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SYNTHETIC APPROACHES TO POLYHYDROXY INDOLIZIDINES AND RELATED AZABICYCLIC SCAFFOLDS†

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Abstract – Approaches to the synthesis of unnatural polyhydroxylated indolizidines are described. Key reactions involve addition of 2-(trimethylsilyloxy)furan to iminium salts, and ring-closure metathesis as second alternative.

INTRODUCTION

Azabicyclic alkaloids belonging to the pyrrolizidine and indolizidine families have been known for many years.[1] Their relevance as important chemotherapeutic agents has been heightened with the activities of polyhydroxylated variants.[2] Thus, castanospermine (**1**),[3] and swainsonine (**2**),[4] are well known inhibitors of glucosidases and mannosidases, with potential applications as anticancer[5] and antiviral agents.[6] (Figure 1).

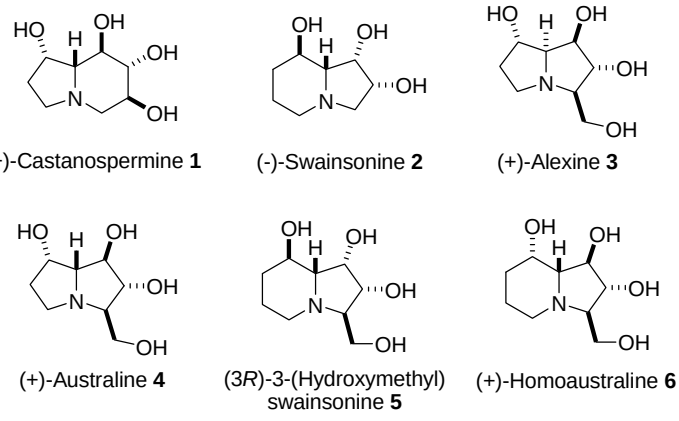


Figure 1. Structures of natural and unnatural polyhydroxylated indolizidine and pyrrolizidine alkaloids.

For these and other reasons, polyhydroxylated indolizidines and their stereochemical variants have been the subject of intensive synthetic efforts.[7] Pyrrolizidine alkaloids such as alexine (**3**)[8] and australine (**4**)[9] have also demonstrated potent glucosidase inhibitory activities. Synthetic efforts have also been directed

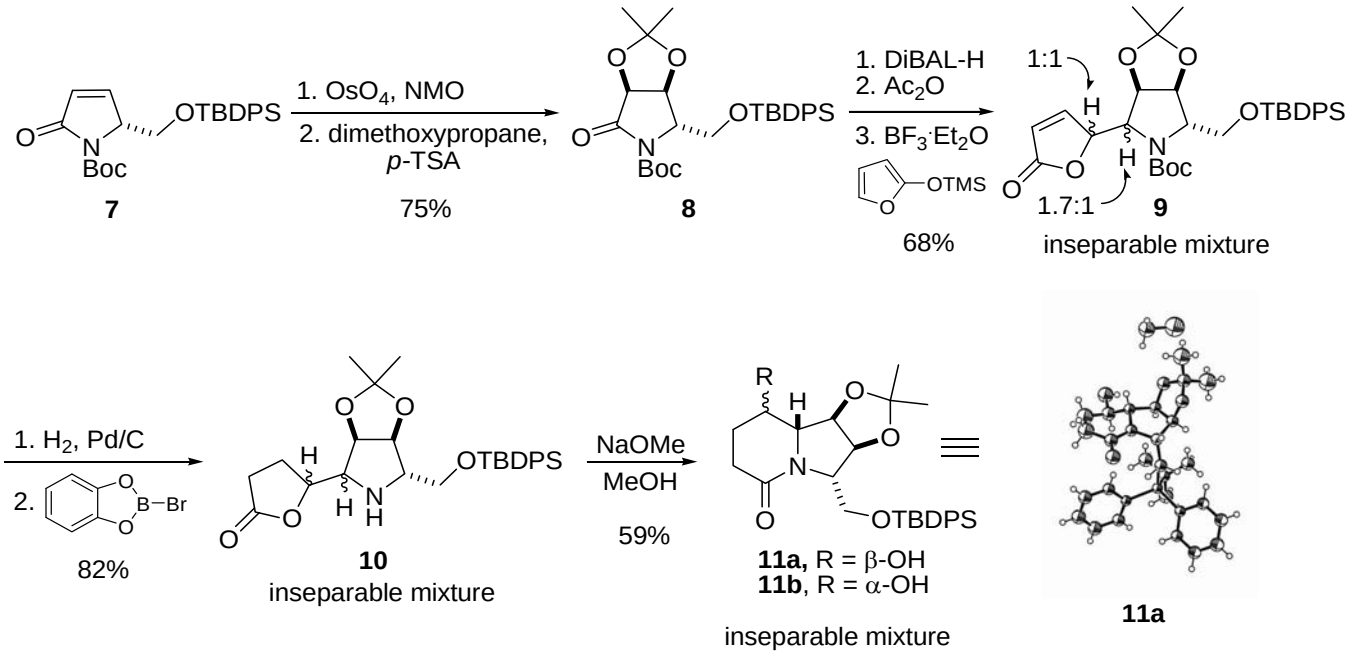
† Dedicated to Professor Steven Weinreb, wishing him the best in chemistry and in life.

at unnatural variants of polyhydroxylated indolizidine alkaloids such as **5** and **6**.[10] A large repertoire of strategies has been reported to construct these azabicyclic motifs, especially with regard to stereocontrolled introduction of various hydroxyl groups.[7] We report herein on two stereocontrolled approaches to the synthesis of polyhydroxylated indolizidines and indolizidinones starting with D- and L-pyroglutamic acid.[11]

RESULTS AND DISCUSSION

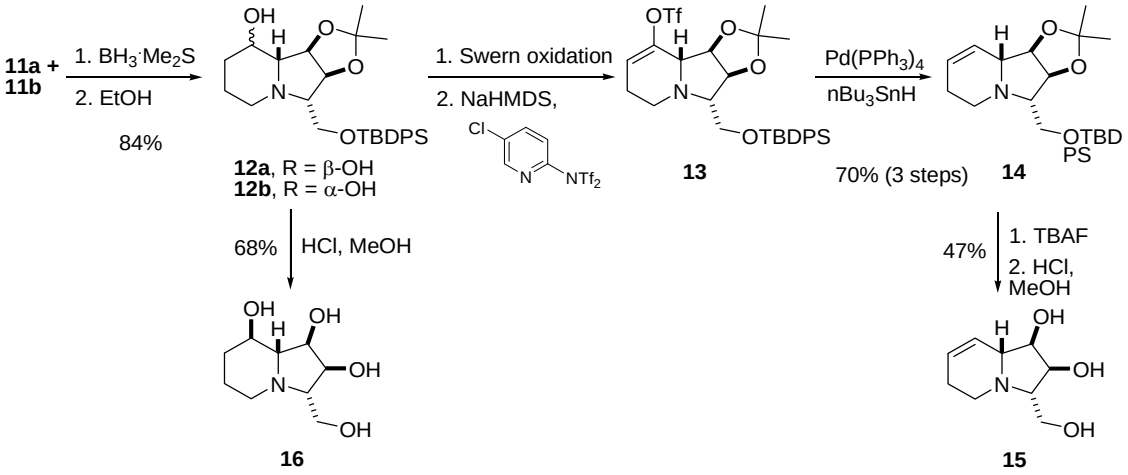
The readily available lactam intermediate (**7**)[12] was dihydroxylated[13] and the diol protected as the acetonide (**8**) in excellent overall yield (Scheme 1). Partial reduction of the lactam carbonyl followed by acetylation gave a mixture of *O*-acyl hemiaminals. Treatment with 2-(trimethylsilyloxy)furan in the presence of $BF_3{\cdot}Et_2O$[14] gave an inseparable mixture of four diastereoisomers (**9**). The ratios were determined later in the synthesis to be 1:1 for the butenolide stereogenic center and 1.7:1 for the pyrrolidine one (the major diastereoisomer is bearing the hydrogen β). On a 2 grams scale, the yield of **9** was 77-81%. The inseparable mixture was hydrogenated under standard conditions using Pd/C, prior to being treated with *B*-bromocatecholborane[15] to remove the *N*-Boc group and afford **10**. During the ring expansion[16] in the presence of NaOMe in MeOH, only the major diastereomer corresponding to the pyrrolidine moiety cyclized to give a mixture of lactams (**11**) in 59% yield. The uncyclized isomer was discarded. Upon standing, one of the diastereoisomers (**11a**) crystallized, the structure and stereochemistry of which were confirmed by a single crystal X-Ray analysis (Scheme 1).

Scheme 1.



Reduction of the mixture of lactams (**11**) with BH_3·DMS in THF led to the *O*-protected indolizidines (**12**) in excellent yield (Scheme 2). At this point, the two diastereoisomers were separable by flash chromatography. In order to further exploit the existing functionality and to provide access to more versatile scaffolds, we converted an epimeric mixture of **12** to the corresponding ketone, which was transformed smoothly to the enol triflate (**13**). This potential Suzuki reaction coupling partner was deoxygenated in the presence of $Pd(PPh_3)_4$ and *n*-Bu_3SnH[17] to the olefin (**14**). Deprotection under standard conditions led to the unsaturated indolizidine triol (**15**). Likewise, the deprotection of **12a** led to the indolizidine tetrol (**16**).

Scheme 2.



The modest ratio of the isomeric butenolide products (**9**) is undoubtedly due to a quasi equally hindered trajectory of approach of the silyloxyfuran nucleophile from either face of the incipient iminium ion (Figure 2).[14] Due to $A^{1,2}$ strain, the hydroxymethyl group with its bulky TBDPS group would adopt a pseudo-axial orientation, impeding α-face approach. Attack from the β-face appears to also be compromised due to the bulky acetal group, although not as much as the α-face, hence the modest selectivity. The importance of $A^{1,2}$ and $A^{1,3}$ strain in such systems is also evident from the pseudo-axial orientation of the hydroxymethyl side-chain in the solid state, as evidenced in the X-Ray structure of the lactam (**11a**) (Scheme 1).[18]

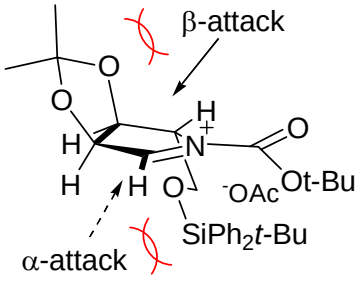
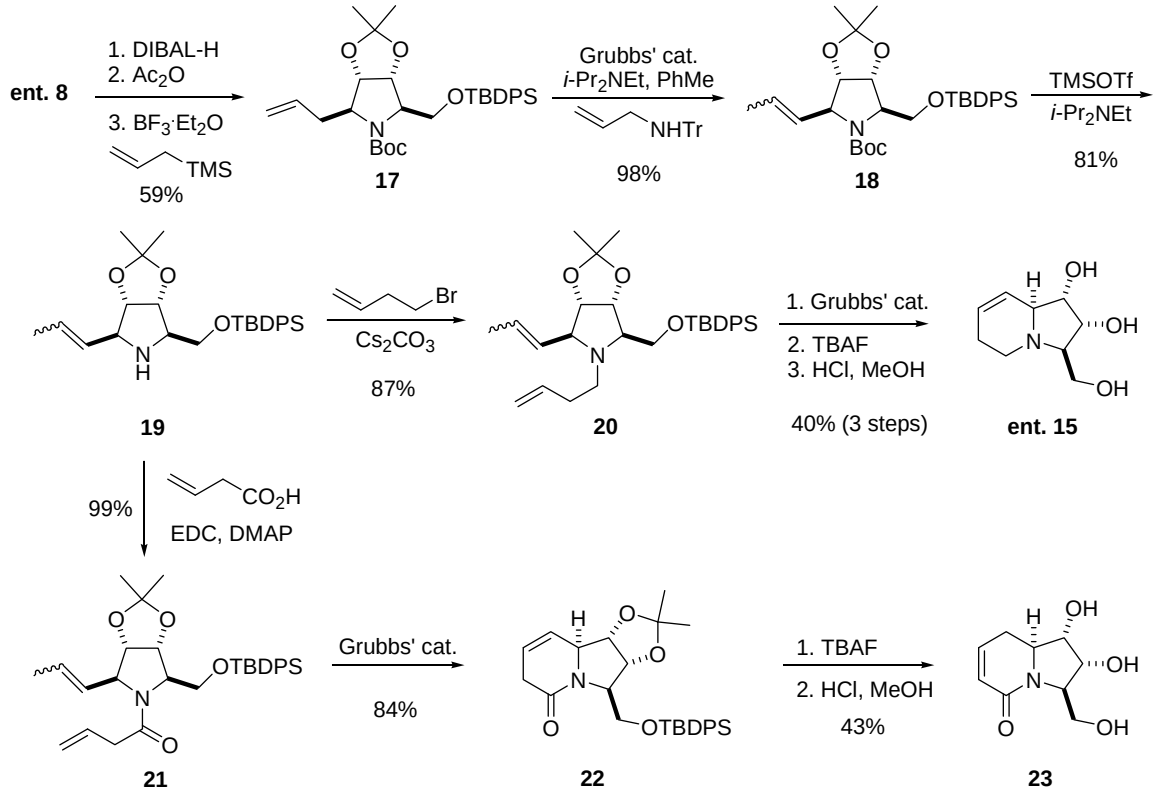


Figure 2. Trajectory of approach of the silyloxyfuran nucleophile onto the incipient iminium ion.

An alternative approach to polyhydroxylated indolizidinones was explored using the versatile ring closure metathesis reaction (Scheme 3).[19] Thus, the enantiomer of **8** obtained from L-pyroglutamic acid was sequentially partially reduced, acetylated, then treated with allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$[20] (Scheme 3). The 2,5-*cis* isomer (**17**) was isolated as the major product. Isomerization of the terminal double bond in the presence of *N*-tritylallylamine and Grubbs' second generation catalyst[21] led to a quantitative yield of the isomerized 2-propenyl compound (**18**). Cleavage of *N*-Boc group with TMSOTf[22] gave the free amine (**19**) which was *N*-alkylated with 4-bromo-1-butene in the presence of Cs_2CO_3[23] to afford the *N*-4-butenyl adduct (**20**). Ring closure metathesis proceeded in 85% yield to give the cyclic olefin. Cleavage of the silyl ether led to the acetal, which was in turn converted to the triol (**ent. 15**).

Scheme 3.

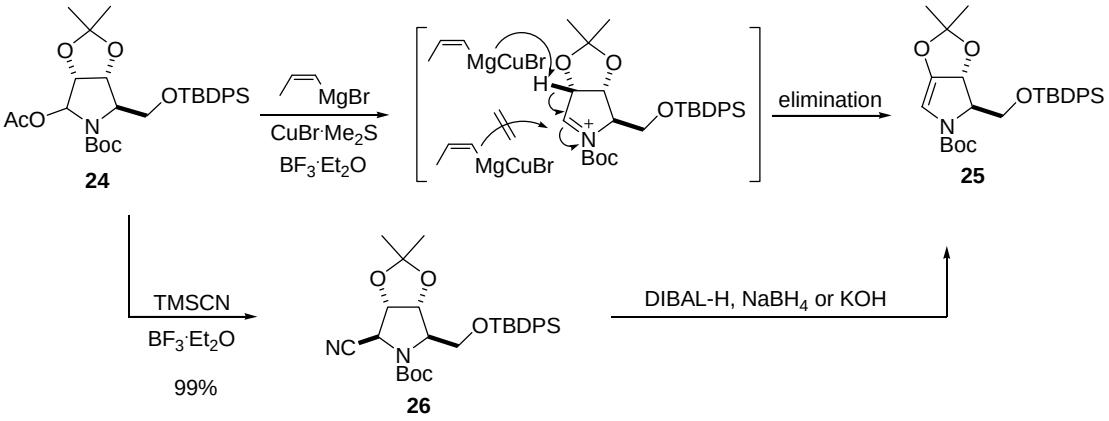


Alternatively, acylation of **19** with 4-butenoic acid gave **21**, which was smoothly converted to cyclic lactam (**22**) in the presence of Grubbs' second generation catalyst. Sequential deprotection of the silyl ether followed by the acetal gave the triol lactam (**23**). Migration of the double bond to the α,β-unsaturated lactam was confirmed by ^{1}H COSY NMR after the silyl ether removal.

Attempts to introduce a 2-propenyl group by reaction of **24** with 1-propenylmagnesium bromide in presence of $CuBr{\cdot}Me_2S$ and $BF_3{\cdot}Et_2O$ led to elimination of the acetate and formation of the ene-carbamate

(**25**) (Scheme 4). The 4-cyanopyrrolidine (**26**) was formed upon treatment of **24** with TMSCN and $BF_3{\cdot}Et_2O$[24] in quantitative yield. However, attempted reduction or hydrolysis led to the eliminated product (**25**).

Scheme 4.



CONCLUSION

In conclusion, we have described two basic approaches for the synthesis of enantiomeric polyhydroxylated indolizidinones starting with D- and L-pyroglutamic acid. These azabicyclic motifs are versatile scaffolds for further manipulation and exploitation as glycosidase inhibitors, or as intermediates in synthesis.

EXPERIMENTAL

Solvents were distilled under positive pressure of dry argon before use and dried by standard methods; THF and ether, from Na/benzophenone; CH_2Cl_2 and toluene, from CaH_2. All commercially available reagents were used without further purification. All reactions were performed under argon atmosphere. NMR (^1H, ^{13}C) spectra were recorded on Bruker AMX-300 and ARX-400 spectrometers in $CDCl_3$ with solvent resonance as the internal standard. Low- and high-resolution mass spectras were recorded on VG Micromass, AEIMS 902, or Kratos MS-50 spectrometers using fast atom bombardment (FAB). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in a 1 dm cell at ambient temperature. Analytical thin-layer chromatography was performed on Merck 60F 254 precoated silica gel plates. Flash column chromatography was performed using (40-60 m) silica gel at increased pressure. All melting points are uncorrected.

(3a*S*,4*S*,6a*S*)-*tert*-Butyl 4-((*tert*-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-6-oxotetrahydro[1,3]-dioxolo[4,5-*c*]pyrrole-5-carboxylate (8). To a 4:1 acetone/water solution (50 mL) of the unsaturated lactam (**7**) (3.66 g, 8.12 mmol) were added OsO_4 (100 mg, 0.41 mmol) and a 50% aqueous solution of

NMO (3.36 mL, 16.23 mmol). After overnight stirring, the reaction was neutralized with a saturated solution of $Na_2S_2O_4$ and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/Hexanes 50:50) to give the diol (3.13 g, 79%). To an acetone solution (21 mL) of that diol (2.55 g, 5.26 mmol), was added 2,2-dimethoxypropane (1.3 mL, 10.52 mmol) followed by *p*-toluenesulfonic acid (30 mg). After stirring for 1.5 h, the solution was neutralized with water and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/Hexanes 20:80) to give the acetal (**8**) (2.64 g, 95%); $[\alpha]_D$ +53.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.61-7.53 (m, 4H), 7.45-7.34 (m, 6H), 4.82 (d, *J* = 5.5 Hz, 1H), 4.55 (d, *J* = 5.4 Hz, 1H), 4.22 (s, 1H), 3.98 (dd, *J* = 2.2, 10.8 Hz, 1H), 3.76 (dd, *J* = 1.2, 10.7 Hz, 1H), 1.45 (m, 12H), 1.38 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.6, 150.0, 135.9, 135.8, 132.9, 132.3, 130.5, 128.3, 112.4, 84.0, 78.7, 76.1, 63.2, 62.3, 28.4, 27.6, 27.2, 26.1, 19.5; IR ($CHCl_3$, cm^{-1}): 2934, 1793, 1763, 1718, 1370, 1370, 1308, 1154, 1104; LRMS (*m/z*) [M^++1]: 526.8; HRMS calcd. for $C_{29}H_{40}NO_6Si$ 526.2625, found 526.2613.

(3a*S*,4*S*,6a*R*)-*tert*-Butyl 4-((*tert*-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-6-(5-oxo-2,5-dihydrofuran-2-yl)tetrahydro[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate (9). To a toluene solution (25 mL) of the lactam (**8**) (1.96 g, 3.73 mmol) at -78 °C, was added a 1.5 M toluene solution of Dibal-H (3.73 mL, 5.59 mmol) and the solution was stirred for 2 h. The solution was cooled to -78 °C, methanol (4 mL) was added and the solution was stirred for 30 min. Then, Et_2O (25 mL) was added and the solution was warmed back to room temperature, followed by the addition of water (1 mL). The gel that formed was filtered on Celite and washed with EtOAc (45 mL). The filtrate was concentrated under vacuum and the crude resulting mixture was used for the next step without further purification. To a CH_2Cl_2 solution (25 mL) of the previous crude material, were added Et_3N (1.56 mL, 11.2 mmol), DMAP (catalytic amount) and Ac_2O (1.05 mL, 11.2 mmol). After overnight stirring, the solution was neutralized with a 10% HCl (5 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/Hexanes 30:70) to give the acetate (1.87 g, 88%). To a CH_2Cl_2 solution (16.5 mL) of the acetate (1.87 g) cooled to -78 °C, was added $BF_3{\cdot}Et_2O$ (0.25 mL, 1.97 mmol) followed by trimethylsilyloxyfurane (0.83 mL, 4.92 mmol). After stirring for 2 h, the solution was neutralized with a 10% HCl solution (3 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/Hexanes 20:80) to give the butenolide (**9**) (1.5 g, 77%) as an inseparable mixture of diastereomers; IR ($CHCl_3$, cm^{-1}): 2933, 1765, 1698, 1383, 1114; LRMS (*m/z*) [M^++1]: 594.4.

5-((3a*R*,6*S*,6a*S*)-6-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo-

[4,5-*c*]pyrrol-4-yl)dihydrofuran-2(3*H*)-one (10). To an EtOAc solution (10 mL) of the butenolide mixture (**9**) (830 mg, 1.40 mmol), was added 10% palladium-on-carbon (15 mg) and the suspension was stirred under a hydrogen atmosphere overnight. The suspension was filtered on Celite, the cake washed with EtOAc (3 x 15 mL) and the filtrate concentrated under vacuum to give a colorless oil. To a CH_2Cl_2 solution (5 mL) of the previous oil, was added *B*-bromocatecholborane (362 mg, 1.82 mmol) in portions. The solution was stirred for 4 h, neutralized with a saturated solution of $NaHCO_3$ (7 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/Hexanes 50:50) to give the amine (**10**) (568 mg, 82%) as an inseparable mixture of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68-7.66 (m, 4H), 7.44-7.26 (m, 6H), 4.66-4.32 (m, 3H), 3.81 (m, 1H), 3.72 (m, 1H), 3.39-3.31 (m, 2H), 2.58-2.50 (m, 3H), 2.34-2.15 (m, 2H), 1.51 (s, 3H), 1.31 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.3, 177.1, 136.0, 135.9, 133.7, 133.6, 130.3, 130.2, 128.2, 128.1, 114.4, 114.3, 82.4, 82.1, 81.9, 81.6, 81.1, 80.3, 67.9, 67.0, 65.6, 65.5, 65.4, 65.0, 60.8, 28.8, 27.8, 27.3, 25.7, 25.6, 24.9, 24.2, 19.7, 19.6; IR ($CHCl_3$, cm^{-1}): 2933, 1781, 1428, 1213, 1113; LRMS (*m/z*) [M^++1]: 496.3.

(3a*S*,4*S*,9a*R*,9b*R*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-9-hydroxy-2,2-dimethylhexahydro[1,3]-dioxolo[4,5-*a*]indolizin-6(9b*H*)-one (11a and 11b). To a methanol solution (10 mL) of the amine (**10**) (430 mg, 0.87 mmol) at 0 °C, was added sodium methoxide (0.5 mL, 25% solution in methanol) and the solution was stirred for 3 h. After concentration under vacuum, a saturated solution of $NaHCO_3$ (3 mL) was added. The solution was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/Hexanes 60:40) to give the indolizidinones (**11a** and **11b**) (253 mg, 59%) as an inseparable mixture of diastereomers with recovery of unreacted minor isomer from **9**; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70-7.63 (m, 4H), 7.48-7.36 (m, 6H), 4.83 (t, *J* = 5.8 Hz, 0.5H), 4.64 (d, *J* = 6.3 Hz, 0.5H), 4.48 (dd, *J* = 4.0, 7.1 Hz, 0.5H), 4.38 (t, *J* = 6.6 Hz, 0.5H), 4.24 (br, 0.5H), 4.09 (br, 0.5H), 3.90-3.82 (m, 1H), 3.74-3.66 (m, 1H), 3.48 (m, 0.5H), 3.23 (br, 0.5H), 2.96 (m, 2H), 2.67 (d, *J* = 4.4 Hz, 0.5H), 2.50 (m, 0.5H), 2.10 (m, 3H), 1.54 (s, 3H), 1.34 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.0, 136.1, 135.9, 133.4, 133.1, 132.9, 130.5, 130.4, 130.3, 128.3, 128.2, 113.0, 82.6, 82.0, 70.2, 69.8, 64.7, 63.2, 62.5, 30.6, 28.4, 27.4, 26.0, 19.7; IR ($CHCl_3$, cm^{-1}): 2934, 1627, 1428, 1113; LRMS (*m/z*) [M^++1]: 496.3. Upon standing, the β-OH isomer (**11b**) crystallized, mp 97-99 °C; HRMS $C_{28}H_{37}NO_5Si$ 492.24410, found 492.24435.

(3a*S*,4*S*,9a*R*,9b*R*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethyl-octahydro[1,3]dioxolo[4,5-*a*]-indolizin-9-ol (12a and 12b). To a THF solution (2 mL) of the indolizidinones (**11a** and **11b**) (260 mg, 0.53 mmol) at 0 °C, was added borane-dimethyl sulfide complex (0.26 mL, 0.53 mmol) and the solution

was stirred for 1 h. The solution was then neutralized with ethanol (1 mL) and concentrated under vacuum. The residue was dissolved again in ethanol (5 mL) and the solution was heated to reflux for 6 h. The solution was concentrated under vacuum and the residue purified by flash chromatography (EtOAc/Hexanes 40:60) to give the indolizidines (**12a** and **12b**) (213 mg, 84%) as a mixture of diastereoisomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.69-7.67 (m, 4H), 7.46-7.38 (m, 6H), 4.58 (t, *J* = 6.7 Hz, 1H), 4.47 (dd, *J* = 4.2, 7.1 Hz, 1H), 4.02 (d, *J* = 10.7 Hz, 1H), 3.82 (dd, *J* = 4.3, 11.0 Hz, 1H), 3.74 (dd, *J* = 3.6, 10.9 Hz, 1H), 2.92 (d, *J* = 7.7 Hz, 1H), 2.63 (d, *J* = 3.9 Hz, 1H), 2.60 (d, *J* = 11.0 Hz, 1H), 2.40 (d, *J* = 5.8 Hz, 1H), 2.09 (m, 1H), 1.88 (d, *J* = 12.2 Hz, 1H), 1.64 (m, 1H), 1.52 (s, 3H), 1.43 (m, 2H), 1.34 (s, 3H), 1.08 (s, 9H); LRMS (*m/z*) [M^++1]: 481.3; HRMS calcd. for $C_{28}H_{39}NO_4Si$ 481.26484, found 481.26497.

(3a*S*,4*S*,9a*R*,9b*R*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethyl-3a,4,6,7,9a,9b-hexahydro-[1,3]dioxolo[4,5-*a*]indolizine (14). To a CH_2Cl_2 solution (3 mL) of oxalyl chloride (0.04 mL, 0.42 mmol) cooled to -78 °C, was added DMSO (0.03 mL, 0.44 mmol). After stirring for 30 min, a CH_2Cl_2 solution (1 mL) of the secondary alcohol (**12**) (100 mg, 0.21 mmol) was added. After stirring for another 30 min, Et_3N (0.58 mL, 4.2 mmol) was added, then the solution was stirred for 1 h, and was neutralized with water (5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 7 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under vacuum to give the ketone (100 mg, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.69 (d, *J* = 7.5 Hz, 4H), 7.45-7.39 (m, 6H), 4.71 (t, *J* = 6.8 Hz, 1H), 4.40 (t, *J* = 4.3 Hz, 1H), 3.85 (dd, *J* = 5.2, 10.9 Hz, 1H), 3.79 (dd, *J* = 3.9, 10.7 Hz, 1H), 3.21 (d, *J* = 10.5 Hz, 1H), 2.93 (d, *J* = 5.7 Hz, 1H), 2.79 (d, *J* = 4.2 Hz, 1H), 2.51-2.42 (m, 2H), 2.29 (m, 1H), 1.96 (m, 1H), 1.64 (m, 1H), 1.52 (s, 3H), 1.34 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 204.6, 136.1, 136.0, 130.2, 128.1, 114.5, 80.1, 76.8, 71.7, 64.2, 50.2, 27.6, 26.7, 25.9, 25.5, 19.7; IR ($CHCl_3$, cm^1): 2932, 2858, 1731, 1428, 1382, 1210, 1113; LRMS (*m/z*) [M^++1]: 480.4. To a THF solution (5 mL) of the previous ketone (100 mg, 0.21 mmol) cooled to -78 °C, was added a 1.0 M THF solution of NaHMDS (0.32 mL, 0.32 mmol). After stirring for 30 min, *N*-(5-chloro-2-pyridyl)triflimide (130 mg, 0.32 mmol) was added, the solution was stirred for 1 h at -78 °C, and then 16 h at rt. The reaction was neutralized by the addition of a saturated solution of NH_4Cl, and the aqueous layer was extracted with Et_2O. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum to give the triflate (**13**) that was used without further purification. To a THF solution (10 mL) of the previous triflate (**13**), was added tetrakis(triphenylphosphine)palladium (4 mg, 0.004 mmol), LiCl (13 mg, 0.63 mmol) and *n*-Bu_3SnH (0.08 mL, 0.27 mmol). After overnight stirring at reflux temperature, the solution was concentrated under vacuum and the residue was purified by flash chromatography (EtOAc/Hexanes 10:90) to give the unsaturated indolizidine (**14**) (68 mg, 71%); $[\alpha]_D$ +28.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400

MHz, $CDCl_3$) δ (ppm): 7.75-7.73 (m, 4H), 7.45-7.37 (m, 6H), 5.94 (td, *J* = 1.2, 10.0 Hz, 1H), 5.75-5.73 (m, 1H), 4.46 (q, *J* = 4.1 Hz, 1H), 4.19 (t, *J* = 7.2 Hz, 1H), 3.95 (dd, *J* = 5.7, 10.5 Hz, 1H), 3.82 (dd, *J* = 5.1, 10.5 Hz, 1H), 3.21 (t, *J* = 6.8 Hz, 1H), 2.96 (m, 1H), 2.84-2.80 (m, 1H), 2.45 (td, *J* = 6.6, 10.9 Hz, 1H), 2.31-2.28 (m, 1H), 2.09-2.00 (m, 1H), 1.55 (s, 3H), 1.35 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 135.6, 133.5, 133.4, 129.6, 127.7, 126.3, 113.5, 81.5, 81.1, 69.8, 67.5, 64.5, 47.0, 27.2, 26.7, 26.1, 25.2, 19.2; IR ($CHCl_3$, cm^{-1}): 2931, 2858, 1428, 1211, 1128; LRMS (*m/z*) [M^++1]: 464.2; HRMS calcd. for $C_{28}H_{37}NO_3Si$ 463.25427; found 463.25446.

(1*R*,2*S*,3*S*,8a*R*)-3-(Hydroxymethyl)-1,2,3,5,6,8a-hexahydroindolizine-1,2-diol (15). To a THF solution (1 mL) of the indolizidine (**15**) (16 mg, 0.03 mmol), was added a 1.0 M THF solution of TBAF (0.05 mL, 0.04 mmol). After stirring overnight, the reaction mixture was neutralized by the addition of a saturated solution of $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc) to give an alcohol (6 mg, 77%); $[\alpha]_D$ +40.7 (*c* 0.68, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.91 (dd, *J* = 1.2, 10.1 Hz, 1H), 5.74-5.72 (m, 1H), 4.62 (dd, *J* = 3.5, 7.0 Hz, 1H), 4.11 (t, *J* = 7.4 Hz, 1H), 3.75 (q, *J* = 9.0 Hz, 2H), 3.06-2.97 (m, 2H), 2.70 (br, 1H), 2.68 (d, *J* = 2.6 Hz, 1H), 2.18 (m, 1H), 2.08-2.02 (m, 1H), 1.49 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 126.8, 126.5, 114.2, 81.7, 81.5, 69.3, 67.7, 59.7, 45.8, 27.7, 26.6, 25.8; IR ($CHCl_3$, cm^{-1}): 3448, 2935, 1210, 1076; LRMS (*m/z*) [M^++1]: 226.1. The alcohol (6 mg) was dissolved in a 1.25 M MeOH solution of HCl (0.5 mL), and stirred overnight. The solvent was evaporated under vacuum, and the residue redissolved in MeOH (1 mL). Dowex Monosphere 550A (OH) anion exchange resin was added, and the mixture was stirred for 30 min. The mixture was filtered, and the resin bed was washed with MeOH. The filtrate was evaporated under vacuum, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH 84:15:1) to give the indolizidine (**15**) (3 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.99 (dt, *J* = 1.2, 10.1 Hz, 1H), 5.84-5.79 (m, 1H), 4.20 (q, *J* = 3.5 Hz, 1H), 3.83 (dd, *J* = 3.3, 11.4 Hz, 1H), 3.75 (dd, *J* = 1.8, 11.4 Hz, 1H), 3.64 (dd, *J* = 6.9, 9.4 Hz, 1H), 3.09 (dd, *J* = 6.3, 9.9 Hz, 1H), 2.96 (d, *J* = 6.7 Hz, 1H), 2.62 (d, *J* = 1.9 Hz, 1H), 2.46-2.30 (m, 2H), 2.16-2.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 126.3, 125.5, 72.5, 71.2, 71.0, 65.1, 58.9, 45.0, 26.2; LRMS (*m/z*) [M^++1]: 186.2; HRMS calcd. for $C_9H_{16}NO_3$ 186.11247, found 186.11302.

(1*R*,2*S*,3*S*,8*R*,8a*R*)-3-(Hydroxymethyl)octahydroindolizine-1,2,8-triol (16). The β-hydroxy indolizidine (**12a**) obtained from **11a** (7 mg, 0.01 mmol) was dissolved in a 1.25 M MeOH solution of HCl (0.5 mL), and stirred overnight. The solvent was evaporated under vacuum, and the residue redissolved in MeOH (1 mL). Dowex Monosphere 550A (OH) anion exchange resin was added, and the mixture was stirred for 30 min. The mixture was filtered, and the resin bed was washed with MeOH. The

filtrate was evaporated under vacuum, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH 84:15:1) to give the indolizidine (**16**) (2 mg, 68%); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 4.28 (s, 1H), 4.10-3.85 (m, 4H), 3.78 (d, *J* = 10.5 Hz, 1H), 3.26 (s, 2H), 3.00 (t, *J* = 12.5 Hz, 1H), 2.15-2.05 (m, 1H), 2.05-1.95 (m, 1H), 1.85-1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 74.4, 70.4, 68.6, 67.1, 61.1, 57.5, 52.4, 28.7, 17.6; HRMS calcd. for $C_9H_{18}NO_4$ 204.12303, found 204.12393.

(3a*S*,4*S*,6*R*,6a*R*)-*tert*-Butyl 4-allyl-6-((*tert*-butyldiphenylsilyloxy)methyl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate (17). The enantiomer of lactam (**8**) was sequentially treated with DIBAL-H and Ac_2O according to the procedure for the preparation of **9**. The acetate obtained (1.39 g, 2.44 mmol) was dissolved in CH_2Cl_2 (16 mL), and to this solution were added $BF_3{\cdot}Et_2O$ (0.61 mL, 4.89 mmol) and allyltrimethylsilane (0.58 mL, 3.66 mmol). After stirring for 3 h, the solution was neutralized with a saturated solution of $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/Hexanes 10:90) to give **17** (793 mg, 59%); $[\alpha]_D$ -32.7 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.67-7.64 (m, 4H), 7.41-7.36 (m, 6H), 5.76 (m, 1H), 5.05 (d, *J* = 10.2 Hz, 1H), 5.01-4.96 (m, 1H), 4.76 (m, 1H), 4.42 (d, *J* = 13.7 Hz, 1H), 4.15-4.00 (m, 2H), 3.89-3.81 (m, 1H), 3.76-3.73 (m, 1H), 2.63 (m, 0.5H), 2.48 (m, 0.5H), 2.20-2.13 (m, 1H), 1.47 (s, 6H), 1.38 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 153.9, 135.4, 135.3, 134.1, 129.7, 127.7, 117.5, 111.4, 79.6, 65.6, 63.8, 61.1, 60.2, 37.4, 28.2, 27.2, 26.9, 25.3, 19.1, 14.0; IR ($CHCl_3$, cm^{-1}): 2934, 2860, 1698, 1393, 1114; LRMS (*m/z*) [M^++1]: 552.3; HRMS calcd. for $C_{32}H_{45}NO_5Si$ 551.30670, found 551.30692.

(3a*R*,4*R*,6*S*,6a*S*)-*tert*-Butyl 4-((*tert*-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-6-(prop-1-enyl)-tetrahydro[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate (18). To a toluene solution (29 mL) of **17** (793 mg, 1.44 mmol), were added allyltritylamine (862 mg, 2.87 mmol), *N*,*N*-diisopropylethylamine (0.25 mL, 1.44 mmol), and Grubbs' 2nd generation catalyst (263 mg, 0.29 mmol). After stirring at reflux temperature for 2 days, the solution was concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc/Hexanes 5:95) to give **18** (780 mg, 98%); $[\alpha]_D$ -35.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71-7.66 (m, 4H), 7.45-7.37 (m, 6H), 5.61 (m, 1H), 5.50 (m, 1H), 4.76 (d, *J* = 5.6 Hz, 1H), 4.49 (d, *J* = 5.2 Hz, 1H), 4.21 (m, 2H), 3.79-3.75 (m, 2H), 1.57 (d, *J* = 6.3 Hz, 3H), 1.50 (s, 3H), 1.44 (s, 9H), 1.35 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 155.3, 136.4 (d), 133.8 (d), 130.7 (d), 130.6, 128.7 (d), 128.3, 112.4, 86.0, 83.5, 80.5, 67.5, 66.5, 64.6, 29.3, 28.2, 27.9, 26.3, 20.1, 18.4; IR ($CHCl_3$, cm^{-1}): 2934, 2860, 1697, 1393, 1113; LRMS (*m/z*) [M^++1]: 552.3.

(3a*R*,4*R*,6*S*,6a*S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethyl-6-(prop-1-enyl)tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole (19). To a CH_2Cl_2 solution (6.5 mL) of **18** (510 mg, 0.92 mmol) cooled at 0 °C, were added *N*,*N*-diisopropylethylamine (0.32 mL, 1.85 mmol) and trimethylsilyl trifluoromethanesulfonate (0.20 mL, 1.11 mmol). After stirring for 30 min, the solution was neutralized with a saturated solution of $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/Hexanes 25:75) to give the amine (**19**) (338 mg, 81%); $[\alpha]_D$ -4.3 (*c* 1.44, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70-7.67 (m, 4H), 7.46-7.38 (m, 6H), 5.76 (dd, *J* = 6.5, 15.3 Hz, 1H), 5.50 (ddd, *J* = 1.5, 7.1, 15.3 Hz, 1H), 4.46 (dd, *J* = 4.3, 7.0 Hz, 1H), 4.29 (t, *J* = 5.4 Hz, 1H), 3.88-3.85 (m, 1H), 3.78 (dd, *J* = 5.4, 10.4 Hz, 1H), 3.60 (t, *J* = 6.1 Hz, 1H), 3.34-3.30 (m, 1H), 2.35-2.30 (m, 1H), 1.72 (d, *J* = 5.8 Hz, 3H), 1.54 (s, 3H), 1.32 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 135.5, 135.4, 133.1, 130.5, 129.6, 127.6, 113.6, 85.6, 82.0, 66.4, 65.2, 64.6, 27.3, 26.8, 25.2, 19.2, 17.8; IR ($CHCl_3$, cm^{-1}): 2933, 2859, 1428, 1211, 1113, 1072; LRMS (*m/z*) [M^++1]: 452.2.

(3a*R*,4*R*,6*S*,6a*S*)-5-(But-3-enyl)-4-((*tert*-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-6-(prop-1-enyl)-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole (20). To an acetonitrile solution (6 mL) of the amine (**19**) (335 mg, 0.74 mmol), were added cesium carbonate (483 mg, 1.48 mmol), and 4-bromo-1-butene (0.83 mL, 0.82 mmol). After stirring the solution at reflux temperature for 4 h, the solution was concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc/Hexanes 5:95) to give **20** (325 mg, 87%); $[\alpha]_D$ -24.8 (*c* 1.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75-7.71 (m, 4H), 7.47-7.38 (m, 6H), 5.76-5.61 (m, 2H), 5.35-5.29 (m, 1H), 4.96 (d, *J* = 6.3 Hz, 1H), 4.93 (s, 1H), 4.49-4.45 (m, 1H), 4.20 (t, *J* = 6.2 Hz, 1H), 3.78 (dd, *J* = 4.5, 10.4 Hz, 1H), 3.61 (dd, *J* = 6.1, 10.4 Hz, 1H), 3.19 (t, *J* = 6.1 Hz, 1H), 3.09-3.04 (m, 1H), 2.67-2.60 (m, 2H), 2.16-2.06 (m, 2H), 1.73 (dd, *J* = 1.4, 6.4 Hz, 3H), 1.56 (s, 3H), 1.34 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 135.6, 135.5, 131.5, 129.6, 128.8, 127.7, 127.5, 115.3, 112.2, 83.4, 81.5, 71.7, 67.7, 65.0, 49.6, 29.6, 27.7, 26.7, 25.6, 19.1, 17.7; IR ($CHCl_3$, cm^{-1}): 2933, 2859, 1428, 1214, 1113; LRMS (*m/z*) [M^++1]: 506.3.

(3a*R*,4*R*,9a*S*,9b*S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethyl-3a,4,6,7,9a,9b-hexahydro-[1,3]dioxolo[4,5-*a*]indolizine (ent. 15). To a CH_2Cl_2 solution (13 mL) of the diene (**20**) (310 mg, 0.61 mmol), was added Grubbs' 2nd generation catalyst (28 mg, 0.03 mmol). After stirring for 3 h, the solution was concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc/Hexanes 10:90) to give the unsaturated indolizidine (**ent. 14**) (241 mg, 85%) with spectral data identical to **14**. The compound was then treated sequentially with TBAF and HCl in MeOH according to the procedure for the preparation of **15**.

1-((3a*R*,4*R*,6*S*,6a*S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethyl-6-(prop-1-enyl)tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-5-yl)but-3-en-1-one (21). To a CH_2Cl_2 solution (10 mL) of the amine (**19**) (799 mg, 1.77 mmol), were added EDC (509 mg, 2.65 mmol), DMAP (324 mg, 2.65 mmol), and 3-butenoic acid (0.22 mL, 2.65 mmol). After stirring for 5 h, the solution was neutralized with a saturated solution of $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/Hexanes 30:70) to give the diene (**21)** (919 mg, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.64-7.60 (m, 4H), 7.40-7.32 (m, 6H), 5.95-5.87 (m, 1H), 5.59-5.54 (m, 2H), 5.14-5.04 (m, 2H), 4.70 (d, *J* = 5.6 Hz, 1H), 4.48 (m, 2H), 4.32 (d, *J* = 6.7 Hz, 1H), 3.82 (d, *J* = 4.3 Hz, 1H), 3.60-3.56 (m, 1H), 3.10-3.01 (m, 2H), 1.53 (d, *J* = 5.1 Hz, 3H), 1.42 (s, 3H), 1.27 (s, 3H), 1.08 (s, 9H); LRMS (*m/z*) [M^++1]: 520.3.

(3a*R*,4*R*,9a*S*,9b*S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethyl-3a,4-dihydro[1,3]dioxolo-[4,5-a]indolizin-6(7*H*,9a*H*,9b*H*)-one (22). To a CH_2Cl_2 solution (35 mL) of the diene (**21**) (905 mg, 1.76 mmol), was added Grubbs' 2nd generation catalyst (80 mg, 0.09 mmol). After stirring for 1.5 h, the solution was concentrated under vacuum and the residue was purified by flash chromatography (EtOAc/Hexanes 30:70) to give the indolizidinone (**22**) (697 mg, 84%); $[\alpha]_D$ -58.2 (*c* 0.78, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.64-7.56 (m, 4H), 7.44-7.34 (m, 6H), 6.14 (d, *J* = 9.5 Hz, 1H), 5.96 (m, 1H), 4.60-4.54 (m, 2H), 4.48 (dd, *J* = 3.1, 10.5 Hz, 1H), 4.26 (s, 1H), 4.16-4.14 (m, 1H), 3.79 (dd, *J* = 2.0, 10.5 Hz, 1H), 2.95-2.90 (m, 2H), 1.55 (s, 3H), 1.36 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.6, 135.2, 132.6 (d), 129.5, 127.3, 124.8 (d), 112.0, 81.4, 80.7, 63.6, 61.9, 60.8, 33.9, 27.9, 26.5, 25.5, 18.9; IR ($CHCl_3$, cm^{-1}): 2933, 2858, 1661, 1429, 1217, 1113, 1078; SM (*m/z*) [M^++1]: 478.3; HRMS calcd. for $C_{28}H_{35}NO_4Si$ 478.33410, found 478.33424.

(1*S*,2*R*,3*R*,8a*S*)-1,2-Dihydroxy-3-(hydroxymethyl)-1,2,3,8a-tetrahydroindolizin-5(6*H*)-one (23). To a THF solution (10 mL) of the indolizidinone (**22**) (690 mg, 1.44 mmol) cooled at 0 °C, was added a 1.0 M THF solution of TBAF (2.17 mL, 2.17 mmol). After stirring for 1 h, the solution was neutralized with saturated $NaHCO_3$, and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc) to give the primary alcohol (206 mg, 60%); $[\alpha]_D$ -130.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.54 (t, *J* = 7.2 Hz, 1H), 5.79 (dd, *J* = 2.6, 9.7 Hz, 1H), 4.53 (d, *J* = 5.5 Hz, 1H), 4.48 (s, 1H), 4.38 (t, *J* = 6.0 Hz, 1H), 4.12 (s, 1H), 3.91 (dd, *J* = 3.1, 11.5 Hz, 1H), 3.70-2.60 (m, 2H), 2.53 (td, *J* = 5.4, 17.2 Hz, 1H), 2.20 (t, *J* = 14.7 Hz, 1H), 1.44 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.3, 140.7, 126.1, 113.0, 83.2, 82.0, 64.0, 63.9, 61.5, 29.1, 28.3, 26.1; IR ($CHCl_3$, cm^{-1}): 3385, 2998, 2938, 1654, 1596, 1446, 1379, 1218, 1079, 808; LRMS (*m/z*) [M^++1]: 240.1. The previous alcohol

(20 mg) was then dissolved in a 1.25 M MeOH solution of HCl (1.0 mL), and stirred overnight. The solvent was evaporated under vacuum, and the residue redissolved in MeOH (1 mL). Dowex Monosphere 550A (OH) anion exchange resin was added, and the mixture was stirred for 30 min. The mixture was filtered, and the resin bed was washed with MeOH. The filtrate was evaporated under vacuum, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH 84:15:1) to give the indolizidine (**23**) (12 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.84 (ddd, *J* = 1.9, 6.5, 9.0 Hz, 1H), 5.91 (dd, *J* = 2.9, 9.7 Hz, 1H), 4.14 (d, *J* = 4.3 Hz, 1H), 4.08 (dd, *J* = 4.3, 9.3 Hz, 1H), 3.97 (t, *J* = 4.1 Hz, 1H), 3.78-3.71 (m, 2H), 3.33 (p, *J* = 1.6 Hz, 1H), 2.67 (ddd, *J* = 5.1, 6.1, 17.4 Hz, 1H), 2.28 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.0, 141.9, 123.5, 75.5, 72.0, 65.4, 59.0, 58.2, 27.6; LRMS (*m/z*) [M^++1]: 200.1; HRMS calcd. for $C_9H_{13}NO_4Na$ 222.07368, found 222.07431.

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