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Olefin Metathesis Based Approach to Diversely Functionalized Pyrrolizidines and Indolizidines; Total Synthesis of (+)-Monomorine

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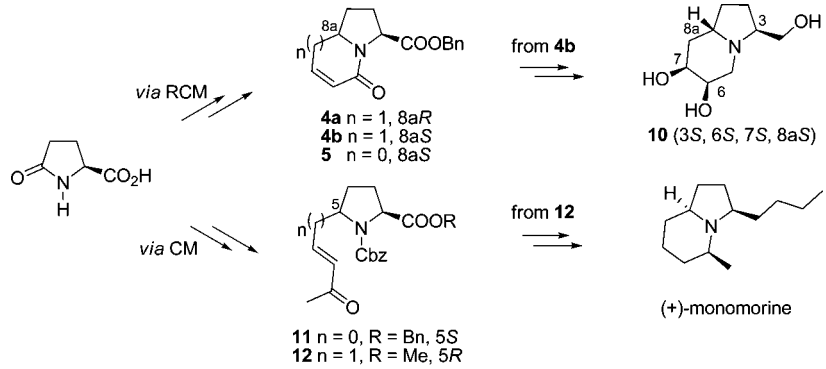
Received July 30, 2008



New scaffolds for the stereoselective synthesis of diversely functionalized chiral enantiopure indolizidines and pyrrolizidines were synthesized from the cross and ring-closing metathesis reactions of appropriate intermediates, readily available from L-pyroglutamic acid. The versatility of this strategy was demonstrated by the synthesis of an indolizidine-based azasugar analogue and of the natural alkaloid (+)-monomorine.

Introduction

The design of small organic molecules derived from natural products is a main issue in organic chemistry, aimed to discover new potentially interesting bioactive compounds. As a matter of fact, most of the drugs currently in use have originated from natural sources.[1] Besides the classical total synthesis approach to complex structures and the combinatorial technique for the generation of libraries, particularly attractive is the development of synthetic methodologies that allow for the preparation of a large number of structurally similar analogs from a few common intermediates.[2] As part of a program aimed at the design and preparation of polyfunctionalized chiral building blocks for the enantiospecific synthesis of natural products,[3] we introduce here new optically pure scaffolds for the stereoselective synthesis of diversely functionalized indolizidines and pyrrolizidines.[4]

Azabicyclic ring skeletons are important structural subunits present in numerous alkaloids and are common scaffolds in biologically active and pharmaceutically significant compounds.[5] For example, polyhydroxylated pyrrolizidines and indolizidines (related to iminosugars) such as swainsonine **1** have increasingly gained attention because of their ability to inhibit glycosidases.[6] More recently, a diverse array of biologically active 3,5 dialkyl-substituted pyrrolizidine and indolizidine alkaloids, such as (−)-xenovenine **2** and (+)-monomorine **3**, have been discovered in

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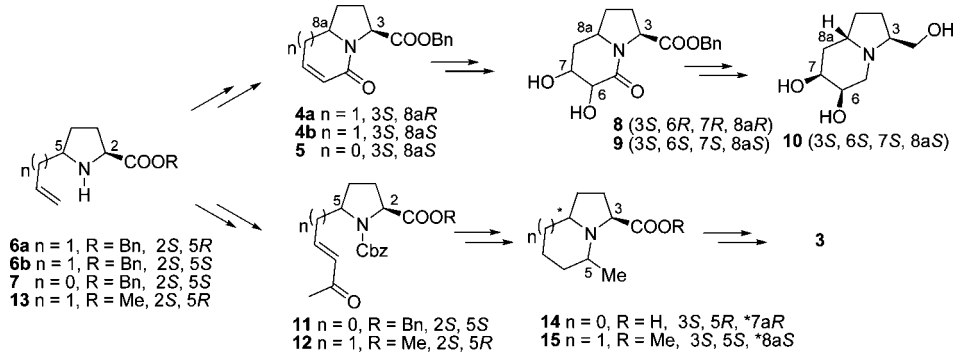
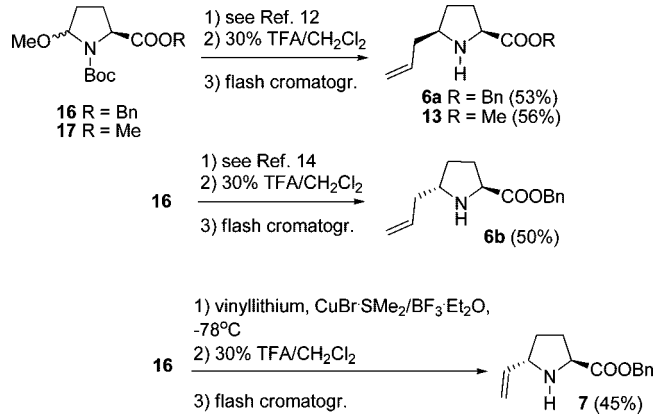
10.1021/jo801638u CCC: $40.75
Published on Web 12/09/2008

SCHEME 1



SCHEME 2



skin extracts of neotropical frogs, mainly *Dendrobates*.[7] It is already well-known that several classes of the amphibian alkaloids exhibit promising pharmacological activity mediated by nicotinic receptor ion channels.[8] The paucity of natural material has made total synthesis the only available avenue to obtain substances for studying the biological activity of these novel compounds. Accordingly, the development of new stereocontrolled synthetic routes to azabicyclic skeletons has received considerable attention[9] and constitutes an area of current interest.

Results and Discussion

Our synthetic strategy (Scheme 1) envisaged compounds **4** and **5** as suitable chiral building blocks for the synthesis of polyfunctionalized pyrrolizidines and indolizidines. Scaffolds **4a,b** and **5** could be obtained by means of ring-closing metathesis (RCM) reactions starting from allyl- or vinylproline derivatives **6a,b** and **7**. Further elaboration of the functional groups present in **4a,b** and **5** makes it possible in principle to obtain many different compounds. As an application of this strategy, we could realize the synthesis of dihydroxylated derivatives **8** and **9** and of the azasugar analogue **10**. Ketopyrrolidines **11** and **12** could be prepared by cross metathesis (CM) reactions with methyl vinyl ketone beginning from precursors **7** and **13**. By means of a stereoselective intramolecular reductive amination, 3,5-disubstituted pyrrolizidine and indolizidine derivatives **14** and **15** can be achieved. Application of this synthetic sequence allowed us to realize an efficient synthesis of (+)-monomorine **3**, a trial pheromone of the pharaoh ant *Monomorium pharaonis L.*[10] Compounds **6a,b**, **7**, and **13** are ultimately derived from commercially available L-pyroglutamic acid, by slight modifications of known stereoselective allylation or vinylation protocols, starting from the known methyl lactamols **16** and **17** (Scheme 2).

Compound **6a**[11] was obtained as the preferred diastereoisomer (8:2 dr) from **16** by use of allyltrimethylsilane according to a reported procedure.[12] Boc deprotection with TFA followed by chromatographic separation yielded **6a** in good yields. The same procedure afforded compound **13**[13] from **17**, in comparable diastereoisomeric excess and yield.

In order to achieve the *trans* isomer **6b**, allylation of **16** was realized using allyl magnesium bromide and $CuBr \cdot SMe_2$ complex, following the protocol by Pedregal.[14] After Boc deprotection and chromatographic separation, the major diastereoisomer **6b** (24:1 dr) was isolated in satisfactory yields.

In our hands, treatment of **16** with the vinyl magnesium bromide/$CuBr \cdot SMe_2/BF_3 \cdot Et_2O$ complex did not give tolerable yields of the expected vinyl derivative. When we changed the reaction conditions using vinyl lithium[15] with an excess $CuBr \cdot SMe_2$, the reaction proceeded smoothly. The desired

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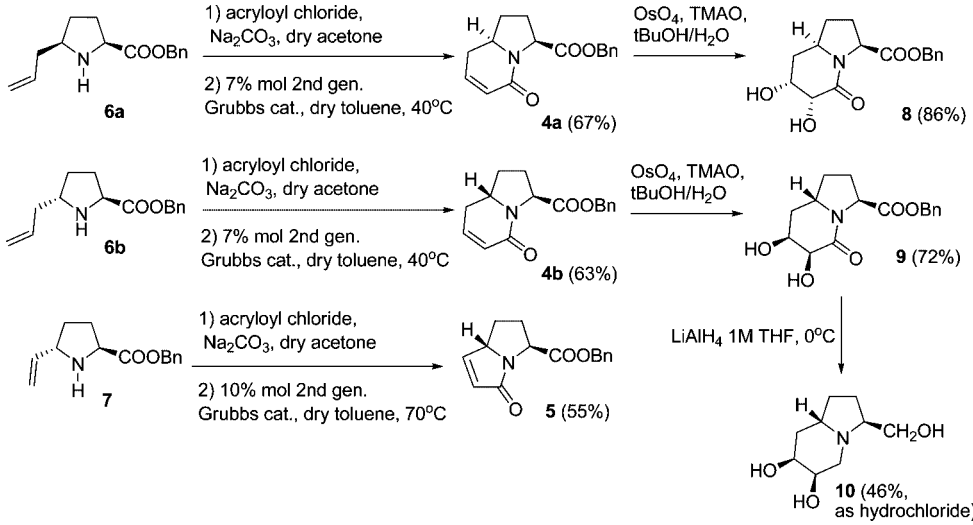
SCHEME 3



product **7** (6:1 dr) was obtained in acceptable yield after Boc deprotection and chromatographic separation. Proline esters derivatives **6a,b** and **7** were reacted with acryloyl chloride and then submitted to a ring-closing metathesis reaction using second generation Grubbs catalyst (Scheme 3).

RCM reactions proceeded promptly in toluene at 40 °C for **6a,b** to afford **4a,b** in good yields. Longer reaction time and higher temperature (70 °C) were required to obtain pyrrolizidin-5-one derivative **5**. Indolizidin-5-ones **4a,b** were then selected for further elaboration of the newly formed double bond by means of a dihydroxylation reaction with catalytic OsO_4 and TMAO. As expected, the reactions showed to be highly stereoselective. Diol **8** was obtained from **4a** as a single diastereoisomer (de >99% by ^{1}H NMR). Osmilation of **4b** afforded mainly compound **9** (de 95% by ^{1}H NMR). The stereochemistry of **8** and **9** was assessed by analysis of the coupling constant values in the ^{1}H NMR spectra and confirmed by NOESY (Figure 2). As an additional structural elaboration, lactam **9** was subjected to reduction with $LiAlH_4$ to cleanly afford the indolizidine **10**, a new hydroxylated azabicyclic compound strictly correlated to biologically active azasugars. Compound **10** was characterized as hydrochloride by means of ^{1}H and ^{13}C NMR spectra, as a 1:1 mixture of *cis* and *trans* indolizidine stereoisomers.

After protection of **7** and **13** as the Cbz derivatives **18** and **19**, cross metathesis reactions were carried out with a stoichiometric amount of methyl vinyl ketone in a 0.05 M dichloromethane solution, using the Grubbs−Hoveyda catalyst (Scheme 4). Reaction proceeded in toluene at 80 °C for **18** to afford **11** in 61% yield and in CH_2Cl_2 at room temperature for **19** to afford **12** in 81% yield.

Both **11** and **12** were subjected to removal of the Cbz group (and cleavage of the benzylic ester moiety for **11**) by treatment with catalytic Pd/C (10%) under hydrogen atmosphere, resulting in concomitant intramolecular reductive amination and cyclization to compounds **14** and **15**.[16] In both cases only the indicated diastereoisomer was obtained as a result of the highly stereoselective palladium-catalyzed reduction from the less hindered face of the rigid cyclic iminium intermediate. 2D NMR NOESY experiments established the configuration of the newly formed stereocenters (Figure 2). For pyrrolizidine **14**, the 5*R* configuration is related to similar literature precedents for iminium-mediated cyclization of disubstituted ketopyrrolidines.[17] For compound **15**, a 5*S* configuration was revealed, also in this case in agreement with literature reports on similar derivatives.[18]

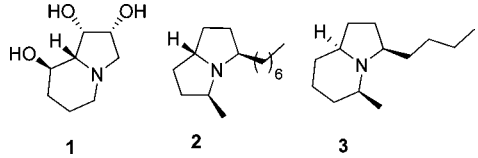


FIGURE 1. Representative naturally occurring pyrrolizidine and indolizidine alkaloids.

Compounds **14** and **15** are advanced intermediates for the synthesis of different 3,5-dialkyl-substituted indolizidines and pyrrolizidines. As an example of possible applications, indolizidine **15** was employed for the enantiospecific synthesis of the natural alkaloid (+)-monomorine **3**[19] (Scheme 5). Reduction of ester **15** with DIBALH afforded the intermediate corresponding aldehyde, which was immediately added to the propyl Wittig ylide to give the *Z*-alkene **20** in satisfactory yield. Finally, Pd-catalyzed reduction of **20** afforded **3**, whose ^{1}H NMR spectrum and optical rotation were consistent with those previously reported for (+)-monomorine.[20]

Conclusions

In summary, we have developed a versatile route to diversely functionalized indolizidine and pyrrolizidine natural and non-natural alkaloids, based on few stereodefined key intermediates (**4a,b**, **5**, **11**, and **12**), readily available from natural (*S*)-pyroglutamic acid. Because every desired stereochemistry (both

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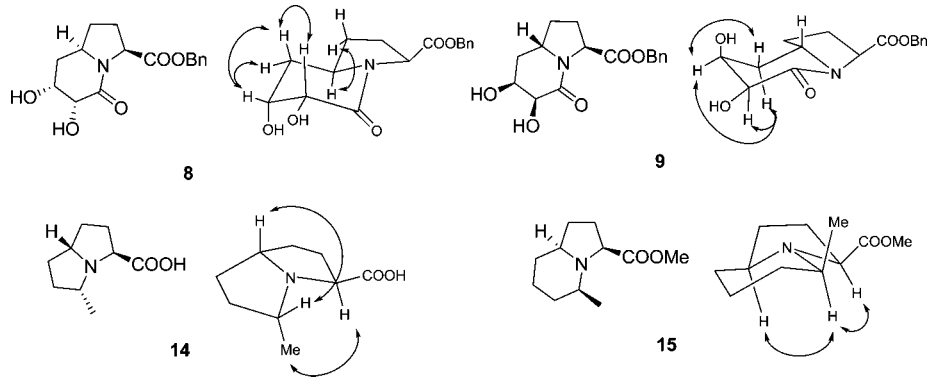
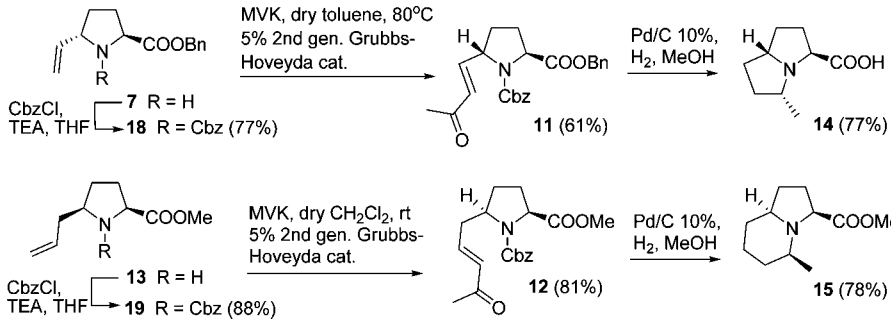
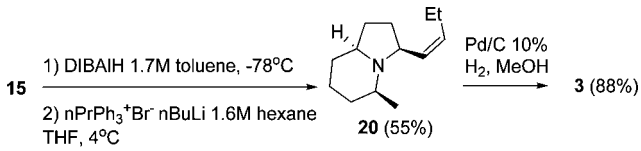


FIGURE 2. Diagnostic NOE contacts for **8**, **9**, **14**, and **15**.

SCHEME 4



SCHEME 5



relative and absolute) is in principle available for these key intermediates, this strategy has the potential to be extremely flexible.

Given their high functional group tolerance, metathesis reactions (RCM and CM) proved to be very suited for our approach, opening up a general efficient and stereoselective entry to this kind of azabicyclic compounds. The usefulness of this strategy was fully demonstrated with the synthesis of the azasugar analogue **10** and of the natural alkaloid (+)-monomorine **3**.

Furthermore, with the accessibility of different α,β-unsaturated ketones (in place of methyl vinyl ketone in Scheme 4), preparation of a variety of 5-alkyl-substituted indolizidines and pyrrolizidines should be possible. Such compounds should find interesting applications in the synthesis of rigid scaffolds that display useful pharmacophores in drug design. Further applications of this strategy for related natural and non-natural compounds is under study.

Experimental Section

General Methods. All solvents were distilled and properly dried, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. All reactions were run under N_2, unless otherwise indicated. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light or by treatment with 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography on silica gel 60 (230−400 mesh). ^{1}H and ^{13}C NMR spectra were recorded using 300 and 400 MHz spectrometers. Chemical shifts (δ) are expressed in ppm relative to TMS at $\delta = 0$ ppm for ^{1}H NMR and to $CDCl_3$ at $\delta = 77.16$ ppm for ^{13}C NMR.

(2*S*,5*R*)-5-Allylpyrrolidine-2-carboxylic Acid Benzyl Ester (6a) and (2*S*,5*R*)-5-Allylpyrrolidine-2-carboxylic Acid Methyl Ester (13). (2*S*,5*R*)-5-Allylpyrrolidine-1,2-dicarboxylic acid-2-benzyl ester,1-*tert*-butyl ester and (2*S*,5*R*)-5-allylpyrrolidine-1,2-dicarboxylic acid-2-methyl ester,1-*tert*-butyl ester were prepared following a previously reported procedure[12] starting from **16** and **17**, respectively. The obtained products were then dissolved in a 30% TFA/CH_2Cl_2 solution (5 mL/mmol). After 4 h the reactions were quenched with saturated aqueous $NaHCO_3$, and the organic layers were separated, dried over Na_2SO_4, and evaporated to dryness. The crude products were purified by flash chromatography (hexane/AcOEt 3:2), to afford respectively **6a** (53%) and **13** (56%), as oils. **6a**:[11] ^{1}H NMR (300 MHz, DMSO) δ 7.38 (s, 5H), 5.82 (m, 1H), 5.12 (s, 2H), 5.05 (d, $J = 17.1$ Hz, 1H), 5.00 (d, $J = 10.6$ Hz, 1H), 3.73 (dd, $J = 8.8$, 5.8 Hz, 1H), 3.32 (br, s, 1H), 3.06 (quint, $J = 6.6$ Hz, 1H), 2.25−1.73 (m, 5H), 1.40−1.23 (m, 1H). HRMS *m*/*z* calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1414. **13**: Spectroscopic data were in agreement with literature values.[13]

(2*S*,5*S*)-5-Allylpyrrolidine-2-carboxylic Acid Benzyl Ester (6b). To a stirred suspension of $CuBr\cdot Me_2S$ (4.80 g, 23.4 mmol) in dry ether (25 mL), at −40 °C under N_2, was added a solution of allyl magnesium bromide 1 M in Et_2O (23.4 mL, 23.4 mmol) dropwise. After stirring for 45 min, the mixture was cooled to −78 °C, and $BF_3\cdot Et_2O$ (2.9 mL, 23.4 mmol) was added dropwise. After 30 min, a solution of **16** (1.96 g, 5.8 mmol) in dry ether (22 mL) was added dropwise. The mixture was stirred for 15 min and allowed to reach room temperature over a period of 3 h. After 1 h at room temperature, the reaction was quenched with aqueous saturated NH_4Cl solution/concentrated NH_3 (1:1, 40 mL), and the mixture was stirred for 1 h. The organic layers were separated, and the aqueous one was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (40 mL), dried, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/

AcOEt 85:15), yielding a mixture of diastereoisomers. The mixture was then dissolved in a 30% TFA/CH_2Cl_2 solution (5 mL/mmol). After 4 h, saturated aqueous $NaHCO_3$ (10 mL) was added, and the organic layer was separated, dried over Na_2SO_4, and evaporated to dryness. The crude was purified by flash chromatography (hexane/AcOEt 3:2) to afford **6b**[11] in 50% yield, as an oil. R_f = 0.27 (hexane/AcOEt 1:1). $[\alpha]^{25}_D = -26.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO) δ 7.45−7.30 (m, 5H), 5.83 (ddt, *J* = 17.4, 11.1, 6.3 Hz, 1H), 5.12 (s, 2H), 5.07 (d, *J* = 17.4 Hz, 1H), 5.00 (d, *J* = 11.1 Hz, 1H), 3.82 (dd, *J* = 9.0, 5.4 Hz, 1H), 3.18 (quint, *J* = 6.6 Hz, 1H), 2.21−2.02 (m, 4H), 1.92−1.68 (m. 2H), 1.40−1.15 (m, 1H). HRMS *m*/*z* calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1419.

(2*S*,5*S*)-5-Vinylpyrrolidine-2-carboxylic Acid Benzyl Ester (7). To a stirred suspension of CuBr·Me_2S (3.70 g, 18 mmol) in dry ether (18 mL), at −40 °C under N_2 was added dropwise a solution of vinyl lithium (16.6 mL, 9.0 mmol, previously prepared from vinyl bromide (2 mL, 21.3 mmol) and *tert*-buthyl lithium (25 mL, 43.5 mmol, 1.7 M in pentane) in dry diethyl ether (12 mL), according to ref 14. After stirring for 1 h, the mixture was cooled to −78 °C, and BF_3·Et_2O (2.3 mL, 18 mmol) was added dropwise. After 30 min, a solution of **16** (1.2 g, 3.6 mmol) in dry ether (22 mL) was slowly added. The mixture was stirred for 1 h and allowed to reach room temperature over a period of 3 h. The reaction was then quenched with saturated aqueous NH_4Cl solution/concentrated NH_3 (1:1, 40 mL) and stirred for 1 h. The organic layer was separated, and the aqueous one was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with saturated $NaHCO_3$ aqueous solution (40 mL), dried, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/AcOEt 9:1), yielding the corresponding mixture of diastereoisomers. The mixture (350 mg, 1.1 mmol) was then dissolved in a 30% TFA/CH_2Cl_2 solution (5 mL/mmol). The reaction was stirred at room temperature for 4 h, then saturated aqueous $NaHCO_3$ (10 mL) was added, and the organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated to dryness. The crude was purified by flash chromatography (hexane/AcOEt 7:3) to afford **7** in 45% yield, as an oil. R_f = 0,16 (hexane/AcOEt 7:3). $[\alpha]^{25}_D = -31.3$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.40−7.27 (m, 5H), 5.90−5.81 (ddd, *J* = 17.1, 10.0, 3.0 Hz, 1H), 5.22 (d, *J* = 17.1 Hz, 1H), 5.20 (s, 2H), 5.08 (d, *J* = 10.0 Hz, 1H), 4.03 (dd, *J* = 8.5, 5.9 Hz, 1H), 3.80 (m, 1H), 3.25 (br, s, 1H), 2.31 (m, 1H), 2.10−1.89 (m, 2H), 1.71−1.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 139.8, 135.6, 128.6−128.2 (5C), 115.4, 66.9, 61.1, 59.1, 31.7, 29.3. HRMS *m*/*z* calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1255.

(3*S*,8a*R*)-5-Oxo-1,2,3,5,8,8a-hexahydroindolizine-3-carboxylic Acid Benzyl Ester (4a). To a solution of **6a** (450 mg, 1.83 mmol) in dry acetone (8 mL) were added aqueous saturated Na_2CO_3 solution (4 mL) and acryloyl chloride (270 μL, 3.29 mmol). The mixture was stirred for 4 h at room temperature and then extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give (2*S*,5*R*)-1-acryloyl-5-allylpyrrolidine-2-carboxylic acid benzyl ester, which was used in subsequent step without further purification. R_f = 0.20 (hexane/AcOEt 7:3). $[\alpha]^{25}_D = -78.5$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, major conformer) δ 7.39−7.28 (m, 5H), 6.50 (m, 2H), 5.90−5.71 (m, 2H), 5.21 (s, 2H), 5.19−5.00 (m, 2H), 4.61−4.52 (m, 1H), 4.12 (m, 1H), 2.58−1.90 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, major conformer) δ 172.3, 164.4, 135.8, 134.1, 128.8, 128.7−127.8 (6C), 118.2, 66.8, 59.8, 58.0, 39.6, 29.7, 27.0. HRMS *m*/*z* calcd for $C_{18}H_{21}NO_3$ 299.1521, found. 299.1529.

(2*S*,5*R*)-1-Acryloyl-5-allylpyrrolidine-2-carboxylic acid benzyl ester (432 mg, 1.44 mmol) was dissolved in dry toluene (36 mL) under nitrogen atmosphere. Second generation Grubbs catalyst (104 mg, 7% mol) was added, and the mixture was stirred for 18 h at 40 °C. The solvent was evaporated, and the residual oil was purified by flash chromatography on silica gel (AcOEt /hexane 9:1) to afford 264 mg of **4a** (67% yield) as a colorless oil. R_f = 0.26 (AcOEt /hexane 7:3). $[\alpha]^{25}_D = -31.5$ (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.30 (m, 5H), 6.60 (ddd, *J* = 10.0, 6.6, 1.9 Hz, 1H), 6.00 (dd, *J* = 10.0, 3.2 Hz, 1H), 5.21 (d, AB system, *J* = 12.4 Hz, 1H), 5.16 (d, AB system, *J* = 12.4 Hz, 1H), 4.72 (br, d, *J* = 7.2 Hz, 1H), 3.85−3.75 (m, 1H), 2.52 (dt, *J* = 17.1, 5.0 Hz, 1H), 2.30 (m, 1H), 2.20−2.04 (m, 3H), 1.89−1.75 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 164.0, 140.1, 136.5, 129.2−128.6 (5C), 126.4, 67.5, 57.9, 57.7, 32.4, 31.3, 28.9. HRMS *m*/*z* calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1211.

(3*S*,8a*S*)-5-Oxo-1,2,3,5,8,8a-hexahydroindolizine-3-carboxylic Acid Benzyl Ester (4b). To a solution of **6b** (222 mg, 0.90 mmol) in dry acetone (4 mL) were added aqueous saturated Na_2CO_3 solution (2 mL) and acryloyl chloride (132 μL, 1.63 mmol) were added. The mixture was stirred for 4 h at room temperature and then extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give (2*S*,5*S*)-1-acryloyl-5-allylpyrrolidine-2-carboxylic acid benzyl ester, which was used in subsequent step without further purification. R_f = 0.26 (hexane/AcOEt 7:3). $[\alpha]^{25}_D = -57.8$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, major conformer) δ 7.40−7.28 (m, 5H), 6.55 (dd, *J* = 17.5, 9.6 Hz, 1H), 6.47 (dd, *J* = 17.5, 2.9 Hz, 1H), 5.76 (dd, *J* = 9.8, 2.9 Hz, 1H), 5.23−5.04 (m, 4H), 4.64 (d, *J* = 9.6 Hz, 1H), 4.24−4.19 (m, 1H), 2.44−2.35 (m, 2H), 2.34−2.10 (m, 3H), 2.06−1.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, major conformer) δ 172.5, 165.3, 136.5, 134.4, 129.3, 129.2−128.6 (6C), 119.0, 67.4, 60.1, 58.2, 40.8, 29.9, 27.2. HRMS *m*/*z* calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1528.

(2*S*,5*S*)-1-Acryloyl-5-allylpyrrolidine-2-carboxylic acid benzyl ester (216 mg, 0,72 mmol) was dissolved in dry toluene (10 mL) under nitrogen atmosphere. Second generation Grubbs catalyst (43 mg, 7% mol) was added, and the mixture was stirred for 18 h at 40 °C. The solvent was then evaporated, and the residual oil was purified by flash chromatography on silica gel (AcOEt/hexane 9:1), to afford 123 mg of **4b** (63% overall yield) as a colorless oil. R_f = 0.10 (hexane/AcOEt 1:1). $[\alpha]^{25}_D = +25.5$ (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 6.55 (ddd, *J* = 9.8, 6.6, 1.9 Hz, 1H), 5.98 (dd, *J* = 9.8, 3.0 Hz, 1H), 5.24 (s, 2H), 4.57 (t, *J* = 8.3 Hz, 1H), 4.08−3.98 (m, 1H), 2.55 (dt, *J* = 17.3, 5.8 Hz, 1H), 2.45−2.37 (m, 1H), 2.31−2.15 (m, 2H), 1.93−1.82 (m, 1H), 1.75−1.64 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 163.9, 139.2, 136.4, 130.3−128.7 (5C), 126.1, 67.5, 58.5, 57.5, 33.5, 31.2, 28.6. HRMS *m*/*z* calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1212.

(3*S*,7a*S*)-5-Oxo-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-3-carboxylic Acid Benzyl Ester (5). To a solution of **7** (100 mg, 0.43 mmol) in dry acetone (2 mL) were added aqueous saturated Na_2CO_3 solution (1 mL) and acryloyl chloride (65 μL, 0.78 mmol). The mixture was stirred for 4 h at room temperature and then extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give (2*S*,5*S*)-1-acryloyl-5-vinylpyrrolidine-2-carboxylic acid benzyl ester, which was used in subsequent reaction without further purification. R_f = 0.43 (hexane/AcOEt 1:1). $[\alpha]^{25}_D = -54.7$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.27 (m, 5H), 6.40 (m, 2H), 5.87 (ddd, *J* = 15.2, 10.3, 4.8 Hz, 1H), 5.70 (dd, *J* = 8.0, 4.3 Hz, 1H), 5.25−5.05 (m, 4H), 4.68 (br, d, *J* = 8.7 Hz, 2H), 2.41−2.28 (m, 1H), 2.22−2.17 (m, 1H), 1.95 (dd, *J* = 13.0, 6.6 Hz, 1H) 1.87 (dd, *J* = 12.2, 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 165.8, 138.8, 136.5, 129.1−128.7 (6C), 116.2, 67.4, 60.6, 60.2, 31.5, 26.8. HRMS *m*/*z* calcd for $C_{17}H_{19}NO_3$ 285.1365, found 285.1359.

(2*S*,5*S*)-1-Acryloyl-5-vinylpyrrolidine-2-carboxylic acid benzyl ester (40 mg, 0.14 mmol) was dissolved in dry toluene (11 mL) under nitrogen atmosphere. Second generation Grubbs catalyst (12 mg, 10% mol) was added, and the mixture was stirred for 18 h at 70 °C. The solvent was then evaporated, and the residual oil was purified by flash chromatography on silica gel (hexane/AcOEt 7:3). Purification afforded 20 mg of **5** (55% yield) as a colorless oil. R_f = 0.25 (hexane /AcOEt 7:3). $[\alpha]^{25}_D = -41.2$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$,) δ 7.40−7.30 (m, 5H), 7.30 −7.25 (dd, *J* = 5.8, 1.7 Hz, 1H), 6.14 (br, d, *J* = 5.8 Hz, 1H), 5.26 (d, AB system, *J* = 12.3 Hz, 1H), 5.20 (d, AB system, *J* = 12.3 Hz, 1H),

4.55−4.48 (m, 1H,), 4.47 (t, J = 8.4 Hz, 1H), 2.81−2.72 (m, 1H), 2.42−2.30 (m, 1H), 2.21−2.12 (m, 1H), 1.37−1.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$,) δ 171.6, 169.6, 149.9, 137.0, 129.3−128.8 (6C), 68.3, 67.7, 55.9, 35.6, 29.5. HRMS *m*/*z* calcd for $C_{15}H_{15}NO_3$ 257.1052, found 257.1025.

(3*S*,6*R*,7*R*,8a*R*)-6,7-Dihydroxy-5-oxooctahydroindolizine-3-carboxylic Acid Benzyl Ester (8). To a solution of **4a** (264 mg, 0.97 mmol) and trimethylamine *N*-oxide (172 mg, 1.55 mmol) in 5 mL of *tert*-butyl alcohol-water (3:1) was added a 2.5% solution of osmium tetraoxide in *tert*-butyl alcohol (0.68 mL, 0.08 mmol). The solution was stirred at 40 °C for 3 h. After cooling to room temperature, sodium bisulfite (100 mg) was added, and stirring was continued for 30 min. The mixture was then concentrated, AcOEt was added, and the solution was filtered through Celite. The filtrate was dried over sodium sulfate and concentrated in vacuo, and the residue was purified by flash chromatography (AcOEt/MeOH 95:5), yielding 256 mg (86%) of **8** as a colorless oil. R_f = 0.11 (hexane/AcOEt 3:7). $[\alpha]^{25}_D$ = −23.5 (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$,) δ 7.40−7.25 (m, 5H), 5.22 (d, AB system, J = 12.3 Hz, 1H), 5.14 (d, AB system, J = 12.3 Hz, 1H), 4.50 (d, J = 9.8 Hz, 1H), 4.35 (t, J = 3.5 Hz, 1H), 4.08 (d, J = 3.5 Hz, 1H), 4.05 (tt, J = 11.7, 4.1 Hz, 1H), 3.60−3.20 (br, s, 2H), 2.40 (dt, J = 13.8, 4.0 Hz, 1H), 2.27−2.15 (m, 1H), 2.07−1.95 (m, 2H), 1.72 (t, J = 13.8 Hz, 1H), 1.72−1.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$,) δ 171.8, 170.8, 136.2, 129.2−128.7 (5C), 71.3, 67.7, 66.7, 58.1, 56.2, 33.1, 31.7, 29.5. HRMS *m*/*z* calcd for $C_{16}H_{19}NO_5$ 305.1263, found 305.1269.

(3*S*,6*S*,7*S*,8a*S*)-6,7-Dihydroxy-5-oxo-octahydroindolizine-3-carboxylic Acid Benzyl Ester (9). To a solution of **4b** (132 mg, 0.49 mmol) and trimethylamine *N*-oxide dehydrate (88 mg, 0.79 mmol) in 3 mL of *tert*-butyl alcohol-water (3:1) was added a 2.5% solution of osmium tetraoxide in *tert*-butyl alcohol (0.34 mL, 0.03 mmol). The solution was stirred at 40 °C for 3 h. After cooling to room temperature, sodium bisulfite (40 mg) was added, and stirring was continued for 30 min. The mixture was then concentrated, AcOEt was added, and the solution was filtered through Celite. The filtrate was dried over sodium sulfate and concentrated in vacuo, and the residue was purified by flash chromatography (AcOEt/MeOH 95:5), yielding 104 mg (72%) of **9** as a colorless oil. R_f = 0.12 (AcOEt). $[\alpha]^{25}_D$ = −164.7 (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.29 (m, 5H), 5.23 (d, AB system, J = 12.9 Hz, 1H), 5.16 (d, AB system, J = 12.9 Hz, 1H), 4.50 (t, J = 9.4 Hz, 1H), 4.34 (t, J = 3.3 Hz, 1H), 4.18−4.08 (m, 2H), 4.04 (d, J = 3.3 Hz, 1H), 3.28 (br, s, 1H), 2.47−2.38 (m, 2H), 2.13−2.06 (m, 1H), 1.93−1.82 (m, 1H), 1.63−1.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 169.6, 135.6, 128.5−128.0 (5C), 70.4, 66.8, 66.3, 57.5, 55.3, 32.4, 32.3, 28.1. HRMS *m*/*z* calcd for $C_{16}H_{19}NO_5$ 305.1263, found 305.1271.

(3*S*,6*R*,7*S*,8a*S*)-3-Hydroxymethyloctahydroindolizine-6,7-diol Hydrochloride (10). $LiAlH_4$ (1 mL, 1 M in THF) was added dropwise over 10 min to a solution of **9** (104 mg, 0.34 mmol) in dry THF (4 mL) cooled to 0 °C. The reaction was kept for 10 min at 0 °C and then refluxed. After 4 h, the reaction mixture was cooled at −5 °C and quenched with saturated aqueous $NaHCO_3$ (3 mL). AcOEt was added, and the mixture was filtered through Celite. The organic phase was separated, dried, and concentrated in vacuo to yield a yellow oil. The residue was suspended in MeOH (6 mL) cooled at 0 °C, and the solution was saturated with gaseous HCl. After 30 min, the reaction was warmed to room temperature and concentrated in vacuo. The residue was crystallized from isopropanol, yielding 37 mg (46%) of **10** (as hydrochloride). $[\alpha]^{25}_D$ = −155.7 (*c* 2.1, MeOH). ^{1}H NMR (400 MHz, DMSO, mixture of two stereoisomers) δ 10.90 (br, s, 0.5H, stereoisomer A), 10.20 (br, s, 0.5H, stereoisomer B), 5.42 (br, s, 0.5H, stereoisomer B), 5.38 (br, s, 0.5H, stereoisomer A), 5.30 (d, 0.5H, J = 5.4 Hz, stereoisomer A), 5.23 (d, 0.5H, J = 5.4 Hz, stereoisomer B), 5.07 (br, s, 0.5H, stereoisomer B), 5.02 (br, s, 0.5H, stereoisomer A), 4.03−3.48 (m, 6H), 3.30−3.08 (m, 2H), 2.20−1.55 (m, 6H). ^{13}C NMR (100 MHz, DMSO, mixture of two stereoisomers) δ 66.8 and 65.6, 65.1 and 63.4, 63.0 and 62.3, 60.1 and 59.2, 58.7 and 57.1, 46.4 and 45.8, 32.9 and 31.1, 28.0 and 27.2, 24.7 and 24.2. HRMS (ESI, M + 1 ion) calcd for $C_9H_{18}NO_3$ 188.1287, found 188.1291.

(2*S*,5*S*)-5-Vinylpyrrolidine-1,2-dicarboxylic Acid Dibenzyl Ester (18). To a solution of **7** (100 mg, 0.43 mmol) and TEA (60 μL, 0.43 mmol) in dry THF (1 mL) was added benzyloxycarbonylchloride (123 μL, 0.86 mmol), and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with AcOEt (3 mL), washed with saturated aqueous NH_4Cl, and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash chromatography (AcOEt/hexane 1:3) to provide **18** (121 mg, 77%) as an oil. R_f = 0.40 (hexane/AcOEt 7:3). $[\alpha]^{25}_D$ = −58.1 (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$, mixture of conformers) δ 7.47−7.23 (m, 10H), 5.81 (m, 1H), 5.30−4.95 (m, 6H), 4.68 (br, t, J = 5.6 Hz, 0.5H, conformer A), 4.62 (br, t, J = 5.6 Hz, 0.5H, conformer B), 4.53 (br, d, J = 9.7 Hz, 0.5H, conformer A), 4.48 (br, d, J = 9.7 Hz, 0.5H, conformer B), 2.32−2.10 (m, 2H), 2.01−1.93 (m, 1H), 1.80−1.72 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of conformers) δ 172.4 and 172.2, 155.0 and 154.0, 137.9 and 137.4, 136.6 and 136.5, 135.7 and 135.5, 128.6−127.7 (10C), 114.6 and 114.3, 67.1 and 67.0, 66.9 and 66.8, 60.1 and 59.7, 59.5, 31.0 and 29.6, 28.4 and 27.2. HRMS *m*/*z* calcd for $C_{22}H_{23}NO_4$ 365.1627, found 365.1831.

(2*S*,5*R*)-5-Allylpyrrolidine-1,2-dicarboxylic Acid 1-Benzylester 2-Methylester (19). To a solution of **13** (385 mg, 2.25 mmol) and TEA (313 μL, 2.25 mmol) in dry THF (4 mL) was added benzyloxycarbonylchloride (642 μL, 4.50 mmol), and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with AcOEt (5 mL), washed with saturated aqueous NH_4Cl, and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash chromatography (AcOEt/hexane 1:4) to provide **19** (600 mg, 88%) as an oil. R_f = 0.38 (hexane/AcOEt 7:3). $[\alpha]^{25}_D$ = −16.1 (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$, mixture of conformers) δ 7.42−7.30 (m, 5H), 5.82 (m, 1H), 5.22−5.01 (m, 4H), 4.39 (m, 1H), 4.02 (m, 1H) 3.79 (s, 1.5H, conformer A), 3.61 (s, 1.5H, conformer B), 2.86−2.75 (m, 0.5H, conformer A), 2.70−2.62 (m, 0.5H, conformer B), 2.32−2.18 (m, 2H), 2.10−2.90 (m, 2H), 1.88−1.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of conformers) δ 173.4 and 173.3, 154.9 and 154.1, 136.6, 135.1, 128.4−127.1 (5C), 117.2, 67.1 and 66.9, 60.2 and 59.9, 58.7 and 58.1, 52.2 and 52.0, 39.0 and 38.2, 29.5 and 28.9, 28.7 and 28.0. HRMS *m*/*z* calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1487.

(2*S*,5*S*)-5-((*E*)-3-Oxobut-1-enyl)-pyrrolidine-1,2-dicarboxylic Acid Dibenzyl Ester (11). To a stirred solution of olefin **18** (100 mg, 0.27 mmol) and methyl vinyl ketone (22 μL, 0.27 mmol) in dry toluene (0.05 M, 5.5 mL) was added second generation Grubbs−Hoveyda catalyst (8 mg, 5% mol). The reaction mixture was stirred under N_2 atmosphere for 4 h at 80 °C. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (AcOEt/hexane 1:1) yielding 70 mg (61%) of **11** as an oil. R_f = 0.11 (AcOEt/hexane 3:7). $[\alpha]^{25}_D$ = −48.7 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two conformers) δ 7.41−7.20 (m, 10H), 6.71 (dd, J = 15.9, 5.5 Hz, 0.5H, conformer A), 6.63 (dd, J = 15.8, 5.8 Hz, 0.5H, conformer B), 6.15 (dd J = 15.8, 1.2 Hz, 0.5H, conformer A), 6.02 (dd, J = 15.8, 1.0 Hz, 0.5H, conformer B), 5.30−4.97 (m, 4H), 4.82 (m, 0.5H,conformer A), 4.72 (m, 0.5H, conformer B), 4.57 (br, d, J = 9.0 Hz, 0.5H, conformer B), 4.50 (br, d, J = 9.0 Hz, 0.5H, conformer A), 2.40−2.18 (m, 2H), 2.28 (s, 1.5H, conformer A), 2.16 (s, 1.5H, conformer B), 2.05−1.98 (m, 1H), 1.85−1.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two conformers) δ 199.8 and 198.8, 171.3, 159.7, 145.7 and 145.4, 136.5, 129.9 and 129.8, 129.7−128.5 (10C), 128.1, 67.4 and 67.3, 67.0 and 66.9, 59.9 and 59.6, 58.6 and 58.2, 29.8 and 28.8, 28.5 and 27.4, 27.6 and 27.5. HRMS *m*/*z* calcd for $C_{24}H_{25}NO_5$ 407.1733, found 407.1738.

(2*S*,5*R*)-5-((*E*)-4-Oxopent-2-enyl)-pyrrolidine-1,2-dicarboxylic Acid 1-Benzylester 2-Methylester (12). To a stirred solution

of olefin **19** (588 mg, 1.93 mmol) and methyl vinyl ketone (161 μL, 1.93 mmol) in dry CH_2Cl_2 (0.05 M, 39 mL) was added second generation Grubbs−Hoveyda catalyst (60 mg, 5% mol). The reaction mixture was stirred under N_2 atmosphere for 12 h. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (AcOEt/hexane 55:45), yielding 539 mg (81%) of **12** as an oil. $R_f = 0.12$ (AcOEt/hexane 3:7). $[\alpha]^{25}_D = +13.7$ (*c* 0.97, $CHCl_3$). ^{1}H NMR (400 MHz, 100 °C, DMSO) δ 7.40−7.29 (m, 5H), 6.85 (dt, $J = 16.0$, 7.2 Hz, 1H) 6.08 (dt, $J = 16.0$, 1.4 Hz, 1H), 5.13 (d, AB system, $J = 12.7$ Hz, 1H), 5.05 (d, AB system, $J = 12.7$ Hz, 1H), 4.38 (dd, $J = 8.2$, 6.8 Hz, 1H), 4.08 (m, 1H), 3.64 (s, 3H), 2.73−2.64 (m, 1H), 2.54−2.45 (m, 1H), 2.30−2.21 (m, 1H), 2.16 (s, 3H), 2.10−1.91 (m, 2H) 1.78−1.69 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, major conformer) δ 198.7, 173.2, 154.1, 144.6, 136.4, 133.4, 128.6−127.7 (5C), 67.1, 59.8, 57.9, 52.5, 37.0, 29.9, 28.9, 26.5. HRMS *m*/*z* calcd for $C_{19}H_{23}NO_5$ 345.1576, found 345.1578.

(3*S*,5*R*,7a*R*)-5-Methylhexahydropyrrolizine-3-carboxylic Acid (14). To a solution of **11** (51 mg, 0.13 mmol) in anhydrous methanol (5 mL) was added Pd/C 10% (5 mg). The resultant mixture was stirred under hydrogen atmosphere at room temperature for 18 h. The mixture was filtered over Celite, and the solvent was evaporated in vacuo to give pure **14** (16 mg, 77%) as an oil. $R_f = 0.2$ (AcOEt/MeOH 8:2). $[\alpha]^{25}_D = -35.8$ (*c* 0.8, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD) δ 11.01 (s, 1H), 4.38 (m, 1H), 4.98 (t, $J = 6.9$ Hz, 1H), 3.50 (m, 1H), 2.55−2.40 (m, 1H), 2.35−2.10 (m, 4H), 2.98−1.70 (m, 3H), 1.47 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 171.9, 69.6, 68.9, 65.2, 32.9, 29.9, 29.7, 29.4, 15.1. HRMS *m*/*z* calcd for $C_9H_{15}NO_2$ 169.1103, found 169.1115.

(3*S*,5*S*,8a*S*)-5-Methyloctahydroindolizine-3-carboxylic Acid Methylester (15). To a solution of **12** (529 mg, 1.53 mmol) in anhydrous methanol (25 mL) was added Pd/C 10% (50 mg) was added. The resultant mixture was stirred under hydrogen atmosphere at room temperature for 18 h. Then the mixture was filtered over Celite, and the solvent was evaporated in vacuo to give pure **15** (234 mg, 78%) as an oil. $R_f = 0.5$ (AcOEt/MeOH 95:5). $[\alpha]^{25}_D = -17.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$) δ 3.72 (s, 3H), 3.07 (dd, $J = 10.2$, 6.2 Hz, 1H), 2.24−2.15 (m, 1H), 2.13−1.91 (m, 2H), 1.89−1.70 (m, 4H), 1.67−1.50 (m, 2H), 1.49−1.14 (m, 3H), 1.01 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 65.9, 65.6, 59.9, 51.8, 34.5, 30.4, 30.3, 26.7, 24.6, 21.2. HRMS *m*/*z* calcd for $C_{11}H_{19}NO_2$ 197.2741, found 197.2745.

(3*S*,5*S*,8a*S*)-3-((*Z*)-But-1-enyl)-5-methyloctahydroindolizine (20). DIBALH (1.7 M in toluene, 734 μL, 1.25 mmol) was added dropwise over 10 min to compound **15** (102 mg, 0.52 mmol) in dry toluene (3 mL) at −78 °C. The reaction mixture was stirred for 1 h, quenched with MeOH, and warmed to room temperature. Diethyl ether was added, and the organic layer was washed twice with water, dried, and concentrated in vacuo to afford the crude aldehyde derivative. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (d, $J = 6.2$ Hz, 1H), 2.97 (m, 1H), 2.41−2.20 (m, 2H), 2.10−1.20 (m, 10H), 1.00 (d, $J = 6.3$ Hz, 3H).

To a stirred solution of propyltriphenylphosphonium bromide (158 mg, 0.41 mmol) in THF (0.9 mL) at −4 °C was added *n*-butyllithium (0.26 mL, 0.41 mmol, 1.6 M in hexane) dropwise. After 15 min a solution of the crude aldehyde (53 mg, 0.32 mmol) in dry THF (1 mL) was added. The reaction was stirred for 15 h at room temperature and then diluted with Et_2O/H_2O (1:2). The aqueous layer was extracted with ether (3 × 10 mL), and the combined organic layers were washed with brine and then dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (AcOEt/MeOH/NH_3 99:0.5:0.5), yielding 38 mg of **20** (55%) as an oil. $R_f = 0.41$ (AcOEt/MeOH 3:1). $[\alpha]^{25}_D = -69.2$ (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$) δ 5.58 (br, t, $J = 10.4$ Hz, 1H), 5.20 (dt, $J = 10.4$, 7.3 Hz, 1H), 3.13−3.25 (m, 1H), 2.20−1.88 m, 4H), 1.73−1.20 (m, 10H), 1.11 (d, $J = 6.3$ Hz, 3H), 0.98 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 128.6, 67.2, 62.6, 61.3, 34.9, 31.9, 31.2, 30.5, 25.5, 25.4, 23.0, 14.1. HRMS *m*/*z* calcd for $C_{13}H_{23}N$ 193.1830, found 193.1835.

(+)-Monomorine (3). To a solution of **20** (24 mg, 0.12 mmol) in anhydrous methanol (3 mL) was added Pd/C 10% (5 mg). The mixture was stirred under hydrogen atmosphere at room temperature for 15 h and then filtered over Celite, and the solvent was evaporated in vacuo to give pure **3** (21 mg, 88%) as an oil. $[\alpha]^{25}_D = +33.8$ (*c* 1.0, *n*-hexane). Lit.:[19] $[\alpha]^{20}_D = +35.7$ (*c* 0.370, *n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (br, t, $J = 9.1$ Hz, 1H), 2.16 (m, 1H), 2.03 (m, 1H), 1.92−1.25 m, 16H), 1.07 (d, $J = 6.2$ Hz, 3H), 0.82 (t, $J = 7.3$ Hz, 3H). HRMS *m*/*z* calcd for $C_{13}H_{25}N$ 195.1987, found 195.1981. Anal. Calcd for $C_{13}H_{25}N$: C, 79.93; H, 12.90; N, 7.17. Found: C, 80.02; H, 12.81; N, 7.23.

Supporting Information Available: NMR spectra of compounds **3**−**15** and **18**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801638U