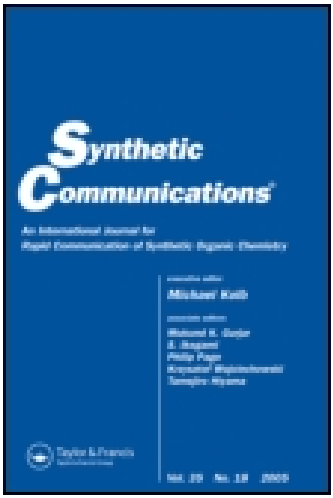

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Preparation of ω-Hydroxy Acids by Reduction of α,ω-Methylene Diesters with $NaBH_4$

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PREPARATION OF ω-HYDROXY ACIDS BY REDUCTION OF α,ω-METHYLENE DIESTERS WITH $NaBH_4$

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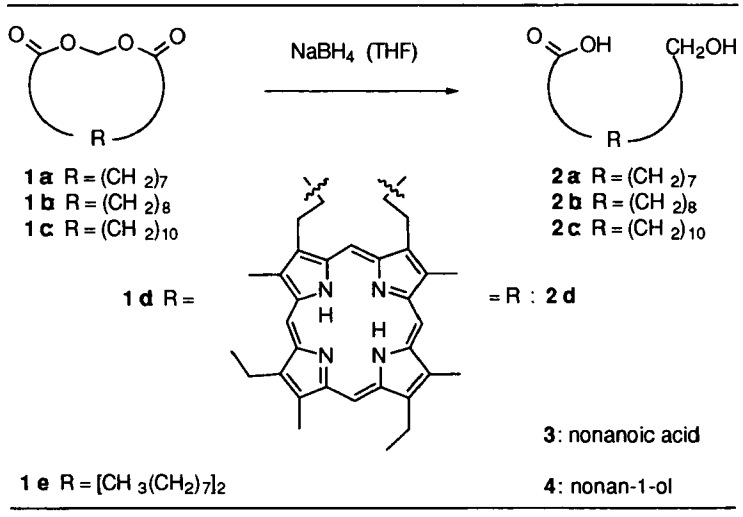
Abstract. By reaction of the dicesium salts of long chain dicarboxylic acids (C atoms > 9) with methylene iodide the corresponding methylene diesters were prepared. These acylals, by reduction with $NaBH_4$ in THF, give the corresponding ω-hydroxy acids.

$NaBH_4$ is sufficiently unreactive with carboxylic esters to permit selective reductions.[1] However, in the presence of electron-withdrawing groups in the α C atom of the alcohol residue the reduction of the ester carbonyl group to primary alcohol can occur. In the case of the methylene diesters of carboxylic acids, owing to the presence of one additional oxygen atom, such an activation effect should be expected. Cyclic acylals of long chain dicarboxylic acids (see Formula Scheme) can be obtained by the reaction of the cesium carboxylates with CH_2I_2 in high dilution conditions. Negative results were obtained in the preparation of the methylene diesters of glutaric and adipic acid through this dicesium salts route.

Treatment of these acylals with NaBH4 in THF results in the selective reduction to the hydroxy acid. Table 1 show the yields of the isolated reaction products for some methylene diester reductions. The cyclic methylene diesters must be purified by recrystallization from the cyclic acylal dimer, which is also obtained in relative high yields. The efficiency of this recrystallization depends on the type of dicarboxylic acid. In the case of azelaic acid, pure acylal **1a** could be obtained. In the case of **1b** and **1c** the used acylal contains dimer in amounts about 3±1 %. In this respect, the dimeric acylal, assuming a 100 % selectivity in the reduction to hydroxy acid, also results in the formation of dicarboxylic acid and diol (stadistical ratio, hydroxy acid: dicarboxylic acid: diol 2:1:1).



In addition to the results of the Table 1 other experimental conditions were tested. NaBH4 reduction of the methylene diesters in the presence of protic solvents (as co-solvents of THF) resulted in the extensive solvolysis of the acylal; to esters in the presence of alcohols and to carboxylic salts in the presence of water. However, reduction in anhydrous conditions results in a reaction rate that is too low for preparative purposes. The stability of the acylals in the experimental conditions corresponding to Table 1 are quite good; *e.*

Table 1. Reduction with NaBH4 (THF) of acylals

Entry	Acylal	Exp.cond.[a]		%				
		h	°C	Acylal[b]	Dicarboxylic acid	Diol[c]	Hydroxy acid	Selectivity[d]
1	**1a**	120	23	<1	<3	2±1	92±3	92±3
2		6	65	<1	<3	6±2	87±3	87±3
3	**1b**	120	23	<1	<3	10±1	79±2	86±2
4		6	65	<1	<3	10±1	82±6	90±6
5	**1c**	120	23	<1	<3	12±3	82±4	86±4
6		6	65	13±7	11±3	6±1	66±4	90±7
7		9	65	<1	9+3	11±2	77+2	90±2
8		6	65[e]	<1	6±3	8±2	85±2	93±2
9	**1d**	6	65	<1	14±3	2±1	71±2	83+2
10	**1e**	120	23	<1	----	66±2[f]	31±2[g]	62±4
11		6	65	5±3	----	49±1f	35±1g	74±2

a) 5:1 Molar ratio $NaBH_4$/acylal. **b)** Detection limit 1 %. **c)** Detection limit 3 %. **d)** Isolated hydroxy acid in respect to that expected for complete selective reduction (corrected for unreacted and hydrolyzed acylal and for the presence of dimeric acylal; see text. **e)** 10:1 Molar ratio $NaBH_4$/acylal. **f)** Yield of **3**. **g)** Yield of **4**.

g. blank experiments without $NaBH_4$ on **1e** at 65°C, with or without NaH, showed an acylal decomposition of 3±1%.

Selectivity in the reduction is higher for the cyclic (entries 1-9) than for the linear methylene diester **1e** (entries 10 and 11). This suggests that the reduction of one of the carbonyl groups is followed by the breaking of the methylene bridge giving a carboxylic acid group (stable to $NaBH_4$) and an aldehyde, which is further reduced to the primary alcohol.

No significant differences in the reduction selectivity could be detected between the reaction at room temperature and refluxing THF (65°C). However, for some dicarboxylic acids the hydrolysis of their acylals was higher in the experiments at 65°C than in the experiments at room temperature (detected through the presence of dicarboxylic acid; see entries 6-8 compared to entry 5). In the experiments at 65°C for some acylals (**1c**, **1e**) unreacted acylal was detected. This can be avoided by increasing the reaction time or better by increasing the ratio $NaBH_4$/acylal; compare entry 6 with entries 7 and 8).

As an example of the application of this route to ω-hydroxy acids entry 9 show the preparation for the first time of the hydroxy acids **2d**. Hydroxy acids similar to **2d** could be interesting substrates to study the interaction porphyrin-protein in hemoproteins. The lower yield of **2d** compared to the yields of **2a** and **2b** is due to the hydrolysis of the acylal. In this case the low solubility of the mesoporphyrin IX derivative (**1d**) in THF does not allow the reduction at room temperature.

Experimental

Compounds **1a**- had been previously described.[2a] They were obtained from the cesium salts of the carboxylic acids by reaction with CH_2I_2 as it has been previously described.[2]

3,8-Diethyl-13,17-(3,7-dioxo-4,6-dioxananomethylen)-2,7,12,18-tetramethylporphyrin (mesoporphyrin IX methylene diester) (1d): Obtained by high dilution reaction of mesoporphyrin IX dicesium salts with CH_2I_2

in DMSO following the procedure previously described for similar bile pigment derivatives.[3] 56 % yield from 350 mg of mesoporphyrin IX. R_f = 0.80 (9:1 $CHCl_3/CH_3OH$); IR (KBr) 1750 cm^{-1}; UV ($CHCl_3$) λ_{max} 400 (ε 149000), 498 (ε 13000), 531 (ε 8000), 567 (ε 6000), 620 (ε 4000): (DMSO) λ_{max} 398 (ε 145000), 496 (ε 13000), 529 (e 8000), 565 (ε 6000), 619 (ε 4000); ^1H NMR (300 mHz, $CDCl_3$) δ 10.06 (s, 2H), 10.05 (s, 1H), 10.01 (s, 1H), 5.54 (s, 2H), 4.42 and 3.25 (m, 4H, ABCD system), 4.05 (q, J =7.5 Hz, 4H), 3.63 (s, 3H), 3.61 (s, 3H), 3.60 (s, 3H), 3.58 (s, 3H), 1.85 (t, 6H), -3.87 (s, 2H); HRFABMS calcd for $C_{35}H_{38}O_4N_4$ *m/z* 578.289 (M^+), found 578.292.

Methylene dinonanoate (1e): 64 % yield from 1 g nonanoic acid. Liquid; Single peak at several chromatographic conditions (TLC, HPLC). IR (film) 1759 cm^{-1}; ^1H NMR (200 mHz, $CDCl_3$) δ 5.75 (s, 2H), 2.35 (t, 4H), 1.63 (m, 4H), 1.27 (s, 20H), 0.88 (t, 3H).

General Reduction Procedure. To a solution of the acylal (≈ 150 mg) in 2 ml THF was added a suspension of $NaBH_4$ (5:1 mols excess) in 5 ml THF. The reductions were performed under stirring at room temperature (5 days) or at reflux (6 h). The reaction mixture was added to 100 ml CH_2Cl_2 and extracted with 2.5% Na_2CO_3 solution (2 x 100 ml). The organic layer was washed with 100 ml water, dried (Na_2 SO_4) and evaporated *in vacuo*. This residue affords the dialcohol in the case of the cyclic derivatives, or the aliphatic alcohol in the case of the non-cyclic acylals. The water extract was acidified with 1 M HCl to pH 1.5 and was extracted with CH_2Cl_2 (5 x 75 ml). The organic extract was washed with 100 ml water, dried (Na_2 SO_4) and evaporated *in vacuo*. This residue affords the hydroxyacid. In some experiments, unreacted acylal was detected in the first organic extract or dicarboxylic acid in the second organic extract (see Table 1). In these cases the yields of Table 1 are corrected from the ratios inferred from the ^1H-NMR analysis of the sample. The entries of Table 2 correspond at least to the mean of two experiments.

Samples were purified by chromatography through a small silica gel column.

The following products were identified according their ^1H NMR and the previous data reported in the literature; nonan-1-ol,[4] nonane-1,10-diol,[5] decane-1,10-diol,[6] dodecane-1,12-diol,[7] 10-hydroxynonanoic acid,[8] 10-hydroxydecanoic acid,[9] 12-hydroxydodecanoic,[10] 3,8-diethyl-13,17-di(1-hydroxypropan-3-yl)-2,7,12,18-tetramethylporphyrin (diol of mesoporphyrin IX).[11]

3,8-Diethyl-13-(3-hydroxypropan-1-yl)-17-(2-carboxyethyl)-2,7,12, 18-tetramethylporphyrin and 3,8-diethyl-17(3-hydroxypropan-1-yl)-13-(2-carboxyethyl)-2,7,12,18-tetramethylporphyrin (hydroxyacid of mesoporphyrin IX) (2d).

The mixture of hydroxyacids obtained following the general procedure was purified by column chromatography on silica gel (1:1, acetone/CH_2Cl_2). 70 % yield from 100 mg **1d**. R_f = 0.22 (9:1 CHCl3/CH_3OH); R_f = 0.54 (10:2:0.2 CHCl3/CH_3OH/CH_3COOH); IR (KBr) 1710 cm^{-1}; UV (CH_3OH) λ_{max} 392 (ε 153000), 496 (ε 12000), 529 (e 8500), 566 (ε 5500), 618 (ε 4000); ^1H NMR (300 mHz, $CDCl_3$) δ 10.27-10.16 (several s, 4H), 4.33 (b t, J≈7, 2H,), 4.15 (b t, J≈7, 2H), 4.10 (m, 4H), 3.77 (t, J=6.4, 2H), 3.64-3.61 (12H), 3.19 (t, J=7.2, 2H), 2.41 (b quint, J≈7, 2H), 1.81 (t, J=7.2, 3H): COSY 4.33-3.19, 4.15-2.41, 4.10-1.81, 3.77-2.41. HRFABMS calcd for $C_{34}H_{41}O_4N_4$ $(M+1)^+$ *m/z* 553.3178, found 553.3191.

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