Article

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Indium-promoted Conversion of Allylic Bromide to Alcohol Moiety and Synthesis of Pipermethystine Skeletons

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Dihydropyridone bromide (**2**) was converted to the corresponding alcohol (**1**) by reaction with indium in air or with indium followed by treatment with a sulfonyloxaziridine. The alcohol (**1**) was transformed in four steps to a phenylsulfone-substituted pipermethystine derivative (**10**). Reductive cleavage of the phenylsulfone did not yield the pipermethystine natural product. Several new pyridone derivatives were synthesized.

Keywords: Aza-Diels–Alder reactions; Pipermethystine synthesis; Organoindium reagents; Allylic bromides.

INTRODUCTION

We had developed a new aza-Diels–Alder reaction of phenylthio-substituted 3-sulfolenes with *p*-toluenesulfonyl isocyanate (PTSI) to give the 2(*1H*)-pyridone derivatives,[1] and used this method to synthesize several natural products.[2] We now report our studies on the synthesis of pipermethystine, a natural product isolated from the leaves of *Piper methysticum*.[3] Only one total synthesis of pipermethystine has been reported.[4] Its biological activities have also been studied.[5] A retrosynthetic analysis of our approach to the synthesis of pipermethystine is shown in Scheme 1. We envision that the desired natural product could be obtained by selective desulfonylation of an intermediate **A**, which would be easily accessible by the oxidation of an intermediate **B**. Compound **B** could be obtained by acylation of an intermediate **C**, which should be readily available from the dihydropyridone precursor **1** we have previously prepared.[1]

RESULTS AND DISCUSSION

Preparation of compound 1 by hydrolysis

Compound **1** was unexpectedly synthesized in our previous work[1] by the reaction of the bromide **2** with sodium nitrite (Scheme 2), but the yield was only 13%. Subsequently, we developed a hydrolysis reaction of compounds **3** bearing a substituent at C-6 to give product **4** in good yield.[2] Under this new reaction condition, however, we found that compound **1** underwent elimination of HBr to give 2-pyridone **5** in 61% yield.[1] Apparently, an alkyl group at C-6 is essential for the substitution reaction. With no substituent at C-6, the elimination reaction of compound **2** would be faster.

We also carried out the hydrolysis reaction of compound **2** without the presence of Et_3N in order to avoid the elimination product **5** (Table 1). In entry 1, treatment of compound **2** with THF/H_2O (1/0.45) in a sealed tube at 70°C gave compound **1** (10%) and elimination product **5** (2%) and recovered the starting material **2** (70%). Increasing the reaction temperature to 120°C (entry 2) only gave the recovered compound **2** (96%). In entry 3, increasing the reaction time to 5.5 days gave similar product yields as in entry 1. Treatment of compound **2** with THF/HOAc (1/1) at 70°C (entry 4) or in a sealed tube at 120°C (entry 5) only gave the recovered starting material **2**. In entry 6, the addition of NH_4OAc to THF/H_2O (1/0.45) at 70°C afforded a mixture of compound **1** (6%) and the elimination product **5** (40%) and recovered the starting material **2** (53%); no OAc substitution product was obtained. Since the highest reaction yield of compound **1** obtained from the hydrolysis condition (Table 1) was only 10%, we wanted to investigate other synthetic routes to compound **1**.

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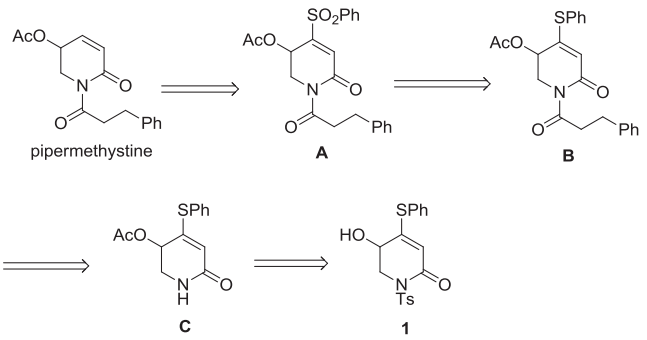
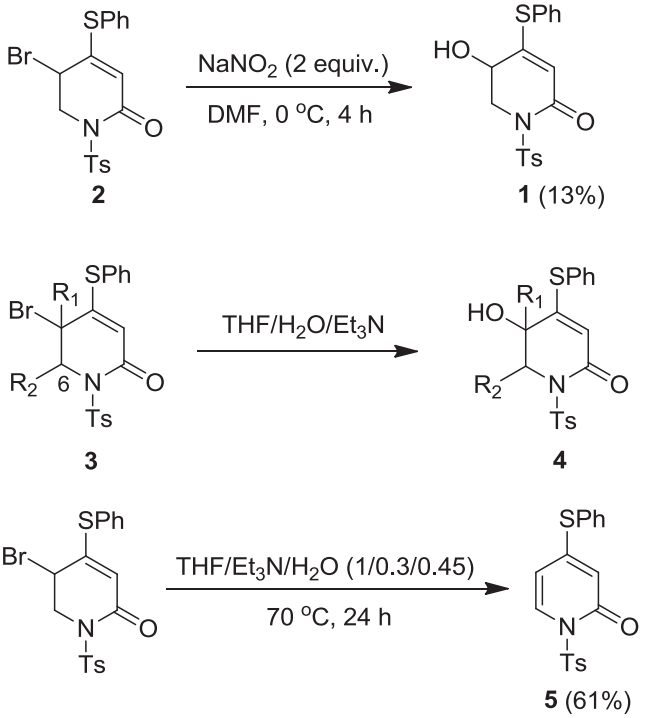


Scheme 1. Retrosynthetic analysis of pipermethystine.



Scheme 2. Previous preparation of compound **1** and derivatives.

Preparation of compound 1 by organometallic reactions

Our second approach to synthesize compound **1** from the bromide **2** was to use a suitable metal[6] to give an organometallic intermediate, which could then react with air[7–10] or other oxidants[11,12] to afford the desired product **1** (Scheme 3). Since compound **2** has carbonyl and tosyl groups that might react with the organometallic reagent, we decided to use less reactive metals. After some preliminary tests we found that indium metal was quite suitable for this type of reaction.[6]

We carried out systematic studies of the reaction conditions (Table 2). In entry 1, treatment of compound **2** with 2 equiv of indium at 70°C in a sealed tube (in air) in THF for 2 days afforded compound **1** (20%), elimination product **5** (7%), and reduction product **6**[1] (72%). However, if 0.2 equiv of indium was used (entry 2), the yield of compound **1** decreased significantly and large amounts of recovered starting material **2** were also obtained. We also tried the reaction of compound **2** with indium in THF with 2.5 bar of O_2 in a pressurized cylinder at room temperature. However, only the starting material **2** was recovered. It is speculated that the high pressure of O_2 might have oxidized the indium metal so that the metal insertion did not occur.

We propose a plausible mechanism for the formation of compound **1** in Scheme 4.[10] Indium insertion into the C–Br bond would give an organoindium intermediate **D**, which would then react with air to give an organoperoxide **E**. Further reaction of **E** with another molecule of the indium intermediate **D** would yield two molecules of an alkoxide intermediate **F**. Aqueous

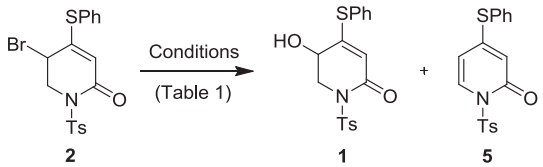
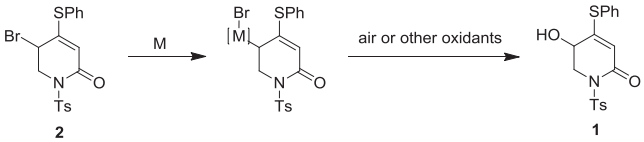


Table 1. Preparation of compound **1** by hydrolysis

Entry	Reaction conditions	Results (% yield)
1	THF/H_2O (1/0.45), sealed tube, 70°C, 24 h	**1** (10), **5** (2), **2** (70)
2	THF/H_2O (1/0.45), sealed tube, 120°C, 24 h	**2** (96)
3	THF/H_2O (1/0.45), sealed tube, 70°C, 5.5 day	**1** (6), **5** (5), **2** (65)
4	THF/HOAc (1/1), 70°C, 24 h	**2** (100)
5	THF/HOAc (1/1), sealed tube, 120°C, 24 h	**2** (80)
6	THF/H_2O (1/0.45), NH_4OAc (3 equiv), sealed tube, 70°C, 24 h	**1** (6), **5** (40), **2** (53)



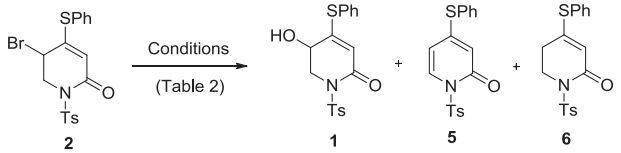
Scheme 3. Proposed preparation of compound **1** by organometallic reagents.

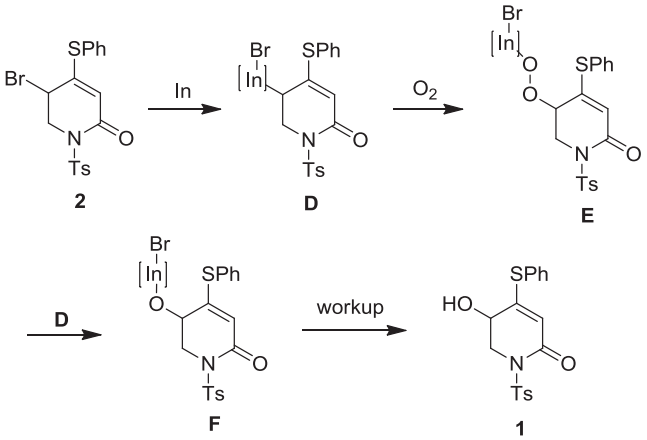
work-up would then give compound **1**.

We also used (−)-(2*S*,8a*R*)-(camphorylsulfonyl) oxaziridine as the oxidant (Table 2, entries 3 and 4).[11] Treatment of compound **2** with 2 equiv of indium and 1.2 equiv of oxaziridine (entry 3) afforded compound **1** (22%) and recovered compound **2** (42%). Increasing the amount of indium and oxaziridine (entry 4) gave compound **1** (29%), elimination product **5** (4%), and recovered compound **2** (15%). So far, the highest yield of compound **1** from bromide **2** was 29%.

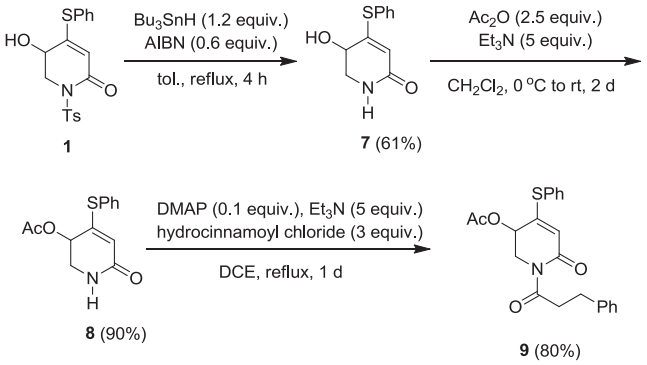
Synthesis of pipermethystine skeletons

We synthesized the pipermethystine skeleton, as shown in Scheme 5. The *N*-tosyl group of compound **1** was cleaved by Parsons' method (Bu_3SnH/AIBN) to give compound **7**.[13] Concentrations of Bu_3SnH and compound **1** were both kept at 0.05 M; lower concentrations led to large amounts of unreacted starting material **1**. Reaction of compound **7** with Ac_2O and Et_3N in CH_2Cl_2 for 2 days provided compound **8** in high yield; the reaction was rather slow, probably because of the low solubility of compound **7** in CH_2Cl_2. Compound **9** was obtained in 80% yield by the reaction





Scheme 4. A plausible mechanism for the formation of compound **1** by reaction of bromide **2** with indium in air.



Scheme 5. Synthesis of the pipermethystine skeletons **9**.

of compound **8** with hydrocinnamoyl chloride in the presence of Et_3N and a catalytic amount of 4-dimethylaminopyridine (DMAP) in refluxing 1,2-dichloroethane.

Table 2. Preparation of compound **1** by reaction with indium

Entry	Reaction conditions[a]	Results (% yield)
1	In (2 equiv), THF, air, 70°C, sealed tube, 2 day	**1** (20), **5** (7), **6** (72)
2	In (0.2 equiv), THF, air, 70°C, sealed tube, 2 day	**1** (7), **5** (6), **6** (14), **2** (51)
3	In (2 equiv), (−)-(2*S*,8a*R*)-(Camphorylsulfonyl)oxazirdine (1.2 equiv), THF, sealed tube, 70°C, 2 day	**1** (22), **2** (42)
4	In (4 equiv), (−)-(2*S*,8a*R*)-(Camphorylsulfonyl)oxazirdine (2.4 equiv), THF, sealed tube, 70°C, 2 day	**1** (29), **5** (4), **2** (15)

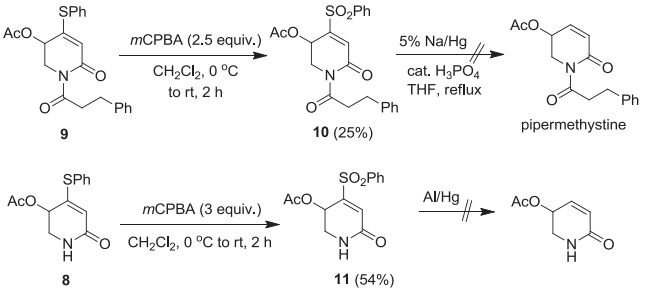
[a] In the eluent of chromatography 2–5% of Et_3N was added.

Oxidation of sulfides to sulfones and desulfonylation

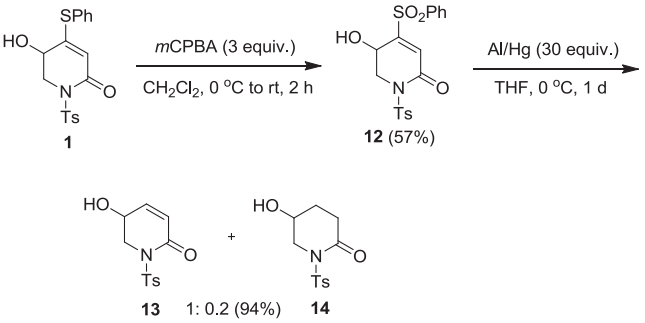
Compound **9** was oxidized by *m*CPBA to give the sulfone **10** in 25% yield (Scheme 6); the low yield of compound **10** was probably due to its instability even in air at room temperature. Attempted desulfonylaion of compound **10** with 5% Na/Hg and a small amount of H_3PO_4 in refluxing THF did not give the desired natural product, pipermethystine.[4] Instead, hydrocinnamoyl acid was obtained, probably by cleaving the *N*-acyl group under the reaction condition.[4] Crude ^{1}H-NMR data indicated that the OAc group of compound **10** was also removed. We also used Al/Hg for the desulfonylation reaction,[14] which gave silmilar results as Na/Hg. Since compound **10** decomposes too easily, we decided to use the sulfone **11**, obtained in 54% yield from the oxidation of compound **8** with *m*CPBA, for the desulfonylation reaction. Unfortunately, treatment of compound **11** with Al/Hg also cleaved the OAc group. From these results, it seemed that the OAc group in compounds **10** and **11** was too labile to survive the reductive condition.

We further studied the desulfonylation of compounds without an OAc group at C-6, as shown in Scheme 7. Treatment compound **1** with *m*CPBA gave the sulfone **12**, which underwent the desulfonylation with Al/Hg in THF at 0°C to give the desired product **13** together with the over-reduction product **14** in the ratio 1:0.2 (94% yield). Unfortunately, these two compounds could not be separated by column chromatography. It should be noted that if the reaction of compound **12** with Al/Hg was carried out at room temperature, the ratio of compounds **13**:**14** was 1:4.7. Thus, compound **14** was obtained by further reduction of compound **13** by Al/Hg.

In conclusion, we discovered that the hydrolysis of bromide **2** bearing no substituent at C-6 under neutral



Scheme 6. Preparation and attempted desulfonylation of sulfones **10** and **11**.



Scheme 7. Preparation and desulfonylation of sulfone **12**.

or basic condition did not yield effectively the desired alcohol **1** due to the dominant elimination reaction. We developed a new and more effective method for the preparation of compound **1** by the reaction of bromide **2** with indium in air or with indium followed by treatment with (camphorylsulfonyl)oxaziridine. Compound **1** was converted in four steps to the sulfone-substituted pipermethystine structure **10**. Intended reductive cleavage of the phenylsulfonyl group of compound **10** did not give the desired natural product pipermethystine because of the presence of a reactive allylic acetate group. We have also synthesized several new pyridone derivatives, the biological activities of which will be studied in future.

EXPERIMENTAL

Melting points were determined with an SMP3 melting apparatus. Infrared (IR) spectra (attenuated total reflection; ATR) were recorded with a Perkin Elmer 100 series Fourier transform IR (FTIR) spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were mostly recorded on a Bruker Avance 300 spectrometer operating at 300 and at 75 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are given in hertz. High-resolution mass spectra (HRMS) were measured with a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Column chromatographic purifications were performed using Merck silica gel 60 (40–60 mm).

4-(Phenylthio)-1-tosyl-1*H*-pyridin-2-one (5). A solution of **2** (50 mg, 0.115 mmol) in THF/Et_3N/H_2O (1 mL/0.3 mL/0.45 mL) was heated at 70°C for 24 h. After cooling, ethyl acetate (30 mL) was added and the mixture washed with brine (30 mL × 2), dried

($MgSO_4$), and evaporated under vacuum. The crude product was purified by column chromatography (ethyl acetate/hexane 1:3) to give product **5** (24.9 mg, 61%).[1]

General procedure for the preparation of compound 1 by hydrolysis (Table 1)

A solution of compound **2** (50 mg, 0.114 mmol) in THF/H_2O (1 mL/0.45 mL) was heated in a sealed tube at 70°C for 24 h. The solvent was then removed under vacuum, and the crude product was purified by column chromatography (ethyl acetate/hexane 1:3 containing 2–5% Et_3N) to give product **1** (4.1 mg, 10%), product **5** (1.0 mg, 2%), and product **2** (34.8 mg, 70%).[1]

General procedure for the preparation of compounds 1 and 6 by organometallic reactions (Table 2, entry 1)

A mixture of compound **2** (50 mg, 0.114 mmol) and indium (26.0 mg, 0.228 mmol) in THF (2 mL) was heated in sealed tube at 70°C for 24 h. Ethyl acetate (10 mL) was added and the reaction was quenched with 1% HCl aqueous solution. The aqueous solution was extracted with ethyl acetate (30 mL × 3), and the organic solution was dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by column chromatography (ethyl acetate/hexane 1:3 containing 2—5% Et_3N) to give compounds **1** (8.6 mg, 20%),[1] **6** (29.8 mg, 72%),[1] and **5** (3.2 mg, 7%).[1]

General procedure for the preparation of compound 1 by organometallic reactions with (−)-(2*S*,8a*R*)-(Camphorylsulfonyl)oxaziridine (Table 2, entry 4)

A mixture of compound **2** (50 mg, 0.114 mmol), indium (52.0 mg, 0.456 mmol), and (−)-(2*S*,8a*R*)-(camphorylsulfonyl)oxaziridine (52.3 mg, 0.228 mmol) in THF (2 mL) was heated in a sealed tube at 70°C for 24 h. Ethyl acetate (10 mL) was added and the reaction was quenched with 1% HCl aqueous solution. The aqueous solution was extracted with EtOAc (30 mL × 3), and the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by column chromatography (ethyl acetate/hexane 1:3 containing 2–5% Et_3N) to give compounds **1** (12.5 mg, 29%), **5** (1.8 mg, 4%), and **2** (7.6 mg, 15%).[1]

5-Hydroxy-4-(phenylthio)-5,6-dihydro-1*H*-pyridin-2-one (7). To a solution of compound **2** (116.5 mg, 0.310 mmol) in degassed toluene (6.2 mL) was slowly added dropwise (1 drop per second) Bu_3SnH (0.10 mL, 0.372 mmol) and AIBN (30.5 mg, 0.186 mmol) in toluene (11.2 mL). After addition, the mixture was heated at reflux for 4 h, and the residue was evaporated under vacuum. The crude product was purified by column chromatography using ethyl acetate containing 10% MeOH as eluent to give product **7** (41.6 mg, 61%) as a white solid: mp 181–184°C, (recryst. MeOH); IR (film, cm^{-1}): *v* 3306, 2955, 2924, 2854, 1645, 1464, 1396, 1292, 1137, 1076, 960, 844, 812; ^1H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.63–7.53 (2H, m), 7.49–7.28 (3H, m), 5.46 (1H, s), 5.29 (1H, *J* = 2.1 Hz), 4.36 (1H, t, *J* = 4.5 Hz), 3.67 (1H, ddd, *J* = 13.2, 4.5, 2.1 Hz), 3.55 (1H, ddd, *J* = 13.2, 4.5, 3.6 Hz); ^{13}C NMR (methanol-d_4, 75 MHz, ppm): δ 165.4, 160.8, 135.2, 129.8, 129.7, 128.3, 113.1, 64.8, 46.2; FAB-MS (relative intensity): *m/z* 222 (M^++H, 9), 207 (19), 166 (11), 154 (22); Exact mass Calcd for $C_{11}H_{11}NO_2S$ (M^+) 221.0510, FAB-HRMS *m/z* 221.0515.

5-Acetoxy-4-(phenylthio)-5,6-dihydro-1*H*-pyridin-2-one (8). A mixture of compound **7** (35.4 mg, 0.160 mmol), Et_3N (0.112 mL) and acetic anhydride (0.038 mL, 0.4 mmol) in dried CH_2Cl_2 was mixed at 0°C and then stirred at room temperature for 2 days. Ethyl acetate (10 mL) was added and the reaction was quenched with saturated sodium bicarbonate (10 mL), and the aqueous solution was extracted with ethyl acetate (30 mL × 3). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by column chromatography using ethyl acetate/hexane (2:1) as eluent to give product **8** (37.9 mg, 90%) as a white solid: mp 142–144°C, (recryst. ethyl acetate); IR (neat, cm^{-1}): *v* 3054, 2987, 2305, 1741, 1666, 1604, 1551, 1421, 1265, 896; ^1H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.54–7.51 (2H, m), 7.47–7.43 (3H, m), 5.93 (1H, s), 5.47 (1H, t, *J* = 4.2 Hz), 5.41 (1H, d, *J* = 1.2 Hz), 3.70 (1H, dd, *J* = 13.8, 4.2 Hz), 3.54 (1H, m), 2.16 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 170.2, 164.2, 153.0, 135.5, 130.3, 130.1, 127.3, 117.7, 65.6, 44.3, 20.9; FAB-MS (relative intensity): *m/z* 264 (M^++H, 43), 204 (43), 95 (29), 69 (60), 55 (100); Exact mass Calcd for $C_{13}H_{13}NO_3S$ (M^+) 263.0616, FAB-HRMS *m/z* 263.0622.

5-Acetoxy-1-(3-phenylpropanoyl)-4-(phenylthio)-5,6-dihydro-1*H*-pyridin-2-one (9). To a solution of compound **8** (38.3 mg, 0.146 mmol) and DMAP (1.8 mg, 0.014 mmol) in 1,2-dichloroethane (2 mL) at room

temperature under nitrogen were added sequentially with a syringe Et_3N (0.10 mL, 0.73 mmol) and hydrocinnamoyl chloride (0.65 mL, 0.438 mmol). The reaction mixture was refluxed for 24 h, and then the solvent was removed under vacuum. Ethyl acetate (10 mL) was added, and the organic solution was washed with 5% HCl (10 mL) and saturated $NaHCO_3$ (10 mL). The organic solution was separated, and the aqueous solution was extracted with ethyl acetate (30 mL × 3), dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography using ethyl acetate/hexane (1:5) as eluent to give compound **9** (46.4 mg, 51%) as a yellow oil; IR (neat, cm^{-1}): *v* 3054, 2987, 2930, 2855, 2305, 1746, 1682, 1603, 1421, 1265, 1078, 1043, 896; ^1H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.64–7.45 (5H, m), 7.43–7.00 (5H, m), 5.76 (1H, t, J = 4.2 Hz), 5.37 (1H, s), 4.47 (1H, dd, J = 14.4, 4.2 Hz), 3.76 (1H, dd, J = 14.4, 3.6 Hz), 3.32–3.14 (2H, m), 3.00–2.94 (2H, m), 2.12 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 175.3, 169.7, 162.6, 157.3, 141.0, 135.4, 130.6, 130.2, 128.5, 128.3, 126.9, 126.0, 118.0, 65.0, 45.3, 40.5, 30.9, 20.8; FAB-MS (relative intensity): *m*/*z* 396 (M^++H, 0.83), 376 (1), 342 (1), 249 (20), 228, (45), 166 (30); Exact mass Calcd for $C_{22}H_{21}NO_4S$ (M^+) 395.1191, FAB-HRMS *m*/*z* 395.1195.

General procedure for oxidation with *m*CPBA

To a solution of the sulfide (0.068 mmol) in CH_2Cl_2 (2 mL) in an ice bath was added *m*CPBA (70–75% in H_2O, 0.17 mmol). After 5 min, the ice bath was removed, and the mixture was further stirred at room temperature for 2 h. To the reaction mixture was then added successively saturated $Na_2S_2O_3$ (10 mL) and saturated $NaHCO_3$ (10 mL), and was extracted with CH_2Cl_2 (20 × 3 mL). The organic solution was dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (ethyl acetate /hexane 1:1 to 2:1) to give purified sulfone products.

5-Acetoxy-1-(3-phenylpropanoyl)-4-(phenylsulfonyl)-5,6-dihydro-1*H*-pyridin-2-one (10). Compound **9** (26.7 mg, 0.068 mmol) with 2.5 equiv *m*CPBA gave compound **10** (7.3 mg, 25%); ^1H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.95–7.75 (2H, m), 7.79–7.70 (1H, m), 7.69–7.58 (2H, m), 7.48–7.11 (5H, m), 7.07 (1H, s), 5.87 (1H, t, J = 2.7 Hz), 4.74 (1H, dd, J = 15.3, 2.1 Hz), 3.43 (1H, dd, J = 15.3, 2.7 Hz), 3.94–3.16 (2H, m), 3.07–2.89 (2H, m), 1.60 (3H, s).

5-Acetoxy-4-(phenylsulfonyl)-5,6-dihydro-1*H*-pyridin-2-one (11). Compound **8** (9.5 mg, 0.036 mmol) with 3 equiv *m*CPBA gave compound **11** (5.7 mg 54%) as a white solid: mp 206–207°C, (recryst. ethyl acetate); IR (neat, cm^{-1}): *v* 3054, 2987, 2686, 2411, 2306, 1750, 1688, 1422, 1265, 1160, 896; ^1H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.92–7.90 (2H, m), 7.74–7.69 (1H, m), 7.63–7.58 (2H, m), 7.05 (1H, d, J = 1.5 Hz), 6.43 (1H, s), 5.77 (1H, s), 3.69 (1H, dd, J = 15, 3.3 Hz), 3.57–3.54 (1H, m), 1.68 (3H,s); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 169.4, 162.4, 147.7, 138.0, 134.6, 132.4, 129.6, 128.9, 60.1, 45.5, 20.3.

5-Hydroxy-4-(phenylsulfonyl)-1-tosyl-5,6-dihydro-1*H*-pyridin-2-one (12). Compound **2** (70 mg, 0.186 mmol) with 3 equiv *m*CPBA gave compound **12** (43.2 mg 57%) as a white solid: mp 143—146°C, (recryst. ethyl acetate); IR (neat, cm^{-1}): *v* 3301, 3054 , 2987, 2685, 2521, 2305, 1697, 1551, 1265, 1156, 896; ^1H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.93–7.91 (4H, m), 7.83–7.72 (1H, m), 7.64–7.56 (2H, m), 7.33–7.31 (2H, m), 6.35 (1H, s), 4.71–4.64 (2H, m), 3.73 (1H, dd, J = 13.8, 3 Hz), 3.00 (1H, s), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 159.7, 153.1, 145.6, 136.8, 135.1, 134.8, 133.6, 129.8, 129.5, 129.0, 128.8, 60.4, 50.5, 21.7.

General preparation of Al/Hg reagent[15]

An aluminum foil was cut to the size 2 × 1 cm (10 mg), put it in 5% NaOH aqueous solution for 1 min, and then washed by distilled water quickly. The washed aluminum foil was put in 5% $HgCl_2$ aqueous solution for 1 min, followed by washing with distilled water, ethanol, and ether.

5-Hydroxy-1-tosyl-5,6-dihydro-1*H*-pyridin-2-one (13) and 5-Hydroxy-1-tosylpiperidin-2-one (14). A mixture of compound **12** (5 mg, 0.0123 mmol), Al/Hg (10 mg, 0.370 mmol) in THF (1 mL) was stirred at 0°C for 1 day. Ethyl acetate (10 mL) was added, and the organic solution was filtered through a flash column of celite. The filtered solution was evaporated under vacuum. The crude product was purified by column chromatography using ethyl acetate/hexane (1:1) containing 2–5% Et_3N as eluent to give compound **13** and compound **14** in the ratio 1:0.2 (3.4 mg, 94%).

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