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**)

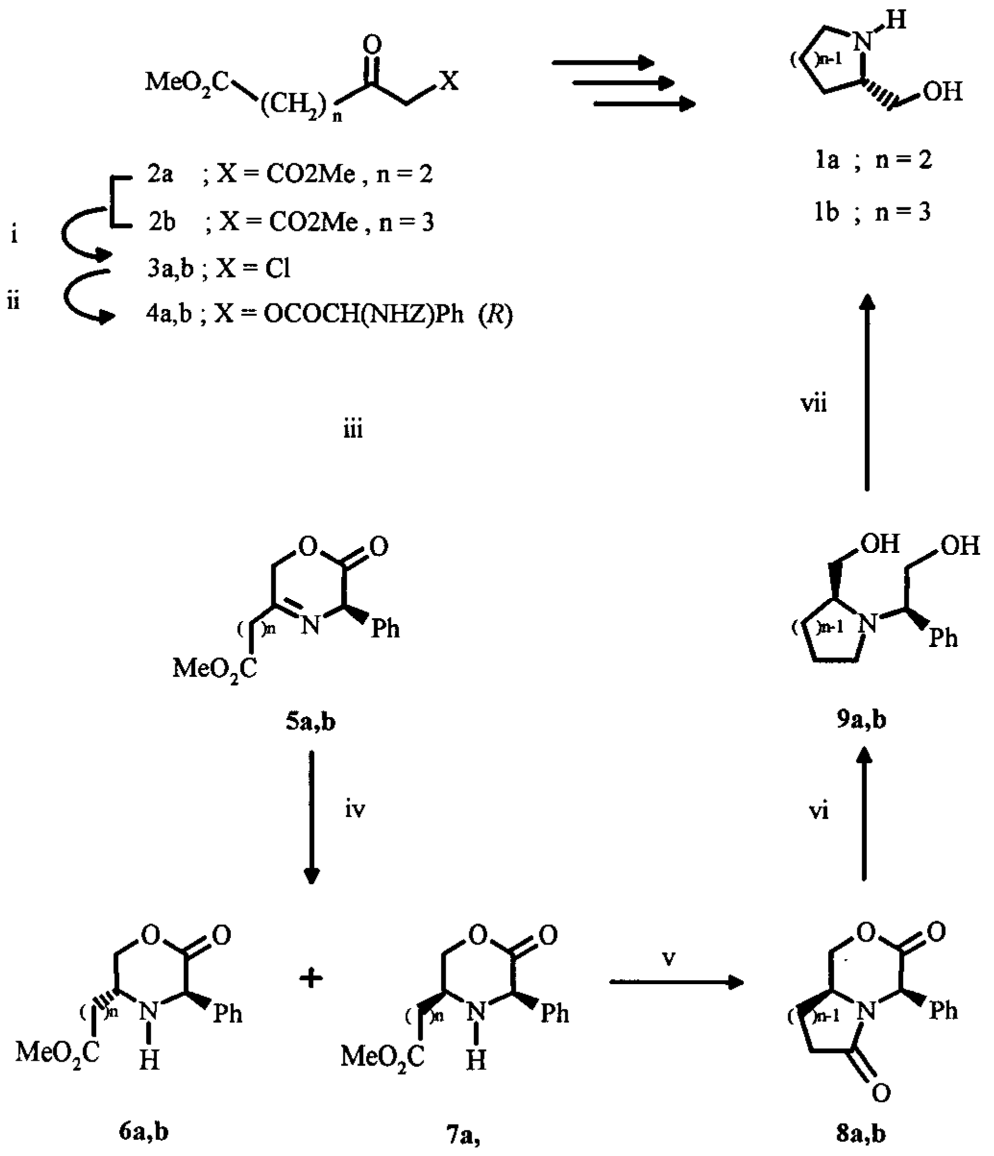
n	Reagents	Temperature (°C)	Time (h)	(7) / (6) *cis / trans*	Morpholinones (7) (%)[a]
3	$NaBH(OAc)_3$-TMSCl / MeCN[b]	20	4	80 / 20	60
3	BH_3 - THF / MeCN[c]	20	3	96 / 4	76
3	"	0	5	90 / 10	68
3	"	-40	5	85 / 15	—
3	BH_3 - THF / THF	20	3	90 / 10	64
2	$NaBH(OAc)_3$-TMSCl / MeCN	20	4	80 / 20	63
2	BH_3 - THF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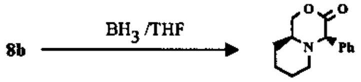
REFERENCES AND NOTES

1. Abstracted from Olivier Lingibé's Thesis, Université P. et M. Curie, Paris, Septembre 1994.
2. O. Lingibé, B. Graffe, M.C. Sacquet, and G. Lhommet, *Heterocycles,* 1994, **37**, 1469.
3. D. Enders, in *Asymmetric Synthesis*, Ed., J.D. Morrison, Academic Press, Inc., London, 1984; Vol. 3 ; Chapter 4. H.S. Moon, N.E. Schore, and M.J. Kurth, *J. Org. Chem.*, 1992, **57**, 6088. J.M. Brunel, M. Maffei, and G. Buono, *Tetrahedron Asymmetry,* 1993, **4**, 2255. C.F. Bigge, J.P.Wu, T.C. Malone, C.P. Taylor, and M.G. Vartanian, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 39. F. Cavelier, S. Gomez, R. Jacquier, and J. Verducci, *Tetrahedron Asymmetry,* 1993, **4**, 2501.
4. M.L. Morris and M.A. Sturgess, *Tetrahedron Lett.*,1993, **34**, 43. T. Sato, K. Tsujimoto, K. Matsubayashi, H. Ishbashi, and M. Ikeda, *Chem. Pharm. Bull.*, 1992, **40**, 2308.
5. J.P. Célérier, E. Marx, and G. Lhommet, *J. Heterocycl. Chem.*, 1988, **25**, 1275.
6. N. De Kimpe, W. De Cock, and N. Schamp, *Synthesis*, 1987, 188.
7. Preparation from acetylsuccinate and 2-acetylglutarate see M.A. Salih, F. Compernolle, S. Van den Branden, W. De Buysser , and G. Hoornaert, *J. Org. Chem.*, 1993, **58**, 690.
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 :



11. Aldrich catalogue 1994-1995.
12. H. Ripperger and K. Schreiber, *Tetrahedron*, 1965, **21**, 1485.

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