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Enantioselective synthesis of (−)-α-conhydrine via cyclic sulfate methodology

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Abstract—An asymmetric synthesis of (−)-α-conhydrine is described using the Sharpless asymmetric dihydroxylation and the regiospecific nucleophilic opening of a cyclic sulfate as the key steps.

Alkaloid mimics with a nitrogen in the ring, including naturally occurring and synthetic monocyclic and bicyclic derivatives, constitute a realm of important functional molecules which have drawn considerable attention by virtue of their potent and varied biological activities.[1] Conhydrine is one of the poisonous alkaloids of the hemlock, *Conium maculatum* whose extracts were used in the ancient Greece for the execution of criminals.[2] Various methods for the synthesis of α- and β-conhydrine (Fig. 1) have been documented in the literature. While a number of auxiliary-supported syntheses or chiral pool approaches have been reported for unnatural β-conhydrine,[3] less attention has been paid to the enantioselective synthesis of α-conhydrine. Recently, the structural assignment of (−)-α-conhydrine and its first asymmetric synthesis based on RAMP/SAMP hydrazone methodology were reported.[4] Surprisingly, there has been no report in the literature about the asymmetric synthesis of conhydrine employing the Sharpless asymmetric dihydroxylation procedure. As part of our research program aimed at developing enantioselective syntheses of naturally occurring lactones[5a,b] and amino alcohols,[5c–f] the Sharpless asymmetric dihydroxylation and subsequent transformation of the diols formed via cyclic sulfites/sulfates were envisioned as powerful tools offering considerable opportunities for synthetic manipulations. Herein we report a new and highly enantioselective synthesis of (−)-α-conhydrine employing the Sharpless asymmetric dihydroxylation as the source of chirality.

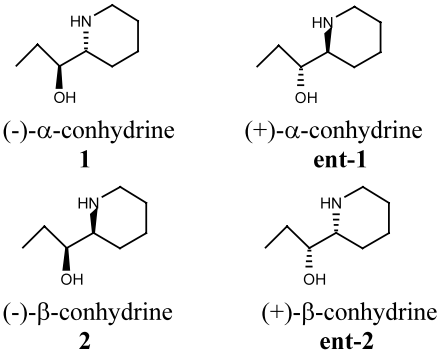

Figure 1.

The synthesis of (−)-α-conhydrine **1** commences from propionaldehyde **3**, a readily available starting material as illustrated in Scheme 1. Thus, treatment of **3** with (methoxycarbonylmethylene)triphenylphosphorane in benzene under reflux conditions gave the Wittig product **4** in 85% yield. The dihydroxylation of **4** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ as chiral ligand under the Sharpless asymmetric dihydroxylation (SAD) conditions[6] gave the diol **5** in 88% yield with 95% ee, having $[\alpha]_D^{20}$ −5.5 (*c* 1.0, $CHCl_3$) [lit.[7] $[\alpha]_D^{20}$ −5.9 (*c* 0.35, $CHCl_3$)]. The diol **5** was then treated with thionyl chloride and triethylamine to give the cyclic sulfite which was further oxidized using $NaIO_4$ and a catalytic amount of ruthenium trichloride to furnish the corresponding cyclic sulfate **6**[8] in excellent yield. The essential feature of our synthetic strategy shown in Scheme 1 was based on the presumption that the nucleophilic opening of the cyclic sulfate **6** would occur in a regiospecific manner at the α-carbon atom.

Indeed the cyclic sulfate **6** reacted with NaN_3 with apparent complete selectivity for attack at the C-2,

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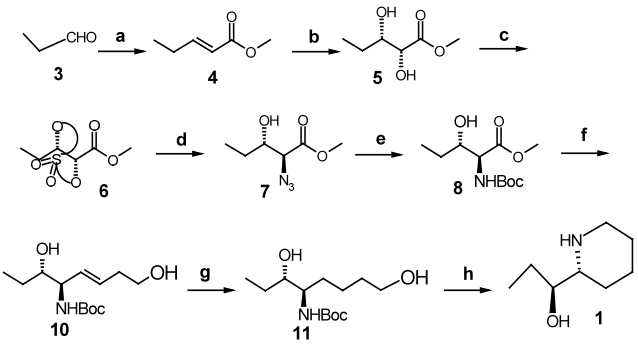

Scheme 1. *Reagents and conditions*: (a) $Ph_3P{=}CHCOOMe$, benzene, reflux, 2 h, 85%; (b) $(DHQ)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 24 h, 0°C, 88%; (c) (i) $SOCl_2$, Et_3N, 15 min, (ii) $RuCl_3/NaIO_4$, 1 h, 88%; (d) NaN_3, acetone, 1 h, 20% aq. H_2SO_4, ether, 10 h, 78%; (e) Boc_2O, Pd/C, H_2, EtOAc, 6 h, 98%; (f) (i) DIBAL-H, −78°C, 1 h, (ii) *n*-BuLi, $^{-}BrPh_3P^{+}(CH_2)_3OH$ **9**, −78°C, 40%; (g) Pd/C, H_2, MeOH, 4 h, 95%; (h) (i) MsCl, Et_3N, −78°C, 1 h; (ii) CF_3COOH, CH_2Cl_2, 74%.

α-position, to furnish the azido alcohol **7** in 78% yield. The carbonyl group must be responsible for the increased reactivity of the α-position.[9] Reduction of the azide under hydrogenation conditions in the presence of Boc_2O gave the Boc protected amino alcohol **8** which on reduction with DIBAL-H to the corresponding aldehyde and subsequent Wittig reaction with phosphonium salt **9**[10] afforded the olefin **10** in moderate yield. The olefin reduction by hydrogenation using Pd/C gave **11** which was subjected to cyclization using methanesulfonyl chloride and triethylamine followed by deprotection of the Boc group to furnish (−)-α-conhydrine **1** having $[\alpha]_D^{20}$ −8.9 (*c* 1.0, ethanol) [lit.[4] $[\alpha]_D^{20}$ −8.6, ethanol]. The physical and spectroscopic data of **1** are in full agreement with the literature data.[4] Similarly, the synthesis of the other isomer (+)-α-conhydrine can be achieved simply by changing the ligand in the SAD step.

In conclusion, we have demonstrated that the enantioselective synthesis of (−)-α-conhydrine can be accomplished by the Sharpless asymmetric dihydroxylation and regiospecific nucleophilic opening of the corresponding cyclic sulfate. To the best of our knowledge, this is the first asymmetric synthesis of (−)-α-conhydrine using Sharpless asymmetric dihydroxylation as the source of chirality. The synthetic strategy described has significant potential for further extension to the synthesis of β-conhydrine and its enantiomer by employing the double inversion concept. Currently studies are in progress in this direction.

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