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A Straightforward Synthesis of (2*S*,3*R*)-3-Hydroxyproline and *trans*-(2*R*,3*S*)-2-Hydroxymethyl-3-hydroxypyrrolidine

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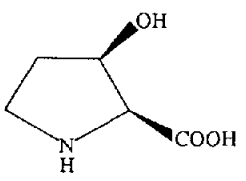
Abstract: A stereocontrolled synthesis of (2*S*,3*R*)-3-hydroxyproline **1**, and *trans*-(2*R*,3*S*)--2-hydroxymethyl-3-hydroxypyrrolidine **2** has been achieved in 21% and 38% yield *via* the homochiral 4,5-disubstituted oxazolidin-2-one **3**. The *trans* relationship in **2** has been introduced by a modified Mitsunobu reaction.

(2*S*,3*R*)-3-Hydroxyproline **1**, formally *cis*-3-hydroxy-L-proline is a known, although rare, β-hydroxy-α-amino acid, which has been found as a component of the antibiotic teleomycin.[1] It has been isolated as minor component in collagenous proteins from carcinoma cell cultures,[2] and it is used in pharmaceutical preparations for antitumor therapy[3] or for treatment of disorders of collagen metabolism.[4] It can be easily converted into the Geissman-Waiss lactone,[5] which is a key intermediate for the preparation of a variety of pyrrolizidine alkaloids, including (+) retronecine,[5,6] (-) platynecine,[6] and (+) croalbinecine.[6] The corresponding protected *cis*-3-hydroxy-L-prolinol has been used by Joullie *et al.* as an intermediate in the synthesis of non-proteinogenic amino acids as detoxinine[7] and in the synthesis of munnularine F.[8]



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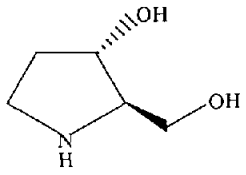

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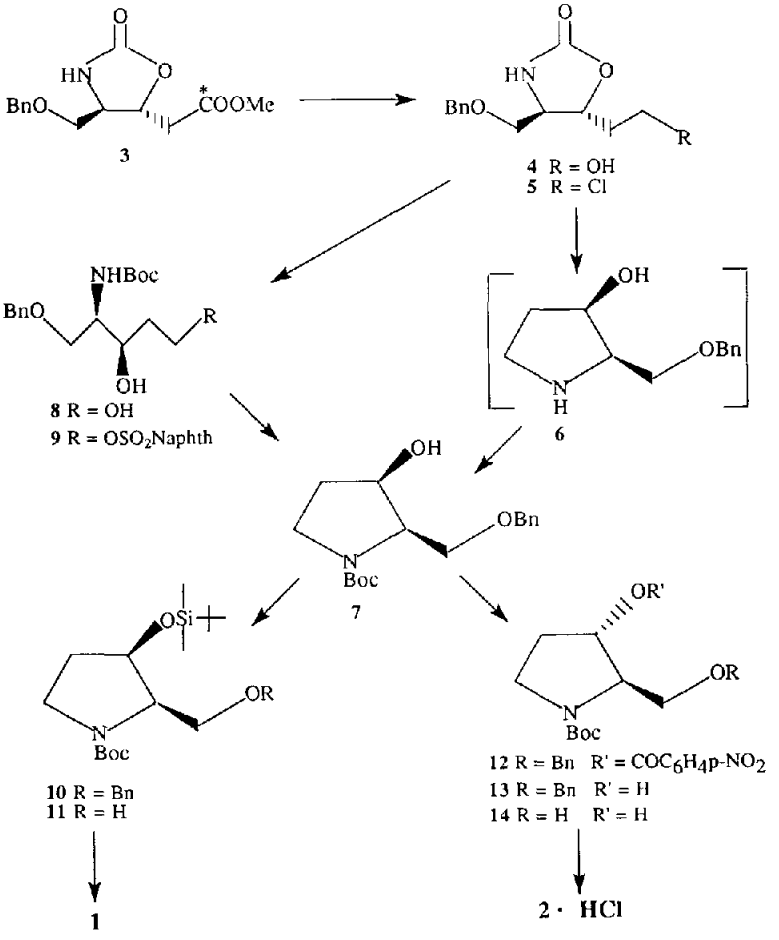
The isomer (2*R*,3*S*)-3-hydroxyproline and the corresponding (2*R*,3*R*)-3-hydroxyprolinol are structural units in indolizidine alkaloids as slaframine[9] and castanospermine[10] and in pyrrolizidine alkaloids, as australine[11] and alexine.[12]

Moreover, the structurally related (2*R*,3*S*)-2-hydroxymethyl-3-hydroxypyrrolidine, or *trans*-3-hydroxy--L-prolinol **2**, occurs in the seeds of the legume *Castanospermum australe*.[13]

Several syntheses of *cis*-3-hydroxyproline[14] and *trans*-3-hydroxy-L-prolinol[15] have been developed. This paper deals with the preparation of the title compounds **1** and **2** through the key intermediate *cis*-3-hydroxypyrrolidine **7**, where the pyrrolidine nucleus is formed by ring closure between the indicated (*) carbon atom and the nitrogen atom in the 4,5-disubstituted oxazolidin-2-one **3**.

We have recently reported[16] a simple and convenient route to **3** *via* an highly stereoselective cyclocarbamation, mediated by iodine, of the methyl (2*Z*,4*R*)-5-benzyloxy-[(benzyloxycarbonyl)amino]--2-pentenoate, readily available from L-serine,[17] followed by tributyltin hydride reduction.

According to the synthetic pathway shown in the Scheme the ester group in **3** was reduced by the use of $NaBH_4$ in THF/MeOH[18] in 88% yield (this is more convenient than the already reported reduction with $LiAlH_4$[16a]).



The alcohol **4** was initially converted into the chloride **5**, m.p. 51-53, $[\alpha]_D$ = +67.5 (*c* = 0.25, $CHCl_3$), in 93% yield, following standard methodology[19] (Ph_3P/CCl_4), and then treated with a solution of NaOH in MeOH/H_2O (80°C), to give the pyrrolidine **6**, through cleavage of the cyclic urethane and displacement of chlorine by nitrogen. The intermediate **6** was directly converted into the N-Boc derivative **7**, $[\alpha]_D$ = –20.0 (*c* = 1.88, MeOH) (65% yield based on **5**), by reaction with Boc_2O in the presence of Et_3N, giving a 61% yield from **4**.

In a less convenient way, the oxazolidin-2-one **4** was initially treated with $Ba(OH)_2$ in MeOH at reflux to cleave the cyclic carbamate, and then converted into the N-Boc amino alcohol **8** in 68%. Regioselective activation of the primary alcohol as β-naphthalensulphonate **9** and ring closure (57% based on **8**) with NaH, gave the desired pyrrolidine **7**, but only in a 40% yield from **4**.

Compound **7** was readily converted into the corresponding *tert*-butyldimethylsilyl ether **10**, followed by removal of the benzyl protecting group by catalytic hydrogenolysis over 10% Pd/C to give the known 2-hydroxymethylpyrrolidine **11**,[20] $[\alpha]_D$ = –33.1 (*c* = 1.2, $CHCl_3$) ⟨Lit[20]: $[\alpha]_D$ = –32.5 (*c* = 1.2, $CHCl_3$)⟩, in 63% yield from **7**. Finally the (2*S*,3*R*)-3-hydroxyproline **1** was obtained by a two step oxidation (TEMPO, NaClO/NaBr[21] and 1 M $KMnO_4$/5% NaH_2PO_4[22]) to give the corresponding acid, which upon treatment with HCl/MeOH afforded the target β-hydroxy-α-amino acid **1**, m.p. 222-228°C, $[\alpha]_D$ = –100.4 (*c* = 1.0, H_2O) ⟨Lit[14e]: $[\alpha]_D$ = –101 (*c* = 1.0, H_2O)⟩, in 21% yield from **3**.

The (2*R*,3*S*)-2-hydroxymethyl-3-hydroxypyrrolidine **2** was obtained from **7** through the following steps. The inversion of the alcohol configuration was achieved by the Mitsunobu reaction,[23] with the modifications (*p*-$NO_2C_6H_4COOH$, diethylazodicarboxylate, Ph_3P, benzene, 25°C) reported by Martin *et al.*[24] for secondary alcohols, because under standard Mitsunobu conditions only starting material has been obtained. The *p*-nitrobenzoate **12** was easily obtained in 90% yield with inversion of configuration, and it was transformed into the *trans*-3-hydroxypyrrolidine **13**, m.p. 67-68°C, $[\alpha]_D$ = –33.4 (*c* = 0.18, MeOH), in 90% yield under alkaline conditions.

The *cis*- and *trans*-relationships between the two substituents in hydroxyprolines **7** and **13** were substantiated by the values of the coupling constants of H-2 and H-3 protons in ^1H NMR spectra ($J_{2,3}$ = 6.5 Hz and 1.5 Hz, respectively).[14h] These data were confirmed by difference NOE experiments, which showed in particular the proximity of H-2α and H-3α in compound **7** and of H-3β and CH_2O in compound **13**.

Fig.: Mutual NOE effects in compounds **7** and **13**

The ^1H- and ^{13}C NMR spectra of N-Boc protected pyrrolidines were not interpretable at room temperature for the presence of a dynamic equilibrium between two rotamers due to the restricted rotation of the nitrogen-carbon bond of the amide group. To overcome this phenomenon NMR spectra were run at 50°C. The chemical shift assignments in ^1H NMR spectra were unambiguously confirmed by decoupling experiments and/or HECTOR measurements. Conversely, in ^{13}C NMR spectra two signals of comparable intensity were still present for most of the carbons and both are reported in the Experimental section. No attempt was made to assign the resonances of each rotamer.

The intermediate **13** was quantitatively converted, by catalytic hydrogenolysis over 10% Pd/C, into the

diol **14**, which was then treated with 3 M HCl/EtOAc[25] to give **2** as hydrochloride, $[\alpha]_D$ = +43.1 (*c* = 0.5, H_2O) ⟨Lit[13]: $[\alpha]_D$ = +46.5 (*c* = 1.0, H_2O)⟩ in 38% yield from **3**.

In summary, we have reported on the easy preparation of (2*S*,3*R*)-3-hydroxyproline and (2*R*,3*S*)-2-hydroxymethyl-3-hydroxypyrrolidine. The present method proves to be a suitable alternative to the known procedures; moreover since the isomer **3** [(4*S*,5*S*)] is readily obtained in optically pure form,[16b] our methodology could be followed to prepare the (2*R*,3*S*)-3-hydroxyproline. Further applications of the above protected pyrrolidines in the total synthesis of biologically relevant alkaloids are currently under investigation.

Experimental

Melting points (uncorrected): open capillaries, Büchi apparatus. – IR spectra (films or in KBr for solids): Nicolet 5DX FT-IR. – ^{1}H- and ^{13}C-NMR (300 MHz and 75 MHz, TMS as internal standard in $CDCl_3$ solutions at 50°C, unless reported otherwise): Varian Gemini 300 spectrometer. – Optical rotations: Perkin-Elmer 243 (measured at 25°C). – Flash chromatography: Merck Kieselgel (particle size 230–400 mesh). All solvents were dried[26] prior to use.

***(4R,5R)-4-(Benzyloxy)methyl-5-(2-hydroxyethyl)-oxazolidin-2-one* (4)**: To a stirred and cooled (–10°C,) solution of the ester **3** (1.925 g, 6.9 mmol) in THF (24 ml) was added $NaBH_4$ (1.03 g, 27.2 mmol) and the mixture was left under stirring for 30 min at the same temperature. After this time MeOH (10 ml) was added dropwise during 30 min and the reaction was stirred ad room temp. overnight. H_2O (1 ml) was added carefully and the reaction was stirred for further 30 min. Most of the organic solvent was removed under reduced pressure and brine (10 ml) was added. The mixture was estracted with EtOAc (3 × 100 ml), the combined organic extracts were washed with brine (100 ml) and dried with Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue which was purified by flash chromatography ($CHCl_3$/MeOH, 9:1) to give **4** (1.524 g, 88% yield): m.p. 72–73°C, $[\alpha]_D$ = +23.1 (*c* = 1.8, $CHCl_3$); ⟨Lit.[16a]: m.p. 71–72°C, $[\alpha]_D$ = +22.8 (*c* = 1.8, $CHCl_3$)⟩. ^{1}H and ^{13}C NMR as reported.[16a]

***(4R,5R)-4-(Benzyloxy)methyl-5-(2-chloroethyl)-oxazolidin-2-one* (5)**: To a solution of the alcohol **4** (0.904 g, 3.6 mmol) in 35 ml of dry CCl_4/CH_2Cl_2 were added successively finely powdered K_2CO_3 (1.0 g, 7.2 mmol) and Ph_3P (2.36 g, 9.0 mmol) and the solution was stirred overnight at 50°C. The solvent was evaporated and the residue was purified by flash chromatography using *n*-hexane/EtOAc (3:7) as eluent to afford the desired alkyl chloride **5** (0.891 g, 93% yield) as a white solid: m.p. 51–53 °C, $[\alpha]_D$ = +67.5 (*c* = 0.25, $CHCl_3$). – IR (KBr): ν = 3279 cm^{-1}, 2846, 1721, 1386, 1242, 1133, 1040, 737. – ^{1}H NMR: δ = 7.40–7.25 (m, 5H, Ph), 5.88 (brs, 1 H, NH), 4.55 (s, 2H, $OC\underline{H}_2Ph$), 4.52 (dt, *J* = 2 × 9.0, 4.5 Hz, 1 H, CHO), 3.69, 3.65 (m, 1 H each, CH_2Cl), 3.67 (dt, *J* = 9.0, 2 × 6.0 Hz, 1 H, CHN), 3.49 (d, *J* = 6.0 Hz, 2 H, CH_2O), 2.24 (ddt, *J* = 15.0, 9.0, 2 × 5.0 Hz, 1 H, $C\underline{H}_AH_B$), 2.04 (dddd, *J* =15.0, 8.0, 6.5, 4.5 Hz, 1 H, $CH_A\underline{H}_B$). – ^{13}C NMR: δ = 158.38 (s, CO), 137.11, 128.57, 128.08, 127.77 (s, 2 × d, d, 2 × d, Ph), 76.14 (d, CHO), 73.59 (t, $O\underline{C}H_2Ph$), 71.33 (t, CH_2O), 56.98 (d, CHN), 39.97 (t, CH_2Cl), 37.70 (t, CH_2). Anal. Calcd. for $C_{13}H_{16}ClNO_3$ (269.7): C, 57.89; H, 5.98; N 5.19. Found: C, 58.21; H, 5.82; N, 5.20.

***(2R,3R)-1-(tert-Butoxycarbonyl)-2-(benzyloxymethyl)-3-hydroxy-pyrrolidine* (7)**: To a solution of chloride **5** (1.076 g, 4.0 mmol) in 10 ml of a 2:1 mixture of MeOH/H_2O was added NaOH (0.48 g, 12.0 mmol), and the mixture was heated at 80°C for 16 h. The solvents were evaporated under reduced pressure, the residue was dissolved in THF (50 ml) and filtered. The filtrate was concentrated and the crude **6** was dissolved in THF (50 ml) followed by the addition of Et_3N (0.6 ml, 4.4 mmol) and Boc_2O (1.05 g, 4.8 mmol). The mixture was stirred for 16 h, concentrated to dryness and the residue was purified by silica gel chromatography

($CHCl_3$/MeOH, 19:1) to give **7** (0.798 g, 65% yield): $[\alpha]_D$ = –20.0 (*c* = 1.88, MeOH). IR (neat): ν = 3410 cm^{-1}, 2927, 1696, 1393, 1253, 1171, 1114. – ^{1}H NMR: δ = 7.42–7.22 (m, 5 H, Ph), 4.56, 4.52 (d, *J* = 12.0 Hz, 1 H each, $OC\underline{H}_2Ph$), 4.45 (q, *J* = 6.5 Hz, 1 H, H-3α), 3.95 (m, 1 H, H-2α), 3.86, 3.76 (m, 1 H each, $C\underline{H}_2OCH_2Ph$), 3.42 (t, *J* = 7.0 Hz, 2H, CH_2N), 2.04 (m, 1 H, $C\underline{H}_AH_B$), 1.93 (dq, *J* = 14.0, 3 × 7.0 Hz, 1 H, $CH_A\underline{H}_B$), 1.45 [s, 9H, $(CH_3)_3$]. – ^{13}C NMR: δ = 154.40 (s, NCO), 137.35, 128.44, 127.80, 127.52 (s, 2 × d, d, 2 × d, Ph), 79.51 [s, $O\underline{C}(CH_3)_3$], 73.48 (t, $O\underline{C}H_2Ph$), 72.74, 72.23 (d each, CHO), 68.49 (t, $\underline{C}H_2OCH_2Ph$), 58.70 (d, CHN), 44.39, 43.77 (t each, CH_2N), 32.89, 32.29 (t each, CH_2), 28.37 [q, $(CH_3)_3$]. Anal. Calcd. for $C_{17}H_{25}NO_4$ (307.4): C, 66.42; H, 8.20; N, 4.56. Found: C, 66.49; H, 7.89; N, 4.64.

***(2R,3R)-1-Benzyloxy-2-(tert-butoxycarbonyl)amino-3,5-pentandiol* (8):** A solution of oxazolidin-2-one **3** (1.92 g, 7.6 mmol) in EtOH (600 ml) was added to a satd. solution of $Ba(OH)_2$ (140 ml) and refluxed overnight. After that time most of the organic solvent was removed under reduced pressure and resulting aqueous solution was poured on the top of an ion-exchange column (Amberlist IR 120) and eluted with H_2O, followed by 30% NH_4OH. The fractions with the amino alcohol were concentrated under reduced pressure and the residue dissolved in THF (100 ml) followed by the addition of Boc_2O (2.18 g, 10.0 mmol) and Et_3N (1.17 ml, 8.4 mmol). The mixture was stirred overnight at room temp. concentrated under reduced pressure and purified by flash column chromatography (Et_2O/EtOAc 3:1) to give **8** (1.68 g, 68% yield): $[\alpha]_D$ = +27.8 (*c* = 0.13, MeOH). IR (neat): ν = 3298 cm^{-1}, 2973, 2929, 1686, 1533, 1367, 1169. – ^{1}H NMR: δ = 7.40–7.25 (m, 5 H, Ph), 5.28 (brd, *J* = 8.0 Hz, 1 H, NH), 4.56 (brs, 2H, $OC\underline{H}_2Ph$), 4.18 (m, 1 H, CHO), 3.93, 3.86 (m, 1 H each, CH_2O), 3.84, 3.77 (m, 1 H each, $C\underline{H}_2OH$), 3.64 (m, 1 H, CHN), 2.80 (brs, 2H, 2 × OH), 1.78, 1.66 (m, 1 H each, CH_2), 1.44 [s, 9H, $(CH_3)_3$]. – ^{13}C NMR: δ = 156.39 (s, NCO), 137.54, 128.44, 128.03, 127.75 (s, 2 × d, 2 × d, d, Ph), 80.07 [s, $O\underline{C}(CH_3)_3$], 73.42 (t, $O\underline{C}H_2Ph$), 71.67 (d, CHO), 67.14 (t, CH_2O), 61.24 (t, CH_2OH), 53.73 (d, CHN), 35.36 (t, CH_2), 28.35 [q, $(CH_3)_3$]. Anal. Calcd. for $C_{17}H_{27}NO_5$ (325.41): C, 62.75; H, 8.36; N, 4.31. Found: C, 62.80; H, 8.43; N, 4.37.

***(2R,3R)-1-Benzyloxy-2-(tert-butoxycarbonyl)amino-5-[(β-naphthyl)sulphonyloxy]-3-pentanol* (9):** To a cooled (–10°C) solution of the alcohol **8** (0.428 g, 1.31 mmol) in dry pyridine (2 ml) was added in one portion the β-naphthalen-2-sulphonyl chloride (0.400 g, 1.76 mmol) and the mixture was stirred at the same temperature for 3 h. Standard work-up gave the crude sulphonate, which was purified by silica gel column chromatography (*n*-hexane/EtOAc 1:1) to give **9** (0.445 g, 67%); $[\alpha]_D$ = +14.4 (*c* = 0.16, MeOH). – IR (KBr): ν = 3360 cm^{-1}, 2920, 1696, 1405, 1200, 1096, 1032. – ^{1}H NMR ($CDCl_3$/CD_3SOCD_3, 7:1): δ = 8.38 (d, *J* = 2.0 Hz, 1 H, H-1' Naphth), 7.93 (dd, *J* = 8.0, 2.0 Hz, 1 H, H-3' Naphth), 7.88–7.80 (m, 2H, H-5', H-8' Naphth), 7.81 (d, *J* = 8.0 Hz, 1 H, H-4' Naphth), 7.50, 7.48 (dt, *J* = 2 × 7.0, 2.0 Hz, 1 H each, H-6', H-7' Naphth), 7.35–7.25 (m, 5 H, Ph), 5.15 (brs, 1 H, NH), 4.55, 4.49 (d, *J* = 11.0 Hz, 1 H each, $OC\underline{H}_2Ph$), 4.46 (m, 1 H, CHO), 3.92 (dd, *J* = 11.0, 8.0 Hz, 1 H, $C\underline{H}_AH_BO$), 3.87 (dd, *J* = 11.0, 6.0 Hz, 1 H, $CH_A\underline{H}_BO$); 3.66 (ddd, *J* = 8.0 Hz, 5.0 Hz and 4.0 Hz, 1 H, CHN), 3.59 (m, 1 H, $C\underline{H}CH_DOSO_2$), 3.40 (ddd, *J* = 12.0, 9.0, 4.0 Hz, 1 H, $CHC\underline{H}_DOSO_2$), 2.18, 2.11 (m, 1 H each, CH_2), 1.44 [s, 9H, $(CH_3)_3$)]. – ^{13}C NMR ($CDCl_3$//CD_3SOCD_3, 7:1): δ = 154.84 (s, NCO), 142.60 (s, C-2' Naphth), 137.47 (s, C-1" Ph), 133.66, 132.41 (s each, C-1', C-4' Naphth), 128.75, 127.60 (d each, C-5', C-8' Naphth), 128.33 (2 × d, C-3", C-5" Naphth), 128.07 (3 × d, C-2", C-6", Ph; C-8' Naphth), 127.79 (d, C-4", Ph), 126.98, 126.46 (d each, C-6', C-7' Naphth), 125.36 (d, C-1' Naphth), 123.39 (d, C-3' Naphth), 80.08 [s, $O\underline{C}(CH_3)_3$], 73.38 (t, $O\underline{C}H_2Ph$), 70.12 (d, CHO), 66.45 (t, CH_2O), 53.71 (d, CHN), 43.43 (t, CH_2OS), 33.46 (t, CH_2), 28.40 [q, $(CH3)_3$]. Anal. Calcd. for $C_{27}H_{33}NO_7S$ (515.64): C, 62.90; H, 6.45; N, 2.72. Found: C, 62.69; H, 6.39; N, 2.69.

(2R,3R)-1-(tert-Butoxycarbonyl)-2-(benzyloxymethyl)-3-hydroxypyrrolidine **(7):** To a cooled (0°C) suspension of NaH (60%, 44 mg, 1.1 mmol, washed three times with petroleum ether) in THF (20 ml) was added dropwise the sulphonate **9** (0.515 g, 1.0 mmol) in THF (5 ml). The mixture was stirred at the same temperature for 3 h, then H_2O was added cautiously. Most of the organic solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$ (3 × 50 ml). Standard work-up gave **7** (0.264 g, 86% yield).

(2R,3R)-1-(tert-Butoxycarbonyl)-2-(benzyloxymethyl)-3-[(tert-butyldimethylsilyl)oxy]-pyrrolidine **(10):** A mixture of (2*S*,3*R*)-**7** (0.614 g, 2.0 mmol), imidazole (0.340 g, 5.0 mmol), DMAP (49 mg, 0.40 mmol), and TBDMSCl (0.452 g, 3.0 mmol) in DMF (10 ml) was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure, the residue was dissolved in EtOAc (25 ml) and filtered. The organic solvent was removed and the residue was purified by flash chromatography over silica gel eluting with *n*-hexane/EtOAC (6:4) to give **10** (0.639 g, 76% yield) as a colorless oil: $[\alpha]_D = -20.0$ ($c = 0.28$, $CHCl_3$). – IR (neat): $\nu = 2934$ cm^{-1}, 2861, 1696, 1393, 1253, 1122. – ^{1}H NMR: $\delta = 7.35$–7.20 (m, 5 H, Ph), 4.53, 4.47 (d, $J = 12.0$ Hz, 1 H each, O$\underline{C}$H$_2$Ph), 4.37 (dt, $J = 8.0$, 2 × 6.0 Hz, 1 H, CHO), 3.82–3.68 (m, 2H, CH$_2$O), 3.72 (m, 1 H, CHN), 3.41 (ddd, $J = 11.0$, 8.0, 5.0 Hz, 1 H, C$\underline{H}_A$H$_B$N), 3.33 (dt, $J = 11.0$, 2 × 8.0 Hz, 1 H, CH$_A\underline{H}_B$N), 1.99 (dq, $J = 12.0$, 3 × 8.0 Hz, 1 H, C$\underline{H}_C$H$_D$), 1.90 (dddd, $\underline{J} = 11.0$, 8.0, 6.0, 5.0 Hz, 1 H, CH$_C\underline{H}_D$), 1.43 [s, 9H, (CH$_3$)$_3$], 0.89 [s, 9H, SiC(CH$_3$)$_3$], 0.07, 0.06 (s, 3H each, Si(CH$_3$)$_2$]. — ^{13}C NMR: 154.64 (s, NCO), 138,92, 128.03, 127.23, 127.05 [s, 2 × d, 2 × d, d, Ph), 79.11 [s, O$\underline{C}$(CH$_3$)], 73.10 (t, O$\underline{C}$H$_2$Ph), 71.72 (d, CHO), 67.49 (t, CH$_2$O), 59.76 (d, CHN), 43.77 (t, CH$_2$N), 32.53 (t, CH$_2$), 28.40 [q, (CH$_3$)$_3$], 25.69 [q, SiC($\underline{C}$H$_3$)$_3$], 17.96 (s, SiC), –4.90, –5.14 [q each, Si(CH$_3$)$_2$]. Anal. Calcd. for $C_{23}H_{39}SiNO_4$ (421.7): C, 65.51; H, 3.32; N, 3.39. Found: C, 65.62; H, 3.37; N, 3.29.

(2R,3R)-1-(tert-Butoxycarbonyl)-2-(hydroxymethyl)-3-[(tert-butyldimethylsilyl)oxy]-pyrrolidine **(11):** A solution of compound **10** (0.696 g, 1.65 mmol) was dissolved in abs. EtOH (25 ml) and hydrogenated over 10% Pd/C at 1 atm for 16 h. After that time the mixture was filtered over Celite, concentrated and purified by silica gel chromatography eluting with $CHCl_3$/MeOH (20:1) to give **11** (0.453 g, 83% yield) as an oil: $[\alpha]_D = -33.1$ ($c = 1.2$, $CHCl_3$) ⟨Lit:[20] $[\alpha]_D = -32.5$ ($c = 1.06$, $CHCl_3$)⟩. – ^{1}H and ^{13}C NMR as reported.[20]

(2S,3R)-3-Hydroxyproline **(1):** A solution of **11** (0.422 g, 1.0 mmol), TEMPO (1.5 mg, 0.01 mmol) and NaBr (0.103 g, 1.0 mmol) in toluene (0.8 ml), EtOAc (0.8 ml) and H_2O (0.05 ml) was cooled at 0°C. To the rapid mechanically stirring mixture, an aqueous solution of NaOCl (0.35 M, 3.14 ml, 1.1 mmol) containing $NaHCO_3$ (269 mg, 32.0 mmol) was added dropwise over a period of 30 min, and stirred for an additional 10 min. The aqueous layer was separated and washed with 10 % aqueous $KHSO_4$ (10 ml) containing KI (0.06 g). The organic layer was then washed with aqueous $Na_2S_2O_4$ (0.2 M, 20 ml), brine, dried (Na_2SO_4), and concentrated to dryness. The resulting aldehyde was dissolved in *tert*-butyl alcohol (2.3 ml) and treated with 5% NaH_2PO_4 (1.53 ml) and $KMnO_4$ (1 M, 2.2 ml) solutions. After 30 min the solution was diluted with Et_2O (10 ml) and cooled at 0 °C. A saturated solution of Na_2SO_3 (1 ml) was added dropwise and acidified to pH 3 with dilute HCl. The aqueous layer was extracted with EtOAc (3 × 50 ml). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness.

To an ice-cooled solution of the above acid in MeOH (2 ml) a satd. solution of HCl in MeOH (3 ml) was added. The mixture was stirred at room temp. for 2 h and then concentrated under reduced pressure. The residue was dissolved in H_2O (2 ml) and purified on an ion-exchange column (DOWEX 50 × 8, 200–400 mesh) using 1.5 M NH_3 as eluent to give 82 mg (63%) of **1** as white crystals; m.p. 222–228°C (dec.), $[\alpha]_D = -100.4$ ($c = 1.0$, H_2O); ⟨Lit.:[14e] m.p. 220-230°C, $[\alpha]_D = -101$ ($c = 1.0$, H_2O)⟩.

***(2R,3S)-1-(tert-Butoxycarbonyl)-2-(benzyloxymethyl)-3-[(4-nitrobenzoyl)oxy]-pyrrolidine* (12):** To a stirred solution of the alcohol **7** (0.460 g, 1.5 mmol), triphenylphosphine (1.96 g, 7.5 mmol) and *p*-nitro benzoic acid (1.1 g, 5.72 mmol) in benzene (30 ml) at room temperature, diethylazodicarboxylate (1.17 ml, 7.5 mmol) was added dropwise. The slightly orange solution was stirred at room temperature for 6 h, whereupon the volatile components were removed under reduced pressure and the residue purified by silica gel chromatography eluting with *n*-hexane/EtOAc (6:4) to give **12** (0.616 g, 90% yield); $[\alpha]_D$ = +13.52 (*c* = 0.15, $CHCl_3$). – IR (neat): ν = 2937 cm^{-1}, 1720, 1657, 1412, 1189, 1106. – ^1H NMR: δ = 8.29, 8.19 (d, *J* = 9.0 Hz, 2H each, *p*-NO_2Ph), 7.40–7.25 (m, 5 H, Ph), 5.57 (dd, *J* =12.0, 5.0 Hz, 1 H, CHO), 4.59, 4.54 (d, *J* = 12.0 Hz, 1 H each, $OC\underline{H}_2Ph$), 4.18 (m, 1 H, CHN), 3.76, 3.68 (m, 1 H each, CH_2O), 3.60, 3.52 (m, 1 H, CH_2N), 2.41 (m, 1 H, $C\underline{H}_AH_B$), 2.12 (brdt, *J* = 14.0, 2 × 5.0 Hz, 1 H, $CH_A\underline{H}_B$), 1.49 [s, 9H, $(CH_3)_3$]. – ^{13}C NMR: δ = 164.10 (s, OCO), 154.21 (s, NCO), 150.60, 135.51, 130.77, 123.54 (s, s, 2 × d, 2 × d, *p*-NO_2Ph), 137.83, 128.43, 127.76, 127.46 (s, 2 × d, d, 2 × d, Ph), 80.07, 79.87 [s each, $OC(CH_3)_3$], 79.00, 78.35 (d each, CHO), 73.37 (t, $O\underline{C}H_2Ph$), 69.27, 68.23 (t each, CH_2O), 63.07 (d, CHN), 45.07, 44.75 (t each, CH_2N), 30.33, 29.36 (t, CH_2), 28.44 [q, $(CH_3)_3$]. Anal. Calcd. for $C_{24}H_{28}N_2O_4$ (456.5): C, 63.15; H, 6.18; N, 6.14. Found: C, 63.02; H, 6.07; N, 6.24

***(2R,3S)-1-(tert-Butoxycarbonyl)-2-(hydroxymethyl)-3-hydroxypyrrolidine* (13):** To a solution of NaOH (0.150 g, 3.75 mmol) in MeOH (30 ml) was added the *p*-nitro benzoate **12** (0.330 g, 0.72 mmol). The mixture reaction was stirred at room temp. overnight, evaporated to dryness, and H_2O (10 ml) was added. The aqueous mixture was extracted with EtOAc (3 × 50 ml), and the combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent removed. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 20:1) to give **13** (0.199 g, 90% yield) as a white solid. M.p. 67–8°C, $[\alpha]_D$ = –33.4 (*c* = 0.18, MeOH). – IR(KBr): ν = 3394 cm^{-1}, 2918, 1655, 1417, 1171, 1106. – ^1H NMR: δ = 7.37–7.24 (m, 5 H, Ph), 4.54, 4.50 (d, *J* = 12.0 Hz, 1 H each, $OC\underline{H}_2Ph$), 4.39 (ddd, *J* = 5.0, 3.0, 1.5 Hz, 1 H, H-3β), 3.78, 3.37 (m, 1 H each, CH_2O), 3.70, 3.25 (m, 1 H each, CH_2N), 3.56 (m, 1 H, $C\underline{H}CH_2O$), 2.05 (ddt, *J* = 13.5, 2 × 9.0, 5.0 Hz, 1 H, $CHC\underline{H}_CH_DCH_2$), 1.82 (ddt, *J* = 13.5, 7.5, 2 × 3.0 Hz, 1 H, $CHCH_C\underline{H}_DCH_2$), 1.44 [s, 9 H, $(CH_3)_3$]. ^{13}C NMR: δ = 154.69 (s, NCO), 138.30, 128.44, 127.70, 127.56 (s, 2 × d, d, 2 × d, Ph), 79.55 (s, OC), 74.83, 74.05 (d each, CHO), 73.49 (t, $O\underline{C}H_2Ph$), 70.24 (t, CH_2O), 65.34 (d, CHN), 44.65, 44.55 (t each, CH_2N), 31.96 (t, CH_2), 28.53 [q, $(CH_3)_3$]. Anal. Calcd. for $C_{17}H_{25}NO_4$ (307.4): C, 66.42; H, 8.20; N, 4.56. Found: C, 66.31; H, 8.10; N, 4.64.

***(2R,3S)-1-(tert-Butoxycarbonyl)-2-hydroxymethyl-3-hydroxypyrrolidine* (14):** Compound **13** (0.250 g, 0.82 mmol) was dissolved in absolute EtOH (20 ml) and hydrogenated over 10% Pd/C at 1 atm for 18 h. After that time the solution was filtered over Celite and concentrated under reduced pressure to give **14** (0.173 g, 98% yield) as a colorless oil, which was used without further purification. $[\alpha]_D$ = –21.5 (*c* = 0.66, MeOH). – IR (neat): ν = 3394 cm^{-1}, 2976, 1671, 1417, 1171, 1122. – ^1H NMR: δ = 4.21 (m, 1 H, CHO), 3.76 (m, 1 H, CHN), 3.68, 3.52 (m, 1 H each, CH_2O), 3.60 (m, 1 H, $C\underline{H}_AH_BN$), 3.38 (ddd, *J* = 11.0, 8.5, 4.0 Hz, 1 H, $CH_A\underline{H}_BN$), 2.03 (m, 1 H, $C\underline{H}CH_D$), 1.86 (ddt, *J* = 14.0, 7.0, 2 × 3.5 Hz, 1 H, $CHC\underline{H}_D$), 1.46 [s, 9 H, $(CH_3)_3$]. – ^{13}C NMR: δ = 156.40 (s, NCO), 80.34 (s, OC), 72.72 (d, CHO), 67.94 (d, CHN), 64.10 (t, CH_2O), 44.96 (t, CH_2N), 31.84 (t, CH_2), 28.40 [q, $(CH_3)_3$]. Anal. Calcd. for $C_{10}H_{19}NO_4$ (217.3): C, 55.28; H, 8.82; N, 6.45. Found: C, 55.31; H, 8.71; N, 6.30.

***(2R,3S)-2-Hydroxymethyl-3-hydroxypyrrolidine Hydrochloride* (2):** Compound **14** (0.150 g, 0.7 mmol) was dissolved in 3 M HCl-EtOAc (1ml). After 30 min the solution was removed under reduced pressure and the oil was triturated with Et_2O to give **2** (97 mg, 91%): m.p. 110–112 °C, $[\alpha]_D$ = +43.1 (*c* = 0.5, H_2O) (Lit.[13]: m.p. 108–112 °C, $[\alpha]_D$ = + 46.5 (*c* = 1, H_2O)). ^1H and ^{13}C NMR as reported.[13]

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