Tetrahedron: *Asymmetry* 22 (2011) 1090–1096

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Silicon-mediated asymmetric synthesis of fagomine and 3,4-di-*epi*-fagomine

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ARTICLE INFO

Article history:
Received 27 April 2011
Accepted 12 May 2011
Available online 14 June 2011

ABSTRACT

The synthesis of D-fagomine and its stereoisomer, D-3,4-di-*epi*-fagomine has been achieved from C_2-symmetric 3,4-bis-silyl substituted adipic acid di-oxazolidin-2-one derivatives via stereocontrolled azidation and silicon to hydroxyl conversion as the key steps. The Evans oxazolidin-2-one controlled the stereochemical outcome of the azidation which supersedes the directing effects of the silyl substituent.

1. Introduction

Polyhydroxylated piperidines (azasugars) have gained increasing synthetic interest due to their remarkable biological activity as glycosidase inhibitors.[1–3] Since glycosidases are involved in numerous biological processes, azasugars are potential therapeutic agents for the treatment of a wide range of diseases, including diabetes, cancer, AIDS, viral infections and many more.[4,5] These important biological properties have led to many synthetic approaches[6,7] towards naturally occurring azasugars and their analogues.

1,2-Dideoxy-azasugars, such as D-fagomine **1** and its stereoisomers **2** and **3** (Fig. 1), have been isolated from the buckwheat seeds of Japanese buckwheat *Fagopyrum esculentum australe* Moench[8] and also from the seeds of *Castanospermum australe* (Leguminosae).[9] More recently, the isomers of fagomine **2** and **3** have been isolated from the leaves and roots of *Xanthocericis zambesiaca*.[10] Fagomine itself has a strong inhibitory activity towards mammalian α-glucosidase, β-galactosidase,[10] and has also been found to have a potent antihyperglycemic effect in streptozocin-induced diabetic mice and a potentiation of glucose-induced insulin secretion.[11,12]

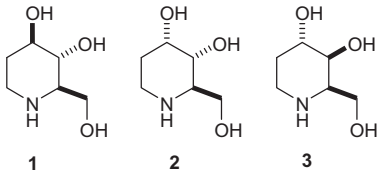

Figure 1. Fagomine **1** and its stereoisomers **2** and **3**.

Several syntheses of D-fagomine **1**[13–25] have been reported from carbohydrates, aminoacids and other precursors. However, the number of syntheses of fagomine isomers such as **2** and **3** are rare. The only synthesis of the stereoisomeric 3,4-di-*epi*-fagomine **3** has been reported as a mixture of diastereoisomers starting from a D-serine-derived Garner aldehyde.[22] In a continuation of our efforts for the silicon-mediated hydroxylated piperidine/pyrrolidine syntheses,[26–30] we herein report the synthesis of D-fagomine **1** and D-3,4-di-*epi*-fagomine **3** from C_2-symmetric 3,4-bis-silyl substituted adipic acid derivatives via stereocontrolled azidation and silicon to hydroxyl conversion as the key steps.

2. Results and discussion

We have recently shown[31] that reductive conditions using an Mg/TMSCl/DMF system on silicon-tethered diacrylic acid *N*-oxazolidin-2-one derivatives favored intramolecular reductive coupling of the two acrylic units with the preferred formation of C_2-symmetric 3,4-bis-silyl substituted adipic acid derivatives with very high selectivity. Thus, disiloxane **4** led to the formation of a mixture of diastereoisomeric cyclic products, *cis*-**5** and two *trans*-products (*trans*-**6**:*trans*-**7** = 60:40) with a strong preference for the desired *trans*-isomers (*trans*:*cis* = 85:15) (Scheme 1). The isolated yield of the mixture of cyclic products was also very high (85%) but the individual isomers were not separable by column chromatography. We adopted simple procedures in which the *trans*-isomers were separated from *cis*-**5** after which the individual *trans*-isomers were separated by crystallisation. Initially, the mixture of *cis*-**5**, *trans*-**6** and *trans*-**7** was dissolved in ethyl acetate and the *trans*-isomers were precipitated out by adding hexane into the solution. After separating the solid mixture of *trans*-**6** and *trans*-**7** (55%), the gummy mixture containing all three isomers (30%) was treated with lithium hexamethyldisilyl amide in THF at −78 °C. Under these conditions, only *cis*-**5** underwent Dieckmann-type cyclisation to cyclic β-keto esters **8a** and **8b** (Scheme 2) while the *trans*-isomers (15%) remained unaffected leading to easy separation by column chromatography. The combined yield of the *trans*-isomers thus improved to 70%. The individual *trans*-isomers were then separated by fractional crystallisation. For this, a

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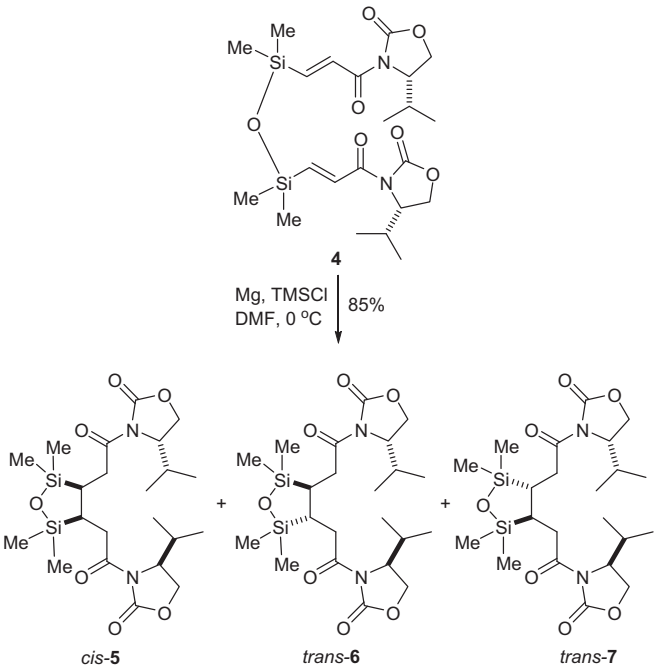
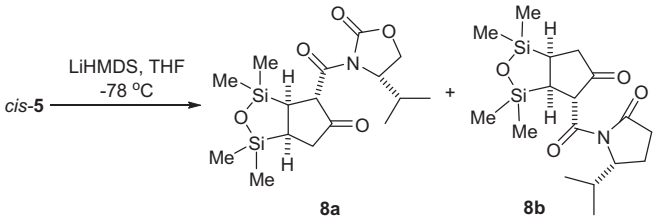
doi:10.1016/j.tetasy.2011.05.004



Scheme 1. Intramolecular reductive coupling induced by magnesium.



Scheme 2. Dieckmann-type cyclisation of *cis*-**5**.

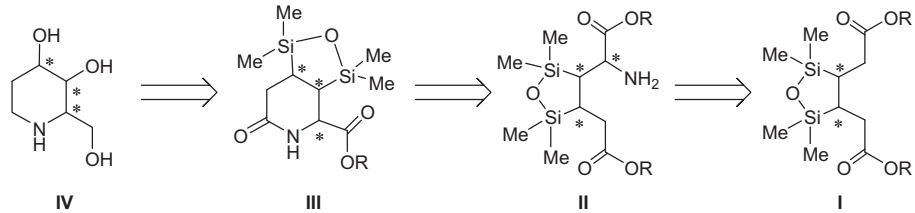
mixture of *trans*-**6** and *trans*-**7** was crystallised from benzene–hexane to give the pure *trans*-**6** product (38%) as needle shaped crystals; the remaining mass was crystallised from hexane–ethyl acetate to give *trans*-**7** (27%) as sugar like crystals.

Our proposed general retrosynthetic strategy (Scheme 3) for the synthesis of fagomine and its stereoisomers from 3,4-bis-silyl substituted adipic acid derivatives **I** is based on; (i) stereoselective introduction of an amino functionality at the α-position of one of the derivatised carboxylic acids to give amine **II**; (ii) intramolecular cyclisation to give lactam **III**; and (iii) the reduction of the carbonyl groups and the conversion of the silicon groups to hydroxyl groups with retention of configuration to give 1,2-dideoxy azasugars **IV**.

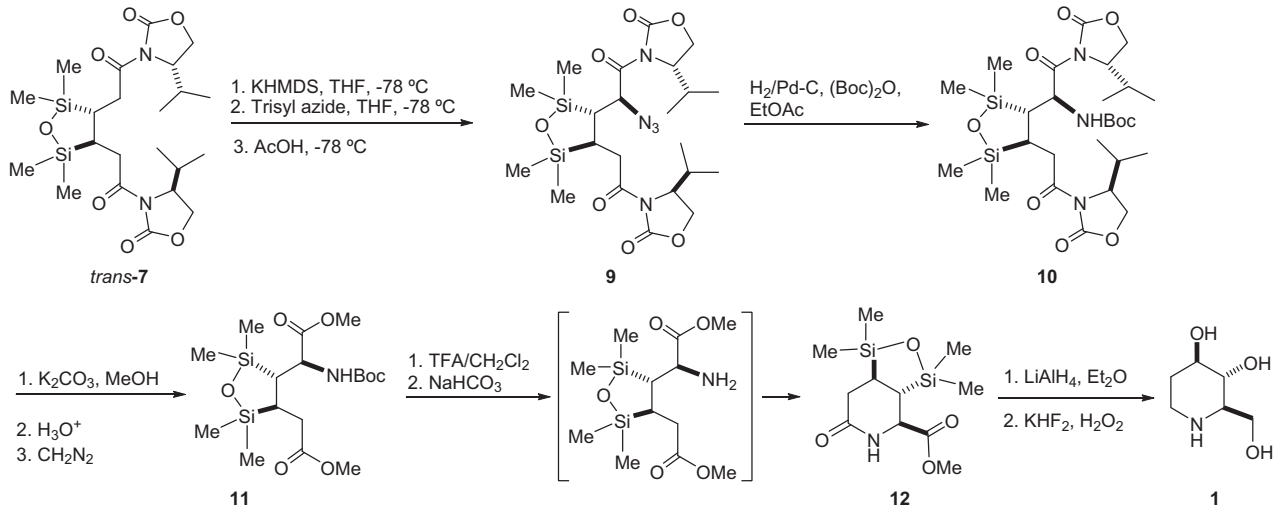
For the synthesis of D-fagomine, 3,4-bis-silyl substituted adipic acid derivative *trans*-**7** was chosen as the starting material because the configurations of the Si-bearing centres matched the configurations required for the OH substituents at the 3- and 4-positions. The introduction of an azido group at the α-position of the carboxamide in *trans*-**7** was carried out following the electrophilic azidation procedure as described by Evans et al.,[32] using KHMDS and trisyl azide. Azide **9** (Scheme 4) was formed as a single diastereoisomer. We were able to observe that the desired stereochemical outcome could be controlled by the valine derived oxazolidin-2-one auxiliary[33] and not by the β-silyl group. The reduction of azide **9** and the in situ protection of the intermediate amine were achieved by the addition of $(Boc)_2O$ in an H_2/Pd–C system to give urethane **10** in excellent yield. The oxazolidin-2-one groups from **10** were removed by treatment with K_2CO_3 in MeOH, resulting in a mixture of dimethyl ester and dicarboxylic acid which upon treatment with diazomethane yielded dimethyl ester derivative **11**. The Boc-protecting group in **11** was removed by treatment with trifluoroacetic acid and the resulting trifluoroacetate salt was basified with $NaHCO_3$ to give the intermediate amine which spontaneously underwent cyclisation to lactam **12**. An $LiAlH_4$ reduction followed by a Fleming–Tamao oxidation[34,35] of lactam **12** using potassium bifluoride and hydrogen peroxide yielded D-fagomine **1**, as confirmed from the ^1H and ^{13}C chemical shift values, and also by comparing the specific rotation values {$[\alpha]_D^{22} = +18.6$ (*c* 0.43, H_2O); lit.[22] $[\alpha]_D^{25} = +18.0$ (*c* 0.92, H_2O)}.

The synthesis of 3,4-di-*epi*-fagomine **3** was achieved in an analogous way as shown for D-fagomine **1**. For this purpose, 3,4-bis-silyl substituted adipic acid derivative *trans*-**6** was chosen as the starting material, because the configurations of the Si-bearing centres matched the configurations required for the OH substituents at the 3- and 4-positions. The stereochemical outcome in the electrophilic azidation in *trans*-**6** was also controlled by the oxazolidin-2-one auxiliary, thus giving azide **13** (Scheme 5) as a single diastereoisomer. Similar to the D-fagomine series, the reduction of azide **13** and the in situ protection of the intermediate amine was achieved by adding $(Boc)_2O$ in an H_2/Pd–C system to give urethane **14**. The oxazolidin-2-one groups from **13** were removed and converted to dimethyl ester derivative **15**. The Boc-protecting group in **15** was removed by treatment with trifluoroacetic acid and the resulting trifluoroacetate salt was basified with $NaHCO_3$ to give the amine **16**. It is interesting to note that amine **16** is stable and did not cyclise to lactam **17**. The cyclisation of amine **16** to lactam **17** was finally achieved by refluxing a xylene solution of amine **16**. An $LiAlH_4$ reduction followed by Fleming–Tamao[34,35] oxidation of lactam **17** using potassium bifluoride and hydrogen peroxide yielded 3,4-di-*epi*-fagomine **3** as confirmed from the ^1H and ^{13}C chemical shift values, and also by comparing the specific rotation values {$[\alpha]_D^{24} = +12.1$ (*c* 0.33, H_2O); lit.[22] $[\alpha]_D^{25} = +13.4$ (*c* 0.32, H_2O)}.

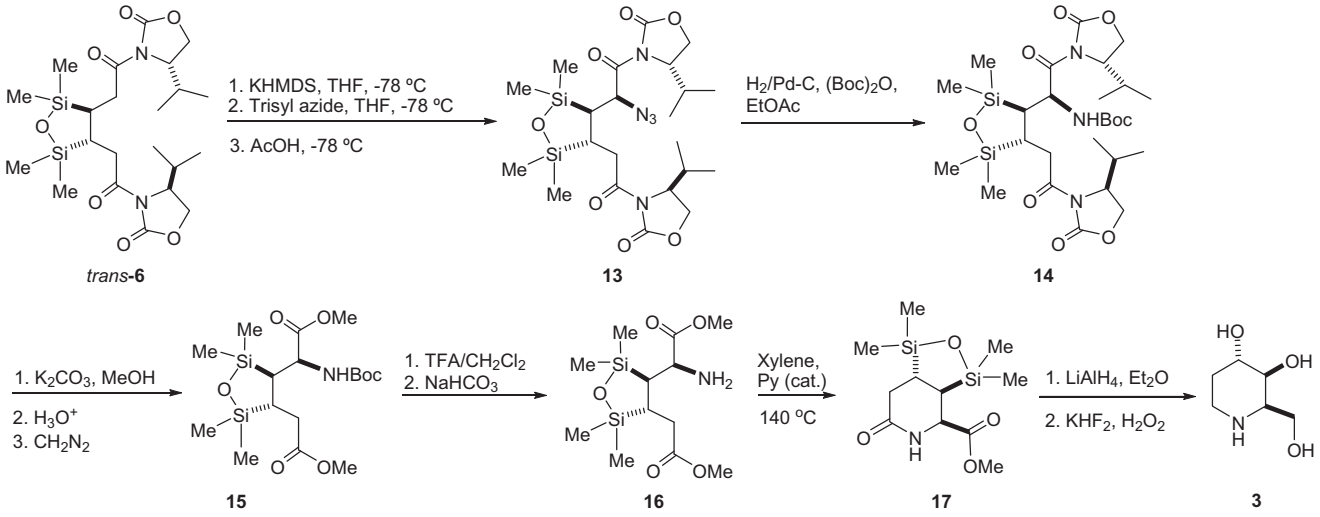
The lactamisation of the intermediate amine derived from **11** was smooth whereas the same sequence for amine **16** to lactam **17** was very difficult, as it required a high temperature and prolonged reaction time. The proposed transition states for both the amines undergoing cyclisation is shown in Scheme 6. While the cyclisation took place, amine **16** had to adopt a conformation wherein the silyl groups have to be disposed axially and the



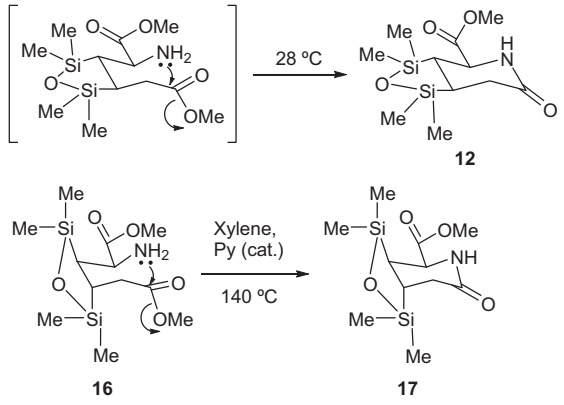
Scheme 3. General retrosynthetic strategy for fagomine stereoisomers.



Scheme 4. Synthesis of D-fagomine.



Scheme 5. Synthesis of D-3,4-di-*epi*-fagomine.



Scheme 6. Proposed transition states for amine cyclisation.

methoxycarbonyl group was in an equatorial position. This makes the system energetically unfavourable, meaning that a very high temperature was required for the lactamisation. On the other hand, for the amine derived from urethane **11**, the silyl groups and methoxycarbonyl group can adopt equatorial positions making the system favourable for lactamisation.

3. Conclusion

In conclusion, we have achieved the stereocontrolled synthesis of D-fagomine and 3,4-di-*epi*-fagomine from C_2-symmetric 3,4-bis-silyl substituted adipic acid di-oxazolidin-2-ones. The Evans' oxazolidin-2-one controlled the stereochemical outcome of the azidation, which supersedes the directing effects of the silyl substituent.

4. Experimental

All reactions were performed in oven-dried (120 °C) or flame-dried glass apparatus under a dry N_2 or argon atmosphere. KHMDS and LiHMDS were freshly prepared, whereas TFA was distilled before use. THF and diethyl ether were distilled over Na/benzophenone. Lithium aluminium hydride, Pd/C (10%), $(Boc)_2O$, trifluoromethanesulfonic acid, KHF_2 and H_2O_2 (30%) were used as received from commercial sources. ^1H and ^{13}C NMR spectra were recorded on Bruker 200/500 MHz spectrometers. Spectra were

referenced to residual chloroform (δ 7.25 ppm, ^{1}H; 77.00 ppm, ^{13}C). Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (pentet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. High resolution mass spectra were recorded at 60–70 eV on a Waters Micromass Q-TOF spectrometer (ESI, Ar). Optical rotations were measured in a JASCO DIP 360 polarimeter. Infrared spectra (IR) were recorded on a JASCO FT IR spectrophotometer in NaCl cells or in KBr discs. Peaks are reported in cm^{-1}. Melting points (mp) were determined on a Fischer John's melting point apparatus and are uncorrected. Analytical thin-layer chromatography was performed using home made silica gel plates (about 0.5 mm). Elemental analyses (C, H, N) were carried out at the Analytical Facility of Bio-Organic Division BARC, Mumbai, India.

4.1. Reductive cyclisation of 4 to give *cis*-5, *trans*-6 and *trans*-7

Freshly distilled trimethylsilyl chloride (21.4 mL, 168.8 mmol) was added to a stirred suspension of magnesium turnings (4.1 g, 168 gatom) in dry DMF (400 mL) at room temperature under an argon atmosphere. After 30 min, the reaction mixture was cooled in an ice-water bath and a solution of disiloxane **4** (7 g, 14.1 mmol) in dry DMF (50 mL) was added slowly over 1.3 h. After the addition was over, the reaction mixture was stirred for 5.5 h and the cold bath was removed. The reaction mixture was allowed to return to room temperature (about 30 min) and then poured into a cold saturated sodium bicarbonate solution and extracted three times with 10% ethyl acetate–hexane. The organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica using hexane–EtOAc as eluent to give a mixture of *cis*-**5**, *trans*-**6** and *trans*-**7** (6 g, 85%). The mixture was dissolved in ethyl acetate and the *trans*-isomers were precipitated out by adding hexane into the solution. The mixture was filtered to give a solid mixture of *trans*-**6** and *trans*-**7** (3.9 g, 55%) and the filtrate was evaporated to give a gummy mixture containing all three isomers (2.1 g, 30%). A pure sample of *cis*-**5** for characterisation purposes was obtained by careful column chromatography of the gummy residue containing a mixture of all isomers.

The gummy mixture of isomers obtained after initial removal of the *trans*-isomers (2.1 g, 4.2 mmol) was dissolved in THF (12 mL) and then added dropwise to a stirred solution of LiHMDS (2.8 mL, 1 M in THF, 2.8 mmol) at −78 °C. After 3 h, the reaction mixture was poured into an aqueous ammonium chloride solution and extracted with ether. The extract was evaporated under reduced pressure and the residue was chromatographed to give a mixture of *trans*-**6** and *trans*-**7** (1.05 g, 50%). The combined solid *trans*-isomeric mixture was crystallised from benzene–hexane to give pure major *trans*-**6** product (2.7 g, 38% overall) followed by crystallisation of the residual mass from hexane–ethyl acetate to give the minor *trans*-**7** product (1.9 g, 27% overall).

4.1.1. Data for (4*S*,4′*S*)-3,3′-(2,2′-((3*S*,4*S*)-2,2,5,5-tetramethyl-1,2,5-oxadisilolane-3,4-diyl)bis(acetyl))bis(4-isopropyloxazolidin-2-one) *trans*-6

Crystalline solid. Mp 162–163 °C (from hexane–EtOAc). $[\alpha]_D^{28} = -5.3$ (*c* 0.87, EtOH). R_f = 0.71 (hexane/EtOAc, 70:30). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H, 2 × SiMe), 0.32 (s, 6H, 2 × SiMe), 0.87 (d, *J* = 7.8 Hz, 6H, 2 × CH*Me*$_A$Me$_B$), 0.92 (d, *J* = 7.8 Hz, 6H, 2 × CHMe$_A$*Me*$_B$), 1.10–1.51 (m, 2H, 2 × Me$_2$Si*H*CH$_2$), 2.27–2.43 (m, 2H, 2 × NCH*H*Me$_2$), 2.81 (dd, *J* = 10.8, 18.6 Hz, 2H, 2 × C*H*$_A$H$_B$CON), 3.43 (dd, *J* = 4.4, 18.6 Hz, 2H, 2 × CH$_A$*H*$_B$CON), 4.17–4.33 (m, 4H, 2 × NCO$_2$*CH*$_2$CH), 4.37–4.44 (m, 2H, 2 × NC*H*CHMe$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.4 (2C), 1.1 (2C), 14.6 (2C), 17.9 (2C), 25.8 (2C), 28.4 (2C), 38.2 (2C), 58.4 (2C), 63.5 (2C), 154.1 (2C), 173.7 (2C). IR ($CHCl_3$ film): 3019, 2966, 1780, 1697, 1388, 1376, 1302, 1252, 1215, 1098, 919, 846, 759 cm^{-1}. *m*/*z* (EI): 483 (M−15, 5%), 327 (27), 328 (100), 260 (81), 228 (15), 213 (19), 199 (71), 174 (34), 149 (32), 133 (66), 117 (19), 73 (22), 69 (21). Anal. Calcd for $C_{22}H_{38}N_2O_7Si_2$: C, 52.98; H, 7.68; N, 5.62. Found: C, 52.95; H, 7.85; N, 5.88.

4.1.2. Data for (4*S*,4′*S*)-3,3′-(2,2′-((3*R*,4*R*)-2,2,5,5-tetramethyl-1,2,5-oxadisilolane-3,4-diyl)bis(acetyl))bis(4-isopropyloxazolidin-2-one) *trans*-7

Crystalline solid. Mp 141–142 °C (from hexane–EtOAc). $[\alpha]_D^{27} = +152.9$ (*c* 0.9, EtOH). R_f = 0.71 (hexane/EtOAc, 70:30). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6H, 2 × SiMe), 0.30 (s, 6H, 2 × SiMe), 0.88 (d, *J* = 7.8 Hz, 6H, 2 × CH*Me*$_A$Me$_B$), 0.92 (d, *J* = 7.8 Hz, 6H, 2 × CHMe$_A$*Me*$_B$), 1.15–1.19 (m, 2H, 2 × Me$_2$Si*H*CH$_2$), 2.28–2.44 (m, 2H, 2 × NCH*H*Me$_2$), 2.82 (dd, *J* = 10.4, 17.8 Hz, 2H, 2 × C*H*$_A$H$_B$CON), 3.41 (dd, *J* = 4.6, 17.8 Hz, 2H, 2 × CH$_A$*H*$_B$CON), 4.17–4.33 (m, 4H, 2 × NCO$_2$*CH*$_2$CH), 4.38–4.45 (m, 2H, 2 × NC*H*CHMe$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.3 (2C), 1.0 (2C), 14.5 (2C), 18.0 (2C), 25.9 (2C), 28.1 (2C), 38.1 (2C), 58.4 (2C), 63.2 (2C), 154.0 (2C), 173.7 (2C). IR ($CHCl_3$ film): 3019, 2965, 2877, 1779, 1696, 1487, 1388, 1302, 1251, 1210, 1096, 920, 846, 751 cm^{-1}. *m*/*z* (EI): 483 (M−15, 5%), 327 (26), 328 (100), 260 (80), 228 (15), 213 (19), 199 (69), 174 (35), 149 (32), 133 (64), 117 (18), 73 (22), 69 (21). Anal. Calcd for $C_{22}H_{38}N_2O_7Si_2$: C, 52.98; H, 7.68; N, 5.62. Found: C, 52.99; H, 7.74; N, 6.21.

4.1.3. Data for (4*S*,4′*S*)-3,3′-(2,2′-((3*R*,4*R*)-2,2,5,5-tetramethyl-1,2,5-oxadisilolane-3,4-diyl)bis(acetyl))bis(4-isopropyloxazolidin-2-one) *cis*-5

Colourless thick gum. $[\alpha]_D^{31} = +58.2$ (*c* 0.67, EtOH). R_f = 0.71 (hexane/EtOAc, 70:30). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.16 (s, 3H, SiMe), 0.17 (s, 3H, SiMe), 0.23 (s, 3H, SiMe), 0.25 (s, 3H, SiMe), 0.88 (d, *J* = 7.0 Hz, 6H, 2 × CH*Me*$_A$Me$_B$), 0.92 (d, *J* = 7.8 Hz, 6H, 2 × CHMe$_A$*Me*$_B$), 1.69–1.73 (m, 1H, Me$_2$Si*H*CH$_2$), 1.82–1.86 (m, 1H, Me$_2$Si*H*CH$_2$), 2.30–2.43 (m, 2H, 2 × NCH*H*Me$_2$), 2.95 (dd, *J* = 9.0, 17.5 Hz, 2H, 2 × C*H*$_A$H$_B$CON), 3.15 (dd, *J* = 6.0, 17.5 Hz, 1H, CH$_A$*H*$_B$CON), 3.22 (dd, *J* = 7.5, 18.0 Hz, 1H, CH$_A$*H*$_B$CON), 4.18–4.23 (m, 2H, NCO$_2$*CH*$_2$CH), 4.26–4.34 (m, 2H, NCO$_2$*CH*$_2$CH), 4.39–4.42 (m, 1H, NC*H*CHMe$_2$), 4.44–4.47 (m, 1H, NC*H*CHMe$_2$). ^{13}C NMR (125 MHz, $CDCl_3$): δ −1.3, −1.1, 0.1, 0.5, 14.5, 14.5, 18.0 (2C), 22.4, 22.9, 28.2, 28.3, 32.9, 33.5, 58.5 (2C), 63.2, 63.3, 154.1, 154.2, 173.4, 173.6. IR ($CHCl_3$ film): 2963, 2977, 1780, 1698, 1387, 1302, 1252, 1208, 1097, 1012, 919 cm^{-1}. *m*/*z* (ESI): 521 (M+Na, 69%), 499 (M+H, 100), 481 (26), 370 (19), 279 (41), 132 (16). HRMS (ESI) calcd for $C_{22}H_{39}N_2O_7Si_2$ [M+H]$^+$: 499.2290; found: 499.2275.

4.2. (*S*)-3-((*R*)-2-Azido-2-((3*R*,4*R*)-4-(2-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetyl)-4-isopropyloxazolidin-2-one 9

A freshly prepared solution of potassium hexamethyldisilazide (KHMDS) (1.3 mL, 1 M solution in THF, 1.3 mmol, 1.3 equiv) was added to a stirred solution of *trans*-**7** (0.5 g, 1 mmol) in dry THF (2.5 mL) at −78 °C. After 30 min, a solution of trisyl azide (0.4 g, 1.3 mmol) in THF (3 mL) was canulated into the reaction mixture and stirred for 8 min. The reaction mixture was quenched with acetic acid (0.3 mL, 5 mmol) at −78 °C and then the temperature was slowly raised to 30 °C. The reaction mixture was evaporated under reduced pressure and the residue was diluted with brine. The reaction mixture was extracted with chloroform and the combined extract was washed with sodium bicarbonate solution, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica using hexane–EtOAc (85:15) as eluent to give azide **9** (0.41 g, 76%) as a thick gum. $[\alpha]_D^{25} = +89.8$ (*c* 1.06, $CHCl_3$). R_f = 0.66 (hexane/EtOAc, 75:25). ^{1}H

NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 3H, SiMe), 0.16 (s, 3H, SiMe), 0.25 (s, 3H, SiMe), 0.34 (s, 3H, SiMe), 0.84–0.97 (m, 12H, 2 × $NCO_2CH_2CHCHMe_2$), 1.41–1.59 (m, 2H, 2 × $Me_2SiCHCH_2$), 2.28–2.44 (m, 2H, 2 × $NCHCHMe_2$), 2.82 (dd, J = 10.2, 18.4 Hz, 1H, CH_AH_BCON), 3.39 (dd, J = 5.4, 18.4 Hz, 1H, CH_AH_BCON), 4.16–4.51 (m, 6H, 2 × NCO_2CH_2CH, 2 × $NCHCHMe_2$), 5.36 (d, J = 6.3 Hz, 1H, CHN_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.0, −0.7, 1.0, 1.3, 14.4, 14.6, 17.7 (2C), 21.7, 28.1, 28.3, 32.9, 38.9, 58.3, 58.8, 63.2, 63.5, 64.0, 153.5, 154.0, 169.7, 173.3. IR ($CHCl_3$ film): 3013, 2965, 2878, 2106, 1780, 1698, 1388, 1252, 1207, 1101, 935, 846 cm^{-1}. Anal. Calcd for $C_{22}H_{37}N_5O_7Si_2$: C, 48.96; H, 6.91; N, 12.98. Found: C, 48.85; H, 6.93; N, 12.81.

4.3. (*S*)-3-((*R*)-2-((*tert*-Butyloxycarbonyl)amino)-2-((3*R*,4*R*)-4-(2-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetyl)-4-isopropyloxazolidin-2-one 10

A catalytic amount of Pd–C (10%) was added to a solution of the azide **9** (0.24 g, 0.44 mmol) and $(Boc)_2O$ (0.3 g, 1.4 mmol) in ethyl acetate (8 mL) and the solution was stirred under hydrogen atmosphere for 24 h at room temperature. The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica using hexane–EtOAc (85:15) as eluent to give the product **10** (0.25 g, 93%) as a colourless solid. Mp 147 °C (from hexane–EtOAc). $[\alpha]_D^{23} = +139.9$ (c 1.07, $CHCl_3$). R_f = 0.54 (hexane/EtOAc, 75:25). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.00 (s, 3H, SiMe), 0.15 (s, 3H, SiMe), 0.30 (s, 3H, SiMe), 0.33 (s, 3H, SiMe), 0.82–0.91 (m, 12H, 2 × $NCO_2CH_2CHCHMe_2$), 1.19–1.52 (m, 2H, 2 × $Me_2SiCHCH_2$), 1.40 (s, 9H, NH*Boc*), 2.29–2.45 (m, 2H, 2 × $NCHCHMe_2$), 2.63 (dd, J = 9.8, 19.0 Hz, 1H, CH_AH_BCON), 3.20 (dd, J = 4.4, 19.0 Hz, 1H, CH_AH_BCON), 4.15–4.47 (m, 6H, 2 × NCO_2CH_2CH, 2 × $NCHCHMe_2$), 5.36–5.50 (m, 2H, *CHNH*Boc). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.2, −0.9, 0.2, 1.0, 14.4, 14.6, 17.8 (2C), 19.1, 28.2 (5C), 33.1, 38.6, 52.0, 58.4, 59.1, 63.3, 64.0, 79.8, 153.4, 154.0, 155.3, 173.4, 174.7. IR ($CHCl_3$ film): 3379, 3019, 2966, 2932, 2877, 1780, 1699, 1489, 1389, 1253, 1207, 929, 846 cm^{-1}. Anal. Calcd for $C_{27}H_{47}N_3O_9Si_2$: C, 52.83; H, 7.72; N, 6.85. Found: C, 52.92; H, 7.73; N, 6.76.

4.4. (*R*)-Methyl 2-((*tert*-butyloxycarbonyl)amino)-2-((3*R*,4*R*)-4-(2-methoxy-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetate 11

Potassium carbonate (138 mg, 1 mmol) was added to a solution of **10** (0.21 g, 0.34 mmol) in methanol (8 mL) at 30 °C and stirred for an hour. After removing the solvent under reduced pressure, the residue was dissolved in water, acidified with dilute HCl and extracted with ethyl acetate. The organic extract was evaporated under reduced pressure and the residue was treated with ethereal diazomethane. The reaction mixture was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane–EtOAc (85:10) as eluent to give the product **11** (0.12 g, 84%) as a colourless liquid. $[\alpha]_D^{25} = +49.2$ (c 1.2, $CHCl_3$). R_f = 0.7 (hexane/EtOAc, 75:25). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 3H, SiMe), 0.11 (s, 3H, SiMe), 0.22 (s, 3H, SiMe), 0.26 (s, 3H, SiMe), 0.87–0.96 (m, 1H, $Me_2SiCHCH_2$), 1.21–1.40 (m, 1H, $Me_2SiCHCH_2$), 1.43 (s, 9H, NH*Boc*), 2.27 (dd, J = 9.7, 16.8 Hz, 1H, $CH_AH_BCO_2Me$), 2.77 (dd, J = 5.0, 16.76 Hz, 1H, $CH_AH_BCO_2Me$), 3.64 (s, 3H, CO_2Me), 3.71 (s, 3H, CO_2Me), 4.39–4.52 (m, 1H, NHC*H*), 5.29 (d, J = 8.6 Hz, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.4, −1.3, 0.6, 0.7, 22.5, 28.3 (3C), 34.3, 35.6, 51.5, 52.1, 53.2, 79.9, 155.2, 173.3, 174.3. IR ($CHCl_3$ film): 3364, 3019, 2955, 2904, 1733, 1715, 1456, 1366, 1254, 1210, 1162, 1055, 933, 847 cm^{-1}. Anal. Calcd for $C_{17}H_{33}NO_7Si_2$: C, 48.66; H, 7.93; N, 3.34. Found: C, 49.08; H, 7.93; N, 2.91.

4.5. (3a*R*,4*R*,7a*R*)-Methyl octahydro-1,1,3,3-tetramethyl-6-oxo-[1,2,5]oxadisilolo[3,4-*c*]pyridine-4-carboxylate 12

Freshly distilled TFA (0.3 mL) was added to a stirred solution of **11** (85 mg, 0.2 mmol) in CH_2Cl_2 (0.3 mL) at 30 °C. After 1 h, the reaction mixture was evaporated and the residue was quenched with an aqueous sodium bicarbonate solution. The reaction mixture was extracted with CH_2Cl_2 and the organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give the cyclised product **12** (57 mg, 99%) as a colourless liquid. $[\alpha]_D^{25} = -20.0$ (c 1.0, $CHCl_3$). R_f = 0.51 ($CHCl_3$/MeOH, 95:5). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.10 (s, 3H, SiMe), 0.21 (s, 3H, SiMe), 0.25 (s, 3H, SiMe), 0.28 (s, 3H, SiMe), 1.02–1.34 (m, 2H, 2 × $Me_2SiCHCH_2$), 2.17 (dd, J = 12.0, 18.0 Hz, 1H, CH_AH_BCON), 2.54 (dd, J = 4.0, 18.0 Hz, 1H, CH_AH_BCON), 3.77 (s, 3H, CO_2Me), 4.12 (d, J = 12 Hz, 1H, *CH*NH), 6.81 (s, br, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ −3.1, −2.5, −0.8, −0.1, 25.4, 30.2, 32.7, 52.3, 58.3, 171.9, 171.8. IR ($CHCl_3$ film): 3303, 3008, 2955, 2898, 1740, 1659, 1469, 1352, 1255, 1201, 1133, 1042, 927, 843 cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{22}NO_4Si_2$ $[M+H]^+$: 288.1087; found: 288.1080.

4.6. D-Fagomine 1

A solution of LAH (91 mg, 2.4 mmol) in dry ether (10 mL) was cannulated into lactam **12** (50 mg, 0.17 mmol) at 0 °C under argon. The reaction temperature was raised to 30 °C and then heated at reflux for 4 h. After cooling to 0 °C, the reaction mixture was diluted with ether and quenched with 15% aqueous NaOH solution and water. The reaction mixture was filtered and the residue was washed well with ether. The combined filtrate was concentrated and hydrogen peroxide (0.5 mL, 30%) was added to it followed by the addition of KHF_2 (90 mg, 1.2 mmol) and THF/MeOH (6 mL, 1:1) as the solvent. After 15 h at 60 °C, the solvent was evaporated under reduced pressure and the white residue was purified by ion-exchange resin to give pure fagomine **1** (17 mg, 68%) as a white solid. $[\alpha]_D^{22} = +18.6$ (c 0.43, H_2O), {lit.[22] $[\alpha]_D^{25} = +18.0$ (c 0.92, H_2O)}. ^{1}H NMR (200 MHz, D_2O): δ 1.35 (dq, J = 4.4, 13 Hz, 1H), 1.80–1.95 (m, 1H), 2.46–2.64 (m, 2H), 2.91–3.04 (m, 1H), 3.09 (t, J = 9.4 Hz 1H), 3.35–3.57 (m, 2H), 3.71 (dd, J = 3.1, 12.0 Hz, 1H). ^{13}C NMR (125 MHz, D_2O): δ 32.0, 42.4, 60.7, 61.0, 72.6, 72.8.

4.7. (*S*)-3-((*R*)-2-Azido-2-((3*S*,4*S*)-4-(2-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetyl)-4-isopropyloxazolidin-2-one 13

Following the procedure for the preparation of **9**, *trans*-**6** (2 g, 4 mmol), KHMDS (8 mL, 1 M solution in THF, 8 mmol, 2 equiv), trisyl azide (2.4 g, 8 mmol) and acetic acid (1.2 mL, 20 mmol) gave azide **13** (1.6 g, 74%) as a colourless solid. Mp 125 °C (from hexane–EtOAc). $[\alpha]_D^{28} = +35.8$ (c 1.01, MeOH). R_f = 0.65 (hexane/EtOAc, 75:25). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 3H, SiMe), 0.24 (s, 3H, SiMe), 0.27 (s, 3H, SiMe), 0.34 (s, 3H, SiMe), 0.82–0.95 (m, 12H, 2 × $NCO_2CH_2CHCHMe_2$), 1.18–1.40 (m, 1H, $Me_2SiCHCH_2$), 1.49–1.59 (m, 1H, $Me_2SiCHCH_2$), 2.23–2.47 (m, 2H, 2 × $NCHCHMe_2$), 2.58 (dd, J = 10.8, 18.0 Hz, 1H, CH_AH_BCON), 3.48 (dd, J = 5.4, 18.0 Hz, 1H, CH_AH_BCON), 4.05–4.59 (m, 6H, 2 × NCO_2CH_2CH, 2 × $NCHCHMe_2$), 5.39 (d, J = 7.6 Hz, 1H, CHN_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.3, −0.9, 0.8, 1.1, 14.4, 14.5, 17.7, 17.8, 23.2, 28.1 (2C), 33.3, 37.2, 58.2, 58.6, 61.9, 63.3, 63.9, 153.7, 154.0, 170.5, 173.2. IR ($CHCl_3$ film): 3019, 2965, 2877, 2105, 1780, 1698, 1387, 1251, 1207, 1102, 934, 844 cm^{-1}. Anal. Calcd for $C_{22}H_{37}N_5O_7Si_2$: C, 48.96; H, 6.91; N, 12.98. Found: C, 49.10; H, 6.96; N, 12.96.

4.8. (*S*)-3-((*R*)-2-((*tert*-Butyloxycarbonyl)amino)-2-((3*S*,4*S*)-4-(2-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetyl)-4-isopropyloxazolidin-2-one 14

Following the procedure for the preparation of **10**, azide **13** (1.5 g, 2.8 mmol) and $(Boc)_2O$ (1.2 g, 5.5 mmol) gave protected amine **14** (1.65 g, 96%) as a colourless solid. Mp 181 °C (from hexane–EtOAc). $[\alpha]_D^{28} = +46.7$ (*c* 1.01, $CHCl_3$). $R_f = 0.5$ (hexane/EtOAc, 75:25). ^1H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 3H, SiMe), 0.11 (s, 3H, SiMe), 0.27 (s, 3H, SiMe), 0.35 (s, 3H, SiMe), 0.82–0.91 (m, 12H, 2 × $NCO_2CH_2CHCH\mathit{Me}_2$), 1.24–1.56 (m, 2H, 2 × $Me_2SiCHCH_2$), 1.40 (s, 9H, NH*Boc*), 2.24–2.45 (m, 2H, 2 × $NCHCHMe_2$), 2.78 (dd, *J* = 10.6, 19.2 Hz, 1H, CH_AH_BCON), 3.72 (dd, *J* = 4.6, 19.2 Hz, 1H, CH_AH_BCON), 4.13–4.37 (m, 6H, 2 × NCO_2CH_2CH, 2 × $NCHCHMe_2$), 4.98 (s, br, 1H, *NH*), 5.69–5.77 (m, 1H, *CH*NHBoc). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.5, −0.2, 0.6, 1.2, 14.4, 14.5, 17.6, 17.7, 21.8, 28.0 (3C), 28.3 (2C), 34.8, 36.9, 52.4, 58.2, 58.5, 63.2, 63.5, 79.6, 153.0, 153.7, 155.0, 173.7, 174.7. IR ($CHCl_3$ film): 3453, 3345, 3019, 2967, 2878, 1782, 1697, 1488, 1389, 1251, 1205, 1101, 919, 844 cm^{-1}. Anal. Calcd for $C_{27}H_{47}N_3O_9Si_2$: C, 52.83; H, 7.72; N, 6.85. Found: C, 53.03; H, 7.70; N, 6.86.

4.9. (*R*)-Methyl 2-((*tert*-butyloxycarbonyl)amino)-2-((3*S*,4*S*)-4-(2-methoxy-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetate 15

Following the procedure for the preparation of **11**, dioxazolidin-2one **14** (1.4 g, 2.3 mmol), K_2CO_3 (1 g, 7.2 mmol), methanol (30 mL) and diazomethane gave the pure product **15** (0.83 g, 86%) as a colourless liquid. $[\alpha]_D^{28} = -11.0$ (*c* 1.02, $CHCl_3$). $R_f = 0.7$ (hexane/EtOAc, 75:25). ^1H NMR (200 MHz, $CDCl_3$): δ 0.10 (s, 3H, SiMe), 0.12 (s, 3H, SiMe), 0.22 (s, 3H, SiMe), 0.30 (s, 3H, SiMe), 1.19–1.52 (m, 2H, 2 × $Me_2SiCHCH_2$), 1.43 (s, 9H, NH*Boc*), 2.18 (dd, *J* = 11.2, 16.2 Hz, 1H, $CH_AH_BCO_2Me$), 2.90 (dd, *J* = 3.5, 16.2 Hz, 1H, $CH_AH_BCO_2Me$), 3.64 (s, 3H, CO_2Me), 3.73 (s, 3H, CO_2Me), 4.44–4.59 (m, 1H, NHC*H*), 4.76 (s, br, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.7, −0.3, 0.3, 0.6, 22.3, 28.0 (3C), 34.7, 35.1, 51.1, 51.8, 52.4, 79.8, 155.1, 173.8 (2C). IR ($CHCl_3$ film): 3517, 3345, 3019, 2954, 2903, 1735, 1718, 1499, 1366, 1253, 1204, 1169, 936, 846 cm^{-1}. Anal. Calcd for $C_{17}H_{33}NO_7Si_2$: C, 48.66; H, 7.93; N, 3.34. Found: C, 48.76; H, 7.91; N, 3.41.

4.10. (*R*)-Methyl 2-(amino)-2-((3*S*,4*S*)-4-(2-methoxy-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetate 16

Freshly distilled TFA (2 mL) was added to a stirred solution of urethane **15** (0.5 g, 1.2 mmol) in CH_2Cl_2 (2 mL) at 30 °C. After 1 h, the solvent was removed under reduced pressure and the residue was diluted with aqueous sodium bicarbonate solution. The mixture was extracted with CH_2Cl_2 and the organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give amine **16** (0.37 g, 96%) as a brown liquid. $[\alpha]_D^{25} = -10.4$ (*c* 1.04, $CHCl_3$). $R_f = 0.35$ (hexane/EtOAc, 75:25). ^1H NMR (200 MHz, $CDCl_3$): δ −0.06 (s, 3H, SiMe), 0.04 (s, 3H, SiMe), 0.06 (s, 3H, SiMe), 0.12 (s, 3H, SiMe), 0.94–1.10 (m, 1H, $Me_2SiCHCH_2$), 1.25–1.39 (m, 1H, $Me_2SiCHCH_2$), 1.56 (s, br, 2H, NH_2), 2.03 (dd, *J* = 11.4, 16.1 Hz, 1H, $CH_AH_BCO_2Me$), 2.39 (dd, *J* = 5.0, 19.2 Hz, 1H, $CH_AH_BCO_2Me$), 3.28 (d, *J* = 7.8 Hz, 1H, *CH*NH_2), 3.49 (s, 3H, CO_2Me), 3.57 (s, 3H, CO_2Me). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.6, −0.8, 0.6, 1.2, 22.8, 34.9, 36.6, 51.2, 51.5, 54.8, 173.8, 177.4. IR ($CHCl_3$ film): 3430, 3394, 3302, 3017, 2953, 2903, 2847, 1735, 1437, 1353, 1252, 1202, 1105, 1008, 930, 846 cm^{-1}.

4.11. (3a*S*,4*R*,7a*S*)-Methyl octahydro-1,1,3,3-tetramethyl-6-oxo-[1,2,5]oxadisilolo[3,4-*c*]pyridine-4-carboxylate 17

A solution of the amine **16** (0.35 g, 1.1 mmol) and pyridine (0.3 mL) in freshly distilled *p*-xylene (45 mL) was gently refluxed at 145 °C under an argon atmosphere. After 9 h, the reaction mixture was evaporated under reduced pressure and the residue was purified by column chromatography on silica using $CHCl_3$/MeOH (97:3) as eluent to give product **17** (0.22 g, 70%) as a colourless liquid. $[\alpha]_D^{27} = +80.9$ (*c* 0.88, $CHCl_3$). $R_f = 0.5$ ($CHCl_3$/MeOH, 95:5). ^1H NMR (200 MHz, $CDCl_3$): δ 0.00 (s, 3H, SiMe), 0.10 (s, 3H, SiMe), 0.20 (s, 3H, SiMe), 0.30 (s, 3H, SiMe), 1.33–1.43 (m, 1H, $Me_2SiCHCH_2$), 1.56–1.72 (m, 1H, $Me_2SiCHCH_2$), 2.16 (dd, *J* = 12.2, 17.7 Hz, 1H, CH_AH_BCON), 2.51 (dd, *J* = 5.1, 17.7 Hz, 1H, CH_AH_BCON), 3.68 (s, 3H, CO_2Me), 4.33 (dd, *J* = 3, 5.9 Hz, 1H, *CH*NH), 7.03 (s, br, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ −3.2, −1.7, −0.4 (2C), 19.8, 29.2, 32.7, 52.1, 55.5, 171.9, 172.9. IR ($CHCl_3$ film): 3301, 3009, 2955, 2899, 1741, 1659, 1469, 1353, 1256, 1201, 1132, 1042, 925, 842 cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{22}NO_4Si_2$ $[M+H]^+$: 288.1087; found: 288.1094.

4.12. D-3,4-Di-*epi*-fagomine 3

Following the procedure for the preparation of fagomine **1**, lactam **17** (70 mg, 0.24 mmol), lithium aluminium hydride (100 mg, 2.6 mmol), hydrogen peroxide (0.6 mL, 30%) and KHF_2 (0.11 g, 1.4 mmol) gave pure 3,4-di-*epi*-fagomine **3** (23 mg, 65%) as a colourless liquid. $[\alpha]_D^{25} = +12.1$ (*c* 0.33, H_2O), {lit.[22] $[\alpha]_D^{25} = +13.4$ (*c* 0.32, H_2O)}. ^1H NMR (200 MHz, D_2O): δ 1.51–1.67 (m, 1H), 1.87–2.06 (m, 1H), 2.90–3.02 (m, 2H), 3.16–3.27 (m, 1H), 3.58–3.66 (m, 2H), 3.66–3.74 (m, 1H), 3.79–3.88 (m, 1H). ^{13}C NMR (50 MHz, D_2O): δ 27.6, 41.0, 57.8, 62.2, 68.2, 69.3.

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