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Syntheses of pyrrolizidines and indolizidines from α,β-unsaturated sugar δ-lactones via Dieckmann condensation

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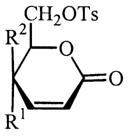
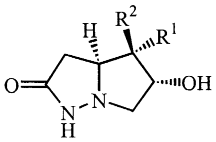
Abstract—Both *N*-methoxycarbonylmethyl- and *N*-methoxycarbonylethyl-derivatives of dihydroxy-(D)-homoproline were subjected to the intramolecular ester condensation to yield ketoesters of pyrrolizidine and indolizidine series, respectively. The former ketoester was transformed into derivative related to australine, while the latter were transformed into the natural lentiginosine as well as its 2-*epi*-, and 7-hydroxy-2-*epi*-derivatives. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Recently, we have reported on the conjugate addition-rearrangement of hydrazine to the α,β-unsaturated sugar δ-lactones **1**–**3**. This transformation constitutes a short and efficient route to the bicyclic pyrazolidinones **4**–**6**, as well as the corresponding mono- and dihydroxy-(D)-homoproline derivatives **7**–**9**,[1] via hydrogenolysis of the N–N bond. Compounds **7**–**9** represent highly functionalized β-amino acids that are suitable for the syntheses of a variety of natural products. Enantioselective syntheses of β-amino acids and their synthetic applications have recently been reviewed.[2]



$R^1 = R^2 = H$ **1**
$R^1 = OBn,\ R^2 = H$ **2**
$R^1 = H,\ R^2 = OBn$ **3**



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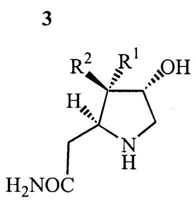

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8
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Some time ago, Buchanan et al.[4] accomplished the synthesis of (+)-crotonecine **11**[4] via initial Dieckmann condensation followed by an additional four-step reaction sequence. The work of Buchanan's group[3] has prompted us to investigate in detail the analogous Dieckmann condensation approach to the synthesis of pyrrolizidine and indolizidine alkaloids,[5–7] starting from (D)-homoproline **8**.

2. Results and discussion

Methanolysis of (D)-homoproline **8** led to the hydrochloride **10** which was silylated at the oxygen atom to give compound **11** in 74% overall yield. N-Alkylation of salt **10** with methyl bromoacetate resulted in formation of the diester **12** in 66% yield. N-Alkylation could also be accomplished using trimethylsilyl bromoacetate. During work-up, the unstable TMS ester underwent facile hydrolysis to provide the corresponding free acid **13** directly.

The presence of a free hydroxyl group in both **12** and **13** offered the possibility of epimerization at the C-4 carbon atom under Mitsunobu conditions, which allowed for easy modification of the stereochemistry of the starting proline **10**. In the case of diester **12**, epimerization proceeded via *p*-nitrobenzoate **15** which was later saponified to give **16**. In the case of acid **13** the epimerization reaction was accompanied by an intramolecular cyclization resulting in the formation of lactone **17**.

Depending on the direction of Dieckmann condensation, application of the Buchanan's methodology[3] to **14** should provide an entry to the skeleton of either heliotridine **18**[8] or australine **19**.[9]

Keywords: δ-lactones; Dieckmann condensation; pyrrolizidines; indolizidines.

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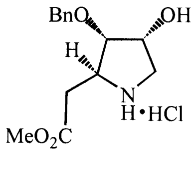

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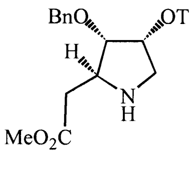

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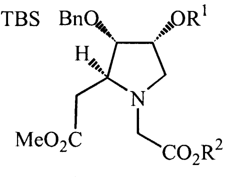
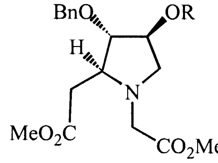
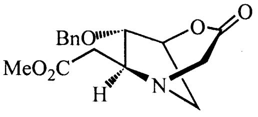


12: $R^1 = H$, $R^2 = Me$
13: $R^1 = R^2 = H$
14: $R^1 = TBS$, $R^2 = Me$



15: R = PNB
16: R = H



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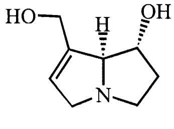

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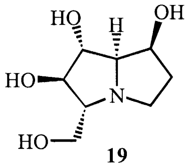

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In the case of compound **14**, our attempts to apply the standard conditions of the Dieckmann condensation that promote formation of the five-membered rings (use of sodium or potassium ethoxide,[7,10] *t*-BuOK,[11] $TiCl_4$,[12] NaH in toluene[13] or diethyl ether,[14] K in toluene,[15] TMS_2NLi[16]) were mostly unsuccessful. Sodium hydride in boiling benzene[13] in the presence of catalytic amount of methanol resulted in racemization at C-2 via a retro-Michael mechanism leading to the formation of a 1:1 mixture of **14** and **20** (Scheme 1).

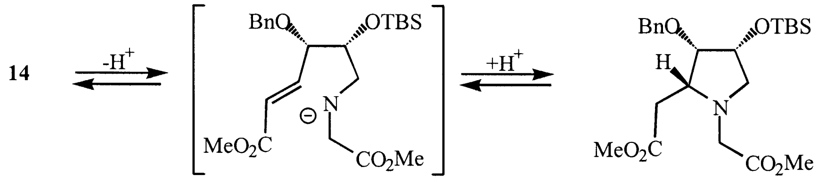
An acceptable yield for the Dieckmann condensation (58%) was finally achieved by employing TMS_2NNa (1 M in THF) at −78°C (Scheme 2). The observed regiochemistry of this reaction was opposite to that reported by Buchanan's group.[3] Ketoester **21**, found to be air-sensitive in the presence of base, was isolated as a sole product.

Reduction of ketoester **21** under an oxygen-free argon atmosphere followed by acetylation of the resulting diol yielded pyrrolizidine **22**. Compound **22** is a structural and configurational isomer of pyrrolizidines such as australine **19**. The stereochemistry assigned to **22** was corroborated by NOE experiments indicating the existence of a spin–spin interaction between H-5, H-6 and H-7a protons. Irradiation of the H-6 signal (at δ 5.22) caused enhancement of resonances of H-7a (δ 3.82) by 1.5%, H-5 (δ 3.04) by 2.9%, and H-7 (δ 2.29) by 4.5%. We detected no spin–spin interactions between H-6 and H-7′ (δ 1.69) and between H-7′ and H-7a protons. The presence of these NOE effects corroborates the configuration assigned to structure **22**.

The regiochemistry of the Dieckmann condensation reported by Buchanan's group[3] is a direct consequence of the presence of a lactone ring, that allows for the desired direction of the condensation reaction exclusively. In our case, however, formation of a carbanion next to the nitrogen atom is preferred. As a result, the insertion of the ketoester fragment occurs at the 5,6- and not at the 6,7-position. Consequently, the reaction yielded products with the skeleton of australine **19**, and not heliotridine **18**.

We decided to investigate whether it would be possible to alter the direction of ester condensation by increasing the electrophilicity of the carbonyl group. We speculated that such an increase could result from attachment of an activator, such as a thiophenol moiety, to the nitrogen atom.

In order to obtain thiophenol derivative **24**, ester **11** was treated with thiophenyl chloroacetate **23**[17] in the presence of pyridine and DMAP. The crude post-reaction mixture was directly treated with TMS_2NLi at −78°C to give indolizidinone **26** and ester **24** in a ratio of about 2:1, respectively, and in 82% overall yield. Compound **26** was identified, after standard acetylation, as the indolizidinone **27**. The presence of both compounds **24** and **26** as products of the ester condensation suggested that the original reaction of ester **11** with thiophenyl chloroacetate **23** led to a mixture of ester **24** and amide **25**. Subsequently, in the presence of lithium amide, *N*-chloroacetyl derivative **25** underwent ester condensation to give indolizidinone **26**, while ester **24** remained unchanged. An attempt to force the Dieckmann



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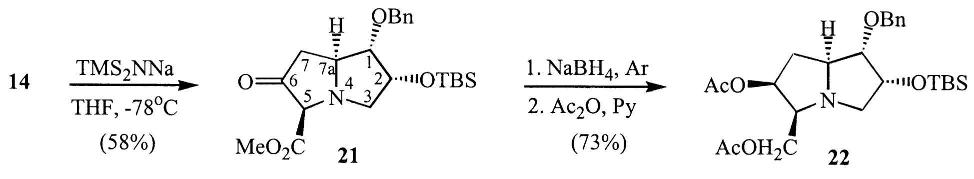
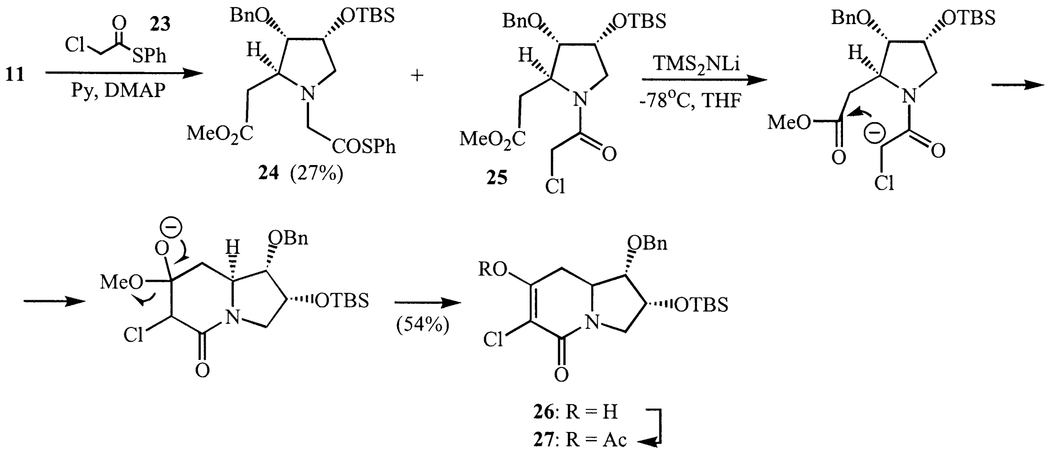
Scheme 1.



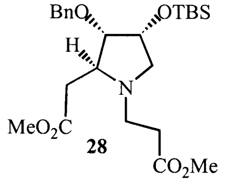
Scheme 2.



Scheme 3.

condensation with ester **24** at higher temperature led to decomposition of the substrate (Scheme 3).

Diester **28** which is a homologue of **14**, formally obtained by an addition of one more carbon atom to the substituent at the nitrogen atom, should provide an entry to indolizidines by the Dieckmann cyclization. Addition of methyl acrylate to the amino group in ester **11**, carried out under standard conditions[18] led to the diester **28** which could be easily transformed into lentiginosine **29** and related compounds. Lentiginosine **29**,[19] isolated from *Astragalus lentiginosus*, 2-*epi*-lentiginosine **30**,[20] isolated from *Rhizoctomia lenguminicola* and 7-hydroxy-lentiginosine **31**[21] are all highly active glycosidase inhibitors. Syntheses of **29**,[22] **30**[23] and **31**[21,22f,g] have been already reported several times in the past.



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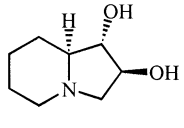

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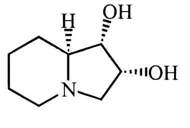

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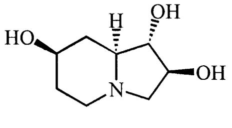

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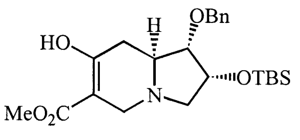
Our attempts to induce the Dieckmann cyclization using diester **28** carried out under standard conditions that should promote the formation of the six-membered ring (use of CH_3ONa in toluene,[24] NaH in benzene with catalytic amount MeOH,[12] K_2CO_3/18-crown-6 in toluene[25]) were unsuccessful. The use of $(TMS)_2NNa$ in THF[26] led to the formation of the expected cyclization product in a low yield (20%). Finally, a satisfactory result was obtained when condensation was carried out using LDA in THF at −78°C. A mixture of two isomeric ketoesters existing as enols **32** and **33**, in approximate ratio 3:1, was obtained in 87% yield. Esters **32** and **33** were separated by chromatography and identified by ^1H NMR spectroscopy.



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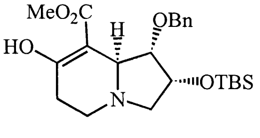

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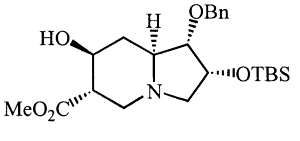

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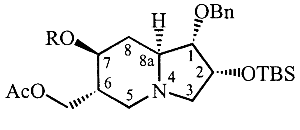


35: R = H
36: R = Ac

We established that the β-keto-ester moiety in the major product **32** can be reduced stepwise with $NaBH_4$ in methanolic solution. Four equivalents of $NaBH_4$ for 15 min at 0°C gave partially reduced ester **34**. When the reduction was carried out at room temperature, with 8 equiv. of $NaBH_4$ for 30 min, both carbonyl functions in ketoester **32** were reduced to give diol **35**, which was identified as diacetate **36**. Separate reduction of monoester **34** under the same conditions led also to diol **35**.

The configuration of diacetate **36** was assigned by NOE experiments in C_6D_6 solution which showed enhancement of the intensity of the H-8a signal (at $\delta=2.50$) by 6% when signal of H-7 ($\delta=4.93$) was irradiated and, conversely, the signal of H-7 was enhanced by 7% when H-8a resonance was irradiated. NOE experiments did not show any interaction between H-6 and H-7 protons. The observed high stereoselectivity of ketoester **32** reduction and configuration found at both C-6 and C-7 in the reduction products **34** and **35** suggest an *exo*-approach of the hydride anion and thermodynamic control of the methoxycarbonyl group position.

Decarboxylation of the mixture of enol esters **32** and **33** in DMSO in the presence of the catalytic amounts of water and NaCl led to the formation of indolizinone **37** in 92% yield.[27] Reduction of ketoester **37** with L-Selectride, followed by acetylation, gave acetate **39** as the sole product. Deoxygenation of ketoester **37** by the modified Wolff–Kishner

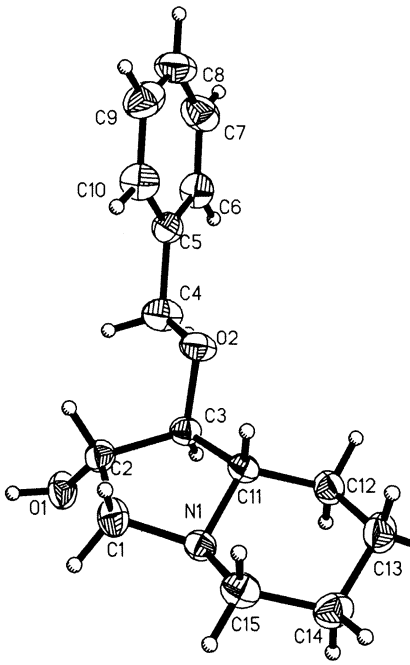
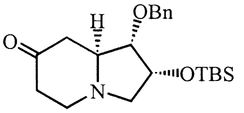


Figure 1. X-Ray structure of 1-*O*-benzyl-lentiginosine (**42**) with crystallographic numbering scheme.

procedure,[22d,28] involving formation of the tosylhydrazone followed by its reduction in situ with $NaBH_3CN$, afforded the 2-*epi*-lentiginosine derivative **40** in 89% yield. The silyl ether in indolizine **40** was removed by treatment with TBAF. The resulting 1-*O*-benzyl-2-*epi*-lentiginosine **41**, treated with *p*-nitrobenzoic acid under Mitsunobu conditions followed by saponification of the intermediate *p*-nitrobenzoate, gave 1-*O*-benzyl-lentiginosine **42**. The structure and absolute configuration of **42** was proved by X-ray crystallography (Fig. 1).[29] It should be noted that the X-ray crystallographic structure of lentiginosine or a simple derivative has not been reported yet. Hydrogenolysis of the benzyl ether in ether **42** with sodium in liquid ammonia led to natural (+)-lentiginosine **29**.



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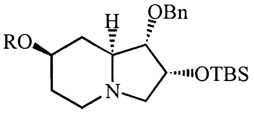
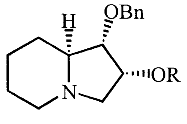
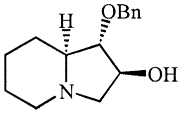


38: R = H
39: R = Ac



40: R = TBS
41: R = H



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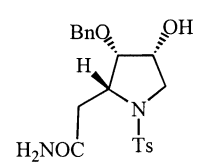
The transformations of diesters **14** and **28** presented above illustrate a convenient synthetic approach to pyrrolizidines and indolizidines with the (*S*)-configuration at the bridgehead carbon atom (C-7a or C-8a, respectively). The configuration at this carbon atom is a direct consequence of the stereochemistry of conjugate addition-rearrangement of hydrazine to the lactones **1–3** with (D)-configuration.

Recently, we have reported on the skeletal rearrangement leading from lactone **43** to the bicyclic compound **45**.[30] Conjugate addition-rearrangement of *N*-benzylhydroxylamine to lactone **43** gave isoxazolidin-5-one **44** which, in turn, was tosylated at the terminal hydroxy group to yield mixture of bicyclic lactones **45** and **46**. Lactone **45** has (L)-homoproline structure (Scheme 4).

Elucidation of the possible reaction pathway leading to these lactones has been proposed by us.[30] Transamination of bicyclic lactone **45** led to the formation of amide **47**. Further debenzylation and detosylation of amide **47** with sodium in liquid ammonia followed by the treatment of resulting intermediate with 2,2-dimethoxypropane and methanolic HCl yielded final ester **48**. Ester **48** represents an entry point to the pyrrolizidines and indolizidines having (*R*)-configuration of the bridgehead carbon atom. The modest overall yield of the transformation of adduct **43** into ester **48** and the presence of non-regiospecific (isopropylidene group) protection of its two hydroxy groups does limit, however, the attractiveness of this reaction sequence when considering further synthetic transformations leading toward swainsonine **49** and related compounds.



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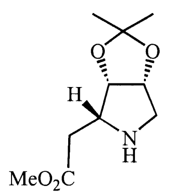

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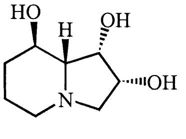

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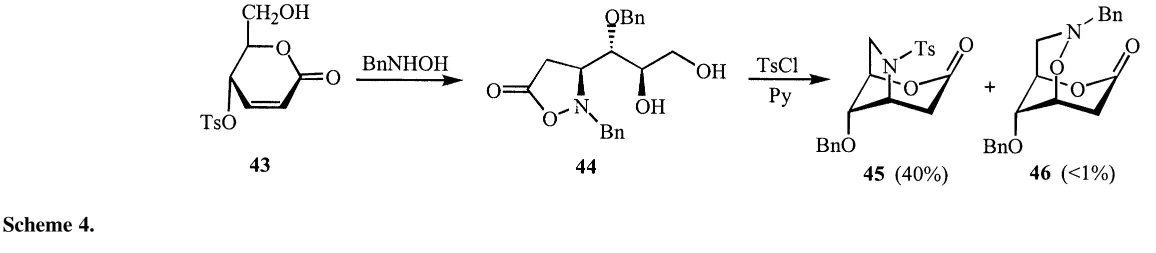
In summary, we have demonstrated that (D)-homoproline derivatives can be employed as attractive starting materials for the syntheses of pyrrolizidines and indolizidines via Dieckmann condensations. This attractiveness was exemplified by the synthesis of pyrrolizidine **22** related to australine, and indolizidines such as natural (+)-lentiginosine **29** (a



Scheme 4.

potent inhibitor of amyloglucosidases) as well as structurally related derivatives **38** and **41**. An early attempt to find an access to the related (L)-homoproline derivatives did not result in a fully satisfactory solution.

3. Experimental

3.1. General

Melting points were determined using a Köfler hot-stage apparatus with microscope. ^1H NMR spectra were recorded on a Bruker Avance 500 and Varian Gemini AC-200 spectrometers for $CDCl_3$ or C_6D_6 solutions using tetramethylsilane as an internal standard and are expressed as δ values. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum 2000 spectrophotometer. Mass spectra were determined using an AMD 604 Inectra GmbH spectrometer. Optical rotation was measured using a JASCO P 3010 polarimeter at ambient temperature. Column chromatography was performed using Merck silica gel (230–400 mesh). All solvents were dried and purified by standard techniques.

Compound **5** was prepared according to the procedure described earlier.[1]

3.1.1. (2*S*,3*S*,4*R*)-3-Benzyloxy-4-*tert*-butyldimethylsiloxy-2-methoxycarbonylmethyl-pyrrolidine (11). Compound **5** (0.20 g, 0.81 mmol) in water (2 mL) was treated with aqueous Raney nickel suspension (600 mg, pH 7). Resulted mixture was stirred for 1.5 h at room temperature. Subsequently, solution was filtered through Celite and evaporated. The crude compound **8** was treated with 10% HCl in methanol (5 mL) and stirred for 4 h. Solvents were removed under reduced pressure and the crude hydrochloride **10** was dissolved in acetonitrile (10 mL), treated with imidazole (0.22 g, 9.24 mmol) and *t*-butyldimethylsilyl chloride (0.18 g, 1.20 mmol). The mixture was stirred overnight at room temperature. Subsequently, the solvent was evaporated and the crude product was purified by chromatography using hexane–ethyl acetate 4:1 v/v and 1% Et_3N as an eluant to give **11** (0.23 g, 74%), syrup, $[\alpha]_D=-101.9$ (*c* 0.4, CH_2Cl_2); IR (film): 3372, 1738, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.74, 4.44 (2d, 2H, J=12.0 Hz, Bn), 4.24 (m, 1H, H-4), 3.64 (s, 3H, OCH_3), 3.60 (m, 1H, H-2), 3.45 (dd, 1H, J=4.5, 7.0 Hz, H-3), 3.11 (dd, 1H, J=4.5, 11.5 Hz, H-5b), 2.93 (dd, 1H, J=4.0, 11.5 Hz, H-5b), 2.62 (dd, 1H, J=4.0, 16.0 Hz, H-1′a), 2.32 (dd, 1H, J=9.0, 16.0 Hz, H-1′b), 0.91 (s, 9H, *t*-Bu), 0.09, 0.10 (2s, 6H, $SiMe_2$); MS (ESI-TOF, HR) *m/z* $(M+H)^+$ calcd for $C_{20}H_{34}NO_4Si$: 380.2252; found: 380.2223.

3.1.2. (2*S*,3*S*,4*R*)-3-Benzyloxy-4-hydroxy-2,*N*-bis-(methoxycarbonylmethyl)-pyrrolidine (12). Hydrochloride **10** obtained as above from **5** (0.90 g, 0.81 mmol) was dissolved in THF (10 mL) and treated with TEA (163 μL, 1.17 mmol) and methyl bromoacetate (54 μL, 0.58 mmol). The mixture was stirred for 5 h at room temperature. Subsequently, it was evaporated and purified by chromatography using hexane–ethyl acetate 3:2 v/v as an eluant to afford **12** (0.18 g, 66%); syrup, $[\alpha]_D=+13.3$ (*c* 1.6, CH_2Cl_2); IR (film): 3485, 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.66, 4.62 (2d, 2H, J=11.5 Hz, Bn), 4.17 (m, 1H, H-4), 3.76 (m, 1H, H-5a), 3.71, 3.65 (2s, 6H, $2OCH_3$), 3.47 (m, 1H, H-2), 3.54, 3.41 (2d, 2H, J=17.2 Hz, H-1′a,1′b), 3.35 (dd, 1H, J=5.8, 12.2 Hz, H-3), 2.71 (dd, 1H, J=4.8, 10.3 Hz, H-5b), 2.56 (dd, 1H, J=5.3, 15.2 Hz, H-1″b), 2.48 (dd, 1H, J=6.8, 15.2 Hz, H-1″b); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{17}H_{24}NO_6$: 338.16037; found: 338.16483.

3.1.3. (2*S*,3*S*,4*R*)-3-Benzyloxy-*N*-carboxymethyl-4-hydroxy-2-methoxycarbonylmethyl-pyrrolidine (13). Compound **13** was obtained according to the procedure described above using TMS bromoacetate; syrup, $[\alpha]_D=-41.5$ (*c* 0.6, CH_3OH); IR (nujol): 3390, 1744, 1627 cm^{-1}; ^1H NMR (CD_3OD) δ: 4.76, 4.54 (2d, 2H, J=11.7 Hz, Bn), 4.39 (m, 1H, H-4), 3.87 (dd, 1H, J=3.8, 8.0 Hz, H-3), 4.01, 3.78 (2d, 2H, J=16.0 Hz, H-1′a,1′b), 3.79 (m, 2H, H-2,5a), 3.65 (s, 3H, OCH_3), 3.26 (dd, 1H, J=2.9, 12.6 Hz, H-5b), 2.87 (d, 2H, H-1″a,1″b); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{16}H_{22}NO_6$: 324.14471; found: 324.14539.

3.1.4. (2*S*,3*S*,4*R*)-3-Benzyloxy-4-*tert*-butyldimethylsiloxy-2,*N*-bis(methoxycarbonylmethyl)-pyrrolidine (14). Silyl ether **11** (0.20 g, 0.53 mmol) in THF (10 mL) was treated with TEA (163 μL, 1.17 mmol), methyl bromoacetate (54 μL, 0.58 mmol) and stirred for 5 h at room temperature. Subsequently, it was evaporated and purified by chromatography using hexane–ethyl acetate 3:2 v/v as an eluant to give **14** (0.20 g, 86%); syrup, $[\alpha]_D=-12.9$ (*c* 0.6, CH_2Cl_2); IR (film): 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.75, 4.52 (2d, 2H, J=11.9 Hz, Bn), 4.27 (m, 1H, H-4), 3.69, 3.60 (2s, 6H, $2OCH_3$), 3.62 (t, 1H, J=4.6 Hz, H-3), 3.57, 3.37 (2d, 2H, J=16.8 Hz, H-1′a,1′b), 3.36 (dd, 1H, J=5.5, 9.4 Hz, H-5a), 3.25 (m, 1H, H-2), 2.66 (dd, 1H, J=6.6, 9.4 Hz, H-5b), 2.54 (dd, 1H, J=5.5, 15.2 Hz, H-1″a), 2.45 (dd, 1H, J=7.0, 15.2 Hz, H-1″b), 0.90, 0.09, 0.07 (3s, 15H, TBS); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{23}H_{38}NO_6Si$: 452.24684; found: 452.24548.

3.1.5. (2*S*,3*S*,4*S*)-3-Benzyloxy-4-hydroxy-*N*-methoxy-carbonylmethyl-pyrrolidine (16). A solution of TPP (0.230 g, 0.89 mmol) and DEAD (140 μL, 0.89 mmol) in dry THF (5 mL) was stirred for 30 min at room temperature and then *p*-nitrobenzoic acid (0.15 g, 0.89 mmol) was added. Stirring was continued for additional 30 min and then compound **12** (0.10 g, 0.29 mmol) in THF (1 mL) was added. The mixture was kept at room temperature for 4 h. Subsequently, solvent was evaporated and residue was extracted with ethyl ether (4×10 mL). Extracts were combined, washed, dried and evaporated. The crude **15** was treated with methanol (5 mL) and K_2CO_3 (0.05 g, 0.32 mmol). After disappearance of the *p*-nitrobenzoate (15 min), the mixture was filtered through Celite and evaporated. The residue was purified by chromatography using hexane–ethyl acetate 4.5:1 v/v as an eluant to afford **16** (0.07 g, 73%); syrup, $[\alpha]_D=+10.7$ (*c* 1.4, CH_2Cl_2); IR (film): 3420, 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.64, 4.57 (2d, 2H, J=11.8 Hz, Bn), 4.11 (m, 1H, H-4), 3.86 (m, 1H, H-3), 3.70, 3.65 (2s, 6H, $2OCH_3$), 3.59, 3.31 (2d, 2H, J=16.8 Hz, H-1′a,1′b), 3.13 (d, 1H, J=10.1 Hz, H-5a), 3.05 (m, 1H, H-2), 2.94 (dd, 1H, J=4.6, 10.1 Hz, H-5b), 2.63 (m, 2H, H-1″a,1″b); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{17}H_{24}NO_6$: 338.16037; found: 338.16091.

3.1.6. (5*S*,6*S*,7*S*)-1-Aza-3-benzyloxy-4-oxa-3-oxo-7-methoxycarbonylmethyl-bicyclo[3.2.1] octane (17). A solution of TPP (0.20 g, 0.75 mmol) and DEAD (118 μL, 0.75 mmol) in dry THF (4 mL) was stirred at room temperature for 30 min and then treated with compound **15** (0.08 g, 0.35 mmol) in THF (1 mL). The mixture was kept at room temperature for 20 h. Subsequently, it was evaporated and purified by chromatography using hexane–ethyl acetate 4:1 v/v as an eluant to give **17** (0.06 g, 82%); syrup, $[\alpha]_D=+16.2$ (*c* 0.9, CH_2Cl_2); IR (film): 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.78 (d, 1H, *J*=1.6 Hz, H-6), 4.65, 4.51 (2d, 2H, *J*=11.8 Hz, Bn), 3.86 (dd, 1H, *J*=2.1, 4.8 Hz, H-5), 3.71 (s, 3H, OCH_3), 3.67 (d, 2H, *J*=0.8 Hz, H-2a,2b), 3.45 (m, 1H, H-7), 3.32 (dd, 1H, *J*=2.1, 12.3 Hz, H-8a), 3.10 (dd, 1H, *J*=12.3 Hz, H-8b), 2.69 (dd, 1H, *J*=6.6, 14.7 Hz, H-1′a), 2.62 (dd, 1H, *J*=9.6, 14.7 Hz, H-1′b); MS (EI, HR) *m/z* M^+ calcd for $C_{16}H_{19}NO_5$: 305.12631; found: 305.12401.

3.1.7. (2*R*,3*S*,4*R*)-3-Benzyloxy-4-*tert*-butyldimethylsiloxy-2,*N*-bis(methoxycarbonylmethyl)-pyrrolidine (20). To a suspension of 60% NaH in mineral oil (0.016 g, 0.39 mmol) in benzene (1 mL) under nitrogen compound **14** (0.055 g, 0.12 mmol) in benzene (1 mL) and methanol (10 μL) was added. The mixture was refluxed for 4 h and then it was cooled to the room temperature, neutralized with acetic acid (250 μL), and poured into saturated solution of $NaHCO_3$. The mixture was extracted with chloroform (3×20 mL). The extract was washed, dried and evaporated. The crude product was separated by chromatography using hexane–ethyl acetate 2:1 v/v as an eluant to give **14** (0.025 g, 45%) and **20** (0.027 g, 49%); syrup, $[\alpha]_D=-15.3$ (*c* 0.2, CH_2Cl_2); IR (film): 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.75, 4.50 (2d, 2H, *J*=11.7 Hz, Bn), 4.45 (m, 1H, H-4), 4.08 (dd, 1H, *J*=4.0, 6.4 Hz, H-3), 3.68, 3.57 (2s, 6H, $2OCH_3$), 3.65 (m, 1H, H-2), 3.60, 3.43 (2d, 2H, *J*=17.9 Hz, H-1′a,1′b), 3.04 (dd, 1H, *J*=3.9, 9.6 Hz, H-5a), 2.99 (dd, 1H, *J*=5.5, 9.6 Hz, H-5b), 2.76 (dd, 1H, *J*=6.4, 16.6 Hz, H-1″a), 2.57 (dd, 1H, *J*=7.0, 16.6 Hz, H-1″b), 0.91, 0.08, 0.07 (3s, 15H, TBS); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{23}H_{38}NO_6Si$: 452.24684; found: 452.24506.

3.1.8. (1*S*,2*R*,5*S*,7a*S*)-1-Benzyloxy-2-*tert*-butyldimethylsiloxy-5-methoxycarbonyl-6-oxo-pyrrolizidine (21). Compound **14** (0.07 g, 0.15 mmol) in dry THF (2 mL) under nitrogen was cooled to −78°C and treated with sodium bis-trimethylsilylamide (TMS_2NNa; 180 μL, 1 M in THF, 0.18 mmol). After 1 h the mixture was poured into saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3×10 mL). The extract was washed, dried, evaporated and purified by chromatography using hexane–ethyl acetate 6:1 v/v as an eluant to give **21** (0.04 g, 58%), syrup, $[\alpha]_D=-91.6$ (*c* 0.4, CH_2Cl_2); IR (film): 3362, 1749, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.70, 4.47 (2d, 2H, *J*=11.9 Hz, Bn), 4.52 (ddd, 1H, *J*=1.3, 4.3, 5.0 Hz, H-2), 4.27 (m, 1H, *J*=6.5, 6.8, 8.6 Hz, H-7a), 3.82 (s, 1H, H-5), 3.81 (dd, 1H, *J*=5.0, 12.8 Hz, H-3), 3.76 (s, 3H, OCH_3), 3.44 (dd, 1H, *J*=4.3, 8.6 Hz, H-1), 3.20 (dd, 1H, *J*=1.1, 12.8 Hz, H-3), 2.38 (dd, 1H, *J*=6.8, 13.9 Hz, H-7), 2.34 (dd, 1H, *J*=6.5, 13.9 Hz, H-7′), 0.91, 0.11, 0.10 (3s, 15H, TBS); MS (ESI-TOF, HR) *m/z* $(M+Na)^+$ calcd for $C_{22}H_{33}NO_5SiNa$: 442.2044; found: 442.2031.

3.1.9. (1*S*,2*R*,5*S*,6*S*,7a*S*)-6-Acetoxy-5-acetoxymethyl-1-benzyloxy-2-*tert*-butyldimethylsiloxy-pyrrolizidine (22). Compound **14** (0.25 g, 0.55 mmol) in dry THF (3 mL) was cooled to −78°C under argon and treated with TMS_2NNa (1.32 mL, 0.6 M solution in toluene, 0.66 mmol). The mixture was stirred for 1 h. Subsequently, it was diluted with CH_2Cl_2 (10 mL), washed with saturated aq. $NaHCO_3$, dried and evaporated. The crude **21** was dissolved in MeOH (2 mL), cooled to 0°C under argon and treated with $NaBH_4$ (0.21 g, 5.5 mmol). The mixture was stirred for 0.5 h, then filtered through Celite and evaporated. The residue was acetylated with acetic anhydride–pyridine mixture 1:2 v/v (10 mL) with addition of DMAP (3 mg). After 4 h, the mixture was evaporated and residue purified by chromatography using hexane–ethyl acetate 9:1 v/v as an eluant to afford **22** (0.19 g, 73%); colorless syrup, $[\alpha]_D=-30.6$ (*c* 0.9, CH_2Cl_2); IR (film): 1743 cm^{-1}; ^1H NMR (C_6D_6) δ: 5.22 (m, 1H, H-6), 4.63, 4.42 (2d, 2H, *J*=12.1 Hz, Bn), 4.31 (m, 1H, *J*=3.1, 4.1, 4.4 Hz, H-2), 4.16 (dd, 1H, *J*=5.6, 11.2 Hz, CH_AH_BOAc), 4.05 (dd, 1H, *J*=6.8, 11.2 Hz, CH_AH_BOAc), 3.82 (m, 1H, H-7a), 3.52 (dd, 1H, *J*=4.1, 7.0 Hz, H-1), 3.36 (dd, 1H, *J*=3.1, 11.1 Hz, H-3), 3.05 (m, 1H, H-5), 2.77 (dd, 1H, *J*=4.4, 11.1 Hz, H-3′), 2.28 (ddd, 1H, *J*=6.2, 7.7, 13.9 Hz, H-7), 1.81 (s, 3H, OAc), 1.69 (m, 1H, H-7′), 1.66 (s, 3H, OAc), 1.08, 0.20, 0.18 (3s, 15H, TBS); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{25}H_{40}NO_6Si$: 478.26249; found: 478.26264.

3.1.10. (2*S*,3*S*,4*R*)-3-Benzyloxy-4-*tert*-butyldimethylsiloxy-*N*-thiophenylcarbonylmethyl-2-methoxycarbonylmethyl-pyrrolidine (24) and (2*S*,3*S*,4*R*)-7-acetoxy-1-benzyloxy-2-*tert*-butyldimethylsiloxy-6-chloro-5-oxo-6-eno-indolizidine (27). Compound **11** (0.20 g, 0.53 mmol) in dry THF (52 mL) was treated with TEA (177 μL, 1.27 mmol), thiophenyl chloroacetate (**23**; 0.12 g, 0.64 mmol) and DMAP (5 mg). The mixture was stirred for 20 h at room temperature. Subsequently, solvent was evaporated and residue was filtered through silica gel bed using hexane–ethyl acetate 4:1 v/v as an eluant. After evaporation of the solvent resulted mixture (**24** and **25**) was dissolved in THF (5 mL), cooled to −78°C and treated under nitrogen with TMS_2NLi (650 μL, 1 M hexane solution, 0.65 mmol) and left for 15 min. Subsequently, acetic acid (250 μL) and acetic anhydride–pyridine mixture 1:2 (10 mL) were added. After 2 h, the solvents were removed under reduced pressure and the mixture was separated by chromatography using hexane–ethyl acetate 4:1 v/v as an eluant to afford **24** (0.08 g, 28%) and **27** (0.13 g, 54%).

Compound **24**: syrup, $[\alpha]_D=-18.5$ (*c* 0.8, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ: 4.70, 4.65 (2d, 2H, *J*=12.1 Hz, Bn), 4.37 (ddd, 1H, *J*=3.6, 4.5, 9.5 Hz, H-5), 4.32 (ddd, 1H, *J*=4.0, 6.6, 7.6 Hz, H-2), 3.79 (dd, 1H, *J*=2.5, 3.9 Hz, H-3), 3.64 (m, 3H, H-1′a, H-5a,5b), 3.59 (s, 3H, OCH_3), 3.51 (dd, 1H, *J*=7.8, 9.5 Hz, H-1′b), 2.88 (dd, 1H, *J*=3.7, 16.2 Hz, H-1″a), 2.36 (dd, 1H, *J*=9.5, 16.2 Hz, H-1″b), 0.90, 0.08, 0.07 (3s, 15H, TBS); MS (LSIMS, HR) *m/z* $(M+Na)^+$ calcd for $C_{28}H_{39}NO_5SiNa$: 552.22059; found: 552.22050.

Compound **27**: mp 124–125°C; $[\alpha]_D=-95.7$ (*c* 0.6, CH_2Cl_2); IR (film): 1771, 1669, 1639 cm^{-1}; ^1H NMR

($CDCl_3$) δ: 4.73 (m, 1H, H-2), 4.73, 4.43 (2d, 2H, *J*=11.8 Hz, Bn), 4.11 (m, 1H, H-8a), 3.59 (m, 3H, H-1,3,3′), 2.67 (dd, 1H, *J*=5.7, 16.6 Hz, H-8), 2.60 (dd, 1H, *J*=13.6, 16.6 Hz, H-8′), 2.26 (s, 3H, OAc), 0.90, 0.12, 0.11 (3s, 15H, TBS); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{23}H_{33}NO_5SiCl$: 446.18165; found: 446.17986.

3.1.11. (2*S*,3*S*,4*R*)-3-Benzyloxy-4-*tert*-butyldimethylsiloxy-*N*-(2′-methoxycarbonylethyl)-2-methoxycarbonylmethyl-pyrrolidine (28). Compound **11** (0.15 g, 0.39 mmol) in ethanol (5 mL) was treated with NEt_3 (324 μL, 2.3 mmol) and methyl acrylate (100 μL, 1.17 mmol). The mixture was stirred for 20 h at room temperature. Subsequently, the solvent was removed under reduced pressure and residue purified by chromatography using hexane–ethyl acetate 7:3 v/v as an eluant to afford **28** (0.16 g, 86%); syrup, $[\alpha]_D=-4.2$ (*c* 1.0, CH_2Cl_2); IR (film): 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.74, 4.53 (2d, 2H, *J*=12.0 Hz, Bn), 4.21 (m, 1H, H-4), 3.63 (t, 1H, *J*=4.5 Hz, H-3), 3.66, 3.61 (2s, 6H, $2OCH_3$), 3.16 (dd, 1H, *J*=5.5, 9.0 Hz, H-5a), 3.08 (m, 2H, H-1′a,2), 2.74 (m, 1H, H-1′b), 2.53 (dd, 1H, *J*=7.5, 9.0 Hz, H-5b), 2.47 (dd, 1H, *J*=5.0, 15.0 Hz, H-1″a), 2.44 (m, 2H, H-2′a,b), 2.37 (dd, 1H, *J*=7.5, 15.0 Hz, H-1″b), 0.91 (s, 9H, *t*-Bu), 0.08, 0.07 (2s, 6H, $SiMe_2$); MS (LSIMS, HR) *m/z* $(M+Na)^+$ calcd for $C_{24}H_{39}NO_6SiNa$: 488.2444; found: 488.24652.

3.1.12. (1*S*,2*R*,8a*S*)-1-Benzyloxy-2-*tert*-butyldimethylsiloxy-7-hydroxy-6-methoxycarbonyl-6-eno-indolizidine (32) and (1*S*,2*R*,8a*S*)-1-benzyloxy-2-*tert*-butyldimethylsiloxy-7-hydroxy-8-methoxycarbonyl-7-eno-indolizidine (33). To the solution of diisopropylamine (78 μL, 0.56 mmol) in dry THF (2 mL), cooled to −78°C under argon *n*-BuLi (2.5 M in hexane, 234 μL, 0.51 mmol) was added. After 20 min, a solution of diester **28** (0.120 g, 0.26 mmol) in THF (1 mL) was added. The mixture was stirred at −30°C for 30 min. Then, while stirring for 15 min, temperature was allowed to rise to room temperature. Subsequently, the mixture was poured into saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3×10 mL). Combined extracts were washed, dried, and evaporated. The residue was separated by chromatography using hexane–ethyl acetate 5:1 v/v as an eluant to afford **32** (0.072 g, 65%) and **33** (0.025 g, 22%).

Compound **32**: syrup, $[\alpha]_D=-137.4$ (*c* 0.7, CH_2Cl_2); IR (film): 1746, 1722, 1662, 1621 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 11.98 (s, 1H, OH), 4.77, 4.47 (2d, 2H, *J*=12.0 Hz, Bn), 4.36 (q, 1H, *J*=6.0 Hz, H-2), 3.75 (s, 3H, OCH_3), 3.60 (d, 1H, *J*=13.5 Hz, H-5), 3.50 (t, 1H, *J*=7.0 Hz, H-1), 3.45 (dd, 1H, *J*=6.0, 10.0 Hz, H-3), 2.91 (dt, 1H, *J*=2.0, 13.5 Hz, H-5′), 2.64 (m, 1H, H-8a), 2.54 (ddd, 1H, *J*=1.5, 4.0, 17.5 Hz, H-8), 2.41 (dd, 1H, *J*=5.5, 10.0 Hz, H-3′), 2.23 (m, 1H, H-8), 0.92 (s, 3H, *t*-Bu), 0.11, 0.10 (2s, 6H, $SiMe_2$); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{23}H_{36}NO_5Si$: 434.2363; found: 434.2344.

Compound **33**: syrup, $[\alpha]_D=-54.4$ (*c* 1.2, CH_2Cl_2); IR (film): 1745, 1718, 1656, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.42 (q, 1H, *J*=6.0 Hz, H-2), 4.74, 4.34 (2d, 2H, *J*=11.0 Hz, Bn), 3.66 (m, 1H, H-1), 3.57 (s, 3H, OCH_3), 3.41 (dd, 1H, *J*=6.5, 9.5 Hz, H-3), 3.27 (m, 1H, H-8a), 3.17 (m, 1H, H-8), 3.05 (dd, 1H, *J*=7.0, 11.0 Hz, H-5), 2.61 (dd, 1H, *J*=3.5, 12.0 Hz, H-6), 2.52 (dd, 1H, *J*=6.5, 12.0 Hz, H-6′), 2.44 (m, 2H, H-3′,5′), 0.90 (s, 9H, *t*-Bu), 0.11, 0.09 (2s, 6H, $SiMe_2$); MS (LSI MS, HR) *m/z* $(M+H)^+$ calcd for $C_{23}H_{36}NO_5Si$: 434.2363; found: 434.2357.

3.1.13. (1*S*,2*R*,6*S*,7*S*,8a*S*)-3-Benzyloxy-2-*tert*-butyldimethylsiloxy-7-hydroxy-6-methoxy-carbonyl-indolizidine (34). To a solution of compound **32** (0.040 g, 0.09 mmol) in methanol (1 mL) at 0°C, $NaBH_4$ (0.014 g, 0.36 mmol) was added over 5 min with stirring. Stirring and low temperature was maintained for 10 min and then the mixture was allowed to warm to room temperature. Subsequently, saturated NaCl solution (5 mL) was added and mixture extracted with chloroform (3×10 mL). The extracts were dried and evaporated. The residue was purified by chromatography using hexane–ethyl acetate 7:3 v/v as an eluant to give **34** (0.031 g, 78%); syrup, $[\alpha]_D=-58.8$ (*c* 0.2, CH_2Cl_2); IR (film): 3461, 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.75, 4.44 (2d, 2H, *J*=12.0 Hz, Bn), 4.39 (m, 1H, H-7), 4.35 (q, 1H, *J*=6.5 Hz, H-2), 3.73 (m, 1H, H-1), 3.71 (s, 3H, OCH_3), 3.36 (m, 2H, H-3,6), 3.01 (dd, 1H, *J*=3.5, 10.0 Hz, H-5), 2.63 (m, 1H, H-8), 2.53 (d, 1H, *J*=2.5 Hz, H-5′), 2.35 (dd, 1H, *J*=6.0, 9.5 Hz, H-3′), 2.15 (dt, 1H, *J*=3.0, 13.5 Hz, H-8a), 1.24 (m, 1H, H-8′), 0.91 (s, 9H, *t*-Bu), 0.09, 0.08 (2s, 6H, $SiMe_2$); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{23}H_{38}NO_5Si$: 436.2519; found: 436.2515.

3.1.14. (1*S*,2*R*,6*S*,7*S*,8a*S*)-7-Acetoxy-6-acetoxymethyl-1-benzyloxy-2-*tert*-butyldimethylsiloxy-indolizidine (36). Compound **34** (0.020 g, 0.04 mmol) in methanol (1.5 mL) was treated with $NaBH_4$ (0.012 g, 0.32 mmol). The mixture was stirred at room temperature for 30 min and filtered through Celite. Filtrate was evaporated under reduced pressure and crude product **35** was acetylated using Ac_2O/Py mixture. The post-reaction mixture was evaporated and purified by chromatography to give **36** (0.016 g, 73%); syrup, $[\alpha]_D=-12.6$ (*c* 0.2, CH_2Cl_2); IR (film): 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.69 (m, 1H, H-7), 4.74, 4.43 (2d, 2H, *J*=12.0 Hz, Bn), 4.34 (q, 1H, *J*=6.5 Hz, H-2), 4.06 (dd, 1H, *J*=3.0, 11.5 Hz, H-1′a), 3.98 (dd, 1H, *J*=6.0, 11.5 Hz, H-1′b), 3.44 (t, 1H, *J*=7.5 Hz, H-1), 3.34 (dd, 1H, *J*=6.5, 9.5 Hz, H-3), 3.07 (dd, 1H, *J*=10.5, 17.0 Hz, H-5), 2.34 (m, 2H, H-8,8a), 2.25 (dd, 1H, *J*=6.0, 9.5 Hz, H-3′), 2.05 (m, 2H, H-5,6), 2.05, 2.03 (s, 6H, 2Ac), 1.25 (m, 1H, H-8′), 0.91 (s, 9H, *t*-Bu), 0.09, 0.08 (2s, 6H, $SiMe_2$); ^1H NMR (C_6D_6) δ: 4.93 (dt, 1H, *J*=5.0, 11.0 Hz, H-7), 4.75, 4.43 (2d, 2H, *J*=12.0 Hz, Bn), 4.25 (m, 1H, H-2), 4.15 (dd, 1H, *J*=3.5, 11.5 Hz, H-1′a), 4.11 (dd, 1H, *J*=6.5, 11.5 Hz, H-1′b), 3.34 (m, 1H, H-1), 3.29 (m, 1H, H-3), 2.96 (dd, 1H, *J*=4.5, 11.0 Hz, H-5), 2.61 (ddd, 1H, *J*=2.5, 5.0, 11.5 Hz, H-8), 2.50 (ddd, 1H, *J*=2.5, 8.0, 11.5 Hz, H-8a), 2.30 (dd, 1H, *J*=5.5, 9.0 Hz, H-3′), 2.20 (m, 1H, H-6), 1.93 (t, 1H, *J*=11.0 Hz, H-5′), 1.78, 1.76 (2s, 6H, 2Ac), 1.40 (m, 1H, H-8′), 1.07 (s, 9H, *t*-Bu), 0.15, 0.13 (2s, 6H, $SiMe_2$); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{26}H_{42}NO_6Si$: 492.2781; found: 492.2763. Reduction of ester **32** under the above conditions yielded **36** (89%) directly.

3.1.15. (1*S*,2*R*,8a*S*)-1-Benzyloxy-2-*tert*-butyldimethylsiloxy-7-oxo-indolizidine (37). To a mixture of **32/33** (0.15 g, 0.33 mmol) dissolved in DMSO (2 mL), water

(18 μL, 0.99 mmol) and NaCl (0.030 g, 0.49 mmol) were added. While stirring, the mixture was kept at 130–140°C under nitrogen for 4 min. Subsequently, it was poured into water and extracted with dichloromethane (3×10 mL). The extracts were dried and evaporated, residue was subject to chromatographic purification using hexane–ethyl acetate 9:1 v/v as an eluant to give **37** (0.12 g, 92%); syrup, $[\alpha]_D=-35.2$ (*c* 0.5, CH_2Cl_2); IR (film): 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.76, 4.43 (2d, 2H, *J*=12.0 Hz, Bn), 4.42 (q, 1H, *J*=6.5 Hz, H-2), 3.52 (t, 1H, *J*=7.0 Hz, H-1), 3.41 (dd, 1H, *J*=6.5, 9.5 Hz, H-3), 3.18 (m, 1H, H-5′), 2.61 (m, 2H, H-8,8a), 2.47 (m, 2H, H-6,6′), 2.35 (dd, 1H, *J*=7.0, 9.5 Hz, H-3′), 2.33 (m, 1H, H-5), 2.13 (dd, 1H, *J*=11.5, 13.5 Hz, H-8′), 0.92 (s, 9H, *t*-Bu), 0.12, 0.10 (2s, 6H, $SiMe_2$); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{21}H_{34}NO_3Si$: 376.2308; found: 376.2318.

3.1.16. (1*S*,2*R*,7*R*,7a*R*)-7-Acetoxy-1-benzyloxy-2-*tert*-butyldimethylsiloxy-indolizidine (39). Compound **37** (0.10 g, 0.27 mmol) in dry THF (2 mL) was cooled to −78°C under argon and treated with L-Selectride (810 μL, 1 M in THF, 0.81 mmol). After 1 h mixture was diluted with THF (10 mL), treated with 3N NaOH (3 mL), 30% H_2O_2 (1 mL) and saturated K_2CO_3 (2 mL). The mixture was stirred for 5 min. Subsequently, organic layer was separated, dried and evaporated. The residue was treated with acetic anhydride–pyridine mixture 1:2 v/v (3 mL) and DMAP (2 mg). After 4 h the mixture was poured into ice/water and extracted with CH_2Cl_2. The extract was dried, evaporated and purified by chromatography to give **39** (0.10 g, 87%); colorless oil, $[\alpha]_D=-53.6$ (*c* 1.6, CH_2Cl_2); IR (film): 1740 cm^{-1}; ^1H NMR (C_6D_6) δ: 4.90 (m, 1H, H-7), 4.75, 4.41 (2d, 2H, *J*=11.9 Hz, Bn), 4.23 (m, 1H, *J*=5.4, 6.5, 6.6 Hz, H-2), 3.44 (dd, 1H, *J*=6.6, 7.9 Hz, H-1), 3.25 (dd, 1H, *J*=6.5, 9.0 Hz, H-3), 2.73 (m, 1H, H-5), 2.46 (m, 2H, H-8,8a), 2.26 (dd, 1H, *J*=3.4, 9.0 Hz, H-3′), 1.95 (m, 2H, H-5′,8′), 1.78 (s, 3H, OAc), 1.70 (m, 1H, H-6), 1.50 (m, 1H, H-6′), 1.04, 0.12, 0.10 (3s, 15H, TBS); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{23}H_{38}NO_4Si$: 420.25701; found: 420.25760.

3.1.17. (1*S*,2*R*,8a*S*)-1-Benzyloxy-2-*tert*-butyldimethylsiloxy-indolizidine (40). Compound **37** (0.060 g, 0.16 mmol) was dissolved in DMF (2 mL), treated with tosylhydrazine (0.060 g, 0.32 mmol) and catalytic amount of *p*-TsOH (2.5 mg). The mixture was heated at 100°C under argon for 1 h. Subsequently it was treated with $NaBH_3CN$ (0.040 g, 0.64 mmol) and heated for additional 2 h. The mixture was then cooled to room temperature, poured into saturated aq. $NaHCO_3$ and extracted with toluene (3×10 mL). The extracts were washed, dried and evaporated. The crude product was purified by chromatography using hexane–ethyl acetate 9:2 v/v as an eluant to afford **40** (0.052 g, 89%); syrup, $[\alpha]_D=-85.8$ (*c* 1.2, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ: 4.77, 4.44 (2d, 2H, *J*=12.0 Hz, Bn), 4.31 (dd, 1H, *J*=6.5, 12.0 Hz, H-2), 3.42 (m, 1H, H-1), 3.34 (dd, 1H, *J*=6.5, 9.5 Hz, H-3), 2.95 (m, 1H, H-5), 2.22 (dd, 1H, *J*=6.0, 9.5 Hz, H-3′), 2.12 (m, 2H, H-8a), 2.05 (m, 2H, H-5′), 1.96 (m, 1H, H-8), 1.77 (m, 1H, H-7), 1.62 (m, 1H, H-6), 1.47 (m, 1H, H-6′), 1.26 (m, 1H, H-7′), 1.14 (m, 1H, H-8′), 0.91 (s, 9H, *t*-Bu), 0.10, 0.09 (2s, 6H, $SiMe_2$); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{21}H_{36}NO_2Si$: 362.2515; found: 362.2536.

3.1.18. (1*S*,2*R*,8a*S*)-1-Benzyloxy-2-hydroxy-indolizidine (41). Compound **40** (0.20 g, 0.55 mmol) in dry THF (5 mL) was treated with TBAF hydrate (0.21 g, 0.66 mmol) and stirred for 30 min. The mixture was poured into water and extracted with toluene (3×10 mL). Combined extracts were dried and evaporated. The crude product was purified by chromatography using hexane–ethyl acetate 4:1 v/v as an eluant to give **41** (0.13 g, 96%); syrup, $[\alpha]_D=-70.5$ (*c* 0.8, CH_2Cl_2); IR (film): 3416 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.67, 4.59 (2d, 2H, *J*=11.5 Hz, Bn), 4.19 (m, 1H, H-2), 3.52 (dd, 1H, *J*=7.0, 8.0 Hz, H-1), 3.45 (dd, 1H, *J*=6.5, 10.0 Hz, H-3), 2.96 (m, 1H, H-5), 2.18 (dd, 1H, *J*=5.0, 10.0 Hz, H-3′), 2.03 (m, 2H, H-5′,8a), 1.93 (m, 2H, H-8), 1.78 (m, 1H, H-7), 1.62 (m, 1H, H-6), 1.47 (m, 1H, H-6′), 1.21 (m, 1H, H-7′,8′); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{15}H_{22}NO_2$: 248.1650; found: 248.1635.

3.1.19. (1*S*,2*S*,8a*S*)-1-Benzyloxy-2-hydroxy-indolizidine (1-*O*-benzyl-lentiginosine) (42). A solution of Ph_3P (0.16 g, 0.60 mmol) in THF (3 mL) was treated with DEAD (95 μL, 0.60 mmol) and stirred for 30 min at room temperature. Subsequently, *p*-nitrobenzoic acid (0.10 g, 0.60 mmol) was added and, after 30 min, compound **41** (0.050 g, 0.20 mmol) in THF (1 mL) was added. The mixture was kept at room temperature until disappearance of the substrate (4 h) and then it was poured into saturated aq. $NaHCO_3$ and extracted with ethyl ether (4×10 mL). Combined extracts were dried and evaporated. Residue was dissolved in methanol (5 mL) and treated with K_2CO_3 (0.03 g, 0.22 mmol). The *p*-nitrobenzoate disappeared after 10 min. Reaction mixture was filtered through Celite, evaporated and purified by chromatography using hexane–ethyl acetate 4:1 v/v to afford **42** (0.041 g, 82%); mp 112–113°C; $[\alpha]_D=-36.0$ (*c* 1.2, CH_2Cl_2); IR (film): 3143 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.70, 4.59 (2d, 2H, *J*=12.0 Hz, Bn), 4.07 (dd, 1H, *J*=1.5, 6.0 Hz, H-2), 3.52 (dd, 1H, *J*=1.5, 7.5 Hz, H-1), 2.98 (m, 1H, H-5), 2.87 (d, 1H, *J*=10.5 Hz, H-3), 2.53 (dd, 1H, *J*=6.0, 10.5 Hz, H-3′), 1.98 (m, 2H, H-5′,8a), 1.89 (m, 1H, H-8), 1.88 (m, 1H, H-7), 1.62 (m, 1H, H-6), 1.54 (m, 1H, H-6′), 1.26 (m, 2H, H-7′,8′); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{15}H_{22}NO_2$: 248.1650; found: 248.1643.

3.1.20. (1*S*,2*S*,8a*S*)-1,2-Dihydroxy-indolizidine, (+)-lentiginosine (29). Compound **42** (0.10 g, 0.405 mmol) in liquid ammonia (2 mL) was cooled to −78°C and treated with sodium (19 mg, 0.83 mmol). Mixture was stirred for 30 min and treated with NH_4Cl until disappearance of color. Ammonia was then evaporated, residue dissolved in THF and filtered through Celite. The solvent was evaporated and residue recrystallized from ethyl acetate–hexane mixture to yield **29** (0.05 g, 78%); mp 106–107°C, $[\alpha]_D=+3.1$ (*c* 0.7, MeOH), lit.[22c] mp 106°C, $[\alpha]_D=+3.0$ (*c* 0.7, MeOH), lit.[22d] mp 106–107°C, $[\alpha]_D=+3.2$ (*c* 0.27, MeOH), lit.[22h] mp 107°C; $[\alpha]_D=+2.8$ (*c* 0.28, MeOH). Spectral data of **29** were identical with those reported previously.[22]

3.1.21. (2*R*,3*S*,4*R*)-3-Benzyloxy-2-carbamoylmethyl-4-hydroxy-*N*-tosyl-pyrrolidine (47). Compound **45** (0.15 g, 0.36 mmol) in THF (1 mL) was treated with 25% aqueous ammonia (2 mL). The mixture was stirred overnight. Subsequently, it was evaporated and purified on a silica gel column using hexane–ethyl acetate 3:2 v/v as an eluant to give **47** (0.14 g, 88%); colorless syrup; $[\alpha]_D=+70.0$ (*c* 0.4, CH_2Cl_2); IR (film): 3455, 3361, 1667, 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.97, 5.61 (2Bs, 2H, NH_2), 4.60, 4.51 (2d, 2H, J=11.5 Hz, Bn), 4.18 (m, 1H, H-4), 3.89 (dd, 1H, J=4.6, 8.9 Hz, H-2), 3.70 (dd, 1H, J=4.6, 7.4 Hz, H-3), 3.45 (dd, 1H, J=3.7, 11.5 Hz, H-5a), 3.25 (dd, 1H, J=5.3, 11.5 Hz, H-5b), 2.94 (s, 1H, H-1a), 2.92 (d, 1H, J=2.1 Hz, H-1′b), 2.43 (s, 3H, Ts); MS (LSIMS, HR) *m/z* $(M+H)^+$ calcd for $C_{20}H_{25}N_2O_5$: 405.1484; found: 405.1486.

3.1.22. (2*R*,3*S*,4*R*)-3,4-*O*-Isopropylidene-2-methoxymethoxycarbonylmethyl-pyrrolidine (48). Compound **47** (0.09 g, 0.22 mmol) in THF (1 mL) was cooled to −78°C and treated with sodium (0.05 g, 2.2 mmol) in liquid ammonia (10 mL). The mixture was stirred at −30°C for 30 min. Subsequently, it was treated with NH_4Cl until disappearance of the color. Ammonia was evaporated, residue dissolved in THF (5 mL) and treated with 2,2-dimethoxypropane (31 μL, 0.31 mmol) and 10% solution of HCl in methanol (3 mL). The mixture was stirred for 24 h. Subsequently the mixture was evaporated and purified by chromatography using hexane–ethyl acetate 1:4 v/v as an eluant to afford **48** (0.043 g, 89%); colorless syrup; $[\alpha]_D=-30.6$ (*c* 1.0, CH_2Cl_2); IR (film): 3356, 1668, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.69 (dd, 1H, J=4.1, 5.6 Hz, H-3), 4.61 (m, 1H, H-4), 3.67 (s, 3H, OMe), 3.03 (m, 1H, H-2), 2.99 (d, 1H, J=13.4 Hz, H-1′a), 2.69 (dd, 1H, J=7.4, 16.4 Hz, H-5a), 2.61 (dd, 1H, J=3.9, 13.4 Hz, H-1′b), 2.58 (dd, 1H, J=6.4, 16.4 Hz, H-5b), 1.27, 1.41 (2s, 6H, CMe_2); MS (ESI-TOF, HR) *m/z* $(M+H)^+$ calcd for $C_{10}H_{18}NO_4$: 216.1221; found: 216.1245.

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