Tetrahedron Letters, Vol.32, No.49, pp 7183 7186, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF (D)- AND (L)-FORMS OF DIFFERENTIALLY PROTECTED 2-PIPERIDINEMETHANAMINE

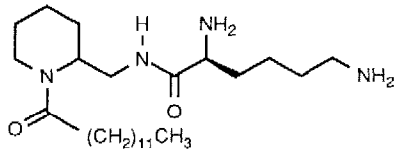
John Perumattam*, Barry G. Shearer, William L. Confer, and Rose M. Mathew

Nova Pharmaceutical Corporation, 6200 Freeport Centre, Baltimore, MD 21224, USA

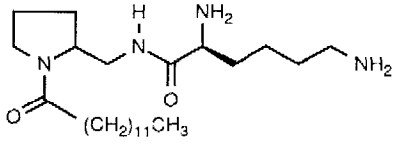
Key Words: Piperidinemethanamine; Pyrrolidinemethanamine; Protein Kinase C Inhibitor

Abstract. (D)- and (L)-isomers of pipecolic acid were converted into (D)- and (L)-2-piperidinemethanamine using an efficient sequence. The amino groups were selectively protected for further functionalization.

2-Piperidinemethanamines are valuable synthons for the preparation of several pharmaceuticals.[1] In all cases a racemic mixture of piperidinemethanamine, derived from the catalytic reduction of readily available pyridine-2-methylamine,[2] was utilized. Recently we have reported that substituted piperidinemethanamine **1** and pyrrolidinemethanamine **2** exhibited potent and selective protein kinase C inhibitory activity.[3]

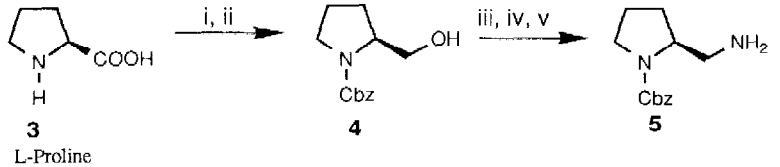


1



2

Thus we required the optical isomers of piperidinemethanamine and pyrrolidinemethanamine. Optically pure forms of pyrrolidinemethanamine were prepared by a general synthetic sequence as outlined below (Scheme 1).



3 L-Proline

4

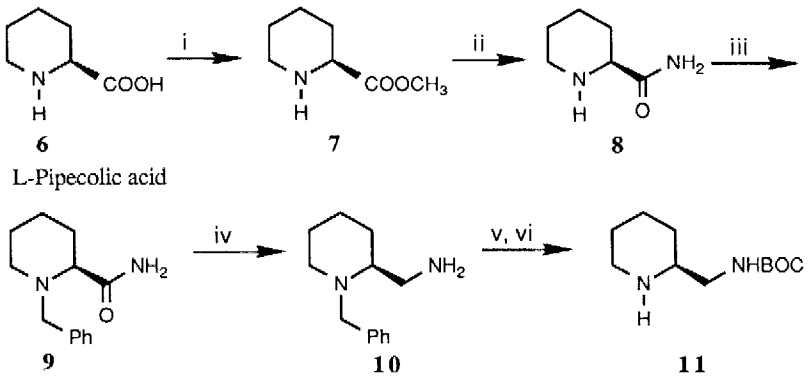
5

i) Cbz-Cl/aq.Na_2CO_3 ; ii) BH_3/THF, 0° C to r.t. ; iii) TsCl/Py, 0° C to r.t.; iv) NaN_3/DMF, reflux; v) PPh_3/NH_4OH/MeOH

Scheme 1

Surprisingly, a similar protocol was unsuccessful in the homologous piperidine system. This observation may be attributed to the flexible nature of the piperidine ring and the strong neighboring group participation of

the ring nitrogen.[4] Attempts to tosylate the N-benzyloxycarbonylpiperidine-2-methanol under basic conditions gave only the cyclized oxazalone. Various other methods of converting the alcohol into the primary amine[5] were not successful. Here we report an efficient synthesis of optically pure protected 2-piperidinemethanamine starting from (D)- and (L)-pipecolic acid (Scheme 2).



i) HCl/MeOH; ii) conc.NH_4OH; iii) BnlBr/Et_3N/CH_2Cl_2; iv) $LiAlH_4$/THF; v) $(t\text{-}BuOCO)_2O$/THF; vi) H_2/10%Pd-C/MeOH

Scheme 2

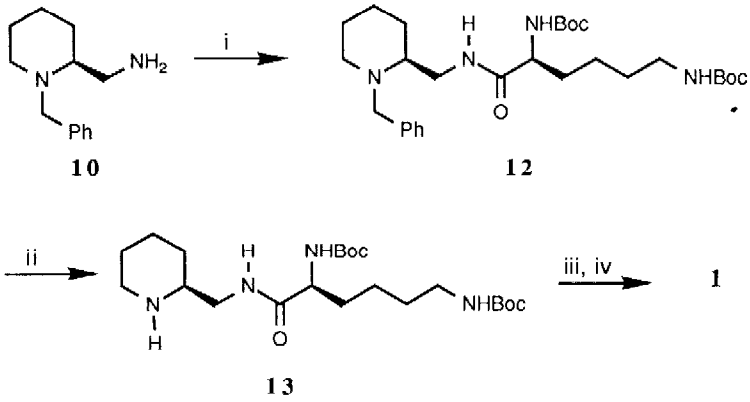
The (D)- and (L)-pipecolic acids are commercially available (Bachem Bioscience) or can be prepared from the DL-mixture by optical resolution technique as described by Hardtman.[6] The corresponding methyl

Table 1

No.	Compound[8]	Yield (%)	m.p. (°C)	Specific Rot. $[\alpha]^{25}D$
6	L-Pipecolic acid		277-279	(-)26.5° (c = 1.6, H_2O)
	D-Pipecolic acid		(decomp)	(+)24.6° (c = 5, H_2O)
7	L-form.HCl	81	170-171	(-)9.1° (c = 3.6, H_2O)
	D-form.HCl	73		(+)9.1° (c = 3.4, H_2O)
8	L-form[9]	75	162-163	(-)32.4° (c = 3.2, EtOH)
	D-form	85		(+)31.6° (c = 2.3, EtOH)
9	L-form	80	103-104	(-)90.7° (c = 2.5, EtOH)
	D-form	80		(+)92.9° (c = 1.9, EtOH)
10	L-form	92	oil	(-)61.2° (c = 3, EtOH)
	D-form	90		(+)58.2° (c = 1.6, EtOH)
11	L-form	93	108-110	(+)9.8° (c = 2.2, EtOH)
	D-form	91		(-)10.0° (c = 1.7, EtOH)

ester 7 of (D)- or (L)-pipecolic acid was then converted into carboxamide[7] **8** using conc.NH_4OH. Benzylation of the ring nitrogen (**9**) and reduction of the amide using $LiAlH_4$ in THF provided the chiral monoprotected piperidinemethanamine **10**. Likewise, protection of the primary nitrogen as BOC, followed by debenzylation of the ring nitrogen yielded the second monoprotected diamine **11**. Compounds **10** and **11** are now available in their protected form and can be used for further synthetic elaboration. Mild conditions are used throughout the synthesis and there was no evidence of any racemization. The yields and the optical rotations of the intermediates are given in Table 1.

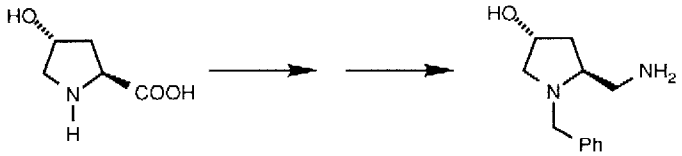
Coupling of the chiral amine **10** with N-BOC-protected L-lysine using EDC/HOBT gave the corresponding amide **12**. Debenzylation (H_2, 10 % Pd-C/MeOH, 55 psi, 20 h) followed by coupling of the secondary nitrogen with tridecanoic acid and deprotection of BOC provided the desired PKC inhibitor **1** in optically pure form as its dihydrochloride salt (Scheme 3).



i) Boc-L-lysine(Boc)-OH, EDC, HOBT, NMM, CH_2Cl_2, rt; ii) H_2, 10%Pd/C, MeOH, 55psi;
iii) $CH_3(CH_2)_{11}CO_2H$, EDC, HOBT, NMM, CH_2Cl_2, rt; iv) HCl/dioxane, rt

Scheme 3

This methodology can also be applied to proline systems with equal efficiency. We have prepared trans-4-hydroxy-L-pyrrolidine-2-methanamine **15** from trans-4-hydroxy-L-proline **14;** the presence of hydroxy group did not affect the reaction sequence.



Acknowledgment: We are grateful to Dr. Carl Kaiser for his advice during the course of this work.

References and Notes

1. Flecainide acetate; R-818: E. H. Banitt and G. J. Conard *J. Labelled Compd. and Radiopharm.* **1981**, 28, 713-719; 7-Chloro-4-(2-piperidylmethylamino)-quinoline: T. R. Norton, A. A Benson, R. A. Seibert, F. W. Bergstrom *J. Am. Chem. Soc.* **1946,** 68, 1330; N-Acyl(aminomethyl)piperidine as analgesics: A. Terada, Y. Iizuka, K. Wachi, K. Fujibayashi Eur. Pat. Appl. EP 356,247, 28 Feb 1990; V. Vecchietti, M. Signorini, A. Giordani Eur. Pat. Appl. EP 260,041, 16 Mar 1988.

2. T. R. Norton, A. A. Benson, R. A. Seibert, F. W. Bergstrom *J. Am. Chem. Soc.* **1946,** 68, 1330; H. J. Beim and A. R. Day *J. Heterocycl. Chem.* **1970,** 7, 355.

3. a) B. G. Shearer, J. P. Sullivan, J. P. Carter, R. M. Mathew, P. Wade, J. R. Connor, C. Ko, R. J. Patch, and R. M. Burch, Abstract No. 25, 202nd American Chemical Society Meeting, New York, August 25-30, 1991; b) B. G. Shearer, J. Perumattam, W. L. Confer, R. M. Mathew, J. P. Carter, J. R. Connor, C. Ko, and R. M. Burch, Abstract No. 26, 202nd American Chemical Society Meeting, New York, August 25-30, 1991.

4. C. F. Hamer, S. R. Heller, J. H. Craig *Tetrahedron,* **1972**, 28, 239; T. Rosen, S. W. Fesik, D. T. W. Chu, A. G. Pernet *Synthesis,* **1988**, 40-44.

5. E. Fabiano, B. T. Golding, and M. M. Sadeghi *Synthesis*, **1987**, 190-192.

6. G. E. Hardtman, W. J. Houlihan, A. Giger, US Patent, 4,760,065, Jul. 26, 1988.

7. See ref. 6.

8. All compounds were characterized by their IR, NMR, and analysis data.

9. As an improved technique (ref.5) we evaporated the aqueous ammonium hydroxide to a solid residue which was then recrystallized to get carboxamide **8** in higher yields.

(Received in USA 5 September 1991)