An enantioselective synthesis of (+)-hygroline and (+)-pseudohygroline *via* Keck allylation and CBS reduction

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Graphical Abstract

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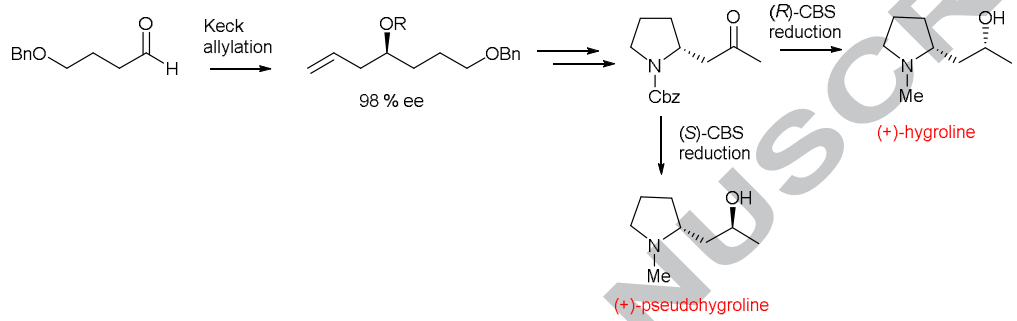

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An enantioselective synthesis of (+)-hygroline and (+)-pseudohygroline *via* Keck allylation and CBS reduction

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ABSTRACT

An enantioselective synthesis of (+)-hygroline and (+)-pseudohygroline have been achieved in high optical purity (98% *ee*) from readily available 1,4-butanediol. The synthesis strategy employs a Keck allylation, CBS reduction and Wacker oxidation.

Introduction

Nitrogen containing heterocycles is extensively studied systems present in natural products and pharmaceutical intermediates. The pyrrolidine ring is widespread in alkaloid natural products and is a common subunit found in several drugs and therapeutic lead compounds.[1] Selected examples include (+)-hygroline (**1**) and (+)-pseudohygroline (**2**) Figure **1**.

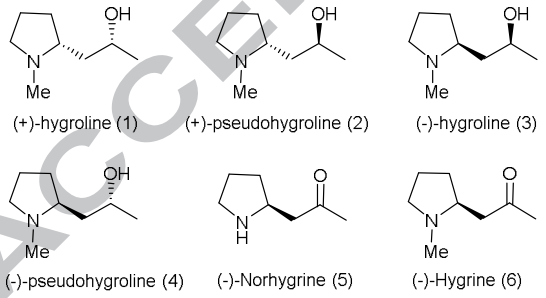

Figure 1. Structures of 2-substituted pyrrolidine

Often 2-substituted pyrrolidines containing 1,3-amino alcohol units display a wide spectrum of biological activities.[2] Hygroline and pseudohygroline were isolated from plant extract of *Carallia brachiata, Erythroxylon coca and Schizanthus hookeri*[3] and both are biosynthetic precursors for the tropane skeleton.[4] Considering its potent biological activity and fascinating structural features, several synthesis of (+)-hygroline (**1**) and (+)-pseudohygroline (**2**) have been reported[5] and the majority of these syntheses is initiated from chiral pool resources[6] and its asymmetric synthesis is rather rare, involving multistep synthesis.[7] As a part of our research program aimed at enantioselective synthesis of biologically active natural products[8] herein, we report an enantioselective synthesis of (+)-hygroline (**1**) and (+)-pseudohygroline (**2**) employing Keck allylation and CBS reductions.

Results and Discussion

Our approach to synthesis of (+)-hygroline (**1**) commenced with the preparation of alcohol **8** in 88% yield by the mono benzyl protection of 1,4-butanediol **7** with benzyl bromide and sodium hydride in dimethyl formamide (Scheme **1**). The terminal hydroxyl group of alcohol **8** was oxidized using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and bis(acetoxy)iodo-benzene (BAIB) in CH_2Cl_2 gave rise to corresponding aldehyde **9** in 93% yield. The aldehyde **9** was then subjected to Keck allylation protocol[9] [(*R*)-BINOL, Ti(O-^{i}Pr)$_4$, (5 mol%), allyl tributyl tin, dichloromethane (CH_2Cl_2), -20 °C] which furnishes homoallylic alcohol **10** in 86% yield and 98% *ee*, $[\alpha]^{25}_D$ = -7.4 (*c*1, $CHCl_3$). The homo allylic alcohol **10** was converted into its mesylate **11** using MsCl and NEt_3 in dichloromethane (CH_2Cl_2), which was further subjected to S_N2 displacement with sodium azide (NaN_3) in DMF afforded azide **12**. Deprotection of benzyl ether in **12** with DDQ afforded alcohol **13** which was readily

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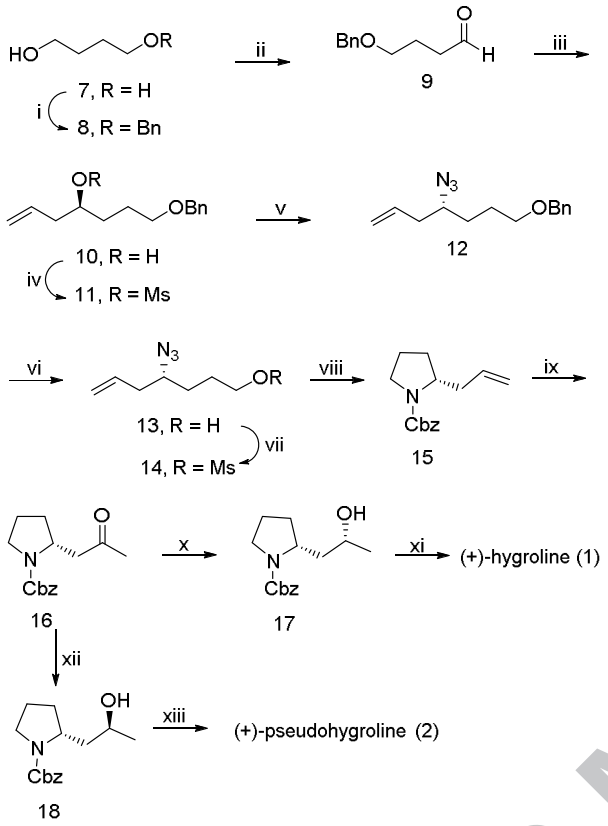
converted into its mesylate **14**. We next sought to prepared pyrrolidine core unit for which the azide functionality in **14** was reduced using Staudinger condition (PPh_3, THF/H_2O) to give free amine, which underwent subsequent intramolecular cyclization,



Scheme 1. Reaction conditions: (i) BnBr, NaH, DMF, 0 °C, 2 h, 88%; (ii) TEMPO, BAIB, CH_2Cl_2, 0 °C, 1 h, 93%; (iii) (*R*)-BINOL, $Ti(OiPr)_4$, allyltributyltin, 4 A° MS, CH_2Cl_2, -20 °C, 24 h, 86%; (iv) MsCl, TEA, CH_2Cl_2, 0 °C, 1 h; (v) NaN_3, DMF, 80 °C, 4 h, 74% (over two steps); (vi) DDQ, H_2O, CH_2Cl_2, 25 °C, 28 h, 95%; (vii) MsCl, TEA, 0 °C, 1 h, 99.5%; (viii) PPh_3, THF, H_2O, 45 °C, 24 h, Cbz-Cl, TEA, CH_2Cl_2, 8 h, 63%; (ix) $PdCl_2$ (10 mol%), CuCl (10 mol%), DMF:H_2O, O_2, 25 °C, 3 h, 76%; (x) (*R*)-CBS Catalyst, BH_3.THF, THF, 25 °C, 30 min, 75%; (xi) $LiAlH_4$, THF, 60 °C, 8 h, 87%; (xii) (*S*)-CBS Catalyst, BH_3.THF, THF, 25 °C, 30 min, 75%; (xiii) $LiAlH_4$, THF, 60 °C, 8 h, 88.8%.

to give pyrrolidine core unit. Followed by *in situ* Cbz-protection of the corresponding cyclic amine to furnishes carbamate derivative **15**. Wacker oxidation[10] [$PdCl_2$ (5 mol%), CuCl (10 mol%), DMF:H_2O] of terminal alkene **15** afforded methyl ketone **16** which was further reduced diastereoselectively using (*R*)-CBS reduction[11] [CBS (10 mol%), BH_3.THF (0.6 mol%), THF] to give secondary alcohol **17** in 75% yield and diastereomeric excess > 23:1. Finally the conversion of *N*-Cbz group in **17** to *N*-methyl group using $LiAlH_4$ to give a target molecule (+)-hygroline (**1**)[5c] in 87% yield with overall yield of 15.4% and high diastereomeric excess in eleven steps (Scheme **1**). Similarly distereoselective reduction of ketone **16** with (*S*)-CBS catalyst[11] to give alcohol **18** in 75% yield and *N*-Cbz group of **18** was converted to *N*-methyl using $LiAlH_4$ to afford (+)-pseudohygroline (**2**) in 88.8% yield with overall yield 15.7% (Scheme **1**).[5c] The ^1H and ^{13}C NMR and other spectral data of compound **1** and **2** were in complete agreement with the values reported in literature[5j]

Conclusion

In conclusion a straightforward enantioselective synthesis of (+)-hygroline (**1**) and (+)-pseudohygroline (**2**) has been achieved with good overall yield and high optical purity. The key reaction employed was asymmetric Keck allylation of aldehyde and diastereoselective CBS reduction of methyl ketone to introduce chirality. The synthetic strategy described here has significant potential for the synthesis of variety of other biologically important pyrrolidine alkaloids.

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Supplementary Material

Supplementary data associated with this article can be found in the online version.