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Synthetic studies towards diazepanone scaffolds

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ABSTRACT

The synthesis of new enantiopure polyfunctionalised diazepanone scaffolds is described. The key steps involve the opening of an azido-epoxide C4 building block derived from L-ascorbic or D-isoascorbic acid by a L-serine derivative followed by a lactonisation–lactamisation two-step sequence.

1. Introduction

The world-wide emergence of bacterial resistance[1] to various antibiotics is becoming a severe public health problem and there is an urgent need for the scientific community to discover novel compounds that are able to treat the resistant bacterial strains. The enzymes involved in peptidoglycan biosynthesis appear as the targets of choice in the development of new antibacterials since peptidoglycan forms part of the bacterial cell wall and protects the cell from osmotic stress. Indeed, most of the enzymes involved in its biosynthesis have been demonstrated to be ubiquitous and essential for bacterial growth.[2] Furthermore, peptidoglycan has no counterparts in eukaryotic cells. To delay the occurrence of bacterial resistance, it is relevant to focus on targets that have not been explored as much as before. Owing to its transmembrane localisation,[3] the translocase MraY, which is an essential enzyme[4] that catalyzes the first membrane step of peptidoglycan biosynthesis,[5] has only recently been purified to homogeneity[6] and characterised and no therapeutic drugs targeting this essential enzyme exist so far. Nevertheless, several families of the naturally occurring inhibitors have been identified,[7] although most of them display limited antibacterial activity in spite of their high in vitro inhibition of the enzymatic activity. Based on the structure of these inhibitors, in an ongoing programme[8] directed to the inhibition of new targets for fighting antibiotics resistance, our goal is to develop efficient access to libraries of compounds that inhibit MraY enzymatic activity in order to contribute not only to the discovery of new antibacterials but also to MraY active site structure elucidation through structure–activity relationships study of families of inhibitors.[9] With that aim, we first focused on the efficient synthesis of polyfunctionalised enantiopure 1,4-diazepan-2-one[10] scaffolds in order to generate a library of potentially active related inhibitors thereafter. Indeed such heterocycles are the central core of several families of MraY natural inhibitors, such as liposidomycins[7b] and caprazamycins[7d,e] (Fig. 1) and no libraries of inhibitors based on such scaffolds have been developed so far.

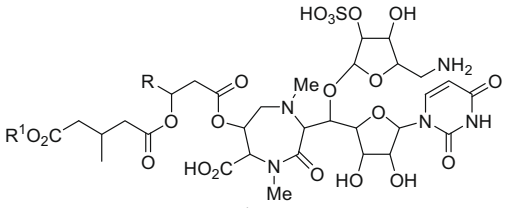

Figure 1. Natural inhibitors of MraY.

Interestingly, one could take advantage of differentiated functions such as amine, amide, primary and secondary alcohols and different configurations at the asymmetric carbon atoms in order to obtain libraries of compounds. We have already described access to these polyfunctionalised skeletons[8f] in a preliminary form but we report herein full results including different synthetic approaches and generalisation of the method to the obtention of these challenging scaffolds in enantiomerically pure form with good yield.

2. Results and discussion

The retrosynthetic analysis towards targeted 1,4-diazepan-2-ones (Fig. 2) relies on two key steps that involve N-alkylation of an α-amino acid by a conveniently protected C4 electrophilic amino-diol building block and a peptidic coupling.

Both synthons can be prepared in an enantiomerically pure form from the chiral pool, allowing potential configurational diversity. Thus, C4 building blocks were derived from either L-ascorbic

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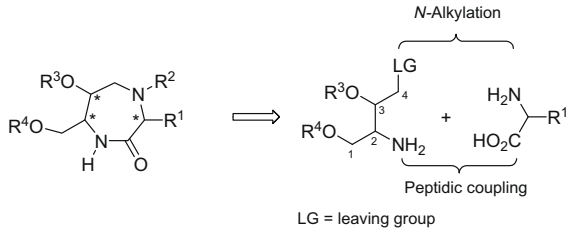


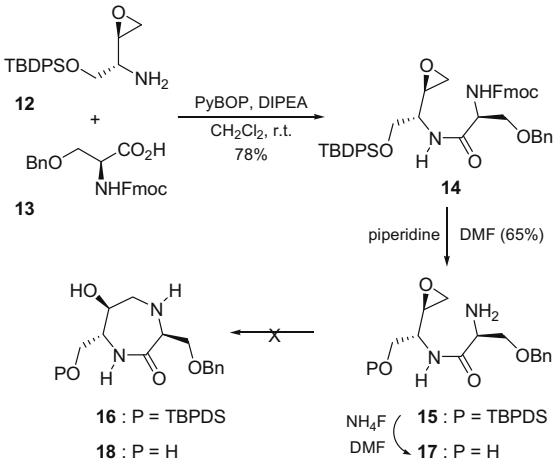
Figure 2. Scaffold with a polyfunctionalised 1,4-diazepan-2-one skeleton and retrosynthesis.

or D-isoascorbic acid, which allows for a (*R*)- or (*S*)-configuration at C3. Moreover, the order of both the proposed key steps was examined with the goal of determining the most powerful strategy to reach the scaffold. Furthermore, we successively focused on the synthesis of various C4 building blocks (Scheme 1) allowing N-alkylation by either reductive amination or regiospecific nucleophilic opening of an epoxide. Subsequently, the achievement of the targeted diazepanone scaffold synthesis from these key building blocks involving first peptidic coupling or N-alkylation was studied (Schemes 2–5). Finally, the best method was also applied to the synthesis of a diastereoisomeric scaffold from D-isoascorbic acid (Scheme 6).

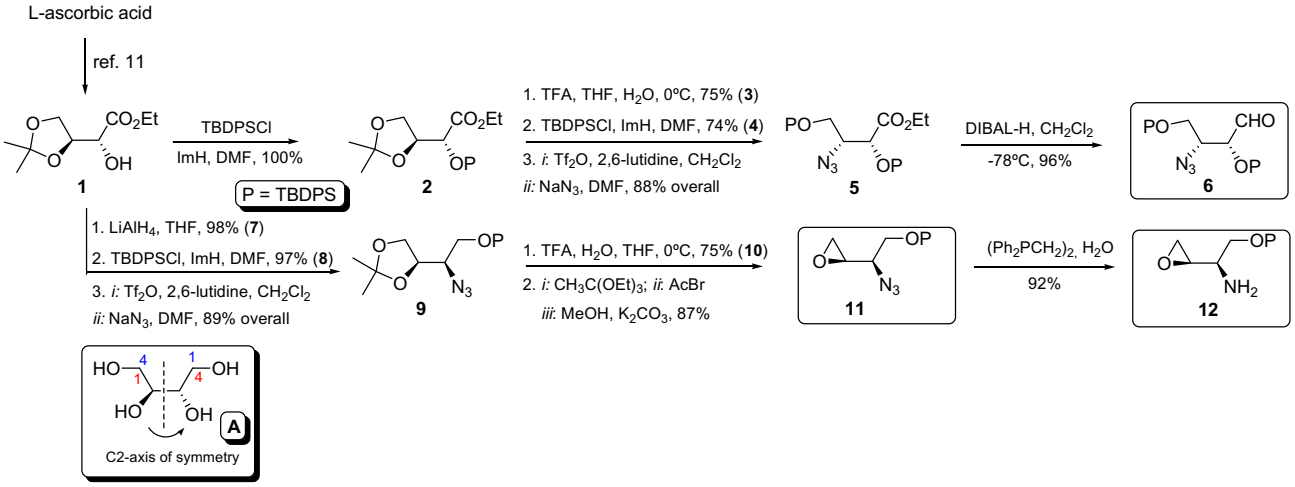
According to the proposed strategy, we first turned our attention to the preparation of C4 building blocks (Scheme 1) via the ethyl 3,4-*O*-ethylidene L-threonate **1**, which can be prepared in three steps and large scale from L-ascorbic acid.[11] It should be noted that this compound can be considered as a masked form of the threitol **A**, which exhibits a *C*2 axis of symmetry.

Careful chemical manipulations of this formal threitol were performed to allow the formation of an electrophilic centre either at C1 or C4, which are equivalent, due to the formal presence of the *C*2 axis of symmetry. With this in mind, the upper part of Scheme 1 is related to the introduction of the electrophilic function at C1, while the lower part is related to its introduction at C4. In addition, compounds which allowed N-alkylation and then peptidic coupling and vice versa were prepared. The building blocks **6**,[12] **11**[8c] and **12** were synthesised from the ethyl 3,4-*O*-ethylidene L-threonate **1** according to classical chemical transformations. The crucial steps were the reduction of an ester into an aldehyde, the nucleophilic substitution of an hydroxy group by an azide ion with inversion of configuration via the triflate intermediate,[8b] the reduction of an azide under Staudinger conditions, and the transformation of an 1,2-diol into an epoxide with retention of configuration under Sharpless conditions.[13] Each of these building blocks was produced in enantiomerically pure form in good to high yields.

With C4 building blocks in hand, we turned our attention to the study of the peptidic coupling (Scheme 2). This involved the C4 synthons **12** which involves a primary amine and the commercially available *O*-benzyl-*N*-Fmoc-L-serine **13**. We showed that the best conditions for this reaction involved PyBOP[14] (benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate) in excess in the presence of DIPEA, which led to the amide bond formation of compound **14** in high yield. It should be noted that the use of HBTU[15] (2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) under the same conditions led to a lower yield (40%). Moreover, in that case, partial epimerisation at the carbon atom at the α-position to the amide was also observed. Towards the diazepanone, the final N-alkylation step needed N-deprotection which could be efficiently performed in the presence of piperidine leading to **15**. The cyclisation was then tentatively carried out by intramolecular nucleophilic opening of the epoxide by the primary amine under various conditions (caesium carbonate, ytterbium triflate or sodium *tert*-butanolate).[16] However, none of these conditions gave the expected diazepanone **16**. In order to exclude a possible π stacking between the aromatic moieties of benzyl- and *tert*-butyldiphenylsilyl-protected groups of the primary alcohols, which could result in a conformation unfavourable to cyclisation, removal of the TBDPS protected group was performed in the presence



Scheme 2.



Scheme 1.

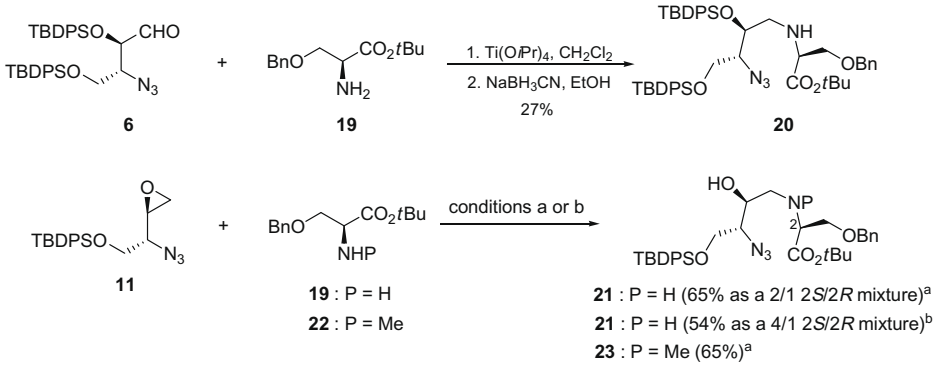
of ammonium fluoride leading to **17**. Cyclisation was then attempted, but again none of the tested conditions resulted in the diazepanone **18**.

In a complementary approach, we examined the diazepanone formation via N-alkylation (Scheme 3) followed by peptidic coupling. N-Alkylation was examined according to two routes.

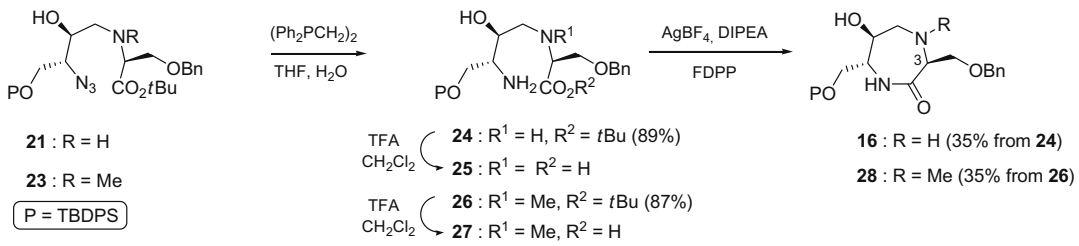
The first route was reductive amination which involved aldehyde C4 building block **6** and *tert*-butyl *O*-benzyl-L-serine **19**. The latter was obtained in quantitative yield from commercially available *N*-Fmoc-*O*-benzyl-L-serine by esterification with *tert*-butyltrichloroacetimidate followed by *N*-Fmoc deprotection in the presence of DBU in DMF.[8f] Reductive amination was performed in the presence of titanium(IV) tetraisopropoxide,[17] followed by sodium cyanoborohydride reduction of the resulting imine. However, the expected secondary amine **20** was produced in a moderate yield (27%). According to a second route, nucleophilic opening of the azido epoxide **11** by *tert*-butyl *O*-benzyl-L-serine **19** in the presence of ytterbium triflate[18] in dichloromethane yielded the corresponding secondary amine **21** in a better yield (65%). Completing this reaction required a long reaction time (up to a week at 20 °C) resulting in partial epimerisation at C_2 (2*S*/2*R* = 2:1). Nevertheless, changing ytterbium triflate with the less acidic calcium triflate[19] Lewis acid and running the reaction in dioxane under microwave irradiation at 110 °C (CEM discover®) limited the epimerisation. Indeed, these conditions allowed the isolation of the expected amine **21** in 54% yield as a 2*S*/2*R* = 4:1 inseparable mixture and 31% of the starting azidoepoxide **11** could be recovered and recycled. The epoxide opening could also be performed with the secondary amine **22**. The latter was prepared from the *N*-Fmoc-*O*-benzyl-L-serine via N-methylation according to Freidinger method,[20] involving the formation of an oxazolidinone in the presence of *p*-formaldehyde and *p*-toluene sulfonic acid, followed by acid-catalyzed reductive alkylation leading to the corresponding amino acid. Next, esterification as previously described and *N*-Fmoc deprotection by piperidine in DMF led to the amine **22**. The nucleophilic opening of the azidoepoxide **11** by amine **22** in the presence of ytterbium triflate in dichloromethane afforded the tertiary amine **23** in 65% yield without epimerisation at C_2.

We next tackled the preparation of the targeted diazepanone scaffold **16** or **28** displaying a secondary or a tertiary amine from the azido *tert*-butyl ester derivative **21** or **23**, respectively (Scheme 4).

Selective azido group reduction under Staudinger conditions led to the corresponding amine **24** or **26**. It should to be noted that the Staudinger conditions were modified by the use of bis-1,2-diphenyl phosphinoethane in the place of triphenylphosphine. This allowed an easier separation of the expected product from the phosphine oxide formed during the reduction in comparison to the one from triphenylphosphine oxide.[21] Acidolysis of the *tert*-butyl ester of **24** or **26** in the presence of trifluoroacetic acid gave **25** or **27**, respectively. Various conditions were then tested for lactam formation but they proved troublesome. For example, the use of EDCI and HOBt[22] as coupling agents was unsuccessful, while that of HATU/HOBt[23] in excess in the presence of diisopropylethylamine required such large excess of reagents that the purification of the resulting compound only led to poor recovery of the expected diazepanone. The best conditions for the lactam formation involved the metal-ion-mediated cyclisation in the presence of silver tetrafluoroborate and pentafluorophenyl diphenylphosphinate (FDPP),[24] which led to **16** or **28** in moderate 35% yield. At this stage, the expected enantiopure diazepanone scaffold **16** could be easily separated from its C_3-epimer by flash chromatography. The absolute configurations of **16** and its C_3-epimer were confirmed by extensive NMR studies. ^{1}H signals were assigned using 2D-COSY and 2D-NOESY experiments. NOE measurements and Molecular Dynamic calculations allowed deduction of the structure of both compounds. For diazepanone **16**, the strong NOEs H3–H5*p*S, H3–H8, H5*p*S–H8 indicate the close proximity of these protons in the lower face of the diazepanone ring (Fig. 3). The coupling constant values measured between H6 and the two H5 protons are nearly the same (2.5 and 2.8 Hz) which indicates that both dihedral angles H5(*p*R or *p*S)–C5–C6–H6 are similar. The coupling constant $^3J_{H6-H7}$ value (7.0 Hz) indicates a pseudo-equatorial position for H6 and H7 with an axial position of the methylene group (CH_2) of TBDPS ether. The axial position was confirmed



Scheme 3. Conditions a: $Yb(OTf)_3$, CH_2Cl_2 up to a week. Conditions b: $Ca(OTf)_2$, dioxane, MW, 110 °C, 35 min.



Scheme 4.

by the NOEs H8–H3 and H8–H5(*p*S). These angles and distances are in good agreement with the conformation shown in this model.

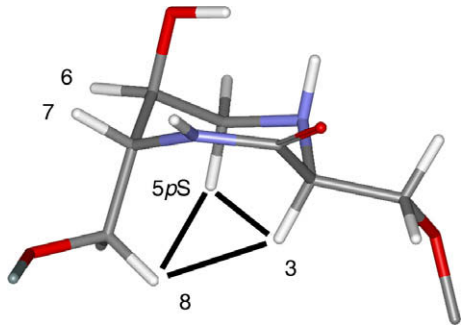


Figure 3. Schematic representation of the NOEs (indicated with dotted lines) found to deduce the structure of **16**. Prochiral ^{1}H is labelled *p*R or *p*S.

For the C_3-epimer of **16**, the strong NOEs H3–H5*p*R, H3–H7, H5*p*R–H7 indicate the close proximity of these protons on the upper face of the diazepanone ring (Fig. 4). The large coupling constant values (8.2 Hz) found between H6 and prochiral H5b (5*p*R) and between H6 and H7 (8.8 Hz) indicate a pseudo-*trans* di-axial

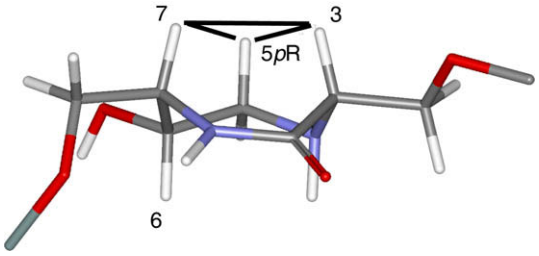
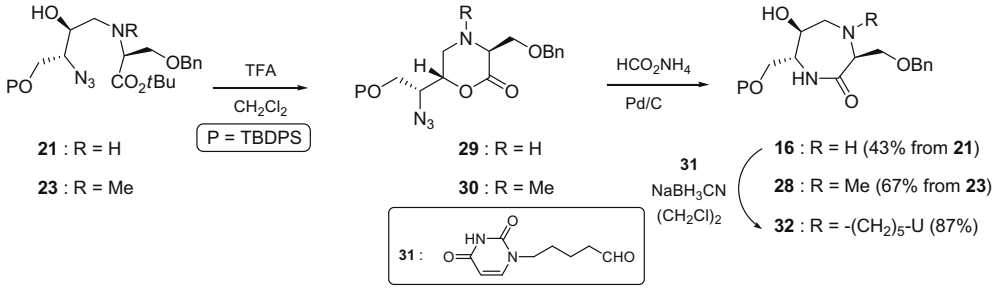


Figure 4. Schematic representation of the NOEs (indicated with dotted lines) found to deduce the structure of the C_3-epimer of **16**. Prochiral ^{1}H is labelled *p*R or *p*S.

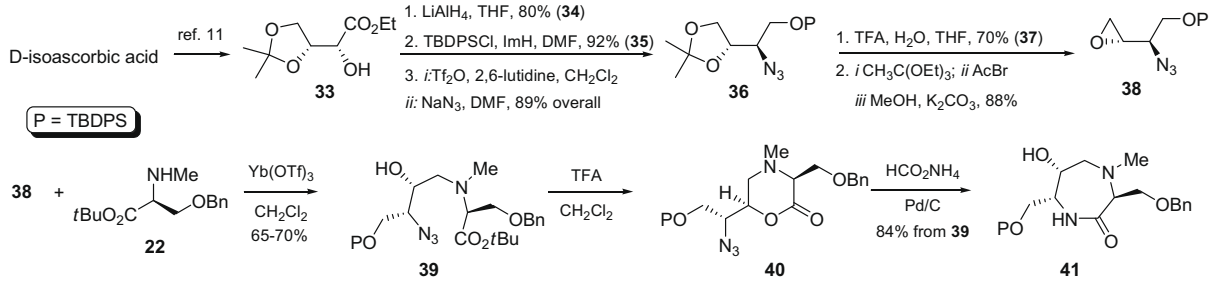
position of H6 relative to prochiral H5*p*R and H7, which is in agreement with the conformation found in the model exhibiting both protective groups in pseudo-equatorial positions.

Having succeeded in the diazepanones synthesis, we turned our attention to the optimisation of their synthesis (Scheme 5). Indeed, the diazepanone formation could be improved and shortened by reversing the order of the last steps of the synthesis. Thus, acidolysis of *tert*-butyl ester **21** or **23** by treatment with trifluoroacetic acid in dichloromethane was first carried out to give the corresponding acid intermediates, which then underwent concomitant lactonisation to give morpholinone **29** or **30**. Subsequent reduction of the azido group of **29** or **30** by hydrogenolysis in the presence of ammonium formate and palladium on charcoal led to the simultaneous isomerisation of the lactones into the target lactam **16** (43% overall yield from **21**, after chromatographic separation of its C_3-epimer) or **28** (67% overall yield from **23**), respectively. The latter conditions involving a lactonisation–lactamisation two-step sequence turned out to be much more efficient, when compared to the initial route, in terms of number of steps, purification and yield. Finally, the synthesis of the targeted diazepanone scaffolds **16** and **28** could be, respectively, performed in 13% and 24% overall yields from the ethyl L-threonate derivative **1**. Furthermore, it should be pointed out that the secondary amine function of scaffold **16** can be used for introducing other structural fragments. For example, with the aim of obtaining bacterial translocase MraY inhibitors, N-alkylation of diazepanone **16**, via a reductive amination of 5-uracilpentanal **31**,[25] could be easily achieved in the presence of sodium cyanoborohydride in dichloromethane affording **32** in high yield (87%).

Finally, in an analogous manner, the diastereoisomeric diazepanone **41** (Scheme 6) could be produced from the azido derivative **38** and the L-serine derivative **22**. The azido epoxide **38** was readily synthesised from D-isoascorbic acid according to the same sequence of reactions as previously described for the azido epoxide **11** from L-ascorbic acid. The enantiomerically pure diazepanone scaffold **41** was obtained in 22% overall yield from the ethyl D-erythronate derivative **33**.



Scheme 5.



Scheme 6.

3. Conclusion

In this study, we have examined various synthetic routes towards polyfunctionalised enantiopure diazepanone scaffolds. Their synthesis entails the preparation of C4 electrophilic amino-diol building blocks prepared from either L-ascorbic or D-isoascorbic acid and L-serine derivatives. We have shown that the best route towards the targeted scaffolds involves the nucleophilic opening of an epoxide followed by a lactonisation–lactamisation sequence. The obtention of 1,4-diazepan-2-ones displaying protected highly differentiated functions should allow the sequential introduction of key structural fragments, which could adopt a spatial distribution that generates essential interactions with the protein and therefore contributes to elucidation of the protein active site structure. In this context, work is currently in progress towards elaboration of a liposidomycin analogues library aiming at the generation of new antibacterials dedicated to the translocase MraY. From a general point of view, the diazepanones described are key skeletons with numerous potential applications, for example, in the field of peptidomimetics,[26] their flexibility allowing topographical modulations that represent a key tool to explore the structure–activity relationships of the related compounds.

4. Experimental

^{1}H NMR (250 MHz) and ^{13}C NMR (63 MHz) spectra were recorded on a Bruker AM250 in $CDCl_3$ (unless indicated). ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker Avance or Avance II. Chemical shifts (δ) are reported in ppm and coupling constants are given in hertz. Optical rotations were measured on a Perkin–Elmer 341 polarimeter with sodium (589 nm) or mercury (365 nm) lamp at 20 °C. Mass spectra, electrospray, chemical ionisation (CI) and high resolution (HRMS) were recorded by the service de Spectrométrie de Masse, ICSN Gif sur Yvette or Ecole Normale Supérieure, Paris. All reactions were carried out under nitrogen atmosphere, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 nm) on glass. Flash chromatography was performed with Merck Kieselgel 60 (200–500 μm); the solvent systems were given v/v. Spectroscopic ^{1}H and ^{13}C NMR, MS and/or analytical data were obtained using chromatographically homogeneous samples.

4.1. Molecular dynamics

The models obtained were consistent with NMR datasets using *ChemDraw 3D Pro 11.0.1*. A molecular dynamic (MD) job of 10,000 steps was carried out using a MM2 forcefield and a target temperature of 300 K. Finally, in order to minimise energy, a molecular mechanics program (MM2) was performed to obtain an RMS gradient value lower than 0.1.

4.2. Ethyl 2-O-*tert*-butyldiphenylsilyl-L-threonate 3

To a solution of acetonide **2** (2 g, 45.2 mmol) in H_2O (40.7 mL) and THF (13.6 mL), trifluoroacetic acid (40.7 mL) was added at 0 °C. After stirring for 3 h, the resulting mixture was neutralised at 0 °C with a 25% aqueous NH_4OH solution until pH 8 and then extracted with Et_2O (5 × 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc, 7:3 then 6:4, R_f 0.27 in cyclohexane/EtOAc, 7:3), led to 1.36 g (75%) of the diol **3** as a yellow oil; $[\alpha]_D$ = +44 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.74–7.35 (m, 10H, $H_{ar.}$), 4.38 (d, 1H, J_{H2-H3} = 4.1 Hz, H_2), 3.93 (2dq, 2H, J = 7.1 Hz, J = 14.3 Hz, CH_2CH_3), 3.89–3.86 (m, 1H, H_3), 3.72 (dd, 1H, J_{H4a-H3} = 6 Hz, $J_{H4a-H4b}$ = 11.4 Hz, H_{4a}), 3.63 (dd, 1H, J_{H4b-H3} = 4.7 Hz, $J_{H4b-H4a}$ = 11.4 Hz, H_{4b}), 1.11 (s, 9H, *t*Bu), 1.03 (t, 3H, J = 7 Hz, CH_3–CH_2); ^{13}C NMR δ 172.0 (C_1), 136.4, 136.2, 133.1, 130.5, 130.4, 128.2, 128.0 ($C_{ar.}$), 74.0 (C_3), 73.5 (C_2), 63.4 (C_4), 61.5 (CH_2CH_3), 27.3, 19.9 (*t*Bu), 14.2 (CH_3CH_2); HRMS calcd for $[M+NH_4]^+$ 420.2206; found 420.2206.

4.3. Ethyl 2,4-di-*O*-*tert*-butyldiphenylsilyl-L-threonate 4

To a solution of the diol **3** (748 mg, 1.86 mmol) in DMF (4 mL) in the presence of imidazole (278 mg, 2.2 equiv, 4.09 mmol), a solution of *tert*-butyldiphenylsilyl chloride (535 μL, 1.1 equiv, 2.05 mmol) in DMF (1 mL) was added dropwise at −10 °C in 1 h. After overnight stirring between −10 °C and 20 °C, the mixture was concentrated in vacuo. The residue was taken up in water (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc, 96:4, R_f 0.46 in cyclohexane/EtOAc, 8:2), afforded 875 mg (74%) of the bis-silyl ester **4** as a yellow oil; $[\alpha]_D$ = +13 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.55–7.28 (m, 20H, $H_{ar.}$), 4.58 (br s, 1H, H_2), 4.32–4.19 (m, 2H, $J_{H1'a-H2'}$ = 7.1 Hz, $J_{H1'a-H1'b}$ = 14.3 Hz, J_{H3-H4a} = 9.6 Hz, J_{H3-H4b} = 4.8 Hz, $H_{1'a}$, H_3), 4.05 (dq, 1H, $J_{H1'b-H2'}$ = 7.1 Hz, $J_{H1'b-H1'a}$ = 14.3 Hz, $H_{1'b}$), 3.81 (dd, 1H, $J_{H4a-H3} \approx J_{H4a-H4b} \approx$ 9.5 Hz, H_{4a}), 3.43 (dd, 1H, J_{H4b-H3} = 4.8 Hz, $J_{H4b-H4a}$ = 9.5 Hz, H_{4b}), 3.04 (s, 1H, OH), 1.26 (t, 3H, $J_{H2'-H1'}$ = 7 Hz, $H_{2'}$), 0.99, 0.98 (2s, 18H, *t*Bu); ^{13}C NMR δ 174.2 (C_1), 136.1, 136.0, 135.9, 135.8, 135.2, 133.9, 133.5, 133.2, 130.3, 130.1, 130.0, 128.0, 127.9 ($C_{ar.}$), 74.7 (C_3), 71.2 (C_2), 63.3 (C_4), 61.9 ($C_{1'}$), 27.2, 27.0, 19.6, 19.5 (*t*Bu), 14.5 ($C_{2'}$); HRMS calcd for $[M+NH_4]^+$ 658.3384; found 658.3382.

4.4. Ethyl (2*R*,3*R*)-3-azido-2,4-di-*tert*-butyldiphenylsilyloxy-butanoate 5

To a solution of the alcohol **4** (3.44 g, 5.38 mmol) in CH_2Cl_2 (190 mL) at −78 °C were successively added dropwise 2,6-lutidine (860 μL, 1.4 equiv, 7.52 mmol) and trifluoromethanesulfonic anhydride (1.17 mL, 1.3 equiv, 6.98 mmol). After 1 h stirring, the temperature was raised to 20 °C and TLC monitoring of the reaction revealed a complete transformation of the alcohol into the corresponding triflate. The mixture was concentrated in vacuo without heating and the residue was taken up in DMF (36 mL) prior to the addition of sodium azide (1.75 g, 5 equiv, 26.9 mmol) at 0 °C. After 2 h stirring at 0 °C, the temperature was allowed to warm to 20 °C overnight and then hydrolyzed (150 mL). After Et_2O extraction (3 × 150 mL), the combined extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the crude (cyclohexane/EtOAc, 96:4, R_f 0.40) led to 3.15 g (88%) of azide **5** as an oil; $[\alpha]_D$ = +7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.68–7.32 (m, 20H, $H_{ar.}$), 4.37 (ddd, 1H, J_{H3-H4a} = 7.9 Hz, J_{H3-H4b} = 4.9 Hz, J_{H3-H2} = 2.8 Hz, H_3), 4.30 (d, 1H, J_{H2-H3} = 2.8 Hz, H_2), 4.19–4.08 (2dq, 2H, $J_{H1'-H2'}$ = 7.2 Hz, $J_{H1'a-H1'b}$ = 14.3 Hz, $H_{1'}$), 3.79 (dd, 1H, J_{H4a-H3} = 8 Hz, $J_{H4a-H4b}$ = 10.1 Hz, H_{4a}), 3.57 (dd, 1H, J_{H4b-H3} = 4.9 Hz, $J_{H4b-H4a}$ = 10.1 Hz, H_{4b}), 1.22 (t, 3H, $J_{H2'-H1'}$ = 7.2 Hz, $H_{2'}$), 1.06, 1.00 (2s, 18H, *t*Bu); ^{13}C NMR δ 168.1 (C_1), 136.3, 136.1, 136.0, 135.9, 133.5, 130.4, 130.1, 128.2, 128.0 ($C_{ar.}$), 71.1 (C_3), 65.2 (C_2), 64.2 (C_4), 62.0 ($C_{1'}$), 27.2, 19.6 (*t*Bu), 14.4 ($C_{2'}$); HRMS calcd for $[M+NH_4]^+$ 683.3449; found 683.3455.

4.5. (2*R*,3*R*)-3-Azido-2,4-di-*tert*-butyldiphenylsilyloxy-butanal 6

To a solution of the azidoester **5** (350 mg, 1 equiv, 0,45 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added dropwise diisobutylaluminium hydride (1.2 M in toluene, 543 μL, 1 equiv, 0.45 mmol). After 2 h stirring at −78 °C, methanol (835 μL) was slowly added and the temperature was allowed to warm to 20 °C. A solution of potassium and sodium tartrate was then added and the mixture was

diluted with Et_2O. After separation, the organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc, 96:4, R_f 0.40) afforded 269 mg (96%) of azidoaldehyde **6** as an oil; ^1H NMR δ 9.52 (s, 1H, H_1), 7.68–7.35 (m, 20H, $H_{ar.}$), 4.45 (ddd, 1H, J_{H3-H4a} = 9 Hz, J_{H3-H4b} = 4.9 Hz, J_{H3-H2} = 2.4 Hz, H_3), 4.19 (d, 1H, J_{H2-H3} = 2.4 Hz, H_2), 3.85 (dd, 1H, J_{H4a-H3} = 9 Hz, $J_{H4a-H4b}$ = 10.1 Hz, H_{4a}), 3.57 (dd, 1H, J_{H4b-H3} = 4.9 Hz, $J_{H4b-H4a}$ = 10.1 Hz, H_{4b}), 1.10, 1.01 (2s, 18H, *t*Bu); ^{13}C NMR δ 195.9 (C_1), 136.2, 136.0, 135.9, 133.0, 130.7, 130.5, 130.2, 128.4, 128.2 ($C_{ar.}$), 75.12 (C_3), 72.0 (C_2), 63.9 (C_4), 27.4, 27.2, 27.1, 19.5, 19.4 (*t*Bu); HRMS calcd for $(M+NH_4)^+$ 639.3187; found 639.3179.

4.6. General procedure for epoxidation

To a solution of the diol **10** or **37** (24 mmol) in CH_2Cl_2 (100 mL) were successively added pyridinium *p*-toluene sulfonate (60 mg, 1 mol %, 0.24 mmol) and trimethylorthoacetate (4.6 mL, 1.5 equiv, 36 mmol) dropwise and the resulting mixture was stirred at 20 °C for 2 h and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (100 mL) and cooled to 0 °C prior to the dropwise addition of triethylamine (70 μL, 2 mol %, 0.48 mmol) and acetyl bromide (2.7 mL, 1.5 equiv, 36 mmol). The mixture was stirred at 20 °C for 2 h and concentrated in vacuo. The residue was taken up in methanol (100 mL) and potassium carbonate (6 g, 1.8 equiv, 43 mmol) was added. The mixture was stirred for 1 h, filtered through a Celite pad and concentrated in vacuo. The residue was then diluted with H_2O (200 mL) and EtOAc (300 mL). After separation and EtOAc extractions, the organic extracts were washed twice with brine, dried ($MgSO_4$), filtered and concentrated in vacuo prior to purification by flash chromatography to give **11** or **38**, respectively.

4.7. (2*R*,3*R*)-3-Azido-4-*tert*-butyldiphenylsilyloxy-1,2-epoxybutane 11

From the diol **10** (9.3 g, 24 mmol), according to the general procedure described above, 7.7 g (87%) of the epoxide **11** was obtained as a colourless oil, after flash chromatographic purification (cyclohexane/EtOAc, 97:3, R_f 0.25).[27]

4.8. (2*R*,3*R*)-3-Amino-4-*tert*-butyldiphenylsilyloxy-1,2-epoxybutane 12

To a solution of the azidoepoxide **11** (203 mg, 0.55 mmol) in THF (1 mL), at 20 °C was added bis-diphenylphosphinoethane (121 mg, 0.55 equiv, 0.30 mmol) and the mixture was stirred overnight. TLC monitoring of the reaction revealed disappearance of the starting material and H_2O (200 μL) was then added while stirring was continued for 24 h. Flash chromatography of the residue (EtOAc/Et_3N, 100:0.5, R_f 0.25) gave 174 mg (92%) of the amino epoxide **12** as a yellow oil; $[\alpha]_D = -4$ (*c* 1.0, CH_2Cl_2); ^1H NMR (CD_3OD) δ 7.68–7.35 (m, 10H, $H_{ar.}$), 3.77 (2dd, 2H, J_{H4a-H3} = 4.1 Hz, J_{H4b-H3} = 5.2 Hz, $J_{H4a-H4b}$ = 10 Hz, H_4), 2.94–2.91 (m, 1H, H_2), 2.84–2.79 (m, 1H, J_{H3-H2} = 4.7 Hz, H_3), 2.66–2.63 (m, 2H, $J_{H1a-H1b}$ = 9.1 Hz, H_1), 1.05 (s, 9H, *t*Bu); ^{13}C NMR (CD_3OD) δ 135.5, 133.4, 133.2, 132.2, 132.0, 131.9, 129.8, 128.6, 128.4, 127.8 ($C_{ar.}$), 65.9 (C_4), 53.5 (C_3), 53.1 (C_2), 44.6 (C_1), 26.9, 19.3 (*t*Bu); HRMS calcd for $(M+H)^+$ 342.1889; found 342.1883.

4.9. (2*R*,3*R*)-3-[(*N*-Fluorenylmethoxycarbonyl-*O*-benzyl-L-serinyl)amino]-4-*tert*-butyldiphenylsilyloxy-1,2-epoxybutane 14

To a solution of the commercially available *N*-Fmoc-*O*-benzyl-L-serine **13** (278.3 mg, 1 equiv, 0.66 mmol) in CH_2Cl_2 (2.44 mL) and in darkness were successively added PyBOP (380 mg, 1.1 equiv, 0.73 mmol), amino epoxide **12** (250 mg, 1.1 equiv, 0.73 mmol) and diisopropylethylamine (320 μL, 2.75 equiv, 1.82 mmol). The progress of the reaction was monitored by TLC and when transformation of the starting material was judged complete, the mixture was concentrated in vacuo prior to flash chromatographic purification (cyclohexane/EtOAc/NEt_3, 7:3:3‰, R_f 0.63) leading to 233.4 mg (78%) of the expected amide **14** as a white foam; $[\alpha]_D$ = +16 (*c* 1.0, CH_2Cl_2); ^1H NMR δ 7.78–7.27 (m, 23H, $H_{ar.}$), 7.06 (d, 1H, J_{NH-H3} = 6.2 Hz, NHCO), 5.72 (d, 1H, $J_{NH-H2'}$ = 5.4 Hz, NHFmoc), 4.59, 4.57 (AB, 2H, J_{AB} = 12.5 Hz, CH_2Ph), 4.41 (m, 2H, $H_{2'}$, CH_{2aFmoc}), 4.31 (dd, 1H, $J_{CHFmoc-CH2Fmoc}$ = 7.1 Hz, $J_{CH2Fmoc}$ = 14.1 Hz, CH_{2bFmoc}), 4.16 (t, 1H, $J_{CHFmoc-CH2Fmoc}$ = 7.1 Hz, CH_{Fmoc}), 3.96 (dd, 1H, $J_{H4a-H4b}$ = 10.2 Hz, J_{H4a-H3} = 2.8 Hz, H_{4a}), 3.91 (dd, 1H, $J_{H3'a-H3'b}$ = 9.3 Hz, $J_{H3'a-H2'}$ = 3.8 Hz, $H_{3'a}$), 3.77 (m, 2H, H_3, H_{4b}), 3.61 (dd, 1H, $J_{H3'b-H3'a}$ = 9.3 Hz, $J_{H3'b-H2'}$ = 7.2 Hz, $H_{3'b}$), 3.14 (m, 1H, H_2), 2.82, 2.80 (AB of ABX, 2H, $J_{H1a-H1b}$ = 10.5 Hz, J_{H1a-H2} = 2.2 Hz, J_{H1b-H2} = 5 Hz, H_{1a}, H_{1b}), 1.12 (s, 9H, *t*Bu); ^{13}C NMR δ 169.8 ($C_{1'}$), 156.2 (CO_{Fmoc}), 143.9, 143.6, 141.3, 137.4, 135.6, 135.5, 132.8, 132.5, 130.0, 128.6, 128.0, 127.8, 127.1, 125.1, 120.1 ($C_{ar.}$), 73.4 (CH_2Ph), 69.6 ($C_{3'}$), 67.4 (CH_{2Fmoc}), 63.3 (C_4), 54.6 ($C_{2'}$), 52.6 (C_3), 51.0 (C_2), 47.1 (CH_{Fmoc}), 46.9 (C_1), 26.9, 19.1 (*t*Bu), HRMS calcd for $(M+H)^+$ 741.3360; found 741.3362. Anal. Calcd for $C_{45}H_{48}N_2O_6Si$: C, 72.94; H, 6.53; N, 3.78. Found: C, 72.80; H, 6.59; N, 3.86.

4.10. (2*R*,3*R*)-3-[(*O*-Benzyl-L-serinyl)amino]-4-*tert*-butyldiphenylsilyloxy-1,2-epoxybutane 15

To the *N*-Fmoc compound **14** (75 mg, 0.1 mmol) at 20 °C was added a 20% (v/v) solution of piperidine in DMF (775 μL). After 30 min, the reaction was completed as monitored by TLC and the mixture was concentrated in vacuo. Flash chromatography of the residue (EtOAc/Et_3N, 1:3‰, R_f 0.10 in EtOAc/cyclohexane/Et_3N, 8:2:3‰) led to 34 mg (65%) of the amino epoxide derivative **15** as a yellow oil; ^1H NMR δ 8.09 (d, 1H, J_{NH-H3} = 8.5 Hz, NH), 7.68–7.27 (m, 15H, $H_{ar.}$), 4.56, 4.54 (AB, 2H, J_{AB} = 12.4 Hz, CH_2Ph), 3.97 (dd, 1H, $J_{H4a-H4b}$ = 10.2 Hz, J_{H4a-H3} = 2.8 Hz, H_{4a}), 3.80 (dd, 1H, $J_{H3'a-H3'b}$ = 9.4 Hz, $J_{H3'a-H2'}$ = 4 Hz, $H_{3'a}$), 3.77 (dd, 1H, $J_{H4b-H4a}$ = 10.2 Hz, J_{H4b-H3} = 3.3 Hz, H_{4b}), 3.76–3.73 (m, 1H, H_3), 3.69 (dd, 1H, $J_{H3'b-H3'a}$ = 9.4 Hz, $J_{H3'b-H2'}$ = 6.6 Hz, $H_{3'b}$), 3.60 (dd, 1H, $J_{H2'-H3'a}$ = 4 Hz, $J_{H2'-H3'b}$ = 6.6 Hz, $H_{2'}$), 3.15 (X of ABX, 1H, J_{AX} = 2.2 Hz, J_{BX} = 5 Hz, J_{H2-H3} = 6.8 Hz, H_2), 2.82, 2.78 (AB from ABX, 2H, J_{AB} = 10.5 Hz, J_{AX} = 2.2 Hz, J_{BX} = 5 Hz, H_1), 1.90 (br s, 2H, NH_2), 1.07 (s, 9H, *t*Bu); ^{13}C NMR δ 172.5 (CONH), 137.9, 135.6, 133.0, 129.9, 128.4, 127.8, 127.7 ($C_{ar.}$), 74.0 (*t*Bu), 73.2 (CH_2Ph), 72.3 ($C_{3'}$), 63.6 (C_4), 55.2 ($C_{2'}$), 52.0 (C_3), 51.1 (C_2), 46.7 (C_1), 26.8 (*t*Bu); HRMS calcd for $(M+H)^+$ 519.2679; found 519.2676. Anal. Calcd for: C, 69.46; H, 7.38; N, 5.40. Found: C, 69.54; H, 7.28; N, 5.44.

4.11. General procedure for the diazepanone formation according to peptidic coupling

To a solution of amino acid **25** or **27** (0.10 mmol) in CH_2Cl_2 (4 mL) at 20 °C were successively added silver tetrafluoroborate (2.25 equiv, 0.23 mmol) and diisopropylethylamine (7.5 equiv, 0.75 mmol) and the resulting mixture was stirred at 20 °C in darkness for 24 h. It was then cooled to 0 °C prior to the addition of pentafluorophenyl diphenylphosphinate (2.25 equiv, 0.23 mmol). The temperature was warmed to 20 °C and the mixture was stirred for 72 h. Then, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution and concentrated in vacuo. The residue was taken up in EtOAc and successively washed with a saturated aqueous $NaHCO_3$ solution and brine. The organic layer was then dried ($MgSO_4$), filtered and concentrated in vacuo and the residue was purified by flash chromatography to afford **16** or **28**, respectively.

4.12. (3*S*,6*S*,7*R*)-3-Benzyloxymethyl-7-*tert*-butyldiphenylsilyloxymethyl-6-hydroxy-1,4-diazepan-2-one 16

From the amino acid **25** (0.27 mmol), the conditions described in the general procedure, followed by flash chromatography (CH_2Cl_2/MeOH, 95:5–9:1, R_f 0.45 in CH_2Cl_2/MeOH, 9:1) led to 49 mg (35%) of the expected diazepanone **16** as a white foam and 24 mg of its C_3-epimer.

From the morpholin-2-one **29** (2.42 mmol), the general conditions described below, for the diazepanone formation according to the lactonisation–lactamisation sequence followed by flash chromatography from EtOAc/Et_3N, 1:3‰ to EtOAc/MeOH/Et_3N, 96:4:3‰ afforded 123 mg of the C_3-epimer of **16** (9.8%, R_f 0.30 in EtOAc/Et_3N, 1:3‰) and 538 mg of the diazepanone **16** (43%, R_f 0.10 in EtOAc/Et_3N, 1:3‰) both as white foams.

Compound **16** $[\alpha]_{365} = -2.5$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.63–7.28 (m, 15H, $H_{ar.}$), 5.82 (br d, 1H, H_1), 4.52, 4.46 (AB, 2H, J_{AB} = 11.9 Hz, CH_2Ph), 3.90 (m, 1H, H_6), 3.82 (dd, 1H, J_{CH2OSi} = 9.5 Hz, $J_{CHaOSi-H7}$ = 3.5 Hz, CH_aOSi), 3.76 (m, 3H, CH_2OBn, H_7), 3.70 (dd, 1H, J_{CH2OSi} = 9.5 Hz, $J_{CHbOSi-H7}$ = 7.4 Hz, CH_bOSi), 3.52 (dd, 1H, $J_{CHaOBn-H3}$ = 7.3 Hz, $J_{CHbOBn-H3}$ = 3.5 Hz, H_3), 3.11 (dd, 1H, J_{H5b-H6} = 2.3 Hz, $J_{H5b-H5a}$ = 14.4 Hz, H_{5b}), 2.96 (dd, 1H, J_{H5a-H6} = 2.7 Hz, $J_{H5a-H5b}$ = 14.4 Hz, H_{5a}), 1.05 (s, 9H, *t*Bu), ^{13}C NMR δ 175.0 (C_2), 138.0, 135.7, 132.8, 130.2, 128.6, 128.1, 128.0, 127.9 (C_{ar}), 73.7 (CH_2Ph); 71.1 (CH_2OBn), 69.1 (C_6), 64.4 (C_3), 63.3 (CH_2OSi), 56.8 (C_7), 51.9 (C_5); 27.1, 19.4 (*t*Bu); HRMS calcd for $(M+Na)^+$ 541.2499; found 541.2521. *C_3-epimer of* **16**: $[\alpha]_D$ = +32 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz) δ 7.70–7.36 (m, 15H, H_{ar}), 5.84 (d, 1H, J_{H1-H7} = 5 Hz, H_1), 4.60, 4.57 (AB, 2H, J_{AB} = 12 Hz, CH_2Ph), 4.02 (dd, 1H, J_{CH2OSi} = 11.0 Hz, $J_{CH2aOSi-H7}$ = 4.0 Hz, $CH_{2a}OSi$), 3.89 (dd, 1H, J_{CH2OSi} = 11.0 Hz, $J_{CH2bOSi-H7}$ = 3.6 Hz, $CH_{2b}OSi$), 3.89 (dd, 1H, J_{CH2OBn} = 10.1 Hz, $J_{CH2aOBn-H3}$ = 4.1 Hz, $CH_{2a}OBn$), 3.69 (ddd, 1H, J_{H6-H5a} = 4.1 Hz, J_{H6-H5b} = 8.2 Hz, J_{H6-H7} = 8.8 Hz, H_6), 3.65 (t, 1H, J_{CH2OBn} = 10.1 Hz, $J_{CH2bOBn-H3}$ = 8.8 Hz, $CH_{2b}OBn$), 3.57 (dd, 1H, $J_{H3-CH2aOBn}$ = 4.1 Hz, $J_{H3-CH2bOBn}$ = 8.8 Hz, H_3), 3.40 (dddd, 1H, $J_{H7-CH2aOSi}$ = 4.1 Hz, $J_{H7-CH2bOSi}$ = 3.6 Hz, J_{H7-H6} = 8.8 Hz, J_{H7-H1} = 5 Hz, H_7), 3.40 (dd, 1H, $J_{H5a-H5b}$ = 13.2 Hz, J_{H5a-H6} = 4.1 Hz, H_{5a}), 2.79 (dd, 1H, $J_{H5a-H5b}$ = 13.2 Hz, J_{H5b-H6} = 8.2 Hz, H_{5b}), 1.1 (s, 9H, *t*Bu); ^{13}C NMR δ 174.4 (C_2), 137.8, 135.5, 132.4, 130.1, 128.4, 128.0, 127.8 (C_{ar}), 73.4 (CH_2Ph), 69.5 (CH_2OBn), 69.2 (C_6), 62.4 (CH_2OSi), 59.9 (C_3), 57.7 (C_7), 56.1 (C_5), 26.8, 19.2 (*t*Bu).

4.13. *tert*-Butyl (2*S*,3*R*)-*N*-(3-azido-2,4-di-*tert*-butyldiphenylsilyloxy-butyl)-*O*-benzyl-L-serine ester 20

To a solution of aldehyde **6** (56 mg, 0.22 mmol), in CH_2Cl_2 (1 mL) at 20 °C was added titanium(IV) tetraisopropoxide (0.294 mL, 1.25 equiv, 1.07 mmol), and 10 min later a solution of the primary amine **19** (216 mg, 1 equiv, 0.86 mmol) in CH_2Cl_2 (0.25 mL) was added. After 3 h stirring, absolute ethanol (1.28 mL) and sodium cyanoborohydride (5.3 equiv, 4.54 mmol) were added at 0 °C and the mixture was stirred at 20 °C overnight. After H_2O (1 mL) addition, the resulting precipitate was filtered and rinsed with absolute ethanol and the filtrate was concentrated in vacuo. The residue was then taken up in EtOAc, filtered and concentrated in vacuo. The so-obtained oil was then diluted with dichloromethane and stirred in the presence of an excess of sodium hydrogenocarbonate for 5 min. The mixture was then filtered and concentrated in vacuo prior to flash chromatographic purification (cyclohexane/EtOAc/Et_3N, 96:4:3‰, R_f 0.52) affording 52 mg (27%) of the secondary amine **20** as a colourless oil; $[\alpha]_D$ = +4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.67–7.27 (m, 25H, $H_{ar.}$), 4.56, 4.52 (AB, 2H, J_{AB} = 12.1 Hz, CH_2Ph), 3.97–3.90 (m, 1H, J_{H3-H2} = 3.2 Hz, H_3), 3.82 (ddd, 1H, J_{H2-H3} = J_{H2-H1a} = 3.2 Hz, J_{H2-H1b} = 9.6 Hz, H_2), 3.72–3.63 (m, 3H, H_{4a}, $H_{3'}$), 3.60 (dd, 1H, J_{H4b-H3} = 4.5 Hz, $J_{H4b-H4a}$ = 9.6 Hz, H_{4b}), 3.28 (dd, 1H, $J_{H2'-H3'a}$ = 4.1 Hz, $J_{H2'-H3'b}$ = 4.9 Hz, $H_{2'}$), 2.92 (dd, 1H, J_{H1a-H2} = 3.2 Hz, $J_{H1a-H1b}$ = 12.5 Hz, H_{1a}), 2.62 (dd, 1H, J_{H1b-H2} = 9.6 Hz, $J_{H1b-H1a}$ = 12.5 Hz, H_{1b}), 2.09 (br s, 1H, NH), 1.48, 1.06, 1.00 (3s, 27H, *t*Bu); ^{13}C NMR δ 172.1 ($C_{1'}$), 138.4, 136.4, 136.2, 136.0, 134.0, 133.6, 133.3, 130.2, 130.0, 128.7, 128.1, 128.0 ($C_{ar.}$), 75.2 (C_3), 73.7 (CH_2Ph), 71.4 ($C_{3'}$), 66.2 (C_2), 64.8 (C_4), 62.4 ($C_{2'}$), 48.2 (C_1), 30.6, 28.5, 27.3, 19.7, 19.5 (*t*Bu); HRMS calcd for $(M+H)^+$ 857.4493; found 857.4496.

4.14. General procedure for epoxide opening

To a solution of azido-epoxide **11** or **38** (12.3 mmol) in CH_2Cl_2 (25 mL), at 20 °C was added ytterbium triflate (0.2 equiv, 2.5 mmol). After 20 min stirring, a solution of *tert*-butyl *O*-benzyl-L-serine ester **19** or **22** (1.3 equiv, 16 mmol) in CH_2Cl_2 (25 mL) was added dropwise. After 5 days stirring at 20 °C, further additions of ytterbium triflate (0.2 equiv, 2.5 mmol) and *tert*-butyl *O*-benzyl-L-serine ester **19** or **22** (0.49 equiv, 6 mmol) in CH_2Cl_2 (12 mL) were carried out. After 6 days stirring, the reaction was quenched by the addition of a saturated $NaHCO_3$ aqueous solution prior to CH_2Cl_2 extraction. The combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the crude afforded **21** (as a 2*S*/2*R* = 2:1 mixture), **23** or **39**, respectively.

4.15. *tert*-Butyl *N*-[(2*S*,3*R*)-3-azido-4-*tert*-butyldiphenylsilyloxy-2-hydroxybutyl]-*O*-benzyl-serine ester 21

From the azido-epoxide **11** (4.5 g, 12.3 mmol) and *tert*-butyl *O*-benzyl-L-serine ester **19** (4 g, 16 mmol), the general procedure described above, followed by flash chromatography (cyclohexane/EtOAc/NEt_3, 8:2:3‰, R_f 0.39 in cyclohexane/EtOAc, 7:3) afforded 4.95 g (65%) of the secondary amine **21**, as a 2*S*/2*R* = 2:1 mixture (yellow oil). In an alternative manner, a suspension of azidoepoxide 11 (0.4 g, 1.09 mmol), serine derivative **19** (0.301 g, 1.1 equiv, 1.20 mmol) and calcium triflate (184 mg, 0.5 equiv, 0.54 mmol) in anhydrous dioxane (6 mL) was stirred for 35 min. at 110 °C in a microwave reactor. After cooling to room temperature, the mixture was concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc/NEt_3, 8:2:3‰) afforded 0.367 g (54%) of the secondary amine **21** as a 2*S*/2*R* = 4:1 mixture and 0.124 g (31%) of the starting azidoepoxide was recovered. ^{1}H NMR δ 7.75–7.29 (m, 15H, Har.), 4.58, 4.52 (AB, 2H, J_{AB} = 12 Hz, CH2Ph), 3.96 (dd, 1H, J_{H4a-H3} = 3.8 Hz, $J_{H4a-H4b}$ = 10.8 Hz, H4a), 3.84 (dd, 1H, J_{H4b-H3} = 6.8 Hz, $J_{H4a-H4b}$ = 10.8 Hz, H4b), 3.72–3.56 (m, 3H, H3′, H2), 3.50 (ddd, 1H, J_{H3-H2} = 6.8 Hz, J_{H3-H4a} = 3.8 Hz, J_{H3-H4b} = 6.8 Hz, H3), 3.33 (dd, 1H, $J_{H2'-H3'a}$ = 4.3 Hz, $J_{H2'-H3'b}$ = 5.2 Hz, H2′), 3.00 (dd, 1H, J_{H1a-H2} = 3.2 Hz, $J_{H1a-H1b}$ = 12.5 Hz, H1a minor),2.81 (dd, 1H, J_{H1a-H2} = 7.2 Hz, $J_{H1a-H1b}$ = 12.7 Hz, H1a major), 2.73 (dd, 1H, J_{H1b-H2} = 4.0 Hz, $J_{H1a-H1b}$ = 12.7 Hz, H1b major), 2.57 (dd, 1H, J_{H1b-H2} = 7.9 Hz, $J_{H1a-H1b}$ = 12.5 Hz, H1b minor), 2.00 (br s, 1H, NH), 1.48, 1.11 (2s, 18H, *t*Bu); ^{13}C NMR δ 172.2 (C1′), 138.2, 136.1, 133.4, 130.3, 128.8, 128.2, 128.1 (Car.), 82.1 (O*t*Bu), 73.8 (CH2Ph), 71.7 (C3′), 68.8 (C2), 66.4 (C3), 65.0 (C4 major), 69.9 (C4minor), 62.2 (C2′), 50.2 (C1), 28.5, 27.4, 27.2, 19.6 (*t*Bu); HRMS calcd for $(M+H)^+$ 619.3316; found 619.3310.

4.16. *tert*-Butyl *N*-[(2*S*,3*R*)-3-azido-4-*tert*-butyldiphenylsilyloxy-2-hydroxybutyl]-*N*′-methyl-*O*-benzyl-L-serine ester 23

From azido-epoxide **11** (2.41 g, 6.6 mmol) and *tert*-butyl *O*-benzyl-L-serine ester **22** (2.2 g, 8.5 mmol), the general procedure described above, followed by flash chromatography (cyclohexane/EtOAc, 4:1, R_f 0.3) afforded 2.7 g (65%) of the secondary amine **23**; $[\alpha]_D = -29$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.66–7.29 (m,

15H, $H_{ar.}$), 4.46, 4.41 (AB, 2H, J_{AB} = 12 Hz, CH_2Ph), 3.86 (dd, 1H, $J_{H4a-H4b}$ = 10 Hz, J_{H4a-H3} = 4.6 Hz, H_{4a}), 3.72 (dd, 1H, $J_{H4a-H4b}$ = 10 Hz, J_{H4b-H3} = 7.0 Hz, H_{4b}), 3.60–3.53 (m, 2H, H_2, $H_{2'}$), 3.48–3.41 (m, 3H, $H_{3'}$, H_3), 2.71 (m, 2H, H_1), 2.37 (s, 3H, NMe), 1.38, 1.01 (2s, 18H, *t*Bu); ^{13}C NMR δ 170.0 ($C_{1'}$), 137.7, 135.7, 133.1, 129.9, 128.5, 128.0, 127.9 ($C_{ar.}$), 81.9 (O*t*Bu), 73.5 (CH_2Ph), 68.0 ($C_{3'}$), 66.6 ($C_{2'}$, C_2), 66.3(C_3), 64.3 (C_4), 55.5 (C_1), 40.2 (NMe), 28.3, 26.9, 19.3 (*t*Bu); HRMS calcd for $(M+H)^+$ 633.3472; found 633.3466.

4.17. General procedure for azide reduction towards amines 24 and 26

To a solution of the azido derivative **21** or **23** (1.99 mmol) in THF (7 mL) at 20 °C were successively added bis-1,2-diphenyl phosphinoethane (0.55 equiv, 1.09 mmol,) and H_2O (700 μL). After stirring overnight, the mixture was concentrated in vacuo and the residue was taken up in cold Et_2O, filtered and concentrated in vacuo. Flash chromatography of the crude afforded **24** or **26**, respectively.

4.18. *tert*-Butyl (2*S*,3*R*)-*N*-(3-amino-4-*tert*-butyldiphenylsilyloxy-2-hydroxy-butyl)-*O*-benzyl-serine ester 24

From the azido derivative **21** (150 mg, 0.24 mmol), the general procedure described above followed by flash chromatography (CH_2Cl_2/MeOH/NEt_3, 95:5:3‰, R_f 0.32) gave 142 mg (quantitative yield) of the amine **24** as an oil; ^{1}H NMR δ 7.72–7.34 (m, 15H, $H_{ar.}$), 4.56, 4.54 (AB, 2H, J_{AB} = 12.2 Hz, CH_2Ph), 3.82 (dd, 1H, J_{H4a-H3} = 3.3 Hz, $J_{H4a-H4b}$ = 9.5 Hz, H_{4a}), 3.75–3.62 (m, 4H, H_{4b}, H_2, $H_{3'}$), 3.37 (dd, 1H, $J_{H2'-H3'a} \approx J_{H2'-H3'b} \approx$ 4.4 Hz, $H_{2'}$), 3.03 (ddd, 1H, J_{H3-H4b} = 6.7 Hz, J_{H3-H4a} = 3.3 Hz, J_{H3-H2} = 3.5 Hz, H_3), 2.98 (dd, 1H, J_{H1a-H2} = 3 Hz, $J_{H1a-H1b}$ = 11.6 Hz, H_{1a}), 2.58 (dd, 1H, J_{H1b-H2} = 8.6 Hz, $J_{H1b-H1a}$ = 11.6 Hz, H_{1b}), 1.48, 1.11 (2s, 18H, *t*Bu); ^{13}C NMR δ 172.4 ($C_{1'}$), 138.3, 136.0, 133.8, 130.2, 128.8, 128.2, 128.1 ($C_{ar.}$), 81.9 (*t*Bu), 73.7 (CH_2Ph), 71.8 ($C_{3'}$), 66.6 (C_4), 66.5 (C_2), 62.2 ($C_{2'}$), 56.0 (C_3), 50.7 (C_1), 28.5, 27.4, 19.7 (*t*Bu); HRMS calcd for $(M+H)^+$ 593.3411; found 593.3408.

4.19. (2*S*,3*R*)-*N*-(3-Amino-4-*tert*-butyldiphenylsilyloxy-2-hydroxy-butyl)-*O*-benzyl-L-serine 25

To a solution of the *tert*-butyl ester **24** (160 mg, 0.27 mmol) in CH_2Cl_2 (2.6 mL) at 20 °C was added dropwise trifluoroacetic acid (865 μL) and the resulting mixture was stirred for 24 h. Concentration in vacuo afforded 207 mg (quantitative yield) of the corresponding acid **25** as its bis-ammonium trifluoroacetate salt.

4.20. *tert*-Butyl (2*S*,3*R*)-*N*-(3-amino-4-*tert*-butyldiphenylsilyloxy-2-hydroxy-butyl)-*N'*-methyl-*O*-benzyl-L-serine ester 26

From the azido derivative **23** (1.26 g, 1.99 mmol) the general procedure described above for azide reduction, followed by flash chromatography (EtOAc/NEt_3, 1:3‰, R_f 0.30) gave 1.05 g (87%) of the corresponding primary amine **26** as an oil; $[\alpha]_D = -19$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ (500 MHz) 7.66–7.20 (m, 15H, $H_{ar.}$), 4.43 (s, 2H, CH_2Ph), 3.79 (dd, 1H, $J_{H4a-H4b}$ = 10 Hz, J_{H4a-H3} = 4.6 Hz, H_{4a}), 3.66 (dd, 1H, $J_{H4a-H4b}$ = 10 Hz, J_{H4b-H3} = 7.0 Hz, H_{4b}), 3.62 (m, 1H, H_2), 3.60 (m, 2H, $H_{3'}$), 3.46 (dd, 1H, $J_{H2'-H3'a}$ = 7.5 Hz, $J_{H2'-H3'b}$ = 6.0 Hz,$H_{2'}$), 2.99 (ddd, 1H, J_{H3-H4} = 7 Hz, J_{H3-H2} = 11 Hz, H_3), 2.71 (m, 2H, H_1), 2.38 (s, 3H, NMe), 1.38, 1.04 (2s, 18H, (*t*Bu); ^{13}C NMR δ 169.8 ($C_{1'}$), 137.4, 135.13, 133.0, 129.3, 127.9, 127.3 (C_{ar}), 80.9 (O*t*Bu), 72.8 (CH_2Ph); 67.8 (C_2, $C_{3'}$), 66.0 ($C_{2'}$), 65.6 (C_4), 55.5 (C_3), 55.1 (C_1), 39.5 (NCH_3), 27.8, 26.5 19.3 (*t*Bu).

4.21. (2*S*,3*R*)-*N*-(3-Amino-4-*tert*-butyldiphenylsilyloxy-2-hydroxy-butyl)-*N'*-methyl-*O*-benzyl-L-serine 27

To the *tert*-butyl ester **26** (1.05 g, 1.73 mmol) at 20 °C were successively added a 3:1 CH_2Cl_2/trifluoroacetic acid mixture (21.7 mL) and H_2O (31 μL, 1 equiv, 1.73 mmol) and the mixture was stirred for 24 h. Concentration in vacuo followed by Et_2O co-evaporations to remove excess of trifluoroacetic acid led to 1.5 g (quantitative yield) of crude carboxylic acid **27** as its bis-trifluoroacetate salt and as a beige foam.

4.22. General procedure for the diazepanone formation according to the lactonisation–lactamisation sequence

To a solution of morpholin-2-one **29**, **30** or **40** (0.35 mmol) in EtOAc (12 mL) were successively added Pd/C 10% (102 mg) and ammonium formate (10 equiv, 3.47 mmol) and the mixture was stirred at 20 °C for 5 h. It was then filtered through a Celite pad and concentrated in vacuo prior to flash chromatographic purification to give **16**, **28** or **40**, respectively.

4.23. (3*S*,6*S*,7*R*)-3-Benzyloxymethyl-7-*tert*-butyldiphenylsilyloxymethyl-6-hydroxy-4-*N*-methyl-1,4-diazepan-2-one 28

From amino acid **27** (1.73 mmol) the conditions described in the general procedure for diazepanone formation by peptidic coupling, followed by flash chromatography (EtOAc/Et_3N, 100:3‰, R_f 0,3) led to 322 mg (35%) of the expected diazepanone **28** as a white foam. Alternatively, from morpholin-2-one **30** (1.2 mmol) the conditions described above followed by flash chromatography in the same conditions as described above afforded 428 mg (67%) of the diazepanone **28**, $[\alpha]_D$ = +20 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.69–7.26 (m, 15H, $H_{ar.}$), 6.1 (d, 1H, J_{H1-H7} = 5 Hz, H_1), 456 (s, 2H, CH_2Ph), 4.01 (m, 1H, H_7), 3.92 (dd, 1H, $J_{CH2bOSi-H7}$ = 3.5 Hz, J_{CH2OSi} = 10.8 Hz, $CH_{2b}OSi$), 3.80 (m, 3H, $J_{CH2OBn-H3}$ = 3.7 Hz, CH_2OBn, H_6), 3.78 (dd, 1H, $J_{CH2aOSi-H7}$ = 3.5 Hz, J_{CH2OSi} = 10.8 Hz, $CH_{2a}OSi$), 3.38 (t, 1H, $J_{H3-CH2OBn}$ = 3.7 Hz, H_3), 3.15 (dd, 1H, $J_{H5a-H5b}$ = 15 Hz, J_{H5a-H6} = 3 Hz, H_{5a}), 2.80 (dd, 1H, $J_{H5a-H5b}$ = 15 Hz, J_{H5b-H6} = 1.5 Hz, H_{5b}), 2.48 (s, 3H, NMe), 1.11 (s, 9H, *t*Bu); ^{13}C NMR δ 173.4 (C_2), 137.9, 135.6, 132.6, 130.0, 128.3, 127.9, 127.6, 127.4 (C_{ar}), 74.8 (C_3), 73.4 (CH_2Ph), 70.0 (CH_2OBn, C_6), 61.8 (CH_2OSi), 60.6 (C_5), 55.3 (C_7), 45.3 (NCH_3), 26.9, 19.3 (*t*Bu); HRMS calcd for $(M+H)^+$ 533.2836; found 533.2830.

4.24. General procedure for morpholinone preparation

To a solution of azido *tert*-butyl ester **21**, **23** or **39** (3.8 mmol) in dichloromethane (35 mL) at 20 °C was added trifluoroacetic acid (7 mL), and the mixture was stirred overnight. The reaction was then quenched at 0 °C with a saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo prior to flash chromatography to afford **29**, **30** or **40**, respectively.

4.25. (1'*R*,3*S*,6*S*)-6-[(1'-Azido-2'-*tert*-butyldiphenylsilyloxy)-ethyl]-3-benyloxymethyl-morpholin-2-one 29

From the *tert*-butyl ester derivative **21** (1.5 g, 2.42 mmol) the conditions described above in the general procedure except that the reaction was carried out in dichloromethane (50 mL) and trifluoroacetic acid (10 mL) afforded the crude morpholinone **29**. A pure sample could be obtained by flash chromatography (cyclohexane/EtOAc, 4:1, R_f 0,19); $[\alpha]_D = -10$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.67–7.27 (m, 15H, $H_{ar.}$), 4.56, 4.50 (AB, 2H, J_{AB} = 12 Hz, CH_2Ph), 4.48 (m, 1H, H_6), 3.88, 3.80 (AB from ABX, 2H, J_{AB} = 12 Hz, J_{AX} = 6 Hz, J_{BX} = 6 Hz, $H_{2'}$), 3.81 (d, 2H, $J_{H3-CH2OBn}$ = 3 Hz, CH_2OBn), 3.67 (t, 1H, $J_{H3-CH2OBn}$ = 3 Hz,

H_3), 3.67–3.60 (m, 1H, $H_{1'}$), 3.15 (dd, 1H, J_{H5b-H6} = 3.6 Hz, $J_{H5b-H5a}$ = 13.6 Hz, H_{5b}), 2.88 (dd, 1H, J_{H5a-H6} = 10.3 Hz, $J_{H5a-H5b}$ = 13.6 Hz, H_{5a}), 1.05 (s, 9H, *t*Bu); ^{13}C NMR δ 167.9 (C_2), 137.6, 135.6, 132.6, 130.1, 128.6, 128.0, 127.9 ($C_{ar.}$), 79.3 (C_6), 73.7 (CH_2Ph), 70.2 (CH_2OBn), 64.3 ($C_{1'}$), 63.5 ($C_{2'}$), 58.5 (C_3), 43.7 (C_5), 26.8, 19.2 (*t*Bu); HRMS calcd for (M+ Na)$^+$ 567.2404; found 567.2417.

4.26. (1′*R*,3*S*,6*S*)-6-[(1′-Azido-2′-*tert*-butyldiphenylsilyloxy)-ethyl]-3-benzyloxymethyl-4-methyl-morpholin-2-one 30

From the *tert*-butyl ester **23** (753 mg, 1.2 mmol) the conditions described above in the general procedure afforded the morpholinone **30** after flash chromatography (cyclohexane/EtOAc, 4:1, R_f 0.2); $[\alpha]_D$ = −2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.67–7.27 (m, 15H, $H_{ar.}$), 4.64 (ddd, 1H, J_{H6-H5b} = 10 Hz, $J_{H6-H1'}$ = 6.5 Hz, J_{H6-H5a} = 2.5 Hz, H_6), 4.55 (s, 2H, CH_2Ph), 3.86, 3.82 (AB from ABX, 2H, J_{AB} = 11 Hz, $J_{A,X}$ = 3.5 Hz, $J_{B,X}$ = 6 Hz, $H_{2'}$), 3.86, 3.78 (A′B′ from A′B′X′, 2H, $J_{A'B'}$ = 11 Hz, $J_{A',X'}$ = 2.5 Hz, $J_{B',X'}$ = 2.5 Hz, CH_2OBn), 3.59 (X from ABX, 1H, $J_{H6-H1'}$ = 6.5 Hz, $J_{A,X}$ = 3.5 Hz, $J_{B,X}$ = 6 Hz, $H_{1'}$), 3.06 (X′ from A′B′X′, 1H, $J_{A',X'}$ = 2.5 Hz, $J_{B',X'}$ = 2.5 Hz, H_3), 3.05 (dd, 1H, $J_{H5a-H5b}$ = 12.5 Hz, J_{H5a-H6} = 2.5 Hz H_{5a}), 2.50 (dd, 1H, $J_{H5a-H5b}$ = 12.5 Hz, J_{H5b-H6} = 10 Hz, H_{5b}), 2.37 (s, 3H, NMe), 1.05 (s, 9H, *t*Bu); ^{13}C NMR δ 163.0 (C_2), 136.2, 135.6, 132.6, 132.2, 130.3, 128.7, 128.4, 128.1 (C_{ar}), 76.7 (C_6), 74.1 (CH_2Ph), 69.0 (CH_2OBn), 67.6 (C_3), 64.4 (C_7), 63.6 ($C_{2'}$), 53.6 (C_5), 43.7 (NCH_3), 26.7, 19.2 (*t*Bu).

4.27. (3*S*,6*S*,7*R*)-3-(Benzyloxymethyl)-7-((*tert*-butyldiphenylsilyloxy)methyl)-4-*N*-(5″-(uracil-1′-yl)pentyl)-6-hydroxy-1,4-diazepan-2-one 32

To a solution of aldehyde **31** (0.353 g, 1.02 equiv, 1.80 mmol) in 1,2-dichloroethane (18.6 mL) was added sodium sulfate (5.11 g, 20 equiv, 36.0 mmol). After stirring under argon atmosphere at 20 °C for 10 minutes, a solution of diazepanone 16 (0.917 g, 1 equiv, 1.77 mmol) in 1,2-dichloroethane (36.7 mL) was added and the reaction mixture was stirred for additional 19 h. Sodium triacetoxyborohydride (1.12 g, 3 equiv, 5.26 mmol) was then added and the reaction mixture was stirred for an additional 24 h. The suspension was filtered through a Celite pad and the reaction was quenched by the addition of saturated water solution of $NaHCO_3$ (20 mL). Phases were separated and the water phase was extracted with CH2Cl2 (3 × 20 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue (EtOAc/MeOH/Et_3N, 96:4:3‰, R_f 0.26) afforded **32** (1.07 g, 87%) as a white foam; $[\alpha]_D$ = +17.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ (500 MHz) 8.62 (br s, 1H, NHuracil), 7.67–7.24 (m, 15H, Har.), 7.06 (d, 1H, $J_{H6'-H5'}$ = 8.0 Hz, H6′), 6.08 (d, 1H, J_{NH-H7} = 5.4 Hz, NH), 5.65 (d, 1H, $J_{H5'-H6'}$ = 7.9 Hz, H5′), 4.56, 4.52 (AB, 2H, J_{AB} = 12.1 Hz, CH_2Ph), 3.96–3.92 (m, 1H, H7), 3.90–3.75 (m, 6H, CH_2OSi, CH_2OBn, H6 and −OH), 3.67 (t, 2H, $J_{H5''-H4''}$ = 7.3 Hz, H5″), 3.60 (t, 1H, $J_{H3-CH2OBn}$ = 3.8 Hz, H3), 3.06 (dd, 1H, J_{H5b-H6} = 3.2 Hz, $J_{H5a-H5b}$ = 15.0 Hz, H5b), 2.84 (dd, 1H, J_{H5a-H6} = 2.2 Hz, $J_{H5a-H5b}$ = 14.9 Hz, H5a), 2.64–2.58 (m, 1H, H1″b), 2.51–2.45 (m, 1H, H1″a), 1.73–1.60 (m, 2H, H4″), 1.57–1.42 (m, 2H, H2″), 1.41–1.22 (m, 2H, H3″), 1.09 (s, 9H, *t*-Bu); ^{13}C NMR 173.8 (C2), 163.6 (C4′), 150.8 (C2′), 144.3 (C6′), 138.0, 135.7, 132.6, 130.1, 128.4, 128.0, 127.9, 127.6 (18Car), 102.2 (C5′), 73.3 (CH_2Ph), 72.2 (C3), 70.4 (CH_2OBn), 69.4 (C6), 61.8 (CH_2O-Si), 57.0 (C5), 55.5 (C7), 54.7 (C1″), 48.5 (C5″), 29.6 (C4″), 28.7, 19.3 (*t*Bu), 26.9 (C2″), 23.8 (C3″); HRMS calcd for (M+H)$^+$ 699.3578, found 699.3571.

4.28. 1-*tert*-Butyldiphenylsilyl-3,4-*O*-methylethylidene-D-erythritol 35

To a solution of the diol **34** (5.2 g, 32 mmol) in DMF (150 mL) at −10 °C were successively added imidazole (4.8 g, 2.2 equiv, 71 mmol) and dropwise a solution of *tert*-butyldiphenylsilyl chloride (9.2 mL, 1.1 equiv, 35 mmol) in DMF (30 mL) and the mixture was stirred at that temperature for 4 h prior to concentration in vacuo. The residue was then taken up in H_2O and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc/NEt_3, 85:15:0.5, R_f 0.2 in cyclohexane/EtOAc, 9:1) afforded 11.8 g (92%) of the silyl ether **35** as a colourless oil; $[\alpha]_D$ = +6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.70–7.32 (2 m, 10H, $H_{ar.}$), 4.07, 4.03 (AB of ABX, 2H, J_{H1a-H2} = 5.8 Hz, J_{H1b-H2} = 4.3 Hz, H_1), 3.95 (X of ABX, 1H, J_{H3-H4a} = 3.8 Hz, J_{H3-H4b} = 5.3 Hz, H_3), 3.81, 3.74 (AB of ABX, 2H, $J_{H4a-H4b}$ = 10.1 Hz, J_{H4a-H3} = 3.8 Hz, J_{H4b-H3} = 5.3 Hz, H_4), 3.66 (X of ABX, 1H, J_{H2-H1a} = 5.8 Hz, J_{H2-H1b} = 4.3 Hz, H_2), 1.32, 1.31 (2s, 6H, CMe_2), 1.06 (s, 9H, *t*Bu); ^{13}C NMR δ 135.5, 132.9, 129.8, 127.7 ($C_{ar.}$), 109.0 (CMe_2), 75.7, 72.4 (C_2, C_3), 66.5, 65.0 (C_1, C_4), 26.8, 19.2 (*t*Bu), 26.6, 25.2 (CMe_2) . Anal. Calcd for $C_{23}H_{32}O_4Si$: C, 68.96; H, 8.05. Found: C, 68.64; H, 8.26.

4.29. (2*R*,3*S*)-2-Azido-1-*tert*-butyldiphenylsilyl-3,4-*O*-methylethylidene-butane-1,3,4-triol 36

To a solution of alcohol **35** (12.7 g, 32 mmol) in CH_2Cl_2 (100 mL) at −78 °C were successively added 2,6-lutidine (4.8 mL, 1.4 equiv, 44 mmol) and dropwise trifluoromethanesulfonic anhydride (6.9 mL, 1.3 equiv, 41 mmol). After 30 min stirring, TLC monitoring revealed the complete transformation of the starting material (cyclohexane/EtOAc, 8:2, R_f 0.4 for the alcohol **35** and R_f 0.6 for the triflate) and the mixture was concentrated in vacuo. The residue was taken up in DMF (100 mL) and the mixture was cooled to 0 °C prior to sodium azide addition (10.4 g, 5 equiv, 158 mmol) and the mixture was allowed to warm to 20 °C overnight. After H_2O addition (100 mL) and Et_2O extractions the combined extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc, 95:5, R_f 0.3) gave 12 g (89%) of the azido derivative **35** as a colourless oil; $[\alpha]_D$ = −15 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.75–7.30 (2 m, 10H, $H_{ar.}$), 4.17 (ddd, 1H, J_{H2-H1a} = 6.5 Hz, J_{H2-H1b} = J_{H2-H3} ≈ 6.3 Hz, H_2), 3.96 (dd, 1H, $J_{H1a-H1b}$ = 8.3 Hz, J_{H1a-H2} = 6.5 Hz, H_{1a}), 3.80–3.68 (m, 3H, H_{1b}, H_4), 3.38 (ddd, 1H, J_{H3-H2} = J_{H3-H4a} = J_{H3-H4b} ≈ 5.8 Hz, H_3), 1.39, 1.32 (2s, 6H, CMe_2), 1.06 (s, 9H, *t*Bu); ^{13}C NMR δ 135.7, 132.8, 130.0, 127.9 ($C_{ar.}$), 109.7 (CMe_2), 75.6 (C_2), 66.4 (C_1), 64.3 (C_3), 64.1 (C_4), 26.4, 25.4 (CMe_2), 26.8, 19.2 (*t*Bu) . Anal. Calcd for $C_{23}H_{31}N_3O_3Si$: C, 64.91; H, 7.34; N, 9.87. Found: C, 64.81; H, 7.48; N, 9.89.

4.30. (2*R*,3*S*)-2-Azido-1-*tert*-butyldiphenylsilyl-butane-1,3,4-triol 37

To a solution of acetonide **36** (9.6 g, 23 mmol) in THF (240 mL) were added H_2O (160 mL) and dropwise, at 0 °C, trifluoroacetic acid (160 mL). The temperature was then warmed to 20 °C and the mixture was stirred for 3 h. A 28% aqueous solution of NH_4OH was then added at 0 °C to adjust the pH of the solution to 8. After Et_2O extractions, the combined extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc, 7:3, R_f 0.4 in cyclohexane/EtOAc, 7:4) gave 6.2 g (70%) of the diol **37** as a colourless oil; $[\alpha]_D$ = −20 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.72–7.32 (2 m, 10H, $H_{ar.}$), 3.90–3.84 (m, 2H, H_{1a}, H_{1b}), 3.76 (dddd, 1H, J_{H3-H2} ≈ 4.8 Hz, J_{H3-H4a} = J_{H3-H4b} ≈ 5.1 Hz, J_{H3-OH} = 5.3 Hz, H_3), 3.68–3.60 (m, 2H, H_4), 3.54 (ddd, 1H, J_{H2-H1a} = J_{H2-H1b} ≈ 5.4 Hz, J_{H2-H3} ≈ 4.8 Hz, H_2), 1.06 (s, 9H, *t*Bu); ^{13}C NMR δ 135.4, 132.5, 129.9, 127.8 ($C_{ar.}$), 71.3 (C_3), 66.4 (C_1, C_2), 63.7 (C_4), 26.6, 18.9 (*t*Bu); HRMS calcd for (M+ NH_4)$^+$ 403.2165; found 403.2166.

4.31. (2*R*,3*S*)-3-Azido-4-*tert*-butyldiphenylsilyloxy-1,2-epoxybutane 38

From diol **37** (6 g, 16 mmol) and according to the general procedure described above for epoxide **11** preparation, 5 g (88%) of the epoxide **38** were obtained as a colourless oil, after flash chromatographic purification (cyclohexane/EtOAc, 97:3, R_f 0.3); $[\alpha]_D = -24$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.75–7.32 (2 m, 10H, $H_{ar.}$), 3.84–3.76 (m, 2H, H_4), 3.25 (ddd, 1H, $J_{H3-H4a} = J_{H3-H4b} = J_{H3-H2} \approx 5.9$ Hz, H_3), 3.04 (ddd, 1H, $J_{H2-H3} = 5.9$ Hz, $J_{H2-H1a} = 4.4$ Hz, $J_{H2-H1b} = 2.5$ Hz, H_2), 2.76 (dd, 1H, $J_{H1a-H2} = 4.4$ Hz, $J_{H1a-H1b} = 4.6$ Hz, H_{1a}), 2.64 (dd, 1H, $J_{H1b-H2} = 2.5$ Hz, $J_{H1b-H1a} = 4.6$ Hz, H_{1b}), 1.06 (s, 9H, *t*Bu); ^{13}C NMR δ 135.5, 132.7, 129.9, 127.8 ($C_{ar.}$), 64.4 (C_3), 64.2 (C_4), 51.7 (C_2), 44.5 (C_1), 26.7, 19.1 (*t*Bu); HRMS calcd for $(M+NH_4)^+$ 385.2060; found 385.2058. Anal. Calcd for $C_{20}H_{25}N_3O_2Si$: C, 65.36; H, 6.86; N, 11.43. Found: C, 65.50; H, 7.01; N, 11.54.

4.32. *tert*-Butyl *N*-[(2*R*,3*R*)-3-azido-4-*tert*-butyldiphenylsilyloxy-2-hydroxybutyl]-*N*′-methyl-*O*-benzyl-L-serine 39

From the azido-epoxide **38** (2.4 g, 6.6 mmol) and *tert*-butyl *O*-benzyl-*N*-methyl-L-serine ester **22** (2.2 g, 8.6 mmol), the general conditions described above for the epoxide opening and for compounds **21** and **23** preparation, followed by flash chromatography (cyclohexane/EtOAc, 4:1, R_f 0.5) afforded 2.7 g (65%) of the tertiary amine **39** as an oil; $[\alpha]_D = -10$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.70–7.28 (m, 15H, $H_{ar.}$), 4.53, 4.48 (AB, 2H, $J_{AB} = 12$ Hz, CH_2Ph), 3.96 (dd, 1H, $J_{4a-4b} = 10.7$ Hz, $J_{H4a-H3} = 7.4$ Hz, H_{4a}), 3.86 (dd, 1H, $J_{H4a-H4b} = 10.7$ Hz, $J_{H4b-H3} = 4.4$ Hz, H_{4b}), 3.75 (m, 1H, H_2), 3.72 (dd, 1H, $J_{H3'a-H3'b} = 10$ Hz, $J_{H3'b-H2'} = 5.7$ Hz, $H_{3'b}$), 3.60 (dd, 1H, $J_{H3'a-H3'b} = 10$ Hz, $J_{H3'a-H2'} = 7$ Hz, $H_{3'a}$), 3.45 (dd, 1H, $J_{H2'-H3'a} = 7$ Hz, $J_{H2'-H3'b} = 5.7$ Hz, $H_{2'}$), 3.35 (m, 1H, H_3), 2.74–2.71 (m, 2H, H_1), 2.34 (s, 3H, NMe), 1.40, 1.07 (2s, 18H, *t*Bu); ^{13}C NMR δ 170.3 ($C_{1'}$), 137.9, 136.7, 136.2, 135.0, 132.9, 130.5, 129.2, 128.5, 127.7, 127.2 ($C_{ar.}$), 81.6 (O*t*Bu), 73.3 (CH_2Ph), 68.3 ($C_{3'}$), 67.6 ($C_{2'}$, C_2), 65.1 (C_3, C_4), 58.4 (C_1), 38.0 (NCH_3), 28.3, 26.9, 19.1 (*t*Bu).

4.33. (1′*R*,3*S*,6*R*)-6-[(1′-Azido-2′-*tert*-butyldiphenylsilyloxy)-ethyl]-3-benzyloxymethyl-4-methyl-morpholin-2-one 40

From the *tert*-butyl ester **39** (2.4 g, 3.8 mmol) and according to the general procedure described above for the morpholinones **29** and **30** preparation, the morpholinone **40** was obtained and was used without further purification in the next reaction. A sample was purified by flash chromatography (cyclohexane/EtOAc, 4:1, R_f 0.25); $[\alpha]_D = -29$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.66–7.25 (m, 15H, $H_{ar.}$), 4,61 (m, 1H, H_6), 4.50, 4.44 (AB, 2H, $J_{AB} = 12$ Hz, CH_2Ph), 3.89, 3.76 (ABX, 2H, $J_{AB} = 10.8$ Hz, $J_{AX} = 3.4$ Hz, $J_{BX} = 5.4$ Hz, $H_{2'}$), 3.86–3.80 (m, 3H, $H_{1'}$, CH_2OBn), 3.24 (t, 1H, $J_{H3-CH2OBn} = 2.6$ Hz, H_3), 2.98 (dd, 1H, $J_{H5a-H5b} = 13.2$ Hz, $J_{H5a-H6} = 5{,}7$ Hz, H_{5a}), 2.65 (dd, 1H, $J_{H5a-H5b} = 13.2$ Hz, $J_{H5b-H6} = 3.6$ Hz, H_{5b}), 2.26 (s, 3H, NMe), 1.04 (s, 9H, *t*Bu); ^{13}C NMR δ 163.0 (C_2), 136.2, 135.6, 132.6, 132.2, 130.3, 128.7, 128.4, 128.1 ($C_{ar.}$), 74.3 (CH_2Ph), 73.5 (C_6), 66.9 ($C_{2'}$), 62.4 (CH_2OBn), 62.2 (C_3), 61.2 ($C_{1'}$), 50.3 (C_5), 40.3 (NCH_3), 26.7, 19.1 (*t*Bu).

4.34. (3*S*,6*R*,7*R*)-3-Benzyloxymethyl-7-*tert*-butyldiphenylsilyloxymethyl-6-hydroxy-4-*N*-methyl-1,4-diazepan-2-one 41

From morpholin-2-one **40** (3.79 mmol) the general procedure described above for the diazepanone **16** and **28** preparation according to the lactonisation–lactamisation sequence was carried out except that the mixture was stirred for 60 h at 20 °C instead of 5 h. This was followed by flash chromatography (EtOAc/Et_3N, 100:3‰, R_f 0.3) and afforded 1.69 g of the diazepanone **41** (84%) as a white foam; $[\alpha]_D = +24$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.69–7.26 (m, 15H, $H_{ar.}$), 6.1 (d, 1H, $J_{H1-H7} = 5$ Hz, H_1), 4.56 (s, 2H, CH_2Ph), 4.01 (m, 1H, H_7), 3.92 (dd, 1H, $J_{CH2bOSi-H7} = 3.5$ Hz, $J_{CH2Osi} = 10.8$ Hz, $CH_{2b}OSi$), 3.80 (m, 3H, $J_{CH2OBn-H3} = 3.7$ Hz, CH_2OBn, H_6), 3.78 (dd, 1H, $J_{CH2aOSi-H7} = 3.5$ Hz, $J_{CH2OSi} = 10.8$ Hz, $CH_{2a}OSi$), 3.38 (t, 1H, $J_{H3-CH2OBn} = 3.7$ Hz, H_3), 3.15 (dd, 1H, $J_{H5a-H5b} = 15$ Hz, $J_{H5a-H6} = 3$ Hz, H_{5a}), 2.80 (dd, 1H, $J_{H5a-H5b} = 15$ Hz, $J_{H5b-H6} = 1.5$ Hz, H_{5b}), 2.48 (s, 3H, NMe), 1.11 (s, 9H, *t*Bu); ^{13}C NMR δ 174.1 (C_2); 137.7, 135.3, 132.6, 129.7, 128.2, 127.7, 127.4, 127.3 ($C_{ar.}$) 73.2 (CH_2Ph), 72.0 (C_3), 68.4 (C_6), 67.8 (CH_2OSi), 63.6 (CH_2OBn), 58.1 (C_5), 55.1 (C_7), 44.8 (NMe), 19.0, 26.7 (*t*Bu); HRMS calcd for $(M+H)^+$ 533.2836; found 533.2829.

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