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A versatile approach to 6-substituted-5-methoxy-δ-lactam framework and application to the formal synthesis of (±)-homopumiliotoxin 223G

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Abstract—Of the various 6-substituted-5-methoxy-δ-lactams **6** were synthesized from α-sulfonyl acetamide **9** in 4 steps in good yield. The key glutarimides **7** were obtained via facile [3+3] annulation. The method featured regioselective introduction of C-6 substituents in glutarimides **7**. Synthesis of tribenzyl lactam **8** and the formal synthesis of (±)-homopumiliotoxin 223G were also reported.

1. Introduction

Naturally occurring 3-piperidinols and polyhydroxylated piperidines such as prosopinine (**1**), mannonolactam (**2**), deoxymannojirimycin (**3**) and homopumiliotoxins (**4**) alkaloids (Fig. 1) have received much attention owing to a variety of their biological activities.[1] Numerous syntheses of these classes of compounds have been reported.[2,4] However, it is still desirable to develop a general synthetic strategy that provides a common pivotal intermediate from which 2,6-disubstituted piperidine-3-ol **5** can be derived. 6-Substituted-5-hyrdoxy-δ-lactams **6** have been reported as precursors for the synthesis of 2,6-disubstituted piperidine-3-ol **5**.[2c,k,r,u,3] In this paper, we described a new and versatile approach to 6-substituted-5-methoxy-δ-lactams **6** starting from glutarimides **7** (Scheme 1). The synthesis of tribenzyl lactam **8** was discussed (Fig. 2). Tribenzyl lactam **8** is a key intermediate for the preparation of prosopinine **1**, mannonolactam **2** and deoxymannojirimycin **3**. The formal synthesis of (±)-homopumiliotoxin 223G **4d** was also reported.

2. Results and discussion

2.1. Synthesis of 5-methoxy-3-tolsyl glutarimides 7a and 7b

Glutarimide **7a** was successfully prepared in just one step. It was taken from α-sulfonyl acetamide **9a** and ester **10** via stepwise [3+3] cycloaddition[5] in 80% yield. The stereochemistry of **7a** was established by X-ray analysis (Fig. 3).[6]

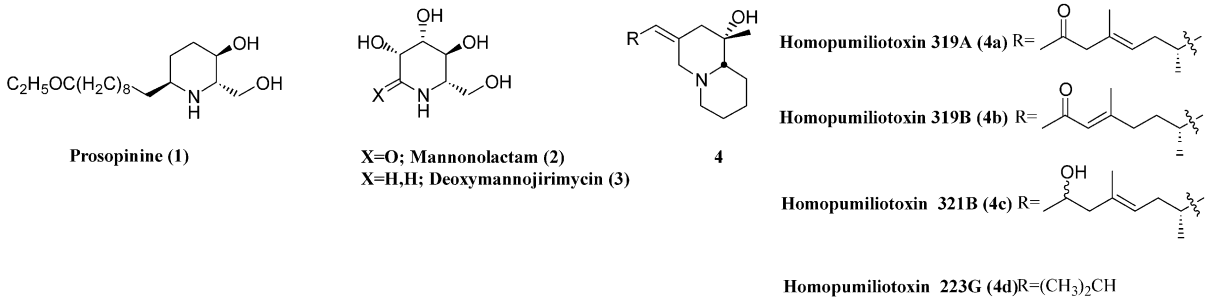

Figure 1.

Keywords: 3-Piperidinol; [3+3] Annulation; Regioselective reduction.
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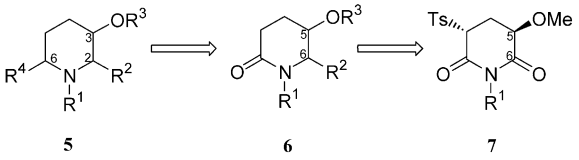


Scheme 1.

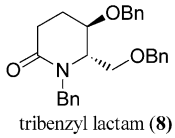


Figure 2.

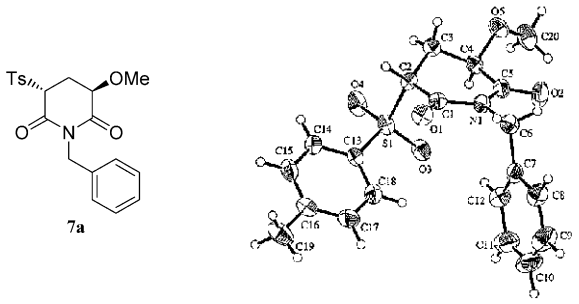
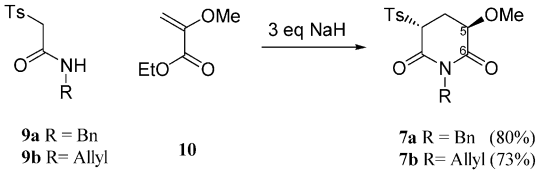


Figure 3. X-ray crystallography of **7a**.

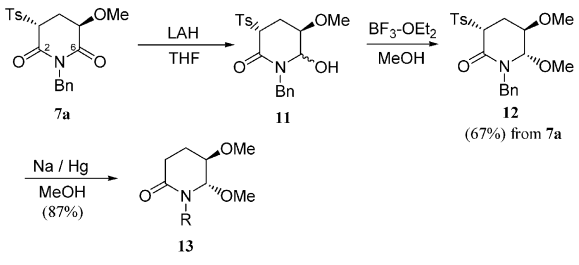


Scheme 2.

Following the same procedure, **7b** was prepared from **9b** in 73% yield (Scheme 2).

2.2. Regioselective introduction of C-6 substituents in 7a

With **7a** in hand, the next step was to introduce substituent regioselectively at C-6 position in **7a**. Such introduction was accomplished by the following procedures. (1) Reduction of **7a** with $LiAlH_4$ afforded hydroxy lactam **11**.[7] Without purification, **11** was converted to 5,6-dimethoxy-δ-lactam **12** in methanol solution in the presence of BF_3–OEt_2. (2) Lactam **12** was desulfonated with sodium amalgam to produce *trans*-5,6-dimethoxy-δ-lactam **13** as *N*-acylimi-nium ion precursor (Scheme 3). The stereochemistry of **13** was established by NMR spectra (Fig. 4). (3) Treatment of **13** with various nucleophiles in the presence of BF_3–OEt_2 furnished the corresponding *N*-benzyl-6-substituted-5-methoxy-δ-lactams **14a**–**14e** as shown in Table 1.[8] Attempts



Scheme 3.

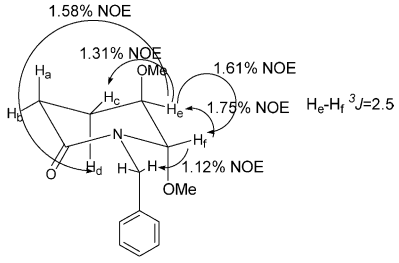


Figure 4. Meaningful NOE and coupling constants for **13**.

to improve the stereoselectivity of the nucleophilic addition with different substituent group at C-5 oxygen (i.e., Ac, TBS) were failed. The stereochemical assignment of *N*-benzyl-6-substituted-5-methoxy-δ-lactams **14a**–**14e** were established by NOE studies and coupling constants. It is noteworthy that the trans isomer **14b** was obtained as the only product when nucleophilic addition with propargyl trimethylsilane was performed. The reason of not observing *cis*-**14b** is not clear.

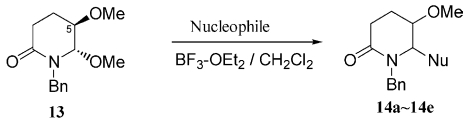
2.3. Preparation of tribenzyl lactam 8, a key intermediate for the synthesis of prosopinine (1), mannonolactam (2) and deoxymannojirimycin (3).[2a,b]

The reaction of propargyl trimethylsilane with dimethoxy δ-lactam **12** in the presence of BF_3–OEt_2 produced allene **15** as the only product. The stereochemistry of **15** was established by NMR spectra (Fig. 5). Compound **15** was transformed into hydroxymethyl product **16** by ozonolysis followed by the reduction of the corresponding aldehyde with $NaBH_4$ in 76% yield in two steps. Subsequently, the acetylation of primary alcohol with acetic anhydride followed by demethylation of the resulting compound **17** with BBr_3 and quenched with $NaHCO_3$ provided alcohol **18**. After removing the sulfonyl group in compound **18** with sodium amalgam, the resulting diol was subsequently treated with sodium hydride and benzyl bromide. δ-Lactam **8** was obtained from **18** in 51% yield (Scheme 4). The spectroscopic data of **8** were identical with those reported in the literature.[2a,b]

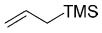
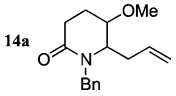
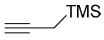
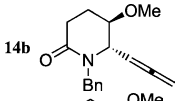
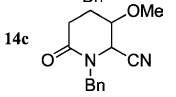
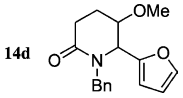
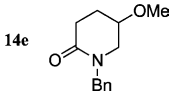
2.4. Formal synthesis of (±)-homopumiliotoxin 223G from 19

For the synthesis of homopumiliotoxin 223G, **7b** was used as starting material. Following the same procedures described in Scheme 3, **19** was obtained in 61% yield from **7b**. In the presence of BF_3–OEt_2, **19** smoothly reacted with allylsilane to yield the diallyl adduct **20** as a mixture of three diastereomers (ca. 33:33:34 as judged by ^1H NMR). This unexpected result might due to part of the C-3 stereocenter epimerized under the reaction condition. Therefore, three diastereoisomers were obtained instead of two. Inasmuch as this mixture would converge to a single compound **24**, the diastereomers were not individually isolated and characterized. The stage was thus set for

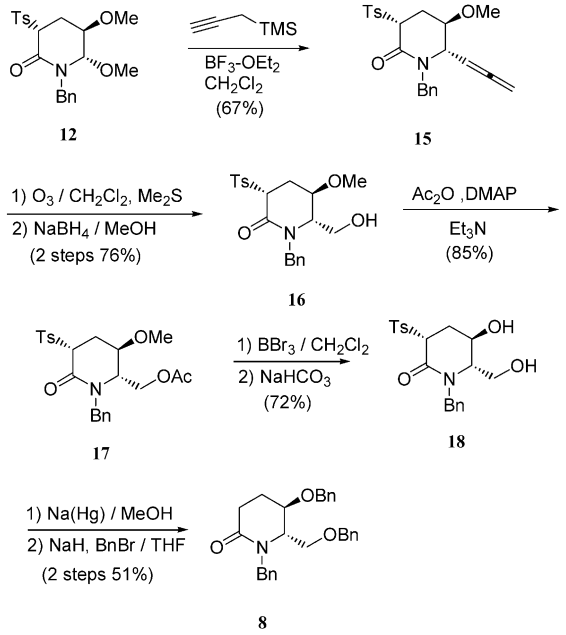
Table 1. Treatment of **13** with various nucleophiles in the presence of BF_3–OEt_2



13 14a~14e

Entry	Nucleophile	Product	(yield)[a]
1		 **14a**	*cis* 62% *trans* 27%
2		 **14b**	71%
3	TMSCN	 **14c**	*cis* 26% *trans* 55%
4		 **14d**	*cis* 41% *trans* 43%
5	Et_3SiH	 **14e**	96%

[a] Isolated yields after column chromatography.



Scheme 4. Preparation of δ-lactam **8**, a key intermediate for the synthesis of prosopinine (**1**), mannonolactam (**2**) and deoxymannojirimycin (**3**).[2a,b]

intramolecular metathesis. Exposure of mixture **20** to the first-generation Grubbs' catalyst at room temperature cleanly provided a mixture of quinolizidinones **21** in 71% yield. Subsequently, the hydrogenation of olefin followed by demethylation of the resulting product with NaI and TMSCl provided mixture **22**. Removal of the sulfonyl function was effected with sodium amalgam to afford

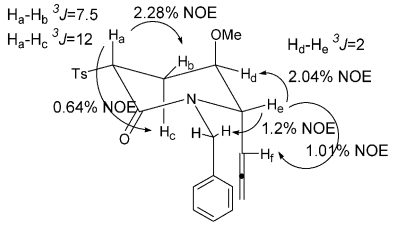
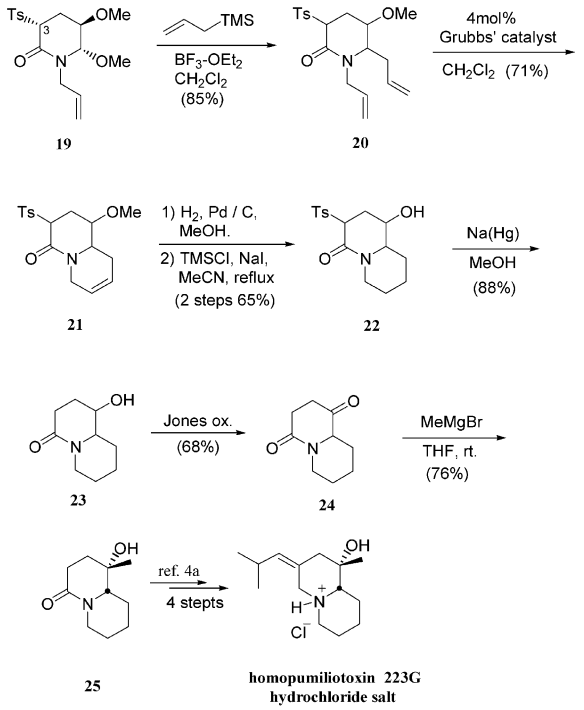


Figure 5. Meaningful NOE and coupling constants for **15**.

hydroxy lactam **23** as a mixture of two isomers (ca. 30:70 as judged by ^1H NMR). After oxidation of **23** with Jones reagent, the resulting ketone **24** underwent stereoselectively 1,2-addition with MeMgBr. The desired **25** was obtained as the only product in the 74% yield (Scheme 5). The spectroscopic data for **25** matched those reported in the literature.[4a] The present work constitutes a formal synthesis of (±)-homopumiliotoxin 223G.

3. Conclusion

In conclusion, the *N*-substituted-5-methoxy-3-tolsyl glutarimides **7** were synthesized in good yield. The glutarimides **7** are versatile intermediate for the preparation of 6-substituted-5-methoxy-δ-lactam **6**. These results were applied to the preparation of δ-lactam **8**, which is a key intermediate for the synthesis of prosopinine **1**, mannonolactam **2** and deoxymannojirimycin **3**. Formal synthesis of (±)-homopumiliotoxin 223G was also reported.



Scheme 5. Formal synthesis of (±)-homopumiliotoxin 223G.

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. Organic layers were dried with anhydrous magnesium sulfate before concentration in vacuo.

4.1.1. Preparation of 2-methoxyacrylic acid ethyl ester (10). A mixture of ethyl pyruvate (5 g, 43.06 mmol) and trimethyl orthoformate (10.9 g, 103.34 mmol) was added dropwise concentrated sulfuric acid (0.1 mL) at room temperature. After being stirred for 6 h, the residue was diluted with water (10 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Without purification, to a solution of above crude product in dry DMF (5 mL), P_2O_5 (3.05 g, 21.52 mmol) was added under strong stirring. The mixture was heated for 6 h at 100 °C, cooled to room temperature, poured on to saturated aqueous $NaHCO_3$ (15 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were washed with water (30 mL), dried, filtered and evaporated. Distillation gave 4.19 g of **10** (75%) as colorless oil.

4.1.2. Procedure of [3+3] cycloaddition to *N*-substituted-5-methoxy-3-tolsyl glutarimides 7. A solution of *N*-substituted-2-(toluene-4-sulfonyl)acetamide (2.0 mmol) **9a**, **9b** 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 room temperature for 15 min, α,β-unsaturated ester **10** (6.0 mmol) was added. The resulting mixture was stirring for 7 h at room temperature, 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 EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel chromatography (hexane/ethyl acetate = 4/1–2/1) produced products.

For **7a**. Yield 80%; white solid; mp 146.6 °C; IR ($CHCl_3$, cm^{-1}) 1685; FAB-MS: $C_{20}H_{21}NO_5S$ *m/z* (%)=91 (100), 137 (36), 154 (35), 388 (M^++1, 12); HRMS (FAB, M^++1) Calcd for $C_{20}H_{22}NO_5S$ 388.1219, found 388.1216; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J*=8 Hz, 2H), 7.32 (d, *J*=8 Hz, 2H), 7.30–7.23 (m, 5H), 4.95 (d, *J*=14.5 Hz, 1H), 4.88 (d, *J*=14.5 Hz, 1H), 4.39 (dd, *J*=4.5, 8.5 Hz, 1H), 4.31 (t, *J*=6.5 Hz, 1H), 3.55 (S, 3H), 2.85 (ddd, *J*=4.5, 6.5, 14.5 Hz, 1H), 2.52 (ddd, *J*=6, 8.5, 14.5 Hz, 1H), 2.64 (S, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.34, 164.22, 145.73, 136.00, 134.52, 129.77 (2C), 129.25 (2C), 128.52 (2C), 128.39 (2C), 127.61, 74.11, 64.30, 59.30, 43.74, 24.44, 21.77. Anal. Calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62; S, 8.28, found C, 61.98; H, 5.44; N, 3.58; S, 8.28. Compound **7a** was recrystallized from ethyl acetate, and as a colorless prism.

For **7b**. Yield 73%; colorless oil; IR ($CHCl_3$, cm^{-1}) 1738, 1687; FAB-MS: $C_{16}H_{19}NO_5S$ *m/z* (%)=91 (100), 151 (38), 155 (9), 182 (14), 337 (M^+, 1); HRMS (FAB, M^++1) Calcd for $C_{16}H_{20}NO_5S$ 337.0978, found 337.0980; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J*=8.0 Hz, 2H), 7.38 (d, *J*=8.0 Hz, 2H), 5.78–5.70 (m, 1H), 5.18 (dd, *J*=1, 17.5 Hz, 1H), 5.14 (dd, *J*=1, 10 Hz, 1H), 4.37–4.30 (m, 4H), 3.85 (s, 3H), 2.83 (ddd, *J*=4, 7, 15 Hz, 1H), 2.55 (ddd, *J*=6, 11.5, 15 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.92, 164.00, 145.74, 134.86, 130.95, 129.79 (2C), 129.25 (2C), 117.75, 74.14, 64.02, 59.20, 42.41, 24.42, 21.74.

4.1.3. Preparation of 1-substituted-5,6-dimethoxy-3-(toluene-4-sulfonyl)piperidin-2-one (12), (19). A solution of glutarimide **7** (2.0 mmol) in THF (20 mL) was added lithium aluminum hydride (2.5 mmol) at −10 °C. The resulting mixture was stirred for 3 h, quenched with saturated aqueous NH_4Cl (1 mL) at the same temperature, filtered and then concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Without purification, to a solution of above crude product in MeOH (20 mL) was treated with BF_3–OEt_2 (0.24 mL, 2.0 mmol) at room temperature. After 15 h, the resulting mixture was diluted with saturated aqueous $NaHCO_3$, concentrated under reduce pressure and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel chromatography (hexane/ethyl acetate=4/1–2/1) produced products.

For **12**. Yield 67%; colorless oil; IR ($CHCl_3$, cm^{-1}) 1654; FAB-MS: $C_{21}H_{25}NO_5S$ *m/z* (%)=91 (100), 69 (61), 372 (8), 404 ($M^+ +1$, 9); HRMS (FAB, $M^+ +1$) Calcd for $C_{21}H_{26}NO_5S$ 404.1532, found 404.1529; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J=8 Hz, 2H), 7.33 (d, J=8 Hz, 2H), 7.27–7.18 (m, 5H), 5.24 (d, J=15.5 Hz, 1H), 4.34 (dd, J=1.5, 3 Hz, 1H), 4.22 (dd, J=7, 11.5 Hz, 1H), 4.06 ((d, J=15.5 Hz, 1H), 3.69 (dt, J=4.5, 2.5 Hz, 1H), 3.35 (S, 3H), 3.20 (S, 3H), 2.76 (ddd, J=2.5, 11.5, 14.5 Hz, 1H), 2.59–2.54 (m, 1H), 2.43 (S, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.51, 144.54, 136.67, 136.17, 129.36 (2C), 129.29 (2C), 128.48 (2C), 127.98 (2C), 127.42, 87.12, 72.52, 62.44, 56.98, 56.72, 48.51, 21.68, 21.42. Anal. Calcd for $C_{21}H_{25}NO_5S$: C, 62.51; H, 6.25; N, 3.47; S, 7.95, found C, 62.52; H, 6.24; N, 3.45; S, 8.00.

For **19**. Yield 61%; colorless oil; IR ($CHCl_3$, cm^{-1}) 1740, 1689; FAB-MS: $C_{17}H_{23}NO_5S$ *m/z* (%)=166 (100%), 91 (12), 168 (7), 354 ($M^+ +1$, 7); HRMS (FAB, $M^+ +1$) Calcd for $C_{17}H_{24}NO_5S$ 354.1375, found 354.1374; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J=8.5 Hz, 2H), 7.34 (d, J=8.5 Hz, 2H), 5.66–5.58 (m, 1H), 5.12 (dd, J=17, 1.5 Hz, 1H), 5.08 (dd, J=10, 1 Hz, 1H), 4.39 (dd, J=15.5, 4 Hz, 1H), 4.37 (d, J=1.5 Hz, 1H), 4.09 (dd, J=11.5, 7 Hz, 1H), 3.68–3.66 (m, 1H), 3.51 (dd, J=15.5, 7 Hz, 1H), 3.33 (s, 3H), 3.32 (s, 3H), 2.62 (ddd, J=14, 12, 2 Hz, 1H), 2.53–2.48 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.82, 144.29, 136.31, 131.96, 129.01 (2C), 128.96 (2C), 171.24, 87.38, 72.31, 61.99, 56.63, 56.53, 48.17, 21.39, 20.96. Anal. Calcd for $C_{17}H_{23}NO_5S$: C, 57.77; H, 6.56; N, 3.96; S, 9.07, found C, 58.02; H, 6.68; N, 3.93; S, 9.39.

4.1.4. 1-Benzyl-5,6-dimethoxypiperidin-2-one (13). Sodium amalgam 6% (Na/Hg, 3.0 g) and sodium phosphate (40 mg) were added to a stirred solution of **12** (806 mg, 2.0 mmol) in MeOH (5 mL), and vigorously stirred for 2 h at room temperature The residue was filtered and washed with MeOH (2×10 mL). The combined organic layers were concentrated to obtain the crude product. The crude product was purified by silica gel chromatography (hexane/ethyl acetate=2/1–1/1) to afford **13** (433 mg, 87%) as colorless oil; IR ($CHCl_3$, cm^{-1}) 1654; FAB-MS: $C_{14}H_{19}NO_3$ *m/z* (%)=91 (100), 69 (43), 218 (16), 250 ($M^+ +1$, 71); HRMS (FAB, $M^+ +1$) Calcd for $C_{14}H_{20}NO_3$ 250.1443, found 250.1442; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.25 (m, 5H), 5.34 (d, J=15 Hz, 1H), 4.34 (dd, J=1.5, 2.5 Hz, 1H), 4.06 (d, J=15 Hz, 1H), 3.52 (dt, J=4.5, 2.5 Hz, 1H), 3.35 (s, 3H), 3.25 (s, 3H), 2.58 (ddd, J=7, 12, 18.5 Hz, 1H), 2.41 (ddd, J=3, 9.5, 17.5 Hz, 1H), 2.14–2.09 (m, 1H), 1.97–1.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.02, 137.14, 128.66, 128.09, 127.68, 127.15 (2C), 88.19, 73.31, 56.75, 56.27, 47.54, 27.20, 20.34.

4.1.5. Preparation of *N*-benzyl-6-substituted-5-methoxy-δ-lactams 14a–14e. To a solution of **13** (0.26 mmol) and the nucleophiles (1.0 mmol) in dry CH_2Cl_2 (5 mL), BF_3–OEt_2 (0.12 mL, 1.0 mmol) was added at 0 °C. The reaction was allowed to warm to room temperature and was monitored by TLC. When the reaction was finished, saturated aqueous $NaHCO_3$ (5 mL) was added and the water layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=2/1–1/1) produced products.

For cis-*6-allyl-1-benzyl-5-methoxypiperidin-2-one* (*cis*-**14a**). Yield 62%; colorless oil; IR ($CHCl_3$, cm^{-1}) 3071, 1638; FAB-MS: $C_{16}H_{21}NO_2$ *m/z* (%)=91 (100), 117 (42), 218 (18), 260 ($M^+ +1$, 69); HRMS (FAB, $M^+ +1$) Calcd for $C_{16}H_{22}NO_2$ 260.1650, found 260.1653; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.21 (m, 5H), 5.87–5.79 (m, 1H), 5.43 (d, J=15 Hz, 1H), 5.13 (dd, J=17.5, 3 Hz, 1H), 5.09 (d, J=10 Hz, 1H), 3.94 (d, J=15 Hz, 1H), 3.49–3.42 (m, 2H), 3.25 (s, 3H), 2.65 (dt, J=18, 5.5 Hz, 1H), 2.59–2.49 (m, 2H), 2.34–2.28 (m, 1H), 1.98–1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.67, 137.22, 135.38, 128.59 (2C), 127.83 (2C), 127.32, 117.77, 75.72, 57.11, 56.36, 48.55, 33.76, 28.59, 22.12.

For trans-*6-allyl-1-benzyl-5-methoxypiperidin-2-one* (*trans*-**14a**). Yield 27%; colorless oil; IR ($CHCl_3$, cm^{-1}) 3076, 1638; FAB-MS: $C_{16}H_{21}NO_2$ *m/z* (%)=91 (100), 133 (52), 260 ($M^+ +1$, 34); HRMS (FAB, $M^+ +1$) Calcd for $C_{16}H_{22}NO_2$ 260.1650, found 260.1651; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.24 (m, 5H), 5.70–5.63 (m, 1H), 5.44 (d, J=15.5 Hz, 1H), 5.12–5.08 (m, 2H), 3.94 (d, J=15.5 Hz, 1H), 3.44–3.43 (m, 2H), 3.12 (s, 3H), 2.64 (ddd, J=8, 11, 18 Hz, 1H), 2.54–2.49 (m, 1H), 2.40 (ddd, J=3, 6.5, 18 Hz, 1H), 2.19–2.13 (m, 1H), 2.05–1.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.79, 137.14, 133.59, 128.47 (2C), 127.78 (2C), 127.16, 118.43, 74.28, 57.71, 55.58, 47.53, 36.67, 27.01, 21.07.

For trans-*1-benzyl-5-methoxy-6-propa-1,2-dienyl-piperidin-2-one* (*trans*-**14b**). Yield 71%; colorless oil; IR ($CHCl_3$, cm^{-1}) 1960, 1648; FAB-MS: $C_{16}H_{19}NO_2$ *m/z* (%)=91 (100), 133 (43), 258 ($M^+ +1$, 26); HRMS (FAB, $M^+ +1$) Calcd for $C_{16}H_{20}NO_2$ 258.1494, found 258.1497; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.24 (m, 5H), 5.32 (d, J=15 Hz, 1H), 5.03 (dd, J=6, 13 Hz, 1H), 4.92–4.90 (m, 2H), 4.00–3.98 (m, 1H), 3.79 (d, J=15 Hz, 1H), 3.43 (dt, J=4.5, 2 Hz, 1H), 3.15 (s, 3H), 2.61 (ddd, J=7.5, 12, 18 Hz, 1H), 2.41 (ddd, J=2, 6.5, 18 Hz, 1H), 2.17–2.20 (m, 1H), 2.00–1.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.56, 169.58, 137.07, 128.54 (2C), 127.95 (2C), 127.15, 90.19, 78.18, 76.31, 57.00, 55.91, 47.42, 27.01, 21.33.

For cis-*1-benzyl-3-methoxy-6-oxopiperidine-2-carbonitrile* (*cis*-**14c**). Yield 26%; colorless oil; IR ($CHCl_3$, cm^{-1}) 2391, 1654; FAB-MS: $C_{14}H_{16}N_2O_2$ *m/z* (%)=154 (100), 91 (70), 137 (72), 245 ($M^+ +1$, 65); HRMS (FAB, $M^+ +1$) Calcd for $C_{14}H_{17}N_2O_2$ 245.1290, found 245.1288; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 5.56 (d, J=15 Hz, 1H), 4.31 (dd, J=1.5, 5 Hz, 1H), 3.91 (d, J=15 Hz, 1H), 3.57 (dt, J=11, 4.5 Hz, 1H), 3.38 (s, 3H), 2.77 (ddd, J=3.5, 6.5, 18.5 Hz, 1H), 2.52 (ddd, J=7, 11, 18.5 Hz, 1H), 2.21–2.17 (m, 1H), 2.16–2.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.17, 135.00, 129.06 (2C), 128.46 (2C), 128.33, 115.42, 73.63, 57.00, 51.18, 48.53, 29.06, 23.82.

For trans-*1-benzyl-3-methoxy-6-oxopiperidine-2-carbonitrile* (*trans*-**14c**). Yield 55%; colorless oil; IR ($CHCl_3$, cm^{-1}) 2303, 1658; FAB-MS: $C_{14}H_{16}N_2O_2$ *m/z* (%)=91 (100), 136 (85), 145 (87), 245 ($M^+ +1$, 42); HRMS (FAB,

$M^+ + 1$) Calcd for $C_{14}H_{17}N_2O_2$ 245.1290, found 245.1291; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 5.67 (d, J=15 Hz, 1H), 4.24 (t, J=2.5 Hz, 1H), 3.86 (d, J=15 Hz, 1H), 3.80 (dt, J=4.5, 2.5 Hz, 1H), 3.17 (s, 3H), 2.70 (ddd, J=7, 12, 18.5 Hz, 1H), 2.54 (ddd, J=2.5, 6.5, 18.5 Hz, 1H), 2.30–2.22 (m, 1H), 2.18–2.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.48, 134.98, 128.91 (2C), 128.25 (2C), 128.11, 116.36, 74.04, 56.61, 49.54, 47.96, 26.88, 23.23.

For cis-*1-benzyl-6-furan-2-yl-5-methoxypiperidin-2-one* (*cis*-**14d**). Yield 41%; colorless oil; IR ($CHCl_3$, cm^{-1}) 3123, 3045, 1638; FAB-MS: $C_{17}H_{19}NO_3$ *m/z* (%)=91 (100), 154 (95), 286 ($M^+ + 1$, 60); HRMS (FAB, $M^+ + 1$) Calcd for $C_{17}H_{20}NO_3$ 286.1443, found 286.1443; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J=1 Hz, 1H), 7.34–7.18 (m, 5H), 6.39 (dd, J=2, 3 Hz, 1H), 6.26 (d, J=3.5 Hz, 1H), 5.46 (d, J=15.5 Hz, 1H), 4.61 (d, J=4.5 Hz, 1H), 3.61 (dt, J=11, 5 Hz, 1H), 3.51 (d, J=15.5 Hz, 1H), 3.31 (s, 3H), 2.77 (ddd, J=3, 7, 18 Hz, 1H), 2.58 (ddd, J=8, 11, 18 Hz, 1H), 2.05–1.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.41, 150.08, 142.86, 136.74, 128.60 (2C), 128.08 (2C), 127.46, 110.31, 109.76, 76.02, 56.70, 55.29, 48.06, 29.62, 22.81.

For trans-*1-benzyl-6-furan-2-yl-5-methoxypiperidin-2-one* (*trans*-**14d**). Yield 43%; colorless oil; IR ($CHCl_3$, cm^{-1}) 3108, 3040, 1641; FAB-MS: $C_{17}H_{19}NO_3$ *m/z* (%)=91 (100), 136 (38), 154 (36), 286 ($M^+ + 1$, 32); HRMS (FAB, $M^+ + 1$) Calcd for $C_{17}H_{20}NO_3$ 286.1443, found 286.1442; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J=2 Hz, 1H), 7.32–7.21 (m, 5H), 6.36 (dd, J=1.5, 3 Hz, 1H), 6.22 (d, J=3 Hz, 1H), 5.60 (d, J=15.5 Hz, 1H), 4.58 (s, 1H), 3.64 (dt, J=4.5, 2.5 Hz, 1H), 3.58 (d, J=15.5 Hz, 1H), 3.20 (s, 3H), 2.71 (ddd, J=7.5, 12.5, 18.5 Hz, 1H), 2.50 (ddd, J=2.5, 6.5, 18.5 Hz, 1H), 2.06–2.00 (m, 1H), 1.96–1.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.89, 151.94, 142.58, 136.80, 128.49 (2C), 127.85 (2C), 127.24, 110.47, 108.06, 75.81, 56.86, 56.16, 47.55, 27.10, 21.84.

For 1-benzyl-5-methoxypiperidin-2-one (**14e**). Yield 96%; colorless oil; IR ($CHCl_3$, cm^{-1}) 1638; FAB-MS: $C_{13}H_{17}NO_2$ *m/z* (%)=91 (59), 220 ($M^+ + 1$, 100); HRMS (FAB, $M^+ + 1$) Calcd for $C_{13}H_{18}NO_2$ 220.1338, found 220.1338; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 4.61 (d, J=15 Hz, 1H), 4.56 (d, J=15 Hz, 1H), 3.59–3.56 (m, 1H), 3.30 (dd, J=4, 13 Hz, 1H), 3.25 (s, 3H), 3.23 (ddd, J=1, 4.5, 13 Hz, 1H), 2.62 (ddd, J=6.5, 16, 17.5 Hz, 1H), 2.40 (dt, J=6, 17.5 Hz, 1H), 2.02–1.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.21, 136.70, 128.40 (2C), 128.77 (2C), 127.17, 72.21, 55.80, 50.19, 49.71, 27.80, 25.08.

4.1.6. 1-Benzyl-5-methoxy-6-propa-1,2-dienyl-3-(toluene-4-sulfonyl)piperidin-2-one (15). To a solution of **12** (564 mg, 1.4 mmol) and the propargyl trimethylsilane (627 mg, 5.6 mmol) in dry CH_2Cl_2 (5 mL), BF_3–OEt_2 (0.7 mL, 5.6 mmol) was added at 0 °C. The reaction was allowed to warm to room temperature and monitored by TLC. When the reaction was finished, saturated aqueous $NaHCO_3$ (5 mL) was added and the water layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate=2/1–1/1) to afford **15** (386 mg, 67%) as colorless oil; IR ($CHCl_3$, cm^{-1}) 1963, 1654; EI-MS: $C_{23}H_{25}NO_4S$ *m/z* (%)=91 (100), 411 (M^+, 0.59); HRMS (FAB, $M^+ + 1$) Calcd for $C_{23}H_{26}NO_4S$ 412.1583, found 412.1584; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J=8.5 Hz, 2H), 7.35 (d, J=8.5 Hz, 2H), 7.32–7.18 (m, 5H), 5.39 (d, J=15 Hz, 1H), 5.10 (dd, J=6.5, 13 Hz, 1H), 5.00–4.91 (m, 2H), 4.28 (dd, J=7.5, 12 Hz, 1H), 3.99 (m, 1H), 3.77 (d, J=15 Hz, 1H), 3.58 (dt, J=4.5, 2.5 Hz, 1H), 3.05 (s, 3H), 2.69 (ddd, J=2, 12, 14 Hz, 1H), 2.59–2.54 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.76, 161.98, 144.52, 136.84, 136.10, 129.37 (2C), 129.17 (2C), 128.44 (2C), 128.17 (2C), 127.43, 89.01, 78.51, 75.54, 62.36, 56.66, 56.19, 47.94, 22.67, 21.68.

4.1.7. 1-Benzyl-6-hydroxymethyl-5-methoxy-3-(toluene-4-sulfonyl)piperidin-2-one (16). A stream of ozone was bubbled through a solution of **15** (197 mg, 0.48 mmol) in CH_2Cl_2 (5 mL) at −78 °C until a pale blue color developed (5 min). Nitrogen was bubbled through the solution to remove excess ozone and dimethyl sulfide (0.5 mL) was added. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 5 h. The solution was concentrated under reduce pressure followed diluted with MeOH (10 mL), $NaBH_4$ (22 mg, 0.58 mmol) was added and monitored by TLC. When the reaction was finished, water (10 mL) was added and then concentrated under reduced pressure. The residue was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate=2/1–1/1) to afford **16** (147 mg, 76%) as a colorless oil; IR ($CHCl_3$, cm^{-1}) 3432, 1660; FAB-MS: $C_{21}H_{25}NO_5S$ *m/z* (%)=117 (100), 91 (43), 219 (12), 404 ($M^+ + 1$, 2); HRMS (FAB, $M^+ + 1$) Calcd for $C_{21}H_{26}NO_5S$ 404.1532, found 404.1532; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J=8.5 Hz, 2H), 7.35 (d, J=8.5 Hz, 2H), 7.28–7.21 (m, 5H), 5.11 (d, J=15.5 Hz, 1H), 4.27 (dd, J=8, 10.5 Hz, 1H), 4.21 (d, J=15.5 Hz, 1H), 3.80–3.78 (m, 3H), 3.58–3.55 (m, 1H), 3.05 (s, 3H), 2.79 (ddd, J=3, 10.5, 15 Hz, 1H), 2.55–2.49 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.65, 144.76, 136.39, 136.35, 129.46 (2C), 129.10 (2C), 128.57 (2C), 127.94 (2C), 127.54, 73.09, 62.77, 62.00, 59.44, 56.09, 49.16, 23.57, 21.71.

4.1.8. Acetic acid 1-benzyl-3-methoxy-6-oxo-5-(toluene-4-sulfonyl)piperidin-2-ylmethyl ester (17). To a solution of **16** (318 mg, 0.79 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (96 mg, 0.79 mmol) in triethylamine (0.5 mL) was added acetic anhydride (2 mL) at room temperature. The reaction mixture was stirred for 3 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ (5 mL) at 0 °C and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate=2/1–1/1) to afford **17** (298 mg, 85%) as colorless oil; IR ($CHCl_3$, cm^{-1}) 1747, 1654; FAB-MS: $C_{23}H_{27}NO_6S$ *m/z* (%)=91 (100), 133 (24), 290 (3), 446 ($M^+ + 1$, 6); HRMS (FAB, $M^+ + 1$) Calcd for $C_{23}H_{28}NO_6S$ 446.1637, found 446.1637; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J=8.5 Hz, 2H), 7.36 (d, J=8.5 Hz, 2H), 7.30–7.21 (m, 5H), 5.27 (d, J=15 Hz, 1H),

4.28–4.23 (m, 3H), 4.06 (d, $J=15$ Hz, 1H), 3.70 (dd, $J=3$, 6.5 Hz, 1H), 3.66–3.63 (m, 1H), 3.03 (s, 3H), 2.68 (ddd, $J=$ 2.5, 10.5, 15 Hz, 1H), 2.62–2.57 (m, 1H), 2.45 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.43, 162.39, 144.75, 136.45, 136.01, 129.46 (2C), 129.13 (2C), 128.53 (2C), 128.14 (2C), 127.59, 73.02, 62.68, 62.42, 56.42, 56.15, 48.74, 23.19, 21.72, 20.76.

4.1.9. 1-Benzyl-5-hydroxy-6-hydroxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (18). To a solution of **17** (298 mg, 0.67 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added dropwise a 1.0 M solution of boron tribromide in dichloromethane (4.0 mL, 4.0 mmol). After stirring the solution for 10 h, the reaction contents was quenched with a saturated aqueous $NaHCO_3$ (10 mL) at 0 °C. The resulting mixture was stirred for 20 min and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 1/1–1/2) to afford **18** (188 mg, 72%) as colorless oil; IR ($CHCl_3$, cm^{-1}) 3401, 1640; FAB-MS: $C_{20}H_{23}NO_5S$ *m/z* (%) = 91 (100), 136 (74), 390 ($M^+ + 1$, 30); HRMS (FAB, $M^+ + 1$) Calcd for $C_{20}H_{24}NO_5S$ 390.1375, found 390.1375; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, $J=$ 8.5 Hz, 2H), 7.36 (d, $J=8.5$ Hz, 2H), 7.33–7.22 (m, 5H), 5.10 (d, $J=15$ Hz, 1H), 4.41–4.39 (m, 1H), 4.33 (t, $J=9$ Hz, 1H), 4.25 (d, $J=15$ Hz, 1H), 3.81–3.79 (m, 2H), 3.40 (dd, $J=4$, 9 Hz, 1H), 2.84 (ddd, $J=2.5$, 9, 14.5 Hz, 1H), 2.44 (s, 3H), 2.42–2.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.60, 144.91, 136.33, 136.22, 129.53 (2C), 129.23 (2C), 128.82 (2C), 127.85 (2C), 127.67, 64.31, 63.69, 63.02, 61.90, 49.16, 26.12, 21.73.

4.1.10. 1-Benzyl-5-benzyloxy-6-benzyloxymethylpiperidin-2-one (8). Sodium amalgam 6% (Na/Hg, 3.0 g) and sodium phosphate (40 mg) were added to a stirred solution of lactam **18** (132 mg, 0.34 mmol) in methanol (5 mL), and vigorously stirred for 2 h at room temperature The residue was filtered and washed with methanol (2×10 mL). The combined organic layers were concentrated to obtain the crude product. Without purification, the solution of above crude product in dry THF (5 mL) was added to a rapidly stirred suspension of NaH (48 mg, 1.2 mmol, 60%) in dry THF (5 mL) at room temperature. The mixture was stirred for 5 min and then benzyl bromide (149 mg, 0.87 mmol) was added. After stirring for 30 min, the reaction was quenched with water (10 mL). The resulting mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 2/1–1/1) to afford **8** (72 mg, 51%) as colorless oil; IR ($CHCl_3$, cm^{-1}) 1640; FAB-MS: $C_{27}H_{29}NO_3$ *m/z* (%) = 91 (100), 154 (86), 416 ($M^+ + 1$, 8); HRMS (FAB, $M^+ + 1$) Calcd for $C_{27}H_{30}NO_3$ 416.2226, found 416.2224; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.19 (m, 15), 5.36 (d, $J=15$ Hz, 1H), 4.45 (d, $J=$ 12 Hz, 1H), 4.41 (d, $J=12$ Hz, 1H), 4.38 (d, $J=12$ Hz, 1H), 4.30 (d, $J=12$ Hz, 1H), 3.97 (d, $J=15$ Hz, 1H), 3.86 (dd, $J=2.5$, 6.5 Hz, 1H), 3.68–3.66 (m, 1H), 3.55 (dd, $J=4$, 10 Hz, 1H), 3.45 (dd, $J=7$, 9.5 Hz, 1H), 2.70 (ddd, $J=8$, 10, 18 Hz, 1H), 2.43 (ddd, $J=4$, 6.5, 18 Hz, 1H), 2.04–2.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.31, 138.03, 137.52, 137.18, 128.50 (2C), 128.45 (2C), 128.29 (2C), 127.91, 127.78 (2C), 127.61 (2C), 127.54, 127.31 (2C), 127.12, 73.30, 71.98, 70.03, 69.36, 58.59, 47.96, 27.41, 22.38.

4.1.11. 1,6-Diallyl-5-methoxy-3-(toluene-4-sulfonyl) piperidin-2-one (20). To a solution of **19** (1 g, 2.9 mmol) and the allylsilane (1.32 g, 11.6 mmol) in dry CH_2Cl_2 (20 mL), $BF_3\cdot OEt_2$ (1.46 mL, 11.6 mmol) was added at 0 °C. The reaction was allowed to warm to room temperature and monitored by TLC. When the reaction was finished, saturated aqueous $NaHCO_3$ (5 mL) was added and the water layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography to afford **20** (897 mg, 85%) as mixture (ca. 33:33:34) of three diastereomers and as colorless oil. For spectroscopic characterization a mixture of the three isomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.77 (comp, 2H), 7.34–7.32 (comp, 2H), 5.88–5.58 (comp, 2H), 5.24–5.07 (comp, 4H), 4.60–4.12 (comp, 1H), 4.16 (t, $J=10$ Hz, 0.3H), 4.11 (t, $J=10$ Hz, 0.3H), 4.06 (tt, $J=5$, 8 Hz, 0.3H), 3.97 (dt, $J=9.5$, 4 Hz, 0.3H), 3.65 (q, $J=3$ Hz, 0.3H), 3.63 (q, $J=4.5$ Hz, 0.3H), 3.57–3.34 (comp, 2.3H), 3.41 (s, 1H), 3.38 (s, 3H), 3.30 (s, 1H), 2.74 (dt, $J=15$, 4.5 Hz, 0.3H), 2.64–2.23 (comp, 6.3H).

4.1.12. 1-Methoxy-3-(toluene-4-sulfonyl)-1,2,3,6,9,9a-hexa hydroquinolizin-4-one (21). 1st Grubbs' catalyst (82 mg, 0.1 mmol) was added to a solution of mixture **20** (881 mg, 2.4 mmol) in CH_2Cl_2 (20 mL) and stirred for 12 h at room temperature The resulting mixture was concentrated and purified by silica gel chromatography (hexane/ethyl acetate = 2/1–1/1) to afford **21** (570 mg, 71%) as a mixture of three diastereomers. For spectroscopic characterization the major isomer was isolated by chromatography; colorless oil; IR ($CHCl_3$, cm^{-1}) 3045, 1639; FAB-MS: $C_{17}H_{21}NO_4S$ *m/z* (%) = 154 (100), 136 (87), 219 (30), 336 ($M^+ + 1$, 28); HRMS (FAB, $M^+ + 1$) Calcd for $C_{17}H_{22}NO_4S$ 336.1270, found 336.1271; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, $J=$ 8 Hz, 2H), 7.34 (d, $J=8$ Hz, 2H), 5.85–5.81 (m, 1H), 5.66–5.63 (m, 1H), 4.55 (dd, $J=3.5$, 18.5 Hz, 1H), 4.10 (t, $J=$ 7 Hz, 1H), 4.04 (ddd, $J=3$, 5, 8 Hz, 1H), 3.57 (dt, $J=11.5$, 4 Hz, 1H), 3.54 (d, br, $J=19$ Hz, 1H), 3.46 (s, 3H), 2.64 (ddd, $J=3$, 7, 14 Hz, 1H), 2.52 (ddd, $J=6$, 9, 15 Hz, 1H), 2.44 (s, 3H), 2.36–2.32 (m, 1H), 2.12 (d, br, $J=17$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.80, 144.63, 136.70, 129.39, 129.30, 129.20, 129.02, 124.31, 123.33, 72.82, 63.45, 57.19, 55.48, 43.14, 26.12, 22.83, 21.64.

4.1.13. 1-Hydroxy-3-(toluene-4-sulfonyl)octahydroquinolizin-4-one (22). Palladium on activated carbon 10% (10 mg) was added to the solution of **21** (577 mg, 1.7 mmol) in MeOH (20 mL) The hydrogen was bubbled into the mixture for 10 min, and the reaction mixture was continued to stir for 3 h at room temperature. The catalyst was filtered through a short plug of celite and washing with MeOH (2×5 mL). The combined organic layers were evaporated. Without purification, sodium iodide (1.27 g, 8.5 mmol) was added to a solution of above crude product in MeCN (10 mL), followed by 8.5 mmol (1.1 mL) of distilled Me_3SiCl added dropwise. The mixture was refluxed for 15 h. After cooling to room temperature, few drops of aqueous 10% NH_4Cl were added, follow by CH_2Cl_2

(2×10 mL) extraction. The organic layer was sequentially washed with aqueous 20% $Na_2S_2O_3$ and brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate=2/1–1/1) to afford **22** (65%) as a mixture of three diastereomers. For spectroscopic characterization the major isomer was isolated by chromatography; white solid; mp 184.6 °C; IR ($CHCl_3$, cm^{-1}) 3447, 1640; FAB-MS: $C_{16}H_{21}NO_4S$ *m/z* (%)=136 (100), 77 (93), 154 (88), 324 (M^++1, 23); HRMS (FAB, M^++1) Calcd for $C_{16}H_{22}NO_4S$ 324.1269, found 324.1270; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J=8 Hz, 2H), 7.33 (d, J=8 Hz, 2H), 4.59 (d, br, J=13.5 Hz, 1H), 4.32–4.29 (m, 2H), 3.35 (d, J=11.5 Hz, 1H), 2.59 (dt, J=13, 6.5 Hz, 1H), 2.49–2.40 (m, 5H), 1.91–1.81 (m, 1H), 1.68–1.63 (m, 2H), 1.52 (ddt, J=13, 3 Hz, 1H), 1.46–1.39 (m, 1H), 1.30 (dtt, J=13, 4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.22, 144.92, 137.06, 129.31 (2C),128.96 (2C), 64.17, 62.42, 60.50, 43.05, 27.26 (2C), 25.21, 23.73, 21.63. Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33; S, 9.92, found C, 59.25; H, 6.58; N, 4.32; S, 9.97.

4.1.14. 1-Hydroxyoctahydroquinolizin-4-one (23). Sodium amalgam 6% (Na/Hg, 3 g) and sodium phosphate (40 mg) were added to a stirred solution of **22** (286 mg, 0.9 mmol) in MeOH (5 mL), and vigorously srirred for 2 h at room temperature The residue was filtered and washed with MeOH (2×10 mL). The combined organic layers were concentrated to obtain the crude product. The crude product was purified by silica gel chromatography (hexane/ethyl acetate=1/1–1/2) to afford **23** (132 mg, 88%) as a mixture of two diastereomers (ca. 70:30) and as colorless oil. For spectroscopic characterization an inseparable mixture of the two isomers; ^1H NMR (500 MHz, $CDCl_3$) δ 4.62–4.59 (comp, 1H), 3.95–3.94 (m, 0.7H), 3.65–3.62 (m, 0.3H), 3.22 (ddd, J=3, 4, 12 Hz, 0.7H), 3.10 (ddd, J=2.5, 4.5, 12 Hz, 0.3H), 2.58–2.46 (comp, 1H), 2.37–2.31 (comp, 1H) 2.27–2.20 (comp, 1H), 1.91–1.09 (comp, 8H).

4.1.15. Hexahydroquinolizine-1,4-dione (24). To an ice-cold solution of **23** (132 mg, 0.8 mmol) in acetone (10 mL) was added dropwise Jones reagent (0.5 mL). After being stirred for 10 min, isopropanol (1 mL) was added and the mixture was concentrated to a residue that was partitioned in CH_2Cl_2 (20 mL) and water (5 mL). The organic layer was separated, washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate=1/1) to afford **24** (89 mg, 68%) as colorless oil; IR ($CHCl_3$, cm^{-1}) 1731, 1638; EI-MS: $C_9H_{13}NO_2$ *m/z* (%)=83 (100), 167 (M^+, 21); HRMS (EI, M^+) Calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0943; ^1H NMR (500 MHz, $CDCl_3$) δ 4.67 (d, br, J=13 Hz, 1H), 3.69 (dd, J=12, 3 Hz, 1H), 2.77–2.64 (m, 4H), 2.48 (dt, J=12.5, 3 Hz, 1H), 2.15 (d, br, J=13 Hz, 1H), 1.79 (d, br, J=13 Hz, 1H), 1.74–1.72 (m, 1H), 1.58–1.34 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.42, 168.06, 64.82, 42.82, 35.37, 30.26, 29.60, 24.55, 24.17.

4.1.16. 1-Hydroxy-1-methyloctahydroquinolizin-4-one (25). To a solution of **24** (89 mg, 0.5 mmol) in THF (5 mL) was added MeMgBr (3 M in THF, 0.27 mL, 0.8 mmol) at room temperature, and the mixture was stirred for 10 min. Water (10 mL) was added to the mixture and the aqueous solution was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=1/1) produced **25** (74 mg, 76%). The ^1H, ^{13}C NMR data was in accordance with the reported in the literature.[4a]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.09.001

References and notes

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