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A versatile synthesis of (+)-deoxoprosopinine and (−)-deoxoprosophylline

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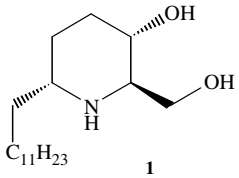
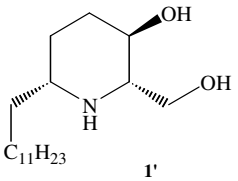
ABSTRACT

An efficient synthesis of (+)-deoxoprosopinine and (−)-deoxoprosophylline was achieved from *N*-benzyl-*N*-Boc serine derivatives (**7**) and (**7′**).

The piperidine ring is a structural feature present in many natural products of biological interest.[1] In the last decade, there has been a growing interest in the enantioselective synthesis of compounds bearing that ring due to the importance of this kind of heterocyclic compounds for the pharmaceutical industry; among these alkaloids are (+)-deoxoprosopinine (**1**) and (−)-deoxoprosophylline (**1′**). To date, several methods for their synthesis have been published.[2,3] Due to the biological importance of these two compounds as well as their structural characteristics, our goal was to find a new method that could use available amino acids and smooth conditions for their synthesis. In this Letter, we report the application of a novel methodology for the synthesis of (+)-deoxoprosopinine and (−)-deoxoprosophylline based on the use of allyl derivatives of N-protected amino aldehydes.



1



1′

As outlined in Scheme 1, our approach starts with *N*-benzyl-*N*-Boc serine derivative **7**.[4] This compound was subjected to hydroboration (BH_3·THF) and subsequently treated with $NaOH/H_2O_2$ affording alcohol **6** with good regioselectivity (8:1). Mesylation of alcohol **6** generated compound **5** (90% yield). Catalytic hydrogenation of the benzyl group in **5** produced an amine that displaced the mesyl group to yield **4** (96% yield). Employing Beak's methodology,[5] the side chain at C-6 of **4** was introduced as follows: its treatment with *sec*-BuLi/TMEDA at −30 °C and reaction of the carbanion formed with DMF (−78 °C) afforded a mixture of aldehydes in a 92:8 ratio from which **3** was obtained in 83% yield after purification by flash column chromatography. Product **3** was then rapidly reacted with the ylide generated in situ from undecyltriphenylphosphonium iodide and *n*-BuLi/THF at −78 °C obtaining compound **2** (91% yield). The formation of this product was highly stereospecific with only a single diasteroisomer observed. Then, in similar fashion as with **3**, compound **2** was immediately used in the final steps of our synthesis; they included catalytic hydrogenation of product **2** (1 atm H_2, 10% Pd–C, EtOH, rt) followed by the cleavage of all protecting groups by Bu_4NF/THF and HCl/MeOH obtaining **1** in 38% overall yield; mp = 87–89 °C (lit.[7] = 89–90 °C); $[\alpha]_D^{25}$ +11.7 (*c* 0.01, $CHCl_3$), (lit.[7] $[\alpha]_D^{23}$ +12.2 (*c* 0.015, $CHCl_3$).

In the same style (as in the synthesis of **1**), compound **7′**[6] was converted to (−)-deoxoprosophylline (**1′**) with an overall yield of 32% yield; mp = 88–90 °C (lit.[7] = 90.5 °C); $[\alpha]_D^{25}$ −14.1 (*c* 0.4, $CHCl_3$), (lit.[7] $[\alpha]_D^{21}$ −13.9 (*c* 0.25, $CHCl_3$) (Scheme 2).

The physical and spectroscopic data of our synthesized compounds **1** and **1′** were in agreement with those described in the literature.[7]

In conclusion, we have developed a versatile, stereocontrolled synthesis of (−)-deoxoprosophylline and (+)-deoxoprosopinine from starting materials **7** and **7′**; this synthetic strategy could be used for the synthesis of other similar alkaloids.[8]

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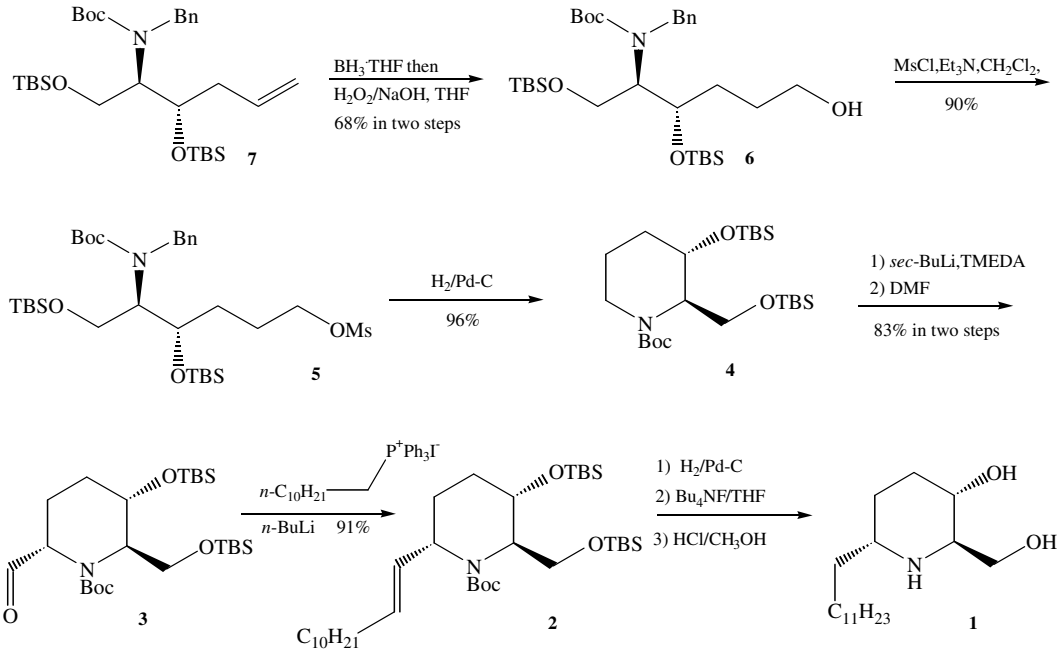
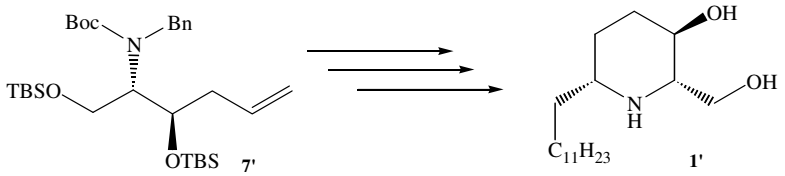


Scheme 1.



Scheme 2.

Acknowledgements

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6. The derivative is obtained via L-serine methyl ester hydrochloride was reacted with 1 equiv of benzaldehyde and 1 equiv of Et_3N/CH_3OH, followed by reduction of the resulting imine with $NaBH_4$. The resulting N-monoprotected methyl ester is reacted with $(Boc)_2O/Et_3N$/THF and then with TBSCl/Imidazole obtaining an N-diprotected, OTBS serine derivative. This product is then treated with DIBAL-H at −40 °C obtaining the desired amino aldehyde. To a suspension of this aldehyde/zinc powder/aqueous solution of NH_4Cl in THF is added allyl bromide at −10 °C; after stirring at room temperature, until the substrate disappeared, the reaction mixture was extracted with Et_2O; then the combined extracts were dried and evaporated in vacuo. The final product is obtained as a mixture of *syn*(minor) and *anti*(major) adducts that can be separated by column chromatography after protection of the hydroxyl moiety with the TBS group.
7. (a) Saitoh, Y.; Moriyama, Y.; Takahashi, T.; Khuong-Huu, Q. *Tetrahedron Lett.* **1980**, *21*, 75; (b) Fuhshuku, K.; Mori, K. *Tetrahedron: Asymmetry* **2007**, *18*, 2104; (c) Takao, K.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Tadano, K.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681; (d) Daniel, L.; Comins, D.; SandelierGrillo, M. J.; Grillo, T. A. *J. Org. Chem.* **2001**, *66*, 6829.
8. It is noteworthy that isomerization on silica gel[5] of the aldehyde **3** (and also **3′**), generates the corresponding diastereomeric products with great regioselectivity. This fact leads to the synthesis of the alkaloids (−)-deoxoprosopinine and (+)-deoxoprosphyline in a similar straight way as presented in Schemes 1 and 2.