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Synthesis and evaluation of substituted indolizidines as peptidomimetics of RGD tripeptide sequence

Delphine Halie [a], Joëlle Pérard-Viret [a,*], Sylvie Dufour [b,†], Jacques Royer [a]

[a] UMR 8638,CNRS/Université Paris Decsartes, Faculté des Sciences Pharmaceutiques et Biologiques, 4 avenue de l'observatoire, 75270 Paris Cedex 06, France
[b] UMR144, CNRS/Institut Curie, 26 rue d'Ulm, 75248 Paris cedex 05, France

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ABSTRACT

The synthesis of seven peptidomimetics of RGD is presented. The indolizidine building block was obtained by condensation of allylglycine with dimethoxydihydrofuran followed by an intermolecular cyclization. The bicyclic ring was functionalised with a carboxylic acid and a guanidinium appendage. The seven peptidomimetics were evaluated by cell-adhesion assays.

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1. Introduction

Integrins are transmembrane receptors, which regulate cell attachment and response to the extracellular matrix. They are involved in many physiopathological processes: coagulation of blood, tumor-induced angiogenesis, osteoporosis, restenosis, acute renal failure, ocular diseases, metastasis formation, and sickle cell anemia and represent an interesting target for therapeutic.[1]

Among the various known integrins the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptors are of great interest since they are involved in angiogenesis, a target for cancer therapy by inhibiting vascularization of tumors.[2]

The tripeptide Arg-Gly-Asp (RGD) is the motif of recognition of most integrins on several matrix proteins (vitronectin (VN), fibronectin (FN)). The specificity of each integrin depends on the conformation of the triad induced by the other residues.[3]

To date, several inhibitors have been imagined and prepared.[4] A cyclic pentapeptide (*c*(–RGDf[*N*Me]V–) cilengitide) was found quite active while a lot of studies have emerged in order to access peptidomimetics.[5] In these series of compounds, azabicycloalkanes have been developed as versatile scaffolds to mimic peptide conformation.[6] Their bicyclic ring backbone gives geometry with fixed dihedral angles, on which the acid (Asp) and basic (Arg) side chains can be placed at an optimal distance of 13 Å allowing the recognition.

We have been interested in developing the synthesis of several new structures as integrin inhibitors since we recently developed an efficient synthesis of indolizin-3-one.[7] We envisaged it as a scaffold, which could be converted into a potent integrin ligand by introducing a carboxylic and a guanidine appendage (Fig. 1).

2. Results and discussion

In this paper, we report the synthesis and the biological activity of RGD peptidomimetics **1**. On this bicyclic compound, the length and the relative geometry of the two side chains bearing the acid and basic functions can be adapted to optimize the affinity with the receptor. The peptidomimetics were evaluated in vitro by cell-adhesion assays.

2.1. Synthesis of the indolizidine building block

The first step was the condensation of dimethoxydihydrofuran[8] (**2**) with racemic allylglycine (**3**) in acidic medium (Scheme 1).

This condensation led to lactam **4**, which was directly cyclized in refluxing formic acid to give only two diastereoisomers at the C7 position **5** and **6** (60:40), which can be separated through column chromatography. Practically, the crude reaction mixture was used. The formiate was hydrolyzed by $KHCO_3$ (1.1 equiv) in MeOH to yield alcohols **7** and **8** in 86% yield. The hydroxyl group was protected as a benzyl

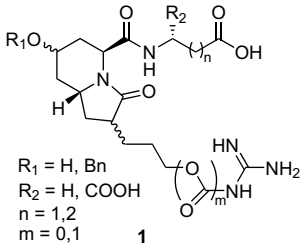

Figure 1.

* Corresponding author. Tel.: +33 1 5373 9748; fax: +33 1 4329 1403.
E-mail addresses: joelle.perard@univ-paris5.fr (J. Pérard-Viret), sylvie.dufour@curie.fr (S. Dufour).
† Tel.: +33 1 5624 6335; fax: +33 1 5624 6349.

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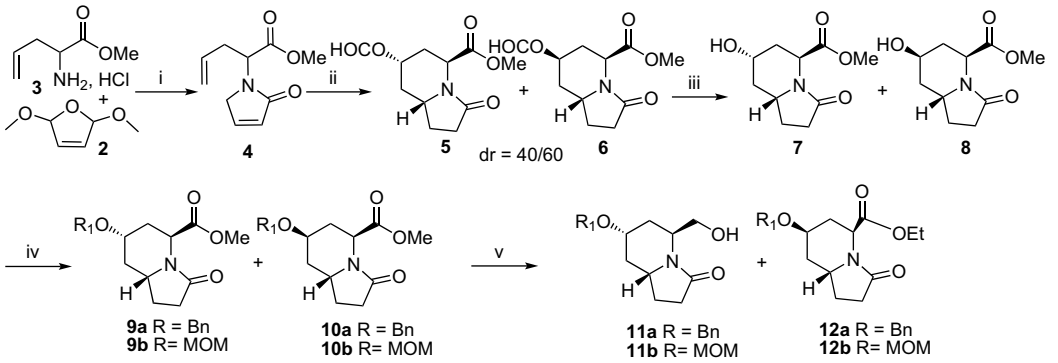


Scheme 1. Synthesis of the indolizidine building block: (i) HCl 1 M; (ii) HCOOH, reflux, 60% (2 steps); (iii) $KHCO_3$ (1.1 equiv), MeOH, 0 °C, 86%; (iv) R_1=Bn, trichloroacetimidate (3 equiv), TfOH (0.25 equiv), C_6H_{12}/CH_2Cl_2, 22 h, 76%; R_1=MOM, $^iPr_2NEt$ (4.5 equiv), MOMCl (4.5 equiv), THF, rt, 2 days, 87%; (v) $NaBH_4$, EtOH, reflux, R_1=Bn, 84%, R_1=MOM, 83%.

or a MOM ether in good yield to give **9a**, **10a** (76%) and **9b**, **10b** (87%), respectively.

Their reaction with $NaBH_4$ in refluxing ethanol allowed an easy separation of the two diastereoisomers. Indeed isomer **10a** and **10b**, which exhibited a cis group were not reduced but just transesterified by ethanol. Compounds **12a**, **12b** and **11a**, **11b** were isolated in 84% and 83% overall yield. NMR studies made it possible to establish a cis-diaxial relationship between the hydroxyl and ester groups in compound **10** (or **12**) and could explain the chemoselectivity of the $NaBH_4$ reduction.

2.2. Functionalization of the indolizidine building block

Having prepared the bicyclic skeleton, we had to introduce the two side chains with an appropriate relative configuration. An allyl group was first introduced (α to the carbonyl of the lactam) to be transformed into the guanidine. This allylation was performed after deprotonation using LDA in tetrahydrofuran and allyl bromide (Scheme 2). Lactams **11a** and **11b** bearing the ether and hydroxyl functions in a trans relationship were deprotonated with 2 equiv of LDA to furnish, after treatment with allyl bromide, **16a**+**17a** (87:13, 46% yield) and **16b**+**17b** (71:29, 54%), respectively. When the allylation was conducted with the diprotected derivative **13** (MOM and TBDMS ether), **14** and **15** were isolated in improved yield and diastereoselectivity (10:90, 88%). It is noteworthy that the diastereoselectivity was inverted compared to the free hydroxyl series. Thus both isomer series can be easily attained by using protected or unprotected alcohol. In all cases, the relative configuration of the allyl group was assigned by NOE experiments.

The next task was to perform the functional group interchanges to obtain the acidic and basic side chains.

We anticipated transforming the allyl group into guanidine. Furthermore, different acid side chains could be obtained from the same intermediates. This transformation was attempted with benzyl ether **16a**. Actually, this synthetic way was not useful: the yield was low (oxidation of the primary alcohol into acid) and purification of the guanidine compound was difficult (several chromatographies were needed). Consequently, we decided to begin with the acid side chain.

In this sequence, we started working on the acid side chain (Scheme 3). Alcohol **16a** was oxidized by Jones reagent to give the acid **18** in good yield (67%). Coupling with β-alanine *tert*-butyl ester and L-aspartic acid di-*tert*-butyl ester furnished **19** (83%) and **20** (88%), respectively.

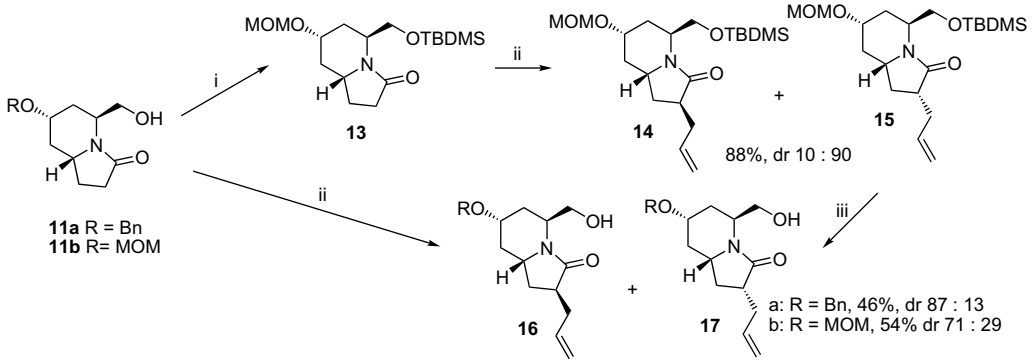
Hydroboration of **19** or **20** gave the alcohols **21** (71%) or **22** (68%). Contrary to several reports, substitution of the hydroxyl group of **21** by a guanidine through a Mitsunobu reaction with DIAD/PPh_3 and di-Boc- or di-Cbz-guanidine was proved to be unsuccessful.[9] We thus investigated the more reactive reagents dipiperidinazodicarboxylate (ADDP) and tributylphosphine (Bu_3P).[10] Surprisingly, use of these reagents led to an unexpected compound: the guanidine carbamate **23**.[11]

Eventually, starting from compound **22**, use of DEAD/PPh_3[4] instead DIAD/PPh_3 permitted to access to the guanidilated product **25**. Boc deprotection with trifluoroacetic acid gave two new mimics **24** and **26**. Hydrogenation on Pd/C of **25** followed by trifluoroacetic acid treatment also gave another analogue **27**.

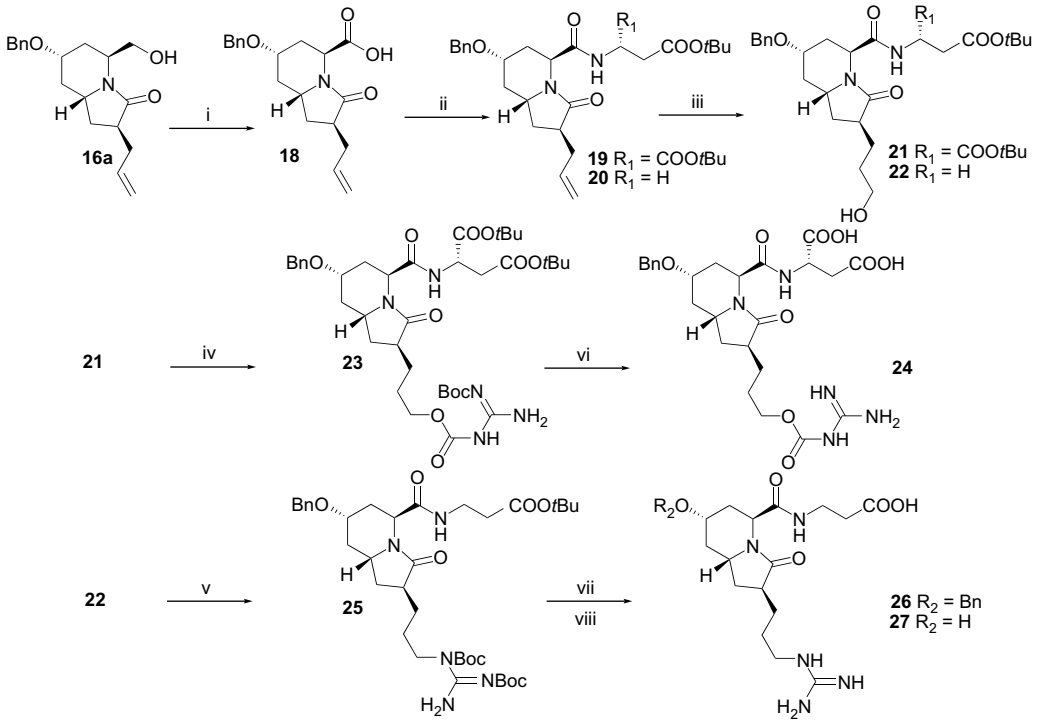
The same sequence was applied to the trans diastereoisomer **17b** (Scheme 4).

Oxidation of alcohol **17b** gave acid **28** in moderate yield (54%), which was coupled with L-glutamic acid di-*tert*-butyl ester (90%). Then after hydroboration of **29** (65%), subsequent reaction of thus obtained **30** with di-Boc-guanidine led to **31** (carbamate) and **33** (guanidinium). TFA-cleavage of the *tert*-butoxy and *tert*-butoxycarbonyl groups of **31** and **33** afforded **32** and **34**, respectively.

We investigated the transformation of compounds **12a**. When these esters reacted with strong bases, a carbanion was



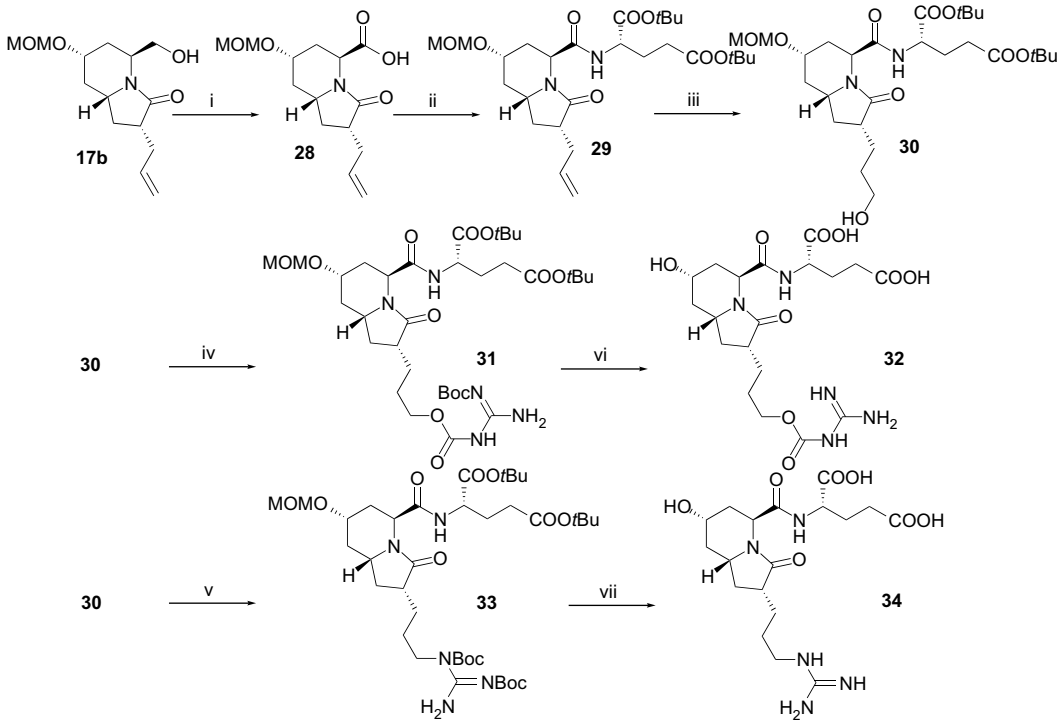
Scheme 2. Allylation of the indolizidine: (i) Et_3N, TBDMSOTf, CH_2Cl_2, −10 °C, 88%; (ii) LDA, −78 °C, allyl bromide, THF; (iii) Bu_4NF, THF, 97%.



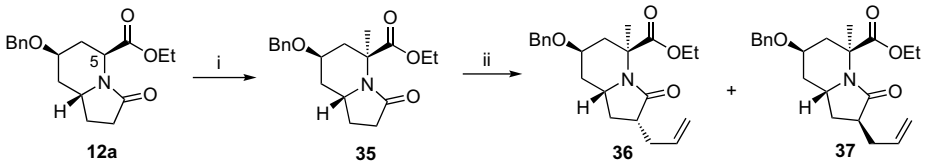
Scheme 3. Functionalization of the cis diastereoisomer: (i) CrO_3, H_2SO_4, acetone, 0 °C, 40 min, 67%; (ii) NMM, ClCOO^{i}Bu, L-BAla-O^{t}Bu or L-Asp(O^{t}Bu)-O^{t}Bu, CH_2Cl_2, R_1=H, 83%, R_1=COO^{t}Bu, 88%; (iii) (a) 9-BBN; (b) H_2O_2, AcONa, R_1=COO^{t}Bu, 68%, R_1=H, 71%; (iv) ADDP, PBu_3, di-Boc-guanidine, toluene, reflux, 2 h, 60%; (v) DEAD, PPh_3, di-Boc-guanidine, THF, rt, 64 h, 92%; (vi) TFA, CH_2Cl_2, 100%; (vii) R_2=Bn, TFA, CH_2Cl_2, 100%; (viii) R_2=H; (a) H_2 Pd/C 10%, 72%; (b) TFA, CH_2Cl_2, 100%.

formed at carbon 5. First, this center was methylated by using KHMDS and methyl iodide in good yield to obtain single diastereoisomer **35** (Scheme 5). Then allylation was performed with the same organic base and allyl bromide, the diastereoselectivity was low (de 20%) and the yield was moderate (55%) (Scheme 5).

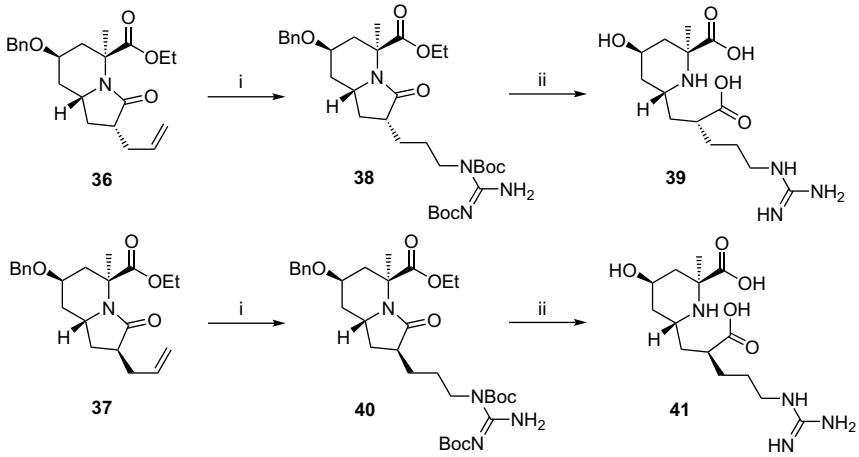
The double bond of **36** and **37** was converted into guanidinium group with DEAD/PPh_3 in good overall yield (54% and 87%, respectively, for 3 steps). Saponification of ethyl ester was very difficult because of the steric hindrance. We checked several bases: NaOH, KOH, KO^{t}Bu, NaSMe, LiSMe, leading to no reaction or degradation of the starting material. Indeed, acidic conditions were



Scheme 4. Functionalization of the trans diastereoisomer: (i) CrO_3, H_2SO_4, acetone, 0 °C, 40 min, 54%; (ii) NMM, ClCOO^{i}Bu, L-Glu(O^{t}Bu)-O^{t}Bu, CH_2Cl_2, 90%; (iii) (a) 9-BBN; (b) H_2O_2, AcONa, 65%; (iv) ADDP, PBu_3, di-Boc-guanidine, THF, reflux, 2 h, 43%; (v) DEAD, PPh_3, di-Boc-guanidine, THF, rt, 64 h, 60%; (vi) TFA, CH_2Cl_2, 100%; (vii) TFA, CH_2Cl_2, 100%.



Scheme 5. Allylation of the trans diaxial diastereoisomer: (i) KHMDS, MeI, THF, 99%; (ii) KHMDS, allyl bromide, 55%, dr 60:40.



Scheme 6. Functionalization and hydrolysis of the trans diaxial diastereoisomer: (i) (a) 9-BBN; (b) H_2O_2, AcONa; (c) DEAD, PPh_3, di-Boc-guanidine, THF, rt (**38**, 54%; **40**, 87%); (ii) EtOH/H_2O, HCl 3 M, 100%.

needed: hydrolysis in aqueous ethanol with 3 M hydrochloric acid at reflux for 20 h gave compounds **39** and **41** of which the amide bond, the benzyl ether were also hydrolyzed (Scheme 6). These compounds **39** and **41** had been also considered as potential peptidomimetics and they have been tested in adhesion assays.

We synthesized seven potential peptidomimetics of RGD in racemic form, in 10 or 11 steps and in 0.6% to 3.4% total yield from racemic allylglycine.

2.3. Biological test of the seven peptidomimetics

The compounds **24**, **26**, **27**, **32**, **34**, **39**, and **41** were evaluated in vitro for their ability to inhibit cell adhesion. Their activity was compared to that of *c*(RGDfV) and GRGES that were used as positive and negative competitors for cell adhesion. We used two different cell lines, mouse sarcoma S180 cells and human vascular endothelial Eahy926 cells. These cells express α5β1 and αvβ3 integrins.[12] The *c*(RGDfV) peptide strongly inhibited S180 cell adhesion to VN (Fig. 2A, black bars) with 19% and 5% of cell adhesion in the presence of 10 μM and 200 μM of its competitor, respectively. This cyclic peptide inhibited less efficiently S180 cell adhesion to FN-coated surface (Fig. 2B, black bars) with 95% and 69% of adhesion in the presence of 10 μM and 500 μM *c*(RGDfV), respectively. In contrast, the control peptide GRGES has no inhibitory effect on the two types of coated surfaces (Fig. 2, white bars). Among the peptidomimetics tested, only compounds **26** and **27** showed inhibitory effect on S180 cell adhesion to VN but they are less efficient compared to the *c*(RGDfV). We measured 65% and 74% of adhesion in the presence of compound **26** or **27** at 200 μM, respectively (Fig. 2A, dashed bars). They did not interfere with S180 cell adhesion to FN-coated surfaces.

The c(RGDfV) peptide also interfered with Eahy926 adhesion to VN but to a lesser extent compared to S180 cell adhesion, with 74.8±7.0% and 9.2±4.4% of adhesion measured at 10 μM and 200 μM *c*(RGDfV). All compounds tested showed no inhibitory effect on Eahy926 adhesion to VN nor FN-coated surfaces.

3. Conclusions

The scaffold of indolizin-3-one was used to prepare seven structures as potential mimics of the RGD tripeptide sequence. These compounds were evaluated in cell-adhesion test. Two of them showed some activities: they possess the acid and guanidine side chains in a cis relationship. This configuration corresponds to the required geometry of a β-turn (type II). Optimization of the length of the side chains and use of optically active allylglycine as starting material are under investigation.

4. Experimental section

4.1. General experimental methods

All commercially available reagents were used without further purification unless otherwise noted. Tetrahydrofuran was freshly distilled from benzophenone ketyl radical under argon prior to use. Column chromatography was performed with silica gel (35–70 mesh). Melting points are reported uncorrected.

NMR spectra were recorded on 300 and 400 MHz Bruker Avance spectrometers. Chemical shifts are reported in parts per million. Coupling constants (*J* values) are reported in hertz. ^{13}C and ^{1}H peak assignments were made based on DEPT, HMQC, HSQC, HSBC, and NOESY data and IR spectra were recorded on a Perkin Elmer 1600 FT-IR spectrometer. MS experiments were performed on a Q-Tof Micromass-1 spectrometer.

4.1.1. (5S,7S*,8aR*)-7-Hydroxy-3-oxo-octahydro-indolizin-5-carboxylic acid methyl ester* **7** *and (5S*,7R*,8aR*)-7-hydroxy-3-oxo-octahydro-indolizin-5-carboxylic acid methyl ester* ***8***

To a solution of formiates **5** and **6** (10.91 g, 45.2 mmol, 1.0 equiv) in 210 mL of anhydrous methanol was added solid $KHCO_3$ (4.54 g, 45.4 mmol, 1.0 equiv) at 0 °C and the reaction was stirred 40 min at 0 °C. $KHCO_3$ was filtered and the filtrate was concentrated in vacuo.

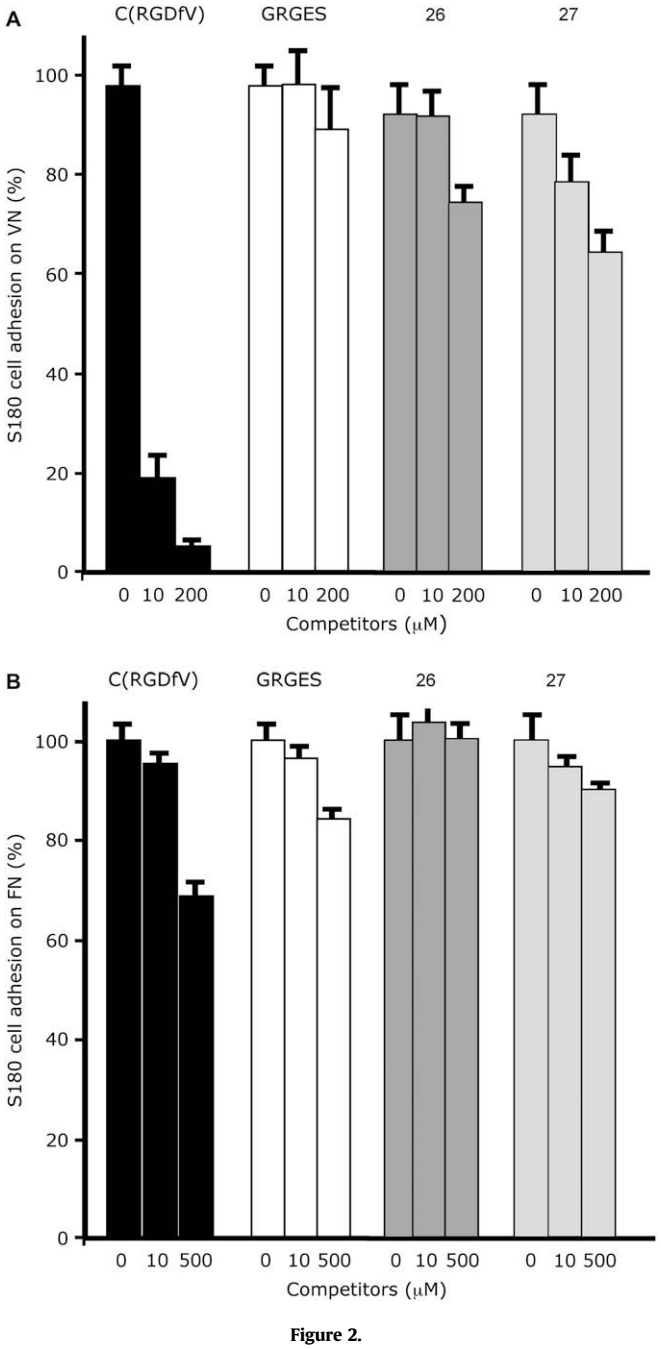


Figure 2.

Purification by flash column chromatography on silica gel (EtOAc/MeOH=95:5 then 90:10) gave **7** and **8** as a yellow solid (8.3 g, 86%).

A sample of each diastereoisomer was obtained.

Compound ***8***: R_f=0.3 (AcOEt/MeOH 90:10), mp: 127 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.30 (1H, ddd, J=13.8, 12.0, 2.2 Hz, H_{8ax}); 1.55 (1H, dddd J=12.4, 9.8, 9.8, 8.5 Hz, H_1); 1.76 (1H, ddd, J=14.3, 7.0, 2.2 Hz, H_{6ax}); 2.01 (1H, dm, J=13.4 Hz, H_{8eq}), 2.23 (1H, dddd, J=12.3, 9.3, 7.1, 3.0 Hz, H_1); 2.3–2.5 (3H, m, $2H_2$, H_6); 3.67 (3H, s, OMe); 4.08 (1H, dddd, J=11.8, 8.0, 8.0, 3.5 Hz, H_{8a}); 4.19 (1H, m, H_{7eq}); 4.68 (1H, d(l), J=6.0 Hz, H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.8 (C_1); 30.2 (C_2); 32.7 (C_6); 38.8 (C_8); 48.1 (C_5); 49.2 (C_{8a}); 52.4 (C_{OMe}); 63.7 (C_7); 171.9, 175.3 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3388, 2962, 1749, 1665, 1441, 1313, 1215, 1090, 1071. MS (ES^+): m/z=236 ($[MNa]^+$). HRMS (ES^+, $[MNa]^+$): calcd for $C_{10}H_{15}NO_4$ 236.0899, found 236.0893.

Compound ***7***: R_f=0.3 (AcOEt/MeOH 90:10), mp: 94 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.1 (1H, ddd, J=11.7, 11.7, 11.7 Hz, H_{8ax}); 1.48 (1H, m, H_6); 1.6 (1H, m, H_1); 2.09 (1H, br d, J=11.8 Hz, H_{8eq}); 2.2 (1H, m, H_1); 2.38 (3H, m, $2H_2$, H_6); 3.66 (4H, br s, OMe, H_7); 3.75 (1H, dddd, J=7.5, 7.5, 7.5, 7.5 Hz, H_{8a}); 4.8 (1H, d(l), J=5.7 Hz, H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.5 (C_1); 30.4 (C_2); 34.7 (C_6); 41.8 (C_8); 50.2 (C_5); 52.6 (OMe); 53.9 (C_{8a}); 65.2 (C_7); 170.9, 174.8 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3432, 2952, 1736, 1666, 1432, 1213. HRMS (ES^+, $[MNa]^+$): calcd for $C_{10}H_{15}NO_4$ 236.0899, found 236. 0909.

4.1.2. (5S,7S*,8aR*)-7-Benzyloxy-3-oxo-octahydro-indolizin-5-carboxylic acid methyl ester* ***9a*** *and (5S*,7R*,8aR*)-7-benzyloxy-3-oxo-octahydro-indolizin-5-carboxylic acid methyl ester* ***10a***

Alcohols **7** and **8** (10.7 g, 50.4 mmol) were dissolved in 40 mL of dichloromethane under argon, and 80 mL of cyclohexane was added. At rt, 19 mL (102 mmol, 2 equiv) of benzyl-trichloroacetimidate was added, followed by 440 μL (5 mmol, 0.1 equiv) of triflic acid. The mixture was refluxed for 16 h, 3 mL of benzyl-trichloroacetimidate was further added and the reflux was continued for 20 h. The mixture was filtered on silica gel and washed with dichloromethane. The filtrate was evaporated and purification by flash column chromatography on silica gel (EtOAc/cyclohexane/MeOH=80:15:5) gave **9a** and **10a** as a colorless oil (13.6 g, 89%).

Compound ***9a***: R_f=0.49 (AcOEt/cyclohexane/MeOH 80:15:5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.16 (1H, ddd, J=11.7, 11.7, 11.7 Hz, H_{8ax}); 1.58 (2H, m, H_1, H_{6ax}); 2.2 (2H, m, H_1, H_{8eq}); 2.38 (2H, m, H_2); 2.55 (1H, dm, J=7, 5 Hz, H_{6eq}); 3.44 (1H, dddd, J=11.3, 11.3, 3.8, 3.8 Hz, H_{7ax}); 3.66 (3H, s, OMe); 3.73 (1H, m, H_{8a}); 4.51 (2H, s, CH_2Ph); 4.89 (1H, d, J=5.6 Hz, H_5); 7.26 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.2 (C_1); 29.9 (C_2); 31.7 (C_6); 38.8 (C_8); 49.8 (C_5); 52.2 (OMe); 53.3 (C_{8a}); 69.9 (CH_2Ph); 72.0 (C_7); 127.4 ($3C_{Ar}$); 128.1 (C_{Ar}); 137.8 ($C_{Ar\text{-}quat}$); 170.9, 174.8 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3352, 2926, 1732, 1682, 1454, 1366, 1291, 1208, 1110. HRMS (ES^+, $[MNa]^+$): calcd for $C_{17}H_{21}NO_4$ 326.1368, found 326.1365.

Compound ***10a***: R_f=0.43 (AcOEt/cyclohexane/MeOH 80:15:5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.29 (1H, ddd, J=13.7, 12.0, 2.2 Hz, H_{8ax}); 1.57 (1H, dddd, J=12.4, 10.5, 10.5, 8.7 Hz, H_1); 1.71 (1H, ddd, J=14.3, 7.0, 2.1 Hz, H_{6ax}); 2.19 (1H, dddd, J=13.4, 13.4, 13.4, 13.4 Hz, H_{8eq}); 2.28 (1H, m, H_1); 2.40 (2H, m, $2H_2$); 2.71 (1H, dddd, J=14.2, 3.3, 1.7, 1.7 Hz, H_{6eq}); 3.51 (3H, s, OMe); 3.84 (1H, br s, H_{7eq}); 4.11 (1H, dddd, J=11.8, 8.4, 8.4, 3.6 Hz, H_{8a}); 4.41 (1H, d, J=11.8 Hz, CH_2Ph); 4.51 (1H, d, J=11.8 Hz, CH_2Ph); 4.74 (1H, d, J=6.0 Hz, H_5); 7.25 (5H, m, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.9 (C_1); 29.3 (C_6); 30.1 (C_2); 37.1 (C_8); 48.2 (C_5); 49.4 (C_{8a}); 52.0 (OMe); 70.1 (CH_2Ph); 70.7 (C_7); 127.0 ($2C_{Ar}$); 127.4 (C_{Ar}); 128.2 (C_{Ar}); 138.2 (C_{Arquat}); 171.0, 174.6 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3448, 2951, 1747, 1696, 1417, 1359, 1293, 1209, 1093. MS (ES^+): m/z 326 ($[MNa]^+$).

4.1.3. (5S,7S*,8aR*)-7-Methoxymethoxy-3-oxo-octahydro-indolizin-5-carboxylic acid methyl ester* ***9b*** *and (5S*,7R*,8aR*)-7-methoxymethoxy-3-oxo-octahydro-indolizin-5-carboxylic acid methyl ester* ***10b***

To alcohols **7** and **8** (371 mg, 1.74 mmol) dissolved in 7 mL of anhydrous THF under argon and cooled to 0 °C, were successively added diisopropylethylamine (860 μL, 5.2 mmol, 3 equiv) and chloromethoxymethane (395 μL, 5.2 mmol, 3 equiv). The mixture was stirred for 20 h, 1.5 equiv of each reagent was added again and stirring was continued for 16 additional hours. After addition of a saturated solution of NH_4Cl, the ester was extracted by CH_2Cl_2, the organic layers were dried ($MgSO_4$), and concentrated under vacuum. Purification by flash column chromatography on silica gel gave 388 mg (87%) of **9b** and **10b**.

Compound ***10b***: R_f=0.39 (AcOEt/cyclohexane/MeOH 80:15:5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.25 (1H, ddd, J=13.6, 11.7, 1.9 Hz, H_{8ax}); 1.52 (1H, m, H_1); 1.66 (1H, ddd, J=14.4, 7.0, 2.0 Hz, H_6); 2.03 (1H,

dm, J=13.4 Hz, H_{8eq}); 2.21 (1H, m, H_1); 2.26–2.44 (2H, m, $2H_2$); 2.48 (1H, br d, J=14.4 Hz, H_{6eq}); 3.26 (3H, s, COOMe); 3.63 (3H, s, OMe); 4.0 (2H, m, H_7, H_{8a}); 4.41 (1H, d, J=6.8 Hz, OCH_2O); 4.55 (1H, d, J=6.8 Hz, OCH_2O); 4.66 (1H, d, J=6.6 Hz, H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.9 (C_1); 29.9 (C_6); 30.2 (C_2); 37.2 (C_8); 48.2 (C_5); 49.5 (C_{8a}); 52.2 (CH_2*OMe*); 55.5 (OMe); 67.7 (C_7); 94.0 (OCH_2O); 171.2, 174.9 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3478, 2950, 1747, 1682, 1417, 1209, 1038, 919. MS (ES$^+$): m/z 280 ([MNa]$^+$). HRMS (ES$^+$, [MH]$^+$): calcd for $C_{12}H_{19}NO_5$ 258.1341, found 258.1351.

Compound ***9b***: R_f=0.46 (AcOEt/cyclohexane/MeOH 80:15:5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.19 (1H, ddd, J=11.7, 11.7, 11.7 Hz, H_{8ax}); 1.61 (2H, m, H1, H_6); 2.24 (2H, m, H1, H_8); 2.3–2.5 (3H, m, H_2, H_6); 3.34 (3H, s, OMe); 3.63 (1H, m, H_7); 3.72 (3H, s, OMe); 3.80 (1H, m, H_{8a}); 4.65 (2H, s, OCH_2O); 4.9 (1H, d, J=5.7 Hz, H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.5 (C_1); 30.2 (C_2); 32.5 (C_6); 39.7 (C_8); 50.1 (C_5); 52.2 (OMe); 53.5 (C_{8a}); 70.9 (C_7); 95.0 (OCH_2O); 170.9, 174.2 (CO, C_3).

4.1.4. *(5S*,7R*,8aR*)-7-Benzyloxy-3-oxo-octahydro-indolizin-5-carboxylic acid ethyl ester* ***12a***

To a mixture of **9a** and **10a** (4.7 g, 15.5 mmol, cis/trans 20:80) dissolved in 250 mL of absolute alcohol, sodium borohydride (6 g, 159 mmol, 10 equiv) was added. The mixture was refluxed for 3 h. After cooling, the solution was concentrated under vacuum, borane precipitates were filtrated and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure and the residue was diluted with CH_2Cl_2 and H_2O, extracted twice by CH_2Cl_2. The organic phase was dried with $MgSO_4$ and evaporated to dryness, where after the residue was purified by flash chromatography on silica gel (EtOAc/MeOH 99:1 to 90:10) to afford 780 mg of **11a** as a light yellow oil (16%, 80% from **10a**) and 2.9 g of **12a** as a white solid (68%, 85% from **9a**).

R_f=0.28 (AcOEt). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.11 (3H, t, J=7.2, CH_3); 1.28 (1H, ddd, J=13.8, 12.0, 2.3 Hz, H_{8ax}); 1.56 (1H, dddd, J=12.4, 9.6, 9.6, 9.1 Hz, H_1); 1.70 (1H, ddd, J=14.4, 7.1, 2.2 Hz, H_{6ax}); 2.10 (1H, ddd, J=13.4, 13.4, 13.4 Hz, H_{8eq}); 2.25 (1H, dddd, J=12.2, 9.4, 6.8, 2.7 Hz, H_1); 2.42 (2H, m, $2H_2$); 2.71 (1H, dddd, J=14.3, 3.2, 1.6, 1.6 Hz, H_{6eq}); 3.83 (1H, m, H_7); 3.92 (1H, dq, J=10.7, 7.2 Hz, OCH_2); 4.02 (1H, dq, J=10.7, 7.2 Hz, OCH_2); 4.11 (1H, dddd, J=11.8, 8.5, 8.5, 3.4 Hz, H_{8a}); 4.41 (1H, d, J=11.9 Hz, CH_2Ph); 4.52 (1H, d, J=11.9 Hz, CH_2Ph); 4.72 (1H, br d, J=5.9 Hz, H_5); 7.27 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 14.0 (CH_3); 26.1 (C_1); 29.3 (C_6); 30.4 (C_2); 37.1 (C_8); 48.4 (C_5); 49.6 (C_{8a}); 61.3 (CH_2O); 70.2 (CH_2Ph); 70.6 (C_7); 94.0 (OCH_2O); 127.1 ($2C_{Ar}$); 127.5 (C_{Ar}); 128.3 ($2C_{Ar}$); 138.4 (C_{Arquat}); 170.7, 174.9 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3468, 2935, 1742, 1694, 1417, 1292, 1198, 1093. MS (ES$^+$): m/z 340 ([MNa]$^+$). HRMS (ES$^+$, [MNa]$^+$): calcd for $C_{18}H_{23}NO_4$ 340.1525, found 340.1534.

4.1.5. *(5S*,7S*,8aR*)-7-Benzyloxy-5-hydroxymethyl-hexahydro-indolizin-3-one* ***11a***

R_f=0.39 (AcOEt/MeOH 90:10), mp: 95 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.17 (1H, ddd, J=11.8, 11.8, 11.8 Hz, H_{8ax}); 1.47 (1H, ddd, J=12.9, 11.6, 6.6 Hz, H_{6ax}); 1.59 (1H, dddd, J=12.5, 9.6, 9.6, 7.3 Hz, H_1); 2.2 (3H, m, H_6, H_{8eq}, H_1); 2.38 (2H, m, H_2); 3.56 (2H, d, J=7.0 Hz, CH_2O); 3.7 (2H, m, H_7, H_{8a}); 4.35 (1H, ddd, J=6.7, 6.7, 6.7 Hz, H_5); 4.54 (2H, s, OCH_2Ph); 7.30 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.7 (C_1); 29.2 (C_2); 29.9 (C_6); 38.4 (C_8); 48.5 (C_5); 52.0 (C_{8a}); 60.5 (CH_2O); 68.7 (CH_2Ph); 70.8 (C_7); 126.2 ($3C_{Ar}$); 127.2 ($2C_{Ar}$); 137.6 (C_{Arquat}); 174.9 (C_3). IR (KBr disc, cm^{-1}): ν_{max} 3319, 2943, 1742, 1664, 1458, 1290, 1100, 1074, 740. HRMS (ES$^+$, [MH]$^+$): calcd for $C_{16}H_{21}NO_3$ 276.1600, found 276.1602. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.33; H, 7.74; N, 4.99%.

4.1.6. *(5S*,7R*,8aR*)-7-Methoxymethoxy-3-oxo-octahydro-indolizin-5-carboxylic acid ethyl ester* ***12b***

To a mixture of **9b** and **10b** 128 mg (0.5 mmol, cis/trans 74:26) dissolved in 10 mL of absolute alcohol, sodium borohydride (189 mg, 5 mmol, 10 equiv) was added. The solution was refluxed for 3 h. After cooling, the solution was concentrated under vacuum, borane precipitates were filtrated, and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure, the residue was diluted with CH_2Cl_2 and 10 mL of H_2O, extracted twice by CH_2Cl_2. The organic phase was dried with $MgSO_4$ and evaporated to dryness, where after the residue was purified by flash chromatography on silica gel (EtOAc/cyclohexane 95:5, 99:1 to EtOAc/MeOH 95:5) to afford 86 mg of **12b** as a colorless oil (63%, 86% from **10b**) and 23 mg of **11b** as a colorless oil (20%, 77% from **9b**).

R_f=0.38 (AcOEt/cyclohexane/MeOH 80:15:5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.10 (3H, t, J=7.2 Hz, CH_2CH_3); 1.25 (1H, ddd, J=13.8, 12.1, 2.2 Hz, H_{8ax}); 1.43 (1H, dddd, J=12.4, 9.8, 9.8, 8.9 Hz, H_1); 1.58 (1H, ddd, J=14.4, 7.1, 2.3 Hz, H_6); 1.95 (1H, ddd, J=13.4, 13.4, 13.4 Hz, H_{8eq}); 2.12 (1H, dddd, J=12.3, 8.3, 5.4, 2.6 Hz, H_1); 2.22 (1H, ddd, J=17.0, 9.7, 2.6 Hz, H_2); 2.29 (1H, m, H_2); 2.40 (1H, dddd, J=14.4, 3.3, 1.7, 1.7 Hz, H_{6eq}); 3.19 (3H, s, OMe); 3.89 (2H, m, H_7, H_{8a}); 3.97 (1H, dq, J=10.8, 7.1 Hz, CH_2O); 4.03 (1H, dq, J=10.8, 7.2 Hz, CH_2O); 4.27 (1H, d, J=6.8 Hz, OCH_2O); 4.43 (1H, d, J=6.7 Hz, OCH_2O); 4.48 (1H, dd, J=6.6, 1.1 Hz, H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 14.1 (CH_3CH_2O); 26.0 (C_1); 29.3 (C_6); 30.3 (C_2); 37.1 (C_8); 48.3 (C_5); 49.5 (C_{8a}); 55.4 (CH_2O*Me*); 61.1 (OCH_2CH_3); 67.7 (C_7); 93.9 (OCH_2O); 170.4, 174.8 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3468, 2938, 1744, 1694, 1417, 1292, 1199, 1038. MS (ES$^+$): m/z 294 ([MNa]$^+$). HRMS (ES$^+$, [MH]$^+$): calcd for $C_{13}H_{21}NO_5$ 272.1498, found 272.1494.

4.1.7. *(5S*,7S*,8aR*)-5-Hydroxymethyl-7-methoxymethoxy-hexahydro-indolizin-3-one* ***11b***

R_f=0.09 (AcOEt/cyclohexane/MeOH 80:15:5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.13 (1H, ddd, J=11.7, 11.7, 11.7 Hz, H_{8ax}); 1.44 (1H, ddd, J=13.2, 13.2, 6.6 Hz, H_6); 1.58 (1H, m, H_1); 2.05 (1H, br d, J=13.2 Hz, H_6); 2.18 (2H, m, H_1, H_{8eq}); 2.35 (2H, m, $2H_2$); 3.30 (3H, s, OMe); 3.57 (2H, br d, J=6.7 Hz, CH_2OH); 3.67 (1H, m, H_{8a}); 3.83 (1H, m, H_7); 4.30 (1H, ddd, J=6.6, 6.6, 6.6 Hz, H_5); 4.62 (2H, br s, OCH_2O). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.4 (C_1); 30.5 (C_2); 31.6 (C_6); 40.3 (C_8); 49.7 (C_5); 53.2 (C_{8a}); 55.4 (CH_2O*Me*); 62.5 (CH_2OH); 70.4 (C_7); 94.9 (OCH_2O); 175.0 (C_3). IR (NaCl disc, cm^{-1}): ν_{max} 2943, 1672, 1656, 1421, 1287, 1111, 1064. HRMS (ES$^+$, [MH]$^+$): calcd for $C_{11}H_{19}NO_4$ 252.1212, found 272.1205.

4.1.8. *(2S*,5S*,7S*,8aR*)-2-Allyl-7-benzyloxy-5-hydroxymethyl-hexahydro-indolizin-3-one* ***16a*** *and (2R*,5S*,7S*,8aR*)-2-allyl-7-benzyloxy-5-hydroxymethyl-hexahydro-indolizin-3-one* ***17a***

A 15 mL LDA solution in THF (from diisopropylamine, 22.1 mmol, 3.1 mL, 2.1 equiv) and BuLi (1.94 M) in hexane (22.1 mmol, 11.4 mL) cooled to −78 °C was cannulated to amide **11a** (10.5 mmol, 2.9 g) in THF (35 mL) maintained at −78 °C under argon. The solution was stirred at the same temperature for 20 min and allyl bromide (11.6 mmol, 1 mL, 1.1 equiv) was slowly added. The mixture was stirred at −78 °C for 2 h and then treated with an aqueous saturated NH_4Cl solution (20 mL). The aqueous phase was extracted several times with CH_2Cl_2. The organic phase was then dried with $MgSO_4$ and the solvent removed in vacuo. The residue was purified by flash chromatography (AcOEt/MeOH 99.5:0.5 to 95:5) to give the two diastereomeric compounds **16a** and **17a** in a 87:13 ratio and a 46% overall yield (827 mg of pure **16a** as a pale yellow oil, 97 mg of pure **17a** as a pale yellow oil and 778 mg of a mixture were isolated).

Compound ***16a***: R_f=0.42 (AcOEt/MeOH: 98/2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 1.17 (1H, ddd, J=11.6, 11.6, 11.6 Hz, H_{8ax}); 1.51 (1H, m, H_6); 1.79 (1H, m, H_1); 2.01 (1H, m, H_1); 2.13–2.28 (3H, m, H_6, H_8, $CH_2CH{=}CH_2$); 2.44 (1H, m, $CH_2CH{=}CH_2$); 2.59 (1H, m, H_2); 3.1 (1H, br s, H–O); 3.5–3.8 (4H, m, CH_2OH, H_{8a}, H_7); 4.38 (1H, ddbr d, J=6.8, 6.8, 6.8 Hz, H_5); 4.55 (2H, s, CH_2Ph); 5.06 (1H, br d, J=9.1 Hz, $CH_2{=}CH$); 5.09 (1H, br d, J=9.1 Hz, $CH_2{=}CH$); 5.77 (1H, dddd, J=16.0, 9.0, 7.0, 7.0 Hz, $CH_2{=}CH$); 7.27 (5H, m, Ar). ^{13}C NMR

(75 MHz, $CDCl_3$): δ_C 30.3 (C_1); 30.8 (C_6); 35.8 ($CH_2CH{=}CH_2$); 39.4 (C_8); 40.9 (C_2); 49.7 (C_5); 51.4 (C_{8a}); 62.4 (CH_2OH); 70.1 (CH_2Ph); 71.8 (C_7); 117.3 ($CH_2{=}CH$); 127.5; 127.6; 128.3 ($2C_{Ar}$, C_{Ar}, $2C_{Ar}$); 135.0 ($CH_2{=}CH$); 138.1 (C_{Arquat}); 176.4 (C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3391, 2942, 1681, 1650, 1454, 1367, 1280, 1094, 917, 739. MS (ES^+): m/z 338 ($[MNa]^+$). HRMS (ES^+, $[MNa]^+$): calcd for $C_{19}H_{25}NO_3$ 338.1732, found 338.1717.

Compound ***17a***: R_f=0.5 (AcOEt/MeOH 98:2). ^1H ($CDCl_3$, 300 MHz): δ_H 1.11 (1H, ddd, J=11.7, 11.7, 11.7 Hz, H_{8ax}); 1.3 (1H, ddd, J=11.3, 11.3, 11.3 Hz, H_1); 1.49 (1H, ddd, J=13.1, 11.6, 6.6 Hz, H_6); 2.1 (2H, m, H_6, $CH_2CH{=}CH_2$); 2.3 (2H, m, H_1, H_8); 2.57 (2H, m, H_2, $CH_2CH{=}CH_2$); 3.1 (1H, br s, H–O); 3.57 (3H, m, H_{8a}, CH_2OH); 3.68 (1H, dddd, J=11.2, 11.2, 4.0, 4.0 Hz, H_7); 4.37 (1H, ddd, J=6.7, 6.7, 6.7 Hz, H_5); 4.52 (2H, s, CH_2Ph); 5.02 (1H, dd, J=10.1, 1.6 Hz, H_{14}, $CH_{2cis}{=}CH$); 5.05 (1H, dd, J=17.1, 1.6 Hz, $CH_{2trans}{=}CH$); 5.71 (1H, dddd, J=16.9, 10.1, 6.8, 6.8 Hz, $CH_2{=}CH$); 7.3 (5H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 31.1 (C_6); 32.4 (C_1); 35.4 ($CH_2CH{=}CH_2$); 40.0 (C_8); 41.3 (C_2); 49.9 (C_5); 51.5 (C_{8a}); 62.5 (CH_2OH); 70.4 (CH_2Ph); 72.0 (C_7); 117.0 ($CH_2{=}CH$); 127.7 ($2C_{Ar}$); 127.8 (C_{Ar}); 128.5 ($2C_{Ar}$); 135.5 ($CH_2{=}CH$); 138.4 (C_{Arquat}); 176.0 (C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3396, 2927, 2867, 1666, 1454, 1367. MS (ES^+): m/z 316 ($[MH]^+$), 338 ($[MNa]^+$), 354 ($[MK]^+$). HRMS (ES^+, $[MNa]^+$): calcd for $C_{19}H_{25}NO_3$ 338.1732, found 338.1732.

4.1.9. *(2S*,5S*,7S*,8aR*)-2-Allyl-5-hydroxymethyl-7-methoxymethoxy-hexahydro-indolizin-3-one* ***16b*** *and (2R*,5S*,7S*,8aR*)-2-allyl-5-hydroxymethyl-7-methoxy-methoxy-hexahydro-indolizin-3-one* ***17b***

The same experimental procedure as described for allylation was applied to lactam **11b** (100 mg, 0.43 mmol) using LDA prepared from diisopropylamine (152 μL, 1.07 mmol, 2.5 equiv) and butyllithium 2.28 M (471 μL, 1.07 mmol, 2.5 equiv). Stirring was maintained 3 h after addition of allyl bromide (41 μL, 0.47 mmol, 1.1 equiv). Flash chromatography on silica gel (AcOEt/MeOH 95:5) allowed the isolation of **16b** and **17b** as a 71:29 ratio in a 54% yield (**17b**: 8 mg as a pale yellow oil, **16b**: 22 mg as a pale yellow oil and 32 mg of a mixture).

Compound ***16b***: R_f=0.38 (AcOEt/MeOH 90:10). ^1H NMR ($CDCl_3$, 300 MHz): δ_H 1.15 (1H, ddd, J=11.7, 11.7, 11.7 Hz, H_{8ax}); 1.33 (1H, m, H_1); 1.55 (1H, ddd, J=13.2, 11.7, 6.7 Hz, H_{6ax}); 2.11 (2H, m, H_{6eq}, $CH_2CH{=}CH_2$); 2.28 (1H, br d, J=12.1 Hz, H_{8eq}); 2.37 (1H, ddd, J=12.6, 8.5, 6.7 Hz, H_1); 2.61 (2H, m, H_2, $CH_2CH{=}CH_2$); 3.39 (3H, s, CH_2OMe); 3.62 (1H, m, H_{8a}); 3.66 (2H, d, J=6.9 Hz, CH_2OH); 3.87 (1H, dddd, J=11.4, 11.4, 4.3, 4.3 Hz, H_{7ax}); 4.4 (1H, ddd, J=6.7, 6.7, 6.7 Hz, H_{5eq}); 4.7 (2H, s, OCH_2O); 5.06 (1H, dd, J=10.1, 1.6 Hz, $CH_2{=}CH$); 5.11 (1H, dd, J=17.1, 1.6 Hz, $CH_2{=}CH$); 5.27 (1H, dddd, J=17.0, 10.1, 6.8, 6.8 Hz, $CH_2{=}CH$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 31.6 (C_6); 32.6 (C_1); 35.4 ($CH_2CH{=}CH_2$); 40.4 (C_8); 41.3 (C_2); 49.8 (C_5); 51.3 (C_{8a}); 55.5 (CH_2OMe); 63.5 (CH_2OH); 70.5 (C_7); 95.0 (OCH_2O); 126.9 ($CH_2{=}CH$); 135.5 ($CH_2{=}CH$); 176.3 (C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3403, 2931, 1667, 1436, 1276, 1151, 1105, 1039, 916. MS (ES^+): m/z 270 ($[MH]^+$), 292 ($[MNa]^+$). HRMS (ES^+, $[MNa]^+$): calcd for $C_{14}H_{23}NO_4$ 292.1525, found 292.1534.

From **15**: to silyl compound **15** (35 mg; 0.87 mmol) dissolved in 14 mL of anhydrous THF was added slowly a solution 1 M of tetrabutylammonium fluoride in THF (2.6 mL, 2.6 mmol, 3 equiv) at 0 °C. Stirring was continued 30 min after removal of the ice bath. At 0 °C 7 mL of water was added and the mixture was extracted three times with dichloromethane. The organic phase was dried with $MgSO_4$ and the solvent removed in vacuo. The residue was purified by flash chromatography (AcOEt/MeOH 97:3) to give **17b** as a pale yellow oil (226 mg, 97%).

Compound ***17b***: R_f=0.44 (AcOEt/MeOH 90:10). ^1H NMR ($CDCl_3$, 300 MHz): δ_H 1.16 (1H, ddd, J=11.6, 11.6, 11.6 Hz, H_{8ax}); 1.48 (1H, ddd, J=13.1, 11.7, 6.7 Hz, H_{6ax}); 1.77 (1H, ddd, J=13.1, 9.5, 6.3 Hz, H_1); 2.0 (1H, m, H_1); 2.07 (1H, ddd, J=13.3, 13.3, 13.3 Hz, H_{6eq}); 2.2 (2H, m, H_{8eq}, $CH_2CH{=}CH_2$); 2.45 (1H, m, $CH_2CH{=}CH_2$); 2.57 (1H, dddd, J=4.3, 4.3, 8.8, 8.8 Hz, H_2); 3.34 (3H, s, CH_2OMe); 3.61 (2H, d, J=7.2 Hz, CH_2OH); 3.65 (1H, m, H_{8a}); 3.85 (1H, dddd, J=11.3, 11.3, 4.2, 4.2 Hz, H_{7ax}); 4.38 (1H, ddd, J=6.7, 6.7, 6.7 Hz, H_{5eq}); 4.65 (2H, d, J=1.2 Hz, OCH_2O); 5.06 (2H, m, $CH_2{=}CH$); 5.76 (1H, dddd, J=17.0, 10.1, 7.0, 7.0 Hz, $CH_2{=}CH$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.3 (C_1); 31.4 (C_6); 35.8 ($CH_2{-}CH{=}CH_2$); 40.0 (C_8); 40.9 (C_2); 49.7 (C_5); 51.4 (C_{8a}); 55.4 (CH_2OMe); 62.5 (CH_2OH); 70.4 (C_7); 94.8 (OCH_2O); 117.3 ($CH_2{=}CH$); 135.1 ($CH_2{=}CH$); 176.4 (C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3397, 2943, 1684, 1441, 1279, 1151, 1105, 1034, 917. MS (ES^+): m/z 270 ($[MH]^+$). HRMS (ES^+, $[MNa]^+$): calcd for $C_{14}H_{23}NO_4$ 292.1525, found 292.1520.

4.1.10. *(5S*,7S*,8aR*)-5-(tert-Butyl-dimethyl-silyloxymethyl)-7-methoxymethoxy-hexahydro-indolizin-3-one* ***13***

Alcohol **11b** (343 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was cooled to −10 °C and triethylamine (525 μL, 3.75 mmol, 2.5 equiv) and *tert*-butyl-dimethylsilyl triflate (444 μL, 1.95 mmol, 1.3 equiv) were added. The solution was stirred between −5 and −10 °C for 30 min and an aqueous saturated $NaHCO_3$ solution (3 mL) was added. The aqueous solution was extracted with CH_2Cl_2. The organic phase was washed with water (2 mL) and then NaCl solution, dried, and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel (ether/MeOH 99.5:0.5). Silyl ether **13** was obtained as a pale yellow oil in 88% yield (453 mg).

R_f=0.45 (ether/MeOH 99:1). ^1H NMR ($CDCl_3$, 300 MHz): δ_H 0.04 (3H, s, SiMe); 0.06 (3H, s, SiMe); 0.89 (9H, s, Si^tBu); 1.15 (1H, ddd, J=11.8, 11.8, 11.8 Hz, H_{8ax}); 1.49 (1H, ddd, J=13.2, 11.8, 6.7 Hz, H_{6ax}); 1.61 (1H, dddd, J=12.4, 9.5, 9.5, 7.5 Hz, H_1); 2.20 (3H, m, H_{6eq}, H_{8eq}, H_1); 2.37 (2H, m, $2H_2$); 3.36 (3H, s, OMe); 3.61 (1H, dd, J=10.0, 4.7 Hz, CH_2O); 3.68 (1H, dd, J=10.0, 6.0 Hz, CH_2OH); 3.76 (1H, dddd, J=11.5, 7.3, 7.3, 3.1 Hz, H_{8a}); 4.06 (1H, dddd, J=11.3, 11.3, 4.2, 4.2 Hz, H_{7ax}); 4.30 (1H, ddd, J=5.8, 5.8, 5.8 Hz, H_{5eq}); 4.68 (2H, s, OCH_2O). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C −5.49, −5.53 (2SiMe); 18.1 ($SiC(CH_3)_3$); 25.7 (C_1); 25.9 ($3SiC(CH_3)_3$); 30.5 (C_2); 32.1 (C_6); 40.1 (C_8); 49.0 (C_5); 54.2 (C_{8a}); 55.3 (OMe); 64.0 (CH_2O); 70.5 (C_7); 94.8 (OCH_2O); 173.8 (C_3). IR (NaCl disc, cm^{-1}): ν_{max} 2886, 1689, 1416, 1257, 1154, 1103, 1041, 837, 777. MS (ES^+): m/z 366 ($[MNa]^+$). HRMS (ES^+, $[MNa]^+$): calcd for $C_{17}H_{33}NO_4Si$ 366.2077, found 366.2072.

4.1.11. *(2S*,5S*,7S*,8aR*)-2-Allyl-5-(tert-butyl-dimethyl-silyloxy-methyl)-7-methoxymethoxy-hexahydro-indolizin-3-one* ***14*** *and (2R*,5S*,7S*,8aR*)-2-allyl-5-(tert-butyl-dimethyl-silyloxy-methyl)-7-methoxymethoxy-hexahydro-indolizin-3-one* ***15***

The same experimental procedure as described for allylation was applied to lactame **13** (120 mg, 0.35 mmol) using LDA prepared from diisopropylamine (63 μL, 0.45 mmol, 1.3 equiv) and butyllithium 2.3 M (195 μL, 0.45 mmol, 1.3 equiv). Stirring was maintained 3 h after addition of allyl bromide (33 μL, 0.39 mmol, 1.1 equiv). Flash chromatography on silica gel (ether) allowed the isolation of **15** and **14** as a 90:10 ratio in a 88% yield (**14**: 12 mg as a yellow oil, **15**: 106 mg as yellow oil).

Compound (2R,5S*,7R*,8aR*)-****15***: R_f=0.66 (AcOEt). ^1H NMR ($CDCl_3$, 300 MHz): δ_H 0.04 (3H, s, SiMe); 0.05 (3H, s, SiMe); 0.87 (9H, s, Si^tBu); 1.1 (1H, ddd, J=11.8 Hz, H_{8ax}); 1.47 (1H, ddd, J=13.6, 11.6, 6.9 Hz, H_{6ax}); 1.73 (1H, ddd, J=13.0, 11.6, 6.9 Hz, H_1); 1.96 (1H, ddd, J=12.9, 7.6, 4.1 Hz, H_1); 2.17 (3H, m, H_6, $CH_2CH{=}CH_2$ H_8); 2.48 (1H, m, $CH_2CH{=}CH_2$); 2.52 (1H, m, H_2); 3.32 (3H, s, OMe); 3.60 (1H, dd, J=10.0, 4.7 Hz, CH_2O); 3.65 (1H, dd, J=10.0, 5.8 Hz, CH_2O); 3.70 (1H, m, H_{8a}); 4.05 (1H, dddd, J=11.3, 11.3, 4.3, 4.3 Hz, H_{7ax}); 4.29 (1H, ddd, J=5.6, 5.6, 5.6 Hz, H_{5ax}); 4.64 (2H, d, J=0.6 Hz, OCH_2O); 5.06 (2H, m, $CH_2{=}CH$); 5.74 (1H, dddd, J=16.9, 10.1, 6.8, 6.8 Hz, $CH_2{=}CH$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C −5.6 (2SiMe); 18.1 ($SiC(CH_3)_3$); 25.8 ($SiC(CH_3)_3$); 30.5 (C_1); 32.1 (C_6); 35.9 ($CH_2CH{=}CH_2$); 39.8 (C_8); 40.7 (C_2); 49.0 (C_5); 52.5 (C_{8a}); 55.6 (OMe); 64.4 (CH_2O); 70.6 (C_7); 94.6 (OCH_2O); 117.1 ($CH_2{=}CH$); 135.2

(CH_2=CH); 175.1 (C_3). IR (NaCl disc, cm^{-1}): ν_{max} 2953, 2856, 1694, 1422, 1257, 1151, 1106, 1037, 916, 837, 777. MS (ES^+): *m/z* 406 ($[MNa]^+$). HRMS (ES^+, $[MNa]^+$): calcd for $C_{20}H_{37}NO_4Si$ 384.2570, found 384.2575.

Compound (2S,5S*,7R*,8aR*)-**14***: R_f=0.86 (AcOEt). ^1H NMR ($CDCl_3$, 300 MHz): δ_H 0.04 (3H, s, SiMe); 0.06 (3H, s, SiMe); 0.89 (9H, s, Si^{t}Bu); 1.1 (1H, ddd, *J*=11.7, 11.7, 11.7 Hz, H_{8ax}); 1.27 (1H, m, H_1); 1.5 (1H, ddd, *J*=11.8, 11.8, 6.9 Hz, H_{6ax}); 2.07–2.28 (3H, m, CH_2 CH=CH_2, H_{8eq}, H_{6eq}); 2.33 (1H, m, H_1); 2.5 (1H, dddd, *J*=9.9, 9.9, 9.9, 3.9 Hz, H_2); 2.65 (1H, ddd, *J*=14.1, 5.3, 5.3 Hz, CH_2 CH=CH_2); 3.36 (3H, s, OMe); 3.64 (3H, m, H_{8a}, CH_2 CH=CH_2); 4.08 (1H, dddd, *J*=11.2, 11.2, 4.0, 4.0 Hz, H_{7ax}); 4.28 (1H, ddd, *J*=5.8, 5.8, 5.8 Hz, H_{5eq}); 4.68 (2H, br s, OCH_2O); 5.06 (2H, m, CH_2=CH); 5.77 (1H, dddd, *J*=17.0, 10.1, 6.9, 6.9 Hz, CH_2=CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C −5.6 (2SiMe); 18.1 (SiC$(CH_3)_3$); 25.8 (SiC$(CH_3)_3$); 32.1 (C_6); 32.9 (C_1); 35.4 (CH_2 CH=CH_2); 40.2 (C_8); 41.3 (C_2); 49.1 (C_5); 52.4 (C_{8a}); 55.2 (OMe); 63.9 (CH_2O); 70.6 (C_7); 94.8 (OCH_2O); 116.7 (CH_2=CH); 135.7 (CH_2=CH); 174.5 (C_3). IR (NaCl disc, cm^{-1}): ν_{max} 2930, 1691, 1419, 1255, 1104, 1042, 840. MS (ES^+): *m/z*=384 ($[MH]^+$), 406 ($[MNa]^+$). HRMS (ES^+, $[MNa]^+$): calcd for $C_{20}H_{37}NO_4Si$ 406.2390, found 406.2386.

4.1.12. (2S*,5S*,7S*,8aR*)-2-Allyl-7-benzyloxy-3-oxo-octahydro-indolizin-5-carboxylic acid ***18***

To alcohol **16a** (757 mg, 2.4 mmol) dissolved in 22 mL in acetone was added dropwise Jones reagent 2.67 M (1.1 mL, 2.9 mmol, 1.2 equiv) at 0 °C. Stirring was continued for 40 min, 10 mL of isopropanol was added, and the mixture was stirred for 20 min at 0 °C. After addition of 0.5 mL of water and 5 mL of 1 M HCl, the mixture was extracted twice with 100 mL of dichloromethane. The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel (AcOEt/MeOH/AcOH 96:2:2) and the carboxylic acid **23** was isolated as a beige solid (67%, 530 mg).

R_f=0.27 (AcOEt/MeOH/AcOH 96:2:2), mp: 146 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H 1.18 (1H, ddd, *J*=11.7, 11.7, 11.7 Hz, H_{8ax}); 1.36 (1H, m, H_1); 1.63 (1H, ddd, *J*=12.1, 12.1, 6.7 Hz, H_6); 2.18 (1H, m, CH_2CH=CH_2); 2.27–2.4 (2H, m, H_1, H_8); 2.58–2.69 (3H, m, H_6, H_2, CH_2CH=CH_2); 3.57 (1H, m, H_7); 3.72 (1H, m, H_{8a}); 4.54 (1H, d, *J*=9.1 Hz, CH_2Ph); 4.59 (1H, d, *J*=9.1 Hz, CH_2Ph); 4.91 (1H, br d, *J*=6.2 Hz, H_5); 5.03–5.13 (2H, m, CH_2=CH); 5.75 (1H, dddd, *J*=16.9, 10.1, 6.8, 6.8 Hz, CH_2=CH); 7.31 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 31.9 (C_6); 32.4 (C_1); 35.0 (CH_2CH=CH_2); 39.2 (C_8); 41.4 (C_2); 50.5 (C_5); 52.4 (C_{8a}); 70.6 (CH_2Ph); 72.7 (C_7); 117.3 (CH_2=CH); 127.7; 127.9; 128.6 ($2C_{Ar}$, C_{Ar}, $2C_{Ar}$); 135.2 (CH_2=CH); 138.1 (C_{Arquat}); 173.1 (COOH); 176.4 (C_3). MS (ES^+): *m/z* 352 ($[MNa]^+$).

4.1.13. (2S)-2-[(2S*,5S*,7S*,8aR*)-(2-Allyl-7-benzyloxy-3-oxo-octahydro-indolizin-5-carbonyl)-amino]succinic acid di-tert-butyl ester ***19***

To carboxylic acid **18** (55 mg, 0.167 mmol) dissolved in 1.5 mL of anhydrous dichloromethane was added *N*-methylmorpholine (NMM) (20 μL, 0.18 mmol, 1.1 equiv) at −10 °C under argon, and the mixture was stirred for 30 min at the same temperature. Isobutyl chloroformiate (23 μL, 0.18 mmol, 1.1 equiv) was added dropwise and stirring was continued for 1 h at −10 °C. The amino acid (51 mg, 0.18 mmol, 1.1 equiv) was dissolved in 1.5 mL of anhydrous dichloromethane under argon and NMM (40 μL, 0.36 mmol, 2.2 equiv) was added at 0 °C. This solution was stirred for 30 min and added via a syringe to the mixed anhydride solution. Stirring was continued for 20 h at rt. The residue was taken off with 10 mL of ethyl acetate, washed with 5 mL of 10% Na_2CO_3 solution, 5 mL of 10% $KHSO_4$ solution, and 5 mL of brine. The organic phase was dried over Na_2SO_4 and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel (AcOEt/cyclohexane 25:75 to 70:30) and the compound was isolated as a white foam (88%, 65 mg).

Two diastereoisomers: R_f=0.53 (AcOEt/cyclohexane 40:60). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 1.16/1.17 (1H, ddd, *J*=11.8, 11.8, 11.8 Hz, H_{8ax}); 1.23–1.52 (20H, m, H_1, H_6, 2C$(CH_3)_3$); 2.11–2.5 (3H, m, H_1, CH_2CH=CH_2, H_8); 2.51–2.9 (5H, m, CH_2CH=CH_2, CH_2CO, H_2, H_6); 3.58–3.89 (2H, m, H_7, H_{8a}); 4.51–4.67 (3H, m, CH_2Ph, NH*CH*CO); 4.85 (1H, br d, *J*=6.2 Hz, H_5); 5.02–5.14 (2H, m, CH_2=CH); 5.67–5.84 (1H, m, CH_2=CH); 6.96/7.20 (1H, d/d, *J*=8.0/8.6 Hz, NH); 7.23–7.37 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 27.9 and 28.0 (C$(CH_3)_3$); 30.8/31.2, 32.2/32.4, 35.1, 37.2/37.3 (C_6, C_1, CH_2CH=CH_2, CH_2CO); 39.6/39.7 (C_8); 40.9/41.0 (C_2); 49.1/49.3, 50.9, 52/52.1 (C_5, C_{8a}, NH*CH*CO); 70.5 (CH_2Ph); 72.4 (C_7); 81.6/81.9 and 82.2/82.4 (C$(CH_3)_3$); 117 (CH_2=CH); 127.6; 128.3 ($2C_{Ar}$, C_{Ar}, $2C_{Ar}$); 135.3 (CH_2=CH); 138.1 (C_{Arquat}); 169.2/169.3, 169.5/169.5, 169.9/170, 175.6/175.7 (3CO, C_3). HRMS (ES^+, $[MNa]^+$): calcd for $C_{31}H_{44}N_2O_7$ 579.3046, found 579.3019.

4.1.14. 3-[(2S*,5S*,7S*,8aR*)-(2-Allyl-7-benzyloxy-3-oxo-octahydro-indolizin-5-carbonyl)-amino]propionic acid tert-butyl ester ***20***

The same experimental procedure as described for peptide coupling was applied to carboxylic acid **18** (136 mg, 0.41 mmol) using NMM (50 μL, 0.45 mmol, 1.1 equiv) and isobutyl chloroformiate (60 μL, 0.45 mmol, 1.1 equiv). Stirring was maintained 20 h after addition of amino acid (82 mg, 0.45 mmol, 1.1 equiv) and NMM (100 μL, 0.9 mmol, 2.2 equiv). Flash chromatography on silica gel (AcOEt/cyclohexane 50:50 to 70:30) allowed the isolation of a colorless oil (83%, 154 mg).

R_f=0.45 (AcOEt/cyclohexane 60:40). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 1.17 (1H, ddd, *J*=11.8, 11.8, 11.8 Hz, H_{8ax}); 1.2–1.5 (11H, m, H_1, H_6, 2C$(CH_3)_3$); 2.18 (1H, m, H_1); 2.29 (1H, br d, *J*=12 Hz, H_8); 2.35 (1H, m, CH_2CH=CH_2); 2.41 (2H, t, *J*=6 Hz, NHCH_2CH_2CO); 2.52–2.7 (3H, m, H_2, H_6, CH_2CH=CH_2); 3.32–3.52 (2H, m, NHCH_2CH_2CO); 3.57 (1H, m, H_{8a}); 3.9 (1H, dddd, *J*=11, 11, 4.5, 4.5 Hz, H_7); 4.57 (1H, d, *J*=11.6 Hz, CH_2Ph); 4.63 (1H, d, *J*=11.6 Hz, CH_2Ph); 4.78 (1H, d, *J*=5.9 Hz, H_5); 5.02–5.12 (2H, m, CH_2=CH); 5.77 (1H, dddd, *J*=15, 12, 5.9, 5.9 Hz, CH_2=CH); 6.65 (1H, br s, NH); 7.25–7.4 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 28.1 (C$(CH_3)_3$); 30.9 (C_6); 32.3 (C_1); 35.1 (CH_2CH=CH_2, NHCH_2CH_2CO); 39.5 (C_8); 41.1 (C_2); 50.9 (C_5); 52.1 (C_{8a}); 70.5 (CH_2Ph); 72.4 (C_7); 81.1 (C$(CH_3)_3$); 117.1 (CH_2=CH); 127.6; 128.4 ($2C_{Ar}$, C_{Ar}, $2C_{Ar}$); 135.2 (CH_2=CH); 138.5 (C_{Arquat}); 169.9, 171.4, 176.4 (2CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3307, 2929, 1727, 1682, 1427, 1278, 1156, 737. MS (ES^+): *m/z* 479 ($[MNa]^+$).

4.1.15. (S)-2-[[(2S*,5S*,7S*,8aR*)-7-Benzyloxy-2-(3-hydroxy-propyl)-3-oxo-octahydro-indolizin-5-carbonyl]-amino]-succinic acid di-tert-butyl ester ***21***

The same experimental procedure as described for hydroboration was applied to alkene **19** (81 mg, 0.14 mmol) using a 0.5 M solution of 9-BBN (1.5 mL, 0.73 mmol, 5 equiv). Stirring was maintained 15 h after addition of sodium acetate 5 M (570 μL, 2.8 mmol, 20 equiv) and a 30% H_2O_2 solution (0.160 mL, 22 equiv). Flash chromatography on silica gel (AcOEt/cyclohexane 50:50 to 90:10) allowed the isolation of a yellow oil (68%, 57 mg).

Two diastereoisomers: R_f=0.16 (AcOEt/cyclohexane 90:10). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 1.13/1.15 (1H, ddd/ddd, *J*=11.7, 11.7, 11.7 Hz, H_8); 1.3–1.98 (23H, m, H_6, 2C$(CH_3)_3$, $CH_2CH_2CH_2OH$); 2.27 (1H, m, H_8); 2.32–2.87 (5H, m, H_1, CH_2CO, H_2, H_6); 3.6–3.66 (3H, m, CH_2OH, H_{8a}); 3.72–3.82 (1H, m, H_7); 4.5–4.64 (3H, m, CH_2Ph, NH*CH*CO); 4.79/4.85 (1H, m, H_5); 6.74/6.82 (1H, d/d, *J*=8.0/8.6 Hz, NH); 7.25–7.35 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.2/27.1 (CH_2); 28.0 and 28.1 (C$(CH_3)_3$); 30.3, 31.0, 31.4, 36.4, 37.3 (CH_2); 39.6/39.7 (C_8); 41.2/41.3 (C_2); 49.1/49.4 (NH*CH*CO); 51.0 (C_5); 52.1/52.3 (C_{8a}); 62.2 (CH_2OH); 70.6 (CH_2Ph); 72.4/72.5 (C_7); 81.7, 82.0, and 82.3/82.5 (C$(CH_3)_3$); 127.6; 128.5 ($2C_{Ar}$, C_{Ar}, $2C_{Ar}$); 138.1 (C_{Arquat}); 169.4/169.6, 170.1, 170.2, 176.7/176.8 (3CO, C_3).

4.1.16. 3-[[(2S,5S*,7S*,8aR*)-7-Benzyloxy-2-(3-hydroxy-propyl)-3-oxo-octahydro-indolizin-5-carbonyl]-amino]propionic acid tert-butyl ester* ***22***

The same experimental procedure as described for hydroboration was applied to alkene **20** (106 mg, 0.23 mmol) using a 0.4 M solution of 9-BBN in hexane (1.5 mL, 0.58 mmol, 2.5 equiv). Stirring was maintained 16 h after addition of sodium acetate 5 M (550 μL, 2.76 mmol, 12 equiv) and a 30% H_2O_2 solution (0.280 mL, 12 equiv). Flash chromatography on silica gel (AcOEt/MeOH 100 to 99:1) allowed the isolation of a yellow oil (71%, 74 mg).

R_f=0.3 (AcOEt/MeOH 95:5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.14 (1H, ddd, *J*=11.8, 11.8, 11.8 Hz, H_{8ax}); 1.22–1.52 (12H, m, H_1, H_6, $CH_2CH_2CH_2OH$, 2C(CH_3)$_3$); 1.6 (2H, q, *J*=11.8 Hz, $CH_2CH_2CH_2OH$); 1.93 (1H, m, CH_2CH_2–CH_2OH); 2.27 (1H, br d, *J*=12 Hz, H_8); 2.39 (2H, t, *J*=6 Hz, $NHCH_2CH_2CO$); 2.41–2.54 (2H, m, H_2, H_1); 2.6 (1H, br d, *J*=12 Hz, H_6); 3.04 (1H, s, OH); 3.2–3.5 (2H, m, $NHCH_2CH_2CO$); 3.63 (1H, m, H_{8a}); 3.63 (2H, t, *J*=6.1 Hz, CH_2OH); 3.88 (1H, dddd, *J*=12, 12, 4.5, 4.5 Hz, H_7); 4.55 (1H, d, *J*=11.7 Hz, CH_2Ph); 4.62 (1H, d, *J*=11.7 Hz, CH_2Ph); 4.74 (1H, d, *J*=5.9 Hz, H_5); 6.79 (1H, t, *J*=6 Hz, NH); 7.2–7.45 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 27.2 ($CH_2CH_2CH_2OH$); 28.1 (C(CH_3)$_3$); 29.7 ($CH_2CH_2CH_2OH$); 31.1 (C_6); 33.3 (C_1); 35.1 ($NHCH_2CH_2CO$); 39.5 (C_8); 41.3 (C_2); 50.9 (C_5); 52.3 (C_{8a}); 62.1 (CH_2OH); 70.5 (CH_2Ph); 72.3 (C_7); 81.1 (*C*(CH_3)$_3$); 127.6; 128.4 (2C_{Ar}, C_{Ar}, 2C_{Ar}); 138.4 (C_{Arquat}); 169.9, 171.4, 176.4 (2CO, C_3).

4.1.17. Guanidine carbamate ***23***

Alcohol **21** (60 mg, 0.1 mmol) and 1,3-bis(*tert*-butoxycarbonyl) guanidine (53 mg, 0.2 mmol, 2 equiv) were dried under vacuo, and dissolved in 2.5 mL of anhydrous toluene under argon. Tributylphosphine (50 μL, 0.2 mmol, 2 equiv) was added to the solution at rt, then dipiperidinazodicarboxylate (ADDP) (52 mg, 0.2 mmol, 2 equiv) at 0 °C. The mixture was refluxed for 4 h. After removal of the toluene under vacuo, the residue was purified by flash chromatography on silica gel (Et_2O/cyclohexane/MeOH 85:14:1) allowed the isolation of **23** as a colorless oil (46 mg, 60%).

Two diastereoisomers: R_f=0.14 (Et_2O/cyclohexane/MeOH 85:14:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 1.01–1.4 (31H, m, H_8, H_6, 3C(CH_3)$_3$, $CH_2CH_2CH_2OH$); 1.5–1.7 (2H, m, $CH_2CH_2CH_2OH$); 1.5–1.7 (1H, m, $CH_2CH_2CH_2OH$); 2.1–2.4 (2H, m, H_1, H_8); 2.4–2.88 (4H, m, CH_2CO, H_2, H_6); 3.48–3.62 (1H, m, H_{8a}); 3.62–3.78 (1H, m, H_7); 4.03 (2H, br s, CH_2OH); 4.43–4.59 (3H, m, CH_2Ph, NH*CH*CO); 4.76 (1H, d, *J*=11.7 Hz, H_5); 7.21/7.26 (1H, d/d, *J*=8.1/8.6 Hz, NH); 7.15–7.29 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 26.7, 27.6/27.7 (CH_2-CH_2CH_2OH); 28.0 and 28.1 (3C(CH_3)$_3$); 29.8/30.4, 30.9/31.3, 33.3/33.4 (C_6, C_1, CH_2CO); 39.6/39.8 (C_8); 41.2/41.3 (C_2); 49.1/49.4, 50.9/51.0, 52.0/52.2 (C_5, NH*CH*CO, C_{8a}); 65.5 (CH_2OH); 70.9 (CH_2Ph); 72.4/72.5 (C_7); 81.7, 81.9, 82.2, and 82.5 (*C*(CH_3)$_3$); 127.7, 127.8, 128.5 (2C_{Ar}, C_{Ar}, 2C_{Ar}); 138.6 (C_{Arquat}); 158.5, 169.4, 169.7, 169.8, 170, 170.1, 170.2, 176/176.2 (C=N, 5CO, C_3). MS (ES^+): *m*/*z* 760 ($[MH]^+$). HRMS (ES^+, $[MNa]^+$): calcd for $C_{38}H_{57}N_5O_{11}$ 782.3952, found 782.3969.

4.1.18. Peptidomimetic ***24***

TFA (0.5 mL, 6.5 mmol) was added to a cooled (0 °C) solution of compound **23** (46 mg, 0.06 mmol) dissolved in CH_2Cl_2 (2 mL) with a droplet of water. The mixture was stirred at rt for 4 h. The mixture was concentrated in vacuo after addition of toluene (2 mL). Two more additions and evaporations of toluene were done and finally the residue was taken in ether (1 mL) and extracted with water (three times). The aqueous phase was lyophilized to leave **24** as a foam in a quantitative yield (33 mg).

Two diastereoisomers: mp: 60 °C. ^{1}H NMR (D_2O, 400 MHz): δ_H 1.07 (1H, ddd, *J*=11.7, 11.7, 11.7 Hz, H_8); 1.32 (2H, m, $CH_2CH_2CH_2O$, H_1); 1.52 (1H, m, H_6); 1.65 (2H, m, $CH_2CH_2CH_2O$); 1.75 (1H, m, $CH_2CH_2CH_2O$); 2.1 (1H, br d, *J*=10.3 Hz, H_8); 2.24 (1H, m, H_6); 2.4 (1H, m, H_1); 2.59 (1H, m, H_2); 2.7–2.88 (2H, m, CH_2COOH); 3.65–3.8 (2H, m, H_7, H_{8a}); 4.12 (2H, t, *J*=6.0 Hz, CH_2OCO); 4.48–4.70 (3H, m, NH*CH*CO, CH_2Ph); 4.70 (1H, m, H_5); 7.29 (5H, m, Ar). ^{13}C NMR (100 MHz, MeOD): δ_C 25.6 ($CH_2CH_2CH_2OH$); 26.6 ($CH_2CH_2CH_2OH$); 32.6 and 32.7 (C_1); 34.4 and 34.5 (C_6); 35.4 (CH_2COOH); 41.0 (C_8); 41.3 (C_2); 48.9 (NH*CH*CO); 51 (C_5); 52.7 and 52.9 (C_{8a}); 64.2 (C_7); 67.0 (CH_2OCO); 70.3 (CH_2Ph); 127.5; 127.7; 128.1 and 128.3 (2C_{Ar}, C_{Ar}, 2C_{Ar}); 138.1 (C_{Arquat}); 153.0 and 155.4 (C=N, OCONH); 170.7; 170.8; 172.6; 173; 173.1 and 177.2 (2NHCO, 2COOH, C_3). HRMS (ES^+, $[MH]^+$): calcd for $C_{25}H_{33}N_5O_9$ 548.2357, found 548.2339.

4.1.19. 3-[[(2S,5S*,7S*,8aR*)-7-Benzyloxy-2-(3-bis(tert-butyloxycarbonyl)guanidino-propyl)-3-oxo-octahydro-indolizin-5-carbonyl]-amino]propionic acid tert-butyl ester* ***25***

Alcohol **22** (76 mg, 0.16 mmol) and 1,3-bis(*tert*-butoxycarbonyl) guanidine (70 mg, 0.27 mmol, 2.1 equiv) were dried under vacuo, and dissolved in 5 mL of anhydrous THF under argon. Triphenylphosphine (87 mg, 0.33 mmol, 2 equiv) was added to the solution at rt, then diethylazodicarboxylate (DEAD) (52 μL, 0.33 mmol, 2 equiv) at 0 °C. The mixture was stirred for 60 h at rt. After addition of dichloromethane, the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel (Et_2O/cyclohexane 90:10) to give a white foam (105 mg, 92%).

R_f=0.22 (Et_2O/cyclohexane 90:10). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.15 (1H, ddd, *J*=11.7, 11.7, 11.7 Hz, H_8); 1.18–1.4 (3H, m, H_1, H_6, $CH_2CH_2CH_2N$); 1.44 (9H, s, C(CH_3)$_3$); 1.49 (9H, s, C(CH_3)$_3$); 1.55 (9H, s, C(CH_3)$_3$); 1.65 (2H, m, $CH_2CH_2CH_2N$); 1.94 (1H, m, $CH_2CH_2CH_2N$); 2.28 (1H, br d, *J*=11.6 Hz, H_8); 2.39 (2H, t, *J*=6 Hz, $NHCH_2CH_2CO$); 2.43–2.49 (2H, m, H_2, H_1); 2.63 (1H, br d, *J*=12.7 Hz, H_6); 3.34–3.49 (2H, m, $NHCH_2CH_2CO$); 3.56 (1H, m, H_{8a}); 3.7–4.05 (3H, m, H_7, CH_2N); 4.55 (1H, d, *J*=11.8 Hz, CH_2Ph); 4.63 (1H, d, *J*=11.8 Hz, CH_2Ph); 4.74 (1H, d, *J*=5.6 Hz, H_5); 6.68 (1H, t, *J*=5.9 Hz, NH); 7.3 (5H, m, Ar); 9.1–9.4 (2H, br s, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 26.2 ($CH_2CH_2CH_2N$); 28.1 and 28.3 (3C(CH_3)$_3$, $CH_2CH_2CH_2N$); 30.8 (C_6); 33.3 (C_1); 35.2 ($NHCH_2CH_2CO$); 39.6 (C_8); 41.1 (C_2); 44.3 ($CH_2CH_2CH_2N$); 50.9 (C_5); 52.3 (C_{8a}); 70.6 (CH_2Ph); 72.4 (C_7); 78.6 81.1 and 83.7 (3C(CH_3)$_3$); 127.6; 128.3 (2C_{Ar}, C_{Ar}, 2C_{Ar}); 138.5 ($C_{Ar\text{-}quat}$); 155, 160.5, and 163.8 (C=N, CON); 169.9, 171.3, 176.4 (2CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3382, 2977, 1715, 1608, 1514, 1368, 1251, 1152, 737. MS (ES^+): *m*/*z* 739 ($[MNa]^+$).

4.1.20. 3-[[(2S,5S*,7S*,8aR*)-7-Benzyloxy-2-(3-guanidino-propyl)-3-oxo-octahydro-indolizin-5-carbonyl]-amino]propionic acid* ***26***

The same protocol for deprotection with TFA was applied to compound **25** (43 mg, 0.06 mmol). Guanidyl compound was obtained as foam in a quantitative yield (28 mg).

^{1}H NMR (D_2O, 300 MHz): δ_H 1.04 (1H, ddd, *J*=11.7, 11.7, 11.7 Hz, H_8); 1.28 (2H, m, H_1, $CH_2CH_2CH_2NH$); 1.48 (3H, m, $CH_2CH_2CH_2NH$, H_6); 1.7 (1H, m, $CH_2CH_2CH_2NH$); 2.21 (1H, br d, *J*=11.7 Hz, H_8); 2.27–2.48 (4H, m, $NHCH_2CH_2CO$, H_6, H_1); 2.55 (1H, m, H_2); 3.06 (2H, t, *J*=6.0 Hz, $CH_2CH_2CH_2NH$); 3.31 (2H, t, *J*=5.7 Hz, $NHCH_2CH_2CO$); 3.51 (1H, m, H_7); 3.65 (1H, m, H_{8a}); 4.47 (1H, s, CH_2Ph); 4.62 (1H, d, *J*=5.6 Hz, H_5); 7.28 (5H, m, Ar). ^{13}C NMR (75 MHz, D_2O): δ_C 25.2 ($CH_2CH_2CH_2NH$); 27.2 ($CH_2CH_2CH_2NH$); 31.6 (C_6); 31.9 (C_1); 33.4 ($NHCH_2CH_2CO$); 35.2 ($NHCH_2CH_2CO$); 38.2 (C_8); 40.8 ($CH_2CH_2CH_2NH$); 41.0 (C_2); 51.6 (C_{8a}); 53.3 (C_5); 70.2 (CH_2Ph); 71.8 (C_7); 128.3; 128.5 and 128.7 (2C_{Ar}, C_{Ar}, 2C_{Ar}); 137.1 (C_{Arquat}); 156.6 (C=N); 171.4, 175.8, 178.6 (2CO, C_3). MS (ES^+): *m*/*z* 460 ($[MH]^+$). HRMS (ES^+, $[MH]^+$): calcd for $C_{23}H_{33}N_5O_5$ 460.2560, found 460.2552.

4.1.21. 3-[(2S,5S*,7S*,8aR*)-[2-(3-Guanidino-propyl)-7-hydroxy-3-oxo-octahydro-indolizin-5-carbonyl]-amino]propionic acid* ***27***

To benzyl ether **25** (45 mg, 0.063 mmol) dissolved in 7 mL of methanol was added 35 mg of palladium on activated carbon (10% Pd). The mixture was put under hydrogen and stirred 24 h. After filtration on Celite, washing with ethyl acetate, the solvents were removed under

vacuo. The residue was purified by flash chromatography on silica gel (ethyl acetate) to give a colorless oil (28 mg, 71%).

R_f=0.36 (AcOEt/MeOH 99:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.14 (1H, ddd, J=11.7, 11.7, 11.7 Hz, H_8); 1.23–1.38 (2H, m, H_1, $CH_2CH_2CH_2N$); 1.38–1.45 (28H, s, H_6, 3C(CH_3)$_3$); 1.59–1.73 (2H, m, $CH_2CH_2CH_2N$); 1.95 (1H, m, $CH_2CH_2CH_2N$); 2.21 (1H, dm, J=12 Hz, H_8); 2.4 (2H, t, J=6.2 Hz, $NHCH_2CH_2CO$); 2.43–2.63 (3H, m, H_2, H_1, H_6); 3.42 (2H, m, $NHCH_2CH_2CO$); 3.59 (1H, m, H_{8a}); 3.8 (1H, m, CH_2N); 4.01 (1H, m, CH_2N); 4.13 (1H, m, H_7); 4.73 (1H, d, J=5.7 Hz, H_5); 6.74 (1H, t, J=4.5 Hz, NH); 9.26 (2H, br s, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 26.2 ($CH_2CH_2CH_2N$); 28.1 and 28.3 (3C(CH_3)$_3$); 33.3, 33.9, 35.1 ($NHCH_2CH_2CO$, C_8, C_6, C_1); 41.1 (C_2); 41.7, 44.3 ($NHCH_2CH_2CO$, $CH_2CH_2CH_2N$); 50.9, 52.3 (C_5, C_{8a}); 65.0 (C_7); 78.6, 81.1, and 83.7 (3C(CH_3)$_3$); 127.6; 128.3 (2C_{Ar}, C_{Ar}, 2C_{Ar}); 138.5 (C_{Arquat}); 155 (C=N); 160.5 and 163.8 (C=N, CON); 169.9, 171.4, 176.5 (2CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3383, 2978, 1715, 1608, 1515, 1251, 1151, 1101, 736. MS (ES$^+$): m/z 626 ([MH]$^+$).

The same protocol for deprotection with TFA was applied to compound described above (28 mg, 0.045 mmol). Guanidyl compound **27** was obtained as an oil in a quantitative yield (17 mg).

^{1}H NMR (D_2O, 400 MHz): δ_H 1.14 (1H, ddd, J=11.7, 11.7, 11.7 Hz, H_8); 1.24–1.35 (2H, m, H_1, $CH_2CH_2CH_2N$); 1.45–1.55 (2H, m, H_6, $CH_2CH_2CH_2N$); 1.69 (1H, m, $CH_2CH_2CH_2N$); 2.12 (1H, dm, J=12.1 Hz, H_8); 2.21 (1H, dm, J=13.2 Hz, H_6); 2.39 (1H, ddd, J=12.6, 8.9, 7.1 Hz, H_1); 2.47 (1H, t, J=6.4 Hz, $NHCH_2CH_2CO$); 2.58 (1H, dddd, J=9.4, 9.4, 9.4, 4.2 Hz, H_2); 3.08 (2H, t, J=6.8 Hz, $CH_2CH_2CH_2N$); 3.35 (2H, t, J=6.4 Hz, $NHCH_2CH_2CO$); 3.65–3.75 (2H, m, H_7, H_{8a}); 4.62 (1H, d, J=5.6 Hz, H_5). ^{13}C NMR (75 MHz, D_2O): δ_C 25.2 ($CH_2CH_2CH_2N$); 27.3 ($CH_2CH_2CH_2N$); 31.5 (C_1); 33.5 ($NHCH_2CH_2CO$); 34.1 (C_6); 35.3 ($NHCH_2CH_2CO$); 40.5 (C_8); 40.8 ($CH_2CH_2CH_2N$); 41.0 (C_2); 51.2 (C_5); 53.3 (C_{8a}); 64.3 (C_7); 156.7 (C=N); 171.7, 176.1, 178.8 (2CO C_3). MS (ES$^+$): m/z 370 ([MH]$^+$), 392 ([MNa]$^+$). HRMS (ES$^+$, [MNa]$^+$): calcd for $C_{16}H_{27}N_5O_5$ 370.2090, found 370.2078.

4.1.22. *(2R*,5S*,7S*,8aR*)-2-Allyl-7-methoxymethoxy-3-oxo-octahydro-indolizin-5-carboxylic acid* ***28***

To alcohol **17b** (105 mg, 0.39 mmol) dissolved in 3.5 mL of acetone was added dropwise Jones reagent 2.67 M (220 μL, 0.58 mmol, 1.5 equiv) at 0 °C. Stirring was continued for 30 min, 3 mL of isopropanol was added, and the mixture was stirred for 10 min at 0 °C. After addition of 1 mL of water and 1 mL of a saturated solution of $KHSO_4$, the mixture was extracted twice with 100 mL of dichloromethane. The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel (AcOEt/MeOH/AcOH 97:1:2) and the carboxylic acid **28** was isolated as a white foam (54%, 60 mg).

R_f=0.35 (AcOEt/MeOH/AcOH 97:1:2). ^{1}H ($CDCl_3$, 300 MHz): δ_H 1.19 (1H, ddd, J=11.8, 11.8, 11.8 Hz, H_{8ax}); 1.58 (1H, ddd, J=12.9, 12.9, 6.8 Hz, H_6); 1.79 (1H, ddd, J=13.0, 9.2, 7.7 Hz, H_1); 2.05 (1H, m, H_1); 2.25 (2H, m, H_8, $CH_2CH{=}CH_2$); 2.55 (3H, m, H_2, H_6, $CH_2CH{=}CH_2$); 3.38 (3H, s, CH_2OMe); 3.70 (1H, dddd, J=11.4, 11.4, 3.9, 3.9 Hz, H_{7ax}); 3.82 (1H, dddd, J=11.6, 8.0, 8.0, 3.8 Hz, H_{8a}); 4.69 (2H, s, OCH_2O); 4.95 (1H, d, J=5.4 Hz, H_{5eq}); 5.06 (1H, br d, J=17.1 Hz, CH_2=CH); 5.09 (1H, dd, J=7.0, 1.3 Hz, CH_2=CH); 5.8 (1H, dddd, J=17.1, 10.1, 7.0, 7.0 Hz, CH_2=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.4 (C_1); 32.3 (C_6); 35.4 (CH_2–CH=CH_2); 39.4 (C_8); 41.0 (C_2); 50.0 (C_5); 52.3 (C_{8a}); 55.4 (CH_2OMe); 70.8 (C_7); 94.7 (OCH_2O); 117.4 (CH_2=CH); 135.3 (CH_2=CH); 172.3 (COOH); 176.4 (C_3). IR (NaCl disc, cm^{-1}): ν_{max} 2936, 2368, 1735, 1651, 1451, 1211, 1112, 1039. MS (ES$^+$): m/z 306 ([MNa]$^+$). HRMS (ES$^+$, [MNa]$^+$): calcd for $C_{14}H_{21}NO_5$ 306.1317, found: 306.1306.

4.1.23. *(2S)-2-[(2R*,5S*,7S*,8aR*)-(2-Allyl-7-methoxymethoxy-3-oxo-octahydro-indolizin-5-carbonyl)-amino]pentanedioic acid tert-butyl ester* ***29***

The same experimental procedure as described for peptide coupling was applied to carboxylic acid **28** (88 mg, 0.31 mmol) using NMM (37 μL, 0.34 mmol, 1.1 equiv) and isobutyl chloroformiate (44 μL, 0.34 mmol, 1.1 equiv). Stirring was maintained 20 h after addition of amino acid (100 mg, 0.34 mmol, 1.1 equiv) and NMM (74 μL, 0.68 mmol, 2.2 equiv). Flash chromatography on silica gel (AcOEt/cyclohexane 80:20) allowed the isolation of a colorless oil (90%, 146 mg).

Two diastereoisomers: R_f=0.6 (AcOEt/cyclohexane 90:10). ^{1}H ($CDCl_3$, 300 MHz): δ_H 1.12 (1H, ddd, J=10.8, 10.8, 10.8 Hz, H_{8ax}); 1.39 (19H, m, 2C(CH_3)$_3$, H_6); 1.72–1.87 (2H, m, $NHCHCH_2CH_2CO$, H_1); 1.98–2.07 (1H, m, $NHCHCH_2CH_2CO$, H_1); 2.1–2.3 (4H, m, $NHCHCH_2CH_2CO$, H_8, $CH_2CH{=}CH_2$); 2.4–2.6 (3H, m, H_2, H_6, $CH_2CH{=}CH_2$); 3.29 (3H, s, CH_2OMe); 3.66 (1H, m, H_{8a}); 3.82/3.92 (1H, dddd/dddd, J=11.3, 11.3, 3.9, 3.9/11.2, 11.2, 3.9, 3.9 Hz, H_{7ax}); 4.33 (1H, m, $NHCHCH_2CH_2CO$); 4.63 (2H, m, OCH_2O); 4.77/4.80 (1H, d/d, J=5.7/6.2 Hz, H_{5eq}); 5.06 (1H, br d, J=17.1 Hz, CH_2=CH); 5.04 (1H, m, CH_2=CH); 5.73 (1H, m, CH_2=CH); 6.66/6.73 (1H, d/d, J=7.7/8.0 Hz, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 27.3/27.4 (2C(CH_3)$_3$); 30.2 (C_1, $NHCHCH_2CH_2CO$); 31.2 (C_6); 31.5 ($NHCHCH_2CH_2CO$); 35.4 (CH_2–CH=CH_2); 39.3 (C_8); 40.4 (C_2); 50.0, 50.9, 52.2 (C_5, C_{8a}, $NHCHCH_2CH_2CO$); 55.3 (CH_2OMe); 70.8 (C_7); 80.65 (C(CH_3)$_3$); 82.1/82.2 (C(CH_3)$_3$); 95.2 (OCH_2O); 117.3:117.5 (CH_2=CH); 135.0/035.3 (CH_2=CH); 169.6/169.7, 170.4/170.6, 171.8 (3CO); 176.4/176.4 (C_3). MS (ES$^+$): m/z 547 ([MNa]$^+$).

4.1.24. *(2S)-2-[[(2R*,5S*,7S*,8aR*)-2-(3-Hydroxy-propyl)-7-methoxymethoxy-3-oxo-octahydro-indolizin-5-carbonyl]-amino]pentanedioic acid tert-butyl ester* ***30***

The same experimental procedure as described for hydroboration was applied to **29** (139 mg, 0.27 mmol) using a 0.5 M solution of 9-BBN (1.6 mL, 0.81 mmol, 3 equiv). Stirring was maintained 15 h after addition of sodium acetate 5 M (0.57 mL, 2.84 mmol, 10.5 equiv) and a 30% H_2O_2 solution (0.33 mL, 12 equiv). Flash chromatography on silica gel (AcOEt/MeOH 98:2 to 95:5) allowed the isolation of a colorless oil (65%, 93 mg).

R_f=0.15 (AcOEt/MeOH 98:2). ^{1}H ($CDCl_3$, 300 MHz): δ_H 1.18 (1H, ddd, J=11.2, 11.2, 11.2 Hz, H_8); 1.3–1.72 (23H, m, 2C(CH_3)$_3$, H_6, $CH_2CH_2CH_2OH$); 1.78–1.99 (3H, m, $NHCHCH_2CH_2CO$, H_1); 1.99–2.12 (1H, m, H_1); 2.12–2.3 (3H, m, $NHCHCH_2CH_2CO$, H_8); 2.45–2.64 (2H, m, H_2, H_6); 3.35 (3H, s, CH_2OMe); 3.62–3.78 (3H, m, CH_2OH, H_{8a}); 3.89/3.99 (1H, dddd/dddd, J=11.2, 11.2, 3.9, 3.9/11.2, 11.2, 4, 4 Hz, H_7); 4.33–4.45 (1H, m, $NHCHCH_2CH_2CO$); 4.67/4.68 (1H, d/d, J=6.8/6.8 Hz, OCH_2O); 4.72/4.73 (1H, d/d, J=6.8/6.8 Hz, OCH_2O); 4.83/4.86 (1H, d/d, J=6/5.3 Hz, H_5); 6.74/6.82 (1H, d/d, J=8.1/7.7 Hz, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.7, 27.4, 27.7 (CH_2); 28.0 (2C(CH_3)$_3$); 30.1, 30.2, 31.5 (CH_2); 31.1 (C_6); 39.3/39.5 (C_8); 40.5/40.6 (C_2); 50.9 (C_5); 52.3 (C_{8a} $NHCHCH_2CH_2CO$); 55.4 (CH_2OMe); 62.3/62.5 (CH_2OH); 70.9 (C_7); 80.8/81.1, 82.5 (C(CH_3)$_3$); 95.2:95.3 (OCH_2O); 169.6/169.7, 170.5/171, 172/172.2 (3CO); 177.1/177.3 (C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3313, 2934, 1730, 1536, 1453, 1369, 1257, 1154. MS (ES$^+$): m/z 565 ([MNa]$^+$). HRMS (ES$^+$, [MNa]$^+$): calcd for $C_{27}H_{46}N_2O_9$ 565.3101, found 565.3084.

4.1.25. *Guanidine carbamate* ***31***

Alcohol **30** (67 mg, 0.127 mmol) and 1,3-bis(*tert*-butoxycarbonyl) guanidine (70 mg, 0.27 mmol, 2.1 equiv) were dried under vacuo, and dissolved in 2.5 mL of anhydrous THF under argon. Tributylphosphine (63 μL, 0.25 mmol, 2 equiv) was added to the solution at rt, then dipiperidinazodicarboxylate (ADDP) (63 mg, 0.25 mmol, 2 equiv) at 0 °C. The mixture was refluxed 2 h. After addition of water and dichloromethane, the mixture was extracted. The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel (Et_2O/MeOH 97:3) to give a white solid (40 mg, 43%).

R_f=0.1 (Et_2O/MeOH 98:2). ^{1}H ($CDCl_3$, 400 MHz): δ_H 1.18 (1H, ddd, J=11.7, 11.7, 11.7 Hz, H_8); 1.27–1.48 (28H, m, 3C(CH_3)$_3$, H_6); 1.5–1.63 (1H, m, $CH_2CH_2CH_2OH$); 1.73–2.28 (10H, m, H_8, $NHCHCH_2CH_2CO$,

$CH_2CH_2CH_2OH$, H_1); 2.43–2.59 (2H, m, H_2, H_6); 3.33 (3H, s, CH_2OMe); 3.64–3.76 (1H, m, H_{8a}); 3.85/3.93 (1H, dddd/dddd, J=11.2, 11.2, 4.0, 4.0/11.2, 11.2, 4.0, 4.0 Hz, H_7); 4.05–4.15 (2H, m, CH_2OH); 4.32–4.43 (1H, m, NH$CH$$CH_2CH_2CO$); 4.65/4.66 (1H, d/d, J=6.8/6.8 Hz, OCH_2O); 4.69/4.695 (1H, d/d, J=6.8/6.8 Hz, OCH_2O); 4.81/4.84 (1H, d/d, J=6/5.8 Hz, H_5); 6.74/6.82 (1H, d/d, J=8.0/7.6 Hz, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 26.5, 26.6, 27.3, 27.4, 28.0 (3C(CH_3)$_3$); 29.6, 31.2, 31.5 (CH_2); 39.0/39.3 (C_8); 40.3 (C_2); 50.9 (C_5); 52/52.1, 52.2/52.4 (C_{8a}, NH$CH$$CH_2CH_2CO$); 55.3 ($CH_2OMe$); 64.9 ($CH_2OH$); 70.9 ($C_7$); 80.8, 82.2, 82.3, 82.7 (C(CH_3)$_3$); 95.2 (OCH_2O); 158.7, 169.7, 169.8, 170.7, 172.0 (5CO, C=N); 176.4/176.8 (C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3403, 2979, 1730, 1554, 1370, 1256, 1156, 1042, 733. MS (ES$^+$): m/z 750 ([MNa]$^+$). HRMS (ES$^+$, [MNa]$^+$): calcd for $C_{34}H_{57}N_5O_{12}$ 750.3901, found 750.3885.

4.1.26. Peptidomimetic **32**

The same protocol for deprotection with TFA was applied to compound **31** (29 mg; 0.04 mmol). Guanidyl compound was obtained as a foam in a quantitative yield (19 mg).

^{1}H NMR (D_2O, 400 MHz): δ_H 1.11 (1H, ddd, J=11.7, 11.7, 11.7 Hz, H_8); 1.4–1.58 (2H, m, H_6, $CH_2CH_2CH_2O$); 1.58–1.7 (3H, m, $CH_2CH_2CH_2O$); 1.72–1.9 (2H, m, NHCHCH_2CH_2COOH, H_1); 1.9–2.17 (5H, m, NHCHCH_2CH_2COOH, H_8, H_1); 2.27 (1H, m, H_6); 2.53 (1H, m, H_2); 3.78–3.9 (2H, m, H_7, H_{8a}); 4.03 (1H, m, NH$CH$$CH_2CH_2COOH$); 4.11 (2H, br s, $CH_2CH_2CH_2O$); 4.68 (1H, m, H_4). HRMS (ES$^+$, [MNa]$^+$): calcd for $C_{19}H_{29}N_5O_9$ 494.1863, found 494.1860.

4.1.27. (2S)-2-[[(2R*,5S*,7S*,8aR*)-2-(3-Bis(tert-butyloxycarbonyl)-guanidino-propyl)-7-methoxymethoxy-3-oxo-octahydro-indolizin-5-carbonyl]-amino]pentanedioic acid tert-butyl ester **33**

The same experimental procedure as described for **25** above was applied to **30** (33 mg, 0.062 mmol) using and 1,3-bis(*tert*-butoxycarbonyl) guanidine (39 mg, 0.15 mmol, 2 equiv), triphenylphosphine (40 mg, 0.15 mmol, 2 equiv), and diethylazodicarboxylate (DEAD) (24 μL, 0.15 mmol, 2 equiv). Stirring was continued for 3 days. Flash chromatography on silica gel (Et_2O/cyclohexane 70:30 to 100:0) allowed the isolation of **33** as a colorless oil (29 mg, 60%) (two diastereoisomers).

R_f=0.45 (Et_2O). ^{1}H ($CDCl_3$, 400 MHz): δ_H 1.21 (1H, ddd, J=11.7, 11.7, 11.7 Hz, H_8); 1.35–1.6 (37H, m, 4C(CH_3)$_3$, H_6); 1.62–2.12 (8H, m, $CH_2CH_2CH_2NH$, H_8, NHCHCH_2CH_2CO, H_1); 2.15–2.3 (3H, m, NHCHCH$_2CH_2$CO, H_8); 2.47–2.63 (2H, m, H_6, H_2); 3.36 (3H, s, CH_2OMe); 3.7–4.06 (4H, m, H_{8a}, $CH_2CH_2CH_2NH$, H_7); 4.09 (1H, m, NH$CH$$CH_2CH_2CO$); 4.67 (1H, d, J=6.8 Hz, OCH_2O); 4.71 (1H, d, J=6.8 Hz, OCH_2O); 4.74 (1H, d, J=5.4 Hz, H_5); 6.72 (1H, d, J=7.6 Hz, NH); 9.26 (2H, br s, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 26.3, 26.5, 27.4 ($CH_2CH_2CH_2NH$ NHCHCH_2CH_2CO); 28.1, 28.3 (4C(CH_3)$_3$); 30.8, 31.5, 31.6 ($CH_2CH_2CH_2NH$, NHCHCH$_2CH_2$CO, C_6, C_1); 38.9/39.2 (C_8); 40.1 (C_2); 44.2 ($CH_2CH_2CH_2NH$); 51, 52, 52.1, 52.3, 55.4 (C_{8a}, C_5, NH$CH$$CH_2CH_2CO$, CH_2OMe); 64; 70.9, 71.0 (C_7); 78.6, 80.8, 82.3, 83.7 (4C(CH_3)$_3$); 95.2 (OCH_2O); 155.0, 160.5, and 163.8 (C=N, N–CO); 169.8, 170.5, 170.7, 172.0, 176.9, 177.2 (4CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3382, 2977, 1715, 1609, 1513, 1368, 1251, 1152, 737. MS (ES$^+$): m/z 784 ([MH]$^+$).

4.1.28. (2S)-2-[[(2R*,5S*,7S*,8aR*)-2-(3-Guanidino-propyl)-7-hydroxy-3-oxo-octahydro-indolizin-5-carbonyl]-amino]pentanedioic acid **34**

The same protocol for deprotection with TFA was applied to compound **33** (46 mg, 0.06 mmol). Guanidyl compound was obtained as a white solid in a quantitative yield (33 mg).

Mp: 60 °C. ^{1}H (D_2O, 400 MHz): δ_H 1.1 (1H, m, H_8); 1.35–1.53 (5H, m, $CH_2CH_2CH_2NH$, H_6); 1.77–1.98 (3H, m, NHCHCH_2CH_2CO, H_8); 1.98–2.15 (2H, m, H_8); 2.21 (1H, m, H_6); 2.31 (2H, br s, NHCHCH$_2CH_2$CO); 2.52 (1H, br s, H_2); 3.06 (2H, t, J=5.9 Hz, $CH_2CH_2CH_2NH$); 3.71 (1H, m, H_7); 3.79 (1H, m, H_{8a}); 4.25 (1H, m, NH$CH$$CH_2CH_2CO$); 4.63 (1H, m, H_5). ^{13}C NMR (100 MHz, D_2O): δ_C 25.5, 25.6 ($CH_2CH_2CH_2NH$ NHCHCH_2CH_2CO); 27.7 ($CH_2CH_2CH_2NH$); 30.1, 30.3 (NHCHCH$_2CH_2$CO, C_1); 34.0 (C_6); 39.8 (C_8); 40.8 (C_2); 40.9 ($CH_2CH_2CH_2NH$); 51.0/51.1 (C_5); 52.4 (NH$CH$$CH_2CH_2CO$); 53.7/53.9 ($C_{8a}$); 64.6 ($C_7$); 156.7 (C=N); 171.9, 172.1 (CONH); 175.1 (NHCHCOOH); 177.1 (COOH); 179.3 (C_3). MS (ES$^+$): m/z 428 ([MH]$^+$). HRMS (ES$^+$, [MH]$^+$): calcd for $C_{18}H_{29}N_5O_7$ 428.2145, found 428.2146.

4.1.29. (5S*,7R*,8aR*)-7-Benzyloxy-5-methyl-3-oxo-octahydro-indolizin-5-carboxylic acid ethyl ester **35**

To **12a** (430 mg, 1.42 mmol) dissolved in 90 mL of anhydrous THF under argon at −78 °C was added 23.3 mL (11.7 mmol, 1.1 equiv) of KHMDS 0.5 M in toluene. After 30 min, methyl iodide (filtered on neutral aluminum oxide; 725 μL, 11.65 mmol, 1.1 equiv) was added. Stirring was continued for 3 h at −78 °C and the reaction was quenched with a saturated solution of NH_4Cl. The product was extracted twice with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. Flash chromatography on silica gel (AcOEt/cyclohexane 50:50) allowed the isolation of **35** as a pale yellow oil (3.5 mg, 99%).

R_f=0.37 (AcOEt/cyclohexane: 70/30). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.12 (3H, t, J=7.1 Hz; CH_3CH_2); 1.36 (1H, ddd, J=13.5, 12.2, 2.6 Hz, H_{8ax}); 1.50 (1H, dddd, J=10.4, 10.4, 10.4, 10.4 Hz, H_1); 1.56 (1H, dd, J=14.4, 2.5 Hz, H_{6ax}); 1.89 (3H, s, Me); 2.12 (2H, m, H_1, H_{8eq}), 2.33 (2H, m, 2H_2); 2.65 (1H, ddd, J=14.4, 3.5, 2.2 Hz, H_{6eq}); 3.77 (1H, dddd, J=2.9, 2.9, 2.9, 2.9 Hz, H_{7eq}); 3.94 (1H, dq, J=10.7, 7.1 Hz, OCH_2CH_3); 3.94 (1H, m, H_{8a}); 4.04 (1H, dq, J=10.7, 7.1 Hz, OCH_2CH_3); 4.40 (1H, d, J=11.9 Hz, CH_2Ph); 4.51 (1H, d, J=11.9 Hz, CH_2Ph); 7.29 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 14.0 (CH_3CH_2); 26.0 (Me); 26.6 (C_1); 31.9 (C_2); 36.7 (C_8); 40.4 (C_6); 52.1 (C_{8a}); 59.2 (C_5); 61.3 (OCH_2CH_3); 70.1 (CH_2Ph); 70.7 (C_7); 127.2 (2C_{Ar}); 127.5 (C_{Ar}); 128.3 (C_{Ar}); 138.5 (C_{Arquat}); 173.1, 177.7 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3460, 2938, 1682, 1455, 1271, 1027, 731. HRMS (ES$^+$, [MNa]$^+$): calcd for $C_{19}H_{25}NO_4$ 354.1681, found 354.1665.

4.1.30. (2R*,5S*,7R*,8aR*)-2-Allyl-7-benzyloxy-5-methyl-3-oxo-octahydro-indolizin-5-carboxylic acid ethyl ester **36** and (2S*,5S*,7R*,8aR*)-2-allyl-7-benzyloxy-5-methyl-3-oxo-octahydro-indolizin-5-carboxylic acid ethyl ester **37**

The same experimental procedure as described for allylation was applied to **35** (1.5 g, 4.53 mmol) using KHMDS 0.5 M (9.5 mL, 4.75 mmol, 1.01 equiv) in 40 mL of THF. After 20 min stirring at −78 °C, solution was cooled at −110 °C before addition of distillated allyl bromide (470 μL, 5.4 mmol, 1.2 equiv) stirring was continued 1 h, then 3h 30 at −78 °C. Flash chromatography on silica gel (AcOEt/cyclohexane 50:50) allowed the isolation of **36** as a pale yellow oil (561 g, 33%) and **37** as a pale yellow oil (366 mg, 22%). Starting material was also recovered (35%).

Compound ***36***: R_f=0.33 (Et_2O/cyclohexane 50:50). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.13 (3H, t, J=7.1 Hz, CH_3CH_2); 1.20 (1H, q, J=10.9 Hz, H_1); 1.32 (1H, ddd, J=14.6, 12.2, 2.4 Hz, H_{8ax}); 1.56 (1H, dd, J=14.4, 2.4 Hz, H_{6ax}); 1.90 (3H, s, Me); 2.18 (3H, m, CH_2CH=CH_2, H_1, H_{8eq}); 2.48 (1H, m, H_2); 2.66 (1H, ddd, J=14.4, 3.4, 1.8 Hz, H_{6equ}); 2.68 (1H, m, CH_2CH=CH_2); 3.77 (1H, br s, H_{7equ}); 3.88 (1H, m, H_{8a}); 3.93 (1H, dq, J=10.7, 7.1 Hz, OCH_2CH_3); 4.04 (1H, dq, J=10.7, 7.1 Hz, OCH_2CH_3); 4.40 (1H, d, J=11.9 Hz, CH_2Ph); 4.52 (1H, d, J=11.9 Hz, CH_2Ph); 5.04 (1H, br d, J=17 Hz, CH_2CH=CH_2); 5.09 (1H, br d, J=17 Hz, CH_2CH=CH_2); 5.80 (1H, dddd, J=17, 10.1, 6.9, 6.9 Hz, CH_2CH=CH_2); 7.28 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.9 (CH_3CH_2); 26.2 (Me); 32.8 (C_1); 35.0 (CH_2CH=CH_2); 36.5 (C_8); 40.2 (C_6); 42.1 (C_2); 49.9 (C_{8a}); 59.1 (C_5); 61.3 (OCH_2CH_3); 70.0 (CH_2Ph); 70.6 (C_7); 116.4 (CH_2CH=CH_2); 127.1 (2C_{Ar}); 127.4 (C_{Ar}); 128.2 (2C_{Ar}); 136.0 (CH_2CH=CH_2); 138.5 (C_{Arquat}); 173.1, 178.5 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 2925, 1737, 1698, 1454, 1396, 1307, 1274, 1207, 1130, 1028, 913, 736. MS (ES$^+$): m/z 394 ([MNa]$^+$). Anal. Calcd

for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.52; H, 7.96; N, 3.77%.

Compound ***37***: R_f=0.2 (Et_2O/cyclohexane 50:50). ^1H NMR ($CDCl_3$, 300 MHz): δ_H 1.14 (3H, t, J=7.2 Hz, CH_3CH_2); 1.34 (1H, ddd, J=13.3 12.3, 2.5 Hz, H_{8ax}); 1.54 (1H, dd, J=14.4, 2.5 Hz, H_{6ax}); 1.60 (1H, m, H_1); 1.89 (3H, s, Me); 1.97 (1H, dd, J=12.7, 6.0 Hz, H_1); 2.10 (1H, ddd, J=13.4, 13.4, 13.4 Hz, H_{8eq}); 2.28 (1H, m, CH_2CH=CH_2); 2.45 (1H, m, H_2); 2.50 (1H, m, CH_2CH=CH_2); 2.64 (1H, ddd, J=14.4, 3.3, 2.2 Hz, H_{6equ}); 3.76 (1H, q, J=2.7 Hz, H_7); 3.95 (1H, dq, J=10.8, 7.1 Hz, OCH_2CH$_3$); 3.98 (1H, m, H_{8a}); 4.04 (1H, dq, J=10.7, 7.1 Hz, OCH_2CH$_3$); 4.38 (1H, d, J=11.9 Hz, CH_2Ph); 4.52 (1H, d, J=11.9 Hz, CH_2Ph); 5.06 (1H, br d, J=10.1 Hz, CH_2CH=CH_2); 5.09 (1H, dd, J=17.1, 1.4 Hz, CH_2CH=CH_2); 5.85 (1H, dddd, J=17, 10.1, 7.8, 6.0 Hz, CH_2CH=CH_2); 7.28 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 14.0 (CH_3CH_2); 25.9 (Me); 30.7 (C_1); 34.7 (CH_2CH=CH_2); 36.8 (C_8); 40.2 (C_6); 41.9 (C_2); 50.0 (C_{8a}); 59.0 (C_5); 61.3 (OCH_2CH$_3$); 70.1 (CH_2Ph); 70.6 (C_7); 116.7 (CH_2CH=CH_2); 127.2 (2C_{Ar}); 127.5 (C_{Ar}); 128.3 (2C_{Ar}); 136.4 (CH_2CH=CH_2); 138.3 (C_{Arquat}); 173.0, 178.8 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 2937, 1736, 1694, 1446, 1396, 1276, 1208, 1132, 1067, 912, 729. MS (ES^+): m/z 394 ($[MNa]^+$).

4.1.31. (2R,5S*,7R*,8aR*)-7-Benzyloxy-2-(3-bis(tert-butyloxycarbonyl)guanidino-propyl)-5-methyl-3-oxo-octahydro-indolizin-5-carboxylic acid ethyl ester* ***38***

trans intermediate alcohol: the same experimental procedure as described for hydroboration was applied to alkene **36** (309 mg, 0.83 mmol) using a 0.5 M solution of 9-BBN in THF (5 mL, 2.49 mmol, 3 equiv). Stirring was maintained 16 h after addition of sodium acetate 5 M (2 mL, 9.9 mmol, 12 equiv) and a 30% H_2O_2 solution (1 mL, 12 equiv). Flash chromatography on silica gel (AcOEt/cyclohexane 90:10) allowed the isolation of a yellow oil (60%, 193 mg).

R_f=0.24 (AcOEt/cyclohexane 95:5). ^1H NMR ($CDCl_3$, 300 MHz): δ_H 1.09 (3H, t, J=7.1 Hz, CH_3CH_2); 1.17 (1H, ddd, J=11.4, 11.4, 11.4 Hz, H_1); 1.31 (1H, ddd, J=13.9, 11.4, 2.4 Hz, H_{8ax}); 1.44 (1H, m, $CH_2CH_2CH_2OH$); 1.54 (1H, dd, J=14.3, 2.3 Hz, H_6); 1.6 (2H, m, $CH_2CH_2CH_2OH$); 1.78–1.95 (4H, s, Me, $CH_2CH_2CH_2OH$); 2.14 (1H, dm, J=11.4 Hz, H_8); 2.25 (1H, ddd, J=11.5, 7.9, 5.4 Hz, H_1); 2.38 (1H, m, H_2); 2.62 (1H, br d, J=14.4 Hz, H_6); 3.6 (2H, t, J=6.3 Hz, $CH_2CH_2CH_2OH$); 3.75 (1H, m, H_7); 3.85 (1H, m, H_{8a}); 3.93 (1H, dq, J=10.7, 7.1 Hz, OCH_2CH$_3$); 3.97 (1H, dq, J=10.7, 7.1 Hz, OCH_2CH$_3$); 4.38 (1H, d, J=11.9 Hz, CH_2Ph); 4.49 (1H, d, J=11.9 Hz, CH_2Ph); 7.29 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.9 (CH_3CH_2); 26.1 (Me); 26.6 ($CH_2CH_2CH_2OH$); 30.1 ($CH_2CH_2CH_2OH$); 33.3 (C_1); 36.4 (C_8); 40.2 (C_6); 42.2 (C_2); 50.0 (C_{8a}); 59.1 (C_5); 61.3 (OCH_2CH$_3$); 62.1 ($CH_2CH_2CH_2OH$); 70.0 (CH_2Ph); 70.5 (C_7); 127.1 (2C_{Ar}); 127.4 (C_{Ar}); 128.2 (2C_{Ar}); 138.3 (C_{Arquat}); 173.0, 179.7 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3412, 2928, 1734, 1681, 1399, 1307, 1273, 1210, 1131, 735. MS (ES^+): m/z 412 ($[MNa]^+$).

The same experimental procedure as described for **25** was applied to intermediate trans (300 mg, 0.77 mmol) using and 1,3-bis(*tert*-butoxycarbonyl) guanidine (311 mg, 1.2 mmol, 1.5 equiv), triphenylphosphine (315 mg, 1.2 mmol, 1.5 equiv), and diethylazodicarboxylate (DEAD) (190 μL, 1.2 mmol, 1.5 equiv). Stirring was continued for 24 h. Flash chromatography on silica gel (Et_2O/cyclohexane 50:50) allowed the isolation of **38** as a white solid (436 mg, 90%).

R_f=0.27 (Et_2O/cyclohexane 50:50), mp: 132 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ_H 1.04 (3H, t, J=7.1 Hz, CH_3CH_2); 1.07 (1H, m, H_1); 1.25 (2H, m, $CH_2CH_2CH_2$N H_8); 1.4–1.55 (19H, m, 2C(CH_3)$_3$ H_6); 1.58 (2H, m, $CH_2CH_2CH_2$N); 1.81 (3H, s, Me); 1.85 (1H, m, $CH_2CH_2CH_2$N); 2.08 (1H, br d, J=12.5 Hz, H_8); 2.34 (2H, m, H_2, H_1); 2.59 (1H, br d, J=14.2 Hz, H_6); 3.62–3.75 (2H, m, H_7, $CH_2CH_2CH_2$N); 3.75–3.89 (2H, H_{8a}, OCH_2CH$_3$); 3.89–4.0 (2H, m, $CH_2CH_2CH_2$N OCH_2CH$_3$); 4.32 (1H, d, J=11.9 Hz, CH_2Ph); 4.45 (1H, d, J=11.9 Hz, CH_2Ph); 7.21 (5H, m, Ar); 9.22 (2H, m, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.9 (CH_3CH_2); 26.1 (Me); 27.6 ($CH_2CH_2CH_2$N); 28.0 and 28.3 ($CH_2CH_2CH_2$N, 2C(CH_3)$_3$); 33.1 (C_1); 36.5 (C_8); 40.3 (C_6); 42.0 (C_2); 44.3 ($CH_2CH_2CH_2$N); 49.9 (C_{8a}); 59.0 (C_5); 61.2 (OCH_2CH$_3$); 69.9 (CH_2Ph); 70.5 (C_7); 78.4 (C(CH_3)$_3$); 83.6 (C(CH_3)$_3$); 127.0 (2C_{Ar}); 127.3 (C_{Ar}); 128.2 (2C_{Ar}); 138.3 (C_{Arquat}); 155.0; 160.5; 163.8 (C=N, NCOO); 173.0, 179.1 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3390, 2881, 1714, 1608, 1271, 1150. MS (ES^+): m/z 653 ($[MNa]^+$).

4.1.32. (2S,4R*,6R*)-6-[(2R*)-2-Carboxy-5-guanidino-pentyl]-4-hydroxy-2-methyl-piperidin-2-carboxylic acid* ***39***

Compound **38** (70 mg, 0.11 mmol) was dissolved in 5 mL of HCl 3 M. The mixture was refluxed for 20 h. The solvent was evaporated under vacuo. To the residue were added 1 mL of diethyl ether and 2 mL of water, insoluble solids were filtered and the product was extracted three times with 2 mL of water. The aqueous phase was lyophilized to leave an orange oil in a 100% yield (38 mg).

^1H NMR (D_2O, 400 MHz): δ_H 1.3–1.65 (8H, m, CH_2CHCOOH, H_5, Me, $CH_2CH_2CH_2$N); 1.67 (1H, br d, J=15.0 Hz, H_3); 1.75–1.95 (3H, m, $CH_2CH_2CH_2$N, CH_2CHCOOH, H_5); 2.3–2.5 (2H, m, H_3, CH_2CHCOOH); 3.0 (2H, br s, $CH_2CH_2CH_2$N); 3.67 (1H, m, H_6); 4.05 (1H, br s, H_4). ^{13}C NMR (75 MHz, D_2O): δ_C 24.4 (Me); 25.4 ($CH_2CH_2CH_2$N); 28.7 ($CH_2CH_2CH_2$N); 33.2 (C_5); 34.4 (CH_2CHCOOH); 37.8 (C_3); 40.7 (CH_2CHCOOH, $CH_2CH_2CH_2$N); 47.5 (C_6); 59.2 (C_2); 61.7 (C_4); 156.6 (C=N); 173.8, 178.6 (CO, C_3). MS (ES^+): m/z 313 ($[M-H_2O]^+$), 331 ($[M-H]^+$). HRMS (ES^+, $[MH]^+$): calcd for $C_{14}H_{26}N_4O_5$ 331.1981, found 331.1965.

4.1.33. (2S,5S*,7R*,8aR*)-7-Benzyloxy-2-(3-bis(tert-butyloxycarbonyl)guanidino-propyl)-5-methyl-3-oxo-octahydro-indolizin-5-carboxylic acid ethyl ester* ***40***

cis intermediate alcohol: the same experimental procedure as described for hydroboration was applied to alkene **37** (178 mg, 0.48 mmol) using a 0.5 M solution of 9-BBN in THF (2 mL, 1 mmol, 2.1 equiv). Stirring was maintained 16 h after addition of sodium acetate 5 M (1.15 mL, 5.76 mmol, 12 equiv) and a 30% H_2O_2 solution (0.6 mL, 5.76 mmol, 12 equiv). Flash chromatography on silica gel (AcOEt/Et_2O 90:10) allowed the isolation of a yellow oil (87%, 162 mg).

R_f=0.18 (AcOEt/Et_2O 90:10). ^1H NMR ($CDCl_3$, 300 MHz): δ_H 1.15 (3H, t, J=7.1 Hz, CH_3CH_2); 1.34 (1H, ddd, J=13.6 11.2, 2.4 Hz, H_8); 1.57 (1H, dd, J=14.4, 2.5 Hz, H_6); 1.61–1.96 (9H, m, *Me*, $CH_2CH_2CH_2OH$, H_1); 2.13 (1H, dm, J=13.5 Hz, H_8); 2.28 (1H, br s, OH); 2.46 (1H, m, H_2); 2.67 (1H, ddd, J=14.4, 3.4, 2.1 Hz, H_6); 3.7 (2H, m, $CH_2CH_2CH_2OH$); 3.78 (1H, m, H_7); 3.93–4.09 (3H, m, H_{8a}, OCH_2CH$_3$); 4.41 (1H, d, J=11.9 Hz, CH_2Ph); 4.53 (1H, d, J=11.9 Hz, CH_2Ph); 7.3 (5H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.1 (CH_3CH_2); 26.0 (Me); 27.2 ($CH_2CH_2CH_2OH$); 30.5 ($CH_2CH_2CH_2OH$); 32.4 (C_1); 34.7 (CH_2CH=CH_2); 36.9 (C_8); 40.3 (C_6); 41.9 (C_2); 50.3 (C_{8a}); 59.1 (C_5); 61.5 (OCH_2CH$_3$); 62.6 ($CH_2CH_2CH_2OH$); 70.2 (CH_2Ph); 70.6 (C_7); 127.3 (2C_{Ar}); 127.6 (C_{Ar}); 128.4 (2C_{Ar}); 138.4 (C_{Arquat}); 173.1 179.6 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3389, 2952, 1651, 1454, 1286, 1066, 910, 728. MS (ES^+): m/z 412 ($[MNa]^+$).

The same experimental procedure as described for **25** was applied to cis intermediate (24 mg, 0.062 mmol) using and 1,3-bis-(*tert*-butoxycarbonyl) guanidine (26 mg, 0.1 mmol, 1.6 equiv), triphenylphosphine (26 mg, 0.1 mmol, 1.6 equiv), and diethylazodicarboxylate (DEAD) (16 μL, 0.1 mmol, 1.6 equiv). Stirring was continued for 44 h. Flash chromatography on silica gel (Et_2O/cyclohexane 70:30) allowed the isolation of **40** as a white solid (40 mg, 100%).

R_f=0.31 (AcOEt/Et_2O 70:30), mp >60 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ_H 1.13 (3H, t, J=7.2 Hz, CH_3CH_2); 1.31 (1H, m, H_8); 1.41–1.62 (20H, m, $CH_2CH_2CH_2$N, 2C(CH_3)$_3$, H_6); 1.63–1.62 (4H, m, $CH_2CH_2CH_2$N, H_1); 1.95 (4H, m, *Me*, H_1); 2.12 (1H, br d, J=13.4 Hz, H_8); 2.4 (1H, m, H_2); 2.67 (1H, br d, H_6); 3.78 (1H, br s, H_7); 3.82–4.09 (5H, m, $CH_2CH_2CH_2$N, H_{8a}, OCH_2CH$_3$); 4.39 (1H, d, J=12 Hz,

CH_2Ph); 4.52 (1H, d, J=12 Hz, CH_2Ph); 7.3 (5H, m, Ar); 9.23 (2H, br s, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 14.0 (CH_3CH_2); 25.9 (Me); 26.8 and 27.3 ($CH_2CH_2CH_2N$, $CH_2CH_2CH_2N$); 28.0 and 28.3 ($2C(CH_3)_3$); 31.6 (C_1); 36.9 (C_8); 40.2 (C_6); 42.0 (C_2); 44.5 ($CH_2CH_2CH_2N$); 50.1 (C_{8a}); 59.0 (C_5); 61.3 (OCH_2CH_3); 70.0 (CH_2Ph); 70.6 (C_7); 78.6 ($C(CH_3)_3$); 83.7 ($C(CH_3)_3$); 127.2 ($2C_{Ar}$); 127.5 (C_{Ar}); 128.3 ($2C_{Ar}$); 138.3 (C_{Arquat}); 155.1, 156.8, 163.9 (C=N, NCOO); 173.0, 179.2 (CO, C_3). IR (NaCl disc, cm^{-1}): ν_{max} 3382, 2930, 1714, 1614, 1454, 1359, 1255, 1152. MS (ES^+): m/z 631 ($[MNa]^+$).

4.1.34. (2S,4R*,6R*)-6-[(2S*)-2-Carboxy-5-guanidino-pentyl]-4-hydroxy-2-methyl-piperidin-2-carboxylic acid **41***

The same experimental procedure as described for **39** was applied to **40** (67 mg, 0.1 mmol) in 5 mL of HCl 3 M. The aqueous phase was lyophilized to leave brown oil in a 100% yield (44 mg).

^1H NMR (D_2O, 400 MHz): δ_H 1.45 (3H, s, Me); 1.46–1.6 (5H, m, $CH_2CHCOOH$, H_5, $CH_2CH_2CH_2N$); 1.75 (1H, br d, J=14.4 Hz, H_3); 1.78–1.93 (3H, m, $CH_2CH_2CH_2N$, $CH_2CHCOOH$, H_5); 2.48 (1H, br d, J=15.1 Hz, H_3); 2.58 (1H, q, J=6.4 Hz, $CH_2CHCOOH$); 3.09 (2H, t, J=6.5 Hz, $CH_2CH_2CH_2N$); 3.75 (1H, m, H_6); 4.09 (1H, br s, H_4). ^{13}C NMR (75 MHz, D_2O): δ_C 24.5 (Me); 25.2 ($CH_2CH_2CH_2N$); 28.2 ($CH_2CH_2CH_2N$); 33.5 (C_5); 34.1 ($CH_2CHCOOH$); 37.7 (C_3); 40.7 ($CH_2CH_2CH_2N$); 40.9 ($CH_2CHCOOH$); 47.8 (C_6); 59.4 (C_2); 61.8 (C_4); 156.6 (C=N); 174.1, 179.1 (CO, C_3). MS (ES^+): m/z 331 ($[M-H]^+$). HRMS (ES^+, $[MH]^+$): calcd for $C_{14}H_{26}N_4O_5$ 331.1981, found 331.1965.

4.2. Cell culture and cell-adhesion assay

S180 and Eahy926 cells were cultured in DMEM+10% FCS and DMEM+20%FCS+HAT, respectively. For adhesion assays, cells were harvested with cell dissociation non-enzymatic solution (SIGMA). Cells were pelleted by centrifugation and resuspended at a density of 1×10^5 cells/ml in PBS/CaMg. Assays of cell adhesion to coated substrates were performed on non-tissue culture treated 96-well plates. The wells were incubated with FN or VN at 10 μg ml^{-1} in PBS overnight at 4 °C followed by a 30-min incubation with 3 mg ml^{-1} bovine serum albumin in PBS (previously heat-inactivated for 3 min at 80 °C). The substrates were thoroughly washed and maintained in PBS until use. The peptidomimetics solutions were prepared either at 20 μM, 400 μM or 1 mM in PBSCaMg. 50 μl of peptidomimetic solution were added to the well with 50 μl of the cell suspension reaching the final peptidomimetic solution to 10 μM, 200 μM or 500 μM for the assay. Each test was done in triplicate. The plates were incubated at 37 °C for 1 h and washed with PBS to remove the non-adherent cells. Then, the wells were fixed in 5% glutaraldehyde in PBS, washed, stained with 1% crystal violet in 200 mM MES, and washed in 200 mM MES buffer, pH 6. The crystal violet fixed to the cells was dissolved in 100 μL of 10% acetic acid and OD was read with a microplate reader at 570 nm. Data are the mean±SD of triplicates and are expressed as the % of cell adhesion obtained on FN in the absence of competitor. The positive and negative controls for the inhibition of cell adhesion were done using the cyclic c(RGDfV) and GRGES peptides, respectively. Two independent experiments were done for each competitor and for each cell type.

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