Novel reduction of 3-hydroxypyridine and its use in the enantioselective synthesis of (+)-pseudoconhydrine and (+)-*N*-methylpseudoconhydrine

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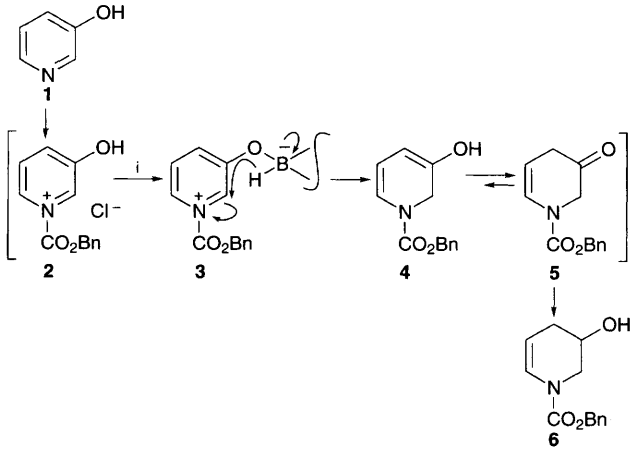
3-Hydroxypyridine is reduced with sodium borohydride in the presence of benzyl chloroformate to give 1-benzyloxycarbonyl-5-hydroxy-2-piperideine which is transformed into (+)-pseudoconhydrine and (+)-*N*-methylpseudoconhydrine in five steps involving a lipase-mediated kinetic resolution.

It is well established that the reduction of pyridine with sodium borohydride furnishes the 1-carbamate ester of 1,2-dihydropyridine when an appropriate chloroformate ester is present.[1,2] We found that 1-benzyloxycarbonyl-5-hydroxy-2-piperideine **6** was formed when 3-hydroxypyridine **1** was treated under the same conditions in the presence of benzyl chloroformate. Here we report our findings and the use of the reduction product **6** as the starting material for the synthesis of two piperidine alkaloids (+)-pseudoconhydrine[3,4] **15** and (+)-*N*-methylpseudoconhydrine[3,5] **17** in natural enantiomeric forms in five steps involving a stereospecific *C*-allylation and a lipase-mediated kinetic resolution.[6]

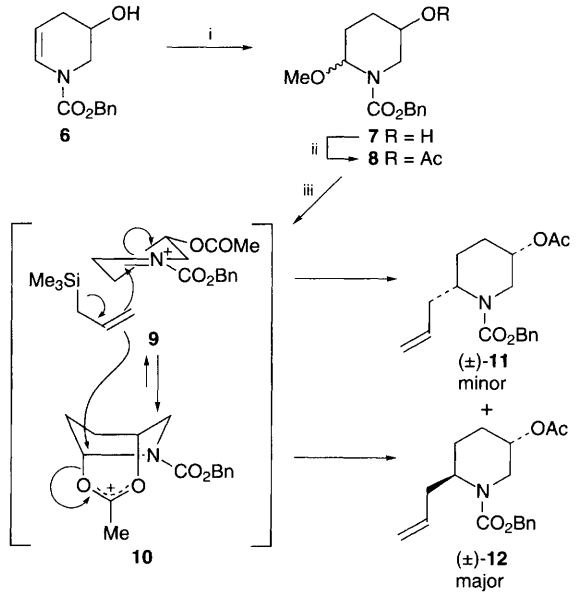
Treatment of 3-hydroxypyridine **1** in methanol containing an excess of sodium borohydride (2.2 equiv.) and sodium hydrogen carbonate (2.0 equiv.) with benzyl chloroformate (1.5 equiv.) at −80 °C afforded 1-benzyloxycarbonyl-5-hydroxy-2-piperideine‡ **6** in 69% yield as the only isolable product. The same reaction occurred in the presence of other chloroformate esters to give the corresponding hydroxy piperideines in comparable yields. The specific generation of the piperideinol **6** may be reasoned by assuming the intervention of the oxygen–boron complex **3** which directed the regiospecific reduction to give initially the 1,2-dihydropyridine **4**. Under these conditions **4** isomerized to the ketone **5** which was then reduced to the alcohol **6** leaving the *N*-acylenamine functionality intact (Scheme 1).

To demonstrate its synthetic potential, the unstable piperideine **6** was first transformed into the more stable 2-alkoxypiperidine ester **8** in 66% overall yield as a diastereoisomeric mixture (1 : 1) *via* **7** on treatment with methanol containing a trace of hydrochloric acid followed by acetic anhydride. Upon reaction with allyltrimethylsilane[5a] in the presence of zinc(II) chloride,[5c] **8** afforded a separable diastereoisomeric mixture (1 : 10) of the *cis*-**11** and the *trans*-**12** in 87% yield.§ The observed rather unexpected high *trans*-selective addition may be due to the anchimeric assistance[7] of the acetate group of **8** which converted the initially generated acyliminium intermediate **9** into the bicyclic oxonium intermediate **10** to allow *anti* addition in preference to the stereoelectronically favoured *syn* addition[7] (Scheme 2).

Without separation of **11** and **12**, the mixture was resolved under hydrolytic conditions using lipase.[6,8] Among tested, the resolution was best carried out in the presence of lipase PS (*Pseudomonas cepacia*, Amano) in a phosphate buffer–acetone mixture (9 : 1) to give the (−)-*trans*-alcohol **13**, $[\alpha]_D^{27}$ −35.5 (*c* 1.1, $CHCl_3$), in 35% yield with >99% ee.¶ The (+)-*trans*-acetate **12**, $[\alpha]_D^{25}$ +19.9 (*c* 1.2, $CHCl_3$), was recovered (39%) with 94% ee¶ accompanied by 6% yield of the acetate‖ of *cis*-**11** and a trace (< 1%) of *cis*-**13**.‖ In order to determine the absolute configuration of the major products, the *trans*-alcohol (−)-**13** thus obtained was hydrogenated on palladium hydroxide in methanol. Concurrent hydrogenation and decarbamoylation gave the saturated secondary amine in 91% yield which was found to be unnatural (−)-pseudoconhydrine **15**, mp 102–104 °C, $[\alpha]_D^{27}$ −10.0 (*c* 1.0, EtOH) [lit.,[9] mp 105–106 °C, $[\alpha]_D^{26}$ −10.8 (*c* 1.68, EtOH)]. This determined unambiguously the stereochemistry of the (−)-alcohol **13** as *trans*-2*R*,5*S* configuration and, consequently, the (+)-acetate **12** as *trans*-2*S*,5*R* configuration (Scheme 3).

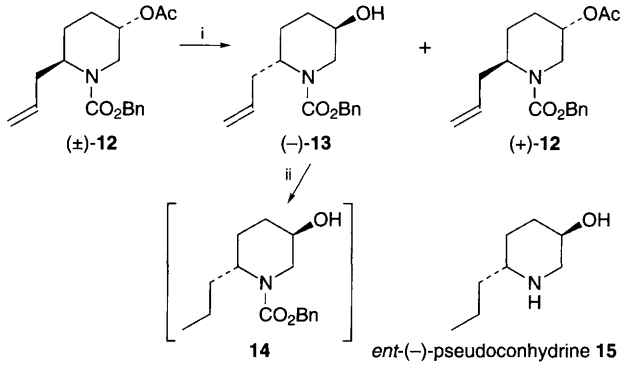


Scheme 1 *Reagents and conditions*: i, $ClCO_2Bn$ (1.5 equiv.), $NaBH_4$ (2.2 equiv.), $NaHCO_3$ (2.0 equiv.), MeOH, −80 °C, 1.5 h, 69%

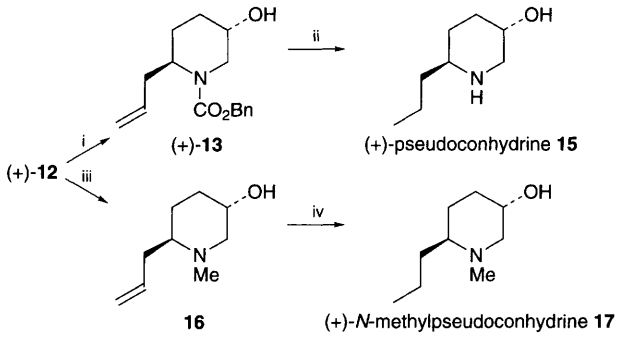


Scheme 2 *Reagents and conditions*: i, conc. HCl–MeOH (0.5%), room temp., 66%; ii, Ac_2O, Et_3N, 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (cat.), CH_2Cl_2, room temp., 99%; iii, allyltrimethylsilane, $Zn^{II}Cl_2$, room temp., 3 d, 87% (**11** : **12** = 1 : 10.2)

Having determined the stereochemistry, the (+)-*trans*-acetate **12** was deacylated to give the (+)-*trans*-alcohol **13**, $[\alpha]_D^{27}$ +34.8 (*c* 1.0, $CHCl_3$), which was hydrogenated as for (−)-**13** to afford natural (+)-pseudoconhydrine **15**, mp 102–104 °C, $[\alpha]_D^{29}$ +11.1 (*c* 1.0, EtOH) [lit.,[9] mp 105–106 °C, $[\alpha]_D^{23}$ +11.1 (*c* 1.72, EtOH)], in 83% overall yield. On the other hand, the (+)-*trans*-acetate **12** was reduced with lithium aluminum hydride to give the unsaturated tertiary amine **16**, $[\alpha]_D^{29}$ +48.0 (*c* 1.0, $CHCl_3$), which was hydrogenated over Adams catalyst to afford natural (+)-*N*-methylpseudoconhydrine **17**, $[\alpha]_D^{27}$ +53.2 (*c* 1.3, $CHCl_3$), [lit.,[4b] $[\alpha]_D^{25}$ +67.8 ($CHCl_3$)], in 86% overall yield (Scheme 4).



Scheme 3 *Reagents and conditions*: i, lipase PS, phosphate buffer-acetone (9 : 1), room temp., 99 h, (−)-**13** (35%) and (+)-**12** (39%); ii, H_2 (1 atm), $Pd(OH)_2$, MeOH, 91%



Scheme 4 *Reagents and conditions*: i, K_2CO_3, MeOH, 92%; ii, H_2 (1 atm), $Pd(OH)_2$, MeOH, 90%; iii, $LiAlH_4$, THF, reflux, 95%; iv, H_2 (1 atm), PtO_2, CH_2Cl_2, 90%

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Footnotes

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‡ Satisfactory spectroscopic (IR, ^1H NMR, MS) and analytical (combustion and/or high resolution MS) data were obtained for all new isolable compounds.

§ The stereochemistry of **11** and **12** could not be determined rigorously at this stage.

¶ Optical purity was determined by HPLC of the acetate **12** using a chiral column (CHIRALCEL OD, elution with Pr^iOH–hexane, 2 : 98).

‖ The absolute configuration was not determined.

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