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Enantioselective synthesis of 2-arylpiperidines from chiral lactams. A concise synthesis of (−)-anabasine

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Cyclodehydration of achiral or racemic aryl-δ-oxoacids with (*R*)-phenylglycinol stereoselectively affords chiral non-racemic bicyclic lactams, from which the enantiodivergent synthesis of (*R*)- and (*S*)-2-phenylpiperidine, the diastereodivergent synthesis of *cis*- and *trans*-3-ethyl-2-phenylpiperidine, and the enantioselective synthesis of the piperidine alkaloid (−)-anabasine is reported.

The search for new methods for the enantioselective synthesis of piperidine derivatives[1] constitutes an area of current interest in pharmaceutical research[2] because this heterocyclic ring is a common moiety in many natural and synthetic biologically active compounds with therapeutic applications.

In previous papers we have described the enantioselective synthesis of diversely substituted piperidines[3] from a chiral bicyclic lactam derived from methyl 5-oxopentanoate and phenylglycinol (Fig. 1, **A**, R_1 = R_2 = H) by successive introduction of the ring substituents. More recently we have reported[4] that the cyclodehydration of racemic δ-ketoacids with (*R*)-phenylglycinol stereoselectively affords one of the four possible chiral bicyclic lactams substituted at the 8 and 8a positions (Fig. 1, **A**, R_1 and R_2 = alkyl or aryl). These lactams can be envisaged as advanced precursors for the synthesis of *cis*- or *trans*-2,3-disubstituted piperidines. The efficiency of this transformation relies on the stereocontrol in the reductive opening of the oxazolidine ring, which involves the 8a stereocentre. In this paper we describe our findings in the stereoselective reduction of 8a-aryl substituted lactams and its application to the enantiodivergent synthesis of 2-arylpiperidines, the diastereodivergent synthesis of *cis*- and *trans*-2-aryl-3-alkylpiperidines, and the enantioselective synthesis of the piperidine alkaloid (−)-anabasine.

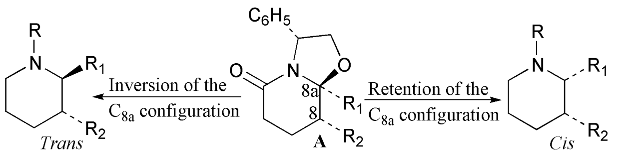
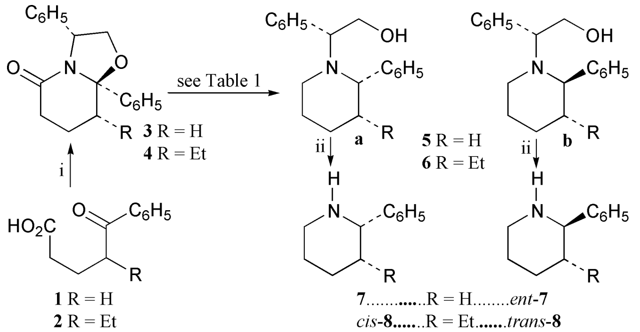


Fig. 1 Stereocontrolled reduction of the C_{8a}-bond.

The 8a-phenyl substituted lactam **3** was readily obtained (90%) as a single stereoisomer from 5-phenyl-5-oxopentanoic acid (**1**) and (*R*)-phenylglycinol (Scheme 1). Treatment of lactam **3** with Red-Al gave 2-phenylpiperidine **5a** as the only stereoisomer detectable by spectroscopic methods (Table 1). However, reduction of **3** with AlH_3 or BH_3 showed poor stereoselectivity, affording mixtures of **5a** and **5b** in which **5a** was the major stereoisomer. Interestingly, treatment of lactam **3** with an excess of 9-BBN provided 2-phenylpiperidine **5b**, resulting from an inversion of the configuration at C-8a, with excellent stereoselectivity. Hydrogenolysis of the benzylic substituent of **5a** and **5b** gave (*S*)-2-phenylpiperidine [**7**, $[\alpha]^{22}_D$ −26.9 (*c* 1.0, MeOH); lit[5] $[\alpha]^{20}_D$ −27.0 (*c* 0.43, MeOH)] and (*R*)-2-phenylpiperidine [*ent*-**7**, $[\alpha]^{22}_D$ +25.2 (*c* 0.4, MeOH; lit[6] $[\alpha]^{24}_D$ +27.6 (*c* 1.0, MeOH)], respectively. The above three-step sequence opens a short enantiodivergent route to 2-arylpiperidines from easily available achiral δ-oxoacids.

Next we turned our attention to the reduction of the 8-ethyl substituted lactam **4**, which was prepared (43%) by cyclocondensation of racemic 4-benzoylhexanoic acid (**2**) with (*R*)-phenylglycinol, in a process involving a dynamic kinetic resolution. The best stereoselectivities in the reduction of lactam **4** were obtained again with Red-Al and 9-BBN, which afforded the *cis*- and *trans*-piperidines **6a** and **6b**, respectively, as single stereoisomers detectable by spectroscopic methods. Reduction of **4** with AlH_3 and BH_3 showed the same level of stereoselectivity we had observed in the reduction of **3**, thus revealing that the C-8 substituent has no influence on the stereoselectivity of the reduction. Removal of the benzylic *N*-substituent of the epimeric piperidines **6a** and **6b** by hydrogenolysis over palladium afforded *cis* and *trans* piperidines **8**, respectively. In this way, starting from easily available racemic γ-substituted δ-oxoacids, the above three-step sequence provides easy access to enantiopure *cis*- and *trans*-3-alkyl-2-arylpiperidines.

The phenyl substituent at the angular 8a-position has a dramatic influence on the stereoselectivity (inversion of configuration) of the above reductions with 9-BBN because 9-BBN reduction of lactam **9**,[4] bearing a 8a-methyl substituent, led to a 9 : 1 mixture (55%) of *cis*-piperidine **10** (retention of the configuration at C-8a) and its C-2 epimer (Scheme 2). As expected, reduction of **9** with Red-Al or AlH_3 afforded *cis*-piperidine **10** as a single stereoisomer, thus providing an efficient entry to enantiopure *cis*-2,3-dialkylpiperidines. Hydro-



Scheme 1 Reagents and conditions: i, (*R*)-phenylglycinol, toluene, reflux; ii, H_2, 10% Pd/C, MeOH, rt, ~70%.

Table 1 Reduction of lactams **3** and **4** to piperidines **5** and **6**

Entry	Lactam	Reductant[a] (equiv.)	Temp./°C (time/h)	Product (**a** : **b** ratio)	Yield (%)
1	**3**	Red-Al (5)	Reflux (8)	**5** (98 : 2)	54
2	**3**	AlH_3 (4)	−78 (1), 25 (2)	**5** (67 : 33)	93
3	**3**	BH_3 (3)	−78 (2), 25 (2)	**5** (60 : 40)	85
4	**3**	BH_3 (3)	Reflux (1)	**5** (73 : 27)	90
5	**3**	9-BBN (10)	Reflux (16)	**5** (3 : 97)	75
6	**4**	Red-Al (2.5)	Reflux (8)	**6** (98 : 2)	56
7	**4**	9-BBN (10)	Reflux (8)	**6** (3 : 97)	86

[a] In THF.

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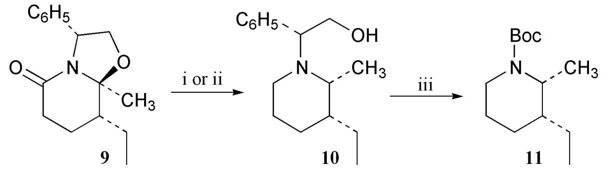
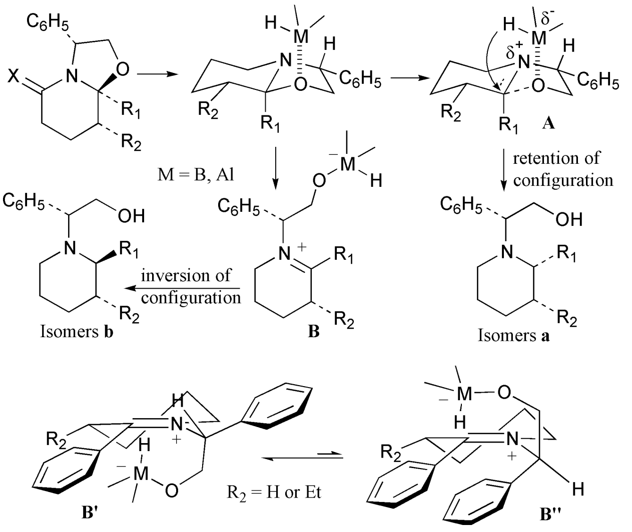


Scheme 2 Reagents and conditions: i, Red-Al, THF, reflux, 8 h, 60%; ii, AlH_3, THF, −78 °C, 90 min, then 25 °C, 2 h, 84%; iii, H_2, $Pd(OH)_2/C$, $(Boc)_2O$, AcOEt, 25 °C, 82%.

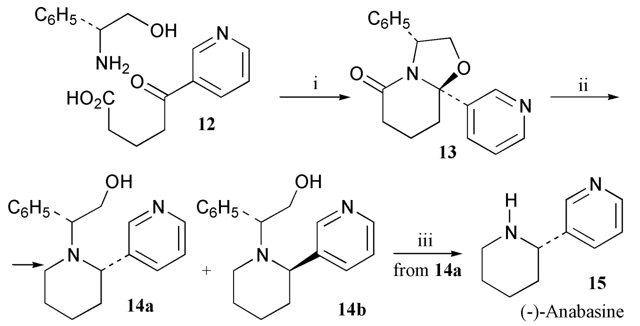


Scheme 3

genolysis of **10** over Pearlman's catalyst in the presence of $(Boc)_2O$ afforded *cis*-2-methyl-3-ethylpiperidine **11**.

The remarkable difference in the stereoselectivity of the above reactions can be explained in terms of the reactive intermediates **A** and **B** as depicted in Scheme 3. Thus, the stereoselectivity in the reduction of related 8a-alkyl substituted lactams ($X = O$, R_1 = alkyl, $R_2 = H$), leading to 2-alkylpiperidines with retention of configuration, has been rationalized[7] by considering that, after the reduction of the carbonyl lactam, the reductive cleavage of the oxazolidine ring takes place through complexation of the oxygen with the reductant, followed by delivery of the hydride from the same face of the C–O bond (**A**). The opposite stereochemical result observed in the reduction of the 8a-aryl substituted lactams **3** and **4** with 9-BBN suggests that, using this reductant, the reaction takes place through a different pathway involving the formation of the ion paired intermediate **B** ($R_1 = C_6H_5$). The intramolecular delivery of the hydride under stereoelectronic control from the preferred conformation **B′** accounts for the stereoselective formation of isomers **b** of piperidines **5** and **6**. Due to steric interactions, the 9-BBN reduction of intermediate **A** is slower than the formation of the iminium salt **B** ($R_1 = C_6H_5$). Moreover, the presence of the 8a-phenyl group in lactams **3** and **4** contributes to the stabilization of this intermediate **B**, making the C–O bond here more prone to undergo cleavage than in 8a-alkyl lactams. This is in agreement with the different stereoselectivity in the 9-BBN reduction of **9**, where **10**, resulting from a retention of configuration, was the major stereoisomer.

To further illustrate the potential of the cyclodehydration-stereocontrolled reduction sequence here developed, we undertook the synthesis of the tobacco alkaloid (−)-anabasine.[8] The required bicyclic lactam **13** was obtained as a single stereoisomer by cyclocondensation of keto-acid **12**[9] with (*R*)-phenylglycinol in refluxing toluene (Scheme 4). Although



Scheme 4 Reagents and conditions: i, toluene, reflux, 24 h, 58%; ii, $LiAlH_4$ (10 equiv.), rt, 15 h; iii, H_2, $Pd(OH)_2$, MeOH, rt, 81%.

treatment of **13** with Red-Al or BH_3 afforded complex mixtures resulting from partial reduction of the heteroaromatic ring, more satisfactorily, reduction of **13** with 9-BBN in refluxing THF provided (73%) a 37:63 mixture of isomers **14a** and **14b**, respectively. The lower stereoselectivity of this reduction as compared with the 9-BBN reduction of the related phenyllactams **3** and **4** probably reflects the lesser ability of pyridine, a π-deficient heterocycle, to stabilize the intermediate iminium ion **B** in comparison with a phenyl group. In this series, the best result regarding stereoselectivity was obtained when **13** was treated with an excess of $LiAlH_4$. The desired piperidine **14a** was obtained in 78% yield along with only minor amounts (6%) of its epimer **14b**. Hydrogenolysis of pure isomer **14a** over Pearlman's catalyst afforded the alkaloid (−)-anabasine [**15**, $[\alpha]^{22}_D$ −74.7 (*c* 0.1, $CHCl_3$); lit.[8] $[\alpha]^{23}_D$ −75.5 (*c* 0.1, $CHCl_3$)].

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