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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. These potentially useful biological properties along with the novel structures have made these compounds and their analogues attractive and important synthetic targets. 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).
During our synthetic studies on the Stemona alkaloids we unexpectedly prepared the novel Meyer-Schuster rearrangement product the enal 1.\textsuperscript{[2]} Intermediate 1 has an $\alpha,\beta$-unsaturated aldehyde moiety which could be potentially useful for the synthesis of polyhydroxylated pyrrolidines, pyrrolizidines and indolizidines. Here we report the diastereoselective 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 \texten(-)-malic acid.\textsuperscript{[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 boron trifluoride-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 TBDPSCI/imidazole in CH\(_2\)Cl\(_2\) to give the TBDPS ether 7 as shown in Scheme 2.

**Scheme 2**

![Scheme 2](image)

Reagents and conditions: a) HCCSiMe\(_3\), nBuLi (1.5 eq) / THF, -78 °C, 1 h and then LiOH, (74%), b) BF\(_3\)-OEt\(_2\), CH\(_2\)Cl\(_2\), 0 °C, 2-5 min (86%), c) NaBH\(_4\)/MeOH, 0 °C, 30 min (97%), d) TBDPSCI, imidazole, CH\(_2\)Cl\(_2\), rt, 2 h (83%).

Having first investigated the stereoselective dihydroxylation of 7 using the Sharpless asymmetric dihydroxylation reaction conditions,\(^{[5]}\) we discovered high trans diastereoselectivities at the pyrrolidine ring (C-4/C-5) but only 1:1 anti/syn diastereoselectivities at the pyrrolidine ring (C-5) and exocyclic stereogenic centre (C-1'). However, when we used K\(_2\)OsO\(_4\).2H\(_2\)O/NMO in acetone and H\(_2\)O (2:1), high trans diastereoselectivities at the pyrrolidine ring (C-4 / C-5) and also high 5:95 anti/syn diastereoselectivities 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\(_3\)SiH/BF\(_3\)-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$_2$OsO$_4$·2H$_2$O, NMO, acetone/H$_2$O, rt, 3 h, (72%), b) Et$_3$SiH/BF$_3$·OEt$_2$, CH$_2$Cl$_2$, 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$_3$·SMe$_2$ in THF and subsequent oxidative work up using H$_2$O$_2$[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$_2$O$^{[8]}$ 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

![Scheme 4](image)

Reagents and conditions: a) BH$_3$.DMS, THF, rt, 12 h, then EtOH, NaBO$_3$.4H$_2$O, 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 pyrrolizidines 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 °C under N2 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 °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 MgSO4 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 MgSO4 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: Rf = 0.28 (7:3 EtOAc/petrol); [α]21D +20.0 (c 1.40, CHCl3); IR (neat, νmax/cm-1) 3278, 2115, 1686, 1403, 1124, 968, 743, 702; δH (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); δC (125 MHz, CDCl3) 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); ESI-MS m/z 343.89 [(M + Na)+ 100%]; HRESIMS calcd. for C20H19NO3Na, (M+Na)+ 344.1272, found: 344.1263.

Minor isomer: Rf = 0.24 (7 : 3 EtOAc/petrol); [α]22D –30.0 (c 1.40, CHCl3); IR (neat, νmax/cm-1) 3278, 2115, 1686, 1403, 1124, 968, 743, 702; δH (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); δC (125 MHz, CDCl3) 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
(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 °C was added dropwise BF₃·Et₂O (0.31 g, 2.18 mmol) at 0 °C under N₂ atm. The reaction mixture was stirred for 2 - 5 minutes at 0 °C. After completion of reaction, the reaction mixture was quenched with saturated NaHCO₃ solution and the aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over MgSO₄ 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%). Rᵣ = 0.60 (7:3 EtOAc/petrol); [α]²⁴<sup>D</sup> + 78.3 (c 0.83, CHCl₃); IR (neat, ν<sub>max</sub>/cm⁻¹) 2919, 1716, 1622, 1403, 1149, 968, 743, 707; δ<sub>H</sub> (500 MHz, CDCl₃) 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<sub>C</sub> (125 MHz, CDCl₃) 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)<sup>+</sup> 30%]; HRESIMS calcd. for C₂₀H₂₀NO₃, (M+H)<sup>+</sup> 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 NaBH₄ (0.21 g, 5.6 mmol) at 0 °C under a N₂ atmosphere. After the addition was completed (4 min), the reaction was stirred at 0 °C for 30 min. Then it was quenched with saturated NaHCO₃ solution and extracted with EtOAc (3 x 40 mL). The combined extracts were washed with brine, dried over MgSO₄ 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%). Rᵣ = 0.28 (2:1 EtOAc/petrol); [α]²⁴<sup>D</sup> + 56.5 (c 0.92, CHCl₃); IR (neat, ν<sub>max</sub>/cm⁻¹) 3380, 2924, 1669, 1419, 1347,1147, 1070, 736, 707; δ<sub>H</sub> (500 MHz, CDCl₃) 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$_3$Na, (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$_2$Cl$_2$ (10 ml) was added DMAP (0.037 g, 0.31 mmol), Et$_3$N (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, $\nu_{\text{max}}$/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), 3.98 (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), 128.4 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 127.9 (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$_3$NaSi, (M+Na)$^+$ 584.2611, found: 584.2597.
(4S,5R)-1-Benzyl-4-(benzyloxy)-5-((R)-2-(tert-butyl diphenylsiloxy)-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 K₂OsO₄·2H₂O (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 MgSO₄ 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%). Rₓ = 0.48 (7:3 EtOAc/petrol); [α]²⁰ D + 6.20 (c 3.64, CHCl₃); IR (neat, ν max/cm⁻¹) 3421, 2929, 1675, 1434, 1112, 825, 748 and 702; δH (500 MHz, CDCl₃) 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); δC (125 MHz, CDCl₃) 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 C₃₆H₄₂NO₅Si, (M+H)+ 596.2853, found: 596.2832.

(4S,5R)-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 CH₂Cl₂ (6 mL) was added BF₃·Et₂O (0.19 g, 1.34 mmol) followed by Et₃SiH (0.39 g, 3.36 mmol) at 0 °C under a N₂ atmosphere. The solution was stirred at 0 °C under N₂ 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 NaHCO₃ solution (5 mL), stirred for a 10 min and diluted with water (5 ml) and extracted with CH₂Cl₂ (3x20 mL). The organic layers were combined, dried over MgSO₄ 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\textsubscript{f} = 0.56 (6:4 EtOAc/petrol); [\alpha]_{D}^{24} + 26.70 (c 2.65, CHCl\textsubscript{3}); IR (neat, v\textsubscript{max}/cm\textsuperscript{-1}) 3334, 2929, 1670, 1424, 1112, 819, 748 and 707; δ\textsubscript{H} (500 MHz, CDCl\textsubscript{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\textsubscript{C} (125 MHz, CDCl\textsubscript{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), 128.3 (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)\textsuperscript{+} 100%]; HRESIMS calcd. for C\textsubscript{36}H\textsubscript{42}NO\textsubscript{4}Si, (M+H)\textsuperscript{+} 580.2892, found: 580.2883.

(S)-1-((2R,3S)-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\textsubscript{4} (0.039 g, 1.03 mmol) at rt under a N\textsubscript{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\textsubscript{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\textsubscript{f} = 0.31 (4:1 EtOAc/petrol); [\alpha]_{D}^{23} – 16.80 (c 0.77, CHCl\textsubscript{3}); IR (neat, v\textsubscript{max}/cm\textsuperscript{-1}) 3370, 2934, 1659, 1444, 1050, 748 and 707; δ\textsubscript{H} (500 MHz, CDCl\textsubscript{3}) 7.37–7.25 (m, 10ArH), 4.54 (1H, d, J = 11.5 Hz), 4.30 (1H, d, J = 11.5 Hz), 4.16-4.00 (1H, m, H-3), 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), 1.80–1.68 (1H, m, H-4); δ\textsubscript{C} (125 MHz, CDCl\textsubscript{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)\textsuperscript{+} 100%]; HRESIMS calcd. for C\textsubscript{20}H\textsubscript{26}NO\textsubscript{3}, (M+H)\textsuperscript{+} 328.1909, found: 328.1913.
(2S,3S)-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); [α]$^D_{22}$ + 4.7 (c 4.0, MeOH); IR (neat, $\nu_{max}$/cm$^{-1}$) 3409, 3365, 2924, 2484, 1634, 1420, 1091, and 1045; δ$_H$ (500 MHz, CD$_3$OD) 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); δ$_C$ (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$_6$H$_{14}$NO$_3$, (M+H)$^+$ 148.0952, found: 148.0974.

(4S,5S)-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$_2$Cl$_2$ (0.36 mL, 0.35 mmol) at 0 °C 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$_2$O (0.032 g, 0.21 mmol) at 0 °C. 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); [α]$^D_{24}$ –0.90 (c 5.40, CHCl$_3$); IR (neat, $\nu_{max}$/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); \(\delta_C\) (125 MHz, CDCl₃) 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_{4}SiNa, (M+Na)^+ 602.2780, found: 602.2703.

\((S)-1-((2S,3S)-1-Benzyl-3-(benzyloxy)pyrrolidin-2-yl)-2-(\text{tert}-\text{butyldiphenylsiloxy})\text{ethanol (12)}\)

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 CH₂Cl₂ (0.69 mL, 0.69 mmol) at 0 °C under a N₂ 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 into ice water and extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried over MgSO₄, 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); \([\alpha]^{24}_D +11.0\) (c 2.08, CHCl₃); IR (neat, \(v_{\text{max}}/\text{cm}^{-1}\)) 3359, 2929, 2858, 1429, 1110, 738 and 702; \(\delta_H\) (500 MHz, CDCl₃) 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, PhCH₂), 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”; \(\delta_C\) (125 MHz, CDCl₃) 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_{5}Si, (M+H)^+ 566.3107, found: 566.3090.

\((2R,3S)-2-((S)-1,2-Dihydroxyethyl)pyrrolidin-3-ol\text{-hydrochloride (3)}\)
To a solution of 12 (0.05 g, 0.088 mmol) in MeOH (4 mL) was added PdCl₂ (47 mg, 0.26 mmol) at rt under a N₂ atmosphere. Then the reaction mixture was flushed with H₂ (balloon) and the solution was stirred at rt under a H₂ 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%). Rᵢ = 0.18 (1:9 MeOH/EtOAc); [α]ᵢᵇ⁺ +5.7 (c 4.0, MeOH); IR (neat, νmax/cm⁻¹) 3409, 3365, 2924, 2484, 1634, 1420, 1091, and 1045; δH (500 MHz, CD₃OD) 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); δC (125 MHz, CDCl₃) 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 C₆H₁₄NO₃, (M+H)+ 148.0991, found: 148.0984.

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REFERENCES


[8] Winqvist, A.; Stromberg, R. Stereoselectivity in the Synthesis of 3'-Deoxy-3'-C-(hydroxymethyl)uridines by Hydroboration and Conversion into a Building Block for
GRAPHICAL ABSTRACT

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

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