# Synthesis of *N*-alkoxycarbonyl-3-substituted tetramic acids and functionalized enols *via C*-acylation reactions of active methylene compounds with *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-α-amino acids

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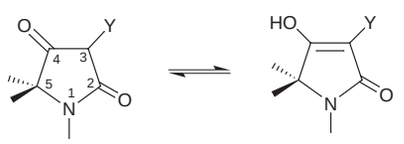
**The *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-α-amino acids react with active methylene compounds (malonic and acyl acetic esters), under basic conditions, to produce *N*-alkoxycarbonyl-3-substituted tetramic acids 7–17; in the case of the *N*-hydroxysuccinimide ester of L-alanine, the corresponding optically active tetramic acids 15 and 16 are obtained. In addition, the *C*-acylation reactions of cyanoacetic esters furnishes the functionalized enols 18–23 in very good yields. Spectral data and physical characteristics for all compounds are reported.**

The basic heterocyclic nucleus, pyrrolidine-2,4-dione (tetramic acid), is an integral part of a number of physiologically active



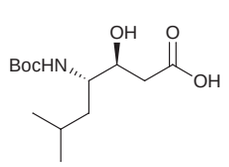

Keto–enol tautomerisation in tetramic acid

natural products. The tetramic acid moiety, in most cases, is present as a 3-acyl derivative. Members of the 3-acyltetramic acid group of compounds such as tenuazonic acid, tirandamycin, streptolydigin, ikaguramycin and erythroskyrine exhibit a range of biological activities from antiviral, antitumor, antibiotic and antimicrobial to inhibition of DNA-directed RNA polymerase and terminal deoxynucleotidyl transferase. Moreover, other members of this class are responsible for the pigmentation of certain moulds and sponges.[1]

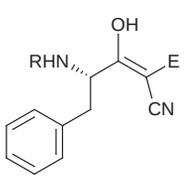
The synthesis of tetramic acids represents a worthwhile and challenging goal for a number of research groups, and a series of publications exist which describe the preparation of the pyrrolidine-2,4-dione nucleus. The first synthetic method for the 3-acyltetramic acids was reported by Lacey.[2] This method has been used for the synthesis of 5-substituted 3-alkoxycarbonyltetramic acids[3] and has been extended to the synthesis of 3-polyenoyltetramic acids.[4] A new strategy for the synthesis of 3-acyltetramic acids was developed by Jones and co-workers using pyrones,[5a] and more recently isoxazole-4-carboxylic esters as precursors.[5b] Moreover, DeShong *et al.* have synthesized 3-acyltetramic acid derivatives starting from 2,5-disubstituted isoxazolium salts.[6] Significant studies in the area of tetramic acids have been made by Ley *et al.*, providing a series of β-keto amides as suitable precursors for the preparation of 3-acyltetramic acids.[7]

The majority of the natural products containing the tetramic acid nucleus possess one or more stereogenic centers and a single enantiomer is responsible for their biological activity; therefore, routes to optically pure materials are becoming increasingly important. The enantioselective Lacey–Dieckmann cyclization has been used by the groups of Boeckmann[8] and Paquette[9] to synthesize (+)-ikaguramycin whereas Jones *et al.*[10] applied a similar strategy for the synthesis of erythroskyrine. Ley *et al.* successfully used their strategy for the synthesis of optically active tetramic acids[7] and, more recently, urethane-*N*-carboxy anhydrides have been used as precursors for the synthesis of enantiomerically pure tetramic acids.[11]

Chiral *N*-protected tetramic acid derivatives are important precursors of β-hydroxy-γ-amino acids and statine analogues. These compounds have been widely used for the synthesis of inhibitors of aspartyl proteases such as renin, a key enzyme in the renin–angiotensin system and HIV.[12] In addition, difunctionalized enols of type **I** possess topographical similarities




Boc-Statine

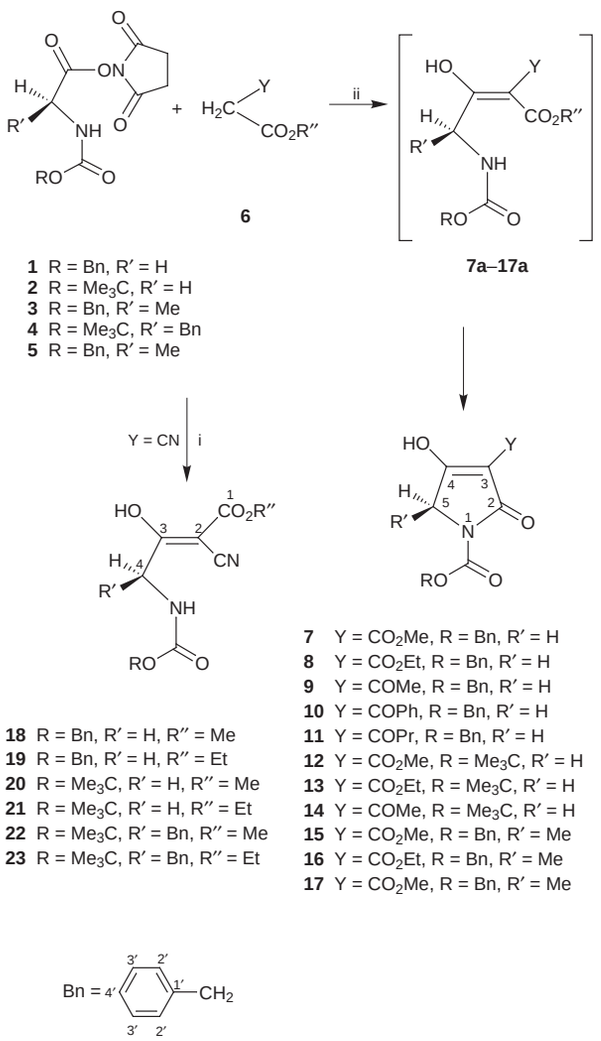



**I** (E = electron withdrawing group)

with Boc-statine, therefore they can be effective as inhibitors of HIV-1 protease.[13]

A strategy for the construction of the 3-substituted pyrrolidine-2,4-dione system through an acylation reaction of an active methylene compound with the *p*-nitrophenyl esters of *N*-benzoyl and *N*-acetyl glycine followed by cyclization of the *C*-acylation compounds, has been developed in our laboratory.[14] Because of the problems associated with this method, we have developed a new methodology, using the *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-α-amino acids as precursors, in which we have attempted to combine ease of operation and good yields with mildness of reaction conditions. This new methodology has been partly reported previously[15] and we hereby wish to present it in full.

The proposed methodology (Scheme 1) involves the *C*-acylation reaction of an active methylene compound with the *N*-hydroxysuccinimide esters of *N*-Boc and *N*-Z-α-amino acids (glycine, L-alanine, D,L-alanine) and *N*-Boc-L-phenylalanine (Boc = *tert*-butoxycarbonyl, Z = benzyloxycarbonyl). The *C*-acylation intermediates **7a**–**17a** (not isolated) undergo an




**Scheme 1** *Reagents and conditions*: i, Bu$^t$OK, Bu$^t$OH, room temp.; ii, NaH, anhydrous benzene, room temp.

*in situ* cyclization reaction to 3-substituted *N*-alkoxycarbonyl tetramic acids **7**–**17**, *via* an intramolecular condensation mechanism.

The requisite *N*-hydroxysuccinimide esters **1**–**5** were easily prepared following a modification of a literature procedure,[16] from the reaction of the corresponding α-amino acid derivatives with *N*-hydroxysuccinimide and DCC in DME, at 0 °C.

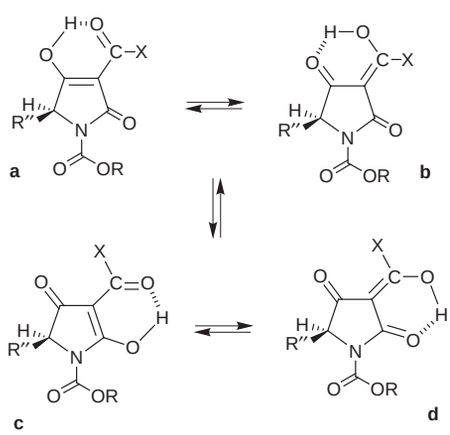
In a typical *C*-acylation–cyclization reaction, 3 equiv. of the active methylene compound **6** were treated with 3 equiv. of sodium hydride in anhydrous benzene, or 2 equiv. of potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature. After *ca*. 60 min, 1 equiv. of the *N*-hydroxysuccinimide ester of the *N*-alkoxycarbonyl-α-amino acid was added to the reaction mixture which was then stirred for 1.5–2 h before treatment with water and diethyl ether; the aqueous layer on acidification gave the *N*-alkoxycarbonyl-3-substituted tetramic acids **7**–**17**, in good yields. In the case of cyanoacetic esters **6** (Y = CN), the *C*-acylation compounds **18**–**23** were isolated in their enolic form, without further cyclization under the reaction conditions.

An important feature of this route has been the use of *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-α-amino acids as acylating agents. These esters are stable, can be stored for a long time and are easily prepared, therefore they are an attractive alternative to other activated amino acid species. These properties also apply to the *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-L-amino acids, which are useful precursors for the synthesis of optically active tetramic acids. The *N*-hydroxysuccinimide formed as a by-product is soluble in water and therefore easily removed from the reaction mixture. Moreover, the *N*-protective groups, Boc and Z, have proved to be very stable under the basic reaction conditions (Bu$^t$OK in Bu$^t$OH, or NaH in anhydrous benzene) allowing for the isolation of the corresponding *N*-alkoxycarbonyl-3-substituted tetramic acids, which are extensively used for the synthesis of β-hydroxy-γ-amino acids and statine analogues.

The application of the suggested methodology to the construction of chiral tetramic acids, with a stereogenic center at C-5 has led to the isolation of optically active *N*-benzyloxycarbonyl-3-alkoxycarbonyl-5-methyltetramic acids **15** and **16**, using the *N*-hydroxysuccinimide ester of *N*-Z-L-alanine. The enantiomeric ratio of compound **15** was 15:85, as determined by means of HPLC using a chiral stationary phase (see Experimental Section). On the other hand, condensation of methyl cyanoacetate with the optically active *N*-hydroxysuccinimide ester of *N*-Boc-L-phenylalanine yielded the functionalized enol methyl 4-*tert*-butoxycarbonylamino-2-cyano-3-hydroxy-5-phenylpent-2-enoate, **22**, which was found to be optically active $[\alpha]_D^{23}$ +78.4 (*c* 1.05, MeOH). This compound has been reported in the literature with an optical rotation $[\alpha]_D^{23}$ +77.9 (*c* 1.04, MeOH).[13a]

The structures of the newly obtained compounds, 3-substituted *N*-alkoxycarbonyl tetramic acids, **7**–**17**, and *C*-acylation compounds, **18**–**23**, were confirmed by elemental analysis and their spectral data (see Experimental Section).

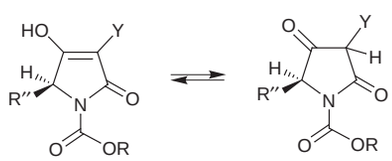
Tetramic acids bearing acyl or alkoxycarbonyl substituents at the 3-position exist in solution as four different enolic forms, a pair of 'external' (**ab** ⟹ **cd**) and a pair of 'internal' (**a** ⟹ **b**; **c** ⟹ **d**) tautomers (Scheme 2).[17] In non-polar solvents (*e.g.*




**Scheme 2**

$CDCl_3$) the interconversion between the 'external' tautomers is often a comparatively slow process on the NMR time-scale, therefore the 'external' tautomers can give separate NMR signals.

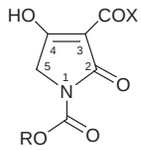
The 3-substituted *N*-alkoxycarbonyl tetramic acids, **7**–**17**, were found to exist in $CDCl_3$ solution in the enolized form. Their $^1$H NMR spectra lacked any resonance characteristic of a methine proton at C-3, corresponding to the keto form (see



Keto–enol tautomerism in the tetramic acids **7**–**17**

diagram) whereas in their $^{13}$C NMR spectra there was no signal attributable to an sp$^3$-CH group at C-3 for the pyrrolidine-2,4-dione system.

**Table 1** $^1$H NMR Chemical shifts for *N*-alkoxycarbonyl-3-acyltetramic acids **9**, **10** and **14** (300 MHz, $CDCl_3$)




**9** X = Me, R = Bn
**10** X = Ph, R = Bn
**14** X = Me, R = $Me_3C$

| Compound | H-5 | | X | | R | OH |
|---|---|---|---|---|---|---|
| | **cd** | **ab** | **cd** | **ab** | | |
| **9** | 4.12 (2H, s) | 4.29 | 2.53 (2H, s) | 2.56 | 5.32 (2H, s) 7.36–7.45 (5H, m) | 12–14 (1H, br) |
| | **cd** : **ab** = 1.36 | | **cd** : **ab** = 1.31 | | | |
| **10** | 4.17 (2H, s) | 4.39 | 5.35 (2H, s) 7.37–8.18 (10H, m) | | | 11–12 (1H, br) |
| | **cd** : **ab** = 1.82 | | | | | |
| **14** | 4.05 (2H, s) | 4.23 | 2.52 (2H, s) | 2.54 | 1.55 (9H, s) | 11–13 (1H, br) |
| | **cd** : **ab** = 2.11 | | **cd** : **ab** = 2.03 | | | |

**Table 2** $^{13}$C NMR Chemical shifts for *N*-alkoxycarbonyl-3-acyltetramic acids **9**, **10** and **14** (75 MHz, $CDCl_3$)

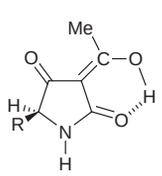
| Compound | | C-4 | COX | C-2 | OCOR | C-3 | C-5 | R | X |
|---|---|---|---|---|---|---|---|---|---|
| **9** | **cd** | 189.20 | 188.69 | 172.80 | 150.21 | 102.96 | 54.54 | 135.22–128.34 68.70 (**cd**) | 20.04 |
| | **ab** | 194.22 | 193.97 | 164.30 | 151.11 | 105.74 | 50.77 | 68.33 (**ab**) | 22.02 |
| | **cd** : **ab** | 1.44 | 1.71 | 1.75 | 1.20 | 1.40 | 1.29 | | 1.19 |
| **10** | **cd** | 186.90 | 182.69 | 174.69 | 149.72 | 100.25 | 54.07 | 134.65–128.21 68.80 (**cd**) | |
| | **ab** | 196.06 | 188.04 | 163.08 | 150.61 | 103.37 | 50.80 | 68.33 (**ab**) | |
| | **cd** : **ab** | | | | | | 1.61 | | |
| **14** | **cd** | 189.64 | 188.31 | 173.16 | 148.83 | 103.15 | 54.71 | 84.18 27.88 | 20.00 |
| | **ab** | 194.06 | 193.97 | 164.63 | 149.85 | 106.06 | 50.78 | 83.51 27.95 | 22.03 |
| | **cd** : **ab** | 1.60 | 1.78 | | | | 1.93 | 1.99 | 1.92 |

In the spectra of tetramic acids bearing an alkoxycarbonyl group at the 3-position only one set of signals was observed for all protons and carbons in $CDCl_3$ solution, indicating that the tautomeric equilibrium shown in Scheme 2 is fast on the NMR time-scale. In this case the observed chemical shifts must be the weighted average of the chemical shifts of the two 'external' tautomeric pairs.

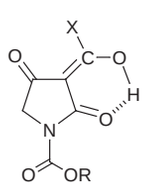
On the other hand, two sets of signals are present in the $^1$H and $^{13}$C NMR spectra of the 3-acyltetramic acids. The $^1$H NMR spectral data for *N*-benzyloxycarbonyl-3-acetyl- and -3-benzoyl-tetramic acids, **9** and **10**, as well as for *N*-*tert*-butoxycarbonyl-3-acetyltetramic acid, **14**, are presented in Table 1. The signals of the C-3 and C-5 substituent protons were split into two parts with an intensity ratio of **cd** : **ab** > 1, showing that the dominant form should be the 'external' tautomer **cd**.

The $^{13}$C NMR assignments of the 3-acyltetramic acids in $CDCl_3$ solution presented in Table 2, are based on the fact that hydrogen-bonded carbonyl carbons appear at lower field than the corresponding non-hydrogen-bonded carbonyls, whereas enolic carbon atoms would be expected to appear at higher field.[18] The chemical shifts observed for C-2 and C-4 (Scheme 2) could be used to deduce the relative stability of the 'external' tautomers. 3-Acyl- *N*-alkoxycarbonyltetramic acids were found to exist to a greater extent as the 'external' pair of tautomers **cd**.

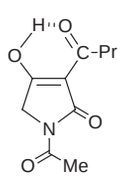
These results are fully in accord with the observations of Steyn and co-workers who found[19] that **d** is the predominant




**II**
(R = $CH_2Ph$, $CHMe_2$)[19]




**III**
[X = Me, Ph; R = $C_6H_5CH_2$, $(CH_3)_3C$]



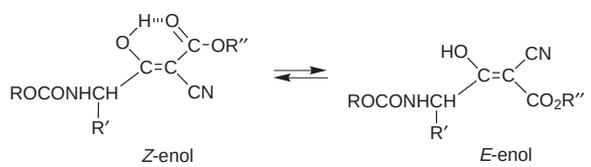

**IV**[20]

tautomer of 3-acetyltetramic acids bearing no substituents on the ring nitrogen (see **II**), as determined from the $^1$H and $^{13}$C NMR spectral results ($CDCl_3$ solutions). This preference is attributed to the ability of the C-2 amide carbonyl group to form a stronger intramolecular hydrogen bond than the C-4 carbonyl-group.

However, when the ring nitrogen is acylated (see **IV**) the major tautomer is **a**, as shown by $^{13}$C NMR spectroscopy and

X-ray crystallography.[20] This difference was attributed to the possibility of hydrogen bonding with the C-4 carbonyl being increased, as the nitrogen lone pair is shared between two carbonyl groups and is no longer able to enhance the proton acceptor ability of the C-2 carbonyl.

The $^1$H and $^{13}$C NMR spectra of the *C*-acylation compounds **18**–**23** clearly indicate that these compounds exist, in $CDCl_3$ solution, in their enolic form. In the case of these compounds the electron withdrawing effect of the −CN substituent causes an increase in the enol population and a decrease in the OH chemical shift[21a] [$\delta_H$(OH) ~ 13–14 ppm, see Experimental Section]. In addition, the *Z*-enol (see diagram) should be the




*E*–*Z* Isomerisation in *C*-acylation compounds **18**–**23**

most stable one due to the presence of the intramolecular hydrogen bond.[21b]

The IR spectra of the *N*-alkoxycarbonyl-3-substituted tetramic acids, **7**–**17**, show a characteristic absorption at 1765–1720 cm$^{-1}$ for the carbonyl group of the urethane substituent. The CO absorption of the lactam (2-CO) appears at 1720–1680 cm$^{-1}$ along with the CO absorption of the keto-form of β-keto ester or β-diketone. The bands at 1680–1630 cm$^{-1}$ can be assigned to the CO stretching of the intramolecular hydrogen bonded carbonyl present in the enol form of β-keto esters or β-diketones. These results indicate that *N*-alkoxycarbonyl-3-substituted tetramic acids exist, in the solid state, as a mixture of the keto- and enol-forms.

The IR spectra of the *C*-acylation compounds **18**–**23** show absorptions at 3320–3300 and 2210 cm$^{-1}$ which are assigned to N–H and C≡N stretching, respectively. In the carbonyl region, the CO absorption of the urethane group appears at 1690–1680 cm$^{-1}$ whereas the intramolecular hydrogen bonded carbonyl of the enol form of the β-keto ester, C(OH)=C-$CO_2$R, absorbs at 1660–1640 cm$^{-1}$. The strong band at 1610–1580 cm$^{-1}$ is attributed to the carbon–carbon double bond of this system. Taking everything into account, it appears that the enolic form of the *C*-acylation compounds is predominating in the solid state.

In the work described above we have developed a novel and advantageous synthetic approach to *N*-alkoxycarbonyl-3-substituted tetramic acids. The synthesis is performed under mild conditions, and short reaction times are required, providing the compounds in satisfactory yields. This methodology has been shown to be applicable to the synthesis of optically active *N*-alkoxycarbonyl-3-substituted-5-methyltetramic acids, providing evidence that partial racemization occurs under these experimental conditions. Apparently, this strategy is a convenient way of preparing tetramic acids and is suitable for the synthesis of compounds of high enantiomeric purity.

Moreover, the *C*-acylation reactions of cyanoacetic esters using the *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-α-amino acids as acylating agents have been performed by a simple experimental procedure providing the functionalized enols **18**–**23** in high yields. The potential of this route for the preparation of optically active functionalized enols has been demonstrated by the synthesis of methyl 4-*tert*-butoxycarbonylamino-2-cyano-3-hydroxy-5-phenylpent-2-enoate, **22**, and ethyl 4-*tert*-butoxycarbonylamino-2-cyano-3-hydroxy-5-phenylpent-2-enoate, **23**.

In conclusion, the base-induced condensation of *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-α-amino acids with active methylene compounds smoothly gives rise to *N*-alkoxycarbonyl-3-substituted tetramic acids and *C*-acylation compounds which can be useful in medicinal chemistry.

## Experimental

Mps were determined on a Galenkamp MFB-595 melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 267 spectrometer. The NMR spectra were recorded on either Varian EM-360 60 MHz, Bruker AC-300 300 MHz or Varian Gemini 2000 300 MHz spectrometers. Chemical shifts are quoted in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad); *J* values are given in Hz. Elemental analyses were obtained from the microanalytical laboratory of CNRS (France) and the University of Liverpool Chemistry Department. The mass spectra were recorded on a Finnigan MAT TSQ 7000 instrument: a solution in methanol or methanol containing 10 mmol sodium acetonate, was analysed in electrospray (ESI) mode by direct infusion with a Harvard Syringe Pump (infusion: 3 μl min$^{-1}$, capillary temp: 200 °C, needle voltage: 4.5 kV, sheath gas: 3.5 units). The proton adduct ions were selected as the parent ions. $[\alpha]_D$ Values are given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. The separation of optical isomers of compound **15** by means of HPLC has been carried out by the JASCO Corporation, LC Application Dept. (Japan), using a packed column, [CHIRALPAK AS (4.6 × 250 mm)] incorporated in an HPLC system consisting of a PU-980 pump, AS-950 auto sampler, CO-965 column oven, Rheodyne 7125 injector, UV-970 and OR-990 detectors and LCSS-905 integrator. The mobile phase was hexane–propan-2-ol (30 : 70)–0.1% (v/v) diethylamine–0.1% (v/v) acetic acid.

### General procedure for the preparation of *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-α-amino acids

A solution of *N*,*N*-dicyclohexylcarbodiimide (9.2 g, 0.044 mol) in *ca*. 15 ml 1,2-dimethoxyethane (DME) was added dropwise to a solution of the *N*-alkoxycarbonyl-α-amino acid (0.04 mol) and *N*-hydroxysuccinimide (4.6 g, 0.04 mol) in 50 ml DME with cooling over a period of 30 min. The reaction mixture was allowed to stand in the refrigerator overnight. The formed dicyclohexylurea was filtered off and washed with DME after which the filtrate was concentrated *in vacuo*. Diethyl ether was added to the white oily residue which soon crystallized to give a white solid that was filtered off and washed with diethyl ether. In the case of the *N*-hydroxysuccinimide ester of *N*-Boc-L-phenylalanine, the oily residue was crystallized after adding isopropyl alcohol instead of diethyl ether.

The *N*-hydroxysuccinimide esters thus obtained were used for the *C*-acylation–cyclization reactions without further purification with the exception of the ester of *N*-Z-L-alanine which was previously recrystallized from dichloromethane–diethyl ether.

***N*-Hydroxysuccinimide ester of *N*-benzyloxycarbonylglycine 1**. Yield: 98%, mp 107–110 °C (from $CH_2Cl_2$–light petroleum) (lit.,[16] mp 113–114 °C); $\nu_{max}$(Nujol)/cm$^{-1}$ 3300m, br (NH), 1820m (CO ester), 1780m (CO ring), 1730s (CO urethane), 1690s (amide II) and 1510m (C=C ring str.); $\delta_H$(60 MHz; $CDCl_3$) 2.77 [4H, s, $(CH_2)_2$], 4.27 (2H, d, *J* 6.8, $NCH_2$), 5.10 (2H, s, $OCH_2C_6H_5$), 5.50 (1H, br, NH) and 7.31 (5H, s, $C_6H_5$).

***N*-Hydroxysuccinimide ester of *N*-*tert*-butoxycarbonylglycine 2.** Yield: 85%, mp 167–169 °C (from $CH_2Cl_2$–$Et_2O$) (lit.,[16] mp 168–170 °C); $\nu_{max}$(Nujol)/cm$^{-1}$ 3300s (NH), 1820m (CO ester), 1785m (CO ring), 1730s (CO urethane) and 1675m (amide II); $\delta_H$(60 MHz; $CDCl_3$) 1.45 [9H, s, $(CH_3)_3$], 2.82 [4H, s, $(CH_2)_2$], 4.18 (2H, d, *J* 6.8, $NCH_2$) and 4.97 (1H, br, NH).

***N*-Hydroxysuccinimide ester of *N*-benzyloxycarbonyl-L-alanine 3.** Yield: 93%, mp 122.5–123.5 °C (from $CH_2Cl_2$–$Et_2O$) (lit.,[16] mp 123–123.5 °C), $[\alpha]_D^{25}$ −37 (*c* 2, dioxane) {lit.,[16] $[\alpha]_D^{25}$ −37.2 (*c* 2, dioxane)}; $\nu_{max}$(Nujol)/cm$^{-1}$ 3300s (NH), 1810m (CO ester), 1780m (CO ring), 1730s (CO urethane), 1710s (amide II) and 1500s (C=C ring str.); $\delta_H$(300 MHz; $CDCl_3$) 1.59

(3H, d, *J* 7.1, CHC$H_3$), 2.82 [4H, s, $(CH_2)_2$], 4.77 (1H, m, C$H$CH$_3$), 5.13 (2H, m, OC$H_2$C$_6$H$_5$), 5.37 (1H, d, *J* 8, NH) and 7.30–7.35 (5H, m, C$_6$H$_5$).

***N*-Hydroxysuccinimide ester of *N*-*tert*-butoxycarbonyl-L-phenylalanine 4.** Yield: 80%, mp 149–151 °C (from $CH_2Cl_2$–$Et_2O$) (lit.,[16] mp 152–153 °C); $[\alpha]_D^{25}$ −19.5 (*c* 2, dioxane) {lit.,[16] $[\alpha]_D^{25}$ −19.0 (*c* 2, dioxane)}; $\nu_{max}$(Nujol)/cm$^{-1}$ 3335s (NH), 1800m (CO ester), 1770m (CO ring), 1730s (CO urethane), 1690s (amide II) and 1510m (C=C ring str.); $\delta_H$(60 MHz; $CDCl_3$) 1.40 [9H, s, $(CH_3)_3$], 2.78 [4H, s, $(CH_2)_2$], 3.20 (2H, br, C$H_2$C$_6$H$_5$), 4.83 (2H, br, NH and CH) and 7.17 (5H, s, C$_6$H$_5$).

***N*-Hydroxysuccinimide ester of *N*-benzyloxycarbonyl-D,L-alanine 5.** Yield: 76%, mp 104–107 °C (from $CH_2Cl_2$–$Et_2O$); $\nu_{max}$(Nujol)/cm$^{-1}$ 3330s (NH), 1820m (CO ester), 1780m (CO ring), 1730s (CO urethane), 1710s (amide II) and 1510s (C=C ring str.); $\delta_H$(300 MHz; $CDCl_3$) 1.59 (3H, d, *J* 7.3, CHC$H_3$), 2.82 [4H, s, $(CH_2)_2$], 4.77 (1H, m, C$H$CH$_3$), 5.13 (2H, m, OC$H_2$C$_6$H$_5$), 5.35 (1H, d, *J* 7.8, NH) and 7.31–7.36 (5H, m, C$_6$H$_5$).

### General procedure for the synthesis of *N*-alkoxycarbonyl-3-substituted tetramic acids

The active methylene compound (0.03 mol) was added dropwise to a mixture of sodium hydride (0.03 mol, 55–60% sodium hydride in oil) in anhydrous benzene (80 ml) and the thick, white or yellow slurry thus formed was stirred at room temperature for 1 h. The *N*-hydroxysuccinimide ester of the appropriate amino acid (0.01 mol) was added to the mixture and stirring continued for 2 h, after which one of the following work-up procedures was followed.

(i) Water and diethyl ether were added to the reaction mixture and the aqueous layer was separated and acidified with 10% hydrochloric acid in an ice–water bath. The 3-substituted-*N*-alkoxycarbonyl tetramic acids were isolated either as crystalline products, formed directly in the acidified solution or as oily products which were extracted with dichloromethane.

(ii) Water was added to the reaction mixture, the white precipitate thus formed was filtered off and dissolved in methanol. The solution was acidified with concentrated hydrochloric acid and evaporated *in vacuo*. The solid residue was dissolved in a small amount of water and extracted with dichloromethane. The organic layer was separated, dried with $Na_2SO_4$ and the organic solvent was evaporated *in vacuo*. Diethyl ether and light petroleum were added to the oily residue and compounds **15**–**17** were isolated as white, crystalline products.

***N*-Benzyloxycarbonyl-3-methoxycarbonyltetramic acid 7.** Following work-up (i) compound **7** was isolated as a white solid, formed directly in the acidified solution (1.6 g, 54%), mp 176–178 °C (from $CH_2Cl_2$–light petroleum) (Found: C, 57.69; H, 4.49; N, 4.62. C$_{14}$H$_{13}$NO$_6$ requires C, 57.73; H, 4.50; N, 4.82%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1720s (CO urethane), 1700s (CO β-keto ester, keto form and 2-CO ring), 1680s (CO β-keto ester, enol form) and 1600s (C=C ring str.); $\delta_H$(300 MHz; $CDCl_3$) 3.93 (3H, s, $CO_2CH_3$), 4.39 (2H, s, $CH_2$ ring), 5.32 (2H, s, OC$H_2$C$_6$H$_5$) and 7.32–7.46 (5H, m, C$_6$H$_5$); $\delta_C$(75 MHz; $CDCl_3$) 185.05 (C-4), 167.64 (C-2), 162.87 (CO ester), 151.25 (*C*OCH$_2$C$_6$H$_5$) 135.41 (C-1′), 128.88 (C-2′), 128.66 (C-4′), 128.25 (C-3′), 99.55 (C-3), 68.39 (*C*H$_2$C$_6$H$_5$), 52.62 (C-5) and 48.18 ($CO_2CH_3$); *m*/*z* (ESI) 291.9 ([M]$^+$, 100%), 225 (9), 128.7 (3), 96.9 (27), 64.8 (11).

***N*-Benzyloxycarbonyl-3-ethoxycarbonyltetramic acid 8.** Following work-up (i) compound **8** was isolated as a white solid, formed directly in the acidified solution (1.83 g, 60%), mp 93–96 °C (from $CH_2Cl_2$–light petroleum) (Found: C, 58.90; H, 5.02; N, 4.72. C$_{15}$H$_{15}$NO$_6$ requires C, 59.01; H, 4.95; N, 4.59%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1720s (CO urethane), 1690s (CO β-keto ester, keto form and 2-CO ring), 1680s (CO β-keto ester, enol form) and 1600s (C=C); $\delta_H$(300 MHz; $CDCl_3$) 1.38 (3H, t, *J* 7, $CH_2CH_3$), 4.38 (2H, s, $CH_2$ ring), 4.40 (2H, q, *J* 7, C$H_2$CH$_3$), 5.32 (2H, s, OC$H_2$C$_6$H$_5$) and 7.33–7.46 (5H, m, C$_6$H$_5$); $\delta_C$(75 MHz; $CDCl_3$) 184.70 (C-4), 167.12 (C-2), 162.37 (CO ester), 151.12 (*C*OCH$_2$C$_6$H$_5$) 135.23 (C-1′), 128.62 (C-2′), 128.41 (C-4′), 128.09 (C-3′), 99.60 (C-3), 68.15 (*C*H$_2$C$_6$H$_5$), 61.81 ($CO_2$-*C*H$_2$CH$_3$), 47.79 (C-5) and 13.94 ($CO_2CH_2CH_3$); *m*/*z* (ESI) 306.0 ([M]$^+$, 100%), 96.9 (23), 64.8 (32).

***N*-Benzyloxycarbonyl-3-acetyltetramic acid 9.** Following work-up (i) the oily product formed in the acidified solution was extracted with dichloromethane and the organic solvent was evaporated *in vacuo*. Diethyl ether and light petroleum were added to the residue and compound **9** was isolated as a yellowish solid (1.98 g, 72%), mp 92–95 °C (from $Et_2O$–light petroleum) (Found: C, 61.11; H, 4.80; N, 5.25. C$_{14}$H$_{13}$NO$_5$ requires C, 61.09; H, 4.76; N, 5.09%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1740s (CO urethane), 1700s (CO β-diketone keto form and 2-CO ring), 1630s (CO β-diketone, enol form) and 1590s (C=C); $\delta_H$(300 MHz; $CDCl_3$) see Table 1; $\delta_C$(75 MHz; $CDCl_3$) see Table 2; *m*/*z* (ESI) 275.8 ([M]$^+$, 76%), 129 (17), 96.7 (100), 65.0 (50).

***N*-Benzyloxycarbonyl-3-benzoyltetramic acid 10.** Following work-up (i) the oily product formed in the acidified solution was extracted with dichloromethane and the organic solvent was evaporated *in vacuo*. Diethyl ether and light petroleum were added to the residue and compound **10** was isolated as a yellowish solid (1.42 g, 42%), mp 97–99 °C (from $Et_2O$/$CH_2Cl_2$–light petroleum) (Found: C, 67.89; H, 4.56; N, 4.21. C$_{19}$H$_{15}$NO$_5$ requires C, 67.89; H, 4.48; N, 4.15%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1760s (CO urethane), 1700s (CO β-diketone keto form and 2-CO ring) and 1590s (C=C); $\delta_H$(300 MHz; $CDCl_3$) see Table 1; $\delta_C$(75 MHz; $CDCl_3$) see Table 2; *m*/*z* (ESI) 337.8 ([M]$^+$, 97%), 128.9 (14), 96.9 (100), 64.9 (59).

***N*-Benzyloxycarbonyl-3-butanoyltetramic acid 11.** Following work-up (i) the oily product formed in the acidified solution was extracted with dichloromethane and the organic solvent was evaporated *in vacuo*. Diethyl ether and light petroleum were added to the residue and compound **11** was isolated as a yellowish solid (1.36 g, 45%), mp 125–127 °C (from $Et_2O$–light petroleum) (Found: C, 58.94; H, 5.10; N, 4.57. C$_{16}$H$_{16}$NO$_5$Na requires C, 59.07; H, 4.96; N, 4.31%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1740s (CO urethane), 1670m (CO β-diketone keto form and 2-CO ring) and 1620s (C=C); $\delta_H$(300 MHz; $CDCl_3$–DMSO) 0.5 (3H, t, *J* 7, $CH_2CH_2CH_3$), 1.16 (2H, m, $CH_2CH_2CH_3$), 2.36 (2H, t, *J* 7, C$H_2$CH$_2$CH$_3$), 3.43 (2H, s, $CH_2$ ring), 4.79 (2H, s, OC$H_2$C$_6$H$_5$) and 6.91–6.96 (5H, m, C$_6$H$_5$); $\delta_C$(75 MHz; $CDCl_3$) 196.06 (C-4), 188.82 (*C*OC$_3$H$_7$), 172.45 (C-2), 150.51 (O*C*OCH$_2$C$_6$H$_5$), 134.85 (C-1′), 127.65 (C-2′), 127.37 (C-4′), 126.92 (C-3′), 101.15 (C-3), 65.90 (*C*H$_2$C$_6$H$_5$), 51.38 (C-5), 32.82 (*C*H$_2$CH$_2$CH$_3$), 17.21 (CH$_2$*C*H$_2$CH$_3$) and 13.09 (CH$_2$CH$_2$*C*H$_3$); *m*/*z* (ESI) 326 ([M + Na]$^+$, 100%), 279 (11), 247 (23), 225 (39) 86.9 (11), 54.9 (28).

***N*-*tert*-Butoxycarbonyl-3-methoxycarbonyltetramic acid 12.** Following work-up (i) compound **12** was isolated as a white solid, formed directly in the acidified solution (1.80 g, 70%), mp 241–243 °C (decomp.) (from $CH_2Cl_2$–light petroleum) (Found: C, 51.71; H, 5.90; N, 5.23. C$_{11}$H$_{15}$NO$_6$ requires C, 51.36; H, 5.88; N, 5.45%); $\nu_{max}$(Nujol)/cm$^{-1}$ 3300m (OH), 1750s (CO urethane), 1680s (CO β-keto ester, keto form and 2-CO ring), 1650m (CO β-keto ester, enol form) and 1600s (C=C); $\delta_H$(300 MHz; $CDCl_3$) 1.54 [9H, s, $(CH_3)_3$C], 3.92 (3H, s, $CO_2CH_3$), 4.33 (2H, s, $CH_2$ ring) and 8.5–9 (1H, br, OH); $\delta_C$(75 MHz; $CDCl_3$) 184.54 (C-4), 167.68 (C-2), 162.66 (CO ester), 149.84 [O*C*OC(CH$_3$)$_3$], 99.70 (C-3), 83.40 [*C*(CH$_3$)$_3$], 52.35 (C-5), 47.83 ($CO_2CH_3$) and 27.97 [C(*C*H$_3$)$_3$]; *m*/*z* (ESI) 257.9 ([M]$^+$, 83%), 201.8 {[M − C(CH$_3$)$_3$]$^+$, 100}, 157.8 {[M − COOC(CH$_3$)$_3$]$^+$, 3}, 96.8 (24), 64.9 (26).

***N*-*tert*-Butoxycarbonyl-3-ethoxycarbonyltetramic acid 13.** Following work-up (i) compound **13** was isolated as a white solid, formed directly in the acidified solution (1.22 g, 45%), mp 140–143 °C (from $CH_2Cl_2$–light petroleum) (Found: C, 53.32; H, 6.33; N, 5.09. C$_{12}$H$_{17}$NO$_6$ requires C, 53.13; H, 6.32; N, 5.16%); $\nu_{max}$(Nujol)/cm$^{-1}$ 3400w (OH), 1760s (CO urethane), 1710m (CO β-keto ester, keto form and 2-CO ring), 1670w (CO

β-keto ester, enol form) and 1590s (C=C); $\delta_H$(300 MHz; $CDCl_3$) 1.38 (3H, t, *J* 7, $CH_2CH_3$), 1.55 [9H, s, $(CH_3)_3C$], 4.31 (2H, s, $CH_2$ ring), 4.39 (2H, q, *J* 7, $CH_2CH_3$) and 8–9 (1H, br, OH); $\delta_C$(75 MHz; $CDCl_3$) 184.81 (C-4), 167.39 (C-2), 162.67 (CO ester), 150.19 [$OCOC(CH_3)_3$], 100.70 (C-3), 83.53 [$C(CH_3)_3$], 61.79 ($CH_2CH_3$), 48.21 (C-5), 28.16 [$C(CH_3)_3$] and 14.23 ($CH_2CH_3$); *m*/*z* (ESI) 271.9 ($[M]^+$, 90%), 215.8 {$[M - C(CH_3)_3]^+$, 100}, 96.8 (12), 64.9 (13).

***N*-*tert*-Butoxycarbonyl-3-acetyltetramic acid 14.** Following work-up (i) the oily product formed in the acidified solution was extracted with dichloromethane and the organic solvent was evaporated *in vacuo*. Diethyl ether and light petroleum were added to the residue and compound **14** was isolated as a white solid (1.5 g, 62%), mp 91–93 °C (from $Et_2O$–light petroleum) (Found: C, 54.36; H, 6.44; N, 5.80. $C_{11}H_{15}NO_5$ requires C, 54.76; H, 6.27; N, 5.81%); $\nu_{max}$(Nujol)/$cm^{-1}$ 3400w (OH), 1765s (CO urethane), 1720s (CO β-keto ester, keto form and 2-CO ring), 1650w (CO β-keto ester, enol form) and 1580s (C=C); $\delta_H$(300 MHz; $CDCl_3$) see Table 1; $\delta_C$(75 MHz; $CDCl_3$) see Table 2; *m*/*z* (ESI) 242 ($[M]^+$, 100%), 185.7 {$[M - C(CH_3)_3]^+$, 24}, 96.9 (22), 64.9 (12).

***N*-Benzyloxycarbonyl-3-methoxycarbonyl-5-methyltetramic acid 15.** Following work-up (ii) compound **15** was isolated as a white solid (1.59 g, 52%), mp 92–95 °C; $[\alpha]_D^{20}$ +41.5 (*c* 1.02, $CH_2Cl_2$) (Found: C, 59.53; H, 5.07; N, 4.92. $C_{15}H_{15}NO_6$ requires C, 59.01; H, 4.95; N, 4.59%); $\nu_{max}$(Nujol)/$cm^{-1}$ 3300m (OH), 1750s (CO urethane), 1710s (CO β-keto ester, keto form and 2-CO ring), 1650m (CO β-keto ester, enol form) and 1620s (C=C ring str.); $\delta_H$(300 MHz; $CDCl_3$) 1.59 (3H, d, *J* 6.8, $CCH_3$), 3.94 (3H, s, $CO_2CH_3$), 4.63 (1H, q, *J* 7, CH ring), 5.29 and 5.37 (2H, AB system, *J* 12.6, $CH_2C_6H_5$) and 7.31–7.48 (5H, m, $CH_2C_6H_5$); $\delta_C$(75 MHz; $CDCl_3$) 188.69 (C-4), 167.51 (C-2), 162.13 (CO ester), 151.01 ($COCH_2C_6H_5$), 135.15 (C-1′), 128.58 (C-2′), 128.27 (C-4′), 127.85 (C-3′), 97.79 (C-3), 68.10 ($CH_2C_6H_5$), 54.99 (C-5), 52.52 ($CO_2CH_3$) and 16.79 ($CCH_3$); *m*/*z* (ESI) 305.9 ($[M]^+$, 100%), 225.0 (27), 96.9 (20), 64.9 (23); HPLC [hexane–propan-2-ol 30 : 70–0.1% (v/v) diethylamine–0.1% (v/v) acetic acid]; $t_R$/min 9.32 (15%) and 11.88 (85%).

***N*-Benzyloxycarbonyl-3-ethoxycarbonyl-5-methyltetramic acid 16.** Following work-up (ii) compound **16** was isolated as a white solid (1.78 g, 55%), mp 84-86 °C; $[\alpha]_D^{20}$ +40.4 (*c* 1.13, $CH_2Cl_2$) (Found: C, 60.04; H, 5.45; N, 4.54. $C_{16}H_{17}NO_6$ requires C, 60.18; H, 5.37; N, 4.39%); $\nu_{max}$(Nujol)/$cm^{-1}$ 1750s (CO urethane), 1710s (CO β-keto ester, keto form and 2-CO ring), 1650s (CO β-keto ester, enol form) and 1610s (C=C ring str.); $\delta_H$(300 MHz; $CDCl_3$) 1.38 (3H, t, *J* 7.1, $CH_2CH_3$), 1.58 (3H, d, *J* 6.7, $CCH_3$), 4.41 (2H, q, *J* 7, $CH_2CH_3$), 4.61 (1H, q, *J* 7, CH ring), 5.30 and 5.36 (2H, AB system, *J* 12.6, $CH_2C_6H_5$) and 7.33–7.46 (5H, m, $CH_2C_6H_5$); $\delta_C$(75 MHz; $CDCl_3$) 188.70 (C-4), 167.27 (C-2), 162.05 (CO ester), 151.17 ($COCH_2C_6H_5$), 135.24 (C-1′), 128.61 (C-2′), 128.31 (C-4′), 127.98 (C-3′), 97.99 (C-3), 68.12 ($CH_2C_6H_5$), 61.93 ($CH_2CH_3$), 54.90 (C-5),16.79 ($CCH_3$) and 14.16 ($CH_2CH_3$); *m*/*z* (ESI) 319.9 ($[M]^+$, 100%), 96.9 (85), 64.7 (5).

***N*-Benzyloxycarbonyl-3-methoxycarbonyl-5-methyltetramic acid (racemic) 17.** Following work-up (ii) compound **17** was isolated as a white solid (1.48 g, 48%), mp 140–142 °C (from MeOH) (Found: C, 59.22; H, 4.99; N, 4.90. $C_{15}H_{15}NO_6$ requires C, 59.01; H, 4.95; N, 4.59%); $\nu_{max}$(Nujol)/$cm^{-1}$ 1750m (CO urethane), 1710s (CO β-keto ester, keto form and 2-CO ring), 1660m (CO β-keto ester, enol form) and 1620s (C=C ring str.); $\delta_H$(300 MHz; $CDCl_3$) 1.57 (3H, d, *J* 6.9, $CCH_3$), 3.92 (3H, s, $CO_2CH_3$), 4.61 (1H, q, *J* 7, CH ring), 5.28 and 5.35 (2H, AB system, *J* 12.5, $CH_2C_6H_5$) and 7.30–7.46 (5H, m, $CH_2C_6H_5$); $\delta_C$(75 MHz; $CDCl_3$) 189.11 (C-4), 167.91 (C-2), 162.43 (CO ester), 151.37 ($COCH_2C_6H_5$), 135.47 (C-1′), 128.87 (C-2′), 128.55 (C-4′), 128.13 (C-3′), 98.05 (C-3), 68.26 ($CH_2C_6H_5$), 55.10 (C-5), 52.66 ($CO_2CH_3$) and 16.84 ($CCH_3$); *m*/*z* (ESI) 305.9 ($[M]^+$, 100%), 224.6 (1), 96.9 (9), 64.8 (11).

**General procedure for the *C*-acylation of cyanoacetic esters with the *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-α-amino acids**

Potassium *tert*-butoxide (1.44 g, 0.0128 mol) was stirred in *tert*-butyl alcohol (60 ml) at room temperature until it dissolved (*ca*. 15 min), after which the active methylene compound **6** (Y = CN, R″ = Me, Et, 0.0192 mol) was added dropwise to the mixture. Stirring was continued for 1 h after which the *N*-hydroxysuccinimide ester of the appropriate *N*-alkoxycarbonyl-α-amino acid (0.0064 mol) was added to the mixture and stirring continued at room temperature for 1.5–2 h. Water and diethyl ether were added to the reaction mixture, after which the aqueous layer was separated and acidified with 10% hydrochloric acid, in an ice–water bath. The *C*-acylation compounds **18**–**23** were isolated as crystalline products, formed directly in the acidified solution.

**Methyl 4-benzyloxycarbonylamino-2-cyano-3-hydroxybut-2-enoate 18.** Yield: 80%, mp 104–105 °C (from $CH_2Cl_2$–light petroleum) (Found: C, 57.35; H, 4.97; N, 9.65. $C_{14}H_{14}N_2O_5$ requires C, 57.93; H, 4.86; N, 9.65%); $\nu_{max}$(Nujol)/$cm^{-1}$ 3300s (NH), 2210s (CN), 1720w (CO β-keto ester, keto form), 1690s (CO urethane), 1640m (CO β-keto ester, enol form) and 1610s (C=C ring str.); $\delta_H$(300 MHz; $CDCl_3$) 3.90 (3H, s, $CO_2CH_3$), 4.33 (2H, d, *J* 6.2, $NHCH_2$), 5.14 (2H, s, $OCH_2C_6H_5$), 5.27 (1H, br, NH), 7.31–7.36 (5H, m, $C_6H_5$) and 13.5–14 (1H, br, OH); $\delta_C$(75 MHz; $CDCl_3$) 185.35 (C-3), 169.85 (C-1), 155.76 ($COCH_2C_6H_5$), 135.49 (C-1′), 128.16 (C-2′), 127.93 (C-4′), 127.79 (C-3′), 112.83 (CN), 79.93 (C-2), 67.13 ($OCH_2C_6H_5$), 52.90 ($CO_2CH_3$) and 42.62 (C-4).

**Ethyl 4-benzyloxycarbonylamino-2-cyano-3-hydroxybut-2-enoate 19.** Yield: 73%, mp 93–96 °C (from $CH_2Cl_2$–light petroleum) (Found: C, 59.51; H, 5.10; N, 9.11. $C_{15}H_{16}N_2O_5$ requires C, 59.20; H, 5.30; N, 9.21%); $\nu_{max}$(Nujol)/$cm^{-1}$ 3300s (NH), 2210s (CN), 1720w (CO β-keto ester, keto form), 1690s (CO urethane), 1650s (CO β-keto ester, enol form) and 1580s (C=C ring str.); $\delta_H$(300 MHz; $CDCl_3$) 1.30–1.38 (3H, m, $CO_2CH_2CH_3$), 4.25–4.37 (4H, m, $CO_2CH_2CH_3$ and $NHCH_2$), 5.13 (2H, s, $OCH_2C_6H_5$), 5.44 (1H, br, NH), 7.30–7.34 (5H, m, $C_6H_5$) and 13.50–14.00 (1H, br, OH); $\delta_C$(75 MHz; $CDCl_3$) 186.27 (C-3), 170.31 (C-1), 156.62 ($COCH_2C_6H_5$), 136.23 (C-1′), 128.83 (C-2′), 128.58 (C-4′), 128.44 (C-3′), 113.64 (CN), 80.62 (C-2), 67.61 ($OCH_2C_6H_5$), 63.12 and 61.93 ($CH_2CH_3$), 43.12 (C-4) and 14.35 and 14.04 ($CH_2CH_3$); *m*/*z* (ESI) 304.9 ($[M]^+$, 100%), 327.0 ($[M + Na]^+$, 82), 231.9 {$[M - CO_2C_2H_5]^+$, 23}, 170.8 ($[M - CO_2CH_2C_6H_5]^+$, 2), 96.9 (14), 64.9 (27).

**Methyl 4-*tert*-butoxycarbonylamino-2-cyano-3-hydroxybut-2-enoate 20.** Yield: 77%, mp 105–107 °C (from $CH_2Cl_2$–light petroleum) (Found: C, 51.44; H, 6.30; N, 10.65. $C_{11}H_{16}N_2O_5$ requires C, 51.56; H, 6.29; N, 10.93%); $\nu_{max}$(Nujol)/$cm^{-1}$ 3330s (NH), 2210s (CN), 1690s (CO urethane), 1650s (CO β-keto ester, enol form) and 1580s (C=C); $\delta_H$(300 MHz; $CDCl_3$) 1.44 [9H, s, $(CH_3)_3$], 3.89 (3H, s, $CO_2CH_3$), 4.24 (2H, d, *J* 6.2, $NHCH_2$), 5.09 (1H, br s, NH) and 13.5–14 (1H, br, OH); $\delta_C$(75 MHz; $CDCl_3$) 186.82 (C-3), 170.49 (C-1), 155.63 [$COC(CH_3)_3$], 113.40 (CN), 80.65 (C-2), 79.98 [$C(CH_3)_3$], 53.16 ($CO_2CH_3$), 42.69 (C-4) and 28.10 [$(CH_3)_3$]; *m*/*z* (ESI) 256.9 ($[M]^+$, 100%), 201 {$[M - C(CH_3)_3]^+$, 9}, 156.7 {$[M - COOC(CH_3)_3]^+$, 23}, 96.8 (12), 64.9 (8).

**Ethyl 4-*tert*-butoxycarbonylamino-2-cyano-3-hydroxybut-2-enoate 21.** Yield: 60%, mp 101–103 °C (from $CH_2Cl_2$–light petroleum) (Found: C, 52.62; H, 6.77; N, 10.20. $C_{12}H_{18}N_2O_5$ requires C, 52.32; H, 6.71; N, 10.37%); $\nu_{max}$(Nujol)/$cm^{-1}$ 3330s (NH), 2210s (CN), 1690s (CO urethane), 1660s (CO β-keto ester, enol form) and 1580s (C=C); $\delta_H$(300 MHz; $CDCl_3$) 1.35 (3H, t, *J* 7, $CH_2CH_3$), 1.44 [9H, s, $(CH_3)_3$], 4.24 (2H, d, *J* 6, $NHCH_2$), 4.34 (2H, q, *J* 7, $CH_2CH_3$), 5.07 (1H, br s, NH) and 13.8–14 (1H, br, OH); $\delta_C$(75 MHz; $CDCl_3$) 186.72 (C-3), 170.19 (C-1), 155.63 [$COC(CH_3)_3$], 113.47 (CN), 80.61 (C-2), 80.18 [$C(CH_3)_3$], 62.83 ($CH_2CH_3$), 42.68 (C-4), 28.11 [$(CH_3)_3$] and 13.85 ($CH_2CH_3$); *m*/*z* (ESI) 292.9 ($[M + Na]^+$, 100%),

270.9 ([M]$^+$, 95), 214.9 {[M − C(CH$_3$)$_3$]$^+$, 17}, 170.8 {[M − COOC(CH$_3$)$_3$]$^+$, 35}, 64.9 (6).

**Methyl 4-*tert*-butoxycarbonylamino-2-cyano-3-hydroxy-5-phenylpent-2-enoate 22.** Yield: 64%, mp 152–153 °C (from $CHCl_3$– light petroleum) (lit.,[13a] mp 152.5–153 °C), $[a]_D^{23}$ +78.4 (*c* 1.05, MeOH) {lit.,[13a] $[a]_D^{23}$ +77.9 (*c* 1.04, MeOH)}; $\nu_{max}$(Nujol)/*cm*$^{-1}$ 3320s (NH), 2200s (CN), 1680s (CO urethane), 1640m (CO β-keto ester, enol form) and 1580m br (C=C); $\delta_H$(300 MHz; $CDCl_3$) 1.38 [9H, s, $(CH_3)_3$], 2.95–3.02 and 3.05–3.14 (2H, 2m, C*H*$_2$C$_6$H$_5$), 3.88 and 3.91 (3H, s, $CO_2CH_3$), 4.92 (2H, br s, NH and NHC*H*), 7.20–7.33 (5H, m, $C_6H_5$) and 13.6–14 (1H, br, OH); $\delta_C$(75 MHz; $CDCl_3$) 187.42 (C-3), 170.65 (C-1), 154.83 [*C*OC(CH$_3$)$_3$], 134.93 (C-1′), 129.27 (C-2′), 128.93 (C-3′), 127.56 (C-4′), 113.38 (CN), 81.55 (C-2), 80.46 [*C*(CH$_3$)$_3$], 54.52 (C-4), 53.19 ($CO_2CH_3$), 38.88 (O*C*H$_2$C$_6$H$_5$) and 28.06 [(CH$_3$)$_3$].

**Ethyl 4-*tert*-butoxycarbonylamino-2-cyano-3-hydroxy-5-phenylpent-2-enoate 23.** Yield: 55%, mp 140–141 °C (from $CHCl_3$–light petroleum); $[a]_D^{23}$ +110.1 (*c* 0.80, $CHCl_3$) (Found: C, 62.25; H, 6.78; N, 8.17. $C_{18}H_{24}N_2O_5$ requires C, 62.05; H, 6.94; N, 8.04%); $\nu_{max}$(Nujol)/cm$^{-1}$ 3310s (NH), 2200s (CN), 1680s (CO urethane), 1640m (CO β-keto ester, enol form) and 1590m br (C=C); $\delta_H$(300 MHz; $CDCl_3$) 1.38 [9H, s, $(CH_3)_3$], 1.29 and 1.36 (3H, t, *J* 7, $CO_2CH_2CH_3$), 2.95 and 3.08 (2H, 2m, C*H*$_2$C$_6$H$_5$), 4.30 and 4.34 (2H, q, *J* 7, $CO_2CH_2CH_3$), 4.93 (2H, br s, NH and NHC*H*), 7.21–7.36 (5H, m, $C_6H_5$) and 13.6-14 (1H, br, OH); $\delta_C$(75 MHz; $CDCl_3$) 188.65 (C-3), 170.33 (C-1), 154.79 [*C*OC(CH$_3$)$_3$], 135.03 (C-1′), 129.29 (C-2′), 128.92 (C-3′), 127.53 (C-4′), 113.46 (CN), 81.57 (C-2), 80.63 [*C*(CH$_3$)$_3$], 62.86 ($CO_2CH_2CH_3$), 54.52 (C-4), 38.95 (O*C*H$_2$C$_6$H$_5$), 28.06 [(CH$_3$)$_3$] and 13.86 ($CO_2CH_2CH_3$).

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