Tetrahedron Letters 49 (2008) 5169–5171

Contents lists available at ScienceDirect

Tetrahedron Letters

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

An asymmetric synthesis of (+)-desoxoprosophylline

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ARTICLE INFO

Article history:
Received 22 April 2008
Revised 9 June 2008
Accepted 17 June 2008
Available online 19 June 2008

Keywords:
Amino alcohol
Asymmetric synthesis
Sulfoxide
N-Cbz-sulfilimine
Desoxoprosophylline

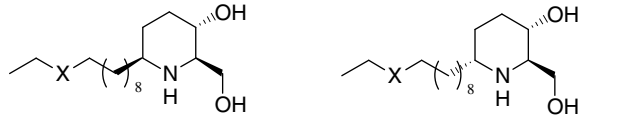
ABSTRACT

An efficient synthesis of (+)-desoxoprosophylline is described. The key steps in the reaction sequence include the preparation of an *N*-Cbz-sulfilimine from the corresponding sulfoxide using the Burgess reagent, regio- and stereoselective hetero-functionalization of an alkene using the pendant sulfilimine as the nucleophile and a stereoselective amidomercuration to form the *cis*-2,6-disubstituted piperidine ring.

2,6-Disubstituted piperidin-3-ols such as (+)-desoxoprosophylline **1**, (+)-prosophylline **2** and related compounds (Fig. 1) occur widely among the alkaloids isolated from the plant genera *Cassia* and *Prosopis*.[1,2] Numerous compounds possessing 2,6-*cis*, 2,6-*trans* and 3α or 3β configurations have been discovered. These alkaloids display a range of bioactivities including acetylcholinesterase inhibitory activity,[3a] cytotoxic,[3b] antibacterial,[3c–f] antimycotic,[3c,e] DNA binding,[3g] anaesthetic and analgesic.[3h,i] Desoxoprosophylline **1** and prosophylline **2** have been isolated from the African mimosa *Prosopis africana* Taub.[4]

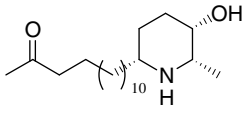
Desoxoprosophylline is characterized by the presence of a polar head group that is known to be essential for glycosidase inhibitory activity[5] and is thereby expected to be useful for the treatment of diseases such as diabetes, arthritis and cancer. The hydrophobic side chain facilitates its transport across lipid membranes.[6] The interesting structural features and the varied biological activity of **1** have attracted the attention of synthetic chemists and several reports detail its synthesis. Many among them rely on chiral pool starting materials[7] and there are only a few reports on asymmetric syntheses.[8]

We describe herein an efficient synthesis of desoxoprosophylline utilizing a methodology that we reported on the oxidative functionalization of alkenes into bromo-sulfonamides mediated by a pendant *N*-Ts sulfilimine.[9] A drawback with the reported methodology was the difficulty in removing the *N*-Ts group in the product to access free *NH*– derivatives. We report herein the preparation of *N*-Cbz sulfilimines from the corresponding sulfoxides and utility for the synthesis of bromo-carbamates, the advantage being that the carbamate moiety can be removed under very mild conditions. The retrosynthetic analysis of **1** is depicted in Scheme 1. (+)-Desoxoprosophylline would be obtained from **7** by a Mitsunobu inversion followed by deprotection. Piperidine derivative **7** was visualized to derive from electrophile promoted cyclization of unsaturated amido compound **8**, which in turn can be derived from amino alcohol derivative **9**. Compound **9** can be obtained from β-siloxy sulfoxide **10**.

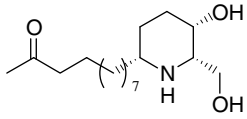


(+)-desoxoprosophylline **1**, X = CH_2
(+)-prosophylline **2**, X = CO

(+)-desoxoprosopinine **3**, X = CH_2
(+)-prosopinine **4**, X = CO



(+)-spectaline **5**



(+)-prosafrinine **6**

Figure 1.

The synthesis began from the known β-siloxy sulfoxide[10] **10**, which on treatment with the Burgess reagent[11] **11** according to the protocol recently described by us[12] yielded sulfilimines **12*anti*** and **12*syn*** in equimolar amounts (78%).[13] These same compounds were also obtained by treatment of **10** with CbzNSO.[10] Reaction of

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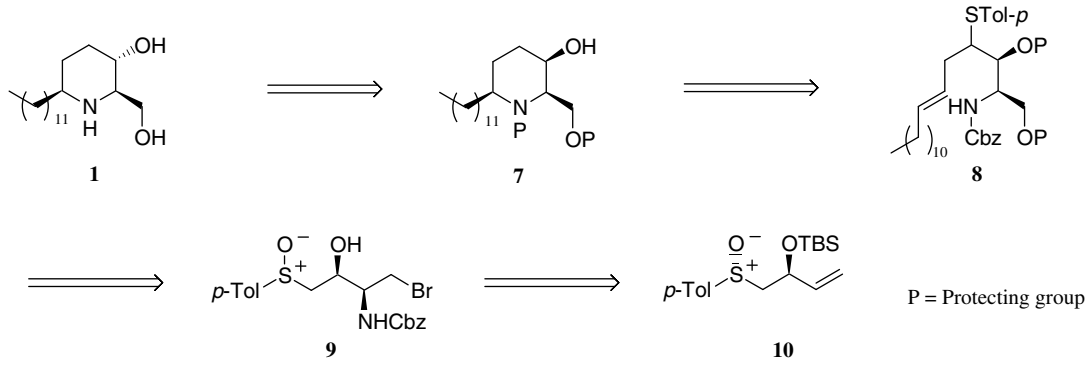
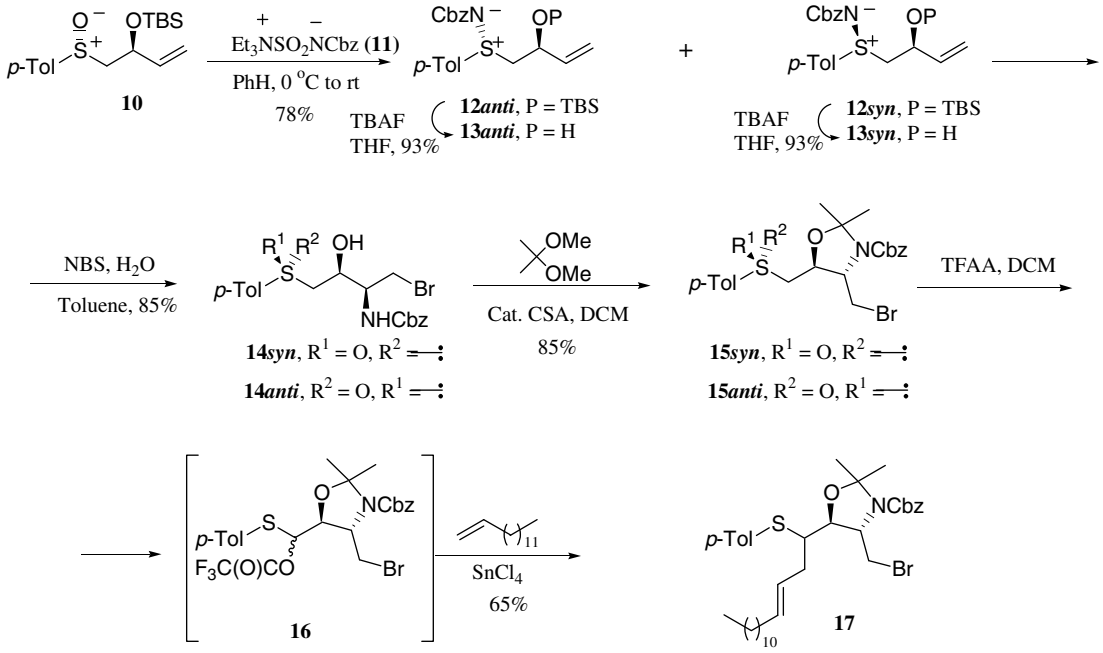
doi:10.1016/j.tetlet.2008.06.074



Scheme 1.



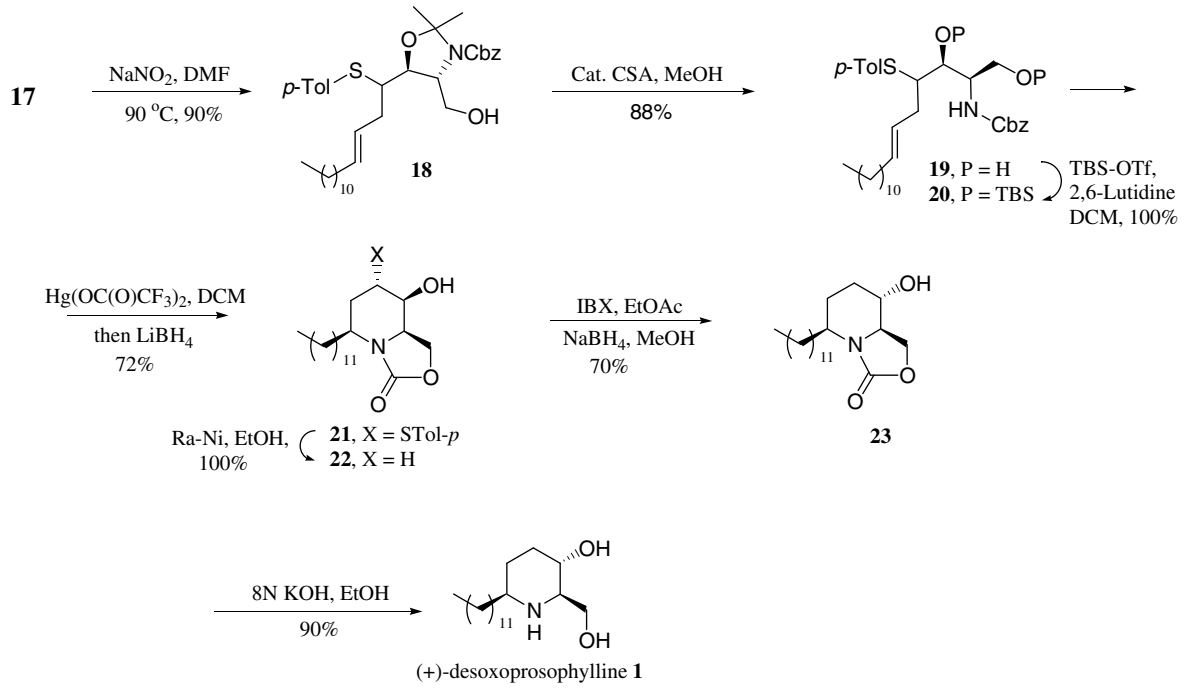
Scheme 2.

sulfilimines[14] **13*anti*** and **13*syn***, obtained by deprotection of **12*anti*** and **12*syn***, with NBS afforded cleanly bromo-carbamates[10] **14*anti*** and **14*syn***, which were further transformed into acetonides **15*anti*** and **15*syn*** (Scheme 2).

Treatment of **15** with TFAA afforded the Pummerer intermediate **16**, which without isolation was reacted with 1-tetradecene in the presence of stoichiometric amounts of $SnCl_4$[15] to yield homoallyl sulfide **17** in 65% yield.[16] Displacement of bromine with a hydroxy group by treatment of **17** with excess sodium nitrite in DMF[17] followed by deprotection of the acetonide furnished diol **19**. It was necessary to protect the hydroxy groups to involve the carbamate selectively in the electrophile promoted cyclization. Thus treatment of **19** with TBS-OTf in the presence of 2,6-lutidine yielded cleanly the disilyl ether **20**. Amidomercuration of **20** using mercuric trifluoroacetate proceeded stereoselectively[18] in DCM to furnish oxazolidinone **21** as the sole product[19] after demercuration and concomitant desilylation using $LiBH_4$ (Scheme 3).[20]

The *p*-tolyl thio group was removed by hydrogenolysis on treatment with Ra-Ni to furnish alcohol **22**, an enantiomeric homolog of desoxosafrinine. Attempted Mitsunobu reaction on **22** using chloroacetic acid[21] as the acid partner only returned unreacted starting material. We therefore resorted to an oxidation–reduction sequence to prepare the inverted alcohol. In the event, treatment of **22** with IBX in refluxing ethyl acetate furnished the corresponding ketone, which was not stable to column chromatography on silica gel. The crude product was reduced with $NaBH_4$[22] to yield alcohol **23** as the sole product. Deprotection of the oxazolidinone was achieved by base promoted hydrolysis[23] to afford (+)-desoxoprosophylline **1** with physical characteristics that were in excellent agreement with those reported in the literature.[7a]

In summary, we have described a novel asymmetric synthesis of desoxoprosophylline in 8.6% overall yield from β-siloxy sulfoxide **10** using a sulfilimine as an intramolecular nucleophile. The sulfilimine was readily obtained from the corresponding sulfoxide using the Burgess reagent as the source of the carbamate moiety. The route disclosed is suitable for the synthesis of several related natural products by varying (a) the nucleophile used for bromide displacement (C-heteroatom and C–C bonds can be made); (b) the chain length of the alkene employed in the Pummerer ene reaction; (c) the conditions of amidomercuration, using kinetic[24] rather than thermodynamic conditions to prepare 2,6-*trans*-di-substituted piperidine derivatives.



Scheme 3.

Acknowledgements

S.R. is thankful to Dr. J. M. Rao, Head, Org. Div. I, and Dr. J. S. Yadav, Director, IICT, for constant support and encouragement. S.M. is thankful to CSIR, New Delhi, for a fellowship. Financial assistance from DST (New Delhi) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.074.

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