Pergamon

Tetrahedron Letters, Vol. 37, No. 11, pp. 1875-1878, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00140-2

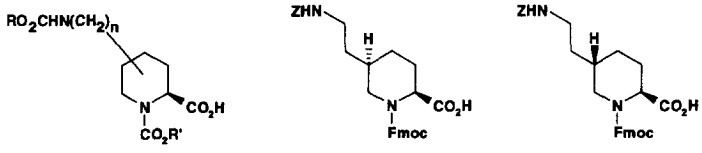
The Enantiospecific Synthesis of Functionalised Pipecolic Acids as Constrained Analogues of Lysine.

Peter John Murray* and Ian D. Starkey.

Glaxo Wellcome-Cambridge Chemistry Laboratory, University of Cambridge Chemical Laboratories, Lensfield Road, Cambridge, CB2 1EW.

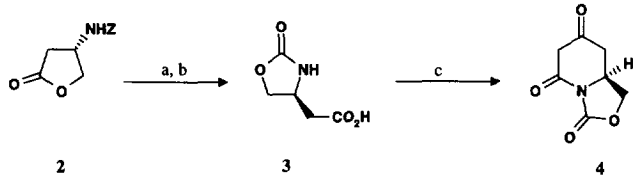
Abstract: Two constrained analogues of (S)- lysine have been prepared, suitably protected for solid phase peptide synthesis, in high optical and diastereomeric purity. The key step is the alkylation of the 6-oxopipecolate derivative (**6**) with iodoacetonitrile.

The design and synthesis of novel, synthetic α-amino acids continues to attract considerable attention from the synthetic community.[1] Of particular interest to the medicinal chemist are structurally constrained analogues of naturally occuring amino acids which can be used to probe the pharmacophoric requirements of peptide binding proteins. In the course of such work we required access to a family of aminoalkyl substituted pipecolic acids **1** in enantio- and diastereomerically pure form, as constrained analogues of lysine and ornithine, suitably protected for incorporation into peptide ligands by solid phase synthesis. Routes to pipecolic acids substituted uniquely at C-3[2], C-4[3], C-5[4] and C-6[5] in the piperidine ring and derivatives containing various other patterns of functionality[6], have been reported recently in the literature. Although several of these were attractive for specific targets a more general approach was considered desirable for our purpose.



1 (n = 1, 2) **1a** **1b**

Our initial aim was to prepare the *cis* and *trans* 5-substituted pipecolates **1a** and **1b**, by elaboration of the novel β-ketopiperidinone **4** (Scheme 1). This densely functionalised intermediate was conveniently made

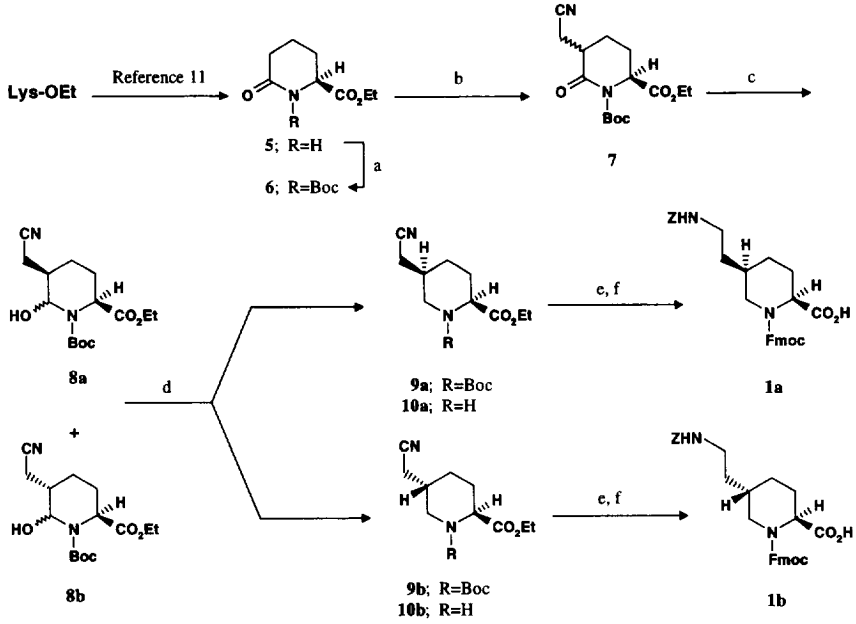


2 **3** **4**

Scheme 1 Reagents: a) NaOMe, MeOH, reflux 50%; b) NaOH, H_2O Dioxan, 90%; c) Isopropenyl chloroformate, DMAP, Meldrum's Acid, then EtOAc reflux, 30%.

from the aspartate-derived lactone[7] **2**, *via* the previously unreported oxazolidinone[8] **3**. Since the ketopiperidone[9] **4** proved to be insoluble in most common organic solvents, and therefore a difficult compound to manipulate, we sought an alternative intermediate for efficient access to substituted pipecolic acids. Very recently Pedregal *et al.*[4a] have reported a route to this class of compound by the stereoselective functionalisation of racemic methyl 6-oxopipecolate. The results of our work in this area, leading to the synthesis of **1a, b** in high enantiomeric purity are the subject of this letter.

(*S*)-Lysine ethyl ester was readily transformed into homochiral ethyl 6-oxopipecolate **5** in an overall yield of 51% using Moloney's procedure[10] and the amide protected as the *tert*-butyl carbamate. Generation of the lactam enolate from the *N*-Boc piperidone **6** with LiHMDS followed by addition of iodoacetonitrile[11] gave a ~1:1 mixture of the diastereomeric nitriles **7**. Partial reduction of the mixture with $LiEt_3BH$ as previously reported[12] gave the hemiaminals **8** which, in contrast to the corresponding lactams **7**, were readily separated[13] by flash chromatography. The hemiaminals were then each reduced[12] independently with Et_3SiH to provide the *cis* and *trans* 5-substituted pipecolates **9a** and **9b** respectively.



Scheme 2 Reagents: a) Boc_2O, DMAP, CH_2Cl_2, 82%; b) LiHMDS, THF, -78°C, then ICH_2CN, 80%; c) $LiEt_3BH$, THF, 68%; d) Chromatography, then Et_3SiH, BF_3OEt_2, CH_2Cl_2, 71-82%; e) i. H_2, PtO_2, EtOH, $CHCl_3$, 87-89%; ii. $ClCO_2CH_2Ph$, Et_3N, CH_2Cl_2, 80-85%; f) i. TFA, CH_2Cl_2, 86%; ii. NaOH, dioxan, H_2O, 90%; iii. FmocCl, Na_2CO_3, dioxan, H_2O, 81%.

The assignment of relative stereochemistry for **9a, b** was made on the basis of the ^1H NMR spectra of these compounds[14] and of the corresponding amines[15] **10** obtained by removal of the *N*-Boc protective group with TFA (Fig. 1).

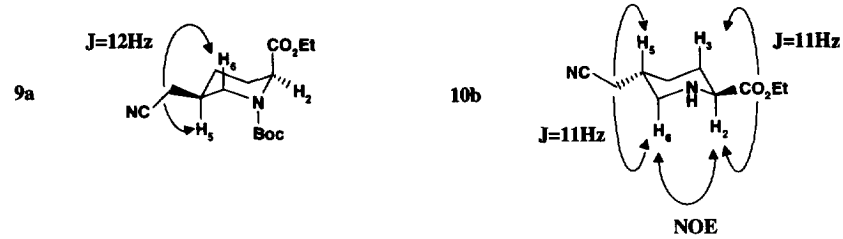
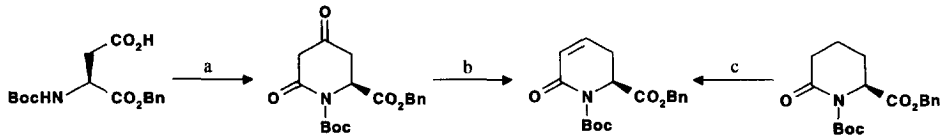


Figure 1 Selected ^{1}H NMR Data and Stereochemical Assignments for the Alkylated Pipecolates **9a** and **10b**

The small coupling constants exhibited by proton H-2 (δ 4.66, dd) in the carbamates **9** are consistent with an axial disposition of the ester group in both compounds. Diastereomer **9a** shows a large coupling constant between protons H-5ax (δ 1.75, m) and H-6ax (δ 2.62, dd) of 12Hz, indicating that this is the *cis* isomer. This assignment was confirmed by the coupling pattern observed for the epimeric *N*-H derivative **10b** which shows large *trans* diaxial coupling constants between protons H-2ax (δ 3.21, dd) and H-3ax (δ 1.46, dddd) and between protons H-5ax (δ 1.78, m) and H-6ax (δ 2.39, dd) of 11Hz. This is fully consistent with a chair conformation for **10b** in which the two substituents are disposed in a *trans* di-equatorial arrangement. The epimeric nitriles **9a** and **9b** were then transformed independently, by straight forward functional group interconversions, into the orthogonally protected *cis* and *trans* 5- substituted pipecolic acids[16] **1a** and **1b**. This route provides these unnatural α-amino acids in high enantiomeric[17] and diastereomeric purity.[18]

We have continued our studies aimed at identifying a suitable ketopiperidone intermediate for the preparation of related compounds and preliminary results are reported herein. The readily available aspartic acid derivative **11**, was condensed, *via* the mixed anhydride, with Meldrum's acid[19] and the crude adduct heated briefly in EtOAc to provide the 4-ketopiperidone[20] **12** in high yield. This compound has been converted into the α,β-unsaturated lactam[21] **13** which has also been prepared independently from the lactam **14**. Further synthetic studies on **12** and **13** are in progress and will be reported in due course.



Scheme 3 Reagents: a) Isopropenyl chloroformate, DMAP, Meldrum's Acid, CH_2Cl_2, 95%; then EtOAc, Δ, 89%; b) i. $NaBH_4$, CH_2Cl_2, AcOH, 9:1, 47%; ii. MsCl, Et_3N, CH_2Cl_2, 70%; c) i. LiHMDS, PhSeBr, 70%; ii. H_2O_2, CH_2Cl_2, 50%.

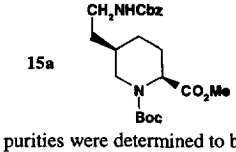
Acknowledgements: The authors wish to thank Mrs C. Kay and Dr. M. Ladlow for helpful discussions and Dr. R. Upton for performing high field and variable temperature NMR experiments.

References and Notes

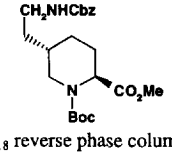
1. For recent reviews of this area see: (a) Duthaler, R.O. *Tetrahedron*, **1994**, *50*, 1539; (b) Williams, R.M. In '*Synthesis of Optically Active α-Amino Acids*'; Organic Chemistry Series, Eds. Baldwin, J.E. and Magnus, P.D.: Pergamon Press, Oxford, 1989, Vol 7; (c) Bailey, P.D.; Clayson, J.; Boa, A.N. *Contemporary Organic Synthesis*, **1995**, 173.
2. (a) Christie, B.D; Rappoport, H. *J.Org. Chem.*, **1985**, *50*, 1239; (b) Angle, S.R.; Arnaiz, D.O. *Tetrahedron Lett.*, **1989**, *30*, 515 and references cited therein.
3. (a) Golubev, A.; Sewald, N.; Burger, K. *Tetrahedron Lett.*, **1995**, *36*, 2037; (b) Jackson, R.F.W.; Graham, L.S.; Rettie, A.B. *Tetrahedron Lett.*, **1994**, *35*, 4417; (c) Argami, C.; Couty, F.; Poursoulis, M.; Vaissermann, J. *Tetrahedron*, **1992**, *48*, 431;

(d) Pellicciari, R.; Natalini, B.; Luneia, R.; Marinozzi, M.; Roberti, M.; Rosato, G.C.; Sadeghpour, B.M.; Snyder, J.P.; Monahan, J.B.; Moroni, F. *Med. Chem. Res.*, **1992**, 2, 491.

4. (a) Ezquerra, J.; Pedregal, C.; Escribano, A.; Carreno, M.C.; Ruano, J.L.G. *Tetrahedron Lett.*, **1995**, *36*, 3247; (b) Hereis, C.; Held, W.A.; Kirfel, A. *Liebigs Ann. Chem.*, **1994**, 1117; (c) Baldwin, J.E.; Adlington, R.M.; Godfrey, C.R.A.; Gollins D.W.; Vaughan, J.G. *J. Chem. Soc., Chem. Commun.*, **1993**, 1434; (d) Ko, K.Y.; Lee, K.-I.; Kim, W.-J.; *Tetrahedron Lett.*, **1992**, *33*, 6651; (e) Bailey, P.D.; Bryans, J.S. *Tetrahedron Lett.*, **1988**, *29*, 2231.
5. (a) Ludwig, C.; Wistrand, L-G. *Acta Chem. Scand.*, **1994**, *48*, 367; (b) Ojima, I.; Tzamarioudaki, M.; Eguchi, M. *J. Org. Chem.*, **1995**, *60*, 7078.
6. Coldham, I.; Collis, A.J.; Mould, R.J.; Rathwell, R.E. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2739; (b) Mc Falane, A.K.; Thomas, G.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2803; (c) Ahman, J.; Somfai, P. *Tetrahedron Lett.*, **1995**, *36*, 303; (d) Bailey, P.D.; Londesbrough, D.J.; Hancox, T.C.; Heffernan, J.D.; Holmes, A.B. *J. Chem. Soc., Chem. Commun.*, **1994**, 2543; (e) Ezquerra, J.; Rubio, A.; Pedregal, C.; Sanz, G.; Rodriguez, J.H.; Ruano, J.L.G. *Tetrahedron Lett.*, **1993**, *34*, 4989; see also reference 2(a).
7. McGarvey, G.J.; Williams, J.M.; Himer, R.N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.*, **1986**, *108*, 4943.
8. All new compounds were fully characterized and gave spectroscopic and analytical data consistent with assigned structures.
9. **4**: m.p. >220°C (dec.); $[\alpha]_D^{20}$ -126 (*c* 0.3, H_2O); ^1H NMR (DMSO, 400MHz) enol tautomer δ: 2.51 (1H, dm, J=16.5 Hz), 2.71 (1H, dd, J=16.5, 11.8 Hz), 4.03 (1H, m), 4.48 (2H, m), 5.01 (1H, s), 11.45 (1H, s br).
10. Hermitage, S.A.; Maloney, M. *Tetrahedron: Asymmetry*, **1994**, *5*, 1463.
11. Addition of the enolate to a stirred solution of benzyl bromide (5 equiv.) gave a separable mixture of *cis* and *trans* alkylation products in 46% isolated yield.
12. Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M.C.; Ruano, J.L.G. *Tetrahedron Lett.*, **1994**, *35*, 2053.
13. Rf (Et_2O/ hexane 2:1); **7**: 0.23, **8a**: 0.28, **8b**: 0.21. The corresponding methyl esters were more difficult to separate.
14. ^1H NMR (DMSO, 400 MHz, 100°C) **9a:** δ: 1.04 (1H, m), 1.19 (3H, t, J=7 Hz), 1.40 (9H, s), 1.65-1.80 (3H, m), 2.14 (1H, m), 2.40-2.52 (2H, m), 2.62, (1H, dd, J=12.5, 12 Hz), 3.96 (1H, dd, J=12.5, 5 Hz), 4.15 (2H, q, J=7 Hz), 4.66 (1H, dd, J=6, 1.5 Hz); **9b:** δ: 1.21 (3H, t, J=7 Hz), 1.40 (9H, s), 1.51 (1H, m), 1.60 (1H, m), 1.84-1.91 (2H, m), 2.10 (1H, m), 2.48 (1H, dd, J=17.5, 7.5 Hz), 2.54 (1H, dd, J=17.5, 8.5 Hz), 3.20 (1H, dd, J=13.5, 4 Hz), 3.69 (1H, dd, J=13.5, 3.5 Hz), 4.14 (2H, q, J=7 Hz), 4.55 (1H, dd, J=5.0, 5.0 Hz).
15. ^1H NMR ($CDCl_3$, 400 MHz, 30°C) **10a:** δ: 1.21 (3H, t, J=7 Hz), 1.47 (1H, m), 1.79 (1H, m), 1.87 (1H, m), 1.92 (1H, m), 2.00 (1H, m), 2.37-2.42 (2H, m), 2.39 (1H, dd, J=12, 7.5 Hz), 2.94 (1H, dd, J=12, 3.5 Hz), 4.08-4.20 (2H, m); **10b:** δ: 1.21 (3H, t, J=7 Hz), 1.27 (1H, m), 1.46 (1H, dddd, J=13, 13, 11, 4 Hz), 1.78 (1H, m), 1.96 (1H, m), 2.03 (1H, dq, J=13, 3 Hz), 2.18 (1H, m), 2.23 (1H, m), 2.39 (1H, dd, J=12, 11 Hz), 3.17 (1H, ddd, J=12, 4, 2 Hz), 3.21 (1H, dd, J=11, 3 Hz), 4.12 (2H, q, J=7 Hz).
16. **1a:** Rf= 0.33 (CH_2Cl_2/ EtOH/ AcOH; 600: 20: 1); $[\alpha]_D^{20}$ -9.8 (*c* 1.2, MeOH); ^1H NMR (DMSO, 400 MHz, 120°C) δ: 0.92 (1H, m), 1.25-1.35 (2H, m), 1.35 (1H, m br), 1.69 (1H, dm, J=13 Hz), 2.11 (1H, dm, J=14 Hz), 2.58 (1H, dd, J=12.5, 11.5 Hz), 3.06 (2H, m), 3.82 (1H, d br), 4.27 (1H, t, J=7 Hz), 4.39 (2H, d, J=7 Hz), 4.63 (1H, dd, J=6, 2 Hz), 5.04 (2H, s), 6.70 (1H, br), 7.26-7.36 (7H, m), 7.39 (2H, t, J=7.5 Hz), 7.60 (2H, dd, J=7.5, 4 Hz), 7.84 (2H, d, J=8 Hz).
1b: Rf= 0.33 (CH_2Cl_2/EtOH/AcOH; 600: 20: 1); $[\alpha]_D^{20}$ -11.9 (*c* 0.5, MeOH); ^1H NMR (DMSO, 400 MHz, 100°C) δ: 1.30-1.54 (4H, m), 1.68-1.88 (3H, m), 3.0 (2H, m), 3.13 (1H, dd, J=13, 3 Hz), 3.60 (1H, d, J=13 Hz), 4.24 (1H, dd, J=6, 6 Hz,), 4.32-4.42 (2H, ddd, J=20, 10, 6 Hz), 4.50 (1H, dd, J=6, 4 Hz), 5.01 (2H, s), 6.74 (1H, s br), 7.20-7.40 (9H, m), 7.60 (2H, d, J=7 Hz), 7.90 (2H, d, J=7 Hz).
17. Enantiomeric purities were determined to be > 98% ee in both the *cis* and *trans* series by HPLC against similarly prepared racemic standards. Conditions: **15a:** Chiralcel OJ column eluted with heptane/ IPA/ Et_3N (95: 4.95: 0.05), 1ml/min at 40°C; **15b:** Chiralcel OJ column eluted with heptane/ EtOH, (95:5) 1ml/min at 25°C.



15a



15b

18. Diastereomeric purities were determined to be > 98% de by HPLC (Dynamax C_{18} reverse phase column; MeCN, H_2O, 0.05% TFA mobile phase) and 400 MHz ^1H NMR.
19. (a) Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc., Perkin Trans. 1.* **1987**, 1177; (b) Tohdo, K.; Hamada, Y.; Shioiri, T. *Syn. Lett.*, **1994**, 105.
20. **12:** Rf= 0.32 (CH_2Cl_2/ EtOH/ AcOH; 600: 20: 1); $[\alpha]_D^{20}$ +88.2 (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) keto tautomer δ: 1.49 (9H, s), 2.84 (1H, dd, J=18, 7 Hz), 3.07 (1H, dd, J=18, 2 Hz), 3.33 (1H, d, J=19 Hz), 3.47 (1H, J=19 Hz), 5.20 (2H, s), 5.26 (1H, dd, J=7, 2 Hz), 7.25-7.40 (5H, m).
21. **13:** Rf= 0.42 (Et_2O/ hexane; 1:1); $[\alpha]_D^{20}$ +16.0 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.48 (9H, s), 2.78 (1H, m), 2.88 (1H, ddd, J=17.5, 6, 1.7 Hz), 5.09 (1H, m), 5.12 (1H, d, J=13 Hz), 5.23 (1H, d, J=13 Hz), 5.95 (1H, dd, J=10, 2.5 Hz), 6.58 (1H, m), 7.32 (5H, m).

(*Received in UK* 6 *December* 1995; *revised* 23 *January* 1996; *accepted* 26 *January* 1996)