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.

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).

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.

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 anionic cyclization, afforded hexahydroindolone 15 in good yield (Scheme 5).
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).

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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REFERENCES


