# Anionic cyclization approach toward perhydroindoles. Total synthesis of montanine-type *Amaryllidaceae* alkaloids\*

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*Abstract:* Hexahydro-1*H*-indol-3-one can be used as a building block for alkaloid synthesis. Radical and anionic cyclization approaches toward this useful structure were developed. Approaches toward total synthesis of montanine-type *Amaryllidaceae* alkaloids using hexahydro-1*H*-indol-3-one as a key intermediate were studied.

Hexahydro-1*H*-indol-3-one **1** [1], containing an enone moiety, can serve as a versatile intermediate for total synthesis of alkaloids of several different classes, (e.g., (-)-brunsvigine **2** [2] and (-)-stenine **3** [3]). We envisage that compound **1** could be subjected to oxidation, ozonolysis, alkylation, 1,2- and 1,4-additions in further transformations, as shown in Scheme 1.



### Scheme 1

We started our investigation with the development of an efficient method for synthesis of hexahydro-1*H*-indol-3-one skeleton. We are interested in a general approach based on either the radical [4] or anionic [5] cyclization, as shown in Scheme 2, because it would be versatile and adaptable to asym-

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metric synthesis. In principle, asymmetric reduction of 2-iodocyclohexen-1-one (9) would afford the chiral allylic alcohol (R)-8 or (S)-8, which could be converted to chiral hexahydroindolone (S)-1 or (R)-1 respectively (Scheme 3).



Scheme 2



### Scheme 3

We first studied the radical cyclization approach (Scheme 4). The precursor **11** for the radical cyclization was prepared from iodo compound **8**. We found that the radical cyclization of **11**, followed by protection of NH group, afforded *exo*-cyclic diene **12** in good yield. However, ozonolysis of **12** gave hexahydroindolone **13** only in 45% yield.



### Scheme 4

We then turned our attention toward anionic cyclization. Iodo compound 14 was prepared from 8 using a Mitsunobu protocol. Metallation of compound 14 with *n*-butyllithium, followed by anioic cyclization, afforded hexahydroindolone 15 in good yield (Scheme 5).



Scheme 5

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Therefore, we conceived a Friedel–Crafts cyclization approach [6] (17 to 16) toward total synthesis of montanine-type Amaryllidaceae alkaloids. The key intermediate 17 would be synthesized via the anionic cyclization (Scheme 6).



Scheme 6

### Scheme 7

Our experimental results toward the realization of this approach are depicted in Scheme 7. Compound 22, prepared from 20, was treated with *n*-butyllithium followed by acidic workup to give compound 23. Friedel–Crafts-type cyclization of 23 was effected with trifluoromethanesulfonic acid to afford montanine-type alkaloid skeleton 24. Furthermore, an alternative approach toward total synthesis of montanine-type alkaloids (i.e., (-)-pancracine and (-)-brunsvigine), based on Pictet–Spengler cyclization [7] is currently under investigation in our laboratory.

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