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Synthesis of Diversely Functionalized Indolizidinones and Related Bicyclic Lactams Using Intramolecular Grubbs Olefin Metathesis and Dieckmann Condensation

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Bicyclic 1-aza-2-oxo ring systems with versatile functionality were synthesized from the Grubbs olefin metathesis of appropriate olefinic precursors, starting with L-pyroglutamic acid. The carbocyclization products were further functionalized utilizing the double bond or by enolate chemistry of the corresponding β,γ-unsaturated bicyclic lactam. In an alternative strategy, indolizidinones were synthesized by application of an intramolecular Dieckmann cyclization. A constrained peptidomimetic thrombin inhibitor was prepared from one of the bicyclic indolizidinones.

Fused bicyclic lactams such as 1-aza-2-oxobicyclo[4.3.0]-nonanes (indolizidinones) with added functionality are among the more versatile of enantiopure nitrogen heterocycles.[1] Their utility as structurally and functionally distinct motifs spans a broad cross-section of areas. Thus, applications can be found in natural products,[2] enzyme inhibitors,[3] ligands for receptors,[4] and mimics of peptide secondary structures[1−5] and as intermediates for synthesis.[6] Substituted 1-aza-2-oxobicyclo[*x.y.z*]alkanes, exemplified by 3*S*-amino-6*S*-indolizidin-2-one-9*S*-carboxylic acid **1** (Figure 1), and related congeners or diastereomers have gained popularity as constrained mimetics of dipeptide β-turns such as Ala-Pro. As a result, several synthetic approaches toward the core 6,5-fused bicyclic lactam have been reported in the past decade. With few exceptions, these methods have relied on an intramolecular reductive amination of δ-keto-bis-α-amino acid derivatives, leading to a 5-branched proline ester, followed by lactam formation (Figure 2). A first short

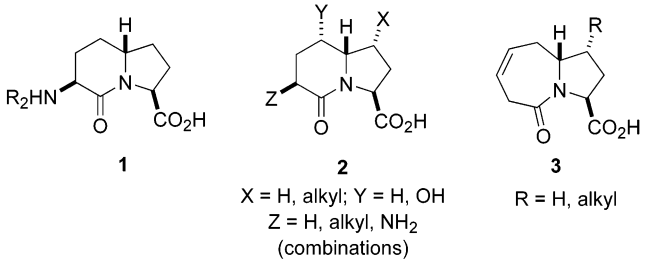

FIGURE 1. Structures of 1-aza-2-oxo-bicyclic amino acids.

synthesis by Mueller and Revesz[7] relied on a Schöllkopf asymmetric alkylation[8] to give the desired bis-amino acid precursor (Figure 2A). Lombart and Lubell[9] utilized an *N*-protected L-glutamic acid precursor in a Claisen condensation to access the δ-keto precursor. The same approach was also adopted by Kim and Kahn[10] utilizing a different *N*-protection (Figure 2B). The method was recently extended to the synthesis of enantiopure 5- and 5,7-di-C-substituted analogues of **1** including 6,6-fused bicyclic lactams.[9c] Hruby and co-workers[11] capitalized on asymmetric catalytic hydrogenation of bis-α,β-unsaturated amino acid derivatives to obtain the desired C_2-symmetrical precursor (Figure 2C). An approach to the synthesis of all possible isomers of **1** was recently reported by Mulzer and co-workers,[12] who started with D- or L-pyroglutamic acid and then elaborated the amino

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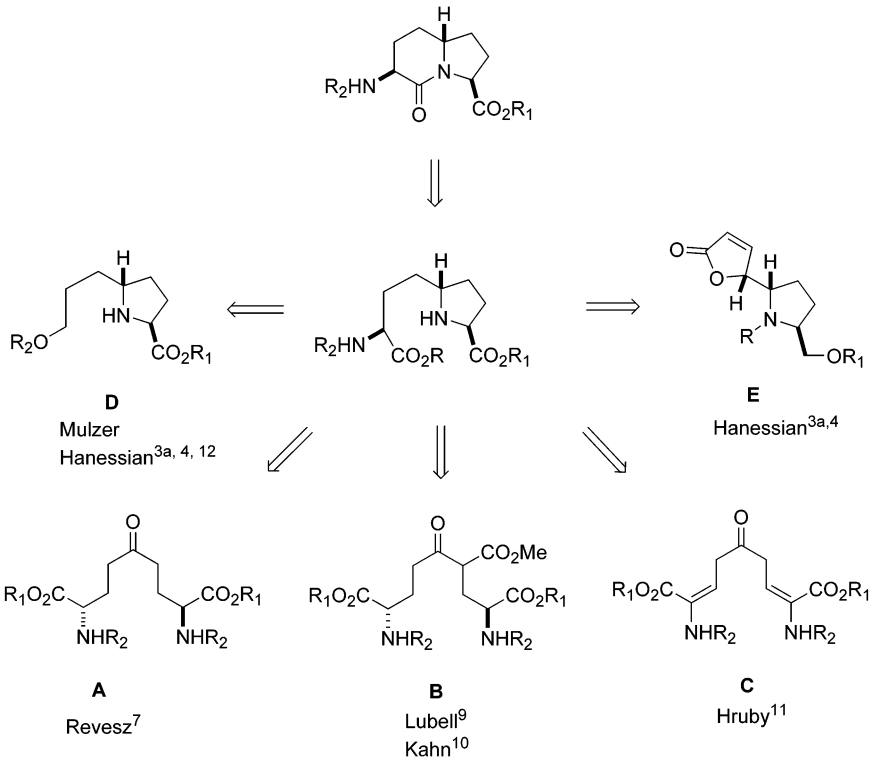

FIGURE 2. Diverse routes to enantiopure indolizidinones.

acid appendage, followed by lactam formation (Figure 2D). Two previous reports from our group that utilized D- or L-pyroglutamic acid as readily available chirons have described the incorporation of appropriate two- and four-carbon branching at C-5, lactam formation, and ultimately the introduction of an azide group as a masked 3-amino group via lactam enolate chemistry[3a,4] (Figure 2D,E). Other methods are also available for the synthesis of enantiopure 6,5-[13] and 7,5-fused[13−15] bicyclic lactams related to the general structure represented by **1**.

We report herein on two versatile methods for the construction of *functionalized* enantiopure 1-aza-2-oxobicyclo[4.3.0]nonane carboxylic acid **2** and the analogous [5.3.0]decenecarboxylic acid **3** (Figure 1). These methods were primarily directed at the synthesis of 4- and 5-substituted 3-amino-2-oxobicyclo[4.3.0]nonane-9-carboxylic acids as prototypical scaffolds in inhibitor[3a] and antagonist design.[4]

The first of these methods demonstrates yet another example of the versatility of the Grubbs olefin metathesis reaction[16] in the carbocyclization of enantiopure precursors to the intended bicyclic lactams.[17] Thus, the readily available chiron **4** was transformed to the known[18] 5*S*-(2-propenyl) derivative **5**, which was further manipulated to afford the diolefin intermediate **6**. Carbocyclization via the Grubbs metathesis reaction afforded **7** in 93% yield while maintaining the position of the double bond. This versatile bicyclic lactam could be easily obtained from **4** in six steps and good overall yield.

Hydrogenation of **7** followed by transformation to the alcohol and silylation afforded **9**. Treatment with LDA and trisyl azide[3a,19] afforded the corresponding 3*S*-azido derivative **10**, as confirmed by a single-crystal X-ray structure (Scheme 1). Treatment of **7** with LDA at −78 °C and addition of 1-cyclohexenylmethyl bromide afforded **12** in 79% yield as a major isomer in a 5:1 mixture. Enolate alkylation of **9**[20] under the same conditions gave the expected C-adduct in only 48% yield with recovery of starting material, reflecting on the versatility and higher reactivity of the allylic lactam enolate derived from **11** compared to **9**, and without affecting the double bond. The 3*S*-stereochemistry in **12** and its 4,5-saturated analogue (not shown)[20] was inferred from the structure of the azide **10**. The double bond in **7** was stereoselectively epoxidized with trifluoroperacetic acid to give **13** as a major isomer in a 9:1 mixture. Treatment with LDA led, as expected, to β-elimination affording the allylic

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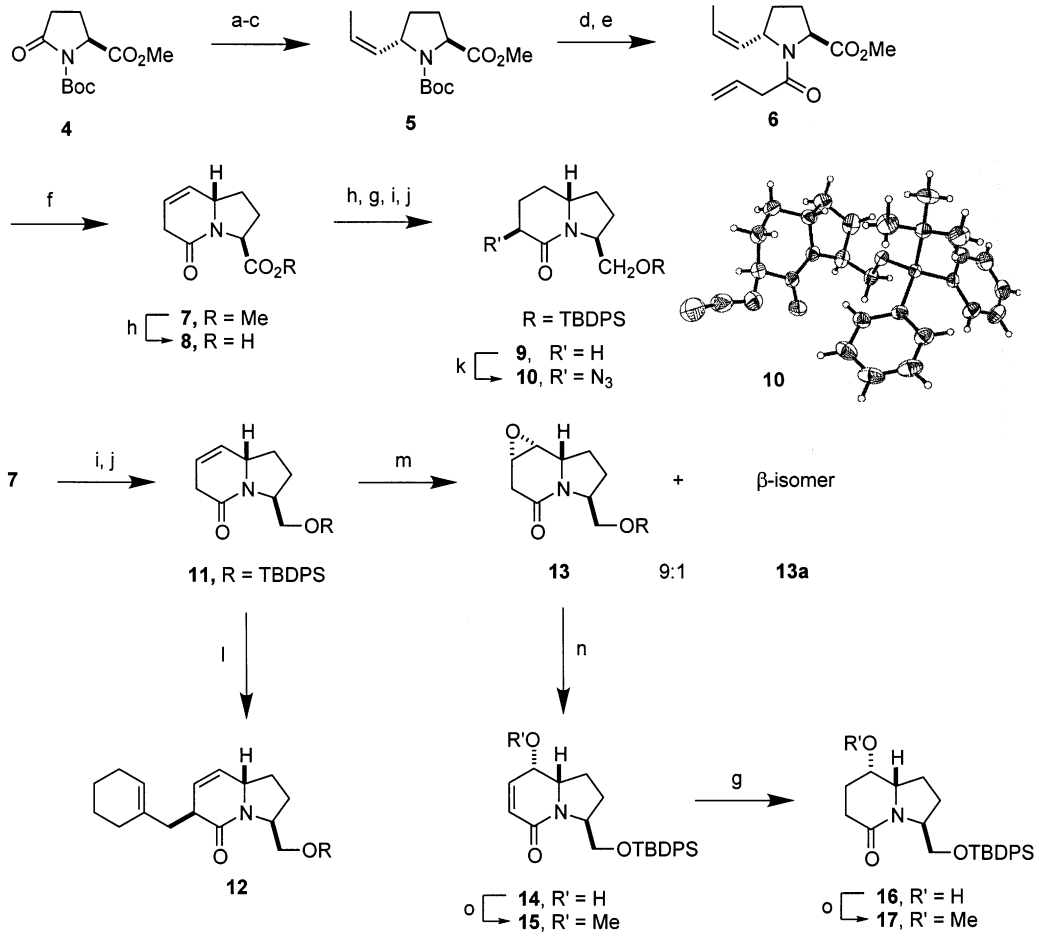
SCHEME 1[a]



[a] Reagents and conditions: (a) $LiEt_3BH$, THF, −78 °C; (b) PTSA, MeOH; (c) (Z)-1-lithiopropene, CuBr·DMS, BF_3·OEt_2, diethyl ether, 92%; (d) TFA, CH_2Cl_2, 99%; (e) vinylacetic acid, EDC, DMAP, CH_2Cl_2, 88%; (f) $Cl_2(Cy_3P)_2Ru{=}CHPh$, CH_2Cl_2, 93%; (g) H_2, Pd/C, MeOH, 97%; (h) LiOH, THF/H_2O, 92%; (i) (i) ethyl chloroformate, Et_3N, THF, (ii) $NaBH_4$, MeOH, 77%; (j) TBDPSCl, imidazole, DMF, 85%; (k) LDA, trisyl azide, THF, −78 °C, 65%, 6:1 syn/anti; (l) LDA, 1-cyclohexenylmethyl bromide, THF, −78 °C, 79%; (m) TFAA, urea−H_2O_2 complex, CH_2Cl_2, 77%; (n) LDA, THF, −78 °C, 92%; (o) KH, MeI, THF, 65%.

alcohol **14**. Catalytic reduction of **14** and its *O*-methyl ether **15** afforded the saturated bicyclic lactams **16** and **17,** respectively. Definitive confirmation for the 4*S*-configuration in **14**, and hence in the α-epoxide **13**, was obtained by comparison with a sample obtained by an independent method.[3a] It is of interest that the epoxidation takes place from the seemingly less accessible concave face of the bicyclic lactam **11**. While it is possible that the bulky *tert*-butyldiphenylsilyl ether may have a steric influence on the epoxidation reaction, a more plausible rationalization of the stereochemical course of α-epoxidation is discussed below following a similar result on a biased system.

We then proceeded to prepare 7-substituted indolizidinones related to **1**, with synthetically relevant functionality in the lactam portion for further manipulation toward the deployment of potential pharmacophores directed at Factor VIIa.[20] Stereoselective alkylation[21] of **4** with a variety of arylalkyl and arylalkenyl bromides led to the corresponding anti-alkylation products **18**−**20** as major isomers (Scheme 2). Following the same sequence of reactions that afforded **5**, the 5-*cis*-(2-propenyl)-L-prolines **21** and **22** were obtained in excellent yields.[22] On the basis of X-ray crystallographic analysis of an advanced intermediate (see below), it was clear that the *cis*-(2-propenyl) group was syn relative to the bulky arylalkyl groups and anti with respect to the ester in the adducts **21** and **22**. Wistrand[23] has suggested that the cuprate reagent coordinates to the ester group, thus shielding the *β*-face of the *N*-acyliminium ion in related cases, which is also applicable to the present case, where the steric bias of the complexed ester group overides that of the *syn*-C-4 arylalkyl chain. Removal of the *N*-Boc group and acylation with vinyl acetic acid afforded **23** and **24**, respectively. These were subjected to a Grubbs metathesis leading to the bicyclic lactams **25** and **26**, respectively. The modest yields compared to the unsubstituted analogue **7** could be due to the effect of the relatively bulky C-4 chain.

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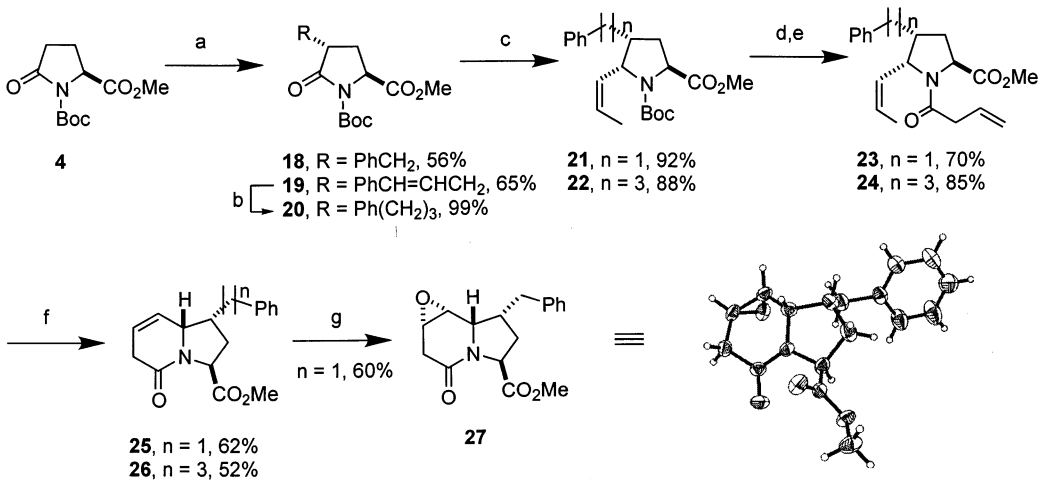
SCHEME 2[a]



[a] Reagents and conditions: (a) (i) LiHMDS, THF, −78 °C, (ii) RBr; (b) H_2, Pd/C, EtOAc; (c) (i) $LiEt_3BH$, THF, −78 °C, (ii) PTSA, MeOH, (iii) (Z)-1-lithiopropene, CuBr·DMS, BF_3·OEt_2, diethyl ether; (d) TFA, CH_2Cl_2; (e) vinylacetic acid, EDC, DMAP, CH_2Cl_2; (f) $Cl_2(Cy_3P)_2Ru$=CHPh, CH_2Cl_2; (g) *m*-CPBA, CH_2Cl_2.

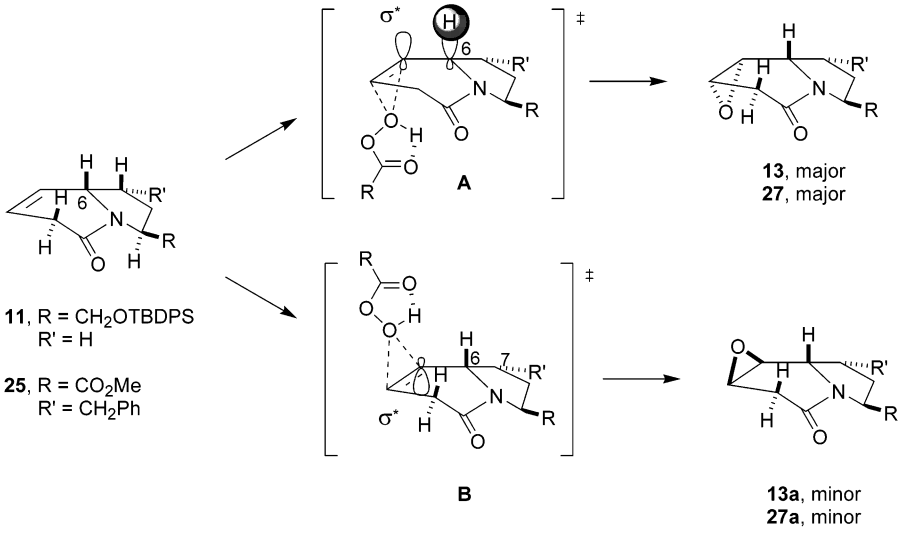


FIGURE 3. Cieplak effect in the transition-state model.

Epoxidation of **25** with *m*-CPBA gave a crystalline product **27**, whose structure was definitively confirmed by an X-ray analysis (Scheme 2). Here too, epoxidation had occurred from the concave face of the indolizidinone despite the presence of a *syn*-C_7 benzyl group. The stereochemical preference for the formation of **13** and **27** as major products can be rationalized by considering a favorable electron-donating ability of the C_6−H σ bond with the developing antibonding orbital in the transition-state model **A** leading to the α-epoxide as illustrated in Figure 3. Approach of the peracid from the convex face is depicted in the transition-state model **B**, in which the less electron-donating C_6−C_7 σ bond would be involved (Figure 3). This stereoelectronic effect (Cieplak effect)[24] could provide a greater stabilization for pathway **A** compared to **B** that overrides the steric effects of a pseudoaxial syn substituent as in **25**. Such a rationalization has been postulated for the epoxidation of an unsubstituted Δ-4,5-unsaturated indolizidinone and in related systems.[25] It may also account for the epoxidation of a sterically biased bicyclo[3:3:0]octene and other alkenes from the more hindered concave side.[26]

It was also of interest to explore synthetic routes to C-7 substituted indolizidinones with an opposite configuration at C-6. We chose the *C*-benzyl- and *C*-(3-phenylpropyl)-substituted *N*-Boc methyl L-pyroglutamates **18** and **20** as substrates (Scheme 3). Transformation to the 3-acetoxy analogues **28** and **29**, respectively, followed by treatment with allytributylstannane or allyltrimethylsilane in the presence of BF_3·Et_2O, led to the 2,5-syn-substituted products **30** and **31**, respectively, in excellent overall yields from **18** and **20,** respectively. Confirmation of stereochemistry was secured from an X-ray analysis

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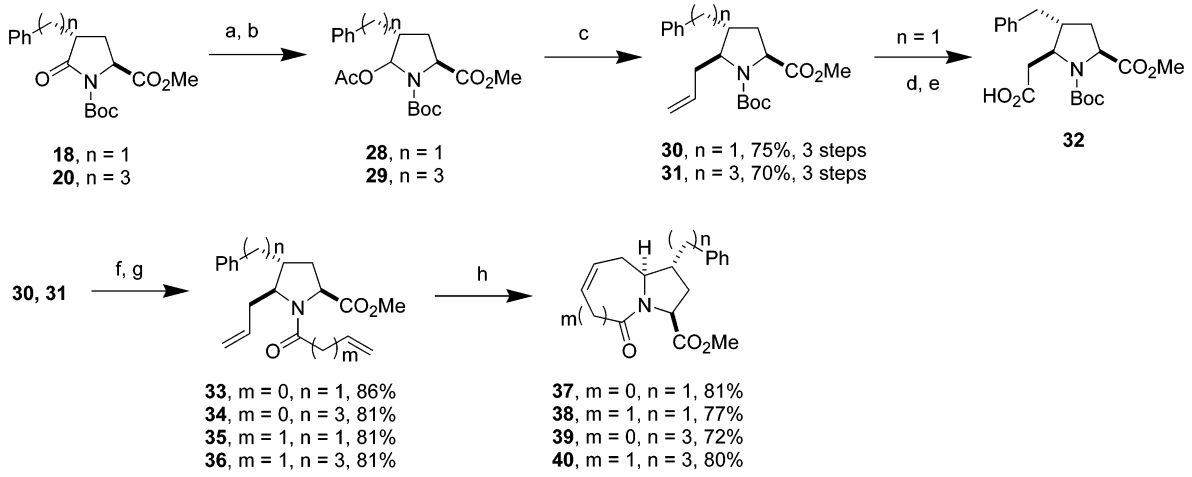
SCHEME 3[a]



[a] Reagents and conditions: (a) $LiEt_3BH$, THF, −78 °C; (b) Ac_2O, DMAP, Et_3N, CH_2Cl_2; (c) allyltributyltin, $BF_3{\cdot}OEt_2$, toluene, −78 °C; (d) $NaIO_4$, OsO_4, THF/H_2O, 83%; (e) Jones' reagent, acetone, 89%; (f) TFA, CH_2Cl_2, 91%; (g) $CH_2{=}CH(CH_2)_nCO_2H$, EDC, DMAP, CH_2Cl_2; (h) $Cl_2(Cy_3P)_2Ru{=}CHPh$, CH_2Cl_2.

of the oxidation product **32** (Scheme 3). There are many examples of C-5-substituted prolines based on the addition of carbon nucleophiles to *N*-acyliminium ions.[18,22,23,27,28] The >20:1 ratio of 4,5-anti-addition products in the addition of allyltributylstannane to the incipient *N*-acyliminium ion generated from **28** and **29**, respectively, is most probably due to the steric effect exerted by the C-4 arylalkyl group. The use of $BF_3{\cdot}Et_2O$ in toluene as solvent was found to be optimal, as compared to dichloromethane (~10:1 4,5-anti/syn) and $Cu(OTf)_2$ in dichloromethane (~6:1). The combination of allyltrimethylsilane and $BF_3{\cdot}Et_2O$ was also highly anti-selective, albeit in somewhat lower yield (71% compared to 81%). In contrast to our results, allylation of an *N*-acyliminium ion related to **28** (C-4-allyl instead of arylalkyl)[29] with allyltributylstannane in the presence of *tert*-butyldimethyl trifluoromethanesulfonate led to a 3:1 mixture of *anti*- and *syn*-5-*C*-allyl prolinates.[30] The dramatic influence of the solvent and catalyst is reflected in the opposite stereochemical outcome when allyltributylstannane and $BF_3{\cdot}Et_2O$ in toluene were used in a related *N*-Cbz derivative.[31] $A^{1,3}$ strain[32] may also play a role in addition to factors related to steric and solvent/catalyst effects in these addition reactions.

Each of the C-branched products **30** and **31** was transformed into the corresponding *N*-acryloyl or *N*-(1-propenoyl) analogues **33**−**36** (Scheme 3). Ring-closure metathesis proceeded smoothly in each case to afford the 3,4-unsaturated fused 7,5-bicyclolactams **37**−**40**.

An alternative approach to the 1-azabicyclo[4.3.0]-nonane-9-carboxylic acid motif was developed on the basis of an intramolecular Dieckmann cyclization of a diester. To the best of our knowledge, cyclizations to afford indolizidinones such as **2** or **3** (Figure 1) have few, if any, precedents and warrant further investigation.[33] Trimethylsilylethyl *N*-Boc L-pyroglutamate **40** was converted to the 5*S*-(2-propenyl) derivative **42** on the basis of the chemistry described above (Scheme 4). Cleavage of the *N*-Boc group and acylation with mono trimethylsilylethyl succinate afforded the *N*-acyl derivative **43**, which was subjected to intramolecular Dieckmann condensation as the K enolate. The resulting β-keto ester **44** was treated with TFA to afford the 5-keto indolizidinone **45** in good yield. Reduction with L-Selectride afforded a single isomer **46** on the basis of NMR data. Oxidative cleavage of the olefinic appendage to the aldehyde, followed by reduction and protection, afforded the 5-hydroxyindolizidinone **16**, which was found to be identical to a sample obtained by the metathesis route (see Scheme 1).

In a previous publication,[3a] we had prepared **16** by a different route and converted it to the thrombin inhibitor **47** (IC_{50} 20 nM). A cocrystal of **47** with thrombin revealed a H-bonding interaction of the tertiary hydroxy group and the lactam carbonyl with Gly-216. Literature precedents[34] of prototypical inhibitors derived from a Phe-Pro-Arg scaffold had shown the same H-bonding with the Phe amino group and the Phe-Pro amide carbonyl. We were therefore interested in the synthesis of a constrained analogue in which the hydroxy group of **47** was replaced by an amino group, and to compare its antithrombin activity to the hydroxy predecessor.

The readily available intermediate **48**[4,35] was transformed via iminium ion chemistry to the anti 2-propenyl adduct **49** (Scheme 5).[18] Cleavage of the *N*-Boc group followed by *N*-acylation gave the expected amide which was subjected to a Grubbs ring-closure metathesis reac-

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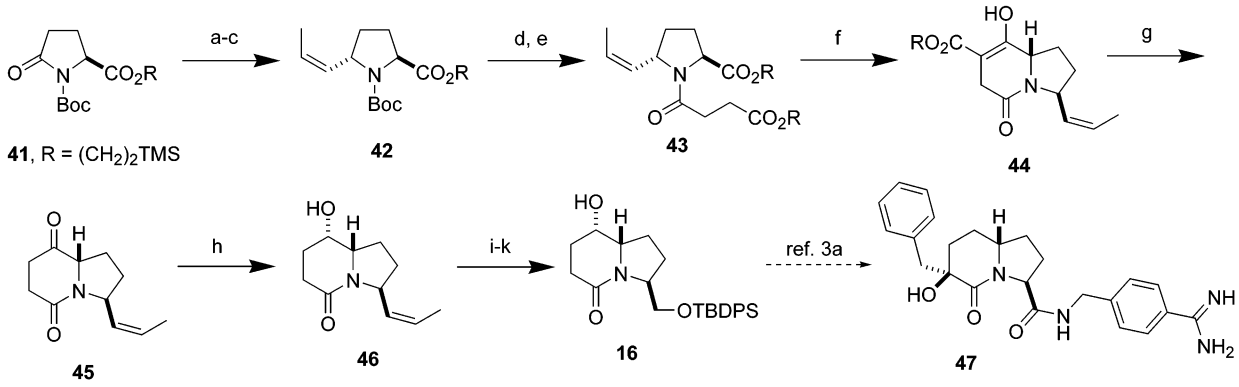
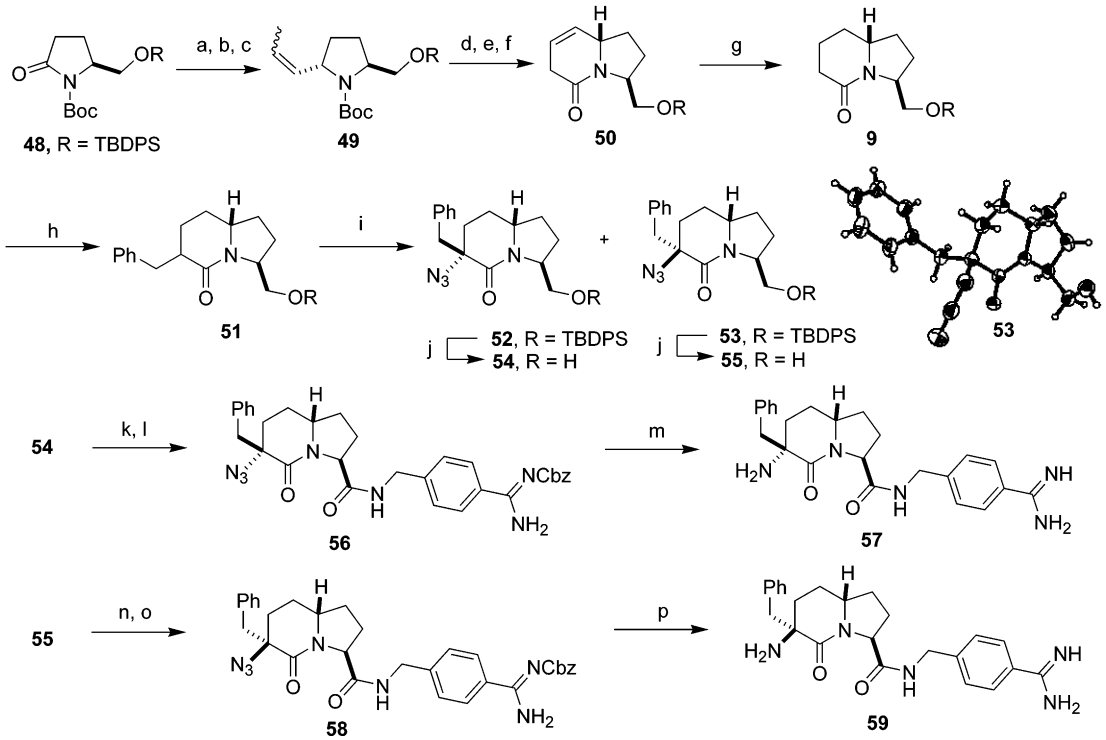
SCHEME 4[a]



[a] Reagents and conditions: (a) DIBAL-H, toluene, THF, −78 °C, 99%; (b) Ac_2O, pyridine, DMAP, CH_2Cl_2, 85%; (c) (*Z*)-1-lithiopropene, CuBr·DMS, BF_3·OEt_2, Et_2O, −78 °C, 67%; (d) TFA, CH_2Cl_2, 80%; (e) $HO_2C(CH_2)_2CO_2(CH_2)_2TMS$, BOP-Cl, *i*-$Pr_2NEt$, CH_2Cl_2, 78%; (f) KHMDS, toluene/THF, −78 °C to rt, then glacial AcOH, 52%, dr > 5:1; (g) TFA, CH_2Cl_2, 67%; (h) L-Selectride, THF, −78 °C, 76%; (i) $NaIO_4$, OsO_4, THF/H_2O; (j) $NaBH_4$, EtOH, 0 °C; (k) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 33% (overall, three steps).

SCHEME 5[a]



[a] Reagents and conditions: (a) DiBAL-H, toluene, −78 °C; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 80%; (c) 1-propenylmagnesium bromide, CuBr·DMS, BF_3OEt_2, Et_2O, −40 to 0 °C, 5 h, 70%; (d) TMSOTf, *i*Pr_2NEt, CH_2Cl_2, 89%; (e) vinylacetic acid, EDC, DMAP, CH_2Cl_2, 85%; (f) $Cl_2(Cy_3P)_2Ru$=CHPh, CH_2Cl_2, 94%; (g) H_2, Pd/C, EtOAc, 96%; (h) *t*-BuLi, BnBr, THF, −78 °C, 67%; (i) *t*-BuLi, trisyl azide, THF, −78 °C, 28% (**52**), 15% (**53**); (j) TBAF, THF, 99%; (k) PDC, wet DMF; (l) EDC, HOBT, *i*Pr_2NEt, *N*-Boc-4-(aminomethyl)benzamidine, DMF, 63% (two steps); (m) H_2, Pd/C, MeOH/HCl, 99%; (j), 90%; (n) PDC, wet DMF; (o) EDC, HOBT, *i*-Pr_2NEt, *N*-Cbz-4-(aminomethyl)benzamidine, DMF, 53% (two steps); (p) H_2, Pd/C, MeOH/HCl, 99%.

tion.[16] The carbocyclization product **50**, obtained in excellent yield, was identical to a product prepared from **7** by reduction of the ester and protection. Catalytic hydrogenation of **50** and alkylation of the lithium enolate with benzyl bromide gave a mixture of *C*-benzyl product **51**, which was treated with *tert*-butyllithium and trisyl azide[19] to give a 1:2 mixture of the desired *S*-azido adduct **53** and its *R*-epimer **52** in modest overall yield. A similar sequence of reactions utilizing the Davis oxaziridine reagent[36] as the electrophile had given the expected *S*-hydroxy precursor to **47** in 63% yield. Evidently, the more sterically demanding azide-transfer reagent coupled with the lower reactivity of the lactam lithium enolate could be responsible for the modest yield. It is of interest that the approach of the reagent from the endo side of the bicyclic ring system was favored, presumably due to the bulky OTBDPS group. The isomeric adducts were

(36) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919; Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241.

each transformed to the respective potential inhibitors **57** and **59** by well-precedented reactions. As expected, the *S*-amino analogue **59** (IC_{50} 4.7 nM) was a stronger inhibitor of thrombin, compared to the epimer **57** (IC_{50} 2.5 μM). It is also of interest that the amino analogue **59** was more active than the hydroxy equivalent **47**, which validated the more effective H-bonding requirement with Gly-216 in thrombin.[3a]

The functionalized indolizidinones reported in this study are not as readily available by other methods. They should find interesting applications in the synthesis of rigid scaffolds that display useful pharmacophores in drug design, in natural product synthesis, and as β-turn mimics.

Experimental Section

(2*S*,5*S*)-1-But-3-enoyl-5-*cis*-propenylpyrrolidine-2-carboxylic Acid Methyl Ester (6). A solution of **5** (4.38 g, 16.3 mmol) was stirred in CH_2Cl_2 (100 mL) at room temperature under argon as TFA (12.5 mL, 163 mmol) was added. The mixture was stirred at room temperature under argon for a period of 2 h and then quenched with saturated aqueous $NaHCO_3$ (50 mL) and adjusted to pH 8 with $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 40 mL), and the organic layer washed with brine and dried with sodium sulfate. The solids were filtered off, and the solvent was removed by evaporation to yield a pale yellow oil which was dissolved in CH_2Cl_2 (5 mL). The mixture was stirred as EDC (6.25 g, 32.6 mmol), 4-(dimethylamino)pyridine (3.98 g, 32.6 mmol), and vinylacetic acid (2.77 mL, 32.6 mmol) were added. The reaction was stirred for 45 min, quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with brine and dried with sodium sulfate. The solids were filtered off, and the solvent was removed by evaporation to give the title compound (**6**) (3.39 g, 88%) as a pale brown oil: $[\alpha]_D$ −3.2 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.96−5.86 (m, 1H), 5.56−5.51 (m, 1H), 5.43−5.37 (m, 1H), 5.14−5.12 (m, 1H), 5.10−5.08 (m, 1H), 4.78 (d, J = 8.1 Hz, 1H), 4.53 (dd, J = 1.6, 9.0 Hz, 1H), 3.68 (s, 3H), 3.12−3.00 (m, 2H), 2.36−2.28 (m, 1H), 2.24−2.13 (m, 1H), 2.00−1.89 (m, 1H), 1.69 (dd, J = 1.7, 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6, 170.3, 131.3, 131.1, 125.3, 117.6, 59.0, 54.9, 52.0, 38.7, 32.2, 27.1, 12.9; HRMS calcd for $C_{13}H_{20}O_3N$ (M + H) 238.14449, found 238.14401.

(3*S*,9*S*)-5-Oxo-1,2,3,5,6,8a-hexahydroindolizine-3-carboxylic Acid Methyl Ester (7). To a solution of **6** (2.70 g, 11.4 mmol) in CH_2Cl_2 (300 mL) at reflux under argon was added Grubbs' catalyst (468 mg, 0.57 mmol) portionwise over a period of 4 h. The mixture was stirred under an air atmosphere for 5 h before being filtered through a 10 cm pad of Florisil/silica. The pad was washed with CH_2Cl_2 (2 × 50 mL), and the solvent was removed by evaporation. The residue was purified by column chromatography (EtOAc−hexanes, 90:10) to yield the title compound (**7**) (2.14 g, 96%) as transparent, colorless needles: $[\alpha]_D$ −133.3 (*c* 1.6, $CHCl_3$); mp 60−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.87−5.83 (m, 1H), 5.80−5.76 (m, 1H), 4.64 (t, J = 8.7 Hz, 1H), 4.30−4.26 (m, 1H), 3.74 (s, 3H), 3.08−3.00 (m, 1H), 2.93−2.85 (m, 1H), 2.43−2.35 (m, 1H), 2.22−2.16 (m, 1H), 2.03−1.93 (m, 1H), 1.90−1.80 (m, 1H), 1.60−1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.8, 166.3, 124.5, 122.7, 59.3, 57.1, 52.2, 32.5, 31.9, 27.4; HRMS calcd for $C_{10}H_{13}O_3NaN$ (M + H + Na) 218.07932, found 218.07900.

(3*S*,9*S*)-5-Oxo-1,2,3,5,6,8a-hexahydroindolizine-3-carboxylic Acid (8). To a mixture of **7** (2.04 g, 10.5 mmol) in THF/water (1:1, 10 mL) was added lithium hydroxide monohydrate (482 mg, 11.5 mmol). The mixture was stirred for 2 h and then acidified to pH 4 with aqueous 1 N HCl. The solvent was removed by evaporation to yield a solid residue which was triturated with MeOH (3 × 20 mL). The solvent was again removed by evaporation to yield the title compound (**8**) (1.79 g, 94%) as a white, crystalline solid: $[\alpha]_D$ −214.0 (*c* 1.0, $CHCl_3$); mp 121−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.55−9.18 (s, 1H), 5.78 (d, J = 10.1 Hz, 1H), 5.70−5.67 (m, 1H), 4.59−4.55 (t, J = 8.7 Hz, 1H), 4.20−4.16 (m, 1H), 3.62−3.01 (m, 2H), 3.01−2.89 (m, 1H), 2.34−2.27 (m, 1H), 2.18−2.10 (m, 1H), 2.03−1.93 (m, 1H), 1.53−1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.9, 166.0, 121.8, 119.4, 57.0, 55.3, 29.4, 29.1, 24.1; HRMS calcd for $C_9H_{12}NO_3$ (M + H) 182.08193, found 182.08217.

(3*S*,9*R*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-hexahydroindolizin-5-one (9). To a solution of **8** (667 mg, 3.68 mmol) in THF (20 mL) at 0 °C under argon were added ethyl chloroformate (0.46 mL, 4.79 mmol) and triethylamine (0.67 mL, 4.79 mmol). The mixture was stirred for 1 h, and then the supernatant was transferred to a second flask and stirred at room temperature as sodium borohydride (557 mg, 14.7 mmol) was added. Methanol (5 mL) was added over 5 min and the mixture stirred for a period of 2 h. The mixture was then adjusted to pH 7 with 1 N aqueous HCl and the solvent removed by evaporation. Water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 15 mL). The organics were dried with sodium sulfate and filtered, and the solvent was removed by evaporation to yield a solid which was purified by column chromatography (EtOAc, 100%) to yield a white crystalline solid that was dissolved in MeOH (15 mL). To the solution was added a catalytic quantity of 10% palladium on carbon, and the mixture was stirred at room temperature under an atmosphere of hydrogen for a period of 14 h. The mixture was filtered over Celite and rinsed with MeOH (3 × 10 mL), and the solvent was removed by evaporation to yield a white solid which was dissolved in DMF (20 mL) and stirred at room temperature under argon as imidazole (330 mg, 4.85 mmol) and TBDPSCl (1.26 mL, 4.85 mmol) were added. The mixture was stirred for 16 h and then quenched with water (20 mL) and extracted with Et_2O (3 × 20 mL). The organic was washed with brine, dried with sodium sulfate, and filtered. The solvent was removed by evaporation to give a residue which was purified by column chromatography (EtOAc−hexanes, 50:50) to yield the title compound (**9**) (871 mg, 58%): $[\alpha]_D$ −60.1 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.65−7.61 (m, 4H), 7.44−7.26 (m, 6H), 4.26 (m, 1H), 4.08 (dd, J = 4.2, 10.1 Hz, 1H), 3.78−3.76 (dd, J = 2.5, 10.1 Hz, 1H), 3.57−3.52 (m, 1H), 2.42 (dd, J = 6.3, 18.1 Hz, 1H), 2.29−2.19 (m, 1H), 2.13−1.99 (m, 4H), 1.91−1.85 (m, 1H), 1.64−1.59 (m, 1H), 1.40−1.35 (m, 1H), 1.28−1.16 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.3, 133.0, 131.1, 127.1, 125.1, 61.6, 57.5, 55.4, 30.6, 29.0, 27.0, 24.4, 22.1, 18.4, 16.8; HRMS calcd for $C_{25}H_{34}O_2NSi$ (M + H) 408.23606, found 408.23598.

(3*S*,6*S*,9*S*)-6-Azido-3-(*tert*-butyldiphenylsilanyloxymethyl)hexahydroindolizin-5-one (10). To a solution of *n*-BuLi (2.6 M/hexanes, 0.81 mmol) in THF (4 mL) at −78 °C under argon was added diisopropylamine (114 μL, 0.81 mmol). The contents were stirred for 10 min before a solution of **9** (250 mg, 0.61 mmol) in THF (6 mL) was added. After 20 min of stirring, trisyl azide (251 mg, 0.81 mmol) was added and the mixture stirred for another 3 h. The mixture was quenched with saturated aqueous AcOH (250 μL, 4.8 mmol) and stirred at 30 °C for 4 h. The mixture was then extracted with CH_2Cl_2 (3 × 20 mL), and the organic was washed with brine (25 mL), dried with sodium sulfate, and filtered. The solvents were removed by evaporation to yield a residue which was purified by column chromatography (EtOAc−hexanes, 90:10) to give the title compound (**10**) (156 mg, 43%) as a white, crystalline solid: $[\alpha]_D$ −68.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.66−7.61 (m, 4H), 7.45−7.39 (m, 6H), 4.25−4.19 (m, 1H), 4.16 (dd, J = 3.8, 10.1 Hz, 1H), 3.71−3.59 (m, 2H), 2.24−2.00 (m, 5H), 1.70−1.56 (m, 2H), 1.44−1.23 (m, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.3, 135.1, 129.1,

127.8, 125.3, 61.6, 57.5, 55.4, 48.6, 29.3, 28.0, 24.3, 23.2, 18.8, 17.0; HRMS calcd for $C_{25}H_{33}O_2N_4Si$ (M + H) 449.23745, found 449.23712.

(3*S*,9*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-2,3,6,-8a-tetrahydro-1*H*-indolizin-5-one (11). To a solution of **8** (550 mg, 3.02 mmol) in THF (20 mL) were added ethyl chloroformate (0.34 mL, 3.62 mmol) and triethylamine (0.51 mL, 3.62 mmol) at 0 °C under argon. The mixture was stirred for 1 h, and then the supernatant was transferred to a second flask and stirred at room temperature as sodium borohydride (557 mg, 14.7 mmol) was added. Methanol (5 mL) was added over 5 min, the mixture was stirred for 2 h and adjusted to pH 7 with 1 N aqueous HCl, and the solvent was removed by evaporation. Water (20 mL) was added, the mixture was extracted with CH_2Cl_2 (4 × 15 mL), the organics were dried with sodium sulfate and filtered, and the solvent was removed to yield a solid which was purified by column chromatography (EtOAc, 100%) to yield a white solid which was dissolved in DMF (20 mL). The mixture was stirred at room temperature under argon as imidazole (246 mg, 3.62 mmol), and TBDPSCl (0.94 mL, 3.62 mmol) were added. The mixture was stirred for 16 h and then quenched with water (20 mL) and extracted with ether Et_2O. The organic was washed with brine and processed to give a residue which was purified by column chromatography (EtOAc−hexanes, 50:50) to yield the title compound (**11**) (772 mg, 63%): $[\alpha]_D$ −99.1 (*c* 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67−7.61 (m, 4H), 7.44−7.33 (m, 6H), 5.80 (d, *J* = 10.1 Hz, 1H), 5.74−5.69 (m, 1H), 4.39−4.31 (m, 1H), 4.21−4.13 (m, 1H), 4.09 (dd, *J* = 4.2, 10.2 Hz, 1H), 3.80 (dd, *J* = 2.6, 10.2 Hz, 1H), 2.95−2.68 (m, 2H), 2.17−1.99 (m, 3H), 1.49−1.40 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.4, 133.0, 131.0, 127.1, 125.1, 122.6, 119.4, 61.9, 57.3, 54.8, 30.3, 29.9, 24.4, 22.2, 16.8; HRMS calcd for $C_{25}H_{32}O_2NSi$ (M + H) 406.22025, found 406.22090.

(3*S*,6*S*,9*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-6-cyclohex-1-enylmethyl-2,3,6,8a-tetrahydro-1*H*-indolizin-5-one (12). To a solution of *n*-BuLi (2.6 M/hexanes, 0.44 mmol) in THF (2 mL) at −78 °C under argon was added diisopropylamine (61 μL, 0.59 mmol). The contents were stirred for 10 min before a solution of **11** (136 mg, 0.34 mmol) in THF (3 mL) was added. After 30 min of stirring, cyclohexenylmethyl bromide was added and the mixture stirred for another 45 min. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 70:30) to give the title compound (**12**) (122 mg, 79%) as a clear, colorless oil: $[\alpha]_D$ −58.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67−7.61 (m, 4H), 7.44−7.35 (m, 6H), 5.82 (dd, *J* = 1.3, 10.0 Hz, 1H), 5.76−5.72 (m, 1H), 5.41, (s, 1H), 4.39−4.34 (m, 1H), 4.20−4.14 (m, 1H), 4.03 (dd, *J* = 4.4, 10.0 Hz, 1H), 3.76 (dd, *J* = 2.6, 10.1 Hz, 1H), 3.03−2.97 (m, 1H), 2.54 (dd, *J* = 3.5, 12.8 Hz, 1H), 2.18−1.97 (m, 8H), 1.62−1.41 (m, 5H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.0, 133.0, 131.7, 131.0, 130.9, 127.1, 125.1, 124.4, 122.0, 121.3, 61.8, 57.0, 54.9, 40.3, 39.1, 30.0, 25.6, 24.3, 22.7, 22.3, 20.4, 19.8, 16.8; HRMS calcd for $C_{32}H_{42}O_2NSi$ (M + H) 500.29866, found 500.29888.

(3*S*,7*S*,8*R*,9*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-7,8-oxahexahydroindolizin-5-one (13). To a solution of **11** (43 mg, 0.11 mmol) in CH_2Cl_2 (4 mL) at 0 °C under argon was added urea−hydrogen peroxide complex (100 mg, 1.11 mmol). The mixture was stirred for 10 min before TFAA (75ul, 0.53 mmol) was added. Stirring was continued for 2 h before the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and washed and processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 50:50) to give the title compound (**13**) (35 mg, 78%) as a clear, colorless oil: $[\alpha]_D$ +45.6 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.66−7.59 (m, 4H), 7.44−7.35 (m, 6H), 4.25−4.21 (m, 1H), 4.10−4.06 (dd, *J* = 4.0, 10.3 Hz, 1H), 3.93−3.89 (dd, *J* = 5.6, 11.2 Hz, 1H), 3.75−3.72 (dd, *J* = 2.4, 10.3 Hz, 1H), 3.44−3.41 (m, 2H), 2.88 (d, *J* = 17.8 Hz, 1H), 2.59 (d, *J* = 17.9 Hz, 1H), 2.22−2.13 (m, 1H), 2.13−1.96 (m, 2H), 1.90−1.82 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.1, 135.4, 133.4, 129.6, 127.5, 64.0, 58.4, 56.9, 51.7, 51.4, 32.6, 29.4, 26.8, 23.6, 19.2; HRMS calcd for $C_{25}H_{31}O_3NSi$ (M + H) 422.21532, found 422.21504.

(3*S*,8*S*,9*R*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-8-hydroxy-2,3,8,8a-tetrahydro-1*H*-indolizin-5-one (14). To a solution of *n*-BuLi (2.6 M/hexanes, 0.59 mmol) in THF (2 mL) at −78 °C under argon was added diisopropylamine (83 μL, 0.59 mmol). The contents were stirred for 10 min before a solution of **13** (191 mg, 0.45 mmol) in THF (3 mL) was added. After 5 min of stirring, *n*-BuLi (2.6 M/hexanes, 0.59 mmol) was added and the mixture stirred for another 20 min. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 80:20) to give the title compound (**14**) (176 mg, 92%) as a white, crystalline solid: $[\alpha]_D$ +80.0 (*c* 2.0, $CHCl_3$); mp 125−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.64−7.58 (m, 4H), 7.44−7.33 (m, 6H), 6.70 (dd, *J* = 5.9, 9.7 Hz, 1H), 5.96 (d, *J* = 9.7 Hz, 1H), 4.18−4.16 (m, 1H), 4.10−4.06 (dd, *J* = 4.7, 10.0 Hz, 1H), 4.01−3.99 (dd, *J* = 3.8, 4.9 Hz, 1H), 3.85−3.80 (m, 1H), 3.78−3.74 (dd, *J* = 2.6, 10.1 Hz, 1H), 2.26−2.2 (m, 1H), 2.18−2.05 (m, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.0, 138.5, 135.4, 133.3, 129.5, 127.5, 127.1, 63.6, 62.4, 61.3, 58.6, 26.7, 26.0, 24.6, 19.1; HRMS calcd for $C_{25}H_{32}O_3NSi$ (M + H) 422.21532, found 422.21599.

(3*S*,8*S*,9*R*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-8-methoxy-2,3,8,8a-tetrahydro-1*H*-indolizin-5-one (15). To a mixture of potassium hydride (0.37 mmol, 35 wt %) in THF (3 mL) was added a solution of **14** (78 mg, 0.19 mmol) in THF (2 mL) at 0 °C under argon. The mixture was stirred for 2 h, iodomethane (23 μL, 0.37 mmol) was added, and stirring was continued for 1 h. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 70:30) to give the title compound (**15**) (50 mg, 62%) as a pale yellow oil: $[\alpha]_D$ +61.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.65−7.60 (m, 4H), 7.44−7.34 (m, 6H), 6.70 (dd, *J* = 5.5, 9.8 Hz, 1H), 6.14 (d, *J* = 9.7 Hz, 1H), 4.25−4.23 (m, 1H), 4.14 (dd, *J* = 4.5, 10.0 Hz, 1H), 3.91−3.86 (m, 1H), 3.79 (dd, *J* = 2.3, 10.0 Hz, 1H), 3.69 (dd, *J* = 4.1, 5.4 Hz, 1H), 3.34 (s, 3H), 2.17−2.03 (m, 4H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.4, 135.4, 135.3, 133.4, 133.3, 129.5, 127.5, 69.9, 63.6, 60.6, 58.0, 56.3, 26.7, 25.8, 24.8, 19.1; HRMS calcd for $C_{26}H_{34}O_3NSi$ (M + H) 436.23080, found 436.23210.

(3*S*,8*S*,9*R*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-8-hydroxyhexahydroindolizin-5-one (16). To a solution of **14** (307 mg, 0.73 mmol) in EtOAc (10 mL) was added a catalytic quantity of 10% palladium-on-carbon. The solution was stirred at room temperature under an atmosphere of hydrogen for a period of 6 h. The mixture was filtered over Celite and then rinsed with MeOH (3 × 10 mL). The solvent was removed by evaporation to give the title compound (**16**) (305 mg, 99%) as a pale yellow oil: $[\alpha]_D$ −64.2, (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.65−7.60 (m, 4H), 7.45−7.33 (m, 6H), 4.23−4.20 (m, 1H), 4.11−4.03 (m, 2H), 3.75 (dd, *J* = 2.3, 10.2 Hz, 1H), 3.64−3.59 (m, 1H), 2.53−2.40 (m, 1H), 2.37−2.30 (m, 1H), 2.08−1.95 (m, 3H), 1.94−1.84 (m, 1H), 1.82−1.71 (m, 1H), 1.05 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.0, 135.4, 133.5, 129.5, 127.5, 64.0, 63.6, 63.0, 58.1, 28.0, 26.8, 26.5, 26.2, 24.4, 19.2; HRMS calcd for $C_{25}H_{34}O_3NSi$ (M + H) 424.23080, found 424.23260.

(3*S*,8*S*,9*R*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-8-methoxyhexahydroindolizin-5-one (17). To a solution of **15** (66 mg, 0.15 mmol) in MeOH (3 mL) was added a catalytic quantity of 10% palladium-on-carbon. The solution was stirred at room temperature under an atmosphere of hydrogen for a

period of 6 h. The mixture was filtered over Celite and rinsed with MeOH (3 × 5 mL), and the solvent was removed by evaporation the title compound (**17**) (66 mg, 100%) as a clear, colorless oil: $[\alpha]_D$ −32.7 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.64−7.61 (m, 4H), 7.43−7.34 (m, 6H), 4.27−4.20 (s, 1H), 4.10 (dd, J = 4.2, 10.1 Hz, 1H), 3.75 (dd, J = 2.2, 10.1 Hz, 1H), 3.68−3.61 (m, 1H), 3.57−3.54 (m, 1H), 3.33 (s, 3H), 2.34−2.19 (m, 3H), 2.06−1.94 (m, 3H), 1.89−1.86 (m, 1H), 1.64−1.59 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 135.4, 133.3, 129.5, 127.5, 72.1, 64.2, 63.0, 57.8, 56.1, 26.8, 26.3, 26.2, 24.2, 23.4, 19.2; HRMS calcd for $C_{26}H_{36}O_3NSi$ (M + H) 438.24662, found 438.24654.

(2*S*,4*R*)-4-Benzyl-5-oxopyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (18). A 50 mL round-bottom flask was flame-dried and charged with 25 mL of dry THF. The contents were stirred at −78 °C under argon as LiHMDS (1.0 M, 9.9 mmol) in THF was added via syringe to the vessel. In a separate, flame-dried, 50 mL round-bottom flask, a solution of **4** (2.0 g, 8.2 mmol) in dry THF (10 mL) was stirred at −78 °C under argon and transferred via cannula to the reaction vessel. The resulting mixture was stirred for 2 h before a solution of benzyl bromide (9.9 mmol) in THF (5 mL) was added via syringe. After 1 h, the contents were quenched with saturated aqueous NH_4Cl (25 mL) and extracted with EtOAc (3 × 30 mL), and the organic extracts were processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexane, 20:80) to give the title compound (**18**) (1.53 g, 56%). The ^{1}H NMR and ^{13}C NMR spectra conform with the reported literature data for the corresponding ethyl ester.[19a]

(2*S*,4*R*)-5-Oxo-4-(3-phenylallyl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (19). A 50 mL round-bottom flask was flame-dried and charged with 25 mL of dry THF. The contents were stirred at −78 °C under argon as LiHMDS (1.0 M, 9.9 mmol) in THF was added via syringe to the vessel. In a separate, flame-dried, 50 mL round-bottom flask a solution of **4** (2.0 g, 8.2 mmol) in dry THF (10 mL) was stirred at −78 °C under argon and transferred via cannula to the reaction vessel. The resulting mixture was stirred for 2 h before a solution of cinnamyl bromide (9.9 mmol) in THF (5 mL) was added via syringe. After 1 h, the contents were quenched with saturated aqueous NH_4Cl (25 mL) and the organic extracts were processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexane, 20:80) to give the title compound (**19**) (1.91 g, 65%) as a white solid. The ^{1}H NMR and ^{13}C NMR spectra conform with the reported literature data.[19a]

(2*S*,4*R*)-5-Oxo-4-(3-phenylpropyl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (20). To a solution of **19** (2.03 g, 5.33 mmol) in MeOH (15 mL) was added a catalytic quantity of 10% palladium on carbon. The solution was stirred at room temperature under an atmosphere of hydrogen for a period of 14 h. The mixture was filtered over Celite and rinsed with MeOH (3 × 10 mL), and the solvent was removed by evaporation to give the title compound (**20**) (1.91 g, 99%) as a pale yellow oil. The ^{1}H NMR and ^{13}C NMR spectra conform to the reported literature data.[19a]

Representative Procedure for the Preparation of *N*-Boc-propenylpyrrolidines. A flame-dried, 50 mL round-bottom flask was charged with **18** (550 mg, 1.65 mmol) and dry THF (10 mL). The solution was stirred at −78 °C under argon for 20 min before Super-Hydride (1.0 M, 1.98 mmol) in THF was added via syringe to the vessel. Stirring was continued for another 1 h, and then the mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and stirred at 0−5 °C with 5 drops of H_2O_2 (30 w/w %) for a period of 1 h. The solvent was then removed by evaporation, and the mixture was extracted with EtOAc (3 × 15 mL), washed with brine, and dried with sodium sulfate. The solids were removed by filtration, the solvent removed by evaporation to yield a residue which was dissolved in MeOH (20 mL), and a catalytic quantity of *p*-toluenesulfonic acid was added. The contents were stirred for 16 h and then quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic was washed with brine and dried with sodium sulfate. The solids were filtered off, and the solvent was removed by evaporation to yield a residue which was dissolved in Et_2O (10 mL). To a separate round-bottomed flask was added copper bromide−dimethyl sulfide complex (746 mg, 3.63 mmol) and Et_2O (10 mL). The mixture was stirred at −40 °C as a solution of *cis*-propenyllithium (0.84 M, 3.47 mmol) in Et_2O was added via syringe. The contents were stirred for 1 h and cooled to −78 °C, boron trifluoride etherate (0.50 mL, 3.96 mmol) was added, and stirring was continued for another 1 h. The solution in Et_2O was then transferred via cannula to the vessel, and the temperature was slowly warmed to 0 °C over a period of 5 h. The mixture was quenched with saturated aqueous NH_4Cl−NH_4OH (1:1, 10 mL) and stirred for 1 h at room temperature. The organic layer was removed and the aqueous layer extracted with Et_2O (3 × 10 mL). The organics were combined and processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 30:70).

(2*S*,4*R*,5*S*)-4-Benzyl-5-*cis*-propenylpyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (21): yield, 79%; $[\alpha]_D$ +20.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30−7.11 (m, 5H), 5.71−5.57 (m, 1H), 5.27−5.18 (m, 1H), 4.79 (dd, J = 7.7, 10.3 Hz, 1H), 4.34 (dd, J = 8.4, 9.3 Hz, 1H), 3.69 (s, 3H), 2.87−2.70 (m, 1H), 2.68−2.46 (m, 2H), 2.06−1.87 (m, 2H), 1.52 (dd, J = 1.8, 6.9 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.3, 154.2, 139.9, 128.7, 128.6, 128.4, 126.9, 126.0, 79.9, 58.2, 56.5, 51.9, 42.3, 35.7, 33.6, 28.4, 13.0; HRMS calcd for $C_{21}H_{30}NO_4$ (M + H) 360.21766, found 360.21750.

(2*S*,4*R*,5*S*)-4-(3-Phenylpropyl)-5-*cis*-propenylpyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (22): yield, 76%; $[\alpha]_D$ +25.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.29−7.25 (m, 2H), 7.19−7.13 (m, 3H), 5.66−5.53 (m, 1H), 5.14−5.07 (m, 1H), 4.77 (dd, J = 7.7, 10.2 Hz, 1H), 4.37 (dd, J = 1.5, 8.3 Hz, 1H), 3.72 (s, 3H), 2.61−2.55 (m, 2H), 2.46−2.36 (m, 1H), 1.99−1.84 (m, 2H), 1.74 (dd, J = 1.8, 7.0 Hz, 3H), 1.60−1.52 (m, 2H), 1.43 (s, 9H), 1.35−1.22 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.8, 154.1, 142.1, 128.1, 128.0, 127.2, 125.9, 125.6, 79.7, 58.6, 56.3, 52.0, 40.9, 35.9, 34.6, 29.8, 28.9, 28.2, 13.2; HRMS calcd for $C_{23}H_{34}NO_4$ (M + H) 388.24896, found 388.24996.

Representative Procedure for the Preparation of *N*-Butenoylpropenylpyrrolidines. To a solution of **21** (1.5 g, 4.17 mmol) in dry CH_2Cl_2 (40 mL) was added trifluoroacetic acid (3.21 mL, 41.7 mmol). The mixture was stirred at room temperature under argon for 2 h, quenched with saturated aqueous $NaHCO_3$ (30 mL), and adjusted to pH 7 with $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the organic washed with brine and dried with sodium sulfate. The solids were filtered off, and the solvent was evaporated to give a residue which was dissolved in CH_2Cl_2 (5 mL). EDC (959 mg, 5.00 mmol) and 4-(dimethylamino)pyridine (614 mg, 5.00 mmol) were added followed by vinylacetic acid (0.43 mL, 5.00 mmol), added drop by drop via syringe, and the solution was stirred for 45 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with brine and dried with sodium sulfate. The solids were filtered off, and the solvent was removed by evaporation to give **23** as a pale yellow oil.

(2*S*,4*R*,5*S*)-4-Benzyl-1-but-3-enoyl-5-*cis*-propenylpyrrolidine-2-carboxylic acid methyl ester (23): yield, 70%; $[\alpha]_D$ +9.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32−7.11 (m, 5H), 6.00−5.88 (m, 1H), 5.75−5.65 (m, 1H), 5.33−5.25 (m, 1H), 5.17−5.06 (m, 2H), 4.77 (dd, J = 7.5, 10.4 Hz, 1H), 4.53 (d, J = 10.2 Hz, 1H), 3.68 (s, 3H), 3.10−2.89 (m, 3H), 2.64−2.53 (m, 2H), 2.09−1.94 (m, 2H), 1.48 (dd, J = 1.8, 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.6, 170.1, 139.2, 131.2, 128.7, 128.4, 127.9, 126.4, 126.1, 117.6, 58.0, 57.1,

52.0, 42.7, 38.4, 35.5, 32.7, 12.8; HRMS calcd for $C_{20}H_{26}NO_3$ (M + H) 323.19144, found 323.19245.

(2*S*,4*R*,5*S*)-1-But-3-enoyl-4-(3-phenylpropyl)-5-*cis*-propenylpyrrolidine-2-carboxylic acid methyl ester (24): yield, 85%; $[\alpha]_D$ +21.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27−7.22 (m, 2H), 7.17−7.07 (m, 3H), 5.97−5.88 (m, 1H), 5.68−5.63 (m, 1H), 5.19−5.11 (m, 2H), 4.73 (dd, J = 7.6, 10.4 Hz, 1H), 4.49 (d, J = 9.1 Hz, 1H), 3.69 (s, 3H), 3.08−2.98 (m, 2H), 2.54 (t, J = 7.5 Hz, 2H), 2.05 (dd, J = 1.7, 7.0 Hz, 1H), 2.01−1.95 (m, 1H), 1.89−1.78 (m, 1H), 1.71 (dd, J = 1.8, 7.1 Hz, 3H), 1.62−1.48 (m, 2H), 1.33−1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.7, 170.1, 141.9, 131.1, 128.2, 128.1, 127.2, 126.5, 125.7, 117.5, 58.1, 57.2, 52.0, 41.6, 38.4, 35.9, 32.9, 29.8, 29.0, 13.1; HRMS calcd for $C_{22}H_{30}NO_3$ (M + H) 356.22274, found 56.22198.

Representative Procedure for the Synthesis of Indolizidinones. To a solution of **23** (184 mg, 0.56 mmol) in CH_2Cl_2 (20 mL) at reflux under argon was added Grubbs' catalyst (23 mg, 0.028 mmol) portionwise over a period of 4 h. The mixture was stirred under an air atmosphere for 5 h before being filtered through a 10 cm pad of Florisil/silica. The pad was washed with CH_2Cl_2 (2 × 10 mL), and the solvent was removed by evaporation. The residue was purified by column chromatography (EtOAc−hexanes, 10:90) to give the products as pale yellow oils.

(1*R*,3*S*,9*S*)-1-Benzyl-5-oxo-1,2,3,5,6,8a-hexahydroindolizine-3-carboxylic acid methyl ester (25): yield, 62%; $[\alpha]_D$ −113.1 (*c* 1.6, $CHCl_3$); mp 170−172 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32−7.16 (m, 5H), 5.94−5.73 (m, 2H), 4.66 (t, J = 9.0 Hz, 1H), 4.59−4.52 (m, 1H), 3.73 (s, 3H), 3.14−2.89 (m, 2H), 2.73 (dd, J = 3.9, 13.9 Hz, 1H), 2.66−2.54 (m, 1H), 2.13 (dd, J = 8.5, 13.2 Hz, 1H), 2.06−1.98 (m, 1H), 1.81−1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6, 166.7, 139.1, 128.9, 128.4, 126.2, 123.9, 122.5, 62.5, 55.4, 52.2, 42.4, 33.6, 32.3, 31.0; HRMS calcd for $C_{17}H_{20}NO_3$ (M + H) 286.14449, found 286.14493.

(1*R*,3*S*,9*S*)-5-Oxo-1-(3-phenylpropyl)-1,2,3,5,6,8a-hexahydroindolizine-3-carboxylic acid methyl ester (26): yield, 52%; $[\alpha]_D$ −60.2 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31−7.23 (m, 2H), 7.20−7.11 (m, 3H), 5.85−5.76 (m, 1H), 5.75−5.70 (m, 1H), 4.57 (t, J = 8.9 Hz, 1H), 3.74 (s, 3H), 3.03−2.92 (m, 1H), 2.90−2.86 (m, 1H), 2.63−2.52 (m, 2H), 2.27−2.20 (m, 2H), 1.92−1.86 (m, 1H), 1.72−1.51 (m, 2H), 1.41−1.30 (m, 1H), 0.96−0.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.7, 166.6, 141.8, 128.2, 128.1, 125.7, 123.6, 122.6, 62.7, 55.6, 52.2, 40.8, 35.8, 32.2, 31.9, 29.1, 27.1; HRMS calcd for $C_{19}H_{24}NO_3$ (M + H) 314.17594, found 314.17345.

(1*R*,3*S*,7*S*,8*R*,9*S*)-1-Benzyl-7, 8-oxa-5-oxooctahydroindolizine-3-carboxylic Acid Methyl Ester (27). To a solution of **25** (47 mg, 0.17 mmol) in dry CH_2Cl_2 (4 mL) was added *m*-CPBA (227 mg, 1.32 mmol). The solution was stirred at room temperature under argon for 16 h and quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2, and the organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc, 100%) to give the title compound (**27**) (30 mg, 60%) as a pale yellow oil: $[\alpha]_D$ −118.3 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33−7.14 (m, 5H), 4.56 (d, J = 8.6 Hz, 1H), 4.33 (d, J = 5.7 Hz, 1H), 3.71 (s, 3H), 3.53 (d, J = 4.2 Hz, 1H), 3.44−3.42 (m, 1H), 3.09 (dd, J = 4.7, 14.3 Hz, 1H), 2.98 (dd, J = 2.1, 17.9 Hz, 1H), 2.89−2.84 (m, 1H), 2.83 (d, J = 18.0 Hz, 1H), 2.46 (dd, J = 11.8, 14.3 Hz, 1H), 2.05−1.99 (m, 1H), 1.80−1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.5, 165.7, 139.2, 128.8, 128.5, 126.3, 59.2, 56.9, 52.2, 50.3, 49.4, 43.2, 34.6, 32.7, 31.0; HRMS calcd for $C_{17}H_{20}NO_4$ (M + H) 301.13941, found 301.13901.

Representative Procedure for the Synthesis of *N*-Boc-5-allylprolines. A flame-dried, 50 mL round-bottom flask was charged with **18** (550 mg, 1.65 mmol) and dry THF (10 mL). The solution was stirred at −78 °C under argon for 20 min before Super-Hydride (1.0M, 1.98 mmol) in THF was added via syringe to the vessel. Stirring was continued for another 1 h, and then the mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and stirred at 0−5 °C with 5 drops of H_2O_2 (30 w/w %) for a period of 1 h. The solvent was then removed, and the mixture was extracted with EtOAc, washed with brine, and dried with sodium sulfate. The solids were removed by filtration, the solvent was removed to yield a residue which was dissolved in CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature under argon as triethylamine (0.69 mL, 4.95 mmol), acetic anhydride (0.47 mL, 4.95 mmol), and 4-(dimethylamino)pyridine (10 mg, 0.082 mmol) were added. The mixture was stirred for 16 h and then quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2. The organic layer was processed as usual to yield a residue which was dissolved in 5 mL of toluene and filtered through 5 cm of silica gel. The silica was washed with toluene (15 mL) and the filtrate transferred to a 50 mL round-bottomed flask. The solution was stirred at −78 °C under argon as allyltributyltin (0.77 mL, 2.48 mmol) was added via syringe to the vessel. After 5 min, boron trifluoride etherate (0.31 mL, 2.48 mmol) was added via syringe, the mixture was stirred for 1 h, and then the contents were quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with toluene. The organic phases were combined, dried with sodium sulfate, and filtered, and the filtrate was concentrated to a residue by evaporation. The residue was purified by column chromatography (EtOAc−hexanes, 30:70) to yield a clear, colorless oil.

(2*S*,4*R*,5*S*)-5-Allyl-4-benzylpyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (30): yield, 75%; $[\alpha]_D$ −24.8 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30−7.11 (m, 5H), 5.81−5.73 (m, 1H), 5.06−5.00 (m, 2H), 4.31 (t, J = 8.1 Hz, 1H), 3.73−3.68 (m, 1H), 3.70 (s, 3H), 2.76−2.65 (m, 1H), 2.54−2.45 (m, 1H), 2.34−2.23 (m, 2H), 1.98−1.93 (m, 2H), 1.46 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.7, 154.4, 139.4, 135.1, 128.8, 128.3, 126.2, 116.8, 79.9, 62.7, 58.6, 51.8, 43.6, 39.3, 38.7, 32.7, 28.2; HRMS calcd for $C_{21}H_{30}NO_4$ (M + H) 360.21766, found 360.21750.

(2*S*,4*R*,5*S*)-5-Allyl-4-(3-phenylpropyl)pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (31): yield, 70%; $[\alpha]_D$ −22.4 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28−7.25 (m, 2H), 7.19−7.14 (m, 3H), 5.87−5.77 (m, 1H), 5.10−4.96 (m, 2H), 4.28 (m, 1H), 3.71 (s, 3H), 2.71−2.50 (m, 3H), 2.31−2.22 (m, 1H), 2.13−1.96 (m, 2H), 1.95−1.86 (m, 1H), 1.63−1.56 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.9, 153.7, 142.0, 135.3, 128.3, 128.2, 125.8, 117.0, 79.9, 63.2, 58.9, 51.9, 42.0, 40.7, 38.2, 35.7, 33.9, 33.0, 28.3; HRMS calcd for $C_{23}H_{34}NO_4$ (M + H) 388.24896, found 388.24905.

(2*S*,4*R*,5*S*)-4-Benzyl-5-carboxymethylpyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (32). To a solution of **30** (1.17 g, 3.26 mmol) in THF/H_2O (25 mL, 50:50) at room temperature under argon were added sodium periodate (1.53 g, 7.16 mmol) and osmium tetroxide (cat.). The mixture was stirred for 3 h and then quenched with water (10 mL). The solids were filtered off over Celite, and the mixture was extracted with EtOAc and dried with Na_2SO_4. The organics were concentrated to yield a crude residue which was purified by column chromatography (EtOAc−hexanes, 30:70) to give a white, crystalline solid. The solid was dissolved in acetone (50 mL) at 0 °C, and Jones' reagent (2.0 M, 10.0 mmol) was added. The mixture was stirred for 20 min and then quenched with saturated aqueous $NaHCO_3$ (10 mL) to pH 10. The organic was extracted with saturated aqueous $NaHCO_3$ and the aqueous layer acidified to pH 3 with 1 N HCl. The mixture was then extracted with EtOAc and processed as usual to yield the title compound (**32**) (911 mg, 89%) as a white, crystalline solid: $[\alpha]_D$ −28.9 (*c* 1.1, $CHCl_3$); mp 164−166 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45−7.10 (m, 5H), 4.35 (t, J = 8.7 Hz, 1H), 4.13−4.07 (m, 1H), 3.72 (s, 3H), 3.05−2.96 (m, 1H), 2.85−2.74 (m, 1H), 2.59−2.44 (m, 2H), 2.43−2.33 (m, 1H), 2.10−1.92 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.3, 173.0, 156.1, 137.3, 128.9, 126.4, 126.2,

90.0, 59.5, 57.8, 52.5, 52.2, 35.1, 34.6, 25.3, 23.9; HRMS calcd for $C_{20}H_{28}NO_6$ (M +) 378.19184, found 378.19127.

Representative Procedure for the Synthesis of *N*-Acyl-5-allylprolines. To a solution of **30** (2.0 g, 5.56 mmol) in dry CH_2Cl_2 (25 mL) was added trifluoroacetic acid (4.29 mL, 55.6 mmol). The mixture was stirred at room temperature under argon for a period of 2 h and then quenched with saturated aqueous $NaHCO_3$ (30 mL) and adjusted to pH 8 with $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with brine and dried with sodium sulfate. The solids were filtered off, the solvent was removed, the residue was dissolved in CH_2Cl_2 (20 mL) at 0−5 °C, and acrylic acid (0.59 mL, 8.67 mmol), EDC (1.66 g, 8.67 mmol), and DMAP (1.06 g, 8.67 mmol) were added. The solution was stirred for 30 min, quenched with saturated aqueous $NaHCO_3$ (10 mL), extracted with CH_2Cl_2, and then processed as usual to give the title compound (**33**) as a clear, colorless oil.

(2*S*,4*R*,5*S*)-1-Acryloyl-5-allyl-4-benzylpyrrolidine-2-carboxylic acid methyl ester (33): yield, 96%; $[\alpha]_D$ −38.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35−7.07 (m, 5H), 6.49−6.37 (m, 2H), 5.79−5.62 (m, 2H), 5.11−5.01 (m, 2H), 4.62 (t, J = 9.0 Hz, 1H), 3.79−3.74 (m, 1H), 3.73 (s, 3H), 2.58−2.51 (m, 2H), 2.50−2.32 (m, 3H), 2.11−2.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.9, 164.7, 138.9, 133.8, 128.9, 128.8, 128.5, 127.5, 125.9, 118.0, 62.3, 58.1, 52.2, 43.7, 39.5, 39.0, 31.2; HRMS calcd for $C_{19}H_{24}O_3N$ (M + H) 314.17563, found 314.17700.

(2*S*,4*R*,5*S*)-1-Acryloyl-5-allyl-4-(3-phenylpropyl)pyrrolidine-2-carboxylic acid methyl ester (34): yield, 86%; $[\alpha]_D$ −38.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.29−7.25 (m, 2H), 7.20−7.13 (m, 3H), 6.44 (m, 2H), 5.81−5.67 (m, 2H), 5.16−5.04 (m, 2H), 4.54 (t, J = 8.8 Hz, 1H), 3.74 (s, 1H), 2.57 (t, J = 7.6, 2H), 2.57−2.51 (m, 1H), 2.41−2.33 (m, 3H), 1.66−1.59 (m, 2H), 1.38−1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.0, 164.7, 141.8, 134.1, 128.8, 128.4, 128.3, 127.7, 125.9, 118.3, 63.4, 58.4, 52.2, 42.2, 40.0, 35.6, 32.9, 32.0, 29.3; HRMS calcd for $C_{19}H_{24}O_3N$ (M + H) 314.17563, found 314.17700.

(2*S*,4*R*,5*S*)-5-Allyl-4-benzyl-1-but-3-enoylpyrrolidine-2-carboxylic acid methyl ester (35): yield, 81%; $[\alpha]_D$ −42.1 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.29−7.10 (m, 5H), 5.99−5.89 (m, 1H), 5.70−5.59 (m, 1H), 5.16−5.09 (m, 2H), 5.08−5.00 (m, 2H), 4.53 (t, J = 9.1 Hz, 1H), 3.70 (s, 3H), 3.68−3.62 (m, 1H), 3.02 (d, J = 6.1 Hz, 2H), 2.55−2.36 (m, 3H), 2.35−2.24 (m, 2H), 2.08−1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.9, 169.9 138.9, 133.9, 131.3, 128.7, 128.4, 126.4, 117.9, 117.8, 62.6, 57.9, 52.0, 43.7, 39.1, 39.0, 38.9, 31.2; HRMS calcd for $C_{20}H_{26}NO_3$ (M + H) 328.19144, found 328.19203.

(2*S*,4*R*,5*S*)-5-Allyl-1-but-3-enoyl-4-(3-phenylpropyl)-pyrrolidine-2-carboxylic acid methyl ester (36): yield, 81%; $[\alpha]_D$ −29.4 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30−7.25 (m, 2H), 7.20−7.13 (m, 3H), 5.97−5.89 (m, 1H), 5.82−5.73 (m, 1H), 5.17−5.0 (m, 4H), 4.47−4.40 (m, 1H), 3.72 (s, 3H), 3.06 (dt, J = 1.3, 6.6 Hz, 1H), 2.63−2.45 (m, 3H), 2.36−2.23 (m, 1H), 2.13−1.97 (m, 2H), 1.95−1.86 (m, 1H), 1.65−1.57 (m, 2H), 1.33−1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.0, 169.9, 141.9, 134.1, 131.3, 128.2, 128.1, 125.8, 118.1, 117.8, 63.4, 59.1, 58.0, 52.0, 42.0, 39.1, 35.5, 32.6, 31.9, 29.3; HRMS calcd for $C_{22}H_{30}NO_3$ (M + H) 356.22274, found 356.22368.

Representative Procedure for the Synthesis of Bicyclic Prolines 37−40. To a solution of **33** (60 mg, 0.19 mmol) in CH_2Cl_2 (10 mL) at reflux under argon was added Grubbs' catalyst (16 mg, 0.019 mmol) portionwise over a period of 4 h. The mixture was stirred under an air atmosphere for 5 h before being filtered through a 10 cm pad of Florisil/silica. The pad was washed with CH_2Cl_2 (2 × 10 mL), the solvent was removed, and the residue was purified by column chromatography (EtOAc−hexanes, 10:90).

(1*R*,3*S*,9*S*)-1-Benzyl-5-oxo-1,2,3,5,8,8a-hexahydroindolizine-3-carboxylic acid methyl ester (37): yield, 80%; $[\alpha]_D$ −63.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35−7.22 (m, 3H), 7.18−7.13 (m, 2H), 6.55−6.49 (m, 1H), 5.97−5.93 (m, 1H), 4.58 (d, J = 9.1 Hz, 1H), 3.71 (s, 3H), 3.55−3.45 (m, 1H), 2.79−2.66 (m, 2H), 2.47−2.38 (m, 1H), 2.22−2.05 (m, 3H), 1.97−1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 163.1, 139.5, 138.8, 128.6, 128.5, 126.5, 125.4, 61.4, 56.3, 52.3, 46.2, 38.0, 34.4, 29.7; HRMS calcd for $C_{17}H_{20}NO_3$ (M + H) 286.14449, found 286.14535.

(1*R*,3*S*,10*S*)-1-Benzyl-5-oxo-2,3,5,6,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylic acid methyl ester (38): yield, 77%; $[\alpha]_D$ −17.6 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33−7.22 (m, 3H), 7.16−7.14 (m, 2H), 5.66−5.60 (m, 1H), 5.57−5.51 (m, 1H), 4.70 (dd, J = 4.2, 8.4 Hz, 1H), 3.95 (m, 1H), 3.71 (s, 3H), (dt, J = 3.6, 16.9 Hz, 1H) 2.91 (dd, J = 8.5, 16.9 Hz, 1H), 2.80 (dd, J = 6.9, 13.6 Hz, 1H), 2.67 (dd, J = 8.3, 13.6 Hz, 1H), 2.52−2.44 (m, 1H), 2.33−2.28 (m, 1H), 2.22−2.15 (m, 1H), 2.14−2.07 (m, 1H), 1.97−1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.6, 171.4, 139.0, 128.6, 128.5, 128.4, 126.5, 119.8, 61.0, 58.5, 52.2, 46.7, 39.5, 36.0, 34.8, 33.5; HRMS calcd for $C_{18}H_{22}NO_3$ (M + H) 300.16014, found 300.16136.

(1*R*,3*S*,9*S*)-5-Oxo-1-(3-phenylpropyl)-1,2,3,5,8,8a-hexahydroindolizine-3-carboxylic acid methyl ester (39): yield, 72%; $[\alpha]_D$ −77.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30−7.26 (m, 2H), 7.20−7.14 (m, 3H), 6.59−6.55 (m, 1H), 6.60−6.55 (m, 1H), 4.55 (d, J = 9.5, 1H), 3.72 (s, 3H), 3.40−3.33 (m, 1H), 2.66−2.60 (m, 2H), 2.51−2.44 (m, 1H), 2.35−2.25 (m, 1H), 2.20−2.13 (m, 1H), 2.12−2.04 (m, 2H), 1.71−1.52 (m, 4H), 1.30−1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.4, 163.1, 141.6, 139.4, 128.2, 128.1, 125.8, 125.4, 61.6, 56.5, 44.5, 35.8, 34.4, 30.9, 29.6, 29.5; HRMS calcd for $C_{19}H_{24}NO_3$ (M + H) 314.17579, found 314.17672.

(1*R*,3*S*,10*S*)-5-Oxo-1-(3-phenylpropyl)-2,3,5,6,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylic acid methyl ester (40): 50 mg, 80%; $[\alpha]_D$ −31.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.21−7.16 (m, 2H), 7.12−7.05 (m, 3H), 5.60−5.53 (m, 1H), 5.52−5.41 (m, 1H), 4.60 (dd, J = 3.4, 8.6 Hz, 1H), 3.73−3.66 (m, 1H), 3.62 (s, 3H), 3.37−3.32 (m, 1H), 2.80 (dd, J = 8.6, 17.0 Hz, 1H), 2.57−2.49 (m, 2H), 2.45−2.33 (m, 1H), 2.13−2.07 (m, 1H), 1.93−1.84 (m, 1H), 1.75−1.67 (m, 1H), 1.62−1.41 (m, 3H), 1.31−1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.7, 171.4, 141.6, 128.4, 128.3, 128.2, 127.9, 125.8, 119.8, 61.6, 58.8, 52.2, 45.1, 36.0, 35.7, 35.1, 33.8, 33.0, 29.8, 29.5; HRMS calcd for $C_{20}H_{26}NO_3$ (M + H) 328.19144, found 328.19111.

(2*S*)-5-Oxo-pyrrolidine-1,2-dicarboxylic Acid 2-Trimethylsilanylethyl Ester 1-*tert*-Butyl Ester. (41). A solution of L-pyroglutamic acid (3.23 g, 0.025 mol) and 2-(trimethylsilyl)ethanol (3.00 mL, 0.021 mol) in benzene (70 mL) was refluxed in the presence of *p*-toluenesulfonic acid (0.400 g, 2.10 mmol), with azeotropic removal of water for 2 h. The reaction mixture was then cooled to room temperature, solid potassium carbonate (5 g) was added, the solvent was removed, and the residue was partitioned between EtOAc and water. The combined organic phases were dried over sodium sulfate and evaporated to yield a white solid which was dissolved in CH_2Cl_2 (50 mL). Di-*tert*-butyl dicarbonate (10.92 g, 0.050 mol), triethylamine (6.97 mL, 0.050 mol), and DMAP (307 mg, 2.50 mmol) were added, and the mixture was stirred at room temperature overnight. The solvent was then removed and the residue partitioned between EtOAc and 10% HCl (aq), and the combined organic extracts were washed with saturated $NaHCO_3$ (aq) and brine and then dried over sodium sulfate and evaporated to yield bright orange oil which was purified by column chromatography (1:10, EtOAc/hexanes as eluent) to afford the title compound (**41**) (3.67 g, 85%) as a pale yellow oil: $[\alpha]_D$ −20.1 (*c* 3.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.01−1.05 (m, 2H), 1.49 (s, 9H), 1.98−2.10 (m, 1H), 2.21−2.72 (m, 3H), 4.23−4.28 (m, 2H), 4.58 (dd, J = 2.9, 9.3 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −2.2, 16.8, 20.8, 27.2, 30.5, 58.2, 63.3, 82.8, 148.6, 170.6, 172.7; ν_{max}/cm^{-1} 2956, 1797, 1745, 1719, 1316; HRMS (FAB) 330 (M + H).

(2*S*, 5*S*)-5-*cis*-Propenyl-pyrrolidine-1,2-dicarboxylic acid 2-trimethylsilanyl-ethyl ester 1-*tert*-butyl ester (42). To a solution of **41** (3.67 g, 0.011 mol) in dry THF (50 mL) at −78 °C under argon, diisobutylaluminum hydride (11.16 mL of a 1.5 M solution in toluene, 0.017 mol) was slowly added. After 1.5 h the reaction mixture was quenched with MeOH (2 mL), allowed to warm to room temperature, and treated with a saturated aqueous solution of potassium sodium l-tartrate tetrahydrate (50 mL) for 1 h. The mixture was then extracted with EtOAc, and the combined organic phases were dried over sodium sulfate and evaporated to give a residue which was dissolved in CH_2Cl_2 (30 mL), to which acetic anhydride (2.08 mL, 0.022 mol), pyridine (1.94 mL, 0.024 mol), and DMAP (0.269 g, 2.20 mmol) were added. The solution was stirred at room temperature for 16 h and then partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The combined organic extracts were washed with saturated solution of copper(II) sulfate (3 × 50 mL) and then brine, filtered through a pad of silica gel, and dried over Na_2SO_4. Evaporation afforded a pale yellow oil which was dissolved in Et_2O (20 mL). To a suspension of copper bromide−dimethyl sulfide complex (4.63 g, 0.023 mol) in anhydrous Et_2O (100 mL) at −55 °C under argon was slowly added *cis*-1-propenyllithium (22.61 mL of a 0.83 M solution in Et_2O, 18.77 mmol). The mixture was allowed to warm to −30 °C over 1 h, forming a very dark red solution. The reaction was then cooled to −78 °C and boron trifluoride diethyl etherate (2.54 mL, 0.021 mol) added dropwise. After 30 min, the solution of the cuprate in Et_2O was slowly added and the reaction allowed to warm to room temperature over 2.5 h. The dark solution formed was treated with NH_4Cl (aq) (50 mL) and NH_4OH (aq) (50 mL) and then extracted with EtOAc. The organic phases were combined, washed with brine, dried over sodium sulfate, and evaporated to yield the title compound (**42**) (2.29 g, 67%) as a colorless oil upon column chromatography (1:10, EtOAc/hexanes as eluent): $[\alpha]_D$ −0.7 (*c* 4.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, two conformations present) δ 0.02 (s, 4.5H), 0.03 (s, 4.5H), 0.93−1.01 (m, 2H), 1.38, 1.40 (s, 9H), 1.57−1.67 (m, 1H), 1.71 (d, J = 1.3 Hz, 1.5H), 1.74 (d, J = 1.3 Hz, 1.5H), 1.89−2.28 (m, 3H), 4.13−4.36 (m, 3H), 4.72 (t, J = 7.5 Hz, 0.5H), 4.80 (t, J = 8.0 Hz, 0.5H), 5.49−5.31 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, two conformations present) δ −2.6, 12.0, 16.2, 16.4, 26.9, 27.2, 27.8, 29.7, 30.4, 53.3, 53.6, 58.3, 58.7, 62.1, 78.6, 122.4, 123.7, 130.8, 131.0, 152.4, 153.3, 171.9, 172.2; ν_{max}/cm^{-1} 2956, 1745, 1699, 1390, 1172; HRMS calcd for $C_{18}H_{34}NO_4Si$ (M + H) 356.22571, found 356.22660.

(2*S*,5*S*)-5-*cis*-Propenyl-1-[3-(2-trimethylsilanylethoxycarbonyl)propionyl]pyrrolidine-2-carboxylic Acid 2-Trimethylsilanylethyl Ester (43). Trifluoroacetic acid (0.13 mL, 1.72 mmol) was added to a solution of **42** (0.122 g, 0.34 mmol) in CH_2Cl_2 (1 mL). The reaction was stirred at room temperature for 30 min and then carefully quenched with saturated $NaHCO_3$. The solution was extracted with CH_2Cl_2,and the combined organic extracts were dried over sodium sulfate and evaporated to give an oil which was dissolved in CH_2Cl_2 (3 mL). A solution of succinic acid mono-2-trimethylsilanylethyl ester (148 mg, 0.68 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (173 mg, 0.68 mmol), and *N*,*N*-diisopropylethylamine (0.36 mL, 2.04 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C for 2 h. The pale yellow solution formed was stirred at room temperature overnight. The solvent was removed, the residue was partitioned between EtOAc and 10% HCl, and the organic extracts were combined and washed with saturated $NaHCO_3$ (aq) and then brine and dried over sodium sulfate. Evaporation yielded a yellow oil which was purified by column chromatography (1:10, EtOAc/hexanes as eluent) to afford the title compound (**43**) (96 mg, 62%) as a colorless oil: $[\alpha]_D$ −11.1 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.03 (s, 9H), 0.94−1.03 (m, 4H), 1.72−1.77 (m, 4H), 1.94−1.98 (m, 1H), 2.19−2.36 (m, 2H), 2.55−2.69 (m, 4H), 4.13−4.22 (m, 4H), 4.52−4.55 (m, 1H), 4.79−4.84 (m, 1H), 5.41−5.48 (m, 1H), 5.54−5.60 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −1.8, 12.7, 16.9, 26.9, 28.5, 28.8, 31.9, 54.7, 59.1, 62.2, 63.0, 125.1, 130.8, 170.4, 171.9, 172.7; ν_{max}/cm^{-1} 2955, 1737, 1653, 1251, 1170; HRMS calcd for $C_{22}H_{42}NO_5Si_2$ (M + H) 456.26016, found 456.26180.

(3*S*,9*R*)-8-Hydroxy-5-oxo-3-*cis*-propenyl-1,2,3,5,6,8a-hexahydroindolizine-7-carboxylic Acid 2-Trimethylsilanylethyl Ester (44). To a solution of **43** (0.486 g, 1.07 mmol) in THF (100 mL) at −78 °C under argon was slowly added potassium bis(trimethylsilyl)amide (3.21 mL of a 0.5 M solution in toluene, 1.61 mmol). A pale orange solution was formed which was allowed to warm to room temperature over 2 h. The reaction was then quenched with glacial acetic acid (0.31 mL, 5.5 mmol) and evaporated. The residue was triturated with Et_2O and filtered, and the filtrate was dried over sodium sulfate and evaporated to yield an orange oil which was purified by column chromatography (1: 4, EtOAc/hexanes as eluent) to yield the title compound (**44**) (0.188 g, 52%) as an unstable colorless solid: $[\alpha]_D$ +1 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 9H), 1.02−1.08 (m, 2H), 1.58−1.75 (m, 2H), 1.79 (dd, J = 1.7 Hz, 6.9 Hz, 3H), 2.28−2.39 (m, 2H), 3.09−3.28 (m, 2H), 4.26−4.32 (m, 3H), 4.97 (q, J = 8.2 Hz, 1H), 5.26−5.33 (m, 1H), 5.56−5.62 (m, 1H), 12.06 (s, 1H); ν_{max}/cm^{-1} 2955, 1726, 1666, 1250, 859, 838; HRMS calcd for $C_{17}H_{28}NO_4Si$ (M + H) 338.17877, found 338.17960.

(3*S*,9*R*)-3-(Cis-Propenyl)hexahydroindolizine-5,8-dione (45). A solution of **44** (167 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) and trifluoroacetic acid (4 mL) was stirred at room temperature for 16 h. The solvent and excess trifluoroacetic acid were removed by evaporation, and the orange residue was purified by column chromatography (EtOAc) to furnish the title compound (**45**) (0.066 g, 67%) as a pale yellow oil: $[\alpha]_D$ −54.3 (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58−1.68 (m, 1H), 1.78 (dd, J = 1.3 Hz, 6.9 Hz, 3H), 1.98−2.07 (m, 1H), 2.10−2.19 (m, 1H), 2.23−2.32 (m, 1H), 2.50−2.80 (m, 4H), 4.09−4.13 (t, J = 7.4 Hz, 1H), 4.95−5.00 (m, 1H), 5.28−5.34 (m, 1H), 5.55−5.62 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.1, 28.7, 32.1, 33.0, 36.4, 56.7, 66.4, 128.5, 131.4, 170.3, 209.0; ν_{max}/cm^{-1} 1730, 1663, 1427; HRMS calcd for $C_{11}H_{15}NO_2$ (M+) 193.110279, found 193.110229.

(3*S*,8*S*,9*R*)-8-Hydroxy-3-(*cis*-propenyl)hexahydroindolizin-5-one (46). To a solution **45** (45 mg, 0.23 mmol) in THF (3 mL) at −78 °C under argon was slowly added L-Selectride (0.35 mL of a 1.0 M in THF, 0.35 mmol). After 1 h, the reaction was quenched with saturated NH_4Cl (0.1 mL) and allowed to warm to room temperature. The solvent was removed, and the residue was redissolved in CH_2Cl_2 and dried over sodium sulfate. Evaporation yielded the title compound (**46**) (33 mg, 76%) as a colorless oil after column chromatography (EtOAc): $[\alpha]_D$ +24.3 (*c* 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50−1.56 (m, 1H), 1.79 (dd, J = 1.7 Hz, 6.9 Hz, 3 H), 1.83−1.97 (m, 3H), 2.00−2.13 (m, 1H), 2.18−2.25 (m, 1H), 2.38−2.45 (m, 1H), 2.49−2.59 (m, 1H), 3.64−3.69 (m, 1H), 4.18 (quintet, J = 2.0 Hz, 1H), 4.86 (q, J = 8.1 Hz, 1H), 5.26−5.31 (m, 1H), 5.54−5.62 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.1, 26.3, 26.8, 28.1, 29.9, 54.4, 62.4, 64.0, 125.2, 131.6, 168.8; ν_{max}/cm^{-1} 3324, 2929, 1614; HRMS calcd for $C_{11}H_{17}NO_2$ (M+) 195.125929, found 195.125737.

(3*S*,8*S*,9*R*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-8-hydroxyhexahydroindolizin-5-one (16). A solution of **46** (32 mg, 0.165 mmol)) in THF (2 mL) and water (0.5 mL) was treated with a solution of osmium tetraoxide in isobutanol (3 drops) and sodium periodate (90 mg, 0.41 mmol) at room temperature overnight. The mixture was then partitioned between water and EtOAc, and the combined organic phases were dried over sodium sulfate and evaporated to yield a pale brown oil which was redissolved in ethanol (0.5 mL). The solution was cooled in an ice bath and sodium borohydride (6 mg, 0.165 mmol) added. The reaction was allowed to warm to room temperature over 1 h and quenched with concentrated HCl (1 drop). The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and dried over sodium sulfate. Evaporation yielded an off-white solid which was dissolved in CH_2Cl_2 (2 mL) and treated with chloro-*tert*-butyldiphenylsilane (43 μL,

0.2 mmol) and triethylamine (50 μL) in the presence of a catalytic amount of DMAP for 2 h at room temperature. The reaction was partitioned between CH_2Cl_2 and 10% HCl, and the organic phases were combined, dried over sodium sulfate, and evaporated to yield the title compound (**16**) (100.5 mg, 33% overall) as a viscous oil upon column chromatography (EtOAc): $[\alpha]_D$ −62.3 (*c* 1.1, $CHCl_3$).

(2*S*,5*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-5-propenylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (49). To a solution of **48** (1.8 g, 3.97 mmol) in dry toluene (5 mL) at −78 °C under argon was slowly added diisobutylaluminum hydride (3.97 mL of a 1.5 M solution in toluene, 5.96 mmol). After 1.5 h, the reaction mixture was quenched with MeOH (7 mL) and stirred for 30 min, Et_2O (20 mL) was added, and the mixture was warmed to 0 °C and stirred for 30 min. Finally, H_2O (1 mL) was added, and the solution was stirred for another 30 min at rt. The resulting gel was filtered through a Celite pad, washed with hot EtOAc (100 mL), and evaporated to give a residue which was dissolved in CH_2Cl_2 (16 mL), and acetic anhydride (1.12 mL, 11.92 mmol), triethylamine (1.66 mL, 11.92 mmol), and catalytic DMAP (135 mg, 1.10 mmol) were added. The solution was stirred at room temperature for 16 h and then partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 20:80) to give a colorless oil. To a suspension of copper bromide−dimethyl sulfide complex (1.67 g, 7.64 mmol) in anhydrous Et_2O (20 mL) at −40 °C under argon was slowly added propenylmagnesium bromide (0.5 M in THF, 13.3 mL, 6.64 mmol). After the mixture was stirred for 40 min, $BF_3{\cdot}OEt_2$ (0.92 mL, 7.30 mmol) was added, followed by a solution of the substrate (1.65 g, 3.32 mmol) in Et_2O (10 mL) via cannula. The reaction mixture was slowly warmed to 0 °C over a period of 4 h. After an additional 1 h at 0 °C, a 1:1 mixture of NH_4Cl and NH_4OH was added. The resulting solution was extracted with EtOAc. The organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 5:95) to give the title compound (**49**) (1.1 g, 70%) as a clear, colorless oil: $[\alpha]_D$ −0.6 (*c* 6.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, two conformations present) δ 7.68−7.64 (m, 4H), 7.44−7.36 (m, 6H), 5.46−5.31 (m, 2H), 4.56 (m, 1H), 4.07−3.96 (m, 1.5H), 3.76 (m, 1H), 3.47 (m, 0.5H), 2.23−2.01 (m, 3H), 1.74−1.48 (m, 4H), 1.39 (s, 4.5 H), 1.30 (s, 4.5H), 1.06 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, two conformations present) δ 154.0, 153.4, 135.3, 133.5, 133.3, 133.2, 132.9, 132.5, 129.4, 129.3, 127.5, 127.4, 124.0, 122.4, 78.8, 78.6, 63.7, 63.6, 58.2, 54.6, 54.5, 31.3, 31.2, 30.1, 28.3, 28.2, 26.6, 26.1, 25.8, 19.0, 13.9, 12.8; ν_{max}/cm^{-1} 2963, 2859, 1694, 1388, 1113; HRMS calcd for $C_{29}H_{42}NO_3Si$ (M + H) 480.29340, found 480.29420.

(2*S*,9*R*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-2,3,6,-8a-tetrahydro-1*H*-indolizin-5-one (50). TMSOTf (1.25 mL, 6.94 mmol) was added to a 0 °C solution of **49** (2.77 g, 5.78 mmol) and *i*-Pr_2NEt (2.01 mL, 11.57 mmol) in CH_2Cl_2 (35 mL). The solution was stirred for 1.5 h, quenched with saturated $NaHCO_3$ (15 mL), extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a colorless oil. The resulting residue was purified by silica gel chromatography (EtOAc−hexanes, 5:95) to give a clear, colorless oil which was dissolved in CH_2Cl_2 (30 mL). EDC (1.47 g, 7.68 mmol), DMAP (937 mg, 7.68 mmol), and vinylacetic acid (0.65 mL, 7,68 mmol) were added dropwise, and the solution was stirred for 45 min. Saturated $NaHCO_3$ was added and the mixture extracted with CH_2Cl_2. The organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 20:80) to give a clear, colorless oil. To a solution of the resulting oil in CH_2Cl_2 (300 mL) at reflux under argon was added Grubbs' catalyst (60 mg, 0.85 mmol) portionwise. The mixture was stirred at reflux 15 h before being filtered through a 10 cm pad of Florisil/silica. The pad was washed with CH_2Cl_2, and the solvent was removed by evaporation. The residue was purified by column chromatography (EtOAc−hexanes, 80:20) to yield the title compound (**50**) (2.14 g, 96%) as a clear, colorless oil: $[\alpha]_D$ −94.8 (*c* 1.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.66−7.62 (m, 4H), 7.43−7.34 (m, 4H), 5.80 (d, *J* = 10.0 Hz, 1H), 5.75−5.70 (m, 1H), 4.35 (m, 1H), 4.18−4.15 (m, 1H), 3.80 (dd, *J* = 10.2, 2.6 Hz, 1H), 2.90−2.84 (m, 2H), 2.17−2.05 (m, 4H), 1.48−1.43 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 136.0, 135.9, 134.0, 130.1, 130.0, 128.1, 128.0, 125.5, 122.4, 64.8, 60.3, 57.7, 32.2, 32.9, 27.4, 25.2, 19.8; ν_{max}/cm^{-1} 3433, 2932, 2858, 1648 (s), 1428, 1112; HRMS calcd for $C_{25}H_{32}NO_2Si$ (M + H) 406.22023, found 406.22223.

(3*S*,9*R*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-hexahydroindolizin-5-one (9). To a solution of **50** (1.6 g, 3.95 mmol) in EtOAc (35 mL) was added a catalytic quantity of 10% palladium on carbon. The solution was stirred at room temperature under an atmosphere of hydrogen for a period of 16 h. The mixture was filtered over Celite and rinsed with EtOAc, and the solvent was removed by evaporation to give the title compound (**9**) (1.54 g, 96%) as a colorless oil.

(3*S*,6*S*,9*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-6-benzylhexahydroindolizin-5-one (51). A solution of **9** (108 mg, 0.27 mmol) in THF (1.4 mL) was cooled to −78 °C under argon atmosphere. *t*-Buli (1.7 M in pentane, 0.17 mL, 0.29 mmol) was added dropwise, and the resulting yellow mixture was stirred at −78 °C for 45 min. Then, the enolate was trapped with slow addition of benzyl bromide (0.04 mL, 0.35 mmol) and stirring was continued for another 1 h at −78 °C. The mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc. The organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 80:20) to give the title compound (**51**) (88 mg, 67%) as a clear, colorless oil: $[\alpha]_D$ −3 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71−7.65 (m, 4H), 7.47−7.40 (m, 6H), 7.30−7.18 (m, 5H), 4.34 (m, 1H), 4.07 (dd, *J* = 10.1, 4.7 Hz, 1H), 3.82 (dd, *J* = 10.1, 2.5 Hz, 1H), 3.59−3.52 (m, 2H), 2.61−2.47 (m, 2H), 2.11−2.03 (m, 4H), 1.78−1.75 (m, 1H), 1.45 (m, 2H), 1.22 (dd, *J* = 13.5, 2.4 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.1, 140.7, 136.0, 134.2, 134.1, 130.1, 129.6, 128.7, 128.1, 126.5, 64.7, 60.9, 58.6, 44.3, 39.2, 33.7, 29.6, 27.4, 25.7, 19.9; ν_{max}/cm^{-1} 2931, 2858, 1633, 1428, 1112; HRMS calcd for $C_{32}H_{40}NO_2Si$ (M + H) 498.28283, found 498.28060

Representative Procedure for the Synthesis of the Indolizidinones (52, 53). A solution of **51** (548 mg, 1.10 mmol) in THF (5.5 mL) was cooled to −78 °C under argon atmosphere. *t*-Buli (1.7 M in pentane, 0.71 mL, 1.21 mmol) was added dropwise, and the resulting yellow mixture was stirred at −78 °C for 50 min. Then, the enolate was trapped with slow addition of trizyl azide (444 mg, 1.43 mmol), and stirring was continued for 6 h at −78 °C. The mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc. The organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 80:20) as a clear colorless oil.

(3*S*,6*S*,9*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-6-azido-6-benzylhexahydroindolizin-5-one (52): yield, 163 mg, 27%; $[\alpha]_D$ −92.6 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71−7.66 (m, 4H), 7.47−7.42 (m, 6H), 7.41−7.26 (m, 5H), 4.31−4.27 (m, 2H), 3.69 (d, *J* = 8.1 Hz, 1H), 3.64 (m, 1H), 3.30 (dd, *J* = 13.8, 27.4 Hz, 2H), 2.15−1.96 (m, 5H), 1.85 (dd, *J* = 3.7, 13.6 Hz, 1H), 1.60 (m, 1H), 1.33−1.22 (m, 2H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.8, 136.0, 134.0, 133.6, 130.6, 130.2, 130.1, 129.0, 128.2, 128.1, 127.6, 64.9, 64.0, 60.6, 59.1, 42.0, 33.6, 30.9, 27.5, 27.3, 26.6, 25.4, 19.8; ν_{max}/cm^{-1} 3435, 2932, 2859, 2105, 1640, 1429, 1113; HRMS calcd for $C_{32}H_{39}N_4O_2Si$ (M + H) 539.28423, found 539.28620;

(3*S*,6*R*,9*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-6-azido-6-benzylhexahydroindolizin-5-one (53): yield, 89 mg, 15%; mp 106 °C; $[\alpha]_D$ −1.4 (*c* 1.48, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.71−7.68 (m, 4H), 7.49−7.41 (m, 6H),

7.28−7.18 (m, 5H), 4.38 (m, 1H), 3.90 (d, J = 3.8 Hz, 2H), 3.37 (m, 1H), 3.27 (dd, J = 13.6, 36.8 Hz, 2H), 2.12−2.01 (m, 3H), 1.87 (dd, J = 3.0, 13.2 Hz, 1H), 1.69−1.58 (m, 2H), 1.49−1.40 (m, 2H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.4, 136.0, 135.9, 134.0, 133.9, 130.8, 130.2, 128.8, 128.2, 128.1, 127.4, 65.2, 64.4, 60.9, 58.9, 42.4, 33.4, 31.7, 27.4, 26.2, 25.8, 19.9; ν_{max}/cm^{-1} 2931, 2859, 2108, 1642, 1429, 1113; HRMS calcd for $C_{32}H_{39}N_4O_2Si$ (M + H) 539.28423, found 539.28596.

(3S,6S,9S)-3-Hydroxymethyl-6-azido-6-benzylhexahydroindolizin-5-one (54). TBAF (1 M in THF, 0.59 mL, 0.59 mmol) was added dropwise to a solution of **52** (160 mg, 0.30 mmol) in THF (2.5 mL). After the mixture was stirred for 1.5 h, a saturated solution of $NaHCO_3$ (10 mL) was added and the resulting mixture extracted with EtOAc. The organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 50:50) to give the title compound (**54**) (89 mg, 99%) as a clear, colorless oil: $[\alpha]_D$ +129.7 (c 0.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31−7.21, 4.73 (br, 1H) (m, 5H), 4.27−4.08 (m, 1H), 3.70 (dd, J = 1.5, 11.6 Hz, 1H), 3.54 (d, J = 13.1 Hz, 1H), 3.47 (dd, J = 7.1, 11.6 Hz, 1H), 3.14−3.09 (m, 1H), 3.00 (d, J = 13.1 Hz, 1H), 2.08−2.04 (m, 1H), 1.94−1.91 (m, 1H), 1.83 (dd, J = 3.3, 13.3 Hz, 1H), 1.72−1.61 (m, 2H), 1.49−1.38 (m, 1H), 1.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.7, 135.6, 130.8, 128.9, 127.6, 67.1, 65.2, 62.0, 60.9, 42.2, 32.7, 31.0, 26.6, 25.6; ν_{max}/cm^{-1} 3369, 2935, 2107, 1619, 1454, 1248; HRMS calcd for $C_{16}H_{21}N_4O_2$ (M + H) 301.16645, found 301.16700.

(3*S*,6*R*,9*S*)-3-Hydroxymethyl-6-azido-6-benzylhexahydroindolizin-5-one (55). TBAF (1 M in THF, 0.32 mL, 0.32 mmol) was added dropwise to a solution of **53** (85 mg, 0.16 mmol) in THF (1.0 mL). After the mixture was stirred for 1.25 h, a saturated solution of $NaHCO_3$ (7 mL) was added and the resulting mixture extracted with EtOAc. The organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 50:50) to give the title compound (**55**) (42 mg, 90%) as a clear, colorless oil: $[\alpha]_D$ −90.5 (c 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33−7.20 (m, 5H), 4.23−4.17 (m, 1H), 3.73 (dd, J = 1.7, 11.8 Hz, 1H), 3.61 (dd, J = 7.7, 11.7 Hz, 1H), 3.50−3.42 (m, 1H), 3.32 (d, J = 13.6 Hz, 1H), 3.15 (d, J = 13.6 Hz, 1H), 2.14−2.09 (m, 1H), 1.99−1.92 (m, 1H), 1.85−1.79 (m, 1H), 1.57 (td, J = 3.2, 14.2 Hz, 1H), 1.46−1.36 (m, 1H), 1.28−1.09 (m, 1H), 0.97−0.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.7, 135.5, 130.5, 129.0, 127.8, 67.5, 65.0, 62.6, 60.2, 42.3, 33.0, 30.8, 26.9, 26.4; ν_{max}/cm^{-1} 3366, 2937, 2870, 2106, 1620, 1441, 1257; HRMS calcd for $C_{16}H_{21}N_4O_2$ (M + H) 301.16645, found 301.16700.

(3*S*,6*S*,9*S*)-6-Azido-6-benzyl-5-oxooctahydroindolizine-3-carboxylic Acid 4-*N*-Cbz-carbamimidoylbenzylamide (56). To a stirred solution of **54** (85 mg, 0.28 mmol) in wet DMF (7 mL) was added PDC (1.07 g, 2.83 mmol). After the mixture was stirred overnight, 10% HCl was added and the resulting mixture extracted with EtOAc. The organic layer was processed as usual to yield a residue which was dissolved in DMF (6.0 mL), and EDC (65 mg, 0.34 mmol), HOBt (46 mg, 0.34 mmol), and *i*-Pr_2NEt (0.11 mL, 0.62 mmol) were successively added. After the mixture was stirred for 20 min, *N*-Cbz-aminomethylbenzamidine (118 mg, 0.37 mmol) was added, and the resulting mixture was stirred overnight and then evaporated to dryness. The residue was dissolved in saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 60:40 to 100:0) to give the title compound (**56**) (104 mg, 63%) as a clear, colorless oil: $[\alpha]_D$ +9.6 (c 1.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.43 (br, 1H), 7.85 (t, J = 5.7 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 7.4 Hz, 2H), 7.35−7.20 (m, 8H), 7.10 (d, J = 7.4 Hz, 2H), 5.17 (s, 2H), 4.62 (t, J = 7.9 Hz, 1H), 4.54 (dd, J = 6.4, 15.5 Hz, 1H), 4.27 (dd, J = 5.3, 15.6 Hz, 1H), 3.44−3.38 (m, 1H), 3.17 (d, J = 13.6 Hz, 1H), 3.05 (d, J = 13.6 Hz, 1H), 2.23−2.16 (m, 1H), 2.11−2.04 (m, 2H), 1.86−1.71 (m, 1H), 1.65 (m, 1H), 1.55−1.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.8, 171.6, 168.4, 164.8, 143.2, 137.1, 135.4, 133.6, 130.6, 128.9, 128.8, 128.6, 128.3, 128.2, 127.8, 127.6, 67.5, 65.0, 61.0, 60.8, 60.4, 43.4, 41.8, 33.2, 31.2, 27.1, 25.4, 21.5, 14.6; ν_{max}/cm^{-1} 3310, 2946, 2108, 1621, 1497, 1262; HRMS calcd for $C_{32}H_{34}N_7O_4$ (M + H) 580.26723, found 580.26900.

(3*S*,6*S*,9*S*)-6-Amino-6-benzyl-5-oxooctahydroindolizine-3-carboxylic Acid 4-Carbamimidoylbenzylamide (57). To a solution of **56** (63 mg, 0.11 mmol) in MeOH (3 mL) and HCl (37%, 1 drop) was added a catalytic quantity of 10% palladium on carbon. The solution was stirred at room temperature under an atmosphere of hydrogen for a period of 14 h. The mixture was filtered over Celite and rinsed with MeOH (3 × 10 mL), and the solvent was removed by evaporation to give the title compound (**57**) (50 mg, 99%) as a white solid: $[\alpha]_D$ +20.2 (c 1.25, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 9.77 (br, 2H), 9.26 (br, 2H), 8.20 (d, J = 9.5 Hz, 2H), 8.05 (d, J = 9.7 Hz, 2H), 7.66 (m, 5H), 4.85−4.70 (m, 3H), 3.76−3.72 (m, 1H), 3.59 (d, J = 18.9 Hz, 1H), 3.22 (d, J = 18.9 Hz, 1H), 2.52−2.46 (m, 1H), 2.41−2.06 (m, 4H), 1.98−1.87 (m, 1H), 1.65 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 163.1, 157.9, 157.8, 143.0, 138.3, 126.8, 124.3, 122.5, 122.0, 121.8, 121.4, 120.9, 120.8, 60.2, 59.8, 57.7, 42.9, 33.9, 31.1, 30.1, 26.8; ν_{max}/cm^{-1} 3268, 1654, 1540, 1496, 1319; HRMS calcd for $C_{24}H_{30}N_5O_2$ (M + H) 420.23995, found 420.23880.

(3*S*,6*R*,9*S*)-6-Azido-6-benzyl-5-oxooctahydroindolizine-3-carboxylic Acid 4-*N*-Cbz-carbamimidoylbenzylamide (58). To a stirred solution of **55** (40 mg, 0.13 mmol) in wet DMF (3.5 mL) was added PDC (500 mg, 1.33 mmol). After the mixture was stirred overnight, 10% HCl was added and the resulting mixture extracted with EtOAc. The organic layer was processed as usual to yield a residue which was dissolved in DMF (3.0 mL), and EDC (31 mg, 0.16 mmol), HOBt (21 mg, 0.16 mmol) ,and *i*-Pr_2NEt (0.05 mL, 0.27 mmol) were successively added. After the mixture was stirred for 20 min, *N*-Cbz-aminomethylbenzamidine (55 mg, 0.17 mmol) was added, and the resulting mixture was stirred overnight then evaporated to dryness. The residue was dissolved in saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was processed as usual to yield a residue which was purified by column chromatography (EtOAc−hexanes, 60:40 to 100:0) to give the title compound (**58**) (41 mg, 53%) as a clear, colorless oil: $[\alpha]_D$ −84.5 (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.77−7.71 (m, 3H), 7.41 (d, J = 7.2 Hz, 2H), 7.36−7.26 (m, 7H), 7.18 (d, J = 6.5 Hz, 2H), 5.19 (s, 2H), 4.59 (t, J = 8.1 Hz, 1H), 4.35 (dd, J = 5.4, 15.6 Hz, 1H), 3.58−3.51 (m, 1H), 3.26 (d, J = 13.7 Hz, 1H), 3.15 (d, J = 13.4 Hz, 1H), 2.29−2.21 (m, 1H), 2.16−2.02 (m, 2H), 1.94−1.91 (m, 1H), 1.86−1.82 (m, 1H), 1.61−1.54 (m, 1H), 1.27−1.17 (m, 1H), 0.99−0.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.3, 170.3, 168.5, 164.7, 143.2, 137.1, 135.3, 133.5, 130.5, 129.1, 128.8, 128.6, 128.4, 128.2, 127.9, 127.7, 67.6, 64.9, 60.1, 43.5, 41.9, 33.3, 30.5, 30.1, 26.1, 26.0; ν_{max}/cm^{-1} 3304, 2938, 2105, 1620, 1497, 1261; HRMS calcd for $C_{32}H_{34}N_7O_4$ (M + H) 580.26723, found 580.26850.

(3*S*,6*S*,9*S*)-6-Amino-6-benzyl-5-oxooctahydroindolizine-3-carboxylic Acid 4-Carbamimidoylbenzylamide (59). To a solution of **58** (35 mg, 0.06 mmol) in MeOH (2 mL) and HCl (37%, 1 drop) was added a catalytic quantity of 10% palladium on carbon. The solution was stirred at room temperature under an atmosphere of hydrogen for a period of 14 h. The mixture was filtered over Celite and rinsed with MeOH (3 × 10 mL), and the solvent was removed by evaporation to give the title compound (**59**) (30 mg, 99%) as a white solid: $[\alpha]_D$ −58.1 (c 1.51, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 9.25 (s, 1H), 8.78 (s, 1H), 7.78 (d, J = 5.3 Hz, 2H), 7.62 (d, J = 5.8 Hz, 2H), 7.37−7.21 (m, 5H), 4.60−4.43 (m, 3H), 3.77 (s, 1H), 3.50 (d, J = 12.0 Hz, 1H), 3.04 (d, J = 11.2 Hz, 1H), 2.41 (m, 1H), 2.33−2.30 (d, J = 11.4 Hz, 1H), 2.17 (m, 1H), 2.06 (m, 1H), 1.94 (m, 1H), 1.80 (m, 1H), 1.18 (m, 1H), 0.95 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 173.5, 167.4, 167.3, 146.0, 143.1, 130.4, 129.2, 128.6, 128.3, 128.2, 128.1, 127.2, 60.9, 60.8, 58.7, 42.8, 42.6, 33.0, 29.8, 29.1, 25.4; ν_{max}/cm^{-1} 3276, 1647, 1540,

1493, 1319; HRMS calcd for $C_{24}H_{30}N_5O_2$ (M + H) 420.23995, found 420.23790.

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Supporting Information Available: ^1H and ^{13}C spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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