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Improved Procedures for the Preparation of (+) - (1R, 2S, 4R)-4-Amino-2-Hydroxy-1-Hydroxymethyl Cyclopentane

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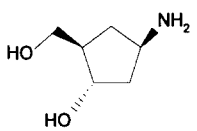
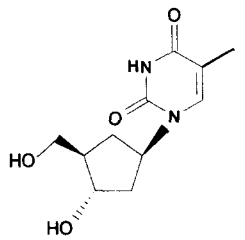
Abstract: Two methods for the stereospecific synthesis of the title compound are described. These short and efficient syntheses provide rapid access to this key intermediate in the construction of 2'-Deoxy Carbocyclic Nucleosides.

Carbocyclic nucleosides display a wide variety of anti-viral activity. [1,2] In addition, the carbocyclic ring confers an increased metabolic stablility over the furanose analogues. [3]

A key intermediate in the construction of a wide variety of 2'-Deoxy carbocyclic nucleosides is the homochiral amino diol (**1**). Ötvös *et. al.* have used this compound to synthesise (+) carbocyclic thymidine(**2**).[4]



(+)
(1)

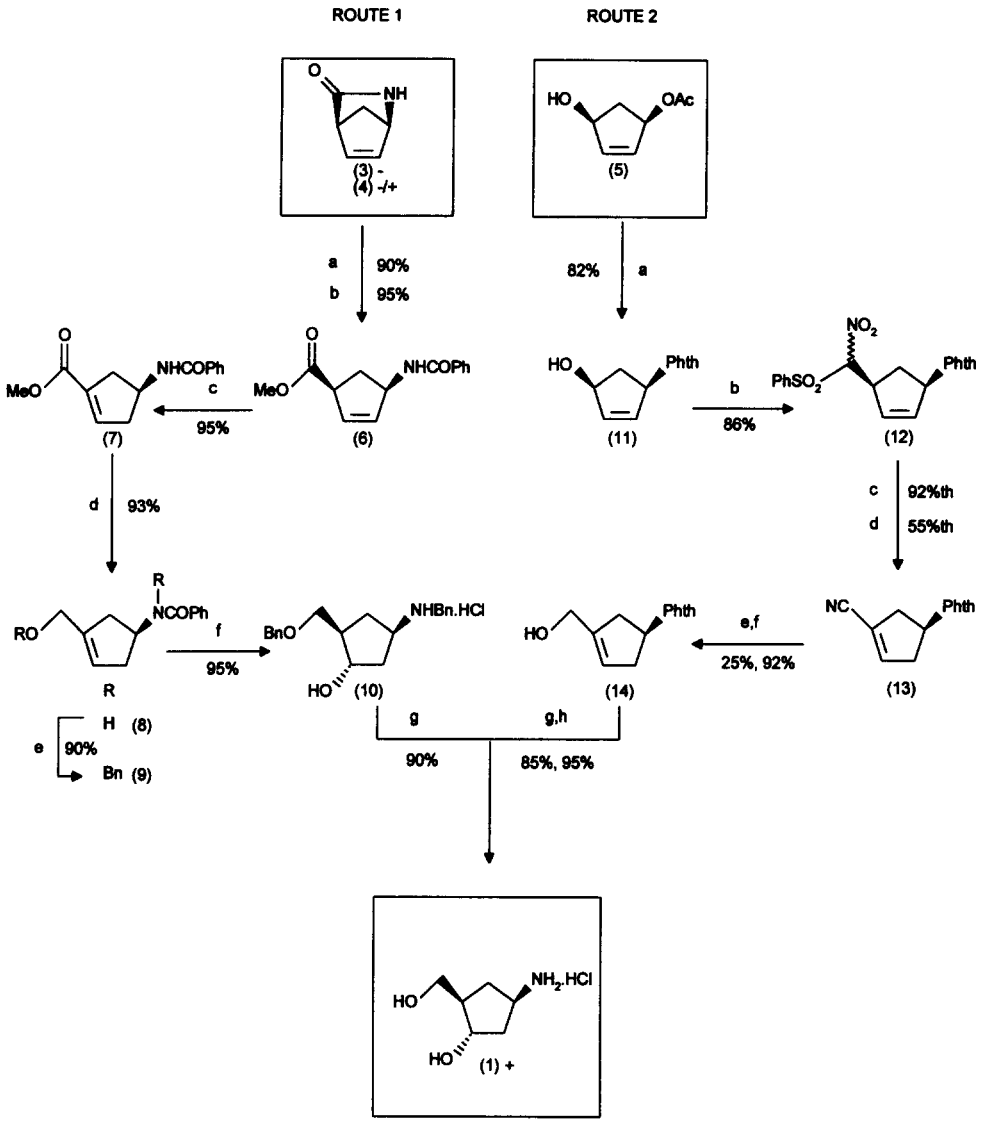


(+)
(2)

Our own interest in this important class of compounds required us to investigate short and commercially viable routes to the amino diol (**1**). We now wish to report two procedures for the preparation of this compound from the available homochiral lactam (**3**)[5] and the cyclopentenyl hydroxyacetate (**5**),[5] both of which represent a significant improvement on existing literature procedures.[6]

Vince *et. al.* synthesised a variety of 2',3' disubstituted cyclopentylamines from the racemic lactam (4).[7,8] Initially (Scheme 1, Route 1), we envisaged that ring opening of the lactam followed by migration of the double bond into conjugation with the ester would give a trisubstituted olefin, the reduction and stereoselective hydroboration of which would incorporate the required 3α-hydroxyl moiety.

Scheme 1



ROUTE 1: a), PhCOCl/Py ; b), H_2SO_4/MeOH ; c), DBU/CH_2Cl_2 ; d), DIBAH/CH_2Cl_2/Toluene ; e), BnBr/Toluene/NaOH/$^tBu_4N^+HSO_4^-$/ $NaHCO_3$; f), BH_3.DMS/2-Methyl-2-butene/THF/NaOH/H_2O_2 ; g), Pd/C,nPrOH

ROUTE 2: a), NaPhth/$Pd(PPh_3)_4$/DMSO/THF; b), CH_3COCN/DMAP/THF;$(AllylPdCl)_2$/PPh_3/$PhSO_2CH_2NO_2$/THF; c), $TiCl_3$/HCl/ MeOH; d), DBU/DMF; e), AcOH/HCl; f), ClCOCOCl/THF/$NaBH_4$/DMF; g), BH_3.DMS/2,3-Dimethyl-2-butene/H_2O_2/NaOH; h), NH_2NH_2/MeOH/HCl/n-PrOH

The homochiral lactam (**3**) was obtained in >99% ee using a microbial transformation.[5] Benzoylation and acid catalysed ring opening of the lactam with methanol gave the crystalline unconjugated ester (**6**); migration of the double bond into conjugation with DBU proceeded smoothly to give the ester (**7**).

Initial attempts to reduce the ester (**7**) using a wide variety of hydride based reducing agents led to complex mixtures of products as a result of competitive 1,2 vs 1,4 reduction. In addition, treatment of the substrate with hydride sources such as REDAL or DIBAH, although 1,2 selective, led to partial reduction of the amide functionality (up to 40% in some cases). We found that it was possible to enhance significantly the chemoselectivity of DIBAH towards reduction of the ester functionality when reductions were carried out in the presence of 1mol equivalent of $AlCl_3$. [9] Under these conditions, the required allylic alcohol (**8**) was isolated as a crystalline solid without any detectable over-reduction.

Brown et. al. had reported that disubstituted hydroborating agents reduced tertiary amides to secondary amines.[10] This observation offered the opportunity, upon benzylation of (**8**), to enhance the steric hinderance around the β face. We reasoned that if the rate of reduction of an amide, such as (**9**), was greater than the rate of hydroboration of the tri-substituted olefin, then participation of an intermediate borate species (in which the benzamide unit had been reduced) could further hinder the top face of the molecule. Thus the tertiary amide (**9**) was prepared using phase transfer catalysed N,O dibenzylation of (**8**) with benzyl bromide and $^{n}Bu_4NHSO_4$. Hydroboration was then achieved using the hindered disiamylborane with a selectivity of >75:1 in favour of the required 3α-hydroxy dibenzylamine (**10**), which was isolated as its hydrochloride salt. Under the same conditions hydroboration of (**8**) led to a loss of selectivity (*ca* 12:1) without concomitant reduction of the amide. Finally, palladium catalysed hydrogenolysis of the benzyl groups afforded the required amino diol (**1**) which was isolated as a crystalline hydrochloride salt. The overall efficiency of this route from the homochiral lactam (**3**) is 58%th and this chemistry has been successfully operated on multikilogram scale.

Concurrently with these investigations (Scheme 1, Route 2), we explored the use of homochiral cyclopentenyl hydroxyacetate (**5**) as an alternative starting material for the synthesis of amino diol (**1**). We planned to introduce nitrogen via a palladium (0) catalysed insertion of a phthalimide group into the C1 allylic position of the cyclopentene ring of (**5**).[11] As in route 1, the 3α-hydroxyl functionality was to be introduced *via* a hydroboration/oxidation strategy. We envisaged that the pthalimide group would show a similar potential to the amide (**9**) in shielding the β face of the cyclopentene ring, provided it was stable to the reaction conditions.

Treatment of the cyclopentenyl hydroxyacetate (**5**) with sodium phthalimide in the presence of catalytic palladium (0) provided the cyclopentenyl hydroxyphthalimide (**11**) as a crystalline solid. Homologation at C4, after activation of the alcohol *in situ* as its methyl carbonate, was achieved using the palladium (0) catalysed insertion of phenylsulfonylnitromethane.[12] The resulting diastereomeric mixture (**12**), was treated with titanium (III) chloride in aqueous hydrochloric acid,[13] followed by double bond migration (catalysed by DBU) to give the α,β unsaturated cyclopentenyl nitrile (**13**). Hydrolysis to the α,β-unsaturated acid and reduction *in situ* of the acid chloride with sodium borohydride, gave the required hydroxycyclopentenyl phthalimide (**14**).

Selective 3 α-hydroxylation of cyclopentenyl phthalimide (**14**) was accomplished with 3eq. of freshly prepared thexylborane with an oxidative workup H_2O_2 (the phthalimide functionality remained intact throughout the reaction).[14] The β-hydroxy isomer was not detected by TLC or proton NMR of the crude

reaction mixture. The phthalimide was removed with hydrazine and amino diol (**1**) was again isolated as a hydrochloride salt by crystallisation from n-propanol. The overall yield from the cyclopentenyl hydroxyacetate (**5**) is 7%th. A comparison with the yield for route 1 is not possible at this stage, since this chemistry has not been operated on a multikilogram scale and remains unoptimised.

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