PERKIN 1 COMMUNICATION

A versatile synthetic route to quinoxaline, pyrazine and 1,2,4-triazine substituted α-amino acids from vicinal tricarbonyls

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A range of novel heterocyclic α-amino acids has been synthesised by the reaction of diamines and amidrazones with α-amino acid vicinal tricarbonyl reactive substrates.

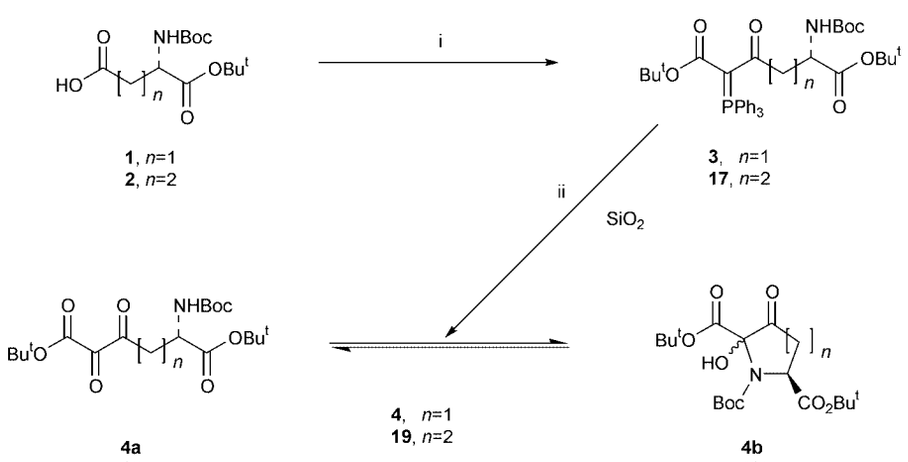
Amino acids play a significant role in the synthesis of novel drug candidates, with the use of non-proteinogenic and unnatural amino acids becoming increasingly important.[1–5] In view of this and of the biological and toxicological properties displayed by many heterocyclic substituted non-proteinogenic α-amino acids we have recently developed versatile synthetic routes towards compounds of this type.[6–8] This was achieved by the incorporation of alkynyl ketone reactive cores into the side chains of suitable amino acids allowing the formation of a range of α-amino acid alkynyl ketones capable of varied heterocyclic construction.

Many groups however have the potential to be suitable reactive cores for introduction into amino acid side chains and subsequent facile heterocyclic construction. It was therefore decided to attempt the formation of new amino acid reactive substrates by incorporation of a vicinal tricarbonyl moiety into our aspartate and glutamate side chains. The vicinal tricarbonyl is a bis-acceptor reactive building block which behaves as a potent electrophile. As such it has been used in the synthesis of many different heterocyclic structures, with Wasserman and co-workers being instrumental in this field.[9–12] One route to vicinal tricarbonyls, developed by Wasserman, involves conversion of carboxylic acids into ketophosphoranes followed by ozonolysis oxidation.[9] Facile formation of the required functionalised α-amino acid reactive substrates thus appeared possible by exploiting the selectively protected amino acids α-*tert*-butyl ester *N*-(*tert*-butoxycarbonyl)-L-aspartate **1** and α-*tert*-butyl ester *N*-(*tert*-butoxycarbonyl)-L-glutamate **2** which we had utilised in the formation of alkynyl ketone α-amino acids.[6–8]

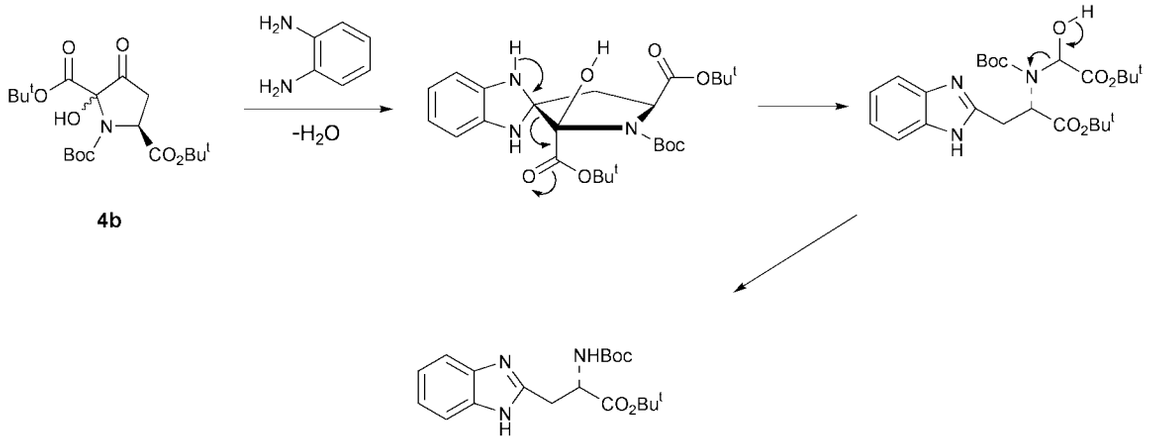
Conversion of **1** to the ketophosphorane **3** was thus carried out, in good yield, by a DCC–DMAP coupling reaction with (*tert*-butoxycarbonylmethylene)triphenylphosphorane in DCM. Ozonolysis of **3** however generated a product **4** which existed as a mixture of two species at equilibrium, the vicinal tricarbonyl α-amino acid **4a** and the 5-membered ring closed species **4b**, which resulted from attack of the α-amino group at the highly electrophilic central carbonyl (Scheme 1).

Initially unperturbed by the equilibrium existence of **4**, trial cyclocondensations with ethylenediamine were carried out, in order to attempt to generate a pyrazine product. These proved to be unsuccessful at a range of temperatures and in a range of solvents, with rapid consumption of **4** being accompanied by the formation of complex unidentifiable products. Condensation reactions with *o*-phenylenediamine were next attempted,[13] however instead of the desired quinoxaline substituted protected amino acid being obtained the benzimidazole **5** was isolated. It is believed that this product is formed by initial condensation of the diamine onto the ketonic carbonyl of **4b** followed by ring cleavage and aromatisation to the benzimidazole. This results in opening of the 5-membered ring, with subsequent elimination of oxoacetic acid *tert*-butyl ester to generate **5** (Scheme 2).

In an effort to effect pyrazine formation with the substrate **4** it was decided to simply prevent the formation of the equilibrium species **4b** by α-amino di-Boc protection.[14,15] *N*-Di-Boc protection of the orthogonally protected aspartate **6**, a precursor in the synthesis of **1**, was thus carried out by reaction of a concentrated acetonitrile solution of **6** with an excess of di-*tert*-butyl dicarbonate and DMAP, which generated **7** in almost quantitative yield. The β-benzyl ester was removed by hydrogenation over Pd–C to give **8**, then acid activation and reaction with (*tert*-butoxycarbonylmethylene)triphenylphosphorane generated **9**. Subsequent ozonolysis of **9** gave the



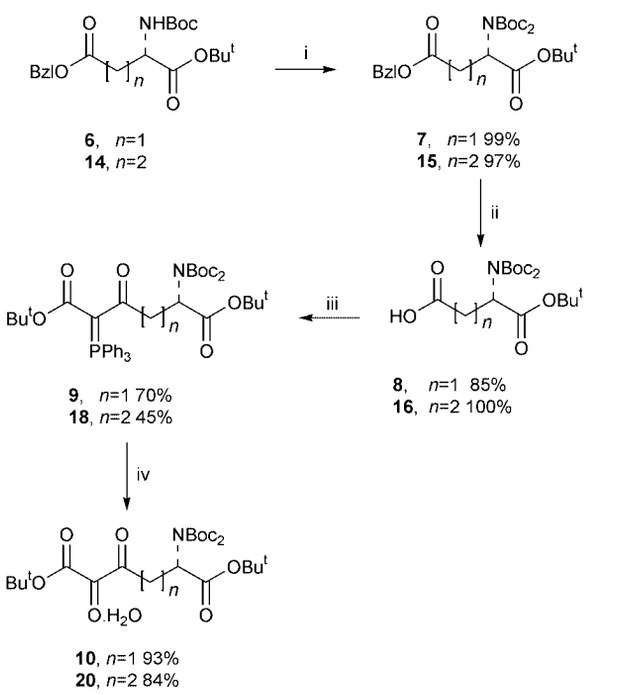
Scheme 1 *Reagents and conditions*: i, (*tert*-butoxycarbonylmethylene)triphenylphosphorane, DCC, DMAP, DCM, 0 °C, 70% (**3**), 63% (**17**); ii, O_3, DCM, −78 °C, 80% (**4**), 75% (**19**).



4b

5

Scheme 2



6, *n*=1
14, *n*=2

7, *n*=1 99%
15, *n*=2 97%

8, *n*=1 85%
16, *n*=2 100%

9, *n*=1 70%
18, *n*=2 45%

10, *n*=1 93%
20, *n*=2 84%

Scheme 3 *Reagents and conditions*: i, Boc_2O, DMAP, MeCN; ii, H_2, (10%) Pd–C, EtOH–H_2O (19 : 1); iii, (*tert*-butoxycarbonylmethylene)-triphenylphosphorane, DCC, DMAP, DCM, 0 °C; iv, O_3, DCM, −78 °C.

vicinal tricarbonyl reactive substrate **10** in good overall yield with no ring closed equilibrium species being observed (Scheme 3).

Reaction of **10**, in ethanol, with ethylenediamine now resulted in a rapid consumption of starting material along with the appearance of a single product, which was not isolated but expected to be the dihydropyrazine. Oxidation was then achieved by the addition of Pd/C, coupled with heating the reaction to reflux and the desired pyrazine substituted amino acid **11** was obtained in high yield (Scheme 4). A cyclocondensation of **10** with *o*-phenylenediamine, in refluxing ethanol, then resulted in quantitative conversion to the quinoxaline substituted amino acid **12** (Scheme 4).

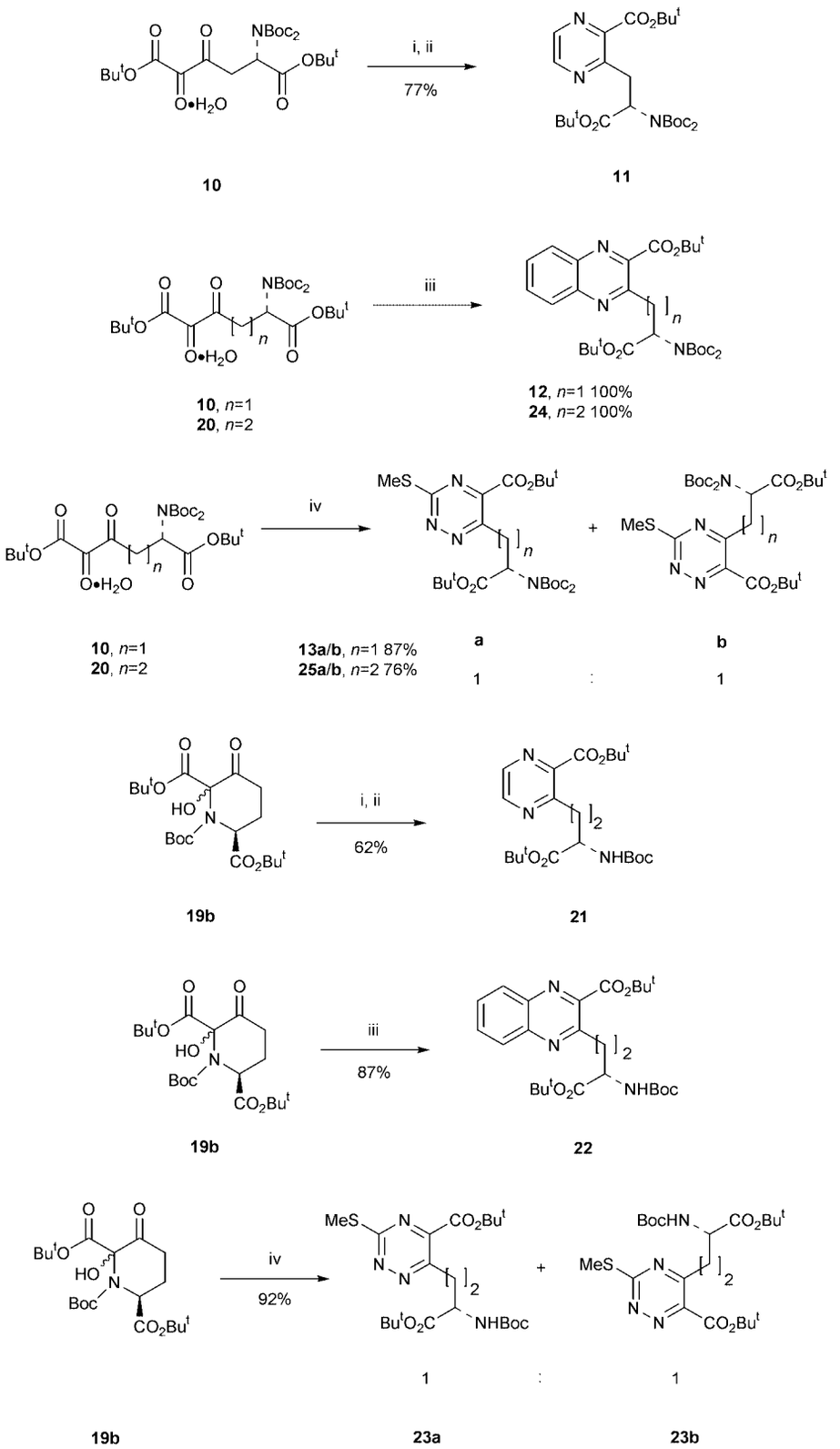
In order to investigate the possibility of 1,2,4-triazine formation,[16] a condensaton reaction of **10** with *S*-methyl isothiosemicarbazide was then attempted. This reaction also proved successful with the desired triazines **13a/b** being isolated, in high yield, as a partially separable 1 : 1 mixture of regioisomers (Scheme 4).

Next, in an attempt to diversify our methodology towards homologous amino acids, it was decided to expand to the glutamate system. Initially γ-benzyl α-*tert*-butyl diester *N*-(*tert*-butoxycarbonyl)-L-glutamate **14** underwent *N*-di-Boc protection, to give **15**, followed by hydrogenolysis to **16**, in excellent overall yield (Scheme 3). Both the mono-Boc and di-Boc, glutamates **2** and **16**, then underwent DCC–DMAP coupling reactions with (*tert*-butoxycarbonylmethylene)triphenylphosphorane to give the ketophosphoranes **17** and **18**, which with subsequent ozonolysis oxidations generated the reactive substrates **19** and **20**. As with the aspartate system the mono-Boc substrate **19** was found to exist as an equilibrium mixture of ring opened vicinal tricarbonyl **19a** and cyclic ketone species **19b**, and the di-Boc system **20** was found to exist exclusively as the vicinal tricarbonyl (Schemes 2 and 3).

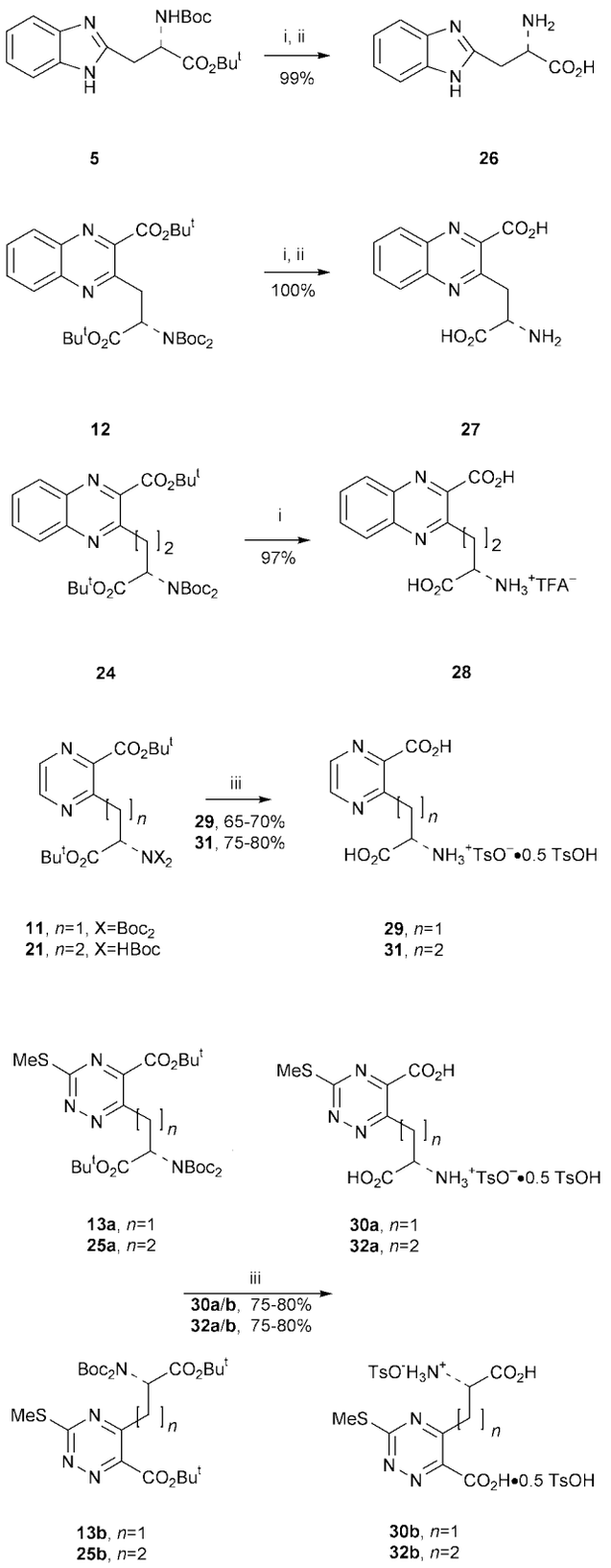
Analogous reactions of **19** with ethylenediamine (followed by Pd/C oxidation), phenylenediamine and *S*-methyl isothiosemicarbazide now resulted in high yielding generation of the pyrazine, quinoxaline and 1,2,4-triazine substituted protected amino acids **21**, **22** and **23a/b**. These results indicated that the equilibrium existence of **19** is not problematic (**19a** > **19b**), as in the aspartate system, which we believed was a consequence of preference for the ring closed form in the aspartate series, *i.e.* **4b** > **4a**. The reaction of **20** with phenylenediamine then allowed the quinoxaline amino acid **24** to be isolated in quantitative yield and cyclocondensation with *S*-methyl isothiosemicarbazide generated the triazine amino acids **25a/b** in high yield (Scheme 4).

Deprotection of the protected amino acids **5**, **12** and **24** was carried out by treatment with TFA–anisole, with the free amino acids **26** and **27** being obtained by ion-exchange chromatography whilst **28** was isolated, after trituration with diethyl ether, as its TFA salt (Scheme 5). Deprotection of the protected amino acids **11**, **13a/b**, **21** and **25a/b** was then carried out by their azeotropic distillation with 1.5 equivalents of $TsOH{\cdot}H_2O$–PhMe, as TFA–anisole conditions had led to decomposition. The amino acids **29**, **30a/b**, **31** and **32a/b** were thus isolated as their tosylate salts with an addtional 0.5 equivalents of TsOH, in high yields, as air and moisture sensitive species (Scheme 5).

In conclusion, by variation of the reactive core to the vicinal tricarbonyl we have been able to access a range of novel heterocyclic substituted non-proteinogenic amino acids.[17] The equilibrium existence of **4**, although initially problematic, allowed an interesting formation of the benzimidazolyl substituted β-alanine **5**, further investigation of which will be reported in due course. This problem was then shown to be easily circumvented, by simple addition of a second *N*-Boc protecting group, or not to be a consideration upon expanding to the glutamate system, from which the desired pyrazine, quinoxaline and 1,2,4-triazine amino acids were readily obtained. Further investigations towards novel heterocyclic systems will be reported.



Scheme 4 *Reagents and conditions*: i, $H_2NCH_2CH_2NH_2$, EtOH, rt; ii, (10%) Pd–C, EtOH, reflux; iii, *o*-$C_6H_4(NH_2)_2$, EtOH, reflux; iv, H_2NHN-(CSMe)NH·HI, Pr^i_2NEt, DCM, reflux.



Scheme 5 *Reagents and conditions*: i, TFA, anisole; ii, Dowex® 50X8-100 ion-exchange resin; iii, $TsOH \cdot H_2O$ (1.5 equiv.), toluene, azeotropic distillation.

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