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Cyclization of a Chiral Oxazolidine as a Key-Step for the Synthesis of Functionalized Piperidines

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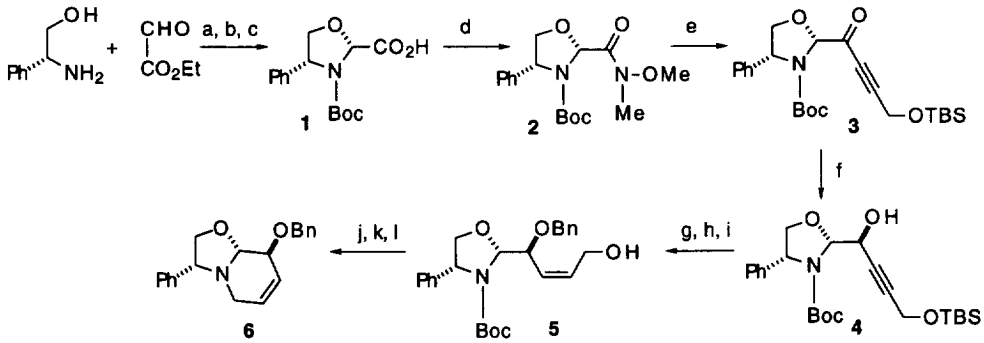
Abstract: Bicyclic oxazolidine **6**, a potential precursor for the synthesis of enantiopure piperidines and indolizidines, was synthesized from (*R*)-phenylglycinol. A stereoselective addition of cyanide anion on this compound afforded ultimately (2*S*,3*S*)-3-hydroxypipecolic acid **9**.

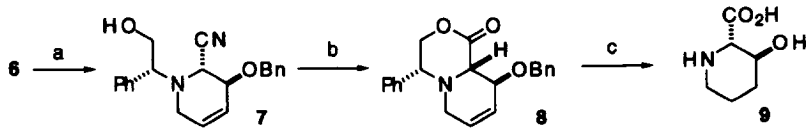
We recently reported the use of *N*-Boc oxazolidines as chiral inductors for stereoselective reactions occurring at an adjacent site.[1] In this paper, we describe the preparation of an oxadehydroindolizidine **6** which could provide a new access to functionalized piperidines or indolizidines. This synthesis is based on a diastereoselective reduction of the acyl group in compound **3** and its stereochemical course was confirmed by the synthesis of enantiopure (2*S*,3*S*)-3-hydroxypipecolic acid **9**.

The sequence of steps which eventually led to compound **6** is displayed in the following scheme. Substrate **1** was stereoselectively obtained from (*R*)-phenylglycinol and ethyl glyoxylate by following our already reported procedure[1a] and was transformed into 2-acyloxazolidine **3** via Weinreb methodology. Product **4** (90% de) was obtained by reduction of the keto group in compound **3**. A chelated cation model can rationalize the observed stereoselectivity: this chelation involves cerium linked to the oxygen atoms of both keto and Boc groups. The completion of this synthesis was straightforward and afforded compound **6** (30 % overall yield).



Reagents and conditions: (a) toluene, reflux (-H_2O); (b) $(Boc)_2O$, reflux; (c) LiOH, THF/EtOH/H_2O, rt (86% overall yield); (d) *N*-methyl morpholine, *i*-BuOCOCl, THF, then $Me(OMe)NH_2^+Cl^-$, NEt_3, DMF, -20° (91%); (e) $LiC{\equiv}CCH_2OSiMe_2t$-Bu, THF, -78°; (f) $NaBH_4$, $CeCl_3.7\ H_2O$, EtOH, -50° (60% from **2**); (g) H_2, Lindlar catalyst, EtOH; (h) NaH, BnBr, DMF, 0°; (i) *n*-Bu_4NF, THF (80% from **4**); (j) MsCl, Et_3N, CH_2Cl_2 0°; (k) CF_3CO_2H, 1,2-dichloroethane, 0°; (l) Et_3N, 1,2-dichloroethane (80% from **5**).

In order to determine the configuration of compound **6**, we decided to use it as a starting material for the synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid **9**. Whereas hydroxypipecolic acids bearing a hydroxy group in various positions have been the subject of many asymmetric syntheses,[2] the first enantioselective synthesis of its *cis*-3-hydroxy isomer **9** has been reported only very recently.[3]



Reagents and conditions: (a) KCN, citric acid, THF/H_2O, 87%; (b) 1N HCl in AcOEt, silica gel, 50% (80% based on recovered **6**); (c) H_2, $Pd(OH)_2$, EtOH, 88%.

To this end, compound **6** was treated with KCN in acidic medium to afford amino nitrile **7** as a single diastereoisomer. No epimerization was observed during the mild hydrolysis of the nitrile function which gave lactone **8**. Finally, hydrogenation over $Pd(OH)_2$ yielded (2*S*,3*S*)-3-hydroxypipecolic acid **9** which was thus obtained in a three-step process from oxadehydroindolizidine **6** (61% overall yield).[4]

As reported above, the formation of amino nitrile **7** occurred in a totally stereoselective way. Nucleophilic attacks on oxazolidines are well-documented and involve the derived iminium ion.[5] In the present case, the starting oxazolidine **6** reacts via its iminium ion **10**. Assuming that the conformation of such a 1,4-cyclohexadiene-like substrate is the classical 1,4-diplanar (boat) form[6] (cf. Fig.1), the stereoselectivity of this addition corresponds to the Felkin-Anh model[7] which favors a transition state with an antiperiplanar position of the strongest acceptor substituent (here the benzyloxy group).

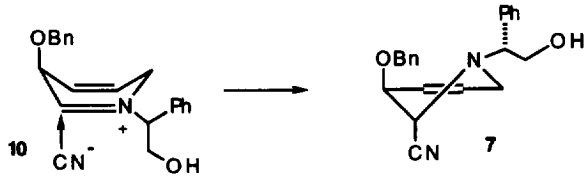


Fig. 1. Felkin-Anh model applied to the stereoselective formation of compound **7**.

There is a general interest in the synthesis of chiral substrates with an indolizidine core[8] since they are related to molecules showing a remarkable biological activity.[9] In this respect, compound **6** might provide an access to polyhydroxylated indolizidines (i.e. analogues of castanospermine) and efforts in this direction are currently being pursued in our laboratory.

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4 Specific rotation of **9**: $[\alpha]_D^{20}$ +15 (*c* 0.5, 10% HCl); lit.[3] $[\alpha]_D^{20}$ +14 (*c* 0.4, 10% HCl).

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