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Synthesis of (−)-hygrine, (−)-norhygrine, (−)-pseudohygroline and (−)-hygroline via Nef reaction

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ABSTRACT

Synthesis of tropane alkaloids (−)-hygrine, (−)-norhygrine and sedum alkaloids (−)-pseudohygroline and (−)-hygroline is described from L-proline via Henry and Nef reactions.

The pyrrolidine members of tropane alkaloids[1a–h] and of sedum alkaloids[1i,j] have been the target of synthesis due to their intriguing biological activities, hallucinogenic characteristics and their utility as pharmacological probes. The representative members of these families include ketone derivatives hygrine **1** and norhygrine **2** which differ only in the substituent on pyrrolidine nitrogen atom and pseudohygroline **3** and hygroline **4** which differ in the stereochemistry of the secondary alcoholic group. The other examples include pyrrolsedamine **5**, pyrrolallosedamine **6**, ruspolinone **7** and cuscohygrine **8**, a bispyrrolidine alkaloid (Fig. 1).

Hygrine **1**, which serves as a biosynthetic precursor for the tropane skeleton, is isolated from several plants[2] and appears to have no detectable optical activity when isolated. (±)-Hygrine was resolved with D-(+)-tartarate to give diastereomeric purity of maximum 80% after several crystallizations. The absolute configurations[1a] of (+)-hygrine and (−)-hygrine were determined by the relative correlations with those of D-proline and L-proline. Later, Park & co-workers confirmed the absolute configuration of (+)-hygrine as '*R*' by its first asymmetric synthesis.[3] The compound norhygrine **2** is found to co-occur with hygrine **1**. Hygroline **3** and pseudohygroline **4** were isolated from *Carallia brachiata*,[4a] *Erythroxylon coca*[4b] and *Schizanthus hookeri*.[4c]

There are seven reports on the synthesis of (±)-hygrine,[5a–g] including the shortest synthesis by Klussmann and co-workers by a direct oxidative coupling using vanadium acetate and L-proline.[5f] Among the chiral syntheses, the first one is by Park and co-workers based on asymmetric phase transfer alkylation,[3] the second is by Arévalo-Garcia and Colmenares from D-proline,[6a] the third and the last is from our own laboratory starting from L-proline using regioselective Wacker oxidation.[6b] This report also includes the first synthesis of (−)-norhygrine.

Pseudohygroline **3** and hygroline **4** have been synthesized by Takahata et al. using Sharpless asymmetric dihydroxylation[7a] and by Knight and Salter via reverse Cope elimination.[7b] The synthesis of hygroline **4** is reported by Murahashi et al. using [1,3]-dipolar cycloaddition of cyclic nitrones to crotonic acid derivatives bearing chiral auxilliaries[7c] and by Louis and Hootelé using asymmetric nitro-vinyl sulfoxide cycloadditions.[7d] Vanucci-Bacqué et al. have achieved the synthesis of **4** by the condensation of (*S*)-phenylglycinol with oxo alkynones.[7e] Pseudohygroline **3** is synthesized by Enierga et.al. using intramolecular oxymercuration.[7f] Recently Davies et al. have synthesized pseudohygroline **3** through a diastereoselective lithium amide conjugate addition,[7g] while Yadav et al. have approached it through stereoselective Prins cyclisation.[7h]

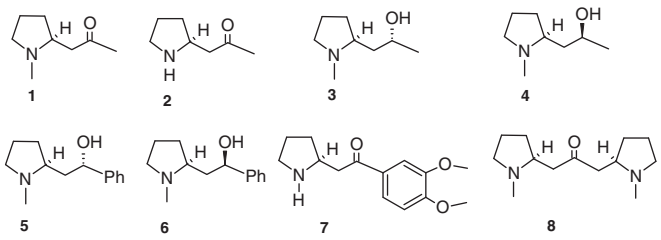

Figure 1. Selected natural pyrrolidine alkaloids.

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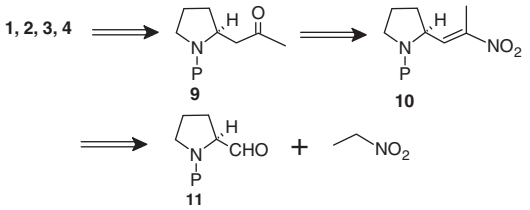
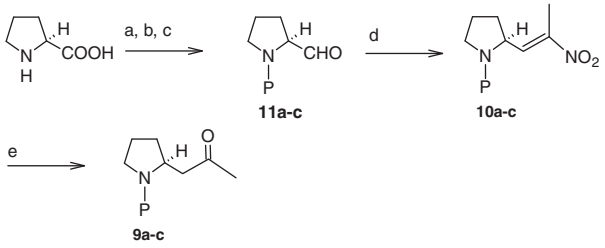


Scheme 1. Retrosynthetic analysis.

Our continuing interest in the synthesis of small molecules[8a–e] prompted us to devise the synthesis of these alkaloids via Henry and Nef reactions. The versatility of the nitro group to be manipulated to carbonyl functionality is well demonstrated[9a–d] in the literature. Our retro synthetic approach is shown in Scheme 1. The required alkaloids could be approached via functional group manipulation of the N-protected pyrrolidine ketone **9**, which in turn can be obtained from the unsaturated nitro compound **10** via Nef reaction. The compound **10** could be realized via Henry reaction between N-protected prolinal and nitroethane. Thus, we started our synthesis from the cheaply available L-proline (Scheme 2). L-Proline was reduced with LAH followed by protection of nitrogen with suitable protecting groups. The Swern oxidation of the prolinols gave N-protected prolinal **11** in a quantitative yield. The Henry reaction with nitroethane gave the corresponding nitro alcohols as diastereomeric mixtures which as such were converted to unsaturated nitro compounds **10**. Of the different methods[9b] tried for Nef reaction, $NaBH_4/MeOH/H_2O_2$ method[9a] worked well in our hands to give moderate yields of the keto pyrrolidines **9a–c**.

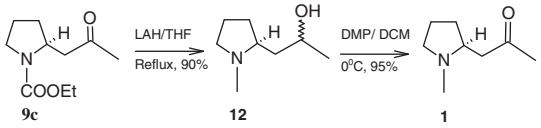
Having obtained the key intermediate **9** through Nef reaction, we proceeded on to the synthesis of alkaloids **1**–**4**. For the synthesis of alkaloid (−)-hygrine **1**, we reduced **9c** (Scheme 3) with LAH to give a mixture of diastereomers of the corresponding *N*-methyl alcohol **12** in 90% yield. The substrate **9c** was preferred to **9a** and **9b** for the reduction, as latter would have given the side products benzyl alcohol and *tert*-butanol which would have required an additional purification step. The alcohol **12** was then oxidized with Dess-Martin periodinane (DMP) to give (−)-hygrine **1** in 95% yield. The optical activity of our synthetic (−)-hygrine. HCl matched very well with the literature values. $[\alpha]_D^{30}$ −33.2 (*c* 0.2, H_2O); Lit.[3] $[\alpha]_D^{30}$ +34.5 (*c* 0.5, H_2O) for *R* isomer; Lit.[6b] $[\alpha]_D^{30}$ −32.1 (*c* 0.25, H_2O) for *S* isomer.

Synthesis of (−)-norhygrine was achieved in a straightforward manner (Scheme 4) by selective hydrogenolysis of **9a** without

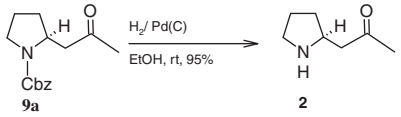


9, 10, 11 **a**, P= -Cbz,
b, P= -Boc
c, P= -COOEt

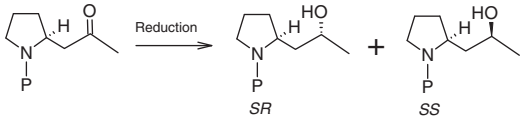
Scheme 2. General synthetic route from L-proline. Reagents and conditions: (a) LAH, THF, reflux, 8 h, 90%; (b) For P = –Cbz: Cbz–Cl, K_2CO_3, CH_3CN, 0 °C, 6 h, 95%; For P = –Boc: $(Boc)_2O$, Et_3N, DCM, 0 °C, 95%; For P = –COOEt: ClCOOEt, K_2CO_3, CH_3CN, 0 °C, 90%; (c) $COCl_2$, DMSO, Et_3N, DCM, −78 °C, 95%; (d) (i) $CH_3CH_2NO_2$, 2 mL of 3 N KOH, two drops of conc. H_2SO_4; (ii) $MeSO_2Cl$, Et_3N, DCM, (85%, two steps); (e) $NaBH_4$, MeOH, K_2CO_3, H_2O_2, rt. 18 h (P = –Cbz, 65%; P = –Boc, 56%; P = –COOEt, 56%).



Scheme 3. Synthesis of (−)-hygrine.



Scheme 4. Synthesis of (−)-norhygrine.



9 **13a**, P=-Cbz; **b**, P=-Boc; **c**, P=-COOEt **14a**, P=-Cbz; **b**, P=-Boc; **c**, P=-COOEt

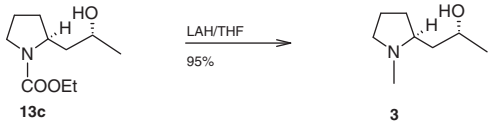
Reducing Agents	P=-Cbz	P=-Boc	P=-COOEt
$Li(t\text{-}OBu)_3AlH$	91.57 : 8.43	98.62 : 1.38	80.88 : 19.12
$Zn(BH_4)_2$	44.69 : 55.31	**14.68 : 85.32**	53.50 : 46.50
$NaBH_4$	50.16 : 49.86	78.90 : 21.10	57.47 : 42.53

: - *diastereomeric ratio* of **13**:**14** was determined by HPLC using kromasil column, Flow rate 1mL/min, eluent 10% IPA + *n*-hexane

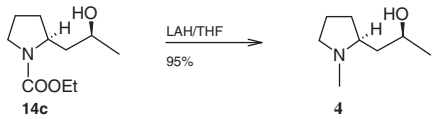
Scheme 5. Diastereoselective reduction of carbonyls.

the reduction of keto group. $[\alpha]_D^{30}$ −30.2 (*c* 0.2, $CHCl_3$); Lit.[6a] $[\alpha]_D^{33}$ −29.6 (*c* 0.14, $CHCl_3$).

For the synthesis of sedum alkaloids (−)-pseudohygroline **3** and (−)-hygroline **4** which differ in their hydroxyl configuration, we probed the selective reduction of **9a–c** with different reducing agents (Scheme 5). Results of these studies show that there is very little diastereoselectivity protecting groups for the ethoxycarbonyl and benzyloxycarbonyl when $NaBH_4$ was used as a reducing agent, while when the *tert*-butoxycarbonyl is the protecting group there was 80% *cis* (*SR*) diastereoselectivity. The *cis* (*SR*) diastereoselectivity is found to increase for all the protecting groups when bulky lithium tri-*tert*-butoxyaluminium hydride was used, the maximum (98%) being for the *tert*-butoxy protecting group. Interestingly, *trans* (*SS*) selectivity of 85% was observed for the *tert*-butoxy protected **9** when $Zn(BH_4)_2$ was used as the reducing agent. The *tert*-butoxycarbonyl group shows a better discrimination for diastereoselective reduction with bulky reducing agent $Li(t\text{-}OBu)_3AlH$ giving maximum *syn* (*SR*) diastereoselectivity while with $Zn(BH_4)_2$, it gave maximum *trans* (*SS*) diastereoselectivity. The normally difficult *trans (SS)* selectivity obtained by $Zn(BH_4)_2$ is noteworthy.[7g,10] For the synthesis of pure (−)-pseudohygroline **3**, the



Scheme 6. Synthesis of (−)-pseudohygroline.



Scheme 7. Synthesis of (−)-hygroline.

cis (*SR*) diastereomer **13c** was reduced with LAH (Scheme 6) and the *trans* (*SS*) **14c** for (−)-hygroline **4** (Scheme 7). The optical rotation of our synthetic products matched well with the literature values. For (−)-pseudohygroline $[\alpha]_D^{28}$ −90 (*c* 0.2, EtOH; Lit.[7f] α_D +70.7 (*c* 2.0, EtOH); Lit.[7a] $[\alpha]_D^{25}$ +97.0° (*c* 3.4, EtOH) for *RS* isomer; for (−)-hygroline, $[\alpha]_D^{23}$ −50 (*c* 0.2, EtOH); Lit.[7a] $[\alpha]_D^{20}$ −50.2 (*c* 0.466, EtOH), Lit.[7a] $[\alpha]_D^{22}$ −49 (*c* 0.4, EtOH).

In summary, tropane alkaloids (−)-hygrine, (−)-norhygrine and sedum alkaloids (−)-pseudohygroline and (−)-hygroline have been synthesized successfully from L-proline via Henry and Nef reactions. The *trans* (*SS*) diastereoselectivity observed for the reduction of *tert*-butyl-(2*S*)-2-(2-oxopropyl)pyrrolidine-1-carboxylate **9b** using $Zn(BH_4)_2$ is noteworthy. Further application of this methodology for the synthesis of piperidine alkaloids is underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.118.

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