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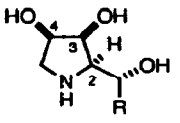
Asymmetric Synthesis of 3S, 4R-Dihydroxypyrrolidines by Regio- and Stereoselective Hydroxylation of 4-Oxoproline Enolate

M. Jesús Blanco and F. Javier Sardina*

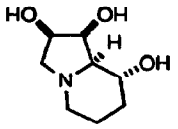
Departamento de Química Orgánica. Universidad de Santiago de Compostela. 15706 Santiago de Compostela. SPAIN

Abstract: A short, efficient and stereoselective synthesis of enantiomerically pure (2*R*, 3*S*, 4*R*) 3,4-dihydroxy-2-hydroxymethylpyrrolidine, a galactosidase inhibitor, from 4-hydroxy-L-proline is presented. The key steps are the regio- and stereoselective hydroxylation of a 4-oxoproline enolate and the stereoselective reduction of the resulting ketoalcohol. An *N*-(9-phenylfluoren-9-yl) moiety is used not only as an *N*-protecting group but as a regio- and stereochemical control element as well.

The (2*R*, 3*S*, 4*R*) 3,4-dihydroxy-2-hydroxyalkylpyrrolidine system is present in a variety of selective glycosidase inhibitors, such as compounds **1**, **2** (swainsonine) and **3**, among others.[1]



1
R = H, CH_3, CH_2F, CH_2OH



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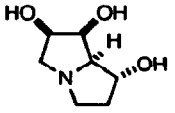


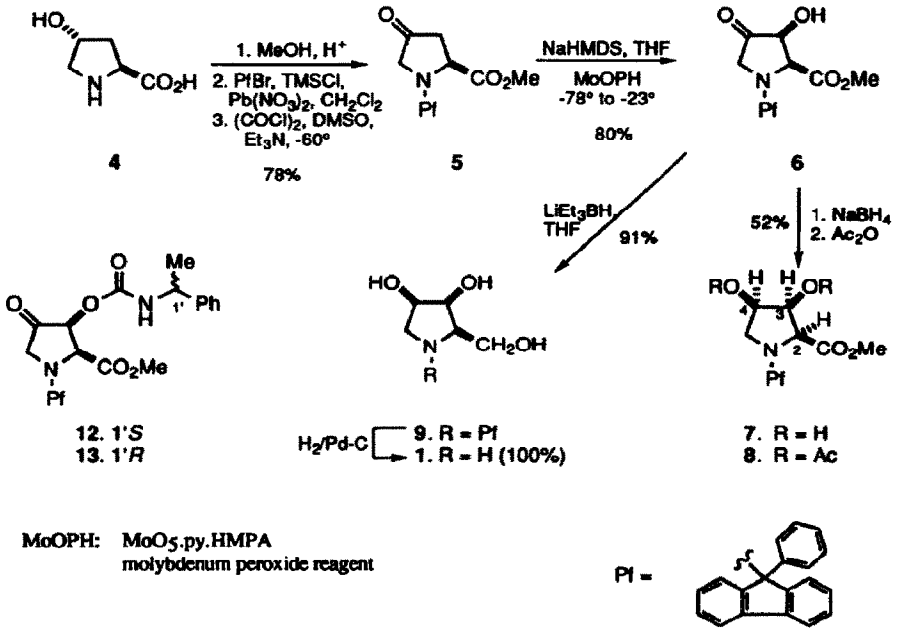
3

The therapeutic potential displayed by these polyhydroxylated pyrrolidines has attracted a good deal of synthetic interest. Fleet has been a major contributor in this area with the development of several approaches to enantiomerically pure **1-3**, and numerous analogues, starting from carbohydrate precursors.[2] Several syntheses of **1-3** from carbohydrate-related starting materials have also been reported by other groups.[3] Glutamic acid has been used as a precursor to **2** and to analogues of **1** as well.[4] Other approaches have made use of the Sharpless epoxidation to induce enantioselection in the syntheses of **2** and of analogues of **1**.[5] Most of these approaches have two important drawbacks: their excessive length (usually more than ten steps are needed to prepare the desired product) and their lack of flexibility (for the preparation of analogues).

Based on synthetic economic criteria we envisioned *trans* 4-hydroxy-L-proline (**4**) as an ideal precursor for the synthesis of **1-3**: it already incorporates the required pyrrolidine ring with a side chain attached at C-2, and the 4-hydroxyl group should be amenable to oxidation to provide a 4-oxoproline (such as **5**) which could, in turn, be manipulated (by α-hydroxylation of the corresponding enolate, followed by ketone reduction) to introduce the *cis* diol system present in the target compounds.[6]

Two problems must be overcome to convert a 4-oxoproline such as **5** into the desired (3*S*, 4*R*)-3,4-dihydroxypyrrolidine system: the ketone group in **5** must be regioselectively enolized by abstraction of H-3, and the resulting enolate has to be stereoselectively hydroxylated *syn* to the methoxycarbonyl group. Garst and co-

workers have explored the enolization of simple *N*-benzyl-3-oxopyrrolidines, and found that mixtures of regioisomeric enolates were formed under kinetic conditions.[7] Besides, the attack of electrophiles or nucleophiles onto an sp^2-hybridized C-3 in proline or pyroglutamate systems always occurs *anti* to the substituent at C-2.[4] Despite these precedents we deemed that the use of the 9-phenylfluoren-9-yl (Pf)[8] group to protect the ring nitrogen should provide the solution to the aforementioned problems. The steric bulk of the Pf group should have a threefold effect: protect the hydrogens at positions 2 and 5 from attack of the base employed to enolize ketone **5** (thus assuring not only the regioselectivity of the ketone enolization towards C-3, but the preservation of the stereochemical integrity of C-2 as well)[8] and block the α face of the enolate towards the attack by the electrophile.[9]



We present herein a short, efficient, stereoselective synthesis of enantiomerically pure pyrrolidine **1** (R = H), a galactosidase inhibitor,[2c] from 4-hydroxy-L-proline (**4**), that makes use of the Pf group as a regio- and stereochemical control element.

Esterification of **4** ($SOCl_2$, MeOH, quant.) followed by selective *N*-protection with 9-Br-9-phenylfluorene (the OH group was transiently protected *in situ* with TMSCl, 82%)[8c] and oxidation[10] of the resulting alcohol gave ketone **5** (95%), as a crystalline solid that is stable for several weeks if stored under Ar at -10 °C.[11]

Regio- and stereoselective introduction of the hydroxyl group at C-3 was achieved by treatment of **5** with NaHMDS, following by oxidation of the resulting enolate with MoOPH.[12] The resulting ketoalcohol **6**, a stable crystalline solid, was obtained as the sole reaction product (80%). The presence of two isolated AB systems (H-5α/H-5β, J=17.8 Hz, and H-2/H-3, J=7.9 Hz) in the ^{1}H-NMR spectrum of **6** clearly established the attachment of the newly introduced OH group to C-3.[11,13,14] In order to assign the stereochemistry of C-3 in ketoalcohol **6**, we proceeded to reduce the keto group with $NaBH_4$ (quant.) and to acetylate the resulting diol **7**, to give **8**

(52%).[11] An NOE experiment performed on **8** showed that the hydrogens H-2, H-3 and H-4 were all *syn* to each other, thus resulting in the stereochemistry depicted in the figure.

To check the enantiomeric purity of ketoalcohol **6** we proceeded to carbamoylate **6** with both *S*(-)- and *R*(+)-phenylethylisocyanate (200 mol%, cat. $CuBr/SMe_2$, THF, rt, quant.). ^{1}H-NMR analysis of the resulting diastereomeric carbamates **12** and **13** showed that **6** had an enantiomeric ratio (er) >99.5:0.5, thus the reaction conditions used do not lead to racemization of the stereogenic centre of the N-Pf-oxoproline **5**.

The desired galactosidase inhibitor **1** was efficiently obtained by exhaustive reduction of **6** with $LiEt_3BH$ (430 mol%, 91%)[15, 16] followed by hydrogenolysis (52 psi, H_2/Pd-C (10%), MeOH-HCl, 2h, rt) of the resulting triol **9**, to give **1**.HCl (quant.) which showed spectral properties identical to those reported in the literature.[2c] In this way, **1** was prepared in 6 steps with a 57% overall yield on a multigram scale. We are currently exploring the application of this methodology to the synthesis of the higher homologues of **1**, to swainsonine (**2**) and to kainic acid derivatives.

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9. Molecular mechanics calculations on various *N*-Pf $\Delta^{3,4}$ dehydroproline model systems showed that the CO_2Me group is locked in an axial position and that the fluorenyl group effectively blocks the α face of the $\Delta^{3,4}$ double bond.
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11. All new compounds showed the expected spectral properties and gave satisfactory elemental analysis. Selected spectral properties: **5**: mp: 136-138 °C (ether/hexanes). $[\alpha]^{25}_D$ -64.2 ° (c 1.42, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.28 (dd, J=2.8, 19.0 Hz, 1H), 2.45 (dd, J=9.0, 17.9 Hz, 1H), 3.20 (s, 3H), 3.48 (d, J=17.9 Hz, 1H), 3.76 (dd, J=3.1, 8.6 Hz, 1H), 3.77 (d, J=17.8 Hz, 1H), 7.23-7.48 (m, 11H), 7.71 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 41.6, 51.5, 55.2, 58.2, 76.0, 120.1, 120.3, 125.5, 126.9, 127.0, 127.6, 127.7, 128.0, 128.6, 128.8, 128.9, 140.3, 140.9, 141.8, 145.3, 146.5, 173.1, 212.9. **6**: mp: 180-182 °C (ethyl acetate/hexanes). $[\alpha]^{25}_D$ -199.8 ° (c 1.04, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.13 (s, 3H), 3.65 (d, J=17.7 Hz, 1H), 3.88 (d, J=17.8 Hz, 1H), 3.95 (d, J=7.9 Hz, 1H), 4.41 (d, J=7.9 Hz, 1H), 7.21-7.44 (m, 11H), 7.71 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 51.3, 51.8, 61.9, 74.9, 75.1, 120.2, 120.3, 125.2, 126.6, 126.8, 127.7, 127.9, 128.2, 128.7, 129.0, 139.9, 141.1, 141.3, 145.2, 146.7, 171.0, 211.8. **8**: $[\alpha]^{25}_D$ +174.9 ° (c 1.33, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.00 (s, 3H), 2.03 (s, 3H), 3.36 (s, 3H), 3.40 (d, J=6.9 Hz, 1H, H-2), 3.45 (d, J=6.6 Hz, 2H, H-5), 5.00 (td, J=4.8, 6.6 Hz, 1H, H-4), 5.22 (dd, J=4.8, 6.9 Hz, 1H, H-3), 7.12-7.75 (m, 13H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 20.6, 20.7, 51.3, 51.4, 51.5, 62.0, 71.0, 72.3, 119.8, 120.2, 125.7, 127.2, 127.3, 127.5, 128.4, 128.5, 128.6, 129.1, 139.5, 141.7, 142.7, 145.7, 146.8, 169.7, 170.3, 171.1. **9**: mp: 174 °C (dec., ethyl acetate/hexanes). $[\alpha]^{25}_D$ +313.6 ° (c 1.06, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.60 (dd, J=4.3, 11.0 Hz, 1H), 2.69 (dd, J=4.2, 8.0 Hz, 1H), 3.21 (dd, J=5.1, 11.9 Hz, 1H), 3.32 (dd, J=2.7, 11.9 Hz, 1H), 3.36 (d, J= 11.1 Hz, 1H), 3.87 (dd, J=4.9, 8.0 Hz, 1H), 3.97 (m, 1H), 7.19-7.75 (m, 13H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 55.4, 59.8, 59.9, 70.9, 73.4, 76.6, 120.1, 120.2, 125.5, 125.9, 127.4, 127.5, 127.9, 128.0, 128.5, 128.6, 128.9, 139.1, 141.8, 142.2, 146.5, 148.9.
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13. The use of LHMDS, LDA or KHMDS led to less stereoselective reactions.
14. The rest of the material isolated from this reaction was mostly unreacted ketone **5**.
15. $LiEt_3BH$ (430 mol%, THF, 45' (-78°C), 2h (rt)). The reaction was worked up with a solution of H_2O_2 (30%) in aq. LiOH (5%) in order to break up the intermediate boronate ester, which is surprisingly stable and could even be purified by column chromatography (silicagel).
16. The use of DIBAL, Red-Al® or $LiAlH_4$ led to the formation of some of the C-4 epimer of **9**.

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