Oxidation-Induced Acyl Group Transfer from Hydroquinone Esters to Nucleophiles

Gerald Reischl[a], Medhat El-Mobayed[a], Rudolf Beißwenger[a], Klaus Regier[a], Cäcilia Maichle-Mössmer[b], Anton Rieker*[,a]

[a] Institute of Organic Chemistry, University of Tübingen, Auf der Morgenstelle 18, D-72076 Tübingen

[b] Institute of Inorganic Chemistry, University of Tübingen, Auf der Morgenstelle 18, D-72076 Tübingen

Z. Naturforsch. **53b,** 765–773 (1998); received April 17, 1998

Acyl Group Transfer, Hydroquinone Esters, Oxidation, Dipeptides, Active Esters

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 *N*-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 trisarylammoniumyl 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, H_2NR *etc.*) preferentially in the *para*-position to give quinol derivatives in yields of 50–97% [3].

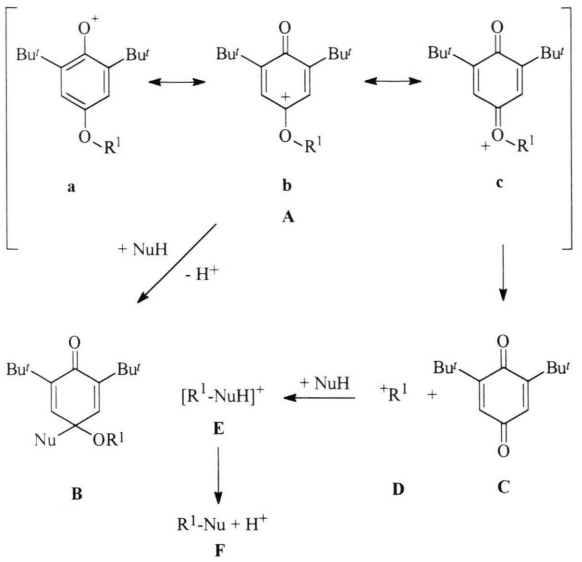
If the substituent in the *para*-position of the phenoxenium ion is an *O*-acyl substituent (O-R^1, R^1 = Acyl, structure **A** in Scheme 1), one would again expect addition of nucleophiles at the *para*-position of the phenoxenium ion to give quinol derivatives **B**. However, there is now also a resonance 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 R^1-bond occurs, the quinone **C** and an acyl-cation **D** would be formed. This acyl-cation **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 oxi-

* All potentials in this publication refer to the Ag/Ag^+ electrode (Ag/0.01 N Ag^+ in CH_3CN).

* Reprint requests to Prof. Dr. A. Rieker.

0932–0776/98/0700–0765 $06.00



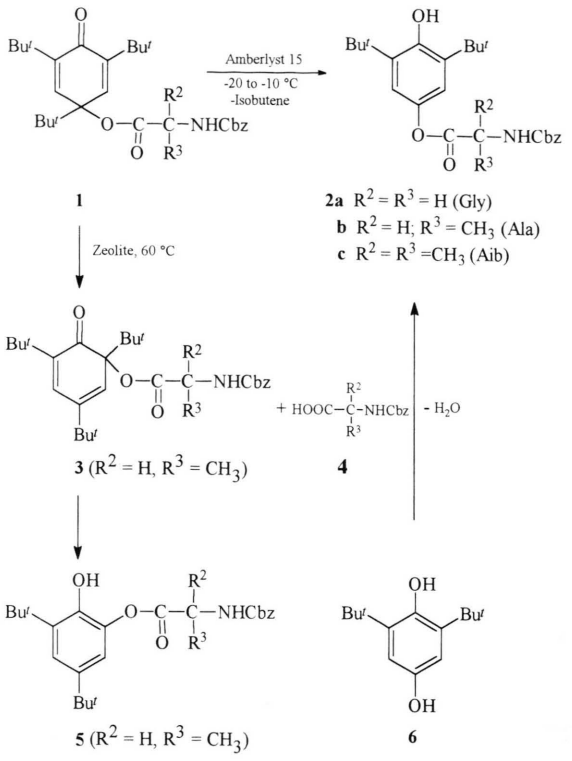
Scheme 1

dation. In this way, aminoacyl groups should be transferable to nucleophiles. If the latter were amino acid esters or carbohydrates with free NH_2 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 payed to mechanistic aspects, as we were able to identify a key intermediate.

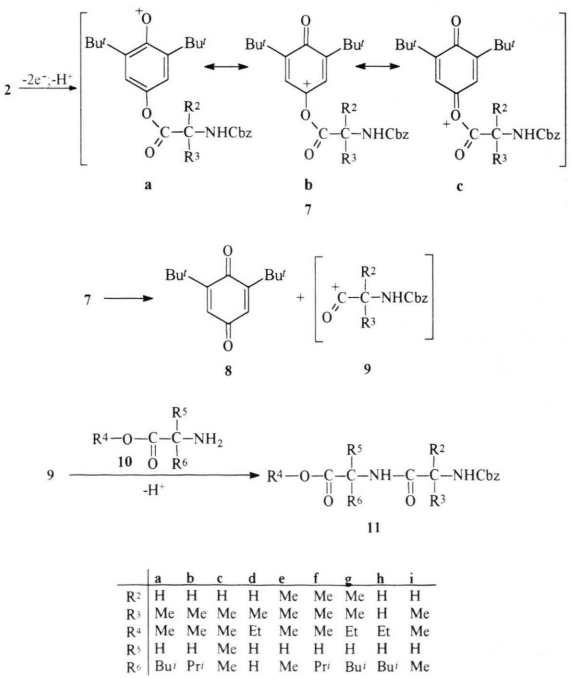
Results and Discussion

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.

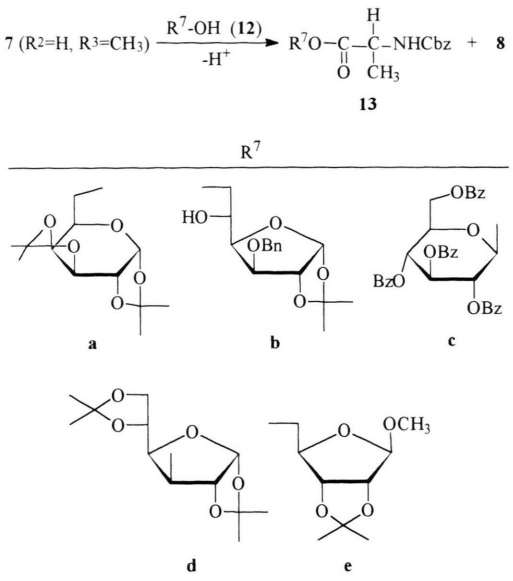
The hydroquinone esters **2**, needed as substrates for the oxidation, could be synthesized either from



Scheme 2



Scheme 3



Scheme 4

hydroquinone **6** and the amino acids **4** with a free C-terminus or from quinol esters **1.** The quinol esters **1** in turn can be obtained by anodic oxidation of the corresponding phenols in the presence of *N*-Cbz-amino acids *via* phenoxenium ions[6]. With acids, the *tert*-butyl group at the sp^3-center should be cleaved to form the hydroquinone ester. Unfortunately, this step proved to be tricky, because always the rearranged *ortho*-product **5**, derived from the 3,5-di-*tert*-butyl-pyrocatechol, was obtained as the main product. Finally, we succeeded by using the sulfonated resin Amberlyst 15 at low temperatures.

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_2Cl_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_2Cl_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)ammoniumyl 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.**

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

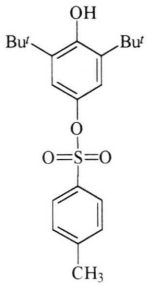
[a] A: direct electrolysis, B: indirect electrolysis with (4-$BrC_6H_4)_3N$, C: chemical oxidation with NBS, D: chemical oxidation with (4-$BrC_6H_4)_3NSbCl_6$; [b] for experimental details see reference 5.

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-$BrC_6H_4)_3N$ or chemical oxidation with (2,4-$Br_2C_6H_3)_3NSbCl_6$, 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.

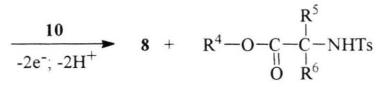
Table I. Reactions of hydroquinone esters with amino acid esters **10.**

Entry	Hydroquinone ester	Nucleophile **10**	Method[a]	Product[b] (yield %)	Reaction time (h)
1	**2b**	H-Ile-OCH_3	A	**11a** (50)[c]	[d]
2	**b**	H-Val-OCH_3	A	**b** (34/44)[c,e]	[d]
3	**b**	H-Aib-OCH_3	A	**c** (11)[c]	[d]
4	**b**	H-Gly-OC_2H_5	A	**d** (42/73)[c,e]	10.0
5	**b**	H-Gly-OC_2H_5	B	**d** (51)	2.5
6	**c**	H-Ala-OCH_3	B	**e** (55)	8.0
7	**c**	H-Val-OCH_3	B	**f** (63)	8.0
8	**c**	H-Leu-OC_2H_5	B	**g** (63)	19.0
9	**a**	H-Leu-OC_2H_5	B	**h** (51)	18.0
10	**b**	H-Val-OCH_3	C	**b** (50/69)[c,e]	0.3
11	**b**	H-Ala-OCH_3	D	**i** (18)	0.8
12	**16**	H-Gly-OC_2H_5	B	**17a** (10)	2.0
13		H-Ala-OCH_3	B	**b** (20)	1.5
14		H-Leu-OC_2H_5	E	**c** (32)	4.0

[a] A: direct electrolysis, B: indirect electrolysis with (4-$BrC_6H_4)_3N$, C: chemical oxidation with NBS, D: chemical oxidation with (4-$BrC_6H_4)_3NSbCl_6$, E: chemical oxidation with (2,4-$Br_2C_6H_3)_3NSbCl_6$; [b] if not mentioned in the Experimental Section, the products were identified through comparison with authentic samples synthesized according to literature procedures [11–14]; [c] for experimental data see reference 5; [d] the reaction was stopped after the current had dropped to 5% of the starting value; [e] the second value gives the yield calculated for the conversion of **2b**.



16



	17a	b	c
R^4	Et	Me	Et
R^5	H	H	H
R^6	H	Me	Bu^i

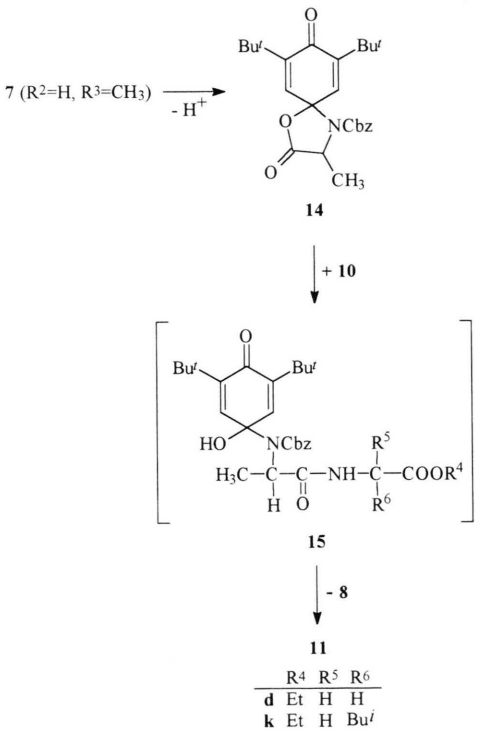
(1)

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 phenoxenium 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 spirocyclus 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 spirocyclus. 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 spirocyclus 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 spirocyclus 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 spirocyclus 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 CF_3 groups [18]



	R^4	R^5	R^6
d	Et	H	H
k	Et	H	Bu^i

Scheme 5

* 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 CF_3 substituted oxazolidones [18], with an envelope conformation of the ring and the nitrogen atom out of the plane.

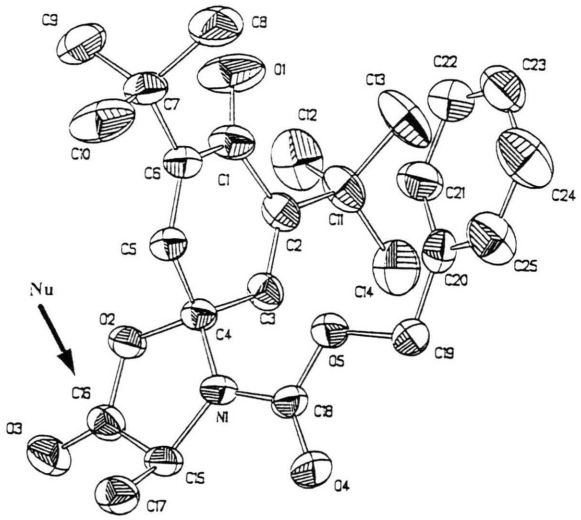
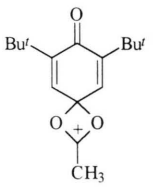


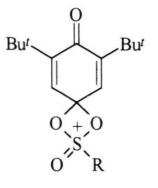
Fig. 1. A perspective ORTEP drawing of the molecule of **14** with the atom numbering scheme. The thermal ellipsoids are scaled at 50% probability.

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 sp^2-hybridized atom (120°). In the case of CF_3 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.



G



H

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 trisarylammoniumyl 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 electrolyses 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 ($CDCl_3$, ^1H NMR: 250 MHz; ^{13}C NMR: 62.9 MHz) refer to Me_4Si 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-Aib-(3,5-di-tert-butyl-4-hydroxyphenyl)ester* (**2c**). *General procedure*: The *N*-Cbz-protected amino acid **4** and **6** were dissolved in 50 ml of CH_2Cl_2, then 1 N DCC in CH_2Cl_2 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% $NaHCO_3$, dried over $MgSO_4$ 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/CH_2Cl_2. Yield 2.3 g (25%), m.p. 76–78 °C (from *n*-hexane). – IR (KBr): 3615; 3410; 2960; 1770; 1710; 1520 cm^{-1}. – MS (FD): m/z = 413 (M^+). – ^1H-NMR: δ (ppm) = 7.35–7.30 (5H, m, Ph Cbz); 6.86 (2H, s, 2,6-H); 5.29 (1H, br s, NH); 5.14 (2H, s,CH_2 Cbz); 5.11 (1H, s, OH); 4.22 (2H, d, *J* 5.5, α-H); 1.40 (18H, s, *t*Bu). – ^{13}C-NMR: δ(ppm) = 169.1; 156.3; 151.6; 143.0; 137.1; 136.2; 128.5; 128.2; 128.1; 117.4; 67.2; 43.0; 34.5; 30.1.

$C_{24}H_{31}NO_5$ (413.5)
Calcd C 69.7 H 7.6 N 3.4%,
Found C 69.8 H 7.7 N 3.1%.

2c. 1.4 g (5.9 mmol) **4c**, 1.3 g (5.9 mmol) **6** and 6.3 ml 1 N DCC/CH_2Cl_2. Yield 1.5 g (58%), m.p. 138–139 °C (from *n*-hexane). – IR(KBr): 3622; 3362; 2958; 1740; 1685; 1515 cm^{-1}. – MS(FD): m/z = 441 (M^+). – ^1H-NMR: δ (ppm) = 7.34–7.27 (5H, m, Ph Cbz); 6.83 (2H, s, 2,6-H); 5.41 (1H, s, NH); 5.10 (2H, s, CH_2 Cbz); 5.08 (1H, s, OH); 1.68 (6H, s, β-H); 1.40 (18H, s, *t*Bu). – ^{13}C-NMR: δ(ppm) = 173.7; 155.0; 151.4; 143.5; 136.9; 136.4; 128.5; 128.0; 127.9; 117.5; 66.6; 56.6; 34.4; 30.1; 25.2.

$C_{26}H_{35}NO_5$ (441.6)
Calcd C 70.7 H 8.0 N 3.2%,
Found C 71.1 H 8.3 N 3.1%.

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 CH_2Cl_2/0.1 N Et_4NBF_4 (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% $NaHCO_3$, washed with water and dried ($MgSO_4$). 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-isopropylidene-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^+). – ^1H-NMR: δ(ppm) = 7.35–7.15 (5H, m, Ph Cbz); 6.18–6.14 (2H, m, 6,10-H); 5.12 (1H, d, *J* 11.9, CH_2 Cbz); 4.96 (1H, br s, CH_2 Cbz); 4.49 (1H, br q, *J* 6.0, 3-H); 1.68 (3H, d, *J* 6.4, 3-CH_3); 1.15 (18H, br s, *t*Bu).- ^{13}C-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.

$C_{25}H_{31}NO_5$ (425.5)
Calcd C 70.6 H 7.3 N 3.3%,
Found C 70.7 H 7.8 N 3.1%.

Second fraction **13e**: colorless oil.- IR(KBr): 3330; 2940; 1715; 1520 cm^{-1}. – MS(FD): m/z = 410 (M^+ + H, 20); 394 (100). – ^1H-NMR: δ(ppm) = 7.38–7.34 (5H, m, Ph Cbz); 5.46 (1H, d, *J* 7.5, NH); 5.12 (2H, s, CH_2 Cbz); 4.98 (1H, s, 1-H); 4.67 (1H, d, *J* 5.9, 2-H or 3-H); 4.60 (1H, d, *J* 5.9, 3-H or 2-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). – ^{13}C-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): $C_{20}H_{27}NNaO_8$ (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 indirect electrochemical oxidation with (4-$BrC_6H_4)_3N$

A solution of $(4\text{-}BrC_6H_4)_3N$ (0.2 mmol) in dry CH_2Cl_2/0.1 N Et_4NBF_4 (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 (*ca.* 1.0 g). The hydroquinone ester (0.6 mmol), the nucleophile (1.5–6.0 mmol) and 2,6-lutidine (excess over the hydroquinone ester) were added to the anodic compartment and the reaction continued at the same potential. The electrolysis was stopped when the current reached a value of 5% of the starting current. The solution was extracted two times with 5% citric acid, once with 5% $NaHCO_3$, washed with water and dried ($MgSO_4$). After evaporation to dryness the resulting product was purified by chromatography. The details are summarized in Table I, entries 5–9,12,13 and Table II, entry 6.

General procedure for the chemical oxidation with NBS

NBS (3.0 mmol) was added to a solution of hydroquinone ester **2b** (0.3 mmol), the nucleophile (1.8 mmol) and 2,6-lutidine (0.9 mmol) in 25 ml of CH_2Cl_2. After 45 min the reaction was quenched with an aqueous solution of $Na_2S_2O_3$/$NaHCO_3$. The organic layer was washed twice with 5% citric acid, then with 5% $NaHCO_3$ and water. After drying over $MgSO_4$ and evaporation of the solvent, the product was purified by chromatography (Table I, entry 10; Table II, entry 7).

Spirocyclus **14**, *chemical oxidation of* **2b** *with PIFA*

2b (250 mg, 0.58 mmol) and 2,6-lutidine (124 mg, 1.16 mmol) were dissolved in 20 ml of CH_3CN. At 0 °C PIFA (260 mg, 0.6 mmol in 20 ml of CH_3CN) was added under argon. After 20 min, water was added and the mixture extracted with ether. The organic layer was washed with saturated NaCl-solution, 5% citric acid, water and dried. After evaporation of the organic phase, the residue was purified by chromatography. Yield: 25 mg (10%).

General procedure for the chemical oxidation with (4-$BrC_6H_4)_3NSbCl_6$

Hydroquinone ester **2b** (0.4 mmol), the nucleophile (2.4 mmol) and 2,6-lutidine (0.8 mmol) were dissolved in 25 ml of CH_2Cl_2 and $(4\text{-}BrC_6H_4)_3NSbCl_6$ (0.8 mmol) was added. At the end of the reaction, the solution was washed with 5% citric acid, 5% $NaHCO_3$ and water. After evaporation, the product was purified by chromatography (Table I, entry 11; Table II, entry 8).

N-Ts-Leu-OC_2H_5 (**17c**)

Hydroquinone monosulfonate **16** (750 mg, 2.0 mmol), H-Leu-OC_2H_5 (1600 mg, 10.0 mmol) and 2,6-lutidine (excess over **16**) were dissolved in 25 ml of CH_2Cl_2 under argon and $(2,4\text{-}Br_2C_6H_3)_3NSbCl_6$ (2100 mg, 2.0 mmol; in 10 ml of CH_2Cl_2) was added. At the end of the reaction (4 h), the solvent was evaporated and the residue extracted with ether. After evaporation, the product was purified by chromatography. Yield 154 mg (32%, calculated for conversion), m.p. 50–52 °C (from *n*-hexane) and 170 mg (23%) **16**. IR(KBr): 3280; 2960; 1740 cm^{-1} . – MS(FD): *m/z* = 313 (M^+). – ^{1}H-NMR: δ(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, α-H); 3.79 (2H, q, *J* 7.1, CH_2CH_3); 2.33 (3H, s, CH_3 Ts); 1.78–1.69 (1H, m, γ-H); 1.45–1.35 (2H, m, β-H); 1.01 (3H, t, *J* 7.1, CH_2CH_3); 0.82 (6H, dd, *J* 6.7 and 3.7 Hz, δ-H).- ^{13}C-NMR: δ(ppm) = 172.3; 143.5; 136.9; 129.5; 127.4; 61.4; 54.4; 42.4; 24.3; 22.7; 21.4; 13.8.

$C_{15}H_{23}NO_4S$ (313.4)

Calcd	C 57.5	H 7.4	N 4.5	S 10.2%,
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 CH_2Cl_2 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-OC_2H_5 (**11d**). H-Gly-OC_2H_5 (7.2 mg, 0.07 mmol), 15 h at rt. Yield: 12 mg (86%).

2. N-Cbz-Ala-Leu-OC_2H_5 (**11k**). H-Leu-OC_2H_5 (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**

$C_{25}H_{31}NO_5$, M = 425.51, triclinic, space group $P\bar{1}$, 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) Å^3, Z = 4, D_c = 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-K_α radiation, λ = 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

This research was supported by the Deutsche Forschungsgemeinschaft. Experimental work by Prof. Dr. R. A. Misra and Dr. A. Hutinec is gratefully acknowledged.

[1] a) B. Speiser, A. Rieker, J. Electroanal. Chem. **102**, 373 (1979);
b) B. Speiser, A. Rieker, J. Electroanal. Chem. **110**, 231 (1980).
[2] a) J. A. Richards, D. H. Evans, J. Electroanal. Chem. **81**, 171 (1977);
b) D. H. Evans, P. J. Jiminez, M. J. Kelly, J. Electroanal. Chem. **163**, 145 (1984).
[3] a) A. Rieker, E.-L. Dreher, H. Geisel, M. H. Khalifa, Synthesis 1978, 851;
b) M. H. Khalifa, G. Jung, A. Rieker, Liebigs Ann. 1982, 1068;
c) E.-L. Dreher, J. Bracht, M. El-Mobayed, P. Hütter, W. Winter, A. Rieker, Chem. Ber. **115**, 288 (1982).
[4] R. W. Johnson, M. D. Bednarski, B. F. O'Leary, E. R. Grover, Tetrahedron Lett. **22**, 3715 (1981).
[5] A. Rieker, R. Beißwenger, K. Regier, Tetrahedron **47**, 645 (1991).
[6] R. Beißwenger, Doctoral thesis, University of Tübingen (1988).
[7] J. H. Jones, G. T. Young, J. Chem. Soc. (C) 1968, 436.
[8] G. Wendlberger, in *Houben-Weyl-Müller*, Methoden der Organischen Chemie, vol. 15/2, p. 70, G. Thieme Verlag, Stuttgart (1974).
[9] W. Schmidt, E. Steckhan, Chem. Ber. **113**, 577 (1980).
[10] Y. Tamura, T. Yakura, J. Haruta, Y. Kita, J. Org. Chem. **52**, 3927 (1987).
[11] H. Faulstich, Chimia **23**, 150 (1969).
[12] I. M. Shaw, A. Taylor, Can. J. Chem. **64**, 164 (1986).
[13] R. Paul, G. W. Anderson, J. Am. Chem. Soc. **82**, 4596 (1960).
[14] E. Fischer, L. v. Mechel, Chem. Ber. **49**, 1355 (1916).
[15] H. Brückner, G. J. Nicholson, G. Jung, K. Kruse, W. A. König, Chromatographia **13**, 209 (1980).
[16] A. Rieker, Z. Naturforsch. **21b**, 647 (1966).
[17] R. Pascal, A. Rousset, A. Commeyras, New J. Chem. **13**, 205 (1989).
[18] K. Burger, M. Gold, R. Simmerl, Chem.-Ztg. **110**, 422 (1986).
[19] G. Hillmann, Z. Naturforsch. **1**, 682 (1946).
[20] K. Regier, Doctoral thesis, University of Tübingen (1989).
[21] G. M. Sheldrick, SHELXS-86, A Program for Structure Solution, University of Göttingen (1986).
[22] G. M. Sheldrick, SHELXL-93, A Computer Program for Crystal Structure Determination, University of Göttingen (1993).