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Total synthesis of natural *cis*-3-hydroxy-L-proline from D-glucose

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ABSTRACT

Synthesis of *cis*-3-hydroxy-L-proline from D-glucose is reported. The methodology involves conversion of D-glucose into *N*-benzyloxycarbonyl-γ-alkenyl amine which on 5-*endo*-*trig*-aminomercuration gave the pyrrolidine ring skeleton with sugar appendage in 25% yield. Alternatively, *N*-benzyloxycarbonyl-γ-alkenyl amine on hydroboration–oxidation, mesylation and intramolecular S_N2 cyclisation afforded pyrrolidine ring compound in high yield. Hydrolysis of 1,2-acetonide functionality, $NaIO_4$ cleavage followed by oxidation of an aldehyde into acid and hydrogenolysis afforded *cis*-3-hydroxy-L-proline in overall 29% yield from D-glucose.

cis-3-Hydroxy-L-proline **1** (Fig. 1), a rare cyclic β-hydroxy-α-amino acid isolated from carcinoma cell cultures,[1] is known to be a therapeutic agent in the treatment of tumour and collagen disorders.[2] It is an important constituent of antibiotic telomycin[1,3] and DNA gyrase inhibitor cyclothialidine **2**[4] and is used as a chiral synthon for the synthesis of the Geissmann–Weiss lactone **3**,[5] retronecine **4**,[6] slaframine[7] and androgen receptor modulator BMS-564929 **5**.[8] The β-hydroxy α-amino acid unit embedded in **1** is considered as a constrained analogue of serine thus permitting its use in conformational ligand binding studies involving bioactive peptides/peptidomimetics[9] and peptide nucleic acids (PNA).[10] In addition chiral hydroxyprolines and their derivatives have attracted great interest due to their direct application as an organo-catalyst[11] in the area of asymmetric synthesis.

A number of racemic and enantio-pure syntheses of β-hydroxyprolines are known in the literature,[12,13] however, less attention has been given on the preparation of optically pure *cis*-isomer due to intricacy in achieving relative *cis*-stereochemistry of the hydroxyl and carboxylic acid functionalities on the adjacent carbon atoms. Amongst chiron approaches, Park and co-workers[13l] have first utilised D-glucono-δ-lactone and gluconic acid-γ-lactone as sugar precursors, in the synthesis of (+)-*cis*-3-hydroxy-D-proline (***ent*-1**) and its *trans*-isomer. Recently, we have reported the first chiron approach from D-glucose for a higher ring homologue of **1**, namely *cis*-3-hydroxy-L-pipecolic acid.[14] In the continuation of same analogy and as a part of our interest in the synthesis of pyrrolidine iminosugars,[15] we are now extending our method in the total synthesis of enantiopure (−)-*cis*-3-hydroxy-L-proline **1** from D-glucose.

As shown in retrosynthetic analysis (Scheme 1), we envisioned the hidden symmetry of **1** in D-glucose wherein the *cis*-relative stereochemistry at C2 and C3 of **1** is in accord with the C3 and C4 of the D-glucose with required C3-hydroxyl functionality of target molecule corresponding to the C4-hydroxy of sugar. The C2-acid functionality could be obtained by cleavage of 1,2-acetonide group, chopping of the C1 followed by oxidation of compound **I**. We planned to synthesise **I** by the mercury acetate mediated five *endo*-*trig* cyclisation of γ-alkenyl amine **II** which could be obtained

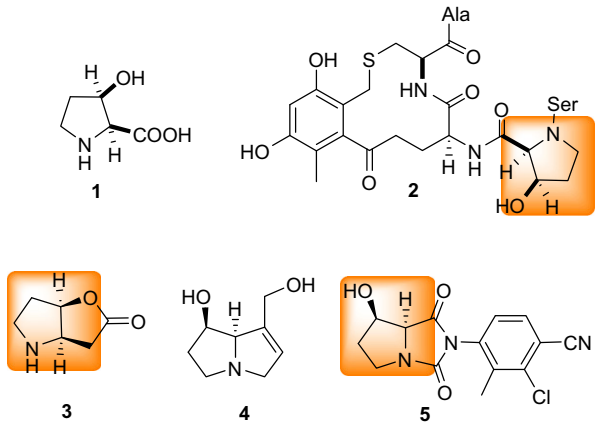

Figure 1. 3-Hydroxyproline and derivatives.

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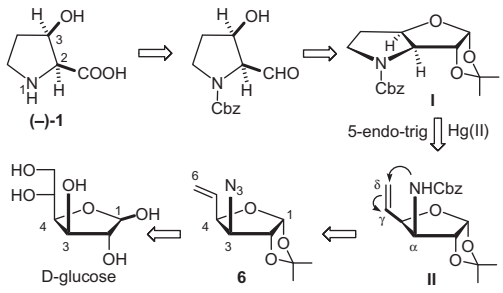
by reduction and *N*-Cbz protection of 3-azido-α-D-*gluco*-hexofuran-5-ene **6** that is, easily obtained from D-glucose. Although few methods for *cis*-3-hydroxyprolines are known in the literature, the synthesis of optically pure **1** from D-glucose, to the best of our knowledge, is not known.

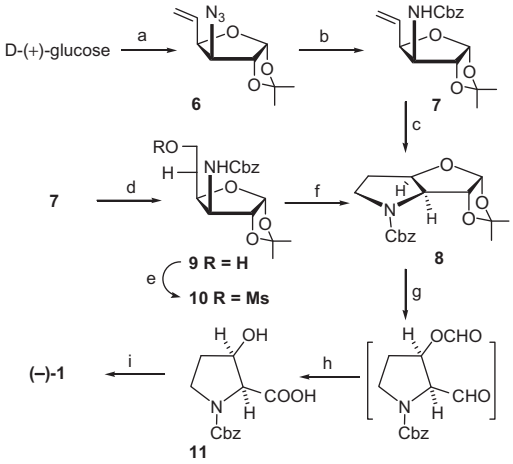
The requisite 3-azido-3,5,6-trideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-hexofuran-5-ene **6** was prepared from D-glucose in 52% overall yield as reported earlier by us.[16] The chemo-selective reduction of azido functionality into amine, in the presence of olefin, under the Staudinger conditions (TPP, THF/water) and subsequent amine protection in the same pot using benzylchloroformate and $NaHCO_3$ afforded *N*-Cbz protected γ-alkenylamine **7** as a solid in 90% yield (Scheme 2). At this stage, we thought of exploiting our methodology of mercury acetate mediated 5-*endo-trig* cyclisation of γ-alkenyl amines to get the pyrrolidine ring skeleton which we have recently used in the synthesis of castanospermine analogues.[17] Thus, *N*-Cbz protected γ-alkenyl amine **7** was treated with mercury (II) acetate in THF/water at room temperature followed by the reductive demercuration with $NaBH_4$ that afforded 5-*endo-trig*-cyclised product **8** in 25% yield. Our attempts to optimise the yield of the reaction under a variety of reaction conditions of solvent, temperature and mole equivalents were unsuccessful.

Alternatively, we thought of hydroboration–oxidation, mesylation and intramolecular S_N2 cyclisation strategy to build pyrrolidene ring skeleton. Thus, the hydroboration of *N*-Cbz γ-alkenylamine **7** with $NaBH_4/I_2$ followed by H_2O_2/NaOH gave primary alcohol **9**[18] in good yield (80%) that on treatment with methanesulfonyl chloride in the presence of pyridine gave *O*-mesyl derivative **10** in 98% yield. Intramolecular S_N2 cyclisation of **10** using NaH and cat TBAI in THF at 0 °C for 1.5 h afforded fused tricyclic pyrrolidine compound **8** in overall 67% yield (three steps). In the next step, treatment of **8** with TFA/water (3:2) afforded an anomeric mixture of hemiacetal (as evident from the ^1H NMR of crude product) that on oxidative cleavage using sodium metaperiodate in acetone/water (to cleave an anomeric carbon) gave aminal as a viscous oil. The crude *N*-Cbz protected α-aminal was subjected to oxidation with sodium chlorite, 30% H_2O_2 and sodium dihydrogen phosphate as a buffer in acetonitrile/water to give *N*-Cbz protected *cis*-3-hydroxyproline **11** as a viscous oil (88% yield in three steps). In the final step, hydrogenolysis of acid **11** using 10% $Pd(OH)_2$ in methanol/H_2O at 80 psi afforded (−)-**1** as a solid in 98% yield. The spectral and analytical data of (−)-**1** were found to be in consonance with that reported.[21] $[\alpha]_D^{20}$ −99.2 (*c* 1.0, H_2O) [lit.[12c] $[\alpha]_D$ −102.7 (*c* 1.0, H_2O), lit.[13a] $[\alpha]_D$ −101.0 (*c* 1.0, H_2O)].

In conclusion, the first chiron approach from D-glucose to *cis*-3-hydroxy-L-proline in overall 29% yield is reported. The overall synthesis is straightforward and makes use of cheap starting material and simple reagents giving high yield of product, which could be elaborated for large scale preparation. Work is in progress to extend the methodology in the synthesis of other naturally occurring β-hydroxy-α-aminoacids, such as (2*S*,3*R*)-3-hydroxyornithine[19] and (2*S*,3*R*)-3-hydroxylysine[20] and its further elaboration into PKC kinase inhibitor (−)-balanol. The investigation of (−)-**1** as a chiral organo-catalyst in the asymmetric reactions is also underway in our laboratory.



Scheme 1. Retrosynthetic analysis for **1**.



Scheme 2. Synthesis of **1**. Reagents and conditions: (a) Ref. 16; (b) Ph_3P, THF−H_2O (4:1), 48 h, rt, then aq $NaHCO_3$, ClCOOBn, 4 h, rt, 90%; (c) $Hg(OAc)_2$, THF−H_2O (1:1), $NaBH_4$, 5 h, 25%; (d) $NaBH_4$, I_2, NaOH, H_2O_2, 3 h, 0 °C to rt, 80%; (e) mesyl chloride, Py, DMAP, 3 h, 0 °C to rt, 98%; (f) NaH, THF, TBAI, 0 °C, 1.5 h, 95%; (g) (i) TFA−H_2O (3:2), 3 h, 0 °C to rt; (ii) $NaIO_4$, acetone/H_2O, 1 h, rt; (h) $NaClO_2$, NaH_2PO_4, 30% H_2O_2, acetonitrile−H_2O, 12 h, 0 °C to rt (three steps, 88%); (i) $H_2/Pd(OH)_2$, MeOH−H_2O (9:1), 80 psi, 12 h, rt, 98%.

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Supplementary data

General experimental methods, procedures and copies of ^1H and ^{13}C NMR spectra of **7**–**11** and (−)-**1**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.086.

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21. Spectral and analytical data: *Data for compound* (**7**): white solid; mp 93–95 °C; R_f 0.40 (*n*-hexane/ethyl acetate = 7/3); $[\alpha]_D^{20}$ −23.1 (*c* 1.3, $CHCl_3$); IR (KBr) 1702, 1628 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3 + D_2O$) δ 1.3 (3H, s, CH_3), 1.50 (3H, s, CH_3), 4.14 (1H, dd, *J* = 7.2 and 3.5 Hz, H-4), 4.60 (1H, d, *J* = 3.0 Hz, H-3), 4.72–4.84 (1H, br, NH), 4.93 (1H, d, *J* = 4.1 Hz, H-2), 5.08 (2H, AB quartet, *J* = 12.3 Hz, *O*-CH_2Ph), 5.30 (1H, bd, *J* = 9.4 Hz, H-6a), 5.46 (1H, bd, *J* = 17.6 Hz, H-6b), 5.70–5.85 (1H, m, H-5) 5.82 (1H, d, *J* = 4.1 Hz, H-1), 7.20–7.40 (5H, br s, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1 (CH_3), 26.4 (CH_3), 58.1 (C-3), 66.8 (*O*-CH_2Ph), 78.0 (strong), 84.2 (C-2), 103.8 (C-1), 111.7, 118.5 (C-6), 128.0, 128.1, 128.4, 130.9 (Ar), 135.1 (C-5), 155.6 (NCOO). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 64.04; H, 6.75; N, 4.62. *Data for compound* (**8**): white solid. Mp 86–88 °C, lit.[6a] mp 88–89 °C; R_f 0.5 (*n*-hexane/ethyl acetate = 6/4); $[\alpha]_D^{20}$ −66.3° (*c* 1.1, $CHCl_3$), lit.[6a] $[\alpha]_D^{20}$ −62.8° ($CHCl_3$); IR (KBr) 1710, 1270, 1078 cm^{-1}; ^1H NMR 300 MHz (DMSO-d_6) δ 1.22 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.68–1.98 (2H, m, H-5), 3.07–3.27 (1H, m, H-6), 4.06 (1H, d, *J* = 4.1 Hz, H-3), 4.66 (1H, d, *J* = 3.8 Hz, H-2), 4.76–4.85 (1H, m, H-4), 5.07 (2H, AB quartet, *J* = 12.3 Hz, *O*-CH_2Ph), 5.82 (1H, d, *J* = 3.8 Hz, H-1), 7.20–7.42 (5H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4 (CH_3), 27.0 (C-5), 30.2 (CH_3), 45.1 (C-6), 66.9 (*O*-CH_2Ph), 67.2 (C-3), 83.1 (C-4), 84.5 (C-2), 105.9 (C-1), 111.7, 127.8, 127.9, 128.2, 128.4, 136.5 (Ar), 154.3 (NCOO). The NMR spectra of **8** showed additional signals due to presence of rotamers (3:2). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.77; H, 6.83; N, 4.67. *Data for Compound* (**9**): viscous oil; R_f 0.5 (*n*-hexane/ethylacetate = 2/3); $[\alpha]_D^{20}$ −14.8 (*c* 0.4, $CHCl_3$); IR (KBr) 3200–3600 (broad) and 1695 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3 + D_2O$) δ 1.30 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.72–1.92 (2H, m, H-5), 3.69–3.86 (2H, m, H-6), 4.20 (1H, d, *J* = 3.0 Hz, H-3), 4.32–4.44 (1H, m, H-4), 4.53 (1H, d, *J* = 3.8 Hz, H-2) 4.72–4.88 (2H, br m, NH, HDO), 5.13 (2H, AB quartet, *J* = 12.0 Hz, *O*-CH_2Ph), 5.80 (1H, d, *J* = 3.8 Hz, H-1), 7.20–7.50 (5H, br, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0 (CH_3), 26.3 (CH_3), 29.7, 30.8 (C-3/C-5), 58.2 (C-6), 60.0 (*O*-CH_2Ph), 67.2 (C-4), 84.5 (C-2), 103.9 (C-1), 111.9, 128.3, 128.5, 130.9, 136.0 (Ar), 155.8 (NCOO). Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.75; H, 7.02; N, 3.95. *Data for compound* (**10**): sticky solid; yield 98%; R_f 0.5 (*n*-hexane/ethylacetate = 7/3); $[\alpha]_D^{20}$ −8.7 (*c* 0.75, $CHCl_3$); IR (KBr) 1710, 1440, 1350 and 1170 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 1.22 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.84–2.0 (2H, m, H-5), 2.92 (3H, s, OMs), 4.10–4.33 (4H, m, H-6, H-3, H-4), 4.43 (1H, d, *J* = 3.8 Hz, H-2), 4.82–4.92 (1H, br, NH), 5.04 (2H, AB quartet, *J* = 12.5 Hz, *O*-CH_2Ph), 5.71 (1H, d, *J* = 3.8 Hz, H-1), 7.20–7.40 (5H, br m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0 (CH_3), 26.3 (CH_3), 28.3 (C-5), 37.2 (C-3), 57.9 (*O*Ms), 66.8 (*O*-CH_2Ph), 67.2 (C-6), 74.7 (C-4), 84.6 (C-2), 103.7 (C-1), 112.0, 128.2, 128.4, 128.6, 128.8, 130.9, 135.9 (Ar), 155.7 (NCOO). Anal. Calcd for $C_{18}H_{25}O_8NS$: C, 52.04; H, 6.07; N, 3.37. Found: C, 52.25; H, 5.92; N, 3.62. *Data for compound* (**11**): viscous oil: R_f 0.5 ($CHCl_3$/MeOH = 7/3); $[\alpha]_D^{20}$ −52.19 (*c* 1.77, $CHCl_3$); IR (KBr) 3600–2800 (br), 1709, 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.85–2.20 (2H, m, H-4), 3.40–3.56 (1H, m, H-5a), 3.56–3.70 (1H, m, H-5b), 4.35–4.48 (1H, m, H-2), 4.50–4.62 (1H, m, H-3) 5.0–5.20 (1H, m, *O*-CH_2Ph), 6.50–7.0 (2H, br s, exchanges with D_2O, COOH, OH), 7.18–7.42 (5H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.1 (C-4), 44.4 (C-5), 63.8 (C-2), 67.3 (C-6), 70.8 (C-3), 127.5, 127.8, 128.3, 128.4, 136.1 (Ar), 155.4 (NCOO), 172.5 (COOH). The NMR spectra of **11** showed additional signals due to presence of rotamers in a ratio 3:1. In NMR data only high intensity signals are given. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 59.01; H, 5.88; N, 5.27. *Data for compound* (−)-**1**: white solid, mp 221–228 °C (decomp.) [lit.[13a] 220–230 °C with decomp., lit.[13e] 222–228 °C, decomp.]; $[\alpha]_D^{20}$ −99.2 (*c* 1.0, H_2O) [lit.[12c] $[\alpha]_D$ −102.7 (*c* 1.0, H_2O), lit.[13a] $[\alpha]_D$ −101.0 (*c* 1.0, H_2O)].