CH_2Cl_2, (15 ml × 3), and dried over Na_2SO_4. After removal of the solvent, the residue was purified through column chromatography using light petroleum–acetate (15:1, v/v) to give the pure **13** as a yellowish oil (0.493 g, 86%). The isomer **10** was prepared in the similar way. ν_{max}/cm^{-1} (KBr) 3052, 2983, 1701, 1630, 1141, 1083; *m/z* (EI) 155(M^+ − 45; δ_H ([$^2H_6$]acetone) 1.11 (3 H, t, *J* = 7.0 Hz), 1.32–1.41 (6 H, m), 3.36–3.72 (2 H, m), 4.44–4.62 (1 H, m), 4.86–5.02 (1 H, m), 5.37–5.54 (1 H, m), 5.94–6.07 (1 H, d, *J* = 10.2 Hz), 6.77 (1 H, dd, *J* = 10.2, 3.2 Hz). (Found: C, 60.03, H, 8.10, $C_{10}H_{16}O_4$ requires C, 59.98; H, 8.06%.) The spectra data of **10**, were identical with those for **13**.

(2R,3S)-6-(1-*Ethoxyethyl*)-2-*methyl*-3,6-*dihydro*-3-*alcohol* **14** *and its Isomer* **11**.—At −40 °C, $NaBH_4$ was added portionwise to a solution of **14** (0.466 g, 2.33 mmol) in methanol (6 ml) containing $CeCl_3 \cdot 7H_2O$ (0.867 g, 2.33 mmol). The reaction was monitored by TLC. The reaction quenched with H_2O (5 ml) and extracted with diethyl ether (20 ml × 3), the ether layer was washed with brine dried over Na_2SO_4. The alcohol **14** was obtained quantitatively as a colorless oil. The synthesis of its isomer **11** was performed in a similar way. ν_{max}/cm^{-1} (KBr) 3427, 3045, 1658, 1380, 1142, 1096; *m/z* (EI) 157 (M^+ − 45, 113; δ_H ([$^2H_6$]acetone) 1.08 (3 H t, *J* = 7.0 Hz), 1.19–1.29 (6 H, m), 2.96 (OH); 3.46–3.74 (4 H, m), 4.80 (1 H, q, *J* = 5.4 Hz), 5.08–5.17 (1 H, m), 5.66–5.75 (1 H, m), 5.90 (1 H, d, *J* = 10.4 Hz); (Found: C, 59.42; H, 8.10. $C_{10}H_{18}O_4$ requires C, 59.39, H, 8.97%.) The spectra data of **14** were same as those for **11**.

(2R,3S)-3-*Acetoxyl*-6-(1-*ethoxyethyl*)-2-*methyl*-3,6-*dihydropyran* **15** *and its Isomer* **12**.—To a solution of **14** (0.086 g, 0.426 mmol) in pyridine (2 ml) was added acetic anhydride (0.065 g, 0.63 mmol) and cat. DMAP, the mixture was stirred for 3 h at room temperature. After completion of the reaction, H_2O (5 ml) was added, and the resultant mixture extracted with acetate (15 ml × 3); the organic layer was then washed with H_2O and brine respectively. Evaporation and chromatography of the residue using light petroleum–acetate (9:1, v/v) as eluant gave **15** as a colorless oil (0.093 g, 90%). Its isomer **12** was prepared in a similar way. ν_{max}/cm^{-1} (KBr) 3048, 2981, 1744, 1375, 1140, 1100; *m/z* (EI) 201 (M^+ − 45), 113; δ_H ([$^2H_6$]acetone) 1.08 (3 H, t, *J* = 7.0 Hz), 1.20–1.31 (6 H, m), 2.05 (3 H, s); 4.83–5.01 (2 H, m), 5.18–5.24 (1 H, m), 5.80 (2 H, *J* = 9.7 Hz); (Found: C, 59.10: H, 8.30. $C_{12}H_{20}O_5$ requires C, 59.00; H, 8.25%.) The spectra data of **15** were the same as those for **12**.

(4S,5R)-*O*-*Acetylosmundalactone* **4** *and its Isomer* **2**.— Compound **15** (0.055 g, 0.223 mmol) was dissolved in acetic acid 92 ml). A solution of CrO_3 (0.022 g, 0.022 mmol) in acetic acid (2 ml) was added to it very slowly. The reaction was monitored by TLC; after completion of the reaction, the mixture was poured into H_2O (4 ml), extracted with diethyl ether, and the organic layer was successively washed with saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. The solvent was then removed at reduced pressure, the residue was purified through column chromatography using light petroleum–acetate (8:1, v/v) as eluant, to give compound **4** as a colorless oil in 70% yield. The isomer **2** was prepared in a similar way. Compound **4**: $[\alpha]_D^{20}$ + 160° (*c*. 2.6, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3050, 2987, 1733, 1634, 1450, 1377; *m/z* (EI) 126 (M^+ − 44), 84, 56; δ_H ($CDCl_3$) 1.26 (3 H, d, *J* = 6.6 Hz), 1.97 (3 H, s), 4.44 (1 H, p, *J* = 6.6 Hz); 5.12, ddd, *J* = 6.6, 3.3, 1.3 Hz), 5.93 (1 H, d, *J* = 10.0 Hz), 6.66 (1 H, dd *J* = 10.0, 3.3 Hz); isomer **2** $[\alpha]_D^{20}$ − 161° (*c*. 2.7, $CHCl_3$ lit.[2] $[\alpha]_D^{20}$ − 172° (*c*. 2.8, $CHCl_3$). (Found: C, 56.50; H, 6.00. $C_8H_{10}O_4$ requires C, 56.47; H, 5.92%). Other spectral data were identical with those for compound **4**.

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