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# Synthesis and Properties of Natural Occurring α-Hydroxyaldehydes

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**Key words:** 2-Hydroxyheptanal, 2-acetoxyheptanal, 2-acetoxyhexadecanal, 9-hydroxy-10-oxo-decanoic acid, 9-acetoxy-10-oxo-decanoic acid, 1-butylamino-2-hydroxyheptane.

**Abstract:** A synthesis for aliphatic α-acetoxyaldehydes **18** is presented. These were converted to free aldehydes **9** by action of hog liver esterase. Aliphatic α-hydroxyaldehydes, recently recognized to be produced in the course of lipid-peroxidation of linoleic and other unsaturated fatty acids, are only stable for short time in solution. They react with amines to give Schiff bases. These are instable, but can be trapped after reduction with $NaBH_4$ to the corresponding amines. Since α-hydroxyaldehydes are produced in the case of lipid peroxidation and were found to stimulate oxidative stress, Schiff base formation might be a physiological important process. α-Hydroxyaldehydes form under physiological conditions mercaptals by reaction with thiols.

## INTRODUCTION

α-Hydroxyaldehydes occur in all biological materials in form of sugars. The aldehyde function of α-hydroxyaldehydes has a much higher carbonyl activity than in unsubstituted ones due to the inductive effect of the adjacent C-OH group. Consequently the aldehyde group of sugars generate hemiacetals containing five- or six-membered rings in an intramolecular reaction with a sterically adjacent OH group. Contrary α-hydroxyaldehydes lacking additional hydroxy groups easily produce dimers in intramolecular reactions.[1-3]

Recently we were able to trap long and short chain α-hydroxyaldehydes lacking additional functional groups in biological material by derivatisation.[4] Later we demonstrated that these aldehydes are generated from two different sources: Short chain α-hydroxyaldehydes are produced by decomposition of bis-dihydroperoxides or hydroxyhydroperoxides of unsaturated fatty acids.[5,6] Long chain α-hydroxyaldehydes are obtained by hydrolysis of plasmalogen epoxides derived from plasmalogens via epoxidation with monohydroperoxides of unsaturated

acids, linoleic acid hydroperoxides (LOOH's)[7,8] or by enzymes which are activated in a cell damaging process. Thus the generation of all hydroxyaldehydes has the same origin - "oxidative stress" - caused by damage of cells:[9] Cell damage obviously activates dormant lipoxygenases which in turn produce LOOH's. Therefore α-hydroxyaldehyde formation is the consequence of many biological processes which may lead to chronic and spontaneous diseases.[9]

Aldehydes were shown to depress in vitro protein synthesis in healthy tissue.[10] In trapped form as α-acetoxyenol ethers they were found to act preferentially against tumor tissue.[10] α-Hydroxyaldehydes, resp. their precursor compounds, increase the oxygen burst[11] in physiological amounts. Consequently production of α-hydroxyaldehydes via LOOH's may introduce a cascade of reactions probably directed against uncontrolled cell growth.[12]

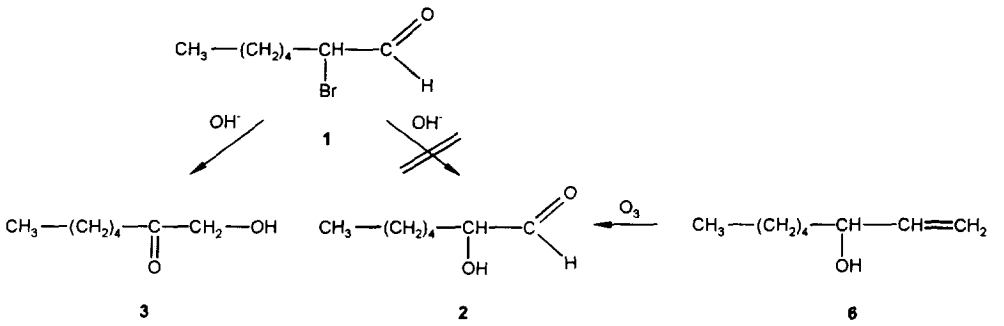
Thus the investigation of the action of α-hydroxyaldehydes with biological material is a challenging problem. This requires that α-hydroxyaldehydes are available by synthesis. We compare in this paper several methods described in the literature for their synthesis and discuss the reasons, why the described methods do not give satisfying results in the synthesis of aliphatic α-hydroxyaldehydes.

We report on an applicable method for the preparation of solutions containing α-hydroxyaldehydes by enzymatic hydrolysis of their acetates. We also describe the synthesis of α-hydroxyaldehydes with a carbomethoxy group at the other chain end.

Finally we present a method to trap Schiff bases produced with these aldehydes.

**Synthesis of Aliphatic α-Hydroxyaldehydes**

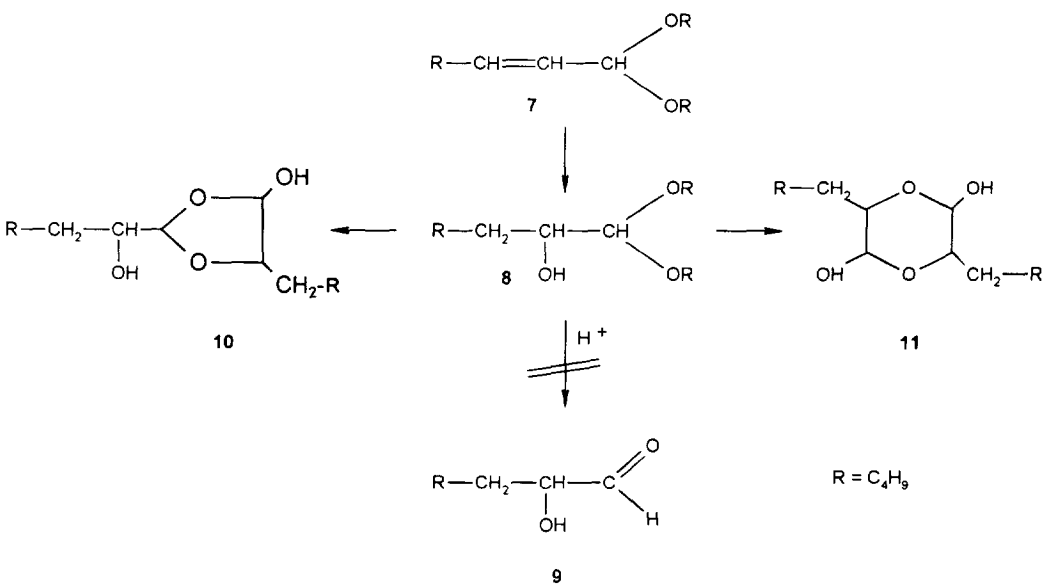
The synthesis of the main α-hydroxyaldehyde 2-hydroxyheptanal (**2**) found after oxidative stress was already claimed to be achieved by reaction of 2-bromo-heptanal (**1**) with 1N KOH.[13] When this reaction was repeated we were only able to detect the isomeric 1-hydroxy-2-heptanone (**3**) in form of 1-trimethylsilyloxy-2-heptanone (**4**) after addition of MSTFA. The rearrangement of α-hydroxyaldehydes to 1-hydroxy-2-heptanone (**3**) is inevitable under alkaline conditions.[14]



**Scheme 1**: Attempt to prepare α-hydroxyaldehydes **9** by hydrolysis of α-bromoaldehydes **1**

Alternatively **2** was reported to have been prepared by ozonolysis of 1-octen-3-ol (**6**) in acetic acid by decomposition of the produced ozonide with zinc dust.[15] We found that this reaction occurs by production of a great number of byproducts, the α-hydroxyaldehyde can be detected in minor amounts only. Complications by ozonolysis of vinylalcohols were reported in the literature.[16]

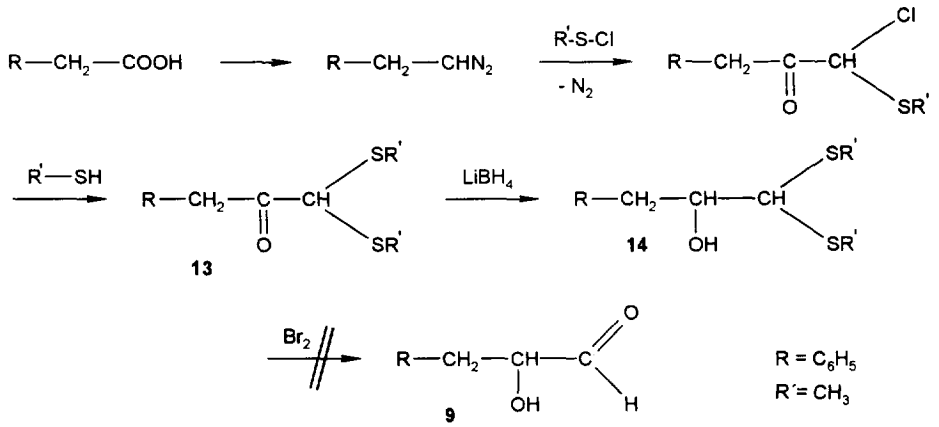
Thus synthesis of free hydroxyaldehydes cannot be achieved by hydrolysis of α-halogenaldehydes. Their generation by ozonolysis is cumbersome. Consequently liberation of the free aldehydes from protected derivatives seems a better strategy for their preparation.



**Scheme 2**: Attempt to prepare α-hydroxyaldehydes **9** from α-hydroxyacetals **8**

Several methods have been described to produce acetals of α-hydroxyaldehydes **8**, starting from α,ß-unsaturated aldehyde acetals **7**.[2,17-20] The liberation of the aldehydic group requires acidic conditions. Even under mild acidic condition[1-3] α-hydroxyaldehydes **9** with an aliphatic chain react by dimerisation to isomeric dimers of type **10** and **11**,[17] only those with an aromatic residue are more stable and can be obtained in pure form (scheme 2). The reported yields of α-hydroxyaldehydes refer in most cases on analysis of reaction products obtained after reaction with carbonyl reagents. Since these react also with dimers measured yields do not indicate the actual amount of hydroxyaldehydes in a solution.

Preparation of α-hydroxyaldehydes was also reported starting from acids which were converted to α-oxomercaptals **13**, reduced by $LiBH_4$ to α-hydroxymercaptals **14** and oxidation ($Br_2$) of the latter[21] (scheme 3). Decomposition of the mercaptals in the presence of $NaHCO_3$ as suggested[22] causes - if applied to aliphatic α-hydroxymercaptals - enolisation to α-hydroxyketones e.g. **5**. Similar difficulties are encountered if the aldehyde group is prepared from other 1,1-disubstituted derivatives.[13,14,18,23,24,25]




**Scheme 3**: Attempt to prepare α-hydroxyaldehydes **9** from α-hydroxythioacetals **14**

Partial reduction of cyanohydrins, a method for preparation of aromatic α-hydroxyaldehydes, requires acidic conditions and therefore also provides dimers.[3]

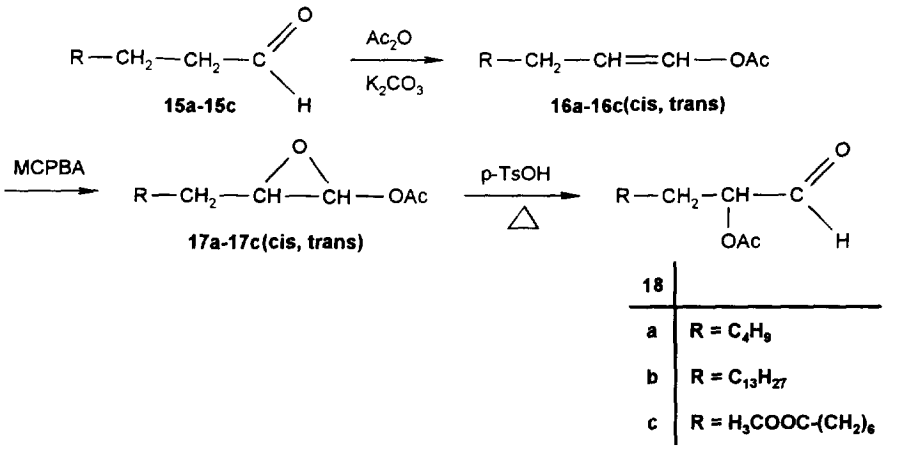
Otherwise the preparation of aliphatic hydroxyaldehydes may be tried by hydrolysis of OH-protected α-hydroxyaldehydes, e.g. acetylated derivatives.[26-28] Their hydrolysis is carried out either in acidic or basic media connected with dimerisation resp. isomerisation to α-hydroxyketones as mentioned above.

The same situation is encountered for α-hydroxylated derivatives, in which the hydroxy group and the aldehyde group are protected at the same time by ring formation.[1,27,29]

Considering the more rigorous condition for liberation of aldehydes from acetals and mercaptals compared with OH-protected ones we prepared O-acetyl derivatives and studied their enzymatic cleavage with esterases, thus avoiding acidic or basic conditions.

**Synthesis of 2-acetoxyheptanal (18a), 2-acetoxyhexadecanal (18b) and 9-acetoxy-10-oxomethyldecanoate (18c)**

Heptanal (**15a**) was converted in analogy to a procedure of Barbier and Benezra[27] by treatment with acetic anhydride in presence of $K_2CO_3$ to its enolacetate **16a**. This was subjected to epoxidation with m-chloroperbenzoic acid to **17a**. In a thermal rearrangement process catalyzed by p-toluene-sulfonic acid the epoxide **17a** was isomerized to the 2-acetoxyheptanal (**18a**) (scheme 4). It is important for the thermal isomeration to use a highly purified compound **17a**, since even traces of m-chloroperbenzoic acid caused fast decomposition. Careful control of the reaction temperature is required also.




**Scheme 4**: Preparation of 2-acetoxyheptanal (**18a**), 2-acetoxy-hexadecanal (**18b**) and 9-acetoxy-10-oxomethyldecanoate (**18c**).

1-Acetoxy-1-hexadecene (**16b**) was prepared in analogy to 2-acetoxyheptanal starting from hexadecanal (**15b**), via the enolacetate **16b** and its corresponding epoxide 1,2-epoxy-1-acetoxy-hexadecane (**17b**) (scheme 4).

The methylester of 9-acetoxy-10-oxodecanoic acid (**18c**) was obtained similarily from the corresponding unsaturated acetate, methyl-10-acetoxy-9-decenoate (**16c**) by epoxidation to 9,10-epoxy-10-acetoxy-methyldecanoate (**17c**) and thermal rearrangement to **18c** (scheme 4).

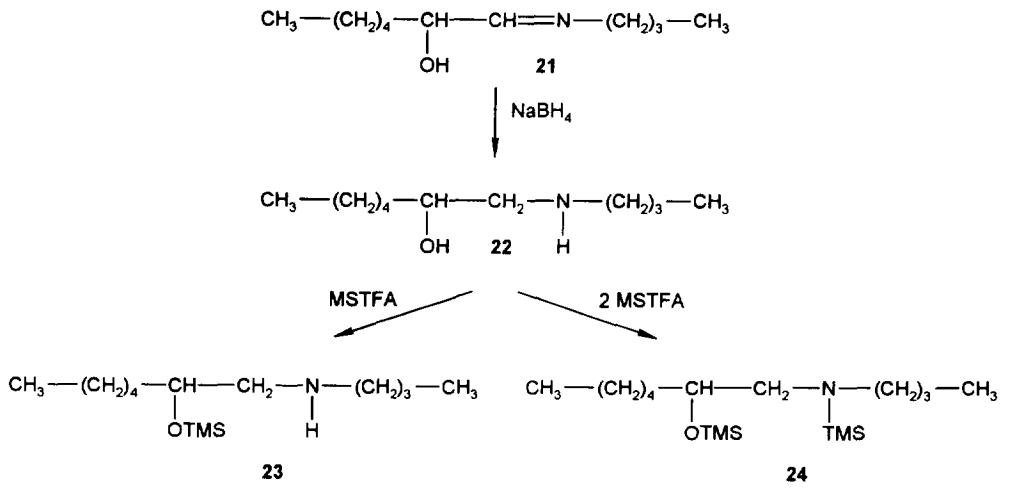
**15c** is either available according to a procedure described by Brown and Subba Rao[30] by reduction of the mono acid chloride of monomethyldidecanoate (**19**) to the corresponding aldehyde using tri-t-butoxyaluminiumhydride in diglyme as solvent, or by ozonolysis of methyl-10-undecenoate (**20**). We preferred the latter procedure since the starting material is easily available, although production of byproducts required separation of the reaction products by thin layer chromatography.

**Generation of α-hydroxyaldehydes from α-acetoxyaldehydes**

If α-acetoxyaldehydes are suspended in aqueous solution and hog liver esterase (Fluka) is added, they are saponified under mild conditions. α-Hydroxyaldehydes are produced, as can be deduced after trimethylsilylation and GC/MS analysis. The α-hydroxyaldehydes can be extracted with an organic solvent, e.g. diethyl ether, but if one tries to remove the solvent even by freeze drying mainly dimers are isolated.

**Trapping of Schiff bases from α-hydroxyaldehydes**

If an amine e.g. butylamine is added to a solution of free 2-hydroxyheptanal (**2**), a Schiff base is formed obviously. Although this Schiff base can not be isolated - if solvent is removed only dimers are obtained - the existence of the amine adducts can be proven by addition of $NaBH_4$ to the solution: The Schiff base is reduced to the corresponding amine. Its structure can easily be deduced from mass spectra after trimethylsilylation: This reaction provides a mono- **23** and a ditrimethylsilylated **24** product. Their structures can be deduced due to the production of prominent α-fragments (scheme 5).

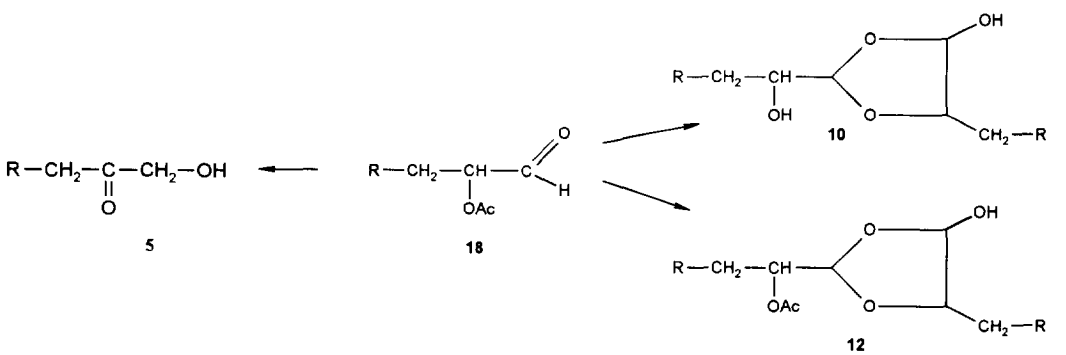



**Scheme 5**: Generation of the trimethylsilyl derivatives **23**, **24** of the Schiff bases of α-hydroxyaldehydes by treatment with $NaBH_4$ and MSTFA

**Properties of α-hydroxyaldehydes with an aliphatic chain and their acetyl derivatives**

α-Acetoxy derivatives of hydroxyaldehydes e.g. 2-acetoxyheptanal (**18a**) can be stored without solvent at -25°C for several weeks under an argon atmosphere. A solution of α-acetoxyaldehydes in dimethyl sulfoxide is stable for several weeks.

In methanolic solution or in other solvents - even under argon atmosphere - they dimerise slowly, probably induced by traces of water.

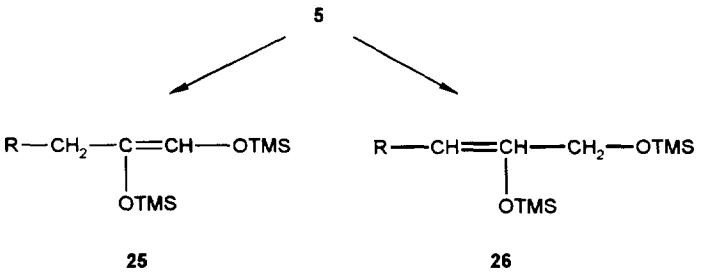



**Scheme 6**: Dimerisation of α-hydroxyaldehydes after hydrolysis in methanolic solution

Acetates of α-hydroxyaldehydes are stable for 1 day in an aqueous 1% solution at room temperature but if kept longer in this solution, they dimerise after partial hydrolysis (scheme 6).

They are readily hydrolysed in basic media, even in a $NaHCO_3$ solution the resulting α-hydroxyaldehydes isomerise fast to 1-hydroxy-2-oxoalkanes (scheme 6).

If the reaction products of 1-hydroxy-2-oxoalkanes **5** are trimethylsilylated partial enolisation occurs to **25** and **26** (scheme 7).

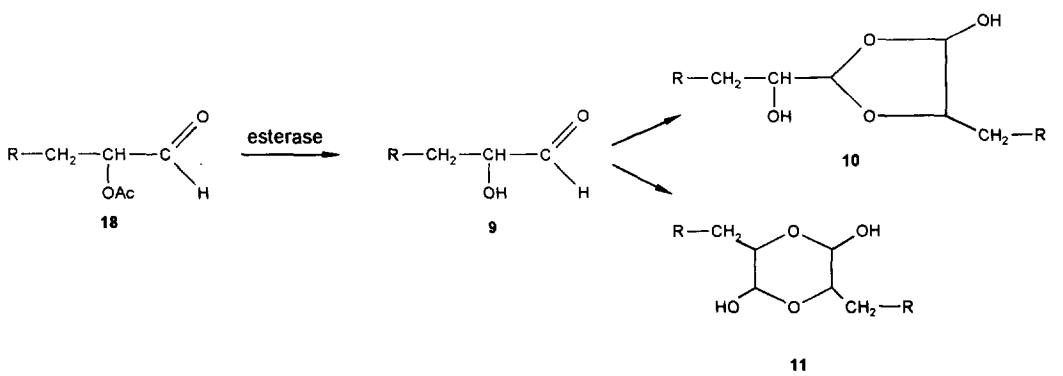



**Scheme 7**: Generation of trimethylsilylated enol ethers of 1-hydroxy-2-oxoalkanes **5**

In basic but also in weak acidic media a slow Cannizzaro reaction was observed producing corresponding 1,2-dihydroxy compounds which can be detected after trimethylsilylation by GC/MS analysis.

**18c** is much less soluble in aqueous solution than **18a**, even if sodium dodecyl sulfate is added. Its solubility can be improved by addition of emulgator Tween ®20 (Aldrich).

If hog liver esterase is added to such a solution the corresponding aldehyde is slowly liberated, but transformed simultaneously to dimers. Therefore the actual concentration of free aldehyde in the solution is in any case rather low (scheme 8).




**Scheme 8**: Hydrolysis of α-acetoxyaldehydes with hog liver esterase

In presence of SH groups mercaptals are formed. They were detected by GC/MS analysis.

## DISCUSSION

A procedure to prepare aliphatic α-hydroxyaldehydes **9** in moderate, but sufficient yield to investigate their properties is reported.

The instability of α-hydroxyaldehydes with an aliphatic chain excludes their isolation in pure form - but they can exist in aqueous emulsion for some time and therefore they can be trapped in biological material. α-Hydroxyaldehydes react with amines by production of instable Schiff bases. It might well be that such instable Schiff bases are also produced with biomolecules. As a consequence such instable adducts may initiate changes in the structure of cell wall proteins and thus induce biological reactions. This possibility is corroborated by the observation that α-acetoxyaldehydes as well as epoxides of plasmalogen model compounds are able to initiate an oxidative burst in stimulated macrophages. This seems to indicate that both types of compounds are hydrolysed in biological media to similar compounds - α-hydroxyaldehydes.[11]

In this connection it seems worth-while to mention that another precursor group - α-acetoxyplasmalogen analogues - are able to inhibit tumor growth in vitro.[31]

The ready reaction of α-hydroxyaldehydes **2** with SH compounds raises the question, if these influence the action of enzymes with SH groups, since they loose their activity if blocked by mercaptal formation. Thus α-hydroxyaldehydes might represent a class of compounds of great physiological potence.

## EXPERIMENTAL SECTION

$^1$H (500 MHZ) NMR spectra were recorded an a Bruker DRX 500 instrument. Samples were dissolved in deuterochloroform. GC/MS spectra were recorded on a MAT 312 double focusing mass spectrometer. Element analyses were performed by Ilse Beetz, Mikroanalytisches Laboratorium, D-96301 Kronach.

### 1-Acetoxy-1-heptene (16a)

1-Acetoxy-1-heptene (**16a**) was prepared in analogy to a procedure of Barbier and Benezra.[27] 28.5 g (250 mmol) heptanal (**15a**) 38.3 g (375 mmol), acetic anhydride and 4.5 g (32.6 mmol) potassium carbonate were refluxed (150°C) overnight in a 250 ml flask. After cooling a 6:1 mixture of cyclohexane (CH) and ethyl acetate (EA) (200 ml) was added and the precipitated potassium carbonate was filtered off. After filtration the solvent was removed.

Yield 34.8 g (89%) brown oil.

A gas chromatogram of the crude reaction products showed 3 peaks: Mass spectra revealed the presence of cis-1-acetyl-1-heptene (**cis-16a**) (Retention index, RI 1060) and trans-1-acetyl-1-heptene (**trans-16a**) (RI 1100) as well as heptanaldiacetate (RI 1337). The byproduct can be removed from the mixture of cis and trans 1-acetoxy-1-heptene (**cis-16a** and **trans-16a**) by column chromatography using CH/EA = 6:1 as elution solvent.

Yield of **cis-16a** and **trans-16a** (mixture): 24.8 g (64%); $RI_{cis}$: 1060, $RI_{trans}$: 1100. DC: $R_f$ = 0.76 (CH/EA = 6:1), mixture of cis and trans; $R_f$ = 0.49 (CH/EA = 6:1) byproduct.

**Epoxidation of 1-acetoxy-1-heptenes (cis-16a) and (trans-16a) to 1-acetoxy-1,2-epoxyheptanes (cis-17a) and (trans-17a)**

24.2 g (155.1 mmol) 1-acetoxy-1-heptenes (mixture), dissolved in 50 ml dry $CH_2Cl_2$, were placed in a 500 ml three necked flask equipped with a dropping funnel and a drying tube by stirring the mixture at room temperature. 29.4 g (170.4 mmol) m-chloroperbenzoic acid (MCPBA) dissolved in 300 ml $CH_2Cl_2$ were added dropwise within 15 min. The temperature was adjusted to room temperature by cooling with water. After stirring overnight the solution was kept for a 3 days in an ice bath, allowing the precipitation of m-chlorobenzoic acid (MCBA) and unchanged MCPBA (22.0 g). An additional part of MCBA and MCPBA was removed by extraction with $NaHCO_3$. Final purification required column chromatography with CH/EA 6:1.

Yield: 8.2 g **cis-16a** and **trans-16a** (mixture) (31%); $RI_{cis}$: 1195, $RI_{trans}$: 1205. DC: $R_f$ = 0.48 (CH/EA = 6:1). MS: m/z (rel. intensity): 143(2), 130(1), 112(2), 99(6), 83(35), 71(5), 57(8), 55(34), 43(100), 41(17).

The compound was stored in the elution mixture under argon at -20°C.

**Thermal rearrangement of 1-acetoxy-1,2-epoxyheptanes (cis-17a) and (trans-17a) to 2-acetoxyheptanal (18a)**

After removal of the solvent ($CH_2Cl_2$) water traces were eliminated by addition of dry benzene which was evaporated off; (the procedure was repeated 3 times). 3.3 g 1-Acetoxy-1,2-epoxyheptanes (mixture) (19.2 mmol) and ca. 45 mg p-toluene sulfonic acid were melted in a glycerol bath at 80°C under argon. The colour of the melting turned to yellow after 2h. After 1h additional 40 mg of p-toluene acid were added, the melting was kept for 4 additional hours at 80°C. After that time the melt turned to brown within 2-3 min. It is important to stop the reaction in this phase by cooling to avoid polymerisation. Purification for removal of small amounts of dimers by column chromatography with cyclohexane/ethyl acetate 3:1 provided 800 mg of 2-acetoxyheptanal (**18a**). - Yield: 800 mg (24%). DC: $R_f$ = 0.41 (CH/EA = 3:1). MS: m/z (rel.

intensity): 143(7), 129(1), 112(2), 94(2), 83(9), 68(6), 56(8), 55(14), 43(100), 41(14). $^1$H NMR: δ 9.52 (s, 1H), 4.98 (dd, J = 8.4 Hz, 1H), 2.17 (s, 3H), 1.68-1.87 (m, 2H), 1.38-1.46 (m, 2H), 1.14-1.38 (m, 4H), 0.88 (t, J = 6.6, 3H). Anal. Calcd. for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.60; H, 9.22%.

**1-Acetoxy-1,2-epoxyhexadecane (17b)**

7.2 g (25.5 mmol) of the 1-acetoxy-1-hexadecenes (**cis-16a**) and (**trans-16a**) were dissolved in 30 ml of dry methylene chloride, and 4.8 g (27.8 mmol) of MCPBA dissolved in 75 ml methylenechloride were added within 15 min. The solution was stirred overnight at room temperature. After 12 h stirring about one third of the solution was evaporated under reduced pressure. After 90 min MCBA and MCPBA precipitated at 4°C. The precipitate was filtered off and the clear solution was kept in a refrigerator for 2-3 days. Additional precipitated MCBA and MCPBA were filtered off, the solvent was removed completely and the residue (9.2 g) subjected to a separation by column chromatography using cyclohexane/ethyl acetate (3:1).

Yield: 3.2 g (**cis-17b**) and (**trans-17b**) (43%); $RI_{cis}$: 2297, $RI_{trans}$: 2310. DC: $R_f$ = 0.72 (CH/EA = 3:1). MS: m/z (rel. intensity): 270(3), 256(3), 238(1), 225(11), 222(3), 209(2), 194(2), 167(1), 153(3), 139(6), 125(11), 111(19), 98(27), 97(34), 83(33), 71(19), 69(22), 57(28), 55(17), 43(100). $^1$H NMR: (mixture of isomeric compounds **17a**, cis:trans ≈ 1:1): (cis) δ 5.52 (d, J = 2.6 Hz, 1H), 2.96 (dt, J = 2.6 Hz, J = 6.0 Hz, 1H), 2.10 (s, 3H), 1.13-1.74 (m, 26H), 0.88 (m, 3H). (trans) δ 5.32 (s, J = 0.9 Hz, 1H), 3.08 (dt, J = 0.9 Hz, J = 5.6 Hz, 1H), 2.08 (s, 3H), 1.13-1.74 (m, 26H), 0.88 (m, 3H). Anal. Calcd. for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.39; H, 11.51.

**Transformation of 1-acetoxy-1,2-epoxyhexadecanes (cis-17b) and (trans-17b) to 2-acetoxyhexadecanal (18b)**

3.1 g (10.4 mmol) 1-Acetoxy-1,2-epoxyhexadecanes (mixture) and a few crystals of p-toluene sulfonic acid were dipped into a water bath of 80°C in an argon atmosphere. Within 5 min the compound reacted to a brown oil which was separated by thin layer chromatography using CH/EA 3:1 as solvent. - Yield: 920 mg 18b (30%); RI: 2052. DC: $R_f$ = 0.53 (CH/EA = 3:1). MS: m/z (rel. intensity): 299(1), 269(7), 256(8), 238(4), 227(7), 225(24), 209(12), 167(1), 153(3), 139(4), 125(7), 111(10), 98(21), 97(15), 83(13), 71(7), 69(8), 57(10). $^1$H NMR: δ 9.52 (s, 1H), 4.98 (dd, J = 4.7 Hz, J = 8.4 Hz, 1H), 2.18 (s, 3H), 1.68-1.87 (m, 2H), 1.36-1.45 (m, 2H), 1.21-1.36 (m, 22H), 0.88 (t, J = 6.9 Hz, 3H). Anal. Calcd. for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.36; H, 11.36.

**Preparation of methyl-10-acetoxy-9-decenoates (cis-16c) and (trans-16c)**

20 g (100 mmol) Methyl-10-oxodecanoate (**15c**), 15.3 g (150 mmol) of acetic anhydride and 1.93 g (14 mmol) $K_2CO_3$ were heated to 150°C over night under stirring and exclusion of moisture. Then 100 ml of potassium hydrogencarbonate solution (1N) were added. The solution was stirred for 10 min at room temperature to destroy the excess of acetic anhydride. The mixture was extracted 3 times with 100 ml of ethyl acetate and dried over sodium sulfate. After extraction and evaporation of the solvent 24.3 g of crude methyl-10-acetoxy-9-decenoates (**cis-16a**) and (**trans-16a**) were obtained. Column separation of the crude product on silica gel using cyclohexane/ethyl acetate = 3:1 as eluent yielded 4.7 g **16a** (mixture); $RI_{cis}$: 1668, $RI_{trans}$: 1709. DC: $R_f$ = 0.56 (CH/EA = 3:1). MS: m/z (rel. intensity): 242 ($M^{\oplus}$, 7%), 211(3), 199(7), 182(6), 169(17), 168(19), 157(5), 150(45), 122 (12), 108(13), 98(17), 87(27), 74(17), 67(14), 55(22), 43(100).

**Preparation of methyl-9,10-epoxy-10-acetoxydecanoates (cis-17c) and (trans-17c)**

A solution of 3.48 g (20.02 mmol) of MCPBA dissolved in 150 ml dry methylenechloride was added to 4.4 g (18.2 mmol) of methyl-10-acetoxy-9-decenoates (**16a**) (mixture) dissolved in 30 ml dry methylenechloride within 5 min. The solution was stirred overnight at room temperature and exclusion of moisture. Then the solvent was evaporated under reduced pressure. GC/MS analysis of a residue sample (7.2 g) revealed the presence of the desired methyl 9,10-epoxy-10-acetoxy-decanoates (**cis-17c**) and (**trans-17c**) but also of starting material **16a** (mixture) and MCBA. Since the latter migrated on thin layer plates together with **17c**, the crude product was treated for 1 min with an etheral solution of diazomethane. After removal of the solvent and excess $CH_2N_2$ the residue was dissolved in a mixture of CH/EA 3:1. This mixture was subjected to separation by thin layer chromatography. The fraction between $R_f$ = 0.42 and $R_f$ = 0.45; contained pure **17c** (mixture). - Yield: 4.1 g (87%); $RI_{cis}$: 1797, $RI_{trans}$: 1811. DC: $R_f$ = 0.44 (CH/EA = 3:1). MS: m/z (rel. intensity): 242(3), 229(3), 227(3), 207(5), 187(7), 185(11), 169(1), 155(38), 138(6), 125(6), 109(14), 97(7), 87(10), 83(10), 74(17), 67(14), 55 (24), 43(100). $^1$H NMR: (mixture of isomeric compounds **17a**, cis:trans ≈ 10:16): (cis) δ 5.52 (d, J = 2.6 Hz, 1H), 3.64 (s, 3H), 2.95 (ddd, 1H), J = 2.6 Hz, J = 5.8 Hz, J = 6.4 Hz), 2.24-2.31 (m, 2H), 2.10 (s, 3H), 1,21-1.69 (m, 12H); (trans) δ 5.30 (d, J = 0.9 Hz, 1H), 3.64 (s, 3H), 3.08 (dt, J = 0.9 Hz, J = 6.1 Hz, 1H), 2.24-2.31 (m, 2H), 2.08 (s, 3H), 1.21-1.69 (m, 12H). Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.49; H, 8.58.

**Preparation of methyl-9-acetoxy-10-oxodecanoate (18c)**

10-Undecenoic acid was converted to its methylester by treatment with methanol and traces of $H_2SO_4$. Methyl-10-undecenoate (**20**) was converted to methyl-10-oxo-decanoate (**15c**) by ozonolysis.[32]

**Preparation methyl-9-acetoxy-10-oxo-decanoate (18c)**

4.0 g (15.5 mmol) **17c** (mixture) and ca. 30 mg of p-toluene sulfonic acid were heated on a glycerol bath to 90°C under an argon atmosphere until the mixture developed to a yellowish brown colour after 10 min. This discolouration requires immediate stopping of heating by sample removal from the glycerol bath. The mixture, 1.4 g, was dissolved in CH/EA = 2:1 and subjected to chromatography on thin layer plates using the same solvent mixture. The fraction between $R_f$ 0.36 and 0.42 was collected and rechromatographed. - Yield: 750 mg (19%); RI: 1754. DC: $R_f$ = 0.38 (CH/EA = 2:1). MS: m/z (rel. intensity): 229(3), 227(3), 197(2), 187(48), 185(34), 166(4), 155(100), 138(10), 125(20), 109(26), 98(15), 97(17), 83(17), 74(16), 67(17), 55(22), 43(74). $^1$H NMR: δ 9.50 (s, 1H), 4.98(dd, J = 4.7 Hz, J = 8.4 Hz, 1H), 3.68 (s, 3H), 2.26-2.32 (m, 2H), 2.17 (s, 3H), 1.67-1.85 (m, 2H), 1.57-1.65 (m, 2H), 1.36-1.44 (m, 2H), 1.25-1.36 (m, 6H). Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.49; H, 8.53.

**Stability of 2-acetoxy-heptanal (18a)**

2-acetoxy-heptanal can be stored in an argon atmosphere at -25° for several weeks. The purity can be checked by GC. If a 1% solution in CH/EA = 3:1 was kept at room temperature in an argon atmosphere for 5 days after trimethylsilylation besides the TMS adduct of 2-acetoxyheptanal also mixed dimers **10** and **12** were detected, after two weeks mainly dimers were found.

In a 10% solution already after one day α-hydroxyaldehyde was observed in 20% yield, probably caused by traces of water.

After 3 days α-acetoxyaldehyde and α-hydroxyaldehyde were present, together with dimers, which could be detected after trimethylsilylation. Two weeks later 1-hydroxy-2-heptanone (**3**) was observed to about 20%.

α-Acetoxyheptanal **18a** is nearly insoluble in water. If its emulsion is stirred in an argon atmosphere for 24 h, besides **18a** also the free α-hydroxyaldehyde **2** - and 1-hydroxy-2-heptanone (**3**) as well as the TMS derivative of 2-hydroxyheptanoic acid were detected.

Products in similar amounts were formed in a solution of $CH_3OH/H_2O$ = 9:1.

The acetate **18a** dissolved in 1N acetic acid was nearly unchanged after standing overnight at room temperature. After 3 days the same products were formed as obtained in an aqueous solution. A solution of 2-acetoxyheptanal **18a** in 0.1N $H_2SO_4$ is also rather stable for 1-2 days at $0^\circ$ in an argon atmosphere, after 2 days about half of the acetate is converted to a mixture of dimers.

After 30 min at 0° in 0.1N NaOH solution the 2-acetoxyheptanal (**18a**) is converted completely to 1-hydroxy-2-heptanone (**3**). If **3** is trimethylsilylated besides compound **4** also the peaks of the enol ethers **25** and **26** were detected, Cannizzaro products were produced as well (see scheme 7).

**Liberation of 2-hydroxyheptanal (2) from 2-acetoxyheptanal (18a) by action of hog liver esterase**

13.1 mg (76 μmol) of 2-acetoxyheptanal (**18a**) were suspended in 100 ml of phosphate buffer (pH 7). To this suspension 0.42 ml hog liver esterase (563 U) were added and the mixture was stirred over night at 35°C under argon. At the next morning the mixture was extracted two times with ether and dried over $Na_2SO_4$. GC/MS analysis showed two peaks: 2-hydroxyheptanal (**2**) and 1-hydroxy-2-heptanone (**3**). After silylation with MSTFA mainly the dimers **10** and **11** were found, also **4** and the MSTFA-adduct [N-(1,2-bis-trimethylsilanyloxy-heptyl)-2,2,2-trifluoro-N-methyl-acetamide] **27**.

**Liberation of 2-hydroxyheptanal (2) from 2-acetoxyheptanal (18a) by action of hog liver esterase in the presence of n-butylamine**

13.1 mg (76 μmol) of 2-acetoxyheptanal (**18a**) were suspended in 100 ml of phosphate buffer (pH 7). To this suspension 0.42 ml hog liver esterase (563 U) and 56.0 mg (760 μmol) n-butylamine were added and the mixture was stirred over night in an argon atmosphere at 35°C. A sample (10 ml) withdrawn after 24 h was extracted with ether. The etheral solution was dried over $Na_2SO_4$, reduced in vacuo and treated with MSTFA. The analysis by GC/MS showed the absence of nitrogen containing products besides n-butylamine.

**Liberation of 2-hydroxyheptanal (2) from 2-acetoxyheptanal (18a) by action of hog liver esterase in the presence of n-butylamine and reaction with sodium borohydride**

To another 10 ml of the mixture withdrawn after 24 hours 2.9 mg (76 μmol) $NaBH_4$ were added. The solution was stirred for 1 hour at room temperature. After extraction with ether and drying over $Na_2SO_4$ the solvent was removed in vacuo. The residue was treated with MSTFA 24 h at room temperature. GC/MS analysis revealed besides the main peak 1,2-

ditrimethylsilyloxyheptane (**28**) the presence of the mono- and disilylated products **23** and **24** (see scheme 5).

**23**: MS: m/z (rel. intensity): 259($M^{\oplus}$, 1%) 244(7), 216(3), 200(1), 188(3), 186(2), 173(8), 157(2), 126(4), 103(5), 86(100), 75(14), 73(21), 57(4), 55(5), 44(9), 41(7).

**24**: MS: m/z (rel. intensity): 331($M^{\oplus}$, 1%) 316(3), 288(1), 260(1), 242(1), 200(1), 173(1), 168(1), 159(12), 158(100), 147(5), 116(6), 101(1), 86(4), 75(3), 73(14), 55(2), 41(2).

**Liberation of 2-hydroxyheptanal (2) from 2-acetoxyheptanal (18a) by action of hog liver esterase and derivatisation with dithioethyleneglycol (DTHEG)**

4.0 mg (23 μmol) 2-Acetoxyheptanal (**18a**) were suspended in 30 ml of phosphate buffer (pH 7). To this suspension 0.13 ml hog liver esterase (174 U) were added and the mixture was stirred overnight at 35°C under argon. The mixture was extracted two times with ether and dried over $Na_2SO_4$. After reduction in vacuo 20 μl DTHEG and 10 μl $BF_3$ ethyletherate were added and the mixture was allowed to react at room temperature 24 h under argon. After removing the excess $BF_3$ ethyletherate by a stream of nitrogen, MSTFA was added to react 24 h at room temperature. GC/MS analysis showed the expected peak of (1-[1,3]dithiolan-2-yl-hexyloxy)-trimethyl-silane) (**29**) besides the main peak of ditrimethylsilylated DTHEG (1,2-bis-trimethylsilanylsulfanylethane) (**30**).

**29**: MS: m/z (rel. intensity): 263(2), 229(1), 208(2), 207(5), 173(60), 147(3), 133(4), 115(5), 103(15), 92(28), 91(45), 75(27), 73(100), 55(13), 44(45), 43(18), 41(16).

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