Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 643–655

Stereoselective synthesis of swainsonines from pyridines

Gerres Heimgärtner, Dirk Raatz and Oliver Reiser*

Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, D-93040, Germany

Received 7 September 2004; revised 27 October 2004; accepted 28 October 2004

Available online 23 November 2004

Abstract—An efficient synthesis of (−)-swainsonine and (−)-2,8a-di-*epi*-swainsonine was developed starting from readily available 2-pyridinecarbaldehyde and 3-hydroxypyridine. In particular, it was demonstrated that the mixture of simple indolizidines, i.e. lentiginosine and *epi*-lentiginosine, being readily available by a number of different synthetic routes, can be directly converted to swainsonine.

1. Introduction

Indolizidines belong to an important class of alkaloids that have received broad attention due to their biological properties such as antimetastatic, antitumor-proliferative, anticancer or immunoregulating activity.[1] Most prominent, (−)-swainsonine (**1b**) is a very potent α-mannosidase inhibitor, being currently under clinical evaluation.[2] Despite their relative simple structure, the synthesis of indolizidines has remained challenging, although a number of elegant routes towards them have been reported[3] (Fig. 1).

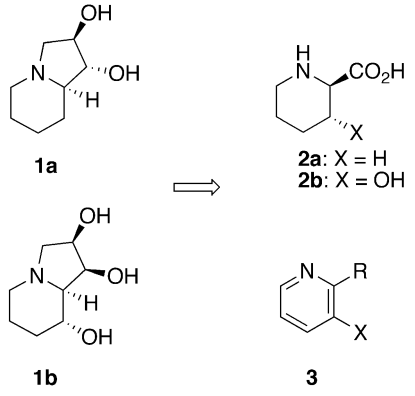


Figure 1. Retrosynthetic analysis of indolizidines.

One obvious approach towards indolizidines would be construction of the five-membered ring by appropriate functionalization of (hydroxylated) pipecolic acids, and indeed, this approach was successfully developed for the synthesis of (−)-lentiginosine (**1a**) and also of (−)-swainsonine (**1b**).[4]

However, even the parent pipecolic acid (**2a**) is not readily available in enantiomerically pure form since it is not available from the chiral pool, and—despite contrary announcements[5]—an efficient chemical large scale process is yet to be developed.

An alternate approach towards indolizidines can be envisioned from pyridines, requiring the efficient transformation of the pyridine into a piperidine ring at some point in the synthesis.[6] Following our interest to use heteroaromatic starting materials such as pyrrols,[7] furans[8] or pyridines[9] for the synthesis of natural products and analogs, we report here such a strategy that leads stereoselectively to (−)-swainsonine (**1b**) and to the epimer (−)-2,8a-di-*epi*-swainsonine.

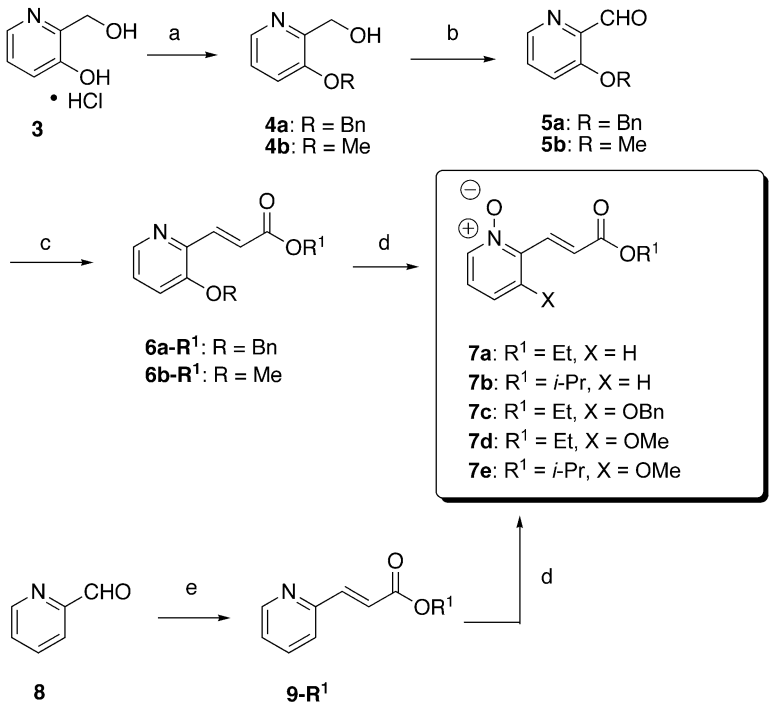
We have reported that acrylates of pyridines cannot be used as substrates in the Sharpless asymmetric aminohydroxylation (AA) due to poisoning of the osmium catalyst by the pyridine nitrogen.[10] However, we demonstrated that the corresponding pyridine *N*-oxides **7** readily underwent this transformation, which was applied to the enantioselective synthesis of pyridine analogous side chains of paclitaxel. Recently, this strategy was taken up for the synthesis of (−)-lentiginosine (**1a**), using an asymmetric dihydroxylation of **7a** as the key step,[11] which prompts us to report our own results for the synthesis of swainsonine epimers.

2. Results and discussion

Asymmetric dihydroxylations of pyridine *N*-oxides **7a–e**, which were readily prepared from pyridines **3** and **8**

Keywords: Indolizidines; Swainsonine; 2,8a-Di-*epi*-swainsonine; Pyridine-*N*-oxides; Asymmetric dihydroxylation.
* Corresponding author. Tel.: +49 941 9434631; fax: +49 941 9434121; e-mail: oliver.reiser@chemie.uni-regensburg.de

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.086

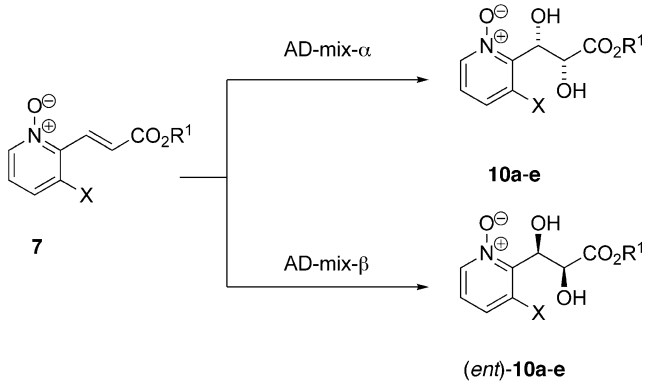


Scheme 1. Reagents and conditions: (a) (i) NaOEt, ethanol; (ii) DMSO, (**4a**: benzyl chloride; **4b**: methyl iodide), 28–39%. (b) SeO_2, dioxane, reflux, 83–84%. (c) LiBr, acetonitrile, NEt_3, $(R^1O)_2POCH_2COOR^1$, 62–84%. (d) Glacial acetic acid, hydrogen peroxide (30%), 60 °C, 77–97%. (e) LiBr, acetonitrile, NEt_3, $(R^1O)_2POCH_2COOR^1$, 62–86%.

(Scheme 1), were investigated using commercially available AD-mix.

7a gave the desired dihydroxylated products **10a**, as recently reported,[11] or (*ent*)-**10a**, respectively, with high enantioselectivity, either by employing AD-mix-α or AD-mix-β (Table 1). Likewise, the alkoxy substituted *N*-oxides **7c** and **7d** could be converted to the corresponding diols with respectable yields, however, the enantioselectivity of the reaction was distinctively dependent on the protecting group at the hydroxyl group in the 3-position on the pyridine ring: while the benzyloxy derivative **7c** gave the diols **10c** or (*ent*)-**10c** with only 53–66% ee, **7d**, substituted with the smaller methoxy group gave rise to the diols **10d** or (*ent*)-**10d** with excellent enantioselectivity. Switching from the ethyl to the isopropyl esters **7b** and **7e** considerably improved the yields by retaining the high selectivities (93–98% ee) of the dihydroxylation reaction due to the increased hydrolytic stability of the starting materials and products.

Table 1. Asymmetric dihydroxylation of **7** to **10a–e** (AD-mix-α) or (*ent*)-**10a–e** (AD-mix-β)[a]



	AD-mix-α		AD-mix-β	
	% ee	Yield (%)	% ee	Yield (%)
7a	97	39	96	36
7b	97	66	98	65
7c	53	55	66	59
7d	97	52	98	54
7e	97	93	93	72

[a] Reagents and conditions: AD-Mix, $MeSO_2NH_2$, *t*-BuOH/H_2O, room temperature, 24–72 h.