Tetrahedron 69 (2013) 6129–6143

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Henry–Nef reaction: a practical and versatile chiral pool route to 2-substituted pyrrolidine and piperidine alkaloids

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ARTICLE INFO

Article history:
Received 15 March 2013
Received in revised form 13 May 2013
Accepted 15 May 2013
Available online 22 May 2013

Keywords:
Pyrrolidine
Piperidine
Henry
Nef
Chiral pool
2-Substituted
Alkaloids

ABSTRACT

The paper describes the synergistic protocol developed by combinatorial Henry and Nef reaction for the synthesis of 2-substituted pyrrolidine and piperidine alkaloids containing 1,3-aminoketone and 1,3-amino alcohol units. The utility of the protocol is demonstrated by asymmetric synthesis of 12 natural products of which asymmetric synthesis of (−)-*N*-methylpelletierine is presented for the first time. The one-carbon homologation described also provides an alternate route for the synthesis of key intermediates homoprolinol and homopipecolinol used as synthetic precursors for several alkaloids and construction of β-amino acids from α-amino acids.

1. Introduction

2-Substituted pyrrolidines and piperidine alkaloids containing a stereogenic nitrogen centre are ubiquitously found in nature and as active components in the various drug candidates.[1] Some of the alkaloids containing 1,3-aminoketone and 1,3-amino alcohol units are depicted in Fig. 1. These alkaloids are isolated from 60 species of the genus *Sedum* and are usually referred as Sedum[2] alkaloids, which are of immense interest due to their memory-enhancing properties and application as anti-Alzheimer agents.[3] Owing to their vast pharmaceutical applications, the access to these motifs is gaining major importance from industrial prospective.[4] These motifs are also potent key building blocks in organic synthesis.[5] As a consequence, the asymmetric synthesis of 2-substituted pyrrolidine and piperidine alkaloids is of current interest and formidable challenge in synthetic organic chemistry. The protocols designed in the earlier days mainly involve racemic synthesis by polar additions, photocyclizations, cycloadditions and radical cyclizations.[6] The modern asymmetric methods encompass chiral pool strategies,[7] chiral auxiliary mediated synthesis using chiral organo metallic reagents[8] and organocatalysis.[9] All these methods have their advantages and limitations. For example, recent development in organocatalysis nevertheless has tremendous potential is yet to develop for practical applications from industrial point of view. On the other hand, 'chiral pool' strategies, wherein the starting material can easily be carved from the naturally available sources like amino acids, though requires large number of synthetic manoeuvring, but still is the best bet for chiral integrity and accordingly for industrial application.[10] Keeping this in mind, we thought of developing a practical and versatile chiral pool strategy for the synthesis of 2-substituted pyrrolidine and piperidine alkaloids from L-proline and L-pipecolinic acid. The molecules of our interest are those containing 1,3-aminoketone and 1,3-amino alcohol units, principal units present in various natural products.[11] Another attraction was the potential of 1,3-amino alcohol units to act as chiral ligands and chiral auxiliaries.[12] A vast variety of methods are available in the literature for the synthesis of these amino alcohols, however, only few asymmetric methods are reported,[13] mainly involving proline catalyzed α-aminoxylation,[13a] rhodium catalyzed asymmetric transformations[13b] and asymmetric Mannich reaction.[13c]

2. Results and discussion

2.1. Henry-Nef reaction on protected prolinols and pipecolinols

In a preliminary communication we had described the development of Henry–Nef protocol for the synthesis of some of the

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0040-4020/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tet.2013.05.055

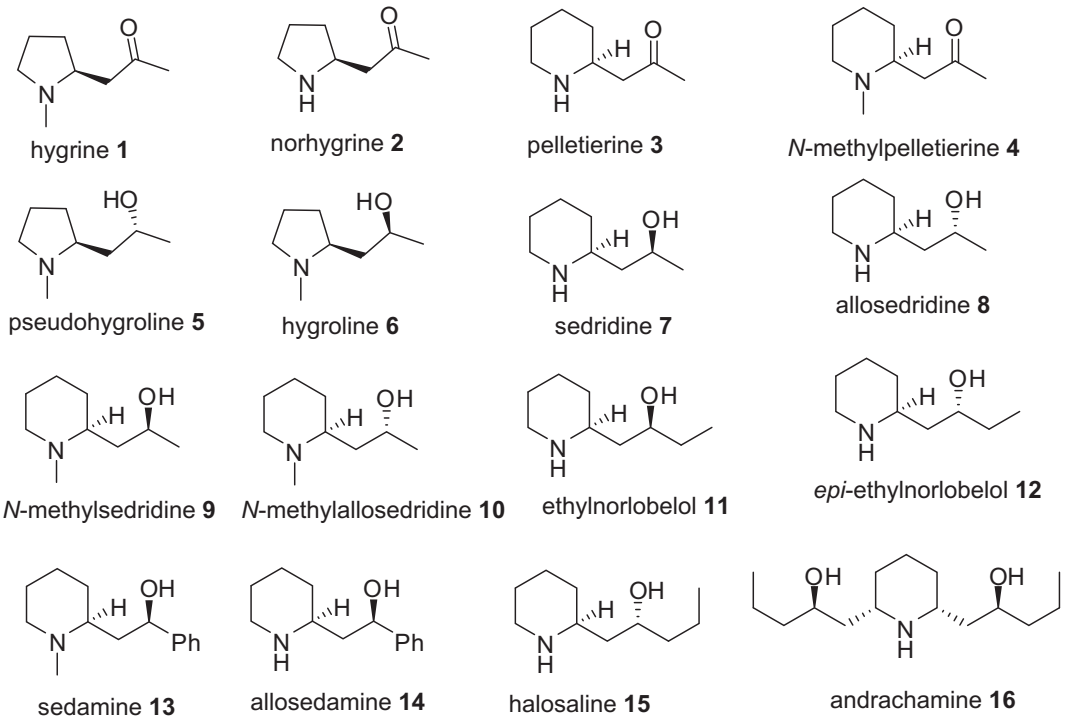
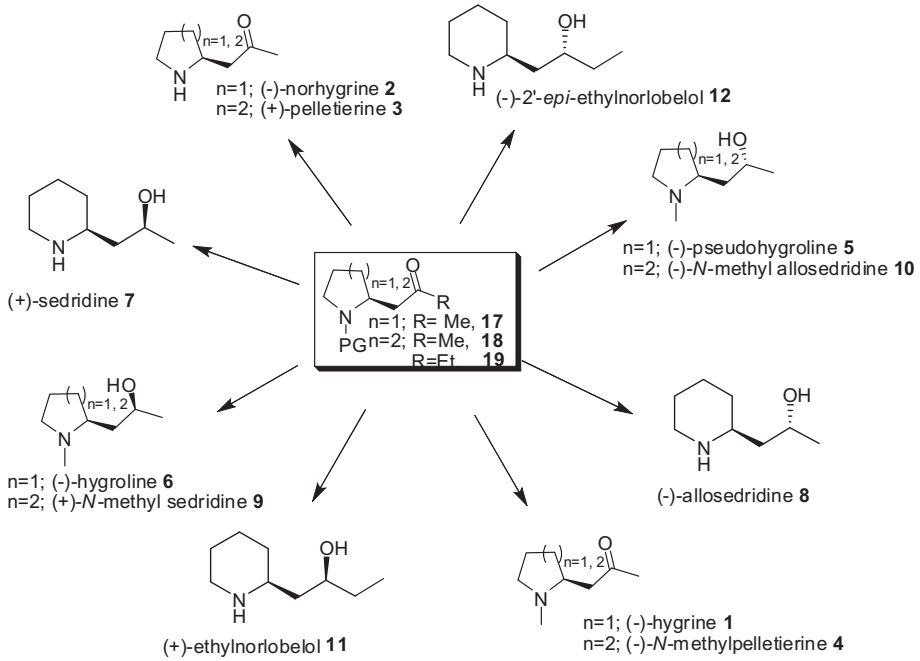


Fig. 1. 2-Substituted pyrrolidine and piperidine alkaloids with 1,3-aminoketone and alcohol units.

pyrrolidine alkaloids.[14] This paper illustrates the full account of application of this protocol for the synthesis of pyrrolidine and piperidine alkaloids and key homologated prolinol and pipecolinol intermediates, known precursors for the synthesis of large pool of alkaloids.

Henry–Nef protocol is in combination involves two major synthetic steps; the formation of the nitro functionality from carbonyls and successive transformation to next carbonyl unit mainly by oxidative or reductive methods. Even though this method is well documented in the literature,[15] surprisingly, not well explored for synthetic applications, turned our synthetic attention in this area. We envisioned the intermediates **17**–**19** can serve as ideal precursors for the synthesis of our targeted alkaloids (Scheme 1). These units could be derived by performing Nef reaction on the corresponding nitroalkenes **20**–**22**. Based on this we formulated a retrosynthetic sequence as outlined in Scheme 2.

At the outset of our study, we undertook several investigative methods to arrive with the nitrofunctional intermediates **20**–**22**. Despite there are numerous reports available on Henry reaction as a tool for natural products, the application for 2-substutited



Scheme 1. Synthetic strategy through common intermediates.