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An Efficient Approach to 3,4-Disubstituted Pyridin-2-ones. Formal Synthesis of Mappicine Ketone

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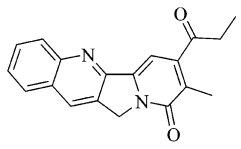
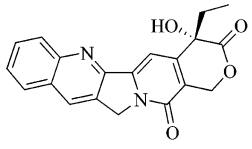
Treatment of 3,4-dihydro-3-tosylpyridin-2-one **5** with sodium hydride and then alkyl halides gave various 3,4-disubstituted pyridin-2-ones **6**. Formal synthesis of mappicine ketone (**1**) was also reported.

Six-membered nitrogen containing heterocycles has been intensively studied in the synthesis of alkaloids, and a great number of them have significant biological activities.[1,2] It is well-known that the pyridin-2-one ring system is a valuable building block in natural product synthesis.[3] Numerous methods for the preparation of substituted pyridin-2-one had been reported in the literature.[4]

In this paper, we described an efficient access to a variety of 3,4-disubstituted pyridin-2-ones **6**, which existed in many alkaloids such as mappicine ketone **1**[5] and camptothecin **2**.[6] A formal synthesis of mappicine ketone **1** is also reported.



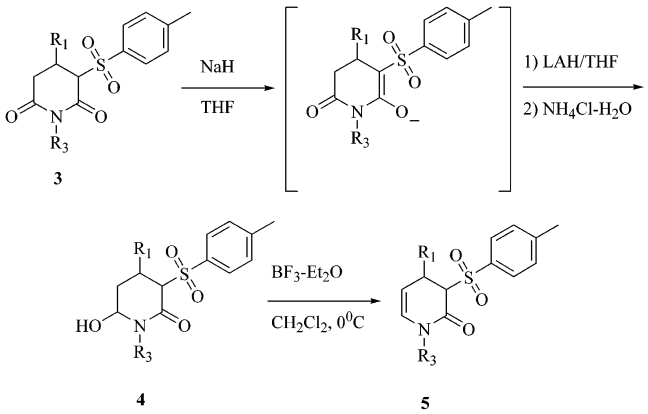
mappicine ketone (1)



camptothecin (2)

Previously, we reported an efficient route to the unsymmetrical glutarimides **3** with a sulfonyl group at the C-3 position.[7] We further discovered that reaction of

SCHEME 1



3 with sodium hydride and then with lithium aluminum hydride could regioselectively reduce various 3-sulfonyl glutarimides **3** to hydroxy piperidones **4**, which were further dehydrated to 3,4-dihydro-3-tosylpyridin-2-one **5** in the presence of boron trifluoride (Scheme 1).[8]

Herein, we further developed an efficient approach to 3,4-disubstituted pyridin-2-ones **6** starting from **5**. As shown in Scheme 2, reaction of 3,4-dihydro-3-tosylpyridin-2-one **5** with 2.2 equiv of sodium hydride at 25 °C in THF for 5 min, the resulting anion reacted with a variety of alkyl halides to afford the corresponding 3,4-disubstituted pyridin-2-ones **6** in good yield, presumably after alkylation, and dehydrosulfonation then followed (Scheme 2). Several examples were examined, and the results are listed in Table 1.

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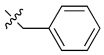
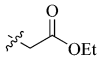
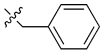
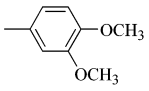
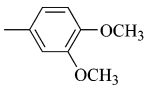
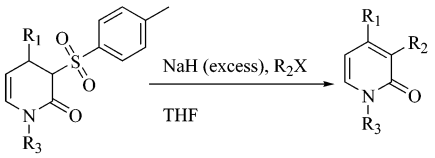
TABLE 1. Reaction of 5 with Excess NaH and Various Alkyl Halide

compd	R_1	R_2	R_3	product (yield %)
5a		$-CH_3$	Bn	**6a** (85)[a]
5b		$-CH_3$	PMB	**6b** (88)[a]
5c			Bn	**6c** (84)[b]
5d			Bn	**6d** (83)[b]
5e			Bn	**6e** (82)[b]
5f			Bn	**6f** (81)[b]
5g		$-CH_3$	PMB	**6g** (86)[a]
5h			PMB	**6h** (82)[b]
5i			Bn	**6i** (81)[b]
5j		$-CH_2CH_3$	Bn	**6j** (82)[b]

[a] Reaction at room temperature. [b] Reaction at reflux temperature.

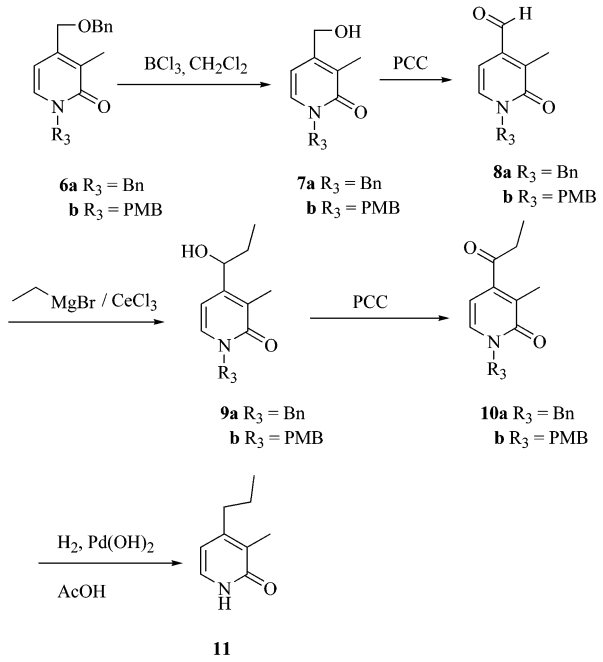
SCHEME 2



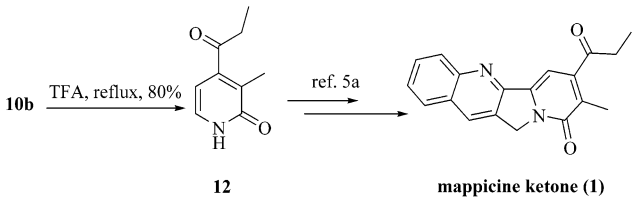
5 **6**

The synthesis of mappicine ketone was carried out as depicted in Scheme 3. Debenzylation of **6a** with BCl_3 at −20 °C to 0 °C obtained alcohol **7a** in 85% yield, and treatment of **7a** with PCC furnished the corresponding aldehyde **8a** in 87% yield. Addition of ethylmagnesium bromide to **8a** in the presence of $CeCl_3$ gave alcohol **9a** in 71% yield,[9] which was further oxidized with PCC to give ketone **10a** in 95% yield. Unfortunately, while we tried to debenzylate pyridinone **10a** with hydrogen gas at 1 atm in the presence of palladium hydroxide catalyst, the unexpected over reduced compound **11** (81%) was

SCHEME 3



SCHEME 4



obtained as the major product accompanied with a small amount of **9a**.

To avoid this over reduction problem, we chose PMB as the N-protecting group. Following the same procedures as described above, pyridinone **10b** was prepared in 43% overall yield starting from **6b**. Finally, reaction of **10b** with TFA in a sealed tube at 100 °C provided the desired ketopyridinone **12** in 80% yield (Scheme 4).[10]

Since compound **12** had already been transformed into mappicine ketone (**1**),[5a] a formal synthesis of **1** was accomplished.

In summary, we have successfully developed an efficient approach to 3,4-disubstituted pyridin-2-ones **6**. This methodology provides greater flexibility for incorporation of an alternative functionality at the 3- and 4-position and proved to be applicable for the synthesis of mappicine ketone (**1**). Further application of these results in the synthesis of analogues of the mappicine and camptothecin is currently underway in our laboratory.

Experimental Section

Before use, THF was distilled from a deep blue solution resulting from sodium and benzophenone under nitrogen. All reagents and solvents were obtained from commercial sources and used without further purification. Thin-layer chromatography (TLC) analysis was performed with precoated silica gel

(9) Direct adding of ethylmagnesium bromide to **8a** gave complex results.

(10) Padwa, A.; Heidellbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368.

(60 f_{254} plates), and column chromatography was carried out on silica (70−230 mesh). All reactions were performed under an atmosphere of nitrogen in dried (except those concerned with aqueous solutions) spherical flasks and stirred with magnetic bars.

General Procedure of Regioselective Reduction of Glutarimides 3 to 3,4-Dihydro-3-tosylpyridin-2-ones 5. To a suspension of sodium hydride (1.2 mmol, 60% dispersion in oil, was washed 3 times with dry hexane) in dry THF (10 mL) was added glutarimides **3** (1.0 mmol) at 25 °C for 5 min, and then 2.0 mmol equiv of LAH was added in one portion and further stirred for 0.5−1.0 h. The reaction was quenched with ammonium chloride solution (1 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered, and concentrated. Without purification, crude **4** was treated with boron trifloride (catalyst) in 20 mL of CH_2Cl_2 at 0 °C for 1 day and quenched with saturated aqueous sodium bicarbonate. The layer was separated, and aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (hexane/AcOEt = 4:1) to afford dehydration product **5**.

General Procedure to 3,4-Disubstituted Pyridin-2-one 6. A solution of **5** (1.0 mmol) in THF (20 mL) was added to a rapidly stirred suspension of sodium hydride (60% dispersion in mineral oil, 2.2 mmol). After the reaction mixture was stirred at room temperature for 10 min, 1.2 mmol of alkyl halide was then added to the suspension mixture. The mixture was stirred for 12 h, quenched with water (5 mL), and extracted with AcOEt (3 × 20 mL). The organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate = 2:1) to give pyridin-2-one **6**.

1-Benzyl-4-[(benzyloxy)methyl]-3-methyl-*1H*-pyridin-2-one (6a). 85% yield; IR ($CDCl_3$, cm^{-1}) 1649; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 10 H), 7.15 (d, J = 7.0 Hz, 1 H), 6.37 (d, J = 7.0 Hz, 1 H), 5.11 (s, 2 H), 4.56 (s, 2 H), 4.40 (s, 2 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 145.7, 137.4, 136.4, 133.4, 128.5 (2C), 128.2 (2C), 127.9 (2C), 127.7, 127.6 (2C), 127.5, 125.6, 105.4, 72.6, 68.2, 52.2, 11.8; HRMS calcd for $C_{21}H_{21}NO_2$ (M^+) 319.4024, found 319.4033.

4-[(Benzyloxy)methyl]-1-(4-methoxybenzyl)-3-methyl-*1H*-pyridin-2-one (6b). 88% yield; IR ($CDCl_3$, cm^{-1}) 1648; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.30 (m, 5 H), 7.26 (d, J = 8.5 Hz, 2 H), 7.16 (d, J = 7.5 Hz, 1 H), 6.85 (d, J = 8.5 Hz, 2 H), 6.37 (d, J = 7.5 Hz, 1 H), 5.07 (s, 2 H), 4.58 (s, 2 H), 4.41 (s, 2 H), 3.78 (s, 3 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 159.2, 145.8, 137.6, 133.4, 129.7 (2C), 128.6, 128.4 (2C), 127.8, 127.7 (2C), 125.8, 114.1 (2C), 105.5, 72.8, 68.4, 55.2, 51.9, 11.9; HRMS calcd for $C_{22}H_{23}NO_3$ (M^+) 349.1678, found 349.1675.

3-Allyl-1-benzyl-4-[(benzyloxy)methyl]-*1H*-pyridin-2-one (6c). 84% yield; IR ($CDCl_3$, cm^{-1}) 1647; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 10 H), 7.19 (d, J = 7.0 Hz, 1 H), 6.41 (d, J = 7.0 Hz, 1 H), 5.91−5.83 (m, 1 H), 5.14 (s, 2 H), 4.99−4.95 (m, 2 H), 4.56 (s, 2 H), 4.44 (s, 2 H), 3.35 (d, J = 6.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 146.9, 137.6, 136.5, 134.8, 134.4, 128.8 (2C), 128.4 (2C), 128.1 (2C), 127.9, 127.8 (2C), 127.7, 127.3, 115.1, 105.5, 72.9, 67.8, 52.3, 30.5; HRMS calcd for $C_{23}H_{23}NO_2$ (M^+) 345.1729, found 345.1731.

1,3-Dibenzyl-4-benzyloxymethyl-*1H*-pyridin-2-one (6d). 83% yield; IR ($CDCl_3$, cm^{-1}); ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.14 (m, 16 H), 6.42 (d, J = 7.0 Hz, 1 H), 5.17 (s, 2 H), 4.51 (s, 1 H), 4.43 (s, 2 H), 3.97 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 147.2, 139.7, 137.5, 136.5, 134.6, 128.8 (2C), 128.7, 128.6, 128.5 (2C), 128.4 (2C), 128.3 (2C), 128.1 (2C), 127.9, 127.8 (2C), 125.9, 105.6, 72.9, 68.2, 52.5, 31.8; MS (EI, 30 eV); 395 (M^+, 6.4%), 91 (100%).

(1-Benzyl-4-benzyloxymethyl-2-oxo-1,2-dihydro-pyridin-3-yl)acetic Acid Ethyl Ester (6e). 82% yield; IR ($CDCl_3$, cm^{-1}) 1731, 1652; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.26 (m, 10 H), 7.22 (d, J = 7.5 Hz, 1 H), 6.37 (d, J = 7.5 Hz, 1 H), 5.14 (s, 2 H), 4.55 (s, 2 H), 4.42 (s, 2 H), 4.12 (q, J = 7.0 Hz, 2 H), 3.65 (s, 2 H), 1.22 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 162.1, 147.9, 137.4, 136.2, 135.1, 128.8 (2C), 128.4 (2C), 128.1 (2C), 127.9 (2C), 127.8, 127.7, 123.3, 105.8, 72.8, 68.4, 60.8, 52.3, 32.0, 14.0; MS (EI, 30 eV); 391 (M^+, 3.3%), 91 (100%).

1,3-Dibenzyl-4-(3-benzyloxy-propyl)-*1H*-pyridin-2-one (6f). 81% yield; IR ($CDCl_3$, cm^{-1}) 1602; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.22 (m, 15 H), 7.11 (d, J = 7.0 Hz, 1 H), 6.02 (d, J = 7.0 Hz, 1 H), 5.14 (s, 2 H), 4.47 (s, 2 H), 4.04 (s, 2 H), 3.43 (t, J = 6.0 Hz, 2 H), 2.61 (t, J = 8.0 Hz, 2 H), 1.76 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 150.8, 140.6, 138.3, 136.7, 134.0, 129.2, 128.8 (2C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.1 (2C), 127.9, 127.6 (2C), 127.6, 125.8, 108.1, 72.9, 69.2, 52.3, 32.1, 29.6, 29.4; HRMS calcd for $C_{29}H_{29}NO_2$ (M^+) 423.2193, found 423.2197.

4-(3,4-Dimethoxtphenyl)-1-(4-methoxybenzyl)-3-methyl-*1H*-pyridin-2-one (6g). 86% yield; IR ($CDCl_3$, cm^{-1}) 1647, 1513; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.5 Hz, 2 H), 7.17 (d, J = 7.0 Hz, 1 H), 6.92−6.83 (m, 4 H), 6.79 (d, J = 2.0 Hz, 1 H), 6.10 (d, J = 7.0 Hz, 1 H), 5.10 (s, 2 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.78 (s, 3 H), 2.13 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 159.2, 148.8, 148.7, 148.5, 132.7, 132.0, 129.8 (2C), 128.6, 126.1, 120.8, 114.1 (2C), 111.5, 110.8, 108.5, 55.8, 55.8, 55.2, 51.8, 14.6; HRMS calcd for $C_{22}H_{23}NO_4$ (M^+) 365.1623, found 365.1625.

3-Allyl-4-(3,4-dimethoxyphenyl)-1-(4-methoxybenzyl)-*1H*-pyridin-2-one (6h). 82% yield; IR ($CDCl_3$, cm^{-1}) 1644, 1614, 1513; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 6.5 Hz, 1 H), 6.90−6.86 (m, 5 H), 6.12−6.03 (m, 2 H), 5.12 (s, 2 H), 5.05−4.95 (m, 2 H), 3.92 (s, 3 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.29 (d, J = 5.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 159.3, 150.0, 148.8, 148.4, 136.7, 133.5, 131.7, 129.8 (2C), 128.6, 127.6, 120.4, 114.8, 114.1 (2C), 111.4, 110.8, 108.6, 55.8, 55.8, 55.2, 51.7, 32.7; HRMS calcd for $C_{24}H_{25}NO_4$ (M^+) 391.1784, found 391.1783.

3-Allyl-1-benzyl-4-phenyl-*1H*-pyridin-2-one (6i). 81% yield; IR ($CDCl_3$, cm^{-1}) 1649; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43−7.26 (m, 10 H), 7.21 (d, J = 7.0 Hz, 1 H), 6.11 (d, J = 7.0 Hz 1 H), 6.05−5.97 (m, 1 H), 5.20(s, 2 H), 4.96 (m, 2 H), 3.27 (d, J = 6.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 149.3, 139.6, 136.6, 133.1, 132.32, 128.8 (2C), 128.4 (2C), 128.3 (2C), 127.9 (2C), 127.8 (2C), 127.7, 108.7, 52.3, 21.6, 13.5; HRMS calcd for $C_{21}H_{19}NO$ (M^+) 301.1467, found 301.1470.

1-Benzyl-3-ethyl-4-phenyl-*1H*-pyridin-2-one (6j). 82% yield; IR ($CDCl_3$, cm^{-1}) 1647; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.18 (m, 10 H), 7.08 (d, J = 7.0 Hz, 1 H), 5.98 (d, J = 7.0 Hz, 1 H), 5.10 (s, 2 H), 2.45 (q, J = 7.5 Hz, 2 H), 1.03 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 149.2, 139.5, 136.6, 133.1, 132.2, 128.8 (2C), 128.4 (2C), 128.3, 127.9 (2C), 127.8, 127.7 (2C), 108.6, 52.2, 21.5, 13.4; HRMS calcd for $C_{20}H_{19}NO$ (M^+) 289.1448, found 289.1461.

1-Benzyl-4-(hydroxymethyl)-3-methyl-*1H*-pyridin-2-one (7a). A solution (1.0 M) of BCl_3 in CH_2Cl_2 (0.95 mL) was added to a cooled solution (−20 °C) of **6a** (200.0 mg, 0.63 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was then warmed slowly to 0 °C (4 h) and quenched with saturated aqueous sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with dichloromethane. The organic layers were washed with brine, dried, filtered, and concentrated. Flash chromatography (hexane/ethyl acetate = 1:1) of the residue followed by filtration through a silica gel column gave 122.8 mg of **7a** (85%). IR ($CDCl_3$, cm^{-1}) 1721, 1643; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5 H), 7.19 (d, J = 7.0 Hz, 1 H), 6.42 (d, J = 7.5 Hz, 1 H), 5.14 (s, 2 H), 4.58 (s, 2 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 148.2, 136.5, 133.8, 128.8 (2C), 128.0 (2C), 127.8, 124.9, 104.9, 61.4, 52.4, 11.7; HRMS calcd for $C_{14}H_{15}NO_2$ (M^+) 229.1096, found 229.1097.

4-(Hydroxymethyl)-1-(4-methoxybenzyl)-3-methyl-*1H*-

pyridin-2-one (7b). 86% yield; IR ($CDCl_3$, cm^{-1}) 1711, 1643; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2 H), 7.18 (d, J = 7.0 Hz, 1 H), 6.85 (d, J = 8.5 Hz, 2 H), 6.39 (d, J = 7.0 Hz, 1 H), 5.06 (s, 2 H), 4.57 (s, 2 H), 3.78 (s, 3 H), 2.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 159.3, 148.0, 133.6, 129.6 (2C), 128.6, 124.9, 114.1 (2C), 104.9, 61.5, 55.2, 52.0, 11.7; HRMS calcd for $C_{15}H_{17}NO_3$ (M^+) 259.1208, found 259.1202.

1-Benzyl-3-methyl-2-oxo-1,2-dihydro-pyridine-4-carbaldehyde (8a). To a stirred solution of alcohol **7a** (200.0 mg, 0.87 mmol) in 20 mL of dichloromethane at 25 °C under nitrogen was added Celite, pyridium chlorochromate (226.3 mg, 1.05 mmol). The reaction mixture was stirred for 1 day. The mixture was filtered through silica gel, and the solid was washed with hexane/ethyl acetate = 2:1. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (elution hexane/ethyl acetate = 2:1) to give ketone **8a** (172.0 mg, 87%). IR ($CDCl_3$, cm^{-1}) 1716, 1648; ^1H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1 H), 7.26−7.19 (m, 5 H), 7.18 (d, J = 7.5 Hz, 1H), 6.45 (d, J = 7.0 Hz, 1 H), 5.07 (s, 2 H), 2.42 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 163.4, 139.2, 135.7, 135.1, 134.3, 128.8 (2C), 128.1, 128.0 (2C), 101.7, 52.8, 11.02; HRMS calcd for $C_{14}H_{13}NO_2$ (M^+) 227.0946, found 227.0947.

1-(4-Methoxybenzyl)-3-methyl-2-oxo-1,2-dihydro-pyridine-4-carbaldehyde (8b). 87% yield; IR ($CDCl_3$, cm^{-1}) 1701, 1619; ^1H NMR (500 MHz, $CDCl_3$) δ 10.39 (s, 1 H), 7.28−7.24 (m, 3 H), 6.87 (d, J = 8.5 Hz, 2 H), 6.52 (d, J = 7.0 Hz, 1 H), 5.09 (s, 2 H), 3.79 (s, 3 H), 2.51 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 163.5, 159.5, 139.2, 135.2, 134.2, 129.8 (2C), 127.8, 114.3 (2C), 101.7, 55.2, 52.4, 11.0; HRMS calcd for $C_{15}H_{15}NO_3$ (M^+) 257.1052, found 257.1052.

1-Benzyl-4-(1-hydroxypropyl)-3-methyl-*1H*-pyridin-2-one (9a). A solution of **8a** (150.1 mg, 0.66 mmol) in anhydrous THF (10 mL) under N_2 was added to anhydrous $CeCl_3$ (325.5 mg, 1.32 mmol). After 30 min, EtMgBr (3.0 M in THF, 0.33 mL) was added to the mixture and stirred at 25 °C for 1 h. The reaction mixture was quenched with the addition of saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (3 × 20 mL); the organic layer was dried $MgSO_4$ and concentrated under reduced pressure. Chromatography (SiO_2, hexane/ethyl acetate = 1:2) afforded **9a** (120.6 mg, 71%). IR ($CDCl_3$, cm^{-1}) 3021, 1617; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.27 (m, 5 H), 7.13 (d, J = 7.5 Hz, 1 H), 6.40 (d, J = 7.5 Hz, 1 H), 5.08 (dd, J = 15.3, 8.7 Hz, 2 H), 4.68 (dd, J = 7.5, 5.5 Hz, 1 H), 2.01 (s, 3 H), 1.67−1.60 (m, 2 H), 0.93 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 152.1, 136.3, 133.5, 128.7 (2C), 128.2 (2C), 127.8, 124.7, 104.3, 70.8, 52.4, 29.9, 12.0, 9.9; HRMS calcd for $C_{16}H_{19}NO_2$ (M^+) 257.1402, found 257.1410. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.63; H, 7.19; N, 5.18.

4-(1-Hydroxypropyl)-1-(4-methoxybenzyl)-3-methyl-*1H*-pyridin-2-one (9b). 87% yield; IR ($CDCl_3$, cm^{-1}) 3020, 1613; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2 H), 7.16 (d, J = 7.0 Hz, 1 H), 6.86 (d, J = 8.5 Hz, 2 H), 6.37 (d, J = 7.0 Hz, 1 H), 5.08 (d, J = 14.0 Hz, 1 H), 5.01 (d, J = 14.0 Hz, 1 H) 4.74 (t, J = 7.0 Hz, 1 H), 3.79 (s, 3 H), 2.08 (s, 3 H), 1.68−1.63 (m, 2 H), 0.95 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 159.3, 151.4, 133.5, 129.8 (2C), 128.5, 124.8, 114.1 (2C), 103.8, 71.1, 55.2, 51.9, 29.9, 12.0, 9.9; HRMS calcd for $C_{17}H_{21}NO_3$ (M^+) 287.1512, found 287.1523. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.33; H, 7.08; N, 4.74.

1-Benzyl-3-methyl-4-propionyl-*1H*-pyridin-2-one (10a). A solution of **9a** (130.2 mg, 0.51 mmol) in CH_2Cl_2 (10 mL) was added to a mixture of PCC (131.4 mg, 0.61 mmol) and Celite in CH_2Cl_2 (10 mL). The reaction mixture was stirred overnight at room temperature and then filtered over a short pad of silica gel with hexane/ethyl acetate = 1:1 to provide 123.7 mg (95%) of pyridone **10a**. IR ($CDCl_3$, cm^{-1}) 1716, 1641; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5 H), 7.22 (d, J = 7.5 Hz, 1 H), 6.06 (d, J = 7.5 Hz, 1 H), 5.14 (s, 2 H), 2.74 (q, J = 7.5 Hz, 2.0 H), 2.16 (s, 3 H), 1.17 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.5, 162.9, 147.1, 135.9, 134.4, 128.8 (2C), 128.2 (2C), 128.1, 126.6, 102.9, 52.6, 35.8, 13.9, 7.6; HRMS calcd for $C_{16}H_{17}NO_2$ (M^+) 255.1252, found 255.1254.

1-(4-Methoxybenzyl)-3-methyl-4-propionyl-*1H*-pyridin-2-one (10b). 91% yield; IR ($CDCl_3$, cm^{-1}) 1717, 1643; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 7.0 Hz, 1 H), 6.87 (d, J = 8.5 Hz, 2 H), 6.04 (d, J = 7.0 Hz, 1 H), 5.07 (s, 2 H), 3.74 (s, 3 H), 2.73 (q, J = 7.5 Hz, 2 H), 2.15 (s, 3 H), 1.17 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 162.9, 159.4, 147.0, 134.2, 129.8 (2C), 128.0, 126.6, 114.2 (2C), 102.8, 55.2, 52.1, 35.8, 13.9, 7.6; HRMS calcd for $C_{17}H_{19}NO_3$ (M^+) 285.1357, found 285.1359.

3-Methyl-4-propyl-*1H*-pydidin-2-one 11. To a solution of 60.1 mg (0.23 mmol) of pyridinone **10a** in 7 mL of acetic acid was added a catalytic amount of $Pd(OH)_2$, and the reaction mixture was stirred under hydrogen overnight. After filtration of the catalyst, the solution was extracted with CH_2Cl_2 and washed with water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 28.2 mg (81%) of **11** as a white solid: mp 108−109 °C. IR ($CDCl_3$, cm^{-1}) 3020, 1616; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 6.5 Hz, 1 H), 6.17 (d, J = 6.5 Hz, 1 H), 2.51 (t, J = 7.5 Hz, 2 H), 2.14 (s, 3 H), 1.59 (q, J = 7.5 Hz, 2 H), 0.98 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 153.1, 130.1, 125.4, 109.7, 35.5, 22.4, 13.9, 11.7; HRMS calcd for $C_9H_{13}NO$ (M^+) 151.0997, found 151.0998.

3-Methyl-4-propionyl-*1H*-pyridin-2-one 12. A solution of 50.3 mg (0.17 mmol) of **10b** in 12 mL of trifluoroacetic acid was heated in a sealed tube at 100 °C for 4 h. The mixture was cooled, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel to give 22.5 mg (80%) of pyridinone **12** as a white solid: mp 128−129 °C. IR ($CDCl_3$, cm^{-1}) 3690, 1706; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 6.5 Hz, 1 H), 6.19 (d, J = 6.5 Hz, 1 H), 2.77 (q, J = 7.0 Hz, 2 H), 2.14 (s, 3 H), 1.92 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 165.4, 149.5, 131.8, 125.9, 103.9, 35.9, 13.1, 7.6; HRMS calcd for $C_9H_{11}NO_2$ (M^+) 165.0790, found 165.0791.

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Supporting Information Available: Additional spectroscopic data for compounds **12**, **10b**, **9b**, **8b**, **7b**, and **6b** (^1H NMR in $CDCl_3$). This material is available free of charge via the Internet at http://pubs.acs.org.

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