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Synthesis of substituted conformationally constrained 6,5- and 7,5-fused bicyclic lactams as dipeptide mimics

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Abstract—Using a convenient and practical route we report the preparation of a series of rigid surrogates of amino acids and dipeptides for application within constrained peptide analogues, and for employment as input for combinatorial science. These substituted 2-oxo-1-azabicycloalkane amino acids have the potential of replicating the backbone geometry and side-chain function of dipeptide residues like serine, lysine, glutamate, and related amino acids.

1. Introduction

Design and synthesis of novel bicyclic lactams as peptidomimetics is currently an area of intensive research in the field of peptide and medicinal chemistry.[1] Because of the intrinsic interest of these substrates as ligands for a wide variety of biological receptors, incorporation of these scaffolds into peptide chains can be used to generate novel structures of significant relevance to biological application. In the course of our studies on peptide secondary structure mimics, we have synthesised several 6,5- and 7,5-fused azabicycloalkane amino acids.[2–7] These structures can be regarded as conformationally restricted substitutes for Ala-Pro and Phe-Pro dipeptide units.[8–10] Functionalizing these molecules with different appendages is a very attractive target, because the side-chains could improve peptide–receptor affinity by interacting with hydrophobic or hydrophilic pockets of the receptor. On the other hand, diversification of bicyclic lactams by tethering of different pharmacophoric groups may generate library members exhibiting different biological activity. Finally, similarly to the unsubstituted constrained dipeptide mimics,[11] these lactams can be incorporated into cyclic pseudopeptides containing the RGD epitope. As such, these molecules can be homed selectively to tissues that over-express these receptors (e.g. epithelial cells involved in vascular growth), and thus can serve to control selective delivery of drugs which may be appended to the lactam substituent.[12]

The generation of different conformationally constrained dipeptide mimetic units broadens the scope of our library of structures. In the light of the importance of amino acid side-chains as sites for interaction in various recognition events, we report here an extension of the versatile approach to the synthesis of azabicyclo[X.Y.0]alkanes[5] that possess hetero-atom-substituted side-chains at the 7 (or 8)-position (Scheme 1).

The synthetic plan relies on the (*Z*)-selective Horner–Emmons/double bond reduction that we have described for the unsubstituted compounds,[5] but uses as starting material the aldehydes **1** and **2**, which carry an appendage on the C4 position of Pro ring. The resulting lactams **5a**,**b** and **6a**,**b** feature a protected hydroxy terminal side-chain. Elaboration of the side-chain through a conversion of the primary hydroxy group into an azide function is also demonstrated starting from **5b**.

2. Results and discussion

2.1. Chemistry

The synthesis of lactams **5a**,**b** and **6a**,**b** was accomplished following the general synthetic plan outlined in Scheme 1. The starting aldehydes **1** and **2** were stereoselectively synthesized from the 3-allyl-pyroglutamic ester **7**

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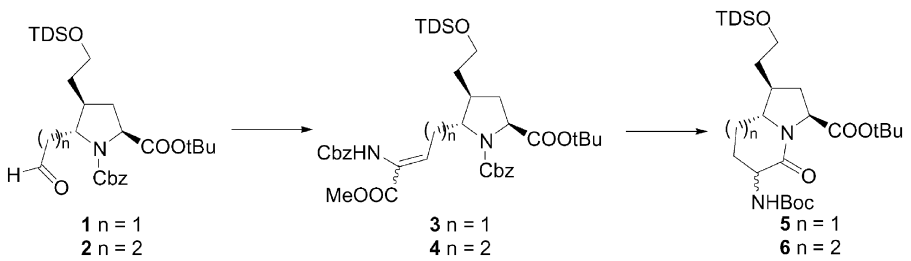


Scheme 1. General scheme for the synthesis of functionalized bicyclic lactams.

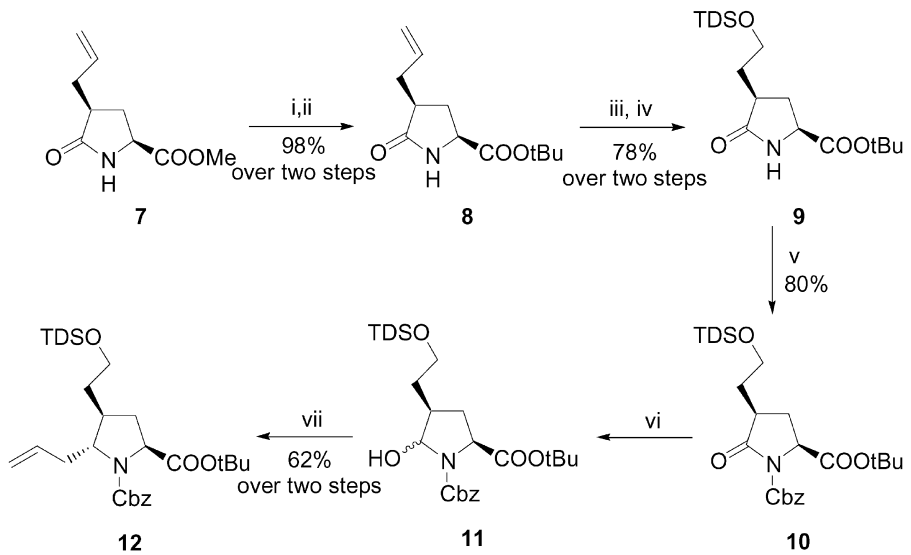
(Scheme 2), readily obtainable from glutamic acid via a known procedure.[13] After the conversion of the methyl ester into the corresponding *tert*-butyl derivative,[14] ozonolysis of **8** followed by treatment with $NaBH_4$ gave the corresponding alcohol which was protected as a thexyldimethylsilyl ether giving **9** in 78% yield over two steps. The lactam **9** was *N*-protected as a *N*-Cbz derivative using LiHMDS and CbzCl in a THF solution[15] affording **10** in 80% yield.

Selective reduction of the imide **10** to the hemiaminal **11** was performed using lithium triethylborohydride at −78°C.[16] The hemiaminal was then treated with allyltributyltin[17] in the presence of *tert*-butyldimethylsilyltriflate[7] in anhydrous CH_2Cl_2 to afford **12** in 62% yield after the two steps as the only isomer. The stereochemistry of the newly formed stereocentre was determined by NOESY experiments. The *trans* arrangement was evidenced by the presence of NOE cross peaks between the proton H5 of the proline moiety and the protons adjacent to the heteroatom on the side-chain in position C4. The nucleophilic addition of the allyl unit selectively occurs *trans* to the adjacent side-chain, as we have already observed in previous work on related systems.[7]

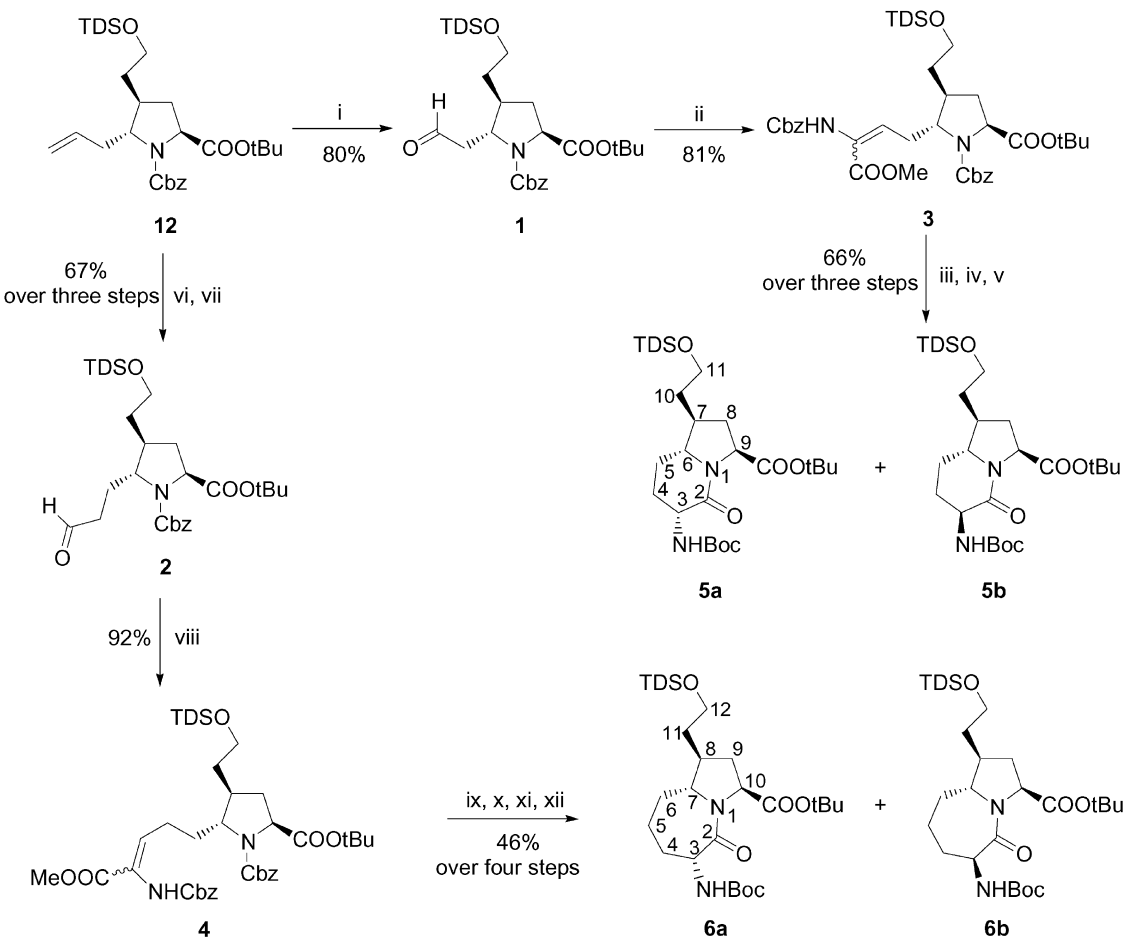
The 5-allyl proline **12** was exploited as the common intermediate for the synthesis of both series of 2-oxoazabicycloalkane **5a**,**b** and **6a**,**b** according to Scheme 3.

Reductive ozonolysis of the double bond in **12** gave the aldehyde **1** which was converted into **3** by standard Horner–Emmons protocol with the commercially available (*Z*)-α-phosphonoglycine trimethyl ester[18] in 65% yield over two steps [9:1 (*Z*)/(*E*) ratio]. The *N*-Cbz group adjacent to the methyl ester was further protected as a Boc derivative and the resulting fully protected compound was submitted to catalytic hydrogenation which effected, in one operation, the removal of both *N*-Cbz protective groups and reduction of the double bond. Final lactam formation was accomplished by refluxing the crude hydrogenation product in methanolic iPr$_2$EtN. The bicyclic lactams **5a** and **b** were thus obtain in 66% yield (over the three steps) as a 2:8 mixture of diastereoisomers. The stereochemistry of the newly formed stereocentre was determined by NOESY experiments. In compound **5a** a strong NOE crosspeaks between H3 and H6 was observed while in compound **5b** this effect was not detected.

The aldehyde **2** was prepared starting from the 5-allyl proline **12** by hydroboration and Swern oxidation (67% over 2 steps). The homologous aldehyde was treated with the (*Z*)-α-phosphonoglycine trimethyl ester to give **4**, mainly as a *Z*-isomer, in 92% yield. *N*-Boc protection followed by methyl ester hydrolysis with NaOH in THF gave the corresponding acid, which was reduced (H_2/Pd–C) and subsequently cyclized with condensing agents HATU, HOAt, 2,4,6-collidine, DMF) to give the easily separated lactams **6a** and **b** in 5.4:1.0 ratio and 46% overall yield. The stereochemistry of the final products was



Scheme 2. *Reagents and conditions*: (i) NaOH, THF, 99%; (ii) *O*-*tert*-butyl-*N*,*N*-diisopropyl-isourea, CH_2Cl_2, reflux, 99%; (iii) O_3, MeOH, $NaBH_4$, 80%; (iv) TBDMSCl, imidazole, DMF, 98%; (v) CbzCl, LiHMDS, THF, 80%; (vi) $LiEt_3BH$, THF, −78°C; (vii) allyltributyltin, TBDSOTf, CH_2Cl_2, −78°C, 62% over two steps.



Scheme 3. *Reagents and conditions*: (i) O_3, MeOH, Me_2S, 80%; (ii) (±)-(*Z*)-α-phosphonoglycine trimethyl ester, *t*BuOK, CH_2Cl_2, −78°C, 81%; (iii) Boc_2O, 4-DMAP, THF, 91%; (iv) H_2, Pd/C, MeOH; (v) MeOH, DIPEA, reflux, 73% over two steps; (vi) 9-BBN, THF, 83%; (vii) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −60°C, 81%; (viii) (±)-(*Z*)-α-phosphonoglycine trimethyl ester, *t*BuOK, CH_2Cl_2, −78°C, 92%; (ix) Boc_2O, 4-DMAP, THF, 87%; (x) NaOH, THF; (xi) H_2, Pd/C, MeOH; (xii) HATU, HOAt, 2,4,6-collidine, DMF, 53% over three steps.

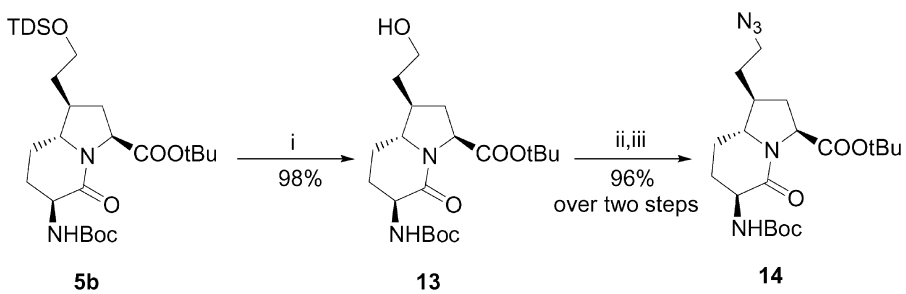
unequivocally determined by NOESY experiments. In the compound **6a** a strong NOE crosspeak between H3 and H12 was observed while in compound **6b** this effect was not detected.

Finally, modification of the lactam side-chain was demonstrated in the case of **5b**, as shown in Scheme 4. Thus, silyl ether deprotection of **5b** (TBAF, THF 98%) and activation of **13** with MsCl followed by nucleophilic displacement with sodium azide in DMF at 80°C gave azide **14**. The azide was isolated in 94% overall yield from **5b**. This structure can be regarded as conformational restricted substitute for Ala-Lys dipeptide unit and can be considered a suitable starting material for the preparation of Ala-Arg dipeptide unit when a guanidine is inserted instead of the azido group.

2.2. Molecular modeling

Computational studies designed to investigate the ability of the new bicyclic scaffolds to adopt reverse-turn conformations were performed on the *N*-acetyl-*N*′-methylamide dipeptide analogues **15a**,**b** and **16a**,**b**[19] (Fig. 1).

Each structure was subjected to an extensive, unconstrained Monte Carlo/Energy Minimization (MC/EM) conformational search[20] by molecular mechanics methods in



Scheme 4. *Reagents and conditions*: (i) TBAF, THF, 98%; (ii) MsCl, TEA, CH_2Cl_2, 0°C; (iii) NaN_3, DMF, 80°C, 96% over two steps.

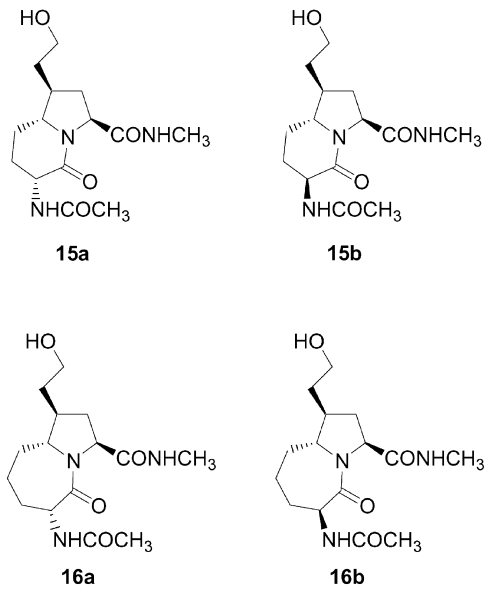


Figure 1. Bicyclic dipeptide mimics used in modelling studies.

water as implicitly represented by the GB/SA solvation model[21] (see Section 4.2). According to the previously reported conformational analysis of unsubstituted azabicycloalkane amino acids,[8] reverse-turn inducing properties of the minimum energy conformations of **15a**,**b**, **16a**,**b** were assessed by computing and analyzing different geometrical parameters (Table 1): the $C\alpha_i - C\alpha_{i+3}$ distance ($d\alpha$) between capping groups on the N- and C termini, the ϕ and ψ backbone torsion angles in residues $i+1$ and $i+2$,[22] the virtual torsion angle β ($C_i - C\alpha_i + 1 - C\alpha_{i+2} - N_{i+3}$),[23] and parameters indicative of hydrogen bonding (distance between the carbonyl oxygen and the amide hydrogen atom, and directional requirements).

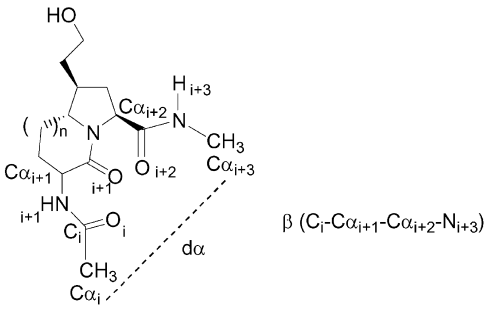
A summary of the reverse-turn mimetic properties of the calculated structures of compounds **15a**,**b** and **16a**,**b** is reported in Table 1. The turn propensity was quantitatively assessed by computing the percentage of conformations within 6 kcal/mol from the global minimum for which the aforementioned parameters assume typical turn values.[24]

The percentage of all conformers with a virtual torsion angle β (absolute value) of less than 30° or 60° shows that **15b** and **16b**, having the carboxy and amino groups on the same face of the bicyclic system (3*S*-Pro Cα *S* configuration) are of potential use as reverse-turn mimetics, although there is a dependence on the lactam ring size. On the contrary, among the (3*R*-Pro Cα *S*) diastereoisomers only the 7,5-fused lactam **16a** is able to enforce a turn which actually induces the peptide backbone to reverse direction.

The percentages of conformers forming intramolecular hydrogen bonds show that the reverse-turn mimetic units **15b** and **16a**,**b** can promote either a γ-turn (7-membered ring H-bond) or a β-turn (10-membered ring H-bond). In the 6,5-fused bicyclic lactam **15a**, the formation of a γ-turn is not sufficient to reverse the peptide direction, as indicated by the values of the torsion angle β and the distance $d\alpha$. The relative stabilities of the principal backbone geometries calculated for compounds **15a**,**b** and **16a**,**b** are given in the last column of Table 1.

The quantitative characterization of the turn propensity of the functionalized azabicycloalkane amino acid scaffolds

Table 1. Quantitative characterization of the reverse-turn forming ability of the conformers (MC/EM, AMBER *, H_2O GB/SA) calculated for dipeptide mimics **15a**,**b**, **16a**,**b**



Compound	% $d\alpha$[a] <7 Å	%$\lvert\beta\rvert$[b] <30°	%$\lvert\beta\rvert$[b] <60°	%H-bond[c] 7-membered ring, γ-turn	%H-bond[c] 10-membd. ring, β-turn	ΔE (kcal/mol) γ-turn/β-turn
15a	0	1	18	29	0+0[d]	0.5[e]/-
15b	32	64	95	27	22+9[d]	0.6[e]/0.3[f]
16a	30	76	97	21	0+20[d]	0.2[e]/2.9[g]
16b	60	26	66	21	24+11[d]	1.8[e]/0.0[h]

[a] % $d\alpha$ is the percentage of all conformers for which the distance between $C\alpha_i$ and $C\alpha_{i+3}$ is <7 Å.
[b] % $\lvert\beta\rvert$ is the percentage of all conformers in which the virtual torsion angle β (absolute value) is <30° (or 60°).
[c] % H-bond is the percentage of all conformers in which H···O distance <2.5 Å, N–H···O bond angle >120°, and H···O=C angle >90°.
[d] Percentage of conformers in which 2.5 Å <H···O distance <4 Å.
[e] Inverse γ-turn.
[f] Type II′ β-turn.
[g] Distorted type II′ β-turn.
[h] Type I β-turn.

suggests that these systems are more effective as reverse-turn than as beta-turn mimics, in agreement with the results obtained for the corresponding unsubstituted bicyclic lactams.[8] Nevertheless, the functionalized bicyclic lactams **15b** and **16b** show β-turn mimetic properties higher than the corresponding unsubstituted scaffolds.[8,25]

The lowest energy conformers mimicking a β-turn of the dipeptide mimics **15b** and **16b** are shown in Figure 2.

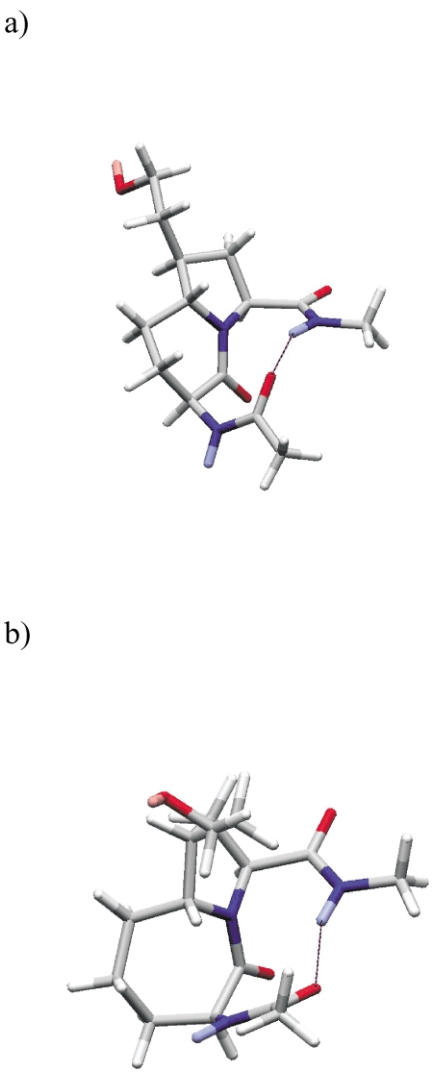


Figure 2. (a) Minimum energy conformer of **15b** featuring the type II′ β-turn. (b) Minimum energy conformer of **16b** featuring the type I β-turn.

3. Conclusion

In conclusion, using a convenient and practical route we have reported the preparation of novel conformationally constrained scaffolds with the potential of replicating the backbone geometry and side-chain function of dipeptide residues like serine, lysine, glutamate, and related amino acids. These amino acid motifs may be used as conformationally constrained entities that mimic segments of natural peptide substrates. Alternatively, the functionalised side-chain could be used as a site to append pharmacologically relevant groups to enhance protein–protein or receptor–substrate interaction. The *trans* relation between the stereocenter in 6 and 9 and 7 and 10, respectively, in the bicyclic lactams, was achieved by a stereoselective allylation of the hemiaminal **11**. After hydrogenation, the lactams were obtained as easily separable mixtures of stereoisomers epimeric at the carbon adjacent to the lactam carbonyl group.

Applications of these compounds as reverse-turn inducers and as scaffolds for the synthesis of biologically active compounds are being studied in our laboratory.

4. Experimental

4.1. Chemistry

General remarks. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution as indicated, at 200 (or 300, 400) and 50.3 MHz, respectively. The chemical shift values are given in ppm and the coupling constants in Hz. Optical rotation data were obtained with a Perkin–Elmer model 241 polarimeter. Thin-layer chromatography (TLC) was carried out using Merck precoated silica gel F-254 plates. Flash chromatography was carried out using Macherey–Nagel silica gel 60, 230–400 mesh. Solvents were dried according to standard procedures, and reactions requiring anhydrous conditions were performed under nitrogen. Solutions containing the final products were dried with Na_2SO_4, filtered, and concentrated under reduced pressure using a rotary evaporator. Elemental analyses were performed by the staff of the microanalytical laboratory in our department. Abbreviations: HATU: *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, HOAt: 1-hydroxy-7-azabenzotriazole, DMAP: 4-(dimethylamino)pyridine, TBAF: tetrabutylammonium fluoride, DMF: *N*,*N*-dimethylformamide, THF: tetrahydrofuran, Boc_2O: di-*tert*-butyl dicarbonate, DMSO: methyl sulfoxide.

General procedure A, preparation of acrylic ester **3** and **4** by Horner–Emmons reaction (Scheme 1). To a stirred solution of *t*BuOK (0.115 mmol) in dry CH_2Cl_2 (1 mL) under nitrogen, a solution of (*Z*)-α-phosphonoglycine trimethyl ester (0.115 mmol) in dry CH_2Cl_2 (0.5 mL) was added at −78°C. The resulting mixture was stirred for 30 min at this temperature and then a solution of the appropriate aldehyde (0.076 mmol) in dry CH_2Cl_2 (1 mL) was added. After 5 h, the solution was allowed to warm to room temperature and neutralised with phosphate buffer. The aqueous phase was extracted with CH_2Cl_2, the combined extracts were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate) to afford the acrylic ester as a (*Z*)/(*E*) diastereoisomeric mixture.

General procedure B, preparation of the *N*-Boc-protected acrylic ester. A solution of the acrylic ester (0.058 mmol), $(Boc)_2O$ (0.117 mmol), and a catalytic amount of DMAP in dry THF (1 mL) was stirred for 30 min under nitrogen. The solution was then quenched with water (1 mL) and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash

chromatography (hexane/ethyl acetate) to yield the Boc-protected acrylic ester.

4.1.1. Synthesis of the intermediate 12 (Scheme 2). *Ester* **8**. To a solution of **7**[13] (1.7 g, 9.34 mmol) in THF (94 mL) was added 2N NaOH (9.34 mL, 18.68 mmol). After stirring for 30 min at room temperature Amberlite IR 120H$^+$ was added and then the reaction mixture was filtered and the solvent was evaporated under reduced pressure to yield 1.56 g of acid (99%) as a white solid; mp 123–124°C. $[\alpha]_D^{20}$=+57.1 (c=0.9, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.95 (m, 1H, –*H*CH–), 2.21 (m, 1H, –*H*CH–), 2.61 (m, 2H, –C*H*$_2$–), 3.71 (m, 1H, –C*H*C=O), 4.32 (m, 1H, –C*H*CO$_2$H), 5.09 (m, 2H, –CH=C*H*$_2$), 5.72 (m, 1H, –C*H*=CH$_2$), 7.52 (bs, 1H, N*H*), 8.35 (bs, 1H, –COO*H*). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=180.6, 174.9, 134.6, 117.5, 54.5, 41.2, 34.7, 30.2. FAB$^+$MS: calcd. For $C_8H_{11}NO_3$ 169.07; found 170. $C_8H_{11}NO_3$ (169.07): calcd. C 56.80, H 6.55, N 8.28; found C 56.71, H 6.52, N 8.29. To a solution of acid (1.58 g, 9.34 mmol) in dry CH_2Cl_2 (93.4 mL) was added *O-tert*-butyl-*N*,*N*-diisopropyl-isourea (6.7 mL, 28.01 mmol) and the mixture was refluxed for 48 h. The solvent was then evaporated and the residue was treated with Et_2O to remove the urea formed as the major by-product. The collected organic solvents were evaporated and the crude was purified by flash chromatography (hexane/ethyl acetate, 3:7) affording 2.08 g of **8** (99%) as a colorless oil. $[\alpha]_D^{20}$=+31.9 (c=1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.48 (s, 9H, C(C*H*$_3$)$_3$), 1.81 (m, 1H, –*H*CH–), 2.17 (m, 1H, –*H*CH–), 2.55 (m, 3H), 4.12 (m, 1H, –C*H*CO$_2$*t*Bu), 5.13 (m, 2H, –CH=C*H*$_2$), 5.71 (m, 1H, –C*H*=CH$_2$), 5.81 (bs, 1H, N*H*). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=178.5, 170.9, 135.2, 117.0, 82.2, 54.3, 40.6, 35.0, 30.4, 27.9. FAB$^+$MS: calcd. For $C_{12}H_{19}NO_3$ 225.14; found 226. $C_{12}H_{19}NO_3$ (225.14): calcd. C 63.98, H 8.50, N 6.22; found C 64.04, H 8.55, N 6.28.

Silyl derivative **9**. A stirred solution of **8** (1.16 g, 5.16 mmol) in MeOH (52 mL) was cooled to −60°C, whereupon O_3 was bubbled through it (flow rate=30 L/h). After 1.5 h N_2 was bubbled through the reaction mixture in order to eliminate the excess of O_3. $NaBH_4$ was then added in portions until the ozonide had completely disappeared. The solvent was evaporated under reduced pressure and the residue was redissolved in EtOAc and washed with brine. The organic phases were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate) to yield 0.946 g of alcohol (80%) as a white solid. Mp 82–83°C. $[\alpha]_D^{20}$=−14.2 (c=1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.48 (s, 9H, –C(C*H*$_3$)$_3$), 1.75 (m, 1H, –*H*CHCH$_2$OH), 1.81 (m, 1H, –*H*CHCHCOO*t*Bu), 2.04 (m, 1H, –*H*CHCH$_2$OH), 2.69 (m, 1H, –C*H*C=O), 2.72 (m, 1H, –*H*CHCHCOO*t*Bu), 3.65 (m, 1H, –HC*H*OH), 3.79 (m, 2H, –HC*H*OH, –O*H*), 4.15 (m, 1H, –C*H*COO*t*Bu), 5.92 (bs, 1H, N*H*). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=179.4, 170.0, 81.8, 60.7, 54.4, 40.0, 33.4, 31.7, 27.3. FAB$^+$MS: calcd. For $C_{11}H_{19}NO_4$ 229.13; found 230. $C_{11}H_{19}NO_4$ (229.13): calcd. C 57.62, H 8.35, N 6.11; found C 57.51, H 8.21, N 6.05. — To a stirred solution of the alcohol (0.708 g, 3.09 mmol), in DMF (4 mL), texyldimethylsilyl chloride (1.82 mL, 9.27 mmol) and imidazole (1.26 g, 18.55 mmol) were added sequentially. After 16 h the solvent was evaporated and the crude was purified by flash chromatography (hexane/ethyl acetate 1:1) to yield 1.12 g of **9** (98%) as a colorless oil. $[\alpha]_D^{20}$=+10.0 (c=1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.12 (s, 6H, –Si(C*H*$_3$)$_2$), 0.83–0.90 (m, 12H, –C*H*$_3$), 1.50 (s, 9H, –C(C*H*$_3$)$_3$), 1.55 (m, 1H, –*H*CHCH$_2$OSi), 1.63 (m, 1H, –C*H*(CH$_3$)$_2$), 1.90 (m, 1H, –*H*CHCH$_2$OSi), 2.15 (m, 1H, –*H*CHCHCOO*t*Bu), 2.60 (m 1H, –C*H*C=O), 2.71 (m, 1H, –*H*CHCHCOO*t*Bu), 3.75 (m, 2H, –C*H*$_2$OSi), 4.12 (m, 1H, –C*H*COO*t*Bu), 6.22 (bs, 1H, N*H*). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=179.1, 170.8, 60.8, 54.4, 38.7, 34.0, 33.8, 32.1, 27.8, 20.2, 18.4, −3.5, −3.6. FAB$^+$MS: calcd. For $C_{19}H_{37}NO_4Si$ 371.25; found 372. $C_{19}H_{37}NO_4Si$ (371.25): calcd. C 61.41, H 10.04, N 3.77; found C 61.51, H 10.10, N 3.87.

N-Cbz-protected silyl derivative **10**. To a solution of **9** (0.552 g, 1.48 mmol) in THF (5 mL) was added LiHMDS 1 M in THF (1.63 mL, 1.63 mmol) at −50°C. After 20 min benzyl chloroformate (0.230 mL, 1.63 mmol) was added and the solution was stirred for 20 min after which a saturated solution of NH_4Cl was added, the aqueous phase was extracted with EtOAc and the organic phase dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (hexane/ethyl acetate 8:2) yielding 0.603 g (80%) of **10** as a colorless oil. $[\alpha]_D^{20}$=−10.6 (c=1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.12 (s, 6H, –Si(C*H*$_3$)$_2$), 0.61 (m, 12H, –C*H*$_3$), 1.48 [s, 9H, –C(C*H*$_3$)$_3$], 1.55 (m, 2H, –*H*CHCH$_2$OSi, –C*H*(CH$_3$)$_2$), 1.75 (m, 1H, –*H*CHCHCOO*t*Bu), 2.11 (m, 1H, –*H*CHCH$_2$OSi), 2.55 (m, 1H, –*H*CHCHCOO*t*Bu), 2.71 (m, 1H, –C*H*C=O), 3.70 (m, 2H, –C*H*$_2$OSi), 4.48 (m, 1H, –C*H*COO*t*Bu), 5.25 (s, 2H, –C*H*$_2$Ph), 7.30 (m, 5H, aromatics). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=175.2, 170.2, 128.4, 128.3, 128.1, 82.2, 68.2, 60.3, 58.0, 39.9, 34.0, 28.1, 27.7, 20.2, 18.4, −3.6. FAB$^+$MS: calcd. For $C_{27}H_{43}NO_6Si$ 505.29; found 506. $C_{27}H_{43}NO_6Si$ (505.29): calcd. C 64.12, H 8.57, N 2.77; found C 64.21, H 8.66, N 2.84.

Hemiaminal **11**. To a solution of **10** (0.754 g, 1.49 mmol) in dry THF (14.8 mL), $LiEt_3BH$ 1 M (1.79 mL, 1.79 mmol) was added at −78°C and the solution was stirred for 3 h, then a saturated NH_4Cl solution (10 mL) was added. The aqueous phase was extracted with EtOAc, the combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude, as a yellowish oil, was submitted to the next reaction without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.12 [s, 6H, –Si(C*H*$_3$)$_2$], 0.81 (m, 12H, –C*H*$_3$), 1.42 [s, 9H, –C(C*H*$_3$)$_3$], 1.55–2.20 (m, 6H), 3.60 (m, 2H, –C*H*$_2$OTDS), 4.20 (m, 1H, –C*H*COO*t*Bu), 5.05 (s, 2H, –C*H*$_2$Ph), 5.41, 5.43 (2 m, 2H, –C*H*OH), 7.3 (m, 5H, aromatics).

Allyl pyrrolidine **12**. To a solution of **11** (0.678 g, 1.34 mmol) and allyltributyltin (0.48 mL, 1.61 mmol) in dry CH_2Cl_2 (13 mL), under argon atmosphere and at −78°C, *tert*-butyldimethylsilyltriflate (0.37 mL, 1.61 mmol) was added dropwise. The reaction mixture was stirred for 1 h, then a $NaHCO_3$ satured solution (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2. The collected organic phases were dried over Na_2SO_4, filtered and evaporated. The crude was purified by flash chromatography (hexane/ethyl acetate 9:1) affording

0.44 g (62% over two steps) of **12** (only *trans*-isomer) as a colorless oil. $[\alpha]_D^{20}=-43.1$ (c=1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ=0.02 (s, 6H, $-Si(CH_3)_2$), 0.85 (m, 12H, $-CH_3$), 1.47 (s, 9H, $-C(CH_3)_3$), 1.53 (m, 1H, $-HCHCH_2OSi$), 1.60 (m, 1H, $-CH(CH_3)_2$), 1.73 (m, 1H, $-HCHCH_2OSi$), 1.78 (m, 1H, $-HCHCHCOOtBu$), 2.30 (m, 2H, $-CH_2CH=CH_2$), 2.40 (m, 1H, $-HCCH_2CH_2OSi$), 2.52 (m, 1H, $-HCHCHCOOtBu$), 3.55 (m, 2H, $-CH_2OSi$), 3.85 (m, 1H, $-CHCH_2CH=CH_2$), 4.21 (m, 1H, $-CHCOOtBu$), 5.1 (m, 4H, $-CH_2Ph$, $CH_2=$), 5.71 (m, 1H, $-CH=CH_2$), 7.35 (m, 5H, aromatics). ^{13}C NMR (HETCOR, 100.6 MHz, $CDCl_3$): δ=129.2, 118.3, 67.2, 64.5, 61.2, 60.1, 38.2, 38.0, 37.5, 34.0, 28.2, 20.1. FAB^+MS: calcd. For $C_{30}H_{49}NO_5Si$ 531.34; found 532. $C_{30}H_{49}NO_5Si$ (531.34): calcd. C 67.76, H 9.29, N 2.63; found C 67.65, H 9.12, N 2.56.

4.1.2. Synthesis of functionalized 6,5-fused bicyclic lactams (Scheme 3). *Aldehyde* **1**. A stirred solution of **12** (0.335 g, 0.63 mmol) in MeOH (6.3 mL) was cooled to −78°C, whereupon O_3 was bubbled through the reaction (flow rate=30 L/h). After 1.5 h N_2 was bubbled through it in order to eliminate the excess of O_3. The solution was then warmed to 0°C by means of an ice bath and Me_2S (39.7 mmol, 0.29 mL) was added. After stirring for 24 h at room temperature, the solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (hexane/ethyl acetate 9:1) to yield 0.268 g of aldehyde **1** (80%) as a colorless oil. $[\alpha]_D^{20}=-26.1$ (c=1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ=0.12 [s, 6H, $-Si(CH_3)_2$], 0.81 (m, 12H, $-CH_3$), 1.40 [s, 9H, $-C(CH_3)_3$], 1.55 (m, 1H, $-HCHCH_2OSi$), 1.65 [m, 1H, $-CH(CH_3)_2$], 1.75 (m, 1H, $-HCHCHCOOtBu$), 1.81 (m, 1H, $-HCHCH_2OSi$), 2.12 (m, 1H, $-CHCH_2CH_2OSi$ –), 2.48 (m, 1H, $-HCHCHCOOtBu$), 2.65 (m, 1H, $-HCHCHO$), 2.85 (m, 1H, $-HCHCHO$), 3.61 (m, 2H, $-CH_2OSi$), 4.22 (m, 1H, $-CHCH_2CHO$), 4.25 (m, 1H, $-CHCOOtBu$), 5.12 (m, 2H, $-CH_2Ph$), 7.28 (m, 5H, aromatics), 9.85, (s, 1H, $-CHO$). ^{13}C NMR (DEPT, 50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ=128.4, 128.2, 128.1, 127.8, 81.4, 67.0, 60.6, 59.8, 59.7, 48.7, 47.5, 40.0, 36.3, 36.2, 34.0, 33.9, 32.7, 27.8, 27.7, 24.9, 20.2, 18.4, −3.7, −3.6. FAB^+MS: calcd. For $C_{29}H_{47}NO_6Si$ 533.32; found 534. $C_{29}H_{47}NO_6Si$ (533.32): calcd. C 65.25, H 8.88, N 2.62; found C 65.38, H 8.96, N 2.72.

Acrylic ester **3**. According to the General Procedure A, **1** was subjected to the Horner–Emmons reaction. The crude product was purified by flash chromatography (hexane/ethyl acetate, 7:3) to afford the acrylic ester **3** in 81% yield [diastereomeric ratio (*Z*)/(*E*)=9:1]. For the sake of characterization, a sample of the diastereomeric mixture was separated by flash chromatography. (*E*)-isomer: ^1H NMR (400 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ=−0.10 [s, 6H, $-Si(CH_3)_2$], 0.85 (m, 12H, $-CH_3$), 1.35 [s, 9H, $-C(CH_3)_3$], 1.55 [m, 1H, $-CH(CH_3)_2$], 1.72–3.03 (m, 7H), 3.55 (m, 2H, $-CH_2OSi$), 3.71 (s, 3H, $-CO_2CH_3$), 3.92 (m, 1H, $-CHCH_2CH=$), 4.30 (m, 1H, $-CHCOOtBu$), 5.10 (m, 4H, $-CH_2Ph$), 6.93 (m, 2H, $-CH=$, $-NH$), 7.40 (m, 10H, aromatics). FAB^+MS: calcd. For $C_{40}H_{58}N_2O_9Si$ 738.39; found 739. $C_{40}H_{58}N_2O_9Si$ (738.39): calcd. C 65.01, H 7.92, N 3.79; found C 65.10, H 7.97, N 3.93. (*Z*)-isomer: ^1H NMR (400 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ=0.10 [s, 6H, $-Si(CH_3)_2$], 0.80 (m, 12H, $-CH_3$), 1.39 [s, 9H, $-C(CH_3)_3$], 1.55 [m, 1H, $-CH(CH_3)_2$], 1.71–2.65 (5 m, 7H), 3.52 (m, 2H, $-CH_2OSi$), 3.70 (s, 3H, $-CO_2CH_3$), 3.82 (m, 1H, $-CHCH_2CH=$), 4.20 (m, 1H, $-CHCOOtBu$), 5.15 (m, 4H, $-CH_2Ph$), 6.53 (m, 1H, $-CH=$), 6.80 (bs, 1H, $-NH$), 7.40 (m, 10H, aromatics). ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ=171.7, 154.5, 154.0, 130.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 81.2, 67.4, 67.1, 66.9, 63.5, 62.6, 60.7, 59.8, 52.2, 39.7, 39.6, 36.6, 33.3, 33.1, 31.5, 27.9, 27.6, 24.9, 20.2, 18.4, −3.61, −3.69. FAB^+MS: calcd. For $C_{40}H_{58}N_2O_9Si$ 738.39; found 739. $C_{40}H_{58}N_2O_9Si$ (738.39): calcd. C 65.01, H 7.91, N 3.79; found C 65.18, H 7.82, N 3.89.

trans-6,5-Fused bicyclic lactams **5a** and **b**. According to the general procedure B, **3** was *N*-Boc-protected. The crude product was purified by flash chromatography (hexane/ethyl acetate, 6:4) to yield the acrylic ester (91%). Mixture of two diastereoisomers: ^1H NMR (400 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ=0.10 [s, 6H, $-Si(CH_3)_2$], 0.85 (m, 12H, $-CH_3$), 1.31 [s, 9H, $-C(CH_3)_3$], 1.40 [m, 1H, $-CH(CH_3)_2$], 1.45 [s, 9H, $-C(CH_3)_3$], 1.74–2.60 (m, 7H), 3.48 (m, 2H, $-CH_2OSi$), 3.74, 3.92 (2 s, 3H, $-CO_2CH_3$), 3.93 (m, 1H, $-CHCH_2CH=$), 4.20 (m, 1H, $-CHCOOtBu$), 5.10 (m, 4H, $-CH_2Ph$), 6.85 (m, 1H, $-CH=$), 7.30 (m, 10H, aromatics). ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ=171.7, 163.7, 151.7, 138.7, 137.7, 136.4, 136.2, 135.2, 130.0, 128.3, 128.2, 128.0, 127.9, 127.8, 83.4, 81.3, 81.2, 68.3, 67.1, 66.9, 62.8, 62.2, 61.2, 61.1, 60.2, 59.6, 52.2, 40.3, 38.8, 36.8, 34.0, 33.9, 32.8, 31.4, 27.8, 27.7, 24.9, 20.2, 18.4, −3.6. FAB^+MS: calcd. For $C_{45}H_{66}N_2O_{11}Si$ 838.44; found 839. $C_{45}H_{66}N_2O_{11}Si$ (838.44): calcd. C 64.41, H 7.93, N 3.34; found C 64.50, H 8.00, N 3.43. A solution of the *N*-Boc-protected compound (0.0647 g, 0.077 mmol) in MeOH (2 mL) containing a catalytic amount of 10% Pd/C was stirred for 16 h under H_2. The catalyst was then removed by filtration through a Celite pad and the filtrate was concentrated to dryness under reduced pressure. The residue was redissolved in MeOH (20 mL) and DIPEA (0.066 mL, 0.38 mmol) was added. The mixture was refluxed for 48 h. The solvent was removed and the two diastereoisomers obtained were separated by flash chromatography (hexane/ethyl acetate, 8:2) to yield 5.7 mg of **5a** and 24.8 mg of **5b** (73% over two steps) in a 1.0:4.3 diastereoisomeric ratio as a colorless oil. **5a**: $[\alpha]_D^{20}=-62.5$ (c=0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=0.10 [s, 6H, $-Si(CH_3)_2$], 0.80 (m, 12H, $-CH_3$), 1.48 (m, 1H, *H*10), 1.50 (m, 1H, *H*5), 1.51 (m, 1H, *H*8), 1.51 [s, 9H, $-C(CH_3)_3$], 1.53 [s, 9H, $-C(CH_3)_3$], 1.60 [m, 1H, $-CH(CH_3)_2$], 1.65 (m, 1H, *H*4), 1.78 (m, 1H, *H*10′), 1.90 (m, 1H, *H*7), 2.11 (m, 1H, *H*5′), 2.40 (m, 1H, *H*4′), 2.52 (m, 1H, *H*8′), 3.38 (m, 1H, *H*6), 3.67 (m, 2H, *H*11), 4.30 (m, 1H, *H*3), 4.37 (m, 1H, *H*9), 5.55 (s, 1H, N*H*). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=171.1, 81.7, 79.6, 61.8, 60.9, 59.0, 50.8, 43.8, 34.8, 34.3, 29.8, 28.1, 27.1, 25.2, 25.0, 20.5, 20.2, 18.6, −3.2. FAB^+MS: calcd. For $C_{28}H_{52}N_2O_6Si$ 540.36; found 541. $C_{28}H_{52}N_2O_6Si$ (540.36): calcd. C 62.18, H 9.69, N 5.18; found C 62.24, H 9.75, N 5.21. **5b**: $[\alpha]_D^{20}=-21.8$ (c=0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=0.00 [s, 6H, $-Si(CH_3)_2$], 0.87 (m, 12H, $-CH_3$), 1.40 (m, 1H, *H*10), 1.45 (m, 1H, *H*5), 1.45 (m,

1H, *H*8), 1.45 [s, 9H, –C(CH_3)$_3$], 1.50 [s, 9H, –C(CH_3)$_3$], 1.60 [m, 1H, –C*H*(CH$_3$)$_2$], 1.70 (m, 1H, *H*4), 1.75 (m, 1H, *H*10′), 1.85 (m, 1H, *H*7), 2.15 (m, 1H, *H*5′), 2.58 (m, 1H, *H*4′), 2.60 (m, 1H, *H*8′), 3.30 (m, 1H, *H*6), 3.65 (m, 2H, *H*11), 4.10 (m, 1H, *H*3), 4.30 (m, 1H, *H*9), 5.55 (s, 1H, N*H*). ^{13}C NMR (50.3 MHz, CDCl$_3$): δ=171.4, 167.5, 156.2, 81.4, 79.5, 64.6, 60.7, 58.1, 52.3, 43.1, 34.7, 34.1, 28.6, 28.3, 28.0, 26.3, 20.3, 18.4, −3.5. FAB$^+$MS: calcd. For $C_{28}H_{52}N_2O_6Si$ 540.36; found 541. $C_{28}H_{52}N_2O_6Si$ (540.36): calcd. C 62.18, H 9.69, N 5.18; found C 62.28, H 9.76, N 5.24.

4.1.3. Synthesis of functionalized 7,5-fused bicyclic lactams (Scheme 3). *Aldehyde* **2**. To a stirred solution of **12** (0.181 g, 0.341 mmol) in dry THF (3.4 mL) was added a 0.5 M solution of 9-BBN in THF (2.1 mL, 1.05 mmol). The reaction mixture was stirred for 3 h, then cooled to 0°C, whereupon water (3 mL), aqueous 3 M NaOH solution (1.03 mL) and 30% H_2O_2 (0.317 mL) were added. The resulting mixture was stirred for 1 h at room temperature and then refluxed for a further 16 h. After cooling, the aqueous phase was extracted with EtOAc and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate 7:3) to yield 0.156 g of the corresponding alcohol (83%) as a yellow oil. $[\alpha]_D^{20}$=−32.9 (c=1.0, CHCl$_3$). ^{1}H NMR (200 MHz, CDCl$_3$) (signals are split due to amidic isomerism): δ=0.10 [s, 6H, –Si(CH_3)$_2$], 0.81 (m, 12H, –CH_3), 1.30 [s, 9H, –C(CH_3)$_3$], 1.40–2.6 (m, 10H), 3.40–3.90 (m, 6H, –CH_2OSi, –CH_2OH, –O*H*, –C*H*N–), 4.20 (m, 1H, –C*H*COO*t*Bu), 5.12 (s, 2H, –CH_2Ph), 7.35 (m, 5H, aromatics). ^{13}C NMR (50.3 MHz, CDCl$_3$) (signals are split due to amidic isomerism): δ=171.9, 171.5, 154.6, 136.3, 134.8, 128.4, 128.2, 128.1, 127.9, 127.8, 127.6, 117.2, 81.2, 67.0, 66.9, 66.8, 63.8, 63.5, 63.0, 62.4, 62.2, 61.3, 60.6, 60.3, 60.0, 59.7, 40.8, 39.1, 39.0, 38.1, 37.0, 34.7, 34.3, 34.1, 33.7, 32.7, 32.1, 30.5, 30.4, 29.7, 28.8, 28.5, 27.8, 27.7, 26.7, 24.9, 20.2, 18.4, −3.6. FAB$^+$MS: calcd. For $C_{30}H_{51}NO_6Si$ 549.35; found 550. $C_{30}H_{51}NO_6Si$ (549.35): calcd. C 65.54, H 9.35, N 2.55; found C 65.63, H 9.38, N 2.53. To a stirred solution of oxalyl chloride (0.093 mL, 1.071 mmol) in CH_2Cl_2 (2 mL), DMSO (0.104 mL, 1.46 mmol), a solution of the alcohol produced in the previous reaction (0.196 g, 0.357 mmol) in CH_2Cl_2 (3 mL), and TEA (0.41 mL, 2.93 mmol) was added at −60°C. The reaction mixture was allowed to warm to room temperature for 1 h at which time water (2 mL) was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude was purified by flash chromatography (hexane/ethyl acetate 8:2) to yield 0.158 g of **2** (81%) as a colorless oil. $[\alpha]_D^{20}$=−41.2 (c=1.0, CHCl$_3$). ^{1}H NMR (200 MHz, CDCl$_3$) (signals are split due to amidic isomerism): δ=0.11 [s, 6H, –Si(CH_3)$_2$], 0.92 (m, 12H, –CH_3), 1.38 [s, 9H, –C(CH_3)$_3$], 1.40–2.61 (m, 10H), 3.45 (m, 2H, –CH_2OSi), 3.63 (m, 1H, –C*H*N–), 4.20 (m, 1H, –C*H*COO*t*Bu), 5.05 (m, 2H, –CH_2Ph), 7.22 (m, 5H, aromatics), 9.45, 9.63 (2 s, 1H. –C*H*O). ^{13}C NMR (50.3 MHz, CDCl$_3$) (signals are split due to amidic isomerism): δ=201.6, 201.1, 171.9, 154.6, 128.5, 128.3, 128.1, 128.0, 81.3, 67.2, 67.0, 66.9, 63.6, 62.8, 61.5, 60.8, 60.6, 60.5, 60.2, 59.8, 40.5, 40.2, 39.2, 38.1, 36.9, 34.2, 33.9, 32.8, 29.7, 27.9, 27.8, 26.6, 26.0, 25.9, 25.1, 20.3, 18.5, −3.5, −5.4. FAB$^+$MS: calcd. For $C_{30}H_{49}NO_6Si$ 547.33; found 548. $C_{30}H_{49}NO_6Si$ (547.33): calcd. C 65.78, H 9.02, N 2.56; found C 65.67, H 8.98, N 2.59.

Acrylic ester **4**. According to the general procedure A, **2** was subjected to the Horner–Emmons reaction. The crude product was purified by flash chromatography (hexane/ethyl acetate, 8:2) to afford the acrylic ester **4** in 92% yield [diastereomeric ratio (*Z*)/(*E*)=9:1] as a yellow oil. Mixture of two geometrical isomers: ^{1}H NMR (200 MHz, CDCl$_3$) (signals are split due to amidic isomerism): δ=0.01 [s, 6H, –Si(CH_3)$_2$], 0.82 (m, 12H, –CH_3), 1.33 [s, 9H, –C(CH_3)$_3$], 1.55 [m, 1H, –C*H*(CH$_3$)$_2$], 1.70–2.52, (m, 9H), 3.57 (m, 2H, –CH_2OSi), 3.72 (s, 3H, –CO$_2$CH_3), 3.78 (m, 1H, –C*H*N–), 4.30 (m, 1H, –C*H*COO*t*Bu), 5.05 (m, 4H, –CH_2Ph), 6.54 (m, 2H, –C*H*═, –N*H*), 7.40 (m, 10H, aromatics). ^{13}C NMR (50.3 MHz, CDCl$_3$) (signals are split due to amidic isomerism): δ=171.9, 154.6, 136.6, 136.3, 128.4, 128.0, 127.8, 126.0, 81.2, 67.2, 66.9, 64.2, 63.5, 60.8, 60.2, 59.8, 52.2, 39.3, 38.2, 37.9, 37.1, 36.9, 34.1, 33.9, 33.3, 32.8, 31.7, 29.6, 27.8, 25.9, 25.0, 24.8, 24.4, 20.3, 18.5, −3.4. FAB$^+$MS: calcd. For $C_{41}H_{60}N_2O_9Si$ 752.41; found 753. $C_{41}H_{60}N_2O_9Si$ (752.41): calcd. C 65.40, H 8.03, N 3.72; found C 65.33, H 8.08, N 3.78.

trans-7,5-Fused bicyclic lactams **6a** and **b**. According to the general procedure B, **4** was *N*-Boc-protected. The crude product was purified by flash chromatography (hexane/ethyl acetate, 8:2) to yield the *N*-Boc derivative (87%). Mixture of two diastereoisomers: ^{1}H NMR (200 MHz, CDCl$_3$) (signals are split due to amidic isomerism): δ=0.10 [s, 6H, –Si(CH_3)$_2$], 0.85 (m, 12H, –CH_3), 1.31 [s, 9H, –C(CH_3)$_3$], 1.40 [m, 1H, –C*H*(CH$_3$)$_2$], 1.45 [s, 9H, –C(CH_3)$_3$], 1.32–2.52 (m, 9H), 3.54 (m, 2H, –CH_2OSi), 3.68 (s, 3H, –CO$_2$CH_3), 3.75 (m, 1H, –C*H*N–), 4.15 (m, 1H, –C*H*COO*t*Bu), 5.10 (m, 4H, –CH_2Ph), 6.78 (m, 1H, –C*H*═), 7.25 (m, 10H, aromatics). ^{13}C NMR (50.3 MHz, CDCl$_3$) (signals are split due to amidic isomerism): δ=171.9, 171.4, 170.8, 164.1, 154.6, 154.3, 153.7, 146.1, 145.8, 141.8, 141.3, 136.5, 135.4, 128.7, 128.4, 128.2, 127.8, 127.6, 83.5, 81.2, 68.7, 68.2, 66.8, 64.6, 64.1, 63.9, 63.5, 61.2, 60.8, 60.1, 52.1, 39.5, 39.1, 38.9, 38.1, 37.8, 34.1, 33.7, 32.9, 32.1, 31.9, 31.0, 30.1, 29.9, 29.3, 27.8, 25.8, 25.0, 24.7, 24.0, 22.6, 20.3, 18.4, −3.4. FAB$^+$MS: calcd. For $C_{46}H_{68}N_2O_{11}Si$ 852.46; found 853. $C_{46}H_{68}N_2O_{11}Si$ (852.46): calcd. C 64.76, H 8.03, N 3.28; found C 64.87, H 7.99, N 3.22. To a solution of the *N*-Boc protected compound (0.15 g, 0.17 mmol) in THF (2 mL) was added 2N aqueous NaOH (1.36 mmol, 0.68 mL) and heated to 50°C. After 16 h the solution was acidified to pH 2 with Amberlite IR 120H$^+$ and then filtered. The solvent was evaporated and the crude residue was used in the next reaction without further purification. Mixture of two diastereoisomers: ^{1}H NMR (200 MHz, CDCl$_3$) (signals are split due to amidic isomerism): δ=0.07 [s, 6H, –Si(CH_3)$_2$], 0.84 (m, 12H, –CH_3), 1.31 [s, 9H, –C(CH_3)$_3$], 1.46 [s, 9H, –C(CH_3)$_3$], 1.45–2.00 (m, 6H), 2.00–2.65 (m, 3H), 3.58 (m, 2H, –CH_2OSi), 3.82 (m, 1H, –C*H*N–), 4.23 (m, 1H, –C*H*COO*t*Bu), 5.10 (m, 2H, –CH_2Ph), 6.05, 6.44 (2 bs, 1H, –N*H*), 6.63 (m, 1H, –C*H*═), 7.30 (m, 5H, aromatics). ^{13}C NMR (50.3 MHz, CDCl$_3$) (signals are split due to amidic isomerism): δ=172.2, 171.8, 168.9, 155.0, 154.8,

141.0, 137.6, 137.5, 136.7, 136.6, 128.6, 128.5, 128.3, 128.2, 128.1, 127.6, 127.1, 81.5, 67.3, 67.2, 65.2, 64.5, 63.8, 61.1, 60.9, 60.3, 59.9, 39.3, 38.1, 37.2, 34.3, 34.0, 32.9, 31.7, 30.5, 29.8, 28.2, 28.3, 27.9, 25.2, 25.0, 20.5, 18.7, −3.2.

A solution of the crude compound in MeOH (1 mL) containing a catalytic amount of 10% Pd/C was stirred for 16 h under H_2. The catalyst was then removed by filtration through Celite and the collected solid was washed with MeOH. The combined filtrate and washings were then concentrated under reduced pressure and the crude was used for the next reaction without further purification.

To a mixture of the aforementioned crude product, HOAt (0.0456 g, 0.335 mmol), and HATU (0.127 g, 0.335 mmol) was added DMF (8 mL) and then 2,4,6-collidine (0.335 mmol, 47 μL). The solution was stirred for 48 h. Thereafter, the solvent was evaporated under reduced pressure, EtOAc was added and washed with a satured solution of $NaHCO_3$ and 1 M HCl. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (hexane/ethyl acetate 8:2) to afford 42.1 mg of **6a** and 7.8 mg of **6b** in a 5.4:1.0 diastereoisomeric ratio (53% over 3 steps). **6a**: $[\alpha]_D^{20}=-19.4$ (c=2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.10 [s, 6H, −Si(CH_3)$_2$], 0.90 (m, 12H, −CH_3), 1.34 (m, 1H, *H*6), 1.45 [s, 18H, −C(CH_3)$_3$], 1.51 (m, 1H, *H*4), 1.52 (m, 1H, *H*11), 1.60 [m, 1H, −C*H*(CH$_3$)$_2$], 1.72 (m, 1H, *H*9), 1.80 (m, 1H, *H*11′), 1.81 (m, 1H, *H*5), 1.89 (m, 1H, *H*6′), 1.95 (m, 1H, *H*5′), 2.10 (m, 1H, *H*4′), 2.10 (m, 1H, *H*8), 2.40 (m, 1H, *H*9′), 3.59 (m, 1H, *H*7), 3.62 (m, 2H, *H*12), 4.24 (m, 1H, *H*3), 4.32 (m, 1H, *H*10), 5.55 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, HETCOR, $CDCl_3$): δ=65.0, 61.7, 61.0, 55.0, 44.0, 37.5, 35.5, 34.9, 33.0, 32.5, 28.0, 20.0. FAB$^+$MS: calcd. For $C_{29}H_{54}N_2O_6Si$ 554.38; found 555. $C_{29}H_{54}N_2O_6Si$ (554.38): calcd. C 62.78, H 9.81, N 5.05; found C 62.87, H 9.88, N 5.02. **6b**: $-[\alpha]_D^{20}=-14.9$ (c=0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.10 [s, 6H, −Si(CH_3)$_2$], 0.85 (m, 12H, −CH_3), 1.36 (m, 1H, *H*11), 1.41 (m, 1H, *H*9), 1.46 [s, 18H, −C(CH_3)$_3$], 1.47 (m, 1H, *H*5), 1.60 [m, 1H, −C*H*(CH$_3$)$_2$], 1.62 (m, 1H, *H*5′), 1.66 (m, 1H, *H*6), 1.80 (m, 1H, *H*11′), 1.86 (m, 1H, *H*8), 2.02 (m, 1H, *H*6′), 2.04 (m, 2H, *H*4), 2.48 (m, 1H, *H*9′), 3.31 (m, 1H, *H*7), 3.65 (m, 2H, *H*12), 4.22 (m, 1H, *H*3), 4.39 (m, 1H, *H*10), 5.74 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=65.0, 61.5, 61.1, 53.2, 43.5, 35.3, 35.1, 34.8, 33.6, 29.1, 28.5, 23.8, 20.9, 19.1, 3.3. FAB$^+$MS: calcd. For $C_{29}H_{54}N_2O_6Si$ 554.38; found 555. $C_{29}H_{54}N_2O_6Si$ (554.38): calcd. C 62.78, H 9.81, N 5.05; found C 62.70, H 9.78, N 5.00.

Synthesis of alcohol **13**. Compound **5b** (27.9 mg, 0.051 mmol) in 1 mL of THF was treated with 1 M solution in THF of TBAF (62 μL, 0.062 mmol) and stirred for 2 h at room temperature. The reaction mixture was washed with brine (1 mL), dried and evaporated. The residue was chromatographed using EtOAc to give the alcohol **13** (21.6 mg, 98%) as a white solid. Mp 144–145°C. $[\alpha]_D^{20}=-36.7$ (c=0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.32 [s, 9H, −C(CH_3)$_3$], 1.49 (m, 1H, −HC*H*CHCOO*t*Bu), 1.50 [m, 2H and 9H, −C(CH_3)$_3$], 1.71 (m, 1H, −HC*H*CHNHBoc), 1.85 (m, 2H), 2.15 (m, 1H), 2.60 (m, 2H, −HC*H*CHCOO*t*Bu, −HC*H*CHNHBoc), 3.38 (ddd, 1H, J=3.9, 10.8, 10.8 Hz, −C*H*N), 3.71 (m, 3H, −CH_2OH, −O*H*), 4.08 (m, 1H, −C*H*NHBoc), 4.32 (dd, 1H, J=8.6, 8.6 Hz, −C*H*COO*t*Bu), 5.32 (bs, 1H, −N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=65.4, 61.5, 58.8, 52.8, 43.6, 35.0, 34.3, 30.1, 29.0, 28.7, 26.5. FAB$^+$MS: calcd. For $C_{20}H_{34}N_2O_6$ 398.24; found 399. $C_{20}H_{34}N_2O_6$ (398.24): calcd. C 60.28, H 8.60, N 7.03; found C 60.32, H 8.66, N 7.09.

Synthesis of azide **14**. Alcohol **13** (17.5 mg, 0.04 mmol) in 3 mL of CH_2Cl_2 was treated with methanesulfonyl chloride (6.2 μL, 0.08 mmol) and Et_3N (13.9 μL, 0.1 mmol) and stirred at 0°C for 1 h. The ice bath was removed, and the reaction mixture was stirred an additional 1 h at room temperature. The solution was diluted with CH_2Cl_2 (1 mL) and washed with a phosphate buffer solution (3 mL), dried, evaporated and used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.45, 1.48 [2 s, 18H, −C(CH_3)$_3$], 1.55–2.21 (m, 7H), 2.55 (m, 2H), 3.01 (s, 3H, −CH_3), 3.37 (m, 1H, −C*H*N−), 4.01 (m, 1H, −C*H*NHBoc), 4.20–4.40 (m, 3H, −C*H*COO*t*Bu, −CH_2OMs), 5.22 (bs, 1H, −N*H*).

The crude residue was dissolved in DMF (3 mL), treated with NaN_3 (7.8 mg, 0.12 mmol) stirred at 80°C for 3 h, and evaporated. The crude was dissolved in EtOAc (2 mL), washed with a phosphate buffer solution (2 mL), dried and evaporated to give **14** (16.2 mg, 96%) as a pale yellow oil. $[\alpha]_D^{20}=-19.3$ (c=1.6, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.43, 1.48 [2 s, 18H, −C(CH_3)$_3$], 1.55–2.03 (m, 6H), 2.12 (m, 1H), 2.51 (m, 2H), 3.38 (m, 3H, −CH_2N$_3$, −C*H*N−), 4.01 (m, 1H, −C*H*NHBoc), 4.32 (dd, 1H, J=9.2, 9.2 Hz, −C*H*COO*t*Bu), 5.25 (bs, 1H, −N*H*). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=171.1, 167.3, 156.1, 81.6, 79.5, 64.3, 57.9, 52.2, 49.5, 43.3, 34.3, 30.2, 29.6, 28.2, 27.9, 26.3. FAB$^+$MS: calcd. For $C_{20}H_{33}N_5O_5$ 423.25; found 424. $C_{20}H_{33}N_5O_5$ (423.25): calcd. C 56.72, H 7.85, N 16.54; found C 56.67, H 7.88, N 16.65.

4.2. Computational methods

Molecular mechanics calculations were performed within the framework of MacroModel[26] version 5.5 using the MacroModel implementation of the Amber all-atom force field[27] (denoted AMBER *) and the implicit water GB/SA solvation model of Still et al.[21] The torsional space of each molecule was randomly varied with the usage-directed Monte Carlo conformational search of Chang, Guida, and Still.[20] Ring-closure bonds were defined in the six- and seven-membered rings of the 6,5- and 7,5-fused bicyclic lactams, respectively. Amide bonds were included among the rotatable bonds.

For each search, at least 2000 starting structures for each variable torsion angle were generated and minimized until the gradient was less than 0.05 kJ/Åmol using the truncated Newton–Raphson method[28] implemented in MacroModel. Duplicate conformations and those with an energy greater than 6 kcal/mol above the global minimum were discarded. The nature of the stationary points individuated was tested by computing the eigenvalues of the second-derivative matrix.

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