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ASYMMETRIC INDUCTION IN THE REDUCTION OF CHIRAL IMINES. STEREOSPECIFIC SYNTHESIS OF 20α-AMINO 5α-PREGNAN 3β-OL (FUNTUPHYLLAMINE A).

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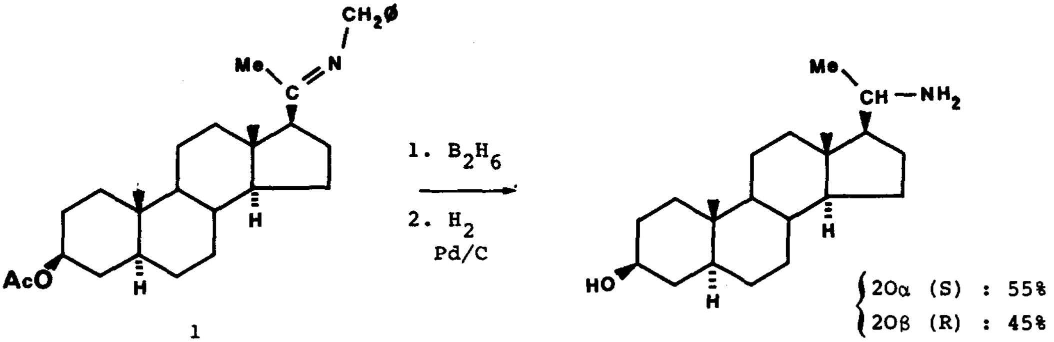
Reduction in smooth experimental conditions of imines containing a chiral center on nitrogen atom has been used as an asymmetric synthesis of amines[1,2,3,4]

We now describe a stereospecific synthesis of a 20α-aminosteroid using reduction of a chiral imine.

The reduction with diborane of the 20-imino 5α-pregnan derivative 1 (without any chiral center on nitrogen atom) affords, after debenzylation, a mixture of the 2 epimeric amines analysed by ^1H NMR on the 18-methyl signal[5]: 55% of 20α (S) amine (δ =0.65 ppm) and 45% of 20β (R) amine (δ= 0.72 ppm).



1

But on introducing (as chiral accessory) an asymmetric center on the nitrogen atom, we have been able to increase drastically the stereoselectivity of the reduction with diborane.

Thus, reduction of imine 2 (prepared by refluxing for 4 days (-)S α-phenyl ethylamine (0.45g.), 3β-acetoxy 5α-pregnan 20-one (1g.), p-toluenesulfonic acid

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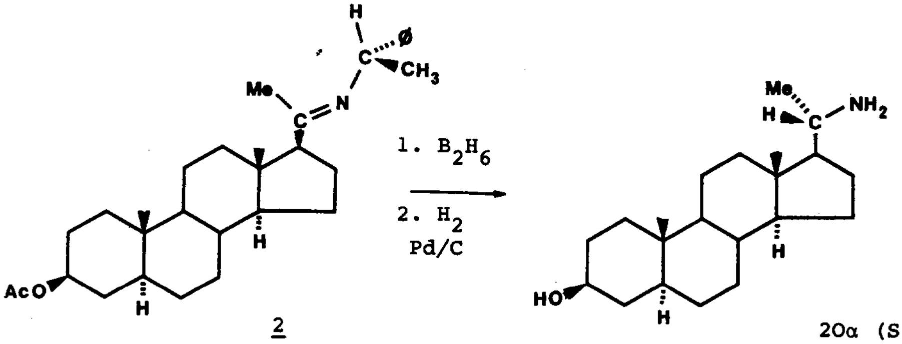
(0.1g.) in toluene),with diborane gives,after debenzylation,the 20α (S) amine[5,6] as unique product:m.p. 175°,$|\alpha|_D$ + 13° (c 1,MeOH);^{1}H NMR:s,$C_{18}H_3$,δ = 0.65 ppm; p-nitrobenzylidene derivative:m.p. 225°,$|\alpha|_D$ + 83° (c 0.1,MeOH).



2

20α (S)

However the asymmetric induction is strongly dependant of the chirality of the group attached on nitrogen.Thus,the reduction,in the same experimental conditions,of the imine prepared from (+)R α-phenylethylamine and 3β-acetoxy 5α-pregnan 20-one gives,after debenzylation,essentially the other epimeric amine : 92% of 20β (R) amine and 8% of 20α (S) amine.

We shall remark that chemical yields for the overall process are quantitative.

Finally,we have shown that reduction of imine 1 with (+) di-3-pinanylborane yields,after debenzylation,a mixture of the 2 epimeric amines:53% of 20α-amine and 47% of 20β-amine.

As it is well established that chemical as well as catalytic reduction of 20-hydroxyimino steroids affords also mixtures of the 2 epimeric amines[5], the reduction of imines having a chiral center on nitrogen appears to be a powerful method to prepare either a 20α-amino or a 20β-amino steroid.

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