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New synthesis and reactions of indolizidine 167E and indolizidine derivatives

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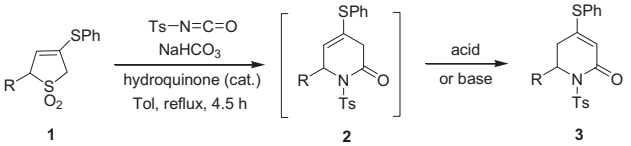
ABSTRACT

Two new methods of synthesizing indolizidines via ring-closing metathesis (RCM) have been developed. One method utilizes an alkene-isomerization, and the other method uses N-vinylation of an amide as the key step. Indolizidine 167E and many derivatives have also been synthesized.

1. Introduction

The piperidine ring is among the most abundant molecular fragments in both natural and synthetic compounds with various biological activities.[1] The aza-Diels–Alder reaction is one of the most versatile routes to substituted piperidines.[2] In general, the use of strongly electron-deficient imines is a prerequisite. We have reported a new aza-Diels–Alder reaction of thio-substituted 3-sulfolenes (**1**) with *p*-toluenesulfonyl isocyanate (PTSI) to give the cyclized products **2**, which upon treatment with acid or base afford the conjugated products **3** (Scheme 1).[3] We have also used this method to prepare some indolizidines and quinolizidines,[4] which are important framework of many natural products.[5] We now report some new synthetic transformations of indolizidines as well as two new methods of synthesizing indolizidines via ring-closing metathesis (RCM).[6] There are only a few examples in the literature for making indolizidines via RCM of piperidine derivatives.[7]



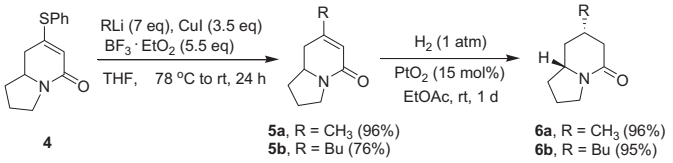
1 2 3

Scheme 1.

2. Results and discussion

2.1. Reactions of indolizidines

The thio-substituted indolizidine **4**[4b] could be converted to the alkyl-substituted compounds **5a**[4f] and **5b** by treatment with an organocopper reagent[8] in the presence of boron trifluoride etherate. Catalytic hydrogenation of compounds **5** was efficiently carried out to give products **6** (Scheme 2). Compound **6a** is identical with the literature report,[9] and compound **6b** has similar spectral data as compound **6a**. Thus, hydrogenation of indolizidines **5** occurs preferentially from the less hindered *exo* face.



4

5a, R = CH_3 (96%)
5b, R = Bu (76%)

6a, R = CH_3 (96%)
6b, R = Bu (95%)

Scheme 2.

Compound **4** was oxidized by *m*CPBA to the sulfone **7**. Further treatment with 5% sodium amalgam gave indolizidine **8** (Scheme 3), which had been prepared by a different route in the literature.[10]

Compound **8** underwent conjugate addition with an organocopper reagent in the presence of boron trifluoride etherate to give products **9a** and **9b** in good yield (Scheme 4). Diastereomeric pairs **6a**/**9a**, and **6b**/**9b** have distinctive ^{13}C NMR absorptions especially at

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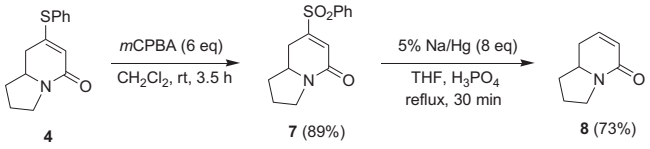
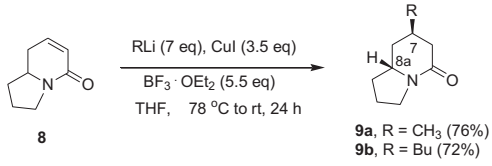


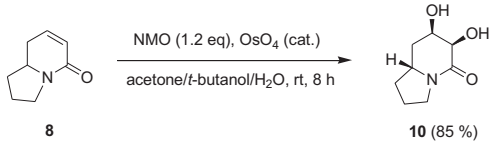
Scheme 3.

C-7 and C-8a (Experimental section). Thus, we can stereoselectively synthesize both the *cis*- and *trans*-7,8a-disubstituted indolizidinones **6** and **9**, respectively. The stereospecific formation of products **9** from compound **8** is probably due to both steric (from the less hindered convex side) and stereoelectronic (axial attack) effects.



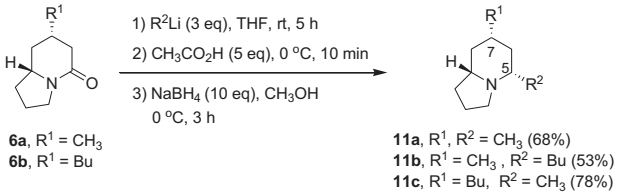
Scheme 4.

Following the literature method of using *N*-methylmorpholine oxide (NMO) and a catalytic amount of OsO_4 for dihydroxylation of alkenes,[11] compound **8** was converted to the *cis*-diol **10** (Scheme 5). The stereochemistry of compound **10** was determined by the NOESY spectrum. This also agrees with the expectation that the dihydroxylation occurs from the less hindered *exo* face of compound **8**.



Scheme 5.

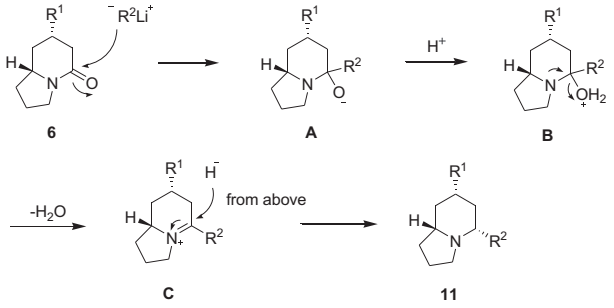
The reaction of compounds **6a** and **6b** with an alkyllithium reagent, followed by sequential treatment with acetic acid and methanolic $NaBH_4$, provided (±)-8a-*epi*-dendroprimine (**11a**) and *cis*-5,7-disubstituted indolizidines **11b** and **11c**, respectively (Scheme 6). The spectral data of compound **11a** is identical with the literature report,[9a,12] and those of compounds **11b** and **11c** are also consistent with the literature trends.[13]



Scheme 6.

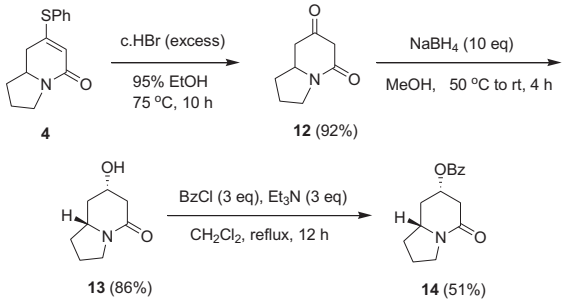
The stereoselective formation of products **11** from compounds **6** can be explained as in Scheme 7. The organolithium reagent attacks the amide **6** to form the intermediate **A**, which upon treatment with an acid would give the intermediate **B**. Further dehydration generates the iminium ion **C**, which is then attacked by the hydride from the less hindered convex side to give products **11**.

Treatment of compound **4** with hot concentrated HBr hydrolyzed the vinyl sulfide group to provide the ketone product **12**. Further reduction with $NaBH_4$ afforded the alcohol **13** (Scheme 8), the stereochemistry of which was determined from the X-ray



Scheme 7.

structure of its benzoate **14** (Fig. 1).[14] Thus, the hydride attacks the ketone **13** from the less hindered *exo* face.



Scheme 8.

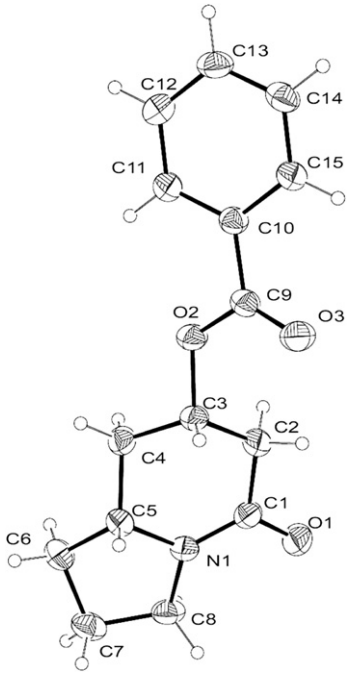
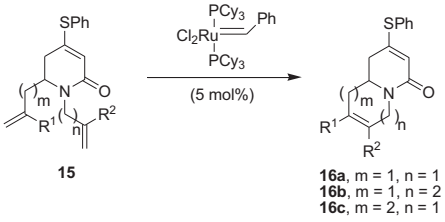


Fig. 1. X-ray crystal structure of compound **14**.

2.2. New synthesis of indolizidines via RCM

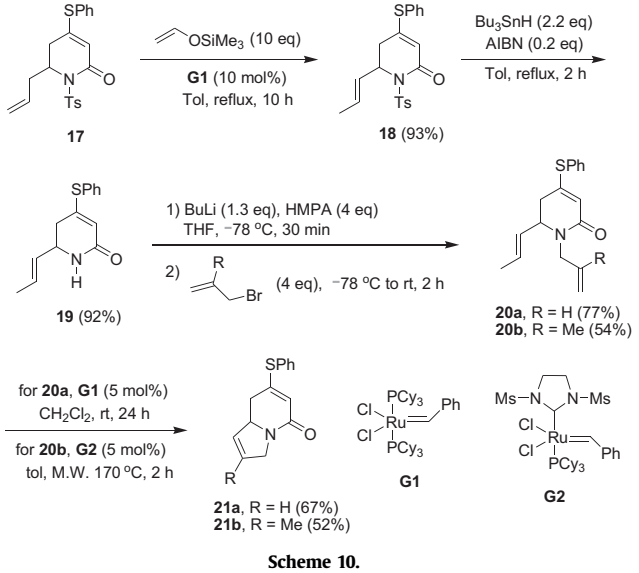
Although we were successful in synthesizing the quinolizidines **16a** and pyridoazepines **16b**,**c** from the piperidines **15** via ring-closing metathesis (RCM) (Scheme 9),[4c] the corresponding indolizidine structures (**16**, m=1, n=0; or m=0, n=1) could not be made because

our methodology could not provide the piperidines **15** with m=0 or n=0. We now report two new methods of synthesizing indolizidines from structurally modified piperidines **15** (m=0 or n=0).



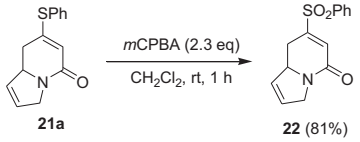
Scheme 9.

Our synthesis of new sulfur-substituted indolizidines **21** is shown in Scheme 10. Following a literature method,[15a] treatment of the allyl-substituted dihydropyridone **17**[3b] with vinyloxytrimethylsilane in the presence of Grubbs' catalyst (**G1**) in refluxing toluene gave the 1-propenyl-substituted product **18** in excellent yield. We propose that under the reaction conditions a ruthenium hydride complex is first generated,[15b] which then undergoes an insertion reaction with the terminal double bond of compound **17**. Subsequent β-hydride elimination would then give the alkene-isomerized product **18**. Compound **18** was detosylated by Parson's method[16] of Bu_3SnH/AIBN to give the amide **19**. Treatment of compound **19** with BuLi at low temperature, followed by reactions with allylic bromides in the presence of HMPA, gave the *N*-allylated products **20a** and **20b**. It was found that compound **20a** reacted with Grubbs' catalyst **G1** at room temperature to yield the indolizidine product **21a**. However, the RCM reaction of the methyl-substituted compound **20b** required the use of Grubbs' catalyst **G2** at higher temperatures; the best reaction condition was to use microwave heating at 170 °C.



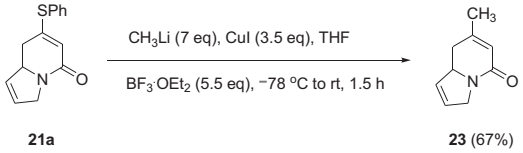
Scheme 10.

We have also carried out some functional group transformations of indolizidine **21a**. Treatment of compound **21a** with *m*CPBA gave the sulfone **22** in good yield (Scheme 11). Further reaction of compound **22** with additional 2.3 equiv of *m*CPBA did not oxidize the C=C bond. Presumably, the ring strain of the expected epoxide product would disfavor its formation.



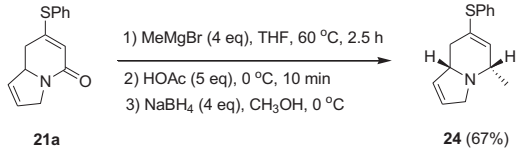
Scheme 11.

Reaction of compound **21a** with CH_3Li/CuI (2:1) with the activation[17] of $BF_3{\cdot}OEt_2$ led to a good yield of the methyl-substituted product **23** (Scheme 12). It should be emphasized that, without the $BF_3{\cdot}OEt_2$ or with insufficient amounts of $BF_3{\cdot}OEt_2$, this reaction did not proceed at all or gave very low yields of the product **23**.



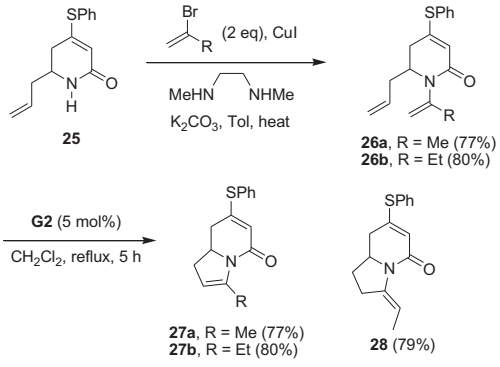
Scheme 12.

Following a reported procedure,[18] treatment of compound **21a** with methylmagnesium bromide, followed by sequential acidification with acetic acid and reduction with sodium borohydride, gave stereospecifically the cis product **24** (Scheme 13). Its stereochemistry was confirmed by NOESY spectrum.



Scheme 13.

Our second new method of constructing the indolizidine skeleton via RCM is shown in Scheme 14. Modifying the literature reaction conditions,[19] amide **25**[3b] underwent N-vinylation with vinyl bromides in the presence of CuI (1 or 2 equiv), base (K_2CO_3 or Cs_2CO_3) and *N*,*N*′-dimethylethylenediamine (1 or 2 equiv) to give the substitution products **26** in fair to excellent yields. The RCM was efficiently carried out with Grubbs' catalyst **G2** in refluxing CH_2Cl_2 to afford the indolizidines **27a** and **27b**. It should be noted that if the RCM of compound **26b** was carried out with the **G2** catalyst in toluene in a sealed tube at 120 °C, the exocyclic alkene **28** was obtained instead of compound **27b**. This is probably because



Scheme 14.

compound **27b** is more strained than compound **28**, and at higher temperature the RCM reaction is reversible to give the more stable product **28**. The X-ray crystal structure of compound **28** (Fig. 2)[14] shows the *E* configuration of the exocyclic double bond. Compound **27b** as compared to compound **28** is quite easily hydrolyzed by aqueous acid. Thus, we would use compound **28** for further synthetic transformations.

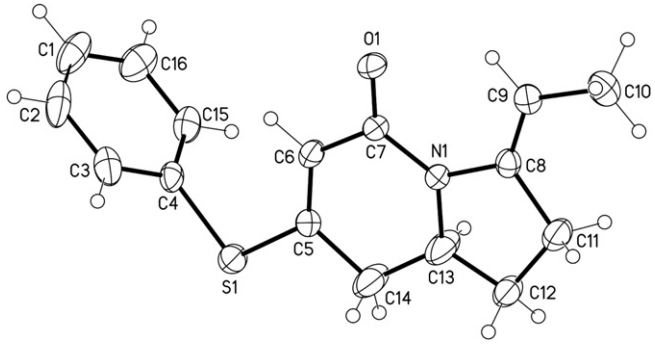
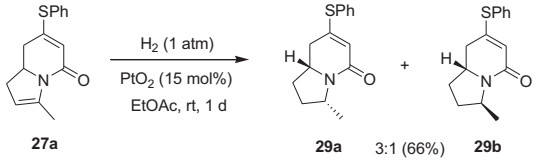


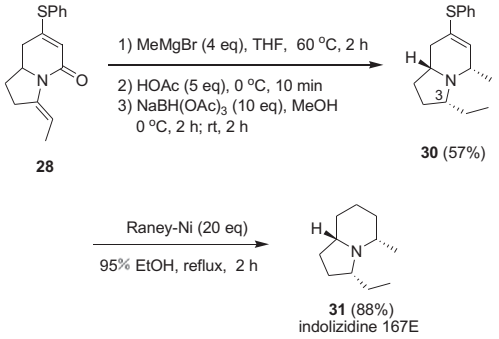
Fig. 2. X-ray crystal structure of compound **28**.

Catalytic hydrogenation of compound **27a** gave a mixture of *cis* and *trans* isomers, **29a** and **29b** in a ratio of 3:1 (Scheme 15). This stereoselectivity is probably due to steric effect. Previously, we reported that mercuric ion promoted the intramolecular cyclization of a secondary amide with the alkene side chain to give a 1:1 mixture of **29a** and **29b**.[4a] Thus, we can now slightly improve the stereoselectivity of the indolizidine formation.



Scheme 15.

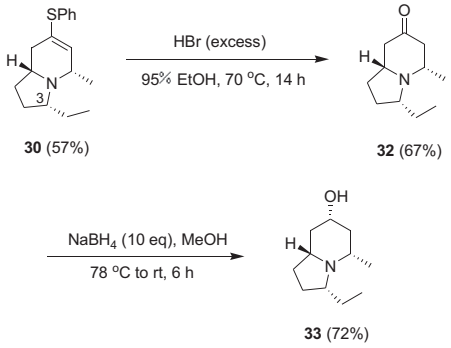
The reaction of compound **28** with methylmagnesium bromide, followed by sequential treatment with acetic acid and methanolic $NaBH(OAc)_3$, led to product **30** (Scheme 16), the stereochemistry of which was proven by its further reaction with Raney nickel to give compound **31**, indolizidine 167E. If $NaBH_4$ or $NaCNBH_3$ were used as



Scheme 16.

the reducing agent, a C-3 epimer would also be obtained. Indolizidine 167E was isolated from the venom of the ant *Solenopsis conjurata*,[20] and has only been synthesized twice before.[21] We have recently reported a tandem cross metathesis and intramolecular aza-Michael reaction to synthesize indolizidine 167E.[22]

Treatment of compound **30** with hot concentrated HBr hydrolyzed the vinyl sulfide group to provide the ketone product **32**. Further reduction with $NaBH_4$ afforded the alcohol **32** (Scheme 17), the stereochemistry of which was proven by X-ray crystallography (Fig. 3).[14] Thus, the hydride attacks the ketone **32** from the less hindered *exo* face. Since the structure of compound **33** has now been established by X-ray crystallography, the structure of indolizidine 167E (Scheme 16) is further confirmed other than by the spectroscopic method provided in the literature.[20]



Scheme 17.

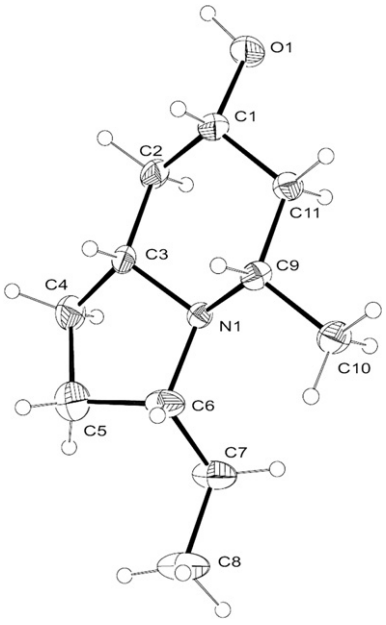


Fig. 3. X-ray crystal structure of compound **33**.

3. Conclusions

We have extended our previously developed method of aza-Diels–Alder reaction to construct new indolizidine structures. We have also established two new methods of synthesizing indolizidines via ring-closing metathesis (RCM). One method utilizes an alkene-isomerization of compound **17** to compound **18**, and the other method uses N-vinylation of amide **25** as the key step. Stereoselective synthesis of indolizidine 167E (**31**) and many derivatives have been achieved.

4. Experimental section

4.1. General

Melting points were determined with a SMP3 melting apparatus. ^{1}H 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) from the internal reference standard tetramethylsilane (TMS), 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. 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 60 H silica gel. The microwave reactions were carried out with a CEM Focused™ Discover-S system.

4.2. General procedure for the $BF_3{\cdot}OEt_2$-promoted cuprate addition reactions

*4.2.1. 7-Butyl-1,2,3,5,8,8a-hexahydro-5-indolizinone (**5b**).* To a mixture of CuI (407 mg, 2.13 mmol) in THF (1.5 mL) at 0 °C was added dropwise a solution of BuLi (2.5 M in THF, 1.71 mL, 4.28 mmol). After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C, and $BF_3{\cdot}OEt_2$ (0.43 mL, 3.36 mmol) was added and stirred for 5 min. Then a solution of compound **4** (150 mg, 0.61 mmol) in THF (1.5 mL), precooled at −78 °C, was added dropwise. The reaction mixture was slowly warmed to room temperature, stirred for another 24 h, and quenched with saturated ammonium chloride. The aqueous solution was extracted with CH_2Cl_2, combined with the organic layer, dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:4–1:2) as eluent to give product **5b** (89 mg, 76%) as a yellow oil: IR (neat) ν 3053, 2959, 2932, 2874, 1658, 1606, 1455, 1265, 895, 867, 736, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.22 (1H, s), 3.77–3.58 (2H, m), 3.50–3.47 (1H, m), 2.40–2.29 (1H, dd, J=16.8, 5.1 Hz), 2.25–2.15 (3H, m), 2.12–1.95 (1H, m), 1.90–1.70 (1H, m), 1.70–1.50 (1H, m), 1.49–1.20 (5H, m), 0.95–0.85 (3H, m); ^{13}C NMR ($CDCl_3$) δ 164.3, 153.8, 119.9, 56.5, 43.8, 36.1, 34.5, 33.4, 28.9, 22.9, 22.2, 13.7; EI-MS (rel intensity) m/z 193 (M^+, 83), 193 (83), 192 (43), 150 (20), 96 (22), 82 (100), 70 (75); EI-HRMS calcd for $C_{12}H_{19}NO$ m/z 193.1467 (M^+), found 193.1468.

*4.2.2. trans-7-Methyl-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (**9a**).* Yellow oil: IR (neat) ν 3054, 2986, 1625, 1550, 1421, 1264, 896 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.70–3.40 (3H, m), 2.45 (1H, dd, J=17.4, 6.3 Hz), 2.30–2.20 (1H, m), 2.19–2.04 (2H, m), 2.03–1.72 (3H, m), 1.55–1.35 (2H, m), 1.05 (3H, d, J=6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 169.3, 54.4, 44.7, 38.5, 34.9, 33.6, 25.8, 22.3, 20.0; EI-MS (rel intensity) m/z 153 (M^+, 23), 138 (60), 86 (22), 84 (40), 83 (42), 49 (28); EI-HRMS calcd for $C_9H_{15}NO$ m/z 153.1154 (M^+), found m/z 153.1153.

*4.2.3. trans-7-Butyl-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (**9b**).* Yellow oil: IR (neat) ν 2955, 2926, 2859, 2622, 1456, 1057 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.71–3.58 (1H, m), 3.58–3.37 (2H, m), 2.44 (1H, dd, J=17.4, 6.3 Hz), 2.19 (1H, d, J=17.4 Hz), 2.11–2.05 (1H, m), 2.05–1.92 (2H, m), 1.88–1.70 (2H, m), 1.50–1.30 (8H, m), 0.93–0.88 (3H, m); ^{13}C NMR ($CDCl_3$) δ 169.5, 54.6, 44.7, 37.1, 33.8, 33.7, 33.2, 31.0, 29.7, 22.8, 22.3, 14.1; EI-MS (rel intensity) m/z 195 (M^+, 59), 194 (55), 139 (22), 138 (74), 111 (38), 83 (91), 82 (24), 70 (100), 55 (27); EI-HRMS calcd for $C_{12}H_{21}NO$ m/z 195.1623 (M^+), found 195.1617.

*4.2.4. 7-Methyl-3,5,8,8a-tetrahydro-5-indolizinone (**23**).* Colorless oil: IR (neat) ν 3075, 2985, 2942, 2909,1667, 1609, 1445, 1372, 1264, 1228, 1217, 908, 730, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.96 (1H, dq, J=6.3, 2.1 Hz), 5.81 (2H, dq, J=6.3, 2.1 Hz), 5.78 (1H, d, J=1.5 Hz), 4.70–4.57 (1H, m), 4.41 (1H, ddt, J=16.5, 4.8, 2.4 Hz), 4.15 (1H, ddt, J=16.5, 3.6, 2.4 Hz), 2.36–2.24 (1H, m), 1.93 (3H, s); ^{13}C NMR ($CDCl_3$) δ 163.1, 149.3, 128.9, 127.4, 121.3, 62.2, 51.4, 35.1, 22.9; EI-MS (rel intensity) m/z 149 (M^+, 89), 148 (50), 82 (100), 68 (50), 54 (24), 39 (32), 17 (32); EI-HRMS calcd for $C_9H_{11}NO$ m/z 149.0841 (M^+), found 149.0841.

4.3. *cis*-7-Methyl-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (6a)

To a solution of compound **5a** (54.2 mg, 0.358 mmol) in ethyl acetate (2 mL) in an Erlenmyer flask was added PtO_2 (12.0 mg). A hydrogen balloon was attached to the flask through a needle. The reaction mixture was vigorously stirred for 1 d, and more ethyl acetate was added to filter the reaction mixture through Celite. The filtrate was dried ($MgSO_4$) and concentrated to give pure product **6a** (52.5 mg, 96%) as a colorless oil: IR (neat) ν 2955, 1619, 1455, 1413, 1324, 920, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.62–3.50 (1H, m), 3.50–3.38 (2H, m), 2.50 (1H, d, J=15.3 Hz), 2.15–2.00 (2H, m), 2.00–1.70 (4H, m), 1.52–1.35 (1H, m), 1.15–0.95 (4H, m); ^{13}C NMR ($CDCl_3$) δ 168.8, 58.9, 44.4, 39.6, 37.4, 33.1, 28.3, 22.1, 21.4; EI-MS (rel intensity) m/z 153 (M^+, 99), 152 (70), 111 (31), 83 (95), 70 (55), 41 (22); EI-HRMS calcd for $C_9H_{15}NO$ m/z 153.1154 (M^+), found 153.1149.

4.4. *cis*-7-Butyl-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (6b)

A similar procedure as for compound **6a** was used. Starting from compound **5b** (89.0 mg, 0.46 mmol), product **6b** (84.9 mg, 95%) was obtained as a colorless oil: IR (neat) ν 2854, 1621, 1455, 1412, 1377, 1339, 755, 726, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.65–3.51 (1H, m), 3.50–3.35 (2H, m), 2.53 (1H, dd, J=16.5, 4.2 Hz), 2.15–2.02 (2H, m), 2.02–1.80 (2H, m), 1.80–1.70 (2H, m), 1.50–1.35 (1H, m), 1.35–1.22 (6H, m), 1.05–0.85 (4H, m); ^{13}C NMR ($CDCl_3$) δ 169.2, 59.1, 44.7, 38.2, 36.1, 35.7, 33.5, 33.5, 28.9, 22.8, 22.4, 14.1; EI-MS (rel intensity) m/z 195 (M^+, 76), 194 (55), 139 (28), 138 (100), 111 (39), 83 (81), 70 (93), 55 (24), 41 (26), 18 (23); EI-HRMS calcd for $C_{12}H_{21}NO$ m/z 195.1623 (M^+), found 195.1626.

4.5. 7-(Phenylsulfonyl)-1,2,3,5,8,8a-hexahydro-5-indolizinone (7)

To a solution of compound **4** (150 mg, 0.61 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added a solution of *m*CPBA (1.27 g, 50% in H_2O, 3.67 mmol) in CH_2Cl_2 (3 mL) in small portions. The reaction mixture was stirred at room temperature for 3.5 h, and saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ were added sequentially. The mixture was then extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:2–1:1) as eluent to give product **7** (143 mg, 85%) as a white solid: mp 96–97 °C (recryst from ethyl acetate/hexane); IR (film) 3054, 2976, 2893, 1657, 1611, 1446, 1308, 1153, 1082, 1019, 741, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.83–7.80 (2H, m), 7.65–7.60 (1H, m), 7.54–7.50 (2H, m), 6.64 (1H, d, J=3.0 Hz), 3.74–3.62 (1H, m), 3.58–3.50 (1H, m), 3.39–3.30 (1H, m), 2.78 (1H, dd, J=16.8, 5.0 Hz), 2.21–2.04 (2H, m), 2.01–1.92 (1H, m), 1.83–1.68 (1H, m), 1.61–1.47 (1H, m); ^{13}C NMR ($CDCl_3$) δ 160.6, 149.4, 137.5, 134.4, 129.6, 129.4, 128.5, 56.9, 44.2, 33.0, 28.7, 22.9; FAB-MS (rel intensity) m/z 278 (M^++H, 100), 154 (62), 149 (24), 147 (25), 137 (40), 136 (63), 91 (25), 73 (100), 69 (28), 55 (24); FAB-HRMS calcd for $C_{14}H_{16}NO_3S$ m/z 278.0851 (M^++H), found 278.0859. Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.37; H, 5.46; N, 4.83.

4.6. 1,2,3,5,8,8a-Hexahydro-5-indolizinone (8)

To a solution of compound **7** (25 mg, 0.09 mmol) in dried THF (3 mL) was added 5% sodium amalgam (349 mg, 0.72 mmol) and two drops of concentrated phosphoric acid. The mixture was heated under nitrogen at 80 °C for 30 min. Upon cooling the mixture was filtered through Celite, rinsed with THF, and evaporated under vacuum. The residue was purified by flash chromatography using ethyl acetate/hexane (1:1–2:1) to give product **8** (9.0 mg, 73%) as a colorless liquid. Its ^{1}H NMR and ^{13}C NMR data were identical with the literature report.[10]

4.7. (6*R**,7*R**,8a*R**)-6,7-Dihydroxy-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (10)

To a solution of compound **8** (36 mg, 0.26 mmol) in *t*-BuOH (1 mL), acetone (1 mL), and H_2O (0.1 mL) was added *N*-methylmorpholine oxide (53 mg, 0.39 mmol). Then a solution of OsO_4 (2.5% in *tert*-butanol, three drops, 3.84×10^{-3} mmol) was added, and stirred at room temperature for 8 h. The reaction mixture was quenched with 10% aqueous $NaHSO_3$, stirred for 1 h, and then extracted with CH_2Cl_2 (10 mL×3). The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using ethyl acetate as eluent to give product **10** (38.0 mg, 85%) as a colorless oil: IR (neat) ν 3397, 2968, 2887, 1622, 1481, 1130, 1101, 1060, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.35–4.30 (1H, m), 4.09 (1H, s, OH), 4.01–3.94 (1H, m), 3.91–3.78 (1H, m), 3.60–3.40 (2H, m), 3.05 (1H, s, OH), 2.40 (1H, dt, *J*=14.1, 4.2 Hz), 2.12–1.95 (2H, m), 1.95–1.77 (1H, m), 1.65–1.40 (2H, m); ^{13}C NMR ($CDCl_3$) δ 169.1, 70.4, 66.1, 54.8, 44.1, 32.8, 32.4, 22.6; ESI-MS (rel intensity) *m*/*z* 194 (M^++Na, 100), 172 (M^++H, 22), 140 (18), 136 (38); ESI-HRMS calcd for $C_8H_{14}NO_3$ *m*/*z* 172.0973 (M^++H), found 172.0961.

4.8. General procedure for the reaction of amides with an organometallic reagent followed by reduction

To a solution of compound **6a** (33.3 mg, 0.22 mmol) in THF (3 mL) at room temperature was added slowly another solution of MeLi (2.2 M in hexane, 0.30 mL, 0.66 mmol). The reaction mixture was stirred at room temperature for 5 h, and then cooled in an ice bath. Acetic acid (0.06 mL, 1.1 mmol) was then added dropwise. The mixture was stirred for 10 min, and $NaBH_4$ (82.3 mg, 2.2 mmol) was added, followed by a dropwise addition of methanol (2 mL). After stirring for 3 h, the solvent was removed under vacuum, and saturated sodium bicarbonate was added. The mixture was extracted with ethyl acetate, dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1:4) as eluent to give the pure product.

4.8.1. (5S,7R*,8aR*)-5,7-Dimethyl-1,2,3,5,6,7,8,8a-octahydroindolizine (**11a**).* Colorless oil: IR (neat) ν 2962, 2926, 2873, 2793, 2698, 1457, 1375, 1265, 739, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.25 (1H, td, *J*=8.4, 2.1 Hz), 2.10–1.40 (11H, m), 1.10 (3H, d, *J*=6.3 Hz), 1.05–0.85 (4H, m); ^{13}C NMR ($CDCl_3$) δ 64.8, 58.2, 51.4, 43.1, 39.4, 31.4, 30.4, 22.0, 21.0, 20.8; EI-MS (rel intensity) *m*/*z* 153 (M^+, 44), 152 (47), 138 (100), 119 (31), 105 (31), 91 (34), 70 (34), 55 (35), 43 (37), 41 (40); EI-HRMS calcd for $C_{10}H_{19}N$ *m*/*z* 153.1517 (M^+), found 153.1513.

4.8.2. (5S,7R*,8aR*)-5-Butyl-7-methyl-1,2,3,5,6,7,8,8a-octahydroindolizine (**11b**).* Colorless oil: IR (neat) ν 2955, 2927, 2871, 1457, 1422, 1377, 1265, 1183, 1132, 1107, 1081, 1032, 895, 739, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.25 (1H, td, *J*=8.4, 1.5 Hz), 2.00–1.60 (9H, m), 1.50–1.20 (8H, m), 0.97–0.85 (7H, m); ^{13}C NMR ($CDCl_3$) δ 64.9, 63.1, 51.3, 39.9, 39.7, 34.4, 31.4, 30.5, 28.2, 23.2, 22.2, 20.9, 14.2; FAB-MS (rel intensity) *m*/*z* 196 (M^++H, 23), 138 (47), 138 (47), 95 (47), 91 (30), 83 (39), 81 (56), 71 (31), 69 (79), 67 (45), 57 (66), 55 (100), 43 (70), 41 (73); FAB-HRMS calcd for $C_{13}H_{25}N$ *m*/*z* 195.1987 (M^+), found 195.1986.

4.8.3. (5S,7R*,8aR*)-7-Butyl-5-methyl-1,2,3,5,6,7,8,8a-octahydroindolizine (**11c**).* Colorless oil: IR (neat) ν 3054, 2986, 1421, 1265, 896, 738, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.22 (1H, td, *J*=8.7, 1.8 Hz), 2.10–1.73 (6H, m), 1.73–1.60 (2H, m), 1.50–1.20 (8H, m), 1.10 (3H, d, *J*=6.3 Hz), 1.02–0.80 (5H, m); ^{13}C NMR ($CDCl_3$) δ 64.8, 58.3, 51.6, 41.3, 37.5, 36.5, 36.4, 30.5, 29.2, 23.0, 21.1, 20.8, 14.2; EI-MS (rel intensity) *m*/*z* 195 (M^+, 49), 194 (54), 180 (44), 138 (100), 83 (43), 70 (65), 55 (30); EI-HRMS calcd for $C_{13}H_{25}N$ *m*/*z* 195.1987 (M^+), found 195.1989.

*4.8.4. cis-5-Methyl-7-(phenylthio)-3,5,8,8a-tetrahydro-indolizidine (**24**).* Colorless oil: IR (neat) ν 3084, 2985, 2943, 2908, 1645, 1447, 1372, 1372, 1300, 1234, 1044, 847, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29–7.19 (5H, m), 5.95 (1H, dq, *J*=6.0, 1.5 Hz), 5.89 (1H, d, *J*=1.2 Hz), 5.81 (1H, dq, *J*=6.0, 1.5 Hz), 3.85 (1H, ddq, *J*=12.9, 4.5, 1.5 Hz), 3.36–3.33 (1H, m), 3.26–3.21 (1H, m), 3.08 (1H, ddq, *J*=12.9, 6.9, 1.5 Hz), 2.40–2.28 (2H, m), 1.21 (3H, d, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 136.2, 134.4, 131.7, 131.6, 131.0, 129.1, 128.8, 126.9, 65.9, 56.6, 56.1, 35.8, 20.1; EI-MS (rel intensity) *m*/*z* 243 (M^+, 8), 176 (20), 134 (100), 132 (27), 118 (32), 117 (35); EI-HRMS calcd for $C_{15}H_{17}NO$ *m*/*z* 243.1076 (M^+), found 243.1082.

4.8.5. (3R,5S*,8aR*)-3-Ethyl-5-methyl-7-(phenylthio)-1,2,3,5,8,8a-hexahydroindolizine (**30**).* Yellow oil: IR (neat) ν 3053, 2985, 2959, 2855, 1454, 1378, 1156, 1078, 1026, 739, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33–7.18 (5H, m), 5.71 (1H, d, *J*=1.2 Hz), 3.16–3.10 (1H, m), 2.60–2.44 (2H, m), 2.19–2.15 (2H, m), 1.91–1.85 (1H, m), 1.79–1.69 (2H, m), 1.56–1.28 (3H, m), 1.21 (3H, d, *J*=6.9 Hz), 0.85 (3H, t, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 136.4, 134.3, 131.0, 130.6, 129.0, 126.7, 65.3, 63.7, 59.9, 36.7, 31.7, 29.7, 29.2, 22.3, 11.1; ESI-MS (rel intensity) *m*/*z* 274 (M^++H, 39), 270 (100), 168 (21); ESI-HRMS calcd for $C_{17}H_{23}NS$ *m*/*z* 273.1551 (M^+), found 273.1541.

4.9. 7-Oxo-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (12)

To a solution of compound **4** (100 mg, 0.408 mmol) in 95% EtOH (10 mL) was added dropwise a 50% aqueous HBr (10 mL). The mixture was heated at 75 °C under nitrogen for 10 h. After cooling, the reaction was carefully quenched with saturated sodium bicarbonate. The solution was extracted with CH_2Cl_2 (30 mL×3), dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:1) as eluent to give product **12** (57.4 mg, 92%) as a colorless oil: IR (neat) ν 3054, 2979, 2884, 1726, 1654, 1449, 1266, 736, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.92–3.81 (1H, m), 3.70–3.50 (2H, m), 3.36–3.19 (2H, m), 2.85 (1H, dd, *J*=16.6, 3.3 Hz), 2.40–2.25 (2H, m), 2.15–2.01 (1H, m), 2.0–1.85 (1H, m), 1.78–1.60 (1H, m); ^{13}C NMR ($CDCl_3$) δ 204.2, 164.8, 54.3, 47.7, 45.5, 45.1, 33.5, 23.1; EI-MS (rel intensity) *m*/*z* 153 (M^+, 100), 83 (25), 70 (89); EI-HRMS calcd for $C_8H_{11}NO_2$ *m*/*z* 153.0790 (M^+), found 153.0793.

4.10. *cis*-7-Hydroxy-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (13)

To a solution of compound **12** (50 mg, 0.33 mmol) in methanol (5 mL) at −50 °C was added in one portion $NaBH_4$ (122 mg, 3.26 mmol). After stirring for 2 h, the solvent was evaporated under vacuum and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (10 mL×3), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography using ethyl acetate and then methanol as eluent to give product **13** (43.5 mg, 86%) as a yellow oil: IR (neat) ν 3390, 2953, 2923, 2877, 1614, 1474, 1324, 1049 cm^{-1}; ^{1}H NMR ($CDCl_3$)

δ 4.20–4.00 (1H, m), 3.72 (1H, s, OH), 3.60–3.45 (1H, m), 3.44–3.33 (2H, m), 2.80 (1H, dd, *J*=17.4, 6.0 Hz), 2.40–2.20 (2H, m), 2.15–2.05 (1H, m), 2.05–1.91 (1H, m), 1.88–1.71 (1H, m), 1.55–1.32 (2H, m); ^{13}C NMR ($CDCl_3$) δ 167.9, 65.5, 56.3, 44.5, 40.9, 38.4, 33.0, 22.4; ESI-MS *m*/*z* 178 (M^++Na), 156 (M^++H); ESI-HRMS calcd for $C_8H_{14}NO_2$ *m*/*z* 156.1024 (M^++H), found 156.1017.

4.11. *cis*-7-Benzoyloxy-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (14)

To a solution of compound **13** (10 mg, 6.4×10^{-2} mmol) in CH_2Cl_2 (2 mL) were added sequentially Et_3N (25 μL, 0.19 mmol) and benzoyl chloride (10 μL, 0.19 mmol). The mixture was refluxed for 12 h, and was poured into saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 (10 mL×3), and dried ($MgSO_4$). The solvent was evaporated and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:1) as eluent to give product **14** (8.6 mg, 51%) as a white solid: mp 142.5–143.5 °C (recryst from CH_2Cl_2/hexane); IR (film) ν 2978, 2886, 1714, 1638, 1451, 1284, 1113, 719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.05–8.00 (2H, m), 7.62–7.54 (1H, m), 7.49–7.42 (2H, m), 5.42–5.28 (1H, m), 3.68–3.42 (3H, m), 3.00 (1H, dd, *J*=17.4, 6.6 Hz), 2.68–2.47 (2H, m), 2.22–2.10 (1H, m), 2.10–1.95 (1H, m), 1.90–1.79 (1H, m), 1.65–1.48 (2H, m); ^{13}C NMR ($CDCl_3$) δ 166.6, 165.9, 133.3, 130.0, 129.7, 128.5, 68.4, 55.7, 44.7, 37.4, 35.2, 33.1, 22.5; EI-MS (rel intensity) *m*/*z* 259 (M^+, 67), 138 (21), 137 (100), 136 (66), 109 (40), 105 (100), 83 (43), 77 (65), 70 (57), EI-HRMS calcd for $C_{15}H_{17}NO_3$ *m*/*z* 259.1208 (M^+), found 259.1211. Crystallographic data: $C_{15}H_{17}NO_3$, formula weight=259.30, temperature=293(2) K, wavelength=0.71073 Å, crystal system=triclinic, space group=*P* −1, *a*=7.8489(3) Å, *b*=9.1149(3) Å, *c*=10.2047(4) Å, α=93.142(2)°, β=108.134(2)°, γ=105.880(3)°, volume=659.45(4) $Å^3$, *Z*=2, density (calculated)=1.306 Mg/m^3, absorption coefficient=0.091 mm^{-1}, *F*(000)=276, crystal size=0.78×0.62×0.4 mm^3, theta range for data collection=2.13–25.02°, index ranges: $-9\le h\le 9$, $-10\le k\le 10$, $-10\le l\le 12$, reflections collected=4112, independent reflections=2267 [*R*(int)=0.0559], completeness to theta=25.02° (97.2%), absorption correction: multi-scan, refinement method: full-matrix least-squares on F^2, data/restraints/parameters=2267/0/172, goodness-of-fit on F^2=1.031, final *R* indices: [*I*>2sigma(*I*)] *R*1=0.0495, *wR*2=0.1307, *R* indices (all data) *R*1=0.0684, *wR*2=0.1462, largest diff. peak and hole=0.215 and −0.298 e $Å^{-3}$.

4.12. 4-(Phenylthio)-6-(*E*-1-propenyl)-1-(toluenesulfonyl)-1,2,5,6-tetrahydro-2-pyridinone (18)

To a solution of compound **17**[3b] (250 mg, 0.63 mmol) in toluene (5 mL) was added vinyloxytrimethylsilane (0.94 mL, 6.30 mmol) and **G1** (25.0 mg, 0.03 mmol). The mixture was heated at reflux for 5 h, and another portion of **G1** (25.0 mg, 0.03 mmol) was added and refluxed for an additional 5 h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:6) as eluent to give product **18** (232 mg, 93%) as a yellow solid: mp 126–127 °C (recryst from ethyl acetate/hexane); IR (film) ν 3081, 2872, 1638, 1612, 1574, 1438, 1425, 1357, 1307, 1212, 1102, 1009, 854, 834, 751, 699, 688, 653 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85 (2H, d, *J*=8.4 Hz), 7.49–7.38 (5H, m), 7.22 (2H, d, *J*=8.4 Hz), 5.78 (1H, ddq, *J*=13.8, 0.6, 6.3 Hz), 5.50 (1H, ddq, *J*=13.8, 7.5, 1.5 Hz), 5.29 (1H, t, *J*=6.6 Hz), 5.17 (1H, d, *J*=2.4 Hz), 3.12 (1H, ddd, *J*=17.6, 6.3, 2.4 Hz), 2.40 (1H, dd, *J*=17.6, 1.8 Hz), 2.38 (3H, s), 1.69 (3H, dd, *J*=6.3, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 161.0, 157.4, 144.4, 136.4, 135.2, 130.33, 130.27, 129.9, 129.3, 128.8, 127.6, 127.3, 113.9, 56.5, 35.5, 21.6, 17.5; FAB-MS (rel intensity) *m*/*z* 400 (M^++H, 100), 229 (66), 155 (23), 91 (62), 77 (23), 73 (22), 42 (22); FAB-HRMS calcd for $C_{21}H_{22}NO_3S_2$ *m*/*z* 400.0963 (M^++H), found 400.0956. Anal. Calcd for $C_{21}H_{21}NO_3S_2$: C, 63.13; H, 5.30. Found: C, 63.18; H, 5.41.

4.13. 4-(Phenylthio)-6-(*E*-1-propenyl)-1,2,5,6-tetrahydro-2-pyridinone (19)

To a solution of compound **18** (570 mg, 1.43 mmol) in degassed toluene (15 mL) at reflux was added dropwise another solution of Bu_3SnH (0.84 mL, 3.58 mmol) and AIBN (47 mg, 0.29 mmol) in toluene (34 mL). The mixture was refluxed for 2 h, and the solvent was removed under vacuum. The crude product was purified by flash chromatography on silica gel prewashed with Et_3N using ethyl acetate/hexane (1:4–1:1) as eluent to give product **19** (323 mg, 92%) as a white solid: mp 139–140 °C (recryst from EA/hexane); IR (film) ν 3070, 2938, 2850, 1645, 1587, 1473, 1393, 1328, 1295, 1217, 1130, 1067, 966, 936, 851, 822, 778, 753, 691, 656 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50–7.39 (5H, m), 5.72 (1H, ddq, *J*=15.3, 0.6, 6.6 Hz), 5.45 (1H, ddq, *J*=15.3, 7.5, 1.5 Hz), 5.38 (1H, s), 5.27 (1H, d, *J*=1.8 Hz), 4.09 (1H, q, *J*=7.5 Hz), 2.48–2.45 (2H, m), 1.74–1.68 (3H, m); ^{13}C NMR ($CDCl_3$) δ 165.8, 154.4, 135.3, 129.9, 129.8, 129.7, 129.0, 128.2, 114.4, 53.3, 35.2, 17.6; EI-MS (rel intensity) *m*/*z* 245 (M^+, 59), 244 (39), 243 (40), 242 (42), 230 (34), 204 (65), 176 (84), 148 (41), 147 (49), 136 (60), 110 (54), 109 (46), 108 (38), 91 (68), 77 (55), 67 (100), 65 (37); EI-HRMS calcd for $C_{14}H_{15}NOS$ *m*/*z* 245.0874 (M^+), found 245.0872. Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.13; H, 6.12; N, 5.36.

4.14. 1-Allyl-4-(phenylthio)-6-(*E*-1-propenyl)-1,2,5,6-tetrahydro-2-pyridinone (20a)

To a solution of compound **19** (250 mg, 1.02 mmol) and HMPA (0.71 mL, 4.08 mmol) in THF (5 mL) at −78 °C was added dropwise a solution of BuLi (2.5 M in hexane, 0.53 mL, 1.33 mmol). The mixture was stirred at −78 °C for 30 min, and allyl bromide (0.35 mL, 4.08 mmol) was added in one portion. After slowly warming to room temperature and further stirring for 2 h, the reaction mixture was quenched with saturated ammonium chloride. The aqueous solution was extracted with ethyl acetate, combined with the organic layer, dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:5) as eluent to give product **20a** (225 mg, 77%) as a yellow oil: IR (neat) ν 3078, 2984, 1634, 1592, 1453, 1441, 1415, 1353, 1264, 993, 966, 907, 853, 727, 704, 691, 646 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.59–7.45 (5H, m), 5.83–5.70 (1H, m), 5.62–5.41 (2H, m), 5.38 (1H, d, *J*=2.1 Hz), 5.17–5.12 (2H, m), 4.67 (1H, ddt, *J*=15.6, 4.5, 1.5 Hz), 3.95 (1H, td, *J*=6.9, 3.0 Hz), 3.30 (1H, dd, *J*=15.6, 7.2 Hz), 2.85 (1H, ddd, *J*=16.8, 6.9, 2.1 Hz), 2.28 (1H, dd, *J*=16.8, 2.4 Hz), 1.70 (3H, d, *J*=5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 162.7, 150.2, 134.9, 133.7, 129.4 (×2), 128.4, 127.6, 116.6, 116.5, 115.3, 56.0, 45.7, 34.3, 17.3; EI-MS (rel intensity) *m*/*z* 285 (M^+, 18), 244 (24), 88 (30), 73 (34), 61 (100); EI-HRMS calcd for $C_{17}H_{19}NO$ *m*/*z* 285.1187 (M^+), found 285.1191.

4.15. 1-(2-Methylallyl)-4-(phenylthio)-6-(*E*-1-propenyl)-1,2,5,6-tetrahydro-2-pyridinone (20b)

A similar procedure as for compound **20a** was used. Starting from compound **19** (70 mg, 0.29 mmol), product **20b** (38 mg, 54%) was obtained as a yellow oil: IR (neat) ν 3054, 1637, 1422, 1365, 1264, 1228, 1217, 908, 730, 704, 650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52–7.40 (5H, m), 5.59–5.50 (2H, m), 5.39 (1H, d, *J*=2.1 Hz), 4.87–4.81 (2H, m), 4.65 (1H, br d, *J*=15.6 Hz), 3.81 (1H, td, *J*=6.6, 2.4 Hz), 3.13 (1H, br d, *J*=15.6 Hz), 2.88 (1H, ddd, *J*=16.8, 6.6, 2.1 Hz), 2.29 (1H, dd, *J*=16.8, 2.4 Hz), 1.72 (3H, br d, *J*=6.6 Hz), 1.70 (3H, br s); ^{13}C NMR ($CDCl_3$) δ 163.1, 150.3, 141.4, 135.3, 135.1, 129.8, 129.7, 128.6, 127.5, 115.5, 111.9, 55.9, 48.8, 34.5, 20.0, 17.5; EI-MS (rel intensity) *m*/*z* 299 (M^+, 17), 258 (30), 89 (31), 88 (29), 73 (33), 70 (52), 61 (100); EI-HRMS calcd for $C_{18}H_{21}NO$ *m*/*z* 299.1344 (M^+), found 299.1347.

4.16. 7-(Phenylthio)-3,5,8,8a-tetrahydro-5-indolizinone (21a)

To a solution of compound **20a** (46.0 mg, 0.16 mmol) and **G1** (6.6 mg, 0.0079 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 24 h. The solvent was then evaporated under vacuum, and the crude product was purified by flash chromatography on silica gel prewashed with Et_3N using ethyl acetate/hexane (1:3–1:1) as eluent to give product **21a** (26 mg, 67%) as a white solid: mp 88–89 °C (recryst from EA/hexane); IR (film) ν 3081, 2872, 1638, 1612, 1574, 1438, 1425, 1357, 1307, 1212, 1102, 1009, 854, 834, 751, 699, 688, 653 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42–7.37 (5H, m), 5.98 (1H, dq, J=6.3, 2.1 Hz), 5.80 (1H, dq, J=6.3, 2.1 Hz), 5.40 (1H, d, J=1.8 Hz), 4.74–4.63 (1H, m), 4.39 (1H, ddt, J=16.5, 5.0, 2.1 Hz), 4.13 (1H, ddt, J=16.5, 3.6, 1.8 Hz), 2.54–2.51 (2H, m); ^{13}C NMR ($CDCl_3$) δ 161.9, 152.1, 135.3, 130.0, 129.9, 128.8, 128.3, 128.0, 116.3, 62.4, 51.5, 34.8; EI-MS (rel intensity) m/z 243 (M^+, 94), 242 (23), 177 (20), 176 (100), 148 (26), 147 (27), 68 (21), 67 (82); EI-HRMS calcd for $C_{14}H_{13}NOS$ m/z 243.0718 (M^+), found 243.0715.

4.17. 2-Methyl-7-(phenylthio)-3,5,8,8a-tetrahydro-5-indolizinone (21b)

A solution of compound **20b** (33.0 mg, 0.11 mmol) and **G2** (4.7 mg, 0.005 mmol) in toluene (2 mL) was heated at 170 °C in a microwave reactor for 2 h. The solvent was then evaporated under vacuum, and the crude product was purified by flash chromatography on silica gel prewashed with Et_3N using ethyl acetate/hexane (1:3–1:1) as eluent to give product **21b** (15 mg, 52%) as a yellow oil: IR (neat) ν 2985, 2942, 2908, 1447, 1372, 1234, 1097, 1043, 938, 847, 786 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48–7.39 (5H, m), 5.41–5.37 (2H, m), 4.68–4.63 (1H, m), 4.28–4.21 (1H, m), 4.06–4.01 (1H, m), 2.48–2.42 (2H, m), 1.81 (3H, s); ^{13}C NMR ($CDCl_3$) δ 161.9, 152.2, 137.9, 135.3, 129.9 (×2), 129.8, 122.2, 116.2, 62.7, 54.6, 35.0, 14.5; EI-MS (rel intensity) m/z 257 (M^+, 100), 256 (36), 255 (38), 148 (43), 147 (45), 118 (21), 109 (23), 82 (83), 67 (97), 65 (21); EI-HRMS calcd for $C_{15}H_{15}NOS$ m/z 257.0874 (M^+), found 257.0878.

4.18. 7-(Phenylsulfonyl)-3,5,8,8a-tetrahydro-5-indolizinone (22)

To a solution of compound **21a** (50.0 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) in an ice bath was added slowly another solution of *m*CPBA (50% in H_2O, 158 mg, 0.48 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was then stirred at room temperature for 1 h, and was then added sequentially saturated $Na_2S_2O_3$ and saturated sodium bicarbonate. The mixture was extracted with CH_2Cl_2, dried (K_2CO_3), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:2–1:1) as eluent to give product **22** (46 mg, 77%) as a white solid: mp 107–108 °C (recryst from ethyl acetate/hexane); IR (film) ν 3052, 2970, 2857, 1661, 1600, 1439, 1356, 1286, 1216, 1152, 1079, 992, 952, 750, 717, 649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (2H, br d, J=7.5 Hz), 7.72–7.68 (1H, m), 7.62–7.51 (2H, m), 6.76 (1H, d, J=3.0 Hz), 6.00–5.98 (1H, m), 5.81–5.79 (1H, m), 4.72–4.67 (1H, m), 4.41 (1H, ddt, J=16.2, 7.2, 1.8 Hz), 4.18 (1H, ddt, J=16.2, 3.6, 1.8 Hz), 2.92 (1H, dd, J=16.8, 4.5 Hz), 2.23 (1H, ddd, J=16.8, 14.4, 3.0 Hz); ^{13}C NMR ($CDCl_3$) δ 160.0, 149.5, 137.6, 134.5, 129.7, 129.4, 128.6, 128.1, 127.8, 62.6, 51.7, 28.2; ESI-MS (rel intensity) m/z 276 (M^++H, 28), 258 (100); ESI-HRMS calcd for $C_{14}H_{13}NO_3S$ m/z 275.0616 (M^+), found 275.0606.

4.19. General procedure for the N-vinylation of amides

In a sample vial for the microwave reaction were added compound **25**[3b] (30.0 mg, 0.1 mmol), a vinyl bromide (0.2 mmol) and K_2CO_3 (40.0 mg, 0.2 mmol) and toluene (1.2 mL). Then CuI (23.0 mg, 0.1 mmol) and *N*,*N*′-dimethylethylenediamine (13.2 μL, 0.1 mmol) were added. The mixture was heated at 160 °C for 2 h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:3–1:2) as eluent to give the pure product.

*4.19.1. 6-Allyl-1-(1-methylvinyl)-4-(phenylthio)-1,2,5,6-tetrahydro-2-pyridinone (**26a**).* Colorless liquid: IR (neat) ν 3075, 2974, 2926, 1646, 1420, 1257, 1154, 998, 918 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46–7.27 (5H, m), 5.78–5.64 (1H, m), 5.36 (1H, d, J=2.1 Hz), 5.18–5.11 (2H, m), 4.99 (1H, q, J=1.2 Hz), 4.89 (1H, s), 3.78–3.71 (1H, m), 2.79 (1H, ddd, J=17.1, 6.3, 2.1 Hz), 2.48–2.38 (3H, m), 2.01 (3H, d, J=1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 162.1, 151.6, 144.9, 135.3, 133.6, 129.9, 129.7, 128.2, 118.8, 115.3, 110.9, 57.1, 36.7, 32.0, 21.5; EI-MS (rel intensity) m/z 285 (M^+, 2), 244 (14), 205 (13), 204 (100), 67 (19); EI-HRMS calcd for $C_{17}H_{19}NOS$ m/z 285.1187 (M^+), found 285.1190.

*4.19.2. 6-Allyl-1-(but-2-enyl)-1,2,5,6-tetrahydro-2-pyridinone (**26b**).* Yellow oil: IR (neat) ν 3060, 2934, 2968, 1647, 1595, 1440, 1304, 1149, 1068, 919, 852, 731, 692, 534 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49–7.39 (5H, m), 5.69 (1H, ddt, J=17.3, 9.9, 7.2 Hz), 5.37 (1H, d, J=2.1 Hz), 5.17–5.11 (2H, m), 5.07 (1H, t, J=1.5 Hz), 4.94 (1H, s), 3.69–3.61 (1H, m), 2.79 (1H, ddd, J=17.2, 5.9, 2.1 Hz), 2.49–2.20 (5H, m), 1.06 (3H, t, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 162.4, 151.5, 150.0, 135.6, 134.0, 130.0, 129.9, 128.4, 119.0, 115.7, 110.0, 57.1, 36.9, 32.0, 27.5, 11.9; EI-MS (rel intensity) m/z 299 (M^+, 27), 298 (74), 284 (29), 271 (69), 258 (100), 257 (42), 256 (53), 242 (53), 216 (72), 204 (45), 86 (31), 84 (48), 55 (66); EI-HRMS calcd for $C_{18}H_{21}NOS$ m/z 299.1344 (M^+), found 299.1339.

4.20. 3-Methyl-7-(phenylthio)-1,5,8,8a-tetrahydro-5-indolizinone (27a)

A mixture of compound **26a** (45.0 mg, 0.16 mmol) and **G2** (6.7 mg, 5 mol %) in CH_2Cl_2 (2 mL) was refluxed under nitrogen for 8 h. The solvent was then removed under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:4) as eluent to give product **27a** (31.3 mg, 77%) as a yellow oil: IR (neat) ν 3075, 2925, 1661, 1629, 1409, 1353, 1148, 1123, 848, 751, 688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44–7.31 (5H, m), 5.37 (1H, d, J=1.8 Hz), 4.84 (1H, t, J=1.3 Hz), 4.01–3.98 (1H, m), 2.67–2.57 (3H, m), 2.39–2.28 (4H, m); ^{13}C NMR ($CDCl_3$) δ 160.7, 152.4, 141.8, 135.2, 129.9, 129.8, 128.8, 117.6, 106.6, 57.8, 35.6, 34.6, 16.1; EI-MS (rel intensity) m/z 257 (M^+, 7), 162 (33), 128 (100), 61 (18); EI-HRMS calcd for $C_{15}H_{15}NOS$ m/z 257.0874 (M^+), found 257.0868.

4.21. 3-Ethyl-7-(phenylthio)-1,5,8,8a-tetrahydro-5-indolizinone (27b)

A mixture of compound **26b** (48.8 mg, 0.16 mmol) and **G2** (13.8 mg, 5 mol %) in CH_2Cl_2 (5 mL) was refluxed under nitrogen for 5 h. The solvent was then removed under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:5) containing 5% EtN as eluent to give product **27b** (38.2 mg, 86%) as a light yellow oil: IR (neat) ν 3054, 2986, 1659, 1628, 1588, 1476, 1409, 1358, 1330, 1266, 1149, 1088, 1024, 896, 855, 737, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.39 (5H, m), 5.38 (1H, d, J=2.1 Hz), 4.90–4.87 (1H, m), 4.10–3.98 (1H, m), 2.75–2.53 (5H, m), 2.31–2.20 (1H, m), 1.10 (3H, t, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 160.4, 152.1, 148.0, 135.1, 129.8 (×2), 128.7, 117.7, 104.8, 58.0, 35.5, 34.6, 22.8, 12.5; EI-MS (rel intensity) m/z 271 (M^+, 71), 180 (57), 179 (50), 178 (33), 176 (29), 117 (32), 105 (51), 97 (47), 91 (41), 84 (34), 83 (57), 82 (31), 81 (34), 71 (41), 69 (61), 68 (37), 67 (39), 57 (83), 56 (33), 55 (100); EI-HRMS calcd for $C_{16}H_{17}NOS$ m/z 271.1031 (M^+), found 271.1035.

4.22. (*E*)-3-Ethylidene-7-(phenylthio)-1,2,3,5,8,8a-hexahydro-5-indolizinone (28)

A mixture of compound **26b** (163.3 mg, 0.55 mmol) and **G2** (23.1 mg, 5 mol %) in toluene (2 mL) was heated in a sealed tube at 120 °C for 5 h. The solvent was then removed under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:5) containing 5% EtN as eluent to give product **28** (117.3 mg, 79%) as a white solid: mp 135.2–136.8 °C (recryst from CH_2Cl_2/hexane); IR (ATR, neat) ν 3045, 2919, 2853, 1630, 1590, 1408, 1389, 1321, 1163, 990, 849, 753, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–7.41 (5H, m), 6.48–6.44 (1H, m), 5.36 (1H, d, J=1.8 Hz), 3.98 (1H, tt, J=11.1, 5.7 Hz), 2.67 (1H, dd, J=15.6, 8.4 Hz), 2.48–2.34 (3H, m), 2.20–2.13 (1H, m), 1.66–1.57 (4H, m); ^{13}C NMR ($CDCl_3$) δ 162.6, 151.6, 138.3, 135.2, 129.9 (×2), 128.8, 117.8, 104.2, 59.3, 35.8, 29.8, 26.5, 13.9; EI-MS (rel intensity) m/z 272 (M^++H, 5), 245 (22), 244 (100), 68 (12); EI-HRMS calcd for $C_{16}H_{17}NOS$ m/z 271.1031 (M^+), found 271.1024. Crystallographic data: $C_{16}H_{17}NOS$, formula weight=271.37, temperature=100(2) K, wavelength=0.71073 Å, crystal system=monoclinic, space group=P 1 21/c 1, a=12.3340(17) Å, b=11.8593(16) Å, c=9.7249(13) Å, α=90°, β=103.183(3)°, γ=90°, volume=1385.0(3) $Å^3$, Z=4, density (calculated)=1.301 Mg/m^3, absorption coefficient=0.225 mm^{-1}, F(000)=576, crystal size=0.17×0.06×0.05 mm^3, theta range for data collection=1.70–26.38°, index ranges: $-15\le h\le 15$, $-14\le k\le 11$, $-12\le l\le 12$, reflections collected=10,231, independent reflections=2832 [R(int)=0.0338], completeness to theta=26.38° (99.9%), max. and min. transmission=0.9486 and 0.8487, refinement method: full-matrix least-squares on F^2, data/restraints/parameters=2832/0/173, goodness-of-fit on F^2=1.034, final R indices [I>2sigma(I)]: $R1$=0.0550, $wR2$=0.1229, R indices (all data) $R1$=0.0753, $wR2$=0.1354, largest diff. peak and hole=0.939 and −0.695 e $Å^{-3}$.

4.23. *cis*-3-Methyl-7-(phenylthio)-1,2,3,5,8,8a-hexahydro-5-indolizinone (29a) and *trans*-3-methyl-7-(phenylthio)-1,2,3,5,8,8a-hexahydro-5-indolizinone (29b)

A mixture of compound **27** (14.0 mg, 0.05 mmol) and PtO_2 (4.9 mg) in ethyl acetate (2 mL) was stirred vigorously under a balloon of hydrogen for 24 h. The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:4) as eluent to give an inseparable 3:1 mixture (determined by ^1H NMR) of products **29a** and **29b** (9.2 mg, 65%)[4a]: IR (neat) ν 3055, 2963, 2926, 2871, 1643, 1582, 1474, 1439, 1426, 1367, 1344, 1305, 1257, 1230, 1175, 1126, 1075, 1022, 1000, 984, 956, 914, 851, 751, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52–7.36 (m), 5.34 (d, J=2.4 Hz), 4.20–4.11 (m), 3.92–3.83 (m), 3.76–3.65 (m), 2.52–2.31 (m), 2.12–1.89 (m), 1.80–1.42 (m), 1.29 (d, J=6.3 Hz), 1.23 (d, J=6.3 Hz); EI-MS (rel intensity) m/z 259 (M^+, 38), 244 (100), 176 (21), 147 (14), 67 (14); EI-HRMS calcd for $C_{15}H_{17}NOS$ m/z 259.1031 (M^+), found 259.1030. Most of the ^1H NMR signals for compounds **29a** and **29b** overlap, but δ 3.76–3.65 (m) and 1.23 (d, J=6.3 Hz) belong to compound **29a**, whereas δ 3.92–3.83 (m) and 1.29 (d, J=6.3 Hz) belong to compound **29b**. The ^{13}C NMR absorptions are distinctive. Compound **29a**: 162.8, 152.6, 135.2, 129.74, 129.71, 128.9, 116.9, 57.9, 51.3, 36.2, 30.8, 30.6, 20.9. Compound **29b**: 162.1, 150.7, 135.1, 129.74, 129.71, 128.9, 117.1, 55.4, 52.5, 35.4, 31.6, 31.5, 19.9.

4.24. (3*S**,5*R**,8a*R**)-3-Ethyl-5-methyl-1,2,3,5,6,7,8,8a-octahydroindolizine (31, indolizidine 167E)

A mixture of compound **30** (54 mg, 0.20 mmol) and a W-2 Raney-Ni (451 mg, 3.95 mmol) in 95% EtOH (3 mL) was heated at reflux under nitrogen for 2 h. The solid was filtered off, washed with methanol, and the residue was evaporated under vacuum in an ice bath. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:4) as eluent to give indolizidine 167E (29.0 mg, 88%) as a yellow oil, the spectral data of which were identical with the literature values.[19]

4.25. (3*R**,5*S**,8a*R**)-3-Ethyl-5-methy-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (32)

To a solution of compound **30** (70.2 mg, 0.26 mmol) in 95% EtOH (3 mL) was added dropwise a 50% aqueous HBr (3 mL). The mixture was heated at 70 °C under nitrogen for 14 h. The reaction was quenched with saturated sodium bicarbonate, extracted with CH_2Cl_2 (10 mL×3), and dried ($MgSO_4$). The solvent was removed under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:6) containing 5% Et_3N as eluent to give product **32** (31.1 mg, 67%) as a colorless oil (29 mg, 91%): IR (neat) ν 2964, 2876, 2793, 1721, 1555, 1461, 1380, 1196, 1124, 932, 825, 734, 618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68–2.51 (2H, m), 2.50–2.44 (2H, m), 2.36–2.18 (3H, m), 2.04–1.91 (1H, m), 1.81–1.73 (1H, m), 1.71–1.47 (3H, m), 1.42–1.30 (1H, m), 1.20 (3H, d, J=6.3 Hz), 0.89 (3H, t, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 209.7, 65.4, 62.6, 57.4, 50.1, 47.4, 32.0, 30.9, 29.8, 22.7, 10.6; FAB-MS (rel intensity) m/z 182 (M^++H, 14), 146 (38), 145 (24), 139 (24), 66 (100); FAB-HRMS calcd for $C_{11}H_{19}NO$ m/z 181.1467 (M^+), found 181.1467.

4.26. (3*R**,5*S**,7*R**,8a*R**)-3-Ethyl-5-methy-7-hydroxy-1,2,3,5,6,7,8,8a-octahydroindolizine (33)

To a solution of compound **32** (27.3 mg, 0.15 mmol) in methanol (5 mL) at −78 °C was added dropwise a solution of $NaBH_4$ (57 mg, 1.5 mmol) in methanol (5 mL). The reaction mixture was slowly warmed to room temperature and stirred for 6 h. The solvent was then evaporated under vacuum and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (10 mL×3), dried (K_2CO_3), and evaporated. The crude product was purified by recrystallization from CH_2Cl_2/hexane to give product **33** (20.0 mg, 72%) as a white solid: mp 69.2–70.2 °C; IR (film) ν 3239, 2967, 2872, 1734, 1560, 1459, 1382, 1312, 1142, 1097, 1040, 947, 824, 618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70–3.63 (1H, m), 2.43 (1H, tt, J=9.6, 2.4 Hz), 2.36–2.25 (1H, m), 2.23–2.14 (1H, m), 2.11–2.04 (1H, m), 1.94–1.80 (2H, m), 1.73–1.61 (3H, m), 1.51–1.42 (2H, m), 1.37–1.21 (3H, m), 1.15 (3H, d, J=6.6 Hz), 0.85 (3H, t, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 69.7, 64.8, 63.3, 57.0, 45.2, 40.3, 32.1, 30.0, 29.9, 22.6, 10.9; EI-MS (rel intensity) m/z 183 (M^+, 14), 184 (100), 182 (75), 166 (23), 149 (74), 139 (31), 82 (18), 71 (25), 66 (28), 63 (45), 62 (23), 55 (37), 53 (48); EI-HRMS calcd for $C_{11}H_{21}NO$ m/z 183.1623 (M^+), found 183.1622. Crystallographic data: $C_{11}H_{23}NO_2$, formula weight=201.30, temperature=200(2) K, wavelength=0.71073 Å, crystal system=triclinic, space group=P −1, a=7.1773(4) Å, b=8.3584(6) Å, c=11.7370(7) Å, α=71.092(4)°, β=75.568(4)°, γ=64.714(4)°, volume=597.22(6) $Å^3$, Z=2, density (calculated)=1.119 Mg/m^3, absorption coefficient=0.076 mm^{-1}, F(000)=224, crystal size=0.69×0.25×0.08 mm^3, theta range for data collection=2.78–25.03°, index ranges: $-8\le h\le 8$, $-9\le k\le 9$, $-12\le l\le 13$, reflections collected=4813, independent reflections=2061 [R(int)=0.0573], completeness to theta=25.03° (97.9%), absorption correction: multi-scan, max. and min. transmission=0.9940 and 0.9497, refinement method: full-matrix least-squares on F^2, data/restraints/parameters=2061/0/128, goodness-of-fit on F^2=1.090, Final R indices [I>2sigma(I)]: $R1$=0.0987, $wR2$=0.2674, R indices (all data): $R1$=0.1329, $wR2$=0.2919, largest diff. peak and hole=0.982 and −0.432 e $Å^{-3}$.

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Supplementary data

NMR spectra (^{1}H, ^{13}C) for all new compounds and indolizidine 167E, and X-ray data for compounds **14**, **28** and **33**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.10.026.

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