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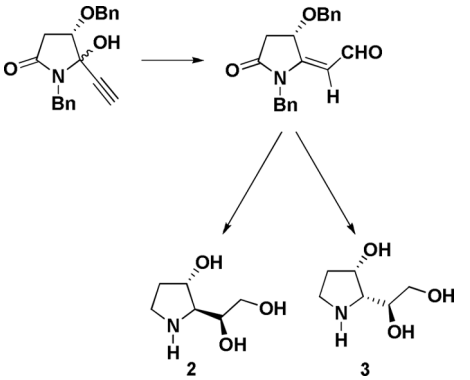
STEREOSELECTIVE SYNTHESIS OF TWO NEW TRIHYDROXYLATED PYRROLIDINES USING A MEYER–SCHUSTER REARRANGEMENT

Nalivela Kumara Swamy and Stephen G. Pyne
School of Chemistry, University of Wollongong, Wollongong, Australia

GRAPHICAL ABSTRACT



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 Meyer–Schuster rearrangement; polyhydroxylated pyrrolidine

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 novel structures, have made these compounds and their analogs 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 (Fig. 1). The polyhydroxylated pyrrolidines include the 1,4-dideoxy-1,4-imino hexitols **A** and **B** (Fig. 1). In many other azasugar compounds the pyrrolidine ring is part of

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Address correspondence to Stephen G. Pyne, School of Chemistry, University of Wollongong, Wollongong, NSW, 2522, Australia. E-mail: spyne@uow.edu.au

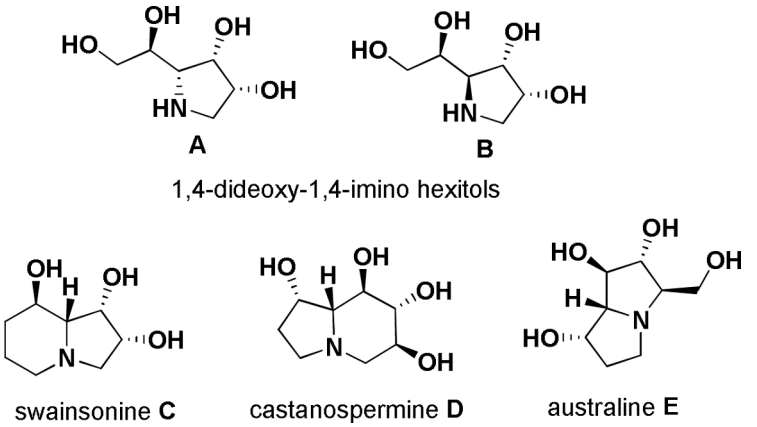
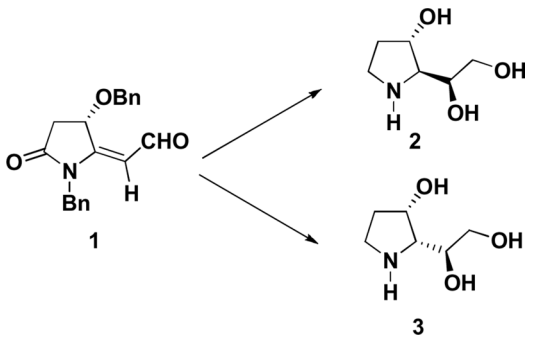


Figure 1. Some polyhydroxylated pyrrolidine ring–containing natural products.



Scheme 1. Target trihydroxylated pyrrolidines **2** and **3**.

a bicyclic heterocyclic system, such as that found in the polyhydroxylated indolizidine and pyrrolizidine alkaloids. Well-known examples include swainsonine **C**, castanospermine **D**, and australine **E** (Fig. 1).

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).

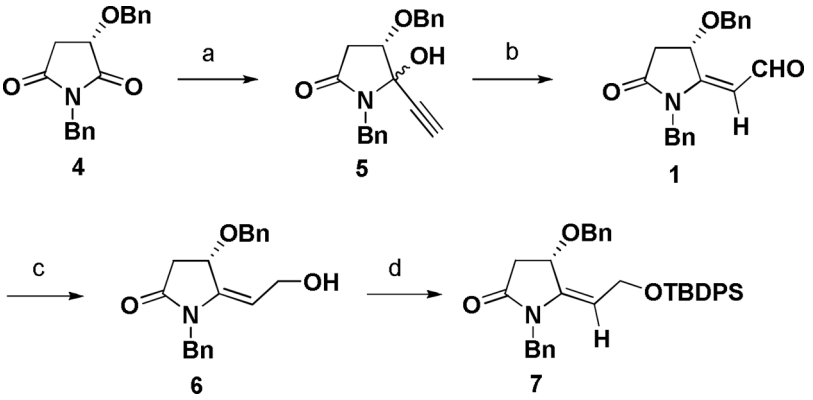
RESULTS AND DISCUSSION

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 trimethylsilane (TMS)–acetylene (1.5 equiv) and *n*BuLi (1.5 equiv). The crude reaction mixture was treated with LiOH, to remove the TMS group and give a mixture (6:4) of diastereomeric hydroxy lactams **2** in 74%

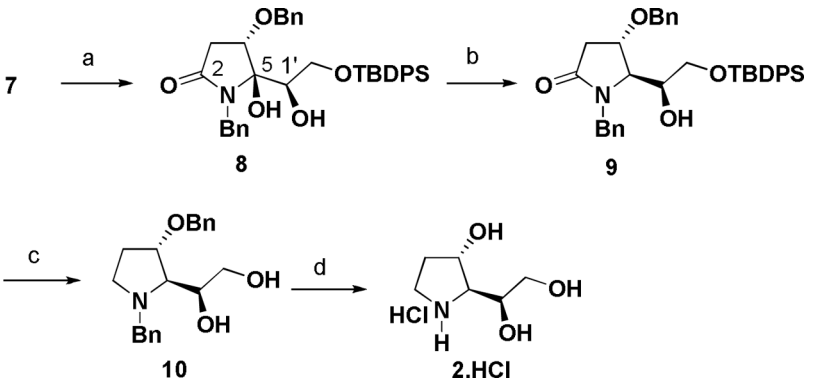
yield. This mixture was treated with borontrifluoride-etherate (1 equiv), which rapidly (2–5 min) gave the Meyer–Schuster rearrangement product **1** as a single *E*-isomer in excellent yield (86%). The *E*-geometry of **1** was established from a nuclear Overhauser effect spectroscopic (NOESY) study 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 *tert*-butyldiphenylsilyl (TBDPS) chloride/imidazole in CH_2Cl_2 to give the TBDPS ether **7** as shown in Scheme 2.

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 center (C-1′). However, when we used $K_2OsO_4 \cdot 2H_2O$/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 center (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 because of 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 (Fig. 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).

Hydroboration of **7** using $BH_3 \cdot SMe_2$ in tetrahydrofuran (THF) and subsequent oxidative workup using H_2O_2[6] in alkaline solution resulted in the formation of an unidentified ultraviolet (UV)–inactive side product and gave the desired



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



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%), and (d) $PdCl_2/H_2$, MeOH, rt, 12 h (99%).

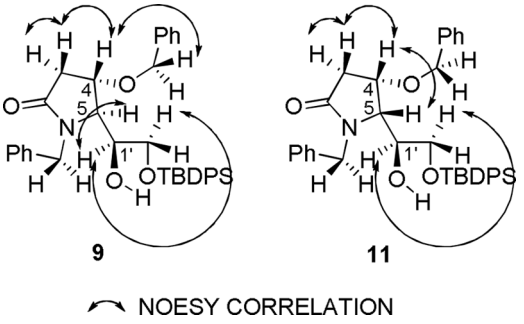
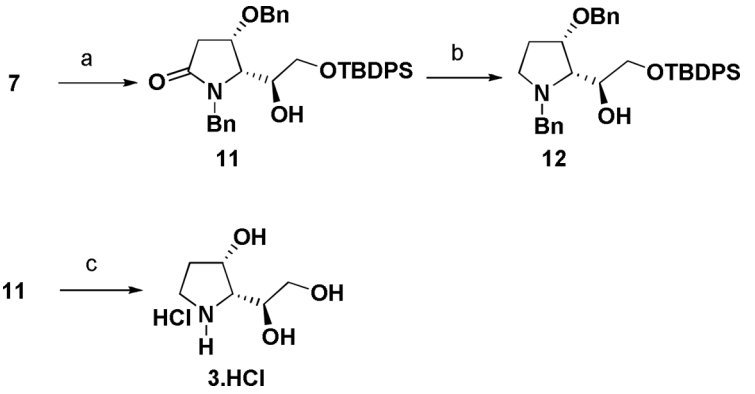


Figure 2. NOESY correlations for compounds **9** and **11**.



Scheme 4. Reagents and conditions: (a) BH_3-Me_2S, THF, rt, 12 h, then EtOH, $NaBO_3 \cdot 4H_2O$, reflux, 3 h (50%), (b) BH_3-Me_2S, THF rt, 12 h, then EtOH reflux, 2 h (72%), and (c) $PdCl_2/H_2$, MeOH, rt 12 h (99%).

product **11** in an unsatisfactory yield of 32% (Scheme 4). However, when the alternative oxidant, $NaBO_3 \cdot 4H_2O$,[8] was used, the yield of **11** was more satisfactory (50%). The configuration of **11** was established by NOESY NMR experiments (Fig. 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-Me_2S in 72% yield. Finally, debenzylation of **12** by hydrogenolysis over $PdCl_2$ gave the hydrochloride salt of **3** in nearly quantitative yield (Scheme 4).

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 synthetic 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 °C under N_2 atm, and the mixture was stirred for 30 min. Then cyclic imide **4** (1 g, 3.39 mmol) dissolved in dry tetrahydrofuran (THF; 10 mL) was added dropwise. Stirring was continued for 30 min at −78 °C, and the reaction was monitored via thin-layer chromatography (TLC). The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc (3 × 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 × 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); δ_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)

BF_3-Et_2O (0.31 g, 2.18 mmol) was added to a solution of **5** (0.70 g, 2.18 mmol) in dichloromethane (10 ml) cooled to 0 °C dropwise at 0 °C under N_2 atm. The reaction mixture was stirred for 2–5 min at 0 °C. After completion of reaction, the reaction mixture was quenched with saturated $NaHCO_3$ solution, and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was chromatographed on silica gel (1:1 EtOAc/petrol) to give the title compound as colorless 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)

$NaBH_4$ (0.21 g, 5.6 mmol) was added in portions to a solution of **1** (0.6 g, 1.86 mmol) in MeOH (10 mL) at 0 °C under a N_2 atmosphere. After the addition was completed (4 min), the reaction was stirred at 0 °C for 30 min. Then it was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3 × 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)

DMAP (0.037 g, 0.31 mmol), Et_3N (0.47 g, 4.64 mmol), and TBDPSCl (1.98 g, 1.85 mmol) were added to a solution of **6** (0.50 g, 1.54 mmol) in dry CH_2Cl_2 (10 ml) at rt under N_2 atmosphere, and the solution was stirred at rt for 2 h under N_2 atmosphere until the disappearance of starting material as shown by thin-layer chromatography (TLC). The reaction mixture diluted with water (10 ml) and extracted with EtOAc (3×30 mL). The organic layers were combined and dried over $MgSO_4$, and the solvent was 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)

$K_2OsO_4 \cdot 2H_2O$ (8.5 mg, 0.023 mmol) and NMO (0.13 g, 1.11 mmol) were added to a solution of **7** (0.26 g, 0.46 mmol) in a mixture of acetone (6 mL) and water (4 mL). The solution was stirred at rt for 3 h until disappearance of starting material as shown by TLC. The reaction mixture was quenched with saturated potassium bisulfite solution (5 mL), stirred for 10 min, diluted with water (5 mL), and extracted with EtOAc (3×10 mL). The organic layers were combined and 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)

$BF_3 \cdot Et_2O$ (0.19 g, 1.34 mmol) was added to a solution of **8** (0.20 g, 0.33 mmol) in dry CH_2Cl_2 (6 mL) followed by Et_3SiH (0.39 g, 3.36 mmol) at 0 °C under a N_2 atmosphere. The solution was stirred at 0 °C under N_2 atmosphere for 15 min and then at rt for 12 h until disappearance of starting material was shown by TLC. The reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL), stirred for 10 min, diluted with water (5 ml), and extracted with CH_2Cl_2 (3×20 mL). The organic layers were combined and 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, 20 ArH), 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)

$LiAlH_4$ (0.039 g, 1.03 mmol) was added to a solution of **9** (0.15 g, 0.26 mmol) in dry THF (5 mL) at rt under a N_2 atmosphere. The solution was stirred at rt for 12 h until disappearance of starting material was shown 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 was 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)

$PdCl_2$ (0.043 g, 0.21 mmol) was added to a solution of **10** (0.07 g, 0.21 mmol) in MeOH (5 mL) 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); 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 $C_6H_{14}NO_3$ $(M+H)^+$ 148.0952, found: 148.0974.

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

A 1 M solution of borane-dimethylsulfide in CH_2Cl_2 (0.36 mL, 0.35 mmol) was added dropwise to a solution of **7** (0.20 g, 0.35 mmol) in THF (4 mL) 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 $NaBO_3 \cdot 4H_2O$ (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 (3 × 20 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)

A 1 M solution of borane-dimethylsulfide in CH_2Cl_2 (0.69 mL, 0.69 mmol) was added dropwise to a solution of **11** (0.10 g, 0.17 mmol) in anhydrous THF (5 mL) 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 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 (3×20 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)

$PdCl_2$ (47 mg, 0.26 mmol) was added to a solution of **12** (0.05 g, 0.088 mmol) in MeOH (4 mL) 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); δ_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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