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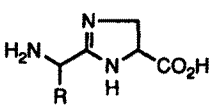
The Synthesis of Unusual Tetrahydropyrimidine Amino Acids

Raymond C F Jones * and Alan K Crockett
(Chemistry Department, Nottingham University, Nottingham NG7 2RD, UK)

Abstract: The synthesis of derivatives of 2-(1-aminoalkyl)-4-carboxy-3,4,5,6-tetrahydropyrimidines, unusual amino acids isolated from bacterial siderophores, is described, from condensation of N-protected amino acids imidates or thioimidates with 2,4-diaminobutyrylglycine methyl ester.

As part of a programme to utilise cyclic amidines as peptide bond isosteres, we have reported the synthesis of peptides incorporating the 2-(1-aminoalkyl)-4(5)-carboxy-4,5-dihydroimidazole unit **1**.[1] A natural extension was to consider the corresponding tetrahydropyrimidine units **2**.



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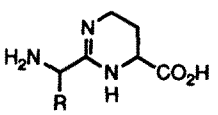
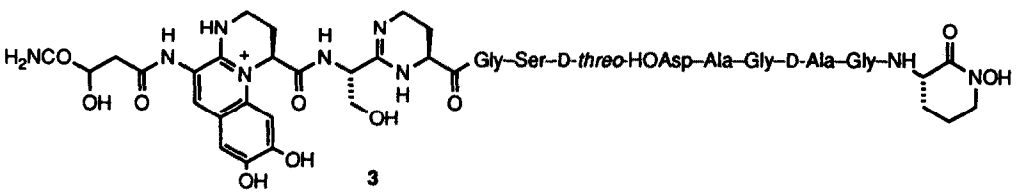


2

These units have also recently been revealed as components of a group of bacterial siderophores, the pyoverdins,[2] e.g. pyoverdin Pf CCM 2798 **3**, excreted from the fluorescent bacterium *Pseudomonas fluorescens* if grown under iron deficient conditions.[2b] They consist of a peptidic portion of 6-10 residues bound to a chromophore derived from 2,3-diamino-6,7-dihydroxyquinoline. Co-occurring with the pyoverdins in some instances are desferriferribactins,[3] e.g. desferriferribactin ATCC 13525 **4**,[3a] which lack the chromophore but contain a tetrahydropyrimidine unit presumably derived from 2,4-diaminobutyric acid and tyrosine, a plausible biogenetic precursor to the pyoverdin chromophore.[3] Acid hydrolysis of these siderophores affords the tetrahydropyrimidine amino acids **2**.[2,3] We report now the first total synthesis of derivatives of this novel type of amino acid.[4]



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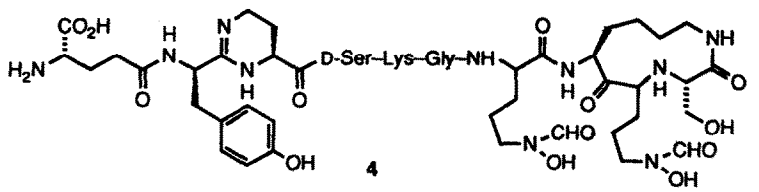
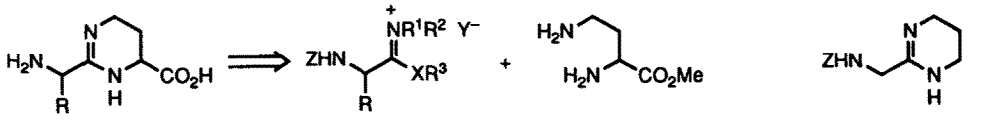


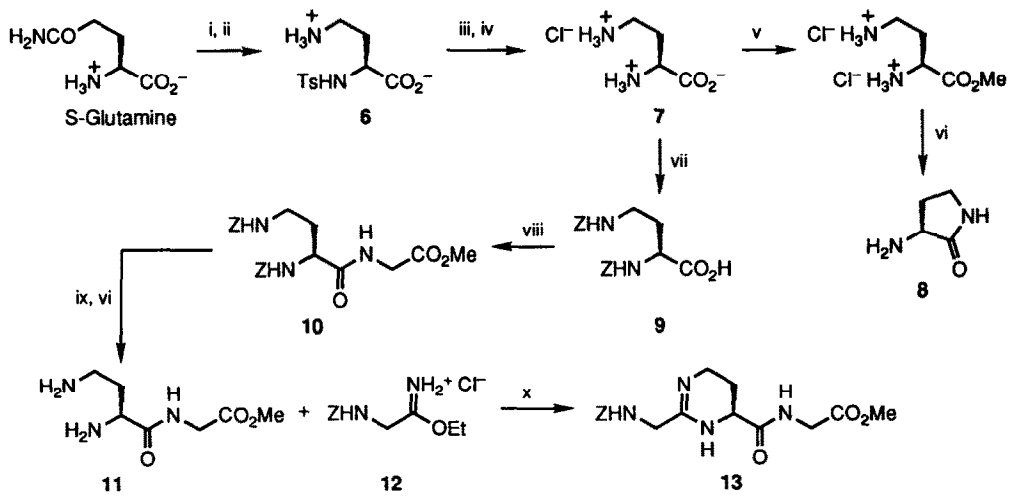
4

Our strategy required a protected form of homochiral 2,4-diaminobutyric acid and a protected amino acid imidate or thioimidate (Scheme 1).[1] As a preliminary test of the condensation conditions needed to form the heterocycle, ethyl benzyloxycarbonylaminoethanimidate hydrochloride [prepared in two steps from amino-acetonitrile hydrochloride: (i) $PhCH_2OCOCl$, aq. NaOH; 71%; (ii) MeCOCl in EtOH; 96%] was treated with 1,3-diaminopropane in ethanol at reflux (3h) to form the "C-seco" tetrahydropyrimidine **5** (71%). These conditions compare with the heating in methanol at reflux that was standard in our dihydroimidazole work,[1] for example to complete the above reaction but using 1,2-diaminoethane as the diamine component.[5]



Scheme 1

To prepare (*S*)-2,4-diaminobutyric acid derivatives we started with (*S*)-glutamine and, after N-protection (p-toluenesulphonyl chloride, MgO, H_2O, 5°C; 92%), performed a Hofmann degradation (Br_2, aq. NaOH, 5°C) to afford N^2-tosyl-2,4-diaminobutyric acid **6** (86%) (Scheme 2).[6] Removal of the tosyl group (HBr–acetic acid, 30 wt %, phenol, 70°C, 16h)[7] gave the (*S*)-diamino acid hydrobromide salt in quantitative crude yield, which was purified as the hydrochloride salt **7** by treatment with hydrogen chloride (from MeCOCl in MeOH, 0°C; 80%). We were able to form the methyl ester dihydrochloride (MeCOCl in MeOH, reflux; 92%) but all attempts to liberate the free diaminoester as we had with methyl 2,3-diaminopropionate (e.g. NH_3–$CHCl_3$ solution, 0°C) led to rapid cyclisation to 3-amino-2-pyrrolidone **8**.[8] An alternative C-protection was required, and we selected amide formation with glycine.[9] Thus, treatment of the diamino acid hydro-

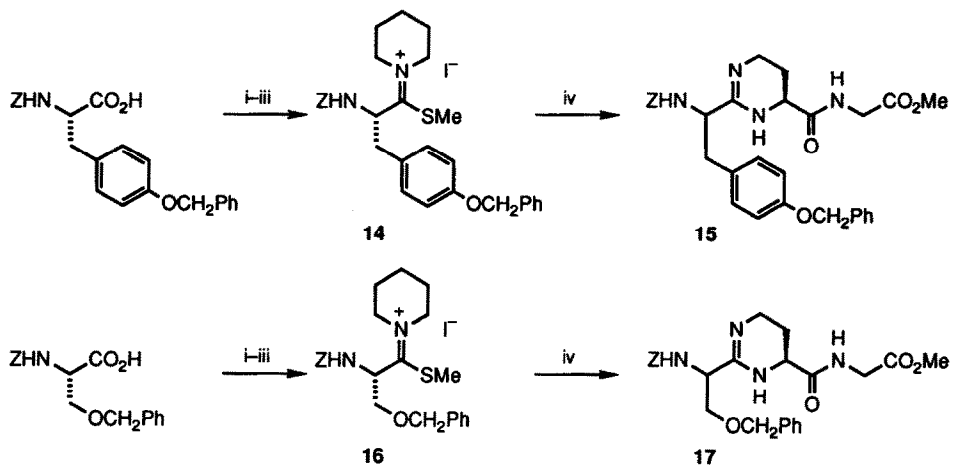


Scheme 2

Reagents: i, TsCl, MgO, H_2O; ii, Br_2, aq. NaOH, 0°C; iii, HBr–acetic acid, phenol, 70°C; iv, MeCOCl in MeOH, 0°C; v, MeCOCl in MeOH, reflux; vi, NH_3–$CHCl_3$ solution, 20°C; vii, $PhCH_2OCOCl$, aq. NaOH, 0°C; viii, Bu^iOCOCl, N-methylmorpholine; then $Cl^-H_3N^+CH_2CO_2Me$, Et_3N; ix, H_2, Pd–C, MeOH–aq. HCl; x, EtOH, reflux.

chloride **7** with benzyl chloroformate (aq. NaOH, 0°C) gave 2,4-bis(benzyloxycarbonylamino)butyric acid **9** (79%) which was coupled to glycine methyl ester by a mixed anhydride protocol [(i) Bu^iOCOCl, N-methylmorpholine, 0°C; (ii) $Cl^- H_3N^+CH_2CO_2Me$, Et_3N] to give the protected dipeptide **10** (82%).[10] Unmasking the N-terminus [(i) H_2, Pd–C, MeOH–aq. HCl; 99%; (ii) NH_3–$CHCl_3$ solution, 0°C; 99%] gave the diamine **11** which could be condensed with the "glycine" imidate **12** (see above) in ethanol at reflux to produce the tetrahydropyrimidine **13** (72%).[11]

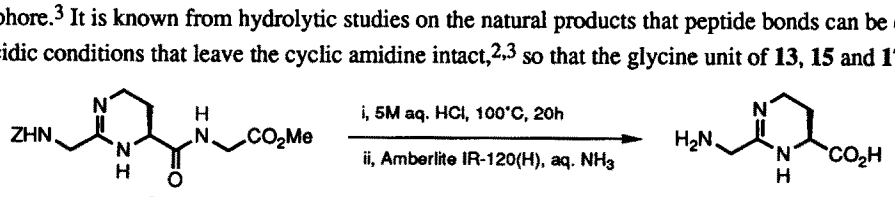
To assemble further derivatives, suitable thioimidates[12] were prepared from tyrosine and serine (Scheme 3).[1,13] Thus, (*S*)-N-benzyloxycarbonyl-O-benzyltyrosine was converted into the piperidine amide (DCC, pentafluorophenol; then piperidine; 85%), which was treated with Lawesson's reagent (toluene, 80°C) to form the thioamide (94%). S-Methylation (MeI, 40°C) afforded thioimidate salt **14** which was promptly condensed with the diamino dipeptide **11** as before (EtOH, reflux) to generate the tetrahydropyrimidine **15** (42%).[14] A similar sequence from (*S*)-O-benzylserine *via* the piperidine amide (92%) and thioamide (91%) gave a thioimidate salt **16** that condensed to form the tetrahydropyrimidine **17**, albeit to date in poor yield (11%).[14,15]



Scheme 3

Reagents: i, DCC, pentafluorophenol; then piperidine; ii, Lawesson's reagent, toluene, 80°C; iii, MeI, 40°C; iv, diamino dipeptide **11**, EtOH, reflux.

The dipeptide protected as **17** forms a part of the peptide sequence in pyoverdin Pf CCM 2798,[2a] whilst the tyrosine-based unit **15** represents the type of tetrahydropyrimidine found in, and isolated as a sub-unit from, the desferriferribactins[3b] and whose oxidative cyclization is suggested to form the pyoverdin chromophore.[3] It is known from hydrolytic studies on the natural products that peptide bonds can be cleaved under acidic conditions that leave the cyclic amidine intact,[2,3] so that the glycine unit of **13**, **15** and **17** can



Scheme 4

be regarded as a true protecting group. We have indeed shown (Scheme 4) that the tetrahydropyrimidine amino acid **18** (i.e. **2**; R = H)[16] can be liberated from protected derivative **13** (5M aq. HCl, 100°C, 20h; then Amberlite IR-120(H), aq. NH_3; 61%). Alternatively, different residues could be used in this 'protecting' role as necessary for assembly of particular siderophore peptide portions. Our efforts in this area are continuing.

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2. (a) Linget, C.; Azadi, P.; MacLeod, J. K.; Dell, A.; Abdallah, M. A. *Tetrahedron Lett.*, **1992**, *33*, 1737-1740, and refs. therein; (b) Demange, P.; Bateman, A.; MacLeod, J. K.; Dell, A.; Abdallah, M. A. *Tetrahedron Lett.*, **1990**, *31*, 7611-7614; (c) Gripp, S.; Hahn, J.; Taraz, K.; Budzikiewicz, H.; Tappe, R.; Schröder, H.; Holneicher, U.; Gwose, I. *Z. Naturforsch., Sect. C*, **1991**, *46*, 535-541.
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4. This work was presented at the 3rd International Congress on Amino Acids, Peptides and Analogues, Vienna, August 23-27 1993; see: Jones, R. C. F.; Crockett, A. K.; Rees, D. C. *Amino Acids*, **1993**, *5*, 119-120.
5. Ward, G. J. *Imidazolines in Peptide Chemistry*, University of Nottingham 1988.
6. By a modification of the method of: Rudinger, J.; Poduska, K.; Zaoral, M. *Collect. Czech. Chem. Commun.*, **1960**, *25*, 2022.
7. *Cf.* Kjöaer, A.; Vesterager, E. *Acta Chem. Scand.*, **1960**, *14*, 961-964.
8. Wunsch, E. Synthese von Peptiden, Teil 1. In *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 4th edn., vol. 15 part 1, 1974; p. 482 *et seq.*, and refs. therein.
9. Initial attempts to form t-butyl 2,4-diaminobutyrate were disappointing.
10. All new compounds gave spectral data (IR, UV, NMR, MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.
11. Selected data for **13**: white solid, m.p. 189-190°C (Found: C, 50.3; H, 5.9; N 13.8%. $C_{17}H_{22}N_4O_5{\cdot}2.5\ H_2O$ requires C, 50.1; H, 5.45; N, 13.75%;); $[\alpha]_D^{25}$ = +301.7° (*c* 0.6 in MeOH); δ_H (250 MHz; CD_3OD) 2.0-2.4 (2H, m, CH_2CH), 3.3-3.6 (2H, m, NCH_2CH_2), 3.72 (3H, s, CO_2Me), 4.00 and 4.21 (each 2H, s, $NHCH_2$ and CH_2CO_2Me), 4.37 (1H, br t, CH_2CH), 5.14 (2H, s, CH_2Ph), and 7.4 (5H, m, ArH); δ_C (100 MHz; CD_3OD) 22.7 (CH_2CH_2CH), 37.6, 42.0, 42.6 (all NCH_2), 52.7 (OCH_3), 52.8 (CH), 68.5 (CH_2Ph), 129.1, 129.3, 129.5 (all ArCH), 137.6 (ArC), 159.0 (N=C–NH), 163.7 (CO, urethane), 171.4 and 172.1 (both CO, amide and ester).
12. Thioimidates were preferred to imidates when it was necessary to prepare a C-activated derivative from an amino acid, cf. the nitrile used to prepare imidate **12**.
13. Clausen, K.; Thorssen, M.; Lawesson, S.-O.; Spatola, A. F. *J. Chem. Soc., Perkin Trans. 1*, **1984**, 785-798.
14. As was observed in the tetrahydroimidazole series (ref. 1), tetrahydropyrimidines α-substituted in the 2-aminomethyl substituent, i.e **15**, **17**, were isolated as mixtures of diastereoisomers. Salts of the tetrahydropyrimidines are configurationally stable at this centre, but undergo epimerisation on basification, because of the C–H acidity at this position (*cf.* Anderson, M. W.; Jones, R. C. F.; Saunders, J. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 205-209).
15. Crude yields are approx. 60-70%, but the compound appears unstable to silica chromatography; we are pursuing alternative purifications.
16. Selected data for **18** (≡ **2**; R = H): ν_{max}/cm^{-1} (film) 3150 and 1620; δ_H (250 MHz; CD_3OD) 2.19 (2H, m, CH_2CH_2CH), 3.47 (2H, m, CH_2CH_2CH), 3.67 (2H, s, CH_2C=N), 4.04 (1H, t, CH); δ_C (68 MHz; CD_3OD) 23.1 (CH_2CH_2CH), 38.5 (CH_2CH_2CH), 41.9 (CH_2C=N), 54.3 (CH), 164.7 (C=N), 176.3 (COOH).

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