Synthesis of Naturally Occurring Dienamides by Palladium-Catalyzed Carbonyl Alkenylation

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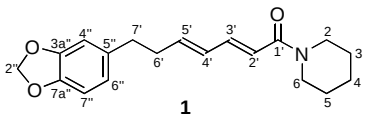
Received October 9th, 1998

Dedicated to Professor Hans-Dieter Martin on the Occasion of his 60th Birthday

Keywords: Eliminations, Alkaloids, Amides, Palladium, Piperdardine, Chingchengenamide A

Abstract. Piperdardine **1** and chingchengenamide A **2**, naturally occurring dienamides, are synthesized in 28% and 16% overall yield, respectively, from commercially available safrole **3**. The key steps involve aldol addition to the enal **5** and mild palladium-catalyzed elimination of the carbonates **7** and **10**.

Recently, we reported on a mild and stereoconvergent palladium-catalyzed alkenylation reaction of α,β-unsaturated aldehydes [1]. Here, the application of this method to a short synthesis of the naturally occurring dienamides piperdardine **1** and chingchengenamide A **2** is described. The amide **1** was recently isolated from the stem of *Piper tuberculatum*, a plant which serves as a sedative and as an antidote for snake bite in Brazil [2]. *Asarum chingchengense*, the source of chingchengenamide A **2**, is used in China as a folk medicine for diaphoresis and as an emetic [3]. According to a recent study, an effect of **2** on the invasion of human MCF-7/6 breast carcinoma cells was not detected [4]. The same amide **2**, a synthesis of which was described recently [5], was also found in *Piper falconeri* and showed insecticidal activity against flies and mosquitoes [6]. Having in hand an easy protocol for the alkenylation of α,β-unsaturated aldehydes, we applied the method to the preparation of chingchengenamide A **2** and to the first synthesis of piperdardine **1**.



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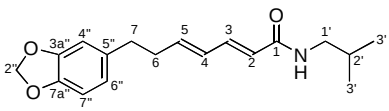

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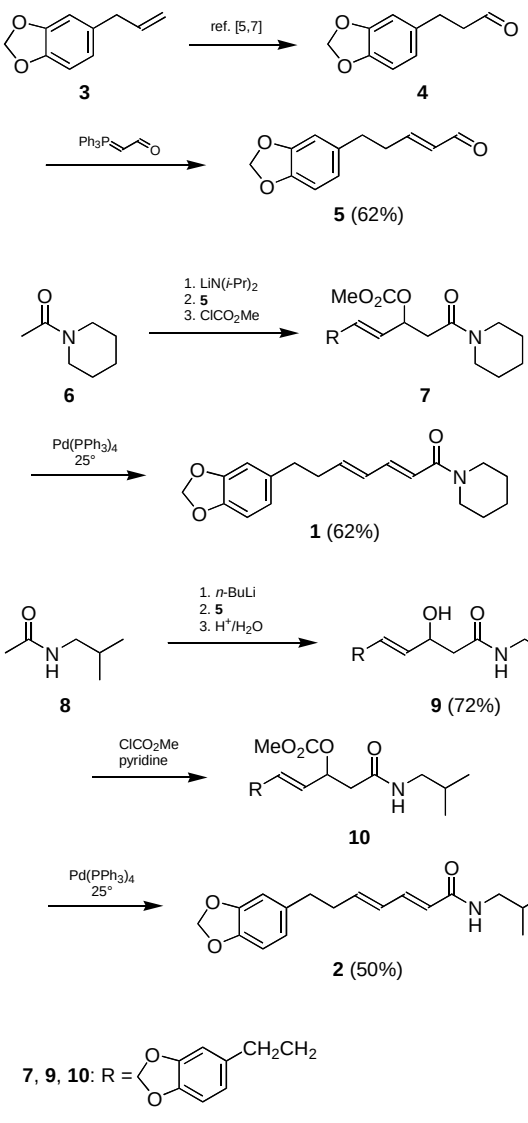
Thus, commercially available safrole **3** was converted into the aldehyde **4** by hydroboration and subsequent oxidation, according to a known protocol [5, 7]. Subsequent treatment with (formylmethylene)triphenylphosphorane followed by acidic hydrolysis [8] led to the enal **5**, which served as the intermediate for the preparation of both amides **1** and **2**. In order to obtain piperdardine **1**, acetyl piperidine **6** was deprotonated to give the lithium enolate, and added to the aldehyde **5**. The alkoxide thus formed was protected *in situ* by addition of methyl chloroformate. When the carbonate **7** obtained thereby was treated with 5 mol% of $Pd(PPh_3)_4$ at room temperature, a smooth conversion into the dienamide **1** occurred. The product **1** turned out to be identical with the natural product. The overall yield of the alkenylation step amounted to 62%, starting from **5**.



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Chingchengenamide A **2** was available in an analogous way. Thus *N-i*-butyracetamide **8** was deprotonated twice and added to the aldehyde **5** to give the allylic alcohol **9** in 72% yield. This was converted into the carbonate **10** by reaction with methyl chloroformate in pyridine and subsequently submitted to the palladium-catalyzed elimination to give the amide **2**, which was found to be identical with chingchengenamide A according to the spectroscopic data.

Compared with established alkenylation methods as *e.g.* the Wittig, the Horner-Wadsworth-Emmons and the Julia reaction, the protocol used here avoids not only the tedious removal of phosphine oxides but also the use of toxic reagents like phosphonates and sodium amalgam [9]. The naturally occurring dienamides **1** and **2** are thus available in a straightforward manner in 28% and 16% overall yield, respectively, starting from safrole **3**.

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. The latter institution also kindly provided a doctoral fellowship to I. S.

Experimental

The following spectrometers were used: NMR spectra: Bruker DRX 500; $CDCl_3$ solutions and TMS as internal standard. The assignment of the signals refers to the numbering given in formulae **1** and **2**. Mass spectra: Varian MAT CH5. IR spectra: Bruker Vector 22. Chromatography: TLC: Silica gel 60 F_{254} (Merck). Column chromatography: Silica gel 60, mesh size 0.04–0.063 mm (Merck). Elemental analyses were carried out by Institut f. Pharmazeutische Chemie, Universität Düsseldorf. Tetrahydrofuran (THF) was predried with KOH and distilled under N_2 from sodium/benzophenone. It was taken from the receiving flask, which was closed by a septum, using syringes or cannulas. Reactions performed at temperatures lower than –20 °C were monitored by introducing a thermocouple, connected to a resistance thermometer (Ebro), through a septum into the reaction mixture. General remarks concerning the handling of lithium enolates and other organolithium compounds are given in ref. [10].

3-(1,3-Benzodioxol-5-yl)-propanal (**4**) was prepared according to ref. [7]

5-(1,3-Benzodioxol-5-yl)-2-pentenal (**5**)

A solution of **4** (0.89 g, 5.00 mmol) and (formylmethylene) triphenylphosphorane (1.59 g, 5.20 mmol) in benzene (50 ml) was refluxed for 24 h. The solvent was removed in a rotary evaporator and the residue was subjected to column chromatography (CH_2Cl_2) to give **5** as a light yellow oil. Yield 0.63 g (62%); R_f = 0.42. – IR: ν/cm^{-1} = 2896, 1688, 1637, 1503, 1490, 1443, 1246, 1188, 1125, 1039, 973, 935, 810. – ^{1}H NMR (500 MHz): δ/ppm = 2.59–2.65 (m, 2H, H-4), 2.75 (t, ^3J = 7.5 Hz, 2H, H-5), 5.93 (s, 2H, H-2'), 6.12 (ddt, ^3J = 15.7 Hz, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, H-2), 6.63 (dd, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1H, H-6'), 6.67 (d, ^4J = 1.7 Hz, 1H, H-4'), 6.74 (d, ^3J = 7.8 Hz, 1H, H-7'), 6.83 (dt, ^3J = 15.7 Hz, ^3J = 6.7 Hz, 1H, H-3), 9.49 (d, ^3J = 7.8 Hz, H-1). – ^{13}C NMR (125 MHz): δ/ppm = 33.8 (C-5), 34.5 (C-4), 100.9 (C-2'), 108.3 (C-4'), 108.7 (C-7'), 121.2 (C-6'), 133.5 (C-2), 134.0 (C-5'), 146.1 (C-7a'), 147.8 (C-3a'), 157.1 (C-3), 193.9 (C-1). – MS (EI, 70 eV): *m/z* (%) = 204 (12), 161 (3), 149 (3), 136 (9), 135 (100). C 70.57, H 5.92; found: C 70.45, H 5.82.

$C_{12}H_{12}O_3$	calcd.:	C 70.57	H 5.92
(204.2)	found:	C 70.45	H 5.82.

1-[7-(1,3-Benzodioxol-5-yl)-1-oxo-2,4-heptadienyl]piperidine (Piperdardine) (**1**)

A 50-ml two-necked flask, connected to a combined nitrogen/vacuum-line, was equipped with a magnetic stirrer and a septum. A thermocouple was introduced through the septum. During the following manipulations an N_2 atmosphere was maintained in all flasks. Anhydrous THF (5 ml) and diisopropylamine (0.15 ml, 1.1 mmol) were injected through the septum by syringes. The mixture was stirred at –78 °C, and a 1.6M solution of BuLi in hexane (0.46 ml, 1.075 mmol) was added in such a way that the temperature did not exceed –70 °C. After stirring for 30 min at 0 °C, the mixture was again cooled to –78 °C. In a 25-ml two-necked flask, connected to the combined nitrogen/vacuum-line, a solution of acetyl piperidine (**6**) (0.13 g, 1.05 mmol) in anhydrous THF (5 ml) was stirred at –78 °C. This mixture was added by a cannula to the slightly evacuated 50-ml flask containing the solution of lithium diisopropylamide. After stirring for 30 min at –78 °C the aldehyde **5** (0.20 g, 1.0 mmol) was added slowly by syringe so that the temperature did not exceed –70 °C, and stirring was continued for 30 min at –78 °C. Methyl chloroformate (0.23 ml, 3.0 mmol) was injected, and the mixture was allowed to reach r.t. overnight. A saturated aqueous solution of NH_4Cl (20 ml) was added. The mixture was transferred into a separatory funnel, and the organic layer was separated. The aqueous phase was extracted with diethyl ether (2 × 50 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$) and concentrated in a rotary evaporator. The crude *1-[7-(1,3-Benzodioxol-5-yl)-3-methoxycarbonyloxy-1-oxo-4-heptenyl]piperidine* (**7**) thus obtained was used without purification in the following step. – ^{1}H NMR (500 MHz): δ/ppm = 1.50–1.67 (m, 6H, H-3, H-4, H-5), 2.30 (dt, ^3J = 15.1 Hz, ^3J = 7.6 Hz, 2H, H-6'), 2.48 (dd, ^3J = 15.2 Hz, ^3J = 5 Hz, 1H, H-2'), 2.60 (t, ^3J = 7.6 Hz, 2H, H-7'), 2.80 (dd, ^3J = 15.2 Hz, ^3J = 7.5 Hz, 1H, H-2'), 3.35–3.58 (m, 4H, H-2, H-6), 3.77 (s, 3H, OC$\underline{H}_3$), 5.48–5.55 (m, 2H, H-3', H-4'), 5.85 (dt, ^3J = 14.2 Hz, ^3J = 7.0 Hz, 1H, H-5'), 5.91 (s, 2H, H-2''), 6.59 (dd, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1H, H-6''), 6.64 (d, ^4J = 1.7 Hz, 1H, H-4''), 6.70 (d, ^3J = 7.8 Hz, 1H, H-7'').

A 10-ml two-necked, was equipped with a magnetic stirrer, and connected to a combined nitrogen/vacuum-line was charged with $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol). Anhydrous THF (5 ml) and the crude carbonate **7** obtained above were added, and the mixture was stirred under N_2 at ambient temperature over night. The solvent was distilled off in a rotary evaporator, and the residue was subjected to column chromatography (hexane/ethyl acetate 1:1) to give **1** as a light yellow oil. Yield 0.19 g (62%); R_f = 0.39. – ^{1}H NMR (500 MHz): δ/ppm = 1.54–1.59 (m, 4H, H-3, H-5), 1.62–1.67 (m, 2H, H-4), 2.42 (dt, ^3J = 7.0 Hz, ^3J = 7.3 Hz, 2H, H-6'), 2.66 (t, ^3J = 7.3 Hz, 2H, H-7'), 3.48 (br s, 2H, H-2), 3.61 (br s, 2H, H-6), 5.92 (s, 2H, H-2''), 6.05 (dt, ^3J = 15.1 Hz, ^3J = 7.0 Hz, 1H, H-5'), 6.18 (dd, ^3J = 15.1 Hz, ^3J = 10.8 Hz, 1H, H-4'), 6.26 (d, ^3J = 14.4 Hz, 1H, H-2'), 6.61 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1H, H-6''), 6.66 (d, ^4J = 1.5 Hz, 1H, H-4''), 6.72 (d, ^3J = 8.2 Hz, 1H, H-7''), 7.22 (dd, ^3J = 14.4 Hz, ^3J = 10.8 Hz, 1H, H-3') – ^{13}C NMR (125 MHz): δ/ppm = 24.6 (C-4), 25.6 (C-3), 26.7

(C-5), 35.0 (C-6', C-7'), 43.2 (C-2), 46.8 (C-6), 100.8 (C-2"), 108.1 (C-7"), 108.8 (C-4"), 119.1 (C-2'), 121.1 (C-6"), 129.5 (C-4'), 135.1 (C-5"), 140.8 (C-5'), 142.4 (C-3'), 145.7 (C-7a"), 147.6 (C-3a"), 165.5 (C-1'). The spectroscopic data are in accordance with those described in the literature [2].

7-(1,3-Benzodioxol-5-yl)-3-hydroxy-N-(2-methylpropyl)-4-heptenamide (**9**)

Under N_2 atmosphere, a solution of *N-i*-butyracetamide **8** (0.13 g, 1.1 mmol) in anhydrous THF (5 ml) was stirred in a 50-ml two-necked flask, equipped with a magnetic stirrer, a septum, and a thermocouple. After cooling to –78 °C, a 1.6M solution of BuLi in hexane (1.38 ml, 2.2 mmol) was added dropwise, and the mixture was stirred at 0 °C for 2 h. After the solution was cooled to –78 °C again, the aldehyde **5** (0.20g, 1.0 mmol) was added slowly by syringe so that the temperature did not exceed –70 °C. The mixture was allowed to reach *r.t.* overnight and worked up according to the procedure described above for **7**. The crude product was submitted to column chromatography (hexane/ethyl acetate 1:4) to afford **9**. Yield 0.23 g (72%); R_f = 0.50. – IR (KBr): ν/cm^{-1} = 3312, 2958, 1636, 1570, 1505, 1446, 1262, 1184, 1098, 1049, 965, 923, 814. – ^{1}H NMR (500 MHz): δ/ppm = 0.91 (d, ^3J = 6.7 Hz, 6H, H-3'), 1.72–1.80 (m, 1H, H-2'), 2.27–2.41 (m, 4H, H-2, H-6), 2.59 (t, ^3J = 7.5 Hz, 2H, H-7), 3.08 (t, ^3J = 6.5 Hz, 2H, H-1'), 3.78 (br s, 1H, OH), 4.42–4.46 (m, 1H, H-3), 5.50 (ddd, ^3J = 15.4 Hz, ^3J = 6.5 Hz, ^4J = 1.4 Hz, 1H, H-4), 5.72 (ddt, ^3J = 15.4 Hz, ^3J = 6.7 Hz, ^4J = 1.0 Hz, 1H, H-5), 5.91 (s, 2H, H-2"), 6.13 (br s, 1H, NH), 6.60 (dd, ^3J = 8.0 Hz, ^4J = 1.7 Hz, 1H, H-6"), 6.65 (d, ^4J = 1.7 Hz, 1H, H-4"), 6.71 (d, ^3J = 8.0 Hz, 1H, H-7") – ^{13}C NMR (125 MHz): δ/ppm = 20.1 (C-3'), 28.4 (C-2'), 34.2 (C-6), 35.2 (C-7), 42.8 (C-2), 46.7 (C-1'), 69.5 (C-3), 100.7 (C-2"), 108.1 (C-7"), 108.9 (C-4"), 121.1 (C-6"), 131.2 (C-5), 131.8 (C-4), 135.5 (C-5"), 145.6 (C-7a"), 147.5 (C-3a''), 171.9 (C-1).

$C_{18}H_{25}NO$	calcd.:	C 67.80	H 7.89	N 4.39
(319.4)	found:	C 67.69	H 8.15	N 4.30.

7-(1,3-Benzodioxol-5-yl)-N-(2-methylpropyl)-2,4-heptadienamide (Chingchengenamide A) (**2**)

In a 10-ml two-necked flask, equipped with a magnetic stirrer and connected to a combined nitrogen/vacuum-line, allylic alcohol **9** (0.16 g, 0.5 mmol) was dissolved in $CHCl_3$ (1 ml) and pyridine (2 ml). A solution of methyl chloroformate (0.16 g, 1.7 mmol) in $CHCl_3$ (1 ml) was added dropwise, and the reaction mixture was stirred for 30 min. The solvent was re-moved in a rotary evaporator, and the residue was dissolved in $CHCl_3$. The organic layer was washed twice with aqueous HCl (1N), twice with aqueous NaOH (2N), once with H_2O and dried with $MgSO_4$. The solvent was removed in a rotary evaporator to give the crude *7-(1,3-Benzodioxol-5-yl)-3-methoxycarbonyloxy-N-(2-methylpropyl)-4-heptenamide* **10** which was used without purification in the following step. – ^{1}H NMR (500 MHz): δ/ppm = 0.89 (d, ^3J = 6.6 Hz, 6H, H-3'), 1.70–1.79 (m, 1H, H-2'), 2.29 (dt, ^3J = 7.7 Hz, ^3J = 7.0 Hz, 2H, H-6), 2.35–2.55 (m, 2H, H-2), 2.59 (t, ^3J = 7.7 Hz, 2H, H-7), 3.06 (t, ^3J = 6.4 Hz, 2H, H-1'), 3.76 (s, 3H, OCH$_3$), 5.41–5.52 (m, 2H, H-3, H-4), 5.82–5.89 (m, 1H, H-5), 5.90 (s, 2H, H-2"), 6.20 (br s, 1H, NH), 6.58 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, H-6"), 6.63 (d, ^4J = 1.5 Hz, 1H, H-4"), 6.71 (d, ^3J = 8.0 Hz, 1H, H-7").

A 10-ml two-necked flask was equipped with a magnetic stirrer, connected to a combined nitrogen/vacuum-line and charged with $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol). Anhydrous THF (5 ml) and the crude carbonate **10** obtained above were added, and the mixture was stirred under N_2 at ambient temperature over night. The solvent was distilled off in a rotary evaporator and the residue was subjected to column chromatography (hexane/ethyl acetate 1:1). Thus chingchengenamide A (**2**) was obtained as a light yellow oil. Yield 0.07 g (50%); R_f = 0.61. – ^{1}H NMR (500 MHz): δ/ppm = 0.92 (d, ^3J = 6.6 Hz, 6H, H-3'), 1.75–1.84 (m, 1H, H-2'), 2.42 (dt, ^3J = 7.2 Hz, ^3J = 7.6 Hz, 2H, H-6), 2.65 (t, ^3J = 7.2 Hz, 2H, H-7), 3.14 (t, ^3J = 6.5 Hz, 2H, H-1'), 5.62 (br s, 1H, NH), 5.76 (d, ^3J = 15.0 Hz, 1H, H-2), 5.92 (s, 2H, H-2"), 6.02–6.16 (m, 2H, H-4, H-5), 6.60 (dd, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1H, H-6"), 6.65 (d, ^4J = 1.7 Hz, 1H, H-4"), 6.72 (d, ^3J = 7.8 Hz, 1H, H-7"), 7.22 (dd, ^3J = 15.0 Hz, ^3J = 10.4 Hz, 1H, H-3) – ^{13}C NMR (125 MHz): δ/ppm = 20.1 (C-3'), 28.6 (C-2'), 35.0 (C-6, C-7), 46.9 (C-1'), 100.8 (C-2"), 108.2 (C-7"), 108.8 (C-4"), 121.2 (C-2), 122.2 (C-6"), 128.9 (C-4), 135.1 (C-5"), 141.0 (C-5), 141.6 (C-3), 145.7 (C-7a"), 147.6 (C-3a"), 166.3 (C-1). The spectroscopic data are in accordance with those described in the literature [3, 5, 6].

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