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Stereoselective syntheses of (+)-α- and (−)-β-conhydrine from L-aspartic acid

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Abstract—An efficient synthesis of (+)-α-conhydrine **1** and (−)-β-conhydrine **2** has been achieved by diastereoselective alkylation of an amino aldehyde derivative **7** with ethylmagnesium bromide or diethylzinc.

Biologically active alkaloids containing a 2-(1-hydroxyalkyl)piperidine unit are abundant in nature.[1] (+)-α-Conhydrine **1** and (−)-β-conhydrine **2**, are two such alkaloids isolated from the seeds and leaves of the poisonous plant *Conium maculatum* L. (Fig. 1).[2] The indolizidine alkaloids such as (−)-castanospermine **3**, (−)-slaframine **4**, and (−)-swainsonine **5** contain a similar structural pattern and are known to exhibit potent glycosidase inhibitor, antiviral, and antitumor properties.[3] Various methods for the synthesis of (+)-α- and (−)-β-conhydrine mainly based on auxiliary-supported or chiral pool approaches have been documented in the literature.[4] We have also recently reported the enantioselective synthesis of (−)-α-conhydrine via cyclic sulfate methodology employing Sharpless asymmetric dihydroxylation as the source of chirality.[5]

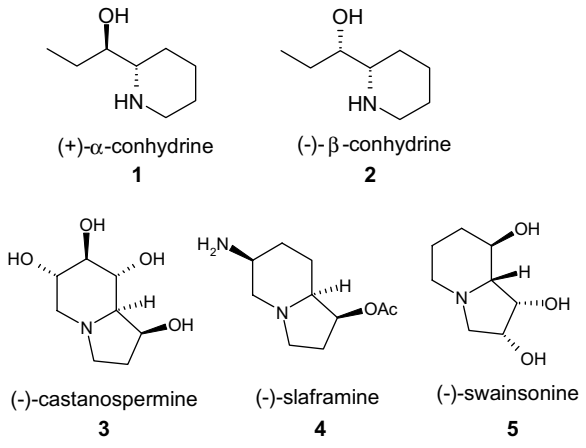

Figure 1.

As part of our research program aimed at developing enantioselective syntheses of naturally occurring amino alcohols[6] and lactones,[7] we became interested in developing a general route capable of providing not only the target molecules **1** and **2** but also their other stereoisomers. Herein, we report a new and convenient synthesis of (+)-α- and (−)-β-conhydrine employing the stereoselective addition of ethylmagnesium bromide or diethylzinc to an aldehyde as the key step.

Our synthetic approach for the synthesis of conhydrine was envisioned via the synthetic route as shown in Scheme 1. The amino aldehyde derivative **7** was visualized as a synthetic intermediate from which both (+)-α- and (−)-β-conhydrine could be synthesized by the stereoselective addition of an organometallic reagent and subsequent synthetic manipulation. The amino aldehyde **7** in turn could be derived from aspartic acid **6** through standard synthetic transformations.

The syntheses of (+)-α-conhydrine **1** and (−)-β-conhydrine **2** started from commercially available L-aspartic acid **6** as illustrated in Scheme 2. L-Aspartic acid **6** was first converted to an amino aldehyde derivative following a literature procedure.[8] The aldehyde **7** was subjected to Grignard reaction with ethylmagnesium bromide to afford the amino alcohol **8a** as a single

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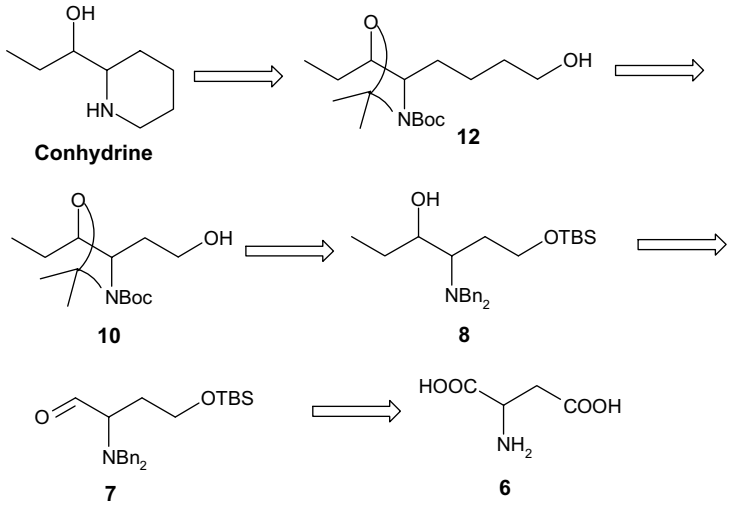
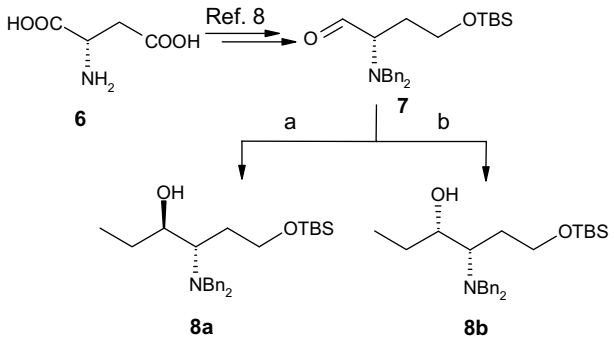


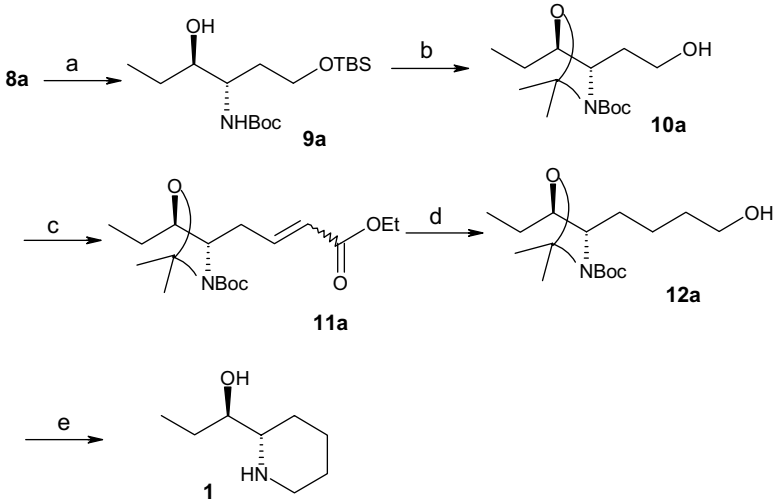
Scheme 1. Retrosynthetic route to conhydrine.



Scheme 2. Reagents and conditions: (a) EtMgBr, dry Et_2O, 0 °C, 2 h, 73%; (b) Et_2Zn, toluene, 0 °C, 8 h, 76%.

diastereomer[9] in 73% yield, $[\alpha]_D^{20}$ +10.9 (*c* 1.0, $CHCl_3$), {lit.[10] $[\alpha]_D^{20}$ +10.7 (*c* 1.0, $CHCl_3$)}. The formation of *anti*-**8a** as a single isomer is in agreement with a non-chelated model.[11] On the contrary, when **7** was treated with diethylzinc, it led to the formation of *syn*-**8b** as a single isomer[9] in 76% yield, $[\alpha]_D^{20}$ +28.2 (*c* 1.0, $CHCl_3$), {lit.[10] $[\alpha]_D^{20}$ +28.3 (*c* 1.0, $CHCl_3$)}. The diastereoselective addition of diethylzinc occurs in favor of the *syn* isomer through a chelated intermediate which is in accordance with a reported observation.[12]

Our next aim was to carry out the two-carbon homologation of **8a** via Wittig reaction. To this end, we first proceeded with protection of the hydroxyl group of **8a** as its benzyl derivative followed by removal of the TBS group to give the corresponding alcohol. The resultant alcohol obtained was then subjected to oxidation under Swern conditions, however, it gave a complex mixture which indicated that the β-amino-γ-hydroxy aldehyde formed during oxidation was unstable due to the dibenzylamino moiety[12] and which decomposed by retro-condensation to the corresponding amine and unsaturated aldehyde.



Scheme 3. Reagents and conditions: (a) $H_2/Pd(OH)_2$, Boc_2O, EtOAc, 12 h, 83%; (b) 2,2-DMP, *p*-TsOH, CH_2Cl_2, 0 °C to rt, 1 h, 87%; (c) (i) $(COCl)_2$, DMSO, dry CH_2Cl_2, −78 °C, Et_3N, −60 °C, 1 h, (ii) $Ph_3P{=}CHCOOEt$, dry THF, rt, 24 h, 96%; (d) $LiAlH_4$, dry THF, rt, 4 h, 78%; (e) (i) MsCl, Et_3N, −78 °C, 1 h, (ii) CF_3COOH, dry DCM, 88%.

Further, in order to achieve the synthesis of target compounds **1** and **2** from **8**, we required a suitable amino protecting group for further synthetic manipulation (Scheme 3). To this end, compound **8a** was subjected to debenzylation by hydrogenation using $Pd(OH)_2$[13] followed by protection of the amino group with $(Boc)_2O$ to afford compound **9a**[14] in 83% yield. The successive protection as the acetonide using 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-TSA and concomitant deprotection of the TBS group afforded **10a** in 87% yield. Compound **10a** was oxidized to the aldehyde by a Swern oxidation,[15] and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane in dry THF at room temperature to furnish the Wittig product **11a** in 96% yield with an *E*:*Z* ratio of 95:5.[16] The olefin and ester reduction of **11a** were carried out in a single step with $LiAlH_4$ to give the corresponding alcohol **12a** in excellent yield which was subjected to cyclization using methanesulfonyl chloride and triethylamine followed by deprotection of the Boc group to furnish (+)-α-conhydrine **1**, $[\alpha]_D^{20}$ +8.9 (*c* 0.85, EtOH), {lit.[4c] $[\alpha]_D^{20}$ +9.0 (*c* 0.85, EtOH)}.

(−)-β-Conhydrine **2** was synthesized from **8b** following an analogous series of reactions as shown in Scheme 3, $[\alpha]_D^{20}$ −34.8 (*c* 0.4, $CHCl_3$), {lit.[4f] $[\alpha]_D^{20}$ −34.1 (*c* 0.4, $CHCl_3$)}. The physical and spectroscopic data of **1** and **2** were in full agreement with the literature data.[4c,f]

In conclusion, practical and stereocontrolled syntheses of (+)-α-conhydrine and (−)-β-conhydrine has been achieved from L-aspartic acid. The synthetic strategy described has significant potential for further extension of the 2-(1-hydroxyalkyl)piperidine unit and to the other isomers, (−)-α-conhydrine and (+)-β-conhydrine. Currently, studies are in progress in this direction.

Acknowledgements

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References and notes

1. Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677–1716.
2. Wertheim, T. *Liebigs Ann. Chem.* **1856**, *100*, 328–330.
3. (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspective*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 5, pp 1–54; (b) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2651–2652; (c) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **1999**, *1*, 1031–1033.
4. (a) Ratovelomanana, V.; Royer, J.; Husson, H. P. *Tetrahedron Lett.* **1985**, *26*, 3803–3806; (b) Masaki, Y.; Imaeda, T.; Nagata, K.; Oda, H.; Ito, A. *Tetrahedron Lett.* **1989**, *30*, 6395–6396; (c) Comins, D. L.; Williams, A. L. *Tetrahedron Lett.* **2000**, *41*, 2839–2842; (d) Guerreiro, P.; Ratevelomanana-Vidal, V.; Genet, J. P. *Chirality* **2000**, *12*, 408–410; (e) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2000**, *41*, 4113–4116; (f) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron* **2001**, *57*, 5393–5401; (g) Enders, D.; Nolte, B.; Raabe, G.; Runsink, J. *Tetrahedron: Asymmetry* **2002**, *13*, 285–291.
5. Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957–1958.
6. (a) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2000**, 3447–3449; (b) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2002**, *43*, 4425–4426; (c) Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2000**, *41*, 10309–10312; (d) Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1035–1037; (e) Gupta, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 4231–4232; (f) Kondekar, N. B.; Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 5477–5479; (g) Pandey, S. K.; Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 5877–5879; (h) Kumar, P.; Bodas, M. S. *J. Org. Chem.* **2005**, *70*, 360–363.
7. (a) Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4797–4802; (b) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2002**, 2921–2923; (c) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 6149–6151; (d) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849–851.
8. (a) Gmeir, P.; Junge, D.; Kartner, A. *J. Org. Chem.* **1994**, *59*, 6766–6776; (b) Oestreich, M.; Frohlich, R.; Hoppe, D. *Tetrahedron Lett.* **1998**, *39*, 1745–1748.
9. The diastereoselectivities of non-chelated **8a** and chelated product **8b** were determined by ^1H NMR spectroscopy and also by comparison with the literature data.
10. Andres, J. M.; Munoz, E. M.; Pedrosa, R.; Perez-Encabo, A. *Eur. J. Org. Chem.* **2003**, 3387–3397.
11. (a) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121–1162; (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531–1546.
12. Andres, J. M.; deElena, N.; Pedrosa, R. *Tetrahedron* **2000**, *56*, 1523–1531.
13. Yoshida, K.; Nakajima, S.; Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Heterocycles* **1988**, *27*, 1167–1168.
14. Spectral data of compound **9a**: $[\alpha]_D^{20}$ +12.98 (*c* 1.0, $CHCl_3$), IR (neat): ν_{max} 3443, 3412, 2931, 1694, 1673, 1394, 1174 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 6H), 0.91 (s, 9H), 0.98 (t, *J* = 7.3, 3H), 1.44 (s, 9H), 1.48–1.55 (m, 2H), 1.70 (br s, 1H) 1.73–1.81 (m, 2H), 3.46–3.57 (m, 2H), 3.73 (t, *J* = 5.9, 2H), 5.34 (d, *J* = 7.3, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.7, 10.3, 18.0, 25.7, 26.5, 28.2, 31.4, 53.2, 59.9, 75.3, 79.0, 155.9. Anal. Calcd for $C_{17}H_{37}NO_4Si$ (347.57): C, 58.75; H, 10.73; N, 4.03. Found: C, 58.80; H, 10.71; N, 4.00.
15. For reviews on the Swern oxidation, see: (a) Tidwell, T. T. *Synthesis* **1990**, 857; (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.
16. The *E*:*Z* ratio of compound **11a** was determined from the ^1H NMR spectrum.