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CHIRAL SYNTHESIS OF 5-HYDROXY-(L)-PIPECOLIC ACIDS FROM (L)-GLUTAMIC ACID

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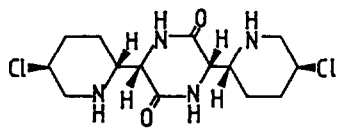
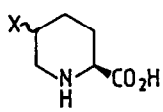
Summary A stereo- and enantio-specific synthesis of the naturally occurring *cis*-5-hydroxy-(L)-pipecolic acid (3) is described, starting from Z-(L)-glutamic acid; the key step involves cyclisation of a protected chlorohydrin, and also gives access to *trans*-5-hydroxy-(L)-pipecolic acid.

As part of work directed towards the asymmetric synthesis of the anti-tumour antibiotic DKP593A (1),[1] and analogues thereof, we have been attempting to devise enantio- and stereo-selective routes to 5-substituted pipecolic acid derivatives (2). The approach described in this paper involves the modification of (L)-glutamic acid, and has enabled us to confirm the optical integrity of our pipecolic acid derivatives by comparison with naturally occurring compounds.

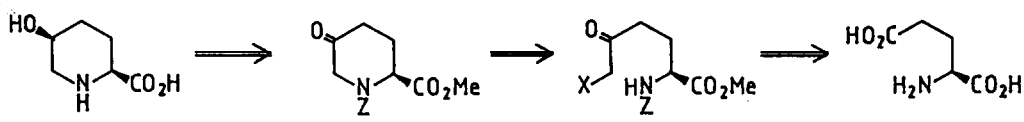


(1)



(2)

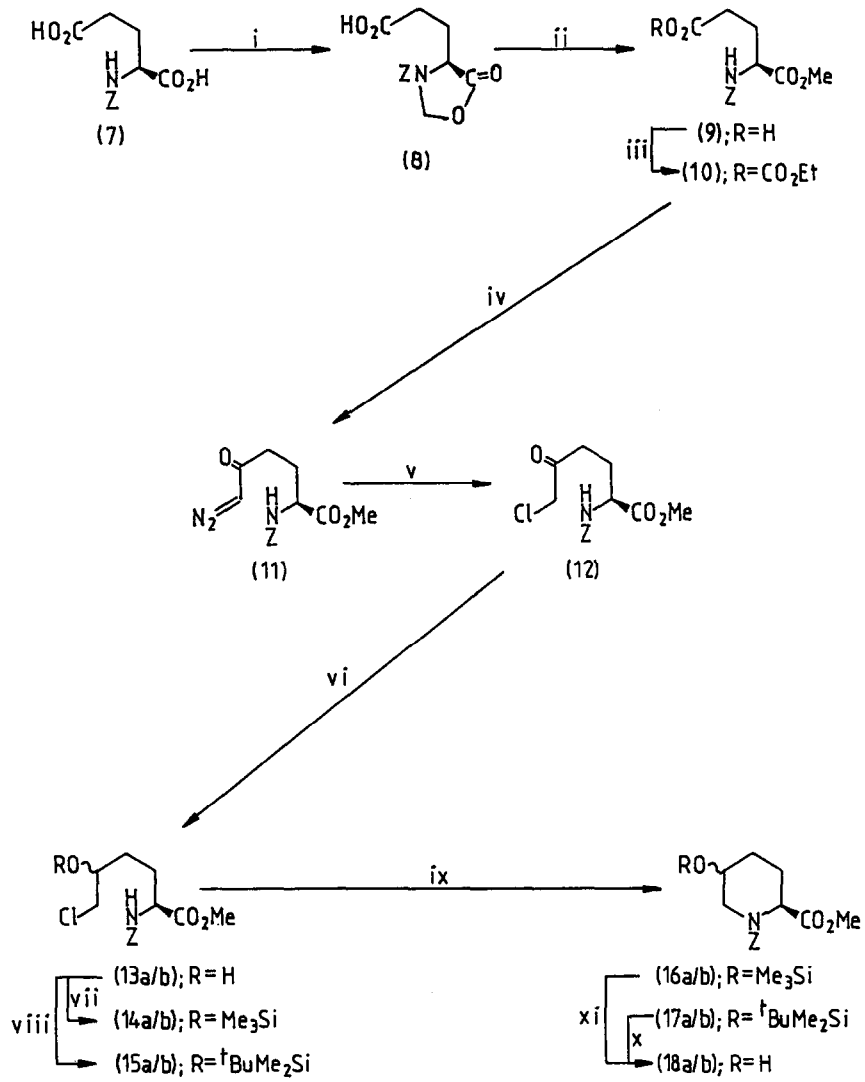
Our intention was to retain the chirality of (L)-glutamic acid (6) whilst carrying out modifications of the carboxylic acid group of the side-chain. Thus, for *cis*-5-hydroxy-(L)-pipecolic acid (3), retro-synthetic analysis (Scheme 1) reveals the importance of intermediates (4) and (5) in which the (S)-amino acid moiety remains intact.



(3) (4) (5) (6)

Scheme 1

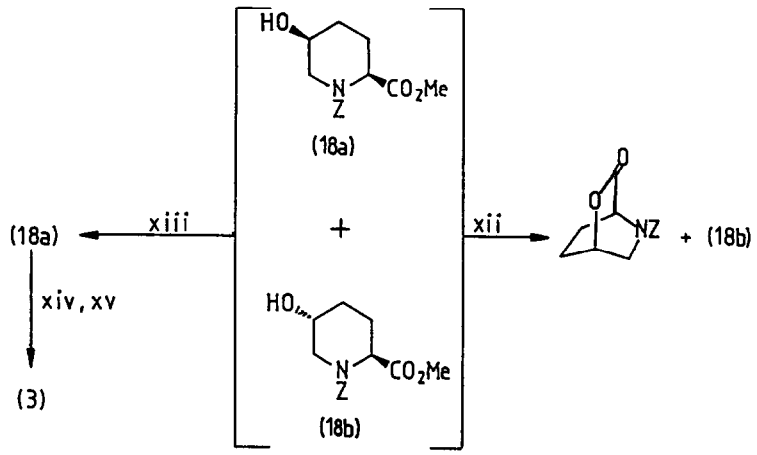
Therefore, starting from the readily available Z-(L)-glutamic acid (7), selective protection of the α-acid was achieved *via* the oxazolidinone (8).[2,3,4] After formation of the mixed anhydride (10), treatment with diazomethane yielded the diazoketone (11), which was converted into the chloroketone (12) using HCl in Et_2O [60% overall yield from (7)].[5]



Scheme 2. Z = CO_2CH_2Ph. Reagents: i, $(CH_2O)_n$/ PTSA/ PhH/ reflux (94%); ii, NaOMe/ MeOH/ Reflux (95%); iii, EtOCOCl/ Et_3N/ CH_2Cl_2/ -5°C (82%); iv, CH_2N_2/ Et_2O/ -5°C (85%); v, HCl/ Et_2O/ -5°C (97%); vi, $NaBH_4$/ MeOH (96%); vii, Me_3SiCl/ Et_3N/ CH_2Cl_2 (66%); viii, $Bu^tMe_2SiOSO_2CF_3$/ 2,6-lutidine/ CH_2Cl_2 (85%); ix, NaH/ DMF/ 85°C (R = TMS, 35%; R = TBDMS, 60%); x, HF/ H_2O/ MeCN (93%); xi, MeOH/ K_2CO_3.

Direct cyclisation to the piperidine ring system was unsuccessful at this stage, presumably due to the reactivity of the carbonyl group.[6] Formation of the piperidine ring was eventually achieved after reduction of the ketone to a diastereomeric mixture (1:1) of alcohols (13a/b), protection as the trialkylsilyl ethers (14a/b) or (15a/b), and treatment with sodium hydride in DMF at 85°C.

Removal of the silyl protection gave an inseparable mixture of the *cis* and *trans* isomers of methyl 5-hydroxy-(L)-pipecolate (18a/b). However, refluxing this mixture in benzene with catalytic p-TsOH gave two separable components, identified as the lactone (19) with $[\alpha]_D^{25}$ - 8.9° (c=0.76 in MeOH) (Lit.[7] $[\alpha]_D^{25}$ -6.3° for c=1.5 in MeOH), and unreacted *trans* hydroxy ester (18b).



Scheme 3. Reagents: xii, PSTA/ PhH/ Reflux; xiii, CrO_3/ Me_2CO then $NaBH_4$/ MeOH (75% overall); xiv, NaOH/ H_2O/ MeOH/ THF (84%); xv, H_2/ Pd-C/ MeOH (75%).

In contrast, oxidation of the mixture of alcohols (18a/b) with CrO_3 in propanone gave the corresponding ketone (4); this was immediately reduced with $NaBH_4$ to give a single diastereoisomer (75% overall), which was identified as being the *cis* isomer (18a)[8] by ^1H NMR spectroscopy.[9] Hydrolysis of the methyl ester group (NaOH/ H_2O/ MeOH/ THF) followed by hydrogenolysis (H_2/ Pd-C) gave the free amino acid (3) [63% from (18a)] with $[\alpha]_D^{25}$ - 26.9° (c=0.48 in MeOH) (Lit[7] $[\alpha]_D^{25}$ - 31.1° for c=0.8 in H_2O).[10]

We have therefore achieved the stereo- and enantio-specific synthesis of 5-substituted (L)-pipecolic acids, including the total synthesis of the naturally occurring *cis*-5-hydroxy derivative. This constitutes an important addition to the chiral methods available for preparing 3-hydroxypiperidines,[11] and is currently being exploited in the synthesis of other natural products.

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1. a) C.O. Gitterman, E.L. Rickes, D.E. Wolf, J. Madas, S.B. Zimmerman, T.H. Stoudt, and T.C. Demny, J. Antibiot., 1970, 23, 305; b) B.H. Arison and J.L. Beck, Tetrahedron, 1973, 29, 2743; c) G.R. Pettit, R.B. Von Dreele, D.L. Herald, M.T. Edgar, and H.B. Wood, J.Amer.Chem.Soc., 1976, 98, 6472.

2. M. Masuo, I. Isaka, M. Takao, and M. Kochidani (Yamanouchi Pharmaceutical Co. Ltd.), Japan.Pat. 68 00,213; Chem.Abs., 1968, 69, 77728a.

3. For DCHA salt $[\alpha]_D^{25}$ - 12.9° (c=1.02 in MeOH). Literature values are: a) $[\alpha]_D^{25}$-10.6° (c=1.53 in MeOH) (E. Klieger, E. Schroeder, and H. Gibian, Ann., 1961, 640, 157); b) $[\alpha]_D^{25}$ -10.9° (c=1.02 in MeOH) (E. Klieger and H. Gibian, Ann., 1962, 655, 195); c) $[a]_D^{25}$ - 10.7° (c=2 in MeOH) (G.H.L. Nefkens and R.J.F. Nivard, Rec.Trav.Chim.Pays-Bas, 1964, 83, 199).

4. All products gave satisfactory NMR (^1H and ^{13}C), mass spectrometry (including accurate mass for parent ions), and infra-red data. Compounds were homogeneous by TLC and (for single diastereoisomers) by HPLC. The NMR spectra were complicated by the presence of rotamers for Z-protected derivatives; e.g. see Note 9.

5. See C.T. Clarke and J.H. Jones, Tetrahedron Lett., 1977, 2367.

6. Deprotonation of the amide nitrogen, replacement of Cl by better leaving groups, or simple protection of the ketone group failed to give access to the piperidine ring system. In all cases, complex mixtures of products were formed, indicated by the presence of many TLC components, and of multiple methyl ester peaks in the proton NMR spectra.

7. B. Witkop and C.M. Foltz, J. Amer.Chem.Soc., 1957, 79, 192.

8. c.f. Ref.7, in which the *cis*-hydroxy-acid is cyclised to the lactone using Ac_2O/AcOH.

9. A mixture of rotamers: δ_H (360 MHz in $CDCl_3$) 1.1-1.25 (1H, m, $H4_{ax}$), 1.65-1.8 (1H, m, $H3_{ax}$), 1.9-2.0 (1H, m, $H4_{eq}$), 1.9-2.3 (1H, br, OH), 2.2-2.3 (1H, m, $H3_{eq}$), 2.64 and 2.76 (1H total, both dd, both J 12.6 and 10.7 Hz, $H6_{ax}$), 3.55-3.65 (1H, m, $H6_{eq}$), 3.69 and 3.72 (3H total, both s, CH_3O), 4.15-4.25 (1H, m, $H5_{ax}$), 4.79 and 4.86 (1H total, both br d, J 5.1 and 4.7 Hz respectively, $H2_{eq}$), 5.05-5.15 (2H, ABq and s, $PhCH_2$), 7.25-7.4 (5H, m, Ph). These assignments were confirmed by selective decoupling experiments.

10. Optical rotations in H_2O are pH dependent.

11. For example: a) R.K. Olson, K.L. Bhat, R.B. Wardle, W.J. Hennen, and G.D. Kini, J.Org.Chem., 1985, 50, 896; b) B.P. Bashyal, H.-F. Chow, and G.W.J. Fleet, Tetrahedron, 1987, 43, 415/423; c) K. Tadano, Y.Iimura, and T. Suami, J.Carbohyd.Chem., 1985, 4, 129; d) C.C. Deane and T.D. Inch, J.C.S.Chem.Commun., 1969, 813.

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