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Regioselective Reduction of 3-Sulfonyl Glutarimides to 3,4-Dihydro-5-sulfonylpyridin-2-ones. Formal Synthesis of the Indolizidine 8a-*epi*-Dendroprimine

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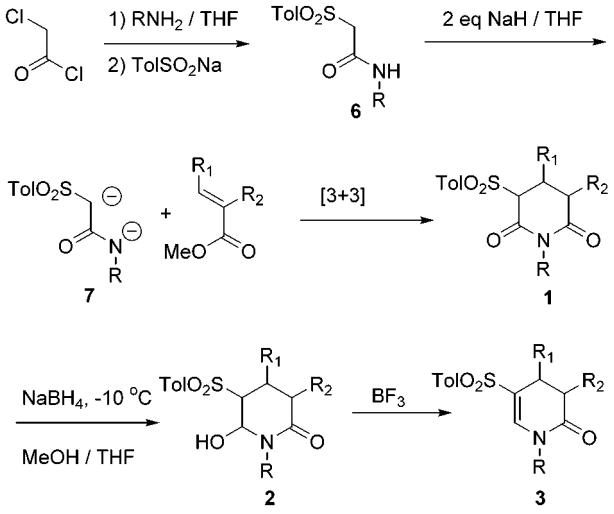
Abstract: Sodium borohydride regioselectively reduced various 3-sulfonyl glutarimides **1** to hydroxy piperidones **2**, which were further dehydrated to 3,4-dihydro-5-sulfonylpyridin-2-ones **3** in the presence of boron trifluoride. Formal synthesis of 8a-*epi*-dendroprimine (**4**) possessing an indolizidine ring system has been accomplished via intramolecular radical cyclization of cyclic vinyl sulfone **5**.

Regioselective reduction of cyclic imides has attracted considerable interest among organic chemists,[1−4] partly because the resulting hydroxylactams can be converted to corresponding *N*-acyliminium intermediates and then further transformed into different alkaloids, such as indolizidines, quinolizidines, isoquinolines, and indoles.[5] In cases of reduction of nonsymmetrically substituted cyclic imides, it was reported that glutarimides seem to be preferentially reduced at the less hindered carbonyl group.[3,4] In this report, we describe a general method which regioselectively reduces the carbonyl group on 3-sulfonyl glutarimides **1** and leads to corresponding hydroxylactams **2**, which are then further converted to 3,4-dihydro-5-sulfonylpyridin-2-ones **3**. Formal synthesis of 8a-*epi*-dendroprimine (**4**) via intramolecular radical cyclization of cyclic vinyl sulfone **5** is also reported.

SCHEME 1



Previously, we reported an efficient synthesis of 4- or 5-substituted 3-sulfonyl glutarimides **1** via a stepwise [3 + 3] cycloaddition.[6] Sequential treatment of chloroacetyl chloride with primary amines and sodium *p*-toluenesulfinate furnished α-toluenesulfonyl acetamide **6** in 90% yield. After the reaction of **6** with 2 equiv of sodium hydride, the resulting dianion **7** reacted with a variety of α,*β*-unsaturated esters to afford the corresponding substituted 3-toluenesulfonyl glutarimides **1**. The *trans* stereochemistry of **1b** was established by X-ray analysis. The stereochemistries of all the other cycloadducts of **1** were compared by their ^{1}H NMR spectra with that of **1b** (a ^{1}H HNR singlet at δ 3.87 was assigned to an equatorial proton on the C_3 carbon in the boat form conformation of **1b**).[6] In the course of our application of **1** in alkaloid synthesis, we found that treatment of **1** with excess sodium borohydride in methanol−tetrahydrofuran (1:2) at −10 °C furnished **2** exclusively. The presence of the strong electron-withdrawing sulfonyl group at the C_3 position increased the electrophilicity of C_2, which may account for the regiochemistry of reduction. To confirm these results, hydroxylactams **2** were treated with boron trifluoride in the presence of anhydrous magnesium sulfate, and the corresponding dehydration products **3** were obtained in moderate to good yields (Scheme 1). Several examples were examined, and the results are listed in Table 1.

For the synthesis of 8a-*epi*-dendroprimine (**4**) shown in Scheme 2,[7] glutarimide **8** was prepared in quantitative yield by treatment of **1b** with aluminum trichloride in refluxing benzene. Compound **8** was converted to chloride **1j**, which, upon treatment with excess sodium borohydride in MeOH−THF solution at −10 °C, furnished hydroxy lactam **2j**.[8] Without purification, subsequent

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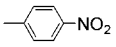
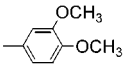
TABLE 1. Synthesis of 3 via Regioselective $NaBH_4$ Reduction of 1[a,b]

entry	R_1	R_2	R	yield of **3**
a	−H	−H	−Bn	45%
b	$-CH_3$	−H	−Bn	91%
c	−H	$-CH_3$	−Bn	68%
d		−H	−Bn	73%
e		−H	−Bn	55%
f		−H	−PMB	80%
g		−H	−PMB	69%
h		−H	−PMB	75%
i	$-CH_3$	−H		95%
j	$-CH_3$	−H	$-(CH_2)_3Cl$	97%

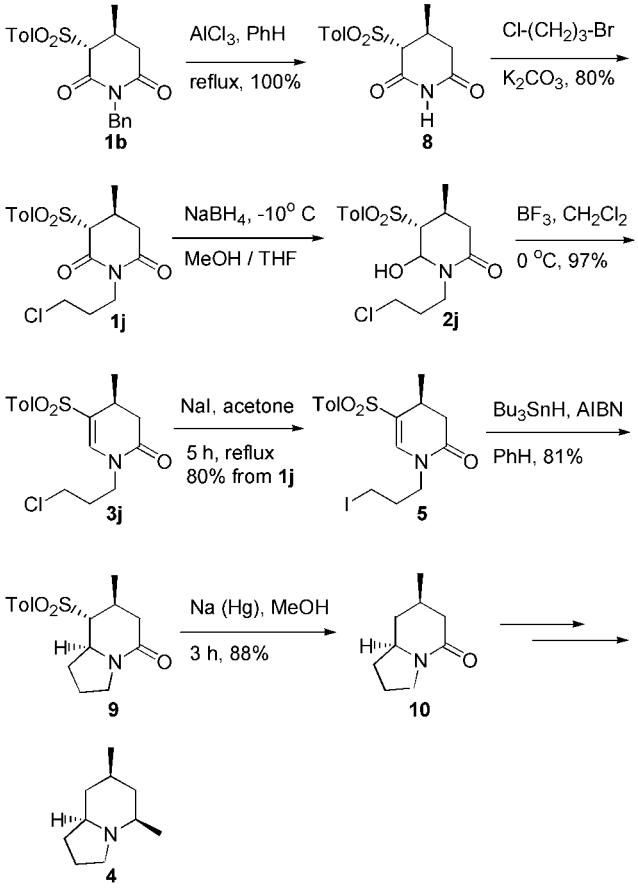
[a] All yields were based on glutarimides **1**. [b] The structures of **1b** and **3g** were confirmed by X-ray analysis.

boron trifloride dehydration of **2j** provided vinyl sulfone **3j** from **1j** in 97% yield.

For the synthesis of an indolizidine skeleton, chloride **3j** was first converted to the corresponding iodide **5** with sodium iodide. Intramolecular radical cyclization of **5** with tributyltin hydride in the presence of AIBN gave indolizidine **9** (81%) as a single diastereomer. To the best of our knowledge, this is the first example of the radical cyclization of cyclic vinyl sulfone to build up an indolizidine carbon skeleton. Reductive desulfonation of **9** with sodium amalgam gave **10** as a single diastereomer in 88% yield.[9] The strucure of **10** was confirmed by comparison of the ^1H and ^{13}C NMR spectra with those of an authentic sample provided by Professor Udo Nubbemeyer.[7a] The diastereoselective production of **9** can be explained by the formation of the more stable intermediate **11a** instead of **11b** in the ring formation step. This rationalization was supported by X-ray crystallography of compound **3g** (Figure 1), prepared in our laboratory. In compound **3g**, the substituents at C_4 and the nitrogen atom are *cis* to each other. Since compound **10** has been transformed into 8a-*epi*-dendroprimine (**4**), this work constitutes a formal total synthesis of racemic 8a-*epi*-dendroprimine (**4**).[7a]

In summary, we successfully performed the regioselective reaction of 3-sulfonyl glutarimides **1**, leading to 3,4-dihydro-5-tosylpyridin-2-ones **3** in moderate to excellent yields and intramolecular radical cyclization of cyclic vinyl sulfone **5** to construct indolizidine carbon skeleton **10**. This methodology has proved applicable for the synthesis of the indolizidine alkaloid 8a-*epi*-dendroprimine (**4**). Further syntheses of piperidine, indolizidine, quinolizidine, and indole alkaloids are currently underway in our laboratory.

SCHEME 2



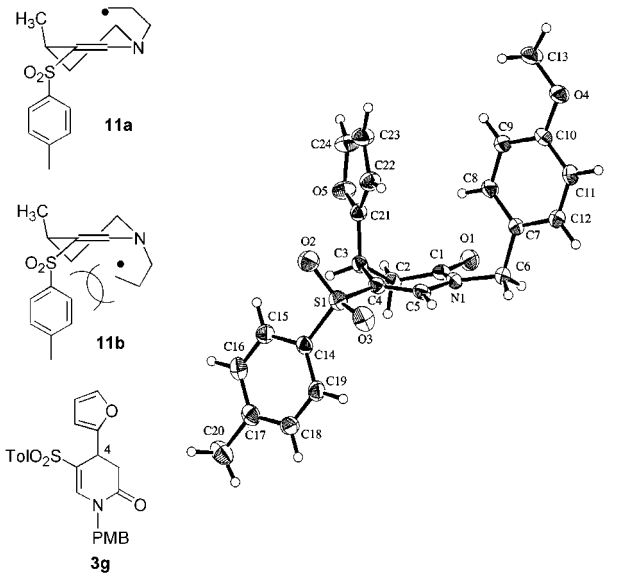


FIGURE 1. Intermediates of **11** and X-ray crystallography of **3g**.

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Experimental Section

Before use, THF and benzene were 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 f_{254} 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.

General Procedure to *N*-Substituted 2-(Toluene-4-sulfonyl)acetamide (6). A mixture of *N*-substituted 2-chloroacetamide (68.5 mmol) and toluene-4-sulfonate sodium salt (1.7 g, 75.4 mmol) in dioxane (30 mL) and water (30 mL) was refluxed for 12 h. The solvent was removed under reduced pressure, and the residue was recrystallized from ethyl acetate to give **6**.

***N*-Benzyl-2-(toluene-4-sulfonyl)acetamide:** 74% yield; IR ($CHCl_3$, cm^{-1}) 3354, 1665; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 2H), 7.37−7.25 (m, 7H), 7.08 (br s, 1H), 4.44 (d, J = 5.5 Hz, 2H), 4.02 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 160.5 (s), 145.6 (s), 137.2 (s), 134.9 (s), 130.1 (d, 2C), 128.8 (d, 2C), 128.1 (d, 2C), 128.0 (d, 2C), 127.7 (d), 61.9 (t), 44.0 (d). Mass *m*/*z* (EI, 70 eV): 303 (M^+, 1%), 148 (100%). HRMS calcd for $C_{16}H_{17}NO_3S$ (M^+): 303.0929. Found: 303.0935. Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.02; H, 5.31; N, 4.56.

General Procedure of [3 + 3] Cycloaddition to Glutarimides 1. To a suspension of sodium hydride (2.00 g, 60% dispersion in oil, washed three times with dry hexane) in dry THF (100 mL) was added 2-sulfonylacetamide (**1**) (20 mmol) in portions. After 20 min, α,β-unsaturated esters (20 mmol) in THF (30 mL) were added to the suspension mixture over a period of 30 min. The mixture was stirred for 12 h at room temperature. The reaction was quenched with aqueous sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate) to give glutarimides **1**.

(3*R,4*S**)-1-Benzyl-4-methyl-3-(toluene-4-sulfonyl)-3,4-dihydro-5*H*-pyridine-2,6-dione (1b):** 95% yield; mp 202−203 °C; IR ($CHCl_3$, cm^{-1}) 1675; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 8.0 Hz, 2H), 7.36−7.24 (m, 7H), 5.09 (d, J = 14.0 Hz, 1H), 4.88 (d, J = 14.0 Hz, 1H), 3.87 (s, 1H), 3.51 (dd, J = 6.0, 18.0 Hz, 1H), 3.21−3.15 (m, 1H), 2.60 (d, J = 18.0 Hz, 1H), 2.43 (s, 3H), 1.13 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3 (s), 164.2 (s), 145.6 (s), 136.4 (s), 134.3 (s), 129.7 (d, 2C), 128.8 (d, 2C), 128.6 (d, 2C), 128.3 (d, 2C), 127.4 (d), 71.7 (d), 117.5 (s), 43.2 (t), 36.0 (t), 23.9 (d), 21.7 (q), 20.3 (q). Mass *m*/*z* (EI, 70 eV): 371 (M^+, 1%), 91 (100%). HRMS calcd for $C_{20}H_{21}NO_4S$ (M^+): 371.1191. Found: 371.1187. Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.20; H, 5.92; N, 3.80.

General Procedure of Regioselective Reduction of Glutarimides 1 to 3,4-Dihydro-5-sulfonylpyridin-2-ones 3. A suspension of sodium borohydride (106 mg, 2.8 mmol) and glutarimides **1** (1.5 mmol) in THF (30 mL) and methanol (15 mL) was stirred for 2 h at −10 °C. After saturated aqueous sodium bicarbonate was added to destroy the excess reduction agent at this temperature, organic solvents were removed under reduced pressure. The residue was extracted with dichloromethane, and the combined organic extracts were washed with brine, dried, filtered, and concentrated to afford **2**. Without further purification, boron trifloride diethyl etherate (0.5 mL) was added to a solution of the residue and anhydrous magnesium sulfate (50 mg) in dichloromethane (20 mL) at 0 °C and stirred at this temperature for 30 min. The reaction mixture was quenched with saturated aqueous sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 2:1) to give 3,4-dihydro-5-sulfonylpyridin-2-ones **3**.

(4*S,5*R**)-1-Benzyl-6-hydroxy-5-(toluene-4-sulfonyl)-4-phenyl-2-piperidinone (2d):** IR ($CDCl_3$, cm^{-1}) 3365, 1653; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 7.11−7.02 (m, 5H), 6.96−6.91 (m, 4H), 5.68 (s, 1H), 5.12 (d, J = 14.5 Hz, 1H), 4.40 (d, J = 14.5 Hz, 1H), 4.13 (br s, 1H), 4.01−3.95 (m, 1H), 3.68 (dd, J = 2.5, 11.5 Hz, 1H), 3.00 (dd, J = 7.5, 18.0 Hz, 1H), 2.52 (dd, J = 9.5, 18.0 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2 (s), 144.2 (s), 139.4 (s), 136.9 (s), 136.3 (s), 129.3 (d, 2C), 128.8 (d, 2C), 128.5 (d, 4C), 128.1 (d, 2C), 127.9 (d, 2C), 127.8 (d), 127.2 (d), 77.5 (d), 68.5 (d), 48.3 (t), 40.0 (t), 35.8 (d), 21.5 (q). Mass *m*/*z* (EI, 30 eV): 435 (M^+, 15.7%), 91 (100%).

1-(3-Chloropropyl)-4-methyl-5-(toluene-4-sulfonyl)-3,4-dihydropyridin-2-one (3j): 97% yield; IR ($CDCl_3$, cm^{-1}) 1692, 1644; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.35 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 3.89 (td, J = 6.5, 13.5 Hz, 1H), 3.65−3.50 (m, 1H), 2.77−2.71 (m, 1H), 2.57 (dd, J = 7.0, 16.0 Hz, 1H), 2.44 (s, 3H), 2.38 (dd, J = 2.0, 16.0 Hz, 1H), 2.10 (quintet, J = 7.0 Hz, 2H), 0.96 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 168.3 (s), 144.3 (s), 138.0 (s), 137.6 (s), 129.9 (d, 2C), 127.6 (d, 2C), 122.8 (s), 45.2 (t), 41.6 (t), 38.7 (t), 31.2 (t), 26.6 (d), 21.6 (q), 18.5 (q). Mass (EI, 70 eV): 343 (M^+, Cl = 37, 18%), 341 (M^+, Cl = 35, 49%), 91 (100%). HRMS calcd for $C_{16}H_{20}ClNO_3S$ (M^+): 341.0852. Found: 341.0848. Anal. Calcd for $C_{16}H_{20}ClNO_3S$: C, 56.21; H, 5.90; N, 4.10. Found: C, 56.30; H, 5.98; N, 3.91.

(3*R,4*S**)-4-Methyl-3-(toluene-4-sulfonyl)piperidine-2,6-dione (8).** A suspension of **1b** (2.00 g, 5.4 mol) and aluminum chloride (3.60 g, 27.0 mmol) in benzene (30 mL) was refluxed for 8 h under nitrogen. After removal of the solvent, water was added to the residue, which was then extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was recrystallized from ethyl acetate to give compound **8** (1.50 g, quantitative). Mp 172−173 °C; IR ($CDCl_3$, cm^{-1}) 3360, 1711; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 3.82 (s, 1H), 3.40 (dd, J = 5.5, 18.0 Hz, 1H), 3.30−3.24 (m, 1H), 2.52 (d, J = 18.0 Hz, 1H), 2.48 (s, 3H), 1.21 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 170.3 (s), 164.1 (s), 146.1 (s), 134.6 (s), 130.0 (d, 2C), 129.0 (d, 2C), 71.0 (d), 35.3 (t), 25.2 (d), 21.8 (q), 20.3 (q). Mass (EI, 70 eV): 282 (M^+, 1%), 91 (100%). HRMS calcd for $C_{13}H_{15}NO_4S$ (M^+): 281.0722. Found: 281.0725. Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.37; N, 4.98. Found: C, 55.41; H, 5.51; N, 4.63.

(3*R,4*S**)-1-(3-Chloropropyl)-4-methyl-3-(toluene-4-sulfonyl)-3,4-dihydro-5*H*-pyridine-2,6-dione (1j).** A solution of **8** (300 mg, 0.10 mol), potassium carbonate (0.5 g), and 1-bromo-3-chloropropane (400 mg, 2.3 mmol) in acetone (15 mL) was stirred at room temperature for 10 h. After removal of the solvent, the residue was added to saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was recrystallized from dichloromethane to afford compound **1j** (300 mg, 80%). Mp 133−134 °C; IR ($CDCl_3$, cm^{-1}) 1677; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 3.96 (dt, J = 2.5, 7.0 Hz, 2H), 3.91 (s, 1H), 3.55 (t, J = 7.0 Hz, 2H), 3.44 (dd, J = 6.0, 18.0 Hz, 1H), 3.21−3.14 (m, 1H), 2.59 (d, J = 18.0 Hz, 1H), 2.48 (s, 3H), 2.03 (quintet, J = 7.0 Hz, 2H), 1.18 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 170.2 (s), 164.5 (s), 146.1 (s), 134.8 (s), 130.0 (d, 2C), 128.8 (d, 2C), 71.8 (d), 42.0 (t), 37.9 (t), 36.0 (t), 30.8 (t), 24.0 (d), 21.8 (q), 20.3 (q). Mass (EI, 70 eV): 360 (M^+ + 1, Cl = 37, 0.6%), 358 (M^+ + 1, Cl = 37, 1.6%), 91 (100%). Anal. Calcd for $C_{16}H_{20}ClNO_4S$: C, 53.70; H, 5.63; N, 3.91. Found: C, 53.38; H, 5.78; N, 3.85.

1-(3-Iodopropyl)-4-methyl-5-(toluene-4-sulfonyl)-3,4-dihydropyridin-2-one (5). A solution of **3j** (1.00 g, 2.90 mol) and sodium iodide (0.40 g, 8.0 mmol) in acetone (20 mL) was refluxed for 5 h. After removal of the solvent, water was added to the residue, which was then extracted with dichloromethane. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was chromatographed on silica

(hexane/ethyl acetate 1:1) to furnish compound **5** (1.00 g, 80%): IR ($CDCl_3$, cm^{-1}) 1691, 1644; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.36 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 3.83 (td, J = 7.0, 13.5 Hz, 1H), 3.53 (td, J = 7.0, 13.5 Hz, 1H), 3.18−3.08 (m, 2H), 2.77−2.71 (m, 1H), 2.57 (dd, J = 7.0, 16.0 Hz, 1H), 2.45 (s, 3H), 2.38 (dd, J = 2.0, 16.0 Hz, 1H), 2.15 (quintet, J = 7.5 Hz, 2H), 0.96 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 168.3 (s), 144.3 (s), 137.9 (s), 137.6 (s), 130.0 (d, 2C), 127.7 (d, 2C), 122.9 (s), 48.1 (t), 38.7 (t), 32.1 (t), 26.6 (d), 21.6 (q), 18.6 (q), 1.3 (t). Mass (EI, 70 eV): 433 (M^+, 18%), 91 (100%). HRMS calcd for $C_{16}H_{20}INO_3S$ (M^+): 433.0209. Found: 433.0206. Anal. Calcd for $C_{16}H_{20}INO_3S$: C, 44.35; H, 4.65; I, 29.29; N, 3.23; O, 11.08; S, 7.40. Found: C, 44.21; H, 4.71; N, 3.05.

(7*S,8*R**,8a*S**)-7-Methyl-8-(toluene-4-sulfonyl)hexahydro-6*H*-indolizin-5-one (9).** To a solution of **5** (300 mg, 0.70 mol) and AIBN (9.5 mg) in benzene (30 mL) was added tributyltin hydride (250 mg) in benzene (30 mL) via syringe pump over a period of 2 h under nitrogen at refluxing temperature. The mixture was refluxed for 4 h. After the addition of water, the layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was chromatographed on silica (hexane/ethyl acetate 1:1) to provide compound **9** (200 mg, 81%): IR ($CDCl_3$, cm^{-1}) 1655; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 2H), 7.41 (s, 1H), 3.88 (dt, J = 6.5, 9.0 Hz, 1H), 3.63−3.58 (m, 1H), 3.40−3.34 (m, 1H), 2.82 (dd, J = 3.0, 9.0 Hz, 1H), 2.73−2.65 (m, 1H), 2.51−2.46 (m, 1H), 2.48 (s, 3H), 2.35−2.28 (m, 1H), 2.15 (dd, J = 2.0, 15.0 Hz, 1H), 1.96−1.89 (m, 1H), 1.83−1.67 (m, 2H), 0.89 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 169.3 (s), 145.5 (s), 134.6 (s), 130.2 (d, 2C), 128.8 (d, 2C), 71.5 (d), 55.3 (d), 44.1 (t), 38.1 (t), 34.8 (t), 29.0 (d), 23.4 (t), 22.6 (q), 21.7 (q). Mass (EI, 70 eV): 308 (M^+, 5%), 136 (100%). HRMS calcd for $C_{16}H_{21}NO_3S$ (M^+): 307.1242. Found: 307.1237.

(7*R,8a*S**)-7-Methylhexahydroindolizin-5-one (10).** A solution of **9** (200 mg, 0.60 mol), disodium hydrogen phosphate (60 mg), and sodium amalgam (2.0 g, 6%) in methanol (10 mL) was stirred at room temperature under nitrogen for 3 h. The mercury was removed, and the solvent was stripped off under reduced pressure. Water was added to the residue, which was then extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was chromatographed on silica (hexane/ethyl acetate 1:1) to afford compound **10** (88 mg, 88%): IR ($CDCl_3$, cm^{-1}) 1625; ^1H NMR (500 MHz, $CDCl_3$) δ 3.62−3.55 (m, 1H), 3.46−3.39 (m, 2H), 2.51 (dd, J = 3.0, 16.0 Hz, 1H), 2.10−2.02 (m, 2H), 1.99−1.86 (m, 3H), 1.81−1.77 (m, 1H), 1.41 (dq, J = 7.0, 11.5 Hz, 1H), 1.07−0.98 (m, 4H), 1.02 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 169.0 (s), 59.0 (d), 44.6 (t), 39.7 (t), 37.6 (t), 33.3 (t), 28.5 (d), 22.2 (t), 21.6 (q). Mass (EI, 70 eV): 153 (M^+, 65%), 83 (100%). HRMS calcd for $C_9H_{15}NO$ (M^+): 153.1154. Found: 153.1157.

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Supporting Information Available: Characterization data for compounds **1d**−**h** and **3a**−**i**. This information is available free of charge via the Internet at http://pubs.acs.org.

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