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Total Synthesis of (-)-Desoxoprosopinine via the Diastereoselective Reduction of Homochiral2-Acyl-N-Boc-Oxazolidines

Claude Agami, François Couty* and Hélène Mathieu

Laboratoire de Synthèse Asymétrique associé au CNRS, Université Pierre et Marie Curie, 4 place Jussieu. 75005 Paris. France

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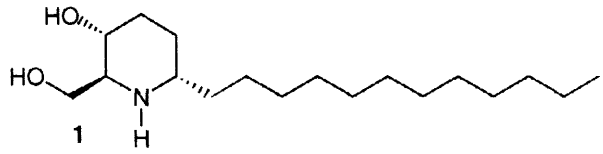
Abstract: (-)-Desoxoprosopinine was synthesised from (*R*)-phenylglycinol as the chiral source. The three distinct steps used for the construction of the three stereogenic centers of the target were all highly diastereoselective. These steps include a reduction of a homochiral N-Boc-2-acyl oxazolidine and the stereoselectivity of this reaction can be explained by a non chelated model. An original N-debenzylation of the phenyl glycinol appendage was devised in this synthesis.

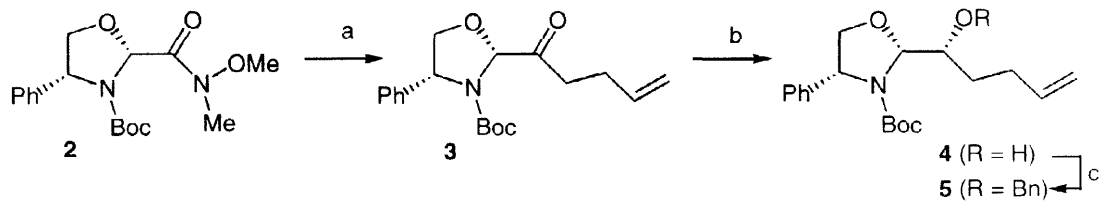
Keywords: oxazolidines, alkaloids, asymmetric synthesis.

The usefulness of homochiral N-Boc-2-acyl oxazolidines as starting substrates for the synthesis of optically pure 1,2-diols[1] or hydroxylated piperidines[2] was recently reported. These asymmetric syntheses were based on highly diastereoselective additions of organometallic reagents onto the ketone moiety adjacent to the heterocyclic ring. We describe here an application of this methodology for the synthesis of (-)-desoxoprosopinine **1**, which is the enantiomer of the reduction product of prosopinine, a natural alkaloid found in *Prosopis africana* Taub.[3,4]



1

Oxazolidine **2**, bearing a Weinreb amide at the 2-position of the heterocycle was used as the chiral starting material for this synthesis. This compound was prepared stereoselectively as already described[2] in four steps from (*R*)-phenylglycinol (78% overall yield). Reaction of **2** with 4-butenylmagnesium bromide was followed by a diastereoselective reduction (ed > 90%) of the produced ketone **3** and this sequence afforded the diasteroisomerically pure homoallylic alcohol **4** after chromatography (84% overall yield). Protection of the latter compound as its benzyl ether derivative afforded **5** (Scheme 1):



2 **3**

Scheme 1 a) 4-Butenylmagnesium bromide, THF, rt; b) $NaBH_4$, EtOH, -78°, 2 steps 84%; c) NaH, BnBr, $N(Bu)_4I$, THF, rt, 98%.

Fax: (33) 1 44 27 26 20; e-mail: couty@ccr.jussieu.fr

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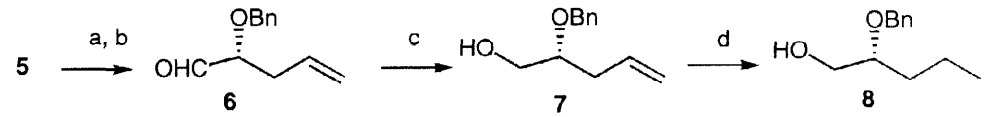
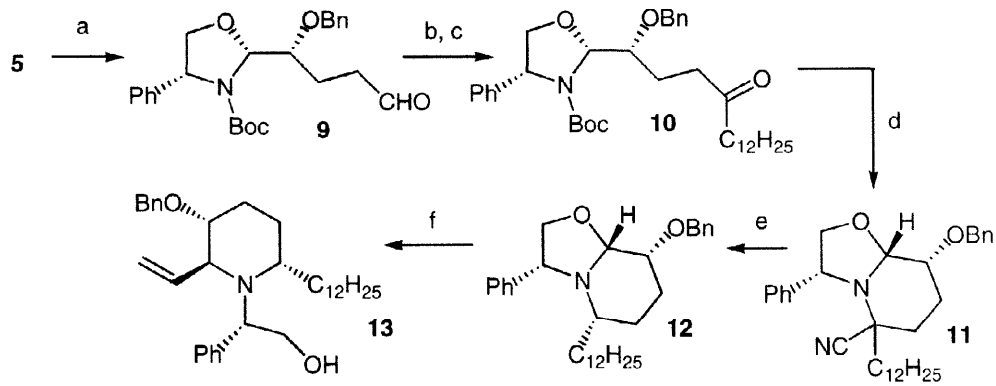
At this stage, the absolute configuration of the newly created chiral center was ascertained by means of a chemical correlation with the known alcohols **7**[5] and **8**,[6] prepared through acidic cleavage of the oxazolidine ring of compound **5** and reduction of the thus released aldehyde **6**. Although partial racemization occurred during this operation at the aldehyde stage, the absolute configuration in **5** was proven to be *R* . by the checking the sign of the optical rotation for **7** and **8** (Scheme 2):



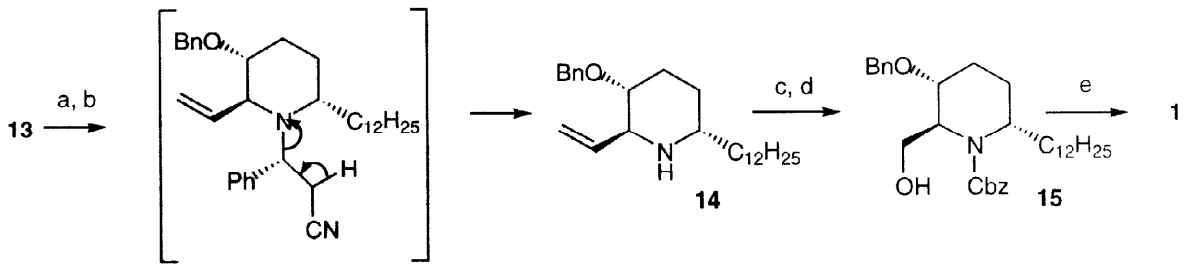
Scheme 2 a) CF_3CO_2H, $ClCH_2CH_2Cl$, rt ; b) THF/H_2O, rt ; c) $NaBH_4$, EtOH, 70 % overall; d) H_2, PtO_2, 66%.

Oxidative cleavage of the ethylenic moiety in compound **5** gave aldehyde **9** which was then transformed into ketone **10** via a two-step sequence involving reaction with undecylmagnesium iodide followed by oxydation of the resulting alcohol. Treatment of compound **10** with trifluoroacetic acid effected the N-Boc cleavage. This operation was followed by an intramolecular condensation of the released amine with the ketone moiety which produced an intermediate iminium ion, in situ transformed into an aminonitrile moiety. Compound **11** was obtained as a 83/17 mixture of diasteromers on the aminonitrile bearing carbon. Reduction of this aminonitrile following the method described by Husson et al.[7] gave stereoselectively bicyclic oxazolidine **12** (ed > 95%). This compound was then treated with an excess of vinylmagnesium bromide in THF in order to give **13**[8] and thereby to set up in a totally stereoselective way the third stereogenic center which is present in the target compound **1** (Scheme 3):



Scheme 3 a) OsO_4 (cat.), $NaIO_4$, THF/water, rt, 78% ; b) $C_{12}H_{25}MgI$, Et_2O, rt; c) PDC, CH_2Cl_2, rt, 60%, 2 steps; d) CF_3CO_2H, $ClCH_2CH_2Cl$, rt, then aqueous KCN, 96%; e) $AgBF_4$, THF, -78°, then $Zn(BH_4)_2$, 78%; f) vinylmagnesium bromide, THF, rt, 86%.

Having compound **13** in hand, we turned our attention to the oxidative cleavage of the vinyl moiety and found that this transformation required a protection of the tertiary amine as a carbamate. A selective N-debenzylation was thus devised as follow: reaction of **13** with thionyl chloride cleanly gave the corresponding primary chloride which was treated with an excess of KCN in DMSO. This operation not only effected a substitution of the chloride by the cyanide ion but also induced a spontaneous β-elimination of the intermediary produced amino nitrile, thus releasing the desired secondary amine **14** in a 86% overall yield. After protection of this amine as a N-Cbz group, the ethylenic double bond in compound **15** was cleaved by ozonolysis, and the resulting aldehyde was reduced by reaction with sodium borohydride to afford compound **15**. Final hydrogenolysis of both the N-CBz and the benzyl ether in **17** gave (-)-desoxoprosopinine **1**[9] (Scheme 4):



Scheme 4 a) $SOCl_2$, THF, rt b) KCN, DMSO/THF (1/1), 86 % two steps; c) CbzCl, DMAP, CH_2Cl_2, rt. 83%; d) O_3, CH_2Cl_2/MeOH, -78°, then $P(Ph)_3$, then $NaBH_4$, 82%; d) H_2, $Pd(OH)_2$/C, EtOH/HCl : 50/1, 88%.

The stereoselectivity of the reactions used in this synthesis deserves some comments. First, the sense of the asymmetric induction observed for the reduction of ketone **3** (cf Scheme 1) is reversed compared to what we previously observed for similar substrates.[1,2] In those cases, in which cerium chloride was present as an additive, a chelated model explained the observed stereoselectivities. In the present case however, a Felkin-Anh model[10] in which the N-Boc moiety is both the larger and the more electron demanding group, accounts for the observed stereoselectivity (Fig 1.). This model was already invoked by some authors[11,12] analysing nucleophilic attacks onto N-tosyl-2-acyl oxazolidines, under non-chelating conditions.

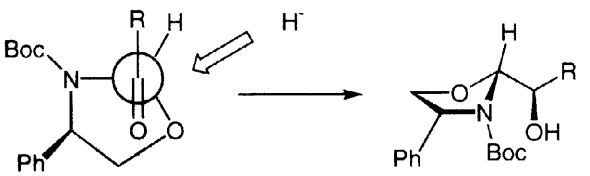
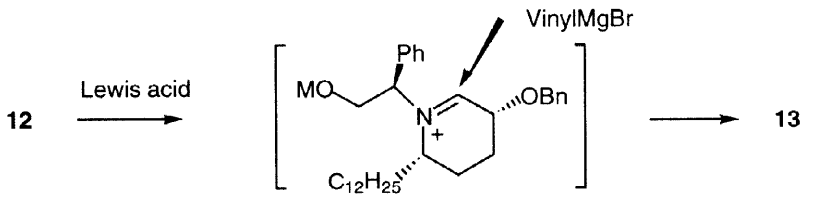


Fig.1. Felkin-Anh model applied to the diastereoselective reduction of **3** leading to alcohol **4**.

As regards the formation of compound **12**, which occurs via an iminium ion generated from amino nitrile **11** following a well documented process, the observed diastereoselectivity is in accordance with previously reported cases.[7] Finally, a complete stereoselectivity was observed for the introduction of the vinyl group in compound **13**. This reaction actually involves the addition of a Grignard reagent onto an intermediate iminium ion resulting from the Lewis acid-mediated opening of the oxazolidine ring. In similar cases featuring formation of 2, 6-dialkylated piperidines, the stereoselectivity was reported to be highly dependant on the nature of the substrate and *cis*[7] as well as *trans*[13] additions were reported. In our case, the outcome of the reaction is governed by the α-benzyloxy group, which directs the attack of the organometallic compound onto the intermediate iminum ion in an *anti* fashion (with respect to both the benzyloxy group and the alkyl side chain):



In conclusion, (-)-desoxoprosopinine **1** was synthesized using three distinct stereoselective steps for the construction of its three stereogenic centers and these reactions were all highly stereoselective. This work highlights the utility of N-Boc-2-acyl oxazolidines as starting material for the enantioselective synthesis of

nitrogen containing heterocycles. Efforts are pursued in our Laboratory towards the synthesis of others enantiopure hydroxy piperidines following this methodology and will be reported in due time.

References and notes

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8. Compound **13**: $[\alpha]_D^{20}$: -40 (c 1.5, $CHCl_3$); ^1H NMR (250MHz, $CDCl_3$): 0.8 (t, J = 6.5, 3H), 1.10-1.18 (m, 22H), 1.36-1.50 (m, 3H), 1.60-1.65 (m, 1H), 2.40 (bs, 1H), 2.89 (bs, 1H), 3.15-3.22 (m, 1H), 3.54 (t, J = 7.7, 1H), 3.59 (dd, J = 6 and 10.3, 1H), 3.77 (dd, J = 9 and 10.3, 1H), 4.17 (dd, J = 6.1 and 8.9, 1H), 4.27 (d, J = 11, 1H), 4.39 (d, J = 11, 1H), 5.26 (dd, 10 and 17, 2H), 5.96 (ddd, J = 7.7, 10.3, 17.6, 1H), 7.17-7.28 (m, 10H); ^{13}C NMR: 14.1, 22.7, 25.1, 25.8, 26.9, 29.3, 29.8, 31.7, 31.9, 51.0, 61.2, 61.3, 62.2, 70.0, 75.8, 79.2, 127.3, 127.5, 127.8, 128.2, 128.3, 128.6, 137.9, 138.6, 140.8.
9. Compound **1**: $[\alpha]_D^{20}$: -16.8 (*c* 0.25, $CHCl_3$), mp 88°; lit. (ref. 3a): $[\alpha]_D^{25}$: -15.9, mp 89.5°.
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