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Asymmetric synthesis of a 3,4-substituted pyrrolidine by L-proline catalyzed direct *enolexo* aldolization

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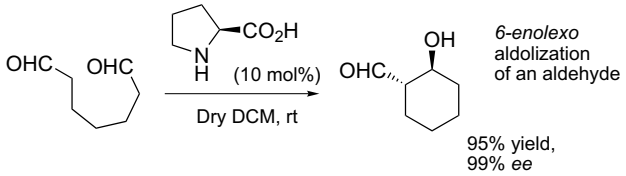
Abstract—The asymmetric synthesis of a 3,4-substituted *N*-tosyl pyrrolidine has been achieved by using L-proline catalyzed 5-*enolexo* aldolization with high enantio and diastereoselectivity.

1. Introduction

The aldol reaction has emerged as one of the most powerful and efficient carbon–carbon bond forming reactions in organic synthesis. Many efforts have been devoted to the development of the catalytic asymmetric aldol reaction using 'preformed and stereo defined stable enolates'.[1] Over the last few years, the direct asymmetric aldol reaction has received a great deal of interest because of its atom economy and involvement of unmodified carbonyl units for 'in situ generated labile enolates' using biocatalysts,[2] metal catalysis,[3] and organo-catalysis[4] under mild conditions. The main attention has been focused on the use of a small organic molecule such as proline as an organo-catalyst for the direct asymmetric aldol reaction due to its ready availability in both L- or D-forms and its importance from both a synthetic as well as mechanistic point of view.[5] Recently, List et al. have shown the first direct 6-*enolexo* aldolization in high enantioselectivity for the synthesis of β-hydroxy cyclohexane carbonyl derivatives (Scheme 1).[6]



Scheme 1.

This led us to propose a new strategy for the synthesis of 1-imino-sugars, which are several times more potent than **2** towards β-glycosidases. Poly-hydroxylated nitrogen heterocyclic compounds with piperidine, pyrrolidine, pyrrolizidine, and indolizidine skeletons (e.g., nojirimycin **1**, 1-deoxynojirimycin **2**, fagomine **3**, swainsonine **4**, and synthetic isofagomine **5**) have been shown to be specific and potent inhibitors of glycosidases.[7] In particular, the development of synthetic methods to create a pyrrolidine skeleton has been of longstanding importance in synthetic chemistry.[8] With the continuation of our program on the direct diastereoselective intermolecular and intramolecular aldol reaction catalyzed by L-proline for the synthesis of

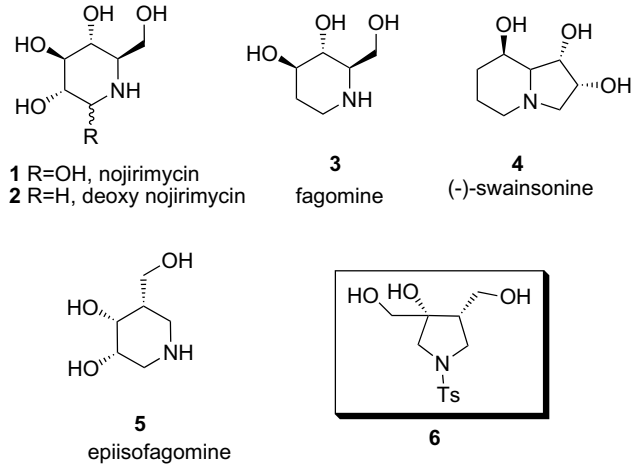


Figure 1.

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amino polyols and amino sugars,[9] we herein report the synthesis of a 3,4-substituted pyrrolidine ring in high enantio- and diastereoselective ratios through a direct 5-*enolexo* aldolization catalyzed by L-proline (Fig. 1).

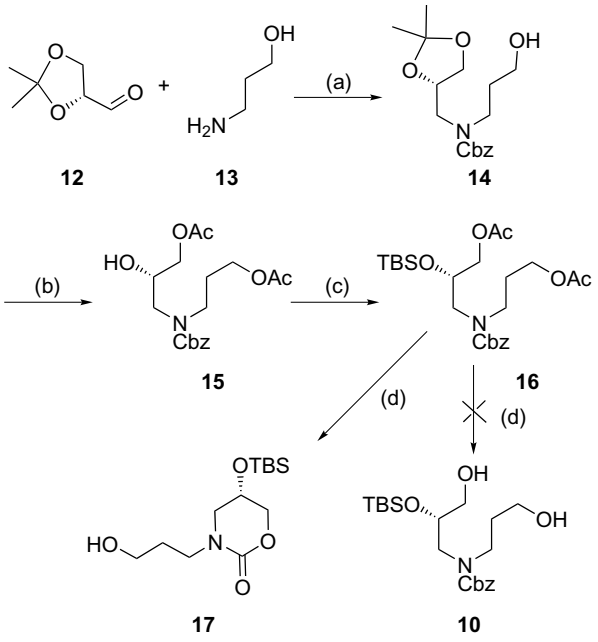
2. Results and discussion

Initially, we started the synthesis of the core structure of the isofagomine alkaloids using a diastereoselective approach with 6-*enolexo* aldolization and the retrosynthetic analysis is shown in Scheme 2. The direct diastereoselective 6-*enolexo* aldolization catalyzed by L-proline is the key step of this approach. The main challenge of this approach is to discriminate between two aldehyde groups by putting a well-defined stereocenter at the active methylene position of one of the aldehyde groups; so that proline catalyzed highly diastereoselective 6-*enolexo* aldolization can occur via an enamine intermediate with another aldehyde functionality. The already existing stereogenic center in synthon **9** may have some impact on the diastereoselective outcome of the direct aldolization reaction. In the retrosynthetic analysis, compound **10** was visualized as a key intermediate, which can be oxidized to dialdehyde **9** for the further step of aldolization.

The first task was to prepare the suitably protected intermediate **10**. Hence, we started from (*R*)-glyceraldehyde **12**; which was easily prepared from commercially available D-mannitol.[10] Reductive amination of glyceraldehyde **12** was carried out with 3-aminopropanol **13**, for 12 h at rt under a hydrogen atmosphere followed by protection with CbzCl under biphasic basic conditions to provide a Cbz-protected alcohol **14** with 85% yield after two steps.[11] Acetonide deprotection of **14** using *p*-TSA/MeOH at rt, followed by protection with AcCl (2.1 equiv) in pyridine/DCM gave diacetyl derivative **15** in 83% yield after two steps.

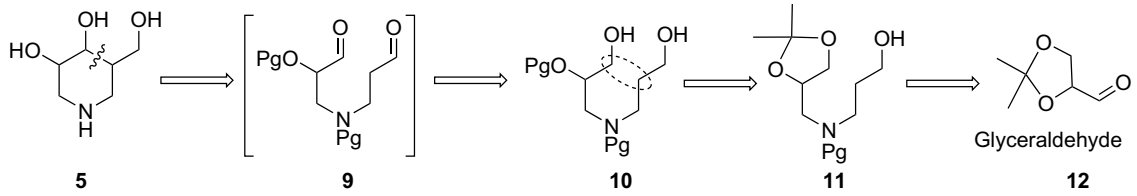
The secondary alcohol of compound **15** was protected with 1.1 equiv of TBSCl/imidazole in dry DCM at 0 °C for 4 h to provide TBS-protected compound **16** in 92% yield. The acetyl deprotection of compound **16** was carried out with a catalytic amount of K_2CO_3/MeOH at rt[12] and surprisingly, we obtained compound **17** as a cyclic carbamate instead of diol **10**. Even though the –OBn group is not a good leaving group, the formation of six member cyclic carbamate might be the driving force for this reaction (Scheme 3).

To overcome this problem, we used benzyl as a protecting group on the amino functionality. This was carried out in two steps from compound **16** by the cleavage of *N*-Cbz, followed by protection with benzyl bromide to provide compound **18** in 87% yield after two steps. The deprotection of –OAc groups from **18** was carried out with K_2CO_3-(cat.)/MeOH at rt to provide diol compound **19** in 92% yield. The resulting diol **19** was then subjected to oxidation under different (IBX, DMP, or Swern) conditions. Unfortunately, all these attempts for the oxidation of compound **19** to the dialdehyde gave a complex reaction mixture which indicated that the β-amino-dialdehyde formed during the oxidation was unstable due to the amino benzyl moiety (Scheme 4).

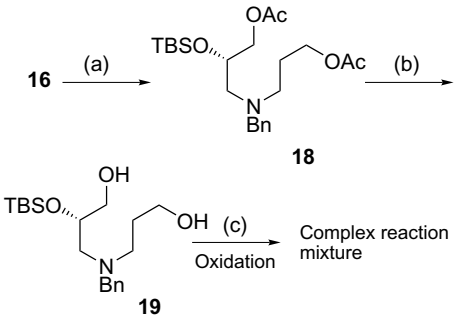


Scheme 3. Reagents and conditions: (a) (i) Pd/C (10 mol %), MeOH, H_2 (1 atm) rt, 12 h; (ii) CbzCl (1.2 equiv), Na_2CO_3 (2.2 equiv), DCM–H_2O (1:1), 0 °C, 3 h, 85% for two steps; (b) (i) *p*-TSA, MeOH, rt, 8 h; (ii) AcCl (2.2 equiv), DCM–pyridine (1:1), 0 °C, 3 h, 83% yield after two steps. (c) TBSCl (1.1 equiv), imidazole, dry DCM, 0 °C, 4 h, 92% yield; (d) K_2CO_3 (cat.), MeOH, rt, 30 min, 93% yield.

These unsuccessful attempts prompted us to find a new protecting group and a tosyl group was considered to be the most suitable candidate. Compound **21** was prepared following the same route described for compound **16** in Scheme 3. The acetyl deprotection of compound **21** was carried out with the standard procedure to provide compound **22** in high yield. The oxidation of compound **22** was carried out with IBX (5.0 equiv) under reflux conditions[13] and the resulting oxidized product was used for direct aldolization without any purification. The direct aldol



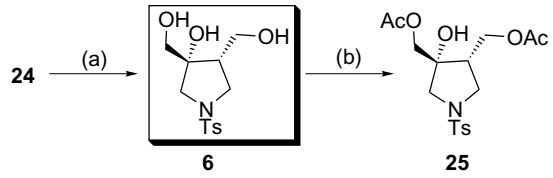
Scheme 2. New retrosynthetic approach for 1-imino-sugar.



Scheme 4. Reagents and conditions: (a) (i) Pd/C (10 mol %), MeOH, H_2 (1 atm), rt; (ii) BnBr (1.2 equiv), Na_2CO_3 (2.2 equiv), DCM–H_2O (1:1), reflux, 3 h, 87% in two steps; (b) K_2CO_3 (cat.), MeOH, rt, 30 min, 92% yield; (c) IBX, DMP or Swern oxidation conditions.

reaction was carried out with L-proline (20 mol %) at 5 °C for 16 h in $CHCl_3$–DMSO (3:1), followed by in situ reduction with $NaBH_4$/MeOH at the same temperature to give a stable diol, whose ^1H and ^{13}C NMR spectral data showed the cyclization. However this product shows four $–CH_2$ groups in ^{13}C-DEPT NMR. A detail interpretation of the spectral data showing four $–CH_2$ at $\delta = 48.88$, 57.38, 59.40, 66.39 in ^{13}C NMR indicates the attachment of these methylenes to the heteroatom which was possible for the product having five membered ring. We found that a 1,2-TBS migration occurred under –OAc deprotection (mild basic) conditions and gave compound **23** with a TBS-group on the primary hydroxyl group. This upon oxidation followed by 5-*endolexo* cyclization gave a 3,4-substituted pyrrolidine ring with high dr 9:1 (^1H NMR) and ee = 90% (major), 18% (minor) of each diastereomer (chiral HPLC, OD-H column) (Scheme 5).

In order to confirm the structure and stereochemical outcome of the aldol product, a further transformation was carried out with the TBS-deprotection of **24** using PTA (cat)/MeOH[14] to quantitatively give triol **6**. Compound **6** was protected with AcCl (2.1 equiv) in DCM/pyridine at 0 °C for 4 h to give the corresponding diacetyl product **25**, which was isolated as the almost pure diastereomer as



Scheme 6. Reagents and conditions: (a) PTA (cat.), MeOH, rt, 30 min. quantitative yield; (b) AcCl (2.1 equiv), DCM–pyridine (1:1), 0 °C, 3 h, 87% yield.

indicated by ^1H and ^{13}C NMR (Scheme 6). The reaction is highly selective, and the stereochemistry of the product was determined by NOESY experiments. The observed NOE correlations between the proton at C-4 and the two proton of $–CH_2OAc$, H^β at C-5 (strong), as well as H^β at C-2 (week); and that between H^β at C-2 and the proton

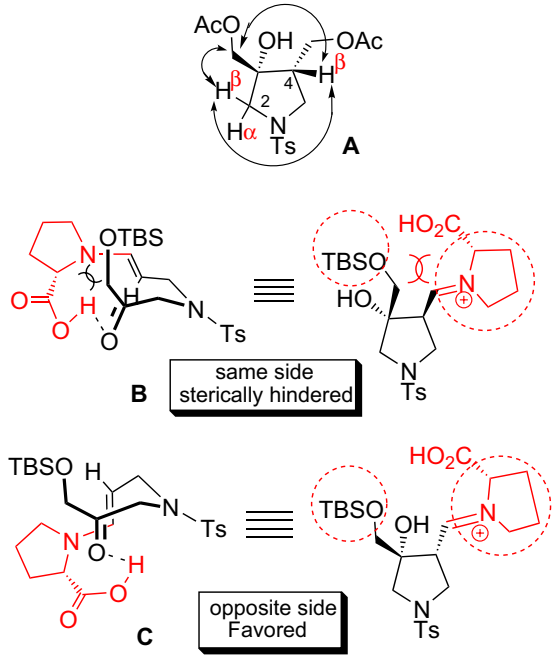
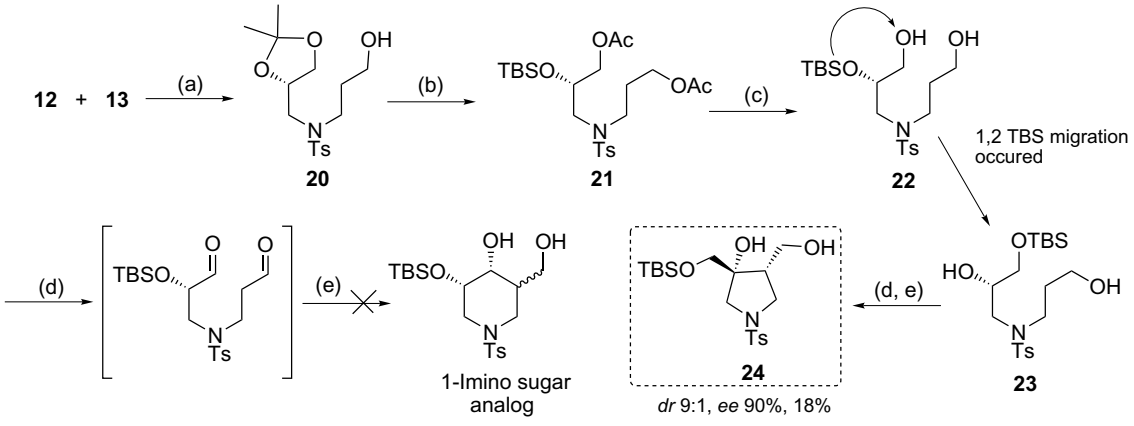


Figure 2.



Scheme 5. Reagents and conditions: (a) (i) Pd/C (10 mol %), MeOH, H_2 (1 atm) rt, 12 h; (ii) TsCl (1.2 equiv), Na_2CO_3 (2.2 equiv), DCM–H_2O (1:1), 0 °C, 3 h, 83% in two steps; (b) (i) *p*-TSA, MeOH, rt, 8 h; (ii) AcCl (2.2 equiv), DCM–pyridine (1:1), 0 °C, 3 h; (iii) TBSCl (1.1 equiv), imidazole, dry DCM, 0 °C, 4 h, 73% yield in three steps; (c) K_2CO_3 (cat.), MeOH, rt, 30 min, 89% yield; (d) IBX (5.0 equiv), EtOAc, reflux, 4.5 h; (e) (i) L-proline (15 mol %), $CHCl_3$–DMSO (3:1), 5 °C, 16 h; (ii) $NaBH_4$, MeOH, 5 °C, 2 h, 65% yield after three steps.

of $-CH_2OAc$ at C-3 in **A** allowed *syn*-selectivity to be attributed.

The high *syn*-selectivity of the reaction can be explained by two different transition states during cyclization, in transition state **B**, the bulky –OTBS group and imminium-ion are on the same side and suffer from steric hindrance while in transition state **C**, these groups are on opposite sides and so are without steric hindrance. This means **C** is energetically more favored than **B** giving the *syn* outcome of this reaction (Fig. 2). Hence, the –OTBS group, due to its bulkiness plays an important role in directing the stereochemistry at C-4 to give *syn* outcome of the reaction.

3. Conclusion

In conclusion, we have demonstrated the synthesis of polyhydroxylated 3,4-substituted pyrrolidine skeleton having one quaternary center using direct 5-*enolexo* aldolization with high diastereo- and enantioselectivity. 1,2-TBS migration, which occurred in the intermediate steps, directed the cyclization in a 5-*enolexo* fashion, as well as controlling the stereochemical outcome of the L-proline catalyzed reaction. The synthesis of the core structure of 1-imino-sugars using 6-*enolexo* aldolization in a diastereoselective fashion will be reported in due course.

4. Experimental

4.1. General methods

All reagents were used as supplied. The reactions involving hygroscopic reagents were carried out under argon atmosphere using oven-dried glassware. THF was distilled from sodium-benzophenone ketyl prior to use. Reactions were followed by TLC using 0.25 mm Merck silica gel plates (60F-254). Optical rotation values were measured using JASCO P-1020 digital polarimeter using Na light. IR spectra were recorded on Perkin–Elmer FT-IR 16 PC spectrometer. The NMR spectra were recorded on a Bruker system (200 MHz for ^1H and 75 MHz for ^{13}C). The chemical shifts are reported using the δ (delta) scale for ^1H and ^{13}C spectra. Choices of deuterated solvents ($CDCl_3$, D_2O) are indicated below. LC–MS was recorded using the electrospray ionization technique. All the organic extracts were dried over sodium sulfate and concentrated under aspirator vacuum at room temperature. Column chromatography was performed using (100–200 and 230–400 mesh) silica gel obtained from M/s Spectrochem India Ltd. Room temperature is referred as rt.

4.2. Benzyl {[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}(3-hydroxypropyl)carbamate 14

To a stirred solution of (*R*)-glyceraldehyde **12** (1.5 g, 11.5 mmol) and 3-aminopropanol **13** (1.0 g, 13.84 mmol) in MeOH (25 ml), was added Pd/C (120 mg, 10 mol %) at rt. The resulting solution was stirred further for 12 h under a hydrogen atmosphere followed by TLC. The reaction mixture was filtered to remove Pd/C and concentrated under reduced pressure to give a slightly yellowish liquid that was diluted in DCM (20 ml). To the resulting solution was added a solution of Na_2CO_3 (2.68 g, 25.36 mmol) in water (20 ml) and CbzCl (2.15 g, 12.694 mmol) at 0 °C and the mixture was stirred further for 2 h at the same temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2×20 ml). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by chromatography on silica gel eluting with hexane–ethyl acetate (8:2–6:4) to give **14** (3.15 g, 85% yield in two steps) as a colorless liquid: $[\alpha]_D^{25} = -7.6$ (*c* 1, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.28$ (s, 3H), 1.35 (s, 3H), 1.72 (m, 2H), 3.15–3.25 (m, 1H), 3.51 (m, 6H), 3.88–4.05 (m, 1H), 4.19 (m, 1H), 5.10 (s, 2H), 7.30 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.09$, 26.85, 30.06, 44.95, 49.85, 58.76, 67.14, 67.34 (overlapping signals), 74.92, 109.18, 127.83, 128.03, 128.46, 136.32, 156.89. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.09; H, 7.82; N, 4.39.

4.3. Benzyl (2*S*)-3-acetoxy-2-hydroxypropyl 3-acetoxypropylcarbamate 15

A solution of **15** (1.2 g, 3.71 mmol) in MeOH (25 ml) was stirred with a catalytic amount of *p*-TSA at rt for 8 h followed by TLC. After completion of the reaction, MeOH was evaporated under reduced pressure to give a pasty residue. This was used further by dissolving in DCM–pyridine (1:1) solvents (14 ml) at 0 °C followed by the addition of the solution of AcCl (0.62 g, 2.1 mmol) in 5 ml dry DCM at the same temperature for 25 min and stirred additionally for 3 h. The reaction mixture was poured into ice water and extracted with (3×20 ml) DCM. The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was further purified by column chromatography to give **15** (1.13 g, 83% in two steps) as a pasty liquid: $[\alpha]_D^{25} = -5.0$ (*c* 1, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.80$–2.10 (m, 8H), 3.30–3.45 (m, 4H), 3.95–4.10 (m, 5H), 5.09 (s, 2H), 7.31 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.54$, 27.39, 45.80, 51.05, 61.74, 66.04, 67.37, 68.87, 127.65, 127.91, 128.32, 136.03, 157.17, 170.77. Anal. Calcd for $C_{18}H_{25}NO_7$: C, 58.84; H, 6.86; N, 3.81. Found: C, 58.91; H, 6.79; N, 3.91.

4.4. Benzyl (2*S*)-3-acetoxy-2-*tert*-butyldimethylsilyloxypropyl 3-acetoxypropylcarbamate 16

To a stirred solution of compound **15** (1.2 g, 3.26 mmol) and imidazole (0.267 g, 3.91 mmol) with a catalytic amount of DMAP in dry DCM (8 ml) was added a solution of TBSCl (0.591 g, 3.92 mmol) in dry DCM (5 ml) at 0 °C for 10 min. The resulting mixture was stirred for a further 2 h at the same temperature followed by 1 h at rt. This reaction was quenched by 20% aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2×10 ml). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel eluting with hexane–ethyl acetate (9:1) to give **16** (1.45 g, 92% yield) as a colorless liquid. $[\alpha]_D^{25} = -9.2$ (*c* 1, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.01$ (t, 6H), 0.85 (s, 9H), 1.75–2.05 (m, 8H),

3.09–3.19 (m, 1H), 3.23–3.70 (m, 4H), 3.89–4.18 (m, 4H), 5.10 (s, 2H), 7.32 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.19$, 17.69, 20.60, 25.49, 27.40, 46.01, 51.13, 61.74, 66.09, 67.10, 68.53, 127.73, 128.09, 128.32, 136.30, 155.93, 170.66. LC–MS (ESI-TOF): m/z $[M+H]^+$ 482.23. Anal. Calcd for $C_{24}H_{39}NO_7Si$: C, 59.85; H, 8.16; N, 2.91. Found: C, 59.79; H, 8.11; N, 2.95.

4.5. (5*S*)-5-*tert*-Butyldimethylsilyloxy-3-(3-hydroxypropyl)-1,3-oxazinan-2-one 17

To a stirred solution of compound **16** (1.0 g, 2.01 mmol) in distilled MeOH (10 ml) was added K_2CO_3 (cat.) at ambient temperature, and the reaction was followed by TLC. The starting material was completely consumed within half an hour. The solvent was evaporated under reduced pressure and the residue was purified by passing through the small pad of silica giving compound **17** (0.56 g, 93% yield) as a colorless liquid. $[\alpha]_D^{25} = -5.3$ (c 1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.12$ (s, 6H), 0.89 (s, 9H), 1.77 (m, 2H), 3.25–3.75 (m, 8H), 4.42 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.20$, 17.92, 25.32, 29.76, 45.52, 50.83, 60.13, 66.94, 72.31, 152.86. LC–MS (ESI-TOF): m/z $[M+H]^+$ 290.13. Anal. Calcd for $C_{13}H_{27}NO_4Si$: C, 53.94; H, 9.40; N, 4.84. Found: C, 53.87; H, 9.32; N, 4.90.

4.6. 3-{[(2*S*)-3-Acetoxy-2-*tert*-butyldimethylsilyloxypropyl](benzyl)amino}propyl acetate 18

To a stirred solution of compound **16** (1.5 g, 3.11 mmol) in distilled MeOH (7 ml) was added Pd/C (32 mg, 10 mol %) at rt. The resulting mixture was hydrogenated under an atmospheric pressure of hydrogen for 3 h, and the reaction was followed by TLC. The resulting mixture was filtered and solvent removed in vacuo to give an oily product that was taken in dichloromethane (10 ml). To the resulting solution was added a solution of Na_2CO_3 (0.726 g, 6.85 mmol) in water (10 ml) and benzyl bromide (0.64 g, 3.37 mmol) and the mixture was refluxed for 3 h. The organic layer was separated and the aqueous layer extracted with dichloromethane (2×10 ml). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was chromatographed over silica gel to give compound **18** (1.18 g, 87% in two steps) as a colorless liquid. $[\alpha]_D^{25} = -12.2$ (c 1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.01$ (s, 6H), 0.82 (s, 9H), 1.73 (m, 2H), 1.92 (s, 3H), 1.96 (s, 3H), 2.47 (m, 4H), 3.52 (d, $J = 13.5$ Hz, 1H, –NCH_2Ar), 3.58 (d, $J = 13.5$ Hz, 1H, –NCH_2Ar), 3.80–3.95 (m, 2H), 4.01 (t, $J = 6.4$ Hz, 2H), 4.17 (dd, $J = 10.5$, 2.5 Hz, 1H), 7.32 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.82$, 17.93, 20.90, 25.60, 26.21, 51.23, 57.63, 59.78, 62.33, 67.21, 69.13, 126.91, 128.12, 128.76, 139.09, 170.68. Anal. Calcd for $C_{23}H_{39}NO_5Si$: C, 63.12; H, 8.98; N, 3.20. Found: C, 63.07; H, 8.91; N, 3.26.

4.7. (2*S*)-2-*tert*-Butyldimethylsilyloxy-3-[benzyl(3-hydroxypropyl)amino]propanol 19

Similar to the acetyl deprotection of compound **16**, deprotection of **18** followed by chromatographic purification over silica gel gave compound **19** (1.12 g, 92% yield from 1.5 g of **18**) as a pasty liquid. $[\alpha]_D^{25} = -13.4$ (c 1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.02$ (s, 6H), 0.85 (s, 9H), 1.63–1.77 (m, 2H), 2.44–2.76 (m, 4H), 3.41–3.58 (m, 3H), 3.65–3.85 (m, 4H), 7.30 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.59$, 18.06, 25.70, 28.60, 52.86, 56.48, 59.07, 62.18, 65.40, 69.02, 127.04, 128.21, 128.98, 138.18. Anal. Calcd for $C_{19}H_{35}NO_3Si$: C, 64.54; H, 9.98; N, 3.96. Found: C, 64.43; H, 9.93; N, 3.98.

4.8. *N*-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-*N*-(3-hydoxypropyl)-4-methylbenzenesulfonamide 20

To a stirred solution of (*R*)-glyceraldehyde **12** (2.0 g, 15.36 mmol) and 3-aminopropanol **13** (1.38 g, 118.44 mmol) in MeOH (32 ml) was added Pd/C (150 mg, 10 mol %) at rt. The resulting solution was stirred further for 12 h under a hydrogen atmosphere followed by TLC. The reaction mixture was filtered to remove Pd/C and concentrated under reduced pressure to give a slightly yellowish liquid that was diluted in DCM (20 ml). To the resulting solution was added a solution of Na_2CO_3 (3.58 g, 33.81 mmol) in water (20 ml) and tosyl chloride (3.50 g, 118.37 mmol) at 0 °C and the mixture was stirred further for 2 h at the same temperature. The organic layer was separated and the aqueous layer extracted with dichloromethane (3×20 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel eluting with hexane–ethyl acetate (8:2 to 7:3) to give **20** (4.38 g, 83% yield in two steps) as a colorless liquid: $[\alpha]_D^{25} = -11.0$ (c 1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.28$ (s, 3H), 1.35 (s, 3H), 1.79 (m, 2H), 2.39 (s, 3H), 2.97 (m, 1H), 3.14 (m, 1H), 3.32–3.48 (m, 2H), 3.60–3.72 (m, 3H), 4.05 (dd, $J = 8.4$, 6.3 Hz, 1H), 4.26 (m, 1H), 7.28 (d, $J = 8.0$ Hz, 2H, Ar), 7.66 (d, $J = 8.3$ Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.22$, 25.09, 26.52, 31.09, 46.50, 51.80, 58.67, 67.23, 74.88, 109.45, 126.95, 129.57, 135.60, 143.38. LC–MS (ESI-TOF): m/z $[M+H]^+$ 344.14, $[M+Na]^+$ 366.12. Anal. Calcd for $C_{16}H_{25}NO_5S$: C, 55.96; H, 7.34; N, 4.08. Found: C, 55.89; H, 7.28; N, 4.15.

4.9. (2*S*)-3-Acetoxy-2-*tert*-butyldimethylsilyloxypropyl-*N*-(3-acetoxypropyl)-4-methylbenzenesulfonamide 21

Following the previous preparation procedure for **16**: $[\alpha]_D^{25} = +5.25$ (c 1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.06$ (s, 6H), 0.85 (s, 9H), 1.85 (m, 2H), 2.01 (s, 3H), 2.05 (s, 3H), 2.41 (s, 3H), 3.06–3.32 (m, 4H), 3.69 (d, $J = 4.3$ Hz, 0.5H), 3.95–4.04 (m, 3H), 4.07–4.16 (m, 2H), 4.20 (d, $J = 4.1$ Hz, 0.5H), 7.29 (d, $J = 8.0$ Hz, 2H, Ar), 7.66 (d, $J = 8.3$ Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.89$, 17.76, 20.66, 21.29, 25.52, 27.49, 47.56, 51.73, 61.61, 65.88, 69.57, 127.13, 129.62, 135.83, 143.46, 170.40, 170.63 (overlapping). LC–MS (ESI-TOF): m/z $[M+H]^+$ 502.14, $[M+Na]^+$ 524.13. Anal. Calcd for $C_{23}H_{39}NO_7SSi$: C, 55.06; H, 7.84; N, 2.79. Found: C, 55.01; H, 7.79; N, 2.83.

4.10. (2*S*)-2-Hydroxy-3-*tert*-butyldimethylsilyloxypropyl-*N*-(hydroxypropyl)-4-methylbenzenesulfonamide 23

To a stirred solution of compound **21** (1.5 g, 2.98 mmol) in distilled MeOH (12 ml) was added K_2CO_3 (cat.) at ambient temperature, followed by TLC. The starting material was

used within half an hour. The solvent was evaporated under reduced pressure and the residue purified by passing through a small pad of silica gel to give compound **23** (1.10 g, 89% yield) as a colorless pasty liquid. $[\alpha]_D^{25} = -7.5$ (*c* 1, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.04$ (s, 6H), 0.86 (s, 9H), 1.80 (m, 2H), 2.40 (s, 3H), 2.68 (br s, 2H, exchangeable) 2.98–3.105 (m, 1H), 3.15–3.31 (m, 3H), 3.54–3.88 (m, 5H), 7.29 (d, $J = 8.0$ Hz, 2H, Ar) 7.62 (d, $J = 8.3$ Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.53$, 18.11, 21.39, 25.73, 31.17, 47.35, 52.53, 58.98, 64.64, 70.89, 127.19, 129.69, 135.52, 143.51. LC–MS (ESI-TOF): *m/z* $[M+H]^+$ 418.11, $[M+Na]^+$ 440.09. Anal. Calcd for $C_{19}H_{35}NO_5SSi$: C, 54.64; H, 8.45; N, 3.35. Found: C, 54.57; H, 8.39; N, 3.41.

4.11. (3*R*,4*S*)-3-Hydroxy-4-(hydroxymethyl)-*N*-[4-methylphenylsulfonyl]pyrrolidin-3-yl-methyl-*tert*-butyldimethylsilylether 24

A mixture of **23** (0.80 g, 1.91 mmol) and IBX (2.67 g, 9.57 mmol) in EtOAc (38 ml) was heated at reflux for 4.5 h at 80 °C, followed by TLC. The reaction temperature was brought to rt and filtered. The filtrate was washed with 20% sol of $NaHCO_3$ (3×20 ml). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting crude oxidized product was used for the cyclization without purification. This slight yellowish material was dissolved in $CHCl_3$–DMSO (3:1, 12 ml) at 5 °C, followed by the addition of L-proline (0.032 g, 15 mol %). The resulting solution was stirred for a further 16 h at the same temperature followed by the addition of 5 ml of MeOH and in situ reduction with $NaBH_4$ (0.075 g, slight excess) for 2 h. The reaction mixture was evaporated in vacuo and poured into cold water (15 ml), followed by the extraction with EtOAc (4×20 ml). The combined reaction mixture was dried over Na_2SO_4 and concentrated under reduced pressure; the resulting pasty mass was purified by flash column chromatography to give **24** (0.51 g, 65% yield after three steps) as a white solid at low temperature. $[\alpha]_D^{25} = -5.1$ (*c* 0.5, MeOH), ^1H NMR (400 MHz, $CDCl_3/D_2O$): $\delta = 0.06$ (s, 6H), 0.87 (s, 9H), 1.63 (br s, 1H, exchangeable), 2.11 (m, 1H), 2.42 (s, 3H), 3.06 (d, $J = 10.8$ Hz, 1H), 3.12 (m, 1H), 3.40 (d, $J = 10.5$ Hz, 1H), 3.47–3.53 (m, 3H), 3.60–3.63 (m, 2H), 7.31 (d, $J = 8.0$ Hz, 2H, Ar), 7.69 (d, $J = 8.3$ Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.74$, 17.98, 21.36, 25.60, 44.53, 48.89 (dept), 57.39 (dept), 59.40 (dept), 66.41 (dept), 80.38, 127.48, 129.54, 132.88, 143.50. LC–MS (ESI-TOF): *m/z* $[M+H]^+$ 416.09, $[M+Na]^+$ 438.08. Anal. Calcd for $C_{19}H_{33}NO_5SSi$: C, 54.91; H, 8.00; N, 3.37. Found: C, 54.83; H, 7.92; N, 3.44.

4.12. (3*R*,4*S*)-3,4-Bis(hydroxymethyl)-1-[(4-methylphenyl)sulfonyl]pyrrolidin-3-ol 6

To a solution of compound **24** (0.50 g, 1.2 mmol) in MeOH (8 ml), was added phosphotungstic acid-hydrate (PTA) in a catalytic amount and stirred further for 30 min at rt. The solvent was removed in vacuo and residue was purified by passing through a small pad of silica gel with $CHCl_3$/MeOH to give triol **6** in almost quantitative yield. $[\alpha]_D^{25} = -3.9$ (*c* 1, MeOH), ^1H NMR (200 MHz, $CDCl_3/D_2O$): $\delta = 2.09$ (m, 1H), 2.41 (s, 3H), 3.06 (m, 2H) 3.15–3.68 (m, 6H), 7.30 (d, $J = 8.0$ Hz, 2H, Ar), 7.68 (d, $J = 8.3$ Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3/D_2O$): $\delta = 21.39$, 42.35, 48.75 (dept), 57.09 (dept), 59.85 (dept), 65.93 (dept), 79.82, 127.41, 129.49, 132.74, 143.55. Anal. Calcd for $C_{13}H_{19}NO_5S$: C, 51.81; H, 6.35; N, 4.65. Found: C, 51.78; H, 6.31; N, 4.68.

4.13. {(3*R*,4*S*)-3-Hydroxy-*N*-[(4-methylphenyl)sulfonyl]pyrrolidine-3,4-diyl}bis(methylene)diacetate 25

To a stirred solution of **6** (0.35 g, 1.16 mmol) and in dry DCM/pyridine (1:1) (8 ml) was added a solution of acetyl chloride (0.19 g, 2.43 mmol) in dry DCM (2.5 ml) at 0 °C for 30 min. The combined reaction mixture was stirred for 2 h at the same temperature and then poured into the cold water (10 ml), which was further extracted with DCM (2×10 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to give diacetyl derivative **25** with 87% yield as a single diastereomer as confirmed by ^1H and ^{13}C NMR. $[\alpha]_D^{20} = +2.9$ (*c* 0.5, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.00$ (s, 3H), 2.07 (s, 3H), 2.31 (m, 1H) 2.42 (s, 3H), 3.09 (t, $J = 9.8$ Hz, 1H), 3.26 (d, $J = 11.0$ Hz, 1H), 3.42 (d, $J = 11.0$ Hz, 1H), 3.56 (t, $J = 8$ Hz, 1H), 3.98 (d, $J = 12.2$ Hz, 1H), 4.00 (dd, $J = 7.0$, 10.5 Hz, 1H), 4.15 (d, $J = 12.2$ Hz, 1H), 4.20 (dd, $J = 7.0$, 11.3 Hz, 1H), 7.32 (d, $J = 8.0$ Hz, 2H, Ar), 7.69 (d, $J = 8.2$ Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.66$, 20.75 (overlapping), 21.51, 43.46, 49.56 (dept), 58.12 (dept), 61.24 (dept), 67.73 (dept), 127.55, 129.78, 133.24, 143.89, 170.78, 171.04. LC–MS (ESI-TOF): *m/z* $[M+H]^+$ 386.38, $[M+Na]^+$ 408.39. Anal. Calcd for $C_{17}H_{23}NO_7S$: C, 52.97; H, 6.01; N, 3.63. Found: C, 52.97; H, 6.05; N, 3.69.

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