Stereoselective Synthesis of *trans-threo-trans*-Oligopyrrolidines: Potential Agents for RNA Cleavage

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Abstract: The 2,5-*trans*-substituted oligopyrrolidines constitute a promising class of novel RNA-binding agents as well as potential building blocks for artificial anion channels. A convergent synthesis of terpyrrolidine **1** and pyrrolidino-THF-pyrrolidine **2** is reported, relying upon convergent coupling of 2,5-*trans*-pyrrolidinecarboxaldehydes through bridging alkyne units under Felkin–Anh control and subsequent closure of the central ring. After complete deprotection, the free polyamine products were isolated in excellent yield and purity. Crystal structure analyses of a terpyrrolidine and a pyrrolidino-THF-pyrrolidine documented their helical privileged conformations. The compounds were then screened for RNA cleavage activity. Unlike the only weakly active simple polyamines, *p*-nitrosulfonamide **33** was found to induce cleavage at mM concentrations under physiologically relevant conditions.

Keywords: helical structures · polyamines · pyrrolidines · RNA binding · synthesis design

Introduction

Polyamines such as spermine play a multitude of roles in biomolecular recognition events.[1–3] Their still emerging functions range from membrane stabilization[4] through the modulation of receptors,[5] enzymes,[6,7] and protein aggregation[8] to a very general interaction with folded oligonucleotides and oligonucleotide–protein complexes.[2,6,9–12] The global association of polyamines with cellular RNA in eukaryotes[1] (50–60% of total content) further highlights the particular affinity of polyamines for RNA and by extension the importance of these polycations for RNA structure integrity. More specifically, the prominent aminoglycoside class of antibiotics can be viewed as closely related polycations, albeit conformationally restricted.[11,13,14] These agents are geared towards binding of folded RNA structures and will interfere with bacterial protein synthesis, mainly through their selective interaction with eubacterial 16S rRNA.[15] Inspired by this natural example of conformational and spatial constraining to tailor specific molecular functions within a specific class of compounds, our goal became the investigation of novel structural motifs for selective anion binding.

By this model, it was envisioned that prototypical *trans-threo-trans*-oligopyrrolidines such as **1** might integrate the potential of an anion-binding polyamine into a flexible backbone with a helical conformational bias (Scheme 1). Molecules of this type are the amine counterparts of the cation-binding oligotetrahydrofurans,[16] which have been synthesized, conformationally characterized and successfully used as building blocks for artificial transmembrane cation channels.[16–20] A privileged helical conformation had been deduced for them from modelling studies, as well as from X-ray structures of synthetic intermediates. In order to advance the corresponding application of oligopyrrolidine subunits in anion channels, as well as to evaluate their potential for selective interaction with RNA, we embarked upon opening up a reliable synthetic route to stereodefined terpyrrolidines **1**. Of additional interest was a synthetic route to pyrrolidine–tetrahydrofuran hybrids **2**, which could link the oligopyrrolidines to the oligotetrahydrofurans characterized previously.

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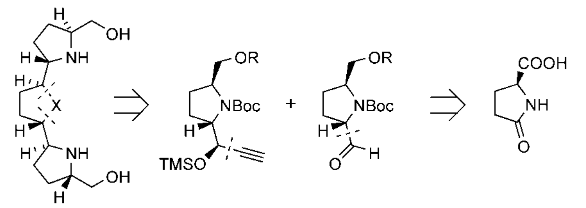
With the exception of spermine/spermidine derivatives, stereochemically complex polyamines are scarcely documented in the literature, completely the opposite to the polyether field. This is most probably due to the infrequent occurrence of polyamine substructures in natural products, especially with regard to oligopyrrolidines. 2,2′-Bispyrrolidine has frequently been applied as a chiral auxiliary, and routes towards its stereoselective synthesis have been devised.[21,22] Vinylogous Mannich reactions have been successfully employed for the synthesis of aza-annonines.[23,24] Recently this reaction has been implemented in an iterative process for the stereodivergent synthesis of 2,5-linked oligotetrahydrofuran-, -pyrrole and -thiophene libraries.[25] However, no fully deprotected oligopyrrolidine products have been reported. Here we give a full account[26] of the stereoselective synthesis of the oligopyrrolidines **1** and **2** on gram scales, their complete structural characterization, protecting groups and deprotection, and further improvements in the synthetic methods. Furthermore, preliminary experiments conducted with RNA oligonucleotides indicate that derivatives of oligopyrrolidines interact with RNA in a selective fashion, and are promising candidates for designed RNA cleavage agents.

Results and Discussion

Our plan for the synthesis of oligopyrrolidines was guided by the necessity to provide the hitherto unknown target molecules in sufficient quantity for structural studies and further experimentation. Therefore, a retrosynthetic analysis of **1** relying on the symmetry of the target structures (Scheme 1) led us to disconnect the central ring into an

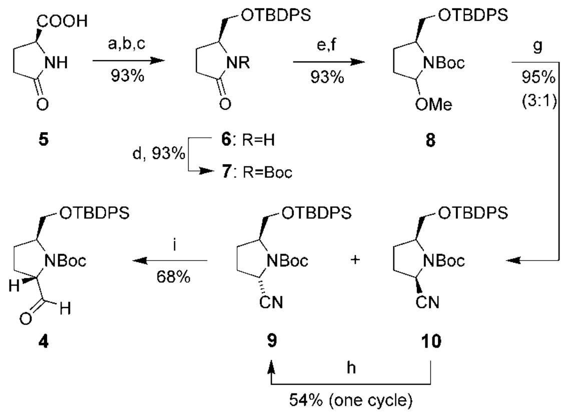


1: X=NH **3** **4** **5**
2: X=O

Scheme 1. Retrosynthetic disconnection of 2,5-*trans-threo-trans*-oligopyrrolidines. R = TBDPS.

open-chain precursor, which would result from a diastereoselective addition of alkyne **3** to aldehyde **4** under Felkin–Anh control. Ring-closure should then be attainable through suitable nucleophilic substitution reactions. The alkyne **3** and its precursor aldehyde **4** should be accessible from readily available pyroglutamic acid (**5**) (Scheme 1), making aldehyde **4** a pivotal building block.

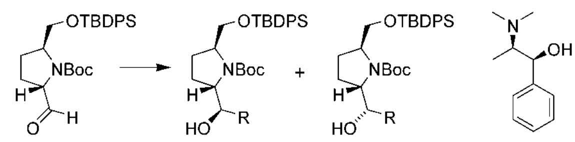
The synthesis of the pyrrolidine carboxaldehyde **4** (Scheme 2) began with the esterification of **5** in order to ease its reduction to the corresponding alcohol, which was



Scheme 2. Synthesis of aldehyde **4**: a) MeOH, dimethoxypropane, H^+, 50°C; b) $NaBH_4$, THF/MeOH; c) TBDPSCl, imidazole, DMF; d) Boc_2O, pyridine, DMAP, CH_2Cl_2; e) $NaBH_4$, CH_2Cl_2/MeOH, −10°C; f) dimethoxypropane, cat. CSA, 0°C; g) TMSCN, cat. TMSOTf, CH_2Cl_2, −35°C; h) cat. KO*t*Bu, *t*BuOH, toluene, 0°C; i) DiBAH, toluene/PE, −70°C→−60°C.

O-protected to give the TBDPS silylether **6** and further transformed[27] into the *N*-Boc-protected lactam **7**. Known procedures were adapted such as to minimize purification efforts along the way. A carefully controlled $NaBH_4$ reduction of **7** in CH_2Cl_2/MeOH at −10°C then yielded the hemiaminal, which was found to be prone to self-condensation and was therefore transformed into the stable aminal **8** by acid-catalysed transacetalization. Treatment of the *N*-acyliminum ion[28] precursor **8** with TMSCN and catalytic amounts of TMSOTf gave a 3:1 mixture of the *trans* nitrile **9** and the *cis* nitrile **10**, independent of aminal stereochemistry. The minor *cis* isomer **10** could easily be separated by column chromatography on 10 g scale, and was further epimerized to **9** under basic conditions. A DIBAH reduction of the nitrile **9** led to the *trans* aldehyde **4**. Neutral workup conditions and a minimal excess of DIBAH were crucial to maximize the yield.

The stereocontrolled addition of carbon nucleophiles to the carbonyl group of the aldehyde **4** was investigated next. The two possible products **11** and **12** (Scheme 3) would be expected, from a Felkin–Anh-type attack in the case of **11** (1′*R*), whereas a chelation-controlled transition state should lead to the 1′*S* alcohol **12**. Felkin–Anh control had been achieved even for acetylide nucleophiles in the case of closely related aldehydes,[29,30] setting the precedent for our planning.



4 **11** **12** **13**

Scheme 3. Addition of C-nucleophiles to aldehyde **4**.

In encouraging first experiments, primary alkyllithium reagents gave the Felkin–Anh product exclusively (Table 1), albeit in moderate yield (entries 1–2).[1] In contrast, Li-acetylides displayed only modest selectivity (entries 3–6), which was also rather insensitive towards solvent composition (hexanes/Et_2O, Et_2O, THF) or temperature. Only the addition of HMPT to the solvent mixture would slightly improve the outcome (entry 5). Partial TMS-group scrambling was difficult to suppress in this case, however, especially on larger scales. Mg-acetylides gave somewhat similar results (data not shown). Use of a less basic organocerium reagent[31] did not improve the stereoselectivity, but did give a much cleaner reaction, allowing essentially quantitative yields (entry 7). A titanium acetylide[32] gave the Felkin–Anh product preferentially, but the aldehyde **4** was found to epimerize slightly under these reaction conditions (entry 8).[2] To overcome these mixed results, we turned our attention to reagent control. Carreira et al. have developed an effective method for the stereocontrolled addition of zinc acetylides to aldehydes by the use of *N*-methylephedrine (**13**) as a chiral ligand.[33] In the event, the chelation-controlled compound **12** was obtained as the main product (entries 9–10). Interestingly, in neither case was the chiral auxiliary **13** able to override the apparent chelating effect of the zinc ion towards aldehyde **4**: (+)-**13** exhibited a mismatched case of double stereodifferentiation (low reactivity, 40% yield and 86:14 selectivity), while (−)-**13** resulted in a perfectly matched case (90% isolated yield, 154:1 stereoselectivity by HPLC).

Table 1. Reaction of aldehyde **4** with nucleophiles.

	R-M	conditions (0.5 mmol scale)	Yield [%][a]	(1′*R*):(1′*S*)
1	MeLi	Et_2O, −100 °C→−78 °C	58[b]	>95:5
2	BuLi	Et_2O, −90 °C→−78 °C	50[b]	>95:5
3	TMS-C≡C-Li	THF, −90 °C→−78 °C, 4 h	80	60:40
4	TMS-C≡C-Li	THF, −78 °C→−60 °C, 2 h	77	51:49
5	TMS-C≡C-Li	THF/HMPT, −90 °C→ −50 °C, 1 h	84[c]	70:30
6	TIPS-C≡C-Li	THF, −78 °C, 1 h	49[b]	62:38
7	TMS-C≡C-$CeCl_2$	THF, −78 °C, 10 min (0.5/15 mmol)	95/93	55:45
8	TMS-C≡C-Ti-Cl(O*i*Pr)$_2$	THF, −40 °C→0 °C, 4 h	88[c]	75:25
9	TMS-C≡C-Zn(OTf)	**13**, toluene, 20 °C, 24 h	40[d]	14:86[e]
10	TMS-C≡C-Zn(OTf)	(*ent*)-**13**, toluene, 20 °C, 24 h	90	1:154[e]

[a] Isolated, (*R*)+(*S*). [b] Not optimized. [c] Side product formation. [d] Incomplete conversion. [e] Determined by HPLC.

The cerium acetylide addition was therefore used routinely in the subsequent course of the terpyrrolidine synthesis (Scheme 4). The aldehyde **4** was converted into the alcohol **14** in 51% yield after chromatographic separation of the undesired epimer. Desilylation of the terminal alkyne (**14**→**15**) and subsequent *O*-TMS protection delivered the alkyne **3** in high yield. Lithiation of alkyne **3** and treatment with the aldehyde **4** gave the two epimeric alcohols **16** and **17** in 95% yield with a 2:1 stereoselectivity in favour of the Felkin–Anh product **16**. In this case the presence of HMPT was beneficial: the addition was unselective otherwise (1:1). After chromatographic separation of the two epimers, compound **16** was deprotected to yield the C_2-symmetric diol **18**, which was saturated (H_2, Pt/C) to give diol **19**.

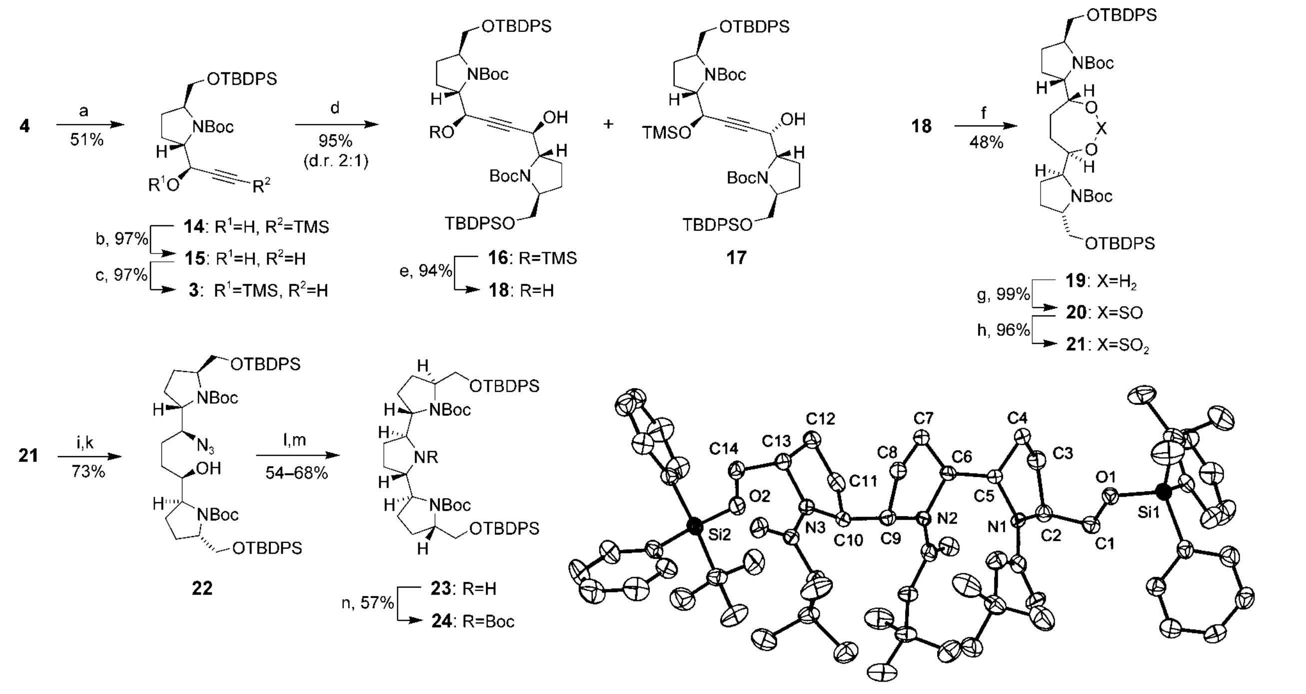
With diol **19** to hand, it was envisaged that substitution of the two OH groups with nitrogen nucleophiles under S_N2 conditions should complete the synthesis of the central pyrrolidine ring. Several attempts treating the ditosylate, dimesylate, or ditriflate of **19** with primary amines or azide proved futile, however, the *N*-Boc groups preferentially attacking the activated positions in an intramolecular substitution reaction, leading to cyclic carbamates. More successful was the conversion of the diol **19** via the cyclic 1,4-sulfite **20** into the cyclic 1,4-sulfate **21** (Scheme 4).[34,35] Treatment of cyclic 1,4-sulfate **21** with LiN_3 under nonbasic conditions in DMF/HMPT occurred without major side reactions of the Boc groups and led to the desymmetrized azido alcohol **22** in good yield. Mesylation of the remaining OH group and hydrogenolytic cleavage of the azide to the amine induced a spontaneous closure of the central pyrrolidine ring to yield the bis-*N*-Boc-protected terpyrrolidine **23**. *N*-Boc-protection of the hindered central pyrrolidine ring nitrogen then gave the tris-*N*-Boc-protected terpyrrolidine **24**.

An X-ray crystal structure analysis of compound **24** showed the correct stereochemical assignment of the *threo-trans-threo*-trispyrrolidine and provided further conformational insights. As can be seen in Scheme 4, the pyrrolidine rings adopt envelope-like conformations with the substituents in the 2- and 5-postions pointing in axial directions. This illustrates the $A^{1,3}$ strain exerted by the *N*-Boc groups.[36] One of the ring connections (C5−C6) is in a *gauche* conformation, whereas the second one (C9−C10) adopts an *anti* arrangement, presumably enforced by the inward-pointing *t*Bu substituent. Overall, the molecule still displays a fairly helical arrangement of the five-membered rings, despite being encumbered with bulky protecting groups.

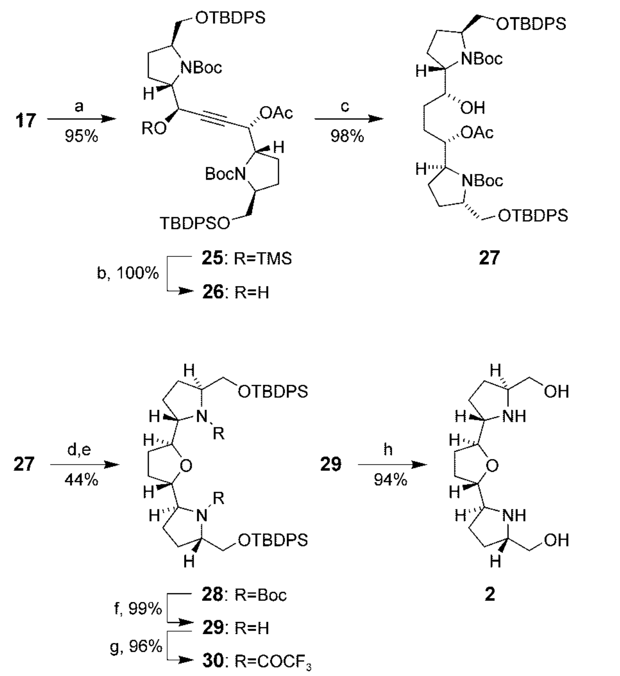
The synthesis of the tricyclic pyrrolidine–tetrahydrofuran hybrid **2** required the stereocontrolled elaboration of a central 2,5-*trans*-disubstituted THF ring (Scheme 5). The propargylic alcohol **17** was envisaged as a suitable synthetic precursor for compound **2**. To this end, alcohol **17** was temporarily protected as its acetate (→**25**). This was desilylated to provide the propargylic alcohol **26**, which was hydrogenated

[1] Stereochemical assignments were made after transformation of the *N*-Boc amino alcohols into cyclic carbamates as reported previously (ref. [26]) and were confirmed by X-ray crystallography of the final products (see above). As a general guide, the -OH resonance of the Felkin–Ahn alcohol product was found to be significantly shifted downfield in the $CDCl_3$ ^1H NMR spectrum in relation to its diastereomer (ca. 1 ppm), indicating a strong hydrogen bond to the neighbouring Boc group.

[2] It should be noted that the presence of sulfonamides (Ts, Ns) instead of Boc protection on the ring nitrogen was found to result in considerable Felkin–Ahn control (6–11:1) for Li-acetylide additions. However, the corresponding aldehydes were difficult to prepare and were also found to be rather sensitive. Moreover, either downstream deprotection was difficult (Ts) or the intermediates were prone to side reactions (Ns). Therefore this route was abandoned.



Scheme 4. Synthesis and X-ray crystal structure of Boc-protected terpyrrolidine **24**: a) TMS-C≡C-$CeCl_2$, THF, −80 °C; b) K_2CO_3, aq. MeOH; c) TMS-Im, CH_2Cl_2, 0 °C; d) 1 equiv *n*BuLi, 2 equiv HMPT, THF, then **4**; e) cat. CSA, THF/MeOH, 0 °C; f) H_2, cat. Pt/C, MeOH; g) 1 equiv $SOCl_2$, NEt_3, CH_2Cl_2, −10 °C; h) cat. $RuCl_3$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$, 0 °C; i) DMF/HMPT (0.2 M), 8 equiv LiN_3, 40 h; k) THF, conc. H_2SO_4, 0 °C; l) MsCl, NEt_3, −20 °C; m) H_2, cat. Pd/C, MeOH/THF; n) Boc_2O, NEt_3, DMF.



Scheme 5. Synthesis of 2,5-*trans*-dipyrrolidino-THF **2**: a) Ac_2O, NEt_3, cat. DMAP, CH_2Cl_2, 0 °C; b) cat. CSA, CH_2Cl_2/MeOH; c) H_2, cat. Pt/C, EtOAc; d) 10 equiv MsCl, NEt_3, −40 °C; e) 2 equiv MeLi, THF, −78 °C→0 °C, then 2 equiv KO*t*Bu; f) TMSOTf, 2,6-lutidine, PhSMe, −78 °C→RT, 1 H; then aq. Na_3PO_4 (pH 12); g) $(CF_3CO)_2O$, pyridine, CH_2Cl_2, −20 °C; h) MeOH/conc. HF 10:1.

to the saturated alcohol **27** with Pt/C as the optimal catalyst. Conversion of **27** into the corresponding mesylate required a large excess of mesyl chloride (10 equiv) and low temperature (−40 °C) in order to avoid migration of the acetoxy group. The closure of the central THF ring was then initiated by cleavage of the acetate with 2 equivalents of methyllithium. The resulting lithium alkoxide reacted sluggishly, but addition of KO*t*Bu to the mixture accelerated the reaction, inducing ring-closure to the target tricycle **28** in 44 % yield. A biscarbamate was inevitably obtained as a by-product in this case, resulting from the nucleophilic and electrophilic properties of the two Boc groups in the molecular neighbourhood. The two *N*-Boc groups of **28** were removed in quantitative yield by use of TMSOTf,[37] to give the bispyrrolidine **29** with the *O*-TBDPS groups intact.[38] HF-mediated cleavage of the two silyl ethers in **29** finally provided the fully deprotected pyrrolidine-tetrahydrofuran-pyrrolidine hybrid **2** in an excellent 94 % yield.

The symmetry of the final product was readily apparent from its NMR spectra. To confirm the stereochemical assignments and to gain further insights into conformational preferences, derivatives of diamine **29** were screened for crystallinity. The bis-trifluoroacetamide **30** (Tfa_2O, 81 %) proved to fulfil this requirement, and crystals of sufficient quality for X-ray structure analysis were obtained. The crystal structure of compound **30** confirmed the *threo-trans-threo* configuration of the two lateral pyrrolidines and the central THF ring (Figure 1). Moreover, the compound adopts an ideal C_2-symmetric conformation in the solid state (coinciding with a crystallographic axis). In comparison with the tris-pyrrolidine **24**, the five-membered rings now do adopt half-chair conformations, with the substituents pointing more in equatorial directions. This is especially apparent at the central THF ring, where a close to ideal *trans*-substituted half chair with two adjacent *gauche*-configured ring

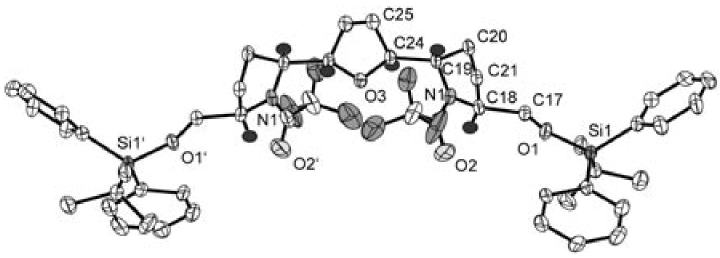
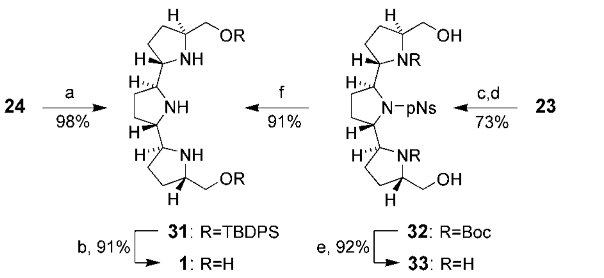


Figure 1. X-ray crystal structure of 2,5-*trans*-bispyrrolidino-THF **30**.

connections is observed, leading to a helical ladder of rings. The documentation of this privileged conformation here validates the design principles that had previously guided the oligo-THF-based ion channels,[17,18,20,39] and should probably also extend to other oligo-THFs and oligopyrrolidines.

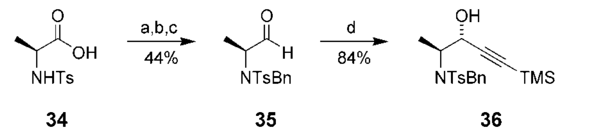
With regard to the terpyrrolidine system, the removal of the *N*-Boc groups and the *O*-silylethers from the fully protected terpyrrolidine **24** was subsequently achieved as follows (Scheme 6). Treatment of tris-*t*Bu-carbamate **24** with



Scheme 6. Deprotection of the terpyrrolidine core (→**1**): a) TMSOTf, 2,6-lutidine, PhSMe, −78 °C→RT, 1 h, then aq. Na_3PO_4 (pH 12); b) MeOH/conc. HF 10:1; c) pNSCl, NEt_3, DMAP, CH_2Cl_2; d) TBAF, THF; e) TFA/CH_2Cl_2 1:1; f) PhSH, K_2CO_3, DMF, 35 °C, 16 h.

TMSOTf generated the corresponding tris-TMS-carbamate through *O*-silylation. After hydrolysis at pH 12 the *O*-TBDPS-protected triamine **31** could still be purified by normal silica gel chromatography. Silyl ether **31** was converted into the fully deprotected target compound **1** by desilylation with methanolic HF. However, attempts to deprotect the bis-Boc-protected terpyrrolidine **23** to give the terpyrrolidine **31** were less clean. The sluggish Boc protection step was therefore circumvented by the introduction of a *p*-Ns (*p*-nitrophenylsulfonyl) group[40] onto the central pyrrolidine nitrogen. After subsequent TBAF-mediated cleavage of the silyl ethers, the diol **32** was obtained. The two *N*-Boc groups in **32** were cleaved with TFA to yield sulfonamide **33**, with the UV-active *p*-Ns group serving as an easily traceable purification tag. This was finally removed with PhSH/K_2CO_3[40] to give the triamino-diol **1** in 91 % yield. Notably, deprotection by-products could easily be removed in this last step by extraction. By this latter route the fully deprotected trispyrrolidine **1** was available from **23** in good yield and excellent purity.

With the synthesis of asymmetrically substituted oligopyrrolidines in mind, the influence of the N-protecting groups on the stereoselective addition of alkynyl nucleophiles to α-amino aldehydes was investigated further.[2] It has been reported that the use of N-benzyl and N-tosyl groups can lead to excellent Felkin–Anh stereocontrol for additions to α-amino aldehydes.[41] The N-benzyl- and N-tosyl-protected amino aldehyde **35** was accessed from *N*-tosyl-L-alanine **34** in three straightforward steps (perbenzylation, ester reduction, Swern oxidation) and was found to be stable and enantiopure after crystallization (Scheme 7). Addition of lithiat-



Scheme 7. a) BnBr, K_2CO_3, DMF; b) $LiAlH_4$, THF; c) $(COCl)_2$, DMSO, EtN(*i*Pr)$_2$, CH_2Cl_2, −65 °C; d) LiC≡CTMS, THF, −78 °C.

ed TMS acetylene to aldehyde **35** gave the secondary alcohol **36** as a single stereoisomer (>95 %), which is exceptionally noteworthy for an alanine derivative, as here methyl and hydrogen substituents are discriminated by a small acetylide nucleophile. The diastereochemical assignment of **36** was verified by X-ray crystallography (Figure 2). Notably,

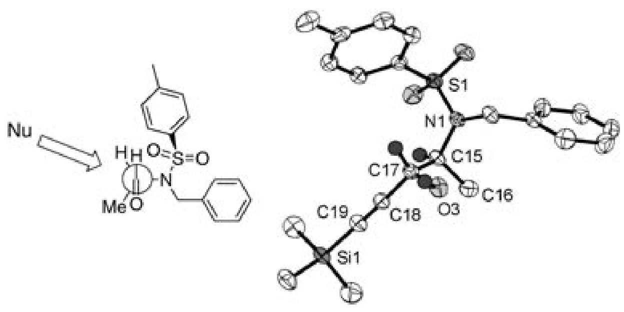
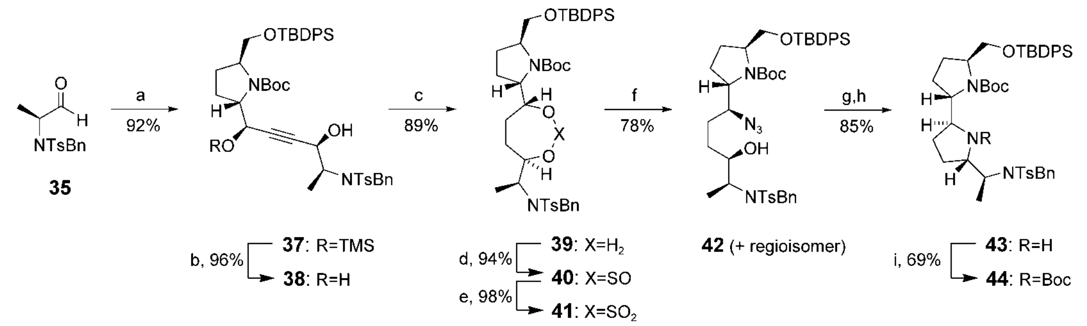


Figure 2. Transition state model for additions to aldehyde **35** and X-ray crystal structure of alcohol **36**.

the ground-state (product) conformation found for **36** in the crystal is in qualitative agreement with the transition state model depicted in Figure 2 and illustrates the role of both N-protecting groups. Firstly, the electron-withdrawing N-tosyl group should lower the σ_{C-N}-orbital and hyperconjugatively affect the adjacent $\pi_{C=O}$-LUMO in the Felkin–Anh-type transition state.[42,43] Secondly, the two N-protecting groups together effectively block one face of the C=O bond, favouring the approach of the nucleophile from the least hindered direction.[44] Furthermore, the asymmetrically substituted nitrogen atom with its bulky SO_2 group enforces an *anti* arrangement of the sulfonamide and methyl substituent, which can in turn lock the carbonyl oxygen on the methyl group side, due to mutual repulsion of the C=O and the N−SO_2 dipoles.[41] Presumably all factors cooperatively contribute to the exceptionally high stereoselectivity observed here.

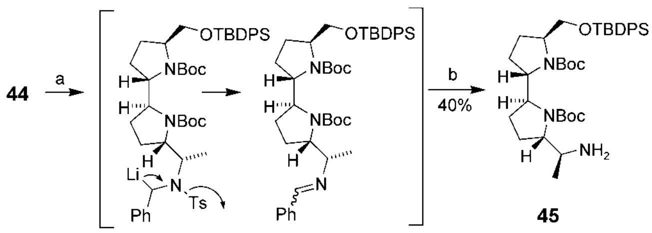
These findings were successfully integrated into the synthesis of bispyrrolidine **45** (Scheme 8). To this end, the diprotected aminoaldehyde **35** was allowed to react with the lithiated alkyne **3**, to provide the Felkin–Anh product **37** in



Scheme 8. Synthesis of bispyrrolidine **41**: a) *n*BuLi, **3**, THF, −78 °C, then **35**; b) cat. CSA, THF/MeOH 1:1; c) H_2, cat. Pt/C, MeOH; d) 1 equiv $SOCl_2$, NEt_3, CH_2Cl_2, −10 °C; e) cat. $RuCl_3$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$, 0 °C; f) $TBAN_3$, THF, 35 °C, then pH 2; g) MsCl, NEt_3, CH_2Cl_2, −20 °C; h) PBu_3, CH_3CN; i) Boc_2O, THF/H_2O, pH 10, 60 °C, 24 h.

high yield as a single stereoisomer. Removal of the TMS group under acidic conditions gave the propargylic diol **38**, which was hydrogenated to deliver the saturated diol **39**. This was converted into the corresponding cyclic 1,4-sulfate (**39**→**40**→**41**) to set up pyrrolidine ring formation. En route, X-ray crystal structure analysis of the 1,4-sulfite confirmed the stereochemical assignments (see Supporting Information). In a search for a substitute for the LiN_3/HMPT ring-opening conditions used earlier, it was then found that treatment of the cyclic 1,4-sulfate **41** with anhydrous tetrabutylammonium azide in THF would give clean results. Under optimized conditions a mixture of the azido alcohol **42** together with its regioisomer was obtained in 78–90 % combined yield. The stereo- and regioconvergent ring-closure of the second pyrrolidine ring was then initiated by conversion of both regioisomers of **42** into the corresponding mesylates. The azido mesylates were found to cyclize spontaneously to the bispyrrolidine **43** under Staudinger conditions[45] with PBu_3 in acetonitrile. In contrast with the reductive process described earlier, no evidence of a free aminomesylate could be found, which could indicate an alternative reaction pathway. Finally, compound **43** was transformed into the bis-*N*-Boc-protected bispyrrolidine **44**, although forcing conditions were again necessary to overcome steric hindrance.

The cleavage of the N-benzyl and N-tosyl groups from bispyrrolidine **44** proved somewhat troublesome under standard conditions. First attempts to cleave the N-tosyl group with Na/NH_3 resulted in complex mixtures, whereas treatment with Na/Hg[46] left the substrate unaffected. Attempts at reductive (Pd black, 10 atm H_2) or oxidative (KO*t*Bu/O_2 or RuO_4) cleavage of the N-benzyl group failed. Finally, benzylic metallation was found to be the method of choice. Whereas use of $LiNEt_2$ at −78 °C selectively metallated the Ts-Me group (65 % yield in a model system, see Supporting Information) and that of LDA led to complex mixtures, the concomitant removal of both protecting groups was cleanly achieved by treatment of **44** with BuLi in THF followed by TMSCl (Scheme 9). The moderate yield can probably be attributed to product isolation problems. No TMS-containing side products were found, indicating a fast fragmentation of the metallated species. Presumably benzylic metallation by BuLi triggers β-elimination of sulfinate[47] from **44** to afford the corresponding imine as intended,[3] and this is subsequently cleaved by hydrolysis to provide the target amine **45**. This route has not only established optimized procedures for oligopyrrolidine synthesis, but should also generally allow the incorporation of amino acid side chains into asymmetric oligopyrrolidines for artificial anion channels.



Scheme 9. Ts/Bn removal: a) *n*BuLi, −78 °C; b) TMSCl, RT.

Beginning to study the potential of oligopyrrolidines for interactions with oligonucleotides, we turned our attention to RNA. RNA is fairly susceptible towards base-induced fragmentation reactions, and this has been explored in the design of artificial nucleases.[48–51] Interestingly, it had been reported that simple diamines can induce ssRNA strand breaks, which triggered our interest.[52,53] However, the conditions used in kinetics experiments (up to 1 M compound)[53] proved impractical for a preliminary screening in our case. Accordingly, assay conditions allowing comparison of the ssRNA cleavage activities of the oligopyrrolidines **1**, **2** and **33** with those of several simple di-, tri- and tetraamines were found (see Supporting Information); some of these had also been covered in work by Komiyama.[53] Under dilute single-turnover conditions (1–5 mM compound, 200 nM ssRNA, 2 mM EDTA, 50 mM TRIS, pH 8.0, 50 °C), simple diamines barely showed any detectable cleavage activity above background. Terpyrrolidine **1** was weakly active, comparable to spermine. The latter compound had earlier been suspected to induce RNA strand breaks nonspecifically under certain conditions.[54] Tetraazacrown 12 C4 gave rise to more cleavage products, which is in qualitative agreement with experi-

[3] Non-chelating imines are fairly inert towards alkyllithium reagents at low temperature. This most likely course of events is also corroborated by model experiments (see Supporting Information).

ments reported by Kalesse.[50] Most interestingly, the pyrrolidino-THF **2** and especially the terpyrrolidine sulfonamide **33** furnished even higher levels of cleavage products in comparison.

These findings were investigated in more detail by comparison of compound **33** with the hairpin ribozyme (Figure 3). The hairpin ribozyme is a self-cleaving endonuclease/self-joining ligase derived from the tobacco ringspot virus satellite RNA.[55–58] Its 50 bp minimal sequence will catalyse the reversible selective cleavage of a suitable 14-mer RNA substrate between the 5- and 6-positions (Figure 3). Ribozyme activity is dependent on the presence of positively charged cofactors, typically magnesium ions, in mM concentrations. However, aminoglycosides or polyamines such as spermine have also been shown to support hairpin ribozyme cleavage, even in the absence of Mg^{2+}.[54,59] In the presence of both Mg^{2+} (10 mM) and the terpyrrolidine **33** (2 mM), three major cleavage products were observed (Figure 3 a–d). In particular, tri-, tetra- and 5-mers were produced. While the 5-mers are expected results of the hairpin ribozyme cleavage reaction, the tri- and tetramers appeared as new additional products. In the absence of Mg^{2+}, only the tri- and tetramer cleavage products were observed (Figure 3 e–h), implying that their formation is directly linked to compound **33**. In this experiment the concentration of **33** was doubled, resulting in a higher rate of tri- and tetramer formation. Strikingly, cleavage rates at 4 mM concentration of compound **33** or 10 mM $MgCl_2$ are virtually the same ($\approx 0.1\ min^{-1}$; for overall conditions refer to Experimental Section). A similar cleavage pattern was observed when the single-stranded RNA substrate was treated with terpyrrolidone **33** in the absence of the ribozyme strand.

The preference for cleavage by pyrrolidine **33** at the 3- and 4-positions is not clear at this point. The previous observations of polyamines influencing the catalytic properties of hairpin ribozymes[54,59,60] might suggest synergistic interactions between compound **33** and the ribozyme. However, polyamine-supported hairpin ribozyme catalysis as described in the literature proceeds with the same specificity as observed for the hairpin ribozyme in the presence of magnesium ions alone, with only the 5-mer cleavage product being obtained.[54,59] Even though it cannot be completely ruled out at this point that **33** interacts with the ribozyme and as a result changes the active conformation of the ribozyme as well as its specificity, production of the tri- and tetramers is more likely to result from direct degradation of the substrate induced by **33** in a dose-dependent manner. This interpretation gains strong support from the observation that cleavage also occurred in the absence of ribozyme and that the cleavage rate was dependent on the concentration of the terpyrrolidine. This strongly suggests that the cleavage reaction was specifically caused by **33**.

It had previously been shown that the chemical stability of phosphodiester bonds of some oligoribonucleotides in the presence of a cofactor such as polyvinylpyrolidine is sequence-dependent.[67] Chemical stability of phosphodiester bonds seems to be "coded" in such a way that structural properties such as the degree of base stacking may be responsible for the stability/instability of certain phosphodiester bonds. The tri- and tetramers obtained in the presence of

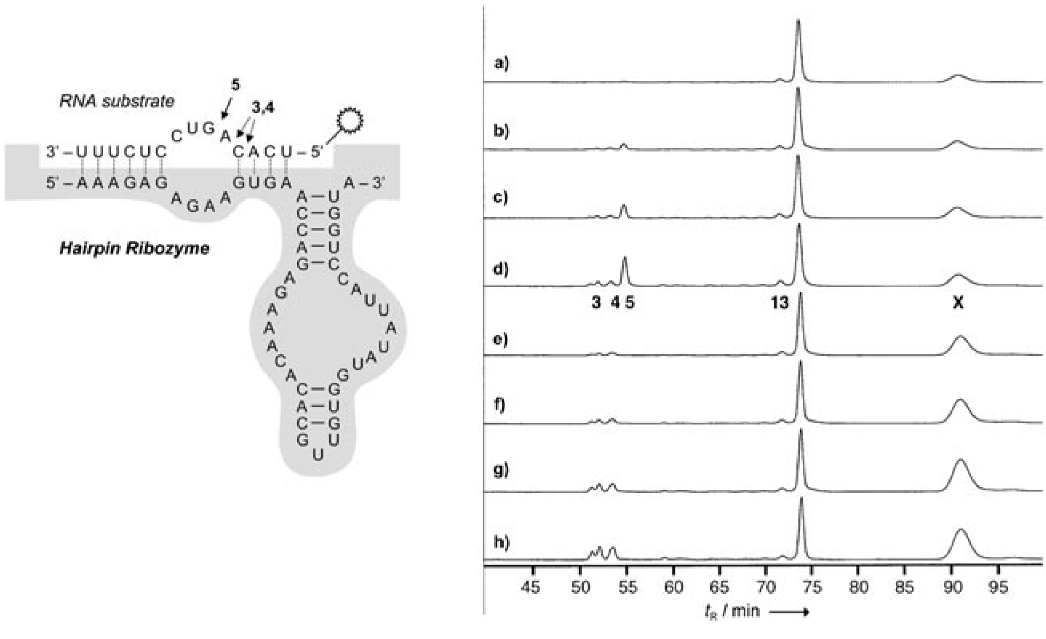


Figure 3. Secondary structure of the hairpin ribozyme with its substrate (left). The solid line arrow denotes the site of cleavage by the ribozyme, dotted line arrows mark the sites of cleavage induced by terpyrrolidine **33**. The substrate RNA carries a fluorescein label at the 5′-end. ALF-recorded traces of RNA cleavage reactions (right; for details see Experimental Section). a)–d) Competition experiment: 10 nM ribozyme, 200 nM substrate, 2 mM **33**, 10 mM $MgCl_2$, 50 mM TRIS-HCl (pH 7.5), 37 °C; a) 5 min, b) 10 min, c) 20 min, d) 35 min; e)–h) conditions as in a)–d), except 0 mM $MgCl_2$ (ribozyme deactivated), 2 mM EDTA and 4 mM **33**; e) 5 min, f) 10 min, g) 20 min, h) 35 min. Peaks marked 3, 4, 5 and 13 refer to 3-, 4-, 5-mer products, respectively. The peak denoted "X" is not a RNA-oligomer but a UV-active substance, most probably compound **33** or a product thereof. The apparent peak splitting for the short oligomers is probably due to stereoisomers in the fluorescent label, as described earlier,[60] or to degradation of the initially formed 2′,3′-cyclic phosphoric acid diester to 2′- or 3′-phosphoric acid monoester.

compound **33** might therefore reflect preferential hydrolysis of phosphodiester bonds at particularly sensitive sites. Alternatively, inherent compound selectivity may account for the observed cleavage products. In either case, compound **33** is a promising lead structure for further functional design. It has been demonstrated to induce RNA cleavage to a considerable extent. CA-rich sequences seem to be most susceptible for terpyrrolidone-induced cleavage, suggesting that **33** may be capable of evolution into a tailored small molecular tool for selective RNA hydrolysis.

Conclusion

In summary, conformationally restricted polyamines are promising candidates for RNA-targeting "shaped" polycations and may become building blocks for artificial anion channels as well. Here we have detailed the stereoselective synthesis of 2,5′-*threo-trans*-configured bis- and terpyrrolidines, which have been stereochemically assigned and investigated by X-ray crystallography. Most importantly, a general preference for helical conformers was found in the solid state, and for the pyrrolidino-THF-pyrrolidine **30** a perfectly helical arrangement was discovered, confirming model calculations made earlier for similar systems.[17] The optimized synthesis was based on diastereoselective additions of alkynes to pyrrolidinecarboxaldehydes, where Felkin–Anh control proved rather difficult to establish. Ligand-accelerated chelation control was found to be operative under Carreira's $Zn(OTf)_2$/*N*-methylephedrine conditions,[33] which in turn allowed completely anti-Felkin–Anh selective addition. On the other hand, perfect Felkin–Anh selectivity was achieved with Ts/Bn protection, which was then utilized for the synthesis of an asymmetric bispyrrolidine. Various amino acid side chains may thus be integrated into the skeleton, paving the way for oligopyrrolidine amino acids in the future.

In incubation experiments with RNA at physiologically relevant temperature (37 °C) and pH (7.5–8), oligopyrrolidine sulfonamide **33** was found to induce RNA cleavage with surprising potency in relation to simple di- and polyamines or terpyrrolidine **1**. In comparison with the evolutionarily tailored hairpin ribozyme, its activity is still about 10^5 times lower. However, in view of the small-molecule nature and singularity of terpyrrolidine **33**, a very promising lead has been found and is likely to evolve in further studies. The synthetic groundwork presented here should allow an approach to this goal.

Experimental Section

General: All reactions sensitive to air or moisture were conducted in flame-dried glassware under an atmosphere of dry Argon. THF and Et_2O were distilled from purple sodium/benzophenone. CH_2Cl_2, toluene, hexanes, pyridine and Et_3N were distilled under Ar from CaH_2. MeOH was distilled from $Mg(OMe)_2$. Organolithium and amide base solutions were titrated against diphenylacetic acid.[61] All starting materials and reagents were used as received unless noted otherwise. Lithium azide,[62] tetrabutylammonium azide[63] and *N*-tosylalanine[64] were prepared by literature procedures. PE: light petroleum, boiling range 40–60 °C; MTBE: methyl *tert*-butyl ether. Thin-layer chromatography (TLC) was performed on glass-supported Merck silica gel plates (60 F_{254}). Spots were viewed under UV light and by heat staining with 2 % molybdophosphoric acid in ethanol. Flash column chromatography (FCC) was performed on Merck silica gel 60 (40–63 μm). Melting points were determined from pulverized material in glass capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on Bruker DPX 300 or AMX 600 spectrometers, respectively. All resonances are referenced to residual solvent signals.[65] IR: Perkin–Elmer FT-IR Spektrum 1600 or BioRad FT-IR 3000 MX. Optical rotations: Perkin–Elmer spectrophotopolarimeter 241, cuvette path length 10 cm. $CHCl_3$ for spectroscopy was filtered over basic aluminium oxide before use. MS: Finnigan MAT 95 (EI: 70 eV; FAB) or MSI Concept 1H (ESI). Elemental analyses: Leco CHNS 932 Analysator (microanalytical facility, HU Berlin).

(*S*)-2-(*tert*-Butyldiphenylsilyloxy)methyl-pyrrolidin-5-one (6): Pyroglutamic acid **5** (33.6 g, 260 mmol) was suspended in anhydrous MeOH (65 mL), and 2,2-dimethoxypropane (65 mL, 0.53 mol, 2 equiv) and conc. HCl (0.54 mL, 6.5 mmol, 2.5 mol %) were added. The mixture was warmed to 50 °C with stirring to give a clear solution. After 6 h the mixture was cooled to 5 °C and neutralized with sat. $NaHCO_3$ solution (approx. 5 mL). The volatiles were evaporated, and the residue was dissolved in EtOAc (200+50 mL) and filtered over a pad of Celite. The filtrate was concentrated, coevaporated with toluene (2×100 mL) and dried to give crude pyroglutamic acid methyl ester **46** (35.5 g, 0.248 mol, 95 %), which was used directly for the next step. R_f = 0.39 in EtOAc/MeOH 8:1.

A 1 L three-necked, round-bottomed flask fitted with a mechanical overhead stirrer was charged with THF/MeOH 3:2 (200 mL), the system was cooled to −10 °C (internal), and $NaBH_4$ (8.2 g, 0.22 mol, 1.1 equiv) was added. A solution of crude ester **46** (28.6 g, 200 mmol) in THF (75 mL) was added dropwise, while the flask temperature was kept below 5 °C. After the addition was complete, the mixture was stirred for 1 h (TLC monitoring, R_f = 0.12 in EtOAc/MeOH 8:1). Occasionally, more $NaBH_4$ (1–2 g) had to be added to complete conversion. Conc. HCl (30 mL) was then added dropwise (**Caution!**) to the stirred, ice-cooled mixture, until the gas evolution had ceased and the pH had reached 2. The mixture was warmed to RT and stirred for 3 h, neutralized with solid $NaHCO_3$ (approx. 20 g), stirred for 30 min and diluted with MTBE (100 mL). $MgSO_4$ (15 g) was added, and the solids were removed by filtration over a pad of Celite. The filtrate was concentrated and coevaporated with toluene (2×100 mL) to give crude pyroglutaminol **47** (23.0 g, 200 mmol, quant.) as a colourless solid.

Crude alcohol **47** (23.0 g, 200 mmol) was dissolved in DMF (200 mL), the mixture was cooled to 0 °C, and imidazole (15.3 g, 220 mmol, 1.1 equiv) was added, followed by TBDPSCl (23 mL, 220 mmol, 1.1 equiv). The mixture was stirred for 3 h at RT. The solvents were removed, and the residue was partitioned between MTBE (200 mL) and water (100 mL). The aqueous layer was extracted with MTBE (3×75 mL), and the combined extracts were washed with brine (100 mL), dried with $MgSO_4$ and concentrated. FCC (900 g, MTBE→MTBE/acetone 4:1→2:1) of the residue gave TBDPS-ether **6** (66.0 g, 187 mmol, 93 %) as a sticky gum, which crystallized from PE/MTBE 10:1 in colourless blocks. R_f = 0.25 (MTBE/acetone 4:1); m.p. 77.5–78 °C; $[\alpha]_D^{20}$ = 15.4 (c = 0.825 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 9H; *t*Bu), 1.69–1.80 (m, 1H; 3-H_{2A}), 2.14 (dt, J = 12.9/7.8 Hz, 1H; 3-H_{2B}), 2.27–2.34 (m, 2H; 4-H_2), 3.52 (dd, J = 10.3, 7.2 Hz, 1H; 1′-H_{2A}), 3.62 (dd, J = 10.3, 4.2 Hz, 1H; 1′-H_{2B}), 3.80 (m, 1H; 2-H), 6.22 (s, 1H; NH), 7.32–7.43 (m, 6H; arom.), 7.63 (d, J = 7.5 Hz, 4H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (Si-$C(CH_3)_3$), 22.7 (C-3), 26.7 (Si-C($CH_3)_3$), 29.7 (C-4), 55.6 (C-2), 67.3 (C-1′), 127.8, 129.8, 132.9, 135.5 (arom.), 178.0 (C-5) ppm; IR (KBr): $\tilde{\nu}$ = 3196 (N−H), 3069, 2929, 2855, 1691 (C=O), 1586, 1472, 1460, 1426, 1391, 1336, 1298, 1238, 1162, 1109, 1034, 996, 951, 870, 824, 793, 745, 706, 639, 616 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{27}NO_2Si$ (353.54): C 71.34, H 7.70, N 3.96; found: C 71.09, H 7.58, N 4.02.

(*S*)-*N*-*tert*-Butoxycarbonyl-2-(*tert*-butyldiphenylsilyloxy)methyl-pyrrolidin-5-one (7): A solution of amide **6** (16.5 g, 46.7 mmol) in CH_2Cl_2 (80 mL) was cooled to 0 °C, and pyridine (5 mL) and DMAP (1.12 g, 9.34 mmol, 0.2 equiv) were added, followed by Boc_2O (10.2 g, 46.8 mmol, 1.0 equiv). The mixture was stirred at 0 °C with continuous gas evolution. After 3 h more Boc_2O (3.0 g, 13.7 mmol, 0.3 equiv) was introduced, and the mixture was stirred overnight at RT. Sat. NH_4Cl solution was added (75 mL), and the well stirred mixture was acidified with 2 N HCl to pH 4 (**Caution!**). The layers were separated, and the aqueous layer was extracted with MTBE (3×75 mL). The combined organic layers were washed with H_3PO_4 (0.1 M), H_2O, and brine (100 mL each), dried with $MgSO_4$, concentrated and coevaporated with toluene (100 mL). Crystallization from hot PE/MTBE 20:1 (5 mL g^{-1}) gave Boc-protected amide **7** (19.7 g, 43.3 mmol, 93 %) as colourless prisms. R_f = 0.33 (MTBE/PE 1:1); m.p. 110 °C; $[\alpha]_D^{20}$ = −38.4 (*c* = 1.30 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (s, 9H; Si-*t*Bu), 1.42 (s, 9H; Boc), 2.05–2.12 (m, 2H; 3-H_2), 2.41 (ddd, *J* = 18/8/4 Hz, 1H; 4-H_2), 2.78 (dt, *J* = 18/11 Hz, 1H; 4-H_2), 3.59 (dd, *J* = 10.4/2.4 Hz, 1H; 1′-H_{2A}), 3.88 (dd, *J* = 10.4/4.2 Hz, 1H; 1′-H_{2B}), 4.20 (m, 1H; 2-H), 7.35–7.45 (m, 6H; arom.), 7.57–7.65 (m, 4H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (Si-*C*(CH_3)$_3$), 21.1 (C-3), 26.8 (Si-C(*C*H_3)$_3$), 28.0 (O-C(*C*H_3)$_3$), 32.3 (C-4), 58.7 (C-2), 64.9 (C-1′), 82.6 (O-*C*(CH_3)$_3$), 127.8, 129.8, 132.6, 133.0, 135.5 (arom.), 149.8 (Boc-C=O), 174.9 (C-5) ppm; IR (KBr): $\tilde{\nu}$ = 3070, 3050, 3030, 2985, 2975, 2954, 2949, 2931, 1748 (-CO-NR_2), 1705 (Boc-C=O), 1580, 1472, 1464, 1432, 1410, 1365, 1310, 1276, 1258, 1156, 1112, 1077, 1034, 999, 896, 860, 821, 742, 706, 620, 597 cm^{-1}; elemental analysis calcd (%) for $C_{26}H_{35}NO_4Si$ (453.66): C 68.84, H 7.78, N 3.09; found: C 69.03, H 7.63, N 3.17.

(2*S*,5*S*)- and (2*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-2-(*tert*-butyldiphenylsilyloxy)methyl-5-methoxy-pyrrolidine (8a and 8b): A solution of amide **7** (25.7 g, 56.6 mmol) in CH_2Cl_2/MeOH 3:1 (650 mL) was cooled to −10 °C, and $NaBH_4$ (6.3 g, 170 mmol, 3 equiv) was added in one portion. The stirred solution became clear within minutes, and was allowed to warm to 0 °C over 2 h. After the starting material was consumed (product R_f = 0.43 in MTBE/PE 1:1), sat. $NaHCO_3$ (200 mL) and H_2O (100 mL) were added, and the ice-cooled mixture was stirred until the gas evolution ceased (2 h). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2×150 mL), and the combined organic layers were washed with brine (100 mL), dried with Na_2SO_4 and carefully concentrated to approx. 70 mL.

2,2-Dimethoxypropane (25 mL, 0.20 mol, 3.6 equiv) was now added at 0 °C, followed by CSA (130 mg, 0.56 mmol, 1 mol %). After conversion of the starting material (15 min) sat. $NaHCO_3$ solution was added (15 mL), and the mixture was washed with H_2O (50 mL). The aqueous layer was extracted with MTBE (2×50 mL), and the organic layers were combined, washed with brine (50 mL), dried (Na_2SO_4) and concentrated. FCC (300 g, PE/MTBE 85:15) gave methyl aminals **8a** and **8b** (24.6 g, 52.6 mmol, 93 %) as a 5:2 diastereomeric mixture, which was separated for analytical purposes only. Elemental analysis calcd (%) for $C_{27}H_{39}NO_4Si$ (469.70): C 69.04, H 8.37, N 2.98; found: C 68.89, H 8.52, N 2.87.

Compound 8a: R_f = 0.36 (PE/MTBE 6:1); m.p. 57–59 °C; $[\alpha]_D^{20}$ = −35.8 (*c* = 0.702 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 2:1 mixture of rotamers): δ = 1.05 (s, 9H; Si-*t*Bu), 1.35/1.45 (each s, 2:1, 9H; Boc), 1.70–1.85 (m, 1H; 3-H_{2A}), 1.87–1.95 (m, 1H; 3-H_{2B}), 2.10–2.25 (br m, 2H; 4-H_2), 3.26 (s, 3H; -OMe), 3.45–3.75 (br m, 1H; 1′-H_{2A}), 3.80–4.00 (m, 2H; 1′-H_{2B}, 2-H), 5.18 (br m, 1H; 5-H), 7.34–7.43 (m, 6H; arom.), 7.65–7.70 (m, 4H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3 (Si-*C*(CH_3)$_3$), 26.9 (Si-C(*C*H_3)$_3$), 27.4 (C-3), 28.0 (O-C(*C*H_3)$_3$), 32.2 (C-4), 55.1 (-OMe), 59.2 (C-2), 67 (b, C-1′), 79.9 (O-*C*(CH_3)$_3$), 89.7 (C-5), 127.6, 129.5, 133.8, 135.5 (arom.); C=O of Boc not detected.

Compound 8b: R_f = 0.28 (PE/MTBE 6:1); ^{1}H NMR (300 MHz, $CDCl_3$, 11:9 mixture of rotamers): δ = 1.06 (s, 9H; Si-*t*Bu), 1.28/1.47 (each s, 56:44, 9H; Boc), 1.71–1.86 (m, 1H; 3-H_{2A}), 1.87–2.00 (m, 1H; 3-H_{2B}), 2.02–2.20 (br m, 2H; 4-H_2), 3.32/3.37 (each s, 55:45, 3H; -OMe), 3.48 (m, 2H; 1′-H_{2A}), 3.70 (m, 2H; 1′-H_{2B}), 3.82–4.03 (m, 1H; 2-H), 4.93/5.05 (each d, *J* = 4.1/4.4 Hz, 1H; 5-H), 7.34–7.43 (m, 6H; arom.), 7.58–7.65 (m, 4H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (Si-*C*(CH_3)$_3$), 24.6/24.4 (C-3), 26.9 (Si-C(*C*H_3)$_3$), 27.7/27.9 (O-C(*C*H_3)$_3$), 29.2/30.5 (C-4), 55.7/56.5 (-OMe), 58.2 (C-2), 63.8/63.9 (C-1′), 79.6/79.8 (O-*C*(CH_3)$_3$), 89.9/90.3 (C-5), 127.7, 129.7, 133.2, 135.5 (arom.), 153.5/153.9 (Boc-C=O).

(2*S*,5*S*)- and (2*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-2-(*tert*-butyldiphenylsilyloxy)methyl-5-cyano-pyrrolidine (9 and 10): Aminal **8** (5:2 diastereomeric mixture, 15.0 g, 32.0 mmol) in CH_2Cl_2 (100 mL) was cooled to −35 °C, and TMSCN (5.0 mL, 40 mmol, 1.25 equiv) was added with stirring. After 10 min, TMSOTf (0.10 mL, 0.33 mmol, 1 mol %) was added dropwise and the system was stirred for 3 min (TLC monitoring). Sat. $NaHCO_3$ (10 mL) and H_2O (60 mL) were added, and the biphasic mixture was vigorously stirred for 15 min. The layers were separated and the aqueous layer was extracted with MTBE (2×50 mL). The organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$) and concentrated. FCC (200 g, PE/MTBE 5:1→3:1) provided *trans*-nitrile **9** (10.7 g, 23.0 mmol, 72 %) as a colourless gum, followed by *cis*-nitrile **10** (3.41 g, 7.34 mmol, 23 %) as a colourless solid, which was crystallized from PE at −20 °C.

Compound 9: R_f = 0.37 (PE/MTBE 4:1); $[\alpha]_D^{20}$ = −39.4 (*c* = 0.900 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 9:11 mixture of rotamers): δ = 1.05 (s, 9H; Si-*t*Bu), 1.34/1.53 (each s, 44:56, 9H; Boc), 2.10–2.55 (m, 4H; 3-H_2, 4-H_2), 3.58/3.87 (each dd, *J* = 10.3, 4.7 Hz, 0.88H; 1′-H_{2A}), 3.67 (dd, *J* = 10.1, 2.7 Hz, 1.12H; 1′-H_{2B}), 3.91/4.05 (each br m, 44:56, 1H; 2-H), 4.46/4.52 (each d, *J* = 8.1 Hz, 1H; 5-H), 7.30–7.45 (m, 6H; arom.), 7.55–7.65 (m, 4H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 (Si-*C*(CH_3)$_3$), 26.9 (Si-C(*C*H_3)$_3$), 26.9 (C-3), 28.1 (O-C(*C*H_3)$_3$), 29.8 (C-4), 48.2 (C-5), 58.3 (C-2), 63.9/64.0 (C-1′), 81.1/81.3 (O-*C*(CH_3)$_3$), 119.1/119.4 (-CN), 127.6, 129.5, 133.8, 135.2 (arom.). 153.1/153.7 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3072, 3050, 2962, 2932, 2859, 2244 (C≡N), 1706 (C=O), 1590, 1474, 1428, 1376, 1338, 1256, 1169, 1113, 1083, 1045, 983, 920, 846, 823, 775, 742, 703, 610 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{36}N_2O_3Si$ (464.68): C 69.79, H 7.81, N 6.03; found: C 69.90, H 7.78, N 6.07.

Compound 10: R_f = 0.17 (PE/MTBE 4:1); m.p. 60.5–61 °C (PE); $[\alpha]_D^{20}$ = +22.3 (*c* = 1.33 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 2:3 mixture of rotamers): δ = 1.07 (s, 9H; Si-*t*Bu), 1.34/1.51 (each s, 42:58, 9H; Boc), 1.97–2.37 (m, 4H; 3-H_2, 4-H_2), 3.60–4.02 (m, 3H; 1′-H_2, 2-H), 4.40/4.57 (each br m, 58:42, 1H; 5-H), 7.37–7.47 (m, 6H; arom.), 7.55–7.65 (m, 4H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (Si-*C*(CH_3)$_3$), 24.4/24.6 (C-3), 26.9 (Si-C(*C*H_3)$_3$), 28.2 (O-C(*C*H_3)$_3$), 29.6/30.3 (C-4), 49.5 (C-5), 59.4 (C-2), 64.1/64.9 (C-1′), 81.4/81.6 (O-*C*(CH_3)$_3$), 119.5 (-CN), 127.7, 129.7, 133.2/133.3, 135.6 (arom.) ppm, C=O of Boc not detected; IR (film): $\tilde{\nu}$ = 3073, 2956, 2932, 2886, 2857, 2238 (C≡N), 1702 (C=O), 1473, 1429, 1391, 1347, 1260, 1166, 1112, 1048, 988, 868, 823, 775, 742, 704, 616 cm^{-1}.

Epimerization of the *cis*-nitrile (10): Compound **10** (4.89 g, 10.5 mmol) in toluene (40 mL) was stirred at 0 °C with *t*BuOH (1 mL) and KO*t*Bu (0.24 g, 2.1 mmol, 0.2 equiv) for 90 min. The mixture was washed with sat. NH_4Cl (50 mL) containing HCl (2 N, 1 mL), the aqueous layer was extracted with MTBE (2×30 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and evaporated. FCC (60 g) gave **9** (2.65 g, 54 %) and **10** (2.05 g, 43 %), identical to the substances described before.

(2*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-2-(*tert*-butyldiphenylsilyloxy)methyl-pyrrolidine-5-carbaldehyde (4): Nitrile **9** (6.97 g, 15.0 mmol) was dissolved in toluene/PE 3:1 (90 mL), and the mixture was cooled to −70 °C (internal). DIBAH (1 M in hexanes, 21 mL, 21 mmol, 1.4 equiv) was added dropwise while the internal temperature was kept under −60 °C. The mixture was stirred until the conversion was complete (1 h). Meanwhile, a mixture of sat. NH_4Cl (200 mL) and Rochelle salt solution (1 M, 60 mL) was adjusted to pH 6.5 with solid tartaric acid (approx. 1 g). MTBE (50 mL) was added, and the stirred suspension was cooled to 0 °C, degassed and saturated with Ar. The reaction mixture was then transferred slowly by cannula into the stirred buffer solution. This biphasic mixture was vigorously stirred until all solids were dissolved (3 h, pH 7.0). The layers were separated, and the aqueous layer was extracted with MTBE (2×100 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4) and concentrated. FCC (100 g, PE/MTBE 3:1) and crystallization (hexanes, −15 °C) provided aldehyde **4** (4.61 g, 9.86 mmol, 66 %) as colourless prisms. R_f = 0.18 (PE/MTBE 4:1); m.p. 70 °C; $[\alpha]_D^{20}$ = −60.1 (*c* = 1.14 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 9:11 mixture of rotamers): δ = 1.06 (s, 9H; Si-*t*Bu), 1.34/1.43 (each s, 45:55, 9H; Boc), 1.88–2.18 (m, 3H; 3-H_2, 4-H_{2A}), 2.20–2.40 (m, 1H; 4-H_{2B}), 3.59 (dd, *J* = 16.8, 6.4 Hz, 0.55H; 1′-H_{2A}), 3.66 (m, 0.9H; 1′-H_2), 3.87 (dd, *J* = 16.8, 4.5 Hz, 0.55H; 1′-H_{2B}), 4.04/4.15 (each m, 45:55, 1H; 2-H), 4.18/4.30 (each m, 1H; 5-H), 7.36–7.46 (m, 6H; arom.), 7.61–7.65 (m, 4H; arom.), 9.53/9.60 (each d, 55:45, *J* = 2.6 Hz, 1H; -C*H*O) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (Si-*C*(CH_3)$_3$), 25.0 (C-3), 26.9 (Si-C(*C*H_3)$_3$), 27.1 (C-4), 28.3 (O-C(*C*H_3)$_3$), 59.2/59.4 (C-2), 63.9/64.3 (C-1′), 65.7/66.0 (C-5), 80.8/80.9 (O-*C*(CH_3)$_3$), 127.7, 129.7/129.8, 132.4/133.5, 135.5 (arom.), 153.4/

154.3 (Boc-C=O), 200.6 (-CHO) ppm; IR (KBr): $\tilde{\nu}$ = 3075, 3055, 2980, 2958, 2929, 2907, 2864, 2808, 1738 (-HC=O), 1697 (Boc-C=O), 1590, 1471, 1428, 1386, 1374, 1176, 1114, 1092, 1061, 1036, 1007, 998, 851, 823, 774, 744, 709, 704, 614 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{37}NO_4Si$ (467.68): C 69.34, H 7.97, N 2.99; found C 69.09, H 7.78, N 3.09.

(2S,5S,1′R)- and (2S,5S,1′S)-*N-tert*-Butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)methyl-2-(1′-hydroxy-3′-trimethylsilyl)-prop-2′-ynyl-pyrrolidine (14 and 48): $CeCl_3\cdot 7H_2O$ (8.8 g, 23.6 mmol, 1.5 equiv) was cautiously dehydrated under high vacuum (0.01 mbar, 1 h at 80 °C, 1 h at 100 °C, 3 h at 150 °C). The resulting fine powder was covered with Ar, cooled to RT, and suspended in THF (100 mL). The suspension was cooled to −60 °C, and a precooled (−70 °C) solution of TMS-ethynyl-lithium (freshly prepared, 23.6 mmol, 1.5 equiv) in THF (40 mL) was added by cannula over 5 min, giving a yellow suspension. The mixture was stirred for 30 min and cooled to −80 °C, and a solution of aldehyde **4** (7.36 g, 15.7 mmol) in THF (50 mL) was added dropwise over 10 min. After the addition was complete, the mixture was stirred for 10 min and poured into an ice-cooled mixture of MTBE (200 mL) and H_2O (200 mL). After stirring for 30 min, the mixture was filtered over a pad of Celite. The layers were separated, and the aqueous layer was extracted with MTBE (3×50 mL). The organic layers were combined, washed with brine (200 mL) and concentrated. FCC (800 g, PE/MTBE 5:1→7:2→3:1) provided (1′R)-alcohol **14** (4.56 g, 8.06 mmol, 51%) followed by (1′S)-alcohol **48** (3.72 g, 6.57 mmol, 42%), each as a colourless gum.

Compound 14: R_f = 0.35 (*n*-hexane/MTBE 10:3); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.16 (s, 9H; TMS), 1.03 (s, 9H; Si-*t*Bu), 1.33 (s, 9H; Boc), 1.76 (m, 1H; 4-H_{2A}), 1.97 (m, 1H; 3-H_{2A}), 2.32 (m, 2H; 3-, 4-H_{2B}), 3.61 (dd, *J* = 9.8, 6.4 Hz, 1H; 1″-H_{2A}), 3.69 (dd, *J* = 9.8, 3.1 Hz, 1H; 1″-H_{2B}), 3.96 (m, 1H; 5-H), 4.14 (d, *J* = 8.5 Hz, 1H; 2-H), 4.40 (dd, *J* = 9.5, 1.0 Hz, 1H; 1′-H), 5.97 (d, *J* = 9.5 Hz, 1H; -OH), 7.32–7.45 (m, 6H; arom.), 7.60–7.66 (m, 4H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = −0.4 (Si-CH_3), 19.0 (Si-*C*(CH_3)$_3$), 26.2 (C-4), 26.6 (Si-C(CH_3)$_3$), 28.1 (O-C(CH_3)$_3$, C-3), 60.7 (C-5), 64.1, 64.5 (C-1″ and C-2), 68.8 (C-1′), 80.4 (O-*C*(CH_3)$_3$), 89.9 (C-2′), 104.9 (C-3′), 127.6, 129.5, 133.2, 133.3, 135.3 (arom.), 156.6 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3369 (-OH), 3072, 3051, 2961, 2932, 2898, 2859, 2172 (C≡C), 1694, 1668, 1473, 1403, 1251, 1174, 1113, 1056, 1010, 978, 844, 760, 741, 702, 614 cm^{-1}; elemental analysis calcd (%) for $C_{32}H_{47}NO_4Si_2$ (565.90): C 67.92, H 8.37, N 2.48; found C 68.07, H 8.58, N 2.51.

Compound 48: R_f = 0.25 (*n*-hexane/MTBE 10:3); ^{1}H NMR (300 MHz, $CDCl_3$, 85:15 mixture of rotamers): δ = 0.17 (s, 9H; TMS), 1.05 (s, 9H; Si-*t*Bu), 1.28/1.47 (each s, 85:15, 9H; Boc), 1.80–2.35 (m, 4H; 3-, 4-H_2), 3.54 (dd, *J* = 9.6, 7.2 Hz, 0.85H; 1″-H_2), 3.58–3.66 (m, 0.3H; 1″-H_2), 3.74 (dd, *J* = 9.6, 3.1 Hz, 0.85H; 1″-H_2), 3.90 (m, 1H; 5-H), 4.05 (m, 1H; 2-H), 4.54 (m, 2H; 1′-H, -OH), 7.30–7.45 (m, 6H; arom.), 7.61–7.65 (m, 4H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = −0.4 (Si-CH_3), 19.0 (Si-*C*(CH_3)$_3$), 25.7, 26.4 (C-3, C-4), 26.6 (Si-C(CH_3)$_3$), 28.0 (O-C(CH_3)$_3$, C-4), 59.5 (C-5), 62.8 (C-2), 63.5 (C-1″), 66.5 (C-1′), 80.5 (O-*C*(CH_3)$_3$), 89.8 (C-2′), 105.0 (C-3′), 127.5, 129.5, 133.2, 135.3 (arom.), 156.3 (Boc-C=O) ppm; HRMS (EI): *m/z*: calcd for $C_{32}H_{47}NO_4Si_2$: 565.3044; found: 565.3049 $[M]^+$.

(2S,5S,1′R)-*N-tert*-Butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)methyl-2-(1′-hydroxy-prop-2′-ynyl)-pyrrolidine (15): TMS-protected alkyne **14** (13.6 g, 24.0 mmol) was dissolved in THF/MeOH (1:1, 200 mL), and the system was cooled to 0 °C. H_2O (1.3 mL, 72 mmol, 3 equiv) and K_2CO_3 (5.0 g, 36 mmol, 1.5 equiv) were added, and the suspension was stirred for 4 h. Acetic acid (4 mL) was added, and the mixture was concentrated in vacuo to approx. 50 mL. The residue was partitioned between EtOAc (150 mL) and brine (75 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. FCC (400 g, PE/MTBE 5:2→2:1→1:1) provided alkyne **15** (11.5 g, 23.2 mmol, 97%) as a clear, viscous oil. R_f = 0.19 (*n*-hexane/MTBE 3:1); ^{1}H NMR (300 MHz, $CDCl_3$, 92:8 mixture of rotamers; data for major rotamer): δ = 1.05 (s, 9H; Si-*t*Bu), 1.33/1.48 (each s, 92:8, 9H; Boc), 1.75 (m, 1H; 3-H_{2A}), 1.98 (m, 1H; 4-H_{2A}), 2.23–2.35 (m, 2H; 3-, 4-H_{2B}), 2.39 (d, *J* = 2.1 Hz, 1H; 3′-H), 3.60 (dd, *J* = 9.8, 6.5 Hz, 1H; 1″-H_2), 3.69 (dd, *J* = 9.8, 3.0 Hz, 1H; 1″-H_2), 4.01 (m, 1H; 5-H), 4.05 (d, *J* = 8.6 Hz, 1H; 2-H), 4.47 (d, *J* = 9.1 Hz, 1H; 1′-H), 5.88 (d, *J* = 9.1 Hz, -OH), 7.33–7.43 (m, 6H; arom.), 7.60–7.66 (m, 4H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (Si-*C*(CH_3)$_3$), 26.5 (C-4), 26.8 (Si-C(CH_3)$_3$), 27.9 (C-3), 28.3 (O-C(CH_3)$_3$, C-4), 60.9 (C-5), 64.3 (C-2, C-1″), 68.0 (C-1′), 73.5 (C-3′), 80.8 (O-*C*(CH_3)$_3$), 83.0 (C-2′), 127.7, 129.7, 133.2, 133.3, 135.5 (arom.), 156.7 (Boc-C=O) ppm; HRMS (EI): *m/z*: calcd for $C_{27}H_{38}NO_4Si$: 468.2570; found: 468.2568 $[M-C_2H]^+$; elemental analysis calcd (%) for $C_{29}H_{39}NO_4Si$ (493.72): C 70.55, H 7.96, N 2.84; found C 70.12, H 8.00, N 2.82.

(2S,5S,1′R)-*N-tert*-Butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)methyl-2-[1′-(trimethylsilyl)oxy]-prop-2′-ynyl-pyrrolidine (3): Alcohol **15** (4.00 g, 8.3 mmol) was dissolved in CH_2Cl_2 (50 mL), and the system was cooled to 0 °C. 1-Trimethylsilyl-imidazole (3.92 mL, 26.8 mmol, 3.2 equiv) and imidazole (68 mg, 1 mmol, 0.1 equiv) were added, and the mixture was stirred for 30 min. Sat. NH_4HCO_3 (100 mL) was added, the mixture was stirred for 10 min, and the layers were separated. The aqueous layer was extracted with MTBE (2×50 mL), and the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and concentrated. FCC (100 g, PE/MTBE 15:1→9:1) gave TMS ether **3** (4.57 g, 8.08 mmol, 97%) as a colourless gum. R_f = 0.28 (*n*-hexane/MTBE 15:1); $[\alpha]_D^{21}$ = −69.7 (*c* = 0.64 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 73:27 mixture of rotamers): δ = 0.11/0.13 (each s, 73:27, 9H; TMS), 1.04/1.05 (each s, 27:73, 9H; Si-*t*Bu), 1.29/1.47 (each s, 73:27, 9H; Boc), 1.95–2.35 (m, 4H; 3-, 4-H_2), 2.34/2.38 (each d, *J* = 2.2 Hz, 73:27, 1H; 3′-H), 3.50 (dd, *J* = 9.6, 7.2 Hz, 1H; 1″-H_2), 3.70 (dd, *J* = 9.6, 3.1 Hz, 1H; 1″-H_2), 3.81–3.95 (m, 2H; 2-H, 5-H), 4.84/5.08 (each t, *J* = 2.0 Hz, 27:73, 1H; 1′-H), 7.32–7.43 (m, 6H; arom.), 7.60–7.67 (m, 4H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = −0.3/−0.2 (TMS), 19.2 (Si-*C*(CH_3)$_3$), 24.4 (C-3), 26.8 (Si-C(CH_3)$_3$), 27.7 (C-4), 28.4/28.6 (O-C(CH_3)$_3$), 59.7/59.9 (C-2), 62.1 (C-1′), 63.1/63.3 (C-5), 63.8/64.2 (C-1′), 72.8/72.9 (C-3′), 79.4 (O-*C*(CH_3)$_3$), 83.9 (C-2′), 127.7, 129.6, 133.4/133.6, 135.5 (arom.), 153.3/153.8 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3310 (C≡C-H), 3072, 3051, 2960, 2932, 2859, 2130 (C≡C), 1693, 1474, 1428, 1392, 1367, 1334, 1253, 1176, 1114, 1043, 925, 883, 844, 742, 703, 615 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{32}H_{47}NO_4Si_2$ 565.3044; found: 565.3036 $[M]^+$; elemental analysis calcd (%) for $C_{32}H_{47}NO_4Si_2$ (565.90): C 67.92, H 8.37, N 2.48; found C 68.03, H 8.49, N 2.40.

(2′S,5′S,2″S,5″S,1R,4R) and (2′S,5′S,2″S,5″S,1R,4S)-1,4-Bis-[*N′-tert*-butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-1-(trimethylsilyl)oxy-2-butyn-4-ol (16 and 17): Alkyne **3** (11.1 g, 19.5 mmol) in THF (400 mL) was cooled to −80 °C, *n*BuLi (8.92 mL, 2.18 M in hexanes, 20.5 mmol, 1.05 equiv) was added dropwise, and the mixture was stirred for 30 min. HMPT (9.0 mL, 50 mmol, 2.5 equiv) was added, and the mixture was stirred for 15 min. Then a precooled solution (−80 °C) of aldehyde **4** (10.1 g, 21.5 mmol, 1.1 equiv) in THF (30+10 mL) was added by cannula over 15 min, and the system was stirred for 1 h. The mixture was warmed over 30 min to −70 °C, and sat. NH_4Cl and H_2O were added (200 mL each). The mixture was warmed to r.t. and the layers were separated. The aqueous layer was extracted with MTBE (2×150 mL), and the combined organic layers were washed with brine (2×100 mL), dried ($MgSO_4$) and concentrated. Triple FCC (300 g, and 2×1000 g, PE/MTBE 7:2→3:1→5:2) gave unconverted alkyne **3** (1.73 g, 3.06 mmol, 16%), followed by (4R)-alcohol **16** (10.9 g, 10.5 mmol, 54%), and (4S)-alcohol **17** (5.23 g, 5.06 mmol, 26%), each as colourless gums (95% yield based on conversion).

Compound 16: R_f = 0.21 (*n*-hexane/MTBE 3:1); $[\alpha]_D^{20}$ = −53.5 (*c* = 1.53 in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, 70:30 mixture of rotamers): δ = 0.09/0.11 (each s, 70:30, 9H; TMS), 1.04 (s, 18H; Si-*t*Bu), 1.28 (s, 35% of 9H; *N′*-Boc), 1.31 (s, 47% of 9H; *N″*-Boc), 1.46 (s, 18% of 9H; Boc), 1.70 (m, 1H; 4″-H_2), 1.90–2.05 (m, 3H; 4′-H_2, 4″-H_2), 2.05–2.25 (m, 3H; 3′-H_2, 3″-H_2), 2.25–2.35 (m, 1H; 3″-H_2), 3.47/3.52 (each m, 70:30, 1H; C*H*$_2$-OSi), 3.60 (m, 1H; C*H*$_2$-OSi), 3.64–3.73 (m, 2H; C*H*$_2$-OSi), 3.83 (m, 1H; 5′-H), 3.90–4.01 (m, 2H; 5″-H, 2′-H), 4.11 (m, 1H; 2″-H), 4.49 (d, *J* = 8.8 Hz, 1H; 4-H), 4.86, 5.08 (each s, 30:70, 1H; 1-H), 5.61/5.79 (each d, *J* = 8.8 Hz, 70:30, 1H; -OH), 7.34–7.40 (m, 12H; arom.), 7.60–7.65 (m, 8H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = −0.03/−0.02 (TMS), 19.0 (Si-*C*(CH_3)$_3$), 24.4 (C-4′), 26.4 (C-4″), 26.6 (Si-C(CH_3)$_3$), 27.4/27.5 (C-3′/C-3″), 28.1/28.5 (*N′*-C(O)O-C(CH_3)$_3$), 28.2 (*N″*-C(O)O-C(CH_3)$_3$), 59.5/59.7 (C-2′), 60.6 (C-5″), 62.1 (CH_2-OSi), 62.9 (C-5′), 63.8 (C-1), 64.0 (CH_2-OSi, C-2″), 67.8/67.9 (C-4), 79.1/79.2 (*N′*-C(O)O-*C*(CH_3)$_3$), 80.5 (*N″*-C(O)O-*C*(CH_3)$_3$), 83.6 (C-3), 85.1, 85.2 (C-2), 127.4, 127.5, 129.4, 129.5, 133.2, 133.3, 133.4, 135.5 (arom.), 153.1/153.3 (*N′*-C=O), 156.3 (*N″*-C=O) ppm; IR (film): $\tilde{\nu}$ = 3409 (-OH), 3072, 3051, 2960, 2930, 2859, 2248 (C≡C), 1694, 1590, 1473, 1428, 1392, 1334, 1253, 1174, 1114, 1036, 909, 883, 845, 824, 775, 739, 703, 614 cm^{-1}; elemental analysis calcd (%) for $C_{59}H_{84}N_2O_8Si_3$ (1033.56): C 68.56, H 8.19, N 2.71; found: C 68.49, H 8.39, N 2.74.

Compound 17: R_f = 0.13 (*n*-hexane/MTBE 3:1); ^{1}H NMR (300 MHz, $CDCl_3$, 73:27 mixture of rotamers): δ = 0.10/0.12 (each s, 73:27, 9H; TMS), 1.05 (s, 18H; Si-*t*Bu), 1.28/1.29/1.46 (each s, 33:47:20, 18H; Boc), 1.85–2.05, 2.05–2.25, 2.25–2.3 (each m, 8H; 3′-H$_2$, 3″-H$_2$, 4′-H$_2$, 4″-H$_2$), 3.37–3.60 (m, 2H; C*H*$_2$-OSi), 3.63–3.78 (m, 2H; C*H*$_2$-OSi), 3.83–4.10 (m, 4H; 2′-H, 5′-H, 2″-H, 5″-H), 4.17/4.35 (each d, *J* = 5.0 Hz, 73:27, 1H; -OH), 4.56 (m, 1H; 4-H), 4.87/5.10 (each s, 27:73, 1H; 1-H), 7.33–7.43 (m, 12H; arom.), 7.60–7.64 (m, 8H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = −0.2/−0.1 (TMS), 19.2 (Si-*C*(CH$_3$)$_3$), 26.7–26.9 (4×, C-3′, C-3″, C-4′, C-4″), 26.8 (Si-C(*C*H$_3$)$_3$), 28.2/28.6 (*N*′-C(O)O-C(*C*H$_3$)$_3$), 28.3 (*N*″-C(O)O-C(*C*H$_3$)$_3$), 59.6/59.7/60.1 (C-5′, C-5″), 62.3/64.1 (C-1), 62.8/63.6 (C-2′), 63.0 (C-2″), 63.7, 64.2 (*C*H$_2$-OSi), 66.1 (C-4), 79.3 (*N*″-C(O)O-*C*(CH$_3$)$_3$), 80.5/80.6 (*N*′-C(O)O-*C*(CH$_3$)$_3$), 84.6, 85.1 (C-2, C-3), 127.6, 127.7, 129.6, 133.2, 133.4, 133.6, 135.6 (arom.), 153.4/153.7 (*N*′-Boc-C=O), 156.4 (*N*″-Boc-C=O) ppm; HRMS (EI): *m*/*z*: calcd for $C_{54}H_{76}N_2O_6Si_3$: 932.5011; found: 932.5013 $[M-\text{Boc}+H]^+$.

(2′*S*,5′*S*,2″*S*,5″*S*,1*R*,4*R*)-1,4-Bis-[*N*′-*tert*-butoxycarbonyl-5′-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-2-butyne-1,4-diol (18): TMS ether **16** (5.17 g, 5.00 mmol) in THF/MeOH (3:1, 100 mL) was cooled to −10 °C, and CSA (23 mg, 0.10 mmol, 2.5 mol %) was added. After 15 min (TLC monitoring), the mixture was partitioned between EtOAc (100 mL) and brine/H_2O (50 mL each). The layers were separated, the aqueous layer was extracted with EtOAc (2×50 mL), and the combined organic layers were washed with brine (50 mL), dried with $MgSO_4$ and concentrated. FCC (120 g, cyclohexane/EtOAc 5:2→2:1) yielded diol **18** (4.54 g, 4.72 mmol, 94 %) as a colourless gum. R_f = 0.22 (*n*-hexane/MTBE 1:1); $[\alpha]_D^{20}$ = −38.7 (*c* = 1.12 in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 18H; Si-*t*Bu), 1.31, 1.47 (each s, 91:9, 18H; Boc), 1.77 (m, 2H; 3′-H$_2$), 1.96 (m, 2H; 4′-H$_2$), 2.18–2.35 (m, 4H; 3′-, 4′-H$_2$), 3.58 (dd, *J* = 9.7, 6.5 Hz, 2H; C*H*$_2$-OSi), 3.67 (dd, *J* = 9.7, 2.9 Hz, 2H; C*H*$_2$-OSi), 4.01 (m, 2H; 5′-H), 4.09 (d, *J* = 8.2 Hz, 2H; 2′-H), 4.58 (d, *J* = 8.2 Hz, 2H; 1-H), 5.48 (d, *J* = 8.2 Hz, 2H; -OH), 7.30–7.44 (m, 12H; arom.), 7.60–7.65 (m, 8H; arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (Si-*C*(CH$_3$)$_3$), 26.6 (Si-C(*C*H$_3$)$_3$), 26.6/26.9 (C-4′, C-4″), 27.4 (C-3′, C-3″), 28.3 (O-C(*C*H$_3$)$_3$), 60.7 (C-5′, C-5″), 63.6 (C-2′, C-2″), 64.1 (*C*H$_2$-OSi), 67.5 (C-1), 80.7 (O-*C*(CH$_3$)$_3$), 84.4 (C-2), 127.7, 129.7, 133.3, 133.5, 135.5 (arom.), 156.5 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3400 (-OH), 3071, 2960, 2931, 2858, 1691, 1668, 1473, 1428, 1403, 1395, 1367, 1256, 1172, 1112, 855, 823, 774, 740, 702, 614 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{51}H_{68}N_2O_6Si_2$: 860.4616; found: 860.4600 $[M-\text{Boc}+H]^+$; elemental analysis calcd (%) for $C_{59}H_{84}N_2O_8Si_3$ (961.382): C 69.96, H 7.97, N 2.91; found: C 70.02, H 8.03, N 2.95.

(2′*S*,5′*S*,2″*S*,5″*S*,1*R*,4*R*)-1,4-Bis-[*N*′-*tert*-butoxycarbonyl-5′-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-butane-1,4-diol (19): Alkyne **18** (4.52 g, 4.70 mmol) was dissolved in MeOH (100 mL), and Pt/C (5 wt %, 100 mg) was added. The flask was filled with H_2, and the mixture was hydrogenated for 16 h (1 atm). The flask was purged with Ar, and the mixture was diluted with EtOAc (50 mL) to redissolve the precipitate, filtered over a pad of Celite and concentrated. FCC (80 g, PE/EtOAc 2:1→1:1) gave diol **19** (4.19 g, 4.34 mmol, 92 %) as a colourless resin, which crystallized from MeOH at −25 °C. R_f = 0.14 (*n*-hexane/EtOAc 3:2), R_f (alkene) = 0.54; m.p. 128.5–129 °C (MeOH); $[\alpha]_D^{20}$ = −40.2 (*c* = 0.560 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.04 (s, 18H; Si-*t*Bu), 1.28/1.45 (each s, 86:14, 18H; Boc), 1.46 (m, 2H; 2-H$_2$), 1.51 (s, 2H; 2-H$_2$), 1.70 (m, 2H; 4′-H$_2$), 1.87–2.20 (m, 6H; 3′-H$_2$, 4′-H$_2$), 3.53 (m, 2H; C*H*$_2$-OSi), 3.68 (m, 2H; C*H*$_2$-OSi), 3.82 (brs, 2H; 1-H), 3.90–4.05 (m, 4H; 2′-H, 5′-H), 4.41/4.62 (each s, 2H; -OH), 7.32–7.44 (m, 12H; arom.), 7.60–7.66 (m, 8H; arom) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.2 (Si-*C*(CH$_3$)$_3$), 25.9 (C-4′), 27.1 (C-3′), 28.3/28.6 (86:14, O-C(*C*H$_3$)$_3$), 30.0 (C-2), 59.5/60.2 (14:86, C-2′), 63.7/63.8 (approx. 10:1, C-5′), 64.1 (*C*H$_2$-OSi), 73.2/74.4 (15:85, C-1), 80.0/80.2 (86:14, O-*C*(CH$_3$)$_3$), 127.7, 129.7, 133.3, 133.5, 135.5 (arom.), 153.8/155.6 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3400 (-OH), 1691, 1668, 1403, 1395, 1112 cm^{-1}; HRMS (FAB): calcd for $C_{56}H_{80}N_2O_8Si_2$: 964.5553; found: 964.5537 $[M]^+$; elemental analysis calcd (%) for $C_{56}H_{80}N_2O_8Si_2$ (965.414): C 69.67, H 8.35, N 2.90; found C 69.31, H 8.20, N 2.92.

(2′*S*,5′*S*,2″*S*,5″*S*,4*R*,7*R*)-4,7-Bis-[*N*′-*tert*-butoxycarbonyl-5′-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-(2-oxo-1,3-dioxa)-thiepane (20): Diol **19** (4.1 g, 4.25 mmol) in CH_2Cl_2 (250 mL) was cooled to −20 °C, and NEt_3 (2.4 mL, 17 mmol, 4 equiv) was added. $SOCl_2$ (340 µL, 4.68 mmol, 1.1 equiv) was added dropwise. After 20 min, sat. $NaHCO_3$ solution (100 mL) was added, and the mixture was stirred for 1 h. The layers were separated, and the aqueous layer was extracted with Et_2O (3×100 mL). The combined organic layers were washed with phosphate buffer (0.5 M, pH 2, 2×100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated. Filtration over silica gel (10 g, Et_2O) gave cyclic sulfite **20** (4.26 g, 4.21 mmol, 99 %) as a colourless gum. R_f = 0.30 (*n*-hexane/MTBE 2:1); $[\alpha]_D^{20}$ = −23.0 (*c* = 1.29 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 18H; Si-*t*Bu), 1.30, 1.33, 1.47, 1.49 (each s, 45:40:8:7, 18H; Boc), 1.62–1.70 (m, 2H; 5-H$_2$), 1.85–2.30 (m, 10H; 5-H$_2$, 3′-H$_2$, 4′-H$_2$), 3.50–3.60 (m, 2H; C*H*$_2$-OSi), 3.65–3.71 (m, 2H; C*H*$_2$-OSi), 3.74/3.85 (each m, 1:1, 2H; 2′-H), 3.88–4.02 (m, 2H; 5′-H), 4.60/4.94 (each d, 1:5, *J* = 10.1 Hz, 1:5, 1H; 4-H), 5.20/5.59 (each m, 1:5, 1H; 4-H), 7.34–7.43 (m, 12H; arom.), 7.60–7.65 (m, 8H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (Si-*C*(CH$_3$)$_3$); 23.8/23.9 (C-4′), 26.8 (Si-C(*C*H$_3$)$_3$), 27.5 (C-3′), 28.2/28.3/28.5 (O-C(*C*H$_3$)$_3$), 30.7 (C-5), 58.8/59.3 (C-5′), 61.2/61.6 (C-2′), 64.5 (*C*H$_2$-OSi), 73.2/74.2 (0.55:0.45, C-4), 79.7 (O-*C*(CH$_3$)$_3$), 127.7, 129.7, 133.5, 135.5, 154.2 (Boc-C=O); MS (ESI): *m*/*z*: calcd for $C_{56}H_{78}N_2O_9Si_2S$: 1033.5; found: 1033.5 $[M+Na]^+$.

(2′*S*,5′*S*,2″*S*,5″*S*,4*R*,7*R*)-4,7-Bis-[*N*′-*tert*-butoxycarbonyl-5′-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-(2,2-dioxo-1,3-dioxa)-thiepane (21): Cyclic sulfite **20** (4.26 g, 4.21 mmol) was dissolved in CCl_4/CH_3CN (1:1, 140 mL), H_2O (50 mL) was added, and the well stirred emulsion was cooled to 0 °C. $NaIO_4$ (3.6 g, 17 mmol, 4 equiv) and $RuCl_3 \cdot H_2O$ (15 mg) were added, and the mixture was stirred for 30 min. After dilution with Et_2O (400 mL), the layers were separated, and the organic layer was washed with H_2O (100 mL) and brine (3×75 mL), dried ($MgSO_4$) and concentrated at RT. Filtration over silica gel (10 g, Et_2O) provided cyclic sulfate **21** (4.20 g, 4.09 mmol, 96 %) as a colourless gum. R_f = 0.38 (*n*-hexane/MTBE 1:1); $[\alpha]_D^{20}$ = −63.5 (c = 1.30 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 18H; Si-*t*Bu), 1.32/1.49 (each s, 88:12, 18H; Boc), 1.60–1.71 (m, 2H; 5-H$_2$), 1.72–1.87 (m, 2H; 5-H$_2$), 1.88–2.05 (m, 4H; 3′-H$_2$, 4′-H$_2$), 2.05–2.28 (m, 4H; 3′-H$_2$, 4′-H$_2$), 3.60 (dd, *J* = 9.8, 6.0 Hz, 2H; C*H*$_2$-OSi), 3.66 (dd, *J* = 9.8 and 2.9 Hz, 2H; C*H*$_2$-OSi), 3.89 (d, *J* = 8.1 Hz, 2H; 2′-H), 3.95 (m, 2H; 5′-H), 5.40 (d, *J* = 8.9 Hz, 2H; 4-H), 7.33–7.44 (m, 12H; arom.), 7.59–7.65 (m, 8H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (Si-*C*(CH$_3$)$_3$), 26.8 (Si-C(*C*H$_3$)$_3$), 26.9 (C-4′), 27.6 (C-3′), 28.3/28.4 (O-C(*C*H$_3$)$_3$), 29.4 (C-5), 58.8 (C-5′), 61.0 (C-2′), 64.5 (*C*H$_2$-OSi), 80.1 (O-*C*(CH$_3$)$_3$), 82.9 (C-4/C-7), 127.7, 129.6, 133.3, 135.5 (arom.), 154.0 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3071, 2958, 2928, 2856, 1690, 1472, 1428, 1392, 1366, 1257, 1199, 1174, 1112, 896, 856, 823, 741, 702, 611 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{56}H_{79}N_2O_{10}Si_2S$: 1027.499; found: 1027.490 $[M+H]^+$.

(2′*S*,5′*S*,2″*S*,5″*S*,1*R*,4*S*)-1,4-Bis-[*N*′-*tert*-butoxycarbonyl-5′-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-4-azido-butan-1-ol (22): Cyclic sulfate **21** (4.10 g, 4.00 mmol) was dissolved in DMF/HMPT (1:1, 20 mL), LiN_3 (1.6 g, 32 mmol, 8 equiv) was added, and the solution was stirred for 40 h at r.t. DMF was removed in vacuo, and the residue was partitioned between $CHCl_3$ (250 mL) and brine/H_2O (1:1, 200 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (4×50 mL). The extracts were concentrated and coevaporated with toluene (80 mL). The crude sulfate (R_f = 0.23 in $CDCl_3$/MeOH 10:1) was dissolved in THF (80 mL), H_2O (700 µL) was added, and the pH was adjusted to 2 with conc. H_2SO_4 (ca. 300 µL). After complete cleavage of the sulfate (12 h, TLC monitoring), the mixture was partitioned between Et_2O and sat. $NaHCO_3$ solution (100 mL each). The layers were separated, and the aqueous layer was extracted with Et_2O (3×75 mL). The combined organic extracts were washed with brine (2×50 mL), dried ($MgSO_4$) and concentrated. FCC (80 g, PE/EtOAc 3:1) gave azide **22** (2.89 g, 2.91 mmol, 73 %) as a colourless gum. R_f = 0.36 (*n*-hexane/EtOAc 5:2); $[\alpha]_D^{20}$ = −32.9 (*c* = 0.917 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.04 (s, 18H; Si-*t*Bu), 1.27/1.28/1.46 (each s, 52:30:18, 18H; Boc), 1.25–1.35 (m, 2H; 3-H$_2$), 1.50–1.60 (m, 2H; 2-H$_2$), 1.66 (m, 1H; 4-H), 1.81 (m, 2H), 1.92 (m, 1H), 1.97 (m, 1H; 4′-H$_2$, 4″-H$_2$), 2.03 (m, 3H; 3′-H$_2$, 3″-H$_2$), 2.22 (m, 1H; 3′-H$_2$), 3.46–3.60 (m, 2H; C*H*$_2$-OSi), 3.63–3.75 (m, 2H; C*H*$_2$-OSi), 3.68 (d, *J* = 8 Hz, 1H; -OH), 3.90 (m, 1H; 2″-H), 3.96 (m, 1H; 2′-H), 4.03 (m, 1H; 1-H), 4.08 (m, 2H; 5′-H, 5″-H), 7.36–7.41 (m, 12H;

arom.), 7.61–7.64 (m, 8H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (Si-*C*(CH_3)$_3$), 24.5 (C-4′), 27.1 (C-3′), 27.2 (Si-C(CH_3)$_3$), 27.4, 28.6 (O-C(CH_3)$_3$), 30.1 (C-2), 59.9/60.8 (C-2′), 60.4 (C-4), 63.3, 63.8 (C-5′), 64.3 (CH_2-OSi), 75.8 (C-1), 80.0, 80.2 (O-*C*(CH_3)$_3$), 128.1, 128.2, 130.0, 130.1, 133.3, 133.5, 135.9, 136.0, 153.8/155.6 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3441 (O−H), 3400 (O−H), 3071, 3050, 2960, 2930, 2858, 2096 (-N_3), 1692, 1676, 1473, 1428, 1392, 1367, 1255, 1174, 1112, 909, 857, 822, 738, 702, 614 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{56}H_{79}N_5O_7Si_2$: 990.560; found: 990.544 [*M*+H]$^+$; elemental analysis calcd (%) for $C_{56}H_{78}N_5O_7Si_2$ (989.442): C 67.98, H 7.95, N 7.08; found C 67.72, H 8.28, N 6.86.

(2*S*,5*S*,2′*S*,5′*S*,2″*S*,5″*S*)-*N*,*N*″-Di-*tert*-butoxycarbonyl-2,5″-bis-[(*tert*-butyldiphenylsilyloxy)methyl]-dodecahydro-terpyrrole (23): Azide **22** (1.95 g, 1.98 mmol) in CH_2Cl_2 (40 mL) was cooled to −25 °C, and NEt_3 (2.3 mL, 16 mmol, 8 equiv) and MsCl (0.63 mL, 8.0 mmol, 4 equiv) were added. The solution was allowed to warm to 0 °C over 2 h, sat. NH_4HCO_3 solution and brine (20 mL each) were then added, and the layers were separated. The organic layer was extracted with Et_2O (3×30 mL), and the combined extracts were washed with citric acid (5%, 2×30 mL) and brine (50 mL), dried ($MgSO_4$), concentrated at 10 °C and dried in vacuo. R_f (mesylate) = 0.52 (*n*-hexane/EtOAc 2:1). The crude mesylate (2.05 g, 1.92 mmol) was dissolved in MeOH/THF (3:2, 100 mL). Pd/C (10 wt%, 200 mg) was added, and the flask was filled with H_2 (1 atm). After complete cleavage of the azide (6 h, TLC monitoring) the flask was purged with Ar, and the mixture was filtered over a pad of silica gel (5 g, MeOH). $NaHCO_3$ (0.35 g, 4.0 mmol, 2 equiv) was added, and the mixture was stirred for 72 h at RT, after which it was concentrated. The residue was partitioned between Et_2O and $NaHCO_3$ (100 mL each). The aqueous layer was extracted with Et_2O (50 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. Triple FCC (2×50 g and 30 g, CH_2Cl_2/MeOH 93:7→90:10) gave terpyrrolidine **23** (1.02 g, 1.08 mmol, 54%) as an off-white resin. R_f = 0.18 (CH_2Cl_2/MeOH 100:8); $[\alpha]_D^{20}$ = −32.9 (*c* = 0.917 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$/TFA 99:1): δ = 1.04 (s, 18H; Si-*t*Bu), 1.28 (s, 18H; Boc), 1.71–1.85 (m, 4H; 4-H_2, 3″-H_2), 2.01–2.22 (m, 8H; 3-H_2, 3′-H_2, 4′-H_2, 4″-H_2), 3.51–3.56 (m, 2H; C*H*$_2$-OSi), 3.71–3.75 (m, 2H; C*H*$_2$-OSi), 3.89–4.01 (m, 2H; 2-H, 5″-H), 4.08–4.24 (m, 4H; 5-H, 2′-H, 5′-H, 2″-H), 7.33–7.45 (m, 12H; arom.), 7.59–7.67 (m, 8H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$/TFA 99:1): δ = 19.1 (Si-*C*(CH_3)$_3$), 26.8 (Si-C(CH_3)$_3$), 25.8, 26.7, 28.0 (C-3, C-3′, C-3″, C-4, C-4′, C-4″), 28.1 (O-C(CH_3)$_3$), 58.7 (C-2′, C-5′), 59.3 (C-2, C-5″), 63.3, 63.4, 63.4 (C-5, C-2″, CH_2-OSi), 81.3 (O-*C*(CH_3)$_3$), 127.7, 129.7, 133.1, 133.2, 135.4, 135.5 (arom.), 156.0 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3353, 3072, 3050, 2959, 2929, 2857, 1691, 1472, 1462, 1428, 1391, 1366, 1334, 1256, 1175, 1112, 940, 858, 823, 774, 740, 702, 614 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{56}H_{80}N_3O_6Si_2$: 946.559; found: 946.555 [*M*+H]$^+$; elemental analysis calcd (%) for $C_{112}H_{164}N_6O_{15}Si_4$ (1946.874, (**23**)$_2$·3 H_2O): C 69.10, H 8.49, N 4.32; found: C 68.92, H 8.48, N 4.25.

(2*S*,5*S*,2′*S*,5′*S*,2″*S*,5″*S*)-*N*,*N*′,*N*″-Tri-*tert*-butoxycarbonyl-2,5″-bis-[(*tert*-butyldiphenylsilyloxy)methyl]-dodecahydro-terpyrrole (24): Terpyrrolidine **23** (381 mg, 402 µmol) was dissolved in DMF (4 mL), NEt_3 (0.16 mL, 1.2 mmol, 3 equiv) and Boc_2O (132 mg, 600 µmol, 1.5 equiv) were added, and the solution was stirred for 24 h at RT. The mixture was diluted with Et_2O (75 mL), washed with sat. $NaHCO_3$, $NaHSO_4$ (1 M), H_2O and brine (15 mL each), dried ($MgSO_4$) and concentrated. FCC (20 g, PE/MTBE 4:1) and recrystallisation from *n*-hexane gave tri-Boc terpyrrole **24** (241 mg, 230 µmol, 57%) as a colourless powder. Crystals suitable for X-ray crystallography were grown from a saturated *n*-hexane solution over 12 weeks. R_f = 0.30 (*n*-hexane/MTBE 3:1); m.p. 175.5–176 °C (*n*-hexane); $[\alpha]_D^{25}$ = −25.9 (*c* = 0.830 in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 18H; Si-*t*Bu), 1.44–1.48 (m, 27H; Boc), 1.85–2.22 (m, 12H; 3-H_2, 3′-H_2, 3″-H_2, 4-H_2, 4′-H_2, 4″-H_2), 3.35–3.85 (m, 4H; C*H*$_2$-OSi), 3.86–4.00 (m, 2H; 2-H, 5″-H), 4.01–4.10, 4.11–4.18 (2×m, 2H; 5-H, 2″-H), 4.20–4.32, 4.38–4.48 (2×m, 2H; 2′-H, 5′-H), 7.33–7.40 (m, 12H; arom.), 7.61–7.64 (m, 8H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (Si-*C*(CH_3)$_3$), 26.9 (Si-C(CH_3)$_3$), 25.2, 26.8, 27.5, 28.1, 28.2, 28.3, 28.5, 28.6 (C-3, C-3′, C-3″, C-4, C-4′, C-4″), 28.6/28.6 (O-C(CH_3)$_3$), 59.5, 60.1, 60.5, 61.0 (C-2, C-2′, C-5′, C-5″), 63.5, 63.6, 63.8 (C-5, C-2″, CH_2-OSi), 79.0, 79.2, 79.4 (O-*C*(CH_3)$_3$), 127.6, 127.7, 129.4, 129.5, 129.6, 129.7, 133.7, 135.5, 135.6 (arom.), 153.7, 153.8, 153.9 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3072, 3051, 2963, 2932, 2887, 2859, 1690, 1474, 1456, 1428, 1393, 1366, 1347, 1175, 1113, 1056, 740, 703, 614 cm^{-1}; HRMS (FAB): *m/z*: calcd for $C_{61}H_{88}N_3O_8Si_2$: 1046.6110; found: 1046.6118 [*M*+H]$^+$; elemental analysis calcd (%) for $C_{61}H_{87}N_3O_8Si_2$ (1046.55): C 70.00, H 8.37, N 4.02; found C 69.90, H 8.28, N 4.05.

General procedure for Boc group cleavage with TMSOTf (GP1): A solution of the compound in CH_2Cl_2 (10 mM) with thioanisole (12 equiv per Boc group) and 2,6-lutidine (6 equiv per Boc group) was cooled to −78 °C, and TMSOTf (3 equiv per Boc group) was added dropwise. After 10 min the cooling bath was removed, and the mixture was allowed to warm to RT (1–2 h). Phosphate buffer (1 M) was added ($^1/_2$ *v*/*v*), and the mixture was stirred for 10 min and partitioned between CH_2Cl_2 (2:1 *v*/*v*) and brine ($^1/_2$ *v*/*v*). The layers were separated, the organic layer was extracted with CH_2Cl_2 (3 ×, 1:1 *v*/*v*), and the combined extracts were washed with brine ($^1/_4$ *v*/*v*), dried (Na_2SO_4) and concentrated to give the crude amine.

(2*S*,5*S*,2′*S*,5′*S*,2″*S*,5″*S*)-2,5″-Bis-[(*tert*-butyldiphenylsilyloxy)methyl]-dodecahydro-terpyrrole (31): Tri-Boc-terpyrrolidine **24** (126 mg, 120 µmol) was deprotected as described in GP1. FCC (10 g, $CHCl_3$/MeOH/HCOOH 100:6:5→100:10:5) provided triamine **31** (88.1 mg, 118 µmol, 98%) as a colourless resin. R_f = 0.15 ($CHCl_3$/MeOH/HCOOH 100:10:5); $[\alpha]_D$ = −9.3 (*c* = 0.518 in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 18H; Si-*t*Bu), 1.39–1.65, 1.80–2.03 (2×m, 12H; 3-H_2, 3′-H_2, 3″-H_2, 4-H_2, 4′-H_2, 4″-H_2), 3.23–3.45 (m, 6H; 2-H, 2′-H, 2″-H, 5-H, 5′-H, 5″-H), 3.57–3.61 (m, 4H; C*H*$_2$-OSi), 7.34–7.43 (m, 12H; arom.), 7.65–7.68 (m, 8H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (Si-*C*(CH_3)$_3$), 26.9 (Si-C(CH_3)$_3$), 28.0, 29.1, 29.2 (C-3/C-4″, C-3′/C-4′, C-3″/C-4), 59.6 (C-2′, C-5′), 60.6 (C-2, C-5″), 62.8 (C-5, C-2″), 65.4 (CH_2-OSi), 127.7, 129.7, 133.3, 135.6 (arom.) ppm; IR (film): $\tilde{\nu}$ = 3414, 3269, 3048, 2958, 2931, 2893, 2858, 1472, 1428, 1112, 999, 824, 740, 703, 614 cm^{-1}; HRMS (FAB): *m/z*: calcd for $C_{46}H_{62}N_3O_2Si_2$: 746.4381; found: 744.4389 [*M*−H]$^+$.

(2*S*,5*S*,2′*S*,5′*S*,2″*S*,5″*S*)-2,5″-Bis-(hydroxymethyl)-dodecahydro-terpyrrol (5): Terpyrrolidine **31** (60.0 mg, 80.4 µmol) was dissolved in MeOH (6 mL, polypropylene flask), conc. HF (0.6 mL) was added (**Caution!**), and the solution was stirred for 24 h at RT. The volatiles were removed in vacuo, and the residue was redissolved in MeOH (5 mL), and the solution was adjusted to pH > 12 with NaOH (2 M). Silica gel (500 mg) was added, and the volatiles were removed in vacuo. FCC of the immobilised material (5 g, CH_2Cl_2/MeOH/aq. NH_3 60:30:5→60:30:8) provided the triaminodiol **1**, which was re-dissolved in $CHCl_3$ and filtered over Celite to yield a colourless oil (19.8 mg, 73.5 µmol, 91%). R_f = 0.27 (CH_2Cl_2/MeOH/aq. NH_3 5:5:1); $[\alpha]_D^{24}$ = 1.3 (*c* = 0.47 in MeOH); ^1H NMR (300 MHz, [D$_4$]MeOH/NaOD 99:1): δ = 1.38–1.52, 1.86–1.99 (2 m, 12H; 3-H_2, 3′-H_2, 3″-H_2, 4-H_2, 4′-H_2, 4″-H_2), 2.96–3.02 (m, 4H; 2′-H, 2″-H, 5-H, 5′-H), 3.24 (dt, *J* = 12.4, 6.0 Hz, 2H; 2-H, 5″-H), 3.42–3.51 (m, 4H; C*H*$_2$-OH) ppm; ^{13}C NMR (75 MHz, [D$_4$]MeOH/NaOD 99:1): δ = 28.8 (C-3/C-4″), 30.2, 30.3 (C-3′/C-4′, C-3″/C-4), 60.6 (C-2, C-5″), 63.4, 63.8 (C-5/C-2″, C-2′/C-5′), 65.5 (CH_2-OH) ppm; HRMS (FAB): *m/z*: calcd for $C_{14}H_{28}N_3O_2$: 270.2181; found: 270.2179 [*M*+H]$^+$.

(2*S*,5*S*,2′*S*,5′*S*,2″*S*,5″*S*)-*N*,*N*″-Di-*tert*-butoxycarbonyl-*N*′-(4‴-nitrophenyl)-sulfonyl-2,5″-bis-[hydroxymethyl]-dodecahydro-terpyrrole (32): Terpyrrolidine **23** (405 mg, 427 µmol) in CH_2Cl_2 (6 mL) was cooled to 0 °C, and NEt_3 (178 µL), *p*NsCl (142 mg, 640 µmol, 1.5 equiv) and DMAP (50 mg, 0.45 mmol, 1.1 equiv) were added. The cooling bath was removed, and the mixture was stirred for 18 h at RT. The solution was diluted with Et_2O (50 mL), washed with $NaHSO_4$ (1 M) and brine (10 mL each), dried ($MgSO_4$) and concentrated. FCC (20 g, PE/EtOAc 5:1→4:1) gave the sulfonamide (421 mg, 312 µmol, 87%) as a yellow foam (R_f = 0.19 in *n*-hexane/EtOAc 5:1). The sulfonamide (304 mg, 269 µmol) was dissolved in THF (5 mL), and TBAF (1.0 M in THF, 0.54 mL, 540 µmol, 2 equiv) was added. After 2 h the mixture was partitioned between EtOAc (50 mL) and NH_4Cl (25 mL), and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic extracts were washed with $NaHSO_4$ (1 M) and brine (10 mL each), dried (Na_2SO_4) and concentrated. FCC (4 g, EtOAc/PE 1:1→5:1) provided diol **98** (146 mg, 225 µmol, 84%) as a colourless solid. R_f = 0.32 (EtOAc/*n*-hexane 5:1); m.p. 156–163 °C; $[\alpha]_D$ = −2.6 (*c* = 1.325 in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45/1.52 (each s, 18H; Boc), 1.23–1.99 (m, 12H; 3-H_2, 3′-H_2, 4′-H_2, 4″-H_2, 4-H_2, 3″-H_2), 3.47–3.61 (m, 2H; C*H*$_2$-OH), 3.61–3.74 (m, 2H; C*H*$_2$-OH), 3.83–4.02 (m, 2H; 2-H, 5″-H), 4.02–4.08, 4.40–4.57, 4.62–4.83 (3×m, 4H; 5-H, 2′-H, 5′-H, 2″-H), 8.01–8.22, 8.32–8.36 (2×m, 4H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 24.6, 25.5, 25.9, 26.9, 27.4 (C-3, C-3′, C-3″, C-4, C-4′, C-4″), 28.5 (O-C(CH_3)$_3$), 59.1, 59.7, 60.4, 60.8, 61.6, 62.0, 62.9, 63.3 (C-2, C-5, C-5″, C-2″, C-2′, C-5′), 63.9, 66.2 (CH_2-OH), 80.2/81.3 (O-*C*(CH_3)$_3$), 124.4, 128.0, 128.2 (arom.), 146.6/146.7 (SO_2-C_{Ar}), 149.5 (NO_2-C_{arom}), 154.0, 155.3/155.4 (Boc-C=O) ppm; IR (KBr): $\tilde{\nu}$ = 3432, 2975, 1691, 1646, 1604, 1532, 1477, 1456, 1395, 1369, 1349, 1308, 1288, 1254, 1168, 1123, 1096, 1056, 1028, 1009, 993, 736, 690, 625 cm^{-1}; HRMS (FAB): *m/z*: calcd for $C_{30}H_{46}N_4O_{10}SNa$: 677.2832; found: 677.2837 [*M*+Na]$^+$.

(2*S*,5*S*,2′*S*,5′*S*,2″*S*,5″*S*)-*N*′-(4‴-Nitrophenyl)sulfonyl-2,5″-bis-(hydroxymethyl)-dodecahydro-terpyrrole (33): Di-Boc-terpyrrolidine **32** (110 mg, 169 µmol) was dissolved in CH_2Cl_2 (2 mL), TFA (2 mL) was added, and the mixture was stirred for 1 h. The volatiles were removed in vacuo, and the residue was coevaporated with toluene/EtOH (2:1, 10 mL). FCC (10 g, $CHCl_3$/MeOH/aq. NH_3 80:10:1→50:10:1→30:10:1) gave diamine **33** (70.2 mg, 156 µmol, 92 %) as a yellow gum. R_f = 0.12 ($CHCl_3$/MeOH/aq. NH_3 50:10:1); $[\alpha]_D^{24}$ = 11.1 (*c* = 0.88 in CH_2Cl_2); ^{1}H NMR (300 MHz, [D$_4$]MeOH/NaOD 99:1): δ = 1.23–1.56, 1.72–1.98 (2×m, 12 H; 3-H_2, 3′-H_2, 3″-H_2, 4-H_2, 4′-H_2,4″-H_2), 3.34–3.40 (m, 4 H; 2″-H, 5-H), 3.44–3.54 (m, 6 H; 2-H, 5″-H, C*H*$_2$-OH), 3.82 (dt, *J* = 6.4, 8.3 Hz, 2 H; 2′-H, 5′-H), 8.22 (d, *J* = 9.0 Hz, 2 H; arom.), 8.43 (d, *J* = 9.0 Hz, 2 H; arom.) ppm; ^{13}C NMR (75 MHz, [D$_4$]MeOH/NaOD 99:1): δ = 28.2, 28.4, 29.8 (C-3′/C-4′, C-3″/C-4, C-3/C-4″), 60.0, 60.1 (C-2/C-5″, C-5/C-2″), 65.9 (*C*H_2-OH), 68.1 (C-2′/C-5′), 125.8, 130.1, 148.8, 151.6 (arom.) ppm; IR (film): $\tilde{\nu}$ = 3333, 2956, 2924, 2872, 1528, 1350, 1309, 1161, 1044, 736, 621 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{20}H_{31}N_4O_6S$: 455.1964, 455.1962 [*M*+H]$^+$.

(2′*S*,5′*S*,2″*S*,5″*S*,1*R*,4*S*)-1,4-Bis-[*N*′-*tert*-butoxycarbonyl-5′-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-1-(trimethylsilyl)oxy-4-acetoxy-2-butyne (25): Alcohol **17** (4.41 g, 4.56 mmol) in CH_2Cl_2 (70 mL) was cooled to 0 °C, NEt_3 (2.5 mL, 18 mmol, 4 equiv), Ac_2O (0.86 mL, 9.1 mmol, 2 equiv) and DMAP (11 mg, 0.09 mmol, 2 mol %) were added, and the mixture was stirred for 1 h at 0 °C and for 1 h at RT. The mixture was diluted with Et_2O and sat. NH_4HCO_3 (100 mL each) and stirred for 15 min, and the layers were separated. The aqueous layer was extracted with Et_2O (2×50 mL), and the combined organic layers were washed with brine (2×30 mL), dried (Na_2SO_4) and concentrated. Double FCC (100 g and 20 g, PE/MTBE 4:1) provided ester **25** (4.67 g, 4.34 mmol, 95 %) as a colourless foam. R_f = 0.30 (*n*-hexane/MTBE 4:1); $[\alpha]_D^{25}$ = −64.5 (*c* = 1.014 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07–0.10 (m, 9 H; TMS), 1.03 (s, 18 H; Si-*t*Bu), 1.27/1.48 (each s, 18 H; Boc), 2.02/2.05 (each s, 3 H; Ac), 1.78–2.28, 2.33–2.50 (2 m, 8 H; 3′-H_2, 3″-H_2, 4′-H_2, 4″-H_2), 3.43–3.74 (m, 3 H; C*H*$_2$-OSi), 3.78–4.07 (m, 5 H; C*H*$_2$-OSi, 2′-H, 5′-H, 2″-H, 5″-H), 5.07 (m, 1 H; 1-H), 5.97–6.08 (m, 1 H; 4-H), 7.33–7.45 (m, 12 H; arom.), 7.59–7.64 (m, 8 H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = −0.2/−0.1 (TMS), 19.2 (Si-*C*(CH_3)$_3$), 20.9 (Ac), 24.9, 26.4, 26.9, 27.7 (C-3′, C-3″, C-4′, C-4″), 26.8 (Si-C(*C*H_3)$_3$), 28.3, 28.4 (2×), 28.6 (O-C(*C*H_3)$_3$), 59.6, 59.7 (C-5′, C-5″), 62.2, 62.4 (C-1, C-4), 62.9, 63.3 (C-2′, C-2″), 64.0, 64.2 (*C*H_2-OSi), 79.4, 79.7, 80.3, 80.6 (O-*C*(CH_3)$_3$), 86.0, 86.4 (C-2, C-3), 127.6, 127.7, 129.6, 129.7, 133.4, 135.5 (arom.), 153.0, 153.7 (Boc-C=O), 169.5 (Ac-C=O) ppm; IR (film): $\tilde{\nu}$ = 3072, 3051, 2960, 2932, 2859, 1750, 1695, 1474, 1462, 1428, 1392, 1367, 1335, 1253, 1230, 1174, 1113, 1036, 927, 882, 845, 823, 740, 703, 613 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{61}H_{87}N_2O_9Si_3$: 1075.572; found: 1075.592 [*M*+H]$^+$; elemental analysis calcd for $C_{61}H_{86}N_2O_9Si_3$ (1075.600): C 68.12, H 8.06, N 2.60; found: C 68.17, H 8.10, N 2.66.

(2′*S*,5′*S*,2″*S*,5″*S*,1*R*,4*S*)-1,4-Bis-[*N*′-*tert*-butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-4-acetoxy-2-butyn-1-ol (26): TMS-ether **25** (4.39 g, 4.08 mmol) was deprotected by the procedure given for compound **16**. FCC (100 g, PE/MTBE 2:1) provided alcohol **26** (4.08 g, 4.07 mmol, 100 %) as a colourless foam. R_f = 0.20 (*n*-hexane/MTBE 2:1); $[\alpha]_D^{24}$ = −54.1 (*c* = 0.194 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 18 H; Si-*t*Bu), 1.28/1.48 (each s, 18 H; Boc), 2.03/2.06 (each s, 3 H; Ac), 1.65–1.71, 1.88–2.17, 2.21–2.48 (3×m, 8 H; 3′-H_2, 3″-H_2, 4′-H_2, 4″-H_2), 3.49–3.66 (m, 4 H; C*H*$_2$-OSi), 3.86–4.08 (m, 3 H; 5′-H, 2″-H, 5″-H), 4.10–4.21 (m, 1 H; 2′-H), 4.49 (dd, *J* = 8.5, 1.5 Hz, 1 H; 1-H), 5.95–6.03 (m, 1 H; 4-H), 7.33–7.45 (m, 12 H; arom.), 7.59–7.64 (m, 8 H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (Si-*C*(CH_3)$_3$), 20.9 (Ac), 26.5, 26.9, 27.0, 27.6 (C-3′, C-3″, C-4′, C-4″), 26.8 (Si-C(*C*H_3)$_3$), 28.2, 28.3, 28.4 (O-C(*C*H_3)$_3$), 59.3, 59.5, 59.6, 59.7, 60.8 (C-5′, C-5″), 63.1 (C-4), 63.6, 63.7 (C-2′, C-2″), 63.9, 64.1 (*C*H_2-OSi), 68.4 (C-1), 79.4, 79.8, 80.0, 80.6, 81.0 (O-*C*(CH_3)$_3$), 127.6, 127.7, 129.6, 133.1, 133.3, 133.6, 135.5 (arom.), 153.1, 153.7, 156.9 (Boc-C=O), 169.2 (Ac-C=O) ppm; IR (film): $\tilde{\nu}$ = 3423, 3072, 3052, 2961, 2932, 2859, 1749, 1694, 1668, 1473, 1428, 1393, 1368, 1231, 1172, 1112, 1023, 849, 823, 740, 703, 614 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{58}H_{79}N_2O_9Si_2$: 1003.532; found: 1003.531 [*M*+H]$^+$; elemental analysis calcd (%) for $C_{58}H_{78}N_2O_9Si_2$ (1003.419): C 69.42, H 7.84, N 2.79; found: C 69.54, H 8.07, N 2.88.

(2′*S*,5′*S*,2″*S*,5″*S*,1*R*,4*S*)-1,4-Bis-[*N*′-*tert*-butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-4-acetoxy-butan-1-ol (27): Alkyne **26** was hydrogenated in EtOAc (100 mL) by the procedure given for compound **19**. Double FCC (100 g + 30 g, *n*-hexane/MTBE/MeOH 66:33:1→59:40:1) gave alcohol **27** (4.00 g, 3.97 mmol, 98 %) as a colourless gum. R_f = 0.21 (*n*-hexane/MTBE/MeOH 66:33:1); $[\alpha]_D^{20}$ = −53.5 (*c* = 1.446 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 18 H; Si-*t*Bu), 1.24, 1.28, 1.48, 1.50 (each s, 18 H; Boc), 2.00/2.04 (s, 3 H; Ac), 1.49–1.61, 1.80–2.21 (2×m, 12 H; 2-H_2, 3-H_2, 3′-H_2, 3″-H_2, 4′-H_2, 4″-H_2), 3.43–3.55 (m, 2 H; C*H*$_2$-OSi), 3.59–3.84 (m, 3 H; C*H*$_2$-OSi, 1-H), 3.86–4.13 (m, 4 H; 2′-H, 5′-H, 2″-H, 5″-H), 4.49 (dd, *J* = 8.5, 1.5 Hz, 1 H; 1-H), 5.39–5.50/5.68–5.88 (each m, 1 H; 4-H), 7.33–7.45 (m, 12 H; arom.), 7.59–7.66 (m, 8 H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (Si-*C*(CH_3)$_3$), 21.2 (Ac), 26.1, 26.8, 26.9, 27.8, 29.0, 29.5 (C-2, C-3, C-3′, C-3″, C-4′, C-4″), 26.8 (Si-C(*C*H_3)$_3$), 28.3/28.5 (O-C(*C*H_3)$_3$), 59.0, 59.2, 59.3 (C-5′, C-5″), 60.2, 60.3 (C-2′, C-2″), 63.6, 63.8 (*C*H_2-OSi), 74.6, 75.0 (C-1, C-4), 79.4, 79.6, 80.2 (O-*C*(CH_3)$_3$), 127.6, 127.7, 129.5, 129.7, 133.4, 133.5, 133.7, 135.5 (arom.), 153.6, 155.6 (Boc-C=O), 170.5 (Ac-C=O) ppm; IR (film): $\tilde{\nu}$ = 3460, 3071, 3050, 2961, 2932, 2858, 1739, 1692, 1473, 1428, 1391, 1367, 1244, 1174, 1113, 702, 613 cm^{-1}; HRMS (FAB): *m/z*: calcd for $C_{53}H_{73}N_2O_7Si_2$: 905.4956; found: 905.4963 [*M*−Boc]$^+$; elemental analysis calcd (%) for $C_{58}H_{82}N_2O_9Si_2$ (1007.451): C 69.15, H 8.20, N 2.78; found: C 68.91, H 8.10, N 2.95.

(2*S*,5*S*,2′*S*,5′*S*,2″*S*,5″*S*)-2,5-Bis-[*N*′-*tert*-butoxycarbonyl-5′-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-tetrahydrofuran (28): Alcohol **27** (2.48 g, 2.46 mmol) and NEt_3 (8.4 mL, 60 mmol, 24 equiv) in CH_2Cl_2 (125 mL) were cooled to −50 °C, and MsCl (2.3 mL, 30 mmol, 12 equiv) was added dropwise. The mixture was slowly was allowed to warm to −15 °C, until conversion was complete (TLC monitoring). The mixture was poured into sat. oxalic acid and H_2O (50+50 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2×75 mL), and the combined organic layers were washed with phosphate buffer (1 M, pH 7) and brine (50 mL each), dried ($MgSO_4$) and concentrated at r.t. Silica gel filtration (30 g, Et_2O) gave the mesylate (2.51 g, 2.31 mmol, 94 %) as a colourless foam. The mesylate (321 mg, 296 µmol) in THF (6 mL) was cooled to −78 °C, and MeLi (640 µL, 0.92 M in cumene/THF, 0.59 mmol, 2 equiv) was added dropwise. The solution was stirred at −78 °C for 30 min and at 0 °C for 30 min. KO*t*Bu (34 mg, 0.30 mmol, 1 equiv) was added, and the mixture was allowed to warmed to r.t. over 30 min. The mixture was partitioned between Et_2O and sat. NH_4Cl (30 mL each), the aqueous layer was extracted with Et_2O (2×15 mL), and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. FCC (10 g, PE/MTBE 4:1→1:1→0:1) provided tetrahydrofuran **28** (123 mg, 130 µmol, 44 %) followed by a dicarbamate side product (86.3 mg, 106 µmol, 36 %), each as a colourless gum.

Compound 28: R_f = 0.28 (*n*-hexane/MTBE 4:1); $[\alpha]_D^{24}$ = −63.1 (*c* = 0.900 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 18 H; Si-*t*Bu), 1.26/1.46 (s, 18 H; Boc), 1.51–1.61 (m, 4 H; 3-H_2, 4-H_2), 1.74–2.09 (m, 8 H; 3′-H_2, 3″-H_2, 4′-H_2, 4″-H_2), 3.42–3.53 (m, 2 H; C*H*$_2$-OSi), 3.61–3.76 (m, 2 H; C*H*$_2$-OSi), 3.84–4.01 (m, 2 H; 5′-H, 5″-H), 4.01–4.10 (m, 2 H; 2′-H, 2″-H), 4.31–4.45 (m, 2 H; 2-H, 5-H), 7.33–7.45 (m, 12 H; arom.), 7.59–7.67 (m, 8 H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 (Si-*C*(CH_3)$_3$), 22.4, 24.3, 25.4, 26.8, 27.2, 27.6 (C-3, C-3′, C-3″, C-4, C-4′, C-4″), 26.6 (Si-C(*C*H_3)$_3$), 28.1, 28.3 (O-C(*C*H_3)$_3$), 59.2, 59.6 (C-2′, C-2″, C-5′, C-5″), 78.8, 78.9 (C-2, C-5), 79.5 (O-*C*(CH_3)$_3$), 127.4, 129.3, 129.4, 133.2, 133.4, 135.3, 135.4 (arom.); 154.0 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3071, 3050, 2963, 2932, 2859, 1694, 1473, 1428, 1392, 1366, 1256, 1176, 1113, 739, 703, 614 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{56}H_{79}N_2O_7Si_2$: 947.543; found: 947.547 [*M*+H]$^+$; elemental analysis calcd (%) for $C_{56}H_{78}N_2O_7Si_2$ (947.399): C 70.99, H 8.30, N 2.96; found C 71.01, H 8.63, N 2.92.

Side product (1,2-bis-[8′-(*tert*-butyldiphenylsilyloxy)methyl]-1′-aza-3′-oxa-bicyclo[3.3.0]octan-2′-on-4′-yl-ethane: R_f = 0.03 (*n*-hexane/MTBE 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (s, 18 H; Si-*t*Bu), 1.85–2.28 (m, 12 H; 1-H_2, 6′-H_2, 7′-H_2), 3.48–3.60 (m, 2 H; C*H*$_2$-OSi), 3.64–3.73 (m, 2 H; C*H*$_2$-OSi), 3.93–4.02 (m, 4 H; 5′-H, 8′-H), 4.30–4.39 (m, 2 H; 4′-H), 7.31–7.44 (m, 12 H; arom.), 7.59–7.67 (m, 8 H; arom.) ppm; ^{13}C NMR

(75 MHz, $CDCl_3$): δ = 19.0 (Si-$C(CH_3)_3$), 26.6 (Si-C(CH_3)$_3$), 27.2 (C-7′), 30.8 (C-1), 31.5 (C-6′), 59.5 (C-8′), 64.7 (C-5′), 65.8 (CH_2-OSi), 78.9 (C-4′), 127.7, 129.6, 133.2, 135.5 (arom.), 160.6 (C-2′).

(2*S*,5*S*,2′*S*,5′*S*,2″*S*,5″*S*)-2,5-Bis-[5′-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-tetrahydrofuran (29): Di-Boc compound **28** (598 mg, 631 μmol) was deprotected as described in GP 1. FCC (15 g, cyclohexane/EtOAc 1:1→EtOAc→EtOAc/MeOH 85:15) gave diamine **29** (464 mg, 621 μmol, 98 %) as a colourless oil. R_f = 0.26 ($CHCl_3$/MeOH/HCOOH 100:5:5); $[\alpha]_D$ = −6.7 (c = 0.867 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 18 H; Si-*t*Bu), 1.30–1.65/1.72–2.00 (m, 12 H; 3-H_2, 4-H_2, 3′-H_2, 3″-H_2, 4′-H_2, 4″-H_2), 2.99–3.17 (m, 4 H; 2′-H, 2″-H, 5′-H, 5″-H), 3.36–3.47 (m, 2 H; CH_2-OSi), 3.48–3.64 (m, 4 H; CH_2-OSi, 2×NH), 3.74–3.85 (m, 2 H; 2-H, 5-H), 7.33–7.42 (m, 12 H; arom.), 7.61–7.66 (m, 8 H; arom.) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): δ = 19.2 (Si-$C(CH_3)_3$), 26.8 (Si-C(CH_3)$_3$), 27.6, 27.7, 29.5 (C-3/C-4, C-3′/C-3″, C-4′/C-4″), 59.0 (CH_2-OSi), 61.8, 66.9 (C-2′/C-2″, C-5′/C-5″), 82.4 (C-2, C-5), 127.6, 129.5, 133.7, 135.6 (arom.) ppm; IR (film): $\tilde{\nu}$ = 3070, 3048, 2959, 2931, 2858, 1472, 1428, 1390, 1112, 1087, 824, 740, 702, 613 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{46}H_{63}N_2O_3Si_2$: 747.438; found: 747.437 $[M+H]^+$.

(2*S*,5*S*,2′*S*,5′*S*,2″*S*,5″*S*)-2,5-Bis-[*N*′-trifluoroacetyl-5′-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-tetrahydrofuran (30): Diamine **29** (73.8 mg, 98.8 μmol) and pyridine (25 μL, 0.3 mmol, 3 equiv) in anhydrous $CHCl_3$ (2 mL) were cooled to −20 °C, and trifluoroacetic anhydride (35 μL, 0.25 mmol, 2.5 equiv) in $CHCl_3$ (0.5 mL) was added dropwise. The mixture was stirred for 1 h, reaching 0 °C, quenched by addition of sat. NH_4HCO_3 (3 mL) and partitioned between MTBE and H_2O (15 mL each). The aqueous layer was extracted with MTBE (3×5 mL), and the combined organic layers were washed with citric acid (5 wt %) and brine (10 mL each), dried ($MgSO_4$) and concentrated. FCC (5 g, *n*-hexane/MTBE 10:3) provided bis-trifluoroacetamide **30** (75.4 mg, 80.3 μmol, 81 %) as a colourless solid. Single crystals for X-ray crystallography were obtained from acetone/*n*-heptane (1:1, 100 mL g^{-1}) by slow evaporation (8 weeks). R_f = 0.23 (*n*-hexane/MTBE 3:1); m.p. 137–139.5 °C (*n*-heptane); $[\alpha]_D^{25}$ = −6.7 (c = 0.46 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, major rotamer): δ = 1.03 (s, 18 H; Si-*t*Bu), 1.52–1.72 (m, 4 H; 3-H_2, 4-H_2, 3′-H_2, 4′-H_2), 1.92–2.19 (m, 7 H; 3-H_2, 4-H_2, 3′-H_2, 4′-H_2, 3″-H_2, 4″-H_2), 2.22–2.46 (m, 1 H; 3″-H_2), 3.61 (dd, *J* = 10.6, 2.6 Hz, 2 H; CH_2OSi), 3.73–3.84 (m, 1 H; 2-H), 3.89–3.97 (m, 1 H; 5-H), 4.12–4.34 (m, 4 H; 2′-H, 2″-H, 5′-H, 5″-H), 7.31–7.43 (m, 12H; arom.), 7.53–7.63 (m, 8 H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (Si-$C(CH_3)_3$), 24.6 (C-4′, C-4″), 26.8 (Si-C(CH_3)$_3$), 28.1 (C-3′, C-3″), 30.1 (C-3, C-4), 60.0, 60.2, 61.0 (C-2′/C-2″, C-5′/C-5″), 62.6 (CH_2-OSi), 79.0, 79.3 (C-2, C-5), 127.7, 127.8, 129.7, 129.9, 133.2, 133.3, 135.5 (arom.) ppm; trifluoroacetyl not detected; IR (film): $\tilde{\nu}$ = 3072, 3050, 2958, 2932, 2858, 1673 (C=O), 1472, 1429, 1229, 1183, 1143, 1112, 1064, 999, 823, 741, 702, 615 cm^{-1}; elemental analysis calcd (%) for $C_{50}H_{60}N_2O_5F_6Si_2$ (939.202): C 63.94, H 6.44, N 2.98; found C 63.98, H 6.44, N 3.15.

(2*S*,5*S*,2′*S*,5′*S*,2″*S*,5″*S*)-2,5-Bis-(5′-hydroxymethyl)-pyrrolidin-2′-yl-tetrahydrofuran (6): TBDPS-ether **29** (207 mg, 277 μmol) was dissolved in MeOH (10 mL, polypropylene flask), conc. HF (1.0 mL) was added (**Caution!**), and the mixture was stirred for 16 h at RT. The volatiles were removed in vacuo, and FCC (15 g, $CHCl_3$/MeOH/aq. NH_3 45:15:1 +0 %→1 %→2 %→5 % H_2O) gave diamino diol **2**, which was taken up in $CHCl_3$ and filtered over Celite to yield a colourless oil (70.1 mg, 259 μmol, 94 %). R_f = 0.20 ($CHCl_3$/MeOH/aq. NH_3/H_2O 45:15:1:3); $[\alpha]_D^{24}$ = 14.7 (*c* = 0.68 in MeOH); ^{1}H NMR (300 MHz, [D$_4$]MeOH/NaOD 99:1): δ = 1.37–1.62, 1.86–2.18 (2 m, 12 H; 3-H_2, 3′-H_2, 3″-H_2, 4-H_2, 4′-H_2, 4″-H_2), 3.07 (dd, *J* = 15.8, 7.6 Hz, 2 H; 2′-H, 2″-H), 3.25–3.33 (m, 2 H; 5′-H, 5″-H), 3.44–3.52 (m, 4 H; CH_2-OH), 3.80 (dd, *J* = 14.0, 7.8 Hz, 2 H; 2-H, 5-H) ppm; ^{13}C NMR (75 MHz, [D$_4$]MeOH/NaOD 99:1): δ = 28.5, 28.6 (C-3′/C-3″, C-4′/C-4″), 30.6 (C-3, C-4), 60.2, 62.9 (C-2′/C-2″, C-5′/C-5″), 65.8 (CH_2-OH), 83.5 (C-2, C-5) ppm; HRMS (FAB): *m*/*z*: calcd for $C_{14}H_{27}N_2O_3$: 271.2021; found: 271.2029 $[M+H]^+$.

(*S*)-*N*-Benzyl-2-(*p*-tolylsulfonyl-amino)propanol (49): *N*-Tosylalanine (10 g, 41 mmol) was dissolved in DMF (75 mL), K_2CO_3 (28 g, 0.2 mol, 5 equiv) and BnBr (17 mL, 0.14 mol, 3.5 equiv) were added, and the mixture was stirred at RT for 2 h. It was then partitioned between MTBE (200 mL) and sat. NH_4Cl solution (75 mL), washed with H_2O and brine (50 mL each), dried ($MgSO_4$), concentrated, coevaporated with toluene (2×150 mL) and dried in vacuo. The crude benzyl ester (approx. 18 g) in THF (30 mL) was added dropwise to an ice-cooled suspension of $LiAlH_4$ (2.0 g, 52 mmol, 1.3 equiv) in THF (60 mL). The mixture was stirred for 1 h. H_2O (2.1 mL, **Caution!**) and NaOH (2 M, 5.8 mL) were then added dropwise. The white suspension was heated at reflux for 10 min, cooled to RT and filtered through a pad of Celite. The volatiles were removed in vacuo, and recrystallization of the residue from hot MTBE provided alcohol **49** (7.88 g, 24.7 mmol, 60 %) as colourless crystals. R_f = 0.14 (*n*-hexane/MTBE 1:1); m.p. 111 °C (MTBE); $[\alpha]_D^{21}$ = −3.2 (*c* = 1.10 in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3 H; 3-H_3), 1.67 (m, 1 H; -OH), 2.43 (s, 3 H; Ts-CH_3), 3.26 (bt, *J* = 5.9 Hz, 2 H; 1-H_2), 4.01 (hex, *J* = 6.9 Hz, 1 H; 2-H), 4.15 (d, *J* = 15.6 Hz, 1 H; N-CH_2-Ph), 4.66 (d, *J* = 15.6 Hz, 1 H; N-CH_2-Ph), 7.27–7.36 (m, 7 H; arom.), 7.72 (d, *J* = 8.3 Hz, 2 H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-3), 21.5 (Ts-CH_3), 47.5 (CH_2-Ph), 55.9 (C-2), 64.8 (CH_2-OH), 127.8, 127.9, 128.7, 129.8, 128.5, 137.7, 138.1, 143.4 (arom.) ppm; IR (KBr): $\tilde{\nu}$ = 3483 (-OH), 2975, 2931, 1320, 1304, 1150, 1090, 1015, 730, 658 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{21}NO_3S$ (319.42): C 63.92, H 6.63, N 4.39, S 10.04; found C 63.91, H 6.54, N 4.41, S 9.97.

(*S*)-*N*-Benzyl-2-(*p*-tolylsulfonyl-amino)propanal (35): DMSO (3.1 mL, 43 mmol, 3.3 equiv) was added dropwise (**Caution!**) to a stirred solution of oxalyl chloride (1.85 mL, 21.6 mmol, 1.7 equiv) in CH_2Cl_2 (60 mL) at −65 °C, and the system was allowed to warm to −55 °C over 20 min. The solution was cooled to −80 °C, alcohol **49** (4.19 g, 13.1 mmol) in CH_2Cl_2 (15 mL) was added dropwise, and the mixture was stirred for 30 min. EtN(*i*Pr)$_2$ (17.5 mL, 0.1 mol, 7.8 equiv) was then added dropwise, and the mixture was allowed to warm to 0 °C and stirred for 20 min. The mixture was extracted with H_3PO_4 (2 M, 100 mL), and the aqueous layer was extracted with Et_2O (2×50 mL). The organic layers were combined, washed with phosphate buffer (1 M, pH 7) and brine (30 mL each), dried (Na_2SO_4), filtered over silica gel (20 g, 50 mL Et_2O rinse) and concentrated at RT. Recrystallization from hexanes/MTBE (1:4, 10 mL g^{-1}) at 4 °C gave aldehyde **35** (3.18 g, 10.0 mmol, 77 %) as colourless needles. R_f = 0.37 (*n*-hexane/MTBE 1:1); m.p. 81.5–82.5 °C (MTBE); $[\alpha]_D^{22}$ = −69.2 (*c* = 1.01 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 7.2 Hz, 3 H; 3-H_3), 2.44 (s, 3 H; Ts-CH_3), 4.17 (q, *J* = 7.2 Hz, 1 H; 2-H), 4.17 (d, *J* = 14.8 Hz, 1 H; N-CH_2-Ph), 4.53 (d, *J* = 14.8 Hz, 1 H; N-CH_2-Ph), 7.29–7.35 (m, 7 H; arom.), 7.75 (d, *J* = 8.3 Hz, 2 H; arom.), 9.28 (s, 1 H; -C*H*O) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1 (C-3), 21.5 (Ts-CH_3), 49.1 (CH_2-Ph), 61.4 (C-2), 127.2, 128.5, 128.8, 129.9, 135.4, 137.0, 143.9 (arom.), 198.9 (*C*HO) ppm; IR (KBr): $\tilde{\nu}$ = 3132, 2923, 1729, 1634, 1598, 1455, 1399, 1386, 1334, 1171, 1155, 832, 736, 659 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{17}H_{20}NO_3S$: 318.1128; found: 318.1131 $[M+H]^+$; elemental analysis calcd (%) for $C_{17}H_{19}NO_3S$ (317.40): C 64.33, H 6.03, N 4.41, S 10.10; found C 64.29, H 6.09, N 4.56, S 10.06.

(3*RS*,4*SR*)-*N*-Benzyl-*N*-tosyl-4-amino-1-trimethylsilyl-1-pentyn-3-ol (36): Trimethylsilylacetylene (0.86 mL, 12 mmol, 4 equiv) in THF (10 mL) was treated at −78 °C with *n*BuLi (2.3 M in hexanes, 1.9 mL, 4.4 mmol, 1.5 equiv) for 15 min, and the mixture was cooled to −90 °C. Racemic aldehyde **35** (934 mg, 2.94 mmol) in THF (10 mL) was added dropwise, and the mixture was allowed to warm to −30 °C in 2 h. The mixture was partitioned between MTBE (30 mL) and HCl (0.5 M, 20 mL), and the aqueous layer was extracted with MTBE (3×25 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. FCC (50 g, PE/MTBE/MeOH 50:10:1→30:10:1) gave racemic *syn*-alcohol **36** (1.03 g, 2.48 mmol, 84 %) as a colourless solid. Single crystals for X-ray crystallography were obtained from *n*-hexane/MTBE (10:1). R_f = 0.46 (*n*-hexane/MTBE 1:1); m.p. 93.5–94.5 °C (*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.14 (s, 9 H; TMS), 1.16 (d, *J* = 7.0 Hz, 3 H; 5-H_3), 2.26 (d, *J* = 5.6 Hz, 1 H; -OH), 2.42 (s, 3 H; Ts-CH_3), 4.09 (m, 1 H; 4-H), 4.33 (t, *J* = 5.6 Hz, 1 H; 3-H), 4.36 (d, *J* = 16.0 Hz, 1 H; N-CH_2-Ph), 4.52 (d, *J* = 16.0 Hz, 1 H; N-CH_2-Ph), 7.25–7.41 (m, 7 H; arom.), 7.70 (d, *J* = 8.3 Hz, 2 H; Ts-arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.1 (TMS), 13.3 (C-5), 21.7 (Ts-CH_3), 48.9 (CH_2-Ph), 58.5 (C-4), 66.2 (C-3), 91.6 (C-2), 104.3 (C-1), 127.3, 127.4, 128.6, 129.9, 137.9, 138.2, 143.6 (arom.) ppm; IR (film): 3492, 3062, 3030, 2959, 2173, 1496, 1455, 1362, 1338, 1249, 1204, 1154, 1117, 1090, 1069, 1010, 921, 844, 816, 762, 733, 698, 666, 602 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{29}NO_3SiS$ (415.622): C 63.58, H 7.03, N 3.37, S 7.72; found: C 63.42, H 7.17, N 3.32, S 7.68.

(2*S*,5*S*,1′*R*,4′*R*,5′*S*)-*N*-*tert*-Butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)-methyl-2-[*N*′-benzyl-5′-(*p*-tolylsulfonyl)amino-4′-hydroxy-1′-(trimethylsi-

lyl)oxy]-2′-hexynyl-pyrrolidine (37): Alkyne **2** (4.73 g, 8.36 mmol, 1.2 equiv) in THF (40 mL) was cooled to −78 °C, and *n*BuLi (2.5 M in hexanes, 3.34 mL, 8.36 mmol, 1.2 equiv) was added slowly with stirring. After 40 min, aldehyde **35** (2.21 g, 6.96 mmol) dissolved in THF (40 mL) was added dropwise (10 min). The mixture was stirred at −78 °C for 2 h, and was then allowed to warm to −25 °C over 1.5 h. The mixture was extracted with NH_4HCO_3/H_2O (1:2, 150 mL), and the aqueous layer was extracted with MTBE (2×50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and evaporated. FCC (2×100 g, CH_2Cl_2/*n*-hexane 3:1→1:0→CH_2Cl_2/acetone 99:1→98:2) delivered alcohol **37** (5.63 g, 6.37 mmol, 92 %) as a colourless gum. R_f = 0.24 (CH_2Cl_2/acetone 98:2); $[\alpha]_D^{20}$ = −38.0 (*c* = 1.00 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 71:29 mixture of rotamers): δ = 0.07/0.10 (each s, 9H; TMS), 1.04/1.06 (each s, 9H; Si-*t*Bu), 1.11 (m, 3H; 6′-H_3), 1.29/1.47 (each s, 71:29, 9H; Boc), 1.89 (d, *J* = 5.7 Hz, 1H, -OH), 1.95–2.23 (m, 4H; 3-, 4-H_2), 2.43 (s, 3H; Ts-Me), 3.48/3.72 (each dd, *J* = 9.4, 7.1 Hz, 2H; 1′′-H_2), 3.79–3.95 (m, 2H; 2-H, 5-H), 4.02–4.14 (m, 1H; 5′-H), 4.37–4.44 (m, 1H; 4′-H), 4.40/4.64 (each d, *J* = 16 Hz, 2H; N-CH_2-Ph), 4.85/5.05 (each t, *J* = 2 Hz, 29:71, 1H; 1′-H), 7.24–7.28 (m, 5H; Bn-arom.), 7.30–7.46 (m, 8H; arom.), 7.63–7.69 (m, 6H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.0 (TMS), 12.6 (C-6′), 19.4 (2×, Si-*C*(CH_3)$_3$), 21.7 (Ts-Me), 24.6 (C-4), 27.0 (Si-C(*C*H_3)$_3$), 27.8 (2×, C-3), 28.5 (2×, O-C(*C*H_3)$_3$), 48.7 (*C*H_2-Ph), 58.3 (C-5′), 59.8 (2×, C-2), 62.3 (C-1′), 63.1 (2×, C-5), 64.3 (C-1′′), 66.0 (2×, C-4′), 79.7 (2×, O-*C*(CH_3)$_3$), 83.5 (2×, C-2′), 86.5 (2×, C-3′), 127.3, 127.8, 127.9, 128.1, 128.7, 129.7, 129.9, 133.5, 133.7, 135.7, 137.8, 138.4, 143.5 (arom.), 153.9 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3453 (O−H), 3067, 2959, 2250 w (C≡C), 1686, 1395, 1337, 1254, 1164, 1112, 1034, 846, 734, 704 cm^{-1}; elemental analysis calcd (%) for $C_{49}H_{66}N_2O_7Si_2S$ (883.31): C 66.63, H 7.53, N 3.17, S 3.63; found C 66.54, H 7.67, N 3.06, S 3.43.

(2*S*,5*S*,1′*R*,4′*R*,5′*S*)-*N*-*tert*-Butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)-methyl-2-[*N*′-benzyl-5′-(*p*-tolylsulfonyl)amino-1′,4′-dihydroxy]-2′-hexynyl-pyrrolidine (37): TMS-ether **37** (4.29 g, 4.86 mmol) in THF/MeOH (1:1, 80 mL) was cooled to 0 °C, and CSA (57 mg, 0.24 mmol, 5 mol %) was added. After 30 min, sat. $NaHCO_3$ solution (10 mL) was added, and the organic solvents were removed in vacuo. The residue was partitioned between EtOAc and brine (50 mL each). The aqueous layer was extracted with EtOAc (50 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. FCC (100 g, PE/EtOAc 3:1→2:1→1:1) gave diol **38** (3.73 g, 4.60 mmol, 95 %) as a colourless gum; R_f = 0.23 (*n*-hexane/EtOAc 2:1); $[\alpha]_D^{24}$ = −15.2 (*c* = 1.43 in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, 93:7 mixture of rotamers): δ = 1.06 (s, 9H; Si-*t*Bu), 1.12 (d, *J* = 6.8 Hz, 3H; 6′-H_3), 1.31/1.48 (each s, 93:7, 9H; Boc), 1.97–2.29 (m, 4H; 3-H_2, 4-H_2), 2.42 (s, 3H; Ts-Me), 3.57–3.70 (m, 2H; 1′′-H_2), 3.86–3.96 (m, 1H; 2-H), 4.05–4.09 (m, 2H; 5-H, 5′-H), 4.42–4.44 (m, 1H; 4′-H), 4.38/4.65 (each d, *J* = 16.2 Hz, 2H; N-CH_2-Ph), 4.54 (d, *J* = 8.3 Hz, 1H; 1′-H), 5.41/5.75 (each d, *J* = 8.3 Hz, 93:7, 1H; -OH), 7.24–7.33 (m, 5H; Bn-arom.), 7.36–7.44 (m, 8H; arom.), 7.62–7.73 (m, 6H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7 (C-6′), 19.2 (Si-*C*(CH_3)$_3$), 21.5 (Ts-Me), 26.7 (C-4), 26.9 (2×, Si-C(*C*H_3)$_3$), 27.4 (C-3), 28.3 (2×, O-C(*C*H_3)$_3$), 48.7 (N-*C*H_2-Ph), 58.4 (C-5′), 60.6 (C-2), 63.8 (C-5), 64.2 (C-1′′), 65.8 (2×, C-4′), 67.1 (C-1′), 80.7 (O-*C*(CH_3)$_3$), 84.4 (C-3′), 85.4 (C-2′), 127.1, 127.4, 127.7, 127.8, 128.5, 129.7, 129.8, 133.2, 133.4, 135.5, 137.7, 138.1, 143.4 (arom.), 156.3 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3405 (O−H), 3068, 2961, 2935, 2862, 2251 (C≡C), 1669, 1456, 1401, 1337, 1259, 1162, 1112, 1017, 913, 818, 734, 704, 658 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{46}H_{59}N_2O_7SiS$: 811.381; found: 811.380 $[M+H]^+$; elemental analysis calcd (%) for $C_{46}H_{58}N_2O_7SiS$ (811.13): C 68.12, H 7.21, N 3.45, S 3.95; found C 67.85, H 7.37, N 3.37, S 3.73.

(2*S*,5*S*,1′*R*,4′*R*,5′*S*)-*N*-*tert*-Butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)-methyl-2-[*N*′-benzyl-5′-(*p*-tolylsulfonyl)amino-1′,4′-dihydroxy]-hexyl-pyrrolidine (39): Alkyne **38** (1.05 g, 1.29 mmol) was dissolved in MeOH (20 mL), and Pt/C (5 %, 50 mg) was added. The mixture was degassed and hydrogenated (1 bar) for 6 h with vigorous stirring. The flask was purged with Ar, the catalyst was filtered off over a pad of Celite, and the solvents were removed in vacuo. FCC (100 g, PE/EtOAc 2:1→1:1) provided saturated diol **39** (936 mg, 1.15 mmol, 89 %) as a colourless foam; R_f = 0.24 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{24}$ = −7.6 (*c* = 0.51 in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, 83:17 mixture of rotamers): δ = 0.96 (d, *J* = 7.1 Hz, 3H; 6′-H_3), 1.05 (s, 9H; Si-*t*Bu), 1.29/1.45 (each s, 83:17, 9H; Boc), 1.30–1.60 (m, 4H; 2′-H_2, 3′-H_2), 1.82–2.28 (m, 4H; 3-H_2, 4-H_2), 2.42 (s, 3H; Ts-Me), 3.13–3.18 (m, 1H; 4′-H), 3.52–3.69 (m, 3H; 1′-H, 1′′-H_2), 3.76–3.83 (m, 1H; 5′-H), 3.90–3.99 (m, 2H; 2-H, 5-H), 4.13/4.70 (each d, *J* = 15.4 Hz, 2H; N-CH_2-Ph), 4.29/5.23 (each s, 2H; OH), 7.26–7.30 (m, 5H; Bn-arom.), 7.35–7.44 (m, 8H; arom.), 7.61–7.71 (m, 6H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9 (C-6′), 19.2 (Si-*C*(CH_3)$_3$), 21.5 (Ts-Me), 26.8 (2×, Si-C(*C*H_3)$_3$), 28.3 (2×, O-C(*C*H_3)$_3$), 26.8, 29.8, 32.6 (C-3, C-4, C-2′, C-3′), 47.9 (N-*C*H_2-Ph), 58.8 (C-5′), 60.4 (C-2), 63.4 (C-5), 64.0 (C-1′′), 74.7 (C-4′), 75.9 (C-1′), 80.5 (O-*C*(CH_3)$_3$), 127.1, 127.4, 127.7, 127.8, 128.4, 128.5, 129.7, 133.2, 133.4, 135.5, 137.9, 138.3, 143.1 (arom.), 156.0 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3384 (O−H), 3070, 2960, 2932, 2859, 1687, 1668, 1456, 1428, 1393, 1367, 1338, 1266, 1166, 1113, 1092, 1007, 860, 821, 775, 736, 703, 659 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{42}H_{53}N_2O_7SiS$: 757.3343; found: 757.3299 $[M-C_4H_9]^+$; elemental analysis calcd (%) for $C_{46}H_{62}N_2O_7SiS$ (815.16): C 67.78, H 7.67, N 3.44, S 3.93; found C 67.59, H 7.64, N 3.37, S 3.65.

(2*S*,4*R*,7*R*,2′*S*,5′*S*,1′′*S*)- and (2*R*,4*R*,7*R*,2′*S*,5′*S*,1′′*S*)-4-[*N*′-*tert*-Butoxycarbonyl-5′-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-7-[1′′-*N*′′-benzyl-(*p*-tolylsulfonyl)amino]-ethyl-2-oxo-1,3-dioxathiepane (40a and 40b): Diol **39** (2.74 g, 3.36 mmol) in CH_2Cl_2 (150 mL) was cooled to −10 °C, and NEt_3 (1.9 mL, 13 mmol, 4 equiv) was added. A solution of $SOCl_2$ (0.27 mL, 3.7 mmol, 1.1 equiv) in CH_2Cl_2 (15 mL) was added dropwise over 20 min, until the mixture became yellow. After complete conversion (5 min, TLC monitoring), the mixture was partitioned between Et_2O (250 mL) and sat. $NaHCO_3$ solution (50 mL). The layers were separated, and the organic layer was washed with H_2O, $NaHSO_4$ (2 M) and brine (50 mL each), dried (Na_2SO_4) and concentrated. FCC (100 g, PE/MTBE 4:1→3:1→2:1→1:1) gave the (2*R*)-sulfite **40a** (1.28 g, 1.48 mmol, 44 %) as a colourless solid, followed by the (2*S*)-sulfite **40b** (1.45 g, 1.68 mmol, 50 %) as a colourless syrup. Compound **40a** crystallized from toluene/*n*-hexane in colourless needles, and X-ray crystallography confirmed the stereochemical assignments (see Supporting Information for details).

Compound 40a: R_f = 0.33 (*n*-hexane/MTBE 3:1); m.p. 153–154 °C (*n*-hexane); $[\alpha]_D^{24}$ = +25.3 (*c* = 0.708 in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, 78:22 mixture of rotamers): δ = 0.62–0.79 (m, 1H; 5-H_2), 0.91 (d, *J* = 6.8 Hz, 3H; 2′′-H_3), 1.01 (s, 9H; Si-*t*Bu), 1.24 (s, 78:22, 9H; Boc), 1.26–1.70 (m, 3H; 5-H_2, 6-H_2), 1.85–2.14 (m, 4H; 3′-H_2, 4′-H_2), 2.42 (s, 3H; Ts-Me), 3.50 (dd, *J* = 9.6, 6.4 Hz, 1H; CH_2-OSi), 3.55–3.66 (m, 2H; CH_2-OSi, 2′-H), 3.82–3.96 (m, 3H; 5′-H, 1′′-H, N-CH_2-Ph), 4.26 (t, *J* = 10.2 Hz, 1H; 7-H), 4.74–4.84 (m, 2H; 4-H, N-CH_2-Ph), 7.21–7.62 (m, 17H; arom.), 7.70 (d, *J* = 8.3 Hz, 2H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (C-2′′), 19.2 (Si-*C*(CH_3)$_3$), 21.5 (Ts-Me), 26.8 (Si-C(*C*H_3)$_3$), 28.3 (O-C(*C*H_3)$_3$), 23.2, 27.4, 28.5, 29.8 (C-3′, C-4′, C-5, C-6), 47.4 (N-*C*H_2-Ph), 56.0 (C-1′′), 59.1(C-5′), 61.3 (C-2′), 64.4 (*C*H_2-OSi), 74.5 (C-4), 74.6 (C-7), 79.7 (O-*C*(CH_3)$_3$), 126.9, 127.0, 127.7, 127.8, 128.8, 129.2, 129.7, 129.9, 133.3, 133.5, 135.4, 137.5, 137.6, 143.5 (arom.), 153.8 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3070, 2960, 2932, 2858, 1687, 1456, 1428, 1394, 1366, 1342, 1210, 1167, 1113, 1086, 1006, 948, 864, 740, 706, 657, 613 cm^{-1}; elemental analysis calcd (%) for $C_{46}H_{60}N_2O_8SiS_2$ (861.20): C 64.16, H 7.02, N 3.25, S 7.45; found C 64.19, H 7.00, N 3.28, S 7.33.

Compound 40b: R_f = 0.14 (*n*-hexane/MTBE 3:1); $[\alpha]_D^{24}$ = +31.6 (*c* = 0.776 in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, major rotamer): δ = 0.99 (d, *J* = 6.8 Hz, 3H; 2′′-H_3), 1.02 (s, 9H; Si-*t*Bu), 1.29 (s, 9H; Boc), 0.85–1.10, 1.22–1.55, 1.60–1.75, 1.93–2.13 (each m, 8H; 5′-H_2, 6′-H_2, 3′-H_2, 4′-H_2), 2.43 (s, 3H; Ts-Me), 3.45–3.56 (m, 1H; CH_2-OSi), 3.56–3.71 (m, 2H; CH_2-OSi, 7-H), 3.72–3.76 (m, 1H; 2′-H), 3.78–3.95 (m, 2H; 1′′-H, 5′-H), 4.00 (d, *J* = 15.1 Hz, 1H; N-CH_2-Ph), 4.63 (d, *J* = 15.1 Hz, 1H; N-CH_2-Ph), 5.37 (d, *J* = 11.3 Hz, 1H; 4-H), 7.30–7.62 (m, 17H; arom.), 7.69 (d, *J* = 8.3 Hz, 2H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9 (C-2′′), 19.2 (Si-*C*(CH_3)$_3$), 21.5 (Ts-Me), 26.8 (Si-C(*C*H_3)$_3$), 28.2 (O-C(*C*H_3)$_3$), 23.4, 27.5, 28.5, 30.9 (C-3′, C-4′, C-5, C-6), 48.0 (N-*C*H_2-Ph), 56.5 (C-1′′), 58.6 (C-5′), 61.0 (C-2′), 64.4 (*C*H_2-OSi), 73.6 (C-4), 78.0 (C-7), 79.7 (O-*C*(CH_3)$_3$), 127.1, 127.7, 127.9, 128.7, 128.8, 129.6, 129.9, 133.5, 135.5, 143.6 (arom.), 153.7 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3070, 2961, 2931, 2858, 1690, 1456, 1428, 1393, 1366, 1342, 1266, 1211, 1168, 1112, 1087, 1043, 1007, 960, 945, 863, 821, 739, 717, 703, 658, 607 cm^{-1}; elemental analysis calcd (%) for $C_{46}H_{60}N_2O_8SiS_2$ (861.20): C 64.16, H 7.02, N 3.25, S 7.45; found: C 64.21, H 7.32, N 3.45, S 7.01.

(2*S*,4*R*,7*R*,2′*S*,5′*S*,1′′*S*)- and (2*R*,4*R*,7*R*,2′*S*,5′*S*,1′′*S*)-4-[*N*′-*tert*-Butoxycarbonyl-5′-(*tert*-butyldiphenylsilyloxy)methyl]-pyrrolidin-2′-yl-7-[1′′-*N*′′-benzyl-(*p*-tolylsulfonyl)amino]-ethyl-2,2-dioxo-1,3-dioxathiepane (41):

Cyclic sulfite **40** (3.46 g, 4.02 mmol, mixture of diastereomers) in CCl_4/CH_3CN (1:1, 170 mL) and H_2O (50 mL) was cooled to 0 °C. $NaIO_4$ (3.4 g, 16 mmol, 4 equiv) and $RuCl_3 \cdot H_2O$ (approx. 1 mg) were added to the vigorously stirred emulsion. The mixture turned brownish-green, and conversion was complete after 20 min (TLC). The mixture was extracted with Et_2O (500 mL), and the organic layer was washed with H_2O (100 mL) and brine (3×100 mL). The organic layer was dried ($MgSO_4$) and concentrated at RT to yield cyclic sulfate **41** (3.64 g, quant.) as a colourless syrup, which was >95% pure (^{1}H NMR). FCC (4 g, *n*-hexane/MTBE 2:1) of 68.0 mg crude material gave pure **41** (64.4 mg, 73.4 µmol, 98%). R_f = 0.25 (*n*-hexane/MTBE 2:1); $[\alpha]_D^{24}$ = −26.0 (*c* = 1.268 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of conformers): δ = 0.90–1.05 (m, 12H; 2″-H$_3$, Si-*t*Bu), 1.28 (s, 9H; Boc), 1.40–1.88, 1.89–2.40 (each m, 8H; 5′-H$_2$, 6′-H$_2$, 3′-H$_2$, 4′-H$_2$), 2.42 (s, 3H; Ts-Me), 3.48–3.70 (m, 3H; C*H*$_2$-OSi, 2′-H), 3.83–4.07 (m, 3H; 1″-H, 5′-H, N-C*H*$_2$-Ph), 4.62–4.81 (m, 2H; N-C*H*$_2$-Ph, 7-H), 5.21 (d, *J* = 11.7 Hz, 1H; 4-H), 7.31–7.66 (each m, 17H; arom.), 7.70 (d, *J* = 8.3 Hz, 2H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4 (C-2″), 19.2 (Si-*C*(CH$_3$)$_3$), 21.6 (Ts-Me), 26.8 (Si-C(*C*H$_3$)$_3$), 28.3 (O-C(*C*H$_3$)$_3$), 23.3, 27.6, 28.7 (C-3′, C-4′, C-5, C-6), 48.0 (N-*C*H$_2$-Ph), 55.6 (C-1″), 58.7 (C-5′), 60.8 (C-2′), 64.5 (*C*H$_2$-OSi), 80.1 (O-*C*(CH$_3$)$_3$), 83.7, 85.1 (C-4, C-7), 127.0, 127.7, 128.2, 129.0, 129.2, 129.7, 130.0, 133.4, 135.5, 137.0, 137.2, 143.9 (arom.), 153.8 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3070, 2960, 2931, 2858, 1750, 1689, 1456, 1428, 1393, 1368, 1342, 1200, 1168, 1112, 1088, 1042, 1007, 961, 908, 893, 854, 821, 766, 731, 704, 659, 614 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{46}H_{60}N_2O_9SiS_2$: 877.359; found: 877.374 [*M*+H]$^+$.

(2*S*,5*S*,1′*S*,4′*R*,5′*S*)-*N*-*tert*-Butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)-methyl-2-[*N*′-benzyl-5′-(*p*-tolylsulfonyl)amino-1′-azido-4′-hydroxy]-hexyl-pyrrolidine and (2*S*,5*S*,1′*R*,4′*S*,5′*S*)-*N*-*tert*-butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)methyl-2-[*N*′-benzyl-5′-(*p*-tolylsulfonyl)amino-4′-azido-1′-hydroxy]-hexyl-pyrrolidine (42a and 42b): $TBAN_3$ (3.4 g, 0.013 mol, 3 equiv) was coevaporated with toluene (50 mL), dried in vacuo (0.01 mbar, 2 h), and added to a solution of 3.57 g (3.88 mmol for 98% purity) of the crude cyclic sulfate **41** in THF (150 mL). The flask was sealed under Ar and stirred at 35 °C, until the conversion was complete (36 h). The flask was cooled to 0 °C, and conc. H_2SO_4 was added dropwise (**Caution!**), until the sulfo monoester began to cleave (approx. 1 mL, pH 1–2, TLC monitoring). After the polar monoester had been consumed (8 h), CO_3^{2-} buffer (2 M, pH 10, 100 mL) and PE (100 mL) were added. The layers were separated, and the aqueous layer was extracted with MTBE (2×100 mL). The combined organic layers were washed with H_2O (30 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated. FCC (60 g, PE/acetone 5:1→4:1) provided the alcohols **42a** and **42b** (2:3 mixture of regioisomers, 2.54 g, 3.02 mmol, 78%), followed by the cyclic carbamate **50** (294 mg, 384 µmol, 10%), each as a colourless foam. The regioisomers **42a** and **42b** could be separated by FCC (CH_2Cl_2/PE/EtOAc 10:10:1→10:10:2→10:10:3), which was done on analytical scale only.

Compound 42a: R_f = 0.29 (CH_2Cl_2/PE/EtOAc 10:10:2); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of conformers): δ = 0.96 (d, *J* = 6.8 Hz, 3H; 6′-H$_3$), 1.03 (s, 9H; Si-*t*Bu), 1.23 (s, 9H; Boc), 1.23–1.31, 1.36–1.50, 1.57–1.75 (m, 4H; 2′-H$_2$, 3′-H$_2$), 1.95–2.17 (m, 4H; 3-H$_2$, 4-H$_2$), 2.42 (s, 3H; Ts-Me), 3.22–3.36 (m, 1H; 4′-H), 3.44–3.52 (m, 1H; 1″-H$_2$), 3.62–3.78 (m, 3H; 1″-H$_2$, 1′-H, 5′-H), 3.83–4.01 (m, 2H; 2-H, 5-H), 4.01/4.67 (each d, *J* = 15.7 Hz, each 1H; N-C*H*$_2$-Ph), 7.26–7.65 (m, 17H; arom.), 7.69 (d, *J* = 8.1 Hz, 2H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (C-6′), 19.2 (Si-*C*(CH$_3$)$_3$), 21.5 (Ts-Me), 26.8 (Si-C(*C*H$_3$)$_3$), 28.3 (O-C(*C*H$_3$)$_3$), 25.2, 26.3, 27.0, 31.5 (C-3, C-4, C-2′, C-3′), 48.2 (*C*H$_2$-Ph), 58.7 (C-5′), 59.3, 59.6 (C-2, C-5), 64.0 (C-1′), 64.0 (C-1″), 74.5 (C-4′), 79.9 (O-*C*(CH$_3$)$_3$), 127.1, 127.7, 127.7, 127.8, 128.3, 128.7, 128.8, 129.6, 129.7, 133.2, 133.4, 135.5, 137.7, 137.9, 143.4 (arom.), 154.3 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3641, 3068, 2959, 2869, 2361, 2337, 2098 (N$_3$), 1688, 1435, 1395, 1371, 1341, 1162, 1113, 705 cm^{-1}; MS (ESI); *m*/*z*: calcd for $C_{46}H_{61}N_5O_6SiSNa$: 862.4; found: 862.3 [*M*+Na]$^+$; HRMS (EI); *m*/*z*: calcd for $C_{42}H_{53}N_5O_6SiS$: 783.3486; found: 783.3497 [*M*−C$_4$H$_9$]$^+$.

Compound 42b: R_f = 0.20 (CH_2Cl_2/PE/EtOAc 10:10:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84–0.90 (m, 3H; 6′-H$_3$), 1.03 (s, 9H; Si-*t*Bu), 1.28 (s, 9H; Boc), 1.25–1.31, 1.44–1.47, 1.55–1.67 (each m, 4H; 2′-H$_2$, 3′-H$_2$), 1.95–2.22 (m, 4H; 3-H$_2$, 4-H$_2$), 2.42 (s, 3H; Ts-Me), 3.19–3.27 (m, 1H; 4′-H), 3.49–3.57 (m, 1H; 1″-H$_2$), 3.60–3.73 (m, 2H; 1″-H$_2$, 1′-H), 3.73–3.85 (m, 1H; 5′-H), 3.88–3.99 (m, 2H; 2-H, 5-H), 4.23 (d, *J* = 15.5 Hz, 1H; N-C*H*$_2$-Ph), 4.47 (d, *J* = 15.7 Hz, 1H; N-C*H*$_2$-Ph), 7.26–7.65 (m, 17H; arom.), 7.69 (d, *J* = 8.3 Hz, 2H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-6′), 19.2 (Si-*C*(CH$_3$)$_3$), 21.5 (Ts-Me), 26.8 (2×, Si-C(*C*H$_3$)$_3$), 28.3 (O-C(*C*H$_3$)$_3$), 26.4, 26.9, 29.4, 31.6 (C-3, C-4, C-2′, C-3′), 48.6 (*C*H$_2$-Ph), 57.6 (C-5′), 60.3 (C-5), 63.6 (C-2), 64.0 (C-1″), 65.8 (C-1′), 74.8 (C-4′), 80.3 (O-*C*(CH$_3$)$_3$), 127.1, 127.3, 127.7, 127.8, 128.3, 128.5, 129.6, 129.7, 133.2, 133.4, 135.5, 137.2, 137.8, 143.2 (arom.), 155.8 (Boc-C=O) ppm; MS (ESI): *m*/*z*: calcd for $C_{46}H_{61}N_5O_6SiSNa$: 862.4; found: 862.3 [*M*+Na]$^+$.

(4*S*,5*S*,8*S*,3′*S*,4′*R*)-4-[*N*′-Benzyl-3′-hydroxy-4′-(*p*-tolylsulfonyl)amino]pentyl-8-(*tert*-butyldiphenylsilyloxy)methyl-1-aza-3-oxa-bicyclo[3.3.0]octan-2-one (50): R_f = 0.04 (*n*-hexane/acetone 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.9 Hz, 3H; 5′-H$_3$), 0.99 (s, 9H; Si-*t*Bu), 1.14–1.60, 1.83–2.18 (several m, 8H; 1′-H$_2$, 2′-H$_2$, 6-H$_2$, 7-H$_2$), 2.36 (s, 3H; Ts-Me), 3.30–3.45 (m, 2H; 8-H, 3′-H), 3.55–3.70 (m, 3H; 4′-H, 1″-H$_2$), 3.85–3.97 (m, 2H; 4-H, 5-H), 4.00/4.60 (2×d, *J* = 15.5 Hz, each 1H; N-C*H*$_2$-Ph), 7.19–7.35 (m, 13H; arom.), 7.55–7.65 (m, 6H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9 (C-5′), 19.3 (Si-*C*(CH$_3$)$_3$), 21.5 (Ts-Me), 26.8 (Si-C(*C*H$_3$)$_3$), 28.5, 30.0, 31.5, 32.0 (C-6, C-7, C-1′, C-2′), 48.5 (*C*H$_2$-Ph), 58.6 (C-4′), 59.4 (C-5), 65.1 (C-8), 65.9 (C-1″), 74.2 (C-3′), 80.7 (C-4), 127.1, 127.7, 127.9, 128.4, 128.8, 129.7, 129.8, 133.3, 135.6, 137.6, 137.8, 143.5 (arom.), 160.7 (*C*=O)) ppm; HRMS (FAB, KI): *m*/*z*: calcd for $C_{42}H_{52}N_2O_6SiSK$: 779.2952; found: 779.2959 [*M*+K]$^+$.

(2*S*,5*S*,2′*S*,5′*S*,1″*S*)-2-[*N*′-*tert*-Butoxycarbonyl-5′-(*tert*-butyldiphenylsilyloxy)-methyl]-pyrrolidin-2′-yl-5-[1″-(*N*″-benzyl-*N*″-tosyl)amino]-ethyl-pyrrolidine (43): Alcohols **40** (mixture of regioisomers, 590 mg, 702 µmol) and NEt_3 (1.2 mL, 8.4 mmol, 12 equiv) in CH_2Cl_2 (30 mL) were cooled to −40 °C, MsCl (0.34 mL, 4.2 mmol, 6 equiv) was added dropwise, and the mixture was allowed to warm to −15 °C over 1 h. The mixture was partitioned between PE (100 mL) and $NaHSO_4$ (1 M, 40 mL), and the aqueous layer was extracted with Et_2O (50 mL). The combined organic layers were washed with H_2O (2×20 mL) and brine (50 mL), dried ($MgSO_4$), concentrated at 10 °C and dried in vacuo to give the corresponding mesylates (650 mg, quant.) as a colourless gum (R_f = 0.14 in *n*-hexane/acetone 4:1). The mesylates (457 mg, 498 µmol) were dissolved in CH_3CN (50 mL), treated with PBu_3 (0.37 mL, 1.5 mmol, 3 equiv), and stirred for 14 h at RT. H_2O (0.1 mL) was added, and the solvents were removed at 40 °C. FCC (50 g, $CHCl_3$/MeOH/HCOOH 100:3:0.3→100:5:0.3→100:5:1; fractions washed with sat. $NaHCO_3$ before concentration) gave bispyrrolidine **43** (330 mg, 423 µmol, 85%) as a colourless oil. R_f = 0.20 ($CHCl_3$/MeOH/HCOOH 100:5:1); $[\alpha]_D^{20}$ = −9.9 (c = 1.056 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$/TFA 99:1): δ = 0.89 (d, *J* = 6.9 Hz, 3H; 2″-H$_3$), 1.00 (s, 9H; Si-*t*Bu), 1.18/1.34 (each s, 9H; Boc-*t*Bu), 1.40–1.60 (m, 2H; 3-H$_2$), 1.78 (m, 2H; 4-H$_2$), 1.95–2.20 (m, 4H; 3′-, 4′-H$_2$), 2.36 (d, 3H; Ts-Me), 3.00 (m, 1H; 5-H), 3.59–3.74 (m, 3H; 2′-H, 1‴-H$_2$), 3.82–4.05 (m, 2H; 2-H, 5′-H), 4.33 (m, 1H; 1″-H), 3.90 (d, *J* = 15.1 Hz, 1H; N-C*H*$_2$-Ph), 4.85 (d, *J* = 15.1 Hz, 1H; N-C*H*$_2$-Ph), 7.19–7.46 (m, 13H; arom.), 7.54–7.75 (m, 6H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$/TFA 99:1): δ = 15.0 (C-2″), 19.2 (Si-*C*(CH$_3$)$_3$), 21.5 (Ts-Me), 26.9 (2×, Si-C(*C*H$_3$)$_3$), 28.3 (2×, O-C(*C*H$_3$)$_3$), 26.4, 26.9, 29.4, 29.7 (C-3, C-4, C-3′, C-4′), 48.6 (*C*H$_2$-Ph), 54.6 (C-1″), 59.5 (C-5′), 60.3 (C-2′), 63.6 (C-1‴), 63.7 (C-5), 63.8 (C-2), 82.8 (O-*C*(CH$_3$)$_3$), 127.4, 127.8, 128.1, 128.8, 129.1, 129.9, 129.9, 133.1, 133.2, 135.5, 136.7, 137.0, 143.6 (arom.), 157.7 (Boc-C=O) ppm; IR (film): $\tilde{\nu}$ = 3410, 3070, 2959, 2932, 2872, 2862, 1687, 1553, 1456, 1428, 1393, 1365, 1342, 1172, 1113, 910, 821, 774, 704, 658, 604 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{46}H_{62}N_3O_5SiS$: 796.4179; found: 796.4171 [*M*+H]$^+$.

(2*S*,5*S*,2′*S*,5′*S*,1″*S*)-4-[*N*′-*tert*-Butoxycarbonyl-5′-(*tert*-butyldiphenylsilyloxy)-methyl]-pyrrolidin-2′-yl-5-[*N*-*tert*-butoxycarbonyl-1″-(*N*″-benzyl-*N*″-tosyl)-amino]-ethyl-pyrrolidine (44): Pyrrolidine **43** (24.0 mg, 30.1 µmol) was dissolved in THF (3 mL), CO_3^{2-}-buffer (pH 10, 1 mL) and Boc$_2$O (26 mg, 0.12 mmol, 4 equiv) were added, and the solution was heated at 60 °C for 24 h. The mixture was partitioned between MTBE (30 mL) and brine (10 mL), and the organic layer was dried with $MgSO_4$ and concentrated. FCC (3 g, *n*-hexane/MTBE 4:1→3:1) provided Boc-protected bispyrrolidine **44** (18.7 mg, 20.9 µmol, 69%) as a colourless gum. R_f = 0.26 (*n*-hexane/MTBE 3:1); $[\alpha]_D^{20}$ = −11.0 (*c* = 1.090 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 7.1 Hz, 3H; 2″-H$_3$), 1.06 (s, 9H; Si-*t*Bu), 1.24/1.28/1.48/1.53 (each s, 18H; 2×Boc), 1.27–1.81, 1.83–2.18 (m, 8H; 3-H$_2$, 4-H$_2$, 3′-H$_2$, 4′-H$_2$), 2.42 (d, 3H; Ts-Me), 3.42–3.51 (m, 1H; 1‴-H$_2$), 3.59–3.68 (m, 1H; 1‴-H$_2$), 3.74–4.16 (m, 4H; 2-H, 5-H, 2′-H, 5′-H), 4.19–4.74 (m, 3H; 1″-H, N-C*H*$_2$-Ph), 7.23–7.72 (m, 17H; arom.), 7.82 (d,

$J = 8.1$ Hz, 2H; arom.) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.0$ (C-2″), 19.2 (Si-*C*(CH_3)$_3$), 21.5 (Ts-Me), 24.4, 25.8, 26.3, 26.8 (C-3, C-4, C-3′, C-4′), 26.4 (Si-C(CH_3)$_3$), 28.3, 28.5 (2×O-C(CH_3)$_3$), 50.0 (CH_2-Ph), 54.5 (C-1″), 59.5, 60.4, 61.3 (C-2, C-2′, C-5, C-5′), 64.0 (C-1‴), 79.1, 79.3 (O-*C*(CH_3)$_3$), 127.1, 127.4, 127.7, 128.0, 128.8, 129.4, 129.7, 133.1, 135.5, 135.6, 138.2, 138.4, 142.5 (arom.), 153.3, 153.7 (Boc-C=O) ppm; IR (film): $\tilde{\nu} = 3066$, 2972, 2931, 2858, 1690, 1474, 1455, 1428, 1391, 1366, 1342, 1255, 1167, 1113, 821, 763, 738, 703, 659 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{51}H_{69}N_3O_7SiS$: 895.4626; found: 895.4652 $[M]^+$.

(2*S*,5*S*,2′*S*,5′*S*,1″*S*)-4-[*N*′-*tert*-Butoxycarbonyl-5′-(*tert*-butyldiphenylsilyloxy)-methyl]-pyrrolidin-2′-yl-5-(*N*-*tert*-butoxycarbonyl-1″-amino-ethyl)-pyrrolidine (45): Pyrrolidine **44** (18.0 mg, 20.1 μmol) in THF (2 mL) was cooled to −78 °C. *n*BuLi (2.4 M in hexanes, 35 μL, 0.084 mmol, 4 equiv) was added dropwise, to give a yellow solution. After 30 min, TMSCl (0.1 mL, 0.7 mmol, 35 equiv) was added, and the mixture was stirred at RT for 2 h. CO_3^{2-} buffer (1 M, 5 mL) was added, and the mixture was stirred for 1 h and partitioned between MTBE (40 mL) and brine (10 mL). The organic layer was dried with Na_2SO_4 and concentrated. FCC (2.5 g, CH_2Cl_2/MeOH/HCOOH 100:5:1→100:10:1→100:10:3) gave amine **45** (5.1 mg, 7.8 μmol, 39 %) as a colourless wax. $R_f = 0.26$ ($CHCl_3$/MeOH/HCOOH 100:10:1); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.84$–0.93 (m, 3H; 2″-H_3), 1.02/1.03 (each s, 1:2, 9H; Si-*t*Bu), 1.22/1.23/1.45/1.47 (each s, 2:2:1:1, 18H; Boc), 1.55–1.69 (m, 2H), 1.75–1.95 (m, 3H), 1.95–2.15 (m, 3H; pyrrolidine 3-H_2, 4-H_2), 3.35–4.45 (m, 7H; pyrrolidine 2-H, 5-H), 7.33–7.42 (m, 6H; arom.), 7.58–7.65 (m, 4H; arom.); MS (ESI): *m*/*z*: calcd for $C_{37}H_{58}N_3O_5Si$: 652.4; found: 652.4 $[M+H]^+$.

CCDC-231 867 (**24**), -231 868 (**30**) and -231 869 (**36**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.uk).

Synthesis of ribozyme and substrate: The hairpin ribozyme was transcribed in vitro from a double-stranded DNA template with the use of T7 RNA polymerase as described previously.[60] The RNA substrate was chemically synthesised and end-labelled with fluorescein with the aid of an automated synthesizer (Gene Assembler Special, Amersham Pharmacia Biotech), then purified as described.[66]

Cleavage experiments: A ribozyme stock solution (100 nM, 10 μL) was added to a stock solution of Tris-HCl (pH 7.5, 1 M, 5 μL) and H_2O (55 μL), and the mixture was heated at 90 °C for 1 min followed by incubation at 37 °C for 15 min. A $MgCl_2$ solution (100 mM, 10 μL) and a solution of terpyrrolidine **33** (10 mM, 20 μL) were added, and the reaction was started by addition of a substrate stock solution (2 μM, 10 μL). Experiments in the absence of $MgCl_2$ were carried out in the same way; instead of $MgCl_2$, a stock solution of EDTA (20 mM, 10 μL) was added in order to bind remaining traces of divalent metal ions and the concentration of **33** was adjusted to 4 mM. Aliquots (10 μL) were taken at suitable time intervals and added to a mixture of EtOH (25 μL) and an aqueous NaOAc solution (3 M, 2 μL) in an Eppendorf tube. Samples were cooled for 5 min at −78 °C to precipitate RNA fragments, and the RNA was isolated by centrifugation. The pellets were taken up in gel loading buffer (7 M urea, 50 mM EDTA) and loaded onto a denaturing polyacrylamide gel (15 %). The gels were analysed with an A.L.F. DNA sequencer (Amersham Pharmacia Biotech); the resulting data were processed with A.L.F. Fragment Manager software as described.[60]

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