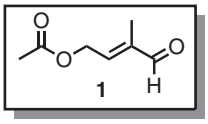
1
C–C Bond Formation

C–C bond formations are essential for the construction of the backbone of any organic compound, and their mechanistic description can be used as a general tool for their classification. Thus, in Sections 1.1–1.8, the focus is on transformations in which nucleophilic, electrophilic, radical, and pericyclic reactions as well as reactions mediated by organometallics and transition-metal compounds play the decisive role.

In Section 1.1, examples are given of nucleophilic additions to the carbonyl group of aldehydes, ketones, and derivatives of carboxylic acids (esters, anhydrides, etc.) as well as addition to acceptor-substituted olefins (Michael addition) and carbonyl olefination. In Section 1.2, alkylation reactions of aldehydes, ketones, carboxylic acids, and β-dicarbonyl compounds at their α- and γ-positions are described. In Section 1.3, reactions of the aldol and Mannich type and in Section 1.4, electrophilic and nucleophilic acylation reactions are depicted. Section 1.5 deals with reactions of alkenes proceeding via carbenium ions and Section 1.6 with transition-metal-catalyzed reactions such as the Heck reaction and Suzuki–Miyaura, Sonogashira, and metathesis reactions. In Section 1.7, pericyclic reactions such as cycloadditions, electrocyclic transformations, and sigmatropic reactions, and, finally, in Section 1.8 some basic radical reactions are described. Further transition-metal-catalyzed transformations such as the Wacker oxidation are described in Chapters 2 and 5.

1.1
Nucleophilic Addition to Aldehydes, Ketones, Carboxylic Acid Derivatives (Esters, Anhydrides), and α,β-Unsaturated Carbonyl Compounds; Carbonyl Olefination

1.1.1
(*E*)-4-Acetoxy-2-methyl-2-butenal



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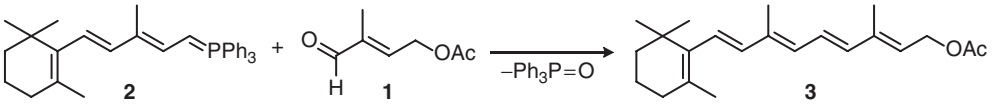
Topics:

- Preparation of a C_5-building block for vitamin A synthesis
- Allylic alcohols from ketones and vinyl Grignard compounds
- Acetylation of an allyl alcohol with allylic inversion
- Kornblum oxidation $R-CH_2-X \rightarrow R-CH{=}O$

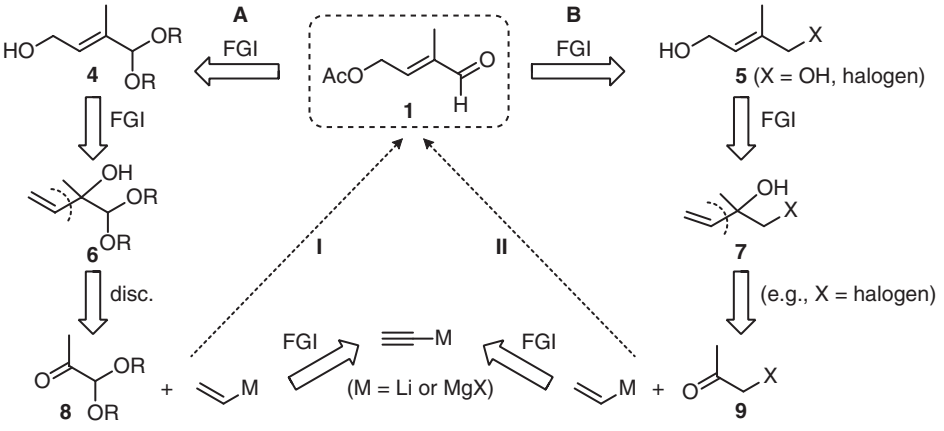
Reactions and Syntheses in the Organic Chemistry Laboratory, Second Edition.
Lutz F. Tietze, Theophil Eicher, Ulf Diederichsen, Andreas Speicher, and Nina Schützenmeister.

(a) **General**

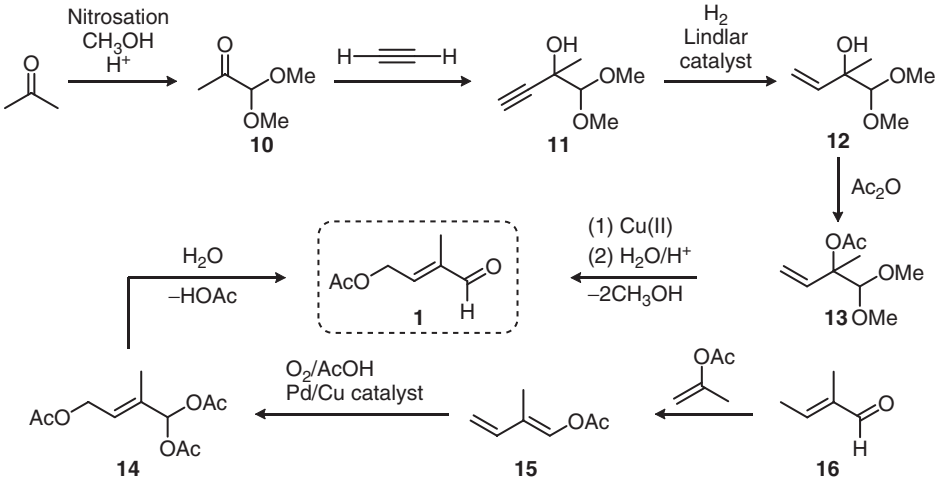
(*E*)-2-Methyl-2-butenal bearing an acetoxy group at the 4-position can be regarded as a functional isoprene unit and is used as a C_5-building block for the synthesis of terpenes by carbonyl olefination [1]. Thus, in the classical industrial vitamin A synthesis of BASF (cf. Section 4.1.5), (*E*)-4-acetoxy-2-methyl-2-butenal (**1**) is combined with the C_{15}-ylide **2** in a Wittig reaction to give vitamin A acetate **3**:



Retrosynthesis of the target molecule **1** can be conducted in two directions (**A**/**B**) via the intermediates **4**/**5** and further by allylic inversions to allyl alcohols **6**/**7**. These should result from the acetone derivatives **8**/**9** either by addition of allyl metals or by ethynylation followed by partial hydrogenation of the primarily formed acetylenic alcohols (approaches **I**/**II**). Both approaches **I** and **II** have been described in Refs [2, 3].

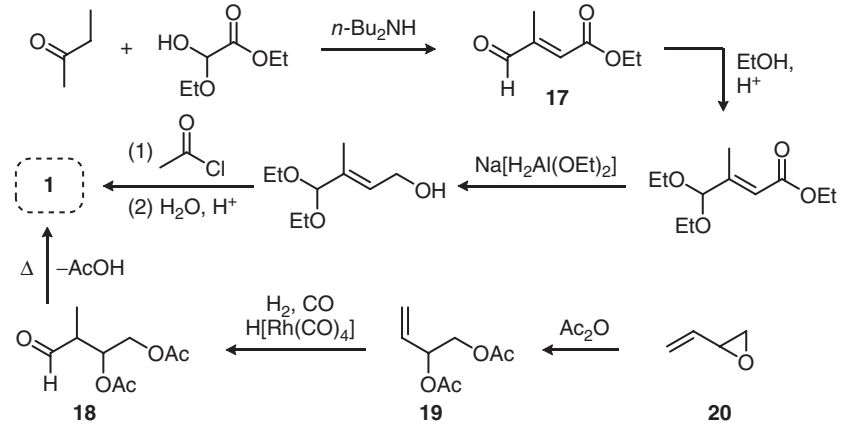


Approach **I** corresponds to a former industrial synthesis of **1** by BASF [2], starting with oxidation (nitrosation in the presence of methanol) of acetone to give methylglyoxal dimethyl acetal (**10**). This is followed by ethynylation with acetylene, partial hydrogenation, and acetylation (**10** → **11** → **12** → **13**). The synthesis is completed by a Cu(II)-catalyzed allylic inversion and acid hydrolysis of the acetal function (**13** → **1**). Alternatively, oxygenation of the dienol acetate **15** with O_2 in glacial acetic acid in the presence of a Pd/Cu catalyst leads to the allyl-inverted acylal **14**. Hydrolysis of the latter gives **1** [4, 5]; **15** can be obtained from the readily available tiglic aldehyde (**16**) and isopropenyl acetate:



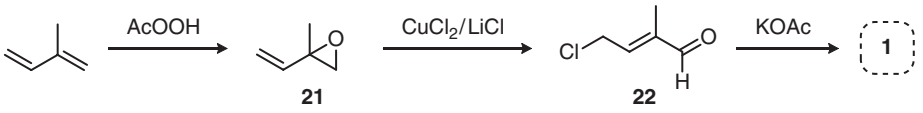
Approach **II** is the basis of a laboratory synthesis of **1** [3], which is described in detail in Section (b).

More recently, two other processes have been introduced for the industrial syntheses of **1** [6], starting from (i) 3-formyl crotonate **17** and (ii) 3,4-epoxy-1-butene

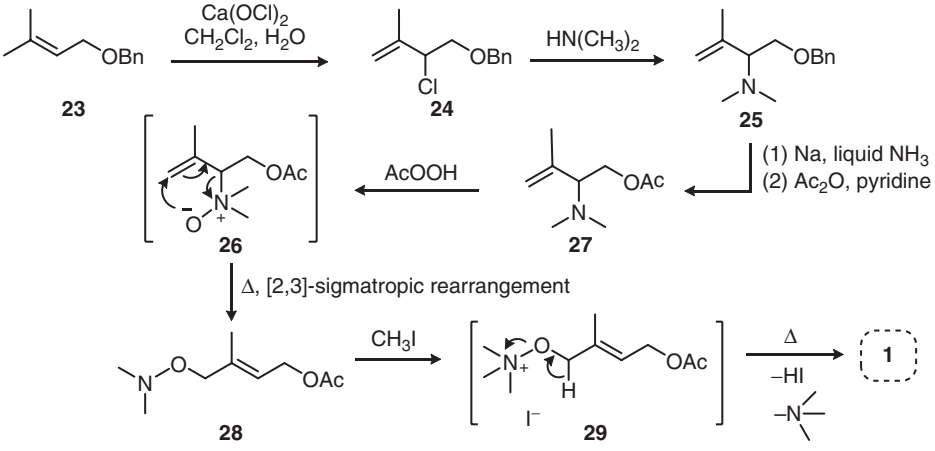


(**20**), respectively. In (ii), the key step is a regioselective Rh-catalyzed hydrocarbonylation (→**18**) of the diacetate **19**, obtained by ring opening of **20** with acetic anhydride.

Likewise, isoprene monoepoxide (**21**) undergoes ring opening with subsequent oxidative chlorination upon reaction with $CuCl_2$/LiCl. The product is (*E*)-4-chloro-2-methyl-2-butenal (**22**), which yields **1** upon substitution of chlorine by acetate [7]:



A more complex synthesis of **1** [8] is initiated by ene-type chlorination [9] of prenyl benzyl ether (**23**) with hypochlorite. In this reaction, the double bond is regioselectively transposed to the *gem*-dimethyl position to give **24**, in which the allylic chlorine can be substituted by dimethylamine (→**25**). The benzyl ether moiety is replaced by acetate, and the formed allylamine **27** is oxidized with peracetic acid to afford exclusively the (*Z*)-configured allyloxyamine **28**. This transformation involves a [2,3]-sigmatropic rearrangement of the primarily formed *N*-oxide **26**. N-Alkylation of **28** with CH_3I followed by a thermal Hofmann-like elimination of $(CH_3)_3N$ finally provides **1** via **29**:



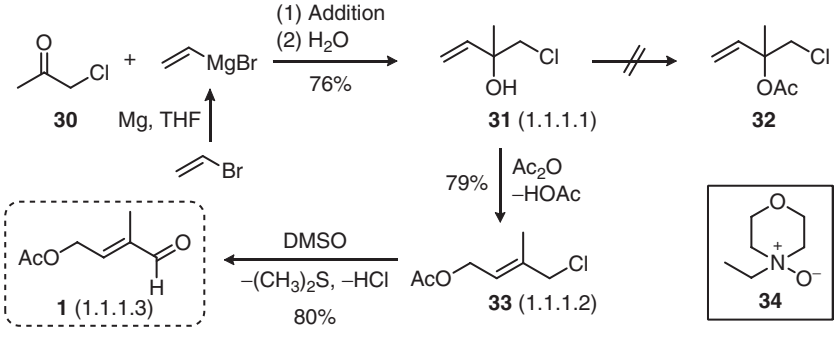
(b) **Synthesis of 1**

The synthesis of **1** starts with the addition of vinyl magnesium bromide to chloroacetone (**30**) to afford the isoprene chlorohydrin (**31**). For the formation and handling of vinyl Grignard compounds, the use of tetrahydrofuran (THF) as solvent is crucial [10]. When the tertiary alcohol **31** is treated with acetic anhydride in the presence of *p*-toluenesulfonic acid, the product is not the tertiary acetate **32** but the thermodynamically more stable primary acetate **33**, resulting from an allylic inversion involving an allylic cation formed from **31** or a Cope rearrangement of **32**.

For the final step of the synthesis, the primary chloride in **33** is converted into the aldehyde group of **1** by means of Kornblum oxidation with dimethyl sulfoxide (DMSO). The disadvantage of the Kornblum oxidation (in particular, odor of $(CH_3)_2S$!) can be avoided by the use of *N*-ethylmorpholine *N*-oxide (**34**),

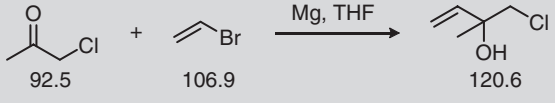
which cleanly oxidizes primary allyl chlorides to the corresponding aldehydes [11, 12].

Thus, the target molecule **1** is obtained in a three-step sequence in an overall yield of 48% (based on **30**).



(c) **Experimental Procedures for the Synthesis of 1**

1.1.1.1 ** **1-Chloro-2-methyl-3-buten-2-ol (isoprene chlorohydrin)** [3]



Magnesium turnings (7.30 g, 300 mmol) are added to anhydrous THF (70 ml) under nitrogen atmosphere, and a small amount of ethyl bromide (~1 g, 0.7 ml) is added to start the reaction. Vinyl bromide (300 mmol, 1 M solution in THF, 0.30 ml) is then added dropwise with stirring at such a rate that the temperature never exceeds 40 °C (approximately 90 min). Stirring is continued for 30 min, the dark-gray solution is cooled to 0 °C, and a solution of chloroacetone (18.5 g, 0.20 mol) (note) in anhydrous THF (70 ml) is added dropwise over 45 min. Stirring is continued at room temperature for 1 h.

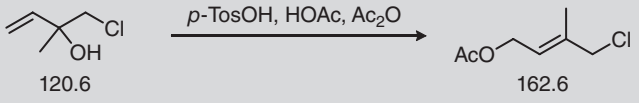
The adduct is hydrolyzed by the dropwise addition of ice-cold saturated aqueous NH_4Cl solution (100 ml) at 0 °C. The phases are separated, and the aqueous phase is extracted with Et_2O (2 × 100 ml). The combined organic phases are washed with 2% aqueous $NaHCO_3$ solution (100 ml) and H_2O (100 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* and the residue is fractionally distilled to give a colorless oil. The yield is 18.3 g (76%), bp_{17} 48–49 °C, $n^{20}_D = 1.4608$.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3420, 3080, 1640.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.89 (dd, 15.0, 9.0 Hz, 1H, 3-H), 5.35 (dd, 15.0, 3.0 Hz, 1H, 4-H_a), 5.18 (dd, 9.0, 3.0 Hz, 1H, 4-H_b), 3.46 (s, 2H, 1-H_2), 2.37 (s_{br}, 1H, OH), 1.38 (s, 3H, CH_3).

Note: Chloroacetone (lachrymator!) is distilled (bp_{760} 118–119 °C) through a short packed column before use.

1.1.1.2 * **(*E*)-1-Acetoxy-4-chloro-3-methyl-2-butene** [3]

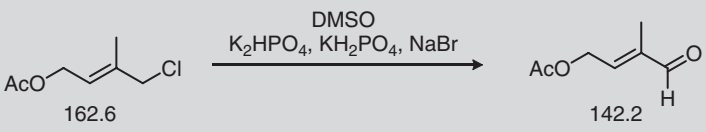


A solution of *p*-toluenesulfonic acid monohydrate (2.54 g, 13.4 mmol) in glacial acetic acid (60.0 ml) is added dropwise to a stirred solution of isoprene chlorohydrin **1.1.1.1** (15.3 g, 127 mmol) in acetic anhydride (20.0 ml) and glacial acetic acid (60.0 ml) at 15 °C over a period of 15 min. The temperature of the bath is raised to 55 °C and stirring is continued for 24 h.

The solution is cooled and carefully poured into a mixture of 10% aqueous NaOH (800 ml) and ice (200 g). The resulting mixture is extracted with Et_2O (3 × 100 ml), and the combined organic phases are dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue is fractionally distilled to give the product as a colorless oil; 16.3 g (79%), bp_{10} 91–93 °C, n^{20}_D = 1.4658; 6 : 1 mixture of the *E*/*Z* stereoisomers.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1740, 1235, 1025, 685.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.65 (t, *J* = 9.0 Hz, 1H, 2-H), 4.59 (d, *J* = 9.0 Hz, 2H, 1-H_2), 4.06, 3.98 (2 × s, 2 × 2H, ratio 1 : 6, *Z*/*E*-CH_2Cl), 2.02 (s, 3H, $OCOCH_3$), 1.79 (s_{br}, 3H, 3-CH_3).

1.1.1.3 * **(*E*)-Acetoxy-2-methyl-2-butenal** [3]



K_2HPO_4 (19.9 g, 114 mmol), KH_2PO_4 (4.14 g, 30.0 mmol), and NaBr (1.20 g, 11.6 mmol) are suspended in a stirred solution of allyl chloride **1.1.1.2** (16.1 g, 99.0 mmol) in anhydrous DMSO (120 ml). The mixture is heated to 80 °C and stirred for 24 h (Hood! formation of dimethyl sulfide!).

The mixture is then cooled and poured into H_2O (400 ml) and CH_2Cl_2 (200 ml). The phases are separated, the aqueous phase is extracted with CH_2Cl_2 (100 ml),

the combined organic layers are dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the yellow residue is fractionally distilled to give the acetoxy aldehyde as a colorless oil; 11.2 g (80%), bp_2 66–72 °C, $n^{20}{}_D = 1.4647$ (note).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2720, 1735, 1690, 1645.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.55 (s, 1H, CHO; *Z*-isomer: δ = 10.23), 6.52 (tq, *J* = 6.0, 1.0 Hz, 1H, 3-H), 4.93 (dq, *J* = 6.0, 1.0 Hz, 2H, 4-H_2), 2.12 (s, 3H, $OCOCH_3$), 1.81 (dt, *J* = 1.0, 1.0 Hz, 3H, C2-CH_3).

Note: If smaller amounts of starting material are used, column chromatography (silica gel, *n*-hexane/Et_2O, 9 : 1) is recommended as the purification procedure.

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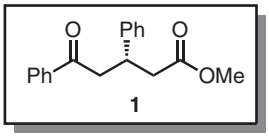
1.1.2

Methyl (*S*)-5-oxo-3,5-diphenylpentanoate



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Topics:

- Knoevenagel condensation, Michael addition
- "Acid cleavage" of acetoacetate, anhydride formation
- Enantioselective asymmetric desymmetrization of a cyclic *meso*-anhydride by a Grignard compound in the presence of (−)-sparteine as a stereocontrolling agent
- Determination of enantiomeric excess by high-performance liquid chromatography (HPLC) on a chiral phase