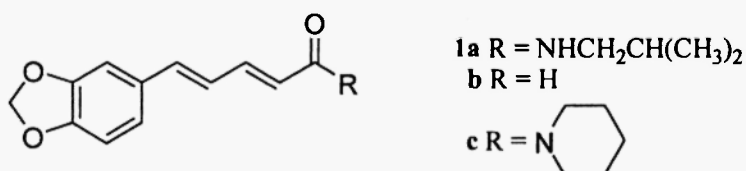# A SIMPLE SYNTHESIS OF PIPERLONGUMININE

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Abstract: A simple and practical method for the synthesis of an alkaloid piperlongumine, an efficient inhibitor of α-melanocyte stimulating hormone, was established by employing Wadsworth-Horner modified Wittig reaction as a key step.

An alkaloid piperolonguminine [*N*-isobutyl-5-(1,3-benzodioxol-5-yl)-2,4-pentadienamide, 1a] was first isolated from *Piper longum* Linn. (1), then also isolated from other *Piper* species (2) as well as other genus (3). *Piper longum*, known as "Pippali", has long been used as an effective drug in the treatment of asthma and chronic bronchitis in the Ayuvedic system of medicine in India (4). Biological properties of the extracts, composed mainly of 1a, piperine (1c), and *N*-isobutyl-(*E,E*)-2,4-decadienamide, were studied to show anti-allergic (5) and tumor inhibitory activity (6). Recent report on the inhibitory activity of 1a on α-melanocyte stimulating hormone-induced tyrosinase synthesis, a key step in melanin biosynthesis, opened a new vista of the 1a as a cosmetic additive (7).

Most of the synthetic methods of piperlongumine employed piperic acid (1b) which could be derived from readily available natural product piperine (8). However, the content of 1c in most pepper plants is low (0.025-6%) and the cost of raw pepper is relatively high.

1a R = NHCH$_2$CH(CH$_3$)$_2$
 b R = H

c R = N (piperidinyl)

The promising potential of piperolongumine as a whitening agent in cosmetic spurred us to design a simple and practical synthetic method to provide sufficient amount for pursuing further biological properties on experimental animals.

Synthetic sequence for 1a was quite straight forward as shown. Wadsworth-Horner modified Wittig condensation (9) of readily available and cheap piperonal (2) with the anion generated from ethyl (*E*)-4-diethylphosphono-2-butenoate (3) gave ethyl piperate (7) in 65% yield. ^{1}H NMR showed a characteristic doublet of doublet (J = 15.3 and 10.5 Hz) for H3 at δ 7.39, a doublet (J = 15.3 Hz) at δ 5.92 for H2, a doublet at δ 6.77 (J = 15.0, 10.0 Hz) for H4, and a doublet (J = 10.3 Hz) at δ 6.70 for H5 for pentadienoic acid moiety. No isomeric product was observed in 250 MHz ^{1}H NMR and 62.5 MHz ^{13}C NMR. The starting phosphono ester 3 was prepared in 90% yield by Arbuzov reaction of commercially available ethyl 4-bromo-2-butenoate (4) and triethyl phosphate. Our attempts for an amination of ethyl piperate by isobutylamine in the presence of sodium methoxide (10) suffered from low yield, which led us to employ an alternative synthetic pathway. The ester was, thus, hydrolyzed to corresponding acid (5), which was condensed with isobutylamine in the presence of catalytic amount of boric acid (11) to yield 1a in 91% two-step yield.

Alternative synthetic route employing aldehyde **7** and triphenylpiperonylphosphonium bromide (**8**) was also pursued to afford the desired ester **4** in similar yield. It is worthy to noting that reaction with **8** gave better yield compared to the reaction with its diethylphosphono congener.
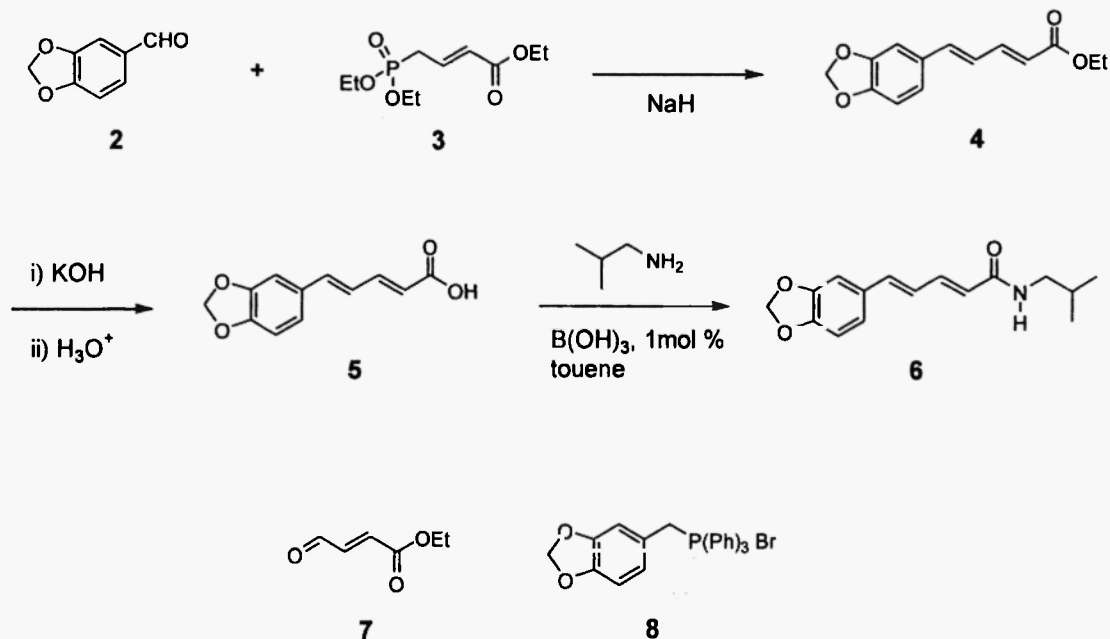
In conclusion, an alkaloid piperlonguminine was streoselectively prepared by employing Wadsworth-Horner modified Wittig reaction as a key step, followed by isobutylamination of piperic acid in presence of 1 mol % $B(OH)_3$.

Experimental

Melting points were determined using a Fischer-Jones melting points apparatus and are not corrected. IR spectra were obtained using a Perkin-Elmer 1330 spectrophotometer. NMR spectra were obtained using a Bruker-250 spectrometer 250 MHz or 400 MHz for ^1H NMR and 62.5 MHz or 100 MHz for ^{13}C NMR and are reported as parts per million (ppm) from the internal standard tetramethylsilane (TMS). The starting **7** (12) and **8** (13) were prepared by employing previously reported method. Chemicals and solvents were commercial reagent grade and used without further purification.

Ethyl (*E*)-4-Diethylphosphono-2-butenoate (2)

Ethyl (*E*)-4-bromo-2-butenonate (18.0 g, 0.10 mol) was added dropwise to triethyl phosphite (18.2 g, 0.104 mol) with stirring. Resulting mixture was heated at 120-130 °C for 2 h. The excess triethyl phosphite was removed under reduced pressure. The residue was distilled under reduced pressure to give 20.2 g (90%) of product as a colorless liquid: bp 109-112 °C (0.01 mmHg, bath temp 160 °C). IR (thin film) υ (1725 (C=O), 1658, 1250, 1025 (P=O), 968 cm^{-1}. ^1H NMR (CDCl$_3$, 250 MHz) δ 6.85 (dtd, J_{trans} = 15.6, ^2J = 7.8, $^3J_{P-H}$ = 7.5 Hz, H3), 5.94 (ddt, J_{trans} = 15.6, ^3J = 1.3, $^4J_{P-H}$ = 6.3 Hz, H2), 4.18 (q, J = 7.2 Hz, 4H), 4.09 (q, J = 7.1 Hz, 2H), 2.72 (ddd, $^1J_{P-H}$ = 22.9, J = 8.0, 1.4 Hz, 2H), 1.30 (t, J = 7.0 Hz, 6H), 1.26 (t, J = 7.5 Hz, 3H).

Ethyl Piperate (4)

NaH (55% in mineral oil 2.3 g, ca 0.05 mol, washed with hexane) was placed in dry DMF (70 mL) under N_2. The slurry was magnetically stirred at 0 °C. Ethyl (*E*)-4-diethylphosphono-2-butenoate (11.2 g, 0.05 mol) in dry DMF (10 mL) was added dropwise. During the addition period the temperature was maintained at 30-35 °C, and cooling was applied if necessary. Resulting mixture was stirred for 4 h. To the reaction mixture was added dropwise over a 20 min period piperonal (MW 150.13, 7.5 g, 0.05 mol) in dry DMF (10 mL). The mixture was kept for 16 h at room temperature, then diluted with water and extracted with ether (4 x 50 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave crude product which was chromatographed on silica gel eluting with CH_2Cl_2. The early fractions (R_f = 0.7 from CH_2Cl_2) afforded 10.90 g (94%) of pale yellow platelets after recrystallization from ether:hexane (1:1): mp 76-77 °C. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.39 (dd, 1H, *J* = 15.3, 10.3 Hz, H3), 6.97 (d, 1H, *J* = 1.5 Hz, H2'), 6.89 (dd, 1H, *J* = 8.0, 1.5 Hz, H6'), 6.77 (dd, 1H, *J* = 15.0, 10.0 Hz, H4), 6.76 (d, 1H, *J* = 8.0 Hz, H5'), 6.70 (d, 1H, *J* = 10.3 Hz, H5), 5.97 (s, 2H, OCH_2O), 5.92 (d, 1H, *J* = 15.3 Hz, H2), 4.20 (q, 2H, *J* = 7.1 Hz), 1.29 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 62.5 MHz) 167.17, 148.49, 148.24, 144.70, 140.07, 130.54, 124.51, 122.91, 120.41, 108.51, 105.82, 101.36, 60.27, 14.31.

Piperic Acid (5)

A mixture of ethyl piperate (2.32, 0.01 mol) and 40% methanolic KOH (100 mL) was heated at 110 °C (bath temp) refluxed for 6 h. Pale yellow precipitate formed was collected and was redissolved in water (60 mL) The resulting aq. solution was acidified with 6 *N* HCl yielded a flocculent yellowish precipitate as piperic acid. The crude piperic acid was recrystallized from CH_3OH to give pale yellow needles in quantitative yield: mp 217-218 °C/lit. mp 217-218 °C (14). ^1H NMR (250 MHz, DMSO-d_6) δ 7.28 (ddd, *J* = 15.0, 4.8, 1.2 Hz, 1H, H3), 7.22 (s, H2'), 7.01-6.89 (m, 4H), 6.03 (s, 2H, -OCH_2O-), 5.91 (d, *J* = 15.0 Hz, H2). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 167.98, 148.40, 148.27, 144.99, 140.14, 130.80, 125.13, 123.46, 121.40, 108.83, 105.99, 101.68.

Piperlonguminine (1a)

Into a stirred solution of piperic acid (6.54 g., 30 mmol) and boric acid (0.02 g, 0.30 mmol) in toluene (88 mL) was added isobutylamine (3.00 g, 40 mmol) in one portion. The resulting mixture was refluxed for 16 h and then ca. 0.6 mL of water was collected in the Dean-Stark trap. The mixture was allowed to cool to room temperature and then poured to hexane (500 mL) leading to the immediate precipitation. Stirring was continued for additional 30 min and then the precipitate was collected to give 7.45 g (91%) of pale yellow solid. Recrystallization from 10% aq. CH_3OH gave fine needles: mp 166-168 °C/lit. mp 166-168 °C (1). ^1H NMR (250 MHz, DMSO-d_6) δ 0.84 (d, 6H, *J* = 6.6 Hz), 1.69 (heptet, 1H), 2.95 (t, 2H, *J* = 6.0 Hz), 6.03 (s, 2H, -OCH_2O-,), 6.10 (d, 1H, *J* = 15.0 Hz, H2), 6.79-6.99 (m, 4H), 7.12 (dd, 1H, *J* = 15.0, 9.5 Hz, H3). 8.03 (t, *J* = 6.7 Hz, NH). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 165.36, 148.13, 147.88, 139.37, 1137.94, 131.09, 125.48, 124.89, 122.85, 108.65, 105.81, 101.46, 46.39, 28.37, 20.41. High resolution mass: 273.33.

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