JOC*Article*

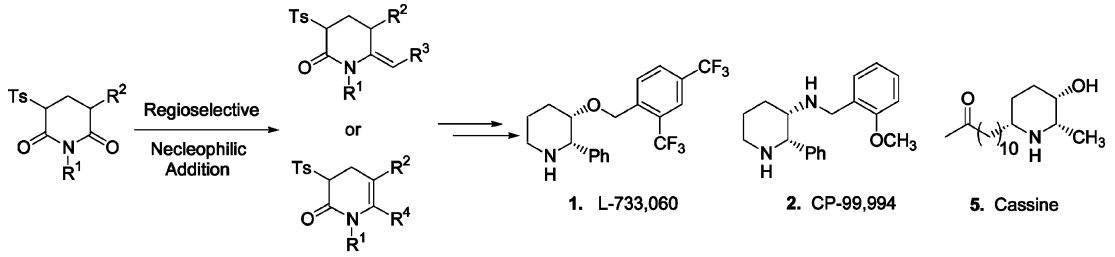
A Novel and Highly Regioselective Approach to 5-Methoxy-6-substituted-3-sulfonyl-δ-enlactams from 5-Methoxy-3-sulfonyl Glutarimide: Synthesis of *cis*-2-Substituted-3-piperidinols

Min-Ruei Tsai, Bo-Fong Chen, Chih-Ching Cheng, and Nein-Chen Chang*

Department of Chemistry, National Sun Yat-Sen University, Kaohsiung 804, Taiwan, ROC

ncchang@mail.nsysu.edu.tw

Received October 29, 2004



A convenient method for the preparation of 5-methoxy-6-substituted-3-sulfonyl-δ-enlactams via regioselective nucleophilic addition to 5-methoxy-3-sulfonyl glutarimide is described. Formal syntheses of L-733,060, CP-99,994, and cassine are also reported.

The piperidine ring continues to be a common moiety in pharmaceutical research. A search of the chemical and patent literature reveals thousands of references to this simple ring system in clinical and preclinical research.[1]

cis-2-Substituted-3-piperidinols such as (+)-L-733,060 (**1**)[2] and (+)-CP-99,994 (**2**)[3] are known to exhibit a variety of biological activities including neurogenic inflammation,[4] pain transmission, and regulation of the immune response.[5] They have been implicated in a variety of disorders including migraine,[6] rheumatoid arthritis,[7] and pain.[8] It has been established that the cis-relationship between the two substituents on the piperidine ring and 2*S*,3*S* configurations are essential for high-affinity binding to the human NK1 receptor.[9] Febrifugine (**3**) and Isofebrifugine (**4**), which show powerful antimalarial potential,[10] are alkaloids first found in the Chinese plant *Dichroafebrifuga* and later in the common hydrangea (Figure 1).

Compounds **1**−**6** are piperidines, which possess different substituents at C-2 and C-3 positions. Introduction of different substituents at C-2 and controlling the stereochemistry of C-2 and C-3 in piperidine has been an important topic.[11] Nucleophilic addition to *N*-acyliminium ions with various carbon-based nucleophiles has been extensively studied[12−18] and reviewed.[19] The alter-

* Address correspondence to this author. Phone: 886-7-525-2000-3914. Fax: 886-7-525-3913.

(1) A substructure search of the piperidine ring using the electronic version of the Drug Data Report (MDL Drug Data Report) revealed a great number of discrete piperidine entities that have been mentioned in clinical or preclinical studies.

(2) (a) Baker, R.; Harrison, T.; Hollingworth, G. J.; Swain, C. J.; Williams, B. J. EP 528,495 A1, 1993. (b) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545.

(3) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911.

(4) Lotz, M.; Vaughan, J. H.; Carson, D. A. *Science* **1988**, *241*, 1218.

(5) Perianan, A.; Snyderman, R.; Malfroy, B. *Biochem. Biophys. Res. Commun.* **1989**. *161*, 520.

(6) Moskowitz, M. A. *Trends Pharmacol. Sci.* **1992**, *13*, 307.

(7) Lotz, M.; Vaughan, J. H.; Carson, D. A. *Science* **1987**, *235*, 893.

(8) Otsuka, M.; Yanagisawa, M. *J. Physiol.* (*London*) **1988**, *395*, 255

(9) (a) Giardina, G. A. M.; Raveglia, L. F.; Grugni, M. *Drugs Future* **1997**, *22*, 1235. (b) Chandrasekhar, S.; Mohanty, P. K. *Tetrahedron Lett.* **1999**, *40*, 5071.

(10) (a) Koepfli, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem Soc.* **1947**, *69*, 1837. (b) Koepfli, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1949**, *71*, 1048.

(11) (a) Calvez, O.; Langlois, N. *Tetrahedron Lett*. **1999**, *40*, 7099. (b) Stadler, H.; Bos, M. *Heterocycles* **1999**, *51*, 1067. (c) Tomooka, K.; Nakazaki, A.; Nakai, T. *J. Am. Chem. Soc*. **2000**, *122*, 408. (d) Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett*. **2001**, *42*, 6223. (e) Bhaskar, G.; Rao, B. V. *Tetrahedron Lett*. **2003**, *44*, 915. (f) Tsuritani, N.; Yamada, K.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett*. **2002**, 276. (g) Yamazaki, N.; Atobe, M.; Kibayashi, C. *Tetrahedron Lett*. **2002**, *43*, 7979. (h) Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett*. **1993**, *34*, 5831.

(12) (a) Kraus, G. A.; Neuenschwander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134. (b) Thaning, M.; Wistrand, L.-G. *Helv. Chim. Acta* **1986**, *69*, 1711. (c) Thaning, M.; Wistrand, L.-G. *J. Org. Chem.* **1990**, *55*, 1406. (d) Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1704. (e) Arai, Y.; Fujii, A.; Ohno, T.; Koizumi, T. *Chem. Pharm. Bull.* **1992**, *40*, 1670.

10.1021/jo048073e CCC: $30.25
Published on Web 02/08/2005

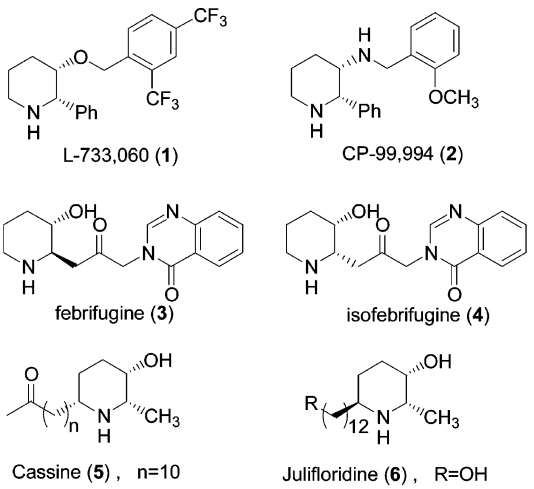
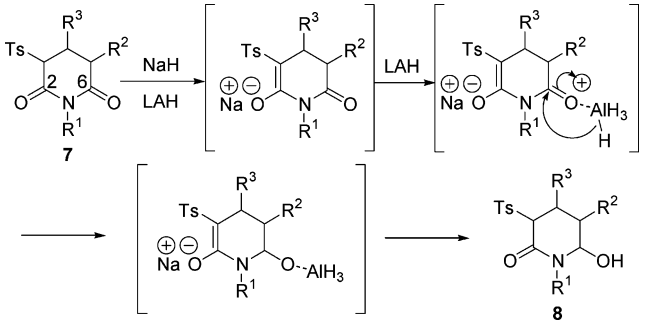


FIGURE 1. Examples of pharmacologically active *cis*-2-substituted-3-piperidinols and 2,6-disubstituted-3-piperidinols

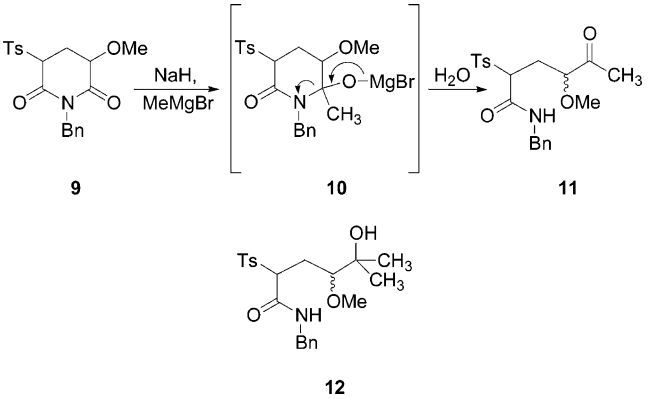
native approaches to 2-substituted piperidines are based on addition of organolithium or Grignard reagents to the symmetric imide followed by reduction of the resulting tertiary hydroxylactams with sodium cyanoborohydride via *N*-acyliminium ions. Although these methods provided general ways to prepare 2-substituted piperidines, two major limitations still existed: (i) acid has to be used as catalyst to generate the *N*-acyliminium intermediate, which is not suitable for acid-sensitive compounds, and (ii) addition of nucleophiles to unsymmetric imides led to poor regioselectivity and yields ring opening products as a mixture. Therefore, the development of new approaches to 2-substitued piperidines is required.

During the course of our study of regioseletive reduction of 3-sulfonyl glutarimides **7** at C-6 carbonyl by sequential addition of sodium hydride and LAH to form hydroxy lactam **8**, the high regioselectivity in the reduction is controlled by the formation of enolate intermediate[20] (Scheme 1). We envisioned that this result can be

SCHEME 1. Regioselective Reduction of Asymmetric Glutarimides



SCHEME 2. Addition of Grignard Reagent to Glutarimide 9



applied to the regioselective introduction of substituent at C-6 in 3-sulfonyl-5-methoxyglutarimide **9** and further converted to *cis*-2-substituted-3-piperidinols. Instead of addition of hydride to C-6 carbonyl in **9**, the addition of organolithium or Grignard reagents should give the same regioselectivity.

Results and Discussion

The starting material 3-sulfonyl-5-methoxy glutarimide **9** was easily prepared via stepwise [3+3] annulation of *N*-benzyl α-sulfonylacetamide with α,*β*-unsaturated ester as we previously described.[20,21] With glutarimide **9** in hand, we then first studied its reaction with methylmagnesium bromide, which although unsuccessful, revealed some interesting chemistry. A mixture of glutarimide **9** and 1.2 equiv of sodium hydride in THF was allowed to react at 25 °C for 5 min, then 2 equiv of methyl Grignard reagent was added in one portion and the solution was further stirred for 30 min. After general workup, the undesired product methyl ketone amide **11** was isolated exclusively (Scheme 2).[22] Since an excess

(13) (a) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *J. Org. Chem.* **1988**, *53*, 3865. (b) Onoue, H.; Narisada, M.; Uyeo, S.; Matsumura, H.; Okada, K.; Yano, T.; Nagata, W. *Tetrahedron Lett.* **1979**, 3867. (c) Kise, N.; Yamazaki, H.; Mabuchi, T.; Shono, T. *Tetrahedron Lett.* **1994**, *35*, 1561.

(14) (a) Yamada, J.; Sato, H.; Yamamoto, Y. *Tetrahedron Lett.* **1989**, *30*, 5611. (b) Ludwig, C.; Wistrand, L.-G. *Acta Chem. Scand.* **1990**, *44*, 707. (c) Wistrand, L.-G.; Skrinjar, M. *Tetrahedron* **1991**, *47*, 573. (d) Collado, I.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **1995**, *60*, 5011. (e) Comins, D. L.; Foley, M. A. *Tetrahedron Lett.* **1988**, *29*, 6711. (f) Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311. (g) Shono, T.; Terauchi, J.; Ohki, Y.; Matsumura, Y. *Tetrahedron Lett.* **1990**, *31*, 6385. (h) Hanson, G. J.; Russell, M. A. *Tetrahedron Lett.* **1989**, *30*, 5751.

(15) (a) Lundkvist, J. R. M.; Wistrand, L.-G.; Hacksell, U. *Tetrahedron Lett.* **1990**, *31*, 719. (b) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **1997**, *119*, 3409.

(16) (a) Thaning, M.; Wistrand, L.-G. *Acta Chem. Scand.* **1989**, *43*, 290. (b) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *50*, 6221. (c) Irie, K.; Aoe, K.; Tanaka, T.; Saito, S. *J. Chem. Soc., Chem. Commun.* **1985**, 633.

(17) (a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. (b) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300. (c) Pilli, R. A.; Russowsky, D. *J. Org. Chem.* **1996**, *61*, 3187.

(18) (a) Shono, T.; Matsumura, Y.; Tsubata, K.; Takata, J. *Chem. Lett.* **1981**, 1121. (b) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299

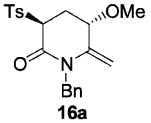
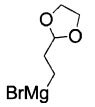
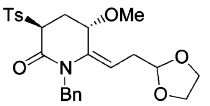
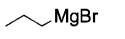
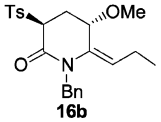
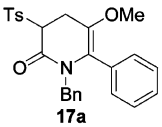
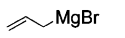
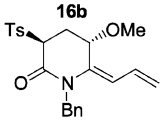
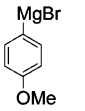
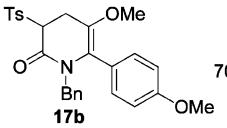
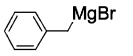
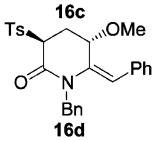
(19) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(20) Chang, B. R.; Chen, C. Y.; Chang, N. C. *Tetrahedron Lett.* **2002**, *43*, 3233.

(21) (a) Chang, M. Y.; Chang, B. R.; Tai, H. M.; Chang, N. C. *Tetrahedron Lett.* **2000**, 41, 10273. (b)Huang, C. G.; Chang, B. R.; Chang, N. C. *Tetrahedron Lett.* **2002**, *43*, 2721. (c) Chang, M. Y.; Chen, S. T.; Chang, N. C. *Tetrahedron* **2002**, *58*, 3623. (d) Chang, M. Y.; Chen, S. T.; Chang, N. C. *Tetrahedron* **2002**, *58*, 5075. (e) Hsu, R. T.; Cheng, L. M.; Chang, N. C.; Tai, H. M. *J. Org. Chem.* **2002**, *67*, 5044. (f) Chang, M. Y.; Chen, S. T.; Chang, N. C. *Heterocycles* **2002**, *57*, 2321. (g) Lin, C. H.; Tsai, M. R.; Wang, Y. S.; Chang, N. C. *J. Org. Chem.* **2003**, *68*, 5688. (h) Chang, M. Y.; Chen, S. T.; Chang, N. C. *Heterocycles* **2003**, *60*, 99. (i) Chang, M. Y.; Chen, S. T.; Chang, N. C. *Synth. Commun.* **2003**, *33*, 1375.

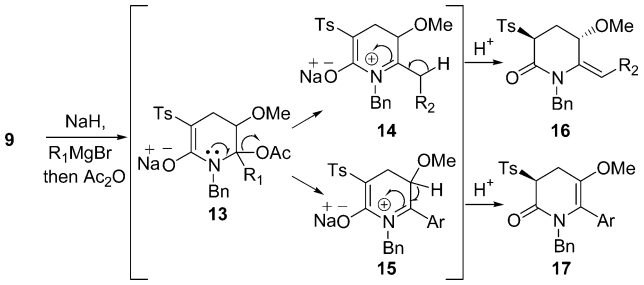
(22) Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P.-Q. *J. Org. Chem.* **2004**, *69*, 6001.

TABLE 1. Regioselective Nucleophilic Addition

entry	Grignard Reagents[a]	Products	yield (%)[b]	entry	Grignard Reagents[a]	Products	yield (%)[b]
1	MeMgBr	 **16a**	90%	5		 **16e**	75%
2		 **16b**	85%	6		 **17a**	82%
3		 **16c**	85%	7		 **17b**	70%
4		 **16d**	70%				

[a] All reactions were at room temperature. [b] All yields were based on 3-sulfonyl glutarimide **9**.

SCHEME 3. Addition of Grignard Reagent to Glutarimide 9 Then Trapping by Ac_2O



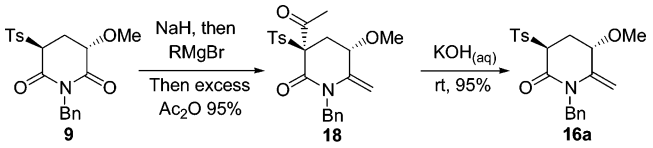
amount of methylmagnesium bromide was employed during the reaction, the lack of formation of tertiary alcohol **12** indicated that **10** was the intermediate before quenching with water.

To avoid the formation of ring opening product **11**, acetic anhydride was added to trap the tertiary alkoxide **10** and afforded δ-enlactam **16a** in 90% yield. Presumably, after the formation of acetate **13** (R_1 = H), *N*-acyliminium intermediate was produced, which further isomerized to δ-enlactam **16a** (Scheme 3). Encouraged by these results, various Grignard reagents were investigated. The corresponding δ-enlactams were obtained in good yield (Table 1). The addition reactions proceeded exclusively at the C-6 position in **9** without the formation of ring-opening product.

The formation of *exo* or *endo* enlactam depends on the type of Grignard reagents. Alkyl Grignard reagents furnished exclusively *exo* olefins (entries 1 to 5). Aryl Grinard reagents produced *endo* olefins (entries 6 and 7) (Table 1). It is evident that in each alkyl Grignard reagent addition, a single geometric isomer was obtained. The structure of **16d** was unequivocally established by single-crystal X-ray analysis.[23] The configuration of

(23) CCDC 250214-250215 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://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).

SCHEME 4. Addition of Grignard Reagent to Glutarimide 9 Then Trapping by Excess Ac_2O



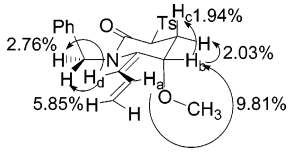
compound **16c** was elucidated by NOESY studies.[24] The stereochemistry of **16a**, **16b** and **16e** was assigned by analogy.

It is interesting to note that when excess acetic anhydride (>2 equiv) was employed in entry 1, the C-3 acylation product **18** was obtained as the only product (Scheme 4). The structure of **18** was unequivocally established by single-crystal X-ray analysis.[23] Treatment of **18** with potassium hydroxide produced **16a**.

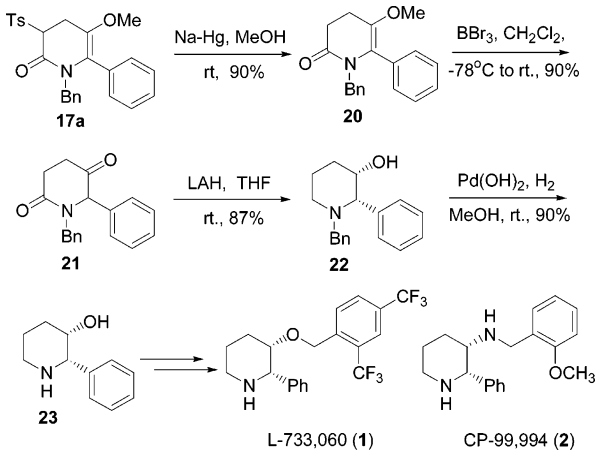
To demonstrate the synthetic utility of this newly developed one-pot procedure, the synthesis of *cis*-2-substituted-3-piperidinols which existed in a number of bioactive natural products and drugs were investigated. L-733,060 (**1**), CP-99,994 (**2**), and cassine (**5**) were chosen as our target molecules.

The synthesis of **1** and **2** was illustrated in Scheme 5. Treatment of **17a** with sodium amalgam furnished desulfonated product **20**, which was further hydrolyzed with boron tribromide to give the corresponding ketolactam **21**. Reduction of dicarbonyl compound **21** with LAH yielded **22** as a single diastereomer.[25] The high diastereoselectivity observed in the reduction of **21** has been rationalized on the basis of Felkin's torsional strain

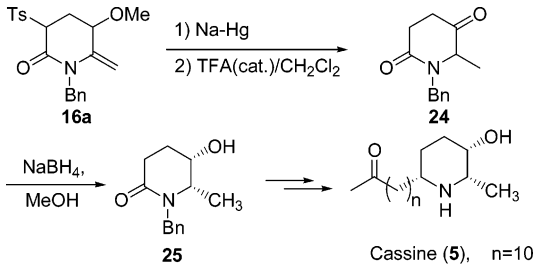
(24) NOESY studies of **16c**: strong NOE correlation between H_a and H_b and the absence of a coupling constant between H_d and H_b are indicative of a chairlike conformation and the equatorial disposition of the sulfonyl group.



SCHEME 5. Formal Synthesis of (+)-L-733,060 (1) and (+)-CP-99,994 (2)



SCHEME 6. Formal Synthesis of Cassine (5)



model, which disfavors the equatorial attack of hydride.[26] The presence of the *N*-benzyl functionality in the six-member ring should flatten the molecule and decrease the 1,3-diaxial steric interactions, further increasing the selectivity. Debenzylation of **22** with $Pd(OH)_2$ as catalyst produced *cis*-2-phenyl-3-pipericinol **23**. The spectral data of **23** were in agreement with those reported in the literature.[27] Compound **23** has been converted to **1** and **2**. Thus, the formal synthesis of **1** and **2** was accomplished.

For the synthesis of cassine (**5**), the key intermediate **25** was readily prepared from **16a**, by sodium amalgam desulfonation followed by hydrolysis of the resulting methyl ether and finally sodium borohydride reduction[28] (Scheme 6).

In conclusion, we have developed a straightforward one-pot reaction procedure, which converted readily available 5-methoxy-3-sulfonyl glutarimide **9** to the corresponding 5-methoxy-6-substituted-3-sulfonyl-δ-enlactames. Various substituents have been introduced to the C-6 position in **9** in high yield. This strategy also provided a rapid access to *cis*-2-substituted-3-piperidinols, and was demonstrated by the formal synthesis of L-733,060 (**1**), CP-99,994 (**2**), and cassine (**5**). Further application of the present methodology to the synthesis of indolizidines, quinolizidines and polysubstituted piperidines is underway in our laboratory.

Experimental Section

1. Preparation of 11. A solution of glutarimide **9** (387 mg, 1 mmol) in dry THF (5 mL) was added to a rapidly stirred suspension of sodium hydride (60 mg, 1.5 mmol, 60%) in tetrahydrofuran (20 mL). After the reaction mixture was stirred at room temperature for 15 min, methylmagnesium bromide (1.3 mmol) was added in one portion by syringe. The resulting mixture was stirred at room temperature for 30 min. After the reaction was accomplished (monitored by TLC), the reaction mixture was quenched with water (2 mL) and filtered through Celite. The organic layer was extracted with EtOAc (3 × 20 mL) and dried with anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 4/1 to 2/1) to afford **11**.

2. General Procedure for the Preparation of 5-Methoxy-6-substituted-δ-enlactams. The procedure for the preparation of **11** was applied to the preparation of **16a**−**e** and **17a**,**b**; however, instead of quenching with water, acetic anhydride (122.4 mg, 1.2 mmol) was added in one portion, and the reaction mixture was stirred for an additional 30 min. After the reaction was finished, the reaction mixture was quenched with a saturated ammonium chloride solution (1 mL) and filtered through Celite. The organic layer was extracted with EtOAc (3 × 20 mL) and dried with anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 4/1 to 2/1) to afford **16a**−**e** and **17a**,**b**.

4-Methoxy-5-oxo-2-(toluene-4-sulfonyl)hexanoic acid benzylamide (11): 88% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58−7.56 (m, 2H), 7.38−7.25 (m, 7H), 6.82 (t, *J* = 5.5 Hz, 0.6H), 6.68 (t, *J* = 5.5 Hz, 0.4H), 4.51−4.43 (m, 1.2H), 4.47−4.36 (m, 0.8H), 4.05 (dd, *J* = 11.0, 2.5 Hz, 0.6H), 3.99 (dd, *J* = 8.5, 3.5 Hz, 0.4H), 3.75 (t, *J* = 7.0 Hz, 0.4H), 3.65(dd, *J* = 10.0, 4.0 Hz, 0.6H), 3.34 (s, 1.2H), 3.26 (s, 1.8H), 2.43 (s, 3H), 2.37−2.22 (m, 1.6H), 2.16−2.10 (m, 0.4H), 2.15 (s, 1.8H), 2.14 (s, 1.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9 (0.4C), 209.0 (0.6C), 163.4 (0.4C), 163.2 (0.6C), 145.7 (0.6C), 145.6 (0.4C), 137.3 (0.6C), 137.2 (0.4C), 133.0 (0.6C), 132.8 (0.4C), 130.0 (1.2C), 129.8 (0.8C), 129.1 (0.8C), 129.0 (1.2C), 128.8 (1.2C), 128.7 (0.8C), 128.1 (2C), 127.8 (0.6C), 127.7 (0.4C), 83.5 (0.4C), 83.2 (0.6C), 67.1 (0.6C), 66.6 (0.4C), 58.4 (0.6C), 58.2 (0.4C), 44.3, 28.6 (0.6C), 28.2 (0.4C), 25.7 (0.6C), 25.6 (0.4C), 21.7; EI-MS $C_{21}H_{25}NO_5S$, *m/z* (%) 91 (100), 404 (M^+ + 1, 0.27).

1-Benzyl-5-methoxy-6-methylene-3-(toluene-4-sulfonyl)-piperidin-2-one (16a): 90% yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3024, 1641, 1219; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.27−7.21 (m, 3H), 7.14 (d, *J* = 7.0 Hz, 2H), 5.0 (d, *J* = 16.0 Hz, 1H), 4.67 (d, *J* = 16.0 Hz, 1H), 4.5 (d, *J* = 1.5 Hz, 1H), 4.47 (dd, *J* = 12.0, 7.0 Hz, 1H), 4.4 (d, *J* = 1.50 Hz, 1H), 4.01 (dd, *J* = 4.0, 2.5 Hz, 1H), 3.11 (s, 3H), 2.74 (ddd, *J* = 14.0, 7.0, 4.0 Hz, 1H), 2.56 (ddd, *J* = 14.0, 12.0, 2.5 Hz 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 144.7, 141.0, 136.3, 136.0, 129.5 (2C), 129.3 (2C), 128.6 (2C), 127.1, 126.0 (2C), 98.3, 75.8, 62.8, 56.0, 47.2, 26.5, 21.8; HRMS *m/z* (ESI, M^+ + 1) calcd for $C_{21}H_{24}NO_4S$ 386.1348, found 386.1422.

1-Benzyl-5-methoxy-6-propylidene-3-(toluene-4-sulfonyl)piperidin-2-one (16b): 85% yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 2997, 1685; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.8 (d, *J* = 8.5 Hz, 2H), 7.32 (m, 6H) 7.16 (d, *J* = 7.0 Hz, 1H), 5.13 (t, *J* = 7.5 Hz, 1H), 5.0 (d, *J* = 15.5 Hz, 1H), 4.73 (d, *J* = 15.5 Hz, 1H), 4.53 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.42 (dd, *J* = 11.5, 7.5 Hz, 1H), 3.03 (s, 3H), 2.74 (ddd, *J* = 14.5, 8.0, 4.5 Hz, 1H), 2.48−2.44 (m, 1H), 2.42 (s, 3H), 2.09 (dq, *J* = 7.5, 7.5 Hz, 2H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 144.6, 136.6, 136.2, 134.2, 129.4 (2C), 129.2 (2C), 128.5 (2C), 126.9,

(25) (a) Bonjoch, J.; Serret, I.; Bosch, J. *Tetrahedron* **1984**, *40*, 2505. (b) Toyooka, N.; Yoshida, Y.; Momose, T. *J. Org. Chem.* **1996**, *61*, 4882. (c) Toyooka, N.; Yoshida, Y.; Yotsui, Y.; Momose, T. *J. Org. Chem.* **1999**, *64*, 4919. (d) Koulocheri, S. D.; Magiatis, P.; Haroutounian, S. A. *J. Org. Chem.* **2001**, *66*, 7915.

(26) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2204. (c) Wu, Y. D.; Trucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018.

(27) Stadler, H.; Bös, M. *Heterocycles* **1999**, *51*, 1067.

(28) Toyooka, N.; Yoshida, Y.; Momose, T. *Tetrahedron Lett.* **1995**, 3715.

126.8 (2C), 117.5, 68.9, 63.1, 55.6, 47.8, 26.6, 21.7, 20.2, 14.7; HRMS *m/z* (ESI, $M^+ + 1$) calcd for $C_{23}H_{28}NO_4S$ 414.1661, found 414.1736.

6-Allylidene-1-benzyl-5-methoxy-3-(toluene-4-sulfonyl)-piperidin-2-one (16c): 85% yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 2975, 1648, 1392; ^1H NMR (500 MHz, $CDCl_3$) δ 7.8 (d, J = 8.0 Hz, 2H), 7.33−7.21 (m, 6H), 7.16 (d, J = 7.5 Hz, 1H), 6.51 (dt, J = 16.5, 11.0 Hz, 1H), 5.8 (d, J = 11.0 Hz, 1H), 5.14 (d, J = 16.5 Hz, 1H), 5.12 (d, J = 16.0 Hz, 1H), 5.11 (dd, J = 10.0, 1.5 Hz, 1H), 4.7 (d, J = 16.0 Hz, 1H), 4.7−4.69 (m, 1H), 4.45 (dd, J = 12.0, 7.5 Hz, 1H), 3.09 (s, 3H), 2.78 (ddd, J = 14.0, 7.5, 4.0 Hz, 1H), 2.57−2.45 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 144.7, 136.1, 136.1, 135.9, 129.9, 129.5 (2C), 129.3 (2C), 128.6 (2C), 127.2, 126.5 (2C), 118.9, 116.0, 68.8, 62.9, 55.9, 47.7, 26.1, 21.7; HRMS *m/z* (EI, M^+) calcd for $C_{23}H_{25}NO_4S$ 411.1504, found 411.1496.

1-Benzyl-6-benzylidene-5-methoxy-3-(toluene-4-sulfonyl)piperidin-2-one (16d): 70% yield; white solid; mp 179−180 °C; IR ($CHCl_3$, cm^{-1}) 2941, 1655, 1281; ^1H NMR (500 MHz, $CDCl_3$) δ 7.8 (d, J = 8.5 Hz, 2H), 7.35−7.17 (m, 10H), 7.05 (d, J = 8.0 Hz, 2H), 6.27 (s, 1H), 5.18 (d, J = 16.0 Hz, 1H), 4.84 (d, J = 16.0 Hz, 1H), 4.58 (dd, J = 4.0, 2.0 Hz, 1H), 4.46 (dd, J = 12.0, 7.5 Hz, 1H), 3.0 (s, 3H), 2.79 (ddd, J = 14.0, 7.5, 4.0 Hz, 1H), 2.52 (ddd, J = 14.0, 12.0, 2.0 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 144.8, 142.5, 137.4, 136.3, 135.1, 129.4 (2C), 129.4 (2C), 129.0 (2C), 128.6 (2C), 128.2, 127.2 (2C), 126.7 (2C), 125.7, 115.3, 69.6, 63.1, 55.5, 47.8, 25.6, 21.6; HRMS *m/z* (EI, M^+) calcd for $C_{27}H_{27}NO_4S$ 461.1661, found 461.1658. Anal. Calcd for $C_{27}H_{27}NO_4S$: C, 70.26; H, 5.9; N, 3.03. Found: C, 70.27; H, 6.01; N, 2.88. Compound **16d** was recrystallized from ethyl acetate as a colorless prism.

1-Benzyl-6-(2-[1,3]dioxolan-2-ylethylidene)-5-methoxy-3-(toluene-4-sulfonyl)piperidin-2-one (16e): 75% yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 2996, 1638; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.29−7.21 (m, 4H), 7.17 (d, J = 7.0 Hz, 1H), 5.19 (t, J = 8.0 Hz, 1H), 5.02 (d, J = 16.0 Hz, 1H), 4.85 (t, J = 3.5 Hz, 1H), 4.75 (d, J = 16.0 Hz, 1H), 4.56 (dd, J = 4.0, 2.0 Hz, 1H), 4.44 (dd, J = 11.5, 7.5 Hz, 1H), 3.85−3.75 (m, 4H), 3.05 (s, 3H), 2.75 (ddd, J = 14.0, 7.5, 4.0 Hz, 1H), 2.49 (ddd, J = 14.0, 12.0, 2.0 Hz, 1H), 2.47−2.43 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 144.7, 137.3, 136.5, 136.3, 129.4 (2C), 129.3 (2C), 128.4 (2C), 127.0, 126.8 (2C), 108.4, 103.0, 69.1, 65.3, 65.1, 63.1, 55.8, 47.7, 31.7, 26.3, 21.7; HRMS *m/z* (ESI, $M^+ + 1$) calcd for $C_{25}H_{30}NO_6S$ 472.1716, found 472.1735.

1-Benzyl-5-methoxy-6-phenyl-3-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-pyridin-2-one (17a): 82% yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 2968, 1714; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.31−7.29 (m, 3H), 7.17−7.15 (m, 3H), 7.09−7.07 (m, 2H), 6.87−6.86 (m, 2H), 4.85 (d, J = 15.5 Hz, 1H), 4.22 (d, J = 15.5 Hz, 1H), 4.15 (q, J = 3.5 Hz, 1H), 3.46 (s, 3H), 3.31 (dd, J = 14.0, 3.5 Hz, 1H), 3.08 (dd, J = 14.0, 3.5 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 145.3, 137.1, 136.0, 131.4, 129.8 (2C), 129.0 (2C), 128.2 (2C), 128.2 (2C), 128.1 (2C), 128.0 (2C), 127.5 (2C), 127.2, 127.1, 65.9, 57.6, 47.0, 22.2, 21.7; HRMS *m/z* (ESI, $M^+ + 1$) calcd for $C_{26}H_{26}NO_4S$ 448.1504, found 448.1612.

1-Benzyl-5-methoxy-6-(4-methoxyphenyl)-3-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-pyridin-2-one (17b): 70% yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3012, 1685; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.26−7.16 (m, 5H), 7.0−6.82 (m, 4H), 4.85 (d, J = 15.5 Hz, 1H), 4.22 (d, J = 15.5 Hz, 1H), 4.15 (dd, 7.0, 3.5 Hz, 1H), 3.86 (s, 3H), 3.45 (s, 3H), 3.29 (dd, J = 17.5, 3.5 Hz, 1H), 3.06 (dd, J = 17.5, 7.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 159.1, 141.7, 138.0, 136.7, 133.7, 131.1, 130.9 (2C), 130.6, 129.2 (2C), 128.1 (2C), 127.4 (2C), 126.8, 126.3, 124.3, 113.4 (2C), 65.4, 55.5, 45.8, 32.1, 21.7, 21.4; HRMS *m/z* (ESI, $M^+ + 1$) calcd for $C_{27}H_{28}NO_5S$ 478.1610, found 478.1721.

3-Acetyl-1-benzyl-5-methoxy-6-methylene-3-(toluene-4-sulfonyl)piperidin-2-one (18): 95% yield; white solid; mp 139−140 °C; IR ($CHCl_3$, cm^{-1}) 1724, 1648, 1278; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.5 Hz, 2H), 7.33−7.24, (m, 6H), 7.22 (d, J = 8.0 Hz, 1H), 5.18 (d, J = 16.0 Hz, 1H), 4.86 (d, J = 16.0 Hz, 1H), 4.51 (d, J = 2.0 Hz, 1H), 4.41 (d, J = 2.0 Hz, 1H), 3.94 (dd, J = 4.0, 2.0 Hz, 1H), 3.21 (dd, J = 14.0, 4.5 Hz, 1H), 3.05 (s, 3H), 2.67 (dd, J = 14.0, 2.0 Hz, 1H), 2.4 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 163.6, 145.4, 140.7, 135.9, 134.0, 131.7 (2C), 129.0 (2C), 128.6 (2C), 127.3, 126.5 (2C), 97.9, 79.8, 75.6, 56.0, 47.1, 32.3, 29.1, 21.7; HRMS *m/z* (ESI, $M^+ + 1$) calcd for $C_{23}H_{25}NO_5S$ 428.1453, found 428.1536. Compound **18** was recrystallized from ethyl acetate as a colorless prism.

3. Synthesis of 1-Benzyl-5-methoxy-6-phenyl-3,4-dihydro-1*H*-pyridin-2-one (20). Sodium amalgam (Na/Hg, 3.0 g) and sodium phosphate (40 mg) were added to a stirred solution of **17a** (800 mg, 1.78 mmol) in MeOH (20 mL), and the solution was 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 (*n*-hexane/ethyl acetate 4/1 to 2/1) to afford **20** (469 mg, 90%) as a colorless oil: 90% yield; colorless oil; IR ($CHCl_3$, cm^{-1}) 3031, 1648, 1233; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29−7.16 (m, 6H), 7.06 (dd, J = 8.0, 3.0 Hz, 2H), 6.88 (dd, J = 8.0, 3.0 Hz, 2H), 4.57 (s, 2H), 3.38 (s, 3H), 2.75 (t, J = 7.0 Hz, 2H), 2.54 (t, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 142.0, 137.9, 132.0, 129.8, 129.7 (2C), 128.8, 128.1 (2C), 127.9, 127.8, 127.3 (2C), 126.8, 56.9, 45.9, 31,9, 21.0; HRMS *m/z* (EI, M^+) calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1413.

4. Synthesis of 1-Benzyl-6-phenylpiperidine-2,5-dione (21). To a solution of **20** (440 mg, 1.5 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C was added dropwise a 1.0 M solution of boron tribromide in dichloromethane (1.0 M, 2.0 mL). After the solution was stirred for 4 h, the reaction contents were 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 (*n*-hexane/ethyl acetate = 6/1 to 3/1) to afford **21** (369 mg, 90%): 90% yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 2996, 1738, 1261; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42−7.26 (m, 8H), 7.17 (d, J = 8.0 Hz, 2H), 5.63 (d, J = 14.5 Hz, 1H), 4.78 (s, 1H), 3.55 (d, J = 14.5 Hz, 1H), 2.84 (dt, J = 17.5, 9.0 Hz, 2H), 2.73 (dd, J = 9.0, 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 170.0, 135.8, 134.0, 129.2 (2C), 128.9 (2C), 128.6 (2C), 128.0 (2C), 126.4 (2C), 68.5, 47.7, 34.9, 29.1; HRMS *m/z* (EI, M^+) calcd for $C_{18}H_{17}NO_2S$ 279.1259, found 279.1257.

5. Synthesis of 1-Benzyl-2-phenylpiperidin-3-ol (22). To a solution of **21** (327 mg, 1.17 mmol) in THF (10 mL) was added lithium aluminum hydride (77 mg, 2.0 mmol) at room temperature. The resulting mixture was refluxed for 3 h, quenched with NH_4Cl (1 mL) at the same temperature, 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 the silica gel (hexane/ethyl acetate = 3/1 to 1/1) produced the product **22** (255 mg, 87%): 87% yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 2994, 1378, 1254; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48−7.22 (m, 10H), 3.88 (d, J = 14.0 Hz, 1H), 3.76 (d, J = 2.0 Hz, 1H), 3.36 (d, J = 1.5 Hz, 1H), 3.01 (d, J = 10.0 Hz, 1H), 2.91 (d, J = 14.0 Hz, 1H), 2.0 (dd, J = 13.5, 2.0 Hz, 2H), 1.98−1.93 (m, 1H), 1.62 (ddt, 16.0, 13.5, 3.0 Hz, 1H), 1.51−1.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 132.3, 128.7 (2C), 128.6 (2C), 128.3 (2C), 128.2 (2C), 127.4, 126.8, 72.3, 69.9, 59.4, 53.3, 31.6, 19.8; HRMS *m/z* (EI, M^+) calcd for $C_{18}H_{21}NO$ 267.1623, found 267.1620.

6. Synthesis of 2-Phenylpiperidin-3-ol (23). Palladium hydroxide (20%) on activated carbon (30 mg) was added to the solution of compound **22** (139 mg, 0.52 mmol) in methanol (100 mL). Then hydrogen was bubbled into the mixture for 1 h, and

the reaction mixture was stirred for 12 h at room temperature. The catalyst was filtered through a short plug of Celite and washed with ethyl acetate (2 × 5 mL), filtered, and concentrated to produce product **23** as a white solid: 90% yield; IR ($CHCl_3$, cm^{-1}) 3645, 3112, 1265; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.34 (m, 5H), 3.86 (br s, 1H), 3.78 (d, J = 1.5 Hz, 1H), 3.21 (dt, J = 11.5, 2.0 Hz, 1H), 2.8 (dt, J = 12.0, 2.5 Hz, 1H), 2.05−2.02 (dm, J = 12.0 Hz, 1H), 1.88 (ddt, J = 12.0, 12.0, 4.0 Hz, 1H), 1.72−1.68 (m, 1H), 1.5 (dm, J = 13.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 128.5 (2C), 127.3, 126.6 (2C), 68.9, 65.0, 47.4, 31.9, 19.8; HRMS *m/z* (ESI, $M^+ + 1$) calcd for $C_{11}H_{16}NO$ 178.1154, found 178.1228.

7. Synthesis of 1-Benzyl-6-methylpiperidine-2,5-dione (24). Sodium amalgam (Na/Hg, 3.0 g) and sodium phosphate (40 mg) were added to a stirred solution of **16a** (365 mg, 0.94 mmol) in MeOH (20 mL), and the solution was 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. Without purification the crude product was dissolved in the CH_2Cl_2 (5 mL) then the trifluroacetic acid (cat.) was added. After the resulting mixture was stirred for 1 h, the solution was concentrated under reduced pressure and the residue was diluted with water (20 mL) and potassium carbonate. After extracted with ethyl acetate (3 × 50 mL), the combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated. The crude product was purified by the silica gel chromatography (*n*-hexane/ethyl acetate = 4/1 to 2/1) to afford **24** (183 mg) as a colorless oil: 90% yield; IR ($CHCl_3$, cm^{-1}) 2989, 1731, 1662; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.23 (m, 5H), 5.25 (d, J = 15.0 Hz, 1H), 4.03 (d, J = 15.0 Hz, 1H), 3.73 (q, J = 7.5 Hz, 1H), 2.84−2.65 (m, 4H), 1.36 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 169.4, 136.4, 128.9 (2C), 128.0 (2C), 127.9, 60.6, 47.4, 35.5, 29.1, 17.5; HRMS *m/z* (EI, M^+) calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1110.

8. Synthesis of 1-Benzyl-5-hydroxy-6-methylpiperidin-2-one (25). To a solution of **24** (95 mg, 0.43 mmol) in methanol (10 mL) was added sodium boron hydride (10.0 mmol) at room temperature. The resulting mixture was stirred for 3 h, quenched with NH_4Cl (1 mL) at the same temperature, 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 chromatography (acetone/ethyl acetate = 1/3 to 1/1) produced the product **25**: 90% yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3627, 3012; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 5.33 (d, J = 15.0 Hz, 1H), 3.99 (dt, J = 10.5, 4.5 Hz, 1H), 3.93 (d, J = 15.0 Hz, 1H), 3.44 (dq, J = 6.5, 5.5 Hz, 1H), 2.64 (ddd, J = 18.5, 7.5, 4.0 Hz, 1H), 2.53 (ddd, J = 17.0, 9.0, 8.0 Hz, 1H), 2.04−1.96 (m, 1H), 1.9 (ddd, J = 17.0, 8.0, 4.0, 1.0 Hz, 1H), 1.22 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 137.3, 128.6 (2C), 127.8 (2C), 127.4, 67.6, 54.8, 47.6, 28.9, 24.9, 13.2; HRMS *m/z* (EI, M^+) calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1321.

Acknowledgment. The authors thank the National Science Council of the Republic of China for financial support.

Supporting Information Available: NMR spectra data of compounds **11** and **16**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048073E