

Oxidation of Partially Protected Carbohydrates at the Nickel Hydroxide Electrode¹

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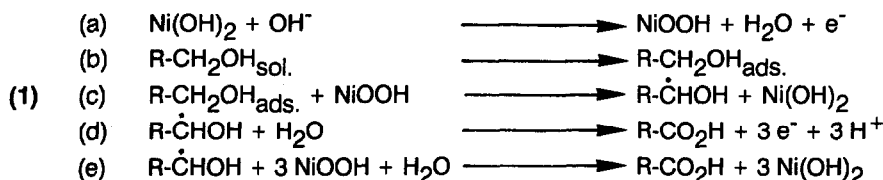
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Abstract: Primary hydroxy groups in pyranoses are oxidized in excellent yields to the corresponding carboxylic acids. In furanose **3** the yield of acid is only moderate. Secondary hydroxy groups are inert, aside from lactols. The different reactivity of secondary and primary hydroxy groups allows the chemoselective oxidation of **8** and **10**.

1. Introduction

The electrode can be used in organic synthesis as a versatile reagent for carbon-carbon bond forming reactions² and functional group interconversions³. Electrochemical conversions can be achieved by direct electron transfer between the electrode and the substrate or by indirect electrolysis, whereby the electrons are transferred by an electrocatalyst (mediator)⁴. Indirect electrolysis can lead to a better selectivity due to the specific interaction of the mediator with the substrate. However, low turnovers and the need to separate the mediator from the product are possible disadvantages. The nickel hydroxide electrode⁵ is fairly free from these disadvantages.

The following mechanism for oxidations at the nickel hydroxide electrode has been proposed by Vertes^{6,7}, Pletcher^{8,9} and Robertson¹⁰ (eq. 1).

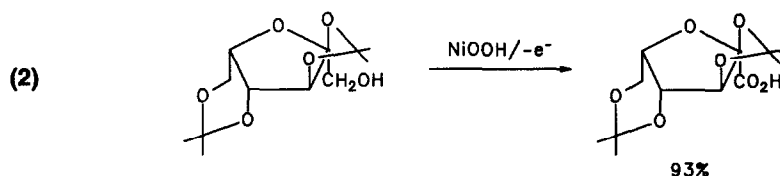


At a nickel metal surface in alkaline aqueous medium a thin film of nickel(II) hydroxide is formed. At +0.63 V (NHE) the film is oxidized to nickel(III) oxide hydroxide (eq. 1a). After adsorption of the substrate at this surface (eq. 1b) hydrogen abstraction at the α -carbon of the substrate occurs in the rate determining step (eq. 1c). The intermediate radical is then further oxidized either directly (eq. 1d) or indirectly (eq. 1e) to the product.

Up to now the nickel hydroxide electrode has been applied in a fair number of conversions, namely in oxidation of primary alcohols to carboxylic acids¹¹ or aldehydes¹², of secondary alcohols to

ketones¹¹, in the selective oxidation of steroid alcohols¹¹, in the cleavage of vicinal diols¹³, in the oxidation of γ -lactones to γ -ketocarboxylic acids¹⁴, of primary amines to nitriles¹⁵, of 2,6-di-*t*-butylphenol to 2,2',6,6'-tetra-*t*-butyldiphenoquinone^{5,16}, of 2-(benzylideneamino)-phenols to 2-phenyl-oxazols^{5,16}, of 1,1-dialkyl hydrazines to tetraalkyltetrazenes^{5,16}. The nickel hydroxide electrode resembles in its applications and selectivity the chemical oxidant nickel peroxide¹⁷. However, the nickel hydroxide electrode has advantages compared to nickel peroxide: it is less expensive, the electrolysis is simple to perform and enables an easy scale-up, nickel(II)salts, that need a careful waste treatment, are not formed as by-products.

The oxidation of carbohydrates at the nickel hydroxide electrode has been addressed in only few papers. Seiler and Robertson^{18,19} developed a technical process, which allows the oxidation of 2,3 : 4,6-di-*O*-isopropylidene-*L*-sorbose to protected gulonic acid. The acid, an intermediate of the vitamin C-synthesis, can be produced in a scale of 2 tons per day at the nickel hydroxide electrode (eq. 2).



Pletcher²⁰ has reported the selective oxidation of methyl- α -D-glucopyranoside at the primary 6-OH group, to the corresponding aldehyde in 60 % yield.

2. Results

In order to estimate the scope for the oxidation of partially protected carbohydrates at the nickel hydroxide electrode, the compounds **1** - **10** have been prepared and electrolyzed. The electrolyses were carried out in a "swiss-roll" - cell^{18,19} with electrolyte circulation (Fig. 1).

In this cell a steel net as cathode, polypropylene fabric as separator and a nickel net as anode are rolled on a nickel rod which serves as current drain. The roll is inserted into a steel tube which functions as electrolysis cell and as current feeder. This cell has several advantages:^{18,19} a) due to the large electrode area, the electrolyses can be conducted at a high current, although the nickel hydroxide electrode allows only low current densities, b) the small electrode distance, the high electrolyte conductivity and the large electrode area allow to maintain a low cell voltage (1.5 to 2.1 V). Before each electrolysis the anode is activated by deposition of nickel oxide hydroxide layers^{5,11} at the anode surface.

2.1 Oxidation of primary hydroxyl groups in **1**, **2**, **3**

The carbohydrates **1**, **2**, **3** have been oxidized at 20° C and pH 8.5 - 14 (Table 1).

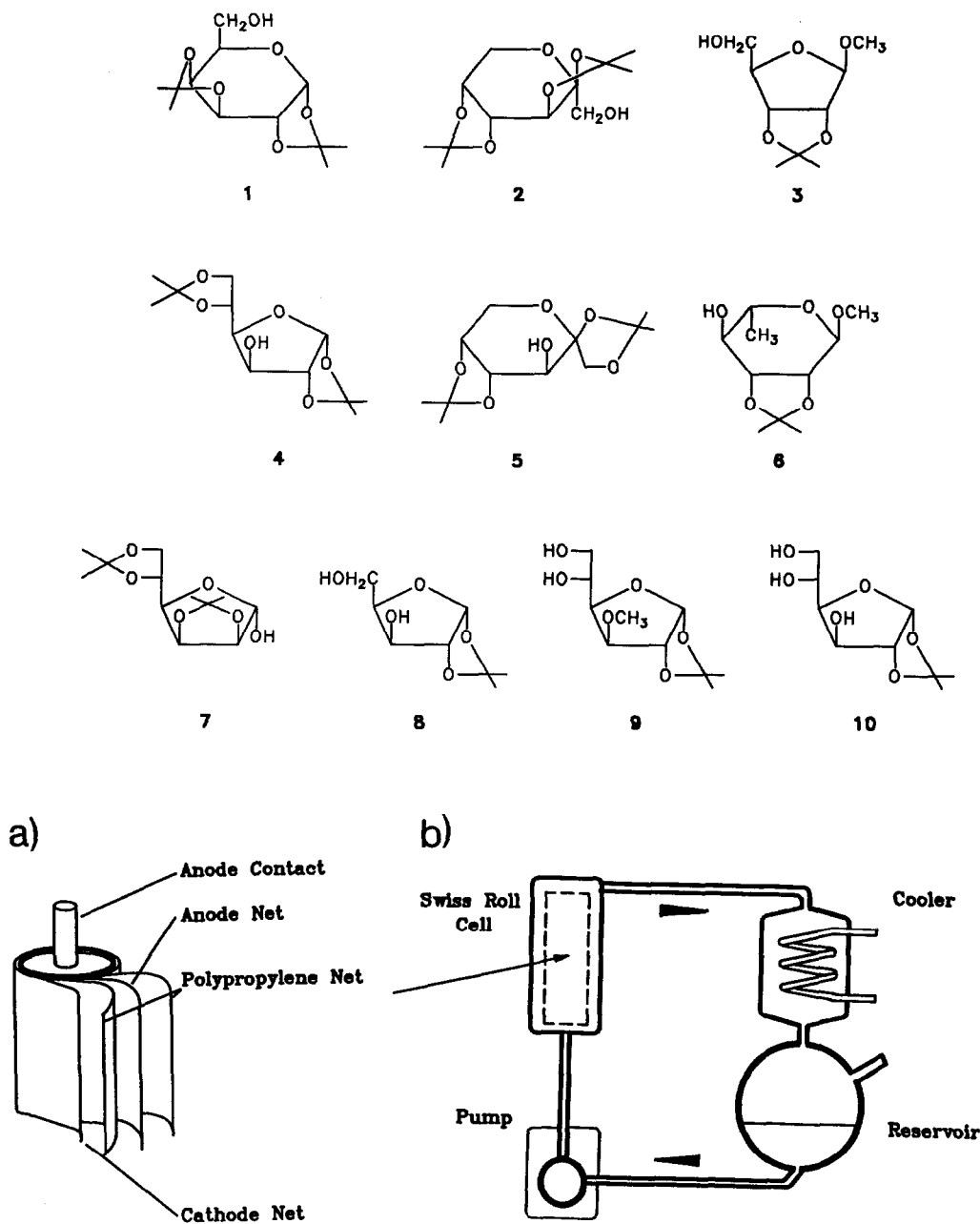
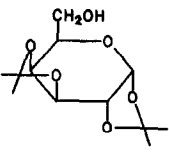
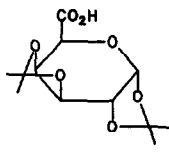
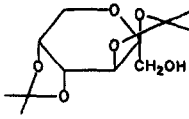
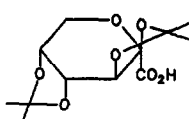
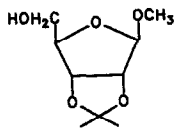
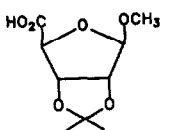


Fig. 1 "Swiss roll" cell with electrolyte circulation (electrode surface: 1500 cm^2 per electrode).

a) arrangements of the electrodes; b) circulation cell

Tab. 1: Oxidation of primary hydroxyl groups in **1**, **2**, **3**

Nr.	Starting compound	Product	Electrolysis-conditions ^a	Current [F/mole]	Yield ^{b)}	
					S	P
1			A	6.0	2%	93%
2			A	6.0	4%	92%
3			A	8.5	3%	54% ^{C)}
4			B	6.0	26%	50%
5			B	10.0	10%	56%
6	3	13	C	6.0	59%	32%
7			D	6.0	92%	7%

a: Current controlled electrolysis at 0.4 A, 20° C;

A: 0.4 M aqueous potassium hydroxide (pH 14),

B: 0.4 M aqueous potassium carbonate (pH 12),

C: 0.2 M aqueous potassium carbonate and 0.2 M potassium hydrogen carbonate (pH 10),

D: 0.4 M aqueous potassium hydrogen carbonate (pH 8.5)

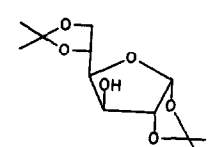
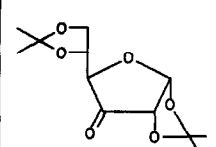
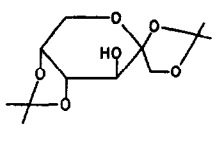
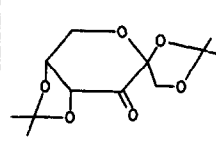
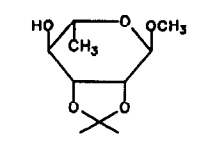
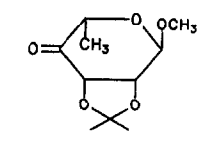
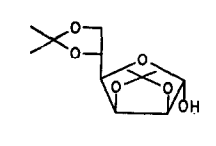
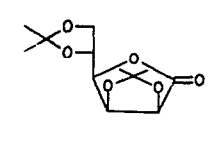
b: Isolated yield, S = starting material, P = product.

As Table 1 shows **1** and **2** are converted to **11** and **12** in high yields. Amounts of 13 g **1** or **2** can be oxidized without problems to afford after consumption of 6 Faraday/mole 92 % **11** or 94 % **12**, respectively. For the oxidation of **3**, however, the maximum yield of 56 % **13** is only moderate. **3** and **13**

2.2. Oxidation of the secondary hydroxyl groups in carbohydrates 4 - 7

The carbohydrates 4 - 7 were oxidized at pH 12 and 20° C (Tab. 3).

Tab. 3: Oxidation of secondary hydroxyl groups in 4 - 7

Nr.	Starting compound	Product	Electrolysis conditions ^{a)}	current [F/mole]	Yield	
					S	P
1	 4	 21	A	5.3	(94%:6%)	
2	 5	 22	A	4.0	(98%:2%)	
3	 6	 23	B	4.0	(95%:2%)	
4	 7	 24	A	6.2	4% ^{c)} 80%	

a: Current controlled electrolysis at 20° C in 0.4 M potassium carbonate

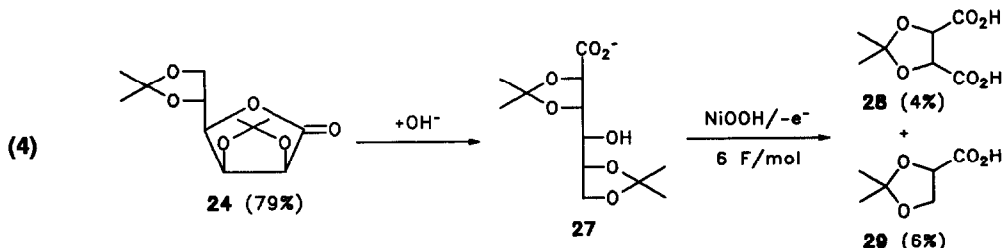
A: "Swiss-Roll"-cell (Fig. 1); B: Analogous "swiss-roll"-cell, but 500 cm² electrode area per electrode.

b: Relative amounts (glc) of starting material and product in the isolated mixture.

c: Isolated yield, S = starting material, P = product.

Whilst the uloses **21** - **23** were only detected in traces by glc, the lactone **24** could be isolated in good yield. Apparently secondary hydroxy groups in the pyranose and furanose rings of **4** - **6** are fairly inert against oxidation at the nickel hydroxide electrode, if they are not additionally activated by a second oxygen as in lactol **7**. A model reaction shows, that the low reactivity of the hydroxy group in **4** - **6** is to

a major part due to steric shielding by the isopropylidene protecting group. 3-Hydroxytetrahydrofuran (**25**) can be oxidized, although only in moderate yield (26 %), to tetrahydrofuran-3-one (**26**). On the other hand lactone **24** is nearly inert against further oxidation at pH 14. After a current passage of 6 Faraday/mole 79 % **24** can be reisolated and only 4 % **28** and 6 % **29** were found as products (eq. 4). In alkaline medium γ -lactones are normally oxidized - after ring opening to the γ -hydroxy-carboxylate, here **27** - in nearly quantitative yield to the corresponding γ -ketoacids¹⁴.



The different reactivities of secondary and primary OH-groups suggested that chemoselective oxidations of the polyols **8** - **10** should be possible.

2.3 Oxidation of the polyols **8** - **10**

The compounds **8** - **10** were oxidized at 20° C and different pH-values (Tab. 4).

8 is indeed oxidized chemoselectively at the primary OH-group to afford furanuronic acid **30** in satisfactory yields. In the glucofuranoses **9** and **10** oxidation occurs with cleavage of the vicinal diol¹³. Tables 4 and 5 show that anodic oxidation can favourably compete with chemical oxidation with respect to yield and chemoselectivity.

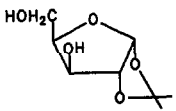
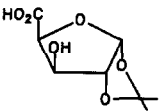
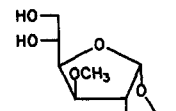
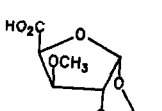
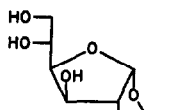
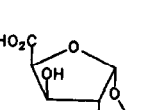
3. Summary

The unprotected primary hydroxy group in pyranoses can be oxidized in excellent yields to the corresponding carboxylic acid. In furanose **3** the oxidation of the primary OH group leads only to moderate yields of furanuronic acid, probably due to a partial oxidative degradation of the acid. Secondary hydroxy groups are inert against oxidation, if activated as in lactols they are oxidized in high yield to the lactone. The different reactivity of primary and secondary OH-groups allows the chemoselective oxidation of polyols as **8** and **10** to the acid **30**. The nickel hydroxide electrode can satisfactorily compete with respect to yield and chemoselectivity with chemical oxidants such as KMnO_4 , RuO_4 or AgCO_3 on celite.

4. Experimental section

4.1. Equipment: Optical rotations were measured with Polarimeter 241 Perkin-Elmer. - Glc - column 1: quartz capillary (30 m, 0.32 mm i.d.) 0.25 μm FS-OV 225; column 2: quartz capillary (50 m, 0.32 mm i.d.) 0.25 μm FS-HP 1; column 3: quartz capillary (25 m, 0.32 i.d.) 0.25 μm FS-OV1. - Current source:

Tab. 4: Oxidation of the polyols **8** - **10**

Nr.	Starting compound	Product	Electrolysis-conditions ^{a)}	current [F/mole]	Yield ^{b)}	
					S	P
1	 8	 30	A	8.0	24%	52%
2	 9	 31	B	8.0	8%	52% ^{c)}
3	 10	 30	B	8.0	10%	53%

a: Current controlled electrolysis at 0.4 A and 20° C; A: 0.4 M aqueous potassium carbonate;

B: 0.4 M aqueous potassium hydroxide. - b: Isolated yield, S = starting material, P = product. -

c: Crude product converted to methyl ester with diazomethane and purified by flash chromatography.

Tab. 5: Oxidation of **8** and **10** with chemical oxidizing agents

Starting compound	Product	Oxidizing agent	Yield (%)	Lit.
8	30	KMnO ₄ /OH ⁻	40 ^a	26
8	30	RuO ₄ /JO ₄ ⁻	23 ^b	24
10	30	KMnO ₄ /OH ⁻	60	27
10	30	AgCO ₃ /Celite	68 ^b	25

a: Isolated as potassium salt; - b: Isolated as methyl ester.

Galvanostat LD 50/10 GB Zentro-Elektrik. - Electrode materials: nickel net (mesh - width: 0.16 mm, thickness: 1 mm) C.M. Pieper, Hagen; steel-net (refined steel, mesh-width: 0.16 mm, thickness 0.1 mm) Dürerer Metalltuch Schoeller Hoesch, Düren; insulator: polypropylene fabric (mesh - width: 1 mm, thickness: 0.3 mm) Reichelt, Chemietechnik, Heidelberg.

4.2. Starting materials and reference compounds

1,2:3,4-Di-O-isopropylidene- α -galactopyranose (**1**) was prepared from D-galactose²⁸, 2,3:4,5-di-O-isopropylidene- β -D-fructopyranose (**2**) from D-fructose²⁹, methyl-2,3-O-isopropylidene- β -D-ribofuranoside (**3**) from D-ribose³⁰, 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose (**4**) from D-glucose²⁸, 1,2:4,5-di-O-isopropylidene- β -D-fructopyranose (**5**) from D-fructose²⁹, 2,3:5,6-di-O-isopropylidene- α -D-mannofuranose (**7**) from D-mannose²⁸, 1,2-O-isopropylidene- α -D-xylofuranose (**8**) from D-xylose³¹, 1,2-O-isopropylidene-3-O-methyl- α -D-glucofuranose (**9**) from **4**^{32,33}, 1,2-O-isopropylidene- α -D-glucofuranose (**10**) from **4**³³.

The reference compound 1,2:5,6-di-O-isopropylidene- α -D-ribo-hexafurano-3-ulose (**21**) was obtained by ruthenium tetroxide oxidation in a two phase system from **4**³⁴, similarly 1,2:4,5-di-O-isopropylidene- β -D-erythro-2,3-hexodiulo-2,6-pyranose (**22**) was prepared from **5**, and methyl-6-desoxy-2,3-O-isopropylidene- α -L-lyxo-hexopyrano-4-ulose (**23**) from **6**, *rac*-2-tetrahydropyranocarboxylic acid (**15**) was obtained by permanganate oxidation from *rac*-2-hydroxymethyltetrahydropyran³⁵.

4.3. General procedure for the electrolyses

The carbohydrate, dissolved in 500 ml electrolyte, is electrolyzed in the "swiss-roll"-cell with an activated anode at controlled current. After consumption of the appropriate number of Faraday/mole the electrolyte is removed and the cell rinsed with 500 ml water : ethyl acetate (1 : 1, v/v). The separated aqueous phase is combined with the electrolyte, acidified to pH 8-10, reduced in volume to 100 - 200 ml at the rotary evaporator, saturated with sodium chloride and the unreacted starting compound extracted with ethyl acetate (6 x 100 ml). Subsequently the aqueous solution is acidified to pH 4 and then extracted with ethyl acetate (6 x 100 ml), whereby the acidity is continuously increased to pH 2. The ethyl acetate solution is dried (MgSO₄), the solvent rotaevaporated and the residual product dried at 0.01 Torr. The purity of the acid is checked after esterification with diazomethane by glc (columns 1-3).

4.4. Electrolyses of 1 - 3, 7 - 10

2.60 g (10 mmol) **1** were converted in 0.4 M aqueous potassium hydroxide at 20° C and 0.4 A after consumption of 6 F/mole into 2.56 g (93 %) 1,2:3,4-di-O-isopropylidene- α -D-galactopyranuronic acid (**11**); $[\alpha]_{\text{D}}^{20} = -87.6^{\circ}$ (c = 1.1 in CHCl₃), mp. 155-156° C, lit.³⁶ 155.5 - 156.5° C.

2.60 g (10 mmol) **2** were electrolyzed as **1** to afford 2.52 g (92 %) 2,3:4,5-di-O-isopropylidene-2-oxo-D-gluconic acid (**12**); $[\alpha]_{\text{D}}^{20} = -47.1^{\circ}$ (c = 1.0 in CHCl₃), mp. 97 - 98° C, lit.²⁴ 97 - 98° C.

2.04 g (10 mmol) **3** in 0.4 M potassium carbonate solution were electrolyzed as **1** to afford 0.53 g (26 %) **3** and 1.09 g (50 %) methyl-2,3-O-isopropylidene- β -D-ribofuranosiduronic acid (**13**); $[\alpha]_{\text{D}}^{20} = -69.4^{\circ}$ (c = 1.4 in CHCl₃), mp. 132 - 134° C, lit.³⁷ 134° C.

2.60 g (10 mmol) **7** were electrolyzed as **3** (different from the general procedure **7** was dissolved in 50 ml t-butanol and before work-up 5 g tartaric acid were added as buffer to the electrolyte) to afford 0.11 g (4 %) **7** and 2.07 g (80 %) 2,3:5,6-di-O-isopropylidene-D-allono-1,4-lactone (**24**); $[\alpha]_{\text{D}}^{20} = +51.3^{\circ}$ (c = 1.4 in CHCl₃), mp. 124 - 125° C, lit.³⁸ 126° C.

1.90 g (10 mmol) **8** were electrolyzed as **3** (current consumption: 8 F/mole) to afford 0.46 g (24 %) **8** and 1.06 g (52 %) 1,2-O-isopropylidene- α -D-xylofuranuronic acid (**30**) $[\alpha]_{\text{D}}^{20} = -32.6^{\circ}$ C (c = 2.1 in acetone). - ¹H-NMR (hexadeuteroacetone): δ (ppm) 1.27 (s, 3H), 1.42 (s, 3H), 4.41 (d, J = 3.3 Hz, 1H), 4.55 (d, J = 3.5 Hz, 1H), 4.69 (d, J = 3.3 Hz, 1H), 5.96 (d, J = 3.5 Hz, 1H).

2.22 g (9.48 mmol) **9** were electrolyzed as **1** (current consumption: 8 F/mole) to afford after conver-

sion of the extracted acid with diazomethane to the methylester and its isolation by flash-chromatography (dichloromethane : ether, 5 : 1, v/v) 0.19 g (8 %) **9** and 1.14 g (52 %) methyl 1,2-O-isopropylidene-3-O-methyl- α -D-xylofuranuronoate (**31**); $[\alpha]_D^{20} = -42.4^\circ$ ($c = 1.1$ in acetone); $^1\text{H-NMR}$ (CDCl_3): δ (ppm) 1.31 (s, 3H), 1.46 (s, 3H), 3.37 (s, 3H), 3.78 (s, 3H), 4.01 (d, $J = 3.7$ Hz, 1H), 4.58 (d, $J = 3.7$ Hz, 1H), 4.79 (d, $J = 3.7$ Hz, 1H), 6.03 (d, $J = 3.7$ Hz, 1H). - MS: m/z (%) 217(41), 185(9), 173(22).

2.20 g (10 mmol) **10** were electrolyzed as **1** (different from the general procedure the acidified aqueous phase is additionally extracted with tetrahydrofuran : ethyl acetate, 7 : 3, v/v) **1** to afford after work-up 0.21 g (10 %) **10** and 1.09 g (53 %) **30**.

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