

Synthetic Studies of Alkaloids Containing Pyrrolidine and Piperidine Structural Motifs

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Synthesis of Pyrrolidine and Piperidine Alkaloids

Our molecules of interest were mainly 2-substituted pyrrolidine and piperidine alkaloids containing 1, 3-aminoketone and 1, 3-aminoalcohol units which are of special synthetic interest (Figure 1). Hygrine and norhygrine belong to the class of tropane alkaloids. The rest of the alkaloids are isolated from 60 species of the genus *Sedum* and are usually referred as *Sedum* alkaloids which are of immense interest due to their memory-enhancing properties and application as anti-Alzheimer agents. These species have now become more important to industry due to their vast pharmaceutical applications. Our method involves "chiral pool" strategies, wherein the starting material can easily be accessed from the naturally available sources like amino acids. Though such a method requires a lot of synthetic maneuvering, it still is the best bet for chiral integrity and suitability for industrial applications.

Commercially available L-proline and L-pipecolic acid, with one existing chiral center, were found to be appropriate chiral sources to access these pyrrolidine and piperidine alkaloids respectively. We developed a Henry–Nef protocol in order to synthesize the key intermediates leading to the total synthesis of these natural products. The Henry–Nef protocol involves two major synthetic steps: the formation of the nitro functionality from carbonyls and the successive transformation to the next carbonyl unit mainly by oxidative or reductive methods. Even though this method is well documented in the literature, surprisingly, it is not well explored for synthetic applications, which got our attention. The

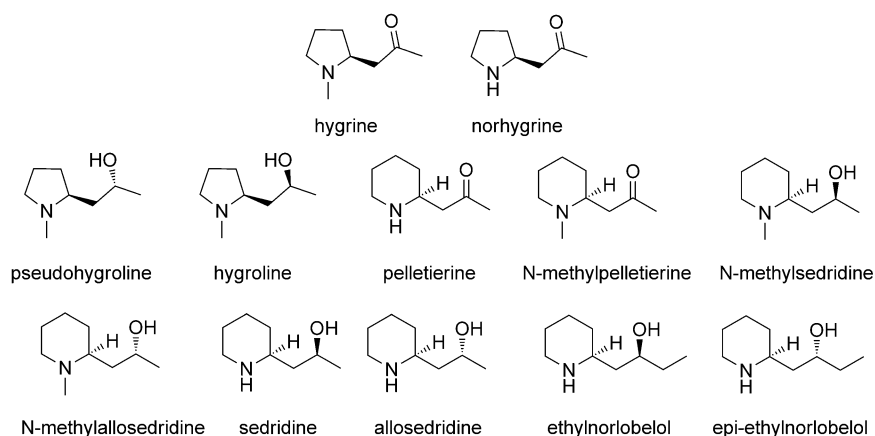


Figure 1. 2-Substituted pyrrolidine and piperidine alkaloids.

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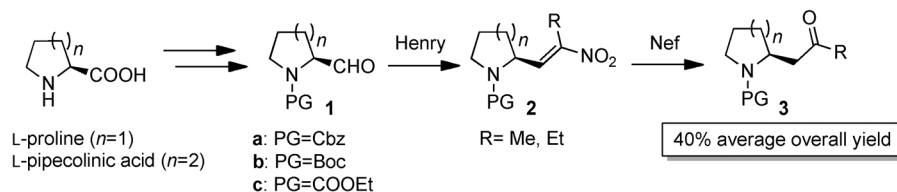
The full thesis is available as Supporting Information on the WWW under <http://dx.doi.org/10.1002/open.201402128>.



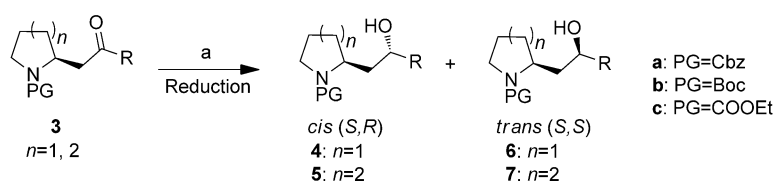
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general synthetic route is shown in Scheme 1. The carbonyl intermediates obtained via Henry–Nef reaction were further subjected to diastereoselective reduction to afford aminoalcohols using different reducing agents (Scheme 2).

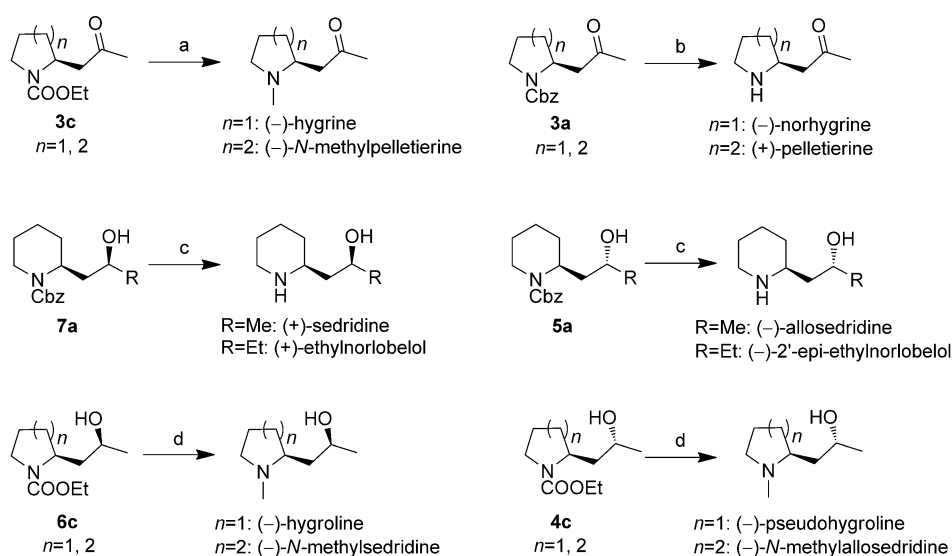


Scheme 1. General method of synthesis.



Scheme 2. Diastereoselective reduction. *Reagents and conditions:* a) Reducing agents: $\text{Li}(\text{O}t\text{Bu})_3\text{AlH}$, NaBH_4 , or ZnBH_4 .

It was observed that, in all the cases the isomer 4 (5) was preferentially formed over 6 (7) except in one case with pyrrolidine carbonyl and $\text{Zn}(\text{BH}_4)_2$ as a reducing agent where 6b was formed diastereoselectively over 4b. The synthesis of all the target natural products was then accomplished following the synthetic Scheme 3.



Scheme 3. Total synthesis of alkaloids. *Reagents and conditions:* a) 1) LiAlH_4 , THF, reflux, 2) Dess–Martin periodinane (DMP), CH_2Cl_2 , rt, 95% ($n=1$), 60% ($n=2$); b) H_2 , Pd/C, EtOH, rt, 81% ($n=1$), 70% ($n=3$); c) H_2 , Pd/C, EtOH, rt, 95% (R=Me), 95% (R=Et); d) LiAlH_4 , THF, reflux, 95% ($n=1$), 90% ($n=2$).

Approaches to Allokainic Acid and Kainic Acid

We next investigated novel and rapid synthetic methods for the formal synthesis of very important kainoids; allokainic acid and kainic acid (Figure 2). We developed two domino and one “one pot” process for the synthesis of the pyrrolidone precursor of allokainic acid. Allokainic acid was first isolated along with its C-4 epimer kainic acid from Japanese marine sponge *Digenea simplex* AG17 in 1953. Over the

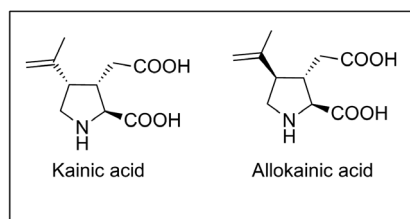
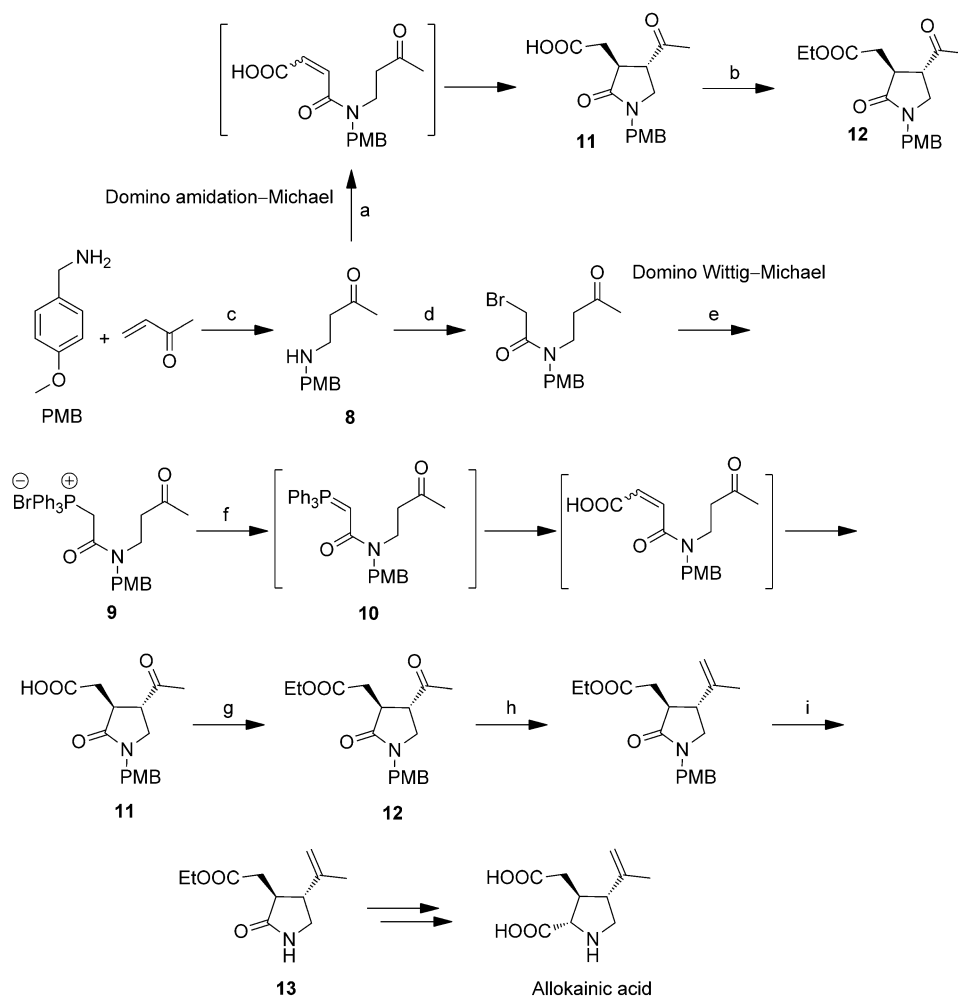


Figure 2. Important members of the kainoid family.

last few decades several kainoids have interested synthetic chemists due to their powerful neuroexcitatory activity in the central nervous system (CNS). A highly functionalized trisubstituted pyrrolidine ring with three contiguous stereogenic centers and global deficiency of these compounds are other factors which make the synthesis of these molecules challenging.

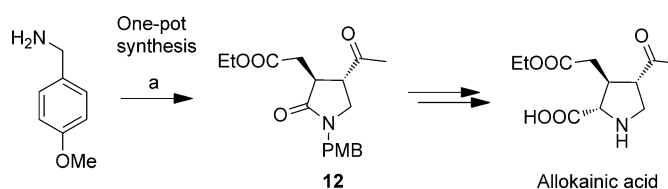
We developed two tandem methods and one 'one-pot' strategy for the synthesis of the key intermediate of allokainic acid. The tandem strategies involved the synthesis of secondary amine **8** from *p*-methoxybenzylamine (PMB) and methyl vinyl ketone (MVK). In the first strategy the secondary amine **8** was converted to the key Wittig salt **9**. When all our attempts to isolate the phosphorane **10** was unsuccessful, we thought of carrying out the Wittig reaction in situ. Thus it was directly condensed with glyoxalic acid in the presence of excess Et₃N by heating in toluene. We observed the formation of cyclic acid **11** in 60% yield after spectroscopic characterization. It was subsequently transformed to ester **13** which is a useful building block for allokainic acid (Scheme 4).



Scheme 4. Domino approaches to allokainic acid. Reagents and conditions: a) Maleic anhydride, toluene, reflux, 92% (**11**); b) SOCl₂, EtOH, rt, 95%; c) THF, rt; d) ClCOCH₂Br, Et₃N, H₂O/CHCl₃ (4:1), rt, 80%; e) PPh₃, toluene, rt, 90%; f) CHO-COOH, Et₃N, toluene, 80 °C, 60% (**11**); g) SOCl₂, EtOH, rt, 90%; h) BrPPh₃CH₃, *n*-BuLi, THF, 0 °C, 60%; i) (NH₄)₂Ce(NO₃)₆, EtOH, rt, 75%.

In another route, the secondary amine **8** was directly condensed with maleic anhydride by refluxing in toluene. The acid **11** was obtained and converted to ester **12**, which can be converted to the key intermediate **13** (Scheme 4).

The methodology was further simplified by achieving the entire sequence in a one-pot manner. The starting materials, PMB and MVK, were mixed in ethanol and stirred for few minutes. Maleic anhydride was then added and stirred for about 30 min followed by the addition of thionyl chloride. The intermediate **12** was isolated in 95 % yield and could be transformed to **13**, the precursor for allokainic acid (Scheme 5).



Scheme 5. One-pot approach to allokainic acid. Reagents and conditions: a) 1) Methyl vinyl ketone, EtOH, rt, 2) maleic anhydride, 3) SOCl₂, rt, 95%.

Diastereoselective Routes to Dexoxadrol, Epidexoxadrol, Conhydrine, and Lentiginosine

In continuation of the asymmetric synthesis of natural products, we undertook the synthesis of a very important *N*-methyl-D-aspartate (NMDA) receptor antagonist, dexoxadrol, which was first synthesized by Hardie et al. in 1960 as an anesthetic drug along with etoxadrol. The subsequent clinical trials revealed that these compounds are efficient NMDA receptor antagonists by binding with 1-(1-phenylcyclohexyl)piperidine (PCP) sites and are found to be more efficient than the available drugs memantine and amantadine (Figure 3). The detailed study on the biological behavior of these molecules showed that the presence of a secondary amine, piperidine ring, five-membered oxygenated ring, and the (*S,S*) stereochemistry altogether play a crucial role for its enhanced activity.

Our synthesis involved the classical synthetic conversion of pipecolic acid to olefin **14a**. The olefin **14a** was then subjected to dihydroxylation via the Upjohn method delivering the diols **15a** and **16a** in the proportion of 3:2 (Scheme 6) determined using high-performance liquid chromatography (HPLC).

The Sharpless “binding pocket” effect for our novel monosubstituted terminal olefin attached to a piperidine system was studied and found to be consistent with this effect. A better discrimination of diastereoselectivity was achieved using hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether ((DHQ)₂PYR) and hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether ((DHQD)₂PYR).

We then proceeded with the synthetic approach to accomplish the total synthesis of dexoxadrol (Scheme 7). Upon hydrogenolysis followed by reaction with dimethoxybenzophenone and *p*-toluenesulfonic acid (PTSA) in isopropyl alcohol held at reflux, **15a** (**16a**) produced dexoxadrol (epidexoxadrol). Incidentally this is the first asymmetric synthesis of (–)-epidexoxadrol.

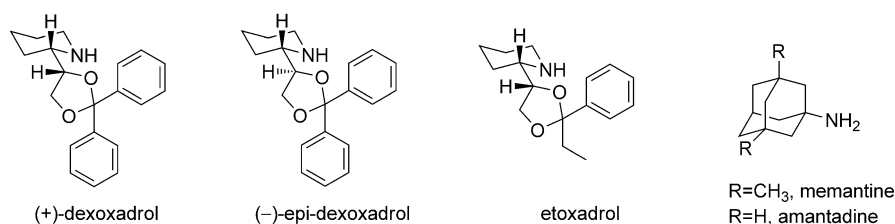
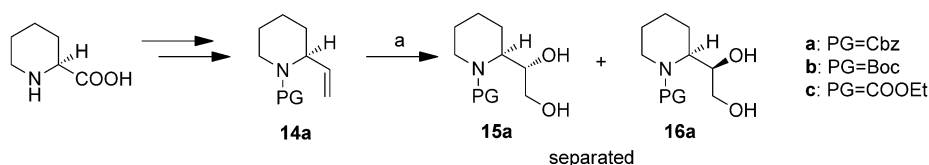
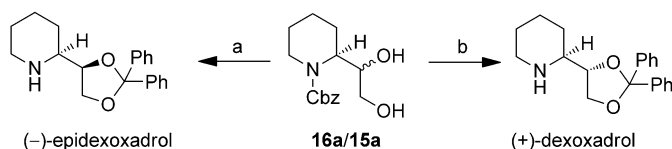


Figure 3. NMDA receptor antagonists.



Scheme 6. Upjohn dihydroxylation. Reagents and conditions: a) OsO₄, *N*-methylmorpholine *N*-oxide, acetone/H₂O (9:1), rt, 80%.

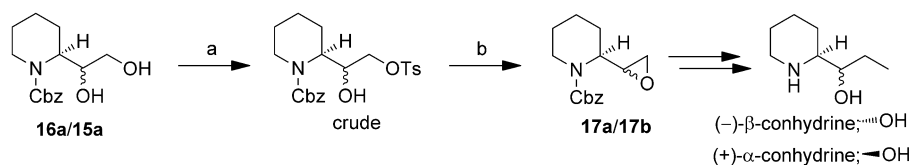


Scheme 7. Synthesis of dioxadrol. *Reagents and conditions:* a) 1) H_2 , Pd/C, EtOH, rt, 98 %, 2) isopropyl alcohol, PTSA, $\text{PhC(OMe)}_2\text{Ph}$, reflux, 60 %; b) H_2 , Pd/C, EtOH, rt, 98 %, 2) isopropyl alcohol, PTSA, $\text{PhC(OMe)}_2\text{Ph}$, reflux, 56 %.

Formal approach to conhydrine

Conhydrine, whose structure was first elucidated in 1933, is an alkaloid of the hemlock family isolated from the leaves and seeds of the plant *Conium Maculatum* L. (+)-Conhydrine has attracted considerable synthetic interest due to its potent antitumor, antiviral, and glycosidase inhibitory activities. The diols **16a**

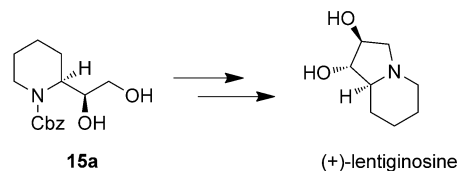
and **15a** were efficiently transformed to **17a** and **17b** respectively to complete the formal synthesis of conhydrine (Scheme 8).



Scheme 8. Formal approach to conhydrine. *Reagents and conditions:* a) TsCl, 4-dimethylaminopyridine, Et_3N , CH_2Cl_2 , 0°C to rt, 2 h, crude; b) K_2CO_3 , MeOH, rt, 58 % (for **17a**), 60 % (for **17b**).

Formal approach to (+)-lentiginosine

The recent synthetic report by Vankar and co-workers describes a total synthesis of (+)-lentiginosine from diol **15a** prepared by synthetic maneuvering of D-mannitol. (+)-Lentiginosine is a naturally occurring isomer first isolated from *Astragalus lentiginosus* in 1990. Being a hydroxylated alkaloid, it serves as a sugar mimic and acts as a potent selective inhibitor of α -glucosidase and amyloglucosidase. Incidentally during our synthetic maneuvering of dioxadrol, the same diol **15a** was obtained from another chiral source (-)-pipecolic acid. Thus the synthesis of diol **15a** provides a straightforward formal synthetic approach to (+)-lentiginosine (Scheme 9).



Scheme 9. Formal approach to lentiginosine.

Keywords: alkaloids • asymmetric synthesis • natural products • piperidines • pyrrolidines

Publications arising from this work:

- C. Bhat, S. G. Tilve, *Tetrahedron Lett.* **2011**, 52, 6566.
- C. Bhat, S. G. Tilve, *Tetrahedron Lett.* **2013**, 54, 245.
- C. Bhat, S. G. Tilve, *Tetrahedron* **2013**, 69, 6129.
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