Nitrate esters in the generation of amino acid radicals

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Nitrate esters, prepared by treatment of β-hydroxy-α-amino acid derivatives with nitric acid, react with tributyltin hydride to give the corresponding alkoxyl radicals. These radicals readily undergo β-scission, providing a convenient route for the regiocontrolled production of α-carbon-centred amino acid radicals. By examining the partitioning of the alkoxyl radicals between the β-scission process and the competing hydrogen transfer reaction, it has been possible to evaluate the influence of electronic and steric effects on the β-scission reaction and the formation of the carbon-centred radicals.

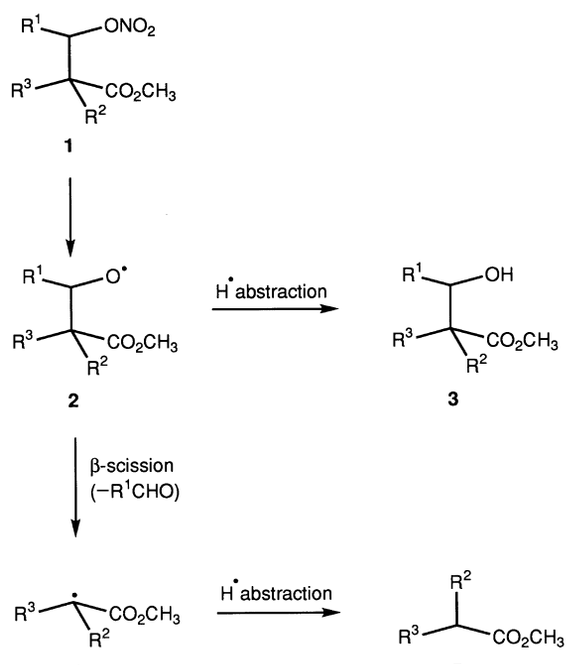
Hydrogen atom transfer reactions of *N*-acyl-α-amino acid derivatives generally favour formation of α-carbon-centred radicals.[1] Reactions of this type occur upon irradiation of proteins[2] and they are involved in the photoalkylation[3] and carboxylation[4] of peptides. Studies of hydrogen atom transfer reactions of amino acid derivatives have shown them to be selective for reaction of glycine residues.[2–6] The reactions are also affected by the nature of the protecting groups applied to the amino and carboxy substituents,[7] and by polar and steric effects.[8] While these effects can be exploited in the regioselective functionalisation of amino acid and peptide derivatives,[3–7] the extent of regiocontrol is limited.

In order to develop the synthetic potential of α-carbon-centred amino acid radicals, halogen[1,6,9] and other functional group[10] transfer reactions have been used as alternative procedures for their generation. In this report we describe a complementary procedure for the synthesis of the amino acid radicals. The conversion of alcohols to nitrate esters is well documented,[11,12] as is the use of reactions of the esters with stannanes to generate radicals.[12,13] Exploiting this methodology and beginning with readily available β-hydroxy-α-amino acid derivatives, reaction with nitric acid affords nitrate esters, which react on treatment with tributyltin hydride and irradiation to give alkoxyl radicals. In turn, the alkoxyl radicals undergo β-scission reactions to give α-carbon-centred radicals.

Alkoxyl radicals also react by hydrogen abstraction to give alcohols. The rate of hydrogen abstraction has been shown to be relatively independent of the nature of the alkoxyl radical.[14,15] For example, the rate constants for hydrogen atom abstraction from benzhydrol (diphenyl methanol) at 27 °C by the primary, secondary and tertiary alkyloxyl radicals, benzyloxyl, cyclohexyloxyl and *tert*-butoxyl, differ by less than a factor of 2.5.[16] Even this variation is likely to be due largely to steric effects, which will be more important with benzhydrol as the hydrogen donor, rather than tributyltin hydride where the hydrogen to be transferred is more exposed. Thus, the ratio of products derived through partitioning of an alkoxyl radical between the β-scission process and hydrogen abstraction from the stannane is a good measure of the efficiency of the former. The β-scission of alkoxyl radicals is dependent upon a number of factors. These include the stability of the product radical,[17,18] the stability of the aldehyde or ketone by-product[13,14] and polar and steric effects[19] which may influence the stability of the reaction transition state. In the present work, a range of amino acid derivatives and related compounds has been studied, in order to evaluate the influence of these effects on the formation of α-carbon-centred amino acid radicals using this approach.

Results and discussion

The nitrate esters **1a–e**, **6a–c** and **11a–c** reacted with tributyltin hydride to give the alcohols **3a-c**, **3e**, **8a–c** and **13a–c**, through hydrogen transfer from the stannane to the corresponding alkoxyl radicals **2a–c**, **2e**, **7a–c** and **12a–c**. In addition, the amino acid derivatives **5a** and **5d**, and the products **10a** and **15** were formed, through β-scission of the alkoxyl radicals **2a**, **2d**, **7a** and **12b**,**c**, followed by hydrogen transfer to the carbon-centred radicals **4a**, **4d**, **9a** and **14** (Schemes 1–3).



a R^1 = H, R^2 = H, R^3 = NHCOPh
b R^1 = Me, R^2 = H, R^3 = NHCOPh
c R^1 = Ph, R^2 = H, R^3 = NHCOPh
d R^1 = H, R^2 = Me, R^3 = NHCOPh
e R^1 = H, R^2 = H, R^3 = PhthN

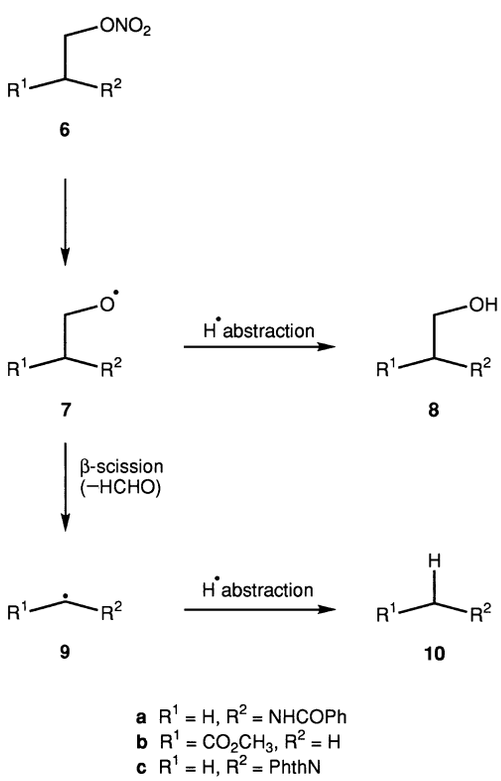
Scheme 1

The ratios of reaction products depended on the reaction conditions. In order to use these ratios to compare the ease of β-scission of the alkoxyl radicals **2a–e**, **7a–c** and **12a–c**, each of

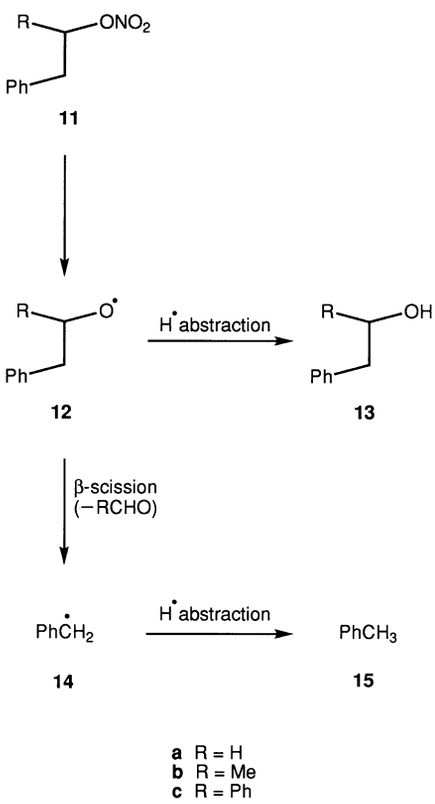
Table 1 Results of irradiation of the nitrate esters **1a–e**, **6a–c** and **11a–c** with tributyltin hydride

Nitrate ester	Alkoxyl radical	β-Scission product[a]		H-abstraction product		Ratio of β-scission to H-abstraction
		Compound	Yield[b] (%)	Compound	Yield[b] (%)	
1a	**2a**	**5a**	17 (17)	**3a**	51 (51)	1:3
1b	**2b**	**5b**	31 (48)	**3b**	14 (22)	2:1
1c	**2c**	**5c**	73 (73)	**3c**	12 (12)	6:1
1d	**2d**	**5d**	88 (88)	**3d**	—	>20:1
1e	**2e**	**5e**	—	**3e**	44 (91)	<1:20
6a	**7a**	**10a**	8 (10)	**8a**	61 (78)	1:8
6b	**7b**	**10b**	—	**8b**	100 (100)	<1:20
6c	**7c**	**10c**	—	**8c**	100 (100)	<1:20
11a	**12a**	**15**	—	**13a**	82 (92)	<1:20
11b	**12b**	**15**	12 (20)	**13b**	18 (30)	2:3
11c	**12c**	**15**	48 (74)	**13c**	17 (26)	3:1

[a] The reactions afford either formaldehyde, acetaldehyde or benzaldehyde as a by-product of the β-scission process. Analysis of the formation of acetaldehyde and benzaldehyde in the reactions of the nitrate esters **1b** and **11c**, respectively, gave yields identical to those of the alternative β-scission products **5b** and **15**. [b] Yields in parentheses are adjusted for unreacted starting materials.



Scheme 2



Scheme 3

the nitrate esters **1a–e**, **6a–c** and **11a–c** (0.2 mmol) was treated with tributyltin hydride (1.0 mmol) in [$^2H_6$]benzene (0.3 ml) under argon, in a sealed quartz ^{1}H NMR tube. The mixtures were irradiated, to initiate reaction, at 40 °C for 2 h. The reaction mixtures were analysed directly using ^{1}H NMR spectroscopy, and product yields were calculated through the use of ethylbenzene (0.2 mmol) as an internal standard. The rate constant for hydrogen transfer to *tert*-butoxyl radical from tributyltin hydride, of 2×10^8 dm^3 mol^{-1} s^{-1} at 22 °C,[20] is almost two orders of magnitude higher than that for the reaction of the alkoxyl radical with ethylbenzene, of 1.05×10^6 dm^3 mol^{-1} s^{-1} at 22 °C.[21] On the basis of this comparison it is reasonable to assume that the extent of reaction of ethylbenzene by hydrogen atom transfer is negligible in the present work, particularly given the excess of tributyltin hydride employed. Products were identified through spectroscopic and chromatographic comparisons with authentic samples. The yields and ratios of the products **3a–c**, **3e**, **5a**, **5d**, **8a–c**, **10a**, **13a–c** and **15** obtained in these experiments are shown in Table 1.

The combined yields of the products **3a–c**, **3e**, **5a**, **5d**, **8a–c**, **10a**, **13a–c** and **15**, corrected for the unreacted starting materials **1a–e**, **6a–c** and **11a–c**, indicate that the β-scission and hydrogen abstraction reactions of the alkoxyl radicals **2a–e**, **7a–c** and **12a–c** represent the major reaction pathways. The use of a five molar excess of tributyltin hydride ensures that the concentration of the stannane does not change substantially during the course of the reactions. Under these conditions, the partitioning of the alkoxyl radicals **2a–e**, **7a–c** and **12a–c** between the β-scission and hydrogen abstraction processes will vary little as a function of the extent of reaction. Then, irrespective of the extent of reaction, the ratios of products formed through β-scission and hydrogen abstraction indicate the relative efficiency of the β-scission processes.

Each of the alkoxyl radicals **2a–c** undergoes β-scission to give the glycyl radical **4a**. This process is slower for the threonine derivative **2b** than for the β-phenylserine derivative **2c**, and even slower for the serine derivative **2a**. These relative reaction rates can be attributed to the release of steric strain accompanying carbon–carbon bond cleavage.[13,14,17–19] The methyl and phenyl

substituents of the radicals **2b** and **2c**, respectively, increase steric interactions that are relieved during the course of the reaction. In addition, β-scission of the radical **2c** is favoured by conjugation[13,14] of the phenyl substituent with the incipient carbonyl group of the reaction by-product, benzaldehyde. The effect of the methyl and phenyl substituents of the radicals **2b** and **2c** is mirrored in the reactions of the radicals **12a–c**, formed from the corresponding nitrate esters **11a–c**, where β-scission is slower for the propoxyl radical **12b** than for the 2-phenylethoxyl radical **12c**, and even slower for the ethoxyl radical **12a**.

The effect of steric strain is also apparent from a comparison of the reactions of the derivatives of serine **1a** and α-methylserine **1d**. β-Scission of the corresponding alkoxyl radicals **2a** and **2d** is much faster for the latter, presumably as a result of the additional methyl group. Apparently, this effect outweighs the normal tendency for more stable radicals to be produced at a faster rate,[17,18] since there is strong evidence[5] that the alanyl radical **4d**, formed through reaction of the alkoxyl radical **1d**, is less stable than the glycyl radical **4a**, which results from β-scission of the radical **1a**.

The reactions of the nitrate esters **1a**, **6a** and **6b** indicate that the alkoxyl radicals **7a** and **7b** undergo β-scission less readily than the serine derivative **2a**. Again this can be attributed to steric effects, since the alkoxyl radicals **7a** and **7b**, respectively, lack the methoxycarbonyl and benzamido substituents of the radical **2a**. It is likely that there is also an additional electronic effect reflected in these reactions, since both the methoxycarbonyl and benzamido substituents would be expected to contribute to the stability and ease of formation of the glycyl radical **4a**.[22]

Each of the benzamides **2a** and **7a** underwent β-scission, at least to some extent, whereas there was no evidence of the analogous reaction for either of the phthalimides **2e** or **7c**, despite the greater bulk of the phthalimido group. These results correlate with the comparative ability of benzamido and phthalimido (PhthN) substituents to stabilise radicals,[7] and they highlight the relationship between the ease of β-scission of an alkoxyl radical and the stability of the product radical.[17,18]

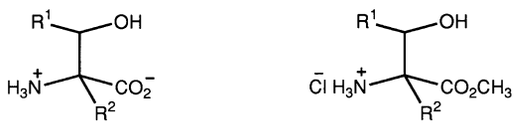
In summary, the reactions described above illustrate a new approach to the generation of amino acid radicals. While alternative procedures[5] are avaliable to access the α-carbon-centred amino acid radicals **4a** and **4d** involved in this work, it seems likely that the new method will be useful for the generation of radicals in peptides where the other procedures would lack regiospecificity. For example, a serine residue in a peptide should serve as a convenient glycyl radical precursor.

Experimental

General

Melting points were determined on a Kofler hot stage melting point apparatus under a Reichert microscope and are uncorrected. Microanalyses were carried out by the Chemistry Department at the University of Otago, Dunedin, New Zealand, and by the Research School of Chemistry at the Australian National University, Canberra, Australia. IR spectra were recorded on a Hitachi 270–30 IR spectrometer and data processor. Samples were prepared either as Nujol mulls or neat liquids, between NaCl plates. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on either a Bruker ACP-300 or a GEMINI 300 spectrometer and refer to deuteriochloroform solutions with chloroform as the internal standard measured at δ_H 7.26 ppm and δ_C 77.04 ppm. Coupling constant values *J* between protons are given in Hertz. Electron impact (EI) and chemical ionisation (CI) mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Accurate mass determinations were carried out by the Chemistry Department at the University of Melbourne, Victoria, Australia, using a JEOL AX505H mass spectrometer. Preparative column chromatography was carried out as either dry flash column chromatography or positive pressure flash chromatography using Merck Kieselgel 60 PF_{254} and Merck Kieselgel 60 (230–400 mesh ASTM). Analytical TLC was performed using Merck Kieselgel 60 F_{254} silica on aluminium backed plates. Detection was *via* either visualisation with ultraviolet light or development with a solution of phosphomolybdic acid in ethanol. R_f values are indicated for those products purified by preparative chromatography and refer to the chromatographic eluent indicated. All solvents and reagents used were purified using standard methods and all organic extracts were dried over $MgSO_4$.

Serine **16a**, threonine **16b** and α-methylserine **16d** were



16 **17**

a R^1 = H, R^2 = H
b R^1 = Me, R^2 = H
c R^1 = Ph, R^2 = H
d R^1 = H, R^2 = Me

purchased as racemates from Sigma Chemical Co. and all derivatives of these compounds were assumed to be racemic. (2*SR*,3*SR*)-β-Phenylserine **16c** was purchased from Aldrich Chemical Co. In subsequent derivatisations no interconversion between diastereomers was observed, indicating no loss of stereochemical integrity. *N*-(2-Hydroxyethyl)phthalimide **8c**, 2-phenylethanol **13a**, 1-phenylpropan-2-ol **13b**, *N*-methylbenzamide **10a,** methyl acetate **10b**, 2-aminoethanol, β-propiolactone and deoxybenzoin were purchased from Aldrich Chemical Co. Samples of *N*-phthaloylserine methyl ester **3e**, *N*-benzoylglycine methyl ester **5a**, *N*-benzoylalanine methyl ester **5d** and *N*-phthaloylglycine methyl ester **5e** were available.[23,24]

General procedure for reaction of the nitrate esters 1a–e, 6a–c and 11a–c with tributyltin hydride

A mixture of nitrate ester (0.2 mmol), tributyltin hydride (0.27 ml, 1.0 mmol) and ethylbenzene (0.2 mmol) in [$^2H_6$]benzene (0.3 ml) in a quartz ^{1}H NMR spectroscopy tube under argon was irradiated with ultraviolet light (300 nm) at 40 °C in a Rayonette Photochemical Reactor for 2 h. The reaction mixture was analysed before and after irradiation using ^{1}H NMR spectroscopy and TLC, by comparison with authentic product samples.

General procedure for the synthesis of the alcohols 3a–d

Thionyl chloride (2.0 equiv.) was added dropwise to a solution of the amino acid **16a–d** in dry methanol (50 ml) at 0 °C under argon. The resulting solution was stirred at room temp. overnight. Removal of solvent under reduced pressure afforded the methyl ester hydrochloride **17a–d** as a white solid. To a solution of this solid and benzoyl chloride (1.1 equiv.) in ethyl acetate (50 ml) was added a solution of sodium hydrogencarbonate (3.0 equiv.) in water (50 ml). The resulting mixture was stirred at room temp. for 4 h. Extraction with ethyl acetate followed by drying and evaporation of solvent under reduced pressure afforded the product **3a–d,** which was purified by either recrystallisation or flash column chromatography.

***N*-Benzoylserine methyl ester 3a.** Serine **16a** (9.62 g, 91.6 mmol) afforded, after chromatography [(95:5) CH_2Cl_2–MeOH], the product **3a** as a colourless, viscous oil (16.50 g, 81%), R_f 0.4 (Found: M^+, 223.0846. Calc. for $C_{11}H_{13}NO_4$: M, 223.0845); ν_{max}/cm^{-1} 3374, 2954, 1747, 1648, 1579, 1528, 1489, 1349, 1225, 1074 and 712; δ_H 3.55 (1 H, br s, OH), 3.77 (3 H, s, CH_3), 4.00 (1 H, dd, *J* 11.4 and 3.6, β-CH), 4.06 (1 H, dd, *J* 11.4 and 3.6, β-CH′), 4.84 (1 H, dt, *J* 7.3 and 3.6, α-CH), 7.22 (1 H, br d, *J* 7.3, NH), 7.34–7.52 (3 H, m, ArH) and 7.80 (2 H, d, *J*

7.3, ArH); δ_C 52.51, 55.00, 62.69, 127.08, 128.48, 131.73, 133.30, 167.78 and 171.02; *m/z* (EI) 223 (M^+, 16%), 206 (17), 192 (13), 164 (13), 160 (10), 146 (14), 122 (12), 106 (14), 105 (100), 77 (43) and 50 (16).

***N*-Benzoylthreonine methyl ester 3b.** Threonine **16b** (3.10 g, 26.1 mmol) afforded the product **3b** as a colourless crystalline solid (5.68 g, 92%), mp 114–117 °C (from CH_2Cl_2–hexane) (Found: MH^+, 238.1064. Calc. for $C_{12}H_{15}NO_4$: MH, 238.1079); δ_H 1.29 (3 H, d, *J* 6.4, CCH_3), 2.60 (1 H, br s, OH), 3.80 (3 H, s, CO_2CH_3), 4.47 (1 H, dq, *J* 2.4 and 6.4, β-CH), 4.84 (1 H, dd, *J* 2.4 and 8.8, α-CH), 6.99 (1 H, br d, *J* 8.8, NH), 7.42−7.56 (3 H, m, ArH) and 7.84–7.87 (2 H, m, ArH); δ_C 20.00, 52.62, 57.69, 68.21, 127.20, 128.57, 131.88, 133.65, 168.00 and 171.62; *m/z* (EI) 238 (M + H^+, 100%), 221 (24), 220 (85), 206 (4), 193 (18), 178 (5), 161 (17), 160 (10), 133 (6), 105 (9), 104 (72) and 76 (20).

(2*SR*,3*SR*)-*N*-Benzoyl-β-phenylserine methyl ester 3c. (2*SR*,3*SR*)-β-Phenylserine **16c** (2.67 g, 14.8 mmol) afforded the product **3c** as a colourless solid (3.10 g, 70%), mp 92–94 °C (from CH_2Cl_2–hexane); δ_H 2.95 (1 H, br s, OH), 3.77 (3 H, s, CH_3), 5.08 (1 H, dd, *J* 8.7 and 3.2, α-CH), 5.40 (1 H, d, *J* 3.2, β-CH), 6.98 (1 H, d, *J* 8.7, NH), 7.26–7.71 (8 H, br m, ArH) and 7.68 (2 H, m, ArH); δ_C 52.58, 58.58, 73.42, 125.68, 127.03, 127.92, 128.29, 128.41, 131.69, 133.45, 139.71, 167.79 and 170.93; *m/z* (EI) 300 (M + H^+, 2%), 268 (2), 240 (10), 193 (77), 161 (72), 133 (32), 105 (100) and 77 (78).

***N*-Benzoyl-α-methylserine methyl ester 3d.** α-Methylserine **16d** (1.50 g, 12.6 mmol) afforded the product **3d** as a colourless, viscous oil (0.94 g, 31%), δ_H 1.66 (3 H, s, CCH_3), 3.83 (3 H, s, CO_2CH_3), 3.90 (1 H, br s, OH), 3.93 (1 H, d, *J* 11.4, β-CH), 4.22 (1 H, d, *J* 11.4, β-CH′), 7.18 (1 H, br s, NH), 7.42–7.56 (3 H, m, ArH) and 7.80 (2 H, d, *J* 8.2, ArH); δ_C 20.14, 53.18, 62.48, 66.60, 127.07, 128.67, 131.93, 134.05, 167.54 and 173.92; *m/z* (EI) 238 (M + H^+, 8%), 220 (7), 219 (15), 207 (23), 206 (26), 178 (33), 175 (15), 160 (14), 122 (36), 105 (31), 104 (94), 101 (26), 78 (13), 77 (100), 76 (9), 51 (35) and 42 (43).

2-Benzamidoethanol 8a

To a solution of 2-aminoethanol (3.00 g, 49.2 mmol) and benzoyl chloride (7.51 g, 53.5 mmol) in ethyl acetate (50 ml) was added a solution of sodium hydrogencarbonate (10.0 g, 66.8 mmol) in water (50 ml). The resulting mixture was stirred at room temp. for 4 h. Extraction with ethyl acetate followed by drying and evaporation under reduced pressure afforded, after chromatography [(95:5) CH_2Cl_2–MeOH], the product **8a** as a colourless solid (5.10 g, 63%), R_f 0.3, mp 52–56 °C (Found: MH^+, 166.0863. Calc. for $C_9H_{12}NO_2$: MH, 166.0868); δ_H 3.07 (1 H, br s, OH), 3.59 (2 H, dt, *J* 4.8 and 4.8, CH_2N), 3.80 (2 H, t, *J* 4.8, CH_2O), 6.94, (1 H, br t, *J* 4.8, NH), 7.37–7.51 (3 H, m, ArH) and 7.76 (2 H, d, *J* 8.3, ArH); δ_C 43.31, 62.00, 127.53, 128.92, 132.01, 134.59 and 169.31; *m/z* (CI) 166 (M + H^+, 96%), 148 (100), 134 (7), 122 (15), 105 (99), 77 (60) and 51 (39).

3-Hydroxypropionic acid methyl ester 8b

A solution of β-propiolactone (1.10 g, 15.3 mmol) and a catalytic amount of toluene-*p*-sulfonic acid in dry methanol (10 ml) was heated at reflux under nitrogen for 4 h and then poured into a sodium hydrogencarbonate solution (1 M, 20 ml). Extraction with CH_2Cl_2 followed by drying and evaporation under reduced pressure afforded, after chromatography [(95:5) CH_2Cl_2–MeOH], the product **8b** as a colourless oil (0.38 g, 24%), R_f 0.35, bp 175–184 °C (lit.,[25] 177–184 °C); ν_{max}/cm^{-1} 3700–2500 (br), 2952, 2892, 1738, 1440, 1366 and 1046; δ_H 2.50 (1 H, br s, OH), 2.59 (2 H, t, *J* 5.6, CH_2O), 3.72 (3 H, s, CH_3) and 3.88 (2 H, t, *J* 5.6, CH_2CO_2); δ_C 36.58, 51.71, 58.18 and 173.23.

1,2-Diphenylethanol 13c

To a solution of deoxybenzoin (5.00 g, 25.5 mmol) in anhydrous EtOH (80 ml) was slowly added sodium borohydride (1.13 g, 30.2 mmol). The resulting clear solution was stirred for 1.5 h and then it was poured cautiously into dilute HCl (200 ml). Extraction with CH_2Cl_2 followed by drying and evaporation under reduced pressure afforded the product **13c** as a colourless solid (5.04 g, 100%), mp 67 °C (lit.,[26] 67 °C).

General procedure for the synthesis of the nitrate esters 1a–e, 6a–c and 11a–c

To a solution of the alcohol **3a–e**, **8a–c** and **13a–c** in acetic anhydride (20 ml) at 0 °C was added a freshly prepared solution of fuming nitric acid (1.1 equiv.) in acetic anhydride (5 ml). The resulting clear solution was stirred for 5 min and then it was poured into an ice-cold saturated sodium hydrogencarbonate solution (100 ml). Extraction with CH_2Cl_2 followed by drying and evaporation under reduced pressure afforded the products **1a–e**, **6a–c** and **11a–c** which were purified by either recrystallisation or flash column chromatography.

***N*-Benzoyl-*O*$^{\beta}$-nitroserine methyl ester 1a.** *N*-Benzoylserine methyl ester **3a** (3.80 g, 17.0 mmol) afforded the product **1a** as a colourless solid (3.63 g, 79%), mp 94−95 °C (from EtOH–H_2O) (Found: C, 49.42; H, 4.40; N, 10.21. $C_{11}H_{12}N_2O_6$ requires C, 49.26; H, 4.51; N, 10.44%); δ_H 3.84 (3 H, s, CH_3), 4.91 (1 H, dd, *J* 3.5 and 11.3, β-CH), 4.98 (1 H, dd, *J* 3.5 and 11.3, β-CH′), 5.15 (1 H, dt, *J* 7.0 and 3.5, α-CH), 6.93 (1 H, d, *J* 7.0, NH), 7.26–7.56 (3 H, m, ArH) and 7.83 (2 H, d, *J* 6.9, ArH); δ_C 51.01, 53.42, 71.31, 127.16, 128.76, 132.30, 132.93, 167.18 and 168.95; *m/z* (EI) 269 (M + H^+, 36%), 268 (M^+, 5), 224 (14), 207 (23), 206 (83), 192 (5), 147 (13), 146 (82), 118 (40), 104 (100), 90 (48), 76 (19) and 50 (9).

***N*-Benzoyl-*O*$^{\beta}$-nitrothreonine methyl ester 1b.** *N*-Benzoylthreonine methyl ester **3b** (1.00 g, 4.2 mmol) afforded the product **1b** as a colourless solid (1.13 g, 95%), mp 82–84 °C (Found: C, 51.34; H, 4.93; N, 9.85. $C_{12}H_{14}N_2O_6$ requires C, 51.06; H, 5.00; N, 9.92%); ν_{max}/cm^{-1} 3308, 1740, 1650, 1632, 1534, 1462, 1282, 1244, 738 and 722; δ_H 1.48 (3 H, d, *J* 6.5, CCH_3), 3.82 (3 H, s, CO_2CH_3), 5.21 (1 H, dd, *J* 2.6 and 8.8, α-CH), 5.73 (1H dq, *J* 2.6 and 6.5, β-CH), 6.73 (1 H, br d, *J* 8.8, NH), 7.46–7.60 (3 H, m, ArH) and 7.86 (2 H, d, *J* 5.8, ArH); δ_C 15.85, 53.24, 54.62, 79.72, 127.22, 128.77, 132.31, 133.05, 167.72 and 169.33; *m/z* (EI) 283 (M + H^+, 51%), 220 (17), 193 (10), 192 (29), 161 (9), 106 (34), 105 (100) and 77 (61).

(2*SR*,3*SR*)-*N*-Benzoyl-*O*$^{\beta}$-nitro-β-phenylserine methyl ester 1c. (2*SR*,3*SR*)-*N*-Benzoyl-β-phenylserine methyl ester **3c** (2.00 g, 6.7 mmol) afforded the product **1c** as a colourless solid (1.50 g, 65%), mp 128–130 °C (from CH_2Cl_2–hexane) (Found: C, 59.46; H, 4.35; N, 8.15. $C_{17}H_{16}N_2O_6$ requires C, 59.28; H, 4.69; N, 8.14%); ν_{max}/cm^{-1} 3372, 1746, 1648, 1640, 1520, 1464, 1292, 714 and 700; δ_H 3.79 (3 H, s, CH_3), 5.42 (1 H, dd, *J* 9.0 and 4.0, α-CH), 6.44 (1 H, d, *J* 4.0, β-CH), 6.87 (1 H, br d, *J* 9.0, NH), 7.32–7.51 (8 H, br m, ArH) and 7.69 (2 H, m, ArH); δ_C 53.25, 55.41, 82.91, 126.17, 127.11, 128.71, 128.90, 129.50, 130.68, 132.15, 133.68, 167.15 and 168.94; *m/z* (EI) 345 (M + H^+, 27%), 298 (8), 283 (36), 282 (100), 264 (25), 105 (6), 104 (59) and 76 (17).

***N*-Benzoyl-*O*$^{\beta}$-nitro-α-methylserine methyl ester 1d.** *N*-Benzoyl-α-methylserine methyl ester **3d** (0.91 g, 3.8 mmol) afforded the product **1d** as a colourless solid (0.78 g, 72%), mp 79–83 °C (from CH_2Cl_2–hexane) (Found: C, 51.46; H, 4.80; N, 9.76. $C_{12}H_{14}N_2O_6$ requires C, 51.06; H, 5.00; N, 9.92%); ν_{max}/cm^{-1} 3268, 1752, 1632, 1536, 1494, 1366, 1330, 1282, 1254, 1134, 982 and 862; δ_H 1.76 (3 H, s, CCH_3), 3.87 (3 H, s, CO_2CH_3), 4.97 (1 H, d, *J* 11.1, β-CH), 5.35 (1 H, d, *J* 11.1, β-CH′), 6.94 (1 H, br s, NH), 7.44–7.54 (3 H, m, ArH) and 7.78 (2 H, d, *J* 7.9, ArH); δ_C 20.62, 53.52, 58.76, 72.13, 126.99, 128.69, 132.07, 133.61, 166.96 and 171.89; *m/z* (CI) 283 (M + H^+, 10%), 236 (35), 220 (17), 208 (60), 160 (20), 148 (26), 105 (100) and 77 (16).

***N*-Phthaloyl-*O*$^{\beta}$-nitroserine methyl ester 1e.** *N*-Phthaloylserine methyl ester **3e** (0.58 g, 2.5 mmol) afforded, after chrom-

atography [(70:30) hexane–ethyl acetate], the product **1e** as a colourless solid (0.36 g, 49%), mp 62–64 °C (Found: $M^+ - NO_3$, 232.0599. Calc. for $C_{12}H_{10}NO_4$: $M - NO_3$, 232.0609); δ_H 3.79 (3 H, s, CH_3), 4.60 (1 H, dd, *J* 9.9 and 11.7, β-CH), 4.92 (1 H, dd, *J* 4.3 and 11.7, β-CH′); 5.18 (1 H, dd, *J* 4.3 and 9.9, α-CH) and 7.76–7.91 (4 H, m, ArH); δ_C 50.65, 52.98, 60.84, 123.66, 131.62, 134.32, 167.18 and 170.42; *m/z* (EI) 294 (M^+, 10%), 293 (43), 292 (100), 250 (19), 233 (37), 232 (96), 219 (23), 200 (17), 190 (50), 187 (48), 172 (26), 133 (15), 132 (17) and 104 (15).

***O*-Nitro-2-benzamidoethanol 6a.** 2-Benzamidoethanol **8a** (2.00 g, 12.1 mmol) afforded the product **6a** as a colourless solid (1.45 g, 57%), mp 117–119 °C (from CH_2Cl_2–hexane) (Found: C, 51.47; H, 4.52; N, 13.08. $C_9H_{10}N_2O_4$ requires C, 51.43; H, 4.80; N, 13.33%); δ_H 3.77 (2 H, apparent q, *J* 5.41, CH_2N), 4.62 (2 H, t, *J* 5.41, CH_2O), 6.87 (1 H, br t, *J* 5.41, NH), 7.38 (2 H, t, *J* 7.14, ArH), 7.49 (1 H, t, *J* 7.14, ArH) and 7.76 (2 H, d, *J* 7.14, ArH); δ_C 37.13, 71.49, 126.85, 128.30, 131.55, 133.40 and 168.20; *m/z* (CI) 211 (M + H^+, 7%), 166 (100), 148 (90), 136 (20), 117 (55) and 105 (75).

***O*$^{\beta}$-Nitro-3-hydroxypropionic acid methyl ester 6b.** 3-Hydroxypropionic acid methyl ester **8b** (0.50 g, 4.8 mmol) afforded, after chromatography [(50:50) CH_2Cl_2–hexane] the product **6b** as a colourless oil (0.49 g, 69%), R_f 0.45 (Found: C, 32.22; H, 4.51; N, 9.66. $C_4H_7NO_5$ requires C, 32.22; H, 4.73; N, 9.39%); ν_{max}/cm^{-1} 2952, 2934, 1746, 1644, 1440, 1372, 1080 and 1018; δ_H 2.73 (2 H, t, *J* 6.25, CH_2CO_2), 3.72 (3 H, s, CH_3) and 4.72 (2 H, t, *J* 6.25, CH_2O); δ_C 31.60, 52.09, 67.85 and 169.74; *m/z* (EI) 149 (M^+, 20%), 118 (70), 105 (14), 83 (12), 76 (65), 71 (100) and 59 (80).

***O*-Nitro-2-phthalimidoethanol 6c.** *N*-(2-Hydroxyethyl)phthalimide **8c** (2.43 g, 12.7 mmol) afforded the product **6c** as a colourless solid (1.95 g, 65%), mp 85–87 °C (from CH_2Cl_2–hexane) (Found: C, 50.70; H, 3.20; N, 11.56. $C_{10}H_8N_2O_5$ requires C, 50.85; H, 3.41; N, 11.86%); ν_{max}/cm^{-1} 1773, 1708, 1608, 1289, 982, 870 and 721; δ_H 4.06 (2 H, t, *J* 5.34, NCH_2), 4.68 (2 H, t, *J* 5.34, CH_2O), 7.70–7.78 (2 H, m, ArH) and 7.81–7.90 (2 H, m, ArH); δ_C 35.07, 69.47, 123.41, 131.57, 134.15 and 167.68; *m/z* (CI) 254 (M + NH_4^+, 75%), 237 (M + H^+, 20), 192 (80), 174 (22), 160 (100), 133 (25) and 104 (27).

***O*-Nitro-2-phenylethanol 11a.** 2-Phenylethanol **13a** (5.00 g, 41.0 mmol) afforded, after chromatography (CH_2Cl_2), the product **11a** as a pale-yellow oil (6.45 g, 94%), R_f 0.9 (Found: C, 57.62; H, 5.23; N, 8.58. $C_8H_9NO_3$ requires C, 57.48; H, 5.43; N, 8.38%); ν_{max}/cm^{-1} 3065–2936 (br), 1625, 1455, 1277, 876, 749 and 701; δ_H 3.01 (2 H, t, *J* 7.11, CH_2Ph), 4.63 (2 H, t, *J* 7.11, CH_2O) and 7.27–7.41 (5 H, m, ArH); δ_C 33.19, 73.31, 127.03, 128.71, 128.80 and 135.96; *m/z* (EI) 167 (M^+, 15%), 105 (21), 91 (100), 77 (8) and 65 (12).

***O*-Nitro-1-phenylpropan-2-ol 11b.** 1-Phenylpropan-2-ol **13b** (5.00 g, 36.7 mmol) afforded, after chromatography (CH_2Cl_2), the product **11b** as a pale-yellow oil (5.80 g, 87%), R_f 0.8 (Found: C, 59.90; H, 5.99; N, 7.95. $C_9H_{11}NO_3$ requires C, 59.66; H, 6.12; N, 7.73%); ν_{max}/cm^{-1} 3089–2898 (br), 1628, 1498, 1455, 1279, 981, 878 and 700; δ_H 1.36 (3 H, d, *J* 6.57, CH_3), 2.82 (1 H, dd, *J* 6.84 and 13.80, CHPh), 3.04 (1 H, dd, *J* 6.27 and 13.80, CH′Ph), 5.29 (1 H, apparant sextet, *J* 6.4, CH) and 7.27–7.41 (5 H, m, ArH); δ_C 23.65, 46.27, 87.24, 132.81, 134.43, 135.20 and 141.75; *m/z* (EI) 181 (M^+, 3%), 149 (3), 119 (5), 91 (100) and 65 (15).

***O*-Nitro-1,2-diphenylethanol 11c.** 1,2-Diphenylethanol **13c** (2.00 g, 10.1 mmol) afforded, after chromatography (CH_2Cl_2), the product **11c** as a pale-yellow oil (2.21 g, 90%) R_f 0.95 (Found: C, 69.47; H, 5.15; N, 5.79. $C_{14}H_{13}NO_3$ requires C, 69.12; H, 5.39; N, 5.76%); δ_H 3.08 (1 H, dd, *J* 6.12 and 14.13, CHPh), 3.27 (1 H, dd, *J* 8.10 and 14.13, CH′Ph), 5.92 (1 H, dd, *J* 6.12 and 8.10, CH) and 7.09–7.36 (10 H, m, ArH); δ_C 40.94, 86.01, 126.49, 126.97, 128.43, 128.60, 128.88, 129.33, 135.50 and 137.25; *m/z* (EI) 243 (M^+, 1%), 197 (15), 181 (32), 165 (15), 105 (35) and 91 (100).

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