An efficient route to the α-methyl ester of L-glutamic acid, and its conversion into *cis*-5-hydroxy-L-pipecolic acid

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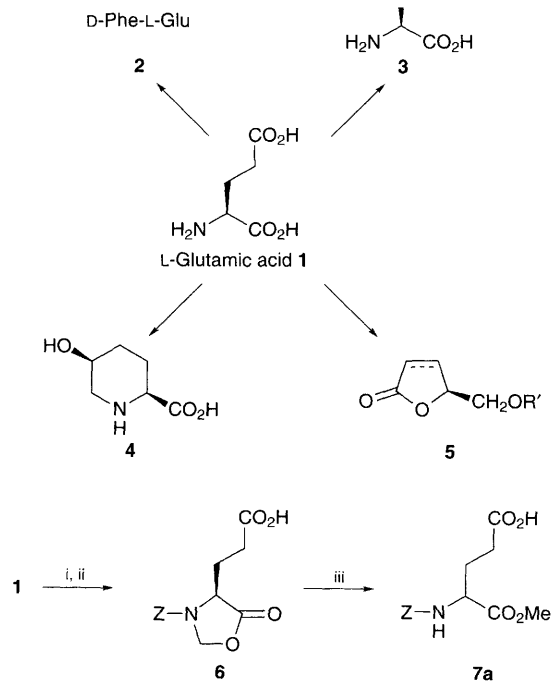
The treatment of the *N*-benzyloxycarbonyl α-methyl esters of L-glutamine or L-asparagine with *tert*-butyl nitrite in refluxing acetonitrile results in selective hydrolysis of the amide group, giving optically pure Z-Glu-OMe (74%) or Z-Asp-OMe (88%); these are versatile chiral building blocks, and an efficient synthesis of *cis*-5-hydroxy-L-pipecolic acid from Z-Glu-OMe is described.

Glutamic acid **1** is an extremely versatile chiral building block, which can be incorporated into peptides (*e.g.* **2**),[1] or can be readily modified to give other amino acids **3**,[2] 5- or 6-membered *N*- heterocycles (*e.g.* **4**),[3a,b] or non-nitrogen containing building blocks such as **5**.[4] In order to use glutamic acid successfully in synthesis, it is necessary to differentiate between the α and side-chain carboxylic acid groups. However, despite the many reportedly high yielding routes to mono-esters of glutamic acid,[2a,5] such compounds are remarkably difficult to prepare, as implied by their high cost.

We required *N*-benzyloxycarbonyl-L-glutamic acid α-methyl ester (Z-Glu-OMe) (Z = benzyloxycarbonyl), both for peptide work and for the synthesis of piperidine natural products such as **4**, but we found that (in our hands) literature methods did not give the yield and/or purity of Z-Glu-OMe that we needed. We report herein two routes to Z-Glu-OMe that are high yielding.

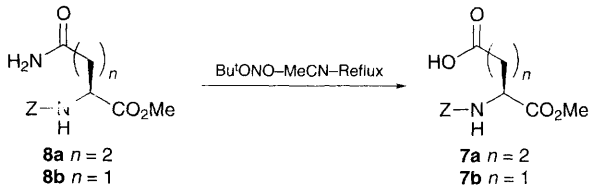
Firstly, we explored the use of the α-amino group to participate in distinguishing the carboxylic esters, *via* formation of the oxazolidinone **6**[2a,6] as shown in Scheme 1. Following formation of **6** in 94% yield, ring-opening with a range of nucleophiles was studied extensively; most efficient was the treatment with 1.05 equiv. of methoxide in refluxing benzene, which led to the formation of the α-ester **7a** in excellent yield (*ca.* 95%), but extensive racemization was often (but not always) observed [*cf.* ref. 2(*a*)]. This route is thus ideal for the synthesis of racemic Z-Glu-OMe, but of limited value for optically active material.



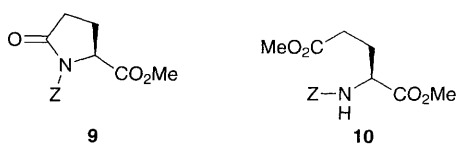
Scheme 1 *Reagents and conditions*: i, ZCl, $NaHCO_3$; ii, $(CH_2O)_n$, 4-$MePhSO_3H$, benzene, reflux; iii, benzene, MeOH (1.1 equiv.), NaH (1.05 equiv.), reflux

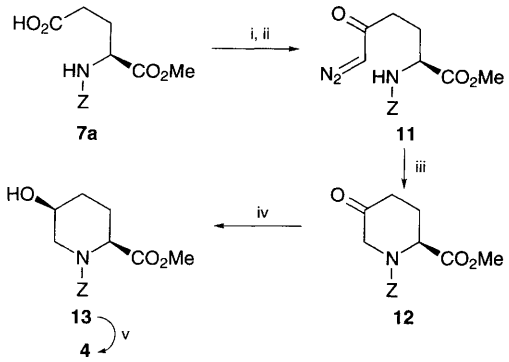
To overcome the racemization problem, we explored the possibility of using glutamine as the chiral starting material, in which the carboxylic groups were already differentiated in this cheap DNA-encoded amino acid. After straightforward conversion of glutamine to the *N*-benzyloxycarbonyl methyl ester **8a**, treatment with *tert*-butyl nitrite in refluxing acetonitrile as a source of $[NO]^+$ led to selective hydrolysis of the side-chain amide group without concommitant hydrolysis of the ester or urethane;† the only by-products were the γ-lactam **9** (8%) and, surprisingly, the di-ester **10** (12%), and these were readily removed by standard washes, generating optically pure **7a** in 74% isolated yield. Similar treatment of Z- Asn-OMe **8b** led to the isolation of **7b** in 88% yield, with no sign of β-lactam formation. This is an excellent method for the preparation of optically pure Z-Glu-OMe and Z-Asp-OMe.

The value of Z-Glu-OMe **7a** as a highly functionalised chiral building block was demonstrated by a short, efficient, asymmetric synthesis of the naturally occurring *cis*-5-hydroxy-L-pipecolic acid **4**. Thus, treatment of **7a** with ethyl chloroformate, followed by reaction of the mixed anhydride with diazomethane generated the diazoketone **11** (82% overall yield), and we studied its direct conversion into protected 5-oxopipecolic acid **12** by carbene insertion into the N–H bond. We initially tried rhodium(II) acetate as the catalyst for carbene generation from **11** which, after sodium borohydride reduction, gave **13** in only 34% yield.[6] Subsequent work by Ko *et al.*[10] resulted in similarly modest yields for this type of insertion reaction. The yield was not improved by the use of copper(I) catalysts, or by using other rhodium(II) salts (trifluoroacetate, butyrate, heptafluorobutyrate), but careful optimisation of reaction conditions using rhodium(II) acetate eventually led to conditions under which **12** could be isolated in 75% yield.§



Scheme 2 *Conditions*: see footnote ‡





Scheme 3 *Reagents and conditions*: i, EtOCOCl; ii, CH_2N_2, Et_2O; iii, $[Rh(OAc)_2]_2$, benzene, reflux; iv, $NaBH_4$, MeOH; v, OH^- (aq.) then H_2, Pd–C

Finally, stereospecific reduction with sodium borohydride gave the *cis*-5-hydroxy-L-pipecolic acid derivative **13** in 93% yield, deprotection of which[3b] gives **4**.

We have therefore developed a cheap and efficient route to α-protected L-glutamic or L-aspartic acids, and have shown that the former can be readily converted into optically pure 5-substituted pipecolic acid derivatives. We thank Dr Justin Bryans and Ms Sarah Alexander for preliminary studies, Dr Alan Boyd and Dr Rod Fergusson for NMR and mass spectra, and EPSRC, The Wellcome Trust and Peboc Ltd for financial support.

Footnotes

† The hydrolysis of amides to acids with other sources of $[NO]^+$ has been reported (*e.g.* $NOBF_4$,[7] N_2O_4,[8] RONO–acid[9]), but yields for the conversion of **8a/b** to **7a/b** were modest using such reagents.

‡ To the amide (**8a/b**) in MeCN at reflux is adder *tert*-butyl nitrite (2 equiv.) rapidly in one portion. (Care! Vigorous foaming). The brown solution is heated at reflux for 90 min, becoming green. After removal of the solvent, the product is extracted into $NaHCO_3$ (aq.), washed with EtOAc and **8a/b** is isolated after acidification and extraction into $CHCl_3$.

§ A concentrated solution of the diazoketone **11** (9.37 g, 27.9 mmol) in benzene (60 cm^3) was added dropwise to a solution of rhodium(II) acetate (124 mg, 1 mol%) at reflux in benzene (500 cm^3, final concentration 0.02 mol dm^{-3}). The solution was heated for a further 30 min. Evaporation of the solvent followed by column chromatography gave **5** as a colourless oil (6.47 g, 21.1 mmol, 75%).

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Received, 19th October 1995; Com. 5/06909B