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SECOND GENERATION PALLADIUM-CATALYZED CYCLOALKENYLATION IN IRIDOID LACTONE SYNTHESIS: TOTAL SYNTHESES OF (±)-ONIKULACTONE AND (±)-MITSUGASHIWALACTONE

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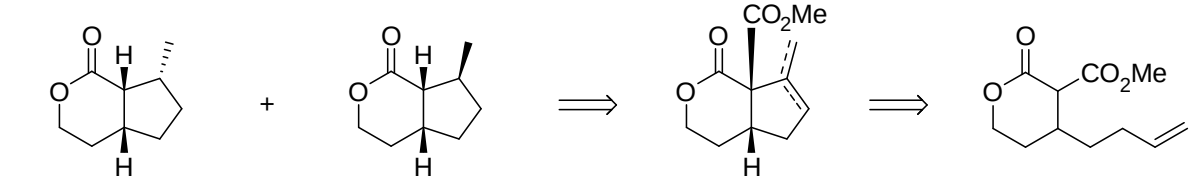
#Dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday.

Abstract – Type-II iridoid lactones, onikulactone (**1**) and mitsugashiwalactone (**2**), were synthesized by employing the second generation palladium-catalyzed cycloalkenylation reaction as the key step.

We recently developed a palladium-catalyzed cycloalkenylation of olefinic keto and lactone esters (second generation palladium-catalyzed cycloalkenylation)[1] and successfully applied this protocol to the total syntheses of (±)-*cis*- and *trans*-195A, a member of the decahydroquinoline class of dendrobatid alkaloids.[2] In an effort to further expand the utility of this catalytic cyclization, we focused on the concise construction of iridoid lactones through strategic application of this reaction. Here, we describe the total syntheses of (±)-onikulactone (**1**) and (±)-mitsugashiwalactone (**2**).

Onikulactone (**1**) and mitsugashiwalactone (**2**) were isolated by Sakan and coworkers as the biological active principles of *Boschniakia rossica* Hult and *Menyanthes trifoliate* L., which have attractive physiological actions on Felidae.[3] Although most natural iridoids include a terpenoid ten-carbon core, onikulactone (**1**) and mitsugashiwalactone (**2**) type-II iridoid lactones are notable exceptions.[4]

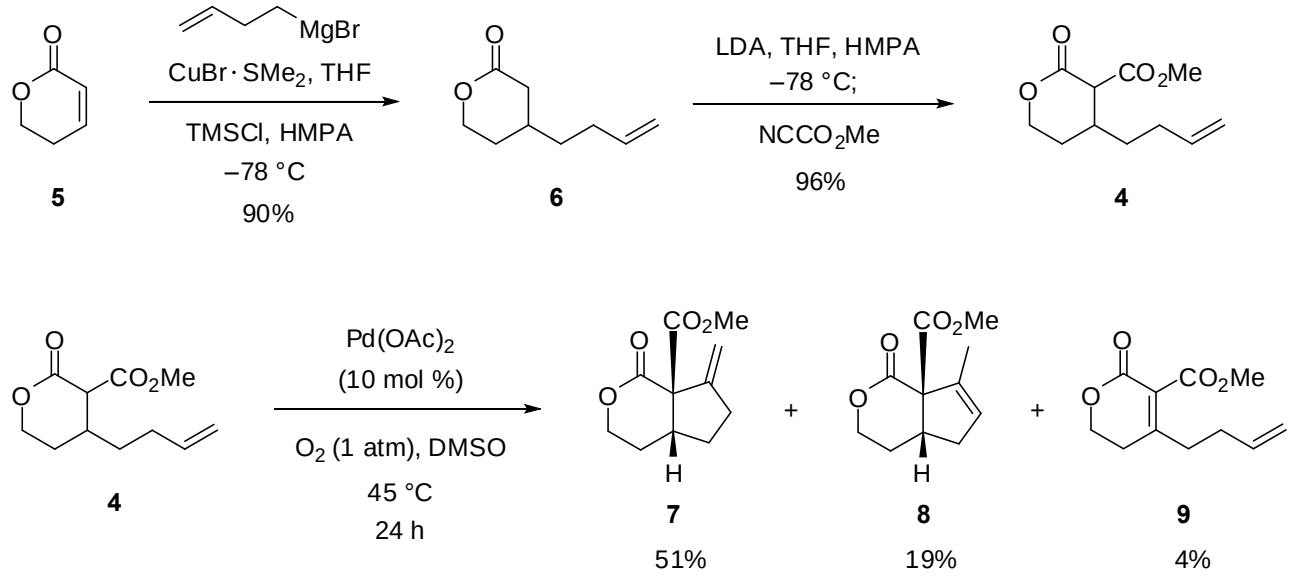


(±)-onikulactone (**1**) (±)-mitsugashiwalactone (**2**) **3** **4**

Scheme 1. Retrosynthetic analysis of onikulactone (**1**) and mitsugashiwalactone (**2**)

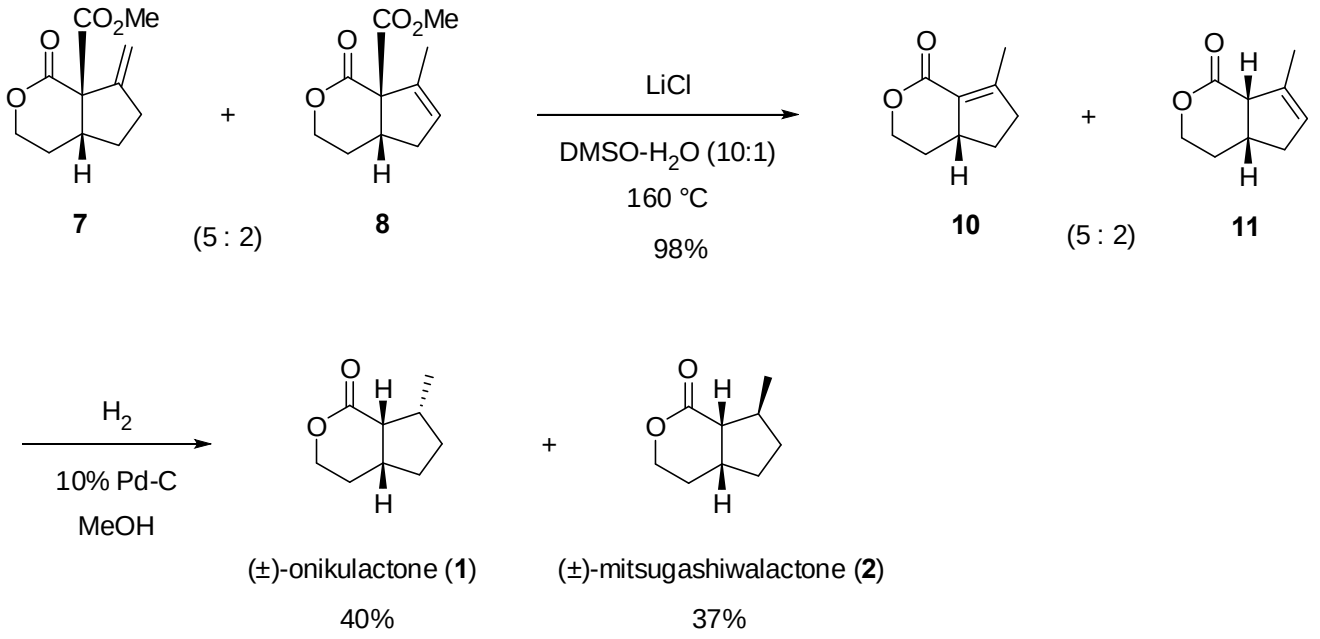
A retrosynthetic analysis of (±)-onikulactone (**1**) and (±)-mitsugashiwalactone (**2**) is shown in **Scheme 1**. We anticipated that both natural products (**1** and **2**) could be synthesized by manipulating the functional groups of the bicyclic lactones **3**, which could be prepared from the olefinic lactone ester **4** by the second generation palladium-catalyzed cycloalkenylation developed by us.[1]

Conjugate addition of homoallyl magnesium bromide to commercially available 5,6-dihydro-2*H*-pyran-2-one (**5**) gave rise to **6**, in 90% yield, which was transformed to the lactone ester **4**[1a] as a 1:3 mixture of diastereoisomers. Surprisingly, application of a tandem conjugate addition–trapping procedure to **5** using methyl cyanoformate provided **6** (< 70%) instead of **4**. The second generation palladium-catalyzed cycloalkenylation of **4** was conducted for 24 h in the presence of 10 mol % $Pd(OAc)_2$ to afford the desired cyclization products **7**[1a] and **8**[5] in 70% total yield together with **9** (4%) (**Scheme 2**).



Scheme 2. Synthesis of bicyclic lactones **7** and **8**.

The Krapcho reaction of the isomeric mixture **3** was performed by application of lithium chloride to give the unsaturated bicyclic lactones **10** and **11**[5] in a 5:2 mixture in 98% yield. The ratio between **10** and **11** appeared to reflect the ratio of the cyclization products **7** and **8**. This was confirmed by individual conversion of **7** and **8** to **10** and **11**, respectively. Finally, hydrogenation of a mixture of unsaturated lactones **10** and **11** furnished (±)-onikulactone (**1**) and (±)-mitsugashiwalactone (**2**) in 40% and 37% yield, respectively. Interestingly, each hydrogenation of **10** and **11** led to (±)-**1** and (±)-**2** as a 1:1 mixture. (±)-Mitsugashiwalactone (**2**) could be generated through *syn*-addition of hydrogen followed by epimerization (**Scheme 3**). Each stereoisomer was easily isolated by flash column chromatography, and the NMR spectral characterizations of the synthetic (±)-**1** and (±)-**2** were identical to the corresponding previously reported spectra.[6]



Scheme 3. Total syntheses of (±)-onikulactone (**1**) and (±)-mitsugashiwalactone (**2**)

EXPEIMENTAL

IR spectra were measured on a SHIMADZU FT-IR 8300 spectrophotometer. ^{1}H NMR spectra were recorded on Varian 400 MR (400 MHz) or JEOL JX-500 (500 MHz) spectrometers with tetramethylsilane (δ 0) or $CHCl_3$ (δ 7.26) as an internal standard. Mass spectra were recorded on JEOL JMS-AX 700 spectrometers.

Onikulactone (**1**) and Mitsugashiwalactone (**2**)

To a stirred solution of a 5:2 mixture of **10** and **11** (3.5 mg, 2.30×10^{-5} mol) in MeOH (1.0 mL) was added 10% Pd-C (0.5 mg) and the resulting mixture was stirred at room temperature for 1.5 h under an atmosphere of hydrogen. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography with hexane-EtOAc (3:1 v/v) as an eluent, giving onikulactone (**1**) (1.4 mg, 40%) and mitsugashiwalactone (**2**) (1.3 mg, 37%) as a colorless oil respectively.

Data for onikulactone (**1**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (1H, ddd, *J* = 11.5, 6.4 and 3.7 Hz), 4.22 (1H, ddd, *J* = 11.5, 8.7 and 3.2 Hz), 3.02 (1H, dd, *J* = 10.1 and 8.7 Hz), 2.63-2.58 (1H, m), 2.50-2.42 (1H, m), 2.01-1.94 (2H, m), 1.79-1.72 (1H, m), 1.65-1.46 (3H, m), 1.10 (3H, d, *J* = 6.8 Hz); LRMS *m/z* 154 (M^+), 99; HRMS calcd for $C_9H_{14}O_2$ 154.0994, found 154.0992.

Data for mitsugashiwalactone (**2**); IR (neat) 1733, 1257, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (1H, ddd, *J* = 11.2, 6.8 and 2.8 Hz), 4.19 (1H, ddd, *J* = 11.2, 8.4 and 2.8 Hz), 2.61-2.51 (1H, m), 2.37 (1H,

dd, *J* = 10.4 and 9.2 Hz), 2.28-2.17 (1H, m), 2.06-1.98 (2H, m), 1.92 (1H, dddd, *J* = 12.0, 6.0, 6.0 and 1.6 Hz), 1.56-1.48 (1H, m), 1.37-1.14 (2H, m), 1.20 (3H, d, *J* = 6.8 Hz); LRMS *m/z* 154 (M^+), 99; HRMS calcd for $C_9H_{14}O_2$ 154.0994, found 154.0992.

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5. Satisfactory analytical data were obtained for all new compounds. Compound **8**: IR (neat) 1745 and 1730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (1H, br s), 4.35 (1H, ddd, *J* = 11.2, 7.6 and 3.2 Hz), 4.28 (1H, dddd, *J* = 11.2, 7.2, 2.8, and 0.4 Hz), 3.78 (3H, s), 3.08-3.01 (1H, m), 2.79-2.70 (1H, m), 2.22-2.06 (2H, m), 1.87 (3H, br s), and 1.77-1.69 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 168.3, 137.0, 131.4, 67.7, 66.9, 53.1, 41.1, 38.1, 29.4, and 14.8. LRMS m/z 210 (M^+). HRMS calcd for $C_{11}H_{14}O_4$ (M^+) 210.0892, found 210.0890. Compound **11**: IR (neat) 1713 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ 5.55 (1H, br s), 4.35-4.20 (2H, m), 3.80-3.50 (1H, m), 3.00-2.84 (1H, m), 2.74 (1H, dddd, *J* = 16.4, 9.2, 4.8, and 2.4 Hz), 2.14-1.98 (2H, m), 1.81 (3H, br s), and 1.72-1.61 (1H, m). LRMS m/z 152 (M^+). HRMS calcd for $C_9H_{12}O_2$ 152.0837, found 152.0836.
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