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Facile Transformation of 2-Azetidinones to 2-Piperidones: Application to the Synthesis of the Indolizidine Skeleton and (8*S*,8a*S*)-Perhydro-8-indolizinol

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Abstract: The highly functionalized bicyclic lactam **7** was prepared from diolefinic-2-piperidone **18** by the use of ruthenium-catalyzed RCM, and in turn, **18** was derived via a two-carbon addition process from readily accessible 4-olefinic-2-azetidinone **13**. Bicyclic lactams **7** and **20** could serve as potentially valuable intermediates for the chiral synthesis of various hydroxylated indolizidine alkaloids as exemplified by the synthesis of (8*S*,8a*S*)-perhydro-8-indolizinol **19**.

Indolizidine alkaloids constitute a family of nitrogen-fused bicyclo[4.3.0]nonanes and have recently received considerable attention due to their wide range of biological activity.[1,2] For example, polyhydroxylated indolizidines such as swainsonine, castanospermine, lentiginosine, and certain natural and synthetic analogues attracted special interest by virtue of their varied and pharmaceutically useful biological actions as potential antiviral, antitumor, and immunomodulating agents. Consequently, the development of efficient synthetic methods for generating the indolizidine skeleton is the subject of recent intense research activity.

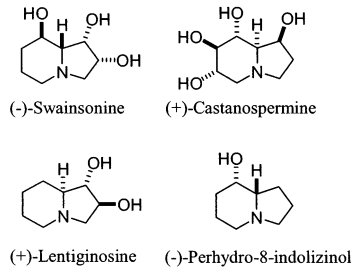
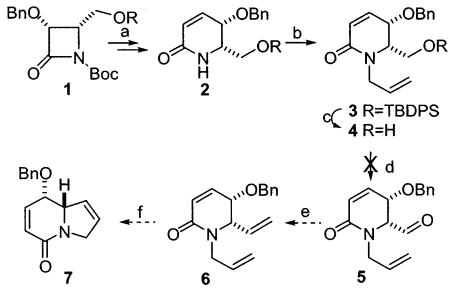


FIGURE 1.

Among the efforts in this area, we recently reported a new synthetic methodology for 2-piperidones that may serve as versatile intermediates for the chiral synthesis of various piperidine and indolizidine alkaloids from readily accessible 2-azetidinones.[3]

Continuing our investigation on the application of this methodology to indolizidine alkaloids, we describe herein the efficient construction of potentially useful highly functionalized indolizidine building block **7** and the synthesis of (8*S*,8a*S*)-perhydro-8-indolizinol **19**.

SCHEME 1[a]



[a] Reaction conditions: (a) ref 3; (b) CH_2=$CHCH_2Br$, NaH, cat. *n*-Bu_4NI, THF, 0 °C, 2 h (88%); (c) *n*-Bu_4NF, THF, 0 °C (95%); (d) oxidation; (e) Wittig; (f) Grubbs' catalyst [$(Cy_3P)_2Cl_2Ru$=CHPh].

As depicted in Scheme 1, we envisaged that ring-closing metathesis (RCM)[4] of diolefinic 2-piperidone **6** could provide a highly functionalized bicyclic lactam **7** that may serve as a valuable precursor of polyhydroxylated indolizidine alkaloids.

Our initial efforts in the synthesis of diolefinic 2-piperidone **6** started from the known 2-piperidone **2**.[3] N-Allylation and desilylation under standard conditions afforded *N*-allyl-2-piperidone **4**. However, subsequent oxidation of **4** to aldehyde **5** turned out to be problematic in our hands. Our attempts to prepare aldehyde **5** from the oxidation of alcohol **4** with various oxidizing agents (Swern,[5] IBX,[6] PCC,[7] TEMPO[8]) were unsuccessful, affording low yields of aldehyde **5**.

Next, we thought that the diolefinic 2-piperidone **6** could be derived from 6-vinyl-2-piperidone by N-allylation and, in turn, 6-vinyl-2-piperidone could be prepared from

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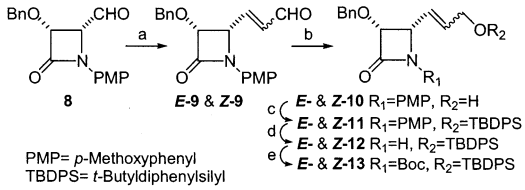
SCHEME 2[a]



[a] Reaction conditions: (a) $Ph_3P{=}CHCHO$, PhH, reflux, 24 h; (b) $NaBH_4$, THF, 0 °C, 1 h (68% from **8**); (c) TBDPSCl, imidazole, DMF, cat. DMAP (94%, *E*:*Z* = 1.7:1); (d) $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O, 0 °C, 30 min (*E*-**12**:61%; *Z*-**12**:47%); (e) $(Boc)_2O$, cat. DMAP, CH_3CN, 10 min (*E*-**13**:97%; *Z*-**13**:84%)

4-vinyl-2-azetidinone by our reported methodology.[3] However, treatment of 2-azetidinone-4-aldehyde **8** with $Ph_3P{=}CH_2$ (Ph_3PCH_3Br/*n*-BuLi) gave a low yield of 4-vinyl-2-azetidinone. We then tried to synthesize 4-substituted vinyl-2-azetidinone **13** as the starting material for preparing 6-olefinic-2-piperidone **17** from the known optically pure 2-azetidinone-4-aldehyde **8**[9] as shown in Schemes 2 and 3.

Thus, treatment of **8** with (triphenylphosphoranylidene)acetaldehyde afforded the α,β-unsaturated aldehyde **9** as an *E* and *Z* mixture. Since it was difficult to separate the (*E*)- and (*Z*)-isomers at this stage, the unsaturated aldehyde (*E*)- and (*Z*)-**9** mixture was subjected to reduction and subsequent protection with TBDPSCl of the resulting alcohol afforded a 1.7:1 mixture of (*E*)-isomer (*E*)-**11** as the major product and (*Z*)-isomer (*Z*)-**11** in 64% overall yield from **8**. Oxidative removal of the PMP protecting group[10] in (*E*)-**11** with CAN and subsequent treatment with $(t\text{-Boc})_2O$ furnished the *N*-Boc-4-olefinic-2-azetidinone (*E*)-**13** in good yields.

Transformation of the *N*-Boc-4-olefinic-2-azetidinone **13** to 6-olefinic-2-piperidone **17** was straightforward using our published two-carbon addition process[3] as shown in Scheme 3.

Thus, (*E*)-**13** was reduced to 3-*N*-Boc-amino alcohol (*E*)-**14** in 95% yield by $LiAlH_4$ in THF at 0 °C for 10 min. Oxidation of 3-*N*-Boc-amino alcohol (*E*)-**14** by IBX (2-iodoxybenzoic acid)[6] in DMSO for 5 h at room temperature cleanly produced highly pure 3-*N*-Boc-amino aldehyde (*E*)-**15**, which was used in the next step without further purification. Aldehyde (*E*)-**15** was dissolved in dry MeOH[11] and treated with methyl (triphenylphosphoranylidene)acetate at room temperature to give an 8:1 mixture of the (*Z*)-α,β-unsaturated ester of (2*Z*,6*E*)-**16** as the major product and its (*E*)-isomer (2*E*,6*E*)-**16** in 86% overall yield from (*E*)-**14**. After separation by flash chromatography, the (*Z*)-*N*-Boc amino ester (2*Z*,6*E*)-**16** was subjected to removal of *N*-Boc protection under mild conditions[12] and in turn cyclized with catalytic DMAP in toluene to give 6-(*E*)-olefinic-2-piperidone (*E*)-**17** in excellent yield from (2*Z*,6*E*)-**16**. 6-(*Z*)-Olefinic-2-piperidone (*Z*)-**17** was also prepared from the *N*-Boc-4-(*Z*)-olefinic-2-azetidinone (*Z*)-**13** through essentially the same procedure for (*E*)-**13** to (*E*)-**17**.

N-Allylation of 6-(*E*)-olefinic-2-piperidone (*E*)-**17** produced the desired diolefinic-2-piperidone **18**. With diolefinic-2-piperidone **18** in hand, we were ready to test the ring-closing metathesis to form the indolizidine skeleton **7**. We were pleased to find that RCM[4] of **18** was indeed successfully effected with Grubbs' ruthenium catalyst to generate the highly functionalized bicyclic lactam **7** despite the steric bulkiness of $TBDPSO-CH_2$ group in 95% yield. (*Z*)-Diolefinic-2-piperidone (*Z*)-**18** was also smoothly converted to the same bicyclic lactam **7** under the same RCM reaction conditions with Grubbs' ruthenium catalyst.

It should be noted that the highly functionalized bicyclic lactam **7** could serve as a potentially valuable intermediate for chiral synthesis of various hydroxylated indolizidine alkaloids.[13] For example, bicyclic lactam **7** was easily converted to (8*S*,8a*S*)-perhydro-8-indolizinol **19**[14] through hydrogenation and amide reduction in good overall yield. On the other hand, regioselective reduction of the 6,7-double bond of the bicyclic lactam **7** with K-selectride[2j] afforded the mono-unsaturated bicyclic lactam **20**, which could be used for the synthesis of swainsonine analogues.

The applications of bicyclic lactams **7** and **20** to the synthesis of various more complex indolizidine alkaloids are under investigation.

In summary, the bicyclic lactam **7** was prepared from diolefinic-2-piperidone **18** by the use of ruthenium-catalyzed RCM and, in turn, **18** was derived via a two-carbon addition process from readily accessible 4-olefinic-2-azetidinone **13**. Bicyclic lactams **7** and **20** could serve as potentially valuable intermediates for the chiral synthesis of various hydroxylated indolizidine alkaloids as exemplified by the synthesis of (8*S*,8a*S*)-perhydro-8-indolizinol **19**.

Experimental Section

Flash column chromatography was performed on silica gel (230−400 mesh). THF and Et_2O were refluxed over sodium in the presence of benzophenone and distilled prior to use. CH_2Cl_2 was distilled from calcium hydride. DMF, benzene, CH_3CN, MeOH, and toluene were dried, distilled, and stored under nitrogen prior to use.[16] All other reagent-grade chemicals obtained from commercial sources were used as received.

(−)-(4*E*)-(2*R*,3*S*)-3-(*t*-Butyloxycarbonyl)amino-2-(benzyloxy)-6-(*t*-butyldiphenylsilyloxy)-4-hexen-1-ol ((*E*)-14). To a suspension of $LiAlH_4$ (0.16 g, 4.09 mmol) in THF (10 mL) was added dropwise a solution of (*E*)-**13** (2.34 g, 4.09 mmol) in THF (10 mL) at 0 °C. After the mixture was stirred at that temperature for 20 min, ice−water (20 mL) and Rochelle salt (20 mL) was added and the reaction mixture was stirred for additional 1 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 40

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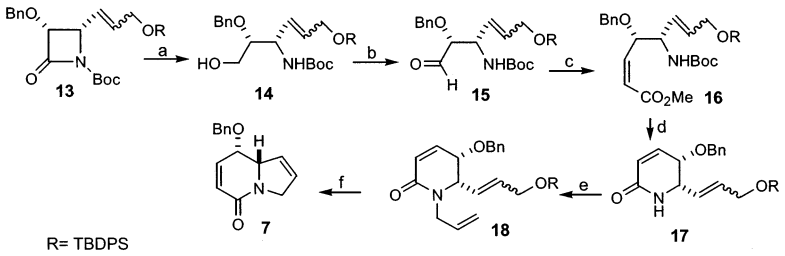
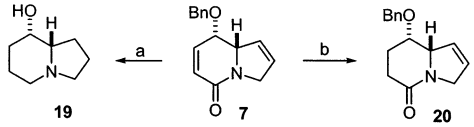
SCHEME 3[a]



[a] Reaction conditions: (a) $LiAlH_4$, THF, 0 °C, 10 min (*E*-**14**:97%; *Z*-**14**:95%); (b) IBX, DMSO, rt, 5 h (*E*-**15**:97%; *Z*-**15**:95%); (c) $Ph_3P{=}CHCO_2Me$, MeOH, rt, 12 h (*E*-**16**:89% (*E*:*Z* =1:8); *Z*-**16**:86% (*E*:*Z* = 1:7)); (d) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, then cat. DMAP, toluene, reflux, 1 h (*E*-**17**:95%; *Z*-**17**:82%); (e) $CH_2{=}CHCH_2Br$, NaH, cat. *n*-Bu_4NI, THF, 0 °C, 2 h (*E*-**18**:88%; *Z*-**18**:73%); (f) 3 mol % $(Cy_3P)_2Cl_2Ru{=}CHPh$, PhH, reflux, 1 h (95%).

SCHEME 4[a]



[a] Reaction conditions: (a) (i) $H_2/Pd(OH)_2$, EtOH, 3 days (98%); (ii) BH_3SMe_2, THF, 0 °C, 4 h (68%). (b) K-Selectride, Et_2O, −78 °C, 30 min (51 %).

mL), washed with $NaHCO_3$ and brine, and dried ($MgSO_4$). After evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (from 7:1 to 5:1 hexane−EtOAc): yield 2.28 g (97%); colorless oil; R_f 0.34 (3:1 hexane−EtOAc); $[\alpha]_D^{21}$ −21.8 (*c* 1.59, $CHCl_3$); IR (NaCl, cm^{-1}) ν 3445, 1716, 1698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.65 (m, 3H), 7.45−7.24 (m, 12H), 5.84−5.73 (m, 2H), 4.86 (d, 1H, J = 9.6 Hz), 4.55 (m, 3H), 4.21 (m, 2H), 3.67−3.45 (m, 3H), 3.24 (br s, 1H), 1.45 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.69, 137.89, 135.48, 133.52, 133.48, 130.54, 129.68, 128.42, 127.94, 127.68, 111.49, 81.27, 80.08, 73.50, 63.69, 60.93, 51.87, 28.29, 26.80, 19.22; MS *m*/*z* 462 (M^+ − 113), 444, 418, 401, 384, 368, 340; HRMS (CI, methane) calcd for $C_{34}H_{45}NO_5Si$ 576.3145 (MH^+), found 576.3148.

(4*E*)-(2*R*,3*S*)-3-(*t*-Butyloxycarbonyl)amino-2-(benzyloxy)-6-(*t*-butyldiphenylsilyloxy)-4-hexenal ((*E*)-15). To a solution of 3-*N*-Boc-amino alcohol (*E*)-**14** (2.81 g, 4.88 mmol) in DMSO (20 mL) was added 2-iodoxybenzoic acid (2.1 g, 7.33 mmol). After stirring at room temperature for 5 h, the reaction mixture was diluted with water (40 mL), filtered over Celite, and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated in vacuo. The crude aldehyde was sufficiently pure to be used in the next step without further purification: yield 2.72 g (97%); pale yellow oil; IR (NaCl, cm^{-1}) ν 2930, 2857, 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.69−7.64 (m, 3H), 7.47−7.25 (m, 12H), 5.82−5.72 (m, 2H), 5.01 (d, 1H, J = 9.4 Hz), 4.74 (d, 1H, J = 11.6 Hz), 4.75−4.73 (m, 1H), 4.58 (d, 1H, J = 11.6 Hz), 4.22−4.20 (m, 2H), 3.89 (br s, 1H), 1.42 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.49, 155.03, 135.47, 133.49, 133.45, 131.43, 129.69, 128.53, 128.21, 128.12, 127.69, 127.68, 84.70, 79.87, 73.19, 63.49, 60.39, 28.27, 26.79, 19.23; MS *m*/*z* 574 (M^+ + 1), 518, 460, 416, 382, 368; HRMS (CI, methane) calcd for $C_{34}H_{43}NO_5Si$ 574.2988 (MH^+), found 574.2997.

Methyl (6*E*)-(4*S*,5*S*)-5-(*t*-Butyloxycarbonyl)amino-4-(benzyloxy)-8-(*t*-butyldiphenylsilyloxy)-2,6-octadienoate ((2*E*,6*E*)- and (2*Z*,6*E*)-16). To a solution of aldehyde (*E*)-**15** (2.48 g, 4.33 mmol) in dry methanol (40 mL) was added $Ph_3P{=}CHCO_2$-Me (1.74 g, 5.19 mmol). The reaction mixture was stirred for 18 h at room temperature, and the solvent was evaporated in vacuo. The crude product was separated to pure (*E*)- and (*Z*)-isomers by flash chromatography (from 15:1 to 10:1 hexane−EtOAc): yield 2.43 g (89%, **2*E***:**2*Z*** = 1:8).

(*E*)-Isomer ((2*E*,6*E*)-16): colorless oil; $[\alpha]_D^{21}$ −2.0 (*c* 0.7, $CHCl_3$); IR (NaCl, cm^{-1}) ν 3070, 3031, 2931, 1724; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.64 (m, 3H), 7.45−7.25 (m, 12H), 6.88 (dd, 1H, J = 6.0, 15.7 Hz), 6.07 (dd, 1H, J = 1.3, 15.7 Hz), 5.87−5.69 (m, 2H), 4.83−4.78 (m, 1H), 4.59 (d, 1H, J = 11.6 Hz), 4.40 (d, 1H, J = 11.6 Hz), 4.31 (m, 1H), 4.20−4.19 (m, 2H), 4.09−4.06 (m, 1H), 3.74 (s, 3H), 1.42 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.23, 155.31, 144.88, 137.42, 135.47, 133.49, 131.07, 129.64, 128.39, 128.06, 127.85, 127.79, 127.65, 123.36, 79.70, 77.20, 71.72, 63.60, 51.92, 51.64, 28.27, 26.77, 19.19; MS *m*/*z* 632 (M^+ + 3), 572, 516, 450, 394, 368, 350, 324, 316, 272; HRMS (CI, methane) calcd for $C_{37}H_{47}NO_6Si$ 630.3250 (MH^+), found 630.3248.

(*Z*)-Isomer ((2*Z*,6*E*)-16): colorless oil; $[\alpha]_D^{21}$ +10.2 (*c* 0.53, $CHCl_3$); IR (NaCl, cm^{-1}) ν 3070, 2931, 1722; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.65 (m, 3H), 7.46−7.25 (m, 12H), 6.25 (dd, 1H, J = 8.4, 11.7 Hz), 5.97 (dd, 1H, J = 1.1, 11.7 Hz), 5.88−5.79 (m, 2H), 5.14−4.97 (m, 2H), 4.53 (d, 1H, J = 11.6 Hz), 4.42 (d, 1H, J = 11.6 Hz), 4.39 (m, 1H), 4.22−4.20 (m, 2H), 3.71 (s, 3H), 1.43 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.03, 155.48, 148.09, 137.91, 135.50, 133.63, 133.61, 130.41, 129.60, 127.95, 127.77, 127.70, 127.64, 122.28, 79.29, 71.87, 63.71, 60.38, 55.69, 51.46, 28.36, 26.79, 19.22; MS *m*/*z* 630 (M^+ + 1), 572, 530, 516, 408, 368, 318, 266, 246; HRMS (CI, methane) calcd for $C_{37}H_{47}NO_6Si$ 630.3250 (MH^+), found 630.3250.

(+)-(5*S*,6*S*)-5-(Benzyloxy)-6-[(*E*)-3-(*t*-butyldiphenylsilyloxy)-1-propen-yl]-1,2,5,6-tetrahydro-2-pyridinone ((*E*)-17). To a solution of (2*Z*)-*N*-Boc amino ester (2*Z*,6*E*)-**16** (1.86 g, 2.95 mmol) and 2,6-lutidine (0.64 g, 5.95 mmol) in CH_2Cl_2 (30 mL) was added TMSOTf (0.8 mL, 4.43 mmol) dropwise at 0 °C. After the reaction mixture was stirred for 1 h at room temperature, the reaction was quenched by addition of saturated $NaHCO_3$ solution (30 mL) and the organic layer was separated and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the resulting oil was dissolved in toluene (20 mL) and DMAP (0.01 g, 0.09 mmol) was added; the reaction mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature and washed with 1 N HCl solution, saturated $NaHCO_3$ (20 mL), and brine (20 mL) successively. After drying ($MgSO_4$) and evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (from 3:1 to 1:1 hexane−EtOAc): yield 1.39 g (95%); colorless oil; R_f 0.05 (3:1 hexane−EtOAc 3:1); $[\alpha]_D^{21}$ +27.9 (*c* 0.61, $CHCl_3$); IR (NaCl, cm^{-1}) ν 3222, 1682, 1615; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.64 (m, 3H), 7.47−7.25 (m, 12H), 6.57 (dd, 1H, J = 3.5, 10.0 Hz), 6.07−5.94 (m, 2H), 5.84 (tt, 1H, J = 4.1, 4.3 Hz), 5.52 (br s, 1H), 4.65−4.53 (m, 2H), 4.25−4.10 (m, 4H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.88, 140.30, 137.48, 135.50, 133.54, 133.42, 133.38, 129.74, 128.48, 127.95, 127.70, 125.50, 124.75, 71.50, 71.36, 63.54, 26.78, 19.19; MS *m*/*z* 497 (M^+), 440, 406, 332, 289, 272, 254, 211, 199; HRMS (EI) calcd for $C_{31}H_{35}NO_3Si$ 497.2386, found 497.2390.

(−)-(5*S*,6*S*)-1-Allyl-5-(benzyloxy)-6-[(*E*)-3-(*t*-butyldiphenylsilyloxy)-1-propenyl]-1,2,5,6-tetrahydro-2-pyridinone ((*E*)-18). To a slurry of NaH (60% in mineral oil, 64 mg, 1.607 mmol) in THF (7 mL) was added a solution of (*E*)-**17** (400 mg, 0.803 mmol) in THF (10 mL) at 0 °C. After the mixture was stirred for 20 min at this temperature, allyl bromide (0.14 mL, 1.607 mmol) and *n*-Bu_4NI (12 mg, 0.032 mmol) were added. The

reaction mixture was stirred for 1 h at room temperature, and the reaction was quenched with saturated NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (from 5:1 to 3:1 hexane−EtOAc): yield 378 mg (88%); colorless oil; R_f 0.35 (3:1 hexane−EtOAc); $[\alpha]_D^{21}$ −26.5 (*c* 2.02, $CHCl_3$); IR (NaCl, cm^{-1}) ν 3070, 1673, 1615; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68−7.63 (m, 3H), 7.45−7.25 (m, 12H), 6.38 (tt, 1H, J = 1.7, 10.2 Hz), 5.85 (dd, 1H, J = 2.4, 10.2 Hz), 5.81−5.61 (m, 3H), 5.20−5.12 (m, 2H), 4.76−4.65 (m, 1H), 4.59−4.51 (m, 3H), 4.23−4.21 (m, 2H), 4.12−4.05 (m, 1H), 3.16 (q, 1H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.18, 140.37, 137.20, 135.49, 133.83, 133.51, 133.43, 129.66, 128.50, 128.00, 127.76, 127.66, 123.99, 122.70, 117.39, 73.95, 71.37, 63.67, 58.91, 46.29, 26.74, 19.18; MS *m*/*z* 537 (M^+), 480, 450, 402, 374, 312, 289, 259; HRMS (EI) calcd for $C_{34}H_{39}NO_3Si$ 537.2699, found 537.2696.

(+)-(8*S*,8a*S*)-8-(Benzyloxy)-3,5,8,8a-tetrahydro-5-indolizidinone (7). A mixture of *N*-allyl-2-pyridone (*E*)-**18** or (*Z*)-**18** (786 mg, 1.46 mmol) and $(Cy_3P)_2Cl_2Ru{=}CHPh$ [Grubbs' catalyst (33 mg, 0.04 mmol)] in benzene (30 mL) was heated to reflux for 1 h. After the mixture was cooled to room temperature, DMSO (0.15 mL, 2 mmol) was added and stirred for 12 h. The reaction mixture was filtered over Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (from 3:1 to 1:1 hexane−EtOAc) to give **7** as a colorless oil: yield 335 mg (95%); R_f 0.17 (1:1 hexane−EtOAc); $[\alpha]_D^{21}$ +135.6 (*c* 1.86, $CHCl_3$); IR (NaCl, cm^{-1}) ν 1665, 1598; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.23 (m, 5H), 6.61 (dd, 1H, J = 5.7, 9.8 Hz), 6.21 (dd, 1H, J = 3.0, 9.8 Hz), 6.07−6.00 (m, 1H), 5.90−5.84 (m, 1H), 4.65−4.61 (m, 1H), 4.56−4.44 (m, 3H), 4.28−4.16 (m, 1H), 4.06 (dd, 1H, J = 3.7, 5.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.27, 137.76, 135.74, 129.46, 128.45, 127.90, 127.66, 127.61, 125.78, 70.46, 67.17, 66.63, 51.81; MS *m*/*z* 241 (M^+), 214, 174, 150, 133, 104, 91; HRMS (EI) calcd for $C_{15}H_{15}NO_2$ 241.1102, found 241.1102.

(−)-(8*S*,8a*S*)-8-Hydroxyindolizidine (19). A mixture of **7** (175 mg, 0.725 mmol) and 20% $Pd(OH)_2$ (88 mg, 50% w/w) in EtOH (8 mL) was shaken for 3 days under 60 psi of hydrogen pressure using a Parr hydrogenator. The mixture was filtered over Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (10:1 EtOAc−MeOH) to give **(−)-(8*S*,8a*S*)-8-hydroxy-5-indolizidinone** as a white solid: yield 100 mg (98%); R_f 0.11 (10:1 EtOAc−MeOH); mp 98−100 °C; $[\alpha]_D^{21}$ −30.6 (*c* 2, $CHCl_3$); IR (KBr, cm^{-1}) ν 3397, 1602; ^1H NMR (500 MHz, $CDCl_3$) δ 4.14−4.13 (m, 1H), 3.52−3.47 (m, 3H), 2.52−2.45 (m, 1H), 2.38−2.32 (m, 1H), 2.09−2.04 (m, 1H), 1.94−1.85 (m, 5H), 1.75−7.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.89, 63.85, 62.44, 45.27, 28.42, 27.63, 26.01, 22.03; MS *m*/*z* 155 (M^+), 138, 127, 111, 98, 83, 70, 55, 41; HRMS (EI) calcd for $C_8H_{13}NO_2$ 155.0946, found 155.0946. Borane−methyl sulfide complex (1.13 mL of 2 M solution in THF, 2.268 mmol) was added dropwise over a period of 10 min at 0 °C to a solution of **(−)-(8*S*,8a*S*)-8-hydroxy-5-indolizidinone** (88 mg, 0.567 mmol) in THF (5 mL). After 30 min, the solution was warmed to room temperature and stirred for another 4 h at that temperature. The reaction was quenched by slow addition of ethanol. Evaporation of the solvent gave a viscous oil, which was redissolved in ethanol (5 mL) and heated to reflux for 2 h. After cooling to room temperature and evaporation under reduced pressure, the residue was purified by flash chromatography (3:1 hexane−EtOAc) giving **19** as a white solid: yield 54 mg (68%); R_f 0.18 (2:1 hexane−EtOAc); mp 101−102 °C; $[\alpha]_D^{21}$ −17.4 (*c* 1.15, $CHCl_3$); IR (KBr, cm^{-1}) ν 3430, 2962, 2372, 1471, 1452; ^1H NMR (500 MHz, $CDCl_3$) δ 4.46−4.42 (m, 1H), 3.36−3.32 (m, 1H), 3.25−3.19 (m, 1H), 3.12−3.08 (m, 1H), 2.79−2.75 (m, 1H), 2.58 (ddd, 1H, J = 3.3, 12.2, 12.2 Hz), 2.18−2.05 (m, 3H), 1.99−1.93 (m, 3H), 1.84−1.81 (m, 1H), 1.68−1.63 (m, 1H), 1.56−1.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.73, 65.23, 64.16, 51.74, 26.30, 22.32, 19.90, 18.91; MS *m*/*z* 141 (M^+), 140, 123, 96, 84, 69, 55, 41; HRMS (EI) calcd for $C_8H_{15}NO$ 141.1153, found 141.1152.

(−)-(8*S*,8a*S*)-8-(Benzyloxy)-3,5,6,7,8,8a-hexahydro-5-indolizidinone (20). To a stirred solution of **7** (80 mg, 0.331 mmol) in Et_2O (3 mL) was added a solution of K-selectride (0.83 mL of a 1 M solution in THF, 0.827 mmol) at −78 °C. After gradual warming to 0 °C and further stirring for 30 min at that temperature, the reaction was quenched by the addition of saturated $NaHCO_3$, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc) to give **20** as a colorless oil: yield 41 mg (51%); R_f 0.24 (EtOAc); $[\alpha]_D^{21}$ −8.4 (*c* 1.31, $CHCl_3$); IR (NaCl, cm^{-1}) ν 1651, 1460, 1409, 1361; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 5.98−5.95 (m, 1H), 5.80−5.76 (m, 1H), 4.62 (d, 1H, J = 12.4 Hz), 4.56−4.53 (m, 1H), 4.49 (d, 1H, J = 12.4 Hz), 4.46−4.43 (m, 1H), 4.09−3.95 (m, 2H), 2.57−2.44 (m, 2H), 2.26−2.09 (m, 1H), 1.98−1.77 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.18, 138.08, 128.38, 127.67, 127.35, 127.14, 126.97, 70.51, 70.20, 67.96, 53.04, 26.80, 24.63; MS *m*/*z* 243 (M^+), 190, 152, 134, 120, 106, 91, 68; HRMS (EI) calcd for $C_{15}H_{17}NO_2$ 243.1259, found 243.1252.

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Supporting Information Available: Full experimental procedures and copies of ^1H and ^{13}C NMR spectra for **7**, **11**−**14**, and **16**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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