Design and Synthesis of a Novel Class of Constrained Tricyclic Pyrrolizidinone Carboxylic Acids as Carbapenem Mimics

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A series of tricyclic pyrrolizidinone carboxylic acids harboring an angular methano group were synthesized as mimics of carbapenems and carbapenams. A key reaction involved a novel intramolecular cyclopropanation mediated by a trimethylstannylmethyl group and an adjacent iminium ion. Enolate chemistry on a tricyclic lactam ring unit allowed the introduction of various substituents. Further elaboration afforded tricyclic pyrrolidinone carboxylic acids, which were found to be inactive as inhibitors against a panel of bacterial strains. However, the antibacterial activity of ceftazidine was enhanced in the presence of the tricyclic analogues.

The unique class of β-lactam antibiotics comprising penams, carbapenems, cephems, and monobactams have occupied a central role in the vigil against bacterial infections over the past several decades.[1] A great deal of synthetic effort has been devoted to the synthesis of new variants or chemically modified analogues.[2] Historically and therapeutically relevant structures such as β-lactam antibiotics are represented by the venerable penicillin G (**1**) and the carbapenem variant thienamycin (**2a**),[3] for example (Figure 1).

The susceptibility of the β-lactam antibiotics toward enzymatic acylation by β-lactamases and target proteins known as penicillin binding proteins (PBPs) is attributed to the partial ketonic character of the carbonyl group as a result of increased pyramidalization of the nitrogen atom.[4] This notion has led to the exploration of penems as potential antibacterials where the original penam nucleus was modified into an unsaturated and highly strained analogue.[5] Relatively little effort has been expended in the design and synthesis of structurally different, strained β-lactams since then.[6]

Previous reports from our laboratory[7a] have shown that the introduction of a 4,5-*trans*-methano bridge in *N*-Boc D-proline (**3**) dramatically flattened the pyrrolidine ring

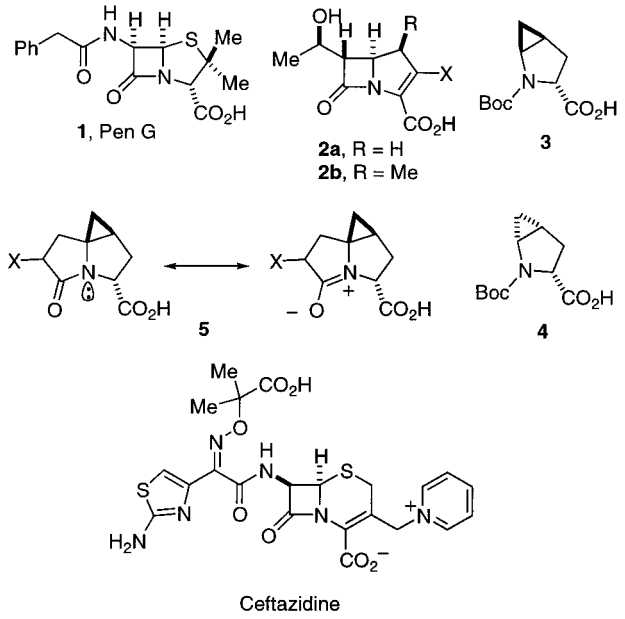

Figure 1.

(rms 0.003 Å), compared to the *cis*-analogue **4** (rms 0.018 Å) and *N*-Boc L-proline (rms 0.013 Å).[8] We surmised that the presence of a methano bridge in a tricyclic pyrrolizidinone carboxylic acid motif such as **5** might be of

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(8) Rms refers to the root-mean-square deviation from planarity expressed in angstroms.

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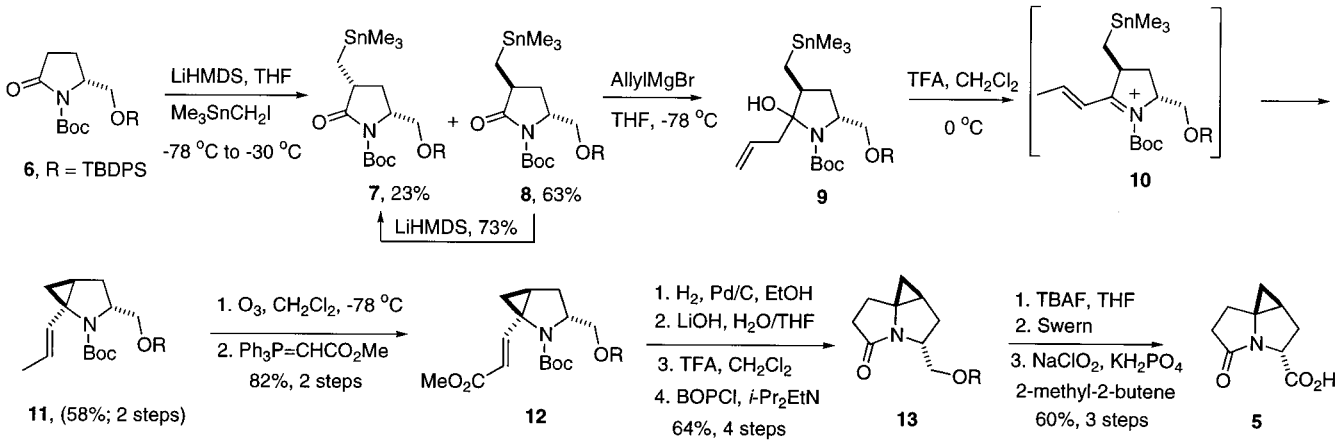
Scheme 1



interest as potential substrates for serine peptidases and transpeptidases (PBPs) (Figure 1). It was not known at the outset if the planarity of the original analogue **3** would also be manifested in the tricyclic structure **5**. This would in effect reduce its acylating power considerably compared to that of a conventional β-lactam such as **1** as a result of a more facile delocalization into the amide bond. In designing **5**, we chose to maintain an α-oriented carboxyl group (penam-like, **1**) and a β-oriented methano bridge (1-methylcarbapenem-like, **2b**). Bicyclic non-β-lactam indolizidinone analogues of penams, penems, and carbapenems[9,10] have been previously made and shown to exhibit moderate to weak antibacterial activity.[11] Tricyclic β-lactams such as the trinems have shown significant interest recently as clinical candidates.[12−15]

The readily available lactam **6**[16] was alkylated via its lithium enolate with trimethylstannylmethyl iodide[17] to afford a separable mixture[7a] of the major *anti*-adduct **8** (63%) and the corresponding *syn*-isomer **7** (23%) (Scheme 1). Treatment of **8** with allylmagnesium bromide afforded the hemiaminal **9**, which when treated with TFA at 0 °C led to the expected 4,5-*trans*-methano-D-proline analogue **11**. The allylic double bond in **11** had migrated, presumably to enter into conjugation with an incipient *N*-Boc iminium ion **10**. It is of interest that cyclopropanation takes place under such mild conditions,[7] presumably via an attack of trifluoroacetate anion on the trimethylstannyl group and subsequent ring closure on the iminium ion. The reaction is also applicable to a 3-trimethylstannyl propyl derivative, which affords the corresponding fused cyclopentane analogue of **3**,[7a] and to oxonium ions to give fused oxabicyclic structures. Ozonolytic cleavage of the 2-propenyl group followed by olefination of the resulting aldehyde gave the α,β-unsaturated ester **12** in excellent yield. Reduction, conventional deprotection and lactam formation gave the tricyclic pyrrolizidinone analogue **13** in 65% yield for four steps.

Desilylation and a two-step oxidation[18] of the hydroxymethyl group afforded the desired prototype **5** (C═O, 1645 cm^{-1}). At this juncture, an X-ray crystal structure of *ent* **13** confirmed its stereochemistry and revealed a rms deviation from planarity for the methano-containing pyrroldine ring of 0.107 Å, indicating considerable flattening compared to **1** and **2** and dimming the prospects of approaching β-lactam-like reactivity. Nevertheless, we pursued our objective of further functionalization of this prototype in the hope of achieving some level of binding to target enzymes. Enolate formation and allylation afforded a *C*-allylated product **14** as the major isomer accompanied by ∼10% of the epimer (Scheme 2). Hydrogenation and a selenoxide-induced elimination led to the endocyclic olefin isomer **16** almost exclusively. Deprotection and oxidation of **16** afforded **17** (C═O, 1639 cm^{-1}). Surprisingly, the carbonyl stretching frequency in **13** and **16** was the same (1679 cm^{-1}) and higher than the corresponding acids **5** or **17**.

Scheme 3 shows our efforts to introduce heteroatom functionality in the lactam ring of **13**. Thus, catalytic reduction of **12** led to **18**, which was subjected to a highly stereoselective enolate α-hydroxylation using the Davis

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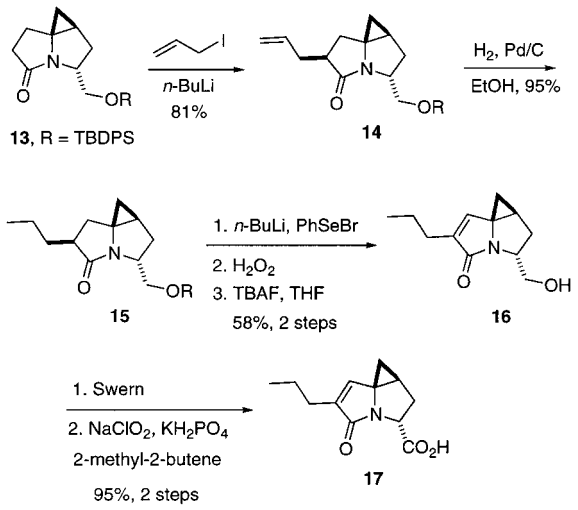
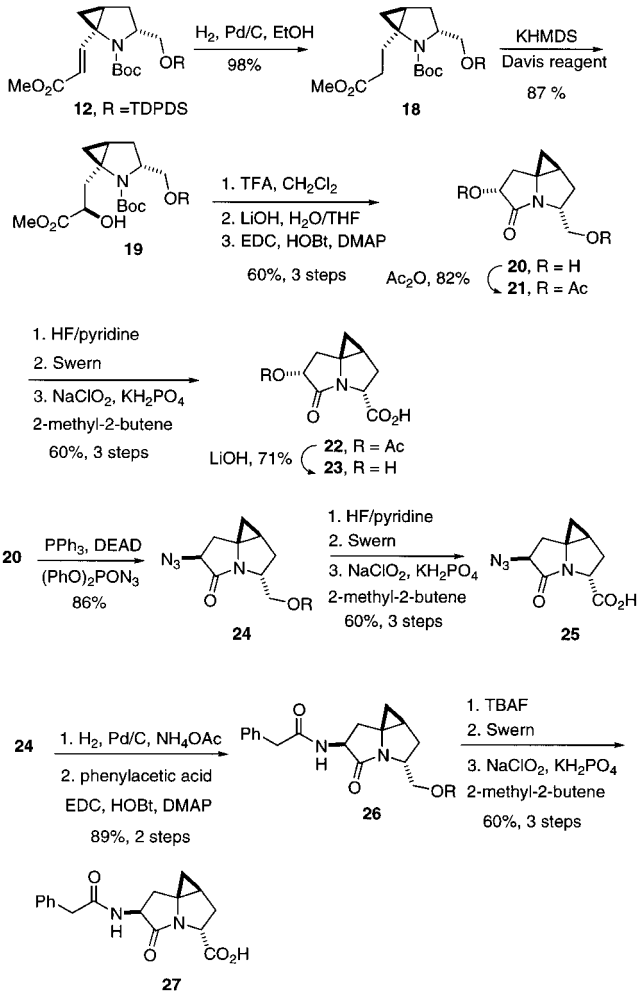
Scheme 2



Scheme 3



reagent (2-benzenesulfonyl-3-phenyloxaziridine)[19] to give **19** as the major isomer, accompanied by 10% of the epimer. The preponderance of **19** is noteworthy, particularly in the absence of a vicinal stereodirecting group on the acyclic chain. Excluding steric effects of the methanopyrrolidine appendage, it is possible that coordination of the K-enolate with the *N*-Boc group is responsible for such a high level of diastereoselectivity. Nuclear Overhauser effect studies on bicyclic analogues confirmed the proposed stereochemistry. Cleavage of the ester and lactam formation gave the α-hydroxy pyrrolizidinone analogue **20** (C=O. 1684 cm^{-1}). Conventional acetylation afforded the acetate ester **21** (C=O, 1711 cm^{-1}) with the highest lactam carbonyl stretching frequency observed among the series of methanopyrrolizidinones so far.[20] Deprotection and oxidation of **21** led directly to the carboxylic acid **22** (C=O, 1694 cm^{-1}), which after treatment with lithium hydroxide afforded the corresponding α-hydroxy analogue **23** (C=O, 1684 cm^{-1}).

Mitsunobu azidation[21] of **20** gave the corresponding inverted azide **24** (C=O, 1702 cm^{-1}), which upon deprotection and oxidation afforded the corresponding carboxylic acid **25** (C=O, 1699 cm^{-1}). Reduction of the azide group in **24** and acylation with phenylacetic acid in the presence of EDC and HOBt led to the phenylacetyl analogue **26** (C=O, 1682 cm^{-1}), which was finally transformed to the carboxylic acid **27** (C=O, 1672 cm^{-1}) as described above.

In view of the topology of the tricyclic ring system in **13**, we also explored the aldol reaction with acetone of the corresponding lithium enolate generated with *sec*-butyllithium. A mixture of adducts was isolated in a combined yield of 71%, which after desilylation and chromatographic separation gave **28** and **29** in a ratio of 3:2 (Scheme 4). The structure and absolute stereochemistry of the slightly more abundant isomer **28** (C=O, 1645 cm^{-1}) were confirmed by X-ray crystallography. Evidently, the *exo*- and *endo*-faces of the enolate from **13** are not sterically differentiated enough toward acetone as an electrophile despite the presence of a bulky *endo*-substituent. A 2-hydroxypropyl appendage can be found in carpetimycin A and its congeners[22] (Scheme 4).

Since the corresponding proline **4** showed less flattening in the solid state compared to **3**,[7a] we undertook the synthesis of the corresponding *cis*-4,5-methanopyrrolizidine analogue. Scheme 5 illustrates the synthesis, which follows the same protocol as for **13**. Enolate formation from **8** with LiHMDS and quenching with 2,6-di-*tert*-butylphenol led to an enrichment of the desired *cis*-isomer **7** (73%, with 13% recovered **8**). Addition of allylmagnesium bromide proceeded uneventfully to give **30**. In this case, the destannylation−cyclopropanation to the intended propenyl analogue **31** proceeded in modest overall yield compared to that of **11**. Ozonolytic cleavage of **31** and further chemistry led to the *cis*-fused methanopyrrolizidinone **33**, whose carbonyl stretching frequency (C=O, 1692 cm^{-1}) showed only a modest shift compared to that of its *trans*-methano isomer **17** (C=O, 1639 cm^{-1}).

In an effort to further constrain the original bicyclic pyrrolidinone motif we explored the possibility of rearranging the 4,5-methanopyrrolizidinone to the corresponding cyclopentane analogue through solvolytic ring

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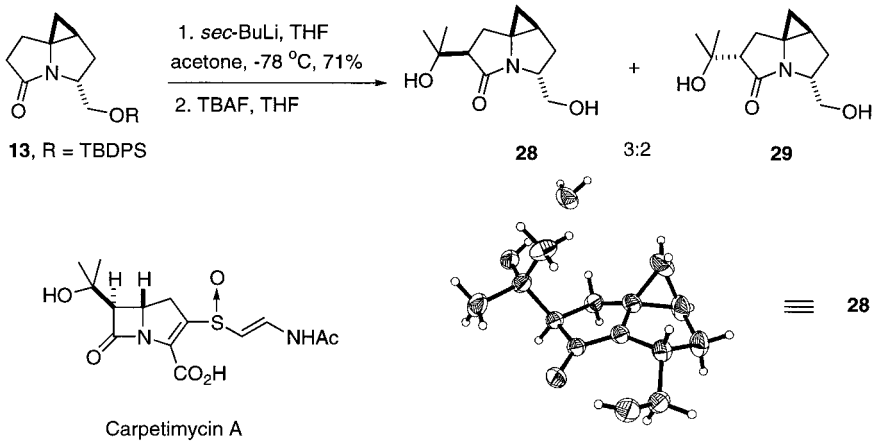
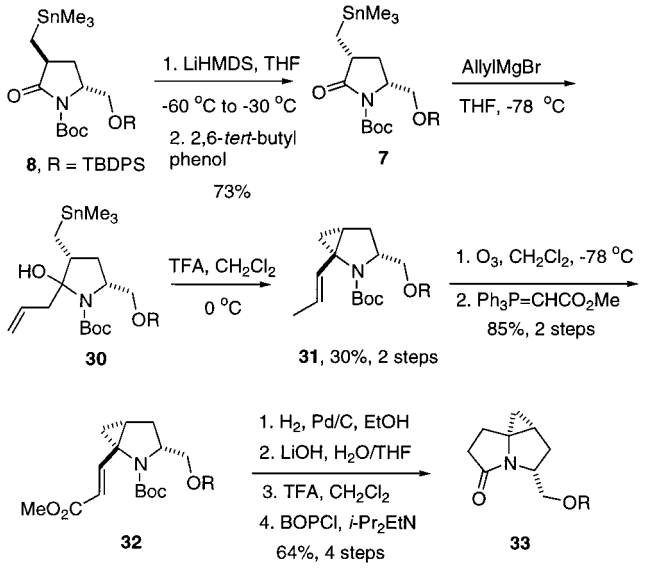
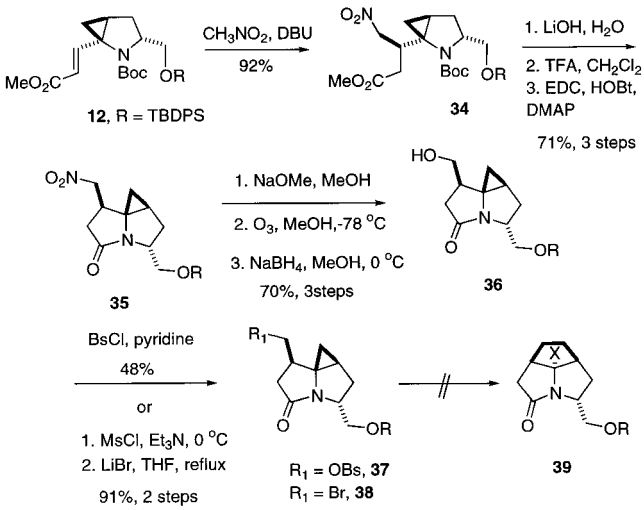
Scheme 4



Scheme 5



Scheme 6



expansion.[23] Base-catalyzed addition of nitromethane to the α,β-unsaturated ester **12** proceeded in high yield to give adduct **34** with a >20:1 selectivity based on NMR data after cyclization (Scheme 6). Lactam formation proceeded uneventfully to give the *cis*-substituted nitromethyl methanopyrrolizidinone **35** as evidenced by detailed NOE studies. Subsequent oxidative cleavage[24] of the sodium nitronate salt of **35** gave the corresponding aldehyde, which was reduced to the alcohol **36**. Brosylation and bromination under standard conditions gave the corresponding brosylate **37** and bromide **38**, respectively. Several attempts to solvolyze these compounds to tricyclic bridged compounds such as **39** were not successful. Thus, refluxing a solution of the bromide **38** in aqueous dioxane left it unchanged. Treatment of the corresponding brosylate **37** with formic acid and pyridine[25] at 100 °C gave the corresponding formate and starting material. Under free radical conditions (Bu_3SnH, AIBN, benzene, reflux), the bromide **38** was simply reduced to the corresponding *C*-methyl derivative. Tricyclic cyclopentapyrrolizidine-2-ones[26] related to **39** also exhibit lower carbonyl stretching frequencies compared to the penams and carbapenems (1695−1700 cm^{-1} compared to 1775−1779 cm^{-1}).

The pyrrolizidinone carboxylic acids **5**, **22**, **25**, and **27** did not show any antibacterial activity when tested on a panel of standard sensitive and resistant strains most likely as a result of their greatly diminished acylating character toward PBPs. However, the activity of the antibiotics ceftazidine (Figure 1) as measured by its MIC against some β-lactamase-producing strains was improved in the presence of a 10 μg/mL concentration of these analogues.[27]

Further work will focus on elucidating the mechanisms of β-lactamase inactivation by nonacylating inhibitors such as the methanopyrrolizidinone carboxylic acids described in this paper. Other modifications that activate the carbonyl or the α-position of these tricyclic γ-lactams toward nucleophilic attack can be envisaged. Structure-based inhibitors of β-lactams have been recently studied with promising results.[28]

Experimental Section

General. Flash chromatography was performed on 230−240 mesh silica gel.[29] Thin-layer chromatography (TLC) was

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(27) Against *Klebsiella* 97P587, the original MIC value of 50 μg/mL for ceftazidine was reduced to 25 μg/mL when 10 μg/mL of **5** and **27** were present. The activity of ceftazidine against *Pseudomonas aeruginosa* PAK (MIC value of 25 μg/mL) was enhanced in the presence of **5** and **25** to MIC 3−12 μg/mL and to 12.5 μg/mL with **22** and **27**.

performed on glass plates coated with a 0.02-mm layer of silica gel 60 F_{254}. All solvents were distilled freshly before use. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were determined in $CDCl_3$ unless otherwise noted. Wherever necessary, ^{1}H NMR assignments were supported by appropriate homonuclear correlation experiments (COSY). Optical rotations were measured at 25 °C at the sodium line.

(3*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-3-trimethylstannanylmethyl-1-*tert*-butyloxycarbonylpyrrolidin-2-one (8). To solution of **6** (5.97 g, 13.2 mmol) in THF (130 mL) was added LiHMDS (1 M in THF, 13.5 mL, 13.5 mmol) dropwise over 1 h using a syringe pump at −78 °C. After another 1 h of stirring at −78 °C, the Me_3SnCH_2I (12.1 g, 40.0 mmol) was added over 5 min, and the temperature was maintained between −25 and −35 °C for 2 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (30 mL) and then diluted with EtOAc (300 mL), and the organic layer was separated. The aqueous layer was then acidified to pH 4 with 0.5M HCl, and this was re-extracted with EtOAc (2 × 200 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography with hexane containing EtOAc (0−10%) to yield **8** as a colorless solid (5.18 g, 63%) and **7** (1.9 g, 23%). For **8**: mp 60−61 °C; $[\alpha]_D$ +13.2 (c = 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.12 (9H, s), 0.88 (1H, dd, J = 8.2, 13.0 Hz), 1.05 (9H, s), 1.16 (1H, dd, J = 7.8, 13.0 Hz), 1.42 (9H, s), 1.74 (1H, m), 2.38 (1H, dd, J = 8.7, 12.6 Hz), 2.95 (1H, m), 3.70 (1H, dd, J = 2.6, 10.4 Hz), 3.84 (1H, dd, J = 4.5, 10.4 Hz), 4.09 (1H, m), 7.36−7.47 (6H, m), 7.60−7.66 (4H, m); ^{13}C NMR ($CDCl_3$) δ −9.1, 13.8, 19.1, 26.8, 27.9, 32.6, 40.7, 56.4, 64.6, 82.5, 127.7, 127.8, 129.8, 132.6, 133.0, 135.4, 135.5, 149.7, 178.2; [M + Na] 654; HRMS, found 654.2007, $C_{30}H_{45}NO_4Si^{120}Sn$ requires 654.2037.

(3*R*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-3-trimethylstannanylmethyl-1-*tert*-butyloxycarbonylpyrrolidin-2-one (7). To a solution of LiHMDS (1 M in THF, 1.7 mL, 1.7 mmol) was added dropwise a solution of **8** (1.0 g, 1.6 mmol) in THF (25 mL) at −60 °C. The reaction mixture was stirred and warmed to −30 °C over a period of 2 h, quenched at this temperature using 2,6-di-*tert*-butyl phenol. The reaction mixture was diluted with EtOAc (50 mL) and washed with a saturated solution of NH_4Cl (15 mL). The organic layer was separated, and the aqueous layer was re-extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography with hexane containing EtOAc (0−10%) to yield **7** as a colorless oil (0.74 g, 73%) and 13% of recovered **8**: $[\alpha]_D$ +16.4 (c = 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.12 (9H, s), 0.94 (1H, dd, J = 9.0, 13.0 Hz), 1.07 (9H, s), 1.27 (1H, dd, J = 7.1, 13.0 Hz), 1.39 (9H, s), 1.76 (1H, ddd, J = 2.0, 7.0, 9.0 Hz), 2.37 (1H, dd, J = 8.1, 11.6 Hz), 2.60 (1H, dd, J = 7.2, 9.1 Hz), 3.84 (2H, m, CH), 4.05 (1H, m), 7.36−7.47 (6H, m), 7.60−7.66 (4H, m); ^{13}C NMR ($CDCl_3$) δ −9.0, 13.9, 19.2, 26.7, 27.8, 31.6, 40.5, 56.3, 64.4, 82.5, 127.6, 127.7, 129.8, 132.9, 133.2, 135.4, 135.5, 149.9, 178.2; [M + Na] 654; HRMS, found 654.2007; $C_{30}H_{45}NO_4Si^{120}$-Sn requires 654.2037.

(2*S*,3*R*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-2-propenyl-2*β*-methano-1-*tert*-butyloxycarbonylpyrrolidine (11). To a solution of lactam **8** (2.0 g, 3.19 mmol) in THF (35 mL) was added allylmagnesium bromide (1 M in Et_2O, 7.98 mL, 7.98 mmol) dropwise over 5 min at −78 °C. The reaction mixture was stirred at −78 °C for 90 min and then quenched with pH 7 buffer (5 mL). This solution was quickly warmed to room temperature and diluted with EtOAc (100 mL). The organic layer was washed with H_2O (2 × 15 mL) and NaCl (15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residual solvent further removed using a vacuum pump (1 h). This crude reaction mixture was dissolved in dry CH_2Cl_2 (125 mL), and TFA (0.90 g, 0.61 mL, 7.90 mmol) was added dropwise at 0 °C. The resulting orange-brown solution was stirred for 10 min, quenched with a saturated solution of $NaHCO_3$ (35 mL), and diluted with EtOAc (300 mL). The organic layer was washed with $NaHCO_3$ (50 mL), followed by H_2O (50 mL) and NaCl (50 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography with hexane containing EtOAc (5%) to yield **11** as a colorless oil (0.91 g, 58%): $[\alpha]_D$ +28.0 (c = 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.73 (1H, t, J = 5.1 Hz), 1.08 (9H, s), 1.30−1.50 (2H, m), 1.41 (9H, s), 1.63 (3H, dd, J = 1.6, 6.5 Hz), 1.90 (1H, m), 2.28 (1H, m), 3.64 (1H, dd, J = 7.0, 9.8 Hz), 3.70 (1H, dd, J = 4.7, 9.8 Hz), 4.09 (1H, br s), 5.37 (1H, dq, J = 6.5, 15.4 Hz), 5.56 (1H, d, J = 15.4 Hz), 7.36−7.45 (6H, m), 7.66−7.72 (4H, m); ^{13}C NMR ($CDCl_3$) δ 17.5, 19.3, 26.7, 26.8, 28.4, 30.4, 48.8, 64.9, 65.3, 79.2, 122.2, 127.6, 129.5, 129.6, 131.2, 133.7, 133.7, 135.6, 155.6; [M + 1] 492; HRMS, found 492.2925; $C_{30}H_{42}NO_3Si$ requires 492.2934.

(2*S*,3*R*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-2-(2′-methoxycarbonylvinyl)-2*β*-methano-1-*tert*-butyloxycarbonylpyrrolidine (12). Through a solution of **11** (1.55 g, 3.14 mmol) in CH_2Cl_2 (55 mL) was bubbled ozone until it became light blue in color at −78 °C. After 5 min, the ozone was replaced with nitrogen and bubbling was continued until the color had dissipated (10 min). Me_2S (1.95 g, 2.30 mL, 31.4 mmol) was then added in one portion, and the reaction mixture was left to warm to room temperature. The solvent and excess Me_2S were removed under reduced pressure, and the residue was purified by silica gel flash chromatography with hexane containing EtOAc (15%) to yield the desired aldehyde as a colorless oil (1.40 g, 93%): $[\alpha]_D$ +31.1 (c = 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.96−1.07 (1H, m), 1.05 (9H, br s), 1.44 (9H, br s), 2.05−2.20 (3H, m), 2.39 (1H, br s), 3.67−3.70 (1H, dd, J = 3.3, 10.2 Hz), 3.89 (1H, br s), 4.18 (1H, br s), 7.36−7.46 (6H, m), 7.64−7.68 (4H, m), 9.84 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.8, 27.8, 28.3, 56.4, 65.2, 80.7, 127.7, 129.7, 129.8, 133.2, 135.4, 135.5, 155.2, 200.0; [M + 1] 480; HRMS, found 480.2559; $C_{28}H_{37}NO_4Si$ requires 480.2570.

To a solution of the aldehyde (1.25 g, 2.61 mmol) in dry benzene (100 mL) was added methyl(triphenylphosphoranylidene) acetate (5.49 g, 16.4 mmol) at room temperature. The reaction mixture was then heated to reflux for a 30 h, the solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel flash chromatography with hexane containing EtOAc (12%). The product **12** (1.27 g, 91%) was obtained as a mixture of *cis*- and *trans*-isomers (1:6), which were easily separable. For the *trans*-isomer: $[\alpha]_D$ −39.5 (c = 2.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.06 (9H, s), 1.05−1.10 (1H, m), 1.41 (9H, s), 1.57 (1H, m), 1.79 (1H, m), 1.96 (1H, m), 2.26 (1H, m), 3.60 (1H, dd, J = 6.8, 9.9 Hz), 3.68 (1H, dd, J = 5.0, 9.9 Hz), 3.69 (3H, s), 4.17 (1H, br s), 5.81 (1H, d, J = 15.5 Hz), 6.80 (1H, d, J = 15.5 Hz), 7.35−7.44 (6H, m), 7.64−7.69 (4H, m); ^{13}C NMR ($CDCl_3$) δ 19.1, 26.7, 28.2, 30.0, 49.3, 51.1, 65.06, 65.10, 80.0, 116.5, 127.6, 129.5, 133.4, 135.5, 150.2, 155.2, 167.0; [M + 1] 536; HRMS, found 536.2851; $C_{31}H_{41}NO_5Si$ requires 536.2832.

(5*S*,6*R*,8*R*)-8-*tert*-Butyldiphenylsilyloxymethyl-5*β*-methano-hexahydropyrrolizidin-2-one (13). To a solution of ester **12** (1.44 g, 2.68 mmol) in EtOH (55 mL) was added 10% Pd/C (500 mg) at room temperature. The suspension was hydrogenated under 1 atm of H_2 for 7 h at room temperature. The suspension was then filtered through a sintered-glass funnel containing Celite, and the solvent was removed under reduced pressure to yield the product as a colorless oil (1.44 g, essentially quantitative): $[\alpha]_D$ +40.9 (c = 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.55 (1H, t, J = 5.0 Hz), 0.92 (1H, dd, J = 5.4, 8.4 Hz), 1.06 (9H, s), 1.30 (1H, m), 1.41 (9H, s), 1.45−1.55 (1H, m), 1.95 (1H, m), 2.17−2.25 (2H, m), 2.34 (1H, ddd, J = 5.6, 9.8, 15.7 Hz), 2.67 (1H, m), 3.50 (1H, m), 3.50 (1H, m), 3.57

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(3H, s), 3.77 (1H, dd, J = 4.8, 9.5 Hz), 3.97 (1H, br s), 7.36−7.45 (6H, m), 7.65−7.69 (4H, m); ^{13}C NMR ($CDCl_3$) δ 19.1, 23.8, 24.4, 26.8, 28.3, 28.8, 30.4, 21.0, 47.7, 51.3, 63.8, 65.4, 79.5, 127.5, 129.5, 133.5, 133.6, 135.4, 156.5, 173.8; [M + 1] 538; HRMS, found 538.2976; $C_{31}H_{43}NO_5Si$ requires 538.2989.

To a solution of the above ester (94.6 mg, 0.174 mmol) in CH_2Cl_2 (3.5 mL) was added trifluoroacetic acid (~0.50 g, 0.35 mL, 4.4 mmol) dropwise at 0 °C. After stirring at this temperature for 2.5 h, a saturated solution of $NaHCO_3$ (5 mL) was added, and the resulting reaction mixture was stirred vigorously for 5 min. EtOAc (50 mL) was added, and the organic layer was washed with $NaHCO_3$ (10 mL) and NaCl (10 mL) and dried (Na_2SO_4). This was filtered and concentrated to give a pale yellow residue, which was used in the next step.

To a solution of crude amine (76.2 mg, 0.174 mmol) in a mixture of THF and water (3.0 mL, 2:1) was added a 1 M LiOH solution (0.348 mL, 0.348 mmol) dropwise at 0 °C. The reaction mixture was stirred for 12 h at room temperature and acidified with a 2% HCl solution (pH <6), and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer were dried (Na_2SO_4) and filtered, and solvent was evaporated to yield the carboxylic acid, which was dissolved (73.6 mg, 0.174 mmol) in CH_2Cl_2 (3.5 mL). Diisopropylethylamine (0.16 g, 0.22 mL, 1.22 mmol) was added followed by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) (66.0 mg, 0.261 mmol) at −10 °C. The reaction mixture was then left to slowly warm to room temperature. After 24 h the reaction mixture was poured into saturated $NaHCO_3$ (5 mL) and diluted with EtOAc (50 mL). The organic layer was washed with a 1 M HCl solution (5 mL) and brine (5 mL) and dried (Na_2SO_4). The residue was purified by silica gel flash chromatography with hexane containing EtOAc (25−45%) to yield **13** as a colorless solid (44.8 mg, 64% for 4 steps): mp 93−94 °C; $[\alpha]_D$ +38.8 (c = 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.68 (1H, dd, J = 5.8, 8.4 Hz), 0.80 (1H, dd, J = 4.2, 5.8 Hz), 1.06 (9H, s), 1.45 (1H, m), 1.96 (1H, ddd, J = 1.4, 9.2, 12.6 Hz), 2.21 (1H, dd, J = 8.0, 12.8 Hz), 2.38−2.62 (3H, m), 2.88 (1H, m), 3.37 (1H, m), 4.06 (1H, dd, J = 2.9, 10.2 Hz), 4.32 (1H, dd, J = 5.7, 10.2 Hz), 7.36−7.44 (6H, m), 7.63−7.72 (4H, m); ^{13}C NMR ($CDCl_3$) δ 15.8, 16.5, 19.3, 24.4, 26.8, 35.0, 36.3, 54.3, 61.3, 127.6, 129.6, 133.4, 133.7, 135.6, 135.7, 171.3; IR (cm^{-1}) 3053, 2931, 1691, 1462, 1410, 1112; [M + 1] 406; HRMS, found 406.2193; $C_{25}H_{32}NO_2Si$ requires 406.2202.

(2*R*,4*R*,5*S*)-4β-Methano-hexahydropyrrolizidin-8-one-2-carboxylic Acid (5). To a solution of **13** (62.5 mg, 0.153 mmol) in THF (1.5 mL) was added TBAF (0.38 mL, 0.38 mmol) dropwise at room temperature. The reaction mixture was stirred for 12 h at room temperature, the solvent was evaporated, and the residue was purified by silica gel flash chromatography with hexane containing EtOAc (80%) to yield the alcohol as a colorless oil (24.6 mg, 95%): $[\alpha]_D$ −81.8 (c = 1.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.68 (1H, dd, J = 6.4, 8.7 Hz), 0.95 (1H, dd, J = 4.2, 6.4 Hz), 1.42 (1H, dd, J = 4.2, 4.4 Hz), 1.77 (1H, symmetrical m), 2.02−2.10 (2H, m), 2.45 (1H, dt, J = 10.1, 12.8 Hz), 2.66 (1H, ddd, J = 2.2, 10.1, 16.9 Hz), 2.92 (1H, ddt, J = 1.6, 9.9, 16.9 Hz), 3.33 (1H, m), 3.65−3.72 (2H, m), 5.04 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 13.7, 16.5, 23.8, 32.6, 35.4, 53.6, 56.8, 62.9, 172.3; IR (cm^{-1}) 3284, 2934, 1659, 1467, 1418, 1057; [M + 1] 168; HRMS, found 168.1030; $C_9H_{14}NO_2$ requires 168.1024.

To a solution of oxalyl chloride (2 M, 0.35 mL, 0.70 mmol) in CH_2Cl_2 (1.0 mL) was added DMSO (0.11 g, 0.10 mL, 1.42 mmol) dropwise at −60 °C. After 20 min, a solution of the above alcohol (29.7 mg, 0.178 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise at −60 °C. The reaction was stirred at −60 °C for 1 h, diisopropylethylamine (0.230 g, 0.31 mL, 1.78 mmol) was added, and the reaction kept below −50 °C for 30 min and then slowly warmed to −10 °C over 1 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (5 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with NH_4Cl (2 × 5 mL) and NaCl (7 mL), then dried (Na_2SO_4), and filtered, and the solvent was evaporated under reduced pressure.

To a solution of crude aldehyde in *tert*-BuOH (2 mL) was added the 2-methyl-2-butene (0.126 g, 0.190 mL, 1.78 mmol) followed by a solution of the $NaClO_2$ (0.158 g, 1.74 mmol) and KH_2PO_4 (0.155 g, 1.14 mmol) in water (1 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h, the *tert*-BuOH was evaporated under reduced pressure, the resulting residue was acidified using a 2% HCl solution, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography with EtOAc containing AcOH (0−5%) to afford **5** as a colorless oil (19.4 mg, 60%): $[\alpha]_D$ +75.5 (c = 0.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.79 (1H, dd, J = 6.4, 8.7 Hz), 0.90 (1H, dd, J = 4.2, 6.4 Hz), 1.63 (1H, dt, J = 4.2, 8.7 Hz), 2.04 (1H, dd, J = 9.5, 12.3 Hz), 2.52−2.67 (3H, m), 2.76, (1H, dd, J = 9.5, 17.0 Hz), 3.04 (1H, dt, J = 10.0, 17.0 Hz), 3.92 (1H, t, J = 8.6 Hz), 5.74 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 14.0, 15.3, 24.2, 35.6, 35.7, 55.0, 55.6, 169.3, 174.1; IR (cm^{-1}) 3650−2200, 1732, 1645, 1470, 1417, 1201; [M + 1] 182; HRMS, found 182.0823; $C_9H_{12}NO_3$ requires 182.0817.

(3*S*,5*R*,6*R*,8*R*)-3-Allyl-8-*tert*-butyldiphenylsilyloxymethyl-5β-methano-hexahydropyrrolizidin-2-one (14). To a solution of **13** (0.13 g, 0.32 mmol) in THF (6.0 mL) was added *n*-BuLi (1.95 mL, 0.44 mmol, 0.227 M in hexanes) dropwise over 5 min at −78 °C. The solution was stirred for 1 h, and then allyl iodide (0.186 g, 0.10 mL, 1.11 mmol) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 2 h and quenched with a saturated solution of NH_4Cl (4 mL), and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with a saturated solution of NaCl (10 mL), dried (Na_2SO_4), filtered, and evaporated under reduce pressure. The residue was purified by silica gel column chromatography with hexane containing EtOAc (20−40%) to yield **14** as colorless oil (114 mg, 81%) and its minor epimer. For **14**: $[\alpha]_D$ +28.6 (c = 1.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.68 (1H, dd, J = 5.7, 8.6 Hz), 0.77 (1H, dd, J = 4.2, 5.7 Hz), 1.07 (9H, s), 1.44 (1H, m), 2.05 (1H, dd, J = 8.2, 12.4 Hz), 2.14−2.23 (3H, m), 2.40 (1H, ddd, J = 5.5, 8.0, 12.8 Hz), 2.69 (1H, m), 3.02 (1H, m), 3.38 (1H, m), 4.04 (1H, dd, J = 2.9, 10.2 Hz), 4.34 (1H, dd, J = 5.6, 10.2 Hz), 5.04 (2H, m), 5.79 (1H, m), 7.35−7.45 (6H, m), 7.65−7.72 (4H, m); ^{13}C NMR ($CDCl_3$) δ 15.6, 16.2, 19.4, 26.5, 26.9, 31.2, 34.7, 35.5, 46.8, 52.1, 54.3, 61.3, 116.4, 127.6, 127.8, 129.6, 133.4, 133.6, 135.6, 135.7, 136.0, 172.0; IR (cm^{-1}) 3079, 2931, 2857, 1689, 1113; [M + 1] 446; HRMS, found 468.2358; $C_{28}H_{35}NNaO_2Si$ requires 468.2335.

For *epi*-**14** (minor isomer): $[\alpha]_D$ +35.4 (c = 0.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.65 (1H, dd, J = 6.2, 8.6 Hz), 0.79 (1H, dd, J = 4.2, 5.8 Hz), 1.06 (9H, s), 1.43 (1H, m), 1.79 (1H, dd, J = 2.0, 12.9 Hz), 2.19 (1H, dd, J = 8.0, 12.7 Hz), 2.34−2.44 (2H, m), 2.52−2.60 (2H, m), 2.78 (1H, m), 3.37 (1H, m), 4.05 (1H, dd, J = 2.8, 10.2 Hz), 4.36 (1H, dd, J = 5.7, 10.2 Hz), 5.05−5.12 (2H, m), 5.82 (1H, m), 7.32−7.44 (6H, m), 7.64−7.73 (4H, m); [M + 1] 446; HRMS, found 468.2359; $C_{28}H_{35}NNaO_2Si$ requires 468.2335.

(3*S*,5*R*,6*R*,8*R*)-8-*tert*-Butyldiphenylsilyloxymethyl-3-propyl-5β-methano-hexahydropyrrolizidin-2-one (15). To a solution of the **14** (76 mg, 0.171 mmol) in EtOH (5.0 mL) was added 10% Pd on carbon (10 mg), and the suspension was stirred under a H_2 for 2 h at room temperature. The suspension was filtered through a sintered glass funnel containing Celite and washed with EtOAc (2 × 5 mL), the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography with hexane containing EtOAc (10−20%) to yield **15** as a colorless oil (72.2 mg, 95%): $[\alpha]_D$ +39.6 (c = 1.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.67 (1H, dd, J = 5.8, 8.5 Hz), 0.77 (1H, dd, J = 4.2, 5.7 Hz), 0.92 (3H, t, J = 7.2 Hz), 1.06 (9H, s), 1.27−1.45 (4H, m), 1.91−1.96 (1H, m), 2.05−2.16 (2H, m), 2.20 (1H, dd, J = 8.0, 12.8 Hz), 2.38 (1H, m), 2.91 (1H, m), 3.38 (1H, m), 4.07 (1H, dd, J = 2.9, 10.2 Hz), 4.29 (1H, dd, J = 5.8, 10.2 Hz), 7.35−7.44 (6H, m), 7.64−7.70 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.2, 15.8, 16.3, 19.6, 20.7, 27.1, 32.0, 33.6, 35.0, 47.5, 52.4, 54.3, 61.7, 127.8, 129.77, 129.79, 133.6, 133.9, 135.8, 135.9, 173.1; IR (cm^{-1}) 2957, 2858, 1690,

1462, 1409, 1113; [M + 1] 448; HRMS, found 470.2498, $C_{28}H_{37}NNaO_2Si$ requires 470.2491.

(3*S*,5*R*,6*R*,8*R*)-8-Hydroxymethyl-3-propyl-5*β*-methanotetrahydropyrrolizidin-2-one (16). To a solution of **15** (82 mg, 0.184 mmol) in THF (3.0 mL) was added dropwise *n*-BuLi (0.227M in hexanes, 1.05 mL, 0.239 mmol) at −78 °C. The solution was stirred for 1 h at −78 °C, and then a solution of PhSeBr (0.122 g, 0.515 mmol) in THF (1.0 mL) was added. The reaction mixture was stirred for 1.5 h at −78 °C, quenched with a saturated solution of NH_4Cl (5 mL), and warmed to room temperature, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with a saturated solution of NaCl (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with hexane containing EtOAc (10%) to yield selenide.

To a solution of the above product in CH_2Cl_2 (5.0 mL) was added pyridine (36 mg, 0.037 mL, 0.46 mmol) followed by a solution of 30% H_2O_2 (0.189 g, 0.166 mmol) in H_2O (0.4 mL) at 0 °C. After 2 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for a further 3 h and diluted with CH_2Cl_2 (25 mL), and a saturated solution of $NaHCO_3$ (15 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were washed with a saturated solution of NaCl (7 mL), then dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane containing EtOAc (10−20%) to yield the product (60% for 2 steps) as a 10:1 mixture of double bond isomers.

To a solution of unsaturated lactam (50 mg, 0.11 mmol) in THF (1.0 mL) was added TBAF (1 M in THF, 0.312 mL, 0.313 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h, the solvent was removed under reduced pressure, and the resulting residue was purified by silica gel column chromatography with hexane containing EtOAc (20−40%) to yield alcohol **16** as a colorless oil (21.5 mg, 97%): $[\alpha]_D$ −211.8 (c = 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 1.38 (1H, m), 1.47 (1H, dd, J = 4.8, 6.1 Hz), 1.58 (2H, m), 1.99−2.06 (2H, m), 2.23−2.32 (3H, m), 3.67−3.78 (3H, m), 4.75 (1H, br s, OH), 6.60 (1H, t, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.7, 16.1, 20.6, 20.9, 28.0, 35.0, 56.8, 62.8 (2), 138.1, 140.6, 171.1; IR (cm^{-1}) 3284, 2957, 2970, 1648, 1458, 1378, 1055; [M + 1] 208; HRMS, found 208.1344; $C_{12}H_{17}NO_2$ requires 208.1337.

(5*S*,6*R*,8*R*)-3-Propyl-5*β*-methano-tetrahydropyrrolizidin-3-en-2-one-8-carboxylic acid (17). To a solution of oxalyl chloride (27 mg, 19 μL, 0.214 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of DMSO (34 mg, 30 μL, 0.429 mmol) in CH_2Cl_2 (0.50 mL) at −60 °C. After 10 min, a solution of alcohol **16** (8.9 mg, 0.0429 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise at −60 °C. After 45 min at this temperature, diisopropylethylamine (67 mg, 90 μL, 0.515 mmol) was added, and the reaction mixture was warmed to −20 °C, stirred for 45 min, and then slowly warmed to 0 °C over 45 min. The reaction mixture was processed as described above.

To a solution of the above aldehyde in *t*-BuOH (2.0 mL) was added 2-methyl-2-butene (30 mg, 45 μL, 0.43 mmol) followed by a solution the $NaClO_2$ (38 mg, 0.420 mmol) and KH_2PO_4 (37 mg, 0.62 mmol) in water (1.0 mL) at room temperature. This reaction mixture was stirred for 12 h at room temperature and processed as described before. The residue was purified by silica gel chromatography with EtOAc containing AcOH (0−1%) to yield **17** as a colorless oil (9.0 mg, 95%): $[\alpha]_D$ +14.7 (c = 0.81, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, t, J = 7.4 Hz), 1.51−1.67 (4H, m), 2.21−2.34 (3H, m), 2.77−2.81 (2H, m), 4.41 (1H, dd, J = 8.4, 9.2 Hz), 6.74 (1H, s), 9.70 (1H, br s, OH); ^{13}C NMR ($CDCl_3$) δ 13.8, 17.0, 20.9, 22.0, 27.9, 38.5, 56.3, 58.1, 140.0, 140.2, 170.5, 171.9; IR/(cm^{-1}) 3400−2000, 2961, 1742, 1639, 1383, 1215; [M + 1] 222; HRMS, found 222.1353; $C_{12}H_{15}NO_3$ requires 222.1357.

(2*S*,3*R*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-2-(2′-methoxycarbonylethyl)-2*β*-methano-1-*tert*-butyloxycarbonylpyrrolidine (18). To a solution of **12** (1.44 g, 2.68 mmol) in EtOH (55 mL) was added 10% Pd on carbon (500 mg), and the suspension was stirred under 1 atm of H_2 at room temperature. After 7 h, the suspension was filtered through a sintered-glass funnel containing Celite, and the filtrate was removed under reduced pressure to yield **18** as a colorless oil (1.44 g, essentially quantitative): $[\alpha]_D$ +40.9 (c = 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.55 (1H, t, J = 5.0 Hz), 0.92 (1H, dd, J = 5.4, 8.4 Hz), 1.06 (9H, s), 1.30 (1H, m), 1.41 (9H, s), 1.45−1.55 (1H, m), 1.95 (1H, m), 2.17−2.25 (2H, m), 2.34 (1H, ddd, J = 5.6, 9.8, 15.7 Hz), 2.67 (1H, m), 3.50 (1H, m), 3.50 (1H, m), 3.57 (3H, s), 3.77 (1H, dd, J = 4.8, 9.5 Hz), 3.97 (1H, br s), 7.36−7.45 (6H, m), 7.65−7.69 (4H, m); ^{13}C NMR ($CDCl_3$) δ 19.1, 23.8, 24.4, 26.8, 28.3, 28.8, 30.4, 21.0, 47.7, 51.3, 63.8, 65.4, 79.5, 127.5, 129.5, 133.5, 133.6, 135.5, 156.5, 173.8; [M + 1] 538; HRMS, found 538.2976; $C_{31}H_{43}NO_5Si$ requires 538.2989.

(2*R*,3*R*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-2-[(2′*R*)-hydroxy-2′-methoxycarbonylethyl]-2*β*-methano-1-*tert*-butyloxycarbonylpyrrolidine (19). To a solution **18** (0.10 g, 0.188 mmol) in THF (2.0 mL) was added KHMDS (0.5 M in toluene, 0.49 mL, 0.244 mmol) dropwise at −78 °C, and the solution was stirred for 45 min. To this a solution of Davis reagent (64 mg, 0.244 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 90 min, quenched with a saturated solution of NH_4Cl (2 mL), and then warmed to room temperature, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with NH_4Cl (2 × 10 mL) and NaCl (10 mL), then dried (Na_2SO_4), filtered, and evaporated under reduce pressure. The resulting residue was purified by silica gel flash chromatography with hexane containing EtOAc (15−25%) to yield **19** as a colorless oil (91 mg, 87%, mixture of two isomers > 10:1). For **19** (major isomer): $[\alpha]_D$ +61.5 (c = 1.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.66 (1H, t, J = 5.0 Hz), 0.87 (1H, m), 1.07 (9H, s), 1.20 (1H, m), 1.35−1.45 (1H, m), 1.40 (9H, s), 1.91 (1H, ddd, J = 1.5, 8.1, 13.4 Hz), 1.97 (1H, br s), 2.23 (2H, m), 3.59 (1H, dd, J = 7.7, 9.8 Hz), 3.69 (3H, s), 3.71 (1H, dd, J = 5.2, 9.8 Hz), 4.06 (1H, m), 4.36 (1H, dd, J = 3.5, 9.2 Hz), 7.36−7.47 (6H, m), 7.65−7.72 (4H, m); ^{13}C NMR ($CDCl_3$) δ 19.2, 23.3, 26.8, 28.2, 30.5, 39.8, 45.2, 52.0, 65.4, 69.5, 80.3, 127.6, 129.5, 129.6, 133.4, 133.4, 135.5, 157.5, 174.2; [M + 1] 554; HRMS, found 554.2959; $C_{31}H_{44}NO_6Si$ requires 544.2938.

(3*R*,5*R*,6*R*,8*R*)-8-*tert*-Butyldiphenylsilyloxymethyl-3-hydroxy-5*β*-methano-hexahydropyrrolizidin-2-one (20). To a solution of **19** (0.99 g, 1.78 mmol) in CH_2Cl_2 (35 mL) was added trifluoroacetic acid (5.18 g, 3.5 mL, 45.4 mmol) dropwise at 0 °C. After 2.5 h at this temperature, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (20 mL), and the resulting solution was stirred vigorously for 10 min. EtOAc (150 mL) was added, and the organic layer was washed with a saturated solution of $NaHCO_3$ (20 mL) and a saturated solution of NaCl (20 mL) and dried (Na_2SO_4). Filtration and concentration gave a pale yellow residue, which was dissolved in a mixture of THF and H_2O (27 mL, 2:1) and treated with a 1 M LiOH solution (3.20 mL, 3.20 mmol) at 0 °C. The reaction mixture was stirred for 16 h at room temperature, acidified with a 2% HCl solution (pH <6), and diluted with EtOAc (30 mL). The layer was separated, the aqueous layer was extracted with EtOAc (3 × 30 mL), and combined organic layers were dried (Na_2SO_4) and filtered, and solvent was evaporated under reduce pressure to give the crude amino acid, which was dissolved in CH_3CN (150 mL). DMAP (0.761 g, 6.23 mmol) was added at 0 °C. After 10 min, HOBt (0.312 g, 2.31 mmol) was added followed by EDC (0.443 g, 2.31 mmol) at 0 °C. The reaction mixture was stirred for 48 h at room temperature, quenched with a saturated solution of $NaHCO_3$ (40 mL), and diluted with EtOAc (150 mL). The layers were separated, and the organic layer was washed with $NaHCO_3$ (2 × 20 mL), NH_4Cl (2 × 20 mL), and NaCl (25 mL), then dried (Na_2SO_4), and filtered. The solvent was evaporated, and the resulting residue was purified by silica gel flash chromatography with hexane containing EtOAc (45−65%) to yield **20** as a colorless oil (452 mg, 60%): $[\alpha]_D$ +84.8 (c = 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.75−0.79 (2H, m), 1.06 (9H, s), 1.50 (1H, m), 2.21 (1H, dd, J = 8.1, 12.9 Hz), 2.36−2.43 (2H, m), 2.47 (1H, dd, J = 9.9, 12.0 Hz), 2.95 (1H, br s), 3.40 (1H, symmetrical m), 4.04 (1H, dd, J = 2.9, 10.3 Hz), 4.32 (1H, dd, J = 5.6, 10.3 Hz), 4.74 (1H, dd, J = 1.2, 7.9 Hz), 7.36−7.45 (6H, m), 7.64−7.71 (4H, m); ^{13}C

NMR ($CDCl_3$) δ 15.3, 15.9, 19.2, 26.7, 33.9, 34.8, 49.9, 55.0, 61.2, 74.2, 127.6, 129.6, 133.1, 133.4, 135.5, 135.6, 171.2; IR (cm^{-1}) 3327, 2931, 2857, 1684, 1427, 1113; [M + 1] 422; HRMS, found 422.2151; $C_{25}H_{32}NO_3Si$ requires 422.2151.

(3*R*,5*R*,6*R*,8*R*)-8-*tert*-Butyldiphenylsilyloxymethyl-3-acetoxy-5β-methano-hexahydropyrrolizidin-2-one (21). To a solution of alcohol **20** (32 mg, 0.077 mmol) in CH_2Cl_2 (1.0 mL) was added DMAP (19 mg, 0.153 mmol) followed by acetic anhydride (15 mg, 14 μL, 0.15 mmol) at 0 °C. This reaction mixture was stirred for 1.5 h at 0 °C and quenched with a saturated solution of NH_4Cl (2 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with a saturated solution of NH_4Cl (5 mL) and a saturated solution of NaCl (5 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography with hexane containing EtOAc (30%) to yield **21** as a colorless oil (29.5 mg, 82%): $[\alpha]_D$ +51.1 (c = 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.75−0.80 (2H, m), 1.07 (9H, s), 1.52 (1H, dt, J = 5.2, 8.1 Hz), 2.13 (3H, s), 2.23 (1H, dd, J = 8.1, 12.9 Hz), 2.38 (1H, m), 2.44 (1H, dd, J = 9.6, 12.4 Hz), 2.55 (1H, dd, J = 8.1, 12.4 Hz), 3.43 (1H, m), 4.07 (1H, dd, J = 2.8, 10.2 Hz), 4.32 (1H, dd, J = 5.8, 10.2 Hz), 5.72 (1H, m), 7.36−7.45 (6H, m), 7.65−7.71 (4H, m); ^{13}C NMR ($CDCl_3$) δ 15.4, 16.2, 19.2, 20.8, 26.7, 22.1, 34.0, 49.7, 54.9, 61.2, 75.0, 127.6, 129.6, 133.1, 133.5, 135.5, 135.7, 166.5, 170.2; IR (cm^{-1}) 2933, 2858, 1749, 1711, 1428, 1233, 1113, 703; [M + 1] 464; HRMS, found 464.2245; $C_{27}H_{34}NO_4Si$ requires 464.2257.

(3*R*,5*R*,6*R*,8*R*)-3-Acetoxy-5β-methano-hexahydropyrrolizidin-2-one-8-carboxylic Acid (22). To a solution of **21** (27.0 mg, 0.058 mmol) in CH_3CN (3.0 mL) was added HF/pyridine (0.067 mL) dropwise at 0 °C. The reaction mixture was stirred for 12 h at room temperature, quenched with a saturated solution of $NaHCO_3$ (1 mL), and diluted with EtOAc (25 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous NaCl (5 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography with hexane containing EtOAc (60−75%) to yield the alcohol as a colorless oil (12.0 mg, 92%): $[\alpha]_D$ −24.5 (c = 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.81 (1H, dd, J = 6.5, 8.8 Hz), 0.97 (1H, dd, J = 4.4 6.5 Hz), 1.52 (1H, dt, J = 4.6, 9.1 Hz), 1.84 (1H, dq, J = 5.0,10.0 Hz), 2.14 (1H, dd, J = 7.5, 12.8 Hz), 2.18 (3H, s), 2.47 (1H, dd, J = 9.5,12.7 Hz), 2.62 (1H, dd, J = 8.5, 12.7 Hz), 3.41 (1H, m), 3.74 (2H, d, J = 5.5 Hz), 5.78 (1H, m); ^{13}C NMR ($CDCl_3$) δ 13.5, 16.3, 20.8, 31.7, 32.5, 49.2, 57.4, 62.6, 74.7, 167.7, 170.0; IR (cm^{-1}) 3334, 2934, 1746, 1681, 1469, 1427, 1233. [M + 1] 226; HRMS, found 226.10730, $C_{11}H_{16}NO_4$ requires 226.10794.

To a solution of oxalyl chloride (31 mg, 21 μL, 0.244 mmol) in CH_2Cl_2 (0.4 mL) was added DMSO (0.038 g, 0.035 mL, 0.488 mmol) dropwise at −60 °C. After 15 min, a solution of the above alcohol (11.0 mg, 0.049 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise at −60 °C. The reaction mixture was stirred at this temperature for 1 h, diisopropylethylamine (76 mg, 0.10 mL, 0.586 mmol) was added, and the reaction was kept below −40 °C for 30 min and then slowly warmed to 0 °C over 1 h. The reaction mixture was processed as described above to give an oil.

To the above aldehyde in *t*-BuOH (1.0 mL) was added 2-methyl-2-butene (34 mg, 52 μL, 0.488 mmol) followed by a solution of $NaClO_2$ (43 mg, 0.478 mmol) and KH_2PO_4 (42 mg, 0.312 mmol) in water (0.5 mL) at room temperature. The reaction mixture was stirred for 12 h at room temperature, the *t*-BuOH was evaporated under reduced pressure, and the residue was acidified using a 2% HCl solution. After usual workup the resulting residue was purified by silica gel chromatography with EtOAc containing AcOH (0−10%) to yield **22** as a pale yellow oil (8.2 mg, 70%): $[\alpha]_D$ +43.2 (c = 0.65, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.85−0.90 (2H, m), 1.69 (1H, m), 2.18 (3H, s), 2.52−2.67 (4H, m), 3.17 (1H, br s), 3.96 (1H, t, J = 8.6 Hz), 5.85 (1H, t, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.7, 15.9, 20.6, 32.6, 35.0, 50.4, 55.3, 74.3, 168.9, 170.1(2); IR (cm^{-1}) 3700−2000, 1738, 1694, 1232; [M + 1] 240; HRMS, found 240.0879; $C_{11}H_{14}NO_5$ requires 240.0872.

(3*R*,5*R*,6*R*,8*R*)-3-Hydroxy-5β-methano-hexahydropyrrolizidin-2-one-8-carboxylic Acid (23). To a solution of **22** (12.6 mg, 0.053 mmol) in THF (1.0 mL) was added a 1 M LiOH solution (80 μL, 0.080 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature and quenched with a 2% HCl solution, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography with EtOAc containing MeOH (0−10%) and acetic acid (0−5%) to yield the product **23** as a viscous colorless oil (7.1 mg, 71%): $[\alpha]_D$ +48.3 (c = 0.53, MeOH); ^{1}H NMR (CD_3OD) δ 0.72 (1H, dd, J = 4.6, 5.5 Hz), 0.81 (1H, dd, J = 5.6, 8.8 Hz), 1.60 (1H, dt, J = 4.6, 8.8 Hz), 2.33−2.47 (3H, m), 2.52 (1H, dd, J = 9.9, 11.9 Hz), 3.58 (1H, t, J = 8.1 Hz), 4.71 (1H, m); ^{13}C NMR (CD_3OD) δ 16.5, 17.7, 24.2, 37.0, 37.5, 51.7, 75.8, 172.8, 180.5; IR (cm^{-1}) 3000−2500, 1696, 1684, 1576, 1418; [M + Na] 220; HRMS, found 220.0592; $C_9H_{11}NO_4Na$ requires 220.0585.

(3*S*,5*R*,6*R*,8*R*)-3-Azido-8-*tert*-butyldiphenylsilyloxymethyl-5β-methano-hydroxypyrrolizidin-2-one (24). To a solution of Ph_3P (0.140 g, 0.534 mmol) in THF (2.2 mL) was added DEAD (0.093 g, 0.084 mL, 0.534 mmol) dropwise at 0 °C. After 15 min, the hydroxy lactam **20** (0.045 g, 0.107 mmol) was added followed by the diphenylphosphoryl azide (0.147 g, 0.115 mL, 0.534 mmol) at 0 °C. The reaction mixture was stirred for 16 h, quenched with a saturated solution of NH_4Cl (5 mL), and diluted with diethyl ether (50 mL). The organic layer was washed with H_2O (5 mL) and NaCl (5 mL), then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography with hexane containing EtOAc (10%) to yield the **24** as a colorless solid (42 mg, 86%): mp 101−102 °C; $[\alpha]_D$ −26.8 (c = 0.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.77 (1H, dd, J = 6.4, 8.7 Hz), 0.90 (1H, dd, J = 4.4, 6.2 Hz), 1.06 (9H, s), 1.55 (1H, m), 1.94 (1H, dd, J = 1.6, 13.9 Hz), 2.20 (1H, dd, J = 7.9, 12.8 Hz), 2.41 (1H, m), 2.72 (1H, dd, J = 8.3, 13.9 Hz), 3.44 (1H, m), 4.00 (1H, dd, J = 2.7, 10.4 Hz), 4.23 (1H, dd, J = 1.6, 8.3 Hz), 4.40 (1H, dd, J = 5.3, 10.4 Hz), 7.34−7.45 (6H, m), 7.64−7.70 (4H, m); ^{13}C NMR ($CDCl_3$) δ 15.6, 16.7, 19.2, 26.7, 31.0, 34.3, 52.4, 54.7, 60.4, 65.3, 127.6, 129.6, 133.0, 133.3, 135.4, 135.6, 166.5; IR (cm^{-1}) 2932, 2104, 1702, 1462, 1428, 1113; [M + 1] 447; HRMS, found 447.2220; $C_{25}H_{31}N_4O_2Si$ requires 447.2216.

(3*S*,5*R*,6*R*,8*R*)-3-Azido-5β-methano-hexahydropyrrolizidin-2-one-8-carboxylic Acid (25). To a solution of **24** (30 mg, 0.068 mmol) in CH_3CN (3.0 mL) was added HF−pyridine (~0.070 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, warmed to room temperature over 1 h, quenched with a saturated solution of $NaHCO_3$ (2 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduce pressure. The resulting residue was purified by silica gel column chromatography with hexane containing EtOAc (60−80%) to yield the alcohol as a colorless solid (13.0 mg, 93%): mp 94−94.5 °C; $[\alpha]_D$ −254.9 (c = 0.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.78 (1H, dd, J = 6.8, 8.7 Hz), 1.06 (1H, dd, J = 4.3, 6.8 Hz), 1.53 (1H, m), 1.81 (1H, ddd, J = 4.9, 10.1, 15.0 Hz), 2.03 (1H, dd, J = 2.0, 14.2 Hz), 2.12 (1H, dd, J = 7.3, 12.7 Hz), 2.72 (1H, dd, J = 8.6, 14.2 Hz), 3.46 (1H, m), 3.70−3.78 (2H, m), 4.36 (1H, dd, J = 2.0, 8.6 Hz), 5.20 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 14.0, 17.0, 30.8, 32.7, 52.1, 57.7, 62.7, 64.9, 168.2; IR (cm^{-1}) 3371, 3020, 2107, 1678, 1216; [M + 1] 209; HRMS, found 209.1035; $C_9H_{13}N_4O_2$ requires 209.1038.

To a solution of oxalyl chloride (43 mg, 30 μL, 0.341 mmol) in CH_2Cl_2 (1.0 mL) was added a solution DMSO (53 mg, 48 μL, 0.68 mmol) in CH_2Cl_2 (0.50 mL) at −60 °C. After 20 min, a solution of the above alcohol (14 mg, 0.062 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise. The reaction mixture was stirred at −60 °C for 1 h, diisopropylethylamine (0.105 g, 0.142 mL, 0.817 mmol) was added and kept below −50 °C for 30 min, and then the reaction was slowly warmed to −10 °C over 1 h. The reaction was processed as described above.

To the above aldehyde in *t*-BuOH (1 mL) was added 2-methyl-2-butene (48 mg, 72 μL, 0.681 mmol) at room

temperature. A solution of $NaClO_2$ (60 mg, 0.667 mmol) and KH_2PO_4 (60 mg, 0.436 mmol) in water (1 mL) was added followed by a 6 M HCl solution (pH ≈ 2−3) at room temperature. The reaction mixture was stirred for 2 h, *t*-BuOH was evaporated under reduced pressure, and the residue was acidified using a 2% HCl solution. The aqueous layer was processed as usual. The residue was purified by silica gel chromatography with EtOAc containing AcOH (0−5%) to yield acid **25** as a pale yellow oil (9.7 mg, 70%): $[\alpha]_D$ −62.7 (*c* = 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86 (1H, dd *J* = 6.2, 8.5 Hz), 0.94 (1H, dd, *J* = 4.3, 6.2 Hz), 1.70 (1H, m), 1.96 (1H, d, *J* = 13.9 Hz), 2.55 (2H, m), 2.88 (1H, dd, *J* = 8.0, 13.8 Hz), 3.91 (1H, m), 4.45 (1H, d, *J* = 8.0 Hz), 8.85 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 15.6, 16.6, 30.8, 35.9, 53.1, 54.7, 64.9, 167.9, 170.5; IR (cm^{-1}) 3700−2000, 2107, 1739, 1699, 1317, 1230; [M + 1] 223; HRMS, found 223.0828; $C_9H_{11}N_4O_3$ requires 223.0831.

(3*S*,5*R*,6*R*,8*R*)-8-*tert*-Butyldiphenylsilyloxymethyl-3-phenylacetamide-5*β*-methano-hexahydropyrrolizidin-2-one (26). To a solution of **24** (74 mg, 0.165 mmol) in EtOH (6 mL) was added NH_4OAc (15 mg) followed by 10% Pd/C (35 mg) at room temperature. The suspension was stirred under 1 atm of H_2 for 30 min at room temperature. The suspension was filtered through a sintered-glass funnel containing Celite and washed with EtOAc, and then the filtrate was washed with a saturated solution of NaCl, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give amine that was used without further purification.

To a solution of phenylacetic acid (67 mg, 0.495 mmol) in CH_3CN (1.0 mL) was added EDC (95 mg, 0.495 mmol) followed by HOBt (67 mg, 0.495 mmol) at 0 °C. After 10 min, a solution of the above amine in CH_3CN (1 mL) was added followed by DMAP (91 mg, 0.747 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature and quenched with a saturated solution of $NaHCO_3$ (10 mL), and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (5 mL), dried (Na_2SO_4), filtered, and evaporated reduced pressure. The resulting residue was purified by silica gel flash chromatography with hexane containing EtOAc (50%) to yield **26** as a colorless solid (80 mg, 89%): mp 142−143 °C; $[\alpha]_D$ +19.2 (*c* = 2.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.59 (1H, dd, *J* = 6.3, 8.5 Hz), 0.80 (1H, dd, *J* = 4.2, 6.3 Hz), 1.04 (9H, s), 1.53 (1H, m), 2.00 (1H, dd, *J* = 4.6, 13.8 Hz), 2.12 (1H, dd, *J* = 7.6, 12.6 Hz), 2.31 (1H, ddd, *J* = 5.2, 8.8, 12.4 Hz), 2.75 (1H, dd, *J* = 9.6, 13.8 Hz), 3.32 (1H, m), 3.58 (2H, s), 4.00 (1H, dd, *J* = 2.8, 10.4 Hz), 4.35 (1H, dd, *J* = 5.5, 10.4 Hz), 4.54 (1H, m), 6.53 (1H, d, *J* = 5.9 Hz), 7.23−7.44 (11H, m), 7.62−7.69 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.3, 17.3, 19.2, 26.7, 31.1, 34.2, 43.3, 51.5, 55.1, 55.9, 60.3, 127.1, 127.6, 128.8, 129.3, 129.6, 133.0, 133.3, 134.6, 135.4, 135.6, 169.3, 171.3; IR (cm^{-1}) 3274, 3068, 2932, 1682, 1541, 1428, 1113; [M + 1] 539; HRMS, found 539.2747; $C_{33}H_{39}N_2O_3Si$ requires 539.2730.

(3*S*,5*R*,6*R*,8*R*)-3-Phenylacetamide-5*β*-methano-hexahydropyrrolizidin-2-one-8-carboxylic acid (27). To a solution of **26** (68 mg, 0.126 mmol) in THF (3.0 mL) was added TBAF (1 M in THF, 0.252 mL, 0.252 mmol) dropwise at 0 °C. The reaction mixture was stirred for 3 h at room temperature, quenched with a saturated solution of $NaHCO_3$ (10 mL), and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel flash chromatography with hexane containing EtOAc (80−100%) to yield the alcohol as a colorless oil (29 mg, 86%): $[\alpha]_D$ −66.3 (*c* = 1.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.63 (1H, dd, *J* = 7.0, 8.4 Hz), 1.03 (1H, dd, *J* = 4.3, 6.7 Hz), 1.52 (1H, dt, *J* = 4.3, 8.4 Hz), 1.71 (1H, m), 2.01−2.16 (2H, m), 2.74 (1H, dd, *J* = 9.8, 14.0 Hz), 3.43 (1H, m), 3.59 (2H, s), 4.11 (2H, d, *J* = 7.2 Hz), 4.68 (1H, dt, *J* = 5.5, 10.0 Hz), 6.66 (1H, d, J 6), 7.25−7.37 (5H, m); ^{13}C NMR ($CDCl_3$) δ 12.8, 17.2, 31.0, 32.3, 43.2, 55.16, 55.26, 57.8, 62.2, 127.2, 128.8, 129.2, 134.4, 170.6, 171.3; IR (cm^{-1}) 3286, 3062, 2936, 1669, 1656, 1540, 1454; [M + 1] 301; HRMS, found 301.1543; $C_{17}H_{21}N_2O_3$ requires 301.1552. To a solution of oxalyl chloride (24 mg, 17 μL, 0.193 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of DMSO (30 mg, 27 μL, 0.386 mmol) in CH_2Cl_2 (0.30 mL) dropwise at −60 °C. After 10 min, a solution of the above alcohol (14.5 mg, 0.048 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise at −60 °C. The reaction was stirred at −60 °C for 1 h, diisopropylethylamine (62 mg, 84 μL, 0.482 mmol) was added, and the reaction kept below −45 °C for 45 min and then slowly warmed to −10 °C over 1 h. The reaction mixture was processed as described above. The oil was dissolved in *t*-BuOH (2.0 mL), and 2-methyl-2-butene (0.068 g, 0.102 mL, 0.964 mmol) was added followed by a solution of $NaClO_2$ (85.0 mg, 0.945 mmol) and KH_2PO_4 (84.0 mg, 0.617 mmol) in water (1.2 mL) at room temperature. The reaction mixture was stirred for 12 h at room temperature then processed as usual, and the residue was purified by silica gel chromatography with EtOAc containing AcOH (0−5%) to yield the **27** as a colorless oil (18 mg, 61%): $[\alpha]_D$ +47.7 (*c* = 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.67 (1H, m), 0.90 (1H, m), 1.26 (1H, s), 1.61 (1H, br s), 1.99 (1H, d, *J* = 12.9 Hz), 2.39 (2H, br s), 2.74 (1H, t, *J* = 11.3 Hz), 3.56 (2H, s), 3.81 (1H, br s), 3.90−4.40 (1H, br s), 4.56 (1H, s), 7.25−7.45 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.7, 17.5, 29.6, 30.3, 35.5, 42.8, 52.1, 55.6, 127.0, 128.6, 129.2, 134.7, 170.1 (2), 171.9; IR (cm^{-1}) 3600−2500, 3284, 1727, 1690, 1672, 1538, 1218; [M + 1] 315; HRMS, found 315.13530, $C_{17}H_{19}N_2O_4$ requires 315.13449.

(3*R*,5*R*,6*R*,8*R*)-3-(1-Hydroxy-1-methyl-ethyl)-8-hydroxymethyl-5*β*-methano-hexahydropyrrolizidin-2-one (28). To a solution of **13** (48 mg, 0.12 mmol) in THF (3 mL) was added dropwise a 1.3 M solution of *sec*-butyllithium (0.18 mL, 0.24 mmol) in cyclohexane at −78 °C. The solution was stirred for 1 h at −78 °C and warmed to −40 °C over a period of 30 min, and then acetone (35 μL, 0.48 mmol) was added at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and quenched with a saturated solution of NH_4Cl (3 mL), and the aqueous layer was extracted with a EtOAc (3 × 5 mL). The combined organic layer was dried (Na_2SO_4) and filtered, and solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel flash chromatography with hexane containing EtOAc (25%) to yield a nonseparable mixture of tertiary alcohols (40 mg, 71%, 3:2) as a colorless oil: IR (cm^{-1}) 3430, 2931, 1667, 1471, 1427, 1401, 1172.

To a solution of the above compound (35 mg, 0.076 mmol) in THF (1.0 mL) was added TBAF (0.23 mL, 0.23 mmol) dropwise at room temperature. The reaction mixture was stirred for 3 h at room temperature, the solvent was evaporated, and the resulting residue was purified by silica gel flash chromatography with hexane containing EtOAc (30% to 50%) to yield **28** as colorless crystals (10 mg, 59%) and **29** as a colorless oil (5 mg; 29%). For **28**: mp 97−100 °C; $[\alpha]_D$ −96.6 (*c* = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.69 (1H, dd, *J* = 6.4, 8.4 Hz), 0.99 (1H, dd, *J* = 4.2, 6.4 Hz), 1.25 (3H, s); 1.29 (3H, s); 1.52 (m, 1H); 1.79 (m, 1H); 2.08 (1H, dd, *J* = 7.2, 12.6 Hz), 2.58 (dd, 1H, *J* = 11.0, 13.8 Hz), 2.97 (1H, dd, *J* = 4.1, 11.0 Hz), 3.41 (m, 1H); 3.74 (1H, d, *J* = 5.8 Hz), 4.11 (2H, br, 2 × OH); ^{13}C NMR ($CDCl_3$) δ 13.6, 17.7, 25.1, 26.4, 27.5, 32.4, 51.9, 56.5, 57.6, 62.2, 71.8, 173.9; IR (cm^{-1}) 3402, 2971, 2934, 2867, 1651, 1459, 1332, 1172; [M + 1] 226; HRMS, found 226.1330, $C_{12}H_{20}NO_3$ requires 226.1435.

(2*R*,3*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-2-propenyl-2α-methano-1-*tert*-butyloxycarbonylpyrrolidine (31). To a solution of **7** (0.75 g, 1.19 mmol) in THF (15 mL) was added allylmagnesium bromide (1 M in Et_2O, 3.00 mL, 3.0 mmol) dropwise over 5 min at −78 °C. The reaction mixture was stirred at −78 °C for 90 min, quenched with pH 7 buffer (5 mL), warmed to room temperature, and diluted with EtOAc (50 mL). The organic layer was washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure, and the residual solvent further removed using a vacuum pump (∼1 h) to give **30**, which was used without further purification. To a solution of the above product in CH_2Cl_2 (50 mL) was then added trifluoroacetic acid (0.23 mL, 2.97 mmol) dropwise at 0 °C. The resulting orange-brown solution was stirred for 10 min and quenched with a saturated solution of $NaHCO_3$ (15 mL), and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with $NaHCO_3$ (25 mL) and NaCl (25 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chroma-

tography with hexane containing EtOAc (5%) to yield the **31** as a colorless oil (0.176 g, 30%): $[\alpha]_D$ +23.9 (c = 3.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.13 (1H, d, J = 4.5 Hz) 0.73 (1H, t, J = 5.1 Hz), 1.07 (9H, s), 1.30−1.50 (2H, m), 1.41 (9H, s), 1.62 (3H, dd, J = 1.5, 6.4 Hz), 1.90 (1H, m), 2.25 (1H, m), 3.64 (1H, d, J = 6.9 Hz), 3.68 (1H, dd, J = 4.7, 9.8 Hz), 4.09 (1H, br s), 5.34 (1H, dq, J = 6.5, 15.3 Hz), 5.54 (1H, d, J = 15.3 Hz), 7.36−7.45 (6H, m), 7.64−7.71 (4H, m); ^{13}C NMR ($CDCl_3$) δ 17.4, 19.2, 26.6, 26.7, 28.3, 30.3, 48.7, 64.8, 65.2, 79.1, 122.0, 127.5, 129.5, 131.1, 133.5, 133.6, 135.5, 155.6; [M + 1] 492; HRMS, found 492.2925; $C_{30}H_{42}NO_3Si$ requires 492.2934.

(2*R*,3*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-2-(2′-methoxycarbonylvinyl)-2α-methano-1-*tert*-butyloxycarbonylpyrrolidine (32). Through a solution of **31** (90 mg, 0.183 mmol) in CH_2Cl_2 (5 mL) was bubbled ozone was until a light blue color persisted at −78 °C. After 10 min, the ozone was replaced with nitrogen, and bubbling was continued until the color had dissipated. Me_2S (0.13 mL, 1.83 mmol) was added, and the reaction mixture was left to warm to room temperature. The solvent and excess Me_2S were removed under reduced pressure, and the reaction residue was purified by silica gel flash chromatography with hexane containing EtOAc (15%) to yield the aldehyde as a colorless oil (75 mg, 85%): ^{1}H NMR ($CDCl_3$) δ 0.94−1.07 (1H, m), 1.05 (9H, br s), 1.44 (9H, br s), 2.04−2.15 (3H, m), 2.40 (1H, br s), 3.67 (1H, dd, J = 3.1, 10.1 Hz), 3.90 (1H, br s), 4.14 (1H, br s), 7.36−7.46 (6H, m), 7.64−7.68 (4H, m), 9.84 (1H, s); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.1, 26.7, 27.6, 28.2, 28.2, 30.1, 33.4, 56.3, 64.7, 65.1, 80.5, 127.6, 129.6, 133.1, 135.3, 135.4, 155.1, 199.8.

To the above aldehyde (70 mg, 0.146 mmol) in benzene (5 mL) was added methyl(triphenylphosphoranylidene) acetate (0.24 g, 0.73 mmol) at room temperature. The reaction mixture was heated to reflux for 30 h and processed as usual to give **32** (70 mg, 85%) as a mixture of *trans*- and *cis*-isomers, which were easily separable. For *trans*-**32** (major isomer): $[\alpha]_D$ −33.5 (c = 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s), 1.05−1.09 (1H, m), 1.41 (9H, s), 1.56 (1H, m), 1.77 (1H, m), 1.90 (1H, m), 2.25 (1H, m), 3.60 (1H, m), 3.66 (1H, m), 3.68 (3H, s), 4.15 (1H, br s), 5.79 (1H, d, J = 15.5 Hz), 6.78 (1H, d, J = 15.5 Hz), 7.34−7.44 (6H, m), 7.64−7.68 (4H, m); ^{13}C NMR ($CDCl_3$) δ 19.1, 26.7, 28.2, 29.9, 49.2, 51.1, 65.1, 79.9, 116.4, 127.5, 129.5, 133.3, 135.4, 150.3, 155.2, 166.9; [M + 1] 536; HRMS, found 536.2851; $C_{31}H_{41}NO_5Si$ requires 536.2832.

(5*R*,6*S*,8*R*)-8-*tert*-Butyldiphenylsilyloxymethyl-5α-methano-hexahydropyrrolizidin-2-one (33). A quantity of **32** (60 mg, 0.11 mmol) was subjected to the four-step sequence as described for the preparation of **13**, to give **33** as a viscous oil (24.0 mg, 64%): $[\alpha]_D$ +2.0 (c = 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.68 (1H, dd, J = 5.8, 8.6 Hz), 0.78 (1H, dd, J = 4.2, 5.7 Hz), 1.05 (9H, s), 1.44 (1H, m), 1.95 (1H, ddd, J = 1.3, 8.8, 12.0 Hz), 2.19 (1H, dd, J = 8.0, 12.8 Hz), 2.41−2.59 (3H, m), 2.86 (1H, m), 3.38 (1H, m), 4.04 (1H, dd, J = 2.8, 10.2 Hz), 4.30 (1H, dd, J = 5.6, 10.2 Hz), 7.36−7.44 (6H, m), 7.65−7.71 (4H, m); ^{13}C NMR ($CDCl_3$) δ 15.7, 16.4, 19.2, 24.2, 26.6, 34.8, 36.1, 54.2, 61.1, 127.5, 129.5, 133.4, 133.7, 135.4, 135.6, 171.2; IR (cm^{-1}) 2932, 1692, 1460, 1428, 1113; [M + 1] 406; HRMS, found 406.2193; $C_{25}H_{32}NO_2Si$ requires 406.2202.

(2*S*,3*R*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-2-[2′-methoxycarbonyl-(1′*S*)-nitromethylethyl]-2*β*-methano-1-*tert*-butyloxycarbonylpyrrolidine (34). To a solution of **12** (0.28 g, 0.523 mmol) in acetonitrile (2.0 mL) was added nitromethane (0.32 g, 0.28 mL, 5.2 mmol) dropwise, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.80 g, 0.78 mL, 5.2 mmol) at room temperature. The resulting yellow-orange reaction mixture was stirred for 36 h at room temperature, then diluted with EtOAc (30 mL), and washed with saturated aqueous NH_4Cl (2 × 5 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel flash chromatography with hexane containing EtOAc (12%) to yield **34** as a pale yellow oil (0.29 g, 92%, ratio >20:1 by ^{1}H NMR): $[\alpha]_D$ +26.2 (c = 1.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62 (1H, t, J = 5.9 Hz), 1.05 (9H, s), 1.11 (1H, dd, J = 5.9, 9.0 Hz), 1.38 (9H, s), 1.57 (1H, m), 2.08 (1H, dd, J = 9.0, 13.3 Hz), 2.23 (1H, m), 2.37 (1H, dd, J = 6.7, 16.6 Hz), 2.47 (1H, m), 3.01 (1H, m), 3.50 (1H, m), 3.52 (3H, s), 3.77 (1H, dd, J = 4.8, 9.4 Hz), 3.92 (1H, m), 4.66 (1H, m), 4.80 (1H, dd, J = 3.4, 13.2 Hz), 7.35−7.45 (6H, m), 7.63−7.67 (4H, m); ^{13}C NMR ($CDCl_3$) δ 19.1, 22.0, 26.7, 28.1, 30.5, 33.9, 36.9, 37.8, 49.8, 51.6, 63.8, 65.6, 78.9, 90.6, 127.6, 129.6, 133.3, 135.39, 156.9, 171.6; [M + 1] 597; HRMS, found 597.2454; $C_{27}H_{37}N_2O_5Si$(M + $C_5H_7O_2$) requires 597.2471.

(4*S*,5*S*,6*R*,8*R*)-8-*tert*-Butyldiphenylsilyloxymethyl-4-nitromethyl-5*β*-methano-hexahydropyrrolizidin-2-one (35). To a solution of **34** (0.252 g, 0.422 mmol) in a mixture THF and water (10 mL, 2:1) was added a 1 M LiOH solution (0.84 mL, 0.84 mmol) at 0 °C. The reaction mixture was stirred for 16 h at room temperature and acidified with a 2% HCl solution (pH <6), and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer were dried (Na_2SO_4), filtered, and concentrated to give the crude acid which was used without further purification.

To a solution of the above acid in CH_2Cl_2 (8.5 mL) was added trifluoroacetic acid (1.2 g, 0.85 mL, 10 mmol) dropwise at 0 °C. The reaction mixture was stirred at this temperature for 2.5 h, the solvent removed under reduced pressure, and the remaining TFA was azeotroped using toluene (3 × 5.0 mL) to give the crude amino acid, which was used directly for cyclization. To a solution of the amino acid in CH_2Cl_2 (30 mL) was added DMAP (0.165 g, 1.35 mmol), followed by HOBt (71 mg, 0.53 mmol) and EDC (100 mg, 0.528 mmol) at 0 °C. The reaction mixture was stirred for 48 h at room temperature and quenched with a saturated solution of $NaHCO_3$ (20 mL), and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with $NaHCO_3$ (2 × 10 mL) and NH_4Cl (20 mL), then dried (Na_2SO_4), filtered, and evaporated under reduce pressure. The resulting residue was purified by silica gel flash chromatography with hexane containing EtOAc (30−50%) to yield **35** as a pale yellow oil (133 mg, 68%): $[\alpha]_D$ +29.5 (c = 0.88, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.70 (1H, dd, J = 4.7, 6.4 Hz), 0.80 (1H, dd, J = 6.4, 9.2 Hz), 1.07 (9H, s), 1.62 (1H, m), 2.23 (1H, dd, J = 8.1, 12.9 Hz), 2.45 (1H, m), 2.60 (1H, ddd, J = 1.1, 10.7, 16.3 Hz), 2.79 (1H, dd, J = 8.9, 16.3 Hz), 3.38 (1H, m), 3.57 (1H, m), 3.96 (1H, dd, J = 2.6, 10.3 Hz), 4.36 (2H, m), 4.44 (1H, dd, J = 5.9, 13.8 Hz), 7.35−7.45 (6H, m), 7.64−7.70 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 16.6, 19.6, 27.1, 33.2, 34.5, 40.1, 54.8, 57.1, 61.1, 76.3, 127.89, 127.92, 129.9, 133.4, 133.7, 135.8, 135.9, 168.2; IR (cm^{-1}) 2932, 1693, 1462, 1428, 1253, 1113; [M + 1] 465; HRMS, found 465.2199; $C_{26}H_{33}N_2O_4Si$ requires 465.2209.

(4*R*,5*S*,6*R*,8*R*)-8-*tert*-Butyldiphenylsilyloxymethyl-4-hydroxymethyl-5*β*-methano-hexahydropyrrolizidin-2-one (36). To a solution of **35** (0.150 g, 0.323 mmol) in MeOH (5.5 mL) was added NaOMe (0.5M in MeOH, 0.68 mL, 0.34 mmol) dropwise at 0 °C. After 15 min, the reaction mixture was cooled to −78 °C, and ozone was then passed through the solution for about 30 min (no obvious change in color). A flow of N_2 was passed through the mixture for several minutes (to remove excess ozone), and $NaBH_4$ (0.122 g, 3.23 mmol) was added in several portions over 1 h and slowly warmed to 0 °C. The reaction mixture was stirred for 30 min at 0 °C and quenched with a saturated solution of NH_4Cl (10 mL), and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with a saturated solution of NaCl (10 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography with hexane containing EtOAc (50−95%) to give **36** as a colorless oil (97.6 mg, 70%): $[\alpha]_D$ +16.1 (c = 1.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.63 (1H, m), 0.99 (1H, dd, J = 5.8, 8.9 Hz), 1.06 (9H, s), 1.48 (1H, dt, J = 4.7, 8.9 Hz), 1.95−2.25 (1H, br s, OH), 2.22 (1H, dd, J = 8.0, 12.8 Hz), 2.42 (1H, ddd, J = 5.6, 8.2, 12.8 Hz), 2.62 (2H, m), 2.94 (1H, m), 3.35 (1H, m), 3.52−3.67 (2H, m), 4.02 (1H, dd, J = 2.8, 10.2 Hz), 4.33 (1H, dd, J = 5.5, 10.2 Hz), 7.32−7.44 (6H, m), 7.65−7.73 (4H, m); ^{13}C NMR ($CDCl_3$) δ 11.7, 16.5, 19.5, 27.0, 34.8, 37.3, 39.4, 54.5, 57.2, 61.3, 63.5, 127.85, 127.87, 129.9, 133.5, 133.8, 135.8, 135.9, 170.3; IR (cm^{-1}) 3378, 3070, 2930, 2856, 1667, 1462, 1427, 1113, 702; [M + 1] 436; HRMS, found 435.2298; $C_{26}H_{33}NO_3Si$ requires 465.2289.

(4*R*,5*S*,6*R*,8*R*)-4-*p*-Bromobenzenesulfonicacid Methyl Ester-8-*tert*-butyldiphenylsilyloxymethyl-5*β*-methano-hexahydropyrrolizidin-2-one (37). To a solution of **36** (15 mg, 0.034 mmol) in pyridine (0.5 mL) was added *p*-bromobenzenesulfonyl chloride (22 mg, 0.086 mmol) at 0 °C. The reaction mixture was stirred for 48 h at room temperature and quenched with a 2% HCl solution (2 mL), and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography with hexane containing EtOAc (20%) to give **37** as a colorless oil (10.6 mg, 48%): $[\alpha]_D$ +9.5 (c = 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.62 (1H, dd, J = 4.6, 6.2 Hz), 0.83 (1H, dd, J = 6.2, 9.1 Hz), 1.04 (9H, s), 1.50 (1H, dt, J = 4.6, 9.1 Hz), 2.20 (1H, dd, J = 8.0, 12.9 Hz), 2.37−2.51 (2H, m), 2.63 (1H, dd, J = 8.9, 16.4 Hz), 3.11 (1H, m), 3.33 (1H, m), 3.93−4.05 (3H, m), 4.33 (1H, dd, J = 5.2, 10.3 Hz), 7.36−7.45 (6H, m), 7.63−7.78 (8H, m); ^{13}C NMR ($CDCl_3$) δ 11.9, 16.4, 19.5, 27.0, 34.4, 34.5, 39.0, 54.6, 56.7, 61.0, 70.5, 127.8, 127.9, 129.5, 129.7, 129.9, 133.0, 133.4, 133.7, 134.7, 135.8, 135.9, 168.7; IR (cm^{-1}) 2931, 1694, 1471, 1367, 1188, 1113; [M + 1,^{79}Br] 654; HRMS, found 654.3356; $C_{32}H_{36}NO_5SSiBr$ requires 654.3350.

(4*R*,5*S*,6*R*,8*R*)-4-Bromomethyl-8-*tert*-butyldiphenylsilyloxymethyl-5*β*-methano-hexahydropyrrolizidin-2-one (38). To a solution of **36** (15 mg, 0.034 mmol) in CH_2Cl_2 (0.5 mL) was added triethylamine (17 mg, 23 μL, 0.17 mmol) followed by methanesulfonyl chloride (10 mg, 0.086 mmol) at 0 °C. The reaction mixture was stirred for 1 h, water (2 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was used without further purification.

To a solution of the above product in THF (2.0 mL) was added LiBr (30 mg, 0.342 mmol) at room temperature. The reaction mixture was heated to reflux for 8 h and quenched with a saturated solution of $NaHCO_3$ (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography with hexane containing EtOAc (50%) to give **38** as a pale yellow oil (15.5 mg, 91%): $[\alpha]_D$ +34.0 (c = 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.64 (1H, dd, J = 4.5, 6.1 Hz), 1.06 (9H, s), 1.08 (1H, m), 1.63 (1H, dt, J = 4.8, 9.3 Hz), 2.24 (1H, dd, J = 8.0, 12.8 Hz), 2.44 (1H, ddd, J = 5.4, 8.0, 12.8 Hz), 2.59 (1H, ddd, J = 1.4, 10.4, 16.4 Hz), 2.75 (1H, dd, J = 8.0, 16.4 Hz), 3.16−3.27 (2H, m), 3.36−3.42 (2H, m), 3.98 (1H, dd, J = 2.7, 10.2 Hz), 4.33 (1H, dd, J = 5.3, 10.2 Hz), 7.36−7.45 (6H, m), 7.64−7.71 (4H, m); ^{13}C NMR ($CDCl_3$) δ 11.5, 16.5, 19.6, 27.0, 32.8, 34.7, 37.7, 42.6, 54.5, 58.0, 61.3, 127.9, 129.9, 133.4, 133.8, 135.8, 135.9, 168.9; IR (cm^{-1}) 2931, 2856, 1693, 1460, 1427, 1113; [M + 1,^{79}Br] 498; HRMS, found 498.3398; $C_{26}H_{32}NO_2SiBr$ requires 498.3489.

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Supporting Information Available: Selected IR and ^{1}H and ^{13}C spectra and X-ray structure data. This material is available free of charge via the Internet at http://pubs.acs.org.

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