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2ND GENERATION PALLADIUM-CATALYZED CYCLOALKENYLATION IN IRIDOID SYNTHESIS: DIASTEREOSELECTIVE TOTAL SYNTHESES OF ISOIRIDOMYRMECIN AND ISODIHYDRONEPETALACTONE

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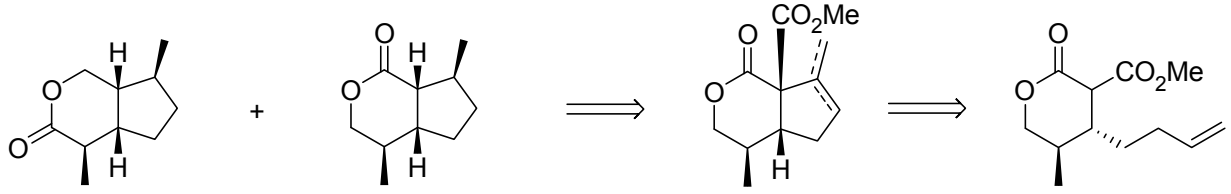
#Dedicated to Professor Albert Padwa on the occasion of his 75th birthday

Abstract – Two different types of iridoids, isoiridomyrmecin and isodihydronepetalactone, were diastereoselectively synthesized using a 2nd generation palladium-catalyzed cycloalkenylation as the key step.

Recently, we described the total syntheses of (±)-onikulactone and (±)-mitsugashiwalactone using a 2nd generation palladium-catalyzed cyclolalkenylation.[1] As a continuing interest in constructing an iridoid skeleton, herein we report that two different types of iridoids, (±)-isoiridomyrmecin (**1**) and (±)-isodihydronepetalactone (**2**), were prepared successfully in the same manner described earlier.

Isoiridomyrmecin (**1**), which was isolated from *Iridomyrmex nitidus* in 1956,[2] exhibits many biological activities.[3] In 1965, isodihydronepetalactone (**2**) was isolated from *Actinidia polygama*.[4] Because iridoids exhibit significant biological activities, numerous synthetic approaches to **1** and **2** have been developed.[5,6]

Scheme 1 outlines our retrosynthetic plan for (±)-isoiridomyrmecin (**1**) and (±)-isodihydronepetalactone (**2**). We envisaged that both **1** and **2** could be obtained by functional group manipulations of cyclization product **3**, which could be synthesized from *trans* substituted lactone ester **4** by employing 2nd generation palladium-catalyzed cycloalkenylation.

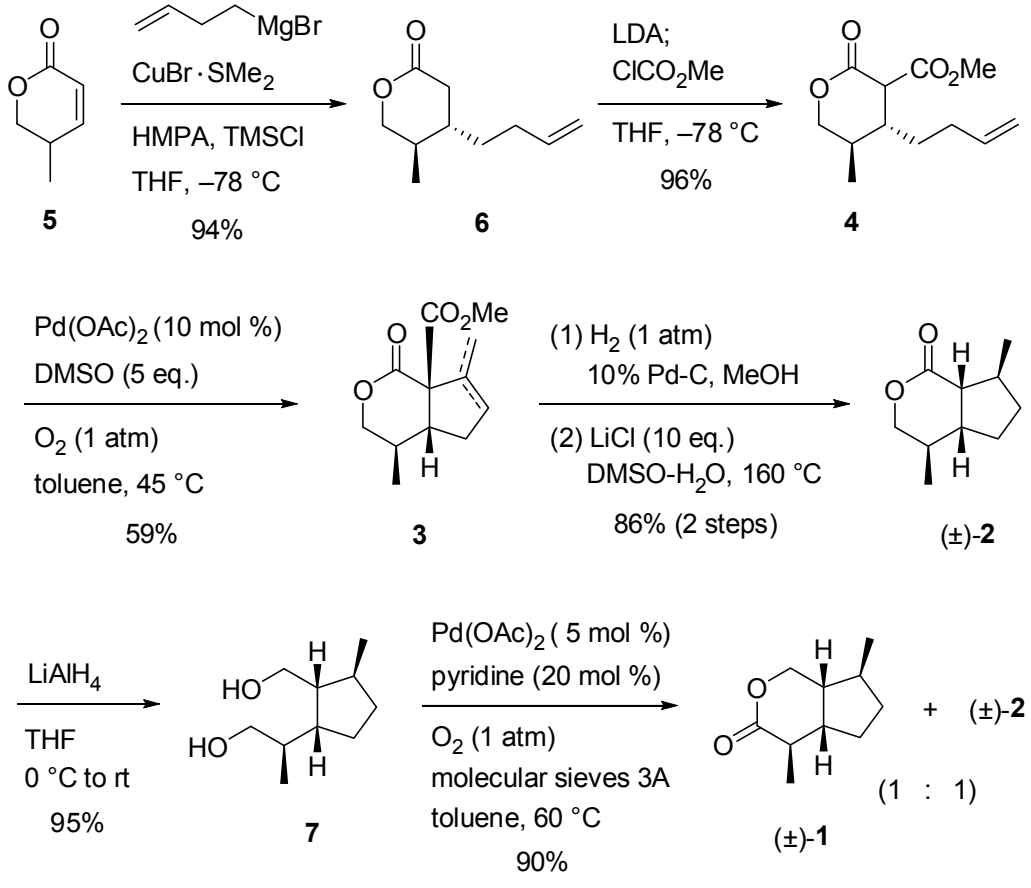


(±)-Isoiridomyrmecin (**1**) (±)-Isodihydronepetalactone (**2**) **3** **4**

Scheme 1. Retrosynthetic analysis of (±)-isoiridomyrmecin (**1**) and (±)-isodihydronepetalactone (**2**)

Conjugate addition of homoallyl magnesium bromide to unsaturated lactone **5** provided **6** (94%) as a single stereoisomer. Compound **6** was then subjected to methoxycarbonylation in the presence of LDA to afford lactone ester **4** in 96% yield as a 3:1 mixture of diastereoisomers. The 2nd generation palladium-catalyzed cycloalkenylation of substrate **4** was subsequently performed in the presence of 10 mol% of $Pd(OAc)_2$ to furnish desired cyclization product **3** in 59% yield as a mixture of olefin isomers. Without separation of the *endo* and *exo* isomers, compound **3** was reduced in the presence of 10% Pd-C under one atmosphere of hydrogen to give the corresponding lactone ester, which was transformed into (±)-isodihydronepatalactone (**2**) in 86% total yield in two steps using the Krapcho reaction. The spectral data of synthetic (±)-isodihydronepetalactone (**2**) were identical to those previously reported.[6a]

To synthesize (±)-isoiridomyrmecin (**1**), compound **2** was reduced with $LiAlH_4$ to give diol **7**, which was subsequently oxidized with catalytic $Pd(OAc)_2$ in the presence of pyridine and molecular sieves 3A[7] to give a 1:1 mixture of the desired product, (±)-isoiridomyrmecin (**1**), and the starting material, (±)-isodihydronepatalactone (**2**), in 90% yield. Each natural product was separated by HPLC, and the ^1H and ^{13}C NMR spectral data of synthetic (±)-isoiridomyrmecin (**1**) were identical to those provided by Professor Tsunoda (**Scheme 2**).[5j]



Scheme 2. Diastereoselective total syntheses of (±)-isoiridomyrmecin (**1**) and (±)-isodihydronepetalactone (**2**)

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EXPERIMENTAL

IR spectra were measured on a SHIMAZU FT-IR 8300 spectrophotometer. ^{1}H NMR spectra were recorded on Varian 400 MR (400 MHz) spectrometer with $CHCl_3$ (δ 7.26) as an internal standard. ^{13}C NMR spectra were recorded on Varian 400 MR (100 MHz) spectrometer with $CHCl_3$ (δ 77.16) as an internal standard. Mass spectra were recorded on JEOL JMS-700 spectrometers. All compounds purified by chromatography were sufficiently pure (> 95% by ^{1}H NMR analysis) for use in subsequent reactions.

(4*S,5*R**)-4-(3-Butenyl)-tetrahydro-5-methylpyran-2-one** (**6**). Copper(I) bromide-dimethyl sulfide complex (172 mg, 0.837 mmol) and HMPA (3.5 mL) were added to a solution of 3-butenylmagnesium bromide, prepared from magnesium turnings (299 mg, 12.3 mmol) and 4-bromo-1-butene (1.25 mL, 12.3 mmol) in THF (25 mL), at –78 °C. After 30 min, a solution of **5** (889 mg, 7.93 mmol) and TMSCl (2.2 mL, 17 mmol) in THF (8 mL) was added dropwise at –78 °C. After 1.5 h, 10% aqueous NH_4Cl solution was added, and the resulting mixture was extracted three times with hexane-EtOAc (3:1 v/v), washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and concentrated. The residue was subjected to flash chromatography (hexane-EtOAc = 3:1 v/v) to provide **6** (1.259 mg, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (1H, ddt, *J*=17.2, 10.0, 6.8 Hz), 5.04 (1H, ddt, *J*=17.2, 1.6, 1.6 Hz), 5.00 (1H, ddt, *J*=10.0, 1.6, 1.6 Hz), 4.26 (1H, dd, *J*=11.2, 4.8 Hz), 3.88 (1H, dd, *J*=11.2, 9.2 Hz), 2.70 (1H, dd, *J*=17.2, 6.0 Hz), 2.20-2.10 (1H, m), 2.19 (1H, dd, *J*=17.2, 8.8 Hz), 2.07-1.96 (1H, m), 1.78-1.57 (3H, m), 1.36-1.28 (1H, m), 1.00 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 13.7, 115.5, 73.5, 37.3, 34.6, 33.58, 33.56, 30.3, 15.7; IR (neat) 2974, 2917, 1746, 1213, 1051 cm^{-1}; HRMS (EI) m/z 168 (M^+) calcd for $C_{10}H_{16}O_2$ 1168.1150, found 168.1146.

Methyl (4*R,5*R**)-4-(3-butenyl)-tetrahydro-5-methyl-2-pyrone-3-carboxylate** (**4**)**.** A solution of **6** (263.1 mg, 1.56 mmol) in THF (3 mL) was added dropwise to a solution of LDA, prepared from diisopropylamine (0.50 mL, 3.6 mmol) and *n*-butyllithium (1.65 M in hexane, 2.0 mL, 3.3 mmol) in THF (8 mL), at –78 °C. After 1 h, methyl chloroformate (0.12 mL, 1.6 mmol) was added dropwise at –78 °C. After 1 h, 10% aqueous NH_4Cl solution was added. The resulting mixture was extracted three times with hexane-EtOAc (3:1 v/v), washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (hexane-EtOAc, 4:1 v/v) to afford **4**

(337.7 mg, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (1H, ddt, *J*=17.2, 10.4, 6.4 Hz), 5.03 (1H, ddt, *J*=17.2, 1.6, 1.6 Hz), 5.00 (1H, ddt, *J*=10.4, 1.6, 1.6 Hz), 4.22 (1H, dd, *J*=11.2, 4.0 Hz), 3.99 (1H, dd, *J*=11.2, 8.4 Hz), 3.80 (3H, s), 3.36 (1H, d, *J*=8.0 Hz), 2.15-2.04 (3H, m), 1.89-1.78 (1H, m), 1.60-1.45 (2H, m), 1.06 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.5, 137.4, 115.7, 72.6, 53.1, 52.5, 40.8, 33.3, 33.0, 30.0, 16.6; IR (neat) 2958, 2929, 1732, 1157 cm^{-1}; HRMS (EI) m/z 226 (M^+) calcd for $C_{12}H_{18}NO_4$ 226.1205, found 226.1214.

Methyl (1*S,5*R**,6*R**)-5-Methyl-9-methylene-2-oxo-3-oxa-bicyclo[4.3.0]nonane-1-carboxylate** (**3**) (**exo isomer**) and **Methyl (1*S**,5*R**,6*R**)-5,9-Dimethyl-2-oxo-3-oxa-bicyclo[4.3.0]nona-8-ene-1-carboxylate** (**3**) (**endo isomer**)**.** To a solution of **4** (202.4 mg, 0.895 mmol) in toluene (8 mL) were added DMSO (0.31 mL, 4.4 mmol) and $Pd(OAc)_2$ (19.8 mg, 88.2 mmol) at ambient temperature and the resulting mixture was stirred at 45 °C under one atmosphere of oxygen. After 84 h, the reaction mixture was filtered through Celite®, and concentrated. The residue was subjected to flash chromatography (hexane-EtOAc, 3:1 v/v) to provide **3** (102.3 mg, 51%, 59%: based upon recovered starting material, exo:endo=2:1) as a colorless oil. Each isomer was separated by HPLC. *Exo isomer***:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (1H, dd, *J*=2.4, 2.4 Hz), 5.31 (1H, dd, *J*=2.0, 2.0 Hz), 4.20 (1H, dd, *J*=11.2, 4.0 Hz), 3.89 (1H, dd, *J*=11.2, 11.2 Hz), 3.78 (3H, s), 2.62 (1H, ddd, *J*=9.2, 6.4, 6.4 Hz), 2.54-2.41 (2H, m), 1.98 (1H, ddq, *J*=8.8, 6.8, 6.8 Hz), 1.84-1.72 (1H, m), 1.57 (1H, dddd, *J*=13.2, 7.6, 7.6, 6.0 Hz), 1.04 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 168.6, 146.7, 113.5, 73.2, 63.0, 53.5, 50.5, 32.3, 31.1, 28.8, 15.4; IR (neat) 2957, 1732, 1236 cm^{-1}; HRMS (EI) m/z 224 (M^+) calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1048. *Endo isomer***:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70-5.60 (1H, m), 4.19 (1H, dd, *J*=11.2, 3.6 Hz), 3.95 (1H, dd, *J*=11.2, 9.6 Hz), 3.78 (3H, s), 2.74 (1H, dddd, *J*=16.4, 8.8, 2.4, 2.4 Hz), 2.66 (1H, ddd, *J*=8.8, 8.8, 4.0 Hz), 2.11 (1H, dddq, *J*=16.4, 4.0, 2.4, 2.4 Hz), 1.89-1.77 (4H, m), 1.05 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 168.9, 137.3, 130.5, 72.4, 70.0, 53.3, 49.2, 37.4, 35.4, 15.8, 15.1; IR (neat) 2957, 1730, 1244 cm^{-1}; HRMS (EI) m/z 224 (M^+) calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1049.

(1*R,5*R**,6*R**,9*S**)-5,9-Dimethyl-3-oxa-bicyclo[4.3.0]nonan-2-one** (**2**)**.** A solution of **3** (89.1 mg, 0.397 mmol) in MeOH (3 mL) in the presence of 10% Pd/C (20 mg) was stirred under an atmosphere of hydrogen. After 42 h, the reaction mixture was filtered through Celite® and concentrated. The residual oil was dissolved in a mixture of DMSO (2.0 mL) and H_2O (0.4 mL). LiCl (181 mg, 4.27 mmol) was added, and the resulting mixture was heated at 160 °C for 8 h. After the mixture was cooled to rt, aqueous NaCl

solution was added, extracted three times with hexane-EtOAc (3:1 v/v), dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (hexane-EtOAc, 3:1 v/v) to afford **2** (57.2 mg, 86% for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (1H, dd, *J*=10.8, 3.2 Hz), 3.87 (1H, dd, *J*=10.8, 10.8 Hz), 2.34 (1H, dd, *J*=10.8, 8.8 Hz), 2.28 (1H, ddd, *J*=10.0, 6.4, 6.4 Hz), 2.13-1.98 (2H, m), 1.86 (1H, dddd, *J*=12.0, 6.0, 6.0, 2.0 Hz), 1.60 (1H, ddqd, *J*=9.6, 9.6, 6.8, 3.2 Hz), 1.23-1.10 (2H, m), 1.20 (3H, d, *J*=6.8 Hz), 0.99 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 73.0, 49.1, 44.8, 38.9, 35.3, 34.5, 32.0, 20.4, 15.9; IR (neat) 2956, 1733, 1182, 1051 cm^{-1}; HRMS (EI) m/z 168 (M^+) calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1161.

(*R)-2-[(1*R**,2*R**,3*S**)-2-(hydroxymethyl)-3-methylcyclopentyl]propan-1-ol** (**7**).[5b] A solution of **2** (65.9 mg, 0.392 mmol) in THF (4 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (44.3 mg, 1.17 mmol) in THF (4 mL) at 0 °C. After 1 h, saturated aqueous Na_2SO_4 solution (0.8 mL) was added dropwise, and then the mixture was allowed to warm to rt. The resulting white solid was filtered off and the filtrate was concentrated. The residue was subjected to flash chromatography (EtOAc) to afford **7** (64.4 mg, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (1H, dd, *J*=10.4, 7.2 Hz), 3.54 (1H, dd, *J*=10.4, 6.0 Hz), 3.49 (1H, dd, *J*=10.4, 5.6 Hz), 3.40 (1H, dd, *J*=10.4, 5.6 Hz), 2.69 (2H, br s), 1.88-1.72 (6H, m), 1.34-1.20 (61H, m), 1.10-0.97 (1H, m), 1.01 (3H, d, *J*=6.8 Hz), 0.90 (3H, d, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.1, 63.6, 50.6, 44.9, 37.2, 35.5, 32.1, 29.3, 22.6, 16.9; IR (neat) 3262, 2949, 2866, 1455, 1016, 830 cm^{-1}.

(1*R,5*R**,6*S**,9*S**)-5,9-Dimethyl-3-oxa-bicyclo[4.3.0]nonan-4-one** (**1**). Pyridine (5.8 mL, 73 μmol), molecular sieves 3Å (180 mg) and $Pd(OAc)_2$ (4.1 mg, 18 μmol) were added to a solution of **7** (62.7 mg, 0.364 mmol) in toluene (4 mL). The mixture was heated at 60 °C under one atmosphere of oxygen. After 12 h, the mixture was filtered through Celite®, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc = 3:1 v/v) to provide **1** and **2** (54.9 mg, 90%, **1**:**2**=1:1) as a colorless oil. Each natural product was isolated by HPLC (hexane/2-propanol = 20:1 v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38-4.33 (1H, m), 3.99-3.92 (1H, m), 2.31 (1H, dq, *J*=10.0, 6.4 Hz), 2.17-1.97 (3H, m), 1.95-1.84 (2H, m), 1.65 (1H, ddq, *J*=10.0, 6.8, 6.8 Hz), 1.37-1.21 (5H, m), 1.19 (3H, d, *J*=6.4 Hz), 1.05 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 69.6, 45.4, 43.3, 39.2, 38.4, 35.4, 33.2, 19.3, 14.1 cm^{-1}; HRMS (EI) m/z 168 (M^+) calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1151.

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