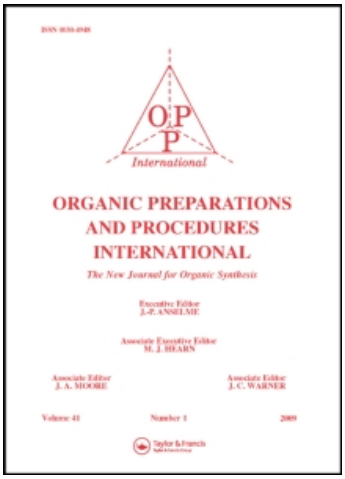


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# A Novel and Practical Synthesis of 2-Amino-5-hydroxypropiophenone

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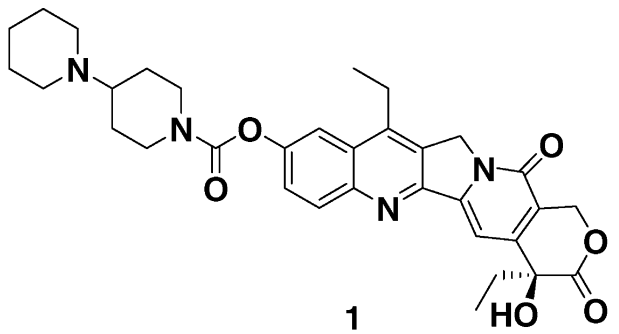
In connection with our recent development of an efficient asymmetric total synthesis of irinotecan (**CPT**-11, **1**), an analogue of the natural product camptothecin, approved by the FDA for treatment of refractory colorectal cancer,[1,2] 2-amino-5-hydroxypropiophenone (**2**) was required as a key intermediate for the construction of the AB ring with (4′*S*)-tricyclic hydroxylactone **3**, another known intermediate bearing CDE ring skeleton for the synthesis of **CPT-11** through a Friedlander condensation strategy.[3] Two precedents for the preparation of this intermediate **2** have been appeared in earlier works based on the

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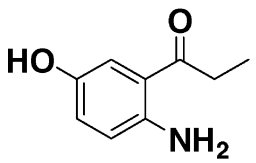


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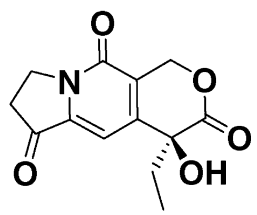


**3**

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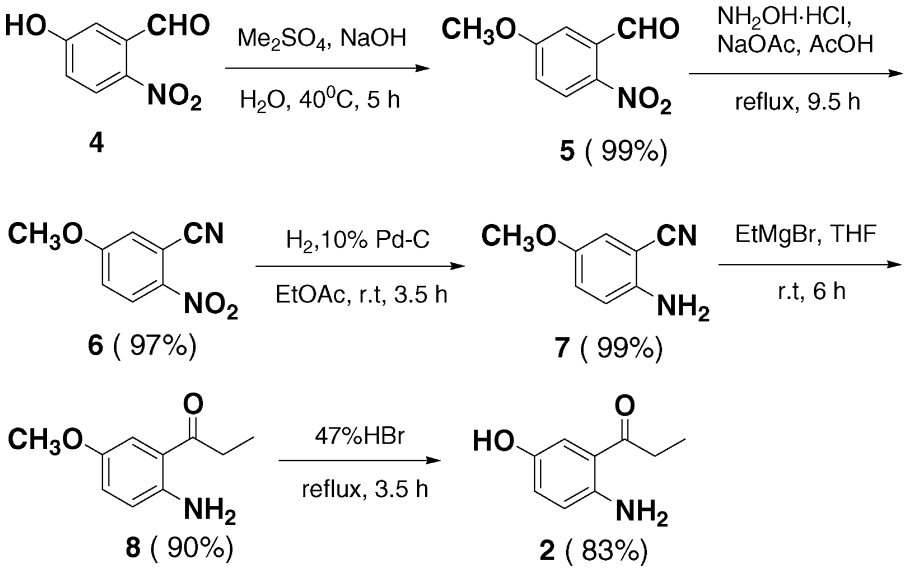
Grignard addition of 5-(benzyloxy)-2-nitrobenzaldehyde with vinylmagnesium bromide and 3-fluorobenzaldehyde with ethylmagnesium bromide as key steps developed by independent groups of Ogawa[4] and Alla[5] in the installation of propionyl group of **2**. However, all these methods suffer from the use of toxic or hazardous reagents, the relatively poor total yield, and tedious handling and chromatographic purification both from a health, safety and technical perspectives, making them impractical for the large scale production in a cost-effective manner. Therefore, an efficient and economic synthetic method remains highly desirable.

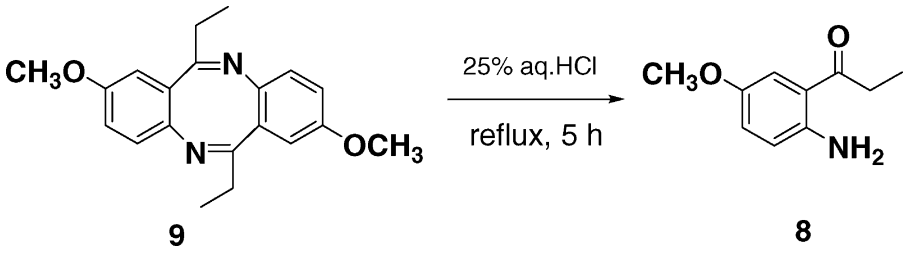
As depicted in *Scheme 1*, our synthesis commenced with 5-hydroxy-2-nitrobenzaldehyde **4**, which can be obtained according to the reported procedure.[6, 7] Compound **4** was then exposed to $Me_2SO_4$ in 30% aqueous NaOH, leading to methyl ether **5** in nearly quantitative yield. Treatment of **5** with $NH_2OH{\cdot}HCl$ in AcOH in the presence of NaOAc under reflux for 9.5 h afforded **6** in 97% yield.

Hydrogenation of **6** in the presence of a catalytic amount of 10% Pd-C at room temperature for 3.5 h gave amine **7** as a pure yellow solid in a nearly quantitative yield. Addition of EtMgBr to **7** in anhydrous THF at 0°C proceeded smoothly to provide propyl ketone **8** as the major product along with 10–15% **9** as by-product. The structure of **9** was confirmed by NMR and GC-MS.[8] Interestingly, compound **9** upon treatment with 25% aqueous HCl under reflux was transformed into **8** in nearly quantitative yield, indicating cleavage of two C=N bonds of **9** could occur *via* acid-hydrolysis (*Scheme 2*). Reaction of a mixture of **8** and **9** with 47%HBr worked well, title compound **2** was obtained in 83% yield, with a GC purity of 98.6%.

In conclusion, a facile and practical process for the preparation of **2** has been developed in an overall yield of 67% starting from the known 5-hydroxy-2-nitrobenzaldehyde **4**. This procedure is amenable to economical and large-scale synthesis of **2**, which avoids tedious




**Scheme 1**




**Scheme 2**

isolation and purification, rigorous reaction conditions, expensive materials and aggressive reagents as found in Ogawa and Alla's preparations.

## Experimental Section

Melting points were measured on a WRS-1B digital melting point apparatus and were uncorrected. Elemental analyses were performed on a Carlo-Erba 1006 elemental analyzer. NMR spectra were recorded with a Bruker Avance-400 spectrometer using TMS as an internal standard. Chemical shifts ($\delta$) are expressed in ppm. GC-MS spectra were recorded on Finnigan Voyager instrument.



### *5-Methoxy-2-nitrobenzaldehyde (5)*

To a stirred solution of 5-hydroxy-2-nitrobenzaldehyde (10.05 g, 59.92 mmol) and $Me_2SO_4$ (30.14 g, 0.24 mol) in $H_2O$ (80 mL) was added dropwise 30% aq. NaOH (30 mL) at 40°C. When the pH of reaction mixture was maintained between 9 and 10, stirring was continued for 5 h at the same temperature. The reaction mixture was cooled to 10°C, the solid was filtered, and the filter cake was washed with cold water (2 × 20 mL), and dried to give **5** (10.78 g, 99% yield, 98.3% purity by GC) as a pale-yellow solid, m.p. 82–83°C ( Lit:[8] 80–81°C); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 10..46 (s, 1H, CHO), 8.14 (d, $J$ = 9.2 Hz, 1H, H-3), 7.31 (d, $J$ = 2.8 Hz, 1H, H-4), 7.14 (dd, $J$ = 9.2, 2.8 Hz, 1H, H-5), 3.95(s, 3H, $OCH_3$), EI-MS (m/z): 181($M^+$), 151($M^+$-NO), 123($M^+$-NO-CO), 108($M^+$-NO-CO-$CH_3$). The $^1$H-NMR is agreement with the data given in the literature.[8]

### *5-Methoxy-2-nitrobenzonitrile (6)*

To a stirred solution of **5** (15.76 g, 87.07 mmol) in glacial acetic acid (40 mL) were added sodium acetate (7.85 g, 95.78 mmol) and hydroxylamine hydrochloride (6.65 g, 95.78 mmol), and the reaction mixture was heated at 110°C for 9.5 h. The reaction mixture was cooled to room temperature. Water (20 mL) was added into the reaction mixture and stirring was continued for 30 min. The precipitated product was filtered, and the filter cake was washed with water (3 × 10 mL), and dried to afford 6 (15.03 g, 97% yield, 98% purity by GC) as a light yellow solid, m.p. 96–97°C ( Lit:[9] 96°C): $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 8.31 (d, $J$ = 9.2 Hz, 1H, H-3), 7.32 (d, $J$ = 2.8 Hz, 1H, H-6), 7.22 (dd, $J$ = 9.2, 2.8 Hz, 1H, H-4), 3.97 (s, 3H, $OCH_3$); EI-MS (m/z): 178($M^+$), 148($M^+$-NO), 117($M^+$-NO-$OCH_3$). The $^1$H-NMR is agreement with the data given in the literature.[9]

***2-Amino-5-methoxybenzonitrile (7)***

To a stirred solution of **6** (5.15 g, 28.4 mmol) in anhydrous EtOAc (30 mL) was added 10% Pd-C (0.5 g), and the mixture was hydrogenated under atmospheric pressure of hydrogen for 3.5 h at 25°C. The mixture was passed through the Celite pad and the solid was rinsed with EtOAc (2 × 5 mL). The combined filtrate was concentrated in vacuo to afford **7** (4.24 g, 99% yield, 99% purity by GC) as a light yellow solid, m.p. 46–47°C ( Lit:[9] 47°C); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 6.96 (dd, $J = 8.8$, 2.8 Hz, 1H, H-4), 6.85 (d, $J = 2.8$ Hz, 1H, H-6), 6.69 (d, $J = 8.8$ Hz, 1H, H-3), 4.23 (s, 2H, $NH_2$), 3.73 (s, 3H, $OCH_3$), EI-MS (m/z): 148($M^+$), 133($M^+$-$CH_3$), 105($M^+$-$CH_3$-CO). The $^1$H-NMR is agreement with the data given in the literature.[9]

***2-Amino-5-methoxypropiophenone (8)***

To a stirred solution of Grignard reagent [prepared from ethyl bromine (12.45 g, 114.1 mmol) and magnesium powder (2.88 g, 119.7 mmol) in dry THF (20 mL) with stirring at reflux for 50 min under nitrogen] was added a solution of **7** (4.2 g, 28.5 mmol) in dry THF (25 mL), while the internal reaction temperature was maintained below 5°C. After completion of the addition, the reaction mixture was stirred at room temperature for 6 h, then cooled to 0°C, and the reaction was quenched by adding 15% aq. HCl (30 mL). The resulting mixture was stirred at room temperature for 2 h, and the pH of the aqueous solution was adjusted to 7 by adding 30% aq. NaOH, then extracted with EtOAc (3 × 15 mL). The organic layer was washed with water (2 × 10 mL) and saturated aq. NaCl (10 mL), then dried over $Na_2SO_4$. The solvent was concentrated *in vacuo* and dried under reduced pressure for 5 h at 40°C to give a mixture of **8** and **9** (5.02 g, **8/9** = 90:10, ratio of GC purity) as a pale yellow solid, and the crude product was recrystallized from EtOH to provide 4.2 g (80% yield) of pure **8** as pale yellow needles, m.p. 63.5–64.5°C ( Lit:[10] 66°C) $^1$H-NMR (400 MHz, DMSO): $\delta$ 7.22 (d, $J = 2.8$ Hz, 1H, H-6), 6.98 (dd, $J = 9.2$, 2.8 Hz, 1H, H-4), 6.82 (s, 2H, $NH_2$), 6.74 (d, $J = 8.8$ Hz, 1H, H-3), 3.71 (s, 3H, $OCH_3$), 2.96 (q, $J = 21.6$ Hz, 2H, $CH_2$), 1.07 (t, $J = 14.4$ Hz, 3H, $CH_3$), EI-MS (m/z): 179($M^+$), 164($M^+$-$CH_3$), 150($M^+$-$CH_2CH_3$),122($M^+$-$COCH_2CH_3$). The $^1$H-NMR is agreement with the data given in the literature.[10]

Although compound **2** was obtained directly from the mixture of **8/9** (*see below*), Compound **9** was isolated as a white solid, mp. 127.4–128.6°C, *via* purification by column chromatography on silica gel (20:1 petroleum ether/ethyl acetate). $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 6.7 (d, $J = 2.4$ Hz, 1H), 6.58 (dd, $J = 8.8$, 2.8 Hz, 1H), 6.47 (d, $J = 8.4$ Hz, 1H), 3.70 (s, 3H), 2.09 (q, $J = 14.8$ Hz, 2H), 0.95 (t, $J = 14.4$, 3H). $^{13}$C-NMR (400 MHz, $CDCl_3$): $\delta$ 153.1(C=N), 137.6(C-O), 128.5(C-N), 117.7(C-1), 113.6(C-3), 110.5(C-4), 67.2(C-6), 55.7(-$OCH_3$), 32.5(-$CH_2$ of Et), 7.9(-$CH_3$ of Et). EI-MS (m/z): 322($M^+$), 307($M^+$-$CH_3$), 292($M^+$-$CH_3$- $CH_3$).

*Anal*. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.58; H, 6.82; N, 8.61

***2-Amino-5-hydroxypropiophenone (2)***

A mixture of **8** and **9** (4.73 g, 26.3 mmol) in 47% aq. HBr (30 mL) was stirred under reflux for 3.5 h, and cooled to 5°C, stirring was continued at this temperature for 1 h. The

precipitate was filtered and washed with cold water (2 × 10 mL), then the wet cake was suspended in water (20 mL) and the pH of the mixture was adjusted to 7–8 by adding 30% aq. NaOH. The resulting suspension was cooled in ice-water bath and stirred for 30 min, and the solid was collected by filtration and washed with water (2 × 10 mL). The solid was dried under reduced pressure at room temperature for 10 h to afford 2 (3.5 g, 83% yield, 98.6% purity by GC) as pale yellow solid, m.p. 144.5–144.9°C ( Lit:[5]147–149°C); $^1$H-NMR (400 MHz, DMSO): $\delta$ 8.63 (s, 1H, OH), 7.10 (d, $J$ = 4 Hz, 1H, H-6), 6.88 (dd, $J$ = 12, 4 Hz, 1H, H-4), 6.64 (d, $J$ = 8 Hz, 1H, H-3), 6.61 (s, 2H, $NH_2$), 2.87 (q, $J$ = 24 Hz, 2H, $CH_2$), 1.05 (t, $J$ = 16 Hz, 3H, $CH_3$), EI-MS (m/z): 165($M^+$), 136($M^+$-$CH_2CH_3$), 108($M^+$-$COCH_2CH_3$); The $^1$H-NMR is agreement with the data given in the literature.[5]

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