

PII: S0040-4039(96)00767-8

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 (2S,3S)-3-hydroxypipecolic acid 9. Copyright © 1996 Published by Elsevier Science Ltd

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 (2S,3S)-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 (-H₂O); (b) (Boc)₂O, reflux; (c) LiOH, THF/EtOH/H₂O, rt (86% overall yield); (d) *N*-methyl morpholine, *i*-BuOCOCl, THF, then Me(OMe)NH₂+Cl⁻, NEt₃, DMF, -20° (91%); (e) LiC=CCH₂OSiMe₂t-Bu, THF, -78°; (f) NaBH₄, CeCl₃.7 H₂O, EtOH, -50° (60% from 2); (g) H₂, Lindlar catalyst, EtOH; (h) NaH, BnBr, DMF, 0°; (i) *n*-Bu₄NF, THF (80% from 4); (j) MsCl, Et₃N, CH₂Cl₂ 0°; (k) CF₃CO₂H, 1,2-dichloroethane, 0°; (l) Et₃N, 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 (2S,3S)-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/H₂O, 87%; (b) 1N HCl in AcOEt, silica gel, 50% (80% based on recovered 6); (c) H₂, 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 (2S,3S)-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) form⁶ (cf. Fig.1), the stereoselectivity of this addition corresponds to the Felkin-Anh model⁷ 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 core⁸ 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.

References and Notes

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(Received in France 12 April 1996; accepted 20 April 1996)