Tetrahedron Letters 59 (2018) 1879–1895

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Digest paper

Recent developments in the synthesis of prosophylline and its derivatives

C. Ande, S. Dubbu, A.K. Verma, Y.D. Vankar *

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208016, India

ARTICLE INFO

Article history:
Received 10 January 2018
Revised 30 March 2018
Accepted 2 April 2018
Available online 3 April 2018

Keywords:
Prosophyllines and derivatives
Garner's aldehyde
D-serine
Asymmetric catalysis
Chiral auxiliaries

ABSTRACT

Several synthetic efforts are reported towards the optically active (−)-prosophylline and (+)-prosophylline, and their derivatives. Interestingly and surprisingly, although only a few synthesis are reported for the parent molecules, there are more reports for the synthesis of their derivatives such as deoxoprosophyllines, deoxoprosopinines, deoxocassines etc. The three main strategies to procure these molecules in optically pure forms are by using (i) chiral synthons (ii) chiral auxiliaries and (iii) asymmetric catalysis. Among these, the chiral synthons are mainly utilized by a number of researchers. This review summarizes the recent developments in the synthesis of optically active prosophyllines and their derivatives, and covers the literature from the year 2000 onwards.

Contents

Introduction

Alkaloids belong to a class of natural products many of which are highly valued since they possess important medicinal properties.[1] Piperidine alkaloids such as prosophyllines and prosopinines belong to the class of *prosopis* alkaloids which are isolated from the leaves of *Prosopis Afrikana Taub*.[2] These have been found to show analgesic, antibiotic, anesthetic and a variety of pharmacological properties such as stimulating central nervous system.[1,2e-i] Because of these important medicinal properties, and also because of their interesting structures a large number of syntheses have been reported.[3] This review aims to compile the recent developments in the synthesis of prosophylline and its derivatives. These include molecules such as (−)- and (+)-prosophylline, (−)- and (+)-deoxoprosophylline, (+)-prosopinine, (−)- and (+)-deoxoprosopinine, (+)-2-*epi*-deoxoprospinine, (−)- and (+)-deoxocassine, (+)-prosopine, and (+)-6-*epi*-prosopinine (Fig. 1) whose syntheses are reported from the year 2000 onwards. A systematic categorization of the syntheses based on different types of approaches are discussed in this review. It is expected that such a review will help future researchers to devise their strategies more efficiently.

* Corresponding author.
E-mail address: vankar@iitk.ac.in (Y.D. Vankar).

https://doi.org/10.1016/j.tetlet.2018.04.004
0040-4039/

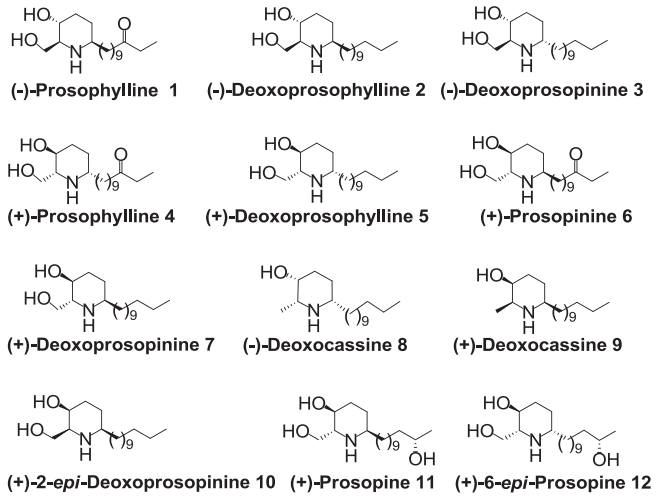


Fig. 1. Prosophyllines and their derivatives.

The synthetic approaches mainly include the utilization of (a) chiral synthons, (b) chiral auxiliaries, and (c) asymmetric catalysis. In the present review, we have categorized the syntheses based on these three categories.

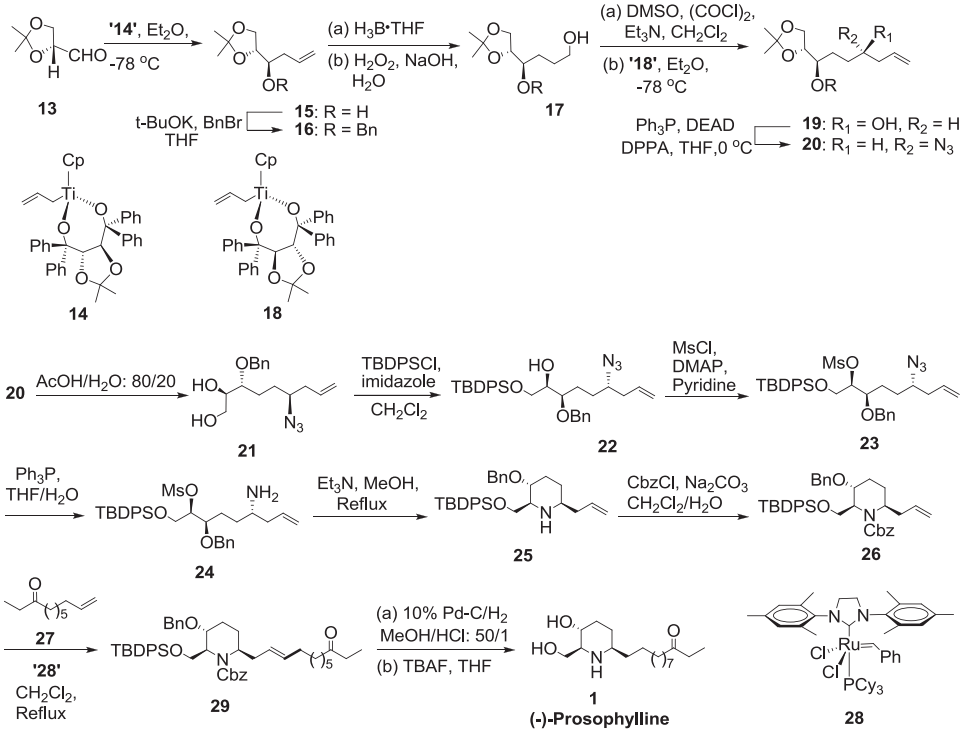
Synthesis of (−)-prosophylline and derivatives

Surprisingly, there is only one synthesis of (−)-prosophylline **1** that has been reported during the period 2000–2017, whereas there are more synthetic efforts towards (−)-deoxoprosophylline, (−)-prosopinine, and (−)-deoxoprosopinine, and (−)-deoxocassine.

(A) Using chiral synthons

Among the chiral synthons, the use of protected glyceraldehyde as a chiral source has been reported only once where the introduction of 'nitrogen' at an appropriate position was carried out at a later stage to lead to the piperidine ring. On the other hand, the utility of D-serine and its protected derivatives, and Garner's aldehyde has been reported by a number of researchers. The 'nitrogen' present in these molecules was effectively utilized and it becomes a ring nitrogen of the piperidine skeletons of the derivatives of prosophyllines.

Synthesis of (−)-prosophylline from protected D-glyceraldehyde **13** (Scheme 1) by employing cross-metathesis as one of the key reactions for elaborating the side chain was reported by Cossy *et al.*[4] Formation of the piperidine ring was accomplished via an intramolecular S_N2 substitution to install the proper absolute configuration at C-2. Thus, aldehyde **13** upon reaction with allyl titanium complex (*S,S*)-**14** led to the known alcohol **15** in 98:2 diastereoselection. Protection of the hydroxyl group to the corresponding benzyl ether **16** followed by hydroboration-oxidation led to the primary alcohol **17**. For the incorporation of the appropriate side chain as well as to introduce an amino functionality with appropriate configuration, the primary alcohol was oxidized to the corresponding aldehyde using Swern oxidation. The aldehyde was then treated with allyltitanium complex (*R,R*)-**18** at −78 °C which proceeded with high diastereoselectivity (98:2) to give the homoallylic alcohol **19**. Incorporation of the azide group with inversion of configuration to obtain **20** was accomplished *via* Mitsunobu reaction using Ph_3P, DEAD and diphenylphosphorylazide (DPPA) at 0 °C to room temperature (RT). Deprotection of the acetonide group in **20** was first done with aqueous AcOH to get **21**, followed by the TBDPS protection of the resultant primary alcohol leading to the azido intermediate **22**. The secondary hydroxyl group was then converted into the corresponding mesylate **23** and the azido group was reduced under the standard Staudinger reaction conditions with Ph_3P-H_2O-THF to get **24**. This was followed by intramolecular S_N2 reaction induced by Et_3N which gave the required piperidine skeleton **25** with correct absolute configurations at the three chiral centers. The side chain was elaborated in two steps that involved protection of the free –NH as a carbamate to obtain **26**, and cross metathesis with olefinic ketone **27** using the



Scheme 1. Synthesis of (−)-prosophylline **1** from a D-glyceraldehyde derivative **13**.