REGIOSELECTIVE REDUCTION OF *N*-ALKYL-3-SULFONYL-GLUTARIMIDE. FORMAL SYNTHESIS OF 1,2,3,4,6,7,12,12b-OCTAHYDROINDOLO[2,3-*a*]QUINOLIZINE AND HOMOBACLOFEN

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Abstract—Reduction of *N*-alkyl-3-sulfonylglutarimides with (1) sodium hydride and then with lithium aluminum hydride, or (2) sodium borohydride yielded two different types of regioselectively reduced hydroxypiperidinones which were further dehydrated to two pyridin-2-ones in the presence of boron trifluoride etherate. Cycloaddition and regioselective reduction were combined to synthesize 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine and homobaclofen.

1. INTRODUCTION

N-Acyliminium ions have been used extensively in the synthesis of alkaloids and compounds with potential biological activities.[1-3] Hydroxypiperidinones are reasonable precursors of *N*-acyliminium ions.[4-6] The regioselective reduction of asymmetrically substituted cyclic imides such as piperidine-2,6-diones to their corresponding hydroxypiperidinones[7-11] is an important pathway to the formation of *N*-acyliminium ions. However, it is difficult to generate specific *N*-acyliminium ions from imide systems.[12,13] Thus, it is important to select appropriate piperidine-2,6-diones with α-sulfonyl group

that features higher selectivity in reduction.

Recently we developed a facile method to produce a wide variety of α-sulfonylpiperidine-2,6-diones by cycloaddition reaction.[14,15] Here, we investigate the regioselective reduction of the α-sulfonylpiperidine-2,6-diones (glutarimides) and use the technique to synthesize natural product (**1**) and a class of potentially drug (**2**). The family of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**), shown in Figure 1, possesses a wide range of biological activities[16,17] and serves as an pharmacological tool. Many synthetic methods for these compounds started with the tetracyclic ring system.[18-40] Krogsgaard-Larsen and Brauner-Osborne[41,42] showed homobaclofen (**2**),[41-44] a homologue of classical GABA$_B$ receptor agonist baclofen,[45-50] to exhibit a quite remarkable functional pharmacological profile. Regioselective reduction is the key connection between α-sulfonylglutarimides (**3**) and the target compounds (**1**) and (**2**) in our synthetic studies.
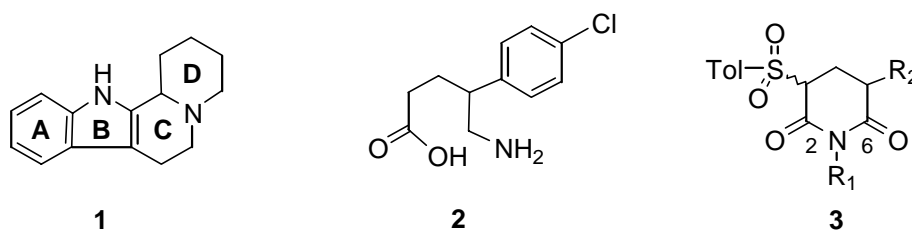

Figure 1. Structure of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**), homobaclofen (**2**) and α-sulfonylglutarimides (**3**)

2. RESULTS AND DISCUSSION

2.1. Regioselective reduction of α-sulfonylglutarimides

Scheme 1 describes the production of α-sulfonylpiperidine-2,6-diones (**3A**) and (**3B**) and the two respective stepwise reduction steps from compounds (**3A**) and (**3B**) to synthesis α-sulfonylpyridinones (**6**) and (**7**). Compounds (**4A**) and (**4B**) were prepared by known procedures.[14,15] Reactions of α-sulfonylacetamides (**4A**) and (**4B**) having *N*-substituents (R$_1$=Tryp and Bn) with the respective acrylates (**5A**) and (**5B**) (R$_2$=H and 4-ClC$_6$H$_4$) yielded products (**3A**) and (**3B**) *via* cycloaddition in basic condition (NaH/THF) at room temperature. The regioselective reduction of α-sulfonylpiperidine-2,6-dione (**3A**) at the C-2 carbonyl group proceed by reduction with sodium borohydride at 4~7 °C, followed by acidic dehydration with boron trifluoride etherate to produce

pyridinone (**6**). The regioselective reduction of α-sulfonylpiperidine-2,6-dione (**3B**) at the C-6 carbonyl group proceeded by proton abstraction using sodium hydride at 25 °C, then reaction with lithium aluminum hydride, followed by dehydration with boron trifluoride etherate to produce pyridinone (**7**). We used **6** and **7** in the formal synthesis of **1** and **2**.
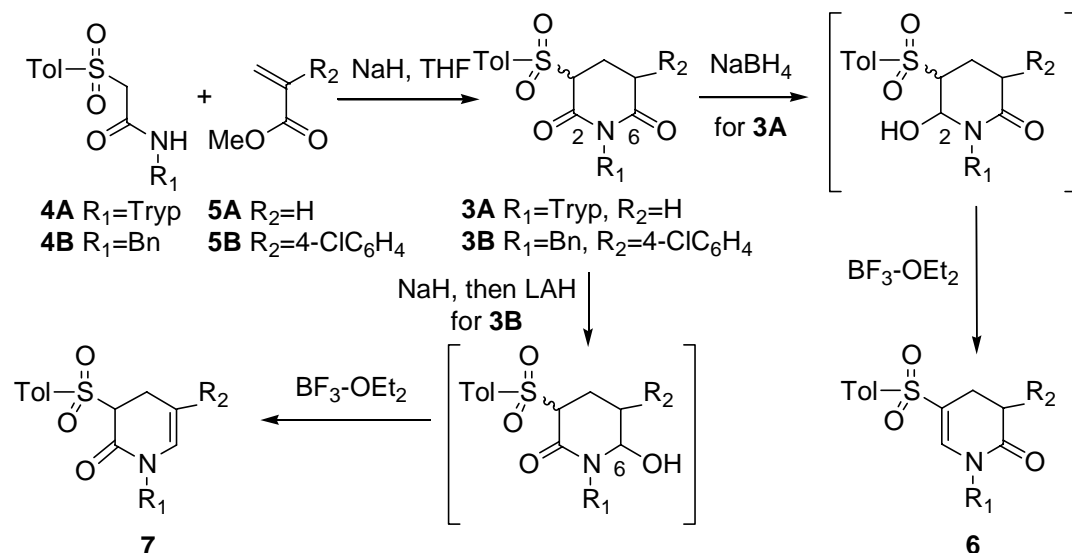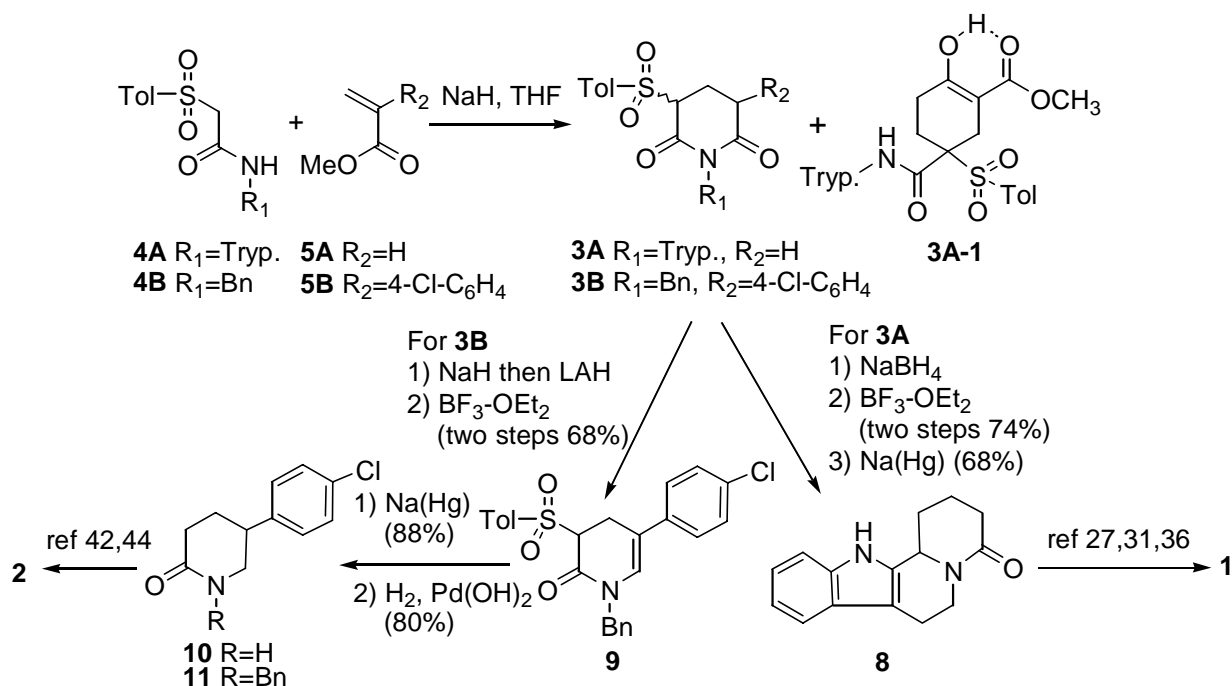

Scheme 1. Regioselective reduction of *N*-alkyl-3-sulfonylglutarimides

2.2. Formal synthesis of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**)

There are many strategies for the synthesis of **1**.[18-40] Our strategy used the key protocols of cycloaddition to form the D-ring *via* α-sulfonylglutarimide (**3A**) and regioselective reduction followed by ring-closure dehydration on the skeleton of compound (**3A**) to synthesize our target (**1**) as shown in Scheme 2. Reaction of tryptamine with chloroacetyl chloride followed by substitution of *p*-toluenesulfonic acid sodium salt gave *N*-tryptaminyl-α-sulfonylacetamide (**4A**) in 87% yield. Deprotonation of acetamide (**4A**) using sodium hydride in THF at room temperature generated the dianion, this is followed by the addition of methyl acrylate (**5A**) to produce cycloadducts (**3A**) and (**3A-1**). The two cycloadducts (**3A**) and (**3A-1**) were formed by Michael addition/cycloaddition and double Michael addition/Dieckmann condensation, respectively. The ratio of cycloadducts (**3A**) to its side product (**3A-1**) was controlled by the rate of addition and the concentration of methyl acrylate in THF. When the rate of addition and concentration of methyl acrylate were 1/10 mL/min and 1/50 g/mL in THF, the ratio of cycloadducts (**3A**) to (**3A-1**) was 3:1 for 72% total yield. Under conditions of 1/20 mL/min and 1/100 g/mL, the cycloadducts ratio was up

to 8:1 for 80% total yield.

Scheme 2. Formal synthesis of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**) and homobaclofen (**2**)

According to related reports,[51-53] the regioselective reduction of piperidine-2,6-dione with sodium borohydride was influenced by the α-substituted group. In our case, chelation between sulfonyl and 2-carbonyl groups of glutarimide (**3A**) was induced by sodium borohydride to produce 2-hydroxypiperidinone. 2-Hydroxypiperidinone was treated with boron trifluoride etherate to produce pyridinone. The ring-closure for C-ring followed sequentially under the same condition. Tetracyclic piperidinone was obtained in 74% yield (two steps). Finally, the lactam (**8**) was obtained from pyridinone by desulfonation with sodium amalgam in methanol. The conversion of lactam (**8**) to target (**1**) has been reported.[27,31,36]

2.3. Formal synthesis of homobaclofen (**2**)

Cycloaddition reaction of compound (**4B**) with **5B** is the key step in the synthesis of homobaclofen (**2**) as shown in Scheme 2. Reaction of benzylamine with chloroacetyl chloride followed by substitution of *p*-toluenesulfonic acid sodium salt gave *N*-benzyl α-sulfonylacetamide (**4B**) in 85% yield. Deprotonation

of acetamide (**4B**) generated the dianion using sodium hydride in THF at refluxed temperature. The α-sulfonylacetamide dianion reacted with acrylate (**5B**) to produce cycloadduct (**3B**). Compound (**3B**) and sodium hydride (1.2 equiv.) in THF was allowed to react at room temperature for 5 min, then, one portion of lithium aluminum hydride (2.0 equiv.) was added and further stirred for 1 h. After normal work-up, hydroxypiperidinone was obtained with the reduction occurring exclusively at C-6 position. To confirm these results, hydroxypiperidinone was treated with boron trifluoride etherate; the corresponding dehydrated product (**9**) was produced in 68% yield. Finally, the lactam (**10**)[42,44] was obtained in two steps by the desulfonation with sodium amalgam in methanol and hydrogenation with palladium hydroxide as a catalyst in acetic acid. A small amount of benzyl lactam (**11**) was also isolated in 10% ratio to the desired product.

3. CONCLUSION

In summary, the formal synthesis of compounds (**1**) and (**2**) has been accomplished through the cycloaddition formation of α-sulfonylacetamide, and the regioselective reduction and dehydration of the α-sulfonylglutarimide.

4. EXPERIMENTAL

General. THF was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Extract was dried with anhydrous magnesium sulfate before concentration *in vacuo*. Crude products were purified using preparative TLC or column chromatography on silica gel. All reported temperatures were uncorrected.

N-[2-(3-Indolyl)ethyl]-2-(4-methylphenylsulfonyl)acetamide (4A)

Chloroacetyl chloride (1.20 g, 10.6 mmol) in THF (20 mL) was added to a solution of tryptamine (1.6 g,

10.0 mmol) and triethylamine (1.11 g, 11.0 mmol) in THF (40 mL) and the mixture was stirred in ice bath for 1 h. After stirring at rt for 4 h, the reaction mixture was concentrated under reduced pressure. Water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (2 x 10 mL), dried, filtered and evaporated. Recrystallization from hexane and ethyl acetate (50 mL : 20 mL) yielded 2.2 g (93%) of chloro compound: mp 145-146 ^{o}C; IR (CHCl$_3$) 3019, 1667, 1214 cm^{-1}; HRMS (EI, M$^+$) calcd for C$_{12}$H$_{13}$N$_2$OCl 236.0178, found 236.0722; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.17 (br s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.22 (t, J = 6.9 Hz, 1H), 7.14 (td, J = 0.9, 6.9 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 6.68 (br s, 1H), 4.01 (s, 2H), 3.64 (dd, J = 6.6, 12.6 Hz, 2H), 3.02 (t, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 165.75, 136.35, 127.07, 122.24, 122.03, 119.50, 118.57, 112.43, 111.24, 42.68, 39.99, 25.10; Anal. Calcd for C$_{12}$H$_{13}$N$_2$OCl: C, 60.89; H, 5.54. Found: C, 60.62; H, 5.52. A stirred solution of chlorocompound (2.0 g, 8.46 mmol) and p-toluenesulfonic acid sodium salt (TolSO$_2$Na-2H$_2$O, 3.21 g, 15.0 mmol) was refluxed in dioxane (50 mL) and water (30 mL) for 10 h. The mixture was concentrated under reduced pressure and the residue was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried, filtered and evaporated. Recrystallization from hexane and ethyl acetate (50 mL : 30 mL) yielded 2.83 g (94%) of **4A**: mp 157-159 ^{o}C; IR (CHCl$_3$) 3042, 1660 cm^{-1}; HRMS (EI, M$^+$) calcd for C$_{19}$H$_{20}$N$_2$O$_3$S 356.1196, found 356.1185; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.42 (br s, 1H), 7.55-7.50 (m, 3H), 7.29 (d, J = 7.8 Hz, 1H), 7.19-7.07 (m, 4H), 7.02 (s, 1H), 6.79 (t, J = 5.4 Hz, 1H), 3.84 (s, 2H), 3.52 (dd, J = 6.6, 12.3 Hz, 2H), 2.92 (t, J = 6.6 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 160.60, 145.30, 136.32, 134.88, 129.79 (2x), 127.91 (2x), 126.94, 122.60, 121.91, 119.18, 118.44, 111.82, 111.36, 61.83, 39.99, 24.68, 21.52; Anal. Calcd for C$_{19}$H$_{20}$N$_2$O$_3$S: C, 64.02; H, 5.66. Found: C, 63.96; H, 5.64.

N-Benzyl-2-(4-methylphenylsulfonyl)acetamide (4B)

Chloroacetyl chloride (5.99 g, 53.0 mmol) in THF (40 mL) was added to a solution of benzylamine (5.35 g, 50.0 mmol) and triethylamine (5.57 g, 55.0 mmol) in THF (100 mL) and stirred in an ice bath for 1 h,

then stirred at rt for 4 h. The mixture was concentrated under reduced pressure. Water (30 mL) was added to the crude product and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (2 x 50 mL), dried, filtered and evaporated. Without purification, the crude product and p-toluenesulfonic acid sodium salt (TolSO$_2$Na-2H$_2$O, 16.05 g, 75.0 mmol) were refluxed in dioxane (150 mL) and water (150 mL) for 10 h. The mixture was concentrated under reduced pressure and the residue was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with brine (2 x 50 mL), dried, filtered and evaporated. Recrystallization from hexane (150 mL) and ethyl acetate (100 mL) yielded 12.88 g (85%, two steps) of **4B** as a solid: mp 157-159 ^{o}C; IR (CHCl$_3$) 2361, 1664, 1528, 1290, 1147 cm^{-1}; ESI-MS: C$_{16}$H$_{18}$NO$_3$S m/z (%) = 91 (100), 154 (65), 304 (M$^+$+1, 85); HRMS (ESI, M$^+$+1) calcd for C$_{16}$H$_{18}$NO$_3$S 304.1008, found 304.1009; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, J = 8.2 Hz, 2H), 7.33-7.24 (m, 7H), 7.06 (br s, 1H), 4.42 (d, J = 5.9 Hz, 2H), 3.99 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 160.64, 145.58, 137.35, 135.12, 130.04, 128.74, 128.16 (4x), 127.97 (2x), 127.70, 62.01, 44.02, 21.70; Anal. Calcd for C$_{16}$H$_{17}$NO$_3$S: C, 63.34; H, 5.65. Found: C, 63.14; H, 5.44.

N-[2-(3-Indolyl)ethyl]-3-(4-methylphenylsulfonyl)piperidine-2,6-dione (3A) and Methyl 5-[2-(3-indolylethyl)ethylcarbamoyl]-2-hydroxy-5-(4-methylphenylsulfonyl)-1-cyclohexene-1-carbo-xylate (3A-1)

A solution of acetamide (**4A**) (1.07 g, 3.0 mmol) in THF (30 mL) was added to a rapidly stirred suspension of sodium hydride (264 mg, 6.6 mmol, 60%) in THF (40 mL). After stirring at rt for 15 min, a solution of methyl acrylate (**5A**) (335 mg, 3.9 mmol) in THF (33.5 mL) was added. The resulting mixture was stirred at rt for *ca.* 11 h, quenched with saturated ammonium chloride solution (2 mL) in ice bath, and concentrated under reduced pressure. Water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 2/1) afforded 873 mg (71%) of **3A** as a solid and 134 mg (9%) of **3A-1** as a viscous oil. Compound (**3A**): mp 177-179 ^{o}C;

IR (CHCl$_3$) 3025, 1667 cm^{-1}; HRMS (EI, M$^+$) calcd for C$_{22}$H$_{22}$N$_2$O$_4$S 410.1300, found 410.1305; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.07 (br s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 6.3 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.18-7.11 (m, 2H), 7.02 (d, J = 2.4 Hz, 1H), 4.11-4.02 (m, 3H), 3.28-3.15 (m, 1H), 2.98 (t, J = 7.8 Hz, 2H), 2.75-2.60 (m, 2H), 2.45 (s, 3H), 2.23-2.15 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 170.64, 164.77, 145.73, 136.05, 134.84, 129.84 (2x), 128.97 (2x), 127.46, 122.33, 121.93, 119.33, 118.87, 112.28, 111.06, 65.64, 40.95, 29.25, 23.31, 21.77, 17.55; Anal. Calcd for C$_{22}$H$_{22}$N$_2$O$_4$S: C, 64.37; H, 5.40. Found: C, 64.62; H, 5.56. Compound (**3A-1**): IR (CHCl$_3$) 3452, 1652 cm^{-1}; HRMS (EI, M$^+$) calcd for C$_{26}$H$_{28}$N$_2$O$_6$S 496.1668, found 496.1678; ^{1}H NMR (300 MHz, CDCl$_3$): δ 12.08 (s, 1H), 8.25 (br s, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.1 Hz, 1H), 7.25-7.11 (m, 4H), 7.04 (d, J = 6.6 Hz, 1H), 6.78 (t, J = 8.1 Hz, 1H), 3.66 (s, 3H), 3.63-3.55 (m, 2H), 3.02 (t, J = 6.6 Hz, 2H), 2.90 (d, J = 15.9 Hz, 1H), 2.78 (d, J = 15.9 Hz, 1H), 2.37 (s, 3H), 2.36-2.28 (m, 3H), 2.15-2.09 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 171.63, 170.05, 164.98, 145.59, 136.42, 131.48, 129.69 (2x), 129.66 (2x), 126.92, 122.45, 122.09, 119.37, 118.50, 112.05, 111.34, 94.20, 70.12, 51.65, 40.48, 26.13, 25.23, 24.69, 24.53, 21.64; Anal. Calcd for C$_{26}$H$_{28}$N$_2$O$_6$S: C, 62.89; H, 5.68. Found: C, 62.71; H, 5.71.

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizin-4-one (8)[27,31,36]

A solution of compound (**3A**) (615 mg, 1.5 mmol) in co-solvent of THF (10 mL) and methanol (5 mL) was stirred at 4-7 ^{o}C, and sodium borohydride (150 mg, 4.0 mmol) was added. The mixture was stirred for 2 h at this temperature. Saturated sodium bicarbonate solution (1 mL) was added to the mixture and the mixture was concentrated under reduced pressure. Water (5 mL) was added to the residue, and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried, filtered and evaporated. Without further purification, the crude hydroxylactam was dissolved in dichloromethane (10 mL) and a catalytic amount of boron trifluoride etherate (0.1 mL) was added. The mixture was stirred for 15 h at rt. Saturated sodium bicarbonate solution (5 mL) was added to the resulting mixture and the mixture was concentrated under reduced pressure. Water (5 mL)

was added to the residue, and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 1/1) afforded 437 mg (two steps 74%) of cyclized product: mp 258-260 $^{\circ}$C; IR (CHCl$_3$) 3240, 1610 cm^{-1}; ESI-MS: C$_{22}$H$_{23}$N$_2$O$_3$S m/z (%) = 58 (48), 136 (50), 149 (88), 238 (72), 391 (57), 395 (M$^+$+1, 100); HRMS (ESI, M$^+$+1) calcd for C$_{22}$H$_{23}$N$_2$O$_3$S 395.1431, found 395.1436; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.75 (br s, 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.4 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 5.39 (d, J = 8.3 Hz, 1H), 4.95 (dd, J = 4.8, 13.2 Hz, 1H), 3.67-3.62 (m, 1H), 3.03-2.90 (m, 2H), 2.75-2.70 (m, 1H), 2.57 (dt, J = 4.5, 17.2 Hz, 1H), 2.49 (s, 3H), 2.20-2.12 (m, 1H), 2.07-1.97 (m, 1H), 1.95-1.88 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.32, 146.44, 136.11, 132.46, 131.49, 130.46 (2x), 129.29, 129.12, 126.47, 122.61, 119.85, 118.45, 111.65, 111.03, 64.32, 52.18, 42.75, 30.08, 22.10, 21.78, 20.56; Anal. Calcd for C$_{22}$H$_{22}$N$_2$O$_3$S: C, 66.98; H, 5.62. Found: C, 66.72; H, 5.66. A solution of sulfonyl compound (394 mg, 1.0 mmol) and sodium phosphate (355 mg, 2.5 mmol) in methanol (15 mL) was stirred, and 6% sodium amalgam (Na/Hg, 1.5 g) was added. The mixture was vigorously stirred for 2 h at rt. The residue was filtered and washed with methanol (2 x 10 mL). The combined organic layers were concentrated to the crude desulfonyl compound. Purification on silica gel (hexane/ethyl acetate = 1/1) afforded 163 mg (68%) of **8**: mp 140-141 $^{\circ}$C; IR (CHCl$_3$) 3230, 1607 cm^{-1}; HRMS (ESI, M$^+$+1) calcd for C$_{15}$H$_{17}$N$_2$O 241.1342, found 241.1339; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85 (br s, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.18 (ddd, J = 1.1, 7.1, 8.0 Hz, 1H), 7.12 (td, J = 0.9, 7.8 Hz, 1H), 5.18-5.11 (m, 1H), 4.81 (m, 1H), 2.94-2.65 (m, 4H), 2.50-2.42 (m, 2H), 2.01-1.72 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.06, 136.27, 132.50, 126.77, 122.46, 120.06, 118.50, 110.97, 109.60, 54.60, 40.92, 31.55, 28.84, 20.91, 18.83.

N-Benzyl-3-(4-chlorophenyl)-5-(4-methylphenylsulfonyl)piperidine-2,6-dione (3B)

A solution of acetamide (**4B**) (0.9 g, 3.0 mmol) in THF (30 mL) was added to a rapidly stirred suspension of sodium hydride (264 mg, 6.6 mmol, 60%) in THF (20 mL). After the reaction mixture was stirred at rt

for 15 min, a solution of methyl acrylate (**5B**) (590 mg, 3.0 mmol) in THF (10 mL) was added. The resulting mixture was stirred at reflux temperature for 30 min, quenched with saturated ammonium chloride solution (2 mL) in ice bath, and concentrated under reduced pressure. Water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 3/1) afforded 1.08 g (77%) of **3B** as a solid: mp 192-194 ^{o}C; IR (CHCl$_3$) 1733, 1669 cm^{-1}; ESI-MS: C$_{25}$H$_{23}$NO$_4$ClS m/z (%) = 91 (26), 136 (61), 154 (100), 307 (32), 468 (M$^+$+1, 19); HRMS (ESI, M$^+$+1) calcd for C$_{25}$H$_{23}$NO$_4$ClS 468.1036, found 468.1033; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85 (d, J = 8.3 Hz, 2/3H), 7.54 (d, J = 8.3 Hz, 4/3H), 7.36-7.24 (m, 9H), 7.12-7.07 (m, 2H), 5.07 (d, J = 13.9 Hz, 2/3H), 4.94 (d, J = 13.9 Hz, 2/3H), 4.92 (d, J = 13.9 Hz, 1/3H), 4.87 (d, J = 13.9 Hz, 1/3H), 4.52 (dd, J = 5.7, 12.8 Hz, 2/3H), 4.32 (dd, J = 5.5, 12.9 Hz, 1/3H), 4.14 (dd, J = 2.8, 5.8 Hz, 2/3H), 3.68 (dd, J = 4.7, 13.9 Hz, 1/3 H), 3.04 (ddd, J = 2.8, 5.8, 14.9 Hz, 1H), 2.81 (td, J = 5.2, 13.4 Hz, 1/3H), 2.63-2.47 (m, 2/3H), 2.46 (s, 1H), 2.44 (s, 2H); Anal. Calcd for C$_{25}$H$_{22}$NO$_4$ClS: C, 64.16; H, 4.74. Found: C, 64.28; H, 4.81.

N-Benzyl-3-[(4-methylphenyl)sulfonyl]-5-(4-chlorophenyl)-3,4-dihydro-2(*1H*)-pyridinone (9)

A solution of **3B** (468 mg, 1.0 mmol) in THF (10 mL) was added to a rapidly stirred suspension of sodium hydride (48 mg, 1.2 mmol, 60%). After the reaction mixture was stirred at rt for 5 min, lithium aluminum hydride (76 mg, 2.0 mmol) was added and the resulting reaction mixture was stirred for 1.0 h, then quenched with a saturated ammonium chloride solution (1 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were washed with brine (2 x 10 mL), dried, filtered and evaporated. Without purification, the crude hydroxylactam was treated with boron trifluoride etherate (0.1 mL) in dichloromethane (20 mL) for 10 h, water (20 mL) was then added. After extraction with dichloromethane (2 x 20 mL), the organic layers were washed with brine (2×10 mL), dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 3/1) afforded 306 mg (68%) of **9** as a solid: mp 153-155 ^{o}C; IR (CHCl$_3$) 1668 cm^{-1}; ESI-MS: C$_{25}$H$_{23}$NO$_3$ClS m/z (%) = 91 (100), 136 (30), 154 (46), 295 (31), 452

(M$^+$+1, 70); HRMS (ESI, M$^+$+1) calcd for C$_{25}$H$_{23}$NO$_3$ClS 452.1087, found 452.1087; ^{1}H NMR(400 MHz, CDCl$_3$) δ 7.68 (d, J = 8.3 Hz, 2H), 7.36-7.14 (m, 11H), 6.20 (d, J = 2.5 Hz, 1H), 4.70 (s, 2H), 4.17 (dd, J = 3.1, 7.9 Hz, 1H), 3.52 (dd, J = 3.1, 18.2 Hz, 1H), 3.19 (ddd, J = 2.5, 7.9, 18.2 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 160.58, 145.30, 135.88, 135.59, 135.49, 133.02, 129.60 (3x), 129.10 (3x), 128.87 (2x), 128.83, 127.97 (2x), 126.17 (2x), 125.51, 115.17, 65.70, 50.32, 24.87, 21.74; Anal. Calcd for C$_{25}$H$_{22}$NO$_3$ClS: C, 66.44; H, 4.91. Found: C, 66.59; H, 4.86.

5-(4-Chlorophenyl)piperidin-2-one (10)[42,44] and N-Benzyl-5-(4-chlorophenyl)piperidin-2-one (11)

A solution of compound (**9**) (450 mg, 1.0 mmol) and sodium phosphate (355 mg, 2.5 mmol) in methanol (15 mL) was stirred, and 6% sodium amalgam (Na/Hg, 1.5 g) was added. The mixture was vigorously stirred for 2 h at rt. The residue was filtered and washed with methanol (2 x 10 mL). The combined organic layers were concentrated to leave the crude desulfonyl compound. Purification on silica gel (hexane/ethyl acetate = 1/1) afforded 260 mg (88%) of desulfonyl compound: mp 80-82 ^{o}C; IR (CHCl$_3$) 1651 cm^{-1}; EI-MS: C$_{18}$H$_{16}$NOCl m/z (%) = 91 (100), 154 (33), 297 (M$^+$, 81); HRMS (EI, M$^+$) calcd for C$_{18}$H$_{16}$NOCl 297.0920, found 297.0924; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34-7.15 (m, 9H), 6.41 (s, 1H), 4.76 (s, 2H), 2.72 (s, 4H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.74, 136.98, 136.75, 132.31, 128.79, 128.70 (4x), 127.66 (2x), 127.62, 126.43, 125.57, 117.69, 49.42, 31.13, 23.65; Anal. Calcd for C$_{18}$H$_{16}$NOCl: C, 72.60; H, 5.42. Found: C, 72.44; H, 5.69. Palladium hydroxide on activated carbon as catalyst (100 mg) was added to a solution of olefin (200 mg, 0.67 mmol) in acetic acid (10 mL). Hydrogen was bubbled into the mixture for 10 min, and the mixture was stirred at rt for 18 h. Filtration through a short plug of Celite and washing with ethyl acetate (3 x 10 mL) resulted in the crude products. Purification on silica gel (hexane/ethyl acetate = 1/1~1/2) produced 112 mg (80%) of compound (**10**) as a solid and 16 mg (8%) of compound (**11**) as a gum. ^{1}H NMR data spectrum of **10** were the same with reference 42. Compound (**11**): IR (CHCl$_3$) 1656 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33-7.14 (m, 9H), 4.69 (d, J = 14.6 Hz, 1H), 4.54 (d, J = 14.6 Hz, 1H), 3.35-3.33 (m, 1H), 3.28-3.23 (m, 1H), 3.06-3.01 (m, 1H), 2.69-2.52 (m, 2H), 2.09-2.02 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.44, 141.69, 136.98,

128.71 (2x), 128.64 (2x), 128.23, 127.47, 127.15, 126.96 (2x), 116.32, 53.68, 50.34, 40.28, 32.06, 28.04; Anal. Calcd for $C_{18}H_{18}NOCl$: C, 72.11; H, 6.05. Found: C, 72.50; H, 5.63.

5. ACKNOWLEDGEMENT

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