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Synthesis and reactions of sulfur-substituted indolizidinones

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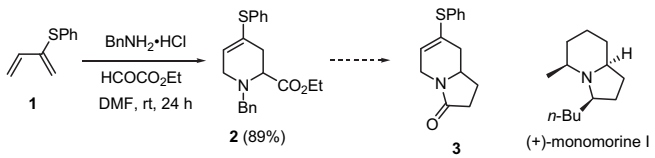
ABSTRACT

An aza-Diels–Alder reaction product **2** was readily converted to a tetrahydropyridine derivative **6**, but its *N*-benzyl group was unexpectedly difficult to cleave under various conditions. On the other hand, the *N*-tosyl α,β-unsaturated ester **14** was transformed in one step by Mg/MeOH/Et_3N to a thio-substituted indolizidinone **3**. This method was also extended to a methyl-substituted diene **16**, which stereoselectively provided the *cis*-2,6-disubstitutedproduct **17**. Further synthetic transformations yielded indolizidinones **20**–**24**, including a formal synthesis of the natural product monomorine I.

1. Introduction

The piperidine ring is a common molecular fragment in both natural and synthetic compounds with various biological activities.[1,2] The aza-Diels–Alder reaction is potentially one of the most versatile and rapid routes to substituted piperidines.[3] However, most imines fail to participate in these [4+2] cycloadditions. In general, a strongly electron-withdrawing group, such as an acyl[4] or a sulfonyl group[5,6] attached to the nitrogen or carbon of the imine is needed.

We have previously reported effective aza-Diels–Alder reactions of thio-substituted dienes with activated or unactivated imines,[7–9] simply by in situ preparation of the iminium salts from amine hydrochlorides and aldehydes. For example, 2-phenylthio-1,3-butadiene (**1**) can give the tetrahydropyridine derivative **2** in good yield. We now report that although the attempted conversion of compound **2** to the thio-substituted indolizidinone **3** failed under various conditions (Scheme 1), the synthesis of compound **3** via an *N*-tosyl analogue succeeded to afford the general structure of indolizidines.[10] We have also completed a formal synthesis of monomorine I,[11] which is a trail pheromone of pharaoh's ants.[12]

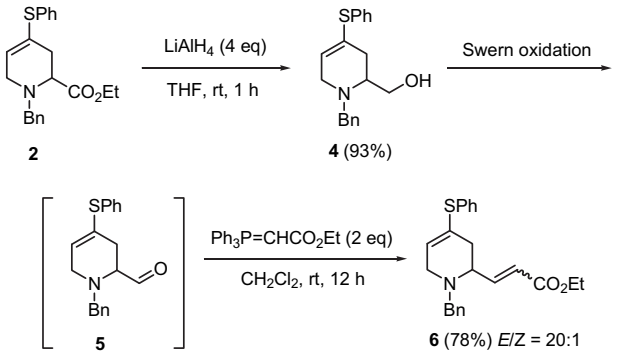


Scheme 1.

2. Results and discussion

Compound **2** was successfully reduced to the alcohol **4** by lithium aluminum hydride in THF (Scheme 2).[13] Swern oxidation of alcohol **4** gave smoothly the expected aldehyde **5**, which decomposed significantly during purification by column chromatography. Thus, after the Swern oxidation, the crude aldehyde **5** was directly treated with (carbethoxymethylene)triphenylphosphorane in CH_2Cl_2 at room temperature to give the α,β-unsaturated ester **6** (*E*/*Z*=20:1).

It was hoped that under catalytic hydrogenation conditions compound **6** could be directly converted to the target molecule **3**.



Scheme 2.

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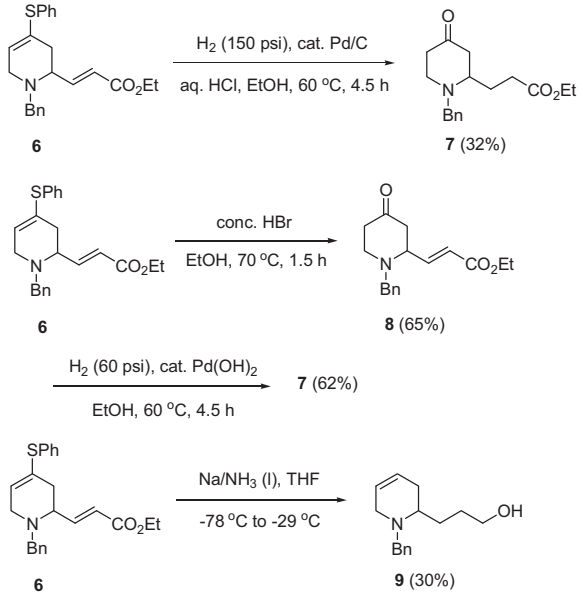
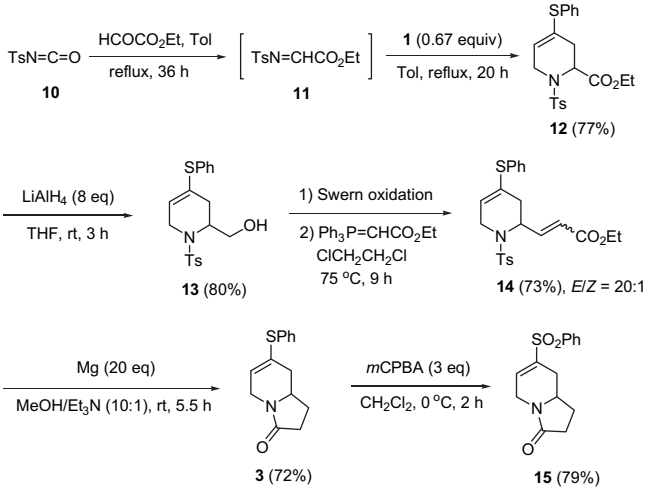
However, after varying the hydrogenation conditions (catalyst, solvent, pressure of H_2, reaction temperature, acidic medium, etc.), the benzyl group of compound **6** could not be cleaved. The keto ester **7** was obtained in 32% yield under a high pressure of hydrogen in aqueous acid. In this reaction, the vinyl sulfide in compound **6** was hydrolyzed under the acidic condition, and the C=C of the α,β-unsaturated ester was reduced by hydrogen. It was speculated that the thio group in compound **6** might poison the palladium catalyst. Thus, compound **6** was first hydrolyzed by concentrated HBr[14] to give the ketone **8**. Further reaction of compound **8** under catalytic hydrogenation condition yielded only the C=C reduction product **7** without cleaving the benzyl group. We also found that treatment of compound **6** with sodium in liquid ammonia[15] gave the thio-cleaved alcohol **9** in 30% yield.



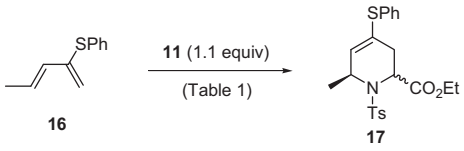
Since the benzyl group of compound **6** was so unexpectedly difficult to cleave, we turned to synthesize piperidine derivatives with a more labile group attached to the nitrogen. A successful synthesis of target molecule **3** is shown in Scheme 3. Following a literature procedure,[16,17] imine **11** prepared in situ from *p*-toluenesulfonyl isocyanate (**10**, PTSI) was directly reacted with diene **1** to give the aza-Diels–Alder product **12** in good yield. The ester **12** was then reduced by lithium aluminum hydride to give alcohol **13**. Swern oxidation of alcohol **13** gave an unstable aldehyde, which was further treated with (carbethoxymethylene)triphenylphosphorane in $ClCH_2CH_2Cl$ at 75 °C to give the α,β-unsaturated ester **14** (*E*/*Z*=20:1). Following a literature procedure,[18] reaction of compound **14** with magnesium in methanol gave compound **3** only in 22% yield. After trying different modifications, it was found that addition of triethylamine to methanol improved the yield of product **3**–72%. Three distinguished steps were involved in this reaction: cleavage of the tosyl group, reduction of the C=C bond, and cyclization of the amino ester intermediate to the product **3**. Compound **3** was further oxidized to the sulfone **15**. It is worth mentioning that the oxidation reaction should be carried out at 0 °C, and no base should be added during the workup because compound **15** was quite sensitive to base.



Scheme 3.

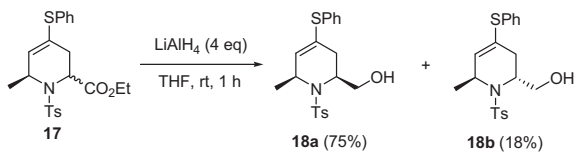
Having established a method for constructing the indolizidinone **3**, we then wanted to apply it to the synthesis of some natural products. Reaction of (*E*)-2-phenylthio-1,3-pentadiene (**16**)[9] with PTSI (**10**) under various conditions provided a different ratio and yield of *cis*/*trans* product **17** (Table 1). Although the cis and trans isomers of compound **17** could not be separated by column chromatography, their ratios were estimated from the ^1H NMR spectra. The reactions carried out in toluene (entries 1 and 2) shows that higher temperature increased the yield of product **17** and the cis/trans ratio. Using 95% EtOH as the solvent (entry 3), only unreacted starting material was recovered. The reaction in DMF (entry 4) was similar to that in toluene (entry 1). The highest cis/trans ratio of compound **17** was obtained in refluxing CF_3CH_2OH (entry 5), but the yield of product **17** was too low. The best reaction condition was to carry out the reaction of diene **16** with imine **11** in CF_3CH_2OH at room temperature (entry 6); the yield was highest and the ratio of cis/trans ratio was about 4:1.

Table 1
Synthesis of compound **17** from diene **16**



Entry	Reaction conditions	Yield of **17** (%)	cis/trans
1	Toluene, rt, 24 h	31	55:45
2	Toluene, reflux, 20 h	55	62:38
3	95% EtOH, reflux, 24 h	S.M.	—
4	DMF, rt, 12 h	36	69:31
5	CF_3CH_2OH, reflux, 20 h	28	87:13
6	CF_3CH_2OH, rt, 12 h	74	79:21

The cis/trans mixture of compound **17** was reduced directly by lithium aluminum hydride in THF at room temperature to the alcohols **18a** and **18b**, which were separated by column chromatography. The structure of compounds **18a** and **18b** was established by X-ray crystallography (Fig. 1 and Fig. 2).[19]



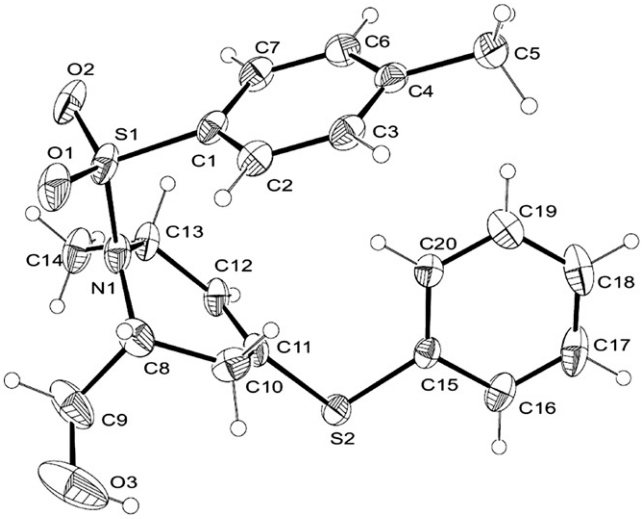


Fig. 1. X-ray crystal structure of compound **18a**.

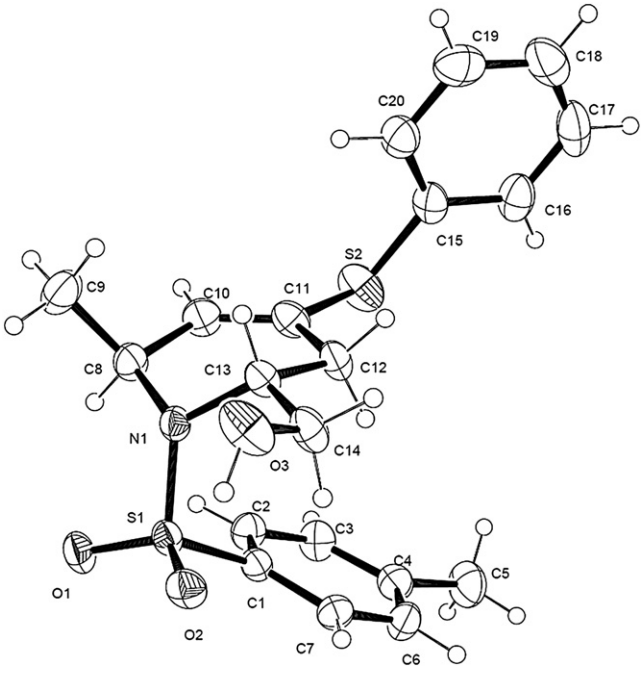


Fig. 2. X-ray crystal structure of compound **18b**.

Swern oxidation of alcohol **18a** gave an unstable aldehyde, which was further treated with (carbethoxymethylene)triphenylphosphorane in CH_2Cl_2 at room temperature to give the α,β-unsaturated ester **19** (*E*/*Z*=8:1). Without separating the *E*/*Z* isomers, compound **19** was successfully converted to the indolizidinone **20** by treatment with magnesium in MeOH/Et_3N (10:1) at room temperature. The *cis*-stereochemistry of compound **20** is clearly shown by the X-ray crystal structure (Fig. 3).[19]

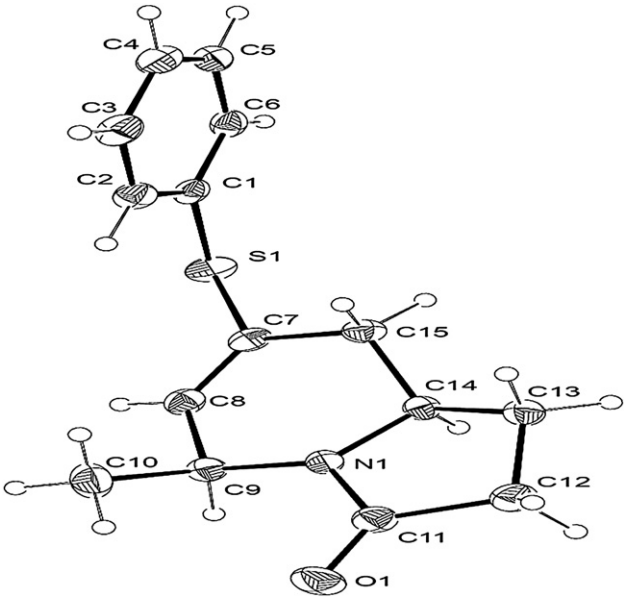
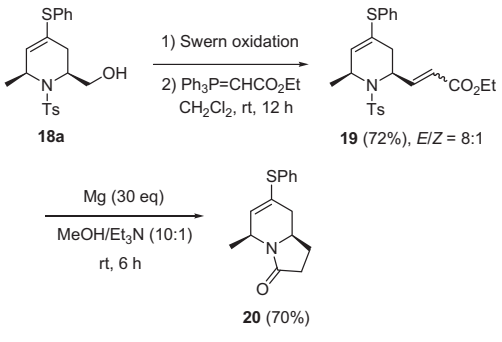
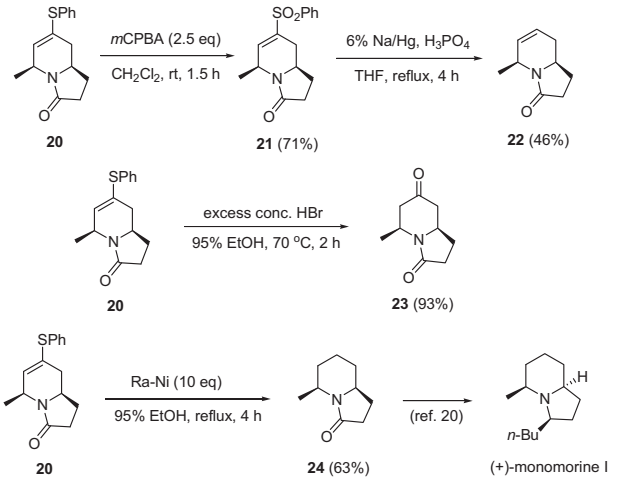


Fig. 3. X-ray crystal structure of compound **20**.

Compound **20** was oxidized to the corresponding sulfone **21** by the reaction with *m*CPBA. Further treatment of compound **21** with 6% sodium amalgam in a small amount of phosphoric acid[20] resulted in the cleavage of the phenylsulfonyl group to give product **22**. On the other hand, the reaction of compound **20** with concentrated HBr solution[21] in 95% EtOH at 70 °C gave the ketone **23** in excellent yield. The *cis*-stereochemistry of compound **23** is clearly shown by the X-ray crystal structure (Fig. 4).[19] Compound **20** also reacted with Raney nickel in refluxing 95% EtOH to afford the bicyclic product **24**, which has been converted to monomorine I.[22]





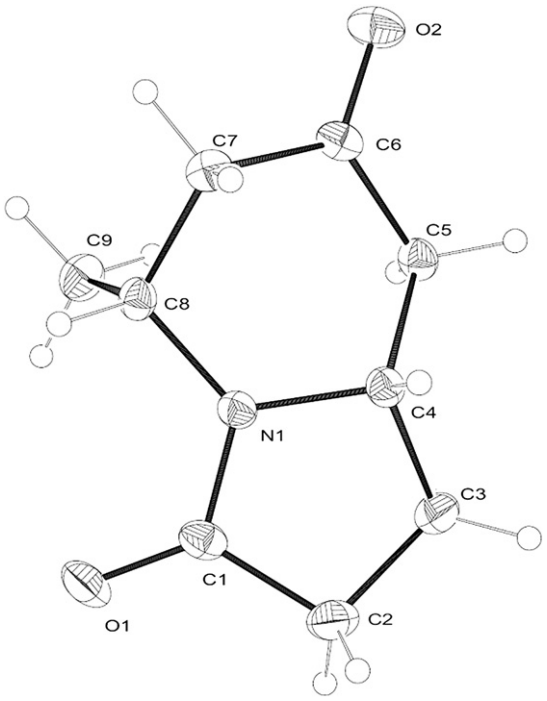


Fig. 4. X-ray crystal structure of compound **23**.

3. Conclusions

Compound **6** was synthesized readily from compound **2** in good yield. The *N*-benzyl group of compound **6** was unexpectedly difficult to cleave under various conditions. On the other hand, the *N*-tosyl α,β-unsaturated ester **14** was converted in one step by Mg/MeOH/Et_3N to the thio-substituted indolizidinone **3**. In this simple procedure, three important transformations were accomplished: cleavage of the *N*-tosyl group, reduction of the C=C bond, and cyclization of the amino ester intermediate. We have also found that the aza-Diels–Alder reaction of imine **15** with methyl-substituted diene **16** could be carried out under suitable condition to give stereoselectively the *cis*-product **17**, which was further transformed to indolizidinones **20**–**24**. Compound **24** has been used to synthesize the natural product monomorine I.

4. Experimental section

4.1. General

Melting points were determined with a SMP3 melting apparatus. Infrared spectra were recorded with a Perkin–Elmer 1600 or 100 series FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer operating at 300 and at 75 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are given in Hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. X-ray crystal structures were obtained with an Enraf–Nonius FR- 590 diffractometer (CAD4, Kappa CCD). Elemental analyses were carried out with Heraeus Vario III-NCSH, Heraeus CHN–O–S-Rapid Analyzer or Elementar Vario EL III. Flash column chromatographic purifications were performed using Merck 60H silica gel.

*4.1.1. 1-Benzyl-2-(hydroxymethyl)-4-(phenylthio)-1,2,3,6-tetrahydropyridine (**4**).* To a solution of **2** (300 mg, 0.85 mmol) in THF (5 mL) under nitrogen was added dropwise a solution of $LiAlH_4$ in THF (1 M, 0.14 mL, 3.39 mmol) at room temperature. After stirring for 1 h, the solvent was removed under vacuum. Saturated NaCl solution was then slowly added. The mixture was extracted three times with ethyl acetate. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography using ethyl acetate/hexanes (1:5) as eluent to give compound **4** (246 mg, 93%) as a yellow oil: IR (film) 3416, 3059, 3027, 2923, 1631, 1582, 1494, 1475, 1453, 1439, 1364, 1335, 1067, 1025, 999, 738, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.22 (10H, m), 5.88 (1H, br s), 3.75 (2H, s), 3.75–3.51 (1H, m), 3.48 (1H, dd, J=5.4, 10.8 Hz), 3.37 (1H, br d, J=19.8 Hz), 3.16–3.10 (2H, m), 2.61 (1H, br s), 2.37 (1H, br d, J=18.0 Hz), 1.90 (1H, dd, J=1.2, 18.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6, 133.5, 131.5, 129.6, 129.2, 128.8, 128.5, 127.4, 127.3 (×2), 61.5, 57.9, 56.6, 47.5, 27.3; EI-MS (rel intensity) m/z 311 (M^+, 0.26), 281 (38), 280 (100), 109 (21), 91 (99), 65 (22); EI-HRMS m/z calcd for $C_{19}H_{21}NOS$ 311.1344, found 311.1348.

*4.1.2. (E)- and (Z)-1-Benzyl-2-[(2-ethoxycarbonyl)ethenyl]-4-(phenylthio)-1,2,3,6-tetrahydropyridine (**6**).* To a solution of oxalyl chloride (0.29 mL, 3.37 mmol) in CH_2Cl_2 (4 mL) at −78 °C under nitrogen was slowly added a solution of DMSO (0.41 mL, 5.73 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred for 5 min, and then a solution of **4** (350 mg, 1.12 mmol) in CH_2Cl_2 (4 mL) was added. After stirring for 30 min, another solution of Et_3N (1.1 mL, 7.87 mmol) in CH_2Cl_2 (4 mL) was added. The mixture was slowly warmed to room temperature, and stirred for another 20 min. Water (15 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic solution was washed with aq K_2CO_3, dried ($MgSO_4$), and concentrated under vacuum. The ^1H NMR of the crude aldehyde product confirmed its structure, but since the aldehyde is quite unstable, it was then immediately dissolved in CH_2Cl_2 (10 mL) and treated with (carbethoxymethylene)triphenylphosphorane (780 mg, 2.25 mmol) at room temperature for 12 h. Saturated ammonium chloride solution was then added. The mixture was extracted with CH_2Cl_2, washed with aq K_2CO_3, dried ($MgSO_4$), and evaporated under vacuum to give crude product **6**. Purification by flash chromatography using ethyl acetate/hexanes (1:5) as eluent gave a mixture of (*E*)- and (*Z*)-**6** (20:1, 333 mg, 78%) as a yellow liquid. The mixture was used for the next step without separation. IR (film) 3059, 3027, 2978, 2925, 2801, 1718, 1649, 1582, 1475, 1439, 1367, 1262, 1176, 1033, 742, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) of (*E*)-**16**: δ 7.38–7.22 (10H, m), 7.01 (1H, dd, J=8.4, 15.7 Hz), 5.90 (1H, d, J=15.7 Hz), 5.89 (1H, s), 4.21 (2H, q, J=6.9 Hz), 3.76 (1H, d, J=13.2 Hz), 3.44 (1H, d, J=13.5 Hz), 3.43 (1H, s), 3.22 (1H, dd, J=2.7, 5.7 Hz), 3.09 (1H, dd, J=2.7, 5.7 Hz). 2.47 (1H, br d, J=18.0 Hz), 2.16 (1H, br d, J=18.0 Hz), 1.30 (3H, t, J=7.2 Hz); (*Z*)-**6** has some characteristic ^1H NMR ($CDCl_3$, 300 MHz) absorptions: δ 6.36 (1H, dd, J=9.3, 11.7 Hz), 4.13–4.07 (2H, m), 1.22 (3H, t, J=6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) of (*E*)-**6**: δ 166.1, 146.6, 138.3, 133.5, 131.6 (×2), 129.1, 128.9, 128.7, 128.4, 127.7, 127.2, 123.6, 60.5, 58.9, 58.5, 50.5, 35.0, 14.3; EI-MS (rel intensity) m/z 379 (M^+, 3), 271 (22), 270 (91), 91 (100); EI-HRMS m/z calcd for $C_{23}H_{25}NO_2S$ 379.1606, found 379.1610.

*4.1.3. 1-Benzyl-2-[2-(ethoxycarboyl)ethyl]-4-oxopiperidine (**7**).* A solution of **6** (100 mg, 0.26 mmol) in absolute ethanol (3 mL) was put in a thick-walled glass bottle for high pressure hydrogenation. To this were added 10% Pd/C (10 mg) and 5 M HCl (1 mL). Hydrogen (150 psi) was filled into the reaction bottle, and the mixture was stirred rapidly at 60 °C for 4.5 h. After cooling to room temperature, Celite was used to filter off the catalyst. The filtrate was then concentrated under vacuum to remove EtOH, and the residue was dissolved in ethyl acetate, dried ($MgSO_4$), and evaporated to give crude product, which was purified by flash chromatography using ethyl acetate/hexanes (1:6) and 5% of Et_3N as eluent to give product **7**

(24 mg, 32%) as a brown liquid: IR (film) 3062, 3030, 2960, 2362, 1728, 1707, 1452, 1371, 1261, 1177, 1113, 1028, 736, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.27 (5H, m), 4.10 (2H, q, J=7.2 Hz), 3.91 (1H, d, J=13.5 Hz), 3.74 (1H, d, J=13.5 Hz), 3.12–3.03 (2H, m), 2.83–2.75 (1H, m), 2.63 (1H, dd, J=1.5, 5.1 Hz), 2.51–2.37 (3H, m), 2.32–2.23 (2H, m), 1.98–1.73 (2H, m), 1.24 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.3, 173.3, 139.0, 128.7, 128.5, 127.4, 60.5, 60.0, 56.3, 47.4, 44.1, 39.0, 30.6, 26.8, 14.3; EI-MS (rel intensity) m/z 289 (M^+, 3), 188 (92), 91 (100); EI-HRMS m/z calcd for $C_{17}H_{23}NO_3$ 289.1678, found 289.1673.

*4.1.4. (E)- and (Z)-1-Benzyl-2-[2-(ethoxycarboyl)ethenyl]4-oxopiperidine (**8**).* A mixture of **6** (250 mg, 0.66 mmol), concentrated HBr (47–49%, 2.5 mL), and EtOH (5 mL) was heated at 75 °C for 1.5 h under nitrogen. After cooling to room temperature, the solvent was removed under vacuum. To the residue was added slowly saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexanes (1:7) as eluent to give a mixture of (*E*)- and (*Z*)-**8** (16:1, 123 mg, 65%) as a yellow oil: IR (film) 3060, 3028, 2977, 2933, 2905, 2806, 1720, 1657, 1649, 1453, 1368, 1252, 1177, 1029, 986, 736, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) of (*E*)-**8**: δ 7.37–7.26 (5H, m), 6.81 (1H, dd, J=8.1, 15.4 Hz), 5.98 (1H, d, J=15.4 Hz), 4.21 (2H, q, J=7.2 Hz), 3.97 (1H, d, J=13.5 Hz), 3.50–3.40 (1H, m), 3.32 (1H, d, J=13.5 Hz), 3.10–3.04 (1H, m), 2.51–2.38 (5H, m), 1.30 (3H, t, J=7.2 Hz); (*Z*)-**8** has some characteristic ^1H NMR ($CDCl_3$, 300 MHz) absorptions: δ 6.31 (1H, dd, J=9.0, 11.7 Hz), 5.91 (1H, d, J=11.7 Hz), 4.52 (2H, q, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.9, 165.6, 148.7, 147.2, 138.6, 138.2, 129.4, 128.7, 128.5, 128.4, 128.2, 127.4, 127.3, 126.9, 123.8, 121.5, 63.2, 60.7, 60.4, 59.6, 59.2, 58.8, 49.8, 49.6, 46.1, 45.8, 41.2, 40.9, 14.3 (×2); EI-MS (rel intensity) m/z 287 (M^+, 2), 196 (36), 91 (100); EI-HRMS m/z calcd for $C_{17}H_{21}NO_3$ 287.1519, found 287.1521.

*4.1.5. 1-Benzyl-2-(3-hydroxypropyl)-1,2,3,6-tetrahydropyridine (**9**).* To a solution of **6** (333 mg, 0.88 mmol) in THF (15 mL) at −78 °C was added liquid ammonia (35 mL) by condensing ammonia with a dry ice condenser. Sodium (about 0.5 g) was cut into small pieces and was quickly added. After stirring for 5 min, the solution turned to dark blue. The reaction mixture was allowed to warm to −29 °C, and powdered ammonium chloride was added till the blue color disappeared. The mixture was warmed to room temperature, and the solvent was evaporated under vacuum. The residue was partitioned between CH_2Cl_2 and water. The organic solution was dried ($MgSO_4$) and concentrated under vacuum to give crude product, which was purified by flash chromatography using ethyl acetate/hexanes (1:6) and 5% Et_3N as eluent to give product **9** (60 mg, 30%) as a light yellow oil: IR (film) 3402, 3026, 2924, 2859, 1652, 1602, 1494, 1453, 1359, 1335, 1062, 1028, 1007, 732, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.23 (5H, m), 5.83–5.77 (1H, m), 5.58–5.53 (1H, m), 3.77–3.56 (4H, m), 3.18–3.0 (2H, m), 2.98–2.90 (1H, m), 2.30–2.24 (1H, m), 1.97–1.53 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 129.3, 128.5, 127.2, 124.8, 123.7, 63.1, 56.5, 54.4, 46.4, 31.3, 30.3, 26.8; EI-MS (rel intensity) m/z 231 (M^+, 2), 172 (100), 91 (68); EI-HRMS m/z calcd for $C_{15}H_{21}NO$ 231.1623, found 231.1620.

*4.1.6. Ethyl 4-(phenylthio)-1-toluenesulfonyl-1,2,3,6-tetrahydro-2-pyridinecarboxylate (**12**).* To a solution of ethyl glyoxylate (50% in toluene, 2 mL, 10 mmol) in toluene (10 mL) was slowly added *p*-toluenesulfonyl isocyanate (PTSI, 1.54 mL, 10 mmol). The mixture was heated at reflux for 36 h under nitrogen to generate the imine **11**. After cooling to room temperature, 2-phenylthio-1,3-butadiene (**1**, 1.1 g, 6.73 mmol) was added. The reaction mixture was then heated at reflux for 20 h. The solvent was removed under vacuum, and to the residue was slowly added 5% aq NaOH (30 mL) to decompose the unreacted *p*-toluenesulfonyl isocyanate. The mixture was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography using ethyl acetate/hexanes (1:6) and 5% Et_3N as eluent to give product **12** (2.18 g, 77%) as a light yellow solid, mp 80–81 °C; IR (film) 3054, 3026, 2980, 2940, 2912, 1739, 1339, 1291, 1195, 1163, 1098, 1027, 931, 814, 744, 732, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (2H, d, J=8.4 Hz), 7.29–7.22 (7H, m), 5.89 (1H, t, J=1.7 Hz), 4.85 (1H, dd, J=0.9, 6.6 Hz), 4.20 (1H, br d, J=10.6 Hz), 4.07–3.95 (2H, m), 3.84 (1H, dd, J=10.6, 7.0 Hz), 2.67 (1H, br d, J=17.1 Hz), 2.52 (1H, d, J=17.1 Hz), 2.42 (3H, s), 1.06 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.5, 143.5, 136.0, 132.7, 131.4, 129.5, 129.0, 128.4, 127.5, 127.2, 125.4, 61.3, 53.5, 43.3, 32.1, 21.5, 13.9; EI-MS (rel intensity) m/z 417 (M^+, 0.12), 263 (22), 262 (100), 188 (69), 91 (62); EI-HRMS m/z calcd for $C_{21}H_{23}NO_4S_2$ 417.1068, found 417.1071.

*4.1.7. 2-(Hydroxymethyl)-4-(phenylthio)-1-toluenesulfonyl-1,2,3,6-tetrahydropyridine (**13**).* To a solution of **12** (1.00 g, 2.39 mmol) in THF (10 mL) under nitrogen was added dropwise a solution of $LiAlH_4$ in THF (1 M, 0.80 mL, 19.0 mmol) at room temperature. After stirring for 2 h, the solvent was removed under vacuum. Saturated NaCl solution was then slowly added. The mixture was extracted three times with ethyl acetate. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography using ethyl acetate/hexanes (1:5) as eluent to give compound **13** as a yellow solid (719 mg, 80%): mp 98.3–99.3 °C; IR (film) 3495, 3056, 2920, 2854, 1636, 1596, 1581, 1474, 1438, 1396, 1326, 1250, 1161, 1103, 1061, 947, 815, 745, 733, 712, 694, 659 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70 (2H, d, J=8.4 Hz), 7.30–7.16 (7H, m), 5.72 (1H, d, J=2.0 Hz), 4.28–4.17 (2H, m), 3.79 (1H, br d, J=15.9 Hz), 3.63 (1H, dd, J=8.4, 11.1 Hz), 3.45 (1H, dd, J=6.6, 11.1 Hz), 2.43 (3H, s), 2.22–2.11 (1H, m), 1.92 (1H, d, J=17.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.6, 137.1, 132.4, 131.9, 130.1, 129.8, 129.1, 127.7, 127.0, 123.0, 61.3, 53.1, 41.8, 29.0, 21.6; EI-MS (rel intensity) m/z 375 (M^+, 0.32), 344 (82), 266 (40), 220 (61), 188 (65), 111 (28) 91 (100), 53 (20); EI-HRMS m/z calcd for $C_{19}H_{21}NO_3S_2$ 375.0963, found 375.0954.

*4.1.8. (E)- and (Z)-2-[(2-Ethoxycarbonyl)ethenyl]-4-(phenylthio)-1-toluenesulfonyl-1,2,3,6-tetrahydropyridine (**14**).* Using a procedure similar to that for the preparation of **6**, compound **13** (540 mg, 1.44 mmol) gave product **14** (466 mg, 73% yield, *E*/*Z*=20:1) as a yellow solid. This mixture of *E*/*Z* products was washed several times with small amounts of diethyl ether/hexanes (1:2) to give pure (*E*)-**14** (420 mg, 66%) as a white solid: mp 68.1–69.1 °C; IR (film) 3057, 2938, 2935, 2905, 2851, 1719, 1656, 1596, 1474, 1440, 1349, 1307, 1163, 1099, 1067, 1034, 981, 927, 815, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (2H, d, J=8.1 Hz), 7.3–7.23 (7H, m), 6.6 (1H, dd, J=5.7, 15.9 Hz), 5.82 (1H, dd, J=1.8, 15.9 Hz), 5.76 (1H, t, J=1.8 Hz), 4.84 (1H, t, J=5.7 Hz), 4.21–4.13 (3H, m), 3.67 (1H, br d, J=16.8 Hz), 2.54 (1H, br d, J=16.8 Hz) 2.43 (3H, s), 2.06 (1H, d, J=16.8 Hz), 1.28 (3H, t, 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4, 143.7, 143.4, 136.2, 132.2, 131.9, 129.7, 129.5, 129.1, 127.7, 127.1, 123.6, 123.5, 60.5, 51.8, 42.2, 33.2, 21.4, 14.2; EI-MS (rel intensity) m/z 443 (M^+, 3), 334 (87), 288 (69), 155 (25), 147 (16), 91 (100); EI-HRMS m/z calcd for $C_{23}H_{25}NO_4S_2$ 443.1225, found 443.1228.

*4.1.9. 7-(Phenylthio)-1,2,3,5,8,8a-hexahydro-3-indolizinone (**3**).* A mixture of **14** (300 mg, 0.68 mmol) and Mg (329 mg, 1.35 mmol) in MeOH (10 mL) and triethylamine (1 mL) was stirred under nitrogen at room temperature for 5.5 h. The solvent was evaporated under vacuum to give crude product, which was purified by flash chromatography using ethyl acetate/hexanes (1:1) and 5% CH_2Cl_2 as eluent to give **3** (119 mg, 72%) as a light yellow liquid: IR (film) 3054, 3030, 2954, 2924, 2852, 1683, 1672, 1653, 1456, 1437, 1418, 1364,

1264, 1023, 752, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.25 (5H, m), 5.87 (1H, dd, J=2.7, 6.0 Hz), 4.37 (1H, ddd, J=3.0, 3.3, 18.9 Hz), 3.74–3.66 (2H, m), 2.45–2.09 (5H, m), 1.72–1.58 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.1, 132.3, 131.9, 130.6, 129.3, 127.7, 124.4, 53.9, 41.2, 37.0, 29.9, 25.0; EI-MS (rel intensity) m/z 246 (M^{+1}, 12), 245 (M, 97), 136 (100), 108 (20); EI-HRMS m/z calcd for $C_{14}H_{15}NOS$ 245.0874, found 245.0881.

*4.1.10. 7-(Phenylsulfonyl)-1,2,3,5,8,8a-hexahydro-3-indolizinone (**15**).* To a solution of compound **3** (100 mg, 0.41 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added dropwise another solution of *m*CPBA (50% in H_2O, 0.42 g, 1.22 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at 0 °C for another 2 h, and was then diluted with more CH_2Cl_2. The solution was washed with saturated aqueous sodium thiosulfate, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography using ethyl acetate/hexanes (1:2) as eluent to give compound **15** (89 mg, 79%) as a light yellow oil: IR (ATR, film) 3065, 2972, 2884, 2838, 2250, 1762, 1680, 1645, 1583, 1446, 1421, 1367, 1305, 1289, 1214, 1197, 1149, 1091, 1071, 1022, 998, 981, 910, 815, 756, 720, 688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87–7.84 (2H, m), 7.69–7.54 (3H, m), 7.04 (1H, dd, J=5.7, 2.7 Hz), 4.60 (1H, dt, J=20.4, 3.3 Hz), 3.78–3.60 (2H, m), 2.70 (1H, d, J=14.1 Hz), 2.43–2.31 (3H, m), 2.04–1.93 (1H, m), 1.74–1.65 (1H, m); ^{13}C NMR ($CDCl_3$) δ 174.1, 138.4, 138.3, 133.7, 133.3, 129.4, 128.1, 52.7, 40.2, 30.2, 29.5, 24.7; FABMS (rel intensity) m/z 278 (M^++H, 3), 147 (21), 119 (21), 105 (25), 95 (39), 81 (52), 69 (70), 55 (100), 41 (93); FAB-HRMS m/z calcd for $C_{14}H_{15}NO_3S$ 277.0695, found m/z 277.0689.

*4.1.11. cis- and trans-Ethyl 2-methyl-4-(phenylthio)-1-tosyl-1,2,5,6-tetrahydro-6-pyridinecarboxylate (**17**).* Using a procedure similar to that for the preparation of **12**, except that the reaction was carried out in CF_3CH_2OH at room temperature for 12 h. Compound **16** (500 mg, 2.84 mmol) gave product **17** (906 mg, 74%) as an inseparable liquid of cis/trans isomers (79:21): IR (film) 3055, 2980, 2933, 1738, 1597, 1582, 1475, 1440, 1338, 1305, 1196, 1162, 1100, 1025, 958, 867, 745, 722, 692 cm^{-1}; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 170.3, 143.5, 143.3, 138.9, 137.4, 132.5 (×2), 132.0, 131.9, 131.7, 129.7, 129.4, 129.2, 129.1, 129.0, 128.8, 128.1, 127.7, 127.5, 127.1 (×2), 61.6, 61.5, 56.4, 52.8, 52.0, 50.7, 32.1, 29.1, 21.8 (×2), 21.5 (×2), 14.0, 13.9; EI-MS (rel intensity) m/z 431 (M^+, 0.39), 416 (12), 358 (16), 322 (12), 277 (14), 276 (100), 202 (42), 188 (29), 91 (28); EI-HRMS m/z calcd for $C_{22}H_{25}NO_4S_2$ 431.1225, found 431.1229. The *cis*-**17** has some characteristic absorptions: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70 (2H, d, J=8.4 Hz), 7.30–7.23 (7H, m), 5.73 (1H, t, J=3.3 Hz), 4.84 (1H, dd, J=6.6, 1.5 Hz), 4.56–4.47 (1H, m), 4.22–4.11 (2H, m), 2.57 (1H, d, J=17.1 Hz), 2.42 (3H, s), 2.20–2.10 (1H, m), 1.33 (3H, d, J=7.2 Hz), 1.19 (3H, t, J=6.3 Hz). The *trans*-**17** has some characteristic absorptions: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.77 (1H, dd, J=1.5, 2.1 Hz), 4.70 (1H, t, J=4.9 Hz), 4.56–4.47 (1H, m), 4.22–4.11 (2H, m), 2.65–2.64 (2H, m), 1.27 (3H, d, J=6.6 Hz), 1.21 (3H, t, J=6.9 Hz).

*4.1.12. 1-Tosyl-2-(hydroxymethyl)-6-methyl-4-(phenylthio)-1,2,3,6-tetrahydropyridine (**18**).* Using a procedure similar to that for the preparation of **4**, compound **17** (50 mg, 0.12 mmol) gave product *cis*-**18a** (34 mg, 75%) and *trans*-**18b** (8 mg, 18%). Compound *cis*-**18a**: white solid, mp 91.3–92.3 °C; IR (ATR, film) 3533, 3055, 2984, 2932, 1644, 1598, 1476, 1334, 1266, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (2H, d, J=8.1 Hz), 7.31–7.17 (7H, m), 5.77–5.75 (1H, m), 4.55–4.50 (1H, m), 4.09 (1H, tt, J=7.8, 3.9 Hz), 3.66–3.59 (1H, m), 3.50–3.42 (1H, m), 2.45 (3H, s), 1.95 (1H, br s), 1.92–1.86 (2H, m), 1.44 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.7, 137.5, 132.6, 131.9, 130.0, 129.2, 128.7 (×2), 127.8, 126.9, 63.2, 52.9, 50.4, 28.0, 24.4, 21.7; FABMS (rel intensity) m/z 390 (M^++H, 18), 358 (40), 234 (54), 214 (85), 155 (41), 154 (100), 137 (58), 136 (100), 91 (82), 88 (44), 77 (52), 73 (43), 69 (60), 67 (42), 57 (72), 55 (77), 43 (66), 41 (64); FAB-HRMS m/z calcd for $C_{20}H_{23}NO_3S_2$ 389.1119, found 389.1122. Compound *trans*-**18b**: white solid, mp 87–88 °C; IR (ATR, film) 3538, 3057, 2976, 2932, 1636, 1598, 1475, 1371, 1266, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69 (2H, d, J=8.1 Hz), 7.31–7.21 (5H, m), 7.15–7.12 (2H, m), 5.75 (1H, dd, J=1.8, 2.7 Hz), 4.78–4.74 (1H, m), 4.07–3.98 (1H, m), 3.81–3.71 (1H, m), 3.66–3.58 (1H, m), 3.20 (1H, dd, J=4.8, 9.9 Hz), 2.47 (3H, s), 1.81 (1H, dd, J=3.9, 17.4 Hz), 1.67 (1H, ddt, J=17.4, 10.2, 1.8 Hz), 1.36 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.6, 139.0, 132.3, 131.9, 130.9, 129.7 (×2), 129.1, 127.6, 126.7, 62.7, 56.1, 53.9, 30.0, 21.5, 20.7.

*4.1.13. cis-(E)- and (Z)-1-Tosyl-2-[(2-ethoxycarbonyl)ethenyl]-6-methyl-4-(phenylthio)-1,2,3,6-tetrahydropyridine (**19**).* Using a procedure similar to that for the preparation of **6**, compound **18a** (100 mg, 0.26 mmol) gave product **19** (85 mg, 72%; *E*/*Z*=8:1) as a yellow liquid. The *E*/*Z* mixture could be recrystallized from CH_2Cl_2/hexanes to give pure *E*-**19** as a white solid: mp 98.6–99.5 °C; IR (ATR, film) 3055, 2987, 1717, 1656, 1600, 1266, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68 (2H, d, J=8.4 Hz), 7.32–7.20 (7H, m), 6.85 (1H, dd, J=5.1, 15.9 Hz), 5.83 (1H, dd, J=1.8, 15.9 Hz), 5.75 (1H, dd, J=2.4, 3.3 Hz), 4.78–4.74 (1H, m), 4.53–4.49 (1H, m), 4.20 (2H, q, J=7.2 Hz), 2.45 (3H, s), 2.15–1.98 (2H, m), 1.37 (3H, d, J=7.2 Hz), 1.30 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.9, 146.6, 143.6, 137.5, 132.2 (×2), 129.9, 129.4, 129.1, 128.4, 127.9, 126.9, 123.0, 60.6, 50.9, 50.8, 30.4, 23.6, 21.6, 14.3; ESI-MS (rel intensity) m/z 458 (M^++H, 26), 348 (70), 302 (71), 282 (100); ESI-HRMS m/z calcd for $C_{24}H_{27}NO_4S_2$ 457.1367, found 457.1372.

*4.1.14. cis-5-Methyl-7-(phenylthio)-1,2,3,5,8,8a-hexahydro-3-indolizinone (**20**).* Using a procedure similar to that for the preparation of **3**, compound **19** (100 mg, 0.22 mmol) gave product **20** (40 mg, 70%) as a white solid: mp 112–114 °C; IR (ATR, film) 3054, 2986, 2870, 1683, 1406, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.28 (5H, m), 5.84 (1H, dd, J=2.4, 3.6 Hz), 4.19 (1H, br s), 3.59 (1H, ddq, J=2.1, 3.9, 6.0 Hz), 2.39–2.31 (3H, m), 2.25–2.11 (2H, m), 1.62–1.52 (1H, m), 1.48 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7, 133.2, 131.7, 131.6, 129.5, 129.3, 127.6, 56.9, 49.6, 36.7, 31.4, 26.4, 20.4; EI-MS (rel intensity) m/z 259 (20), 245 (17), 244 (100), 150 (94), 134 (19); EI-HRMS m/z calcd for $C_{15}H_{17}NOS$ 259.1031, found 259.1025. Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40; S, 12.36. Found: C, 69.36; H, 6.43; N, 5.33; S, 12.66.

*4.1.15. cis-5-Methyl-7-(phenylsulfonyl)-1,2,3,5,8,8a-hexahydro-3-indolizinone (**21**).* Using a procedure similar to that for the preparation of **15**, compound **20** (100 mg, 0.39 mmol) gave product **21** (80 mg, 71%) as a white solid: mp 130.4–131.4 °C; IR (ATR, film) 3054, 2987, 2927, 1727, 1604, 1551, 1422, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88–7.86 (2H, m), 7.69–7.55 (3H, m), 6.96 (1H, dd, J=3.0, 3.6 Hz), 4.33 (1H, br s), 3.45 (1H, ddq, J=2.4, 3.6, 6.6 Hz), 2.65 (1H, ddd, J=15.9, 3.6, 1.5 Hz), 2.40–2.31 (2H, m), 2.25–2.17 (1H, m), 2.11–2.01 (1H, m), 1.66–1.51 (1H, m), 1.57 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7, 139.6, 138.7, 136.9, 133.8, 129.5, 128.1, 55.8, 49.0, 31.2, 30.6, 26.2, 19.0; EI-MS (rel intensity) m/z 291 (M^+, 8), 276 (50), 150 (100), 125 (60), 84 (37), 67 (16), 17 (19); EI-HRMS m/z calcd for $C_{15}H_{17}NO_3S$ 291.0929, found 291.0932.

*4.1.16. cis-5-Methyl-1,2,3,5,8,8a-hexahydro-3-indolizinone (**22**).* To a solution of compound **21** (40 mg, 0.14 mmol) in dried THF (4 mL) was added 6% sodium amalgam (1.4 mmol) and two drops of concentrated phosphoric acid. The mixture was heated at reflux for 4 h. Upon cooling the mixture was filtered through Celite, rinsed with ethyl acetate, and evaporated under vacuum. The residue was purified by flash chromatography using ethyl acetate/hexanes (1:2 to 1:1) to give product **22** (9 mg, 46%) as a colorless

liquid: IR (ATR, film) 2985, 2936, 1681, 1651, 1457, 1409, 1377, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.79 (1H, ddt, J=9.9, 6.6, 1.5 Hz), 5.66 (1H, dt, J=9.9, 3.3 Hz), 4.11 (1H, br m), 3.50 (1H, ddq, J=2.1, 3.9, 6.0 Hz), 2.38–2.29 (3H, m), 2.22–2.16 (1H, m), 2.06–1.96 (1H, m), 1.66–1.51 (1H, m), 1.46 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.2, 131.1, 122.8, 55.8, 48.7, 32.1, 31.3, 26.9, 20.5; EI-MS (rel intensity) m/z 151 (M^+, 54), 138 (28), 136 (100), 108 (50), 96 (21), 84 (43), 68 (29), 67 (21); EI-HRMS m/z calcd for $C_9H_{13}NO$ 151.0997, found 151.0991.

*4.1.17. cis-5-Methyl-1,2,3,5,8,8a-hexahydro-3,7-indolizinedione (**23**).* To a solution of compound **20** (50 mg, 0.19 mmol) in 95% EtOH (4 mL) was added dropwise a 50% HBr (3 mL). The mixture was heated at 70 °C under nitrogen for 2 h. The solvent and excess HBr solution were removed under vacuum, and saturated sodium bicarbonate was slowly added. The solution was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate as eluent to give product **23** (30 mg, 93%) as a white solid: mp 91.2–92.2 °C; IR (ATR, film) 2986, 2873, 2904, 2832, 1723, 1683, 1457, 1417, 1377, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.25–4.09 (2H, m), 2.84 (1H, dd, J=15.9, 6.6 Hz), 2.75 (1H, dd, J=18.3, 3.6 Hz), 2.49–2.26 (5H, m), 1.64 (1H, m), 1.32 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.0, 174.1, 54.6, 46.7, 44.9, 44.8, 31.4, 27.3, 21.9; FABMS (rel intensity) m/z 168 (M^++H, 37), 166 (10), 102 (100), 84 (10); FAB-HRMS m/z calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0947.

*4.1.18. cis-5-Methyl-1,2,3,5,6,7,8,8a-octahydro-3-indolizinone (**24**).* A mixture of compound **20** (50 mg, 0.19 mmol) and a W-2 Ra-Ni (198 mg) in 95% EtOH (3 mL) was heated at reflux under nitrogen for 4 h. The solid was filtered off with Celite, washed with methanol, and the solvent was evaporated under vacuum in an ice bath. The crude product was purified by flash chromatography using ethyl acetate/hexanes (1:2 to 1:1) as eluent to give product **24** (19 mg, 63%) as a colorless liquid. The spectral data were identical with the literature report:[22] IR (ATR, film) 2987, 1638, 1422, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.33–3.27 (2H, m), 2.35–2.28 (2H, m), 2.17–2.05 (1H, m), 1.87–1.79 (2H, m), 1.70–1.60 (4H, m), 1.58–1.18 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7, 59.4, 52.6, 33.9, 32.7, 32.0, 25.7, 23.0, 20.0; EI-MS (rel intensity) m/z 138 (15), 124 (15), 110 (100), 104 (25), 91 (26), 84 (24), 55 (15), 41 (16); EI-HRMS m/z calcd for $C_9H_{15}NO$ 153.1154, found 153.1151.

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