ASYMMETRIC SYNTHESIS WITH CHIRAL HYDROGENOLYSABLE AMINES : A NEW ROUTE TO ENANTIOPURE CYCLIC β-AMINO ALCOHOLS

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Abstract - Enantiopure prolinol and pipecolinol have been obtained *via* diastereoselective chemical reduction of chiral 2,3-dihydro-6*H*-1,4-oxazin-2-ones (5).

We have recently described[2] a new general synthesis of enantiopure aliphatic ethanolamines based on a catalytic diastereoreductive amination of α-halomethyl ketones. The chiral auxiliary we used was α-phenylglycine as both enantiomers were commercially available and inexpensive.

We report here preparation and chemical diastereoselective reduction of cyclic imines (5) which have allowed to obtain optically pure prolinol (**1a**) and pipecolinol (**1b**) (Scheme 1).The prolinol was commonly used as chiral auxiliary [3] or as building block in alkaloid synthesis.[4]

Thus, chloroketo esters (**3**) were readily obtained in good yields from keto diesters (**2**)[5] using monochlorination with sulfuryl chloride, acidic hydrolysis and decarboxylation (**3a**: 72 % ;**3b**: 80 %).[6,7] The condensation of potassium (*R*)-*N*-carbobenzyloxy-α-phenylglycinate with chloroketo esters (**3**) in DMF at room temperature for 14-16 h gave the desired keto diesters (**4**) in excellent yields (**4a**: 94 % ; **4b**: 98 %) . Amine deprotection of (4) with hydrobromic acid followed by neutralisation of the resulting hydrobromides furnished chiral oxazinones (**5**) (**5a**: 94 % ; **5b**: 95 %).

The oxazinones (**5**) were reduced with sodium cyanoborohydride, sodium triacetoxyborohydride or diborane in various conditions (Table 1) yielding a mixture of morpholinones (**6**) and (**7**) with 60-92 % d.e.[8] The best diastereoselectivity and chemical yields were obtained with diborane-THF in acetonitrile at room temperature. The major *cis* diastereomer (**7**)[9] was isolated by chromatography in good yield.

Cyclisation of *cis*-morpholinones (**7**) in toluene provided bicyclic lactams (**8**) (**8a**: 85 % ; **8b**: 92 %). These lactams underwent effective reduction[10] to produce cyclic amino diols (**9**) in excellent yields (Table 2).

The amine deprotection of **9** was easily performed by hydrogenolysis (H_2, 1 atm, 10 % Pd-C, MeOH, 2 h) in 90 % yield leading to (*S*)-prolinol (**1a**) $[\alpha]_D^{21}$ + 30.4° (c 1, toluene)[lit.,[11]: + 31° (c 1, toluene)] and (*S*)-pipecolinol (**1b**) $[\alpha]_D^{21}$ + 15.9° (c 2.5, ethanol)[lit.,[12]: -16.0° (c 2.34, ethanol)].

Table 1 : Reduction of oxazinones (**5**)

n	Reagents	Temperature (°C)	Time (h)	(7) / (6) *cis* / *trans*	Morpholinones (7) (%)[a]
3	$NaBH(OAc)_3$-TMSCl / MeCN[b]	20	4	80 / 20	60
3	BH_3 - THF / MeCN[c]	20	3	96 / 4	76
3	"	0	5	90 / 10	68
3	"	-40	5	85 / 15	—
3	BH_3 - THF / THF	20	3	90 / 10	64
2	$NaBH(OAc)_3$-TMSCl / MeCN	20	4	80 / 20	63
2	BH_3 - THF / MeCN	20	3	95 / 5	80

[a] Chromatographed products

[b] $NaBH(OAc)_3$ (1.6 eq) , TMSCl (1.2 eq)

[c] BH_3- THF (1 $mol.l^{-1}$) (1.4 eq)

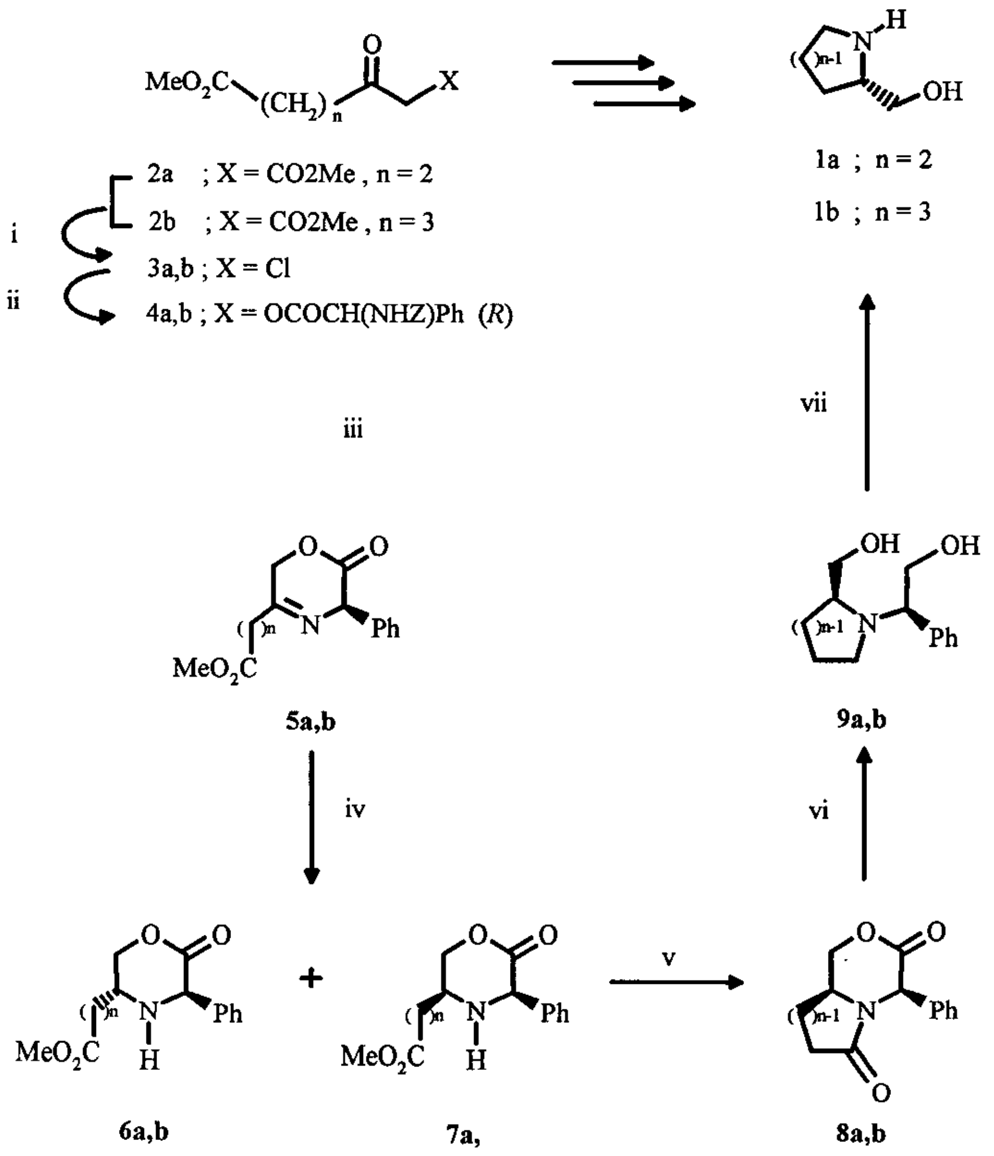
Table 2 : Reduction of lactams (**8**)

n	Reagents	Temperature (°C)	Time (h)	Cyclic Amino diols(9) (%)[a]
3	$LiAlH_4$ / THF[b]	20	2	82
2	"	20	2	77
3	BH_3 -THF / THF[c]	20	3	90
2	"	20	3	88

[a] Chromatographed products.

[b] $LiAlH_4$ (6 eq)

[c] BH_3-THF (1 $mol.l^{-1}$) (2.5 eq)



(i) SO_2Cl_2 then H_2SO_4 ; (ii) (*R*)- Ph (NHZ) CO_2K, DMF, room temperature ; (iii) HBr-AcOH (33 %) ; (iv) reduction (Table 1), chromatographic separation ; (v) Toluene reflux, 10-20 h ; (vi) reduction (Table 2) ; (vii) MeOH, H_2 ,1 atm, 10 % Pd-C, room temperature ,2 h.

Scheme 1

In summary, the enantioselective synthesis of cyclic β-amino alcohols has been accomplished. The strategy presented here provides a convenient synthesis of (-)-or (+)-prolinol and -pipecolinol from two commercially available enantiomers of α-phenylglycine with respectively an overall yield of 48 % and 53 %.

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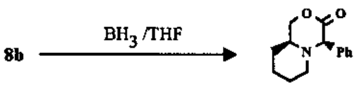
8 Diastereomeric ratios were determined analysing crude products by ^{1}H nmr (200 MHz) and glc.
9. The *cis* stereochemistry of the predominant diastereomer was established unambigously by NOE experiment between hydrogens H-3 and H-5.
10. With 2.2 eq of BH_3, reduction exclusively occurs on the lactam function :



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