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Alternative route towards the convergent synthesis of a human purine nucleoside phosphorylase inhibitor—forodesine HCl

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ABSTRACT

Forodesine HCl is being investigated as a potential target for the control of T-cell proliferation. Herein we present an alternative route for the synthesis of the target molecule with addition of lactam to the lithiated deazahypoxanthine (generated in situ). The lactam was synthesized in five steps starting from L-pyroglutamic acid.

Purine nucleoside phosphorylase (PNP) enzyme has been investigated widely due to its importance in the purine salvage pathway. PNP catalyzes the reversible phosphorolysis of ribonucleosides and 2′-deoxyribonucleosides to the respective base and deoxyribose-α-1-phosphate.[1]

The importance of PNP enzyme to the integrity of the immune system has become apparent with the discovery of a rare form of immune deficiency found in children who are genetically deficient in PNP enzyme.[2,3] Children lacking the enzyme have severe T-cell immunodeficiency and in most cases they maintain a normal or high B-cell function.

In the past decade, Schramm and co-workers have identified several potent inhibitors of PNP enzyme.[4,5] This has led to the discovery of several novel classes of inhibitors that are extremely potent against PNP. These compounds are the aza-C-nucleosides, and one of them, forodesine is currently being investigated by BioCryst Pharmaceuticals Inc. for control of T-cell proliferation (see Fig. 1).

A number of earlier publications by Tyler and co-workers have described the synthesis of forodesine.[6–10] The key step in the synthesis involved addition of the imine (generated in situ from the aza-sugar) to the lithiated 9-deazahypoxanthine, followed by the removal of the protecting groups to furnish forodesine. The synthesis of aza-sugar was first reported by Fleet and co-workers starting from D-gulonolactone. Since D-gulonolactone is no longer available commercially a new synthetic route to make the aza-sugar had to be explored.[11] The coupling of the imine with the lithiated 9-deazahypoxanthine gave reproducible results, but the process involved cumbersome manipulation that was not suitable for large-scale operations. Hence there was a need to explore other synthetic routes to make the aza-sugar and forodesine HCl.

Herein we describe an alternate route to make the aza-sugar using L-pyroglutamic acid (see Scheme 1).[12] L-Pyroglutamic acid is commercially available and cheap source of starting material. L-Pyroglutamic acid was converted to the ester followed by reduction of the ester with sodium borohydride to give the alcohol, **1** in 75% yield.[13,14] Compound **1** was treated with benzaldehyde in the presence of an acid catalyst (*p*-TsOH) to furnish **2** as a solid in 80% yield.[15] Transformation of compound **2** to the unsaturated lactam, **3** was accomplished using the Myers reagent in 65% yield.[16] Cis-dihydroxylation of compound **3** was accomplished using a catalytic

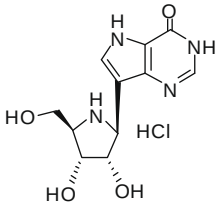
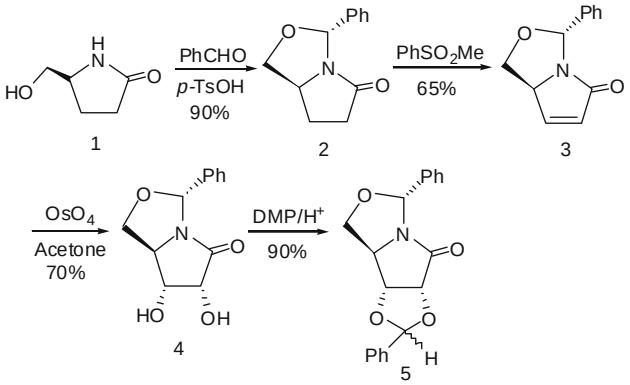


Figure 1. Structure of forodesine HCl.



Scheme 1. Synthesis of the aza-sugar moiety (**5**).

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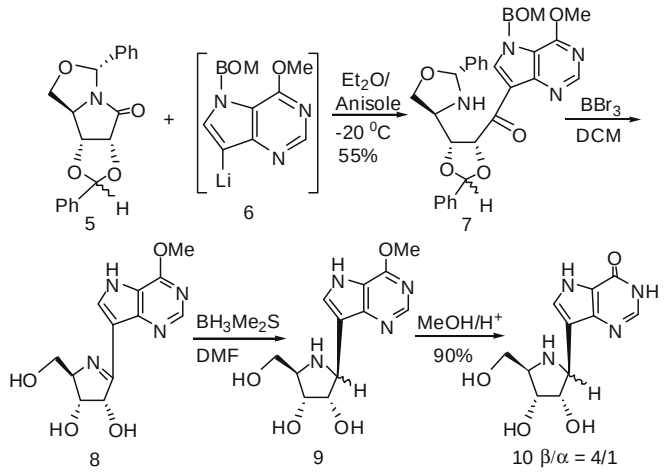
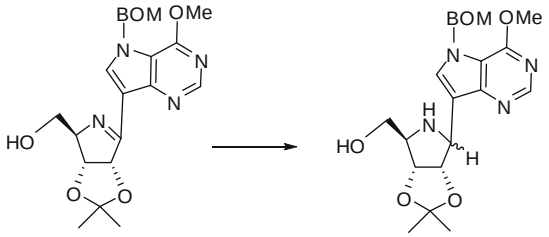


Scheme 2. Progress towards the synthesis of forodesine HCl (**1**).

Table 1
Reaction conditions for reduction of the imine using various reducing agents



11 12

No.	Solvent	Reducing reagent	β/α ratio
1	THF	$NaCNBH_3$	1: 1
2	THF	L-Selectride + $NaCNBH_3$	1:4
3	THF	R-MeCBS + BH_3Me_2S	1:4
4	THF	S-MeCBS + BH_3Me_2S	1:4
5	THF	STAB	1:4
6	THF	$NaBH_4$	1:1
7	**THF**	**BH_3Me_2S**	**2:1**

amount of OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) in aqueous acetone to furnish the diol, **4** with the desired stereochemistry in 70% yield.[17] The diol was further protected as a benzylidene acetal mixture, **5** under standard conditions in 90% yield.[18]

The key step was the addition of the lactam to the lithiated 9-deazahypoxanthine (see Scheme 2). Compound **6** (generated in situ by reacting the 9-bromo deazahypoxanthine[10] with *n*-BuLi) was coupled to the N,O-protected lactam, **5** at −20 °C and stirred for 20 min. The reaction mixture was slowly warmed to 0 °C and then stirred further for 1 h.[19] Workup of the reaction furnished the crude product. The crude was purified by column chromatography to furnish **7** as a foam in 55% yield.[20] Compound **7** was treated with BBr_3 in DCM and stirred at rt for 2 h. Workup of the reaction mixture gave the cyclized adduct, **8** which was taken directly to the next step without any further purification.[21]

At this stage a number of reducing agents and reaction conditions were attempted on a model compound **11**[10] to selectively reduce the imine to furnish the target compound (see Table 1). Reduction of the imine, **11** with bulky reducing agents predominantly gave the undesired α-anomer as the major product. This result was further supported by molecular modelling studies of compound **11**. The best anomeric ratio was obtained using BH_3–Me_2S reagent to give **12** with β/α anomeric ratio of 2:1 (Table 1, see entry 7). The ratio was determined by HPLC using authentic forodesine HCl as a reference.[6]

Based on the results from Table 1, **8** was reacted with BH_3–Me_2S reagent to furnish **9** as a mixture with β/α ratio of 4:1.[22] Hydrolysis of **9** was carried out in MeOH and concd HCl under reflux conditions for 1 h to give product **10** in 90% yield. The two compounds were finally isolated by column chromatography.[23] The β-anomer was characterized and was found to be identical in all respects with the compound published in the literature.[10]

In conclusion, an alternative route to synthesize forodesine HCl has been demonstrated. Work on improving the synthetic route is still in progress.

Acknowledgement

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21. 9-Bromo deazahypoxanthine (1 g, 2.9 mmol) dissolved in Et_2O/anisole mixture at −20 °C was treated with *n*-butyl lithium solution (1.6 M, 1.9 mL, 3.0 mmol) and stirred for 10 min. Compound **5** (0.9 g, 2.9 mmol) pre-dissolved in Et_2O/anisole mixture was added slowly via a cannula to the reaction mixture containing **6** (formed in situ) at −20 °C for 20 min and then warmed to 0 °C and stirred further for 1 h. Upon completion of the reaction, the mixture was quenched with satd NH_4Cl solution, extracted in Et_2O, washed with H_2O, dried and evaporated to dryness. The product was purified by column chromatography using hexanes/EtOAc 1:9 as eluent. The appropriate fractions were pooled together to furnish compound **7** as a foam (0.95 g, 55%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.15 (s, 1H), 7.11–7.62 (m, 15H), 5.60–5.80 (m, 6H), 4.42–4.71 (m, 5H), 4.15 (s, 3H, OMe), 3.90 (dd, 1H).
22. Compound **7** (0.25 g, 0.43 mmol) was dissolved in DCM (10 mL) followed by slow addition of BBr_3 (0.16 mL, 1.75 mmol) and stirred at rt for 2 h. Upon completion of the reaction (as indicated by TLC) the reaction mixture was neutralized with solid $NaHCO_3$. The solids were filtered and the filtrate was concentrated. The crude was taken directly to the next step without any further purification.
23. Compound **8** (87 mg, 0.3 mmol) was dissolved in DMF (5 mL) followed by addition of BH_3–Me_2S (39 μL, 0.6 mmol) and stirred for 1 h. Workup of the reaction furnished **9** which was then hydrolyzed using MeOH/concd HCl (1:1,

2 mL) under reflux conditions to furnish **10** as a mixture. Compound **10** (α-anomer) was isolated by column chromatography and fully characterized. ^{1}H NMR (500 MHz, D_2O) δ 7.96 (s, H-2, 1H), 7.75 (s, H-8, 1H), 4.97 (d, H-1′,1H), 4.41 (m, H-3′, 1H), 4.37 (m, H-2′, 1H), 3.94, 3.96 (dd, H-5′, 2H), 3.69 (m, H-4′, 1H); ^{13}C NMR (125 MHz, D_2O) δ 155.3, 143.3, 142.7, 129.8, 117.3, 106.7, 72.2, 71.9, 62.0, 58.6, 56.3; IR (thin film) ν 3087.9, 2941.4, 1661.6 cm^{-1}. HRMS: Calcd for $C_{11}H_{15}N_4O_4$ ($M+H^+$): 267.1082; Found: 267.1080.