A SHORT AND PRACTICAL SYNTHESIS OF (+)-PSEUDOCONHYDRINE AND (+)-*N*-METHYLPSEUDOCONHYDRINE *VIA* OSMIUM CATALYZED ASYMMETRIC DIHYDROXYLATION[1]

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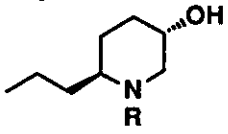
Absatrct - A short and practical synthesis of (+)-pseudoconhydrine (**1**) and (+)-*N*-methylpseudoconhydrine (**2**) has been achieved by starting with asymmetric dihydroxylation of the α-amino acid-derived *N*-alkenylurethane (**3**).

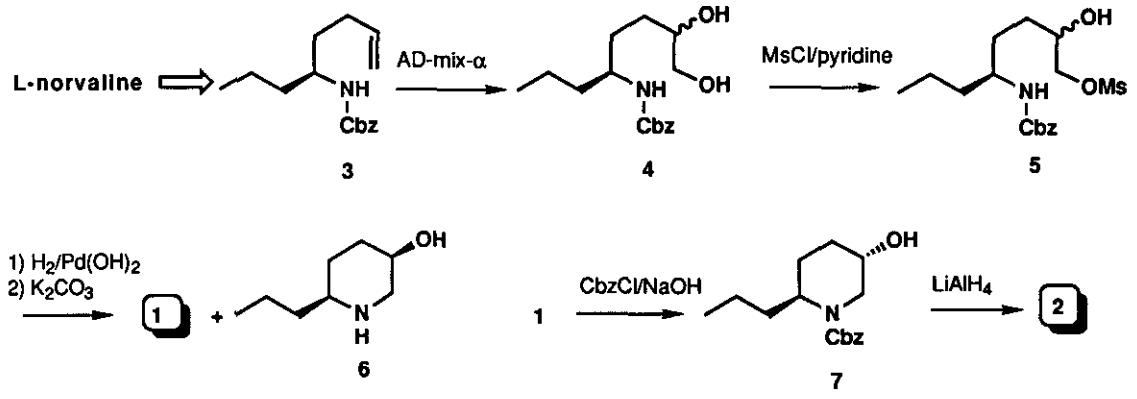
Alkaloids containing the β-hydroxypiperidine system are abundant in nature and many of them exhibit pivotal biological activities.[2] Accordingly, they offer attractive targets for asymmetric synthesis. Two are found in the *Conium* alkaloids: (+)-pseudoconhydrine (**1**),[3] one of the alkaloidal constituents of the poison hemlock isolated from *Conium matculatum* L. (Umbelliferae), and (+)-*N*-methylpseudoconhydrine (**2**)[4] yielded from the South African *Conium* sp. So far, the synthesis of **1** has been reported several times in its racemic form[5] and only once in its chiral one[6] and that of **2** has been described one example in both racemic[4b] and chiral[7] forms. In connection with our program directed towards the development of methodology for the asymmetric synthesis of biologically active nitrogen-containing compounds,[8] we disclose a short and practical synthesis of **1** and **2** *via* osmium-catalyzed asymmetric dihydroxylation of the homochiral (*S*)-5-[(benzyloxy)carbonyl]amino-1-octene (**3**), readily available from L-norvaline.



1: R = H
2: R = Me

The reaction of osmium tetroxide with alkenes is perhaps one of the most reliable and selective transformation in organic synthesis.[9] Recently, the Sharpless asymmetric dihydroxylation (AD) of olefins has attained high levels of enatioselectivity and practicality based in large part on the development of more effective *Cinchona* alkaloid-derived ligands.[10] In addition, the reaction has been performed by using commercially available[11] AD-mix-α (dihydroquinine-based ligand) or -β (dihydroquinidine-based ligand) under a single set of the experimental conditions.[10b] Our synthesis of **1** began with the catalytic asymmetric dihydroxylation of the *N*-alkenylurethane (**3**) prepared from L-norvaline according to the known procedure[12]. Asymmetric dihydoxylation of **3** with AD-mix-α in ^{t}-BuOH-H_2O afforded a mixture of the diastereomeric diols (**4**) in 84% yield. Selective mesylation of the primary hydroxyl in **4** provided **5** in quantitative yield. Exposure of **5** to an atmosphere of hydrogen in the presence of $Pd(OH)_2$ as a catalyst in MeOH caused simultaneous debenzyloxycarbonylation and cyclization (6-exo-tet.)[13,14] to give the piperidine salt, which was, by treatment with K_2CO_3, converted into the desired **1**[15] {$[\alpha]^{25}_D$ +12.68° (EtOH), lit.,[16] $[\alpha]^{23}_D$ +11.1° (EtOH)} and 3-*epi*-pseudoconhydrine (**6**)[17] in 54% and 13% yields, respectively. Spectral data (^{1}H and ^{13}C nmr) for **1** were completely identical with those reported.[5a] It appears that the ratio of the products (**1**) and (**6**) presumably reflects the diastereoselectivity (enantioselectivity) for the dihydroxylation of **3**.[18]

In addition, the synthesis of **2** was achieved in two steps from **1**. Benzyloxycarbonylation of **1** provided **7** {$[\alpha]^{25}_D$ +15.8° ($CHCl_3$)}, in 98% yield, which was reduced with lithium aluminum hydride to give **2** [19]{2-HCl mp 171-3 °C, lit.,[7] 169-170 °C; $[\alpha]^{25}_D$ +24.4° (MeOH), lit.,[4] $[\alpha]^{23}_D$ +25.0° (MeOH)} in 96% yield. ^{1}H Nmr spectrum for **2** was in accord with that reported.[4]



In summary, starting from the homochiral *N*-alkenylurethane (**3**), available from L-norvaline, **1** and **2** were prepared concisely in good yields. This methodology, based on the asymmetric dihydoxylation of *N*-alkenylurethanes and subsequent aminocyclization,[20] provides a new and promising access to the

stereoselective construction of the pyrrolidine and piperidine ring, which could be convertible to related biologically active compounds, and the results will be described in due course.

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14. At the biginning, cyclization (6-endo-trig)[13] of **3** and its derivatives using metal acetates {$Hg(OAc)_2$, $Cu(OAc)_2$, and $Pd(OAc)_2$} was attempted. However, all reactions underwent undesired cyclization (5-exo-trig.)[13] to give the pyrrolidines. Accordingly, it is judged the annulation (6-end-trig.) of *N*-alkenylurethanes bearing no substituents at terminal olefin is difficult.

15. **1**: mp 92-3 °C, lit.,[16] mp 91.5-92 °C; HCl salt of **1**; mp 220 °C;$[\alpha]_D^{25}$ +3.06° (MeOH); Anal. Calcd for $C_8H_{18}NOCl$: C, 53.47; H, 10.10; N, 7.80. Found: C, 53.46; H, 10.39; N, 7.66.

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17. **6**: HCl salt of **6**; mp 158 °C; ^{1}H nmr (270 Mz, D_2O) δ 0.79 (3 H, t, *J*= 7.2 Hz), 1.24-1.93 (6 H, m), 2.99-3.18 (3 H, m), 4.67 (1 H, br s); ^{13}C nmr (D_2O) δ 62.3, 57.38, 49.95, 35.8, 28.5, 23.5, 18.6, 13.7; $[\alpha]_D^{25}$ +9.24° (MeOH); Anal. Calcd for $C_8H_{18}NOCl$: C, 53.47; H, 10.10; N, 7.80. Found: 53.15; H, 10.08; N, 7.67.

18. Since the diasteroseectivity is not so high, AD using other ligands is under investigation; G. A. Crispino, K.-S. Jeong, H. C. Kolbe, Z.-M. Wang, and K. B. Sharpless, *J. Org. Chem.*, 1993, **58**, 3785.

19. **2**: $[\alpha]^{25}_D$ +67.8° ($CHCl_3$); ^{1}H nmr (300 Mz, $CDCl_3$) δ 0.90 (3H, t, *J*= 7.0 Hz), 1.20-1.99 (10H, m), 2.26 (3H, s), 2.97 (1H, ddd, *J*= 11, 4, 2 Hz), 3.73 (1H, m); ^{13}C nmr ($CDCl_3$) δ 67.2 (CH), 63.6 (CH_2), 62.5 (CH), 42.8 (CH_3), 33.9 (CH_2), 33.2 (CH_2), 28.4 (CH_2), 18.8 (CH_2), 14.5 (CH_3).

20. We beleive this protocol is valuable as substitute for the 6-end-trig cyclization.[14]

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