Oxidation-Induced Acyl Group Transfer from Hydroquinone Esters to Nucleophiles

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Bivalent oxidation of 3,5-di-tert-butyl-hydroquinone monoesters leads to phenoxenium ions, which can transfer an acyl group to nucleophiles. Based on this principle, dipeptides, glyco-amino acids and Ar-sulfonyl-amino acids were synthesized from hydroquinone esters of amino acids and p-toluenesulfonic acid. For this reaction, direct anodic and indirect mediated oxidation, as well as chemical oxidation with NBS or trisarylaminium yl salts, was used. The mechanism of the acyl transfer is discussed in terms of a direct and/or a mediated process. A spirocyclic key intermediate was isolated and its molecular structure determined by X-ray crystallography.

Introduction

For the anodic oxidation of sterically hindered phenols two selective pathways are possible [1,2], either a CE process (one-electron oxidation) to the phenoxy radical or an ECE process (two-electron oxidation) to the phenoxenium ion (C: chemical step, E: electrochemical step, tert-Butyl groups ortho to the hydroxy group prevent undesired reactions (e.g. dimerization) and stabilize the intermediates of higher oxidation states. The ECE process occurs under neutral conditions, where the phenol is present in undissociated form. Here, the phenol is first oxidized at high potentials (1.0–1.5 V)* to the cation radical. This species is very acidic and deprotonates to the neutral phenoxy radical, which is immediately further oxidized at the applied high potential to give selectively the phenoxenium ion. The latter ion adds many types of nucleophiles NuH, (e.g. ROH, RCOOH, ArOH, H2NR etc.) preferentially in the para-position to give quinol derivatives in yields of 50–97% [3].

If the substituent in the para-position of the phenoxenium ion is an O-acyl substituent (O-R1, R1 = Acyl, structure A in Scheme 1), one would again expect addition of nucleophiles at the para-position of the phenoxenium ion to give quinol derivatives B. However, there is now also a resonance structure with the positive charge at the acyl ether oxygen (Ac), in other words, the cation species reveals a phenoxenium/carbenium/quinoxonium ion charge distribution (Aa ↔ Ab ↔ Ac). In the quinoxonium ion resonance structure, a quinone is “preformed”, and if a heterolytic cleavage of the R1-bond occurs, the quinone C and an acylation D would be formed. This acylation D, instead of the phenoxenium ion, could now react with the nucleophile to give an acylated nucleophile F and a proton via the adduct E. This transformation would not necessarily have to proceed via a free acyl cation, one could also think of an incipient cation, being formed during the encounter of the quinoxonium ion and the nucleophile with a simultaneous cleavage of the quinone moiety.

Johnson et al. [4], had reported reactions in which acyl groups were formally transferred to water or monofunctional alcohols on oxidation of mono-acylated hydroquinones or aminophenols. Our idea was to employ hydroquinone esters of N-protected amino acids as substrates for the ox-
In this way, aminoacyl groups should be transferable to nucleophiles. If the latter were amino acid esters or carbohydrates with free NH₂ or OH groups, a new synthetic route to dipeptides or glyco-amino acids would be opened. Some of our early results with carbohydrates and amino acid derivatives as nucleophiles were mentioned in a review on general aspects of the anodic oxidation of phenols and its application to the synthesis of natural products [5]. Here, we report on scope and limitation of the application of this general electron-transfer induced reaction to peptide and glyco-amino acid synthesis in detail. Special regard is paid to mechanistic aspects, as we were able to identify a key intermediate.

**Results and Discussion**

As acyl donors we used di-tert-butyl-hydroquinone esters 2 of N-protected amino acids (Scheme 2), as nucleophiles we tested oxygen or nitrogen functions, namely amino acid esters 10 (Scheme 3) with a free amino group and hexoses or pentoses 12 (as pyranoses or furanoses, Scheme 4), with one free OH group and the others protected. The only exception is 12b with two free exocyclic (one primary and one secondary) hydroxy groups.

The hydroquinone esters 2, needed as substrates for the oxidation, could be synthesized either from...
It is known that pyrocatechol monoesters of amino acids react without further activation with amino acid esters to form dipeptides [7,8]. And also the 3,5-di-tert-butyl-pyrocatechol ester 5 reacted with alanine methylester hydrochloride in CH$_2$Cl$_2$ in the presence of N-methylmorpholine at rt to form N-Cbz-Ala-Ala-OMe in a yield of 54% within 24 h [6].

In contrast to pyrocatechol monoesters, hydroquinone monoesters 2 do not undergo aminolysis in the presence of amino acid esters. However, after oxidation, they react as acylating agents, as outlined above. For the oxidation of the esters 2 we used both electrochemical and chemical methods. Electrochemical oxidations were performed in a divided cell using CH$_2$Cl$_2$ and platinum electrodes containing 10% of iridium, under neutral conditions. Anodic oxidations generally have the advantage that no oxidant is necessary, however, in the present case they led to long reaction times due to adsorption phenomena at the anode, a problem that was partly circumvented through indirect electrolysis with tris-(4-bromophenyl)amine [9] as mediator.

Among the chemical oxidants tested was NBS, which acts as a clean two-electron oxidant. Since the positions ortho to the phenolic hydroxy group are substituted in 2, the usual bromination of the aromatic ring is not possible here. Alternatively, the hypervalent iodine compound phenyliodoso(III) bis(trifluoroacetate) (PIFA) [10] was employed, or tris-(4-bromophenyl) ammonium hexachloro antimonate [9], a stable salt with the tris-(4-bromophenyl) ammoniumyl radical cation as oxidizing agent. The reaction is similar to that using this reagent in the indirect electrolysis (see above), however, stoichiometric amounts are necessary, because there is no mediated oxidation to regenerate the oxidant. By all these two-electron oxidation methods the phenoxenium/quinoxonium ion A is formed, either in a free or incipient form (see mechanistic considerations).

The results of the oxidations of hydroquinone esters 2 of N-protected amino acids with amino acid esters 10 are summarized in Table I. As expected, we directly get the dipeptides 11 in reasonable yields, without racemization*, as well as the quinone 8 as second product (Scheme 3), which can be easily reduced to 6 with Zn/HCl. After this regeneration 6 is again available for the synthesis of 2.

The yields and reaction times were mainly dependent on the chosen method of oxidation. Anodic oxidations (entries 1–4) produced variable quantities of products. The yields were better and more constant in the mediated process with tris-(4-bromophenyl)amine (entries 5–9). The reaction times depended on the nature of the amino acid ester. Along with increasing steric hindrance went an increase in reaction time. Nevertheless, the product yields were in the same range for all

* Tests for racemization were performed by GC analysis according to ref. [15].
five experiments. In general, the reaction times for chemical oxidations were very short (entries 10,11), but only with NBS the product yield was as high as the yields with indirect electrolysis.

Using the hydroquinone ester of N-Cbz-alanine 2b and partially protected monosaccharides 12 as nucleophiles, we obtained the corresponding glyco-amino acid esters 13 (Scheme 4, Table II). For the hexoses the yields depended on the type of the free OH group; they decreased from 12a, b (primary exocyclic OH) over 12c (anomeric OH) to 12d (secondary ring OH). In the case of 12b with a free primary and a free secondary exocyclic OH group, 7b reacted regiospecifically with the primary OH group (direct electrolyses; entries 1–4). Reaction with the pentose 12e gave the lowest yields (entry 5).

As in the case of the formation of the dipeptides 11, the method of choice was the indirect electrolysis (entry 6), with much shorter reaction times and significantly higher yields compared to the direct anodic oxidation. With NBS (entry 7) we received as much product as through direct electrolysis, but with a rate even faster than that of indirect electrolysis. The use of the radical salt in stoichiometric amounts (entry 8) again proved to be the least effective.

Table II. Reactions of 2b with monosaccharides 12.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Method</th>
<th>Product (yield %)</th>
<th>Reaction time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12a</td>
<td>A</td>
<td>13a (52)b</td>
<td>48.0</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>A</td>
<td>b (59)b</td>
<td>65.0</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>A</td>
<td>c (33)b</td>
<td>20.0</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>A</td>
<td>d (19)b</td>
<td>43.0</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>A</td>
<td>13e(16)/14(6)</td>
<td>22.0</td>
</tr>
<tr>
<td>6</td>
<td>e</td>
<td>B</td>
<td>13e(26)/14(20)</td>
<td>2.5</td>
</tr>
<tr>
<td>7</td>
<td>e</td>
<td>C</td>
<td>13e(15)/14(6)</td>
<td>0.8</td>
</tr>
<tr>
<td>8</td>
<td>e</td>
<td>D</td>
<td>13e(12)/14(8)</td>
<td>7.0</td>
</tr>
</tbody>
</table>

a: direct electrolysis, B: indirect electrolysis with (4-BrC₆H₄)₃N, C: chemical oxidation with NBS, D: chemical oxidation with (4-BrC₆H₄)₃NSbCl₆; b: for experimental details see reference 5.

We also examined the oxidation of a hydroquinone monosulfonate 16 [16] in the presence of amino acid esters as nucleophiles, in order to see whether a transfer of sulfonyl groups was possible in this way (eq. (1)). Using indirect electrochemical oxidation with (4-BrC₆H₄)₃N or chemical oxidation with (2,4-Br₂C₆H₃)₃NSbCl₆, a transfer of a sulfonyl group from 16 to amino acid esters was indeed observed (Table I, entries 12–14), the yields, however, were relatively low.

Table I. Reactions of hydroquinone esters with amino acid esters 10.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydroquinone ester</th>
<th>Nucleophile</th>
<th>Method</th>
<th>Product (yield %)</th>
<th>Reaction time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>H-Ile-OCH₃</td>
<td>A</td>
<td>11a (50)c</td>
<td>d</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>H-Val-OCH₃</td>
<td>A</td>
<td>b (34/44)c-e</td>
<td>d</td>
</tr>
<tr>
<td>3</td>
<td>2b</td>
<td>H-Ala-OCH₃</td>
<td>A</td>
<td>c (11)c</td>
<td>d</td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>H-Gly-O₃C₅H₆</td>
<td>A</td>
<td>d (42/73)c-e</td>
<td>10.0</td>
</tr>
<tr>
<td>5</td>
<td>2b</td>
<td>H-Gly-O₃C₅H₆</td>
<td>B</td>
<td>d (51)</td>
<td>2.5</td>
</tr>
<tr>
<td>6</td>
<td>2b</td>
<td>H-Ala-OCH₃</td>
<td>B</td>
<td>e (55)</td>
<td>8.0</td>
</tr>
<tr>
<td>7</td>
<td>2b</td>
<td>H-Val-OCH₃</td>
<td>B</td>
<td>f (63)</td>
<td>8.0</td>
</tr>
<tr>
<td>8</td>
<td>2b</td>
<td>H-Leu-O₃C₅H₆</td>
<td>B</td>
<td>g (63)</td>
<td>19.0</td>
</tr>
<tr>
<td>9</td>
<td>2b</td>
<td>H-Leu-O₃C₅H₆</td>
<td>B</td>
<td>h (51)</td>
<td>18.0</td>
</tr>
<tr>
<td>10</td>
<td>2b</td>
<td>H-Val-OCH₃</td>
<td>C</td>
<td>i (18)</td>
<td>0.8</td>
</tr>
<tr>
<td>11</td>
<td>2b</td>
<td>H-Ala-OCH₃</td>
<td>C</td>
<td>j (18)</td>
<td>0.8</td>
</tr>
<tr>
<td>12</td>
<td>16</td>
<td>H-Gly-O₃C₅H₆</td>
<td>B</td>
<td>17a (10)</td>
<td>2.0</td>
</tr>
<tr>
<td>13</td>
<td>16</td>
<td>H-Ala-OCH₃</td>
<td>B</td>
<td>b (20)</td>
<td>1.5</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
<td>H-Leu-O₃C₅H₆</td>
<td>E</td>
<td>c (32)</td>
<td>4.0</td>
</tr>
</tbody>
</table>

a: direct electrolysis, B: indirect electrolysis with (4-BrC₆H₄)₃N, C: chemical oxidation with NBS, D: chemical oxidation with (4-BrC₆H₄)₃NSbCl₆; b: for experimental details see reference 5.
Mechanistic Considerations

As already indicated, there is the pertinent question, whether the active species in the acyl transfer is a free or an incipient acyl cation. Moreover, there might be a completely different mechanism. Therefore, we intensively looked for an intermediate in the reaction. In the case of the synthesis of 13e in the co-oxidation of hydroquinone ester 2b and the sugar nucleophile 12e, we isolated a substance as a by-product (Table II), which turned out to be the spiro-aminal ester 14 according to its spectroscopic data. It may be formed via an intramolecular nucleophilic attack of the NHcbz group, bound by the acyloxy spacer, in the para-position of the intermediate phenoxonium ion (Scheme 5), as a reaction competing for the intermolecular attack of the added nucleophile. If the oxidation of the hydroquinone ester 2 was performed in the absence of any nucleophile*, again the spirocycle could be detected by mass spectrometry in all cases, and in the case of the alanine derivative 2b, it was even possible to isolate it (14, direct electrolysis: 18%; PIFA: 10%). However, in the case of the reaction of a hydroquinone ester 2 in the presence of an amino acid ester 10 as nucleophile, we could not detect the spirocycle. This can be either explained by the fact that the amino acid ester is a better nucleophile than the sugar and reacts completely with the quinoxonium ion, and no spirocycle is formed, or the latter also reacts with the amino acid ester. Such a reaction might proceed via the attack of the added nucleophile to the carbonyl group to give a semi-

aminal (15, Scheme 5), which would be cleaved to the quinone and the dipeptide or the glyco-amino acid. In the case of the dipeptide the equilibrium might be far on the side of this product, and no spirocycle would be detectable.

In fact, the isolated 14 reacted in the expected way with amino acid esters in the absence of any coupling reagent at ambient temperature to give high yields of the dipeptides (Scheme 5; 14 with H-Gly-OEt, 11d 86%; with H-Leu-OEt, 11k 100%). The transformation of the hydroquinone ester 2b to the spirocycle effected an activation of the carbonyl group (cyclic active ester) for nucleophilic attack.

It is known from the literature that other oxazolidones are also active coupling agents in peptide synthesis [17,18]. This rises the question, which structural element is responsible for the activation of the carbonyl C-atom in oxazolidones towards nucleophilic attack, as, regardless, whether the substituents at position 2 of the ring are simply hydrogen atoms [17] or CF₃ groups [18].

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*Especially water should be excluded, because 14 is easily hydrolyzed to 8 and N-Cbz-Ala-OH 4b.
or even the bulky quinonoidal ring (see 14), all these oxazolidones show activation towards nucleophiles.

For a more detailed examination we determined the crystal structure of 14 (Fig. 1). The planes through the quinonoidal six-membered ring and the five-membered ring are perpendicular to each other. The quinonoidal ring shows the typical boat form, but surprisingly all five atoms of the five-membered ring are in one plane, in contrast to Burger's CF₃ substituted oxazolidones [18], with an envelope conformation of the ring and the nitrogen atom out of the plane.

Thus, it can be assumed that the major effect of the activation in 14 results from the ring tension in the planar oxazolidone ring and especially from the reduced angle between C₁₅-C₁₆-O₂ (110.9°), compared to the ideal angle at an sp²-hybridized atom (120°). In the case of CF₃ substituted oxazolidones electronic effects may be also responsible for the activation.

Altogether, it could be shown that in the present case active spirocycles as 14 are intermediates in the acyl transfer from 7 to nucleophiles. On the other hand, a competitive acyl transfer via a free or an incipient acyl cation cannot be ruled out definitely. But even in the cases of an acetyl transfer [4] or the sulfonyl transfer (see above), we may have intermediate spirocyclic quinone acetals of the type shown (G and H), where the nucleophile can add at the positive carbon or sulfur center, to give the acylated or sulfonylated products after hydrolysis.

Conclusions
The present work demonstrates the successful utilization of hydroquinone esters as starting materials to form dipeptides (without racemization), glyco-amino acids or N-tosyl-amino acids in a preparative scale. This is achieved via a formal acyl transfer from phenoxenium/quinoxonium ions, created by oxidation of these esters. A spirocyclic quinol derivative could be isolated as intermediate and structurally characterized.

The various oxidation procedures employed show a strong impact on the product yields. The method of choice is in all cases the indirect electrolysis with trisarylamines as mediators, leading to the highest yields in short reaction times at low potentials. In the direct anodic oxidation the reaction times were very long, due to adsorption phenomena at the anode, and the yields were always low. Also chemical oxidations with NBS or trisaryl-ammoniumyl radical salts generally were less effective. This type of acyl transfer represents another expansion of the application of electrochemical oxidations and outlines the advantages of electrocatalysts.

Experimental
General
Electrochemical oxidations were carried out potential-controlled at platinum electrodes (Pt/Ir 90/10) with AMEL or Wenking potentiostats. For the divided cells, a ceramic tube (Haldenwanger, ABS) was used as diaphragm. The purification of solvents and preparation of the supporting electrolytes have been described elsewhere [5]. All electrolysers were performed under an argon atmosphere at room temperature. The mediator, the
ammoniumyl salts [9], the amino acid esters [19] and the sugar nucleophiles [20] were prepared according to literature procedures. Chromatography was performed on silica gel with n-hexane/ethyl acetate gradients. NMR values (CDCl₃, 1H NMR: 400 MHz; 13C NMR: 100 MHz) refer to Me₄Si as internal standard. J values are given in Hz. Syntheses of 11a,b and 13a-d have been described previously [5].

**Monoesters of 2,6-di-tert-butyl-hydroquinone**

The syntheses of 2b [5] and 16[16] have been described previously.

N-Cbz-Gly-(3,5-di-tert-butyl-4-hydroxyphenyl)-ester (2a), N-Cbz-Ala-(3,5-di-tert-butyl-4-hydroxyphenyl)ester (2c). General procedure: The N-Cbz-protected amino acid ester 4 and 6 were dissolved in 50 ml of CH₂Cl₂, then 1 N DCC in CH₂Cl₂ together with 30 mg of DMAP was added dropwise at 0 °C. After 1 h at 0 °C, 24 h at rt and 72 h at 40 °C the reaction was quenched with 5 ml of 5% citric acid. The layers were separated and the organic layer was washed with 5% NaHCO₃, dried over MgSO₄ and evaporated to a small volume. On addition of n-hexane the colorless product precipitated and was recrystallized from n-hexane.

2a. 4.6 g (22 mmol) 4a, 5.0 g (22 mmol) 6 and 28 ml 1 N DCC/CH₂Cl₂. Yield 2.3 g (25%), m.p. 76–78 °C (from n-hexane). - IR (KBr): 3622; 1795; 1710 cm⁻¹. - MS (FD): m/z = 425 (M⁺).

Second fraction 13e: colorless oil. - IR (KBr): 3330; 2940; 1715; 1520 cm⁻¹. - MS (FD): m/z = 410 (M⁺ + H, 20); 394 (100). - 13C-NMR: δ (ppm) = 7.38–7.34 (5H, m, Ph Cbz); 5.46 (1H, d, J 5, 5.5, 2-H or 3-H); 4.60 (1H, d, J 5.9, 2-H or 3-H); 4.67 (1H, d, J 5.9, 2-H or 3-H); 4.60 (1H, d, J 5.9, 2-H or 3-H); 4.48–4.33 (2H, m, α-H Ala, 4-H); 4.24–4.10 (2H, m, 5-H); 3.30 (3H, s, OMe); 1.48 (3H, s, i-Pr); 1.43 (3H, d, J 7.1, β-H Ala); 1.31 (3H, s, i-Pr). - 13C-NMR: δ (ppm) = 172.5; 155.6; 136.3; 128.6; 128.2; 128.1; 112.6; 109.7; 85.2; 84.1; 81.7; 66.9; 65.5; 55.0; 49.7; 26.4; 24.9; 18.7.

HRMS (FAB, NBA + NaCl): C₂₀H₂₇NNaO₈ (432.1647)

Found 432.1647.

**Anodic oxidation without nucleophile**

2b (500 mg, 1.17 mmol), 42 h. Yield of 14: 90 mg (18%).

**General procedure for the anodic oxidation**

Hydroquinone ester 2b (1.4 mmol), the nucleophile (4–5 mmol) and 2,6-lutidine (excess over 2b) in dry CH₂Cl₂/0.1 N Et₄NBF₄ (150 ml) were anodically oxidized in a divided cell at 1400 mV. The cathodic compartment contained the same supporting electrolyte and lutidinium perchlorate (ca. 1.0 g). The electrolysis was terminated after disappearance of 2b (TLC). The solution was extracted two times with 5% citric acid, once with 5% NaHCO₃, washed with water and dried (MgSO₄). After evaporation the product was purified by chromatography (Table I, entries 1–4; Table II, entries 1–5).

5-O-(N-Cbz-Ala)-2,3-O-isopropyliden-1.O.methyl-β-D-ribofuranoside (13e) and 4-N-Cbz-7,9-di-tert-butyl-3-methyl-4-aza-1-oxa-spiro[4,5]-deca-6,9-dien-2,8-dione (14) (Table II, entry 5). First fraction 14: m.p. 97–98 °C (from n-hexane). - IR(KBr): 2960; 1795; 1710 cm⁻¹. - MS (FD): m/z = 425 (M⁺).

6.0, 3-H); 1.68 (3H, d, J 6.4, 3-CH₃); 1.15 (18H, br s, tBu). - 13C-NMR: δ (ppm) = 185.4; 171.5; 150.4; 135.0; 134.0; 132.9; 128.6–128.5; 87.6; 68.0; 52.3; 35.03; 34.97; 29.2; 18.4.

C₂₅H₃₁NO₅ (425.5)

Calcd C 70.6 H 7.3 N 3.3%.

Found C 70.7 H 7.8 N 3.1%.
General procedure for the indirect electrochemical oxidation with (4-BrC₆H₄)₃N

A solution of (4-BrC₆H₄)₃N (0.2 mmol) in dry CH₂Cl₂/0.1 N Et₄NBF₄ (150 ml) was preoxidized in a divided cell for 30 min at 800 mV under argon. The cathodic compartment contained the same supporting electrolyte and lutidinium perchlorate in a divided cell for 30 min at 800 mV under argon. CH₂Cl₂/0.1 N Et₄NBF₄ (150 ml) was preoxidized two times with 5% citric acid, once with 5% of the starting current. The solution was extracted stopped when the current reached a value of 5% tin (excess over the hydroquinone ester) were added (ca. 10 mg, 0.06 mmol), 50 h at 45 °C. Yield: 17 mg (23%) 16. IR(KBr): 3280; 2960; 1740 cm⁻¹. MS(FD): m/z = 313 (M⁺). -¹H-NMR: (3(ppm) = 7.65 (2H, d, J 8.0, Ph); 7.19 (2H, d, J 8.0, Ph); 5.10 (1H, d, J 10.0, NH); 3.91–3.80 (1H, m, a-H); 1.45–1.35 (2H, m, β-H); 1.01 (3H, t, J 7.1, CH₃CH₃); 0.82 (6H, dd, J 6.7 and 3.7 Hz, δ-H). -¹³C-NMR: δ(ppm) = 172.3; 143.5; 136.9; 129.5; 127.4; 61.4; 42.4; 22.4; 22.7; 21.4; 13.8.

C₁₅H₂₃N₀₅ (313.4)
Calcd C 57.5 H 7.4 N 4.7 S 10.0%
Found C 57.2 H 7.3 N 4.7 S 10.0%

Dipeptides from the active ester 14

General procedure. 20 mg (0.047 mmol) of the spirocyclus 14 and the corresponding amino acid ester were dissolved in 5 ml of CH₂Cl₂ and stirred until 14 had reacted completely (TLC). Then the solvent was evaporated in vacuo and the crude product purified by chromatography.

1. N-Cbz-Ala-Gly-OC₂H₅ (11d). H-Gly-OC₂H₅ (7.2 mg, 0.07 mmol), 15 h at rt. Yield: 12 mg (86%).
2. N-Cbz-Ala-Leu-OC₂H₅ (11k). H-Leu-OC₂H₅ (10 mg, 0.06 mmol), 50 h at 45 °C. Yield: 17 mg (99%). Identified through comparison with an authentic sample [11].

Crystal data and structure refinement of 14

C₂₃H₃₁NO₅, M = 425.51, triclinic, space group P1, a = 10.8011(8), b = 15.0951(12), c = 15.900(2) Å, α = 83.118(7), β = 73.209(8), γ = 82.776(7)°, V = 2452.7(4) Å³, Z = 4, D = 1.152 Mg m⁻³, F(000) = 912, μ(Cu-Kα) = 0.646 mm⁻¹, colorless crystal 0.5 × 0.2 × 0.2 mm.
The data collection was carried out with a CAD-4 diffractometer by using graphite-monochromated Cu-Kα radiation, $\lambda = 1.54056$ Å. Scan = $\omega/2\theta$. Unit cell determination and refinement were carried out with 25 reflections of the reference list. All 9792 recorded reflections merged to give 9185 unique reflections [$I > 2\sigma(I)$, $R_{int} = 0.0471$]. The structure was solved by direct methods using the SHELXS-86 program [21]. The full-matrix least-squares structure refinement was performed with the SHELXL-93 program [22] against $F^2$. All hydrogen atoms were found on a difference Fourier map and considered in the structure factor calculation. The structure afforded a final $R_1$ value of 0.043 and $wR_2 = 0.1143$. The results of the crystal structure analysis unequivocally support the structure of 14.

Further details can be requested to the Cambridge Crystallographic Data Centre, The Director CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, quoting the full literature citation and the reference number 101748.

Acknowledgments
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