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Regioselective reduction of *N*-alkyl-3-sulfonyl glutarimides to δ-lactams. Formal synthesis of (±)-paroxetine and (±)-tacamonine☆

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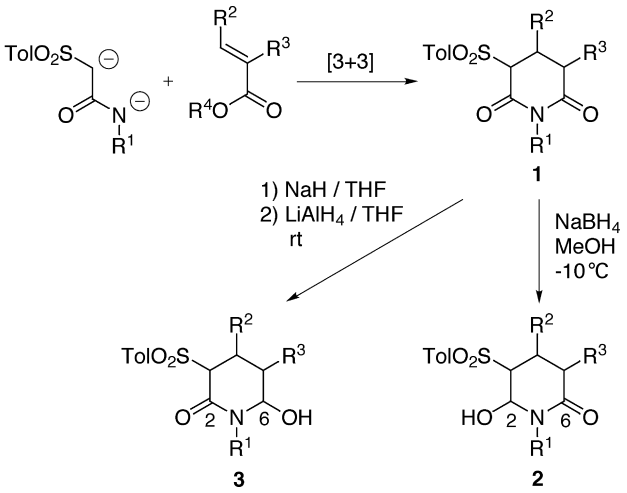
Abstract—A convenient method for the preparation of 4- or 5-substituted 3-sulfonyl-δ-lactams via regioselective reduction of *N*-alkyl-3-sulfonyl glutarimides is described. Formal synthesis of (±)-paroxetine and (±)-tacamonine is also reported.

1. Introduction

Six-membered nitrogen-containing heterocycles are abundant in nature and exhibit diverse and important biological properties.[1] Alkaloids that contain the piperidine ring continue to be the targets of extensive synthetic interest, partly because there are many biologically active natural products of this type.[2] Accordingly, the development of a general method for the preparation of piperidine derivatives has been the subject of considerable synthetic efforts.[3] δ-Lactams have been generally regarded as the precursors of the corresponding piperidines. It is well documented that one of the most widely used methods for the construction of the tetracyclic carbon skeleton of indole alkaloids is to synthesize an appropriate δ-lactam, which is then cyclized to indole alkaloids via the Bischler–Napieralski reaction. Herein, we report a convenient method for the preparation of 4- or 5-substituted 3-sulfonyl-δ-lactams from *N*-alkyl-3-sulfonyl glutarimide **1**.

Recently, we developed an efficient route to the unsymmetrical glutarimides with a sulfonyl group at C-3 position.[4,5] The feature of this approach is the utility of a sulfonyl group to control subsequent regioselective functionalizations that lead to a variety of hydroxy δ-lactams with diverse substituents.[5] Regioselective reduction of C-2 carbonyl of glutarimide **1** was accomplished with $NaBH_4$.[5a,b] This was attributed to the chelation of the reducing agent with both the 3-sulfonyl and C-2 carbonyl. The sulfonyl group also increased the electrophilicity of C-2 carbon. Regioselective reduction of the C-6 carbonyl of glutarimide **1** was accomplished by protection of the C-2 carbonyl as an enolate[5c] (Scheme 1).



Scheme 1. Regioselective reduction of *N*-alkyl-3-sulfonyl glutarimide **1** to hydroxy lactam.

2. Results and discussion

2.1. Regioselective reduction of *N*-alkyl-3-sulfonyl glutarimide 1 to δ-lactam 5 with $LiAlH_4$

It was reported that reduction of glutarimides with $NaBH_4$ or $LiAlH_4$ yielded hydroxy lactams or over-reduced product hydroxy amides.[6] However, reduction of glutarimides directly to δ-lactams has never been achieved. We discovered that treatment of glutarimide **1** with 1.2 equiv.

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Keywords: glutarimide; δ-lactam; regioselective reduction; paroxetine; tacamonine.

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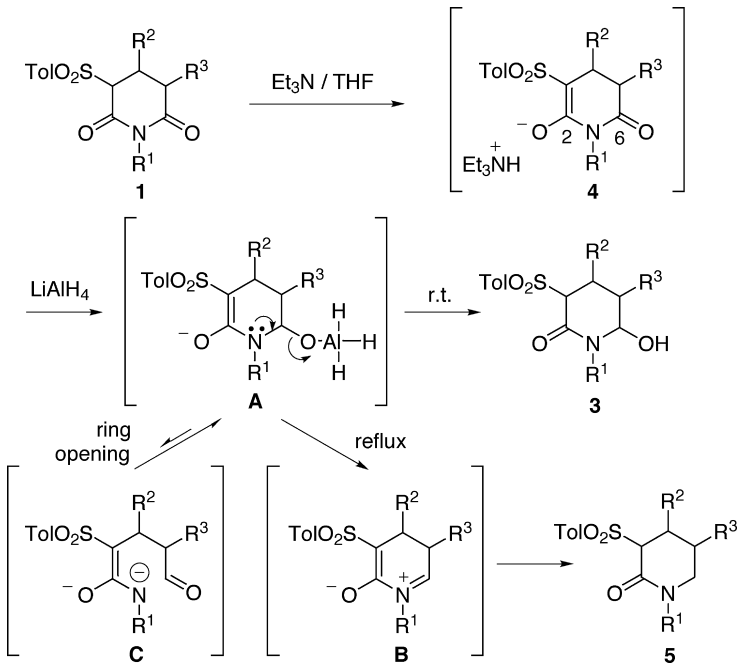


Scheme 2. Regioselective reduction of *N*-alkyl-3-sulfonyl glutarimide **1** with $LiAlH_4$.

Et_3N at 25°C for 30 min followed by addition of 5 equiv. of $LiAlH_4$, the resulting mixture was further refluxed in THF solution for 3 h, δ-lactam **5** was obtained in good yields (Scheme 2).

In order to examine the generality of this new method for the preparation of δ-lactam **5**, several examples were tested; the results are listed in Table 1. The regioselective reduction of **1** and the formation of δ-lactam **5** could be rationalized by the formation of enolate **4**, which prevented the C-2 carbonyl group from $LiAlH_4$ reduction. It is worth noting that when reduction of **1** proceeded at rt (25°C), hydroxy lactam **3** was obtained exclusively. Nevertheless, when the reaction mixture was heated to refluxing temperature in THF solution, the corresponding δ-lactam **5** was yielded as the only product, presumably via B intermediate. Since dianion intermediate C is more unstable compared with A and B, the corresponding hydroxy amides (ring opening products) were not observed at elevated temperature.

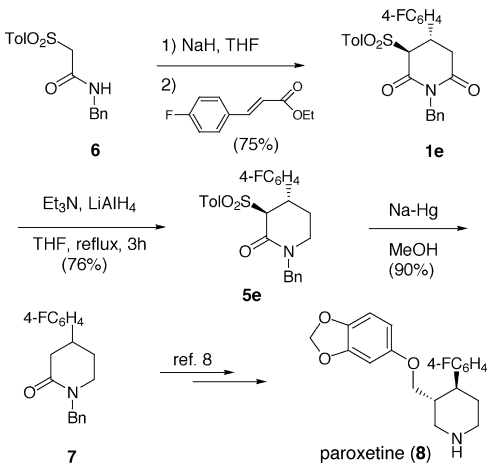
Table 1. Synthesis of **5** via regioselective $LiAlH_4$ reduction

No.	1	R^1	R^2	R^3	5 (yield[a], %)
1	**1a**	Bn	H	H	**5a** (75)
2	**1b**	Bn	Me	H	**5b** (86)
3	**1c**	Bn	Ph	H	**5c** (78)
4	**1d**	Bn		H	**5d**[b] (95)
5	**1e**	Bn	4-FC_6H_4	H	**5e** (76)
6	**1f**	PMB		H	**5f** (88)
7	**1g**	Tryp	H	H	**5g** (85)
8	**1h**	Tryp	H	Et	**5h** (83)

[a] All yields were based on glutarimide **1**.
[b] The structure of **5d** was confirmed by X-ray analysis (see Ref. 7).

2.2. Formal synthesis of (±)-paroxetine

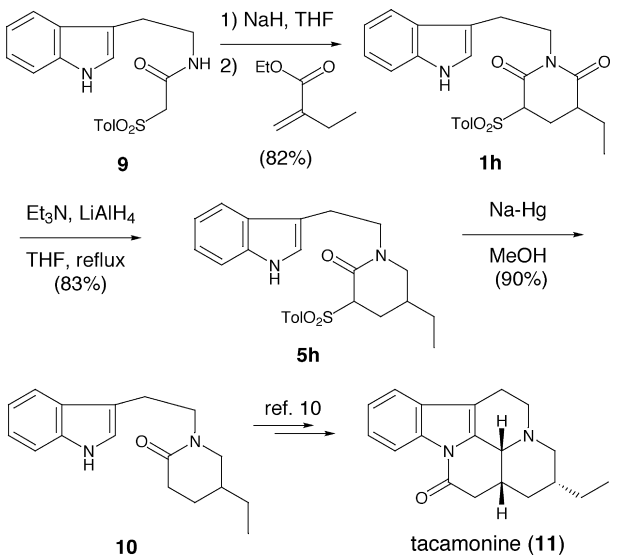
To demonstrate the synthetic utility of this methodology, the efficient formal synthesis of (±)-paroxetine (**8**), which is marketed as the hydrochloride Paxil/Seroxat, a selective serotonin reuptake inhibitor, was reported. Reductive desulfonylation of **5e** with sodium amalgam in methanol solution furnished **7** in good yield, which had been readily converted into (±)-paroxetine (**8**) by Yu.[8] The spectroscopic data for **7** were identical to those reported in the literature (Scheme 3).



Scheme 3. Formal synthesis of (±)-paroxetine.

2.3. Foral synthesis of (±)-tacamonine

Tacamonine (**11**), one of the few indole alkaloids of the tacamane type, was isolated in 1984 from *Tabernaemontana eglandulosa*,[9] which possess vasodilator and hypotensive activities. Lactam **10** has been converted to **11** in three steps via Bischler–Napieralski cyclization.[10] As shown in



Scheme 4. Formal synthesis of (±)-tacamonine.

Scheme 4, following the same procedures as described in the synthesis of **5e**, the key intermediate **10** was obtained in 3 steps from **9** (61% overall yield). The spectroscopic data for **10** matched those reported in the literature.[10a] The present work constitutes a formal synthesis of (±)-tacamonine (**11**).

3. Conclusion

In conclusion, we have developed a convenient method for the preparation of substituted δ-lactams in good yield. We also successfully accomplished the formal synthesis of (±)-paroxetine and (±)-tacamonine. Further application of this methodology in the synthesis of other alkaloids is currently underway in our laboratory.

4. Experimental

4.1. General

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 (60 f254 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.

4.2. Procedure of [3+3] cycloaddition to *N*-alkyl-3-sulfonyl glutarimide 1

A solution of *N*-substituted-2-(toluene-4-sulfonyl) acetamide (2.0 mmol) in THF (15 mL) was added to a rapidly stirred suspension of sodium hydride (4.4 mmol, 60%) in THF (10 mL). After the reaction mixture was stirred at rt for 15 min, a solution of α,β-unsaturated ester (2.0 mmol) in THF (10 mL) was added. The resulting mixture was refluxed for 30 min, quenched with NH_4Cl (1 mL) in an ice bath, and concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=4/1–2/1) produced products.

4.2.1. 3-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-5-(toluene-4-sulfonyl)piperidine-2,6-dione (1h). 82% Yield; mp 168–170°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (brs, 0.7H), 8.04 (brs, 0.3H), 7.87 (d, J=8.5 Hz, 0.7H), 7.72–7.63 (m, 2.3H), 7.36 (t, J=8.0 Hz, 2.1H), 7.31 (t, J=8.0 Hz, 0.9H), 7.18–7.14 (m, 1H), 7.12–7.08 (m, 1H), 7.01 (d, J=2.5 Hz, 0.7H), 6.95 (d, J=2.5 Hz, 0.3H), 4.15–3.96 (m, 3H), 3.13–3.07 (m, 0.7H), 2.99–2.95 (m, 1.3H), 2.90–2.85 (m, 0.7H), 2.78–2.74 (m, 0.7H), 2.61–2.56 (m, 0.3H), 2.44 (s, 3H), 2.31–2.25 (m, 0.3H), 2.05–1.87 (m, 2H), 1.59–1.48 (m, 1H), 0.93 (t, J=8.0 Hz, 2.1H), 0.90 (t, J=8.0 Hz, 0.9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.15 (0.7C), 172.52 (0.3C), 165.01 (0.3C), 164.66 (0.7C), 145.72 (0.7C), 145.34 (0.3C), 136.07, 135.50 (0.3C), 135.01 (0.7C), 129.86, 129.57, 128.94, 127.52 (0.7C), 127.40 (0.3C), 122.35, 121.91, 119.34, 118.89, 112.34 (0.7C), 112.19 (0.3C), 111.06, 65.86 (0.7C), 65.70 (0.3C), 41.94, 41.25, 39.21, 23.84, 23.39 (0.3C), 23.24 (0.7C), 22.59 (0.7C), 22.46 (0.3C), 21.71 (0.7C), 21.69 (0.3C), 10.61 (0.3C), 10.46 (0.7C); IR ($CHCl_3$, cm^{-1}) 3025, 1667. Mass *m/z* (EI, 30 eV) 438 (M^+, 8.26%), 143 (100%), 130 (76.27%); HRMS calcd for $C_{24}H_{26}O_4N_2S$: 438.1613, found: 438.1617. Anal. calcd for $C_{24}H_{26}O_4N_2S$: C, 65.73; H, 5.98; O, 14.59; N, 7.31, found: C, 65.79; H, 5.96; O, 14.55; N, 7.28.

4.3. Procedure of regioselective reduction of glutarimide 1 to δ-lactam 5

A solution of glutarimides **1** (2.0 mmol) in THF (20 mL) was added to a stirred solution of triethylamine (2.4 mmol) in THF (10 mL). After the reaction mixture was stirred at rt for 30 min, lithium aluminum hydride (10.0 mmol) was added. The resulting mixture was refluxed for 3 h, quenched with NH_4Cl (1 mL) in an ice bath, filtered and then concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=3/1–1/1) produced products.

4.3.1. 1-Benzyl-3-(toluene-4-sulfonyl)piperidin-2-one (5a). 75% Yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J=7.5 Hz, 2H), 7.31–7.22 (m, 7H), 4.74 (d, J=14.5 Hz, 1H), 4.43 (d, J=14.5 Hz, 1H), 4.03 (t, J=7.0 Hz, 1H), 3.37–3.32 (m, 1H), 3.24–3.18 (m, 1H), 2.75–2.69 (m, 1H), 2.44 (s, 3H), 2.31–2.17 (m, 2H), 1.81–1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.01, 144.67, 136.67, 136.23, 129.46 (2C), 129.10 (2C), 128.67 (2C), 127.77 (2C), 127.50, 65.86, 50.56, 47.16, 22.08, 21.70, 20.39; IR ($CHCl_3$, cm^{-1}) 3027, 1662. Mass *m/z* (EI, 30 eV) 349 (M^++1, 3.66%), 91 (100%); HRMS calcd for $C_{19}H_{21}O_3NS$: 343.1242, found: 343.1236.

4.3.2. 1-Benzyl-4-methyl-3-(toluene-4-sulfonyl)piperidin-2-one (5b). 86% Yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J=8.5 Hz, 2H), 7.35–7.26 (m, 7H), 4.67 (d,

J=15.0 Hz, 1H), 4.52 (d, J=15.0 Hz, 1H), 3.76 (d, J=4.0 Hz, 1H), 3.41–3.36 (m, 1H), 3.25–3.20 (m, 1H), 3.09–3.05 (m, 1H), 2.44 (s, 3H), 2.39–2.33 (m, 1H), 1.57–1.50 (m, 1H), 1.19 (d, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.82, 144.73, 136.40, 136.33, 129.49 (2C), 128.99 (2C), 128.67 (2C), 127.81 (2C), 127.52, 72.52, 50.77, 44.27, 27.67, 27.57, 21.71, 20.22; IR ($CHCl_3$, cm^{-1}) 3025, 1668. Mass m/z (EI, 30 eV) 358 (M^++1, 1.36%), 202 (100%), 91 (86.07%); HRMS calcd for $C_{20}H_{23}O_3NS$: 357.1399, found: 357.1392.

4.3.3. 1-Benzyl-4-phenyl-3-(toluene-4-sulfonyl)piperidin-2-one (5c). 78% Yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J=8.0 Hz, 2H), 7.35–7.21 (m, 10H), 7.10 (d, J=7.0 Hz, 2H), 4.73 (d, J=15.0 Hz, 1H), 4.56 (d, J=15.0 Hz, 1H), 4.30–4.27 (m, 2H), 3.38–3.36 (m, 1H), 3.06–3.00 (m, 1H), 2.66–2.60 (m, 1H), 2.43 (s, 3H), 1.89–1.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.05, 144.83, 141.36, 136.28, 136.06, 129.47 (2C), 128.99 (2C), 128.80 (2C), 128.59 (2C), 127.97 (2C), 127.54, 127.18, 126.95 (2C), 70.59, 50.85, 44.00, 37.75, 28.57, 21.66; IR ($CHCl_3$, cm^{-1}) 3030, 1658. Mass m/z (EI, 30 eV) 420 (M^++1, 2.29%), 264 (95.59%), 91 (100%); HRMS calcd for $C_{25}H_{25}O_3NS$: 419.1555, found: 419.1549.

4.3.4. 1-Benzyl-4-dimethoxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (5d)[7]. 95% Yield; mp 96–98°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J=8.0 Hz, 2H), 7.40 (d, J=8.0 Hz, 2H), 7.34–7.27 (m, 5H), 4.61 (dd, J=15.0, 4.0 Hz, 2H), 4.35 (d, J=5.6 Hz, 1H), 4.13 (d, J=2.5 Hz, 1H), 3.38 (s, 1H), 3.37 (s, 1H), 3.35 (t, J=4.5 Hz, 1H), 3.28–3.23 (m, 2H), 2.46 (s, 3H), 2.36–2.31 (m, 1H), 1.87–1.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.75, 144.71, 136.27, 136.22, 129.45, 128.93, 128.51, 127.80, 127.39, 104.88, 66.82, 54.96, 54.37, 50.75, 44.62, 34.83, 21.65, 20.73; IR ($CHCl_3$, cm^{-1}) 3030, 2928. Mass m/z (EI, 30 eV) 418 (M^++1, 1.32%), 262 (58.37%), 91 (100%); HRMS calcd for $C_{22}H_{27}O_5NS$: 417.1610, found: 417.1604. Single-crystal X-ray diagram: crystal of **5d** was grown by slow diffusion of ethyl acetate into a solution of **5d** in dichloromethane to yield colorless prism. The compound crystallizes in the primitive orthorhombic crystal system, space group $P2_1/c$ (#14), a=10.634(2) Å, b=24.581(4) Å, c=8.383(2) Å, V=2133.1(7) Å^3, Z=4, d_{calcd}=1.300 g/cm^3, F(000)=888.00, 2θ range 16(20.5–27.9°).

4.3.5. 1-Benzyl-4-(4-fluorophenyl)-3-(toluene-4-sulfonyl)piperidin-2-one (5e). 76% Yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J=8.5 Hz, 2H), 7.34–7.29 (m, 7H), 7.09–7.06 (m, 2H), 6.97–6.93 (m, 2H), 4.68 (d, J=14.5 Hz, 1H), 4.59 (d, J=14.5 Hz, 1H), 4.26–4.23 (m, 1H), 4.21 (d, J=2.5 Hz, 1H), 3.42–3.38 (m, 1H), 3.07–3.02 (m, 1H), 2.62–2.56 (m, 1H), 2.44 (s, 3H), 1.86–1.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.96, 160.81, 145.00, 137.33, 136.16, 136.02, 129.55 (2C), 129.06 (2C), 128.68 (2C), 128.66, 128.59, 128.08 (2C), 127.70, 115.81, 115.63, 71.00, 50.99, 44.11, 37.41, 28.91, 21.71; IR ($CHCl_3$, cm^{-1}) 3021, 1616. Mass m/z (EI, 30 eV) 438 (M^++1, 6.47%), 282 (23.70%), 91 (100%); HRMS calcd for $C_{25}H_{24}O_3NSF$: 437.1461, found: 437.1464.

4.3.6. 1-Benzyl-4-[1,3]dithian-2-yl-3-(toluene-4-sulfonyl)piperidin-2-one (5f). 88% Yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J=8.5 Hz, 2H), 7.35 (d, J=8.5 Hz, 2H), 7.18 (D, J=8.5 Hz, 2H) 6.86 (d, J=8.5 Hz, 2H), 4.62 (d, J=14.5 Hz, 1H), 4.51 (d, J=3.0 Hz, 1H) 4.40 (d, J=14.5 Hz, 1H), 4.01 (d, J=7.5 Hz, 1H), 3.80 (s, 3H), 3.39–3.33 (m, 2H), 3.21–3.17 (m, 1H), 3.00–2.91 (m, 2H), 2.90–2.73 (m, 2H), 2.45 (s, 3H), 2.35–2.33 (m, 1H), 2.11–1.90 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.46, 159.31, 145.10, 136.46, 129.81 (2C), 129.50 (2C), 129.19 (2C), 128.42, 114.29 (2C), 68.93, 55.50, 50.30, 50.03, 44.00, 36.71, 29.34, 29.15, 25.57, 23.99, 21.98; IR ($CHCl_3$, cm^{-1}) 3045, 1682. Mass m/z (EI, 30 eV) 491 (M^+, 1.28%), 336 (91.88%), 121 (100%); HRMS calcd for $C_{24}H_{29}O_4NS_3$: 491.1259, found: 491.1252.

4.3.7. 1-[2-(1*H*-Indol-3-yl)ethyl]-3-(toluene-4-sulfonyl)-piperidin-2-one (5g). 85% Yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (brs, 1H), 7.80 (d, J=8.5 Hz, 2H), 7.58 (d, J=5.0 Hz, 1H), 7.33–7.30 (m, 3H), 7.16 (t, J=7.5 Hz, 1H), 7.09 (t, J=2.5 Hz, 1H), 7.05 (s, 1H), 3.96 (t, J=6.0 Hz, 1H), 3.75–3.70 (m, 1H), 3.50–3.45 (m, 1H), 3.15–3.10 (m, 1H), 3.04–2.98 (m, 4H), 2.59–2.54 (m, 1H), 2.40 (s, 3H), 2.09–2.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.54, 144.62, 136.25, 129.43 (2C), 128.99 (2C), 127.21, 122.62, 121.80, 119.15, 118.45, 112.38, 111.30, 65.80, 51.09, 49.08, 48.76, 22.85, 21.93, 21.62, 20.40; IR ($CHCl_3$, cm^{-1}) 3052, 1688. Mass m/z (EI, 30 eV) 396 (M^+, 1.35%), 143 (100%); HRMS calcd for $C_{22}H_{24}O_3N_2S$: 396.1507, found: 396.1510.

4.3.8. 5-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-3-(toluene-4-sulfonyl)piperidin-2-one (5h). 83% Yield; mp 173–175°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (brs, 1H), 7.82 (d, J=8.5 Hz, 1H), 7.79 (d, J=8.5 Hz, 1H), 7.61 (d, J=8.0 Hz, 0.5H), 7.57 (d, J=8.0 Hz, 0.5H), 7.35–7.31 (m, 3H), 7.18 (t, J=7.5 Hz, 1H), 7.12–7.08 (m, 1H), 7.02 (d, J=2.5 Hz, 1H), 4.05 (dd, J=3.5, 7.5 Hz, 0.5H), 3.92 (dd, J=2.5, 4.5 Hz, 0.5H), 3.78–3.73 (m, 0.5H), 3.69–3.65 (m, 0.5H), 3.55–3.44 (m, 1H), 3.15–3.12 (m, 0.5H), 3.04–3.01 (m, 0.5H), 3.03–2.85 (m, 2H), 2.75 (t, J=10.5 Hz, 1H), 2.44–2.39 (m, 0.5H), 2.42 (s, 3H), 2.27–2.24 (m, 0.5H), 1.96–1.89 (m, 0.5H), 1.68–1.61 (m, 1H), 1.53–1.48 (m, 0.5H), 1.30–1.14 (m, 2H), 0.82 (t, J=7.5 Hz, 1.5H), 0.77 (t, J=7.5 Hz, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.86 (0.5C), 161.51 (0.5C), 144.63 (0.5C), 144.50 (0.5C), 136.84 (0.5C), 136.61 (0.5C), 136.24, 129.46 (0.5C), 129.35 (0.5C), 129.17, 128.98, 127.26, 122.55 (0.5C), 122.36 (0.5C), 121.97 (0.5C), 121.93 (0.5C), 119.30 (0.5C), 119.28 (0.5C), 118.54, 112.62, 111.22 (0.5C), 111.20 (0.5C), 65.71 (0.5C), 65.54 (0.5C), 53.99 (0.5C), 53.80 (0.5C), 49.12 (0.5C), 49.01 (0.5C), 34.95, 31.58, 27.67 (0.5C), 27.42 (0.5C), 26.01 (0.5C), 26.00 (0.5C), 22.87 (0.5C), 22.82 (0.5C), 21.67, 11.00 (0.5C), 10.94 (0.5C); IR ($CHCl_3$, cm^{-1}) 3053, 1687. Mass m/z (EI, 30 eV) 424 (M^+, 1.18%), 143 (100%); HRMS calcd for $C_{24}H_{28}O_3N_2S$: 424.1821, found: 424.1817. Anal. calcd for $C_{24}H_{28}O_3N_2S$: C, 67.90; H, 6.65; O, 11.31; N, 6.60, found: C, 67.93; H, 6.61; O, 11.25; N, 6.58.

4.4. Procedure of reductive desulfonylation of 3-sulfonyl lactam 5

6% Sodium amalgam (Na/Hg, 3.0 g) and sodium phosphate (40 mg) were added to a stirred solution of 3-sulfonyl lactam **5** (2.0 mmol) in methanol (5 mL), and vigorously

stirred for 2 h at rt. The residue was filtered and washed with methanol (2×10 mL). The combined organic layers were concentrated to obtain the crude product. Purification on silica gel (hexane/ethyl acetate=2/1–1/1) produced products.

4.4.1. 1-Benzyl-4-(4-fluorophenyl)piperidin-2-one (7). 90% Yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.32 (m, 2H), 7.30–7.27 (m, 3H), 7.15 (dd, J=5.0, 8.5 Hz 2H), 7.01 (t, J=8.5 Hz, 2H), 4.74 (d, J=14.5 Hz, 1H), 4.55 (d, J=14.5 Hz, 1H), 3.33–3.24 (m, 2H), 3.12–3.06 (m, 1H), 2.80 (ddd, J=2.0, 5.5, 17.0 Hz, 1H), 2.55 (dd, J=11.0, 17.0 Hz, 2H), 2.08–2.03 (m, 1H), 1.94–1.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.04, 162.57, 139.05, 136.98, 128.60 (2C), 128.14 (2C), 127.93, 127.87, 127.44, 115.57, 115.41, 49.98, 46.19, 39.57, 37.94, 30.26; IR ($CHCl_3$, cm^{-1}) 3027, 1618. Mass m/z (EI, 30 eV) 283 (M^+, 2.48%), 91 (100%); HRMS calcd for $C_{18}H_{18}ONF$: 283.1367, found: 283.1362.

4.4.2. 5-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]piperidin-2-one (10). 90% Yield; mp 147–149°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (brs, 1H), 7.66 (d, J=8.0 Hz, 1H), 7.35 (d, J=8.0 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 7.11 (t, J=7.5 Hz, 1H), 7.04 (s, 1H), 3.70–3.59 (m, 2H), 3.17–3.14 (m, 1H), 3.03 (t, J=7.5 Hz, 2H), 2.86 (t, J=10.5 Hz, 1H), 2.50–2.45 (m, 1H), 2.38–2.31 (m, 1H), 1.85–1.81 (m, 1H), 1.58–1.54 (m, 1H), 1.38–1.32 (m, 1H), 1.28–1.22 (m, 2H), 0.83 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.94, 136.25, 127.51, 121.94, 121.92, 119.26, 118.75, 113.20, 111.13, 53.82, 48.39, 35.52, 31.62, 26.87, 26.01, 22.93, 11.29; IR ($CHCl_3$, cm^{-1}) 3050, 1681. Mass m/z (EI, 30 eV) 424 (M^+, 1.18%), 143 (100%); HRMS calcd for $C_{17}H_{22}ON_2$: 270.1732, found: 270.1729. Anal. calcd for $C_{17}H_{22}ON_2$: C, 75.52; H, 8.21; O, 5.92; N, 10.36, found: C, 75.68; H, 8.15; O, 5.90; N, 10.34.

5. Supplementary Material

Experimental procedures and photocopies of spectral data for **1h**, **5a**–**5h**, **7**, **10** (^{1}H NMR in $CDCl_3$) were supported.

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7. CCDC 219521 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
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