Malonaldehyde, Succinaldehyde, and Glutaraldehyde Monoacetals: Syntheses and Applications

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Methods for synthesizing 1,3-, 1,4-, and 1,5-dialdehyde monoacetals or monothioacetals published from 1930 up to 1983 are reviewed. Open-chain and cyclic acetals or thioacetals are considered. A short survey of the most important applications of these compounds is also included.

1. Introduction

Bi-functional compounds are useful building-blocks in organic synthesis. Particularly attractive are those which have one of the functions suitably masked, so that it becomes possible to transform them in different ways and at different steps of the synthetic sequence.

Dialdehydes, in which an aldehyde group is acetalized with alcohols or thiols, namely dialdehyde monoacetals and their substitution products belong to this class of compounds.

\[
\begin{align*}
O=CH-(CH_2)_n-CH(OH)R & \quad \text{or} \\
O=CH-(CH_2)_n-CH(SR) & 
\end{align*}
\]

\( n = 1, 2, 3 \)

The aim of this review is to provide organic chemists, particularly those who deal with the preparation of complex molecules, with a survey of the main methods to obtain dialdehyde monoacetals. Special attention is devoted to those synthetic routes which are experimentally more accessible and give higher yields and higher selectivities. A short outline of some important synthetic applications of the title compounds is also reported.

2. Synthesis of Malonaldehyde Monoacetals

Few methods of general applicability are reported in the literature for the preparation of malonaldehyde monoacetals: they are discussed in the following Sections 2.1 to 2.6. It is to be pointed out that only the method described in Section 2.1 produces the desired dialdehyde monoacetal with high selectivity, whereas the others yield a mixture of two or more products, from which the pure title compound can be isolated customarily by fractional distillation, and hence with a low-to-moderate yield.

2.1. Oxidative Cleavage of 1,1-Dialkoxy-3-alkenes

1,1-Dialkoxy-3-alkenes can be oxidized to malonaldehyde monoacetals via hydroxylation reaction with neutral potassium permanganate at 0°C.\(^5\) followed by cleavage of the resulting glycol with lead (IV) acetate\(^1\) or sodium periodate\(^6\). The hydroxylation step can be accomplished by other methods, for instance by epoxidation of the double bond and hydrolysis of the oxirane ring\(^3\). The overall yields obtained with these two-step oxidative methods are not very high, ranging between 10 and 30%\(^4,5\).

\[
\begin{align*}
& \text{R}^1\text{O} + \text{HCO} \rightarrow \\
& \text{R}^1\text{CONHCO} \quad \text{R}^1\text{CONHCO} \quad \text{R}^1\text{CONHCO} 
\end{align*}
\]

3,3-Dithioxypropanal\(^1,4\):

To a solution of 4,4-dithioxy-1,2-butanediol (71.2 g, 0.4 mol) in anhydrous benzene (800 ml), lead (IV) acetate (177.2, 1 mol) is added in small portions in order to avoid a too rapid increase in temperature. Then excess oxidant is reacted by adding a further amount of the glycol to the mixture. The reaction is complete after 1–2 h at room temperature. The mixture is filtered, the filtrate is concentrated in vacuo at 35°C to one-fourth of its volume, diluted with diethyl ether (5 vol), neutralized with aqueous potassium carbonate solution, and distilled to afford 3,3-dithioxypropanal; yield: 33.8 g (58%); b.p. 74–75°C/20 torr.

Higher yields of malonaldehyde monoacetals are achieved by cleavage with ozone of the dialkoxyolefin\(^5\), e.g., 1,1-di-\(n\)-butoxy-3-buten in ethyl acetate gives 78% of 3,3-di-\(n\)-butoxypropanal by treatment with ozone at -50°C followed by catalytic reduction of the ozonide\(^5\).

\[
\begin{align*}
& \text{O}_3/\text{AcO}CH_2\text{H}_4, \quad -50°C \\
& \text{H}_2/\text{Pd}+\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} 
\end{align*}
\]

Closely related to this method is the oxidation of the hydroxyethyl group of 3,3-ethanediol oxypropanol and its substitution products to an aldehyde group. Thus, 2,2-dimethyl-3,3-ethanediol oxypropanol is obtained in 75% yield by oxidation of the corresponding alcohol with pyridinium chlorochromate in dichloromethane\(^6,7\).
2.2-Dimethyl-3,3-ethanediolxypropanol^9,10^: To a suspension of pyridinium chlorochromate\(^7\) (0.32 g, 1.5 mmol) in dichloromethane (2 ml) a solution of 2,2-dimethyl-3,3-ethanediolxypropanol\(^8\) (0.15 g, 1 mmol) in the same solvent (1 ml) is rapidly added at room temperature. After 3 h the oxidation is complete. The black reaction mixture is diluted with anhydrous diethyl ether (5 vol); the solvent is decanted and the black solid washed twice with ether. Filtration of the organic extracts through Florisil and evaporation of the solvent at reduced pressure affords 2,2-dimethyl-3,3-ethanediolxypropanol; yield: 0.11 g (75\%).

2.2. Partial or Selective Hydrolysis of Malonaldehyde Bis-acetals

The partial hydrolysis of malonaldehyde bis-acetals\(^9,10\) is sometimes employed\(^2,10,11,12\) to obtain monooacetals. The selectivity is rather low, even though yields of up to 43\% can be achieved by carefully controlling the reaction conditions.

\[
\begin{array}{c}
R^1O\end{array}CH\end{array}C\end{array}R^2O + H_2O \xrightarrow{\text{H}_2O^+} \begin{array}{c}
R^1O\end{array}CH=CH=\end{array}O
\]

\(R^1 = \text{CH}_3, \ C_6H_5\)

\(R^2, R^3 = \text{H, alkyl}\)

Orthophosphoric acid (6–10\%) was found to be the best acid catalyst for this reaction\(^11,12\); an equimolecular amount of water is used and the alcohol is distilled off as soon as it is formed. As expected, alcohol elimination to \(\beta\)-alkoxyacroleins is observed as an undesired side-reaction if one \(\alpha\)-hydrogen atom at least is present in the starting bis-acetal\(^2,10\).

2.2-Dimethyl-3,3-dimethoxypropanol^11,12^: A mixture of 1,1,3,3-tetramethoxy-2,2-dimethylpropane\(^13\) (20 g, 10.4 mmol) and 6\% aqueous orthophosphoric acid (2 ml) is heated at 100 °C for 30 min, removing the methanol formed by distillation. After this time the mixture is stirred for 30 min with calcium carbonate (1 g), filtered, and distilled to give 2,2-dimethyl-3,3-dimethoxypropanol; yield: 6.63 g (43\%), b.p. 160 °C/760 torr.

The fact that cyclic aldehyde acetals are significantly more stable towards acid hydrolysis than acetals formed with monohydroxy alcohols has been conveniently exploited to prepare a cyclic monoacetal of malonaldehyde\(^14\). Reaction of 1,1,3,3-tetramethoxypropane with an equimolecular amount of 2,2-dimethyl-1,3-propanediol in the presence of sulfuric acid gives the mixed bis-acetal; subsequent hydrolysis of this product with oxalic acid in 1,2-dichloroethane/tetrahydrofuran at 60 °C produces the desired monoacetal in 55\% yield\(^14\).

Another interesting example of selective hydrolysis of a malonaldehyde bis-acetal has been reported\(^15\): 1,1-diethoxy-3,3-(1,3-propanediylidithio)-propane\(^16\) is smoothly hydrolyzed at the \(O\)-acetyl moiety due to the well-known stability of the 1,3-dithiane ring in acidic media.

3-(1,3-Propanediylthio)-propanol\(^15\): A solution of 1,1-diethoxy-3,3-(1,3-propanediylthio)-propane\(^16\) (50.1 g, 21.2 mmol), perchloric acid (60 ml) and water (100 ml) in dioxan (400 ml) is stirred at room temperature for 0.5 h. The mixture is extracted with diethyl ether (4 × 250 ml), the combined ether layers are washed with a saturated aqueous sodium chloride solution (6 × 200 ml) and dried with anhydrous sodium sulfate. The solution is concentrated in vacuo to give crude 3,3-propanediylthiopropanol as a brown oil of sufficient purity for most purposes; yield: 31.8 g (93\%). Further purification is achieved by distillation to give the product as a colorless oil; yield: 23.3 g (68\%), b.p. 62–68 °C/0.2 torr.

2.3. Hydroformylation Reaction of Acrolein Acetals Catalyzed by Rhodium or Cobalt Complexes

Acrolein acetals can be hydroformylated to methylmalonaldehyde monoacetals\(^17,18\), as expected, these products are formed together with the isomeric succinaldehyde monoacetals (see Section 3.3.).

\[
\begin{array}{c}
\text{CH}_2\end{array} + \text{CO} + \text{H}_2\text{O} \xrightarrow{\text{HCOOH} + \text{SiO}_2 / \text{CICH}_2\text{CH}_2\text{CH}_2\text{Cl} + \text{THF}} \begin{array}{c}
\text{CH}_3\end{array} + \begin{array}{c}
\text{CH}_3\end{array} \]

65\%

35\%

The hydroformylation reaction of acrolein acetals has been extensively investigated, since the o xo-product can be converted by hydrolysis and subsequent catalytic hydrogenation to commercially valuable diols\(^17,18\).

Use of cobalt carbonyl catalysts gives rise to complex mixtures of products, which originate from subsequent reactions of the formed o xo-aldehydes\(^19\), when acrolein diethyl acetal is employed as the substrate. Hydroformylation of this acetal using rhodium carbonyl catalysts results in a mixture of the expected aldehydes in a linear-to-branched isomer ratio\(^19\) of 1:2.

Hydroformylation of Acrolein Diethyl Acetal\(^20\): Acrolein diethyl acetal (39.0 g, 0.3 mol), rhodium oxide (129.6 mg, 0.5 g/l as Rh) and benzene (104 ml) are charged in a 300 ml stainless-steel autoclave. A hydrogen and carbon monoxide mixture (1:1) is then introduced up to 200 atm, after the air in the reactor has been replaced by these gases. The autoclave is kept at 110 °C for 30 min. After cooling, the gas mixture is purged and the catalyst is decomposed with triphenylphosphine. Filtration and removal of the solvent under reduced pressure affords a mixture of 1,1-diethoxy-2-formylpropane and 1,1-diethoxy-3-formylpropane in the ratio 1:82:1 (determined by \(^1\)H-N.M.R. spectrometry); yield: 29.9 g.
Acrolein cyclic acetals, either with cobalt or rhodium catalysts, produce the typical oxo-aldehydes mixture; however, the linear isomer always prevails in the cobalt-catalyzed hydroformylation, reaching up to 82% of the crude reaction mixture. The highest yield (75%) of methylmalonaldehyde monoacetal is achieved when the reaction is carried out at 600 atm of carbon monoxide/hydrogen and at 80°C using rhodium carbonyls in the absence of complexing agents. A convenient separation of the two isomeric dialdehyde monoacetals can be effected by a careful fractional distillation using an efficient standard or spinning-band distillation column.

2.4. Oxidative Conversion of the Phenylthiomethyl to the Aldehyde Group in Acetalated 3-Phenylthiopropanals

Recently, a new route to malonaldehyde monooacetals that promises general applicability has been discovered: this route is based on a mild and experimentally easy conversion of a phenylthiomethyl to an aldehyde group. The yields range between 67 and 72%, the only by-product being the diphenyl thiaoacetal of the aldehyde product.

\[
\begin{align*}
R-C\text{-CH}_2\text{-SC}_{\text{H}_5} \overset{\text{SO}_2\text{Cl}_2/CH_2\text{Cl}_2, 0^\circ C}{\rightarrow} R-C\text{-CH(Cl)}\text{-SC}_{\text{H}_5} \\
H_2O/\text{SiO}_2 \rightarrow R-C\text{-CH=O} + C_{\text{H}_6}\text{SH}
\end{align*}
\]

The starting 3-phenylthiopropan aldehydes are accessible by phenylthiocetylation of trimethylsilyl enol ethers with chloromethyl phenyl sulfide in the presence of zinc bromide.

Malonaldehyde Cyclic Monoacetals: General Procedure:
Sulfuryl chloride (8.9 ml, 110 mmol) is added to a solution of the appropriate 3-phenylthiopropionaldehyde acetal (109 mmol) in dry dichloromethane (300 ml) at 0°C. The mixture is stirred for 3 min, the solvent is evaporated at 10 torr at room temperature. The residue is purified through a 2% water-activated silica gel (900 g) dry packed column. After elution with dichloromethane, the dialdehyde monoacetal is isolated in 72% yield and the corresponding diphenyl thiaoacetal in 11% yield.

2.5. Alcohol Addition to Propynal Catalyzed by Tertiary Amines

Propynal is reported to react with alcohols under alkaline conditions to give different addition products; among them 3,3-dialkoxypropanals can be formed in up to 80% yield.

\[
\begin{align*}
\text{ROH/ base} \rightarrow R-C\text{-CH=O} \\
\text{RO-C\text{-CH2-CH=O} + RO-C\text{-CH=CH=O}}
\end{align*}
\]

X = CH, C_{2}H_{5}

The reaction is catalyzed by tertiary aliphatic amines. More recently, 3,3-dimethoxypropionaldehyde containing 10% of 3-methoxyacrolein was obtained in 80% yield by adding two equivalents of methanol to propynal in the presence of N-methylpiperidine. The preparation of the same dialkoxyaldehyde according to the previously described procedure has been repeated by another group.

2.6. Other Methods

Mono- and dialkyl-substituted malonaldehyde having one carbonyl group protected as a thioacetal have been prepared by alkylation of the morpholino-enamines of aliphatic aldehydes by 2-chloro-1,3-dithiane. This method is obviously applicable only to aldehydes bearing at least one α-hydrogen atom. Yields between 50 and 70% are claimed for this type of formylation reaction.

2,2-Dimethyl-3,3-(1,3-propanediylidithio)-propanal:
A 100 ml 3-necked round-bottomed flask, fitted with two addition funnels and a magnetic stirring bar, is cooled with an ice bath and dry diethyl ether (10 ml) is added. Under nitrogen, a solution of 2-chloro-1,3-dithiane (3.1 g, 20 mmol) in dry tetrahydrofuran (10 ml)/dry diethyl ether (10 ml), and another solution of 1-morpholino-2-methylpropene (2.82 g, 20 mmol) in dry diethyl ether (20 ml) are added simultaneously over 15 min. During this time a solid precipitates. After the addition is complete, the mixture is vigorously stirred at room temperature for 10 min and 10% hydrochloric acid (20 ml) is added. The two-phase mixture is stirred for 0.5 h, the ether layer separated and the aqueous phase extracted with ether (2 x 10 ml). The combined ether extracts are dried with sodium sulfate, then filtered, and the solvent evaporated. The residual oil gives by distillation under reduced pressure 2,2-dimethyl-3,3-(1,3-propanediylidithio)-propanal; yield: 2.77 g (73%) b.p. 56–57°C/760 torr (sublimates).

Halo-malonaldehyde monoacetals are valuable intermediates for many syntheses of heterocyclic compounds. A unique route has been reported for these reactive compounds, which starts from 1,1,3-triethoxypropene. This olefin is in turn obtained in good yields (up to 86%) from acrolein following different procedures. Halogen addition and subsequent careful dehydrohalogenation affords the 3-halomalonaldehyde monoacetal in a yield of up to 66%.
2-Bromo-3,3-diethoxypropanal**: To a solution of 1,3,3-triethoxypropane (425 g, 2.44 mol) in dry diethyl ether (1050 ml) is added with stirring at 0–10 °C over a period of 30 min, bromine (355 g, 2.22 mol) until a slight orange color of the reaction mixture remains. Most of the solvent is evaporated in vacuo with a maximum bath temperature of 30 °C. The yellow residue is then added in 40 min to a mixture of sodium hydrogen carbonate (323 g), dioxan (765 ml), and water (256 ml), maintaining the temperature between 5–10 °C. Stirring is maintained for an additional 2 h at 0–5 °C. The mixture is extracted with ether and the organic layer dried with sodium sulfate. Removal of the solvent under reduced pressure and distillation through a Vigreux column gives 2-bromo-3,3-diethoxypropanal; yield: 330 g (66%); b.p. 65–70 °C/4 torr.

Reaction of dialkoxyacetinitrile with 2-lithio-1,3-dithiane in tetrahydrofuran at −78 °C followed by acid hydrolysis gives 2-oxomalonaldehyde monoacetaetals; however, 2-oxo-3,3-(1,3-propanediylidithio)-propanal is obtained in poor yield from 2,2-dithoxyacetinitrile by this method. Only higher 2,2-dialkoxyalkenetenitriles are converted into the corresponding 2-(2-oxoalkanoyl)-1,3-dithianes in good yields (68–78%)..

\[
\begin{align*}
\text{C}_2\text{H}_5\text{O} & \quad \text{CH-CN} \quad \text{Li} \quad \text{THF, -78 °C, 40 min} \\
\text{C}_2\text{H}_5\text{O} & \quad \left[ \begin{array}{c}
\text{C}_2\text{H}_5\text{O} \\
\text{CH-CN} \quad \text{Li} \\
\text{C}_2\text{H}_5\text{O}
\end{array} \right] \quad \text{r.t., 2 h} \\
4% \text{HCl} & \quad \text{O=CH-S-C-O}
\end{align*}
\]

3. Synthesis of Succinaldehyde Monoacetaetals

3.1. Oxidative Cleavage of 1,1-Dialkoxy-4-alkenes

Succinaldehyde monodiethyl acetal has been prepared in high yields by classical oxidative breakdown of 1,1-diethoxy-4-pentene with potassium permanganate at 0 °C followed by cleavage of the intermediate glycol with lead(IV) acetate. Similarly good results can be obtained by ozonolysis of the double bond according to the procedure described for 1,1-di-n-butoxy-3-butene (see Section 2.1.3).

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{OC} & \quad \text{OC}_2\text{H}_5 \\
\text{OC}_2\text{H}_5 & \quad 1. \text{KMnO}_4, 0 °C \\
2. \text{Pb(OAc)}_2 & \quad \text{H} & \quad \text{OC}_2\text{H}_5 \\
\text{OC}_2\text{H}_5 & \quad 8% \text{HClO}_4, \text{H}_2\text{O}/\text{dioxan} & \quad \text{H}
\end{align*}
\]

This method appears to be very convenient, since y,δ-unsaturated aldehydes are easily available through Claissen rearrangement of suitable allyl enol ethers.

2-Aryl substituted half-protected succinaldehyde has been obtained in four steps from phenylacetinitriles in 46% overall yield. The key step of this synthetic route consists in the oxidation of 2-aryl-4-pentenal cyclic acetal with the osmium tetroxide/sodium periodate system to the target compound.

3-(p-Methoxyphenyl)-4,4-ethanediylidioxbutanal**: 4-(p-Methoxyphenyl)-5,5-ethanediylidiox-1-pentene (0.5 g, 2 mmol) is partitioned between diethyl ether (12 ml) and distilled water (10 ml). Osmium tetroxide (51 mg, 0.2 mmol) is added to the vigorously stirred solution, producing the black osmate ester. Sodium metaperiodate (5 g, 23 mmol) is added in portions over 20 min and the mixture stirred for 20 h. The phases are separated, the aqueous phase extracted with ether (2 x 10 ml), the combined organic phase dried with magnesium sulfate, and concentrated. The resulting oil, filtered through neutral alumina (5 g) using benzene/chloroform 2:1, gives the mono-protected aldehyde; yield: 0.4 g (80%).

3.2. Alkylation of 1,3-Dithiane with Suitable Reagents

The carbonium generated from 1,3-dithiane by the action of n-butyllithium undergoes alkylation in excellent yield with 3-halo-propanal acetals. The formed bis-acetal can be easily and selectively hydrolyzed (see Section 2.2.) to a monothioacetal of the succinaldehyde.

\[
\begin{align*}
\text{X} & \quad \text{Cl}, \text{Br} \\
\text{OR} & \quad 8% \text{HClO}_4, \text{H}_2\text{O}/\text{dioxan}
\end{align*}
\]

A variety of substituted half-protected succinaldehydes can be prepared in this way by suitably selecting the structure of the alkylating bromoacetal.

Acetoxy-succinaldehydes with both carbonyl functions simultaneously protected by different masking groups are obtainable by reaction of 3,3-dialkoxy-1,2-epoxypropanes with lithiated 1,3-dithianes, followed by acetylation of the resulting diacet-alcohol. Selective deacetalization at the dithiane moiety carried out with the
mercury(II) oxide/boron trifluoride reagent in aqueous tetrahydrofuran gives 3-acetoxy-4,4-dialkoxybutanals in good overall yield (up to 72%).

Moreover, a facile 1,2-elimination of acetic acid by treatment of the acetoxyacetals with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) gives rise to 4,4-dialkoxy-2-butenals, these in turn can be selectively hydrogenated at the C=C double bond to give succinaldehyde monoacetals in good yield.

Cyclic succinaldehyde monothioacetals can be directly obtained in poor-to-moderate yield through an 1,4-addition of lithiated 1,3-dithianes to a variety of acroleins in tetrahydrofuran/hexamethylphosphoric triamide solution at low temperature. This type of substrate appears to be more prone towards conjugate addition under these reaction conditions, although 1,2-addition products are customarily predominant.

Thus, α-methylacrolein, when treated with 2-lithio-1,3-dithiane at −70°C for 30 min affords 2-methyl-4,4-trimethylenebis(dithio) in about 40% yield (determined by 1H-N.M.R. spectrometry).

3.3. Hydroformylation of α,β-Unsaturated Aldehyde Acetals

In spite of serious limitations due to both the use of high-pressure apparatus and selectivity problems, the hydroformylation of acetals of α,β-unsaturated aldehydes is an important method for preparing succinaldehyde monoacetals. Rhodium carbonyl complexes are the catalysts of choice: they give customarily higher chemoselectivities and yields, and are more generally applicable.

The hydroformylation of acrolein cyclic acetals has received particular attention in the recent patent literature as a route to 1,4-butanedio[42,43]. The influence of various reaction parameters on the regioselectivity towards the formation of the linear oxo-aldehyde has been thoroughly investigated: Table 1 reports the most interesting results among those obtained in many hydroformylation experiments carried out with the purpose of maximizing the yield of succinaldehyde monoacetals. By modifying the rhodium catalytic precursors with tertiary phosphines or phosphites and carefully selecting the reaction pressure, the carbon monoxide partial pressure, and the reaction temperature, up to 95% formylation in the terminal position of the olefinic substrate has been reached.

Only cyclic acetals of acrolein produce the typical oxo-aldehydes mixture when hydroformylated in the presence of cobalt carbonyl complexes (see Section 2.3.): in general, good yields (up to 82%) of the linear isomer are achieved.

The presence of an alkyl or aryl substituent (even a methyl group) in the 2-position of an acrolein acetal is sufficient to force the introduction of the formyl group on the terminal carbon atom of the vinylidene double bond.

The results obtained in several hydroformylation experiments using various unsaturated acetals as substrates and rhodium complexes as catalytic precursors are listed in Table 2. The yields range from 75 to 90%; the final product can be isolated from the crude reaction solution by simple fractional distillation over anhydrous potassium carbonate.

Also, cinnamaldehyde diethyl acetal is smoothly hydroformylated under the above-mentioned conditions giving phenylsuccinaldehyde monoacetal in about 90% selectivity (Table 2).

Unfortunately, this marked tendency for α-formylation of a double bond conjugated with an aromatic ring is
Table 1. Hydroformylation of Acrolein Cyclic Acetals to give Succinaldehyde Monoacetals

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalytic Precursor</th>
<th>Modifying Ligand&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Temperature&lt;sup&gt;b&lt;/sup&gt; [°C]</th>
<th>Pressure&lt;sup&gt;b,c&lt;/sup&gt; [atm]</th>
<th>Yield&lt;sup&gt;d&lt;/sup&gt; [%]</th>
<th>Selectivity&lt;sup&gt;e&lt;/sup&gt; [%]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH—CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) &lt;sub&gt;12&lt;/sub&gt;</td>
<td>(H&lt;sub&gt;2&lt;/sub&gt;CO) &lt;sub&gt;2&lt;/sub&gt;P</td>
<td>110°</td>
<td>6.5</td>
<td>88</td>
<td>81</td>
<td>44</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) &lt;sub&gt;12&lt;/sub&gt;</td>
<td>(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;O) &lt;sub&gt;2&lt;/sub&gt;P</td>
<td>90°</td>
<td>2.7</td>
<td>95</td>
<td>95.5</td>
<td>45</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) &lt;sub&gt;12&lt;/sub&gt;</td>
<td>(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;O) &lt;sub&gt;2&lt;/sub&gt;P</td>
<td>85°</td>
<td>6.1</td>
<td>—</td>
<td>&gt;95</td>
<td>46, 47</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) &lt;sub&gt;12&lt;/sub&gt;</td>
<td>(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;O) &lt;sub&gt;2&lt;/sub&gt;P</td>
<td>105°</td>
<td>5.3</td>
<td>89</td>
<td>85</td>
<td>48</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;C═CH</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) &lt;sub&gt;12&lt;/sub&gt;</td>
<td>(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;O) &lt;sub&gt;2&lt;/sub&gt;P</td>
<td>150°</td>
<td>70</td>
<td>85&lt;sup&gt;f&lt;/sup&gt;</td>
<td>81</td>
<td>49</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;C═CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) &lt;sub&gt;12&lt;/sub&gt;</td>
<td>(H&lt;sub&gt;2&lt;/sub&gt;CO) &lt;sub&gt;2&lt;/sub&gt;P—R&lt;sup&gt;g&lt;/sup&gt;</td>
<td>150°</td>
<td>70</td>
<td>89</td>
<td>82</td>
<td>49</td>
</tr>
</tbody>
</table>

<sup>a</sup> All phosphine and phosphite ligands are present in a molar excess over rhodium.
<sup>b</sup> Initial pressure at room temperature (1:1 mixture of carbon monoxide/hydrogen).
<sup>c</sup> The carbon monoxide partial pressure is gradually reduced by addition of hydrogen up to 0.7 atm within 40 min.
<sup>d</sup> Total yield of hydroformylation products.
<sup>e</sup> Selectivity [%] = mol of succinaldehyde monoacetals × 100
| total mol of oxo-products |
<sup>f</sup> Composed of 67% aldehyde and 19% alcohol.
<sup>g</sup> R = C<sub>20</sub>—C<sub>26</sub> alkyl group.

Table 2. Hydroformylation of α,β-Unsaturated Aldehyde Acetals in the Presence of Rhodium Catalysts<sup>a</sup>

<table>
<thead>
<tr>
<th>Substrate&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Amount [mol/l]</th>
<th>Catalyst (Amount [mol/l])</th>
<th>Pressure&lt;sup&gt;c&lt;/sup&gt; [atm]</th>
<th>Temperature&lt;sup&gt;b&lt;/sup&gt; [°C]</th>
<th>Reaction Time [h]</th>
<th>Yield&lt;sup&gt;d&lt;/sup&gt; [%]</th>
<th>Selectivity&lt;sup&gt;e&lt;/sup&gt; [%]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH—CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.33</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) [P(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>100&lt;sup&gt;f&lt;/sup&gt; (2.41)</td>
<td>80°</td>
<td>1.5</td>
<td>98</td>
<td>58</td>
<td>52</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH—CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2.12</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) [P(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>100&lt;sup&gt;f&lt;/sup&gt; (2.97)</td>
<td>80°</td>
<td>2</td>
<td>76</td>
<td>98</td>
<td>52</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH—CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.20</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) [P(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>100&lt;sup&gt;f&lt;/sup&gt; (2.20)</td>
<td>105°</td>
<td>5.5</td>
<td>75</td>
<td>98</td>
<td>52</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH—CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.62</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) [P(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>20&lt;sup&gt;f&lt;/sup&gt; (4.00) (24.00)</td>
<td>110°</td>
<td>73</td>
<td>60</td>
<td>98</td>
<td>52</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH—CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.23</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) [P(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>100&lt;sup&gt;f&lt;/sup&gt; (5.82)</td>
<td>95°</td>
<td>5</td>
<td>85</td>
<td>98</td>
<td>52</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH—CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.00</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) [P(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>100&lt;sup&gt;f&lt;/sup&gt; (2.48)</td>
<td>90°</td>
<td>5.5</td>
<td>80&lt;sup&gt;f&lt;/sup&gt;</td>
<td>98</td>
<td>52</td>
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<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH—CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3.21</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) [P(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>100&lt;sup&gt;f&lt;/sup&gt; (7.97)</td>
<td>80°</td>
<td>3</td>
<td>90</td>
<td>70</td>
<td>53</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH—CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0.76</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO)</td>
<td>120&lt;sup&gt;f&lt;/sup&gt; (9.84)</td>
<td>120°</td>
<td>9</td>
<td>—&lt;sup&gt;i&lt;/sup&gt;</td>
<td>—</td>
<td>53</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C═CH—CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2.00</td>
<td>Rh&lt;sub&gt;3&lt;/sub&gt;(CO) [P(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>100&lt;sup&gt;f&lt;/sup&gt; (2.80)</td>
<td>80°</td>
<td>—&lt;sup&gt;j&lt;/sup&gt;</td>
<td>75</td>
<td>90</td>
<td>54</td>
</tr>
</tbody>
</table>

<sup>a</sup> Solvent: benzene.
<sup>b</sup> Reaction mixture contains 0.70–0.75 mol triethylamine/mol substrate.
<sup>c</sup> 1:1 mixture of carbon monoxide/hydrogen.
<sup>d</sup> Yield of formylation products isolated by distillation.
<sup>e</sup> Selectivity [%] = mol of succinaldehyde monoacetal × 100
| total mol of oxo-products |
<sup>f</sup> Initial pressure at room temperature.
<sup>g</sup> Experiment performed at constant pressure.
<sup>h</sup> 5% Rhodium on charcoal.
<sup>i</sup> Hydrogenation products of substrate (15%) detected by G. L. C. and 1H-N. M. R. analysis.
<sup>j</sup> Only hydrogenation product of substrate found in reaction mixture.
<sup>k</sup> Not detected.
not maintained in aliphatic substrates: thus, the regioselectivity in the hydroformylation of crotonaldehyde ethanediol esters, for the α-formylation from 90 to 70% (Table 2).

Surprisingly, no reaction was noticed during the hydroformylation of the ethanediol ester of 4-methylhex-2-enal at 100°C and 100 atm (carbon monoxide/hydrogen = 1:1) using rhodium(III) oxide as the rhodium carbonyl precursor; at 120°C and 120 atm only hydrogenation of the double bond occurs (Table 2).\(^{13}\)

Optically active 2-alkylacrolin acetalts having the asymmetric center adjacent to the double bond can be hydroformylated with rhodium/tertiary phosphine complexes under standard conditions without appreciable racemization (~4%)\(^{12}\); indeed, it is well known\(^{16}\) that this type of catalyst does not promote double bond isomerization, which, in this case, induces loss of optical activity.

Hydroformylation of 2-Alkyl- or 2-Aryl-α,β-unsaturated Aldehyde Acetals, General Procedure\(^{22,34}\).

Method A: Into an evacuated 0.21 autoclave containing carbonyl rhodiumbis[triphenylphosphine] chloride (0.300 g), a solution of the unsaturated acetal (0.1 mol) and triethylamine (11.5 ml) in dry benzene (40 ml) is introduced by suction. A mixture of carbon monoxide and hydrogen (1:1) is then introduced to a pressure of 100 atm; the autoclave is then rocked and heated to 80°C. Reaction starts immediately and is allowed to proceed until no more pressure drop is observed. After cooling and release of the pressure, the slightly yellow reaction mixture is evaporated under reduced pressure (100 torr) and the residue is distilled under vacuum over potassium carbonate to give the 2-alkyl- or 2-arylsuccinylaldehyde acetal as a colorless liquid; yield: 60–80%.

Method B: Following the same experimental procedure, the unsaturated acetal (0.4 mol) in benzene (200 ml) is hydroformylated in a 0.51 autoclave using 5% rhodium on charcoal (2.0 g) and triethylamine (0.5 ml) at 20 atm and 110°C; yield: 73%.

Following the experimental procedure described in Method A, cinnamaldehyde diethylacetal in benzene containing triethylamine is hydroformylated in to 2-phenyl-4,4-dihydroxybutanone (≥ 90% selectivity) using carbonyl rhodiumbis[triphenylphosphine] chloride as the catalyst (0.15–0.2 mol%) with respect to substrate\(^{34}\); yield: 75%.

3.4. Alkylation of Lithium Derivatives of Aldimines with Bromoacetaldehyde Acetals

A direct and fast synthesis of succinaldehyde monoacetals has been described\(^{57}\); according to this procedure aldimine carbonates react with α-bromoacetals in hexamethyldiphosphoric triamide at low temperature to give the corresponding acetal-imines in good yield. These products are then selectively hydrolyzed with a tartaric acid solution at 0°C\(^{57}\). Aldimine carbonates are easily prepared from aldimes by the action of "activated lithium amides"\(^{35,58}\).

2-n-Butyl-4,4-ethanediolbutanal\(^{57}\):
To a stirred solution of lithium dialkylamide\(^{18}\) (4.4 g, 0.06 mol) in hexamethyldiphosphoric triamide (10 ml) and benzene (10 ml) a solution of n-hexanal cyclohexylamine (10.9 g, 0.06 mol) in tetrahydrofuran (10 ml) is added at −60°C. The mixture is stirred and heated up to −10°C within 2 h; then it is cooled again to −60°C and 2-bromocarbonyl-1,3-dioxolane (8.35 g, 0.05 mol) in tetrahydrofuran (10 ml) is added. This mixture is allowed to warm up and hydrolyzed at 0°C by stirring for 5 h with aqueous tartaric acid. Separation of the organic layer, drying, and evaporation of the solvent affords the crude half-protected aldehyde, which is purified by distillation in vacuo; yield: 85%; b.p. 99°C/0.01 torr.

3.5. Other Methods

An interesting example of the preparation of 1,4-dialdehyde monoacetals was reported\(^{59}\): 4-halo-2,3-ununsaturated aldehydes are directly converted to the desired products by the action of alkali metal alkoxides or phenoxides under mild reaction conditions.

γ-Acetal esters have been described as a source of succinaldehyde dialkyl monoacetals\(^{60}\); these compounds are obtained in yields higher than 90% by reducing the ester function with diisobutylaluminium hydride (DIBAH) at −70°C. The starting compounds can be prepared in satisfactory yields (40% overall) from formylsuccinic acid dialkyl esters\(^{60}\).
4.4-Diethoxybutanal\(^{16}\)

To a solution of disobutyldialuminium hydride (3.5 g, 24.5 mmol) in anhydrous diethyl ether (10 ml) a solution of 4,4-diethoxybutanoic acid ethyl ester (2.5 g, 12.2 mmol) in anhydrous ether (20 ml) is slowly added at \(-70^\circ C\) under argon atmosphere. After 1 h the mixture is poured into a saturated solution of ammonium chloride and stirred vigorously; an excess of 20\% orthophosphoric acid is added at 0\(^\circ C\). The phases are separated, the ether solution is washed with saturated sodium chloride solution and then with saturated sodium hydrogen carbonate solution. Drying with sodium sulfate and removal of the solvent gives 4,4-diethoxybutanal; yield: 1.8 g (92\%, crude).

4. Synthesis of Glutaraldehyde Monoacetals

These compounds are only sparingly described in the literature; some individual members of this class have been prepared as intermediates in organic syntheses. However, several methods successfully employed in the preparation of malonaldehyde and succinaldehyde monoacetals can also be used in principle for obtaining glutaraldehyde monoacetals.

4.1. Oxidative Methods

4-(1,3-Dioxolan-2-yl)butanal has been obtained in 65\% yield by ozonolysis of cyclopentene in ethyl acetate at \(-15\) to \(-20^\circ C\) in the presence of ethyleneglycol and p-toluenesulfonic acid followed by reduction of the ozonide with palladium on charcoal at pH 8.5\(^{16}\). This method is claimed to be of general application also for the preparation of homologous half-protected dialdehydes.

\[
\begin{align*}
\text{H}_2\text{O} + \text{C}_\text{H}_2\text{OAc} + \text{TFA} + \text{CH}_2\text{C}_\text{H}_4 \\
\text{H}_2\text{PtOAc} - \text{C} & \rightarrow \text{C}_\text{H}_2\text{OAc} + \text{CH}_3\text{CHO} \\
\end{align*}
\]

Anodic oxidation of cyclopentane-1,2-diols in methanol containing tetraethylammonium sulfonate as an supporting electrolyte brings about the formation of the methyl mono- and bis-acetals of glutaraldehyde\(^{2,2}\); however, the synthetic value of this method is strongly reduced by the unfavorable ratio of the desired dimethoxy with respect to the tetramethoxy-derivative\(^{62}\).

The ethyleneglycol monoacetal of 2-methylene glutaraldehyde has been prepared in five steps from the easily available ethyl 2-ethoxy carbonyl-4-formyl-butanate\(^{6,2}\); the final step of this reaction scheme consists in the oxidation of an allyl alcohol with manganese dioxide to the corresponding unsaturated aldehyde. The overall yield is 10\%.

2-Methylene-5,5-ethanediylidioxypentanol\(^{16}\).

A mixture of 2-methylene-5,5-ethanediylidioxypentanol (12 g, 76 mmol), carbon tetrachloride (200 ml), and active manganese dioxide (80 g, 0.32 mol) is stirred at room temperature for 6 h, then filtered, and the solvent removed. The residue is chromatographed over alumina and the fraction obtained by eluting with benzene/petroleum ether (20:80) is taken up on. On vacuum distillation, this fraction gives 2-methylene-5,5-ethanediylidioxypentanol; yield: 7 g (51\%) in b.p. 105\(^\circ C/12\) torr.

A synthetic method which is worthy of particular attention and seems to have the merit of general applicability is that reported recently\(^{44,65}\): readily accessible allyl alcohols are used as starting materials and converted to 5,5-diethoxy pentanols through Claisen rearrangement of the corresponding vinyl ethers.

\[
\begin{align*}
\text{R} + \text{H}_2\text{C} \rightarrow \text{R} & \rightarrow \text{R} \rightarrow \text{R} \\
\text{CH}_3\text{OH} / \text{HCl} & \rightarrow \text{R} \rightarrow \text{R} \\
\text{2. BnH-THF/CH}_2\text{OH/normal NaOH} \\
\text{R} + \text{H}_2\text{C} \rightarrow \text{R} & \rightarrow \text{R} \\
\end{align*}
\]

Each step runs with excellent yield; the final oxidation reaction of the primary alcohol group is carried out with chromium trioxide/pyridine complex or with pyridinium chlorochromate and proceeds in 68 - 76\% yield\(^{44,65}\). It is to be pointed out that this synthetic route has made available 3,3-disubstituted half-masked glutaraldehydes not easily accessible by other methods.

4.2. Partial Hydrolysis of Glutaraldehyde Bis-Acetals or Alcoholysis of Dihydropyran or Tetrahydropyran Derivatives

Partial hydrolysis of bis-ethanediol diacetals of glutaraldehyde has been accomplished in the presence of acid catalysts; the reaction mixture contains 48\% of the desired monoacetal\(^{66}\). It is interesting to note that the same product is obtained in 40\% yield by partial acetalization of glutaraldehyde with ethyleneglycol (2:1 molar ratio) at 150\(^\circ C\).\(^{67}\) Monoacetals of the same dialdehyde are obtained together with variable amounts of the corresponding bis-acetal by reacting 2-alkoxy-2,3-dihydro-2H-pyran with alcohols\(^{68}\) or glycols\(^{69}\) under acidic conditions; the highest yield (31\%) has been achieved when
an equimolecular mixture of 2-methoxy-2,3-dihydro-2H-pyran and ethyleneglycol are heated in the presence of a catalytic amount of the cationic resin SKIB at 90 °C for 30 min.

\[
\begin{align*}
R^2 - \text{OH} & \rightarrow R^2O - \text{CH} \\
\text{OH} & / \text{SKIB, 90 °C, 30 min} \\
\end{align*}
\]

\( R^1 = \text{H, alkyl, aryl, aralkyl, } R^2 = \text{alkyl} \)

The starting material is easily available by cycloaddition reaction between an \( \alpha,\beta \)-unsaturated aldehyde and a vinyl ether\(^7\). Also, 1,6-dialkoxytetrahydropyrans have been employed as a source of glutaraldehyde monoacetals\(^7\); they are transformed in the corresponding half-masked 1,5-dialdehydes by reaction with glycols in the presence of acid catalysts. Yields are not reported.

\[
\begin{align*}
\text{R}^1\text{O} & \text{H} \quad \text{C}_2\text{H}_5\text{O} \\
\text{HCl, 88 °C} & \quad \text{R}^2\text{O} - \text{CH} \\
\end{align*}
\]

\( R = \text{H}_2\text{C} = \text{CH}^– \).

### 4.3. Homologation Reaction of Succinaldehyde Monoacetals

A remarkable method for obtaining glutaraldehyde monoacetals consists of the homologation of succinaldehyde monoacetals. One of the best ways to accomplish such a transformation is the Wittig reaction using \( \alpha \)-alkoxy- or \( \alpha \)-alkyliodotriphenylphosphonium salts\(^2,13,12\).

In principle, this reaction can be successfully used to convert also half-protected malonaldehydes into succinaldehyde monoacetals.

Thus, (S)-2-(s)-butylsuccinaldehyde diethyl monoacetal was treated under phase-transfer conditions with a slight excess of methylthiomethyl-triphenylphosphonium chloride\(^7\): the Wittig adduct, obtained in 75% yield, can be selectively hydrolyzed at the thienol ether moiety to 2-alkyl-substituted glutaraldehyde diethyl monoacetal\(^7\).

\[
\begin{align*}
\text{R} & \quad \text{C}_2\text{H}_5\text{O} \\
\text{HCl} & / \text{CH}_2\text{Cl}_2/50 \% \text{ NaOH} \\
\end{align*}
\]

\( R = (S)-s - \text{C}_6\text{H}_5 \)

Another route to the same compounds has been recently proposed\(^7\). Although this method has not yet been conveniently optimized and needs a higher number of steps, it appears to permit interesting developments. The additional carbon atom is introduced into the succinaldehyde skeleton through a condensation reaction with nitromethane under basic conditions.

\[
\begin{align*}
\text{R}^2\text{O} - \text{CH} & \quad \text{H}_3\text{C} - \text{NO}_2/ \\
\text{10 % NaOH} & \quad \text{C}_2\text{H}_5\text{O} - \text{C}_2\text{H}_5 \\
\end{align*}
\]

Dehydration of the nitro alcohol, sodium borohydride reduction of the formed nitroolefin and hydrogen peroxide oxidation of the nitromethyl group to an aldehyde group in the presence of potassium carbonate produces 2-alkylglutaraldehyde monoacetal in 10% overall yield\(^7\). The poor selectivity found in the last step is responsible for the low yield obtained.

### 4.4. Rhodium-Catalyzed Hydroformylation of \( \beta,\gamma \)-Unsaturated Aldehyde Acetals

The rhodium-catalyzed hydroformylation of acetals or thiocacetals of \( \beta,\gamma \)-unsaturated aldehydes proves to be a very useful method for the production of half-protected 1,5-dialdehydes. Thus, 1,1-diethoxy-3-butene is smoothly converted at 110 atm (carbon monoxide/hydrogen = 1:1) and 100 °C in the presence of rhodium(III) oxide (1.4% with respect to the substrate) without any solvent to o xo-aldehydes in 70% yield; the regioselectivity of the reaction is slightly in favour of the branched isomer (56%)\(^7\).

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{C}_2\text{H}_5\text{O} \\
\text{110 atm, 100 °C} & \quad \text{H}_3\text{C} \text{O} - \text{C}_2\text{H}_5 \\
\end{align*}
\]

As expected, a single hydroformylation product is formed, if the acetal of the \( \beta,\gamma \)-unsaturated aldehyde bears an alkyl substituent in the \( \beta \)-position.
Accordingly, (S)-2-s-butyl-4,4-(1,3-propanediylidithio)or (S)-2-s-butyl-4,4-diethoxy-1-butene give, on hydroformylation catalyzed by HRh(CO)\([\text{P(C}_8\text{H}_8\text{H}_3\text{H}_2\text{Cl}_2]}\) and RhCl(CO)\([\text{P(C}_8\text{H}_8\text{H}_3\text{Cl}_2]}\) respectively, under standard conditions, the desired o xo-products in 50–60% yield (based on the starting allyl halide)78,79. Remarkably, the presence of sulfur atoms in the substrate is tolerated by the rhodium catalysts. The reaction occurs with almost complete retention of optical activity at the asymmetric center present in the molecule.

\[(S)-3\text{-s-butyl-5,5-(1,3-propanediylidithio)-pentanal}^{80}\]

\[(S)-2\text{-s-butyllallyl)-1,3-dithiane (23.8 g, 0.11 mol) in dry benzene (100 ml) is hydroformylated with a mixture of carbon monoxide and hydrogen (1:1) at 100 atm and 100 °C in the presence of HRh(CO)\([\text{P(C}_8\text{H}_8\text{H}_3\text{H}_2\text{Cl}_2]}\) (0.2 g). After 36 h, > 90% of the substrate has reacted (G.L.C.). After cooling and releasing of the pressure, the mixture is evaporated under reduced pressure (20 torr) and the residual aldehyde is directly purified through its hydrogen sulfite derivative; Quite pure \((S)-3\text{-s-butyl-5,5-(1,3-propanediylidithio)-pentanal}^{80}\) is recovered by distillation in vacuo as a pale yellow oil; yield: 18.9 g (70%), b. p. 128–130°C/0.04 torr.

\[(S)-3\text{-s-butyl-5,5-diethoxypentanal}^{80}\]

\[(S)-2\text{-s-butyl-4,4-diethoxy-1-butene (20 g, 0.1 mol) in dry benzene (40 ml) containing triethylamine (6.42 g, 83 mmol) is hydroformylated with a mixture of carbon monoxide/hydrogen (1:1) at 100 atm and 80–100 °C in the presence of RhCl(CO)\([\text{P(C}_8\text{H}_8\text{H}_3\text{Cl}_2]}\) (0.30 g). After 36 h no more pressure drop is observed. After cooling and releasing of the pressure, the mixture is evaporated under reduced pressure (100 torr) and the residuum distilled in vacuo over anhydrous potassium carbonate to give \((S)-3\text{-s-butyl-5,5-diethoxypentanal, 95 % pure by G.L.C.}; yield: 16.1 g (70%); b. p. 74 °C/0.05 torr.

### 4.5. Other Methods

Recently, O-silylated dienolates were reported to react with 1,3-dithienium tetrafluoroborate giving mixtures of glutaric aldehyde and 2-alkenyl-malonaldehyde monothioacetals80.

In the case of \(R = H\), the reaction is regiospecific and only the monothioacetal of glutaric aldehyde is formed in 30% yield. This compound might be considered as an interesting precursor of variously substituted glutaraldehyde monothioacetals.

#### 5. Selected Applications of Dialdehyde Monoacetals or Monothioacetals

Dialdehyde monoacetals or monothioacetals are widely used as intermediate compounds in many organic syntheses: diols, protected hydroxylaldehydes, aldehydes, formyl-carboxylic acids, bocarboxylic acids. Other useful bifunctional compounds have been, or can be, prepared through very simple reduction, oxidation, and condensation reactions.

The most important application from a quantitative viewpoint of succinaldehyde monoacetals consists in the industrial preparation of 1,4-butenediols, a valuable monomer for the production of engineering thermoplastic polybutene terephthalate83. This method has been developed in particular by Du Pont de Nemours & Co.; however, no commercial plants are working according this route up to date. Tetrahydrofuran can be also produced by dehydration of 1,4-butenediol84.

Other interesting applications from the industrial viewpoint of succinaldehyde cyclic monoacetals consist in the conversion of such compounds into N-protected glutamic acid \(\gamma\)-semialdehyde acetals; these intermediates give in turn racemic proline and tryptophan by hydrogenation over palladium on carbon in 0.5 normal hydrochloric acid and treatment with phenyldiazine, respectively82,83,84.

The Wittig reaction with various phosphorus ylids has been extensively employed to transform the simple dialdehyde monoacetals into more valuable synths85. The neutral or basic conditions required for this type of reaction allow to preserve the protection of the aldehyde group, which can react after hydrolysis in a selected step of a reaction sequence according to the synthesis strategy.

Particularly interesting is the application of the Wittig reaction to the synthesis of natural products such as dihydroagatone from 2-methyl-4,4-ethenodiyldioxo-5,5-butanal85. 5,5-ethenediyldioxypentanal85. Ethyl \((Z)-2\text{-bromo-6,5-dimethyl-7,7-dimethoxy-2-heptenoate, an important building-
block for marasmic acid, a unique sesquiterpene antibiotic, was prepared in 90% yield from 3,3-dimethylglutaraldehyde dimethyl monoacetal by treatment with (α-hydrindomethyl)-methylentriphenylphosphorane. The same mono-protected glutaraldehyde reacts with 3-(O,O-dimethylphosphonomethyl)-4-hydroxy-2-butenoic acid lactone to give a versatile diene-aldehyde intermediate for many synthetic applications.

Other authors report a direct conversion of the above monoacetal into the corresponding ethyl 2-(isopropylthiomethyl)-acrylate, a useful intermediate for the synthesis of the sesquiterpene α-methylene-f-lactones. An intramolecular Wittig reaction, which involves reaction of the anion of 2-(2-oxoalkanoyl)-1,3-dithianes with vinyltriphenylphosphonium salts leading to functionally substituted cyclopentenones has been described.

Many other nucleophilic additions to the free aldehyde group of both dialdehyde monoacetals and monoacetalcs are reported: Grignard reagents react under standard conditions with half-protected malonaldehydes and sucinaldehydes giving the expected secondary alcohols in satisfactory-to-good yields.

Other organometallic compounds like lithium or sodium acetylenides have been used to improve the functionality of half-masked malonaldehydes. Interestingly, organocuprates have been found to add with very high stereoselectivity to α-asymmetric aldehydes bearing a β-oxygen substituent: thus, reaction of lithium dimethylcuprate with monoethynediylloxymethylmalonaldehyde in diethyl ether at −78°C affords 1,1-ethanediylidioxy-2-methyl-3-hydroxybutanal with 92% threeo-configuration in 93% yield. Addition of 2-lithiopyridine to (S)-3-3-buty-5,5-diethoxypentalan in diethyl ether at −70°C proceeds smoothly leading to the expected pyridyl-carbinol in 50% yield: this is easily converted in three steps into (S)-2-(2'-pyridyl)-4-3-butylicypyrnidine, the first optically active member of the class of 2,2-bipyridines.

Carbanions generated from nitroalkanes react in high yields with the free aldehyde group of malonaldehyde and sucinaldehyde monoacetals leading to the corresponding nitro-alcohols: by suitably selecting the structure of the nitro compound, a very large number of versatile intermediates for organic syntheses are produced.

The condensation adduct between malonaldehyde monoacetal and ethyl propanoate has been employed as the starting material for the synthesis of the antimalarial and antitumor terpenoid apiladiaphanginosine.

The one-pot synthesis of a scecolagene analog has been accomplished by cycloaddition reaction of alkényl ethers with the condensation product obtained from a malonaldehyde cyclic monoacetal and the sodium salt of malonaldehyde.

The (E)-vinloxyborane, derived from S-phenylpropanediol, 9-boracycloxovanone triflate and disopropylethylamine, reacts stereospecifically with 3,3-(1,3-propanediylidithio)-prop-1-anal to give the corresponding erythro-3-hydroxy-2-methylpentanoate; such types of compounds are used advantageously in the synthesis of antibiotics.

One example of conversion of an alkyl substituted half-protected glutaraldehyde to the corresponding methyl ketone with diazomethane in 70% yield was described.

Difunctional linear compounds for polymer cross-linking are obtained by transforming the aldehyde group of dialdehyde monoacetals into a primary amino group either by lithium aluminium hydride reduction of the corresponding aldoxime or by reductive amination in the presence of nickel catalysts. Reductive alkylation in the presence of palladium catalysts has been used to join together a protected malonaldehyde with ethyl p-aminobenzoate and dimethyl p-aminobenzoylglycinate: the former product is an important intermediate for the synthesis of a pyrimidine analog of tetrahydrohomofolic acid. The free aldehyde group of 3-(p-methoxyphenyl)-4,4-ethanediylidioxysuccinaldehyde was cleanly transformed into a dimethylamino group in 60% yield through reductive amination using dimethyamine hydrochloride and sodium cyanoborohydride.

Dialdehyde monoacetals give under controlled pH conditions the usual products with hydroxylamine and hydrazine derivatives: treatment of the tosylhydrazone of 2,2-dimethyl-3,3-dimethoxymalonaldehyde with sodium methoxide in diglyme at 160–180°C brings about the formation of 1-methylcyclopropenecarboxaldehyde dimethyl acetal, a precursor of 1-methylcyclobutene.

Like tetraacetals, malonaldehyde monoacetals can be used as starting material for the synthesis of pyrazoles, isoxazoles, and pyrimidines with various substituents by reaction with hydrazine, hydroxylamine, and guanidine in acidic media. 2-Chloro- and 3-bromomalonaldehyde diethyl monoacetals have been used as building-blocks for the preparation of peridines: the total synthesis of pteroylglutamic acid, an important vitamin of B complex, was performed by condensation of 2,4,5-triamino-6-hydroxypririmidine with 2-bromomalonaldehyde diethyl monoacetal.

The four-membered heterocyclic ring of azeidinones, crucial synthons for obtaining thienamycin and its analogs, a class of exceptionally powerful broad-spectrum antibiotics, has been often formed using malonaldehyde monoacetals or monoacetalcs as convenient precursors.

Five-membered heterocyclic compounds are readily obtained from half-protected succinaldehydes: various acetals of 4-hydroxyaldehydes, available by reduction of the aldehyde group with lithium aluminium hydride or by addition of Grignard reagents, have been cyclized in the presence of ammonium nitrate at 160–230°C to 2-ethoxycarboxyhydrofurans, which in turn undergo dealkoxylation reaction catalyzed by phosphorous pentoxide to substituted 2,3-dihydrofurans. As expected, treatment of alkyl or aryl substituted succinaldehyde monoacetals with dilute aqueous acids produces 3-alkyl- or 3-aryl furans; the corresponding thiophenes and pyroles are formed in the presence of hydrogen sulfide or
ammonia, respectively. This method is particularly convenient for the synthesis of optically active 3-alkylfurans, thiophenes, and pyrroles; chemical yields up to 73% and optical yields up to 80% have been achieved.

Glutaraldehyde monoacetals are important precursors for pyridines: the classical reaction of these compounds with hydroxylamine hydrochloride represents the method of choice to prepare pyridine derivatives. Starting with monoacetals or monothioacetals of 1,5-dialdehydes having chiral substituents, optically active 3- or 4-substituted pyridines with high optical purity have been obtained. The yields of this cyclization reaction are between 40 and 60%.

6. Addendum

The addition of 2-lithio-1,3-dithiane to α,β-unsaturated aldehydes was further investigated. It was found that the ratio 1,2- to 1,4-addition remarkably depends on the reaction medium; the extent of the conjugate addition of the lithium derivative to crotonaldehyde, cinnamaldehyde, 3-methyl-2-butenal, and α-methylacrolein was always less than 5% when the reaction was carried out in tetrahydrofuran at −78 °C. This percentage rose to 45% and 55% in the case of crotonaldehyde and α-methylacrolein, respectively, when the reaction was accomplished in tetrahydrofuran/hexamethylphosphoric triamide (80/20) at the same temperature.

The products of conjugate additions consist of half-protected substituted succinaldehydes.

$$\text{H}_2\text{C}-\text{C}=\text{O} + \text{S-Li} \xrightarrow{\text{THF/HMPA}} \text{S-CH}_2=\text{O}$$

Succinaldehyde with an aldehyde group protected as a cyclic thioacetate was prepared in 75% overall yield by the following scheme:

$$\text{Li} + \text{Br} \xrightarrow{\text{THF/HMPA}} \text{THF/HMPA}$$

This compound proved to be a very useful building block for the synthesis of the trans-fused decalin system bearing a single angular methyl group, a ubiquitous structural subunit in terpenoid and steroid natural products.

Another example of the use of monothioacetalized malonaldehyde as starting product for the synthesis of a d6-6-phenylalmino-1-carbapen-2-εm derivative, a non-classical β-lactam antibiotic, was recently reported.

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