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Enantioselective Synthesis of 2-Aminomethyl and 3-Amino Pyrrolidines and Piperidines through 1,2-Diamination of Aldehydes

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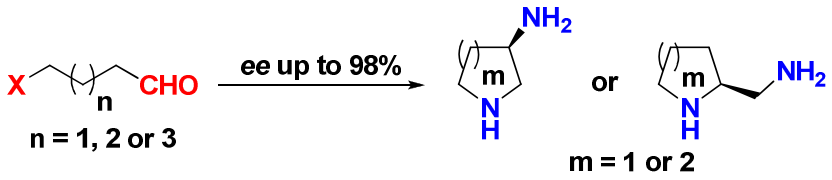
TOC Graphic



Abstract: An efficient method for the synthesis of 1,2-diamines from aldehydes through proline-catalyzed asymmetric α-amination followed by reductive amination is reported. The products resemble those obtained through direct asymmetric diamination of terminal alkenes. The methodology is used to synthesize 2-aminomethyl and 3-amino pyrrolidines and piperidines in high yields and with good enantioselectivity. The usefulness of the method is demonstrated through the synthesis of a 2-aminomethyl iminocyclitol.

Introduction

1,2-diamino units are widely found in natural products and in a number of biologically active synthetic compounds.[1] In addition to being used as synthetic building blocks for heterocyclic compounds; they are also used as chiral ligands and catalysts.[2] A wide range of approaches are available in the literature towards the synthesis of this ubiquitous motif. While metal-catalyzed diamination reactions[3-5] are the most common approach towards their synthesis, methods based on the functionalization of nitro alkanes,[6] amino acids,[7] aziridines,[8] β-chloro amines[9] and aldehydes through umpolung reactions[10] are also available. Recently, Masson and coworkers have reported an efficient method for the asymmetric synthesis of 1,2-diamines through amination of enecarbamates.[11] 1,2-diamines are often part of aza-heterocyclic compounds as masked units, eg. natural products such as balanol and pseudodistomins and azasugars containing 2-aminomethyl groups (Figure 1). We envisaged that a general method for the synthesis of such heterocyclic compounds can be achieved through intramolecular S_N2 displacement of a leaving group by one of the 2-amino groups introduced by α-amination followed by reductive amination of an aldehyde (Scheme 1).

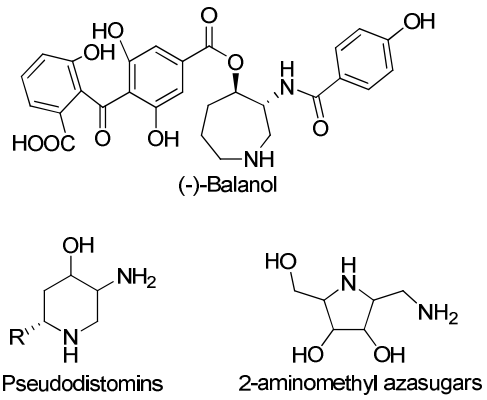


Figure 1. Aza-heterocyclic compounds containing 1,2-diamino units

Proline-catalyzed α-amination of aldehydes using dibenzyl azodicarboxylate (DBAD) is a widely used synthetic strategy that allows the stereoselective introduction of an amino group in the α-position of aldehydes.[12] The intermediate, an α-hydrazino aldehyde obtained from the initial reaction is prone to racemization and hence is reduced in situ into an alcohol or is functionalized

further by aldol,[13] Wittig,[14] Barbier[15] or Passerini[16] reactions in one-pot. Reductive amination of this α-hydrazino aldehyde to get a 2-hydrazino amine, which could then be converted to a terminal 1,2-diamine has not been explored yet. However, the α-hydroxylation of aldehydes followed by reductive amination to get β-amino alcohols has already been reported[17] and we have used this method for the synthesis of hydroxy diamino acid derivatives.[18] Here we report enantioselective syntheses of four compounds (Figure 2), viz. (*R*)-3-aminopiperidine (**1**), (*R*)-3-aminopyrrolidine (**2**), (*R*)-2-aminomethylpyrrolidine (**3**) and (*R*)-2-aminomethylpiperidine (**4**) using the strategy outlined in Scheme 1.

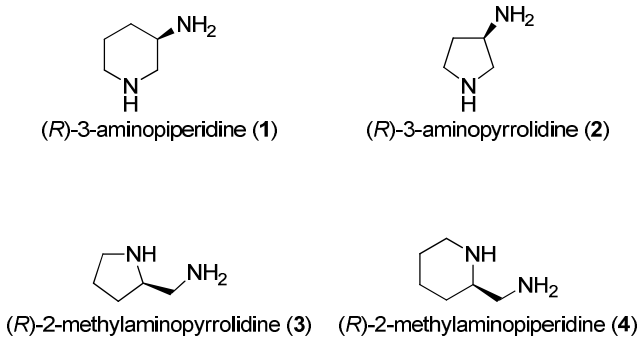


Figure 2. Molecules synthesized in this study

Although, we carried out the synthesis of compounds **1-4** to establish the usefulness of the methodology reported here, a literature search revealed that enantioselective synthesis of these targets are of importance. These compounds also have the potential to be used as chiral ligands for transition metals and as oragnocatalysts. A general method that can be used to synthesize compounds **1-4** is not available. Zhang et al. have recently reported the synthesis of **1** as its hydrochloride salt, which is a synthetic intermediate for linagliptin and alogliptin. The synthesis was achieved by the cyclization followed by reduction of an ornithine derivative, which in turn was synthesized from asymmetric reduction of a dehydroamino ester derivative.[19] Compound **1** has been used as a component in the design of hybrid molecules for the inhibition of dipeptidyl peptidase-4.[20] Davies et al. have reported a general method for the synthesis of 3-aminopyrrolidines, including compound **2**, by the conjugate addition of homochiral lithium amides to methyl 4-(*N*-benzyl-*N*-allylamino)but-2-enoates followed by cyclization, enolate functionalization and deprotection.[21] The reaction proceeds in essentially four steps with stereoselectivity achieved in excess of 98%. An earlier report on the synthesis of **2** used optically pure *N*-benzyl-3-pyrrolidinol as the starting material.[22] Recently, **2** was incorporated on to

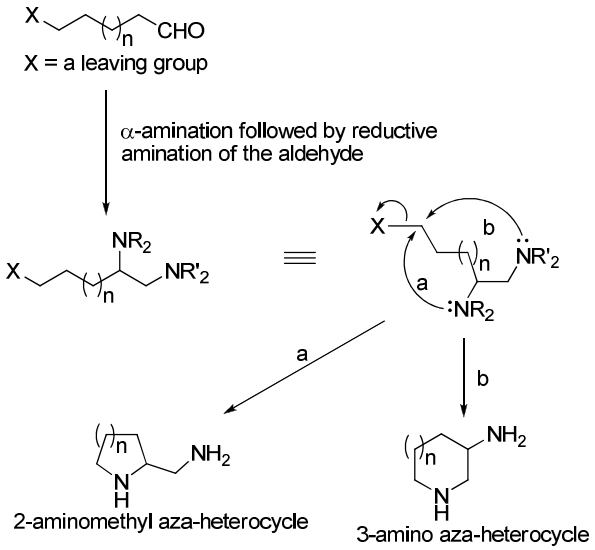
known glutaminase isomerase C inhibitors, resulting in molecules with nanomolar potency and improved *C*log*P* values.[23] Compound **2** has also been incorporated as a structural unit to design histamine H_4 receptor antagonists.[24] Compound **3** is probably the easiest to prepare using methods other than we have reported here. The synthesis of **3** can be achieved by reduction of prolinamides[25] or from glutamic acid.[26] As our method relies on the incorporation of an amino function enantioselectively; it has the potential to be used for the synthesis of substituted derivatives of **3**, which may not be possible on using commercially available chiral derivatives of amino acids. **3** has been used to develop inhibitors targeting calcium-dependent protein kinase-1.[27] Quirion, Husson and coworkers have reported an interesting strategy for the synthesis of **4** and other 2-aminomethyl piperidines using (-)-2-cyano-6-phenyloxazolopiperidine, which in turn is prepared from (R)-(-)-phenylglycinol, glutaraldehyde and KCN.[28] O'Hagan and coworkers have reported a rather straight forward route to **4** through the cyclization of lysine.[29]

Thus, most of the available syntheses of **1-4** rely on the use of enantiomerically pure starting materials, which are commercially available. This limits their application to the synthesis of those derivatives, for which an exact chiron is available. Therefore, a general method that depends on the enantioselective installation of amino groups to synthesize 1,2-diamines is very relevant.

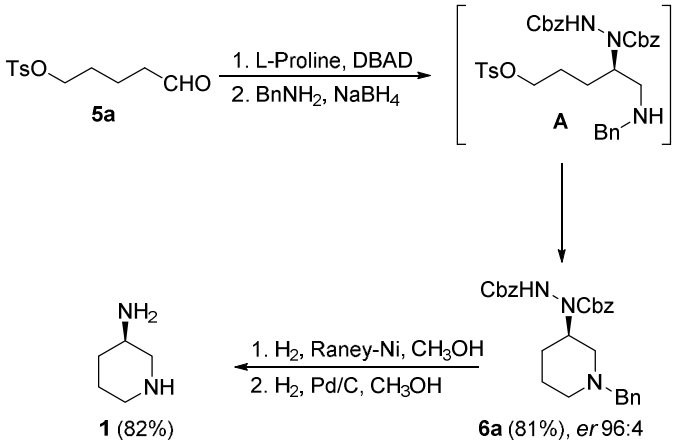
Results and Discussion

(*R*)-3-aminopiperidine (**1**) was synthesized from the aldehyde **5a**, which in turn can be derived from 1,5-pentanediol.[30] The aldehyde **5a** was subjected to α-hydrazination using DBAD in the presence of L-proline (0 ºC – r. t., 3 h, CH_3CN). The crude product was subjected to reductive amination using benzylamine and triacetoxy sodium borohydride ($NaBH(OAc)_3$, 0 ºC – r. t., 2.5 h). Under the reaction conditions the hydrazino amine intermediate, **A** underwent cyclization to give the 3-hydrazinopiperidine derivative **6a** in 79% yield over the two steps. HPLC analysis of **6a** was carried out and the peaks were compared with those obtained for a racemic mixture of **6a** derived from **5a** through α-functionalization using DL-proline. The L-proline-catalyzed reaction yielded **6a** with a moderate *ee* of 68%. The reduced *ee* in comparison with L-proline catalyzed α-amination reactions in general, may be attributed to partial racemization of the aldehyde or the imine before it is reduced to the benzylamine derivative. Carrying out the reaction at lower temperatures substantially reduced the rate of conversion and a significant improvement in

enantioselectivity could not be achieved. To our surprise, when sodium borohydride ($NaBH_4$) was used instead of $NaBH(OAc)_3$ for reductive amination, the enantioselectivity of the reaction improved substantially and **6a** was isolated in 81% yield and with 92% *ee* (Scheme 2). Hydrogenolysis of **6a**, first using *Raney*-Ni® and then with 5% Pd/C yielded **1** in 82% yield. Thus, the synthesis of **1** from **5a** was achieved in an overall yield of 66% and with high enantioselectivity.



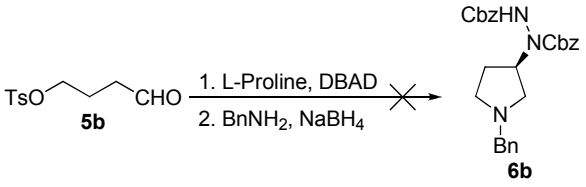
Scheme 1. Strategy for the synthesis of amino aza-heterocycles



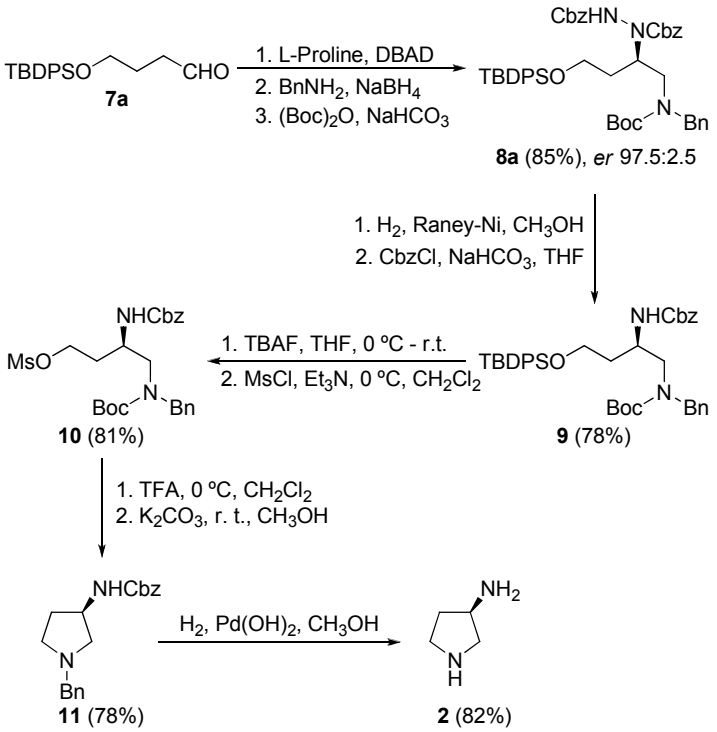
Scheme 2: Synthesis of (*R*)-3-aminopiperidine (**1**)

Encouraged by the success achieved in the synthesis of **1**, we assumed that a similar sequence of reactions would yield (*R*)-3-aminopyrrolidine (**2**) from **5b**, the lower homologue of **5a**. However, the aldehyde **5b** did not give the expected product **6b**, on L-proline catalyzed α-hydrazination

followed by reductive amination. A complex reaction mixture was obtained and no products could be isolated and characterized after multiple attempts at different conditions (Scheme 3).



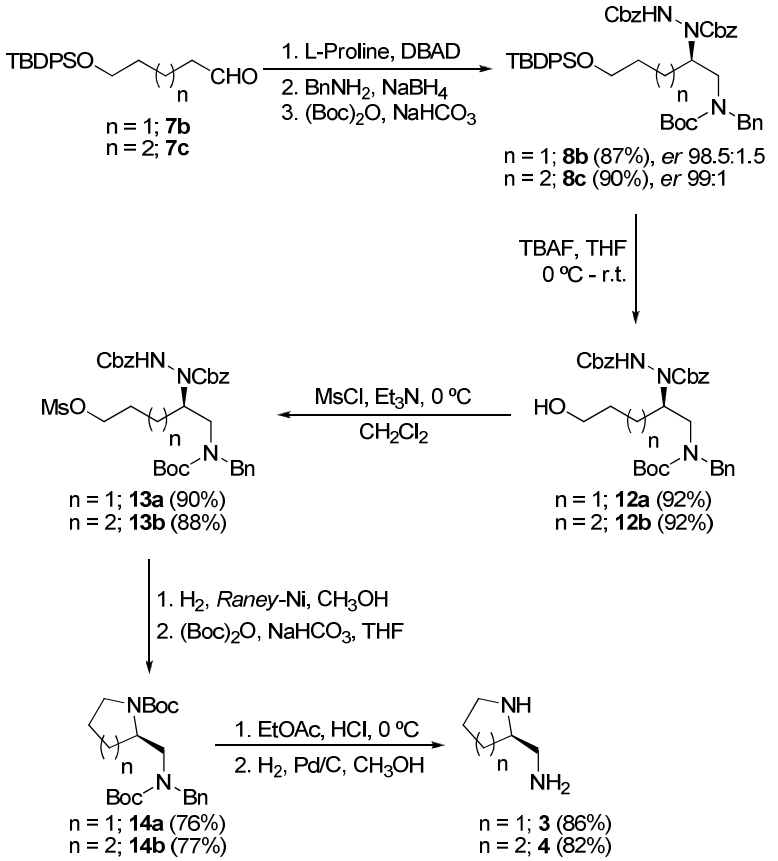
Scheme 3. An unsuccessful attempt towards the synthesis of **2** from **5b**



Scheme 4: Synthesis of (*R*)-3-aminopyrrolidine (**2**)

It was realized that **2** could be prepared from a slightly longer route from the aldehyde **7a**[31] (Scheme 4). L-proline-catalyzed α-hydrazination followed by reductive amination and Boc-protection of **7a** yielded **8a** in 85% yield over the 3 steps and with an *ee* of 95%. Hydrogenolysis of the N–N bond with *Raney*-Ni® and protection of the resultant amine with CbzCl gave the diamine derivative **9** (78%). The silyl protecting group in **9** was removed using TBAF (0 ºC – r.t., THF) and the primary hydroxyl group was mesylated (MsCl, Et_3N, 0 ºC, CH_2Cl_2) to get **10**. Removal of the *N*-Boc protection using TFA (50% in CH_2Cl_2) and treatment of the crude TFA

salt of the amine with K_2CO_3 (CH_3OH, r.t.) gave the 3-aminopyrrolidine derivative **11**, which on hydrogenolysis using $Pd(OH)_2$ in CH_3OH yielded **2** in 64% yield over the three steps.

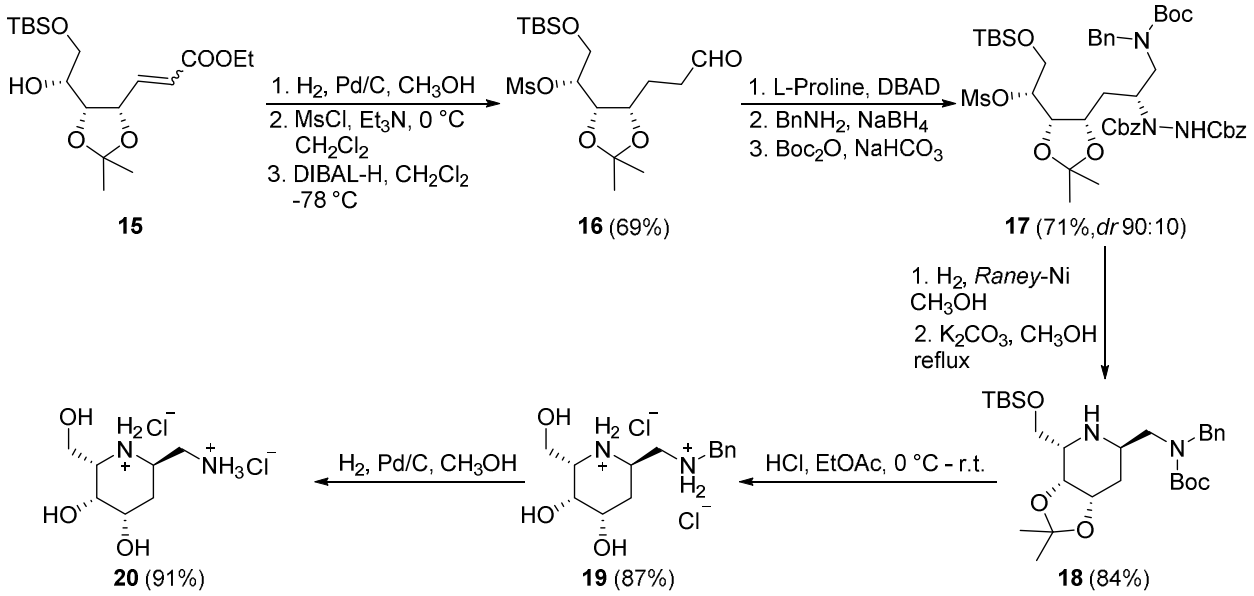


Scheme 5. Synthesis of (*R*)-2-aminomethylpyrrolidine (**3**) and (*R*)-2-aminomethylpiperidine (**4**)

(*R*)-2-aminomethylpyrrolidine (**3**) and (*R*)-2-aminomethylpiperidine (**4**) were prepared from aldehydes **7b** and **7c**, respectively (Scheme 5). **7b** and **7c** were subjected to L-proline-catalyzed α-hydrazination and subsequently to reductive amination using benzylamine and $NaBH_4$. The resultant amines were treated with Boc anhydride to get the Boc-derivatives **8b** and **8c** in 87% and 90% yields over the three steps and with 97% and 98% *ee*, respectively. The *O*-TBDPS groups were deprotected (TBAF, THF, 0 ºC – r.t.) to get primary alcohols **12a** (92%) and **12b** (92%), which were then converted to the mesylates **13a** (90%) and **13b** (88%) by treating with MsCl (Et_3N, 0 ºC, CH_2Cl_2). Hydrogenolysis of the N–N bond using *Raney*-Ni® and subsequent Boc-protection (Boc_2O, $NaHCO_3$, THF) of the free amine directly, yielded the corresponding cyclized products **14a** (76%) and **14b** (77%). The *N*-Boc groups were removed by acidolysis

(HCl in EtOAc, 0 ºC) and the *N*-benzyl groups were removed by hydrogenolysis (H_2, Pd/C, CH_3OH) to get **3** and **4** in 86% and 82% yields from **14a** and **14b**, respectively (Scheme 5).

In order to demonstrate the applicability of the current methodology for the synthesis of highly functionalized molecules, we prepared a 2-aminomethyl iminocyclitol using α-amination followed by reductive amination of an aldehyde as the key step (Scheme 6). The unsaturated ester derivative **15** was prepared from D-ribose following a reported procedure.[32] Reduction of the double bond and the ester group and mesylation of the hydroxyl group yielded the aldehyde **16** in 69% yield. L-proline-catalyzed α-hydrazination followed by reductive amination and Boc protection of **16** yielded **17** in 71% yield and in 9:1 diastereomeric ratio. Multiple attempts at different conditions towards improving the diastereoselectivity for this reaction were not successful. The reaction of the aldehyde function with benzylamine was found to be slower than those observed for the unhindered aldehydes **5a** and **7a-c**. The increased reaction time in this case may have resulted in partial stereo randomization of the newly generated chiral center. Hydrogenolysis of **17** and treatment of the resulting amine with K_2CO_3 in methanol resulted in the piperidine derivative **18** in very good yield. Acidolysis of **18** yielded **19** (87%), which was subjected to hydrogenation to remove the *N*-benzyl group to get the desired 2-aminomethylpiperidine derivative **20** in 80% yield over the two steps.



Scheme 6. Synthesis of a 2-aminomethyl iminocyclitol (**20**)

Conclusion

In conclusion, we have developed a reliable method for the enantioselective synthesis of terminal 1,2-diamines from aldehydes through proline-catalyzed asymmetric amination followed by reductive amination. High enantioselectivity and very good yields are achieved in these reactions. This methodology is successfully explored in the synthesis of 2-aminomethyl and 3-amino pyrrolidines and piperidines. The methodology will be useful for the synthesis of natural products containing 1,2-diamino units in them, which was demonstrated by the synthesis of a 2-aminomethyl iminocyclitol.

EXPERIMENTAL SECTION

All the chemicals were purchased from commercial sources. The ^{1}H NMR spectra of compounds containing the hydrazino group were complex at r. t. due to the presence of rotamers. They were therefore recorded at 80 °C in DMSO-*d6*. Column chromatography was done with silica gel (particle size 60-120 and 100-200 mesh) purchased from Merck. The enantiomeric ratios were determined by chiral HPLC analysis using Daicel chiralpak OD-H and IC columns with a mixture of hexane and isopropanol as eluent at 25 °C. Optical rotation was measured using a 5.0 mL cell with 10 dm path length and is reported as $[\alpha]_D^{25}$ (*c* in g per 100 mL solvent).

*(R)-dibenzyl 1-(1-benzylpiperidin-3-yl)hydrazine-1,2-dicarboxylate (**6a**)*. To a stirred solution of the aldehyde **5a** (1.10 g, 4.29 mmol) in CH_3CN (13 mL) dibenzylazodicarboxylate (DBAD, 1.53 g, 5.14 mmol) and L-proline (0.043 g, 10 mol%) were added at 0 °C and was stirred for 2 h. The stirring was continued at room temperature until the solution turned colorless from yellow. The reaction mixture was again cooled to 0 °C and benzyl amine (0.46 mL, 4.29 mmol) and sodium borohydride (0.32 g, 8.58 mmol) were added and was stirred for 30 min at 0 °C and further for 2 h at r. t. The reaction was quenched with saturated NH_4Cl solution (15 mL) at 0 ºC. The product was extracted with EtOAc (3 × 40 mL); organic layers were combined and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the product was isolated by column chromatography (60:40 petroleum ether/EtOAc) as a colorless oil (1.64 g, 81%); $[\alpha]_D^{25}$ − 19.935 (*c* 0.26, CH_2Cl_2, 92% ee); ^{1}H NMR (DMSO-*d6* 400 MHz, 80 °C) δ 9.23 (s, 1H), 7.41-7.13 (m, 15H), 5.04 (s, 4H), 4.04 (s, 1H), 3.43 (m, 2H), 2.84 (s, 1H), 2.68 (d, *J* = 10.8 Hz, 1H), 1.91 (s, 1H), 1.83-1.69 (m, 2H), 1.61 (d, *J* = 12.2 Hz, 1H), 1.47 (m, 1H), 1.29 (m, 1H) ppm; ^{13}C NMR (DMSO-*d6*, 100 MHz, rotamers) δ 157.2, 155.4, 138.9, 138.7, 136.9, 136.8, 129.2, 128.9,

128.6, 128.5, 128.2, 127.8, 127.7, 127.3, 67.3, 66.6, 62.7, 56.4, 54.8, 53.1, 27.9, 27.4, 24.48, 24.41; IR (thin film): 3290, 3030, 3032, 2937, 2807, 1755, 1713, 1496, 1454, 1408, 1348, 1300, 1257, 1224, 1173 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{28}H_{32}N_3O_4$ 474.2393, found 474.2377; HPLC (Diacel IC column, 90:10 hexane/IPA, detection wavelength λ = 254 nm, flow rate of 1 mL/min) retention times: 21.5 min (major isomer, 96%) and 27.2 min (minor isomer, 4%).

*(R)-3-aminopiperidine (**1**)*. To a stirred solution of **6a** (1.00 g, 2.11 mmol) in CH_3OH (15 mL), *Raney*-Ni® (0.80 g, prewashed with absolute ethanol) and 0.10 mL of acetic acid were added and the stirring was continued for 14 h at r. t. under a hydrogen atmosphere. The reaction mixture was filtered through a celite pad and concentrated under reduced pressure to get 1-benzyl-3-aminopiperidine, which was dissolved in CH_3OH (5 mL) and 10% Pd/C (0.05 g) was added. The mixture was stirred for 14 h at r. t. under a hydrogen atmosphere. The reaction mixture was filtered through a celite pad and the solvents were removed under reduced pressure to get **1** as a colorless oil (0.17 g, 82%); $[\alpha]_D^{25}$ +3.880 (*c* 0.30, CH_3OH); ^1H NMR (D_2O, 500 MHz) δ 3.74 (m, 1H), 3.70-3.62 (m, 1H), 3.54-3.45 (m, 1H), 3.11 (m, 1H), 3.04 (m, 1H), 2.30 (d, *J* = 12.9 Hz, 1H), 2.20-2.09 (m, 1H), 1.94-1.81 (m, 1H), 1.74 (m, 1H) ppm; ^{13}C NMR (D_2O, 125 MHz) δ 44.9, 44.6, 43.4, 26.2, 20.1 ppm; IR (thin film): 3426, 2958, 2031, 1619, 1513, 1454, 1302, 1164 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_5H_{13}N_2$ 101.1079, found 101.1074.

General procedure for α-hydrazination followed by reductive amination of 7 to 8. To a stirred solution of the aldehyde **7a** (0.88 g, 2.69 mmol) at 0 °C in CH_3CN (20 mL), dibenzylazodicarboxylate (DBAD) (0.96 g, 3.22 mmol) and L-Proline (0.031 g, 10 mol%) were added. The reaction mixture was stirred for 2 h at 0 °C and then at r. t. until the solution turned colorless from yellow. After the colour change, the reaction mixture was again cooled to 0 °C and benzyl amine (0.29 mL, 2.69 mmol) and sodium borohydride (0.20 g, 5.38 mmol) were added one after the other. The reaction mixture was stirred for 30 min at 0 °C and further for 2 h at r. t. and then Boc anhydride (0.74 mL, 3.22 mmol) and $NaHCO_3$ (0.45 g, 5.38 mmol) were added and the mixture was stirred for an additional 4 h. The reaction mixture was quenched with saturated NH_4Cl solution (15 mL) and the product was extracted with EtOAc (3 × 50 mL), the extractions were pooled, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography to get **8a**. The same procedure was used to convert **7b** and **7c** to **8b** and **8c**, respectively.

*(R)-dibenzyl 1-(9-benzyl-2,2,12,12-tetramethyl-10-oxo-3,3-diphenyl-4,11-dioxa-9-aza-3-silatridecan-7-yl)hydrazine-1,2-dicarboxylate (**8a**).* column chromatography (90:10 petroleum ether/EtOAc); clear oil (1.86 g, 85%); $[\alpha]_D^{25}$ + 5.738 (*c* 0.36, CH_2Cl_2, 95% ee); ^{1}H NMR (DMSO-*d6*, 500 MHz, 80 °C) δ 7.58 (s, 4H), 7.43-7.18 (m, 19H), 7.12 (s, 2H), 5.04 (s, 4H), 4.65 (s, 1H), 4.32 (s, 2H), 3.77 (s, 1H), 3.69 (s, 1H), 3.21 (s, 1H), 1.74 (s, 1H), 1.58 (s, 1H), 1.32 (s, 9H), 0.97 (s, 9H) ppm; ^{13}C NMR (DMSO-*d6*, 125 MHz, rotamers) δ 156.5, 156.3, 156.1, 138.8, 138.7, 138.5, 136.8, 135.5, 133.8, 133.7, 130.2, 128.9, 128.9, 128.8, 128.7, 128.5, 128.3, 128.1, 128.0, 127.9, 127.6, 127.3, 127.1, 79.5, 67.9, 67.4, 66.8, 60.4, 50.4, 47.5, 32.3, 32.0, 31.8, 28.7, 28.4, 27.1, 19.2 ppm; IR (thin film): 3302, 3067, 3032, 2959, 2930, 2856, 1755, 1718, 1676, 1472, 1454, 1424, 1392, 1366, 1337, 1249, 1218, 1140, 1111 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{48}H_{58}N_3O_7Si$ 816.4044, found 816.4045, HPLC (Diacel OD-H column, 98:2 hexane/IPA, detection wavelength λ = 254 nm, flow rate of 1 mL/min) retention times: 9.0 min (minor isomer, 2.5%) and 20.8 min (major isomer, 97.5%).

*(R)-dibenzyl 1-(10-benzyl-2,2,13,13-tetramethyl-11-oxo-3,3-diphenyl-4,12-dioxa-10-aza-3-silatetradecan-8-yl)hydrazine-1,2-dicarboxylate (**8b**).* column chromatography (90:10 petroleum ether/EtOAc); clear oil (1.99 g, 87%); $[\alpha]_D^{25}$ +8.429 (*c* 0.22, CH_2Cl_2, 97% ee); ^{1}H NMR (DMSO-*d6*, 500 MHz, 80 °C) δ 7.58 (d, *J* = 6.4 Hz, 4H), 7.39 (m, 6H), 7.33-7.23 (m, 11H), 7.22-7.16 (m, 2H), 7.13 (s, 2H), 5.06 (s, 4H), 4.33 (s, 3H), 3.57 (d, *J* = 23.6 Hz, 2H), 3.20 (s, 2H), 1.69 (s, 1H), 1.45 (s, 3H), 1.31 (s, 9H), 0.98 (s, 9H) ppm; ^{13}C NMR (DMSO-*d6*, 125 MHz, rotamers) δ 156.9, 156.1, 156.0, 138.9, 138.8, 136.8, 135.5, 134.2, 130.1, 128.8, 128.4, 128.2, 128.1, 127.6, 127.4, 79.9, 67.6, 66.8, 64.0, 50.9, 48.9, 29.4, 28.5, 27.3, 25.7, 19.3 ppm; IR (thin film): 3302, 3067, 3032, 2959, 2930, 2856, 1755, 1718, 1676, 1496, 1426, 1392, 1337, 1248, 1208, 1140, 1111 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{49}H_{60}N_3O_7Si$ 830.4201, found 830.4202, HPLC (Diacel OD-H column, 98:2 hexane/IPA, detection wavelength λ = 254 nm, flow rate of 1 mL/min) retention times: 15.7 min (minor isomer, 1.5%) and 21.6 min (major isomer, 98.5%).

*(R)-dibenzyl 1-(11-benzyl-2,2,14,14-tetramethyl-12-oxo-3,3-diphenyl-4,13-dioxa-11-aza-3-silapentadecan-9-yl)hydrazine-1,2-dicarboxylate (**8c**).* column chromatography (90:10 petroleum ether/EtOAc); clear oil (2.1 g, 90%); $[\alpha]_D^{25}$ +14.262 (*c* 0.30, CH_2Cl_2, 98% ee); ^{1}H NMR (DMSO-*d6*, 500 MHz, 80 °C) δ 7.62 (d, *J* = 6.7 Hz, 4H), 7.48-7.37 (m, 6H), 7.31 (s, 11H), 7.21 (m, 4H), 5.09 (s, 4H), 4.57-4.07 (m, 3H), 3.60 (s, 2H), 3.22 (s, 1H), 1.47 (s, 4H), 1.35 (s, 9H),

1.26 (s, 2H), 1.01 (s, 9H) ppm; ^{13}C NMR (DMSO-*d6*, 125 MHz, rotamers) δ 155.9, 155.5, 136.9, 136.8, 135.5, 133.8, 130.2, 128.9, 128.7, 128.5, 128.3, 128.2, 127.5, 79.5, 67.3, 66.7, 63.9, 55.4, 50.7, 32.3, 28.7, 28.4, 27.1, 22.6, 19.3 ppm; IR (thin film): 3292, 3031, 2931, 2931, 2856, 1756, 1716, 1676, 1472, 1426, 1366, 1337, 1288, 1249, 1218, 1160, 1111 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd. for $C_{50}H_{65}N_4O_7Si$ 861.4623, found 861.4627, HPLC (Diacel OD-H column, 98:2 hexane/IPA, detection wavelength λ = 254 nm, flow rate of 1 mL/min) retention times: 14.1 min (minor isomer, 1%) and 21.6 min (major isomer, 99%).

*Tert-butyl (R)-benzyl(2-(((benzyloxy)carbonyl)amino)-4-((tert-butyldiphenylsilyl)oxy)butyl)carbamate (**9**).* To a stirred solution of **8a** (1.10 g, 1.34 mmol) in CH_3OH (15 mL), *Raney*-Ni® (0.90 g, prewashed with absolute ethanol) and 0.1 mL of acetic acid were added and the stirring was continued for 14 h at r. t. under a hydrogen atmosphere. The reaction mixture was then filtered on a celite pad and concentrated under reduced pressure. The crude amine was dissolved in THF (10 mL) and cooled to 0 °C. $NaHCO_3$ (0.34 g, 4.02 mmol) and benzyl chloroformate (50% solution in toluene 0.57 mL, 2.01 mmol) were added to the solution. The reaction mixture was stirred for 5 h and then filtered, concentrated and purified by column chromatography (80:20 petroleum ether/EtOAc) to get **9** as a colorless oil (0.696 g, 78%). $[\alpha]_D^{25}$ +6.832 (*c* 0.44, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.62 (d, *J* = 6.7 Hz, 4H), 7.45-7.15 (m, 16H), 5.52 (s, 1H), 5.08 (s, 2H), 4.61 (d, *J* = 15.5 Hz, 1H), 4.44-4.20 (m, 1H), 4.04 (s, 1H), 3.76 (s, 1H), 3.68 (m, 1H), 3.56 (s, 1H), 3.14 (d, *J* = 10.4 Hz, 1H), 1.74 (s, 1H), 1.68 (s, 1H), 1.42 (d, *J* = 25.5 Hz, 9H), 1.02 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.8, 156.4, 138.2, 136.8, 136.7, 135.6, 133.5, 133.4, 133.4, 133.3, 129.7, 128.5, 128.5, 127.9, 127.7, 127.3, 127.2, 80.2, 66.4, 61.0, 50.6, 49.3, 48.6, 35.3, 28.4, 26.8, 19.1 ppm; IR (thin film): 3340, 3068, 2959, 2931, 2857, 1720, 1696, 1514, 1497, 1454, 1427, 1392, 1365, 1248, 1168, 1111 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{40}H_{51}N_2O_5Si$ 667.3567, found 667.3563.

*(R)-4-(benzyl(tert-butoxycarbonyl)amino)-3-(((benzyloxy)carbonyl)amino)butyl methanesulfonate (**10**).* To a stirred solution of **9** (0.70 g, 1.05 mmol) at 0 °C in dry THF (10 mL), TBAF (1 M solution in THF, 1.36 mL, 1.3 equiv.) was added and the reaction mixture was stirred for 2 h. After the complete disappearance of starting material on TLC, the reaction was quenched with saturated NH_4Cl solution (12 mL) and the product was extracted with EtOAc (2 × 20 mL) and dried over Na_2SO_4. Solvents were removed under reduced pressure and the alcohol was purified through column chromatography (60:40 petroleum ether/EtOAc) to get *tert*-butyl

(*R*)-benzyl(2-(((benzyloxy)carbonyl)amino)-4-hydroxybutyl)carbamate as an oil (0.404 g, 90%). $[\alpha]_D^{25}$ +16.455 (*c* 0.38, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.11 (m, 10H), 5.92 (d, *J* = 6.6 Hz, 1H), 5.10 (d, *J* = 8.9 Hz, 2H), 4.66 (m, 1H), 4.23 (d, *J* = 15.7 Hz, 1H), 3.98 (d, *J* = 7.2 Hz, 1H), 3.74-3.56 (m, 3H), 2.91 (d, *J* = 12.2 Hz, 1H), 1.67 (s, 1H), 1.45 (d, *J* = 45.3 Hz, 10H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.1, 157.5, 137.8, 136.6, 128.7, 128.5, 128.1, 127.9, 127.5, 127.2, 80.8, 66.8, 58.4, 51.0, 49.7, 48.1, 36.4, 28.3 ppm; IR (thin film): 3338, 3031, 2973, 2931, 1696, 1523, 1496, 1454, 1415, 1365, 1248, 1168 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{24}H_{32}N_2NaO_5$ 451.2209, found 451.2209.

To a stirred solution of the primary alcohol obtained as above (0.41 g, 0.95 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C, triethylamine (0.26 mL, 1.86 mmol) and methanesulfonyl chloride (0.11 mL, 1.40 mmol) were added and the reaction mixture was stirred for 3 h. Reaction was monitored through TLC and after the complete disappearance of the alcohol, reaction mixture was quenched with saturated citric acid solution (5 mL), extracted with CH_2Cl_2 (3 × 10 mL) and dried over Na_2SO_4. Solvents were removed under reduced pressure and the crude product was purified through column chromatography (70:30 petroleum ether/EtOAc) to get **10** as a colorless oil (0.435 g, 91%). $[\alpha]_D^{25}$ +4.146 (*c* 0.58, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56-7.05 (m, 10H), 5.53 (d, *J* = 6.3 Hz, 1H), 5.07 (s, 2H), 4.60 (d, *J* = 15.2 Hz, 1H), 4.24 (d, *J* = 13.9 Hz, 3H), 3.95 (s, 1H), 3.72 – 3.53 (m, 1H), 3.11–2.95 (m, 1H), 2.93 (s, 3H), 1.89 (m, 1H), 1.80-1.68 (m, 1H), 1.45 (d, *J* = 44.1 Hz, 9H). ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.1, 156.7, 137.8, 136.6, 128.7, 128.5, 128.1, 127.9, 127.5, 127.3, 80.8, 67.1, 66.7, 50.9, 49.4, 47.9, 37.2, 33.0, 28.3 ppm; IR (thin film): 3338, 3031, 2973, 2931, 1696, 1523, 1496, 1454, 1415, 1365, 1248, 1168 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd. for $C_{25}H_{38}N_3O_7S$ 524.2430, found 524.2434.

*Benzyl (R)-(1-benzylpyrrolidin-3-yl)carbamate (**11**).* To a stirred solution of **10** (0.15 g, 0.30 mmol), trifluoroacetic acid (0.30 mL) in CH_2Cl_2 (4 mL) was added at 0 °C. After the complete disappearance of the starting material on TLC, reaction mixture was concentrated under reduced pressure and K_2CO_3 (0.06 g, 0.44 mmol) was added in CH_3OH (3 mL) and stirred for 14 h. The reaction mixture was filtered through a celite pad and the solvents were removed under reduced pressure and the crude product was purified by column chromatography (40:60 petroleum ether/EtOAc). **11** was obtained as an oil (0.071 g, 78%). $[\alpha]_D^{25}$ −3.006 (*c* 0.20, CH_2Cl_2); ^{1}H

NMR ($CDCl_3$, 500 MHz) δ 7.33 (m, 8H), 7.31-7.26 (m, 2H), 5.34 (s, 1H), 5.08 (s, 2H), 4.28 (s, 1H), 3.66 (s, 2H), 2.92 (s, 1H), 2.72-2.60 (m, 2H), 2.38 (m, 1H), 2.29 (s, 1H), 1.70 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.8, 136.6, 129.0, 128.5, 128.5, 128.1, 127.5, 66.6, 60.5, 59.8, 52.5, 50.3, 32.4 ppm; IR (thin film): 3326, 3029, 2974, 2922, 2851, 1717, 1528, 1453, 1377, 1344, 1253 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{19}H_{23}N_2O_2$ 311.1760, found 311.1768.

*(R)-3-aminopyrrolidine (**2**)*. To a stirred solution of **11** (0.120 g, 0.386 mmol) in CH_3OH (5 mL), $Pd(OH)_2/C$ (0.05 g) was added along with a few drops of acetic acid and the reaction and the mixture was stirred for 14 h at r. t. under a hydrogen atmosphere. The reaction mixture was filtered through celite pad and the solvents were removed under reduced pressure to get **2** as a wax (0.027 g, 82%). $[\alpha]_D^{25}$ −1.046 (*c* 0.46, CH_3OH); ^1H NMR (D_2O, 500 MHz) δ 4.25-4.17 (m, 1H), 3.86 (m, 1H), 3.68-3.59 (m, 1H), 3.56-3.45 (m, 2H), 3.07 (s, 1H), 2.61 (m, 1H), 2.24 (m, 1H) ppm; ^{13}C NMR (D_2O, 125 MHz) δ 48.7, 47.7, 44.6, 28.5 ppm; IR (thin film): 3429, 2987, 1600, 1476, 1446, 1401, 1295, 1245, 1224 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_4H_{11}N_2$ 87.0922, found 87.0928.

*Dibenzyl (R)-1-(1-(benzyl(tert-butoxycarbonyl)amino)-5-hydroxypentan-2-yl)-2λ^2-diazane-1,2-dicarboxylate (**12a**)*. To a stirred solution of **8b** (1.21 g, 1.47 mmol) at 0 °C in dry THF (15 mL), TBAF (1 M solution in THF, 1.91 mL, 1.3 equiv.) was added and the stirring was continued for 2 h. After the complete disappearance of **8b** on TLC, the reaction was quenched with saturated NH_4Cl solution (15 mL) and the product was extracted with EtOAc (3 × 20 mL) and the solution was dried over Na_2SO_4. Solvents were removed under reduced pressure and column chromatography (60:40 petroleum ether/EtOAc) was performed to get **12a** as colorless oil (0.80 g, 92%). $[\alpha]_D^{25}$ +8.558 (*c* 0.20, CH_2Cl_2); ^1H NMR (DMSO-*d6*, 500 MHz, 80 °C) δ 7.33 (s, 12H), 7.25 (d, *J* = 7.0 Hz, 1H), 7.18 (s, 2H), 5.10 (s, 4H), 4.35 (s, 3H), 4.07 (s, 1H), 3.36 (s, 2H), 3.20 (s, 1H), 1.60 (s, 1H), 1.43 (s, 3H), 1.36 (s, 9H) ppm; ^{13}C NMR (DMSO-*d6*, 125 MHz) δ 156.4, 155.9, 155.5, 139.0, 136.8, 128.9, 128.8, 128.5, 128.4, 128.2, 127.8, 127.6, 127.5, 79.6, 67.8, 67.4, 66.7, 61.0, 50.7, 47.9, 29.7, 28.4, 25.7 ppm; IR (thin film): 3503, 3288, 3032, 2974, 1752, 1714, 1672, 1496, 1478, 1420, 1366, 1338, 1249, 1162 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{33}H_{42}N_3O_7$ 592.3023, found 592.3027.

12b was prepared from **8c** using the same procedure.

*Dibenzyl (R)-1-(1-(benzyl(tert-butoxycarbonyl)amino)-6-hydroxyhexan-2-yl)-2λ²-diazane-1,2-dicarboxylate (**12b**).* Column chromatography (60:40 petroleum ether/EtOAc); clear oil (0.675 g, 92%); $[\alpha]_D^{25}$ +5.980 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (DMSO-*d6*, 500 MHz, 80 °C) δ 7.45-7.06 (m, 15H), 5.10 (s, 4H), 4.35 (s, 3H), 4.06 (s, 1H), 3.35 (s, 2H), 3.21 (s, 1H), 1.49-1.24 (m, 15H) ppm; ^{13}C NMR (DMSO-*d6*, 125 MHz) δ 156.4, 155.9, 155.5, 136.9, 136.8, 136.7, 128.9, 128.8, 128.5, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 80.0, 79.6, 67.7, 67.3, 66.7, 61.1, 50.8, 32.9, 28.9, 28.4, 22.7 ppm; IR (thin film): 3503, 3290, 3064, 3032, 2968, 2932, 1753, 1715, 1674, 1496, 1478, 1420, 1366, 1339, 1284, 1224, 1137 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{34}H_{44}N_3O_7$ 606.3179, found 606.3171.

*Dibenzyl (R)-1-(1-(benzyl(tert-butoxycarbonyl)amino)-5-((methylsulfonyl)oxy)pentan-2-yl)-2λ²-diazane-1,2-dicarboxylate (**13a**).* To a solution of **12a** (0.78 g, 1.31 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C, triethylamine (0.36 mL, 2.62 mmol) and methanesulfonyl chloride (0.15 mL, 1.97 mmol) were added and the reaction mixture was stirred for 3 h. Reaction was monitored through TLC and after the complete disappearance of **12a**, reaction was quenched with saturated citric acid solution (10 mL), product was extracted with CH_2Cl_2 (3 × 20 mL) and dried over Na_2SO_4. Solvents were removed under reduced pressure and the crude product was purified further through column chromatography (70:30 petroleum ether/EtOAc) to get **13a** as oil (0.790 g, 90%). $[\alpha]_D^{25}$ −0.594 (*c* 0.24, CH_2Cl_2); ^{1}H NMR (DMSO-*d6*, 500 MHz, 80 °C) δ 7.45-7.09 (m, 15H), 5.12 (s, 4H), 4.37 (s, 3H), 4.13 (s, 2H), 3.26 (s, 2H), 3.09 (s, 3H), 1.89 (s, 1H), 1.66 (s, 1H), 1.48 (s, 2H), 1.38 (s, 9H) ppm; ^{13}C NMR (DMSO-*d6*, 125 MHz) δ 156.5, 155.9, 155.5, 138.9, 136.7, 128.9, 128.8, 128.6, 128.6, 128.4, 128.3, 127.9, 127.9, 127.8, 127.6, 127.5, 127.4, 80.3, 70.8, 67.5, 66.9, 55.2, 50.6, 47.9, 37.0, 28.4, 28.4, 28.3, 25.3, 25.0 ppm; IR (thin film): 3285, 3032, 2974, 1752, 1716, 1672, 1496, 1478, 1420, 1353, 1296, 1247, 1057 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd. for $C_{34}H_{47}N_4O_9S$ 687.3064, found 687.3060.

13b was prepared from **12b** using the same procedure.

*Dibenzyl (R)-1-(1-(benzyl(tert-butoxycarbonyl)amino)-6-((methylsulfonyl)oxy)hexan-2-yl)- 2λ²-diazane-1,2-dicarboxylate (**13b**).* Column chromatography (70:30 petroleum ether/EtOAc); oil (1.292 g, 88%); $[\alpha]_D^{25}$ +0.363 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (DMSO-*d6*, 500 MHz, 80 °C) δ 7.44-7.07 (m, 15H), 5.11 (s, 4H), 4.35 (s, 3H), 4.12 (s, 2H), 3.24 (s, 2H), 3.10 (s, 3H), 1.59 (s, 2H), 1.46 (d, *J* = 10.0 Hz, 2H), 1.37 (s, 9H), 1.27 (m, 2H) ppm; ^{13}C NMR (DMSO-*d6*, 125 MHz) δ

156.4, 156.4, 136.8, 136.8, 136.7, 128.9, 128.8, 128.5, 128.3, 127.9, 127.8, 127.6, 127.5, 79.6, 70.8, 67.8, 67.4, 66.8, 60.2, 55.4, 50.8, 37.1, 28.9, 28.4, 22.3, 21.2, 14.6 ppm; IR (thin film): 3287, 3031, 2936, 2932, 1753, 1715, 162, 1496, 1467, 1420, 1353, 1289, 1220, 1028 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd. for $C_{35}H_{49}N_4O_9S$ 701.3220, found 701.3222.

*t-Butyl (R)-2-((benzyl(tert-butoxycarbonyl)amino)methyl)pyrrolidine-1-carboxylate (**14a**).* To a solution of **13a** (1.25 g, 1.86 mmol) in CH_3OH (20 mL), *Raney*-Ni® (1.30 g, prewashed with absolute ethanol) was added followed by 0.10 mL of acetic acid and stirred for 14 h at r. t. under a hydrogen atmosphere. The reaction mixture was then filtered through a celite pad and the solution was concentrated under reduced pressure. The crude product was dissolved in THF (10 mL) and $NaHCO_3$ (0.408 g, 4.86 mmol) and $(Boc)_2O$ (0.55 mL, 2.43 mmol) were added to the solution. The reaction mixture was stirred for 5 h and then filtered, concentrated and purified by column chromatography (90:10 petroleum ether/EtOAc) to get **14a** as a white solid (0.55 g, 76%). $[\alpha]_D^{25}$ −2.377 (*c* 0.24, CH_2Cl_2); m.p.: 89 °C; ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 7.30 (d, *J* = 4.3 Hz, 2H), 7.24 (s, 2H), 7.18 (s, 1H), 4.64-4.34 (m, 2H), 3.96 (d, *J* = 54.6 Hz, 1H), 3.63-3.06 (m, 4H), 1.94 (s, 1H), 1.84 (s, 3H), 1.52-1.36 (m, 18H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.3, 154.5, 128.5, 128.3, 127.4, 127.1, 126.7, 80.0, 79.7, 55.5, 50.9, 50.0, 46.2, 28.7, 28.6, 28.4, 28.3, 23.6, 22.7 ppm; IR (thin film): 2974, 2931, 2862, 1693, 1496, 1478, 1454, 1392, 1365, 1343, 1251, 1162, 1111 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{22}H_{35}N_2O_4$ 391.2597, found 391.2598.

14b was prepared from **13b** using the same procedure.

*t-Butyl (R)-2-((benzyl(tert-butoxycarbonyl)amino)methyl)piperidine-1-carboxylate (**14b**).* column chromatography (90:10 petroleum ether/EtOAc); white solid (0.363 g, 77%); $[\alpha]_D^{25}$ +4.600 (*c* 0.24, CH_2Cl_2); m.p.: 97 °C; ^{1}H NMR (DMSO-*d6*, 500 MHz, 80 °C) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.28-7.18 (m, 3H), 4.44-4.32 (m, 3H), 3.87 (d, *J* = 13.0 Hz, 1H), 3.48 (s, 1H), 3.21-3.12 (m, 1H), 2.87 (t, *J* = 12.7 Hz, 1H), 1.52 (s, 4H), 1.41 (d, *J* = 10.6 Hz, 20H) ppm; ^{13}C NMR (DMSO-*d6*, 125 MHz): δ 155.3, 154.5, 139.1, 128.9, 128.9, 127.7, 127.5, 127.4, 79.0, 78.9, 49.0, 45.3, 45.2, 28.6, 28.4, 25.5, 19.5, 19.4 ppm; IR (thin film): 2975, 2933, 2865, 1693, 1495, 1476, 1453, 1391, 1365, 1340, 1271, 1246, 1161, 1104 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{23}H_{37}N_2O_4$ 405.2753, found 405.2755.

*(R)-2-aminomethylpyrrolidine (**3**)*. 4N HCl in EtOAc (1.5 mL) was added to **14a** (0.14 g, 0.36 mmol) and the solution was stirred for 1 h. After the complete disappearance of the starting material on TLC, the solvent was decanted carefully and the crude product was washed with EtOAc (3 × 5 mL). The solution was concentrated (to approximately 3 mL) and $NaHCO_3$ (0.08 g, 0.95 mmol) was added and the mixture was stirred for 10 min to neutralize any residual acids present. The solids were filtered off and the solution was concentrated and the residue was dissolved in CH_3OH (4 mL). The solution was stirred with 10% Pd/C (0.05 g) for 14 h in a hydrogen atmosphere at r. t., filtered through a celite pad and the solvents were removed under reduced pressure to get **3** as a clear oil (0.030 g, 86%). $[\alpha]_D^{25}$ +5.034 (*c* 0.34, CH_3OH); ^1H NMR (D_2O, 500 MHz) δ 4.00-3.89 (m, 1H), 3.55-3.35 (m, 4H), 2.39 (m, 1H), 2.23-2.14 (m, 1H), 2.13-2.04 (m, 1H), 1.86 (m, 1H); ^{13}C NMR (D_2O, 125 MHz) δ 57.1, 46.0, 39.8, 28.2, 22.8; IR (thin film): 2974, 2931, 1693, 1496, 1478, 1454, 1392, 1365, 1343, 1251, 1162, 1111 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_5H_{13}N_2$ 101.1079, found 101.1076.

*(R)-2-aminomethylpiperidine (**4**)*. **4** was prepared from **14b** using the same procedure that was used for the preparation of **3** from **14a**. Oil (0.05 g, 82%); $[\alpha]_D^{25}$ +1.380 (*c* 0.60, CH_3OH); ^1H NMR (D_2O, 500 MHz) δ 3.53 (d, *J* = 11.3 Hz, 1H), 3.49 (d, *J* = 2.1 Hz, 1H), 3.35 (m, 1H), 3.24 (m, 1H), 3.06 (m, 1H), 2.09 (d, *J* = 9.3 Hz, 1H), 1.92 (d, *J* = 15.3 Hz, 2H), 1.75-1.64 (m, 1H), 1.63-1.50 (m, 2H); ^{13}C NMR (D_2O, 125 MHz) δ 53.8, 45.2, 41.1, 26.0, 21.4, 20.9 ppm; IR (thin film): 2974, 2931, 1693, 1496, 1478, 1454, 1392, 1365, 1343, 1251, 1162, 1111 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_6H_{15}N_2$ 115.1235, found 115.1238.

*(R)-2-((tert-butyldimethylsilyl)oxy)-1-((4S,5S)-2,2-dimethyl-5-(3-oxopropyl)-1,3-dioxolan-4-yl)ethyl methanesulfonate (**16**)*. To a stirred solution of the α,β-unsaturated ester **15** (1.50 g, 4.01 mmol) in CH_3OH (30 mL), Pd/C (0.10 g) was added and the reaction was stirred for 1 h at r. t. under a hydrogen atmosphere. The reaction mixture was filtered through a celite pad and the solvents were removed under reduced pressure. The crude product was dissolved in dry CH_2Cl_2 (30 mL) and at 0 °C, triethyl amine (1.09 mL, 7.85 mmol) and methane sulfonyl chloride (0.45 mL, 5.88 mmol) were added and the reaction mixture was stirred for 2 h. After complete disappearance of the alcohol, reaction was quenched with citric acid solution (15 mL), extracted with CH_2Cl_2 (3 x 20 mL) and dried over Na_2SO_4. Solvents were removed under reduced pressure and the compound was purified through column chromatography (90:10 petroleum ether/EtOAc) to get the mesyl derivative (1.63 g, 90%). The mesyl derivative (1.63 g, 3.59 mmol) was

dissolved in dry CH_2Cl_2, at -78 °C and DIBAL-H (1 M solution in toluene, 5.38 mL, 1.5 equiv.) was added and the reaction mixture was stirred for 0.5 h. Reaction was monitored through TLC and after the complete disappearance of the ester, it was quenched with saturated NH_4Cl (15 mL) and the product was extracted with CH_2Cl_2 (3 x 20 mL) and was dried over Na_2SO_4. Solvents were removed under reduced pressure and the aldehyde was purified through column chromatography (85:15 petroleum ether/EtOAc) to give an aldehyde (1.13 g, 77%). $[\alpha]_D^{25}$ +6.666 (*c* 0.30, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.79 (s, 1H), 4.72 (m, 1H), 4.26 (dd, *J* = 7.3, 5.9 Hz, 1H), 4.19 (m, 1H), 4.04 (dd, *J* = 12.1, 2.3 Hz, 1H), 3.89 (dd, *J* = 12.1, 5.4 Hz, 1H), 3.13 (s, 3H), 2.64 (q, *J* = 7.0 Hz, 2H), 2.08 (m, 1H), 1.87 (m, 1H), 1.39 (s, 3H), 1.30 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.7, 108.6, 81.1, 76.4, 75.0, 62.8, 40.7, 39.4, 27.8, 25.9, 25.4, 22.5, 18.4, -5.3, -5.4 ppm; IR (thin film): 2986, 2954, 2858, 1725, 1463, 1413, 1359, 1255, cm^{-1}. HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd. for $C_{17}H_{38}NO_7SSi$ 428.2138, found 428.2136.

*dibenzyl 1-((R)-1-(benzyl(tert-butoxycarbonyl)amino)-3-((4S,5S)-5-((R)-2-((tert-butyldimethylsilyl)oxy)-1-((methylsulfonyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-yl)hydrazine-1,2-dicarboxylate (**17**)*. **17** was prepared from **16** using the same procedure that was used for the preparation of **8** from **7**. column chromatography (85:15 petroleum ether/EtOAc); clear oil (1.30 g, 71%); $[\alpha]_D^{25}$ + 10.082 (*c* 0.21, CH_2Cl_2, 90:10 dr); ^{1}H NMR (DMSO-*d6*, 400 MHz, 80 °C) δ 7.36 – 7.17 (m, 13H), 7.13 (s, 2H), 5.07 (s, 4H), 4.64 – 4.07 (m, 6H), 3.90 (d, *J* = 11.9 Hz, 1H), 3.79 (dd, *J* = 11.5, 5.1 Hz, 1H), 3.27 (bs, 1H), 3.12 (s, 1H), 3.07 (s, 3H), 1.93 (s, 1H), 1.73 (s, 1H), 1.45 (s, 3H), 1.32 (s, 9H), 1.21 (s, 3H), 0.85 (d, *J* = 4.4 Hz, 9H), 0.03 (s, 6H) ppm; ^{13}C NMR (DMSO-*d6*, 100 MHz, rotamers) δ 155.6, 155.5, 146.7, 138.7, 136.7, 128.9, 128.8, 128.5, 128.4, 128.3, 127.5, 127.4, 127.1, 126.9, 112.3, 108.0, 103.4, 86.8, 86.1, 84.0, 81.5, 81.2, 80.3, 79.8, 75.3, 73.8, 70.2, 67.7, 67.6, 67.3, 67.0, 62.7, 50.5, 37.3, 31.8, 28.7, 28.3, 27.8, 27.3, 26.6, 18.5, -5.0 ppm; IR (thin film): 3290, 3065, 2930, 2856, 1715, 1677, 1472, 1454, 1424, 1392, 1366, 1252, 1218, 1174 cm^{-1}. HRMS (ESI-TOF) m/z: $[M - H]^+$ calcd. for $C_{45}H_{64}N_3O_{12}SSi$ 898.3980, found 898.3989, HPLC (Diacel IC column, 90:10 hexane/IPA, detection wavelength λ = 250 nm, flow rate of 1 mL/min) retention times: 8.4 min (major isomer, 90%) and 16.3 min (minor isomer, 10%).

*tert-butyl benzyl(((3aR,4S,6R,7aS)-4-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethylhexahydro-[1,3]dioxolo[4,5-c]pyridin-6-yl)methyl)carbamate (**18**)*. To a stirred solution of **17** (1.30 g, 1.44 mmol) in CH_3OH (30 mL), *Raney*-Ni® (1.00 g, prewashed with absolute ethanol) and 0.10 mL of acetic acid were added and the reaction mixture was stirred for 14 h at r. t. under a hydrogen atmosphere. The reaction mixture was filtered through a celite pad and concentrated under reduced pressure, the crude mixture obtained was dissolved in CH_3OH (20 mL) and K_2CO_3 (0.39 g, 2.88 mmol) was added. The mixture was refluxed for 3 h and was filtered through a celite pad and the solvents were removed under reduced pressure. The crude product obtained was purified through column chromatography (80:20 petroleum ether/EtOAc) to get **18** as a colorless oil (0.63 g, 84%). $[\alpha]_D^{25}$ -10.031 (*c* 0.42, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 – 7.26 (m, 2H), 7.21 (dd, *J* = 13.4, 5.9 Hz, 3H), 4.72 – 4.53 (m, 1H), 4.45 (dd, *J* = 16.9, 7.9 Hz, 2H), 4.23 (dd, *J* = 7.7, 1.9 Hz, 1H), 3.54 (m, 2H), 3.30 (d, *J* = 31.7 Hz, 2H), 3.16 – 2.92 (m, 2H), 2.82 (d, *J* = 18.4 Hz, 1H), 1.83 (d, *J* = 16.2 Hz, 1H), 1.59 (s, 1H), 1.47 (s, 3H), 1.45 (s, 3H), 1.40 (s, 6H), 1.31 (s, 3H), 0.88 (s, 9H), 0.05 (d, *J* = 0.9 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 128.5, 127.8, 127.2, 127.1, 107.8, 79.8, 71.7, 71.6, 63.6, 52.3, 51.5, 51.2, 46.5, 46.3, 28.5, 26.5, 26.0, 24.2, 18.4, -5.2, -5.3 ppm; IR (thin film): 3330, 2929, 2857, 1696, 1495, 1462, 1365, 1249, 1164, cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{28}H_{49}N_2O_5Si$ 521.3411, found 521.3414.

(2S,3R,4S,6R)-6-((benzylammonio)methyl)-3,4-dihydroxy-2-(hydroxymethyl)piperidin-1-ium chloride (***19***). 4N HCl in EtOAc (5 mL) was added to **18** (0.30 g, 0.57 mmol) at 0 °C and the reaction mixture was stirred for 24 h at r. t. The reaction mixture was concentrated under reduced pressure and the solid was washed with EtOAc (5 x 3 mL) and dried under reduced pressure to get **19** as a wax (0.17 g, 87%). $[\alpha]_D^{25}$ -18.750 (*c* 0.16, CH_3OH); ^{1}H NMR (D_2O, 400 MHz) δ 7.36 (d, *J* = 7.1 Hz, 5H), 4.20 (s, 2H), 3.96 (d, *J* = 13.3 Hz, 2H), 3.89 – 3.82 (m, 1H), 3.75 (m, 2H), 3.49 – 3.37 (m, 3H), 2.17 – 2.06 (m, 1H), 1.89 – 1.81 (m, 1H) ppm; ^{13}C NMR (D_2O, 100 MHz) δ 130.0, 129.9, 129.8, 129.3, 65.6, 63.8, 58.8, 56.2, 52.0, 48.9, 45.5, 27.0 ppm; IR (thin film): 3390, 2958, 2795, 1619, 1457, 1446 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{14}H_{23}N_2O_3$ 267.1709, found 267.1700.

(2S,3R,4S,6R)-6-(ammoniomethyl)-3,4-dihydroxy-2-(hydroxymethyl)piperidin-1-ium chloride (***20***). To a solution of **19** (0.10 g, 0.29 mmol) in CH_3OH (3 mL), Pd/C (0.020 g) was added and the reaction mixture was stirred for 20 h at r. t. under a hydrogen atmosphere. The reaction mixture was filtered through a celite pad and the solvents were removed under reduced pressure to get **20** as a wax (0.66 g, 91%). $[\alpha]_D^{25}$ -9.328 (*c* 0.16, CH_3OH); ^1H NMR (D_2O, 500 MHz) δ 3.95 (s, 1H), 3.91 (d, *J* = 10.7 Hz, 1H), 3.85 (d, *J* = 4.4 Hz, 1H), 3.78 – 3.73 (m, 2H), 3.39 – 3.29 (m, 3H), 2.15 – 2.04 (m, 1H), 1.85 (d, *J* = 14.4 Hz, 1H) ppm; ^{13}C NMR (D_2O, 125 MHz) δ 66.0, 64.1, 59.3, 55.9, 49.4, 38.3, 26.9 ppm; IR (thin film): 3390, 2922, 2852, 1457 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_7H_{16}N_2O_3$ 177.1239, found 177.1700.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website

^1H and ^{13}C spectra for all the compounds

HPLC data for **6a**, **8a**, **8b** and **8c**

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Notes

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