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SYNTHESES VIA ANODICALLY PRODUCED PHENOXENIUM IONS. APPLICATIONS IN THE FIELD OF PEPTIDES AND CARBOHYDRATES

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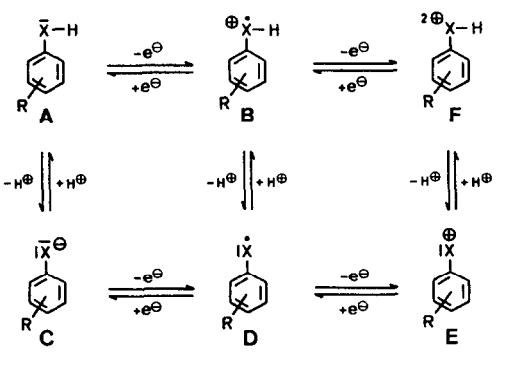
Abstract: Sterically hindered phenols are anodically oxidized to the corresponding phenoxenium ions which react with O- and N-nucleophiles to give cyclohexadienyl-protected nucleophiles. 4-Acyloxy substituted phenoxenium ions can transfer the acyl group to nucleophiles. A synthesis of dipeptides and glycoamino acids based on this principle is developed.

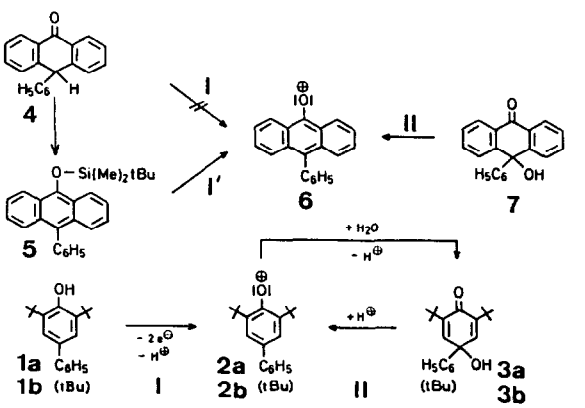
Phenoxenium ions, prominent species in the anodic oxidation of hindered phenols

Phenols are phenyl-X systems (Scheme 1, X=O). Their oxidation may be described by a "scheme of squares", in which the individual species are correlated by *electron transfers* (horizontally) and *proton transfers* (vertically). Thus, proton and electron transfers are the fundamental processes in this description, the electron transfer being denoted as "E" process, the proton transfer as "C" (from chemical) process. In Scheme 1, from left to right, the oxidation potential of the species is increasing, and so is its acidity, i.e. the tendency to deprotonate. Starting with a neutral phenol **A**, the dication **F** may be formed by two successive one-electron transfers *via* the cation radical **B**. All three species (**A**, **B** and **F**) are in equilibrium with their deprotonated forms, the phenolate **C**, the neutral phenoxy radical **D**, and the phenoxenium cation **E**, respectively. On the other hand, **C**, **D** and **E** are again interrelated by two consecutive one-electron transfers. The real system is even more complicated, since every species may react with each of the others *via bimolecular electron* or *proton transfers* to give two other species of the system. Setting the proper potential and adjusting the suitable proton concentration, it should be possible to generate the desired species **A** - **F** selectively as the main component in the coupled equilibria.

Scheme 1:



Scheme 2:



Since phenoxenium ions of type **E** are not easily prepared by chemical reactions[1], we were mainly interested in *these* species. Cyclic voltammetric and other electroanalytic investigations[2,3] revealed that

E may be obtained from phenol **A** via two routes, provided that dimerization of the radicals **B** and **D** by means of sterically hindering substituents (e.g. *tert*-butyl groups) in the positions *ortho* to the phenolic OH-group is prohibited and that all species are further stabilized by substituents in *para*-position.

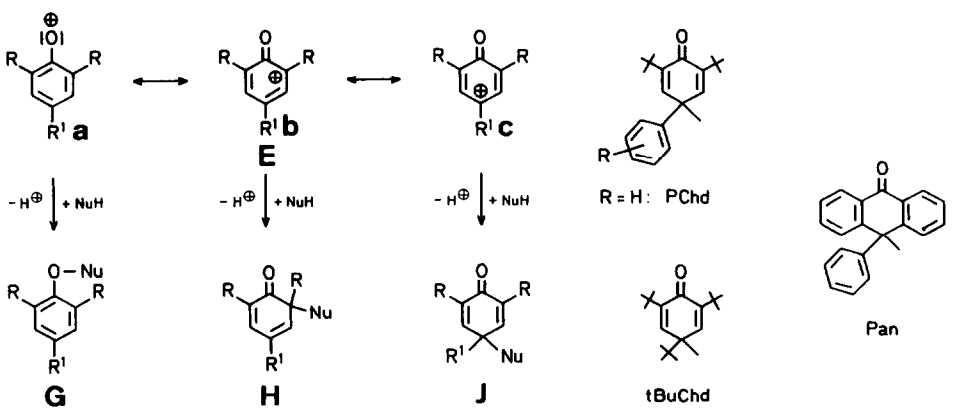
In the *absence of a base*, phenol **A** is oxidized at a "high potential" (ca. 1000 - 1400 mV#) in a one-electron transfer to give the cation-radical **B**. This deprotonates to the neutral phenoxyl **D**, which is further oxidized at the applied potential to the desired cation **E**. Alternatively, **B** and **D** may react in a homogeneous redox reaction to produce **A** and again **E**.

In the *presence of a base*, the corresponding phenolate **C** is anodically oxidized in two successive one-electron transfers to give the phenoxy radical **D** first (-300 to +300 mV), and, finally, the cation **E** (+700 to 800 mV). Oxidation at the "low potential" (-300 to +300 mV) is the preferential method to produce phenoxy radical **D** selectively. For the synthesis of phenoxenium ion **E**, however, oxidation of the phenol **A** under neutral or weakly acidic conditions (see above) proved to be the method of choice, since the cation **E**, although formed under basic conditions from **D**, is not generally stable towards the base.

In practice, we used two procedures (Scheme 2). The *direct technique*, denoted by I, involves direct anodic oxidation of the phenol (e.g. **1a,b**) in the presence of the nucleophile NuH. The resulting phenoxenium ion (e.g. **2a,b**) then reacts with the nucleophile (see below). The *indirect technique*, denoted by II, uses water as the nucleophile. Thereby, the *para*-quinol (e.g. **3a,b**) is first formed. Then, the nucleophile of choice is added together with an acid. Again, the phenoxenium ion is formed and adds to the new nucleophile, whereas water is removed by azeotropic distillation. Alternatively, the quinol (**3a,b**) may be isolated and treated with the nucleophile and acid separately. The indirect method has advantages over the direct one, if: (i) the nucleophile would be adsorbed or oxidized at the anode, (ii) the quinol is available by other methods, whereas the phenol does not exist. The latter is the case with 9-phenylanthranol, which exists only in the tautomeric anthrone form (**4**), which cannot be oxidized to the phenoxenium ion. Here, method II, starting with the available oxanthrone (**7**), is the method of choice. A direct anodic oxidation, however, is possible, if 9-phenylanthrone is first transformed into the silyl ether (**5**)[4], which can also be oxidized anodically to the phenoxenium ion (**6**) (pathway I'). The acids used for the indirect method II are $ZnCl_2$ for quinol **3a** and *para*-toluene sulfonic acid for **7**. The quinol **3b** cannot be used for pathway II, because the tBu group at the quinol center is not stable towards acids.

It should be mentioned that 2,6-di-*tert*-butyl-4-(4-dimethylaminophenyl)phenoxenium ion can be isolated as the perchlorate at room temperature[2]. It reacts only with very strong nucleophiles.

Scheme 3:



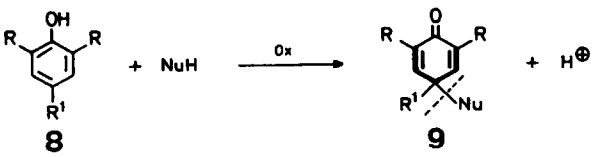
#All potentials in this publication refer to the (Ag/0.01 M Ag^+) electrode.

Phenoxenium ions, electrophiles par excellence

Phenoxenium ions should react with nucleophiles NuH (Scheme 3) to give the adducts **G** (aryloxy-substituted nucleophile), **H** (*ortho*-quinol derivative), or **J** (*para*-quinol derivative), depending on the nature of R, R^1 and Nu. In most cases, the *para*-adduct **J** dominates. Especially **H** and **J** are potential synthons for the synthesis of aromatics, quinones, quinol epoxides, oxepins, cyclohexenes, etc.[5]

Compounds **H** and **J** may also be regarded from another point-of-view: they are nucleophiles, in which the nucleophilic functions are protected by cyclohexadienyl groups. In this respect it may be useful to use abbreviations like PChd, tBuChd, Pan (Scheme 3).

Scheme 4:



8 **9**

R = CH_3, $C(CH_3)_3$, C_6H_5, Br

R^1 = CH_3, C_2H_5, $CH(CH_3)_2$, $C(CH_3)_3$, CH_2-CH_2-CN, $CH_2-COOCH_3$, $CH_2-CH_2-NH-CHO$, $C\equiv C-C_6H_5$, C_6H_5, 4-$H_3C-C_6H_4$, 4-MeO-C_6H_4, 4-$O_2N-C_6H_4$, 4-$Me_2N-C_6H_4$, Mesityl

NuH = HOH, ROH, ROOH, RCOOH, ArOH, $\diagdown C=N-OH$, H_2N-R, H_2N-CH_2-CN, $H_2N-CHR-COOR^1$, $H_2N-CO-NH_2$, H_2N-Ar, $\diagdown C=NH$, $H_2N-CO-R$, $Na^{\oplus}\,{}^{\ominus}CH(COOR)_2$

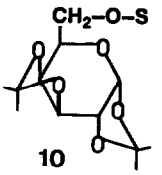
Scheme 4 shows the structural features of the reaction partners for the direct anodic oxidation (pathway I). Substituents R in the phenols were CH_3, $C(CH_3)_3$, C_6H_5, or Br, with a preponderance of the *tert*-butyl groups. The substituents R^1 comprised alkyl and aryl groups. As nucleophiles we tested oxygen[6] or nitrogen[7] functions and carbanions[2e]. The yields of quinol derivatives **9** are generally between 50 and 97%, if we use *undivided cells* (cathodic and anodic compartments are not separated by a diaphragm), potential control, solvents such as dichloromethane, acetonitrile or undiluted nucleophiles, and sodium perchlorate ($NaClO_4$), tetrabutylammonium perchlorate (Bu_4NClO_4) or tetrafluoroborate (Bu_4NBF_4) as supporting electrolytes. Reactions of anodically produced phenoxenium ions with O-nucleophiles and halogens have also been reported by Ronlan and Parker[8a]. A general discussion of the anodic oxidation of phenols is given in ref.[8b].

In the following, we present a few characteristic examples, restricting ourselves to HO-nucleophiles. The protection of HN-nucleophiles and the use of PChd protected amino acid derivatives for peptide synthesis has been reported elsewhere [7,9,10,11].

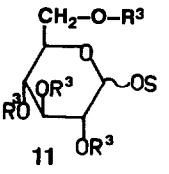
As we have shown earlier[6], the yields of alcohol adducts in the direct anodic oxidation (pathway I), starting with *tert*-butylated phenols **1** and **8** (Scheme 4; R = tBu; R^1 is the substituent in 4-position), decrease in passing from methanol to primary, secondary and tertiary alcohols, which reflects a steric effect.

The same graduation may be found for *sugar* OH-groups[12]. Let us consider the simplest case, where only one OH-group is free, using pyranoses as examples (Table 1). If the exocyclic primary OH is free, we can protect it as in other alcohols by method I or II (e.g. **10**). The yields are drastically reduced with increasing steric hindrance of the groups. The anomeric OH-group can also be protected by both methods (**11**), however, we observe some peculiarities: (i) tBuChd cannot be introduced, probably due to steric hindrance. (ii) The yields obtained by method I are much lower than those by method II. (iii) The substituents R^3 exert a special effect, regardless of the group to be introduced. Thus, the yields for tetra-acetyl substitution are always lower than those for tetra-benzoyl substitution.

Table 1. Yields of cyclohexadienyl protected pyranoses



10



11

S	Yield of 10[a] (%) I	II	S	R^3	Yield of 11[a,b] (%) I (α:β)	II	(α:β)
Pan	78	75	Pan	Me	-	60	(72:28)
PChd	-	50	PChd	Me	-	56	(59:41)
tBuChd	20	-	Pan	COMe	-	30[55]	(31:69)
			Pan	COC_6H_5	45 (0:100)	90	(59:41)
			PChd	COMe	14[46] (0:100)	33[66]	(0:100)
			PChd	COC_6H_5	-	70[82]	(0:100)

[a] Based on Pan, PChd, tBuPChd. [b] The yields in brackets refer to conversion of phenols or quinols.

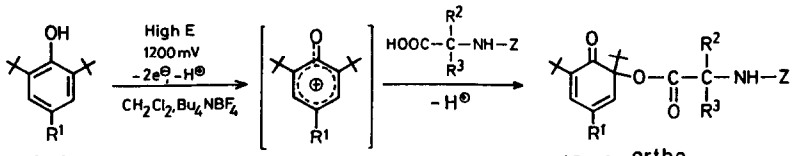
For the case of protection of the anomeric OH, the α:ß ratio is of high interest. For Pan we observe various ratios using method II. The direct electrochemical method, however, produces only the ß-isomer. For PChd, in the case of acetyl *and* benzoyl (however, not methyl) we observe regiospecifity in favor of the ß-isomer for both methods.

A selective deprotection of Pan and PChd from compounds **10** and **11** in the presence of isopropylidene and benzoyl groups can be achieved by cathodic reduction (Hg-pool, 0.05 M HCl, -1000 mV) or catalytic hydrogenation (Pd/charcoal) in 88 to 100% yield[12].

A selectivity of Pan, PChd, and tBuChd towards exocylic primary and secondary OH-groups as well as secondary ring OH- groups has been found in furanoses (e.g. furoglucose)[12]. Other examples for a successful OH-protection are disaccharides (maltose)[12], nucleosides (thymidine)[4,12] and amino acids with a side-chain OH-function (serine, threonine)[4].

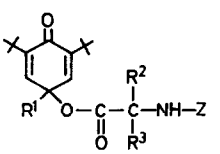
The protection of the carboxyl OH-groups in amino acids is demonstrated in Scheme 5. The anodic oxidation of the corresponding phenols **1a,b** at potentials of about +1100 mV leads again to the phenoxenium ion, which reacts with the Z-amino acid present to give the *ortho*- and *para*-adduct. Here, we have one of the rare cases, in which both quinolide systems, **12** and **13**, are formed simultaneously, the

Scheme 5:



1a,b **12a,b** ortho +

R^1	R^2	R^3	Yield (%) ortho	para
tBu	H	H	18	50
tBu	H	Me	11	74
tBu	Me	Me	1	75
Ph	H	H	66	3
Ph	H	Me	62	0
Ph	Me	Me	6	77

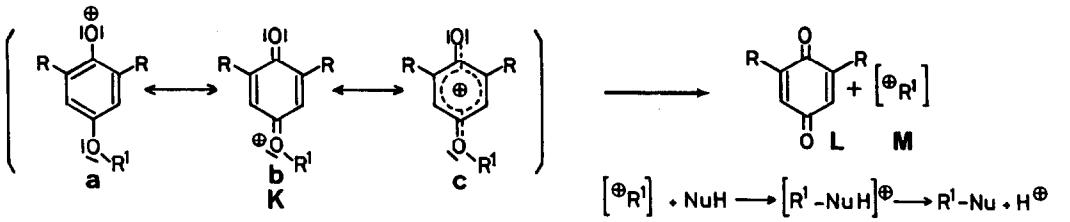


13a,b para

ortho:*para* ratio being dependent on R^1 of the starting phenol and on the steric surroundings of the C^{α} -atom of the amino acid (glycine, alanine and aminoisobutyric acid were tested).

In every case, the more alkyl groups are bound to C^{α}, the more *para*-adduct is formed, however, the effect is most impressive for R^1 = Ph. This means that the steric effect is larger in the *ortho*-quinol system than in the *para*-quinol system. These reactions can be performed only by the direct electrochemical method I and not *via* the acid catalyzed method II.

Scheme 6:



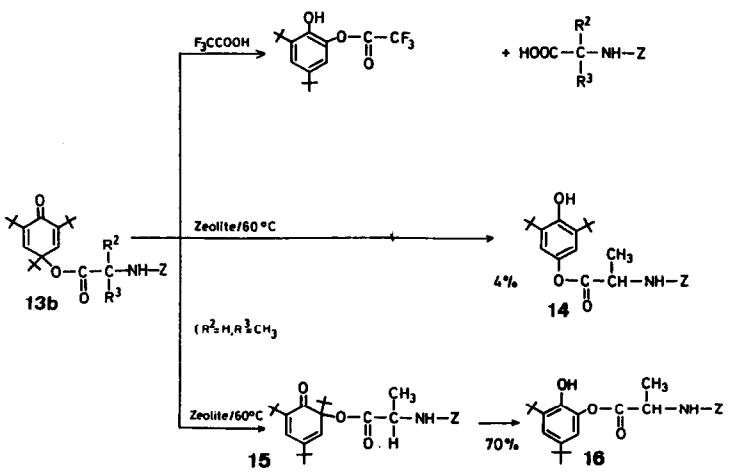
Acyl transfer from phenoxenium /quinoxonium ions

The underlying principle of this reaction is shown in Scheme 6. The phenols oxidized now bear acyloxy groups in *para*-position. The resulting phenoxenium ions **Ka** are again stabilized by resonance with carbenium ion structures (in the ring) (**c**) and, additionally, with an oxonium ion structure (**b**). On the other hand, in the oxonium ion structure (we may call it a *quinoxonium* ion) a quinone is preformed, and the R^1-O^+-bond is weakened. If it is cleaved, the quinone (**L**) and an acyl cation (**M**) should be formed. The latter would react with nucleophiles present to give the substituted nucleophiles and protons. The acyl cations must not necessarily be free, but have, presumably, incipient (S_N2-type) character.

Such reactions have been reported by Johnson et al.[13] for the acylation of alcohols and amines; however, no application to peptide syntheses has been mentioned.

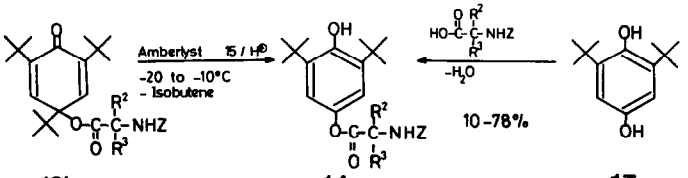
For this latter goal, we need hydroquinone esters **14** of protected amino acids (Schemes 7 and 8). One idea was to start with amino acids having a tBuChd protecting group at the C-terminal (**13b**), the synthesis of which has already been demonstrated (Scheme 5). We expected that in the tBuChd system the *para*-quinolide *tert*-butyl group would be eliminated by acid catalysis to produce the desired hydroquinone ester **14** similar to a dienone-phenol rearrangement.

Scheme 7:



With trifluoroacetic acid, however, the result was quite different: The *ortho-tert*-butyl group was eliminated and the amino acid part released (Scheme 7). As a result, we avoided the application of nucleophilic acids. Indeed, Lewis acids as $ZnCl_2$ or Zeolite Y can be used with partial success. In the case of alanine as the amino acid moiety (**13b**, R^2= H, R^3= CH_3) Zeolite Y at 60 °C produced about 4% of the desired hydroquinone ester **14** (R^2=H, R^3=CH_3). The main product (in 70% yield), however, was the corresponding pyrocatechol ester **16**. Since pyrocatechol esters are so-called "active esters" and couple directly with amino acid esters to dipeptides in high yields[10], we have found a useful way to transform a C-terminal protective group (i.e. tBuChd) into an active coupling agent. Obviously, **16** is formed, because at temperatures of about 60 °C the *para*-quinolide Chd system **13** equilibrates with the *ortho*-quinolide system (**15** = **12b**). Although the *para*-quinolide structure is totally predominant in the equilibrium, an *ortho*-quinolide *tert*-butyl group fragments more easily than a *para*-quinolide one. Therefore, finally, most of the molecules react *via* this pathway to **16**.

Scheme 8:

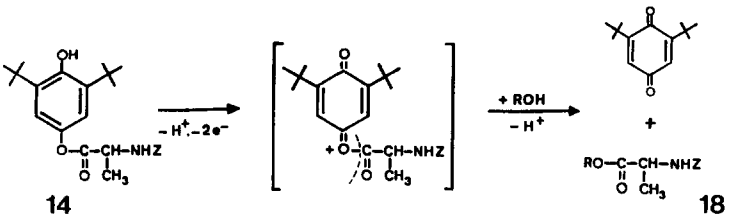


	R^2	R^3	Yield* para	Yield* ortho
Gly	H	H	65	10
Ala	H	Me	92	–
Aib	Me	Me	69	20 (-15 to -5°C)
			83	5 (-20 to -10°C)

* from **13b**

In order to get higher yields of the hydroquinone ester **14**, we had to lower the temperature, but Zeolite Y and other Lewis acids are unreactive at room temperature or below. Therefore, we tried proton acids at lower temperatures. Trifluoroacetic acid in dichloromethane at -20 °C to -30 °C, indeed, produces up to 33% of the desired hydroquinone ester.

Scheme 9:



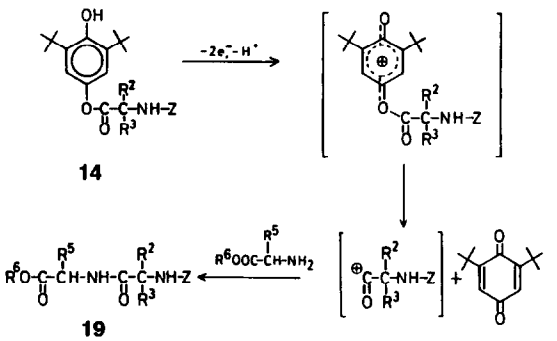
R	Yield (%)	R	Yield (%)
	52 a		59 c
	33 b		19 d

The catalyst of choice, however, is Amberlyst 15, a macro porous ion-exchange resin in its H^+-form. It works at -20 °C to -10 °C and produces the hydroquinone esters (**14**) in yields high enough for preparative purposes (Scheme 8). Alternatively, those esters can be prepared from the hydroquinone (**17**) and the Z-amino acids by direct condensation in yields of 10-78%.

The crucial steps are shown in Schemes 9 and 10. Anodic oxidation of **14** (R^2=H, R^3=CH_3) in the presence of some sugars in dichloromethane at potentials of about 1300 mV produces the *glycoamino-acid esters* **18** in medium yields *via* transfer of the (aminoalkyl)acyl group (Scheme 9). The acyl ester **18b** is formed selectively in the ß-conformation. The same behavior has been observed for the synthesis of thioglucoside esters and was explained in terms of a higher reactivity of the ß-anomer in the α/β equilibrium of the starting sugar in solution[14]. If the hydroquinone ester **14** is anodically oxidized under the same conditions, however, in the presence of amino acid esters, the corresponding *dipeptides* **19** are obtained from the intermediate quinoxonium ions, as expected (Scheme 10). Interestingly, *chemical* two-electron oxidants such as N-bromo-succinimide are also effective in inducing this coupling.

During the synthesis of **18** and **19** adsorption phenomena occur at the anode, which seem to be responsible for the long electrolysis times in the reaction with the carbohydrates. The yields decrease with increasing steric hindrance. This may be taken as indication that the intermediate species is not a free but an incipient acylium ion.

Scheme 10:



a Z-Ala-Gly-OEt : 73 % (Anode)
b Z-Ala-Ile-OMe: 50 % (Anode)
c Z Ala-Val-OMe: 44 % (Anode), 69 % (N-Bromosuccinimide)

The reaction with aminoacid esters presents a new type of peptide coupling, and, taking into account the synthesis of the intermediate hydroquinone esters **14** from tBuChd protected amino acids **13b** (Schemes 5 and 8), constitutes a successful example of transformation of a protecting group into an active reagent. Moreover, the synthetic power of aryloxenium ions and anodic oxidation is further demonstrated.

Experimental Section

General. Techniques of the anodic oxidations of phenols as well as the preparation and purification of the supporting electrolytes have been previously described[6]. PAR 373, AMEL 552, and Wenking potentiostats were used. Working and counter electrodes consisted of Pt/Ir (90/10) (Degussa). In the case of divided cells, a ceramic tube (Haldenwanger, ABS) was used as diaphragm. The reference electrode consisted of Ag/0.01 M Ag^+ in *acetonitrile*. All electrolyses were carried out under N_2-gas and cooling to 25° C. Spectroscopic measurements were performed with standard instruments. All NMR values refer to TMS (= 0 ppm) as internal standard. The assignments indicated by an asterisk may be exchanged. Further detailed procedures and spectroscopic data are available in the theses listed in the references, which can be ordered from the Central Library of the University of Tübingen, D-74 Tübingen, P.O. Box 2620, F.R.G.

Protection of OH-nucleophiles.

Carbohydrates.

1. **General procedure for anodic Pan protection:** Silylether **5**[4,12] (0.5 mmol), the carbohydrate (3 - 5 mmol), and 2,6-lutidine (ca. 1 mL) in CH_2Cl_2/0.1 M Et_4NBF_4 (150 mL) were electrolyzed in a divided cell at +600 to +700 mV. The cathodic compartment contained also CH_2Cl_2/0.1 M Et_4NBF_4 and lutidinium perchlorate (ca. 1 g). After complete disappearance of **5** (6-8 h), the mixture was washed two times with 5% citric acid (50 mL), once with 5% $NaHCO_3$ and water. After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue chromatographed or crystallized.

2. **1,2:3,4-Di-O-isopropylidene-6-O-Pan-'''-D-galactopyranose (10, S = Pan)**[4,12]: 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (1.22 g, 4.09 mmol), silylether **5** (185 mg, 0.48 mmol), 2,6-lutidine (800 mg, 7.48 mmol) were treated for 6 h according to the general procedure. Yield: 200 mg (78 %), mp 162 - 164 °C, after chromatography (silica gel 60, 70 - 230 mesh; gradients: petroleum ether bp 70 - 90 °C --> CH_2Cl_2 or petroleum ether --> ethyl acetate). IR (KBr): 1665, 1660 cm^{-1}. MS (FD): m/z = 528 (M^+). ^{13}C NMR ($CDCl_3$): 24.4, 24.9, 25.7, 26.1, 62.7, 67.1, 70.5, 70.7, 71.0, 78.1, 96.2, 108.5, 109.1, 125.5, 126.6, 126.9, 128.2, 128.7, 128.9, 131.6, 131.7, 133.6, 134.0, 144.6, 144.8, 146.3, 183.4. Anal. calcd. for $C_{32}H_{32}O_7$: C 72.71, H 6.10; found: C 72.83, H 6.27.

3. **PChd-2,3,4,6-tetra-O-acetyl-ß-D-glucopyranoside (11, R^3 = $COCH_3$, S = PChd):** 2,6-Di-*tert*-butyl-4-phenylphenol (**1a**) (280 mg, 1.0 mmol), 2,3,4,6-tetra-O-acetyl-ß-D-glucopyranose (348 mg, 1.0 mmol), and 2,6-lutidine (210 mg, 2.0 mmol) were oxidized in a divided cell at +1200 mV. The cathodic compartment contained the supporting electrolyte and lutidinium perchlorate (ca. 1.0 g). After 30 min again 1.0 mmol of **1a** was added and the electrolysis continued for 60 min. Work-up as in the general procedure for Pan-protection yielded 88 mg (46%, calculated for conversion) as a syrup (after chromatography). ^1H NMR ($CDCl_3$): 1.226 (9H, s, tBu), 1.234 (9H, s, tBu), 1.991 (3H, s, CH_3CO), 2.003 (3H, s, CH_3CO), 2.046 (3H, s, CH_3CO), 2.057 (3H, s, CH_3CO), 3.55 (1H, dt, J = 3.8, J = 2.2 Hz, H-5), 4.07 (1H, dd, J = 12.5, J = 2.2 Hz, H-6b), 4.23 (1H, dd, J = 12.5, J = 3.8 Hz, H-6a), 4.48 (1H, d, J = 7.8 Hz, H-1), 5.10-5.18 (3H, m, H-2,3,4), 6.27 (1H, d, J = 3.0 Hz, H-olefinic), 6.71 (1H, d, J = 3.0 Hz, H-olefinic), 7.25-7.32 (5H, m, H-phenyl). ^{13}C NMR ($CDCl_3$): 20.5, 20.6, 20.7 (4 CH_3-CO), 29.47 (tBu), 29.50 (tBu), 34.96 (tBu), 34.99 (tBu), 61.9 (C-6), 68.2 (C-4), 71.1 (C-2), 72.9 (C-3), 78.2 (C-quinol), 96.6 (C-1), 125.4, 128.0, 128.8, 138.7 (6 C-phenyl), 139.8, 141.0, 146.5, 148.2 (4 C-olefinic), 169.0, 169.3, 170.2, 170.5 (4 $COCH_3$), 186.2 (CO). The signals of chemically equivalent carbons of the cyclohexadienone system of the PChd group are doubled due to the magnetic nonequivalence as a result of chiral centers in the sugar moiety.

Amino acids.

1. **C-terminal tBuChd-protection. N-(benzyloxycarbonyl)alanine (1,3,5-tri-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-yl)ester (13b, R^2 = H, R^3 = CH_3):** N-(benzyloxycarbonyl)alanine (1.2 g, 5.4 mmol) and 2,6-lutidine (640 mg, 6 mmol) were dissolved in 0.1 M Et_4NBF_4/CH_2Cl_2 (80 mL) and transferred to the *anodic* compartment of a divided cell, which contained also molecular sieve for drying. Into the cathodic compartment lutidinium perchlorate (1.1 g, 5.6 mmol) and supporting electrolyte were added. After applying an anode potential of +1100 mV, a solution of 2,4,6-tri-*tert*-butylphenol **1b** (787 mg, 3.0 mmol) in CH_2Cl_2 was slowly dropped into the stirred solution of the anodic compartment (20-25 °C). The current did not exceed 100 mA. After 2.2 F/ mol had passed, the solvent was evaporated *in vacuo*. The residue was extracted several times with ether, the ether was evaporated and the extract chromatographed (silicia gel 60, $CHCl_3$/petroleum ether bp 60-90 °C) to give 3 fractions: phenol **1b**, 180 mg (23%); **13b** (R^2=H, R^3=CH_3), 800 mg (74%, calculated for conversion), mp 84-86 °C; N-(benzyloxycarbonyl)alanine 1,3,5-tri-*tert*-butyl-6-oxo-2,4-cyclohexadien-1-yl)ester **15**, 120 mg (11%, calculated for conversion), mp 75-76 °C.

Physical data of **13b** (R^2 = H, R^3 = CH_3): 2% D-Ala (hydrolysis: 24 h, 110 °C, 6N HCl). IR (KBr): 3355, 2960, 1743, 1702, 1669, 1648, 1530 cm^{-1}. MS (FD), m/z= 483 (M^+), 967 $(2M+H)^+$. ^1H NMR ($CDCl_3$): 0.94 (9H, s, tBu), 1.20 (18H, s, 2 tBu), 1.45 (3H, d, J = 7 Hz, CH_3-Ala), 4.40 (1H, quint, J = 7 Hz, CH-Ala), 5.08 (2H, s, CH_2-Z), 5.29 (1H, d, J = 7 Hz, NH), 6.37 (1H, d, J = 2.7 Hz, H-2,6), 6.45 (1H, d, J = 2.6 Hz, H-2,6), 7.28-7.33 (5H , m, Phenyl-Z). ^{13}C NMR ($CDCl_3$): 18.64 (CH_3-Ala), 25.38 (tBu), 29.25 (2tBu), 34.88 (tBu), 34.93 (tBu), 40.82 (tBu), 49.85 (CH-Ala), 66.75 (CH_2-Z), 82.55 (C-1, tBuChd), 127.95 (Z), 128.04 (Z), 128.39 (Z), 136.18 (Z), 137.48 (C-2,6, tBuChd), 137.96 (C-2,6, tBuChd), 147.55 (C-3,5, tBuChd), 147.90 (C-3,5, tBuChd), 155.50 (CO-Z), 171.06 (CO-Ala), 186.27 (C-4, tBuChd). Anal. calcd. for $C_{29}H_{41}NO_5$: C 72.02, H 8.55, N 2.90; found: C 72.59, H 8.83, N 2.79.

Physical data of **15**: 2.1 % D-Ala (hydrolysis: 2 h, 110 °C, 6 N HCl). IR (KBr): 3334, 2960, 1725, 1678, 1654, 1525 cm^{-1}. MS (FD): m/z = 483 (M^+). ^1H NMR: ($CDCl_3$): 0.91 (9H, s, tBu), 1.12 (9H, s, tBu), 1.20 (9H, s, tBu), 1.43 (3H, d, J = 7 Hz, CH_3-Ala), 4.43 (1H, quint, J = 7 Hz, CH-Ala), 5.09 (2H, s, CH_2-Z), 5.32 (1H, d, J = 7 Hz, NH), 5.74 (1H, s, broad, H-2,4), 6.82 (1H, d, J = 2.5 Hz, H-2,4) 7.27 - 7.37 (5H, m, Phenyl-Z). ^{13}C NMR ($CDCl_3$): 18.62 (CH_3-Ala), 24.54 (tBu), 28.76 (tBu), 29.31 (tBu), 34.51 (tBu), 34.84 (tBu), 40.14 (tBu), 49.84 (CH-Ala), 66.75 (CH_2-Z), 86.59 (C-1, Chd), 127.99 (Z), 128.02 (Z), 128.43 (Z), 134.75 (C-2,4, Chd), 136.36 (Z), 144.21 (C-3,5, Chd), 145.67 (C-3,5, Chd), 155.51 (CO-Z), 170.60 (CO-Ala), 198.26 (C-6, Chd). Anal. calcd. for $C_{29}H_{41}NO_5$: C 72.02, H 8.55, N 2.90; found: C 72.31, H 8.64, N 2.67.

2. **Aminoacid (3,5-di-*tert*-butyl-4-hydroxyphenyl)ester 14.**

2a. **Fragmentation of tBuChd. N-(benzyloxycarbonyl)alanine (3,5-di-*tert*-butyl-4-hydroxyphenyl)ester 14 (R^2 = H, R^3 = CH_3):** N-(benzyloxycarbonyl)alanine (1,3,5-tri-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-yl)ester (**13b**, R^2=H, R^3=CH_3) (210 mg,

0.43 mmol) was dissolved in toluene (25 mL) and stirred with Amberlyst-15®(2.0 g) for 12 h at -18 to -5 °C. Afterwards, the ion exchange resin was filtered and washed with toluene and acetone. The combined filtrates were evaporated and the residue was treated with petroleum ether bp 60-90 °C to give colorless **14**. Yield: 170 mg (92%), mp 142-145 °C. 1.1% D-Alanine (hydrolysis: 24 h, 110 °C, 6N HCl). IR (KBr): 3620, 3340, 2960, 1765, 1690, 1530 cm^{-1}. MS (FD): m/z = 427 (M^+), 222. ^1H NMR ($CDCl_3$): 1.40 (18H, s, 2 tBu), 1.57 (3H, d, J=7 Hz, CH_3-Ala), 4.62 (1H, quint, J=7 Hz, CH-Ala), 5.12 (2H, s, CH_2-Z), 5.16 (1H, s, OH), 5.40 (1H, d, J= 8 Hz, NH), 6.85 (2H, s, H-2,6), 7.30-7.35 (5H, m, Phenyl-Z). ^{13}C NMR ($CDCl_3$): 18.83 (CH_3-Ala), 30.05 (2tBu), 34.42 (2tBu), 49.80 (CH-Ala), 66.97 (CH_2-Z), 117.42 (C-2,6), 128.06, 128.14, 128.50, 136.21 (Phenyl-Z), 137.01 (C-3,5), 143.03 (C-1), 151.56 (C-4), 155.57 (CO-Z), 172.08 (CO-Ala). Anal. calcd. for $C_{25}H_{33}NO_5$: C 70.23, H 7.78, N 3.28; found: C 70.32, H 7.61, N 3.26.

2b. **Condensation with hydroquinone. 14 (R^2=H, R^3=CH_3)**: N-(benzyloxycarbonyl)alanine (5.0 g, 22.5 mmol) and 2,6-di-*tert*-butylhydroquinone (5.0 g, 22.5 mmol) in CH_2Cl_2 (60 mL) were stirred with 1 N dicyclohexylcarbodiimide (DCC)/CH_2Cl_2 (28 mL) for 1 h at 0 °C, then for 12 h at 25 °C, and, finally, for 2 h at 50 °C. The reaction was interrupted by addition of citric acid/water (5 %) (5 mL). After filtration, the solution was washed several times with $NaHCO_3$/water (5 %), dried and evaporated to a small volume. Addition of petroleum ether bp 60 - 90 °C precipitated colorless **14** (R^2=H, R^3=CH_3). Yield: 7.3 g (76 %), mp 143 °C, identical to a sample prepared by method 2a.

Glycoaminoacid esters *via* acyl group transfer.

1. **General procedure:** Z-alanine hydroquinone ester **14** (R^2=H, R^3=CH_3) (1.0-1.2 mmol), the corresponding carbohydrate (1.8 - 3.3 equivalents) and 2,6-lutidine (excess over **14**) in dry CH_2Cl_2/0.1 M Et_4NBF_4 (150 mL) were anodically oxidized in a divided cell at +1300 to +1350 mV. The cathodic compartment contained the same supporting electrolyte and lutidinium perchlorate (ca. 1 g). The electrolysis was terminated after disappearance of **14** (thin-layer chromatography). 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.

2. **1,2:3,4-Di-O-isopropylidene-6-O-(Z-Ala)-α-D-galacto-pyranose (18a)**: **14** (R^2=H, R^3=CH_3) (500 mg, 1.17 mmol), 1,2:3,4-di-O-isopropylidene-α-D-galactose (1.0 g, 3.8 mmol), 48 h at 1300 mV. Yield: 282 mg (52%), oil. IR (film): 3340, 1730-1720, 1520 cm^{-1}. MS (FD): m/z = 466 (M^++1), 465 (M^+), 450, 407, 91. ^1H NMR ($CDCl_3$): 1.30 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.42 (3H, d, J=7.4 Hz, CH_3-Ala), 1.43 (3H, s, CH_3), 1.48 (3H, s, CH_3), 3.99 (1H, t, J=6 Hz, H-5), 4.19 (1H, d, J=7.9 Hz, H-4), 4.28 - 4.34 (3H, m, H-2, H-6), 4.40 (1H, quint, J=7.4 Hz, CH-Ala), 4.59 (1H, dd, J=7.9, J=2.5 Hz, H-3), 5.06 (1H, d, J=12.5 Hz, CH_2-Z), 5.10 (1H, d, J=12.5 Hz, CH_2-Z), 5.31 (1H, d, broad, J=7.4 Hz, NH), 5.50 (1H, d, J=5 Hz, H-1) 7.28 - 7.41 (5H, m, Phenyl-Z). ^{13}C NMR ($CDCl_3$): 18.8 (CH_3-Ala), 24.4 (CH_3), 24.9 (CH_3), 25.93 (CH_3), 26.0 (CH_3), 49.7 (CH-Ala), 64.2 (C-6), 66.0 (C-5), 66.9 (CH_2-Z), 70.4 (C-2,3), 70.7 (C-2,3), 71.0 (C-4), 96.2 (C-1), 108.8 [*C*(CH_3)$_2$], 109.7 [*C*(CH_3)$_2$], 128.0 (Z), 128.1 (Z), 128.5 (Z), 136.3 (Phenyl-Z), 155.5 (CO-Z), 172.7 (CO-Ala).

3. **2,3,4,6-Tetra-O-benzoyl-1-O-(Z-Ala)-ß-D-glucopyranose (18b)**: **14** (R^2=H, R^3=CH_3) (490 mg, 1.15 mmol), 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranose (1.26 g, 2.11 mmol), 20 h at 1320 mV. Yield: 300 mg (33 %); mp 88 - 90 °C, from methanol. IR (KBr): 3390, 1768, 1740 - 1710, 1600, 1510 cm^{-1}. MS (FD): m/z = 802 (M^++1), 801 (M^+), 579, 473, 105. ^1H NMR ($CDCl_3$): 1.35 (3H, d, J=7.1 Hz , CH_3-Ala), 4.29 (1H, ddd, J=9.8, J=4.8, J=2.7 Hz, H-5), 4.36 (1H, quint, J=7.1 Hz, CH-Ala), 4.47 (1H, dd, J=12.3, J=4.8 Hz, H-6b), 4.61 (1H, dd, J=12.3, J=2.7 Hz, H-6a), 4.95 (1H, d, J=12.2 Hz, CH_2-Z), 5.00 (1H, d, J=12.2 Hz, CH_2-Z), 5.21 (1H, d, J=7.6 Hz, NH), 5.68 (1H, dd, J=9.6, J=8.1 Hz, H-2), 5.74 (1H, t, J=9.6 Hz, H-3 or H-4), 5.95 (1H, t, J=9.6 Hz, H-3 or H-4), 6.09 (1H, d, J=8.1 Hz, H-1), 7.25 - 7.56 (17H, m, Phenyl-Z, Benzoyl), 7.81 - 8.02 (8H, 4d, J=8.0 Hz, Benzoyl). ^{13}C NMR ($CDCl_3$): 18.2 (CH_3-Ala), 49.6 (CH-Ala), 62.6 (C-6), 66.9 (CH_2-Z), 69.1 (C-4*), 70.8 (C-2*), 72.7 (C-5*), 73.3 (C-3*), 92.8 (C-1), 128.0, 128.1, 128.29, 128.34, 128.4, 128.6, 129.5, 129.72, 129.74, 129.8, 129.9, 133.1, 133.3, 133.5 (Phenyl-Z, Benzoyl), 136.1 (Phenyl-Z), 155.3 (CO-Z), 165.0, 165.6, 166.0 (CO-Benzoyl), 171.1 (CO-Ala).

4. **3-O-Benzyl-1,2-O-isopropylidene-6-O-(Z-Ala)-α-D-glucofuranose (18c)**: **14** (R^2=H, R^3=CH_3) (450 mg, 1.05 mmol), 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (1.07 g, 3.45 mmol), 65 h at 1300 mV. Yield: 320 mg (59 %), oil. IR (Film): 3340, 3060, 3040, 2980, 2935, 1750 - 1690, 1520 cm^{-1}. MS (FD): m/z = 516 (M^+), 1030 (M^++M). ^1H NMR ($CDCl_3$): 1.32 (3H, s, CH_3), 1.42 (3H, d, J=7.2 Hz, CH_3-Ala), 1.47 (3H, s, CH_3), 2.64 (1H, d, J=6.4 Hz, OH, H-->D exchange), 4.09 - 4.45 (6H, m, CH-Ala, H-3, H-4, H-5, H-6a, H-6b), 4.56 (1H, d, J=11.8 Hz, CH_2-Benzyl), 4.60 (1H, d, J=3.8 Hz, H-2), 4.70 (1H, d, J=11.8 Hz, CH_2-Benzyl), 5.04 (1H, d, J=11.8 Hz, CH_2-Z), 5.11 (1H, d, J=11.8 Hz, CH_2-Z), 5.44 (1H, d, broad, J=7.3 Hz, NH), 5.92 (1H, d, J=3.8 Hz, H-1), 7.26 - 7.36 (10H, m, Phenyl-Z, Benzyl) . ^{13}C NMR ($CDCl_3$): 18.5 (CH_3-Ala), 26.4 (CH_3), 26.9 (CH_3), 49.9 (CH-Ala), 67.0 (C-5), 67.1 (CH_2-Z), 68.3 (C-6), 72.3 (CH_2-Benzyl), 79.5 (C-4), 81.6 (C-2*), 82.2 (C-3*), 105.3 (C-1), 112.0 [*C*(CH_3)$_2$], 127.9, 128.1, 128.2, 128.27, 128.30, 128.6, 128.8 (Phenyl-Z, Phenyl-Benzyl), 136.2 (Phenyl-Z), 137.2 (Phenyl-Benzyl), 155.8 (CO-Z), 173.1 (CO-Ala). Anal. calcd. for $C_{27}H_{33}NO_9$: C 62.90, H 6.45, N 2.72; found: C 62.13, H 6.82, N 2.64.

5. **1,2:5,6-Di-O-isopropylidene-3-O-(Z-Ala)-α-D-glucofuranose (18d)**: **14** (R^2=H, R^3=CH_3) (440 mg, 1.03 mmol), 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (850 mg, 3.27 mmol), 43 h at 1350 mV. Yield: 91 mg (19 %), oil. IR (KBr): 3395, 2985, 2960, 2880, 1750, 1715, 1520 cm^{-1}. ^1H NMR ($CDCl_3$): 1.27 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.40 (3H, d, J=7.2 Hz, CH_3-Ala), 1.49 (3H, s, CH_3), 3.98 (1H, dd, J=8.6, J=4.3 Hz, H-6b), 4.05 (1H, dd, J=8.6, J=5.4 Hz, H-6a), 4.13 -

4.20 (2H, m, H-2, H-4), 4.38 - 4.43 (2H, m, CH-Ala, H-5), 5.06 (1H, d, J=12.1 Hz, CH_2-Z), 5.11 (1H, d, J=12.1 Hz, CH_2-Z), 5.26 (1H, d, J cannot be determined due to overlap, NH), 5.27 (1H, d, J=2.3 Hz, H-3), 5.79 (1H, d, J=3.5 Hz, H-1), 7.27 - 7.39 (5H, m, Phenyl-Z). ^{13}C NMR ($CDCl_3$): 18.5 (CH_3-Ala), 25.2 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 49.8 (CH-Ala), 67.0 (CH_2-Z), 67.3 (C-6), 72.4 (C-5), 76.9 (C-3), 79.8 (C-4), 83.2 (C-2), 105.1 (C-1), 109.4 [$C(CH_3)_2$], 112.4 [$C(CH_3)_2$], 128.1, 128.3, 128.6, 136.1 (Phenyl-Z), 155.5 (CO-Z), 171.4 (CO-Ala).

Dipeptides *via* acyl group transfer.

1. **Z-Ala-Gly-OEt (19a)**: N-(benzyloxycarbonyl)alanine (3,5-di-*tert*-butyl-4-hydroxyphenyl)ester **14** (R^2 = H, R^3 = CH_3) (600 mg, 1.4 mmol) and glycine ethylester (464 mg, 4.5 mmol) were dissolved in 0.1 M Et_4NBF_4/CH_2Cl_2 (200 mL) and electrolyzed at +1400 mV in the anodic compartment of a divided cell. This compartment contained also molecular sieve for drying. In the cathodic compartment only supporting electrolyte was present. After the current had dropped to a constant value of about 20 mA, the reaction was terminated and the solvent evaporated *in vacuo*. The solid residue was extracted several times with petroleum ether (bp 60-90 °C) and finally with ether. The petroleum ether fractions gave 250 mg (42%) of unreacted **14**. The ethereal extract was washed twice with 5% citric acid, water, and 5% $NaHCO_3$, respectively. After drying (Na_2SO_4) and concentrating the solution, the dipeptide was precipitated with petroleum ether. Yield: 185 mg, 73% (calculated for conversion); mp 97-98 °C (lit.[15] mp 98-99 °C). R_f : 0.56. 1.2 % D-alanine. IR (KBr): 3300, 1768, 1695, 1653, 1535 cm^{-1}. MS (FD): m/z= 308 (M^+). ^1H NMR ($CDCl_3$): 1.26 (3H, t, J=7 Hz, OCH_2CH_3), 1.38 (3H, d, J=7 Hz, CH_3-Ala), 3.99 (2H, d, J=5 Hz, CH_2-Gly), 4.19 (2H, q, J=7 Hz, OCH_2-CH_3), 4.30 (1H, m, CH-Ala), 5.09 (2H, s, CH_2-Z), 5.33 (1H, d, J= 8 Hz, NH-Ala), 6.59 (1H, s, broad, NH-Gly), 7.32 - 7.33 (5H, m, Phenyl-Z).

2. **Z-Ala-Val-OMe (19c)**: **14b** (R^2=H, R^3=CH_3) (428 mg, 1.0 mmol), lutidine (214 mg, 2.0 mmol), valine methylester (131 mg, 1.0 mmol) in 1 M Et_4NBF_4/CH_2Cl_2 were electrolyzed in an undivided cell at constant current (10 mA). The cathodic compartment (with the same supporting electrolyte) contained also lutidinium tetrafluoroborate (390 mg, 2.0 mmol). During the electrolysis a solution of additional valine methylester (197 mg, 1.5 mmol) in CH_2Cl_2 was added dropwise. The reaction was terminated after 2.4 F/mol had passed. The solvent was evaporated *in vacuo* and the residue extracted with ethyl acetate. The extract was washed twice with 5% citric acid, water, and 5% $NaHCO_3$, respectively. After drying (Na_2SO_4), the ethyl acetate was evaporated. The residue was chromatographed on silica gel 60 with petroleum ether bp 60 - 90 °C/ethyl acetate (1:1, with increasing polarity) to give **19c** (115 mg, 44 %, calculated on conversion of **14**), mp 81-82 °C (from ether/petroleum ether) (lit.[16] mp 82 °C). ^{13}C NMR ($CDCl_3$): 17.68, 18.31, 18.82 (CH_3-Ala, CH_3-Val), 31.19 (C-ß-Val), 50.58 (CH-Ala), 52.03 (OCH_3), 57.21 (C-α-Val), 67.01 (CH_2-Z), 127.98, 128.10, 128.47, 136.27 (Phenyl-Z), 155.99 (CO-Z), 171.16, 172.10 (CO).

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