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# Deprotection of *t*-Butyl Esters of Amino Acid Derivatives by Nitric Acid in Dichloromethane

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**Abstract**—The extension of the deprotection procedure of *t*-butylated carboxyl function using $HNO_3$ in $CH_2Cl_2$ to a number of appropriately selected *N*-Z-derivatives of natural amino acid esters was investigated. The method was found to work effectively with alanine, phenylalanine, serine and the dipeptide aspartame, but the reagent brought about a number of unwanted transformations with tyrosine, methionine and tryptophan. Suitable protection of functions present in the latter ones allowed selective ester dealkylation, but tyrosine underwent unavoidable fast preliminary ring nitration. 

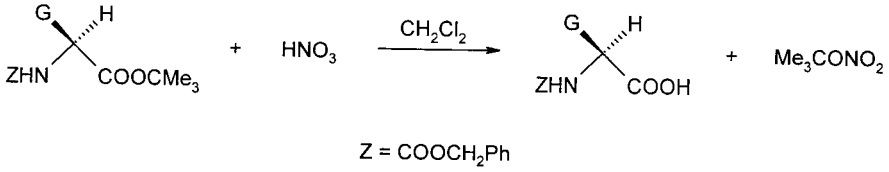
## Introduction

*t*-Butylation of free carboxylic acids is a widespread procedure for the protection of the carboxyl function, receiving continuous attention in many fields of chemistry.[1] Moreover, this kind of protection has found a variety of applications in peptide synthesis, both in the semipermanent masking of the α-carboxyl group of amino acids[2] and for the purpose of protecting some side chain functions.[3] We have recently published a convenient method of deprotection of *t*-butyl esters of carboxylic acids employing $HNO_3$ in $CH_2Cl_2$:[4] therefore, it appeared of interest to test the procedure with *t*-butyl esters of amino acids presenting an *N*-acyl substituent and possibly bearing sensitive groups in their side chain.

We chose a common acyl moiety, namely the phenylmethoxycarbonyl (benzyloxycarbonyl, Z) group, which is widely used as an easily removable amino protection in peptide synthesis, in order to obtain *N*-acyl derivatives of a number of natural amino acids: this choice should permit us to simultaneously observe the compatibility of the presence of a sensitive urethane with the procedure to be tested (Scheme 1). Moreover, removal of the *t*-butyl protection, usually accomplished with $CF_3COOH$ (TFA),[5] incurred in the formation of side products in some instances,[6] mainly owing to the alkylating action of the *t*-butyl cation,[7] therefore avoidance of these inconveniences would be highly desirable. The selection of the six amino acids to be tested, namely L-alanine (L-Ala, **1a**), L-phenylalanine (L-Phe, **2a**), L-serine (L-Ser, **3a**), L-tyrosine (L-Tyr, **4a**), L-methionine (L-Met, **5a**) and L-tryptophan (L-Trp, **6a**), as well as the dipeptide *N*-L-α-aspartyl-L-phenylalanine 1-methyl ester (aspartame, APM, **7a**), was effected with the aim of collecting experimental indications on the viability of the use of $HNO_3$ in the presence of a variety of chemical functions (see Fig. 1).

## Results and Discussion

In the course of this work, besides the common *N*-Z-derivatives **3b** and **4b** of the hydroxylated amino acids outlined above (**3a** and **4a**), it seemed of interest to prepare the




**Scheme 1.**

*Keywords*: amino acids and derivatives; deblocking; esters; nitric acid and derivatives; protecting groups.
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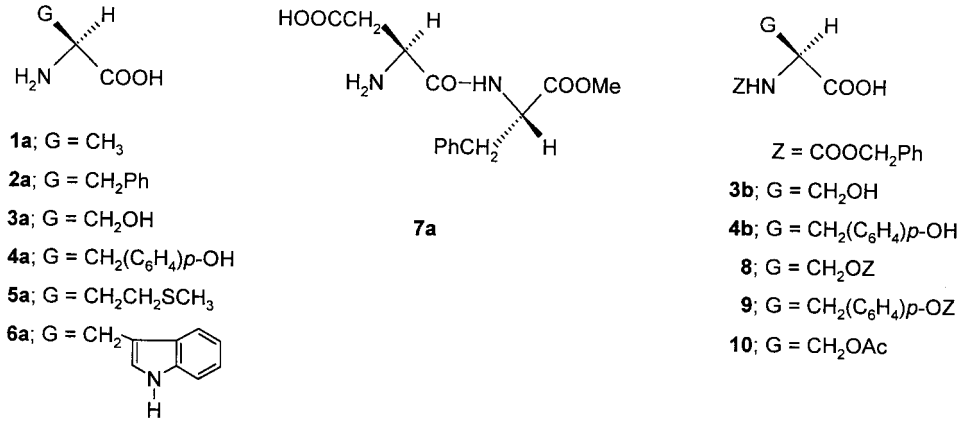
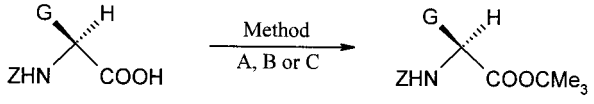



**Figure 1.**

corresponding side chain protected compounds, in the form of phenylmethoxy carbonates **8** and **9**. In the case of L-Tyr (**4a**), the goal was easily obtained by using the well established Bergmann and Zervas procedure,[8] affording the *N*,*O*-diprotected derivative **9** in excellent yield; whereas, under the same conditions, the corresponding L-Ser derivative **8** was formed only in poor yields. Even direct treatment of Z-L-Ser (**3b**) with benzylchloroformate according to a described method[9] gave unsatisfactory results, most likely owing to the faster decomposition of the acylating agent caused by the amine used as a catalyst.[10] At variance with an indication reported in the literature,[11] we found that the use of AcCl in $CH_2Cl_2$[12] on **3b** gave the *O*-acetyl protected *N*-Z-Ser (**10**) in excellent yield, which in turn could be easily transformed into the corresponding *t*-butyl ester **11**; the acetyl group in the latter could be selectively removed by hydrazine affording **3c**.

Convenient preparation of the selected protected amino acid *t*-butyl esters implied experiments apt for evaluating the relative advantages of the use of some procedures among the many reported in the literature:[13] (A) *t*-BuOH in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP),[1b] (B) 2-methylpropene under acid catalysis,[14] and (C) *t*-butyl bromide and $K_2CO_3$ in the presence of a phase transfer agent[15] (Scheme 2, Table 1). Method A, considered of choice because of its simplicity on the laboratory scale, gave satisfactory results with Z-L-Ala (**1b**), Z-L-Phe (**2b**), Z-L-Met (**5b**), Z-L-Trp (**6b**) and $N^{in}$-formyl-Z-L-Trp (**12**), but failed with the side chain OH-unprotected Z-L-Ser (**3b**), Z-L-Tyr (4**b**) and 3-nitro-*N*-Z-L-Tyr (**13**) which, as expected,[16] gave intractable polymeric mixtures. The procedure proved to be equally unsuitable in the case of *N*,*O*-diZ-L-Tyr (**9**), affording a complex mixture of decomposition products, as well as for L-Ser *O*-acyl derivatives **8** and **10** which, besides the expected esterification, underwent an elimination reaction to 1,1-dimethylethyl 2-[(phenylmethoxy)carbonyl]amino-2-propenoate (**14**), most likely induced by the presence of DMAP (Scheme 3).[17] On the other hand, any attempt at avoiding the use of the base was unsuccessful, because it is essential to induce the reaction between formed acylurea **15** and *t*-BuOH.[18] Method B, *a priori* preferred in transforming the dipeptide Z-APM (**7b**) into the ester **7c** (88% isolated yield), in the case of compounds **3b** and **4b** afforded the corresponding di-*t*-butyl derivatives **16** and **17** in good yields; this procedure proved to be quite efficient in converting the *O*-acetyl derivative of Z-L-Ser (**10**) and *N*,*O*-diZ-L-Tyr (**9**) into the corresponding esters **11** and **18**, respectively, whereas failed with the di[(phenylmethoxy)carbonyl] derivative **8** which, under these conditions, evidenced instability of the carbonate moiety. Method C was then used successfully for the preparation of **3c**, **4c**, the nitro derivative **19** and the *N*,*O*-diZ ester **20**, although in the latter case some unavoidable elimination to **14** occurred to depress the yields (Scheme 4).

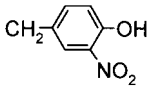
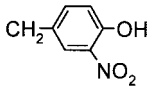
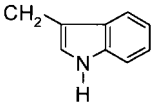
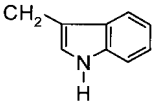
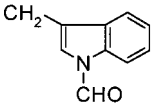
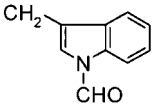



**Scheme 2.**

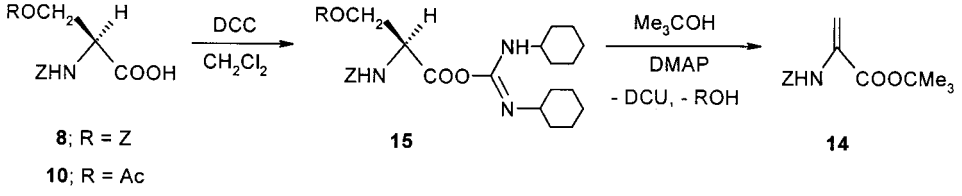
Deprotection of the carboxylic function of the examined *t*-butyl esters by the proposed method (Scheme 1) proceeded smoothly by the action of 3–4 equiv. of $HNO_3$ in $CH_2Cl_2$ at 0°C during 2 h (Table 2) with some exceptions (see below). Remarkable features of the procedure are: the optical activity was fully preserved for all the tested compounds; no ring nitration occurred on L-Phe derivative **2c**; no side chain oxidation and/or nitration was observed in the case of the L-Ser derivative **3c**; the diacylated L-Ser derivatives **11** and **20** underwent selective removal of the *t*-butyl group from the ester function. It is noteworthy that the present conditions effected, although to a partial extent, the seldom reported[19] selective removal of the carboxyl protection on the di-*t*-butylated product **16** (Scheme 5, Table 2): the so far standard deprotection procedure using TFA could not be induced to exhibit such behaviour to any extent.[20] The case of the *t*-butyl derivative of APT (**7c**) is significant because of the selectivity shown in the removal of only one alkyl ester group (Scheme 6).

Since we found that the L-Tyr derivatives **4b** and **4c** underwent prompt quantitative ring nitration at the 3-position to **13** and **19**, respectively, when exposed to only 1 equiv. of $HNO_3$, it was not surprising that the fully protected derivative **17** evidenced rapid 3-nitration, although accompanied by dealkylation of the sole phenol oxygen to yield **19**. Nevertheless, when the nitrolysis reaction was performed

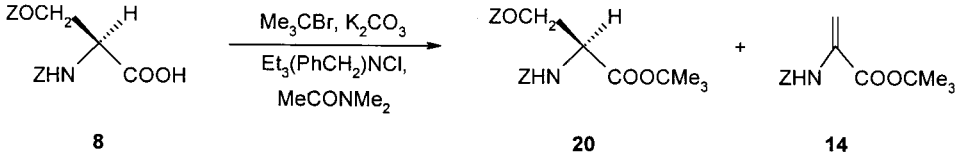
**Table 1.** *t*-Butyl esters of Z-amino acids and derivatives prepared according to Scheme 2

| Entry | Substrate | G | Method[a] | Product | G | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **1b** | $CH_3$ | A | **1c** | $CH_3$ | 58 |
| 2 | **2b** | $CH_2Ph$ | A | **2c** | $CH_2Ph$ | 71 |
| 3 | **3b** | $CH_2OH$ | C | **3c** | $CH_2OH$ | 73 |
| 4 | **3b** | $CH_2OH$ | B | **16** | $CH_2OCMe_3$ | 80 |
| 5 | **8** | $CH_2OZ$ | C | **20** | $CH_2OZ$ | 30[c] |
| 6 | **10** | $CH_2OAc$ | B | **11** | $CH_2OAc$ | 70 |
| 7 | **4b** | $CH_2(C_6H_4)p$-OH | C | **4c** | $CH_2(C_6H_4)p$-OH | 60 |
| 8 | **4b** | $CH_2(C_6H_4)p$–OH | B | **17** | $CH_2(C_6H_4)p$-$OC(CH_3)_3$ | 57 |
| 9 | **9** | $CH_2(C_6H_4)p$-OZ | B | **18** | $CH_2(C_6H_4)p$-OZ | 63 |
| 10 | **13** |  | C | **19** |  | 67 |
| 11 | **5b** | $(CH_2)_2$–S–$CH_3$ | A | **5c** | $(CH_2)_2$-S-$CH_3$ | 58 |
| 12 | **6b** |  | A | **6c** |  | 30 |
| 13 | **12** |  | A | **23** |  | 82 |

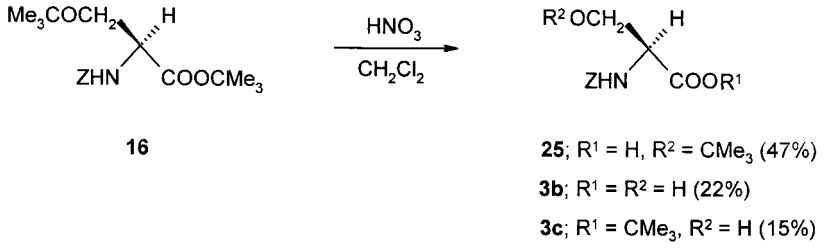
[a] See Experimental.
[b] Yields refer to isolated products.
[c] Some 12% of 1,1-dimethylethyl 2-[[(Phenylmethoxy)carbonyl]amino]-2-propenoate (**14**) was also isolated.




**Scheme 3.**




**Scheme 4.**




**Scheme 5.**

**Table 2.** Nitrolysis of *t*-butyl esters of Z-amino acids and derivatives according to Scheme 1

| Entry | Substrate | $HNO_3$[a] | Conversion (%)[b] | Product | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | **1c** | 3 | 98 | **1b** | 95 |
| 2 | **2c** | 3 | 98 | **2b** | 96 |
| 3 | **3c** | 3 | 96 | **3b** | 89 |
| 4 | **16** | 3 | 84 | **25** | 47[d] |
| 5 | **20** | 4 | 94 | **8** | 82 |
| 6 | **11** | 4 | 95 | **10** | 91 |
| 7 | **4c** | 3 | 99 | **4b** | 0[e] |
| 8 | **17** | 3 | 68 | **4b** | 0[f] |
| 9 | **18** | 4 | 95 | **9** | 91 |
| 10 | **5c** | 3 | 99 | **5b** | 0[g] |
| 11 | **22** | 4 | 92 | **21** | 85 |
| 12 | **6c** | 3 | 99 | **6b** | 0[h] |
| 13 | **23** | 4 | 94 | **12** | 91 |
| 14 | **7c** | 3 | 95 | **7b** | 89 |

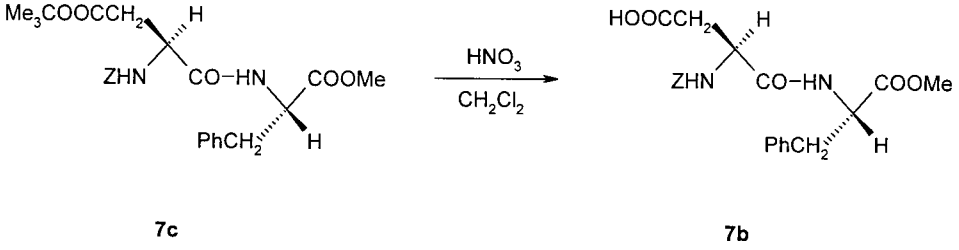
[a] $HNO_3$ (mol) per mole of substrate.
[b] Reported conversions were determined by $^1H$ NMR, on intact reaction mixtures after dilution with $CH_2Cl_2$, washing with 30% aqueous NaCl, drying over $Na_2SO_4$, evaporation of the solvent and redissolution in $CDCl_3$.
[c] Yields refer to isolated products.
[d] Compounds **3b** (22%) and **3c** (15%) were also formed.
[e] Complete 3-nitration accompanied by some 36% nitrolysis of the ester was observed. Compounds **4b** and **4c** were promptly 3-nitrated in the presence of 1.1 equiv. of $HNO_3$.
[f] Essentially compound **19** was formed.
[g] Complete oxidation to sulfoxide was observed. Compound **5b** was transformed into the sulfoxide **21** by treatment with 1.2 equiv. of $HNO_3$.
[h] An intractable tarry mixture was obtained.

on the diacylated ester **18**, a suitable building block in peptide synthesis,[21] ring nitration did not occur and selective deblocking of the carboxyl function was achieved affording **9**. The L-Met derivatives **5b** and **5c** under nitrolytic conditions underwent faster transformation to the corresponding sulfoxides **21** and **22**, after a well known pattern of reaction.[22]

The sulfoxide **22** was then completely and selectively deprotected at the ester function to **21**: this reaction might be of use in some peptide syntheses when L-Met, due to its known sensitivity to oxidation,[23] is first introduced in the form of its sulfoxide to be eventually reduced.[24]

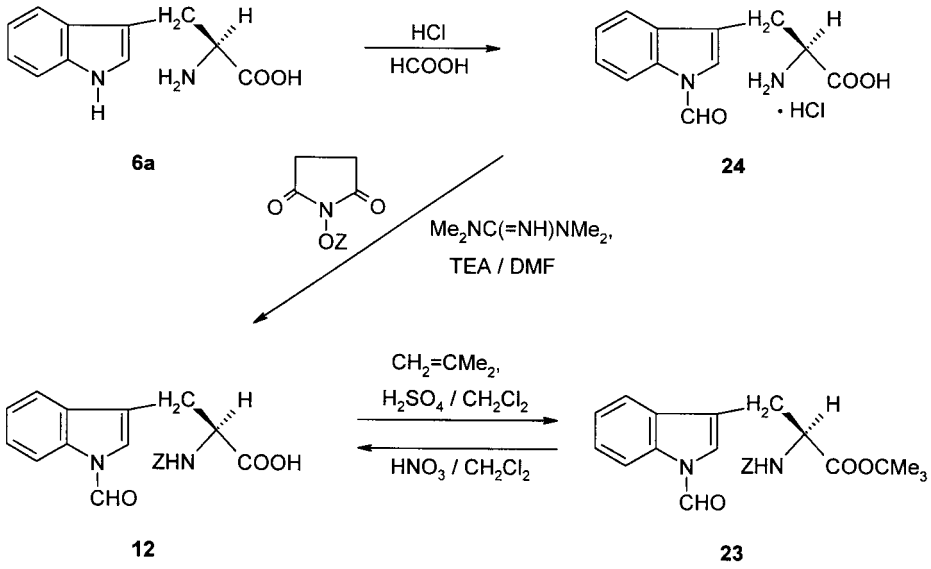
As could be expected by the ascertained sensitivity of the indole system to the action of strong acids,[25] the nitrolysis procedure on the L-Trp derivative **6c** gave an intractable tarry reaction mixture. Following the indication reported in the literature[25] that $N^{in}$-formylation is widely employed as a suitable protection of the ring, we prepared the $N^{in}$-protected derivative **23** as reported in Scheme 7. Subsequent nitrolysis of the ester **23** proceeded as desired to **12**.

In conclusion, the present work has firmly established the feasibility of the selective nitrolysis deprotection of amino acid *t*-butyl esters in general and supplied alternatives in the cases where it could not be applied.




**7c** **7b**

**Scheme 6.**




**6a** **24** **12** **23**

**Scheme 7.**

## Experimental

### General

Unless otherwise specified, reagents and solvents were commercially available (Aldrich Italia, Milano, Italy) and used as received. Commercial 100% $HNO_3$ (d=1.51) was purchased from Hydro Chemicals France (Nanterre, France) and kept at 4°C in the dark to avoid decomposition; the acid was freshly distilled and its titre, averaging ca. 24 M, alkalimetrically checked prior to use. Anhydrous $K_2CO_3$ was finely ground and activated by keeping it in vacuo at 150°C for 1 h. TLC analyses and column chromatography were performed on silica gel 60 from Merck (Darmstadt, Germany). The course of all the described reactions was monitored by TLC and by a parallel accurate $^1H$ NMR quantitative evaluation. Melting points were determined in open ended capillary tubes by using a Mettler FP 61 automatic apparatus and are uncorrected. Elemental analyses were obtained by a Carlo Erba CHN/OS 1106 analyzer for all isolated compounds and found satisfactory. Optical activities were measured at 20°C by an Atago Polax-D polarimeter at 589 nm in a 1.0 dm tube. IR spectra were recorded on a Nicolet FTIR Magna 550 spectrophotometer using the KBr technique. Unless otherwise indicated, $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ on a Bruker AC-200 spectrometer at 200 and 50 MHz, respectively (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad, sym: symmetrical). The proton chemical shifts are reported in ppm on the $\delta$ scale relative to TMS as an internal reference (0.00); the carbon chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ triplet (77.00) or, when $Me_2SO$-$d_6$ was the solvent, the center line of the corresponding heptet (39.50). The coupling constants are given in Hz. MS measurements were carried out with a Fisons TRIO-2000 apparatus, working in the positive-ion electron impact mode (70 eV), by direct introduction of the sample into the ion source and heating from 50 to 300°C. The five most intense peaks and the molecular peak for each individual compound with bracketed intensity values are reported.

Occasionally, we prepared large amounts of the *N*-[(phenylmethoxy)carbonyl]-L-amino acids **1b**–**6b**, essentially according to a described procedure,[26] encountering some difficulties in obtaining consistently reproducible yields, probably due to the known aptitude of these compounds to form very stable complexes with the corresponding salts.[27] A definite improvement was obtained by pouring the final basic reaction mixtures in one lot into an excess of well stirred 1 M HCl at room temperature. Some of the substrates (**4a**, **6a** and **7a**), were initially dissolved in the $NaHCO_3$–$H_2O$ system by heating and, in the first two instances, kept in solution on cooling and during the course of the reaction by the addition of an equal volume of MeOH, the latter being evaporated at reduced pressure previous to the final work up. In the case of the tyrosine derivative **6b**, in order to reverse the unavoidable formation of the diacylated derivative **9** (ca. 11%), the procedure described by Ismailov[28] was successfully employed.

***N*-[*N*-[(Phenylmethoxy)carbonyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester (7b).** Pale brownish solid (89% yield): mp (from $Et_2O$) 117°C; $[\alpha]_D^{20}=-15.9$ ($c$=1.6; MeOH). [Lit.[29]: mp 120–122°C; $[\alpha]_D^{20}=-14.8$ ($c$=0.5; MeOH)]. $^1H$ and $^{13}C$ NMR.[30]

***N*-[(Phenylmethoxy)carbonyl]-L-serine phenylmethyl carbonate (8).** The compound was obtained by the classic Bergmann and Zervas's procedure.[8] Benzyl chloroformate (168.0 mmol) was added dropwise during 30 min into a well stirred solution of L-serine (**3a**, 80.0 mmol) in 4 M NaOH (20.0 mL) at 0°C, maintaining constant pH by simultaneous addition of 4 M NaOH (42.0 mL). After completion of the addition, the reaction mixture was allowed to reach room temperature, left under stirring for 1 h, washed with $Et_2O$ (2×100 mL) and the pH adjusted to ca. 3 by careful addition of concentrated HCl. The obtained suspension was extracted with EtOAc (3×100 mL), then the combined organic phase was washed with 30% aqueous NaCl, dried over $Na_2SO_4$ and the solvent evaporated off: pure **8** was obtained by repeated fractional crystallizations of the oily residue. White solid (27% yield): mp (from $C_6H_6$) 73°C; $[\alpha]_D^{20}=+5.0$ ($c$=1.0; EtOH). [Lit.[31]: mp 83–84°C; $[\alpha]_D^{20}=+4.4$ ($c$=1.0; EtOH)].

***N*-[(Phenylmethoxy)carbonyl]-L-serine ethanoate (10).** The compound was obtained by a described procedure.[12] Pale brownish solid (93% yield): mp (from cyclohexane–EtOAc) 86°C; $[\alpha]_D^{20}=-20.0$ ($c$=2.0; DMF). [Lit.[32]: mp 88–89°C; $[\alpha]_D^{20}=-18.5$ ($c$=2.0; DMF)]. $^1H$ NMR.[33]

***N*-[(Phenylmethoxy)carbonyl]-L-tyrosine phenylmethyl carbonate (9).** The compound was obtained by the procedure employed for **8**, the only modification being the careful control of pH between 9 and 11 during the whole course of the reaction. White solid (85% yield): mp (from $CCl_4$) 115°C; $[\alpha]_D^{20}=+5.0$ ($c$=10.0; AcOH). [Lit.[34]: mp 85–86°C; $[\alpha]_D^{20}=+3.7$ ($c$=10.0; AcOH)].

**3-Nitro-*N*-[(phenylmethoxy)carbonyl]-L-tyrosine (13).** The nitro derivative was obtained by direct nitration of the *N*-protected amino acid **4b**.[35] A solution of 100% $HNO_3$ (16.0 mmol) in $CH_2Cl_2$ (1.5 mL) was added dropwise into a stirred solution of **4b** (15.0 mmol) in $CH_2Cl_2$ (8.5 mL) at 0°C. After completion of the addition, the reaction mixture was allowed to reach room temperature, left under stirring for 1 h, diluted with $CH_2Cl_2$ (100 mL), washed with 30% aqueous NaCl, dried over $Na_2SO_4$ and the solvent evaporated off. Yellow solid (85% yield): mp (from cyclohexane—*t*-butyl methyl ether) 109°C; $[\alpha]_D^{20}=+10.0$ ($c$=1.0; MeOH). [Lit.[36]: mp 110°C; $[\alpha]_D^{20}=+12.5$ ($c$=2.9; MeOH)].

**4-(Methylsulfinyl)-2-[[(Phenylmethoxy)carbonyl]amino]-(2*S*)-butanoic acid (21).** The sulfoxide **21** (as diastereoisomeric mixture) was prepared by direct oxidation of the protected amino acid **5b** according to a reported procedure.[37] Orange oil (98% yield): $[\alpha]_D^{20}=-11.1$ ($c$=0.9; MeOH). [Lit.[38]: mp 89–104°C; $[\alpha]_D^{20}=+(0.5–5.5)$ (AcOH)]. IR (film) $\nu_{max}$: 3316s, br; 1715s; 1534m; 1455w; 1410w; 1229s; 1050w; 1003m; 739w; 700w $cm^{-1}$. $^1H$ NMR $\delta$ (ppm): 9.14 (br s, 1+1H, COO*H*); 7.45–7.20 (m, 5+5H, $C_6H_5$); 6.17 (d, $J$=7.5 Hz, 1H, N*H*); 6.09 (d, $J$=7.5 Hz, 1H, N*H*); 5.08 (s, 2+2H, PhC$H_2$); 4.55–4.28 (m, 1+1H, C*H*); 2.98–2.67 (m, 2+2H, OSC$H_2$); 2.59 (s, 3H, OSC$H_3$); 2.55 (s, 3H, OSC$H_3$); 2.43–2.03 (m, 2+2H, C$H_2$). $^{13}C$ NMR $\delta$ (ppm): 172.95+172.89; 156.08+156.12;

136.05; 128.46; 128.13; 128.06; 66.97; 52.81+52.53; 49.10+49.02; 37.23+37.12; 25.79+25.35. MS ($T$=100°C) $m/z$: 91 (100); 108 (57); 79 (52); 107 (40); 77 (33); 299 ($M^+$, <1). Anal. Calcd for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.73; N, 4.68. Found: C, 51.33; H, 5.87; N, 4.52.

**1-Formyl-*N*-[(phenylmethoxy)carbonyl]-L-tryptophan (12).** Compound **12** was obtained starting from 1-formyl-L-tryptophan monohydrochloride (**24**),[39] according to a reported method (Scheme 7).[40] White solid (88% yield): mp (from diisopropyl ether) 80°C; $[\alpha]_D^{20}$=+4.5 ($c$=1.1; MeOH). [Lit.[40]: mp 108–110°C]. IR (pellet) $\nu_{max}$: 3325s, br; 2971s, br; 1702s; 1522w; 1459m; 1385m; 1335w; 1196s; 1053m; 793w; 747m; 697w $cm^{-1}$. $^1H$ NMR $\delta$ (ppm): (isomer ratio due to formyl protection $E$:$Z$=1:1.8)[41] 9.23 [br s, 0.35H, C*H*O ($E$)]; 9.07 (br s, 1H, COO*H*); 8.87 [br s, 0.65H, C*H*O ($Z$)]; 8.42–8.20 (m 0.65H, indole-*H* ($Z$)]; 7.75–7.12 (m, 8.35H, indole-*H*+$C_6H_5$); 7.06 [br s, 0.65H, indole 2-*H* ($Z$)]; 6.74 [br s, 0.35H, indole 2-*H* ($E$)]; 5.59 (d, $J$=7.9 Hz, 1H, N*H*); 5.15–4.92 (m, 2H, PhC$H_2$); 4.83–4.52 (m, 1H, C*H*); 3.39–2.97 (m, 2H, C$H_2$). $^{13}C$ NMR $\delta$ (ppm): [predominant isomer ($Z$)] 174.73; 159.79; 156.03; 135.87; 134.07; 131.19; 128.45; 128.19; 128.02; 125.37; 124.55; 118.87; 118.15; 116.07; 109.61; 67.12; 53.53; 27.34. MS ($T$=120°C) $m/z$: 130 (100); 158 (74); 77 (26); 108 (24); 79 (23); 366 ($M^+$, <1). Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.43; H, 5.02; N, 7.29.

**Synthesis of 1,1-dimethylethyl esters.**

**General procedure.** *Method A.*[1b] A solution of dicyclohexylcarbodiimide (DCC, 20.8 mmol) in $CH_2Cl_2$ (4.0 mL) was added dropwise at 0°C and under vigorous stirring into a solution containing the substrate (20.0 mmol), 2-methyl-2-propanol (40.0 mmol) and 4-(dimethylamino)pyridine (DMAP, 3.2 mmol) in $CH_2Cl_2$ (8.0 mL). After the addition was complete, the reaction mixture was allowed to reach room temperature and stirred overnight; the formed dicyclohexylurea (DCU) was filtered off, the solvent evaporated and the residue dissolved in $Et_2O$ (40 mL). The obtained solution was additionally filtered, if necessary, washed with 0.5 M HCl (3×20 mL), 5% aqueous $NaHCO_3$ (2×20 mL), 30% aqueous NaCl (20 mL), dried over $Na_2SO_4$ and the solvent evaporated off. The obtained esters were suitably purified by column chromatography; yields are reported in Table 1.

*Method B.*[14] An excess of 2-methylpropene (ca. 20 mL) was condensed at −25°C into a solution of the substrate (10.0 mmol) in $CH_2Cl_2$ (25 mL) and, after the addition of 0.3 mL of 96% $H_2SO_4$, the reaction mixture was transferred into a pressure vessel, allowed to reach room temperature and vigorously stirred for 12 h. After this time, the excess of 2-methylpropene and the solvent were carefully evaporated at reduced pressure and room temperature and the residue dissolved in $Et_2O$ (50 mL); the obtained solution was washed with 5% aqueous $NaHCO_3$ (2×30 mL), 30% aqueous NaCl (30 mL), dried and processed as for Method A.

*Method C.*[15] Finely ground anhydrous $K_2CO_3$ (260 mmol) was added in one lot into a solution of the substrate (10.0 mmol) and benzyltriethylammonium chloride (10.0 mmol) in *N*,*N*-dimethylacetamide (75 mL) and the resulting suspension kept under vigorous mechanical stirring. 2-Bromo-2-methylpropane (480 mmol) was added dropwise and the resulting mixture stirred at 55°C for 24 h. After that time, the reaction mixture was cooled at room temperature, poured under stirring into cold $H_2O$ (1000 mL) and the oily residue which separated was extracted with EtOAc (2×200 mL). The combined organic phase was washed with 30% aqueous NaCl (2×200 mL), dried and processed as for Method A.

***N*-[(Phenylmethoxy)carbonyl]-L-alanine 1,1-dimethylethyl ester (1c).** Colourless oil (58% yield): $[\alpha]_D^{20}$=−22.9 ($c$=1.2; EtOH). [Lit.[42]: $[\alpha]_D^{20}$=−23.8 ($c$=3.6; EtOH)].

***N*-[(Phenylmethoxy)carbonyl]-L-phenylalanine 1,1-dimethylethyl ester (2c).** White solid (71% yield): mp (from petroleum ether–EtOAc) 82°C; $[\alpha]_D^{20}$=−7.5 ($c$=1.0; EtOH). [Lit.[43]: mp 81–82°C; $[\alpha]_D^{20}$=−7.8 ($c$=1.0; EtOH)].

***N*-[(Phenylmethoxy)carbonyl]-L-serine 1,1-dimethylethyl ester (3c).** White solid (73% yield): mp (from hexane–$Et_2O$) 95°C; $[\alpha]_D^{20}$=−15.9 ($c$=1.1; EtOH). [Lit.[11]: mp 93–95°C; $[\alpha]_D^{20}$=−16.5 ($c$=1.0; EtOH)].

***O*-(1,1-Dimethylethyl)-*N*-[(phenylmethoxy)carbonyl]-L-serine 1,1-dimethylethyl ester (16).**[20] White solid (80% yield): mp (from hexane–$CH_2Cl_2$) 65°C; $[\alpha]_D^{20}$=+5.0 ($c$=1.4; $CH_2Cl_2$). IR (pellet) $\nu_{max}$: 3445s, br; 2977w; 1729s; 1508m; 1387w; 1368m; 1343w; 1157m; 1068w; 740w; 697w $cm^{-1}$. $^1H$ NMR $\delta$ (ppm): 7.42–7.27 (m, 5H, $C_6H_5$); 5.59 (d, $J$=9.1 Hz, 1H, N*H*); 5.12 (s, 2H, PhC$H_2$); 4.35 (ddd, $J$=9.1, 3.0, 2.7 Hz, 1H, C*H*); 3.79 (dd, $J$=8.7, 2.7 Hz, 1H, *t*-BuOCH*H*); 3.53 (dd, $J$=8.7, 3.0 Hz, 1H, *t*-BuOCH*H*); 1.46 [s, 9H, COOC(C$H_3$)$_3$]; 1.13 [s, 9H, $CH_2OC(CH_3)_3$]. $^{13}C$ NMR $\delta$ (ppm): 169.57; 156.11; 136.45; 128.46; 128.06 (2 overlapped signals); 81.71; 73.02; 66.82; 62.26; 54.95; 27.99; 27.28. MS ($T$=50°C) $m/z$: 91 (100); 57 (64); 148 (63); 209 (57); 150 (42). Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.94; H, 8.32; N, 3.99. Found: C, 66.11; H, 8.46; N, 3.85.

***N*-[(Phenylmethoxy)carbonyl]-L-serine phenylmethyl carbonate 1,1-dimethylethyl ester (20).** White solid (30% yield): mp (from hexane–$CH_2Cl_2$) 88°C; $[\alpha]_D^{20}$=+20.0 ($c$=1.0; $CH_2Cl_2$). IR (pellet) $\nu_{max}$: 3361m, br; 2978w; 1751s; 1515m; 1457w; 1371w; 1269s; 1157m; 1062w; 755w; 698m $cm^{-1}$. $^1H$ NMR $\delta$ (ppm): 7.39–7.27 (m, 10H, $C_6H_5$); 5.60 (d, $J$=6.9 Hz, 1H, N*H*); 5.13 (s, 2H, PhC$H_2$); 5.10 (s, 2H, PhC$H_2$); 4.60–4.33 (m, 3H, C*H*–C$H_2$); 1.42 [s, 9H, OC(C$H_3$)$_3$]. $^{13}C$ NMR $\delta$ (ppm): 167.84; 155.72; 154.68; 136.12; 134.92; 128.55 (2 overlapped signals); 128.46; 128.29; 128.11; 128.03; 83.11; 69.88; 67.64; 67.04; 53.89; 27.81. MS ($T$=65°C) $m/z$: 91 (100); 107 (38); 92 (20); 57 (16); 181 (14). Anal. Calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 65.73; H, 6.42; N, 3.18.

**1,1-Dimethylethyl 2-[[(phenylmethoxy)carbonyl]amino]-2-propenoate (14).** Side product from the preparation of **20**. Colourless oil (12% yield). IR (film) $\nu_{max}$: 3412m; 2928m; 1743s; 1708s; 1640w; 1516s; 1371w; 1334s;

1228w; 1164m; 1068s; 893w; 747w; 698m $cm^{-1}$. $^1H$ NMR $\delta$ (ppm): 7.43–7.29 (m, 5H, $C_6H_5$); 7.27 (br s, 1H, N*H*); 6.16 [s, 1H, NC=C*H* (*Z*)]; 5.69 [d, *J*=1.5 Hz, 1H, NC=C*H* (*E*)]; 5.15 (s, 2H, PhC$H_2$); 1.51 [s, 9H, OC(C$H_3$)$_3$]. $^{13}C$ NMR $\delta$ (ppm): 162.67; 153.13; 135.94; 132.11; 128.53; 128.26; 128.13; 104.87; 82.75; 66.85; 27.86. MS (*T*=25°C) *m*/*z*: 91 (100); 57 (46); 176 (37); 92 (21); 41 (20). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.86; H, 6.99; N, 4.98.

***N*-[(Phenylmethoxy)carbonyl]-L-serine ethanoate 1,1-dimethylethyl ester (11).** Yellowish oil (70% yield): $[\alpha]_D^{20}$=+35.0 (*c*=1.0; $CHCl_3$). IR (film) $\nu_{max}$: 3347m, br; 2981m; 1734s; 1522m; 1457w; 1370w; 1227s; 1158m; 1059m; 845w; 754m; 698w $cm^{-1}$. $^1H$ NMR $\delta$ (ppm): 7.40–7.22 (m, 5H, $C_6H_5$); 5.60 (d, *J*=7.7 Hz, 1H, N*H*); 5.12 (s, 2H, PhC$H_2$); 4.56–4.23 (m, 3H, C*H*–C$H_2$); 2.02 (s, 3H, C$H_3$); 1.46 [s, 9H, OC(C$H_3$)$_3$]. $^{13}C$ NMR $\delta$ (ppm): 170.31; 168.23; 155.66; 136.09; 128.45; 128.12; 128.06; 82.86; 67.00; 64.36; 53.78; 27.80; 20.48. MS (*T*=50°C) *m*/*z*: 91 (100); 57 (38); 108 (15); 92 (14); 107 (13). Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 62.20; H, 6.71; N, 3.98.

***N*-[(Phenylmethoxy)carbonyl]-L-tyrosine 1,1-dimethylethyl ester (4c).** Pale brownish solid (60% yield): mp (from hexane–$Et_2O$) 86°C; $[\alpha]_D^{20}$=−0.5 (*c*=1.0; EtOH). [Lit.[15]: mp 88°C; $[\alpha]_D^{20}$=−0.4 (*c*=1.0; EtOH)].

***O*-(1,1-Dimethylethyl)-*N*-[(phenylmethoxy)carbonyl]-L-tyrosine 1,1-dimethylethyl ester (17).**[20] Yellowish oil (57% yield): $[\alpha]_D^{20}$=+31.5 (*c*=1.1; $CH_2Cl_2$). IR (film) $\nu_{max}$: 3342m, br; 2379m; 1725s; 1609w; 1507s; 1368m; 1237m; 1161s; 1057m; 899w; 847w; 751w; 698w $cm^{-1}$. $^1H$ NMR $\delta$ (ppm): 7.38–7.28 (m, 5H, $C_6H_5$); 7.09–6.99 (m, 2H, HOC$_6H_4$); 6.94–6.83 (m, 2H, HOC$_6H_4$); 5.29 (d, *J*=8.3 Hz, 1H, N*H*); 5.09 (s, 2H, PhC$H_2$); 4.50 (sym m, 1H, C*H*); 3.03 (d, *J*=6.1 Hz, 2H, C$H_2$); 1.37 [s, 9H, COOC(C$H_3$)$_3$]; 1.32 [s, 9H, $CH_2$OC(C$H_3$)$_3$]. $^{13}C$ NMR $\delta$ (ppm): 170.49; 155.47; 154.25; 136.30; 129.84; 129.01; 128.40; 128.03; 127.97; 123.96; 82.09; 78.24; 66.74; 55.20; 37.78; 28.73; 27.82. MS (*T*=70°C) *m*/*z*: 107 (100); 91 (86); 220 (79); 164 (61); 57 (36); 427 ($M^+$, <1). Anal. Calcd for $C_{25}H_{33}NO_5$: C, 70.23; H, 7.78; N, 3.28. Found: C, 69.65; H, 7.83; N, 3.25.

***N*-[(Phenylmethoxy)carbonyl]-L-tyrosine phenylmethyl carbonate 1,1-dimethylethyl ester (18).** White solid (63% yield): mp (from hexane–$CH_2Cl_2$) 118°C; $[\alpha]_D^{20}$=+15.0 (*c*=1.0; $CH_2Cl_2$). IR (pellet) $\nu_{max}$: 3357m, br; 2979m; 1763m; 1725s; 1509s; 1457w; 1370w; 1243s; 1156w; 1055m; 913w; 847w; 737m; 698w $cm^{-1}$. $^1H$ NMR $\delta$ (ppm): 7.48–7.28 (m, 10H, $C_6H_5$); 7.19–7.03 (m, 4H, ZOC$_6H_4$); 5.28 (d, *J*=8.0 Hz, 1H, N*H*); 5.26 (s, 2H, OCOOC$H_2$Ph); 5.10 (s, 2H, NCOOC$H_2$Ph); 4.51 (sym m, 1H, C*H*); 3.07 (d, *J*=6.1 Hz, 2H, C$H_2$); 1.38 [s, 9H, OC(C$H_3$)$_3$]. $^{13}C$ NMR $\delta$ (ppm): 170.32; 155.50; 153.51; 150.12; 136.31; 134.76; 133.97; 130.47; 128.72; 128.66; 128.47 (2 overlapped signals); 128.13; 128.09; 120.87; 82.47; 70.28; 66.87; 55.13; 37.79; 27.90. MS (*T*=150°C) *m*/*z*: 91 (100); 197 (45); 92 (19); 107 (16); 108 (8). Anal. Calcd for $C_{29}H_{31}NO_7$: C, 68.90; H, 6.18; N, 2.77. Found: C, 66.26; H, 6.33; N, 2.71.

**3-Nitro-*N*-[(phenylmethoxy)carbonyl]-L-tyrosine 1,1-dimethylethyl ester (19).** Orange oil (67% yield): $[\alpha]_D^{20}$=−14.5 (*c*=0.7; MeOH). IR (film) $\nu_{max}$: 3332m, br; 2980m; 1734s; 1630w; 1540s; 1430w; 1327w; 1217m; 1156m; 1082w; 843w; 754m; 698w $cm^{-1}$. $^1H$ NMR $\delta$ (ppm): 10.41 (s, 1H, ArO*H*); 7.88 (d, *J*=2.0 Hz, 1H, Ar*H*); 7.44–7.21 (m, 6H, $C_6H_5$+Ar*H*); 7.04 (d, *J*=8.6 Hz, 1H, Ar*H*); 5.37 (d, *J*=7.8 Hz, 1H, N*H*); 5.09 (sym m, 2H, PhC$H_2$); 4.51 (sym m, 1H, C*H*); 3.08 (sym m, 2H, $^{Tyr}$C$H_2$); 1.44 [s, 9H, OC(C$H_3$)$_3$]. $^{13}C$ NMR $\delta$ (ppm): 169.88; 155.47; 154.06; 138.92; 136.16; 133.17; 128.67; 128.51; 128.23; 128.09; 125.34; 119.92; 83.05; 66.98; 54.97; 37.14; 27.96. MS (*T*=50°C) *m*/*z*: 91 (100); 57 (44); 152 (24); 92 (20); 41 (14); 416 ($M^+$, <1). Anal. Calcd. for $C_{21}H_{24}N_2O_7$: C, 60.57; H, 5.81; N, 6.73. Found: C, 58.23; H, 5.95; N, 6.81.

***N*-[(Phenylmethoxy)carbonyl]-L-methionine 1,1-dimethylethyl ester (5c).** Yellowish oil (58% yield): $[\alpha]_D^{20}$=−29.0 (*c*=2.8; EtOH). [Lit.[44]: $[\alpha]_D^{20}$=+14.0 (*c*=2.1; $CHCl_3$)].

**1,1-Dimethylethyl 4-(methylsulfinyl)-2-[[(phenylmethoxy)carbonyl]amino]-(2*S*)-butanoate (22).** The sulfoxide **22** (as diastereoisomeric mixture) was prepared by direct oxidation of the ester **5c** as previously described for **21**. Pale yellowish oil (98% yield): $[\alpha]_D^{20}$=−43.9 (*c*=0.6; MeOH). [Lit.[44]: $[\alpha]_D^{20}$=−19.3 (*c*=1.3; MeOH)].

***N*-[(Phenylmethoxy)carbonyl]-L-tryptophan 1,1-dimethylethyl ester (6c).** White solid (30% yield): mp (from hexane–$CH_2Cl_2$) 68°C; $[\alpha]_D^{20}$=−5.0 (*c*=1.0; EtOH). [Lit.[13b]: mp 70–71°C; $[\alpha]_D^{20}$=−5.2 (*c*=1.0; MeOH)].

**1-Formyl-*N*-[(phenylmethoxy)carbonyl]-L-tryptophan 1,1-dimethylethyl ester (23).** Pale yellowish oil (82% yield based on **12**):[40] $[\alpha]_D^{20}$=+5.0 (*c*=1.0; MeOH). IR (pellet) $\nu_{max}$: 3344m, br; 2980m; 1717s; 1609w; 1522m; 1459m; 1370s; 1231s; 1156s; 1050m; 845w; 793w; 751m; 698w $cm^{-1}$. $^1H$ NMR $\delta$ (ppm): (isomer ratio due to formyl protection *E*:*Z*=1:1.8)[41] 9.36 [br s, 0.35H, C*H*O (*E*)]; 8.97 [br s, 0.65H, C*H*O (*Z*)]; 8.37 (d, *J*=7.3 Hz, 0.65H, indole-*H* (*Z*)]; 7.74–7.18 (m, 8.7H, indole-*H*+$C_6H_5$); 7.12 [br s, 0.65H, indole 2-*H* (*Z*)]; 5.48 (d, *J*=7.8 Hz, 1H, N*H*); 5.19–4.98 (m, 2H, PhC$H_2$); 4.64 (sym m, 1H, C*H*); 3.22 (sym m, 2H, C$H_2$); 1.36 [s, 9H, OC(C$H_3$)$_3$]. $^{13}C$ NMR $\delta$ (ppm): [predominant isomer (*Z*)] 170.39; 159.02; 155.58; 136.14; 134.05; 131.27; 128.39; 128.06; 128.00; 125.31; 124.39; 119.05; 118.47; 115.97; 109.43; 82.50; 66.77; 54.07; 27.92; 27.75. MS (*T*=60°C) *m*/*z*: 158 (100); 91 (74); 130 (72); 215 (38); 57 (20); 422 ($M^+$, <1). Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 67.96; H, 6.35; N, 6.62.

***N*-[*N*-[(Phenylmethoxy)carbonyl]-L-α-aspartyl]-L-phenylalanine 4-(1,1-dimethylethyl) 1-methyl ester (7c).** White solid (88% yield): mp (from hexane–$CH_2Cl_2$) 71°C; $[\alpha]_D^{20}$=−15.0 (*c*=1.0; MeOH). [Lit.[45]: mp 71–73°C; $[\alpha]_D^{20}$=−16.2 (*c*=1.0; MeOH)].

## Nitrolysis of 1,1-dimethylethyl esters.[4]

**General procedure.** A chilled solution of 100% $HNO_3$ in $CH_2Cl_2$ (60.0 mmol in 8.0 mL) was added dropwise at 0°C and under stirring to a solution of the substrate (Scheme 1,

Table 2) in $CH_2Cl_2$ (20.0 mmol in 12.0 mL) and the homogeneous mixture was stirred for 2 h at 0°C with protection from the light. Then, the reaction mixture was diluted with $CH_2Cl_2$ (100 mL), washed with 30% aqueous NaCl (2×100 mL), dried over anhydrous $Na_2SO_4$ and the solvent fully evaporated. The obtained residue was suitably purified, when needed, by crystallization or column chromatography: results and yields are reported in Table 2. In order to complete the deprotection reaction, some substrates (**11**, **18**, **20**, **22** and **23**) required 4 equiv. of $HNO_3$.

**Hydrazinolysis of *N*-[(phenylmethoxy)carbonyl]-L-serine ethanoate 1,1-dimethylethyl ester (11).** Hydrazine monohydrate (30.0 mmol) was added dropwise to a solution of the acetyl derivative **11** in EtOH (15.0 mmol in 30 mL) at 0°C under stirring. The reaction mixture was allowed to reach room temperature and stirring was continued until complete conversion was observed (12 h); then EtOH was evaporated at reduced pressure and the yellowish oily residue dissolved in EtOAc (50 mL), washed with 1 M HCl (30 mL), 30% aqueous NaCl (30 mL) and dried over $Na_2SO_4$. The white solid residue from evaporation of the solvent (91% yield) was found to be identical to **3c**.

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