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Synthesis and biological evaluation of conformationally constrained analogues of the antitubercular agent ethambutol

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Abstract—Three (*S*)-prolinol-derived conformationally restricted analogues of the antitubercular agent ethambutol were prepared and tested against *Mycobacterium tuberculosis*.

1. Introduction

The World Health Organization's reports on tuberculosis (TB) are alarming.[1] Almost 9 million new cases occurred in 2004 and TB kills nearly 2 million people over the world every year. It is estimated that one-third of the world's population is infected by *Mycobacterium tuberculosis*, the bacillus responsible for TB. Moreover, the global TB incidence is growing at 1% a year due to a rapid increase in Africa. Indeed, association with HIV has contributed to the resurgence of this curable disease. The worldwide emergence of multi-drug resistant TB is also considered to aggravate the current pandemic.

Ethambutol (EMB) (**1**) (Fig. 1) is a long-known front-line antimycobacterial agent used against TB.[2] Despite its moderate bacteriostatic activity, this reliable and well-accepted drug belongs to the standard anti-TB chemotherapeutic regimen. About 10 years ago, EMB was shown to inhibit the biosynthesis of the mycobacterial cell wall.[3] Its primary site of action is thought to be the arabinosyltransferases responsible for building the arabinan core of both the mycolyl-arabinogalactan and lipoarabinomannan units. However, an accurate understanding of its molecular mechanism of action is still hampered by lack of structural data concerning its enzymatic targets.

The possibility that EMB could act as a cation chelate is inherent to its discovery and historically led to the introduction of the hydroxyl groups in the β-position of the amines. Although EMB has been shown to affect trace metal metabolism in animal models, its hypothetical action through mycobacteria cation inactivation is still open to debate.[4]

In the context of the TB pandemic, the rather simple structure of EMB renders the search for new analogues attractive.

2. Results and discussion

2.1. Design and synthetic approach

Reports concerning the structural optimization of EMB have remained rather scarce for many years.[5] Studies have, however, elegantly led to the preparation of EMB-saccharide and -iminosaccharide hybrid molecules that proved, in fact, inactive.[6] Lately, the occurrence of a 'better ethambutol' has been systematically investigated through virtual screening[7] or a combinatorial approach.[8] Several 1,2-diamines, such as SQ 109 (**2**), displaying up to 14- to 35-fold improved in vitro antimycobacterial potencies and promising pharmacokinetic

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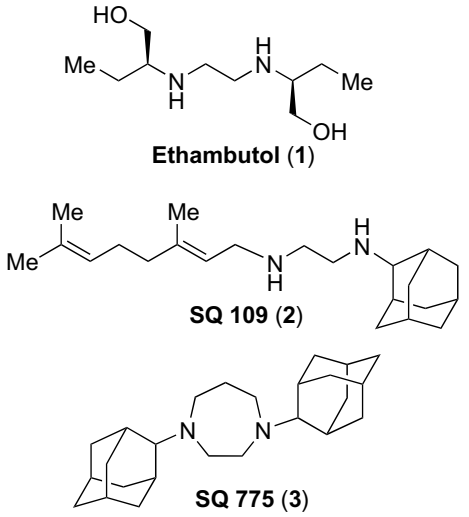


Figure 1. Structure of ethambutol and of two analogues thereof.

properties have thus been reported (Fig. 1).[9] New cyclic diamine scaffolds with in vivo activity against *M. tuberculosis* have similarly been identified, like for example the homopiperazine SQ 775 (**3**).[10] Ferrocenyl diamines also lacking the EMB hydroxymethyl appendages have been recently reported.[11] Despite being conceptually derived from EMB, these achiral compounds all contrast by their pronounced lipophilicity.

We would like to report here our approach towards new EMB analogues based on the identification of (*S*)-prolinol (**4**) as a rigidified equivalent of the key aminobutanol fragment (Fig. 2). The relevancy of the prolinol framework in the design of new antimycobacterial arabinosyltransferase inhibitors has already been demonstrated by us and by J. Prandi.[12] According to the present strategy, either mono- or bicyclic conformation-restricted EMB analogues, such as **5** or **7**, respectively, could be targeted (Scheme 1). Such compounds would retain several important structural features of EMB: low molecular weight, reduced lipophilic character and, for the bicyclic analogues, possibility of C_2 symmetry. Additionally, the metal chelating capacity of these analogues may be modulated due to their con-

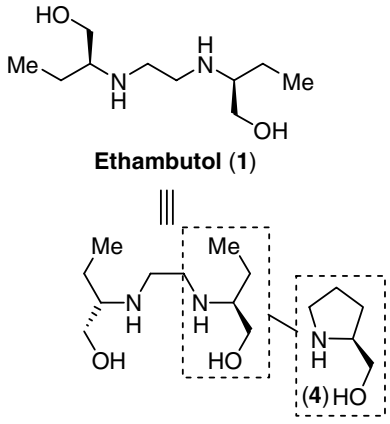
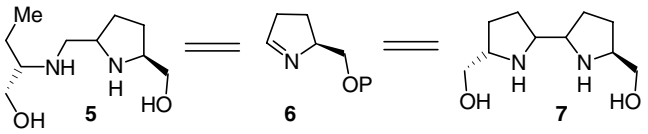


Figure 2. Structural homology between ethambutol (**1**) and prolinol (**4**).



Scheme 1. Targeted rigidified EMB analogues and their key imine precursor.

strained conformation.[13,14] It thus seemed interesting to evaluate the incidence on antimycobacterial activity of such a specific structural alteration in light of the original 'metal chelate hypothesis.'

A synthetic route was delineated allowing direct assembly of the central 1,2-diamine pharmacophore. An original prolinol-derived imine **6**, ready for functionalization at the 5-position of the pyrrolidine framework, was selected as a pivotal intermediate.

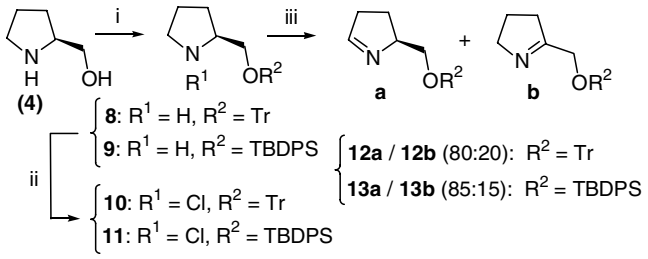
2.2. Preparation of the pivotal imine

With regard to the preparation of the pivotal imine, we chose the method described by V.L. Schramm and P.C. Tyler for the synthesis of aza-*C*-nucleosides and developed by B.G. Davies for the synthesis of various *C*-substituted iminosugars.[15,16] This route relies on the regioselective dehydrochlorination of an *N*-chloramine intermediate. We selected two primary hydroxyl protecting groups on the basis of their large steric bulk in order to ensure an optimal level of regiocontrol: triphenylmethyl (Tr) and *tert*-butyldiphenylsilyl (TBDPS).

O-Tr prolinol **8** was prepared using a previously described 3-step procedure requiring intermediate N-protection as a formamide.[17] On the other hand, the O-silylation of prolinol to give **9** was straightforward. The N-chlorination of **8** and **9** was efficiently accomplished by the use of NCS in Et_2O. The crucial elimination step required careful optimization due to the high sensitivity of the desired imines towards traces of moisture and acids. Freshly prepared lithium tetramethylpiperidine (LiTMP) was slowly added, at −78 °C, to the starting chloramine until complete consumption of the latter. At this point, it was found that direct filtration of the reaction medium over neutral Al_2O_3 smoothly delivered the imines in fairly good yield and appreciable purity. As estimated by ^1H NMR analysis of this crude mixture, the regioisomeric ratio ranged from 80/20 for the *O*-Tr derivative to 85/15 for *O*-TBDPS analogue. Both thermodynamic imines were prepared separately for identification by treatment of the corresponding *N*-chloramine with DBU. If required, the desired imines **12** and **13** could be rapidly purified over neutral grade I alumina and isolated in 88% and 73% yield, respectively, as a mixture of isomers. On the basis of this study, we carried out the rest of this work with the more readily accessible imine **13** (Scheme 2).

2.3. Access to the semi-rigidified EMB analogues

Functionalization of the 5-position of prolinol was then undertaken by means of a hydrocyanation reaction of



Scheme 2. Reagents and conditions: (i) R = Tr: Ref. 17; for R = TBDPS: TBDPSCl (1.1 equiv), Et_3N (2.5 equiv), THF, rt, quant.; (ii) NCS (1.1 equiv), Et_2O, rt, 91% for R = Tr, 72% for R = TBDPS; (iii) LiTMP (1.7 equiv), THF, −78 °C, 88% for R = Tr, 73% for R = TBDPS.

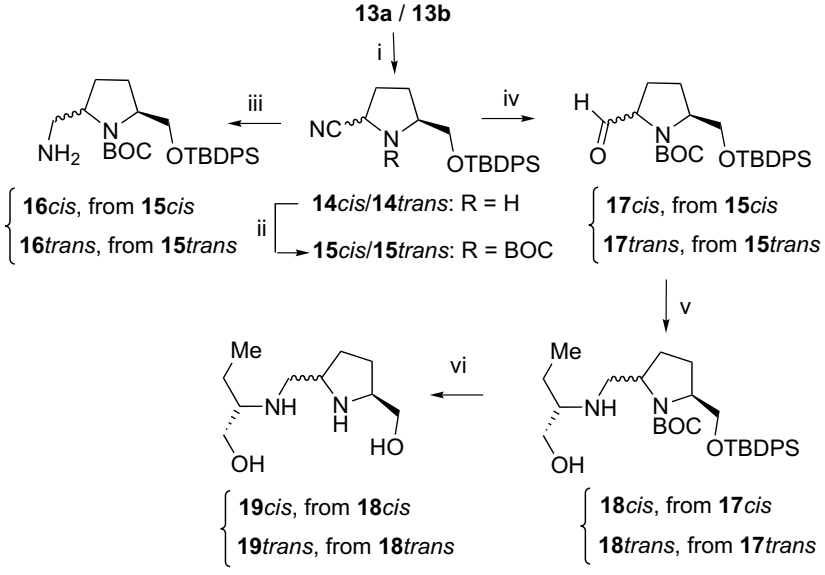
derivative **13**. The resulting nitriles were then well suited for the branching of the missing aminobutanol unit via conversion either to an aldehyde or an amine, followed by reductive amination.

Preliminary studies on a purified sample of imine **13** showed that treatment with TMSCN (1.5 equiv) in the presence of $Yb(OTf)_3$ (0.1 equiv) (CH_2Cl_2, 0 °C, MS 4 Å) afforded the expected aminonitriles in 66% yield as a 50/50 diastereoisomeric mixture (not shown).[18] The same result was obtained using diethyl phosphorocyanidate (DEPC) (1.5 equiv) and imidazole (1.5 equiv) (THF, rt) (Scheme 3).[19] Hydrocyanation product of the minor imine **13b** could not be detected. These conditions were conveniently applied to the crude imines allowing isolation of the aminonitriles in ca. 50% combined yield from the *N*-chloramine. The N-protection was achieved by introduction of a Boc group using a large excess of Boc anhydride in a 1 M aqueous NaOH/THF mixture at rt, allowing the two isomers **15***cis* and **15***trans* to be separated by column chromatography. The relative configuration at C-5 was confirmed by ^1H NMR analysis. Differential NOE experiments clearly demonstrated the cis relationship between H-2 and H-5 in **15***cis* and between H-2 and CH_2OTBDPS in **15***trans*. Finally, this 3-step sequence was efficiently conducted without purification of the aminonitrile intermediates affording the expected *N*-Boc aminonitriles **15***cis* and **15***trans* in 29% and 24% overall yield (an average of 81% combined yield for each step) from the starting *N*-chloramine.

We then studied introduction of the required aminobutanol fragment. In principle, this can be achieved in two ways: a) complete reduction of the nitrile to the corresponding primary amine and reductive amination with 1-hydroxybutan-2-one or b) conversion of the nitrile to an aldehyde and reductive amination with (*S*)-2-aminobutan-1-ol.

Treatment of the *N*-Boc aminonitriles **15***cis* or **15***trans* by Raney Ni (5 bars H_2, EtOH–NH_3, rt) cleanly delivered the corresponding primary amines (58% or 67% yield, respectively) (Scheme 3). However, because of the expected lack of stereocontrol at the newly formed asymmetric centre during the reductive amination with 1-hydroxybutan-2-one, we chose the alternative route.

Access to the desired sensitive aminoaldehydes was secured by action of DIBAL-H in a strongly apolar medium followed by careful hydrolysis of the imine intermediate. After meticulous optimization, it was found that treatment with a simple saturated aqueous solution of potassium hydrogen tartrate (pH 3–4) allowed clean isolation of the expected *N*-Boc aminoaldehyde **17***cis* or **17***trans* (58% or 77% yield, respectively)



Scheme 3. Reagents and conditions: (i) DEPC (1.5 equiv), imidazole (1.5 equiv), THF, rt; (ii) $(Boc)_2O$ (9.0 equiv), aqueous NaOH/THF, rt; 29% in **15***cis* and 24% in **15***trans* based on the starting *N*-chloramine **11**; (iii) Raney Ni, 5b H_2, EtOH–NH_3, 58% in **16***cis* from **15***cis* and 67% in **16***trans* from **15***trans*; (iv) DIBAL-H (2.0 equiv), petroleum ether/toluene, −78 °C then tartrate buffer, rt, 58% in **17***cis* from **15***cis* and 77% in **17***trans* from **15***trans*; (v) (*S*)-2-aminobutan-1-ol (1.1 equiv), $NaBH(OAc)_3$ (1.4 equiv), 4 Å MS, CH_2Cl_2, rt, 58% in **18***cis* from **17***cis* and 65% in **18***trans* from **17***trans*; (vi) MeOH–HCl, rt, 85% in **19***cis* from **18***cis* and 86% in **19***trans* from **18***trans*.

(Scheme 3). Importantly, any epimerization was avoided. The spectral data for the isomer **17***trans* were in good agreement with those reported previously.[20]

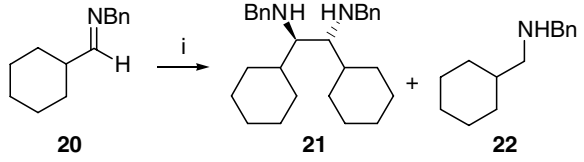
Reductive amination with (*S*)-2-aminobutan-1-ol was achieved better using sodium triacetoxyborohydride than sodium cyanoborohydride, the latter giving rather confused and poorly reproducible transformations.[21] Thus, the expected aminoalcohol **18***cis* or **18***trans* was formed in a stereospecific manner (58% or 65% yield, respectively) under these smooth and neutral conditions (Scheme 3).

For the final deprotection step we selected conditions avoiding an aqueous work up in view of the expected high polarity of the EMB analogues. Action of HCl in methanol at rt followed by treatment with DOWEX cation exchange resin cleanly delivered the targeted 1,2-diamines (Scheme 3).

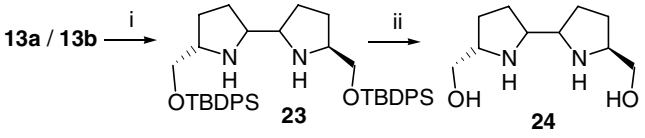
2.4. Access to the bipyrrolidine analogue of EMB

The most straightforward access to the targeted bipyrrolidine skeleton was the pinacol type coupling of pivotal imine **13**. However, procedures useful for the reductive coupling of enolisable alkylimine are scarce, mainly because of their sluggish reactivity and their tendency to rather suffer simple reduction.

R. Yanada reported the use of in situ generated SmI_2 for the reductive coupling of aromatic imines.[22] These conditions proved ineffective with aliphatic substrates and a model study was conducted with the representative imine **20** (Scheme 4). After considerable experimentation, the Sm(0)/I_2/Ti(O*i*-Pr)$_4$ system was found to allow efficient and complete *d,l* selective coupling.[23] These conditions compare well in terms of stereoselectivity, practicality and innocuousness with the few methods reported to be useful with the same imine.[24]



Scheme 4. Reagents and condition: Ti(O*i*-Pr)$_4$ (1.0 equiv), Sm(0) (1.1 equiv), I_2 (0.1 equiv) DME, rt, 80% in **21** and 20% in **22**.



Scheme 5. Reagents and conditions: (i) Ti(O*i*-Pr)$_4$ (1.0 equiv), Sm(0) (1.1 equiv), I_2 (0.1 equiv) DME, rt, 20%; (ii) MeOH–HCl, rt, 66%.

When applied to the prolinol-derived imine **13** this procedure gave, as a single diastereoisomer, the expected bipyrrolidine **23** in 20% yield, along with *O*-TBDPS prolinol (Scheme 5). While NMR analysis clearly indicated the C_2 symmetry of compound **23**, NOE measurements were unable to distinguish between (2*S*,2′*S*) and (2*R*,2′*R*). We proposed the all-*S* configuration as it corresponds to the combination of the intermediate radical species by the less hindered face (Scheme 6). The presence of an unsubstituted methylene α to the intermediate radical species, likely to favour the concurrent disproportionation pathway, may explain the lower efficiency of this transformation in comparison to the model study. The direct access to the bipyrrolidine framework afforded by this highly reproducible procedure was found to compensate its modest efficiency.

The final deprotection was again achieved by the action of HCl in methanol at rt followed by treatment with DOWEX cation exchange resin, cleanly delivering the targeted bipyrrolidine EMB analogue **24** (Scheme 5).

2.5. Biological evaluation

The antimycobacterial activities of our three EMB analogues were evaluated against the *M. tuberculosis* H_{37}Rv strain (Fig. 3). The semi-rigid analogue **19***cis* exerted a modest growth inhibition at concentrations of over 60 μg/mL, whereas MIC of EMB under the same conditions is around 2 μg/mL. The second diastereoisomer

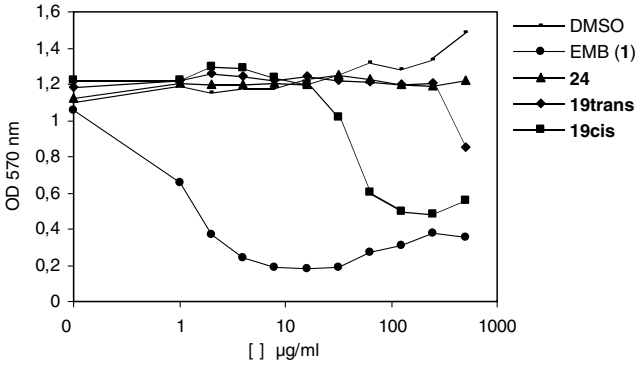
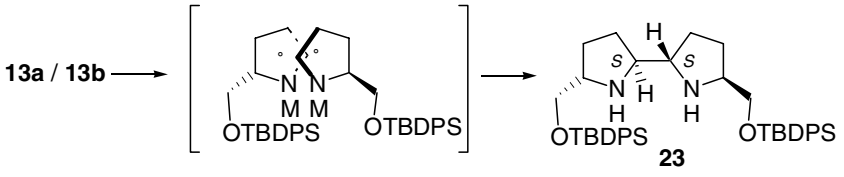


Figure 3. Activity against *M. tuberculosis* H_{37}Rv strain.



Scheme 6. Proposed stereochemical course for the reductive coupling of imine **13**.

19*trans* and the bicyclic analogue **24** did not display any appreciable activity.

It seems likely that conformational restrictions profoundly affected the activities of our analogues. This might imply that the high degree of conformational flexibility of EMB is critical for its overall activity against mycobacteria. Interestingly, a pronounced gap in growth inhibitory potency was observed between the two diastereoisomeric derivatives **19***cis* and **19***trans*.

3. Conclusion

We designed, synthesised and tested against *M. tuberculosis* three conformationally constrained EMB analogues. Our synthetic approach was based on the pivotal prolinol-derived imine **13**, prepared in three steps with a 53% yield. Two semi-rigidified EMB analogues **19***cis* and **19***trans* were accessed via a route including imine hydrocyanation, conversion to an aldehyde and reductive amination. The bipyrrolidine scaffold of the rigidified analogue **24** was secured by means of an original pinacolic type reductive coupling procedure based on the $Sm(0)/I_2/Ti(O\textit{i}\text{-}Pr)_4$ system. Biological evaluation revealed that only the semi-rigidified EMB analogue **19***cis* retained some antimycobacterial activity, displaying a 30-fold reduced potency as compared to the parent drug. This synthetic work thus paves the way for the preparation of other rigidified EMB analogues in order to further evaluate the influence of the rigidity on the antimycobacterial activity and provides new insights into the structure–activity relationships with respect to the historical 'metal chelate hypothesis'.

4. Experimental

4.1. Chemistry

4.1.1. General methods. Unless otherwise stated, all reactions requiring anhydrous conditions were carried out under nitrogen. The following solvents and reagents were dried prior to use: CH_2Cl_2, MeOH (from calcium hydride), 1,2-dimethoxyethane (DME), Et_2O, petroleum ether, THF, toluene (freshly distilled from sodium/benzophenone), 2,2,6,6-tetramethylpiperidine (TMP), Et_3N (from calcium hydride, stored over potassium hydroxide pellets). Analytical thin layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} precoated plates. Chromatograms were observed under UV light and/or were visualised by heating plates that were dipped in 10% phosphomolybdic acid in ethanol or Dragendorff reagent. Standard column chromatography was performed with SDS 70–200 μm silica gel or Merck 70–230 mesh neutral alumina (Brockman grade I). Flash column chromatography was carried out with SDS 35–70 μm silica gel. NMR spectroscopic data were obtained with Bruker AC 250, Advance 300, ARX 400 and Advance 500 operating with ^1H spectra at 250, 300, 400 and 500 MHz, respectively, ^{13}C spectra at 63, 75, 100 and 125 MHz, respectively. Chemical shifts are quoted in parts per million (ppm) relative to residual solvent peak and coupling constants are given in Hertz. Doubled ^{13}C chemical shifts correspond to signals with $\Delta\delta < 0.05$ ppm. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR 1725X spectrometer. Mass spectrometry (MS) data were obtained on a ThermoQuest TSQ 7000 spectrometer. High resolution mass spectra (HRMS) were recorded on a ThermoFinnigan MAT 95 XL spectrometer. Optical rotations were measured on a Perkin-Elmer model 241 spectrometer.

4.1.2. (*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)pyrrolidine (9). To a solution of (*S*)-prolinol (**4**) (8.97 g, 88.7 mmol) in anhydrous THF (222.0 mL) under inert atmosphere were successively added Et_3N (31.0 mL, 223 mmol) and *tert*-butyl-diphenylchlorosilane (25.3 mL, 97.5 mmol). The reaction mixture was stirred overnight before being filtered through Celite. THF was then evaporated off under reduced pressure to afford **9** (30.2 g, quant.) as a yellow oil. An analytical sample was purified by flash column chromatography on silica gel (EtOAc/MeOH/NH_4OH 97:1:2): colourless oil; $R_f = 0.35$ (EtOAc/MeOH/NH_4OH 97:1:2); $[\alpha]_D^{25} -1.6$ (*c* 1.1, $CHCl_3$); IR (neat) $\nu_{max} = 3048, 2959, 2856$ (C–H), 1425 (N–H), 1264 (C–O) cm^{-1}; NMR ^1H (300 MHz, $CDCl_3$) $\delta = 1.10$ (s, 9H, $SiC(CH_3)_3$), 1.47–1.55 (m, 1H, H-3), 1.70–1.86 (m, 3H, 2× H-4, H-3′), 2.34 (sl, 1H, NH), 2.83–3.04 (m, 2H, 2× H-5), 3.22–3.30 (m, 1H, H-2), 3.65 (AB part of an ABX, $^2J = 10.1$ Hz, $^3J = 6.0$ Hz, $^3J = 5.0$ Hz, $\delta a - \delta b = 16.8$ Hz, 2H, CH_2O-Si), 7.37–7.47 (m, 6H, H-Ph), 7.68–7.72 (m, 4H, H-Ph) ppm; NMR ^{13}C (75 MHz, $CDCl_3$) $\delta = 19.2$ (Si*Cq*), 25.3 (C-4), 26.8 ($SiC(CH_3)_3$), 27.4 (C-3), 46.4 (C-5), 59.9 (C-2), 66.5 (CH_2OSi), 127.6, 129.6 (CH-Ph), 133.6 (Cq-Ph), 135.5, 135.5 (CH-Ph) ppm; MS (DCI, NH_3): $m/z = 340$ (100) $[M+H^+]$; HRMS (DCI, NH_3): calcd for $C_{21}H_{30}NOSi$ $[M+H^+]$ 340.2097, found 340.2093.

4.1.3. General procedure A: synthesis of *N*-chloramines. *N*-chlorosuccinimide (1.1 equiv) was added to a 0.07 M solution of *O*-protected prolinol (1.0 equiv) in anhydrous Et_2O under inert atmosphere. The reaction mixture was stirred until TLC analysis showed disappearance of starting material (1–4 h) and was then diluted with Et_2O (30 mL/mmol). The organic phase was successively washed with water (3× 15 mL/mmol) and brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure.

4.1.3.1. (*S*)-1-Chloro-2-(trityloxymethyl)pyrrolidine (10). Compound **8** (330 mg, 0.96 mmol) was treated according to general procedure A. The crude product was purified by column chromatography on silica gel (2 g, pentane/EtOAc 95:5) to give **10** (330 mg, 91%): colourless oil; $[\alpha]_D^{25} -65.1$ (*c* 0.8, $CHCl_3$); IR (neat) $\nu_{max} = 3054, 2975, 2870$ (C–H), 1595, 1489 (C=C), 1263 (C–O) cm^{-1}; NMR ^1H (300 MHz, $CDCl_3$) $\delta = 1.65–1.94$ (m, 3H, H-3, 2× H-4), 2.04–2.15 (m, 1H, H-3′), 2.98–3.07 (m, 1H, H-5), 3.14–3.21 (m, 2H, H-2, H-5′), 3.37–3.43 (m, 1H, CH_2O), 3.51–3.58 (m, 1H, CH'_2O), 7.24–7.36 (m, 9H, H-Ph), 7.50–7.53 (m, 6H, H-Ph) ppm; NMR ^{13}C (75 MHz, $CDCl_3$) $\delta = 21.6$ (C-4), 26.2 (C-3), 62.5 (C-5), 64.8 (CH_2O), 71.4 (C-2), 86.6 (O*Cq*), 127.0, 127.8, 128.8

(CH-Ph), 144.1 (Cq-Ph) ppm; MS (DCI, NH_3): m/z = 378 (100) [M+H$^+$].

4.1.3.2. (*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-1-chloropyrrolidine (11). Compound **9** (2.00 g, 5.87 mmol) was treated according to general procedure A. The crude product was purified by column chromatography on silica gel (11 g, petroleum ether/EtOAc 95:5) to give **11** (1.58 g, 72% from (*S*)-prolinol): colourless oil; R_f = 0.32 (petroleum ether/EtOAc 95:5); $[\alpha]_D^{25}$ −60.7 (*c* 2.0, $CHCl_3$); IR (neat) ν_{max} = 3087, 3085, 2928, 2853 (C–H), 1112 (C–O) cm^{-1}; NMR ^{1}H (300 MHz, $CDCl_3$) δ = 1.08 (s, 9H, SiC(CH_3)$_3$), 1.71–1.93 (m, 3H, 2× H-4, H-3), 2.03–2.11 (m, 1H, H-3′), 2.97–3.03 (m, 1H, H-5), 3.10–3.17 (m, 1H, H-2), 3.48–3.53 (m, 1H, H-5′), 3.68 (dd, ^2J = 10.4 Hz, ^3J = 6.3 Hz, 1H, CH_2OSi), 3.92 (dd, ^2J = 10.4 Hz, ^3J = 4.3 Hz, 1H, CH'_2OSi), 7.38–7.47 (m, 6H, H-Ph), 7.69–7.72 (m, 4H, H-Ph) ppm; NMR ^{13}C (100 MHz, $CDCl_3$) δ = 19.3 (Si*Cq*), 21.6 (C-4), 25.8 (C-3), 26.8 (SiC(*C*H$_3$)$_3$), 62.5 (C-5), 65.0 (*C*H$_2$OSi), 72.7 (C-2), 127.6, 127.6, 129.5, 129.6 (CH-Ph), 133.5, 133.6 (Cq-Ph), 135.6, 135.6 (CH-Ph) ppm; MS (DCI, NH_3): m/z = 374 (100) [M+H$^+$].

4.1.4. General procedure B: synthesis of kinetic imines. To a 0.2 M solution of TMP (1.9 equiv) in anhydrous THF at 0 °C and under inert atmosphere was slowly added *n*-BuLi (1.6 M solution in hexane, 1.8 equiv). The mixture was allowed to react with stirring for 30 min at this temperature. In another flask, a 0.08 M solution of *N*-chloramine (1 equiv) in anhydrous THF was cooled to −78 °C. The LiTMP solution was then added dropwise to the *N*-chloramine (flow rate: 10 mL h^{-1}) until TLC analysis showed disappearance of starting material. The reaction mixture was then cannulated under inert atmosphere onto an alumina pad (6 g/mmol, 70–230 mesh neutral alumina Brockman grade I) and the products were eluted with anhydrous THF (3× 5 mL/mmol). The resulting THF solution was concentrated under reduced pressure.

4.1.4.1. (*S*)-2-(Trityloxymethyl)-3,4-dihydro-2H-pyrrole (12a). Compound **10** (401 mg, 1.06 mmol) was treated according to general procedure B. The 80:20 (**12a**/**12b**) regioisomeric ratio was determined by NMR ^{1}H analysis (integrating the H-2 signal of **12a** and the CH_2O signal of **12b**). The crude imines were purified by column chromatography on alumina (22 g, dehydrated by heating under vacuum before use, Et_2O/EtOAc 100:0, 50:50 and 0:100) to give a mixture of imines **12a** and **12b** (320 mg, 88%): yellow oil; R_f = 0.50 (EtOAc/CH_2Cl_2 50:50).

Major regioisomer **12a**. NMR ^{1}H (250 MHz, $CDCl_3$) δ = 1.57-1.71 (m, 1H, H-3), 1.82–2.02 (m, 1H, H-3′), 2.45–2.65 (m, 2H, 2× H-4), 3.20–3.31 (m, 2H, CH_2O), 4.21–4.34 (m, 1H, H-2), 7.19–7.32 (m, 9H, H-Ph), 7.45–7.47 (m, 6H, H-Ph), 7.80 (s, 1H, H-5) ppm; NMR ^{13}C (75 MHz, $CDCl_3$) δ = 23.8 (C-3), 37.0 (C-4), 66.3 (*C*H$_2$O); 73.0 (C-2), 86.8 (O*Cq*), 126.8, 127.7, 128.7 (CH-Ph), 144.1 (Cq-Ph), 167.3 (C-5) ppm; MS (DCI, NH_3): m/z = 342 (100) [M+H$^+$].

4.1.4.2. (*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-3,4-dihydro-2H-pyrrole (13a). Compound **11** (400 mg, 1.07 mmol) was treated according to general procedure B. The 85:15 (**13a**/**13b**) regioisomeric ratio was determined by NMR ^{1}H analysis (integrating the H-2 signal of **13a** and the CH_2O signal of **13b**). When required, the crude imines were purified by column chromatography on alumina (18 g, dehydrated by heating under vacuum before use, Et_2O/EtOAc 100:0, 50:50 and 0:100) to give a mixture of imines **13a** and **13b** (265 mg, 73%): colourless oil, R_f = 0.54 (EtOAc/CH_2Cl_2 50:50), IR (neat) ν_{max} = 3047, 2930, 2856 (C–H), 1622 (C=N), 1263 (C–O) cm^{-1}.

Major regioisomer **13a**. NMR ^{1}H (250 MHz, $CDCl_3$) δ = 1.03 (s, 9H, SiC(CH_3)$_3$), 1.77–1.99 (m, 2H, 2× H-3), 2.45–2.68 (m, 2H, 2× H-4), 3.82 (AB part of an ABX, ^2J = 10.1 Hz, ^3J = 4.9 Hz, ^3J = 4.0 Hz, $\delta a - \delta b$ = 23,7 Hz, 2H, CH_2OSi), 4.17–4.28 (m, 1H, H-2), 7.34–7.42 (m, 6H, H-Ph), 7.65–7.68 (m, 5H, H-Ph, H-5) ppm; NMR ^{13}C (100 MHz, $CDCl_3$) δ = 19.5 (Si*Cq*), 23.4 (C-3), 27.0 (SiC(*C*H$_3$)$_3$), 37.5 (C-4), 66.6 (*C*H$_2$OSi), 74.7 (C-2), 127.8, 127.9, 129.8, 129.8 (CH-Ph), 133.8, 134.0 (Cq-Ph), 135.8, 135.9 (CH-Ph), 167.7 (C-5) ppm; MS (DCI, NH_3): m/z = 338 (100) [M+H$^+$].

4.1.5. General procedure C: synthesis of thermodynamic imines. DBU (1.05 equiv) was added to a 0.04 M solution of *N*-chloramine (1 equiv) in anhydrous Et_2O at room temperature and under inert atmosphere. The mixture was stirred for 24 h before being filtered through Celite. The solution was concentrated under reduced pressure.

4.1.5.1. 5-(Trityloxymethyl)-3,4-dihydro-2H-pyrrole (12b). Compound **10** (100 mg, 0.27 mmol) was treated according to general procedure C to give **12b** (120 mg). The crude imine was analysed by ^{1}H NMR. ^{1}H NMR (250 MHz, $CDCl_3$) δ = 1.82–1.94 (m, 2H, 2× H-3), 2.69 (t, 2H, ^3J = 13.2 Hz, 2× H-4), 3.79–3.88 (m, 2H, 2× H-2), 3.90 (s, 2H, CH_2O), 7.20–7.33 (m, 9H, H-Ph), 7.44–7.48 (m, 6H, H-Ph) ppm.

4.1.5.2. 5-((*tert*-Butyldiphenylsilyloxy)methyl)-3,4-dihydro-2H-pyrrole (13b). Compound **11** (100 mg, 0.27 mmol) was treated according to general procedure C to give **13b** (116 mg). The crude imine was analysed by ^{1}H NMR. ^{1}H NMR (250 MHz, $CDCl_3$) δ = 1.07 (s, 9H, SiC(CH_3)$_3$), 1.80–1.93 (m, 2H, 2× H-4), 2.61–2.70 (m, 2H, 2× H-3), 3.78–3.87 (m, 2H, H-2), 4.42 (s, 2H, CH_2OSi), 7.34–7.47 (m, 6H, H-Ph), 7.64–7.69 (m, 4H, H-Ph) ppm.

4.1.6. (2*S*,5*R*) and (2*S*,5*S*)-2-((*tert*-Butyldiphenylsilyloxy)-methyl)-5-cyanopyrrolidine (14*cis*/14*trans*). To a solution of the crude imines **13a**/**13b** (obtained from 1.07 mmol of *N*-chloramine **11**) in anhydrous THF (5.4 mL) under inert atmosphere were added diethyl phosphorocyanidate (215 μL, 1.60 mmol) and imidazole (109 mg, 1.60 mmol). The mixture was stirred for 1 h 30 min before evaporating off the THF under reduced pressure. The residue was taken up in Et_2O and filtered through Florisil 60–100 mesh (4 g) to give a crude mixture of diastereoisomeric aminonitriles **14***cis*/**14***trans* (536 mg).

The crude products were then used in the next step. An analytical sample of each diastereoisomer was purified by flash column chromatography on silica gel (pentane/EtOAc 80:20 to 65:35).

4.1.6.1. Less polar diastereoisomer. R_f = 0.20 (pentane/EtOAc 80:20); $[\alpha]_D^{25}$ −18.2 (*c* 1.7, $CHCl_3$); IR (neat) ν_{max} = 3470 (N–H), 3016, 2930 (C–H), 2207 (C≡N), 1214 (C–O) cm^{-1}; NMR ^1H (400 MHz, $CDCl_3$) δ = 1.07 (s, 9H, SiC(CH_3)$_3$), 1.60–1.52 (m, 1H, H-3), 1.81–2.25 (m, 4H, 2× H-4, H-3′, NH), 3.50–3.56 (m, 2H, H-2, CH_2OSi), 3.63–3.68 (m, 1H, CH'_2OSi), 4.05 (dd, ^3J = 7.3 Hz, ^3J = 3.8 Hz, 1H, H-5), 7.38–7.47 (m, 6H, H-Ph), 7.65–7.71 (m, 4H, H-Ph) ppm; NMR ^{13}C (100 MHz, $CDCl_3$) δ = 19.2 (Si*Cq*), 25.8 (C-3), 26.8 (SiC(CH_3)$_3$), 30.2 (C-4), 47.4 (C-5), 58.8 (C-2), 66.5 (CH_2OSi), 121.6 (*C*N), 127.7, 129.8 (CH-Ph), 133.2, 133.2 (Cq-Ph), 135.5, 135.5 (CH-Ph) ppm; MS (DCI, NH_3): *m*/*z* = 365 (100) [M+H$^+$], 382 (8) [M+NH_4^+].

4.1.6.2. More polar diastereoisomer. R_f = 0.12 (pentane/EtOAc 80:20); $[\alpha]_D^{25}$ +13.8 (*c* 1.5, $CHCl_3$); NMR ^1H (400 MHz, $CDCl_3$) δ = 1.09 (s, 9H, SiC(CH_3)$_3$), 1.65–1.75 (m, 1H, H-3), 1.89–1.97 (m, 1H, H-3′), 2.13–2.17 (m, 2H, 2× H-4), 3.40 (pseudoqd, ^3J = 7.0 Hz, ^3J = 5.3 Hz, 1H, H-2), 3.67 (AB part of an ABX, ^2J = 10.2 Hz, ^3J = 6.9 Hz, ^3J = 5.3 Hz, $\delta a - \delta b$ = 7.2 Hz, 2H, CH_2OSi), 4.01 (dd, ^3J = 6.5 Hz, ^3J = 6.0 Hz, 1H, H-5), 7.39–7.49 (m, 6H, H-Ph), 7.68–7.74 (m, 4H, H-Ph) ppm; NMR ^{13}C (100 MHz, $CDCl_3$) δ = 19.2 (Si*Cq*), 26.8, 26.8 (C-3, SiC(CH_3)$_3$), 30.9 (C-4), 46.7 (C-5), 60.0 (C-2), 67.0 (CH_2OSi), 121.8 (*C*N), 127.7, 129.7 (CH-Ph), 33.3 (Cq-Ph), 135.5, 135.6 (CH-Ph) ppm; MS (DCI, NH_3): *m*/*z* = 365 (100) [M+H$^+$].

4.1.7. (2*S*,5*S*)-*tert*-Butyl 2-((*tert*-butyldiphenylsilyloxy)-methyl)-5-cyanopyrrolidine-1-carboxylate (15*cis*) and (2*S*, 5*R*)-*tert*-butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-5-cyanopyrrolidine-1-carboxylate (15*trans*). To the crude mixture of aminonitriles **14***cis*/**14***trans* (obtained from 1.07 mmol of *N*-chloramine **11**) in THF (10.0 mL) were added 1 M aqueous NaOH (12.9 mL, 12.9 mmol) and $(Boc)_2O$ (534 mg, 2.45 mmol). After stirring overnight at room temperature, three additional portions of $(Boc)_2O$ were added (3× 534 mg, 3× 2.45 mmol) over 3 h. Stirring was maintained for a further 1 h before quenching the reaction by addition of water (50.0 mL). The aqueous layer was extracted with Et_2O (3× 125.0 mL) and the combined organic phases were washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (49 g, pentane/EtOAc 95:5 to 80:20) to give the diastereoisomers **15***trans* (142 mg, 29% from *N*-chloramine **11**) and **15***cis* (120 mg, 24% from *N*-chloramine **11**). The relative configuration at C-5 for the two compounds was determined by differential NOE experiments.

4.1.7.1. Diastereoisomer 15*cis*. Colourless oil; R_f = 0.19 (pentane/EtOAc 90:10); $[\alpha]_D^{25}$ +10.3 (*c* 2.0, $CHCl_3$); IR (neat) ν_{max} = 3071, 3050, 2960, 2931, 2858 (C–H), 2288 (C≡N), 1703 (C=O), 1589, 1473 (C=C), 1112 (C–O) cm^{-1}; NMR ^1H (500 MHz, $CDCl_3$) δ = (*as a 50/50 mixture of rotamers A and B*) 1.09 (s, 9H, SiC(CH_3)$_3$), 1.35 (sl, 4.5H, OC(CH_3)$_{3B}$), 1.53 (sl, 4.5H, OC(CH_3)$_{3A}$), 1.95–2.39 (m, 4H, 2× H-4, 2× H-3), 3.62–4.02 (m, 3H, H-2, CH_2OSi), 4.41–4.51 (m, 0.5H, H-5$_A$), 4.51–4.64 (m, 0.5H, H-5$_B$), 7.37–7.45 (m, 6 H, H-Ph), 7.66–7.70 (m, 4H, H-Ph) ppm; NMR ^{13}C (125 MHz, $CDCl_3$) δ = (*as a mixture of rotamers A and B*) 19.2 (Si*Cq*), 26.8 (SiC(CH_3)$_3$), 28.2 (OC(CH_3)$_3$), 29.3, 29.7, 30.0 (C-4$_A$, C-4$_B$, C-3$_A$, C-3$_B$), 48.1 (C-5), 59.4 (C-2), 63.8, 64.6 (CH_2OSi_A, CH_2OSi_B), 81.2, 81.5 (O*Cq*$_A$, O*Cq*$_B$), 119.1, 119.3 (*C*N$_A$, *C*N$_B$), 127.7, 129.7 (CH-Ph), 133.3 (Cq-Ph), 135.6 (CH-Ph), 153.1, 153.8 (*C*=O$_A$, *C*=O$_B$) ppm; MS (DCI, NH_3): *m*/*z* = 465 (100) [M+H$^+$], 482 (45) [M+NH_4^+]; HRMS (DCI, NH_3): calcd for $C_{27}H_{37}N_2O_3Si$ [M+H$^+$] 465.2573, found 465.2573.

4.1.7.2. Diastereoisomer 15*trans*. Colourless oil; R_f = 0.42 (pentane/EtOAc 90:10); $[\alpha]_D^{25}$ −70.8 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} = 3071, 3051, 2959, 2931, 2858 (C–H), 2303 (C≡N), 1704 (C=O), 1589, 1472 (C=C), 1112 (C–O) cm^{-1}; NMR ^1H (300 MHz, $CDCl_3$) δ = (*as a 60/40 mixture of rotamers A and B*) 1.07 (s, 9H, SiC(CH_3)$_3$), 1.37 (s, 3.6H, OC(CH_3)$_{3B}$), 1.55 (s, 5.4H, OC(CH_3)$_{3A}$), 2.14–2.54 (m, 4H, 2× H-4, 2× H3), 3.59–3.65 (m, 0.4H, CH_2OSi_B), 3.68–3.72 (m, 1H, CH'_2OSi), 3.88 (dd, ^2J = 10.2 Hz, ^2J = 4.9 Hz, 0.6H, CH_2OSi_A), 3.95–3.99 (m, 0.4H, H-2$_B$), 4.07–4.11 (m, 0.6H, H-2$_A$), 4.47–4.50 (m, 0.6H, H-5$_A$), 4.53–4.56 (m, 0.4H, H-5$_B$), 7.37–7.48 (m, 6H, H-Ph), 7.61–7.66 (m, 4H, H-Ph) ppm; NMR ^{13}C (75 MHz, $CDCl_3$) δ = (*as a mixture of rotamers A and B*) 19.2 (Si*Cq*), 26.8 (SiC(CH_3)$_3$), 27.0 (C-3$_A$), 27.7 (C-3$_B$), 28.2 (OC(CH_3)$_{3B}$), 28.3 (OC(CH_3)$_{3A}$), 28.8 (C-4$_B$), 30.0 (C-4$_A$), 48.2 (C-5$_B$), 48.3 (C-5$_A$), 58.4 (C-2$_B$), 58.5 (C-2$_A$), 64.0 (CH_2OSi_A), 64.2 (CH_2OSi_B), 81.2 (O*Cq*$_B$), 81.5 (O*Cq*$_A$), 119.1 (*C*N$_B$), 119.4 (*C*N$_A$), 127.7, 127.7, 129.7, 129.8 (CH-Ph$_A$, CH-Ph$_B$), 133.1, 133.2 (Cq-Ph$_A$, Cq-Ph$_B$), 135.4 (CH-Ph), 152.7, 153.2 (*C*=O$_A$, *C*=O$_B$) ppm; MS (DCI, NH_3): *m*/*z* = 465 (100) [M+H$^+$], 482 (20) [M+NH_4^+]; HRMS (DCI, NH_3): calcd for $C_{27}H_{37}N_2O_3Si$ [M+H$^+$] 465.2573, found 465.2572.

4.1.8. General procedure D: reduction of aminonitriles into amines. To a 0.1 M solution of aminonitrile in absolute ethanol saturated with gaseous NH_3 was added Raney Ni. The mixture was hydrogenated at 5 bars for 20 h before being first filtered through Celite, then through a GELMAN 0.45 μm filter to remove traces of catalyst. The solution was then concentrated under reduced pressure.

4.1.8.1. (2*S*,5*R*)-*tert*-Butyl 5-(aminomethyl)-2-((*tert*-butyldiphenylsilyloxy)methyl)pyrrolidine-1-carboxylate (16*cis*). Compound **15***cis* (110 mg, 0.24 mmol) was treated according to general procedure D. The crude product was purified by flash column chromatography on silica gel (9 g, EtOAc/MeOH/NH_4OH 97:1:2 to 94:4:2) to give **16***cis* (65.7 mg, 58%): colourless oil; R_f = 0.53 (AE/MeOH 99:1 under a saturated atmosphere of NH_3); $[\alpha]_D^{25}$ −16.1 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} = 3414 (N–H), 2955, 2932, 2852 (C–H), 1690 (C=O), 1471 (C=C), 1109 (C–O) cm^{-1}; NMR ^1H (300 MHz, $CDCl_3$) δ = 1.05 (s, 9H, SiC(CH_3)$_3$), 1.36 (sl, 9H, OC(CH_3)$_3$), 1.56–2.16 (m, 6H, NH_2, 2× H-4, 2× H-3), 2.76 (AB part

of an ABX, ^2J = 12.8 Hz, ^3J = 6.7 Hz, ^3J = 5.4 Hz, $\delta a - \delta b$ = 55.5 Hz, 2H, CH_2NH$_2$), 3.46–4.01 (m, 4H, H-5, H-2, CH_2OSi), 7.33–7.46 (m, 6H, H-Ph), 7.61–7.68 (m, 4H, H-Ph) ppm; NMR ^{13}C (75 MHz, $CDCl_3$) δ = 19.2 (Si*Cq*), 26.8 (SiC(*C*H$_3$)$_3$), 27.4 (C-4 or C-3), 28.4 (OC(*C*H$_3$)$_3$), 29.6 (C-4 or C-3), 46.1 (*C*H$_2$NH$_2$), 59.6 (C-5), 61.2 (C-2), 64.9 (*C*H$_2$OSi), 79.4 (O*Cq*), 127.6, 129.6 (CH-Ph), 133.4 (Cq-Ph), 135.4, 135.5 (CH-Ph), 155.3 (*C*=O) ppm; MS (DCI, NH_3): *m*/*z* = 469 (100) [M+H$^+$]; HRMS (DCI, NH_3): calcd for $C_{27}H_{41}N_2O_3Si$ [M+H$^+$] 469.2886, found 469.2883.

4.1.8.2. (2*S*,5*S*)-*tert*-Butyl 5-(aminomethyl)-2-((*tert*-butyldiphenylsilyloxy)methyl)pyr-rolidine-1-carboxylate (16*trans*). Compound **15***trans* (159 mg, 0.34 mmol) was treated according to general procedure D. The crude product was purified by flash column chromatography on silica gel (14 g, EtOAc/MeOH/NH_4OH 97:1:2 to 88:10:2) to give **16***trans* (106 mg, 67%): colourless oil; R_f = 0.35 (EtOAc/MeOH 99:1 under a saturated atmosphere of NH_3); $[\alpha]_D^{25}$ −44.6 (*c* 1.3, $CHCl_3$); IR (neat) ν_{max} = 3370 (N–H), 3067, 3045, 2961, 2855 (C–H), 1691 (C=O), 1587, 1471 (C=C), 1110 (C–O) cm^{-1}; NMR ^{1}H (300 MHz, $CDCl_3$/D_2O) δ = (*as a 65:35 mixture of rotamers A and B*) 1.05 (s, 9H, SiC(CH_3)$_3$), 1.28 (s, 5.9H, OC(CH_3)$_{3A}$), 1.46 (s, 3.1H, OC(CH_3)$_{3B}$), 1.65–2.22 (m, 4H, 2× H-4, 2× H-3), 2.56 (dd, ^2J = 12.6 Hz, ^3J = 8.0 Hz, 1H, CH_2NH$_2$), 2.89 (dd, ^2J = 12.6 Hz, ^3J = 2.7 Hz, 0.35H, *CH*$'_2$NH$_{2B}$), 2.99 (dd, ^2J = 12.6 Hz, ^3J = 3.5 Hz, 0.65H, *CH*$'_2$NH$_{2A}$), 3.46 (dd, ^2J = 9.4 Hz, ^3J = 7.8 Hz, 0.65H, CH_2OSi$_A$), 3.65–3.99 (m, 3.35H, H-5, H-2, *CH*$'_2$OSi, CH_2OSi$_B$), 7.32–7.45 (m, 6H, H-Ph), 7.60–7.68 (m, 4H, H-Ph) ppm; NMR ^{13}C (75 MHz, $CDCl_3$) δ = (*as a mixture of rotamers A and B*) 19.1 (Si*Cq*$_A$), 19.1 (Si*Cq*$_B$), 25.8, 25.9, 26.0 (C-4$_A$, C-3$_A$, C-4$_B$ or C-3$_B$), 26.7 (SiC(*C*H$_3$)$_3$), 27.0 (C-4$_B$ or C-3$_B$), 28.2 (OC(*C*H$_3$)$_{3A}$), 28.4 (OC(*C*H$_3$)$_{3B}$), 44.0 (*C*H$_2$NH$_{2A}$), 44.8 (*C*H$_2$NH$_{2B}$), 58.7 (C-5$_A$), 58.7 (C-5$_B$), 60.5 (C-2$_A$), 60.6 (C-2$_B$), 63.4 (*C*H$_2$OSi$_B$), 63.7 (*C*H$_2$OSi$_A$), 79.1 (O*Cq*$_B$), 79.2 (O*Cq*$_A$), 127.5, 127.6, 127.6, 129.4, 129.5 (CH-Ph$_A$, CH-Ph$_B$), 133.2, 133.4, 133.6 (Cq-Ph$_A$, Cq-Ph$_B$), 135.4, 135.4 (CH-Ph), 153.7 (*C*=O$_B$), 153.9 (*C*=O$_A$) ppm; MS (DCI, NH_3): *m*/*z* = 469 (100) [M+H$^+$]; HRMS (DCI, NH_3): calcd for $C_{27}H_{41}N_2O_3Si$ [M+H$^+$] 469.2886, found 469.2884.

4.1.9. General procedure E: synthesis of aminoaldehydes from aminonitriles. A saturated potassium hydrogen tartrate solution (pH 3–4) was prepared by adding potassium hydrogen tartrate (1.90 mg, 10.1 mmol) to water (40.0 mL). DIBALH (2.0 equiv, as a 20% solution in toluene) was added to a 0.1 M solution of aminonitrile (1.0 equiv) in anhydrous toluene/petroleum ether (2:1) at −78 °C and under inert atmosphere. The mixture was stirred for 2 h 30 min at this temperature and saturated potassium hydrogen tartrate solution (4× the volume of the reaction mixture) was added. The reaction mixture was allowed to warm up to 0 °C and was then stirred at this temperature for 5 h. The phases were separated and the aqueous layer was extracted with Et_2O (4×). The combined organic phases were successively washed with water and brine, dried with Na_2SO_4 and concentrated under reduced pressure.

4.1.9.1. (2*R*,5*S*)-*tert*-Butyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-2-formylpyrrolidine-1-carboxylate (17*cis*). Compound **15***cis* (59.0 mg, 127 μmol) was treated according to general procedure E. The crude product was filtered through Florisil 60–100 mesh (1 g, CH_2Cl_2) to give **17***cis* (34.4 mg, 58%): colourless oil; R_f = 0.35 (pentane/EtOAc 90:10); NMR ^{1}H (300 MHz, $CDCl_3$) δ = (*as a 60/40 mixture of rotamers A and B*) 0.97 (s, 9H, SiC(CH_3)$_3$), 1.21–1.41 (m, 9H, OC(CH_3)$_3$), 1.80–2.13 (m, 4H, 2× H-3, 2× H-4), 3.53–4.15 (m, 4H, H-2, H-5, CH_2OSi), 7.22–7.41 (m, 6H, H-Ph), 7.48–7.65 (m, 4H, H-Ph), 9.33 (d, ^3J = 3.1 Hz, 0.6H, C*H*O$_A$), 9.40 (sl, 0.4H, C*H*O$_B$) ppm; NMR ^{13}C (75 MHz, $CDCl_3$) δ = (*as a mixture of rotamers A and B*) 19.2 (Si*Cq*), 25.1 (C-3$_B$ or C-4$_B$), 26.4 (C-3$_A$ or C-4$_A$), 26.8, 26.9 (OC(*C*H$_3$)$_{3A}$, OC(*C*H$_3$)$_{3B}$), 27.1 (C-3$_A$ or C-4$_A$), 27.9 (C-3$_B$ or C-4$_B$), 28.3 (SiC(*C*H$_3$)$_3$), 59.4 (C-2$_B$ or C-5$_B$), 59.6 (C-2$_A$ or C-5$_A$), 64.4 (*C*H$_2$OSi$_A$), 64.6 (*C*H$_2$OSi$_B$), 66.2 (C-2 or C-5), 80.6, 80.8 (O*Cq*$_A$, O*Cq*$_B$), 127.7, 129.8 (CH-Ph$_A$, CH-Ph$_B$), 133.2 (Cq-Ph), 135.5, 135.6 (CH-Ph$_A$, CH-Ph$_B$), 153.9 (*C*=O), 201.1, 201.2 (*C*HO$_A$, *C*HO$_B$) ppm.

4.1.9.2. (2*S*,5*S*)-*tert*-Butyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-2-formylpyrrolidine-1-carboxylate (17*trans*). Compound **15***trans* (50.0 mg, 108 μmol) was treated according to general procedure E. The crude product was filtered through Florisil 60–100 mesh (1 g, CH_2Cl_2) to give **17***trans* (39.0 mg, 77%): colourless oil; R_f = 0.35 (pentane/EtOAc 90:10); NMR ^{1}H (300 MHz, $CDCl_3$) δ = (*as a 55/45 mixture of rotamers A and B*) 1.05 (s, 9H, SiC(CH_3)$_3$), 1.34 (s, 4H, OC(CH_3)$_{3B}$), 1.42 (s, 4H, OC(CH_3)$_{3A}$), 1.83–2.41 (m, 4H, 2× H-3, 2× H-4), 3.62 (dd, ^2J = 9.9 Hz, ^3J = 6.4 Hz, 0.45H, CH_2OSi$_B$), 3.67–3.75 (m, 1H, CH_2OSi$_A$, *CH*$'_2$OSi$_B$), 3.94 (dd, ^2J = 10.2 Hz, ^3J = 5.0 Hz, 0.55H, *CH*$'_2$OSi$_A$), 4.00–4.06 (m, 0.45H, H-5$_B$), 4.13–4.21 (m, 1.10H, H-2$_A$, H-5$_A$), 4.30 (dpseudot, ^3J = 9.4 Hz, ^3J = 1.6 Hz, 0.45H, H-2$_B$), 7.33–7.46 (m, 6H, H-Ph), 7.61–7.67 (m, 4H, H-Ph), 9.53 (d, ^3J = 2.6 Hz, 0.55H, C*H*O$_A$), 9.60 (d, ^3J = 1.8 Hz, 0.45H, C*H*O$_B$) ppm; NMR ^{13}C (75 MHz, $CDCl_3$) δ = (*as a mixture of rotamers A and B*) 19.2, 19.2 (Si*Cq*$_A$, Si*Cq*$_B$), 25.0, 26.6 (C-3$_A$, C-3$_B$ or C-4$_A$, C-4$_B$), 26.8, 26.8 (OC(*C*H$_3$)$_{3A}$, OC(*C*H$_3$)$_{3B}$), 27.0 (C-3 or C-4), 28.3 (SiC(*C*H$_3$)$_3$), 59.1, 59.3 (C-2$_A$, C-2$_B$ or C-5$_A$, C-5$_B$), 63.9, 64.3 (*C*H$_2$OSi$_{A+B}$), 65.7, 66.0 (C-2$_A$, C-2$_B$ or C-5$_A$, C-5$_B$), 80.4, 80.5 (O*Cq*$_A$, O*Cq*$_B$), 127.7, 127.7, 127.7, 127.8, 129.7, 129.7 (CH-Ph$_A$, CH-Ph$_B$), 133.2, 133.3, 133.3, 133.4 (Cq-Ph$_A$, Cq-Ph$_B$), 135.5, 135.5, 135.5 (CH-Ph$_A$, CH-Ph$_B$), 153.4, 154.3 (*C*=O$_A$, *C*=O$_B$), 200.7, 200.7 (*C*HO$_A$, *C*HO$_B$) ppm.

4.1.10. General procedure F: reductive amination. To a 0.1 M solution of aldehyde (1.0 equiv) in anhydrous CH_2Cl_2 under inert atmosphere were successively added 4Å molecular sieves, (*S*)-2-aminobutan-1-ol (1.1 equiv) and $NaBH(OAc)_3$ (1.4 equiv). After being stirred overnight at room temperature, the reaction was quenched by addition of solid $NaHCO_3$ and a few drops of saturated aqueous $NaHCO_3$ solution. The mixture was extracted directly in the reaction flask with EtOAc. The combined organic phases were dried with Na_2SO_4 and concentrated under reduced pressure.

4.1.10.1. (2*S*,5*R*)-*tert*-Butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-5-(((*S*)-1-hydroxy-butan-2-ylamino)methyl)pyrrolidine-1-carboxylate (18*cis*). Compound **17***cis* (34.4 mg, 73.7 μmol) was treated according to general procedure C. The crude product was purified by flash column chromatography on silica gel (3 g, EtOAc/MeOH/NH_4OH 98:0:2 to 97:1:2) to give **18***cis* (20.7 mg, 52%): colourless oil; R_f = 0.46 (EtOAc/MeOH/NH_4OH 97:1:2); $[\alpha]_D^{25}$+0.4 (*c* 1.8, $CHCl_3$); IR (neat) ν_{max} = 3435 (O–H), 3071, 3050, 2962, 2931, 2858 (C–H), 1690 (C═O), 1589, 1473 (C═C), 1112 (C–O) cm^{-1}; NMR ^1H (300 MHz, $CDCl_3$) δ = (*as a 70/30 mixture of rotamers A and B*) 0.84 (t, ^3J = 7.5 Hz, 3 H, CH_3), 1.06 (s, 9 H, SiC(CH_3)$_3$), 1.23–1.48 (m, 11H, OC(CH_3)$_3$, CH_3CH_2), 1.72–2.13 (m, 4H, 2× H-4, 2× H-3), 2.44–2.55 (m, 1H, C*H*NH), 2.60–2.71 (m, 1H, CH_2NH), 2.77 (dd, ^2J = 11,6 Hz, ^3J = 4.5 Hz, 1H, CH'_2NH), 3.20 (dd, ^2J = 10.6 Hz, ^3J = 6.8 Hz, 1H, CH_2OH), 3.48–3.64 (m, 0.3H, CH_2OSi$_B$), 3.54 (dd, ^2J = 10.6 Hz, ^3J = 4.0 Hz, 1H, *CH'*$_2$OH), 3.69–4.03 (m, 3.7H, H-5, H-2, *CH'*$_2$OSi, CH_2OSi$_A$), 7.34–7.45 (m, 6H, H-Ph), 7.62–7.68 (m, 4H, H-Ph) ppm; NMR ^{13}C (75 MHz, $CDCl_3$) δ = 10.3 (*C*H_3), 19.3 (Si*Cq*), 24.2 (CH_3CH_2), 26.9 (SiC(*C*H_3)$_3$), 26.9, 28.1 (C-4, C-3), 28.4 (OC(*C*H_3)$_3$), 49.9 (*C*H_2NH), 59.0 (C-5), 59.7 (C-2), 60.1 (*C*HNH), 62.5 (*C*H_2OH), 64.9 (*C*H_2OSi), 79.5 (O*Cq*), 127.6, 129.6 (CH-Ph), 133.5 (Cq-Ph), 135.5 (CH-Ph), 155.1 (*C*═O) ppm; MS (DCI, NH_3): *m*/*z* = 541 (100) [M+H^+]; HRMS (DCI, NH_3): calcd for $C_{31}H_{49}N_2O_4Si$ [M+H^+] 541.3462, found 541.3464.

4.1.10.2. (2*S*,5*S*)-*tert*-Butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-5-(((*S*)-1-hydroxy-butan-2-ylamino)methyl)-pyrrolidine-1-carboxylate (18*trans*). Compound **17***trans* (18.8 mg, 40.3 μmol) was treated according to general procedure F. The crude product was purified by flash column chromatography on silica gel (2 g, EtOAc/MeOH/NH_4OH 98:0:2 then 97:1:2) to give **18***trans* (14.2 mg, 65%): colourless oil; R_f = 0.46 (EtOAc/MeOH/NH_4OH 97:1:2); $[\alpha]_D^{25}$−35.3 (*c* 2.0, $CHCl_3$); IR (neat) ν_{max} = 3435 (O–H), 3135, 3071, 3049, 2963, 2858 (C–H), 1690 (C═O), 1589, 1473 (C═C), 1113 (C–O) cm^{-1}; NMR ^1H (300 MHz, $CDCl_3$) δ = (*as a 70/30 mixture of rotamers A and B*) 0.87–0.94 (m, 3H, CH_3), 1.05 (s, 9H, SiC(CH_3)$_3$), 1.29 (s, 6.3H, OC(-CH_3)$_{3A}$), 1.34–1.50 (m, 2H, CH_3CH_2), 1.46 (s, 2.7H, OC(CH_3)$_{3B}$), 1.75–2.17 (m, 4H, 2× H-4, 2× H-3), 2.32–2.39 (m, 0.3H, CH_2NH$_B$), 2.43 (dd, ^2J = 11.4 Hz, ^3J = 8.0 Hz, 0.7H, CH_2NH$_A$), 2.49–2.58 (m, 1H, C*H*NH), 2.94 (dd, ^2J = 11.3 Hz, ^3J = 2.3 Hz, 0.3H, *CH'*$_2$NH$_B$), 3.02 (dd, ^2J = 11.4 Hz, ^3J = 3.6 Hz, 0.7H, *CH'*$_2$NH$_A$), 3.26 (dd, ^2J = 10.6 Hz, ^3J = 6.1 Hz, 1H, CH'_2OH), 3.46 (dd, ^2J = 9.5 Hz, ^3J = 7.7 Hz, 0.7H, CH_2OSi$_A$), 3.59 (dd, ^2J = 10.6 Hz, ^3J = 4.0 Hz, 1H, CH'_2OH), 3.68–3.98 (m, 3.3H, H-5, H-2, CH_2OSi$_B$, *CH'*$_2$ OSi), 7.33–7.46 (m, 6H, H-Ph), 7.60–7.67 (m, 4H, H-Ph) ppm; NMR ^{13}C (75 MHz, $CDCl_3$) δ = (*as a mixture of rotamers A and B*) 10.4 (CH_{3B}), 10.5 (CH_{3A}), 19.2 (SiCq_A), 19.3 (SiCq_B), 24.4 (CH_3CH_2B), 24.7 (CH_3CH_2A), 25.9 (C-4$_B$ or C-3$_B$), 26.2 (C-4$_A$ or C-3$_A$), 26.8 (SiC(*C*H_3)$_3$), 27.8 (C-4 or C-3), 28.3 (OC(*C*H_3)$_{3A}$), 28.6 (OC(*C*H_3)$_{3B}$), 49.3 (*C*H_2NH$_B$), 49.4 (*C*H_2NH$_A$), 58.4 (C-5$_A$), 58.5 (C-5$_B$), 58.7 (C-2$_B$), 58.8 (C-2$_A$), 60.2 (*C*HNH$_A$), 60.5 (*C*HNH$_B$), 62.3 (*C*H_2OH$_A$), 62.7 (*C*H_2OH$_B$), 63.5 (*C*H_2OSi$_B$), 63.8 (*C*H_2OSi$_A$), 79.2 (OCq_B), 79.4 (OCq_A), 127.6, 127.7, 127.7, 129.5, 129.6, 129.7 (CH-Ph$_A$, CH-Ph$_B$), 133.4, 133.5, 133.7 (Cq-Ph$_A$, Cq-Ph$_B$), 135.5, 135.5 (CH-Ph$_A$, CH-Ph$_B$), 153.7 (*C*═O$_B$), 154.1 (*C*═O$_A$) ppm; MS (DCI, NH_3): *m*/*z* = 541 (100) [M+H^+]; HRMS (DCI, NH_3): calcd for $C_{31}H_{49}N_2O_4Si$ [M+H^+] 541.3462, found 541.3462.

4.1.11. General procedure G: final deprotection. 1 M Methanolic HCl was prepared by slow addition of acetyl chloride (344 μL, 5.00 mmol) to anhydrous MeOH (5.0 mL) under inert atmosphere. A 0.05 M solution of protected compound in 1 M methanolic HCl was stirred overnight at room temperature under inert atmosphere. The reaction mixture was then concentrated under reduced pressure. The crude product was dissolved in MeOH/water 2:1 (25 mL/mmol), acidic resin (Dowex 50 WX8-200, 12 g/mmol) was added, and the suspension was stirred slowly for 1 h. The resin was then successively washed with water (500 mL/mmol) and MeOH (150 mL/mmol), taken up in 3 M aqueous NH_4OH (85 mL/mmol) and the mixture stirred slowly for 1 h. The suspension was then filtered and the resin rinsed with 3 M aqueous NH_4OH (850 mL/mmol). The resulting solution was then concentrated to dryness under reduced pressure.

4.1.11.1. (2*S*,5*R*)-2-(Hydroxymethyl)-5-(((*S*)-1-hydroxybutan-2-ylamino)methyl)pyrrolidine (19*cis*). Compound **18***cis* (39.4 mg, 73.0 μmol) was treated according to general procedure G. The crude product was purified by column chromatography on silica gel (0.8 g, CH_2Cl_2/MeOH/NH_4OH 76:20:4) to give **19***cis* (12.5 mg, 85%): colourless oil; R_f = 0,33 (CH_2Cl_2/MeOH/NH_4OH 76:20:4); $[\alpha]_D^{25}$+7.1 (*c* 1.3, MeOH); NMR ^1H (300 MHz, CD_3OD) δ = 0.90 (t, ^3J = 7.5 Hz, 3H, CH_3), 1.31–1.57 (m, 4H, H-4, H-3, CH_3CH_2), 1.77–1.95 (m, 2H, H-4′, H-3′), 2.43–2.51 (m, 1H, C*H*NH), 2.62 (AB part of an ABX, ^2J = 11.6 Hz, ^3J = 7.8 Hz, ^3J = 5.0 Hz, $\delta a - \delta b$ = 46.4 Hz, 2H, CH_2NH), 3.38 (dd, ^2J = 11.1 Hz, ^3J = 6.7 Hz, 1H, CH_2OH), 3.49 (AB part of an ABX, ^2J = 10.9 Hz, ^3J = 6.0 Hz, ^3J = 5.4 Hz, $\delta a - \delta b$ = 16.8 Hz, 2H, CH_2OH), 3.61 (dd, ^2J = 11.1 Hz, ^3J = 4.2 Hz, 1H, *CH'*$_2$OH) ppm; NMR ^{13}C (75 MHz, CD_3OD) δ = 10.8 (*C*H_3), 24.8 (CH_3CH_2), 28.4 (C-3), 30.4 (C-4), 53.2 (*C*H_2NH), 59.9 (C-5), 61.6 (C-2), 62.4 (*C*HNH), 63.8 (*C*H_2OH), 66.1 (*C*H_2OH) ppm; MS (DCI, NH_3): *m*/*z* = 203 (100) [M+H^+]; HRMS (DCI, NH_3): calcd for $C_{10}H_{23}N_2O_2$ [M+H^+] 203.1760, found 203.1760.

4.1.11.2. (2*S*,5*S*)-2-(hydroxymethyl)-5-(((*S*)-1-hydroxybutan-2-ylamino)methyl)pyrrolidine (19*trans*). Compound **18***trans* (33.6 mg, 62.2 μmol) was treated according to general procedure G. The crude product was purified by column chromatography on silica gel (0.8 g, CH_2Cl_2/MeOH/ NH_4OH 74:20:6) to give **19***trans* (10.8 mg, 86%): colourless oil; R_f = 0.29 (CH_2Cl_2/MeOH/NH_4OH 74:20:6); $[\alpha]_D^{25}$+22.7 (*c* 1.1, MeOH); NMR ^1H (300 MHz, CD_3OD) δ = 0.92 (t, ^3J = 7.5 Hz, 3H, CH_3), 1.33–1.56 (m, 4H, H-4, H-3, CH_3CH_2), 1.84–2.03 (m, 2H, H-4′, H-3′), 2.45–2.53 (m, 1H,

C*H*NH), 2.60 (d, ^3J = 6.5 Hz, 2H, CH_2NH), 3.19–3.30 (m, 2H, H-5, H-2), 3.46 (d, ^3J = 5.9 Hz, 2H, CH_2OH), 3.48 (AB part of an ABX, ^2J = 11.1 Hz, ^3J = 6.7 Hz, ^3J = 4.4 Hz, $\delta a - \delta b$ = 51.8 Hz, 2H, CH_2OH) ppm; NMR ^{13}C (75 MHz, CD_3OD) δ = 10.8 (*C*H_3), 24.8 (CH_3CH_2), 28.7 (C-3), 30.7 (C-4), 52.6 (*C*H_2NH), 58.6 (C-5), 60.4 (C-2), 62.1 (*C*HNH), 64.0 (*C*H_2OH), 65.5 (*C*H_2OH) ppm; MS (DCI, NH_3): *m/z* = 203 (100) [M+H$^+$]; HRMS (DCI, NH_3): calcd for $C_{10}H_{23}N_2O_2$ [M+H$^+$] 203.1760, found 203.1759.

4.1.12. (5*S*,5′*S*)-5,5′-Bis((*tert*-butyldiphenylsilyloxy)eméthyl)-2,2′-bipyrrolidine (23). To the purified mixture of imines **13a/13b** (221 mg, 656 μmol) in anhydrous and degassed DME (0.6 mL) under argon was added Ti(O*i*-Pr)$_4$ (196 μL, 656 μmol). After 5 min, Sm(0) (109 mg, 727 μmol) and I_2 (100 μL of a 1 M solution in degassed DME, 0.1 mmol) were successively added. The reaction mixture was stirred for 2 h at room temperature before being diluted with CH_2Cl_2 and quenched by addition of a 15% aqueous NaOH saturated with NaCl (4.0 mL). The organic layer was separated, the aqueous phase treated again with a 15% aqueous NaOH saturated with NaCl (2.0 mL) and extracted with CH_2Cl_2. The combined organic phases were then filtered through Celite. The filtrate was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (22 g, CH_2Cl_2/MeOH/NH_4OH 98.3:0.5:1.2) to give **23** (45.2 mg, 20%) and **9** (65.8 mg, 30%). Compound **23**: yellow oil; $[\alpha]_D^{25}$ −3.0 (*c* 1.9, $CHCl_3$); NMR ^{1}H (300 MHz, $CDCl_3$) δ = 1.06 (s, 9H, SiC(CH_3)$_3$), 1.33–1.42 (m, 2H, 2× H-3), 1.43–1.52 (m, 2H, 2× H-4), 1.78–1.88 (m, 4H, 2× H-3′, 2× H-4′), 1.92–2.15 (m, 2H, 2× NH), 2.91–3.02 (m, 1H, 2× H-2), 3.31–3.36 (m, 2H, 2× H-5), 3.56 (d, ^3J = 5.8 Hz, 4H, 2× CH_2OSi), 7.35 (m, 6H, H-Ph), 7.64–7.68 (m, 4H, H-Ph) ppm; NMR ^{13}C (75 MHz, $CDCl_3$) δ = 19.3 (Si*C*q), 26.9 (SiC(*C*H_3)$_3$), 27.8 (C-4), 29.1 (C-3), 59.2 (C-5), 62.6 (C-2), 66.6 (*C*H_2OSi), 127.6, 129.6 (CH-Ph), 133.6, 133.6 (Cq-Ph), 135.6, 135.6 (CH-Ph) ppm; MS (DCI, NH_3): *m/z* = 677 (100) [M+H$^+$]; HRMS (DCI, NH_3): calcd for $C_{42}H_{57}N_2O_2Si_2$ [M+H$^+$] 677.3959, found 677.3958.

4.1.13. (5*S*,5′*S*)-5,5′-Bis(hydroxymethyl)-2,2′-bipyrrolidine (24). Compound **23** (49.5 mg, 73.2 μmol) was treated according to general procedure G with a 2 M methanolic HCl. The crude product was purified by column chromatography on silica gel (2 g, CH_2Cl_2/MeOH/NH_4OH 74:20:6) to give **24** (9.7 mg, 66%): yellow oil; R_f = 0.26 (CH_2Cl_2/MeOH/NH_4OH 74:20:6); $[\alpha]_D^{25}$ +21.7 (*c* 0.7, MeOH); NMR ^{1}H (300 MHz, CD_3OD) δ = 1.36–1.54 (m, 4H, 2× H-3, 2× H-4), 1.85–1.99 (m, 4H, 2× H-3′, 2× H-4′), 2.98–3.06 (m, 2H, 2× H-2), 3.22–3.30 (m, 2H, 2× H-5), 3.48 (AB part of an ABX, ^2J = 10.9 Hz, ^3J = 6.3 Hz, ^3J = 5.5 Hz, $\delta a - \delta b$ = 12.1 Hz, 4H, 2× CH_2OH) ppm; NMR ^{13}C (75 MHz, CD_3OD) δ = 28.8 (C-4), 30.2 (C-3), 60.7 (C-5), 63.6 (C-2), 65.3 (*C*H_2OH) ppm; MS (DCI, NH_3): *m/z* = 201 (100) [M+H$^+$]; HRMS (DCI, NH_3): calcd for $C_{10}H_{21}O_2N_2$ [M+H$^+$] 201.1603, found 201.1600.

4.2. Biological tests

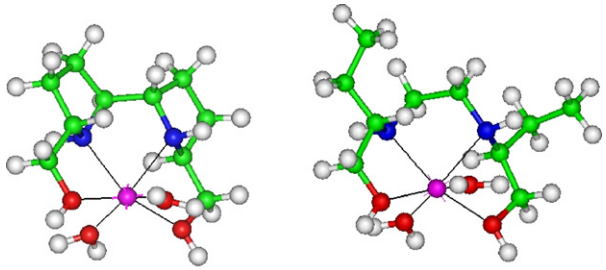
Susceptibility of *M. tuberculosis* H_{37}Rv to compounds **19***cis*, **19***trans* and **24** was tested by determining the minimum inhibitory concentration (MIC). We used a colorimetric microassay based on the reduction of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Sigma) to formazan by metabolically active cells.[25] Briefly, serial twofold dilutions of each drug were prepared in 7H9 broth (Middlebrook 7H9 broth base (Difco)) using 96-well microtitre plates and 100 μl of *M. tuberculosis* H_{37}Rv suspension in 7H9 broth was added to each well. After 6 days incubation, MTT was added (50 μl, 1 mg/ml). After one day incubation, solubilisation buffer was added to each well. The optical densities were measured at 570 nm. The MIC was determined as the lowest concentration of drug that inhibited bacterial growth (absorbance from untreated bacilli was taken as a control for growth).

References and notes

1. World Health Organisation Tuberculosis Fact Sheet N° 104, 2006. See: http://www.who.int/mediacentre/factsheets/fs104/en.
2. (a) Wilkinson, R. G.; Sheperd, R. G.; Thomas, J. P.; Baughn, C. *J. Am. Chem. Soc.* **1961**, *83*, 2212; (b) Sheperd, R. G.; Baughn, C.; Cantrall, M. L.; Goodstein, B.; Thomas, J. P.; Wilkinson, R. G. *Ann. N.Y. Acad. Sci.* **1966**, *135*, 686.
3. (a) Lee, R. E.; Mikušová, K.; Brennan, P. J.; Besra, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 11829; (b) Khoo, K.-H.; Douglas, E.; Azadi, P.; Inamine, J. M.; Besra, G. S.; Mikušová, K.; Brennan, P. J.; Chatterjee, D. *J. Biol. Chem.* **1996**, *271*, 28682.
4. (a) Cole, A.; May, P. M.; Williams, D. R. *Agents Actions* **1981**, *11*, 296; (b) Solecki, T. J.; Aviv, A.; Bogden, J. D. *Toxicology* **1984**, *31*, 207; (c) King, A. B.; Schwartz, R. *J. Nutr.* **1987**, *117*, 704.
5. Häsler, H.; Kawakami, R. P.; Mlaker, E.; Severn, W. B.; Stütz, A. E. *Bioorg. Med. Chem.* **2001**, *11*, 1679.
6. Reynolds, R. C.; Bansal, N.; Rose, J.; Friedrich, J.; Suling, W. J.; Maddry, J. A. *Carbohydrate Res.* **1999**, *317*, 164.
7. García-García, A.; Gálvez, J.; De Julián-Ortiz, J.; García-Domenech, R.; Muñoz, C.; Guna, R.; Borráz, R. *J. Biomol. Screen.* **2005**, *10*, 206.
8. Lee, R. E.; Protopopova, M.; Crooks, E.; Slayden, R. A.; Terrot, M.; Barry, C. E., III *J. Comb. Chem.* **2003**, *5*, 172.
9. (a) Jia, L.; Tomaszewski, J. E.; Hanrahan, C.; Coward, L.; Noker, P.; Gorman, G.; Nikonenko, B.; Protopopova, M. *Br. J. Pharmacol.* **2005**, *144*, 80; (b) Jia, L.; Tomaszewski, J. E.; Noker, P. E.; Gorman, G. S.; Glaze, E.; Protopopova, M. *J. Pharm. Biomed. Anal.* **2005**, *37*, 793.
10. Bogatcheva, E.; Hanrahan, C.; Nikonenko, B.; Samala, R.; Chen, P.; Gearhart, J.; Barbosa, F.; Einck, L.; Nacy, C. A.; Protopopova, M. *J. Med. Chem.* **2006**, *49*, 3045.
11. Razafimahfa, D.; Ralambomanana, D. A.; Hammouche, L.; Pélinski, L.; Lauvagie, S.; Bebear, C.; Brocard, J.; Maugein, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2301.
12. Marotte, K.; Ayad, T.; Génisson, Y.; Besra, G. S.; Baltas, M.; Prandi, J. *Euro. J. Org. Chem.* **2003**, 2557.
13. The chiral 2,2′-bipyrrolidine scaffold has already been successfully exploited in asymmetric catalysis and has been shown to give well-characterized complexes with $ZnCl_2$: (a) Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew Chem. Int. Ed.*

2000, *39*, 4093; (b) Denmark, S. E.; Fu, J.; Lawler, M. J. *Organic Synthesis* **2006**, *83*, 121.

14. The compared ability of EMB and our analogues to act as tetradentate ligands was assessed by simple molecular mechanics structural optimization (MSI/Insight II/Discover 3/esff force field). For example, energetically minimized zinc chelates generated from the all-*S* isomer of the targeted bipyrrolidine **24** (**A**) and the parent drug EMB (**B**) displayed comparable geometry.



A **B**

15. (a) Horenstein, B. A.; Zabinski, R. F.; Schramm, V. L. *Tetrahedron Lett.* **1993**, *34*, 7213; (b) Furneaux, R. H.; Limberg, G.; Tyler, P. C. *Tetrahedron* **1997**, *53*, 2915; (c) Evans, G. B.; Furneaux, R. H.; Gainsford, G. J.; Schramm, V. L.; Tyler, C. T. *Tetrahedron* **2000**, *56*, 3053; (d) Evans, G. B.; Furneaux, R. H.; Hutchison, T. L.; Kezar, H. S.; Morris, P. E., Jr.; Schramm, V. L.; Tyler, C. T. *J. Org. Chem.* **2001**, *66*, 5723; (e) Evans, G. B.; Furneaux, R. H.; Gainsford, G. J.; Hanson, J. C.; Kicska, G. A.; Sauve, A. S.; Schramm, V. L.; Tyler, C. T. *J. Med. Chem.* **2003**, *46*, 155.
16. (a) Davis, B. G.; Maughan, M. A. T.; Chapman, T. M.; Villard, R.; Courtney, S. *Org. Lett.* **2002**, *4*, 103; (b) Chapman, T. M.; Courtney, S.; Hays, P.; Davis, B. G. *Chem. Eur. J.* **2003**, *9*, 3397.
17. vandenBroeck, L. A. G. M.; Porskamp, P. A. T. W.; Haltiwanger, R. C.; Zwanenburg, B. *J. Org. Chem.* **1984**, *49*, 1691.
18. Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049.
19. Harusawa, S.; Hamada, Y.; Shiori, T. *Tetrahedron Lett.* **1979**, *48*, 4663.
20. Arndt, H.-D.; Polborn, K.; Koert, U. *Tetrahedron Lett.* **1997**, *38*, 3879.
21. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
22. Yanada, R.; Negoro, N.; Okaniwa, M.; Miwa, Y.; Taga, T.; Yanada, K.; Fujita, T. *Synlett* **1999**, *5*, 537.
23. This study will be reported independently in due course.
24. Tanaka, H.; Dhimane, H.; Fujita, H.; Ikemoto, Y.; Torii, S. *Tetrahedron Lett.* **1988**, *29*, 3811; Taniguchi, Y.; Kuno, T.; Nakahashi, M.; Takaki, K.; Fujiwara, Y. *Appl. Organomet. Chem.* **1995**, *9*, 491; It was also reported that treatment with an excess of SmI_2 in refluxing THF delivered a 69% yield in coupling product. In our hands however, the reaction essentially yielded the reduction product: Enholm, E. J.; Forbed, D. C.; Holub, D. P. *Synth. Commun.* **1990**, *20*, 981.
25. Hansen, M. B.; Nielsen, S. E.; Berg, K. *J. Immunol. Methods* **1989**, *119*, 203; Gomez-Flores, R.; Gupta, S.; Tamez-Guerra, R.; Mehta, R. T. *J. Clin. Microbiol.* **1995**, *33*, 1842.