Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 8, pp. 1463-1464, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00209-6

A SHORT APPROACH TO FUNCTIONALISED HOMOCHIRAL PIPERIDINONES

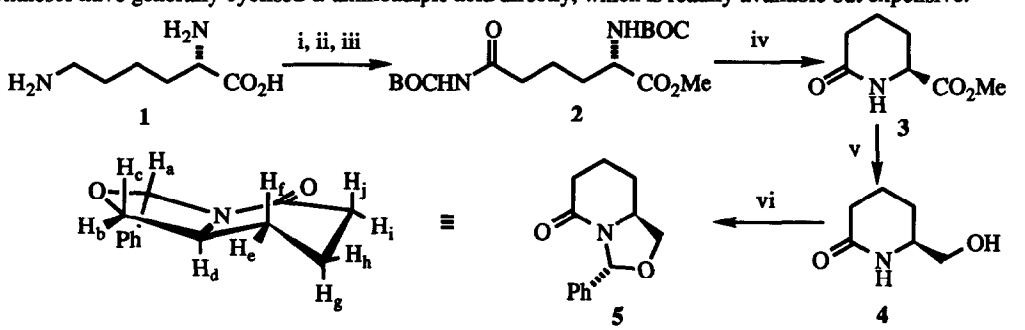
Stephen A. Hermitage and Mark G. Moloney*

The Dyson Perrins Laboratory, University of Oxford, South Parks Rd, Oxford. OX1 3QY.

Abstract: The preparation of homochiral lactam **4** in 5 steps from *(S)*-lysine is described. Conversion to bicyclic *O,N*-acetal **5** provides a useful template for further elaboration to highly substituted piperidinones with excellent diastereoselectivity.

Because of the widespread occurrence of the piperidine ring skeleton in naturally occurring compounds[1-3], and their importance in pharmacologically active compounds[4-6], the preparation of such saturated heterocycles has attracted considerable attention[7-16]. However, more general methods for the preparation of substituted piperidines, which allow functionalisation at any or all positions of the heterocyclic ring with a wide variety of substituents, and in a stereocontrolled manner, are lacking[17]. We report here a method for the convenient preparation from *S*-lysine of homochiral methyl 6-oxopipecolate and its further conversion to more highly substituted bicyclic piperidinones *via* a chiral bicyclic template that permits diastereoselective functionalisation around the piperidine ring.

(S)-Lysine(e.e. 92%) **1** was readily converted[18] to the protected *(S)*-α-aminoadipic acid derivative **2** by esterification, *N*-protection, and oxidation of the ω-amino function with ruthenium dioxide/sodium periodate using literature procedures[19] in 73% yield over the three steps (Scheme 1). The preparation of α-aminoadipic acid and its derivatives has attracted considerable attention.[20, 21] Adipamide **2** could be easily cyclised to the corresponding lactam in refluxing trifluoroacetic acid, to give methyl 6-oxopipecolate **3**. The α-ester function was reduced to the alcohol **4** with sodium borohydride (37% yield over the two steps). The optical purity of this compound, determined from the MTPA ester[22] was 90%[23]. This represents an efficient synthesis of protected homochiral 6-oxopipecolic acid, from a readily available and inexpensive starting material; previous syntheses have generally cyclised α-aminoadipic acid directly, which is readily available but expensive.[24-26]

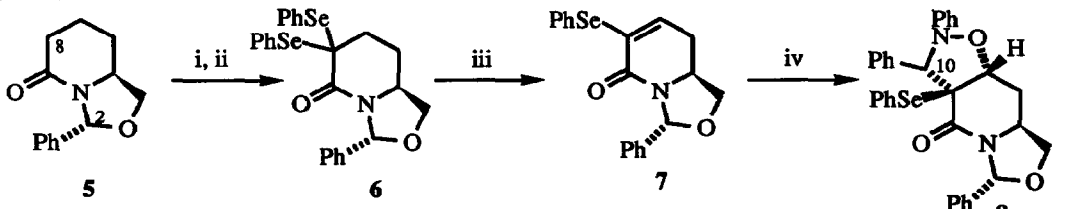


(i) $(MeO)_2CMe_2$, HCl, MeOH ; (ii) BOC_2O, $NaHCO_3$, MeOH, sonicate; (iii) RuO_2, $NaIO_4$, EtOAc, H_2O; (iv) TFA ; (v) $NaBH_4$, EtOH ; (vi) $PhCH(OMe)_2$,TsOH, 80°C, 72h

Scheme 1

Treatment of lactam alcohol **4**, obtained directly from the reduction step, with benzaldehyde dimethyl acetal gave the bicyclic benzylidene *O,N* acetal **5** in 68% yield[27]. ^1H NMR spectroscopic investigations of **5** suggest that the most stable solution conformation is as shown in Scheme 1, as evidenced by n.O.e. results, and a clear W-coupling in the 2D ^1H COSY spectrum between H_e and H_i.

Deprotonation of **5** with LiHMDS in THF, followed by phenylselenyl chloride (2 equivalents) gave the selenoacetal **6**, which could be cleanly converted to the vinylselenide **7** in 26% over 2 steps using the standard oxidation and elimination conditions(mCPBA). No evidence for oxidation of both phenylselenyl groups was observed. Related alkylations both in simple piperidinones[28-30], and in a related homochiral bicyclic lactam[31], have been described. Reaction of **7** with *N*,α-diphenyl nitrone gave the cycloadduct **8** as a single diastereomer in 98% yield (based on recovered starting material), in which the nitrone dipole had approached exclusively from the *exo*-face of the substrate with the expected regiochemistry; however, the stereochemistry at C-10 could not be established. Similar selectivity is simple lactones has been recently observed[32].



5 **6** **7** **8**

(i) LiHMDS, THF ; (ii) 2PhSeCl, THF ; (iii) mCPBA, CH_2Cl_2 ; (iv) $PhCH{=}N^{+}(Ph)O^{-}$

Scheme 2

These results demonstrate the preparation and utility of the templates **5** and **7** for the construction of substituted piperidines, and further work in this area will be reported in due course.

Acknowledgements: MGM gratefully acknowledges Zeneca for a Strategic Research Award.

References

1. Baliah, V., Jeyeraman, K. and Chandrasekaran, L., *Chem. Rev.*, 1983, **83**, 379-423.
2. Pinder, A.R., *Nat. Prod. Rep.*, 1990, **7**, 447-455 and earlier reports.
3. Attygalle, A.B. and Morgan, E.D., *Chem. Soc. Rev.*, 1984, **13**, 245-278.
4. Houpis, I.N., *et al.*, *Tetrahedron Lett.*, 1993, **34**, 2593-2596.
5. Skiles, J.W., *et al.*, *Biorg. Med. Chem. Lett.*, 1993, **3**, 773-776.
6. Perumattam, J., Shearer, B.G., Confer, W.L. and Mathew, R.M., *Tetrhedron Lett.*, 1991, **32**, 7183-7186.
7. Lu, Z.-H. and Zhou, W.-S., *J. Chem. Soc., Perkin Trans. 1*, 1993, 593-596.
8. Jefford, C.W. and Wang, J.B., *Tetrahedron Lett.*, 1993, **34**, 2911-2914.
9. Keck, G.E. and Palani, A., *Tetrahedron Lett.*, 1993, **34**, 3223-3224.
10. Knight, D.W., Lewis, N., Share, A.C. and Haigh, D., *Tetrahedron:Asym*, 1993, **4**, 625-628.
11. Gomez-Monterrey, I., Gonzalez-Muniz, R., Herranz, R. and Garcia-Lopez, M.T., *Tetrahedron Lett.*, 1993, **34**, 3593-3594.
12. Beak, P. and Lee, W.K., *J. Org. Chem.*, 1993, **58**, 1109-1117.
13. Bailey, P.D., Brown, G.R., Korber, F., Reed, A. and Wilson, R.D., *Tetrahedron:Asymmetry*, 1991, **2**, 1263-1282.
14. Jones, R.C.F., Turner, I. and Howard, K.J., *Tetrahedron Lett.*, 1993, **34**, 6329-6332.
15. Caballero, E., Puebla, P., Medarde, M. and Feliciano, A.S., *Tetrahedron*, 1993, **49**, 10079-10088.
16. Royer, J. and Husson, H.-P., *Janssen Chimica Acta*, 1993, **11**, 3-8.
17. Oppolzer, W. and Merifield, E., *Helv. Chim. Acta*, 1993, **76**, 957.
18. All new compounds gave satisfactory spectroscopic and high resolution mass spectroscopic or analytical data.
19. Yoshifuji, S., Tanaka, K.-I. and Nitta, Y., *Chem. Pharm. Bull.*, 1987, **35**, 2994-3001.
20. Bergmeier, S.C., Cobas, A.A. and Rapoport, H., *J. Org. Chem.*, 1993, **58**, 2369-2376.
21. Amoroso, R., Cardillo, G., Romero, M.S. and Tomasini, C., *Gazz. Chim. Ital.*, 1993, **123**, 75-8.
22. Dale, J.A. and Mosher, H.S., *J. Am. Chem. Soc.*, 1969, **95**, 512-519.
23. Huang, S.-B., Nelson, J.S. and Weller, D.D., *Syn. Commun.*, 1989, **19**, 3485-3496.
24. Miller, S.M. and Nutt, R.F., 1980, British Patent 1,569,486.
25. Greenstein, J.P., Birnbaum, S.M. and Otey, M.C., *J. Am. Chem. Soc.*, 1953, **75**, 1994-1995.
26. Prassad, K.U., Roeske, R.W., Weitl, F.L., Vilchez-Martinez, J.A. and Schally, A.V., *J. Med. Chem.*, 1976, **19**, 492-495.
27. Crab, T.A., Jackson, D. and Patel, A.V., *Adv. Heterocycl. Chem.*, 1990, **49**, 193-275.
28. Baens, N.P., Compernolle, F., Toppet, S.M. and Hoornaert, G.J., *Tetrahedron*, 1993, **49**, 3193-3202.
29. Meyers, A.I., Kunnen, K.B. and Still, W.C., *J. Am. Chem. Soc.*, 1987, **109**, 4405-4407.
30. Hagen, T.J., *Syn. Lett.*, 1990, 63-66.
31. Meyers, A.I., Lefker, B.A., Aitken, R.A. and Warner, K.T., *J. Org. Chem.*, 1986, **51**, 1936-1938.
32. Rispens, M.T., Keller, E., Lange, B.d., Zijlstra, R.W.J. and Feringa, B.L., *Tetrahedron:Asymmetry*, 1994, **5**, 607-624.

(*Received in UK* 16 *June* 1994)