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Asymmetric total synthesis of (−)-deoxoprosophylline

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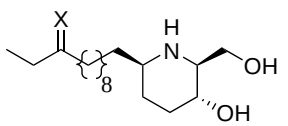
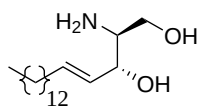
Abstract—Asymmetric syntheses of (−)-deoxoprosophylline from chiral L-*N*,*N*-dibenzyl serine (TBDMS) aldehyde is reported. A highly diastereoselective intramolecular reductive amination of ω-oxo amino diol is a key step of the present synthesis.

2,6-Dialkylated piperidine alkaloids have been found abundantly in nature and are key structural units in many medicinally important compounds.[1] Prosopis alkaloids, isolated from *Prosopis africana*, forms a subgroup possessing a characteristic 3-hydroxy function.[2] Structurally, these compounds, possessing a polar head group and a hydrophobic aliphatic tail, can be considered as cyclic analogues of membrane lipid sphingosine.[3] Indeed, interesting bioactivities including analgesic, anaesthetic and antibiotic have been reported for prosophylline, prosopinine and their deoxygenated derivatives (**1**–**4**, Fig. 1). Although many elegant syntheses of piperidine alkaloids have been developed,[4] asymmetric syntheses of optically pure prosopis alkaloids appeared only recently.[5] As an extension of our work on the L-(*N*,*N*-dibenzylamino)serine (TBDMS) aldehyde (L-**6**),[6–8] we thought to synthesize both deoxoprosophylline **1** and deoxoprosopinine **3** from ω-oxo-amino diol **7** featuring a key intramolecular reductive amination. Compound **7** can be synthesized by a nucleophilic addition of Grignard reagent **8** to the serine aldehyde L-**6**. Alternatively, it can be obtained by a stepwise homologation of the same starting chiral pool via an aldehyde **10** (Scheme 1). We report herein a concise synthesis of (−)-deoxoprosophylline (**1**) according to the latter strategy.

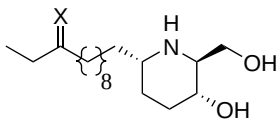
Bromide **16**, a precursor of Grignard reagent **8**, was synthesized as shown in Scheme 2. Mono alkylation of methyl acetoacetate by 1-bromoundecane gave the homologated β-keto ester (**13**) in 70% yield.[9] Formation of dioxolane followed by reduction of ester gave the primary alcohol **15**. The one-step transformation of hydroxyl function to bromide was best realized using a couple (Ph_3P–CBr_4) in the presence of a base (Et_3N). Without adding Et_3N, the reaction was low-yielding due to probably the in situ generation of hydrogen bromide, that can hydrolyze the dioxolane function and provoke side-reactions thereof.[10] Unfortunately, under diverse reaction conditions varying the magnesium sources, the equivalents of dibromoethane and the temperature, we were unable to convert **16** into the adduct **17**. When the reaction was carried out at or below room temperature, no addition reaction occurred and only a proto-debromination product of **16** was isolated after aqueous workup. To probe the reactivity of this magnesium, we investigated its reaction with heptanal and benzaldehyde. However, in neither of these two cases was the secondary alcohol produced. The low reactivity of this type of Grignard reagent has been observed previously and has been explained by an



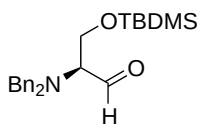
1 X = H, H, (-)-deoxoprosophylline
2 X = O, (-)-prosophylline



5 sphingosine



3 X = H, H, (-)-deoxoprosopinine
4 X = O, (-)-prosopinine



L-**6**

Figure 1.

Keywords: hydroxypiperidine; deoxoprosophylline; *N*,*N*-dibenzyl serine (OTBS) aldehyde; facial selectivity; intramolecular reductive amination.

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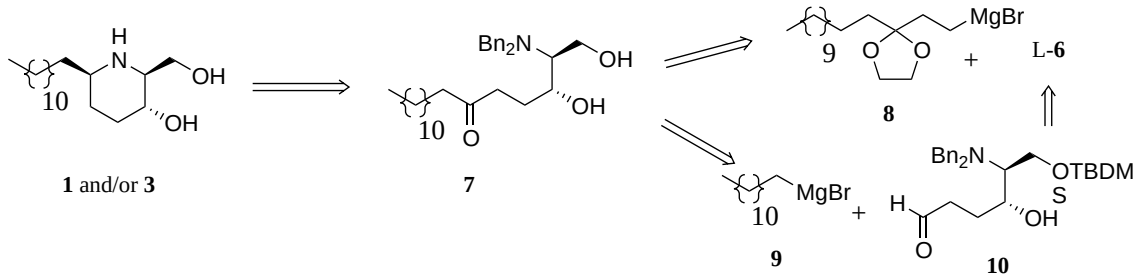
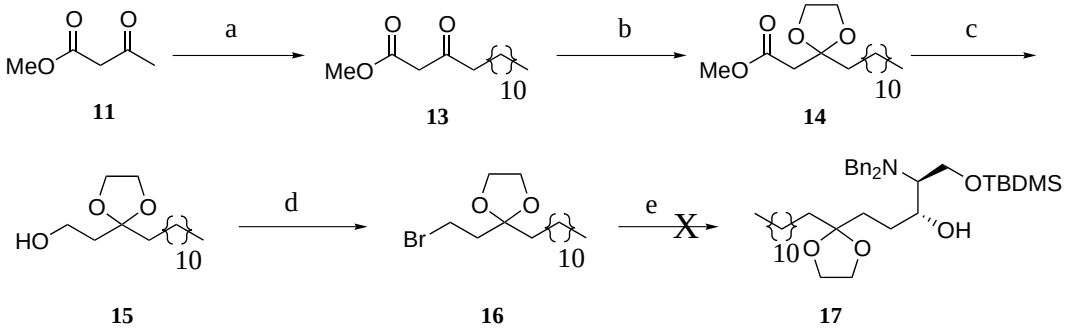


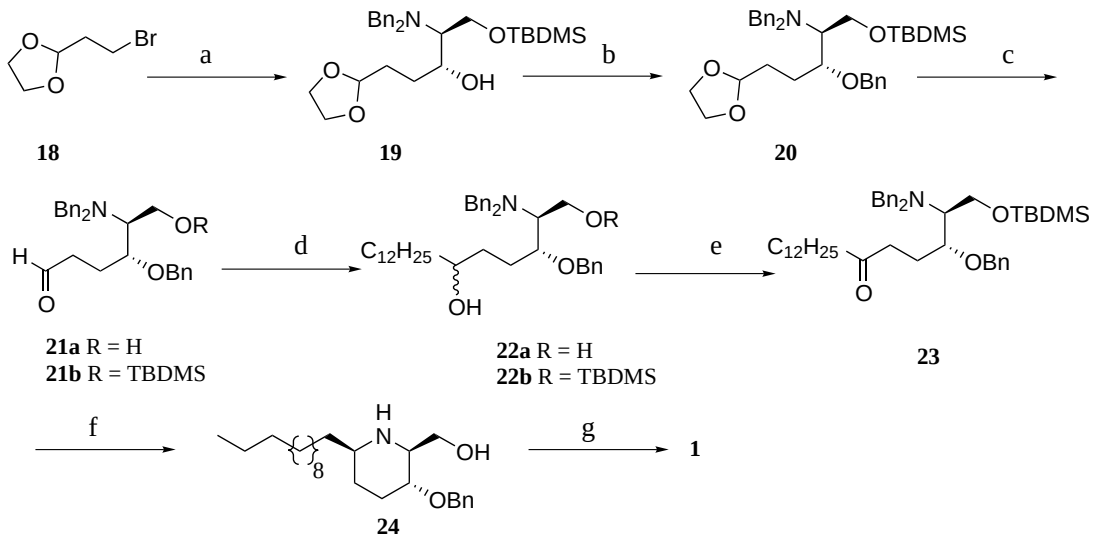
Scheme 1. Retro-synthetic analysis of deoxoprosophylline and deoxoprosopinene.



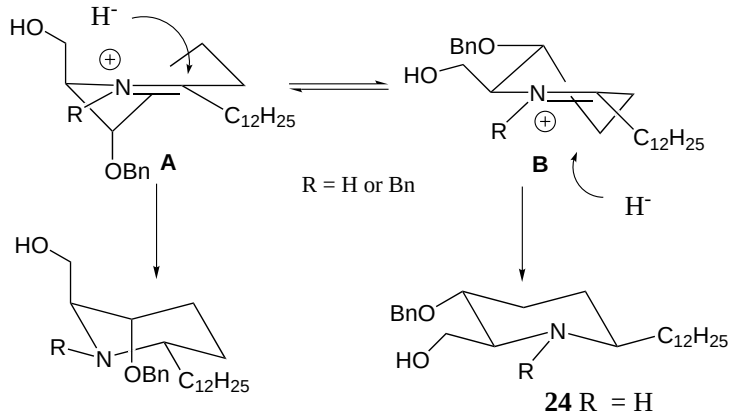
Scheme 2. *Reagents and conditions*: (a) LDA (2.2 equivalents), then $C_{11}H_{23}Br$ (**12**), THF, 70%; (b) TMSCl, $HOCH_2CH_2OH$, CH_2Cl_2, 88%; (c) $LiBH_4$, Et_2O–MeOH, 97%; (d) PPh_3, CBr_4, CH_2Cl_2, 89%; (e) Mg, THF, then L-**6**.

internal solvolysis of the magnesium by the dioxolane oxygen.[11] When the reaction was performed at 60°C or under sonification conditions,[12] a complex reaction mixture was obtained due to probably the degradation of both the aldehyde and the magnesium.[13]

Synthesis of (−)-deoxoprosophylline was finally accomplished as depicted in Scheme 3. Addition of Büchi's Grignard reagent,[14] prepared in situ from the corresponding bromide **18**, to the aldehyde L-**6** gave the amino diol **19** in excellent yield and diastereoselectivity (*anti*/*syn* = 15/1). The major stereomer was assumed to be *anti* according to the Felkin–Anh model[15] and this is corroborated by the synthesis of the final compound. Protection of the secondary alcohol as benzyl ether followed by acidic hydrolysis of dioxolane gave the aldehyde **21a**. Reaction of aldehyde **21a** with an excess of dodecylmagnesium bromide afforded alcohol **22a** as a mixture of two diastereomers in a 1:1 ratio.[16] On the other hand, a moderate diastereoselectivity (*dr* 7/3) was



Scheme 3. *Reagents and conditions*: (a) Mg, THF, room temperature, then L-**6**, 86%; (b) NaH, BnBr, BuNI, THF, 0°C, then room temperature, 85%; (c) (i) 3N HCl–THF, (ii) TBDMSCl, imidazole, DMF, room temperature, 90%; (d) $C_{12}H_{25}Br$, Mg, dibromoethane, THF, then **21b**, 70°C, 80%; (e) DMSO, $(COCl_2)$ then Et_3N, 84%; (f) $Pd(OH)_2$, cyclohexene, EtOH, reflux, (g) Pd/C, MeOH, 73%.



Scheme 4. Stereochemical issue.

observed when the Grignard addition was performed on the fully protected aldehyde **22b**.[17] This lack of diastereoselectivity was nevertheless of no consequence since the chiral centre in question was anyway thought to be introduced at the end of the synthesis via reduction of a cyclic iminium.

Swern oxidation of alcohol **22b** afforded ketone **23** in 84% yield. Catalytic hydrogenation of **22b** under acidic conditions (3N HCl, MeOH, Pd/C, H_2) furnished directly the (–)-deoxoprosophylline (**1**) in 63% yield. However, this process is found to be non-reproducible and an alternative two-step process was developed. Thus, under catalytic transfer hydrogenolysis conditions developed recently by Bajwa and co-workers [$Pd(OH)_2$, cyclohexene, EtOH, HOAc reflux],[18] a chemoselective *N*-debenzylation followed by a reductive amination occurred to provide *O*-benzyl deoxoprosophylline which, without purification, was *O*-debenzylated (Pd(OH)/C, EtOH, cyclohexene, reflux)[19] to afford (–)-deoxoprosophylline (**1**) in 73% yield.[20] The deoxoprosopinine was not detectable from the ^{1}H NMR spectrum of the crude reaction mixture indicating the high diastereoselectivity in the reduction step. The physical and spectroscopic data of our synthetic material are identical with those described in the literature. Thus from the serine aldehyde L-**6**, we were able to synthesize the (–)-deoxoprosophylline (**1**) in seven steps with a 32% overall yield.

The cyclic iminium, the intermediate en route to **24** from **23** can exist in either of the two conformations shown in Scheme 4. Since we knew the stereochemistry of the final product, it is reasonable to ascertain that conformer B predominants over A. Considering the balance between the allylic strain and the 1,3-diaxial interaction, two factors that determine the relative stability of two conformers,[21] we thought that the bis *N*-debenzylation preceded the reduction of iminium in the transformation from **23** to **24** (i.e. R = H in Scheme 4). It is reasonable to predict that deoxoprosopinine (**3**) could be synthesized from the same intermediate if a structural element was introduced to favor the conformer A. Work in this direction is in progress and will be reported in due course.

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