Tetrahedron: Asymmetry Vol. 4, No. 2, pp. 205-206, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

The Synthesis of Homochiral Naturally Occurring Hydroxy Amides

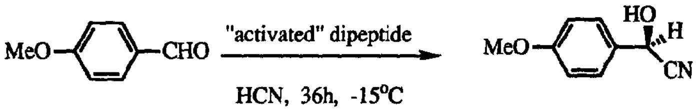
Roger F.C.Brown, W. Roy Jackson and Tom D. McCarthy*
Department of Chemistry, Monash University, Wellington Road, Clayton, 3168, Victoria, Australia.

(*Received in UK 7 January* 1993)

Abstract: The chiral naturally occurring hydroxy amides, (-)-tembamide and (-)-aegeline, have been synthesised in two steps from (R)-2-hydroxy-2-(4-methoxyphenyl)acetonitrile

Tembamide (3) and aegeline (4) are naturally occurring hydroxyamides isolated from various members of the family Rutaceae.[1,2,3,4] These hydoxyamides have been reported to have adrenaline-like and insecticidal activity[5] and extracts of *Aegle marmelos* Corr., which contain tembamide(3), have been used in traditional Indian medicines and show hypoglycaemic activity.[6]

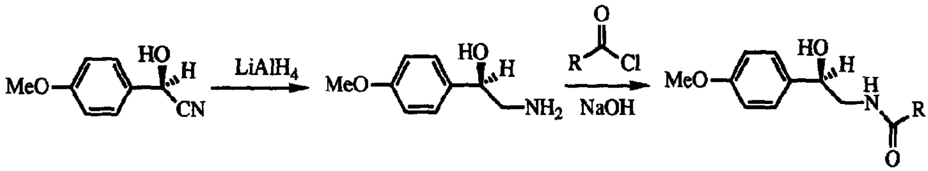
Tembamide (1) and aegeline (2) possess a stereogenic centre and have been isolated as total or partial racemates.[7] We were interested in synthesising both enantiomers of tembamide (1) and aegeline (2) for use in biological testing. Previous synthetic work has led to racemic samples of tembamide (1) and aegeline (2)[5] while both enantiomers of tembamide (1) and aegeline (2) have been prepared by a resolution of racemic aminoalcohol (2).[7] We now report a high yielding synthesis of the (R) enantiomer of tembamide (1) and of aegeline (2) in three steps from *para*-methoxybenzaldehyde.[8]



1

Method of Activation	Conversion	%e.e.
Freeze dried	96%	92%
Precipitation	98%	>99%

para-Methoxybenzaldehyde was treated with hydrogen cyanide in the presence of (S,S)-cyclo(phenylalanylhistidyl), the "Inoue catalyst"[9,10,11], to give the (R)-cyanohydrin (1)[12,13]. The method of activation of the catalyst has an effect on the enantioselectivity of the reaction. If the dipeptide is freeze dried[14] prior to its addition to the reaction, cyanohydrin (1) is obtained with an enantiomeric excess of 92%.[15] Recrystallisation of the crude product from dichloromethane/light petroleum gave pure (R)-cyanohydrin (1) in 87% yield. However if the dipeptide was precipitated from a methanol solution by the addition of ether[16], the enantiomeric excess of the (R) enantiomer increased to >99% at 98% conversion. Recrystallisation of this material gave pure (R)-cyanohydrin (1) in 94% yield.



1 $[\alpha]_D^{24}$=+48.8 **2** $[\alpha]_D^{24}$=-36.6 **3** R=Ph $[\alpha]_D^{24}$=-59.8

4 R=(*E*)-Ph-CH=CH- $[\alpha]_D^{24}$=-35.6

Lithium aluminium hydride reduction of cyanohydrin (1) overnight at room temperature gave the amino alcohol (2)[17] in 85% yield. Diborane has been reported to be superior to $LiAlH_4$ for this reduction[5], however if the reaction with $LiAlH_4$ is not allowed to rise above room temperature and the excess hydride is destroyed with sodium potassium tartrate, good yields of the amino alcohol can be obtained. Acylation of the aminoalcohol (2) with benzoyl chloride gave (-)-tembamide (3) in 90% yield. When the aminoalcohol (2) was treated with *trans*-cinnamoyl chloride (-)-aegeline (4) was produced in 93% yield. The optical rotations were in good agreement with those reported in the literature.[7]

Formal syntheses of both enantiomers of tembamide (3) and aegeline (4) are thus available as the (S)-enantiomer of cyanohydrin (1) can be prepared using (R, R)-cyclo(phenylalanylhistidyl) as a catalyst.

Acknowledgements: We thank H. Jacobs for initial experiments and the Australian Research Council (ARC) for financial support.

References and Notes

1. Kuck, A.M., Albonico, S.M. and Deulofeu,V., *Chem. and Ind.*, (1966), 945.
2. Chatterjee, A. and Bose, S., *J. Indian Chem. Soc.*, (1952), **29**, 425.
3. Johns, S.R., Lamberton, J.A. and Price, J.R., *Aust. J. Chem.*, (1967), **20**, 2795.
4. Johns, S.R., Lamberton, J.A., Tweeddale, H.J. and Willing, R.I., *Aust. J. Chem.*. (1969), **22**, 2233.
5. Somanathan, R., Aguilar, H.R. Ventura, R. and Smith, K.M., *Syn. Comm.*, (1983), **13**, 273.
6. Shoeb, A., Kapil, R.S., Popli, S.P., *Phytochemistry*, (1973), **12**, 2071.
7. Kuck, A.M., Albonico, S.M. and Deulofeu,V., *J. Chem. Soc., Section C*, (1967), 1327.
8. All compound discussed in this communication gave satisfactory ^1H n.m.r., i.r. and mass spectra. The optical rotations and melting points agreed with those reported in the literature.
9. Tanaka, K., Mori, A., Inoue, *J.Org.Chem.*, (1990), **55**,181 and references cited therein.
10. Jackson, W.R., Jayatilake, B.R., Matthews, B.R. and Wiltshire, C., *Aust. J. Chem.*, (1988), **41**, 203.
11. Jackson, W.R., Jacobs, H.A., Jayatilake, B.R., Matthews, B.R. and Wiltshire, C., *Aust, J. Chem.*, (1988),**41**, 1697.
12. Brussee, J., Roos, E.C. and Van Der Gen, A., *Tetrahedron letters*, (1988), **29**, 4485.
13. The optical rotation and melting point for (R)-2-hydroxy-2-(4-methoxyphenyl)acetonitrile previously reported by us (ref. 11) were incorrect. The optically pure material used in this work had $[\alpha]_D^{24}$=+48.8, c=1, $CHCl_3$ and m.p. 74-76°C. These values are in good agreement with those reported in the literature (ref. 12).
14. Stoutamire, D.W., Tienan, C.W. and Dong, W., Shell Oil Co., U.S. Pat. Applications 443,513; 443763 and 443764 (filed 22 November 1982); Stoutamire, D.W. and Dong, W., Shell Oil Co., U.S. Pat. 4,594,196 (granted 10 June 1986).
15. The enantiomeric excess of the cyanohydrin (1) was obtained from the ^1H n.m.r. spectra of the derived (R)-Mosher's ester.
16. Danda, H., *Synlett*. (1991), 263.
17. Brussee, J., Dofferhoff, F., Kruse, C.G. and Van Der Gen, A., *Tetrahedron*, (1990), **46**, 1653.