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Stereoselective synthesis of two new trihydroxylated pyrrolidines using a meyer-schuster rearrangement

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Abstract

The synthesis of two new trihydroxylated pyrrolidines, in a highly diastereoselective manner, has been developed using the Meyer-Schuster rearrangement as a key step. C 2011 Taylor & Francis Group, LLC.

Keywords

Stereoselective, synthesis, two, trihydroxylated, pyrrolidines, using, meyer, schuster, rearrangement, CMMB

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A STEREOSELECTIVE SYNTHESIS OF TWO NEW TRIHYDROXYLATED PYRROLIDINES USING A MEYER-SCHUSTER REARRANGEMENT

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Abstract: The synthesis of two new trihydroxylated pyrrolidines, in a highly diastereoselective manner, has been developed using the Meyer-Schuster rearrangement as a key step.

Keywords: polyhydroxylated pyrrolidine, Meyer-Schuster rearrangement.

INTRODUCTION

The polyhydroxylated pyrrolidine, piperidine, indolizidine, pyrrolizidine and nortropane alkaloids have glycosidase inhibitory activities and thus have potential utility as antiviral, anticancer, antidiabetic and antiobesity drugs.[1] These potentially useful biological properties along with the novel structures have made these compounds and their analogues attractive and important synthetic targets.[1] A large majority of the polyhydroxylated bioactive alkaloids or azasugars contain a pyrrolidine ring moiety decorated with one or two hydroxyl group functionalities (Figure. 1). The polyhydroxylated pyrrolidines include the 1,4-dideoxy-1,4-imino hexitols **A** and **B** (Figure 1). While in many other azasugar compounds the pyrrolidine ring is part of a bicyclic heterocyclic system such as that found in the polyhydroxylated indolizidine and pyrrolizidine alkaloids. Well know examples include swainsonine **C**, castanospermine **D** and australine **E** (Figure 1).

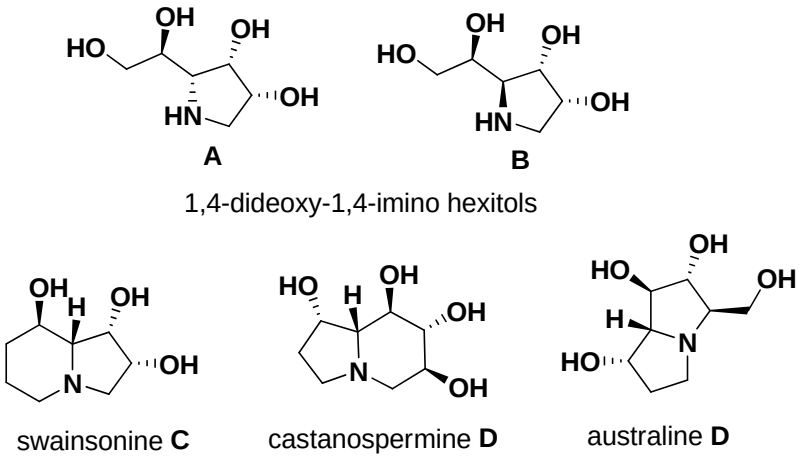
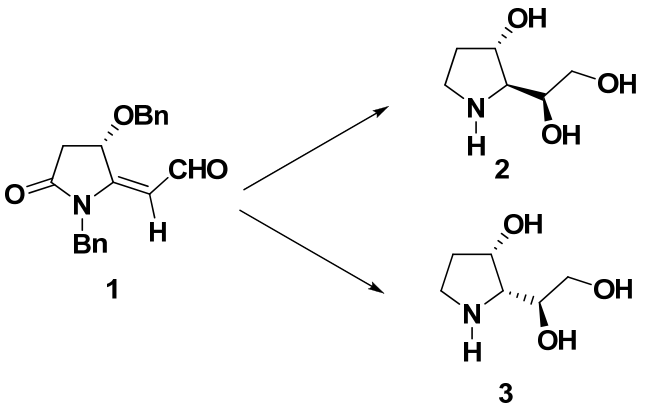


Figure 1. Some Polyhydroxylated Pyrrolidine ring containing Natural Products.

During our synthetic studies on the Stemona alkaloids we unexpectedly prepared the novel Meyer-Schuster rearrangement product the enal **1**.[2] Intermediate **1** has an α,β-unsaturated aldehyde moiety which could be potentially useful for the synthesis of polyhydroxylated pyrrolidines, pyrrolizidines and indolizidines. Here we report the diastreoselective synthesis of the two new trihydroxylated pyrrolidines **2** and **3** from the aldehyde **1** (Scheme 1).

Scheme 1

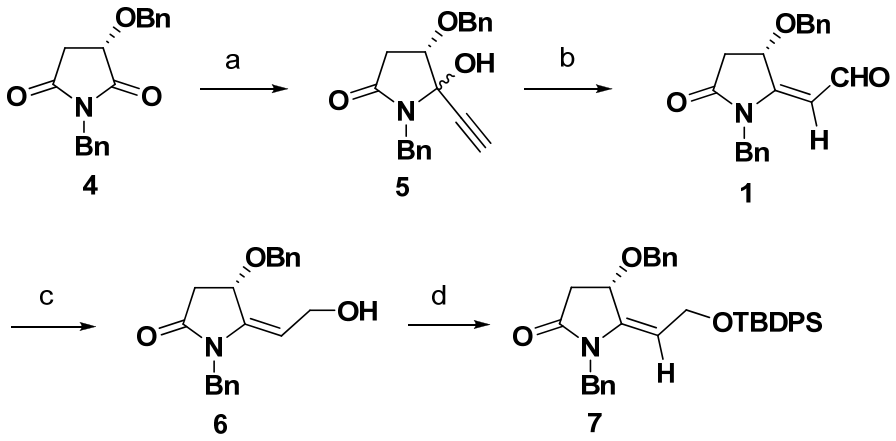


RESULTS AND DISCUSSION

Our synthetic approach started from enantiopure imide **4,** which can be readily synthesized from (-)-malic acid.[3] Imide **1** was alkynylated with lithium trimethylsilylacetylide, which was prepared from TMS-acetylene (1.5 equiv) and *n*BuLi (1.5 equiv). The crude reaction mixture was treated with LiOH, to remove the

TMS group, to give a mixture (6:4) of diastereomeric hydroxy lactams **2** in 74% yield. This mixture was treated with borontrifluoride·etherate (1 equiv) which rapidly (2-5 min) gave the Meyer-Schuster rearrangement product **1** as a single *E*-isomer in excellent yield (86%). The *E*-geometry of **1** was established from a NOESY study that showed a cross peak between the *N*-benzyl methylene protons and the alkene proton. The *E*-isomer was also expected from the work of Huang on related compounds.[4] The aldehyde **1** was reduced to the alcohol **6** using $NaBH_4$ in MeOH, followed by hydroxyl group protection with TBDPSCl/imidazole in CH_2Cl_2 to give the TBDPS ether **7** as shown in Scheme 2.

Scheme 2

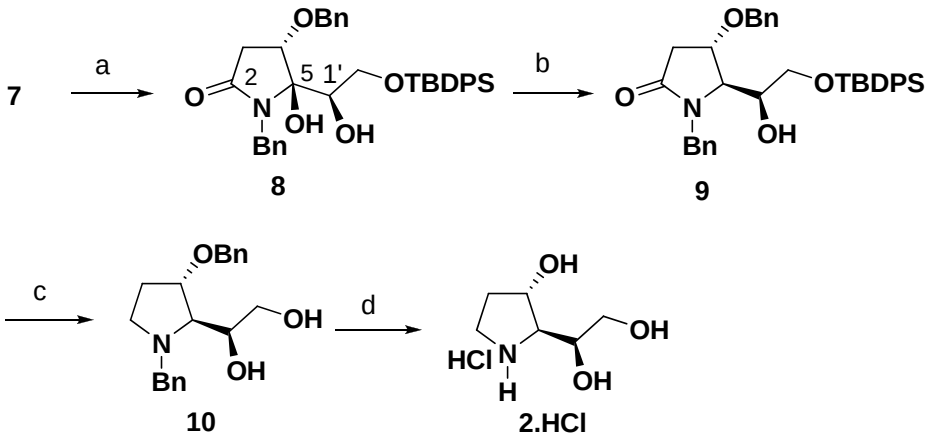


Reagents and conditions: a) $HCCSiMe_3$, nBuLi (1.5 eq) / THF, -78 ^oC, 1 h and then LiOH, (74%), b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 ^oC, 2-5 min (86%), c) $NaBH_4$/MeOH, 0 ^oC, 30 min (97%), d) TBDPSCl, imidazole, CH_2Cl_2, rt, 2 h (83%).

Having first investigated the stereoselective dihydroxylation of **7** using the Sharpless asymmetric dihydroxylation reaction conditions,[5] we discovered high *trans* diastereoselectivites at the pyrrolidine ring (C-4/C-5) but only 1:1 *anti/syn* diastereoselectivites at the pyrrolidine ring (C-5) and exocyclic stereogenic centre (C-1'). However, when we used $K_2OsO_4.2H_2O$/NMO in acetone and H_2O (2:1), high *trans* diastereoselectivites at the pyrrolidine ring (C-4 / C-5) and also high 5:95 *anti/syn* diastereoselectivites at the pyrrolidine ring (C-5) and exocyclic stereogenic centre (C-1') were observed. This resulted in isolation of the diol **8** in 72% yield (Scheme 3).[6] The configuration at the aminol carbon (C-5) was not unequivocally established. Reductive of **8** with $Et_3SiH/BF_3{\cdot}OEt_2$ gave only the *trans* diastereomer **9** in 77% yield. The stereochemical outcomes of this reaction was expected due to the

stereodirecting effect of the C-3 pyrrolidine substituent in **8**.[4] Evidence for the configuration of **9** was obtained from NOESY NMR experiments which showed a significant correlation between H-5 and H-1' and no correlation between H-4 and H-5 (Figure 2). Further, $J_{4,5}$ was 0 Hz, consistent with the 4,5-*trans* configuration.[7] Lactam **9** was reduced to the pyrrolidine **10** using $LiAlH_4$ in 83% yield. Finally debenzylation of **10** by hydrogenolysis over $PdCl_2$ gave the hydrochloride salt of **2** in nearly quantitative yield (Scheme 3).

Scheme 3



Reagents and conditions: a) $K_2OsO_4 \cdot 2H_2O$, NMO, acetone/H_2O, rt, 3 h, (72%), b) $Et_3SiH/BF_3 \cdot OEt_2$, CH_2Cl_2, rt, 12 h, (77%), c) $LiAlH_4$/THF, rt, 12 h, (83%), d), $PdCl_2/H_2$, MeOH, rt, 12 h, (99%).

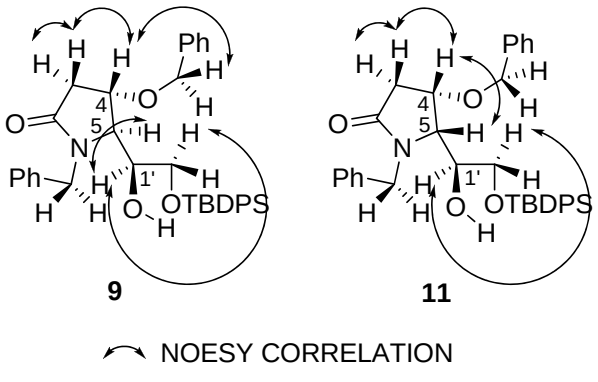
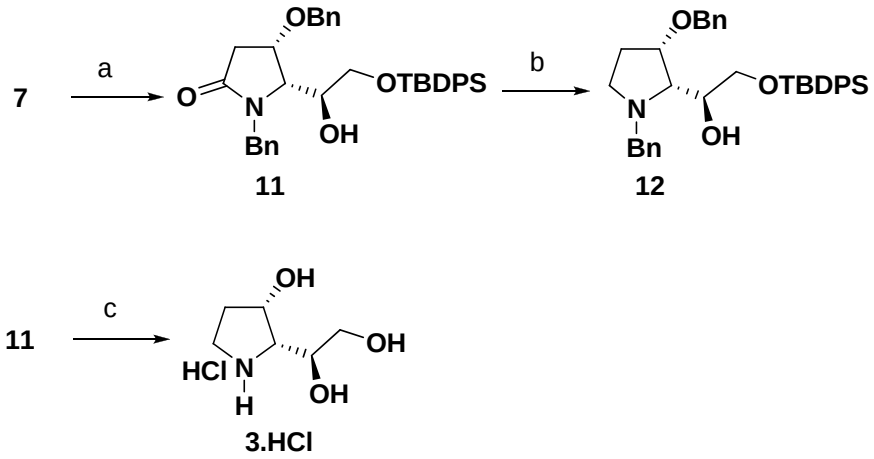


Figure 2. NOESY correlations for compounds **9** and **11**.

Hydroboration of **7** using $BH_3 \cdot SMe_2$ in THF and subsequent oxidative work up using H_2O_2[6] in alkaline solution resulted in the formation of an unidentified UV-inactive

side product, and gave the desired product **11** in an unsatisfactory yield of 32% (Scheme 4). However, when the alternative oxidant, $NaBO_3.4H_2O$[8] was used the yield of **11** was more satisfactory (50%). The configuration of **11** was established by NOESY NMR experiments (Figure 2). Further, $J_{4,5}$ was 6.0 Hz, consistent with the 4,5-*cis* configuration.[7] Lactam **11** was reduced to the pyrrolidine **12** using BH_3·DMS in 72% yield. Finally debenzylation of **12** by hydrogenolysis over $PdCl_2$ gave the hydrochloride salt of **3** in nearly quantitative yield (Scheme 4).

Scheme 4



Reagents and conditions: a) BH_3·DMS, THF, rt, 12 h, then EtOH, $NaBO_3.4H_2O$, reflux, 3 h (50%), b) BH_3·DMS, THF rt, 12 h, then EtOH reflux, 2 h (72%) c) $PdCl_2/H_2$, MeOH, rt 12 h, (99%).

CONCLUSIONS

The synthesis of two new trihydroxylated pyrrolidines, in a highly diastereoselective manner, has been developed using the Meyer-Schuster rearrangement as a key step. The trihydroxylated pyrrolidine **2** was obtained as its hydrochloride salt in eight synthetic steps from **4** in 23% overall yield, while the hydrochloride salt of **3** was obtained in seven synthetic steps and 18% overall yield from **4**. This methodology could, in principle, be extended to the synthesis of natural and unnatural polyhydroxylated pyrollizidines and indolizidines.

EXPERIMENTAL

General methods were as previously described.[7]

(*S*)-1-Benzyl-4-(benzyloxy)-5-ethynyl-5-hydroxy pyrrolidin-2-one (5)

To a solution of trimethylsilyl acetylene (0.50 g, 5.08 mmol) in dry THF (10 mL) was added dropwise 2.5 M *n*-butyllithium solution (2.40 mL) at -78 ^{o}C under N_2 atm and stirred for 30 min. Then cyclic imide **4** (1 g, 3.39 mmol) dissolved in dry THF (10 mL) was added dropwise. Stirring was continued for 30 min. at -78 ^{o}C, monitoring the reaction via TLC, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo.* The residue was dissolved in THF (10 mL) and treated with saturated LiOH solution (2 mL) to cleave the TMS group. The mixture was then diluted with water and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed on silica gel (2 : 1 EtOAc/petrol) to afford a 60 : 40 mixture of two diastereomeric products as an pale yellow gum (0.80 g, 74%). **Major isomer**: R_f = 0.28 (7:3 EtOAc/petrol); $[\alpha]_D^{21}$ +20.0 (*c* 1.40, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 3278, 2115, 1686, 1403, 1124, 968, 743, 702; δ_H (500 MHz, $CDCl_3$) 7.37–7.19 (m, 10ArH), 4.73 (1H, d, *J* = 11.5 Hz), 4.66 (1H, d, *J* = 11.5 Hz), 4.65 (1H, d, *J* = 15.0 Hz), 4.50 (1H, d, *J* = 15.0 Hz), 4.24 (1H, t, *J* = 6.5 Hz, H-4), 2.65 (1H, dd, *J* = 6.0, 17.0 Hz, H-3), 2.63 (1H, s, H-2`), 2.50 (1H, dd, *J* = 6.0, 17.0 Hz, H-3); $\delta_C$ (125 MHz, $CDCl_3$) 171.0 (CO), 137.4 (ArC), 136.3 (ArC), 128.5 (ArCH), 128.3 (ArCH) , 128.2 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 127.1 (ArCH), 83.97 (C-2`), 80.87 (C-1`), 78.02 (C-4), 75.0 (C-5), 72.64 (C-4`), 43.7 (C-3`), 32.2 (C-3); ESIMS *m/z* 343.89 [(M + Na^+) 100%]; HRESIMS calcd. for $C_{20}H_{19}NO_3Na$, $(M+Na)^+$ 344.1272, found: 344.1263. **Minor isomer**: R_f = 0.24 (7 : 3 EtOAc/petrol); $[\alpha]_D^{22}$ –30.0 (*c* 1.40, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 3278, 2115, 1686, 1403, 1124, 968, 743, 702; δ_H (500 MHz, $CDCl_3$) 7.32–7.16 (m, 10ArH), 4.84 (1H, d, *J* = 11.5 Hz), 4.70 (1H, d, *J* = 15.0 Hz), 4.60 (1H, d, *J* = 11.5 Hz), 4.40 (1H, d, *J* = 15.0 Hz), 4.00 (1H, apparent t, *J* = 6.5 Hz, H-4), 2.69 (1H, s, H-2`), 2.67 (1H, dd, *J* = 6.0, 17.0 Hz, H-3) , 2.40 (1H, dd, *J* = 6.0, 17.0 Hz, H-3); δ_C (125 MHz, $CDCl_3$) 172.2 (CO), 137.3 (ArC), 137.29 (ArC), 128.32 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 127.2

(ArCH), 88.4 (C-2`), 80.4(C-1`), 78.6 (C-4), 77.4 (C-5), 72.4 (C-4`), 43.4 (C-3`), 36.0 (C-3); ESIMS *m/z* 343.88 [$(M+Na)^+$ 100%]; HRESIMS calcd. for $C_{20}H_{19}NO_3Na$, $(M+Na)^+$ 344.1251, found: 344.1263.

(*S,E*)-2-(1-Benzyl-3-(benzyloxy)-5-oxopyrrolidin-2-ylidene) acetaldehyde (1)

To a solution of **5** (0.70 g, 2.18 mmol) in dichloromethane (10 ml) cooled to 0 ^oC was added dropwise $BF_3{\cdot}Et_2O$ (0.31 g, 2.18 mmol) at 0 ^oC under N_2 atm. The reaction mixture was stirred for 2 - 5 minutes at 0 ^oC. After completion of reaction, the reaction mixture was quenched with saturated $NaHCO_3$ solution and the aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was chromatographed on silica gel (1:1 EtOAc/petrol) to give the title compound as colourless gum (0.60 g, 86%). R_f = 0.60 (7:3 EtOAc/petrol); $[\alpha]_D^{24}$ + 78.3 (*c* 0.83, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 2919, 1716, 1622, 1403, 1149, 968, 743, 707; δ_H (500 MHz, $CDCl_3$) 9.75 (1H, d, *J* = 8.0 Hz, CHO), 7.38–7.18 (m, 10ArH), 5.54 (1H, d, *J* = 8.0 Hz, H-1`), 5.17 (1H, dd, *J* = 2.5, 7.5 Hz, H-3), 4.37 (2H, s, H-3`), 4.64 (1H, d, *J* = 11.0 Hz), 4.55 (1H, d, *J* =11.0 Hz), 2.89 (1H, dd, *J* = 7.5, 18.5 Hz, H-4) , 2.80 (1H, dd, *J* = 2.5, 18.5 Hz, H-4); δ_C (125 MHz, $CDCl_3$) 189.3 (CHO), 173.2 (CO), 160.1 (C-2), 135.8 (ArC), 133.8 (ArC), 128.9 (ArCH), 128.8 (ArCH) , 128.7 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.2 (ArCH), 126.9 (ArCH), 107.0 (C-2), 71.3 (C-4`), 70.0 (C-3), 44.2 (C-3`), 35.1 (C-4); ESIMS *m/z* 321.9 [$(M+H)^+$ 30%]; HRESIMS calcd. for $C_{20}H_{20}NO_3$, $(M+H)^+$ 322.1458, found: 322.1443.

(*S,E*)-1-Benzyl-4-(benzyloxy)-5-(2-hydroxyethylidene)pyrrolidin-2-one (6)

To a solution of **1** (0.6 g, 1.86 mmol) in MeOH (10 mL) was added in portions $NaBH_4$ (0.21 g, 5.6 mmol) at 0 ^oC under a N_2 atmosphere. After the addition was completed (4 min), the reaction was stirred at 0 ^oC for 30 min. Then it was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 40 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was chromatographed on silica gel (2:1 EtOAc/petrol) to give the title compound as colorless gum (0.59 g, 97%). R_f = 0.28 (2:1 EtOAc/petrol); $[\alpha]_D^{24}$ + 56.5 (*c* 0.92, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 3380, 2924, 1669, 1419, 1347,1147, 1070, 736, 707; δ_H (500 MHz, $CDCl_3$) 7.38–7.16 (m, 10ArH), 5.14 (1H, t, *J* = 7.5 Hz, H-1`), 4.83

(1H, apparent bd, *J ca* 7 Hz, H-4), 4.70 (1H, d, *J* = 15.5 Hz), 4.64 (1H, d, *J* = 15.5 Hz), 4.58 (1H, d, *J* = 11.5 Hz), 4.47 (1H, d, *J* = 11.5 Hz), 4.13 (1H, dd, *J* = 7.5, 12.5 Hz, H-2`), 3.99 (1H, dd, *J* = 7.5, 12.5 Hz, H-2`), 2.80 (1H, dd, *J* = 8.0, 18.0 Hz, H-3), 2.70 (1H, dd, *J* = 2.5, 18.0 Hz, H-3); δ_C (125 MHz, $CDCl_3$) 172.98 (CO), 143.6 (C-5), 136.3 (ArC), 135.3 (ArC), 128.7 (ArCH), 128.6 (ArCH) , 128.5 (ArCH), 128.4 (ArCH), 128.39 (ArCH), 128.35 (ArCH), 127.9 (ArCH), 127.4 (ArCH), 127.0 (ArCH), 105.3 (C-1`), 71.0 (C-4`), 70.2 (C-4), 57.7 (C-2`), 43.6 (C-3`), 35.8 (C-3); ESIMS *m/z* 345.9 [$(M+Na)^+$ 100%]; HRESIMS calcd. for $C_{20}H_{21}NO_3Na$, $(M+Na)^+$ 346.1425, found: 346.1419.

(*S*,*E*)-1-Benzyl-4-(benzyloxy)-5-(2-(*tert*-butyldiphenylsilyloxy)ethylidene)pyrrolidin-2-one (7)

To a solution of **6** (0.50 g, 1.54 mmol) in dry CH_2Cl_2 (10 ml) was added DMAP (0.037 g, 0.31 mmol), Et_3N (0.47 g, 4.64 mmol) and TBDPSCl (1.98 g, 1.85 mmol) at rt under N_2 atmosphere, and the solution was stirred at rt for 2 h under N_2 atmosphere until disappearance of starting material by TLC. The reaction mixture diluted with water (10 ml) and extracted with EtOAc (3 x 30 mL). The organic layers were combined, dried over $MgSO_4$ and solvent concentrated *in vacuo.* The crude product was chromatographed on silica gel (1:2 EtOAc/petrol) give the title compound as a colorless liquid (0.72 g, 83%). R_f = 0.84 (2:1 EtOAc/petrol); $[\alpha]_D^{24}$ + 56.5 (*c* 0.92, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 2929, 1685, 1429, 1112, 830, 743 and 707; δ_H (500 MHz, $CDCl_3$) 7.59–7.08 (m, 20ArH), 4.98 (1H, dd, *J* = 4.5, 9.0 Hz, H-1`), 4.65 (1H, d, *J* = 15.5 Hz), 4.55 (1H, d, *J* = 15.5 Hz), 4.32 (1H, dd, *J* = 4.5,12.5 Hz, H-2`), 4.27 (1H, d, *J* = 11.5 Hz), 4.15 (1H, dd, *J* = 3.0, 12.5 Hz, H-2`), 4.12 (1H, d, *J* = 11.5 Hz), 3.89 (1H, d, *J* = 3.0 Hz, H-4), 2.46 (2H, d, *J* = 2.5 Hz, H-3); δ_C (125 MHz, $CDCl_3$) 173.1 (C=O), 140.7 (C-5), 136.8 (ArC), 135.8 (ArC), 135.6 (ArC), 135.57 (ArC), 135.45 (ArCH), 135.43 (ArCH), 135.3 (ArCH), 134.8 (ArCH), 133.7 (ArCH), 133.6 (ArCH), 129.6 (ArCH) , 129.5 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.44 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.85 (ArCH), 127.8 (ArCH), 127.6 (ArCH), 127.4 (ArCH), 127.3 (ArCH), 106.2 (C-1`), 70.0 (C-4`), 69.7 (C-4), 59.9 (C-2`), 43.5 (C-3`), 36.2 (C-3), 26.7 (3Me-tBu), 19.0 (C-tBu); ESIMS *m/z* 583.8 [$(M+Na)^+$ 100%]; HRESIMS calcd. for $C_{36}H_{39}NO_3NaSi$, $(M+Na)^+$ 584.2611, found: 584.2597.

(4*S*,5*R*)-1-Benzyl-4-(benzyloxy)-5-((*R*)-2-(*tert*-butyldiphenylsiloxy)-1-hydroxyethyl)-5-hydroxypyrrolidin-2-one (8)

To a solution of **7** (0.26 g, 0.46 mmol) in a mixture of acetone (6 mL) and water (4 mL) was added $K_2OsO_4.2H_2O$ (8.5 mg, 0.023 mmol) and NMO (0.13 g, 1.11 mmol). The solution was stirred at rt for 3 h until disappearance of starting material by TLC. The reaction mixture was quenched with saturated potassium bisulfite solution (5 mL), stirred for a 10 min and diluted with water (5 mL) and extracted with EtOAc (3x10 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent was concentrated *in vacuo.* The crude product was chromatographed on silica gel (3:1 EtOAc/petrol) to give the title compound as a colorless liquid (0.2 g, 72%). R_f = 0.48 (7:3 EtOAc/petrol); $[\alpha]_D^{22}$ + 6.20 (*c* 3.64, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 3421, 2929, 1675, 1434, 1112, 825, 748 and 702; δ_H (500 MHz, $CDCl_3$) 7.60–7.15 (m, 20ArH), 4.56 (1H, d, *J* = 15.5 Hz), 4.54 (1H, d, *J* = 11.5 Hz), 4.43 (1H, d, *J* = 15.5 Hz), 4.35 (1H, d, *J* = 11.5 Hz), 4.14 (1H, d, *J* = 5.0 Hz, H-1`), 3.96 (1H, s, OH), 3.84-3.79 (m, 2H, H-2`, H-4), 3.52 (1H, dd, *J* = 7.0, 10.0 Hz, H-2`), 2.76 (1H, dd, *J* = 7.0, 17.0 Hz, H-3), 2.46 (1H, d, *J* = 17.0 Hz, H-3), 2.46 (1H, s, OH), 1.02 (9H, s, 3Me); δ_C (125 MHz, $CDCl_3$) 172.9 (C=O), 138.7 (ArC), 136.7 (ArC), 135.8 (ArC), 135.7 (ArC), 133.2 (ArCH), 132.9 (ArCH), 130.2 (ArCH), 130.1 (ArCH), 128.8 (ArCH), 128.7 (ArCH), 128.5 (ArCH) , 128.1 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.4 (ArCH), 92.2 (C-5), 72.8 (C-1`), 72.0 (C-4`), 71.88 (C-4), 64.1 (C-2`), 42.3 (C-3`), 37.3 (C-3), 27.1 (3Me-tBu), 19.4 (C-tBu); ESIMS *m/z* 595.7 [$(M+H)^+$ 100 %]; HRESIMS calcd. for $C_{36}H_{42}NO_5Si$, $(M+H)^+$ 596.2853, found: 596.2832.

(4*S*,5*R*)-1-Benzyl-4-(benzyloxy)-5-((*S*)-2-(*tert*-butyldiphenylsiloxy)-1-hydroxyethyl) pyrrolidin-2-one (9)

To a solution of **8** (0.20 g, 0.33 mmol) in dry CH_2Cl_2 (6 mL) was added $BF_3.Et_2O$ (0.19 g, 1.34 mmol) followed by Et_3SiH (0.39 g, 3.36 mmol) at 0 ^oC under a N_2 atmosphere. The solution was stirred at 0 ^oC under N_2 atmosphere for 15 min and then at rt for 12 h until disappearance of starting material by TLC. The reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL), stirred for a 10 min and diluted with water (5 ml) and extracted with CH_2Cl_2 (3x20 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent concentrated *in vacuo.* The crude product was chromatographed (3:1 EtOAc/petrol) to give the title compound as a

colorless liquid (0.15 g, 77%). R_f = 0.56 (6:4 EtOAc/petrol); $[\alpha]_D^{24}$ + 26.70 (*c* 2.65, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 3334, 2929, 1670, 1424, 1112, 819, 748 and 707; δ_H (500 MHz, $CDCl_3$) 7.60–7.11 (m, 20ArH), 5.10 (1H, d, *J* = 15.5 Hz), 4.32 (2H, s), 4.13 (1H, d, *J* = 6.5 Hz, H-4), 4.05 (1H, d, *J* = 15.5 Hz), 3.97–3.96 (1H, m, H-1`), 3.67 (1H, s, H-5), 3.65 (1H, dd, *J* = 7.0, 10.5 Hz, H-2`), 3.56 (1H, dd, *J* = 7.0, 10.5 Hz, H-2`), 3.29 (1H, d, *J* = 3.0 Hz, OH), 2.77 (1H, dd, *J* = 6.5, 17.5 Hz, H-3), 2.46 (1H, d, *J* = 17.5 Hz, H-3), 0.98 (9H, s, 3Me); δ_C (125 MHz, $CDCl_3$) 174.0 (C=O), 137.5 (ArC), 136.0 (ArC), 135.47 (ArC), 135.46 (ArC), 132.8 (ArCH), 132.76 (ArCH), 129.95 (ArCH), 129.93 (ArCH), 128.7 (ArCH), 128.3 (ArCH), 127.83 (ArCH) , 127.81 (ArCH), 127.67 (ArCH), 127.5 (ArCH), 71.9 (C-4), 70.3 (C-4`), 68.65 (C-1`), 64.8 (C-5), 64.3 (C-2'), 44.1 (3`), 38.5 (C-3), 26.8 (3Me-tBu), 19.1 (C-tBu); ESIMS *m/z* 580.3 [$(M+H)^+$ 100%]; HRESIMS calcd. for $C_{36}H_{42}NO_4Si$, $(M+H)^+$ 580.2892, found: 580.2883.

(*S*)-1-((2*R*,3*S*)-1-Benzyl-3-(benzyloxy)pyrrolidin-2-yl)ethane-1,2-diol (10)

To a solution of **9** (0.15 g, 0.26 mmol) in dry THF (5 mL) was added $LiAlH_4$ (0.039 g, 1.03 mmol) at rt under a N_2 atmosphere. The solution was stirred at rt for 12 h until disappearance of starting material by TLC. The reaction mixture was quenched with saturated ammonium chloride solution until a precipitate was formed. The solution was filtered and the solids were washed with EtOAc. The organic layer was dried over $MgSO_4$ and the solvent concentrated *in vacuo*. The crude product was chromatographed (3:1 EtOAc/petrol) to give the title compound as a colorless liquid (0.07 g, 83%). R_f = 0.31 (4:1 EtOAc/petrol); $[\alpha]_D^{23}$ – 16.80 (*c* 0.77, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 3370, 2934, 1659, 1444, 1050, 748 and 707; δ_H (500 MHz, $CDCl_3$) 7.37–7.25 (m, 10ArH), 4.54 (1H, d, *J* = 11.5 Hz), 4.30 (1H, d, *J* = 11.5 Hz), 4.15-4.00 (1H, m, H-3), 4.08 (1H, d, *J* = 13.0 Hz), 3.89 (1H, dd, *J* = 5.5, 8.5 Hz, H-2), 3.74–3.65 (2H, m, H-2`), 3.41 (1H, d, *J* = 13.0 Hz), 2.93 (1H, t, *J* = 8.5 Hz, H-5), 2.80 (1H, apparent t, *J* = 3.5 Hz, H-1`), 2.56 (1H, dd, *J* = 7.0, 17.0 Hz, H-5), 1.90 (1H, dd, *J* = 7.0, 13.0 Hz, H-4), 1.84–1.68 (1H, m, H-4); δ_C (125 MHz, $CDCl_3$) 138.5 (ArC), 137.8 (ArC), 128.8 (ArCH), 128.52 (ArCH), 128.45 (ArCH), 128.0 (ArCH), 127.3 (ArCH), 79.1 (C-3), 72.6 (C-1`), 71.1 (C-4`), 69.2 (C-2), 64.4 (C-2`), 59.04 (C-3`), 52.1 (C-5), 30.1 (C-4); ESIMS *m/z* 328.1 [$(M+H)^+$ 100%]; HRESIMS calcd. for $C_{20}H_{26}NO_3$, $(M+H)^+$ 328.1909, found: 328.1913.

(2*S*,3*S*)-2-((*S*)-1,2-Dihydroxyethyl)pyrrolidin-3-ol·hydrochloride (2)

To a solution of **10** (0.07 g, 0.21 mmol) in MeOH (5 mL) was added $PdCl_2$ (0.043 g, 0.21 mmol) at rt under a N_2 atmosphere. Then the reaction mixture was flushed with H_2 (balloon) and the solution was stirred at rt under a H_2 atmosphere for 12 h. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with MeOH. The solvent was concentrated *in vacuo* and then residue was triturated with ether for several times to get rid of all nonpolar-impurities. This gave the pure title compound as a colorless gum (0.039 g, 99%). R_f = 0.18 (1:9 MeOH/EtOAc); $[\alpha]_D^{22}$ + 4.7 (*c* 4.0, MeOH); IR (neat, ν_{max}/cm^{-1}) 3409, 3365, 2924, 2484, 1634, 1420, 1091, and 1045; δ_H (500 MHz, CD_3OD) 4.45 (1H, apparent t, *J* = 2.5 Hz, H-3), 3.77 (1H, dd, *J* = 5.0, 9.5 Hz,H-1`), 3.63 (1H, dd, *J* = 5.0, 11.0 Hz, H-2`), 3.65 (1H, dd, *J* = 5.0, 11.0 Hz, H-2`), 3.45 (1H, bs, H-2), 3.30 (2H, apparent t, *J* = 7.5 Hz, H-5), 2.18 – 2.10 (1H, m, H-4), 1.91 – 1.85 (1H, m, H-4); $\delta_C$ (125 MHz, $CDCl_3$) 70.76 (C-3), 69.8 (2C-C-2 and C-1`), 64.5 (C-2`), 45.34 (C-5), 34.5 (C-4); ESIMS *m/z* 148.1 [$(M+H)^+$ 100%]; HRESIMS calcd. for $C_6H_{14}NO_3$, $(M+H)^+$ 148.0952, found: 148.0974.

(4*S*,5*S*)-1-Benzyl-4-(benzyloxy)-5-((*S*)-2-(*tert*-butyldiphenylsiloxy)-1-hydroxyethyl)pyrrolidin-2-one (11)

To a solution of **7** (0.20 g, 0.35 mmol) in THF (4 mL) was added dropwise a 1 M solution of borane·dimethylsulfide in CH_2Cl_2 (0.36 mL, 0.35 mmol) at 0 ^oC under a N_2 atmosphere. The reaction mixture was stirred at rt for 12 h. The reaction mixture was quenched with ethanol (1.2 mL) and treated with $NaBO_3.4H_2O$ (0.032 g, 0.21 mmol) at 0 ^oC. The reaction mixture was then heated at reflux for 3 h. After being cooled, the reaction mixture was poured into ice water and was extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The residue was chromatographed on silica gel (2:1 EtOAc/petrol) to give the title compound as a colorless gum (0.103 g, 50%). R_f = 0.48 (6:4 EtOAc/petrol); $[\alpha]_D^{24}$ –0.90 (*c* 5.40, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 3390, 2939, 1680, 1424, 1112, 819, 753 and 712; δ_H (500 MHz, $CDCl_3$) 7.61–7.13 (m, 20ArH), 5.10 (1H, d, *J* = 15 Hz), 4.43(1H, d, *J* = 12.0 Hz), 4.23 (1H, d, *J* = 12.0 Hz), 4.20 (1H, d, *J* = 15.0 Hz), 4.13–4.10 (1H, m, H-1`), 4.00 (1H, apparent q (ddd), *J* = 6.0 Hz, H-4), 3.74 – 3.69 (2H, m, H-2`), 3.64 (1H, apparent t, *J* = 6.0 Hz, H-5), 2.67 (s, OH),

2.66 (1H, dd, *J* = 6.0, 16.0 Hz, H-3) , 2.53 (1H, dd, *J* = 6.0, 16.0 Hz, H-3); δ_C (125 MHz, $CDCl_3$) 173.1 (C=O), 136.94 (ArC), 135.5 (ArC), 132.9 (ArC), 132.8 (ArC) , 129.89 (ArCH), 129.86 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 127.9 (ArCH), 127.77 (ArCH), 127.7 (ArCH), 127.5 (ArCH), 127.2 (ArCH), 73.7 (C-4), 71.4 (C-4`), 70.7 (C-1`), 65.2 (C-2`), 60.6 (C-5), 45.5 (C-3`), 36.8 (C-3), 26.8 (3Me), 19.1 (tBuC); ESIMS *m/z* 602.1 [$(M+Na)^+$ 100%]; HRESIMS calcd. for $C_{36}H_{41}NO_4SiNa$, $(M+Na)^+$ 602.2780, found: 602.2703.

(*S*)-1-((2*S*,3*S*)-1-Benzyl-3-(benzyloxy)pyrrolidin-2-yl)-2-(*tert*-butyldiphenylsiloxy)ethanol (12)

To a solution of **11** (0.10 g, 0.17 mmol) in anhydrous THF (5 mL) was added dropwise a 1 M solution of borane·dimethylsulfide in CH_2Cl_2 (0.69 mL, 0.69 mmol) at 0 ^oC under a N_2 atmosphere. The reaction mixture was stirred at rt for 12 h. The reaction mixture was quenched with ethanol (1 mL). The resulting mixture was heated at reflux for 2 h. After cooling, the reaction mixture was poured in to ice water and extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The residue was chromatographed on silica gel (2:1 EtOAc/petrol) to give the title compound as colorless gum (0.07 g, 72%). R_f = 0.62 (6:4 EtOAc/petrol); $[\alpha]_D^{24}$ +11.0 (*c* 2.08, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 3359, 2929, 2858, 1429, 1110, 738 and 702; δ_H (500 MHz, $CDCl_3$) 7.69–7.23 (m, 20ArH), 4.52 (1H, d, *J* = 12.0 Hz), 4.45 (1H, d, *J* = 12.0 Hz), 4.10-4.04 (3H, m, H-2, H-3, PhC*H*), 3.75 (1H, dd, *J* = 6.0, 10.0 Hz, H-2`), 3.69 (1H, dd, *J* = 7.5, 10.0 Hz, H-2`), 3.54 (1H, d, *J* = 14.0), 3.33 (1H, dd, *J* = 3.0, 8.0 Hz, H-1`) , 3.01-2.97 (1H, m, H-5), 2.38-2.36 (1H, m, H-5), 1.97-1.94 (1H, m, H-4), 1.86-1.85 (1H, m, H-4); δ_C (125 MHz, $CDCl_3$) 138.2 (ArC), 135.6 (ArC), 134.7 (ArC), 133.5 (ArC), 129.7 (ArCH), 129.6 (ArCH) , 128.8 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.35 (ArCH), 128.34 (ArCH), 128.1 (ArCH), 127.8 (ArCH), 127.6 (ArCH), 127.5 (ArCH), 127.3 (ArCH), 127.2 (ArCH), 126.9 (ArCH), 78.9 (C-3), 71.5 (C-4`), 68.0 (C-2), 65.8 (C-2`), 64.0 (C-1`), 61.3 (C-3`), 50.3 (C-5), 30.6 (C-4), 26.8 (3Me, tBu), 19.2 (tBuC); ESIMS *m/z* 566.1 [$(M+H)^+$ 100%]; HRESIMS calcd. for $C_{36}H_{44}NO_3Si$, $(M+H)^+$ 566.3107, found: 566.3090.

(2*R*,3*S*)-2-((*S*)-1,2-Dihydroxyethyl)pyrrolidin-3-ol·hydrochloride (3)

To a solution of **12** (0.05 g, 0.088 mmol) in MeOH (4 mL) was added $PdCl_2$ (47 mg, 0.26 mmol) at rt under a N_2 atmosphere. Then the reaction mixture was flushed with H_2 (balloon) and the solution was stirred at rt under a H_2 atmosphere for 12 h. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with MeOH. The solvent was concentrated *in vacuo* and then the residue was triturated several times with ether to get rid of all nonpolar-impurities. This gave the pure title compound as a colorless gum (0.016 g, 99%). R_f = 0.18 (1:9 MeOH/EtOAc); $[\alpha]_D^{23}$ +5.7 (*c* 4.0, MeOH); IR (neat, ν_{max}/cm^{-1}) 3409, 3365, 2924, 2484, 1634, 1420, 1091, and 1045; δ_H (500 MHz, CD_3OD) 4.41 (1H, bs, H-3), 4.05–4.03 (1H, m, H-1`), 3.73 (1H, dd, *J* = 1.50, 11.5 Hz H-2`), 3.65 (1H, dd, *J* = 3.5, 11.5 Hz, H-2`), 3.45 (1H, bs, H-2), 3.43 (1H, bs, H-5), 3.25 (1H, bs, H-5), 2.18 – 2.16 (1H, m, H-4), 2.10–2.05 (1H, m, H-4); $\delta_C$ (125 MHz, $CDCl_3$) 70.7 (C-3), 69.6 (C-1`), 67.5 (C-2), 64.7 (C-2`), 44.0 (C-5), 34.9 (C-4); ESIMS *m/z* 148.1 [$(M+H)^+$ 100%]; HRESIMS calcd. for $C_6H_{14}NO_3$, $(M+H)^+$ 148.0991, found: 148.0984.

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GRAPHICAL ABSTRACT

A STEREOSELECTIVE SYNTHESIS OF TWO NEW TRIHYDROXYLATED PYRROLIDINES USING A MEYER-SCHUSTER REARRANGEMENT

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