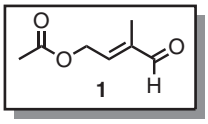
1
C–C Bond Formation

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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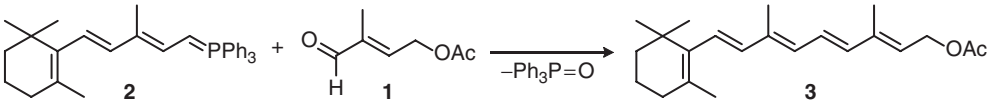
Topics:

- 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 $R-CH_2-X \rightarrow R-CH{=}O$

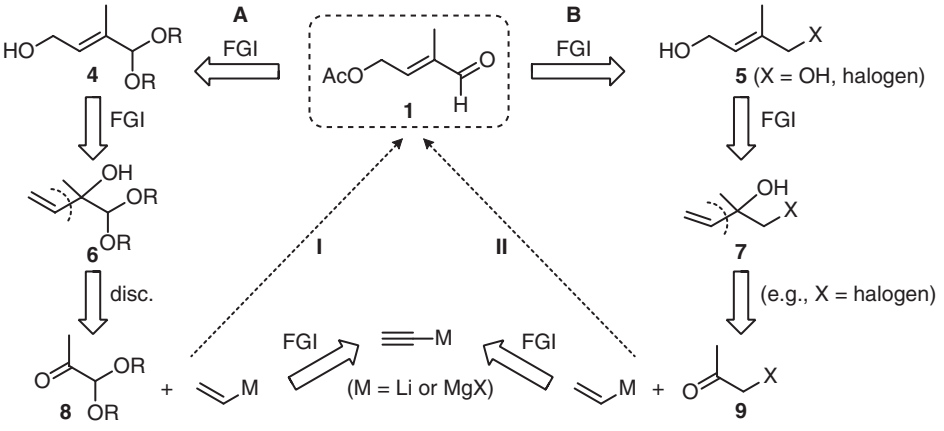
Reactions and Syntheses in the Organic Chemistry Laboratory, Second Edition.
Lutz F. Tietze, Theophil Eicher, Ulf Diederichsen, Andreas Speicher, and Nina Schützenmeister.

(a) **General**

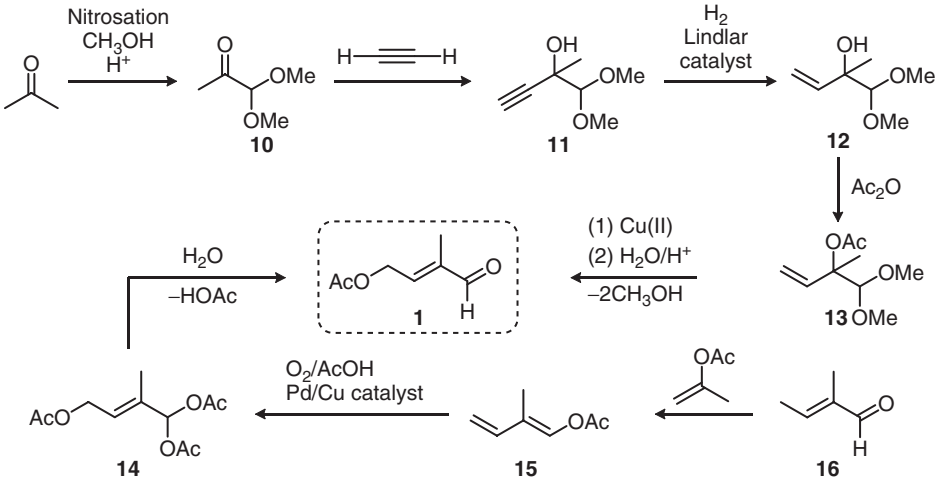
(*E*)-2-Methyl-2-butenal bearing an acetoxy group at the 4-position can be regarded as a functional isoprene unit and is used as a C_5-building block for the synthesis of terpenes by carbonyl olefination [1]. Thus, in the classical industrial vitamin A synthesis of BASF (cf. Section 4.1.5), (*E*)-4-acetoxy-2-methyl-2-butenal (**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].

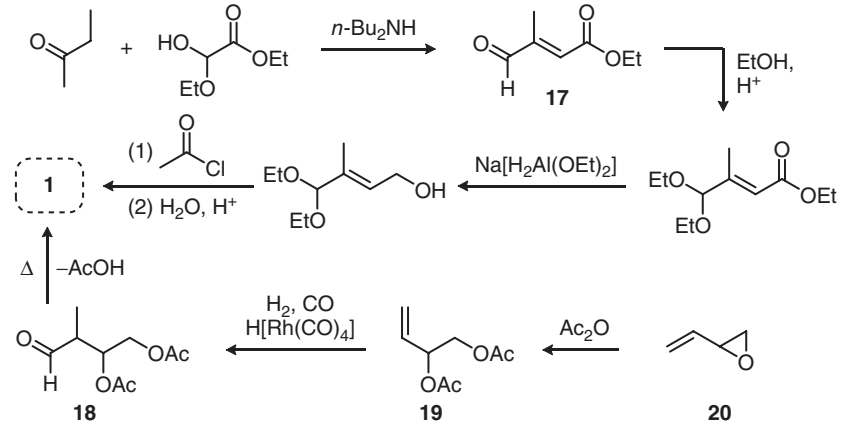


Approach **I** corresponds to a former industrial synthesis of **1** by BASF [2], starting with oxidation (nitrosation in the presence of methanol) of acetone to give methylglyoxal dimethyl acetal (**10**). This is followed by ethynylation with acetylene, partial hydrogenation, and acetylation (**10** → **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:



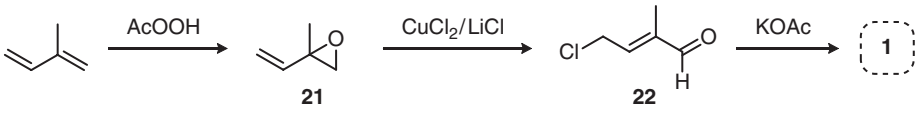
Approach **II** is the basis of a laboratory synthesis of **1** [3], which is described in detail in Section (b).

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

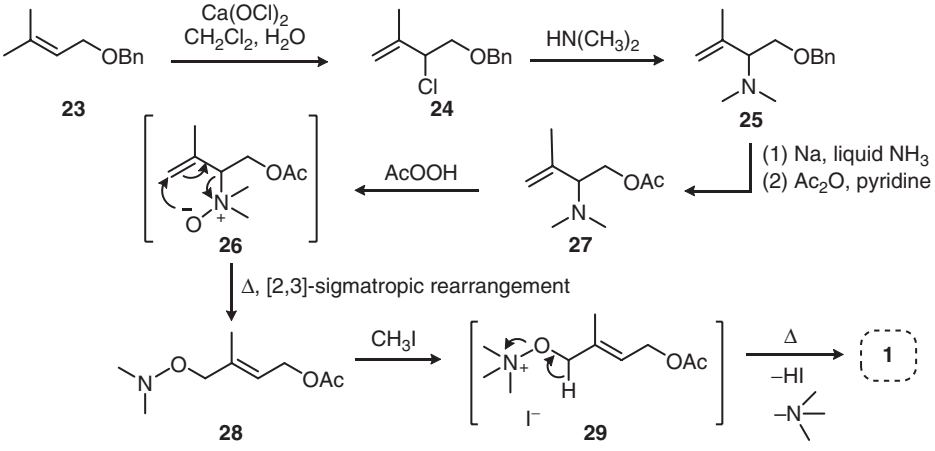


(**20**), respectively. In (ii), the key step is a regioselective Rh-catalyzed hydrocarbonylation (→**18**) of the diacetate **19**, obtained by ring opening of **20** with acetic anhydride.

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**:



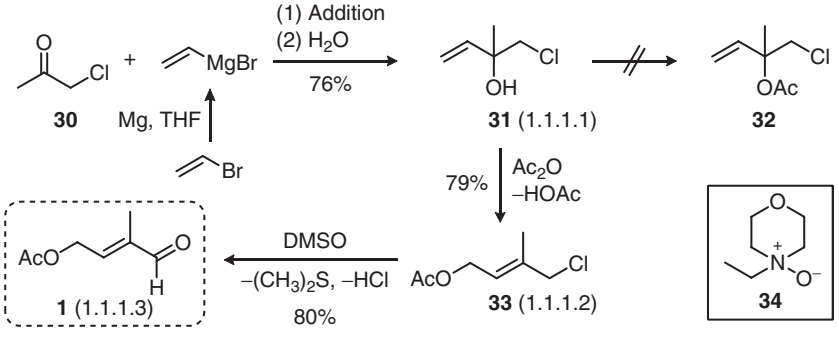
(b) **Synthesis of 1**

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**),

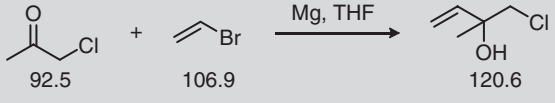
which cleanly oxidizes primary allyl chlorides to the corresponding aldehydes [11, 12].

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.

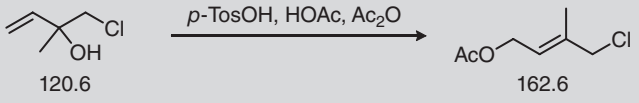
The adduct is hydrolyzed by the dropwise addition of ice-cold saturated aqueous NH_4Cl solution (100 ml) at 0 °C. The phases are separated, and the aqueous phase is extracted with Et_2O (2 × 100 ml). The combined organic phases are washed with 2% aqueous $NaHCO_3$ solution (100 ml) and H_2O (100 ml), 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]

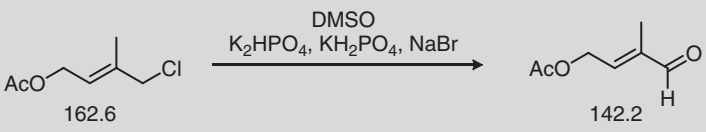


A solution of *p*-toluenesulfonic acid monohydrate (2.54 g, 13.4 mmol) in glacial acetic acid (60.0 ml) is added dropwise to a stirred solution of isoprene chlorohydrin **1.1.1.1** (15.3 g, 127 mmol) in acetic anhydride (20.0 ml) and glacial acetic acid (60.0 ml) at 15 °C over a period of 15 min. The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

References

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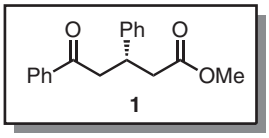
12. Sulfoxides anchored on ionic liquids are reported to represent nonvolatile and odorless reagents for Swern oxidation: He, X. and Chan, T.H. (2006) *Tetrahedron*, **62**, 3389–3394.

1.1.2

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



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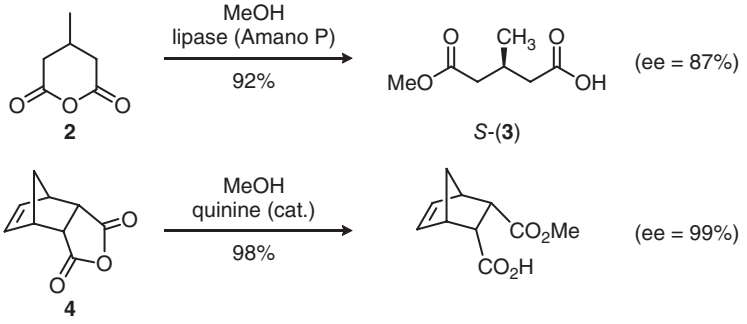
Topics:

- 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

(a) **General**

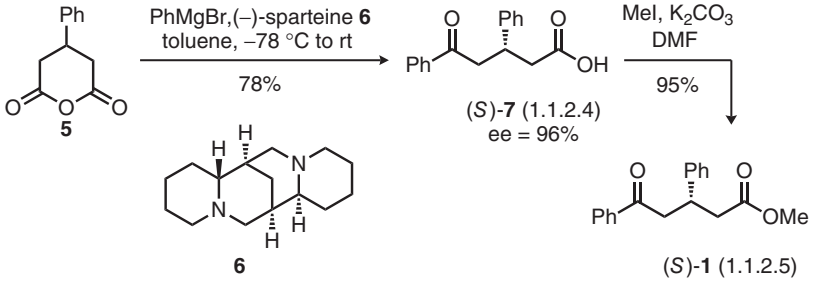
The desymmetrization of meso and other prochiral compounds represents an important approach in asymmetric synthesis [1]. The desymmetrization of five- and six-membered cyclic anhydrides of the meso type (such as **2** and **4**) by ring-opening attack of nucleophiles at one of the enantiotopic carbonyl groups is broadly possible (i) by chiral alcohols or amines and (ii) by achiral alcohols in combination with enzymes or other organocatalysts [2]. Clearly, the catalytic variant is by far the more attractive route for reasons of atom economy and preparative efficiency,[1)] for example:



Only a few examples of the desymmetrization of cyclic anhydrides with carbon nucleophiles have been described [2]. Recently, asymmetric ring-opening reactions of 3-substituted glutaric anhydrides (such as **2**) were found [3] to occur with Grignard compounds in the presence of (–)-sparteine as a chiral complexing ligand system, which has been shown [4] to be a very versatile organocatalyst [5] for asymmetric stereocontrol in reactions of organolithium compounds.

As described in Section (b), a simple synthesis of the chiral target molecule **1** [6] can be achieved by the application of the above protocol.

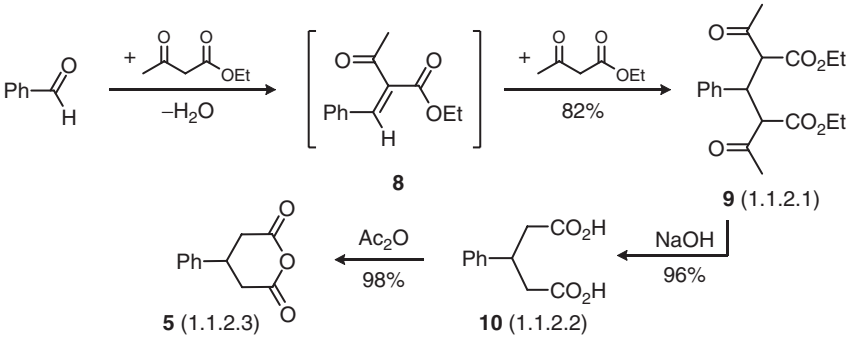
(b) **Synthesis of 1**



1) Although the ring opening of *meso* cyclic anhydrides by enantiomerically pure alcohols, amines, and other chiral nucleophiles is highly diastereoselective, the preparative value is limited by the amounts of chiral nucleophile required and by the necessity of further reactions for removal of the chiral auxiliary (see Ref. [2]).

3-Phenylglutaric anhydride (**5**) is reacted with phenylmagnesium bromide in toluene at −78 °C in the presence of 1.3 equiv of (−)-sparteine (**6**) as a stereocontrolling agent to give the δ-keto acid **7** in 78% yield and with high enantioselectivity (ee = 96%) [3]. The enantiomeric purity of **7** may be determined by HPLC on a chiral phase of the methyl ester **1**, easily accessible from the acid **7** by O-alkylation of its potassium salt with methyl iodide.

The *meso*-anhydride **5** is conventionally prepared [7] starting from benzaldehyde and 2 equivalents of ethyl acetoacetate. The product **9** of this base-catalyzed, three-component reaction results from a domino process involving Knoevenagel condensation of the first molecule of acetoacetate with benzaldehyde followed by Michael addition of the second acetoacetate to the primary condensation product **8** in the presence of piperidine:

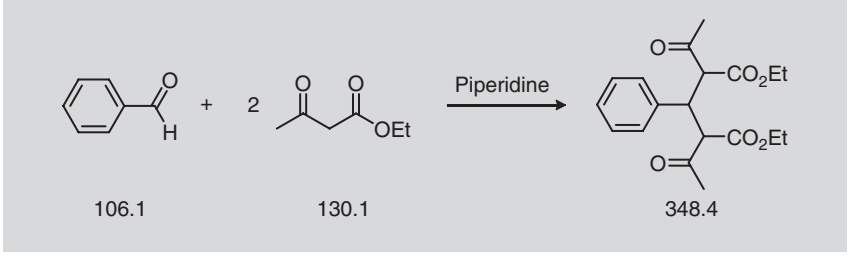


The diester **9** undergoes a twofold "acid cleavage" of the acetoacetate moieties upon treatment with NaOH in EtOH, which results in the loss of two molecules of acetate and saponification of the carboxylic acid ester moieties to give 3-phenylglutaric acid (**10**). Finally, the diacid **10** is transformed to the cyclic anhydride **5** using acetic anhydride.

Thus, the target molecule **1** is obtained in a four-step sequence with an overall yield of 60% (based on benzaldehyde).

(c) Experimental Procedures for the Synthesis of 1

1.1.2.1 * Diethyl 2,4-diacetyl-3-phenylpentanedioate [7]



Ethyl acetoacetate (75.5 g, 580 mmol, note 1) and benzaldehyde (28.5 g, 269 mmol) are dissolved in anhydrous EtOH (160 ml). Piperidine (4.0 ml) is added, and the solution is heated to reflux for 10 min and then stirred for 12 h at room temperature. The product begins to crystallize after 2–3 h (note 2).

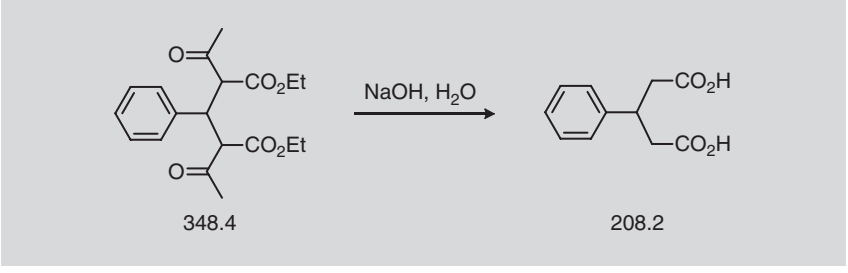
The slurry is cooled to −20 °C (MeOH/dry ice), and the product is collected by filtration and washed with cold EtOH (−20 °C) until the washings remain colorless. The residue is dried *in vacuo*. The product is obtained as colorless crystal; 77.2 g (82%), mp 150–152 °C (note 3).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3515, 2980, 1740, 1720, 1500, 1470, 1380, 1190, 830.
^{1}H NMR (300 MHz, $CDCl_3$): very complex because of enolization and different *E*/*Z* geometries.

Notes:

1) Ethyl acetoacetate is freshly distilled prior to use (bp_{15} 76–77 °C).
2) If the slurry becomes too viscous for stirring, it is diluted with additional EtOH (50–100 ml).
3) The product is sufficiently pure according to thin-layer chromatography (TLC) (SiO_2/Et_2O). It may be recrystallized from EtOH, which increases the mp to 154–155 °C.

1.1.2.2 * 3-Phenylglutaric acid [7]



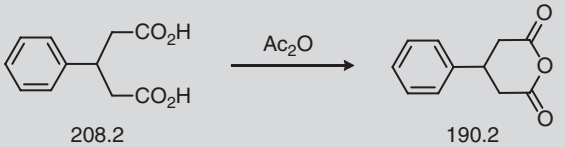
348.4 208.2

The diester **1.1.2.1** (69.7 g, 194 mmol) is added to a mixture of 50% aqueous NaOH (200 ml) and EtOH (200 ml), and the resulting mixture is heated to reflux for 3 h.

The slurry is diluted with H_2O (200 ml), concentrated to dryness *in vacuo*, and the residue is taken up in H_2O (400 ml). The resulting solution is acidified to pH 2 using concentrated HCl, and the phenylglutaric acid is extracted with Et_2O (3 × 150 ml). The combined extracts are dried over Na_2SO_4, filtered, and concentrated to a volume of 100–120 ml. Cooling to −20 °C results in crystallization of the product, which is collected by filtration, washed with a small amount of cold Et_2O (−20 °C), and dried *in vacuo*. The acid is obtained as colorless crystals; 40.0 g (96%), mp 145–147 °C; the product is sufficiently pure for further use.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3200 – 2500, 1720, 1705, 1495, 1450, 1420, 820.
^{1}H NMR (300 MHz, [D_6]acetone): δ (ppm) = 10.88 (s_{br}, 2H, 2 × CO_2H), 7.25 (m_c, 5 H), 3.66 (quintet, J = 6.7 Hz, 1H, 3-H), 2.72 (d, J = 6.7 Hz, 4H, 2-H_2, 4-H_2).

1.1.2.3 * 3-Phenylglutaric anhydride [7]

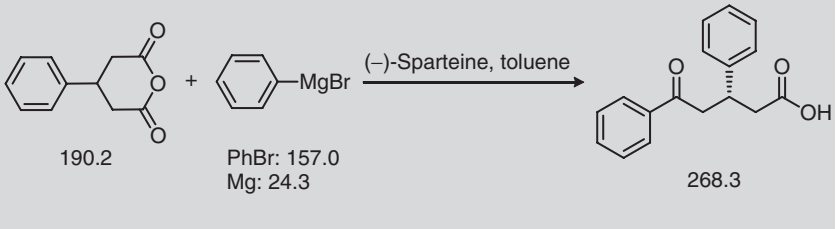


The dicarboxylic acid **1.1.2.2** (26.0 g, 125 mmol) in acetic anhydride (140 ml) is heated under reflux for 2 h.

The reaction mixture is then concentrated to dryness. The residue is suspended in Et_2O (100 ml), filtered off, washed with Et_2O, and dried *in vacuo*. The yield is 23.3 g (98%) as colorless crystals, mp 103 – 105 °C; the product is sufficiently pure for further use.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3034, 2980, 1809, 1751, 1243, 1172, 1066, 953, 763, 702, 605, 591.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.40 (t, J = 7.4 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 7.25 Hz, 2H, 2 × Ar – H), 3.42 (m_c, 1H, 3-H), 3.11 (dd, J = 17.3, 4.4 Hz, 2H, 2-H_A, 4-H_A), 2.89 (dd, J = 17.3, 11.4 Hz, 2H, 2-H_B, 4-H_B).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 165.8 (C-1, C-5), 139.1, 129.4, 128.2, 126.3 (6 × Ph – C), 37.2 (C-3), 34.1 (C-2, C-3).

1.1.2.4 *** (*S*)-5-Oxo-3,5-diphenylpentanoic acid [3]



Approximately one-fifth of a solution of bromobenzene (1.02 g, 6.50 mmol) in anhydrous Et_2O (10 ml) is added to magnesium turnings (158.0 mg, 6.50 mmol)

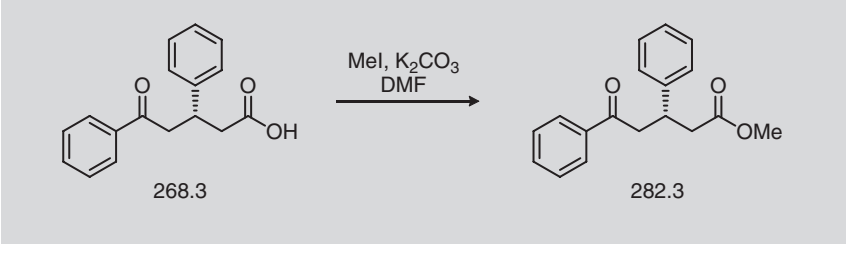
under a nitrogen atmosphere. Once the Grignard reaction has started, the remaining bromobenzene solution is added dropwise. The solution is then heated to reflux until all of the magnesium turnings have reacted.

The Grignard solution is added dropwise to a solution of (−)-sparteine (1.52 g, 6.50 mmol) in anhydrous toluene (25 ml) at room temperature under nitrogen atmosphere. The solution is stirred for 3 h and then cooled to −78 °C. A solution of 3-phenylglutaric anhydride **1.1.2.3** (951 mg, 5.00 mmol) in toluene (10 ml) is added dropwise to the Grignard/(−)-sparteine solution at −78 °C. The mixture is stirred at this temperature for an additional 3 h before being allowed to warm to room temperature.

The solution is quenched with 2 M NaOH (50 ml), stirred thoroughly, and extracted with Et_2O (3 × 20 ml). The aqueous layer is separated and acidified with concentrated HCl under ice cooling. The carboxylic acid precipitates and is collected by suction filtration, washed with H_2O (2 × 20 ml), and air-dried to give the acid as colorless crystals; 1.05 g (78%), mp 126–127 °C.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3030, 1734, 1698, 1682, 1595, 1578.
^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 12.06 (s_{br}, 1H, CO_2H), 7.91 (d, J = 7.3 Hz, 2H, 2 × ArH), 7.60 (t, J = 7.6 Hz, 1H, ArH), 7.48 (t, J = 7.6 Hz, 2H, 2 × ArH), 7.26 (d, J = 7.0 Hz, 2H, 2 × ArH), 7.23 (t, J = 7.6 Hz, 2H, 2 × ArH), 7.13 (t, J = 7.3 Hz, 1H, ArH), 3.66 (quintet, J = 7.9 Hz, 1H, 3-H), 3.44 (dd, J = 17.1, 7.9 Hz, 1H, 2-H_a), 3.37 (dd, J = 17.1, 6.3 Hz, 1H, 2-H_b), 2.69 (dd, J = 15.8, 6.3 Hz, 1H, 4-H_a), 2.56 (dd, J = 15.8, 8.5 Hz, 1H, 4-H_b).
^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 198.4 (C-5), 172.9 (C-1), 143.8, 136.7, 133.1, 128.6, 128.1, 127.8, 127.5, 126.2 (12 × Ar–C), 44.0, 40.4, 37.2 (C-2. C-3, C-4).

1.1.2.5 * **Methyl (*S*)-5-oxo-3,5-diphenylpentanoate** [3]



Methyl iodide (2.84 g, 20.0 mmol; Caution: carcinogenic!) is added dropwise with stirring to a solution of the carboxylic acid **1.1.2.4** (268 mg, 1.00 mmol), anhydrous K_2CO_3 (207 mg, 1.50 mmol), and *N*,*N*-dimethylformamide (DMF) (5 ml). The resulting mixture is stirred overnight at room temperature.

It is then quenched with 10% aqueous K_2CO_3 solution (10 ml). The product is extracted with Et_2O (5 × 10 ml), and the combined ethereal extracts are washed with brine (3 × 10 ml), dried over Na_2SO_4, and filtered. The solvent is removed

in vacuo, and the product is allowed to crystallize; one obtains 268 mg (96%) as colorless crystals, mp 82 °C, $[\alpha]^{20}_{D} = +1.8$ ($c = 0.85$, $CHCl_3$), 96% ee.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 2970, 2870, 1735, 1680, 1596, 1578, 1496.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.91 (d, J = 6.9 Hz, 2H, ArH), 7.53 (t, J = 7.6 Hz, 1H, ArH), 7.43 (t, J = 7.9 Hz, 2H, ArH), 7.26 (m, 3H, ArH), 7.19 (m, 2H, ArH), 3.88 (quintet, J = 7.3 Hz, 1H, PhC<u>H</u>), 3.58 (s, 3H, OCH_3), 3.39 (dd, J = 16.7, 6.9 Hz, 1H) and 3.33 (dd, J = 16.7, 6.9 Hz, 1H, C<u>H_2</u>CO_2Me), 2.82 (dd, J = 15.3, 7.3 Hz, 1H), and 2.69 (dd, J = 15.3, 7.3 Hz, 1H, PhCOC<u>H_2</u>).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 198.13, 172.29, 143.36, 136.95, 133.09, 128.62, 128.07, 127.33, 127.18, 126.82, 51.55, 44.55, 40.58, 37.53.

The enantiomeric ratio of 98 : 2 (96% ee) was determined by HPLC on a Daicel Chiralcel® OD-H column (4.6 × 250 mm; isopropanol/*n*-hexane (20 : 80), 0.5 ml min^{-1}; UV 254 nm, baseline separation). A reference sample of racemic 5-oxo-3,5-diphenylpentanoic acid methyl ester may be obtained by performing the reaction **1.1.2.4** in the absence of sparteine and then generating the methyl ester according to the procedure described above.

References

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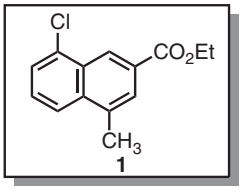
1.1.3
Ethyl 8-chloro-4-methylnaphthalene-2-carboxylate

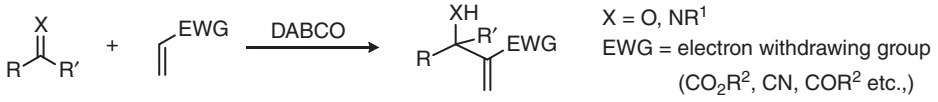


1

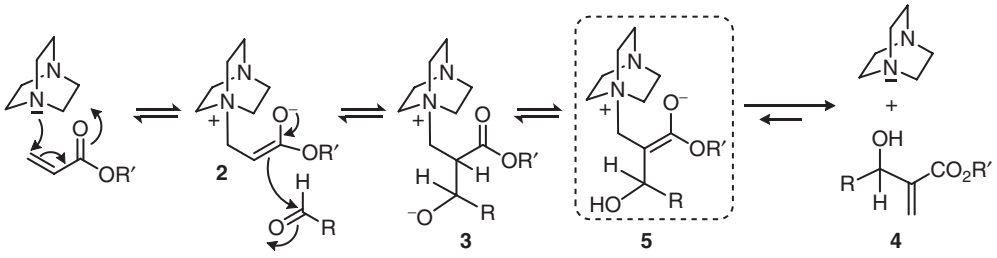
Topics:
- Baylis–Hillman reaction of an aryl aldehyde with an acrylate in the presence of DABCO
- Acetylation of an OH functionality
- Transformation of an acetylated Baylis–Hillman adduct to a functionalized naphthalene system by reaction with nitroalkane/base (domino process)

(a) **General**

The addition of carbonyl compounds, mainly aldehydes or aldimines, to acceptor-substituted alkenes (e.g., acrylates, acrylonitrile, enones, etc.) induced by tertiary amines (or phosphines), preferentially 1,4-diazabicyclo[2.2.2]octane (DABCO), is known as the *Baylis–Hillman reaction* [1, 2]:



The generally accepted mechanism for the Baylis–Hillman process is illustrated by the reaction of an aldehyde with acrylate under the catalytic influence of DABCO:



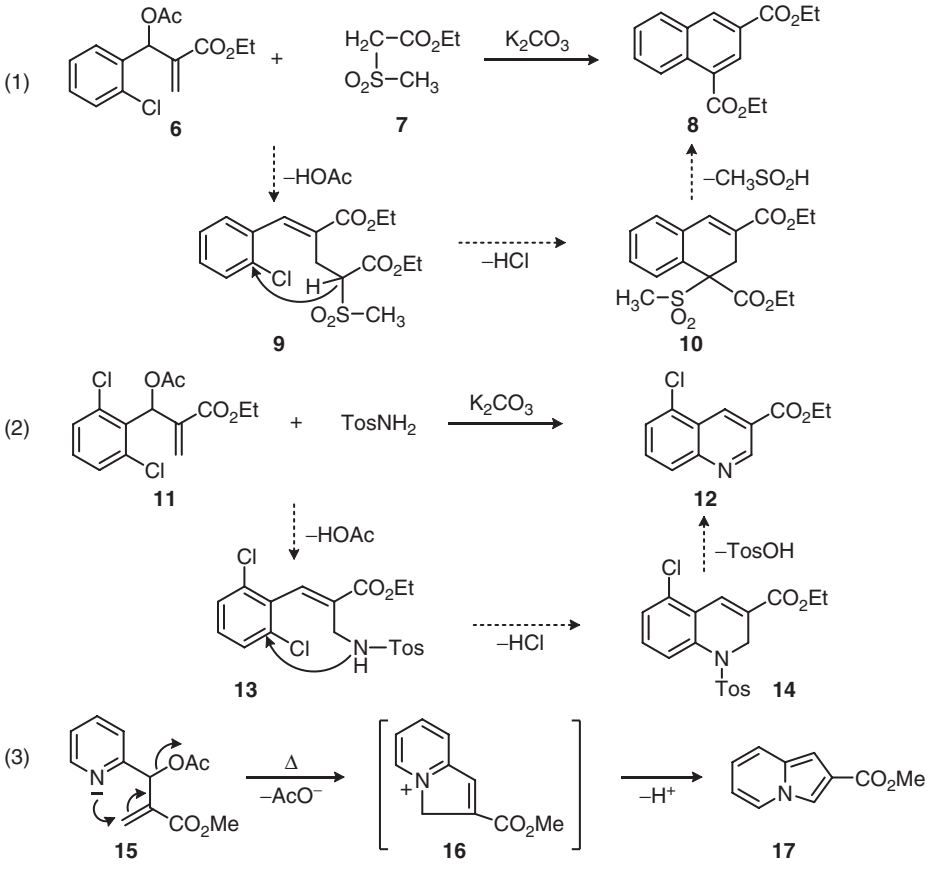
The first step involves a Michael-type addition of DABCO to the acrylate to produce the zwitterionic enolate betaine **2**, which then adds as a nucleophile to the aldehyde carbonyl group in an aldol-like manner to give the zwitterion **3**. Subsequent proton transfer (**3** → **5**) and release of the tertiary amine complete the catalytic cycle and provide the Baylis–Hillman adduct **4**.

The product **4** contains three different functionalities and is therefore capable of undergoing several different transformations [2]. Moreover, if the electrophilic component in the Baylis–Hillman reaction carries additional functionalities, domino reactions [3] can be induced, which lead to the formation of carbocyclic and heterocyclic compounds [4], as illustrated by the following examples (1)–(3).

In (1), the acetylated Baylis–Hillman adduct **6** (obtained from 2-chlorobenzaldehyde and ethyl acrylate with subsequent acetylation) reacts with the sulfone **7** in the presence of a base. The product is the naphthalene derivative **8**, which is formed via S_N' attack (→**9**), intramolecular S_NAr reaction (→**10**), and finally elimination of sulfinic acid [5].

In (2), the acetylated Baylis–Hillman adduct **11** (obtained as above from 2,6-dichlorobenzaldehyde) is reacted with *p*-toluenesulfonamide/base to give the quinoline derivative **12** in a sequence analogous to (1) (**11** → **13** → **14** → **12**) [6].

In (3), the acetylated Baylis–Hillman adduct **15** (obtained from pyridine-2-aldehyde and methyl acrylate with subsequent acetylation) is transformed into the indolizine derivative **17** by thermolysis. The process involves an S_N' substitution of the allylic acetate moiety in **15** to give the indolizinium ion **16** followed by deprotonation [7].



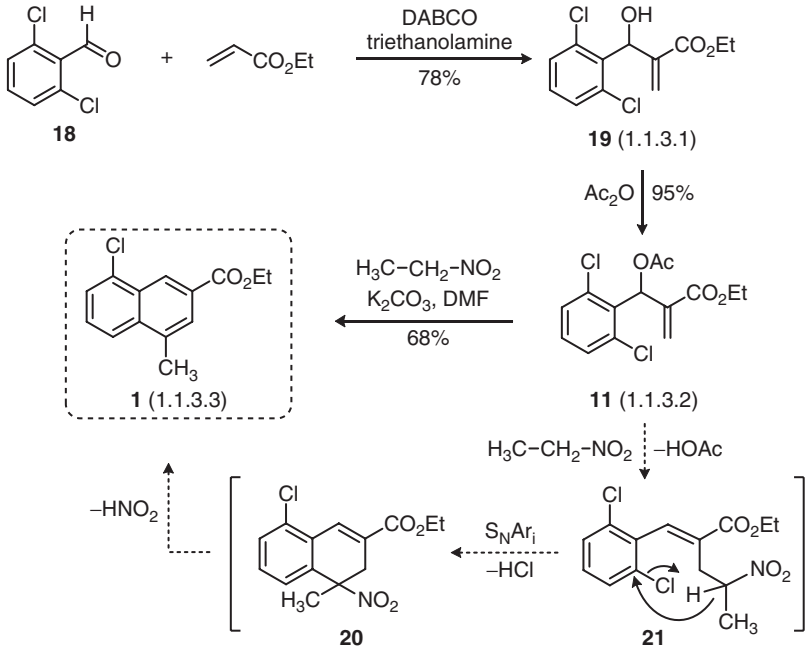
As a further example, the synthesis of **1** is described in detail in Section (b)[2] [8].

(b) **Synthesis of 1**

The synthesis of **1** [8] starts with the reaction of 2,6-dichlorobenzaldehyde (**18**) and ethyl acrylate in the presence of DABCO, which provides the Baylis–Hillman adduct **19**. As in most cases, this DABCO-initiated Baylis–Hillman process

2) To date, a conventional synthesis of the target molecule **1** has not been reported in the literature.

requires a long reaction time of 5 days for completion, probably in this case due to steric hindrance in the o,o′-disubstituted benzaldehyde **18**. In other cases, the reaction time may be decreased to approximately 12 h by the use of a catalytic system consisting of DABCO, triethanolamine, and the Lewis acid $La(OTf)_3$ [9]. Such acceleration, however, could not be observed for the transformation **18** → **19**. Nevertheless, triethanolamine was used as solvent, which proved to be more effective even than octanol [9c]. In the next step, the adduct **19** is acetylated using acetic anhydride to give the acetate **11**:

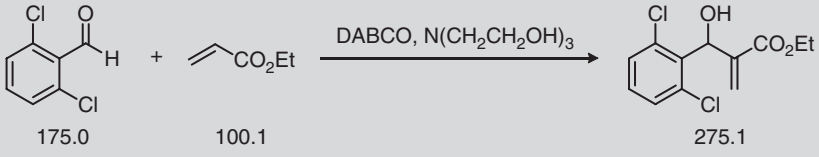


The acetate **11** reacts smoothly with nitroethane in DMF in the presence of K_2CO_3 as a base to provide the target molecule **1** in good yield (68%). Again, the functionalized naphthalene system is formed by way of a three-step domino process. First, the nitronate anion from nitroethane displaces acetate in **11** in an S_N'-like mechanism to give the cinnamic ester **21**; second, one of the arene *ortho*-halogens (activated by the α,β-unsaturated ester moiety) is substituted by the nitronate in **21** in an intramolecular S_NAr reaction to afford **20**; third, aromatization of the 1,2-dihydronaphthalene intermediate **20** takes place by base-induced elimination of HNO_2.

Thus, the naphthalene-2-carboxylic ester **1** is obtained in a three-step sequence with an overall yield of 50% (based on aldehyde **18**).

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

1.1.3.1 * **2-[(2,6-Dichlorophenyl)hydroxymethyl]-acrylic acid ethyl ester** [9]

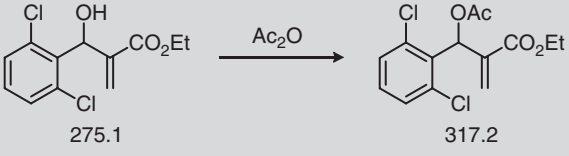


To a stirred mixture of ethyl acrylate (4.51 g, 45.0 mmol) and 2,6-dichlorobenzaldehyde (5.25 g, 30.0 mmol) at room temperature under inert gas are added DABCO (3.37 g, 30.0 mmol) and triethanolamine (1.99 ml, 15.0 mmol).

After 5–7 days, the reaction is quenched by dilution with Et_2O (150 ml), and the mixture is washed sequentially with 2% aqueous HCl (100 ml) and H_2O (100 ml). After drying over $MgSO_4$ and filtration, the solvent is removed *in vacuo*. The crude product is purified by column chromatography (SiO_2; petroleum ether/Et_2O, 2 : 1); yield 6.44 g (78%); colorless crystalline solid, mp 67–68 °C.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3492, 1694, 1288, 1191, 1047, 964, 762.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.31 (d, J = 7.8 Hz, 2H, Ar–H), 7.17 (t, J = 7.8 Hz, 1H, Ar–H), 6.41 (d, J = 1.6 Hz, 1H, =CH_a), 6.34 (dt, J = 9.0, 1.9 Hz, 1H, C<u>H</u>OH), 5.79 (d, J = 1.9 Hz, 1H, =CH_b), 4.18 (m, 2H, C<u>H</u>$_2$$CH_3$), 3.37 (d, J = 9.0 Hz, 1H, OH), 1.23 (t, J = 7.3 Hz, 3H, CH_2CH_3).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 166.0, 139.8, 135.6, 135.5, 129.5, 129.4, 126.1, 70.1, 61.0, 14.0.

1.1.3.2 * **2-[Acetoxy-(2,6-dichlorophenyl)methyl]acrylic acid ethyl ester** [10]



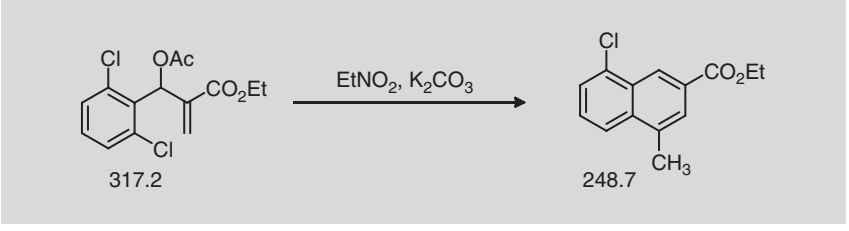
To a mixture of the benzyl alcohol **1.1.3.1** (4.13 g, 15.0 mmol) in acetic anhydride (50 ml) (note) is added one drop of concentrated H_2SO_4. After stirring for 30 min, the mixture is diluted with cold 2 M NaOH (100 ml) and then stirred for 1 h at room temperature.

The mixture is then extracted with chloroform (3 × 30 ml). The combined extracts are washed with 10% aqueous $NaHCO_3$, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo* to give 4.54 g (95%) of a colorless, viscous oil.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1747, 1436, 1370, 1228, 1027.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.33 (t, J = 1.9 Hz, 1H, C<u>H</u>OAc), 7.31 (d, J = 8.2 Hz, 2H, 2 × Ar–H), 7.17 (t, J = 7.6 Hz, 1H, Ar–H), 6.48 (d, J = 1.3 Hz, 1H, =CH_2), 5.69 (d, J = 1.9 Hz, 1H, =CH_2), 4.20 (m, 2H, C<u>H_2</u>CH_3), 2.12 (s, 3H, C(O)C<u>H_3</u>), 1.24 (t, J = 7.3 Hz, 3H, CH_2C<u>H_3</u>).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 169.4, 166.0, 136.2, 136.1, 132.5, 129.9, 129.4, 127.9, 70.3, 61.1, 20.7, 14.0.

Note: Acetic anhydride has to be distilled before use, bp_{760} 140–141 °C.

1.1.3.3 * Ethyl 8-chloro-4-methylnaphthalene-2-carboxylate [8]



Nitroethane (1.44 ml, 20.0 mmol) is added to a stirred solution of well-ground K_2CO_3 (4.14 g, 30.0 mmol) (note) in DMF (30 ml) at room temperature. After stirring for 10 min, a solution of the acrylic ester **1.1.3.2** (3.17 g, 10.0 mmol) in DMF (10 ml) is added dropwise over a period of 20 min at the same temperature. The reaction mixture is stirred for 17 h at 50–60 °C.

The yellow reaction mixture is then poured into dilute HCl (150 ml) (Caution: foaming!). The aqueous mixture is extracted with Et_2O (3 × 50 ml), and the combined extracts are washed with H_2O (50 ml), dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo* to give the crude product as a brown oil. It is purified by column chromatography (SiO_2, *n*-hexane/CH_2Cl_2, 1 : 1) to give 1.70 g (68%) of a yellow crystalline solid; mp 52–53 °C.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 1708, 1269, 1236, 1186, 765.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.88 (s, 1H, Ar–H), 7.95 (s, 1H, Ar–H), 7.92–7.48 (m, 3H, Ar–H), 4.46 (q, J = 7.1 Hz, 2H, CO_2C<u>H_2</u>CH_3), 2.72 (s, 3H, Ar–CH_3), 1.46 (t, J = 7.1 Hz, 3H, CO_2CH_2C<u>H_3</u>).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 166.6, 135.9, 135.3, 134.0, 130.4, 128.3, 127.7, 126.7, 125.7, 123.3, 61.3, 19.7, 14.4.

Note: It is recommended that K_2CO_3 is dried for 24 h at 80 °C before use.

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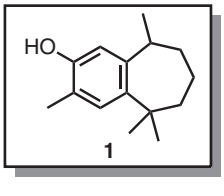
1.1.4

(±)-4-Hydroxy-*ar*-himachalan



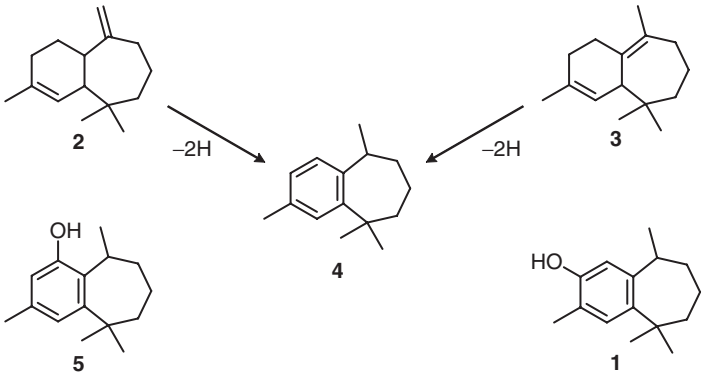
1

Topics:

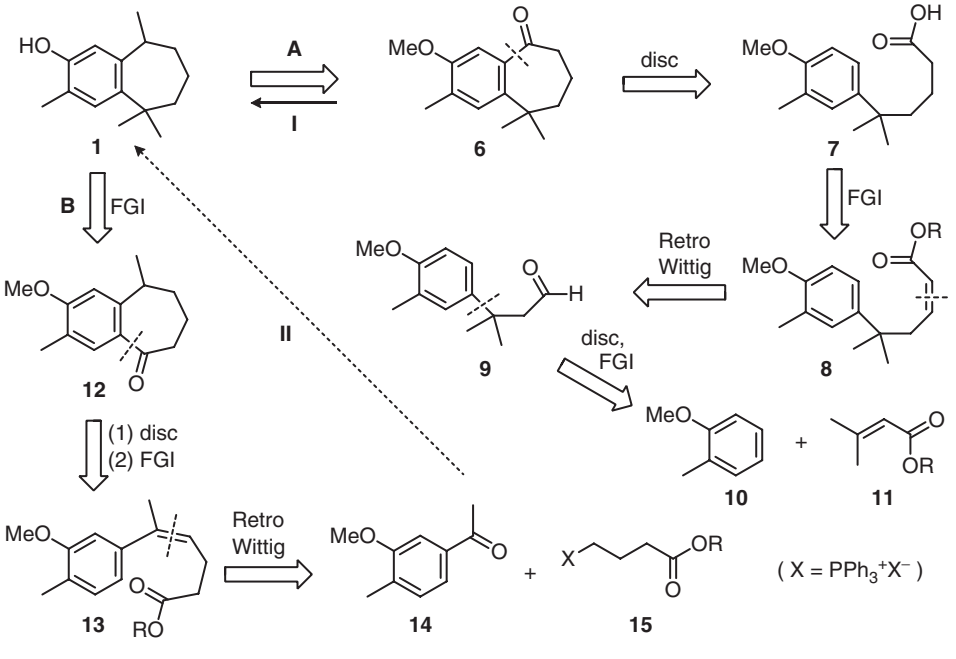
- Synthesis of a phenolic sesquiterpene
- Intramolecular Friedel–Crafts acylation
- Wittig reaction
- Transformation $Ar-NO_2 \rightarrow Ar-NH_2 \rightarrow Ar-OH$
- Demethylation of $Ar-O-CH_3$
- Ti-induced geminal dialkylation of a ketone

(a) General

Himachalans constitute a long-known but rather rare family of sesquiterpenes possessing a methyl-substituted seven-membered ring system. α- and β-Himachalens (**2**/**3**) can be dehydrogenated to *ar*-himachalan **4**, the structure of which has been proven by independent synthesis [1]. More recently, phenolic derivatives of **4** have been isolated from the plant *Lasianthaea podocephala* (**5** [2]) and from the liverwort *Lepidozia incurvata* (**1**) [3]. Himachalans are ingredients of precious perfumes.



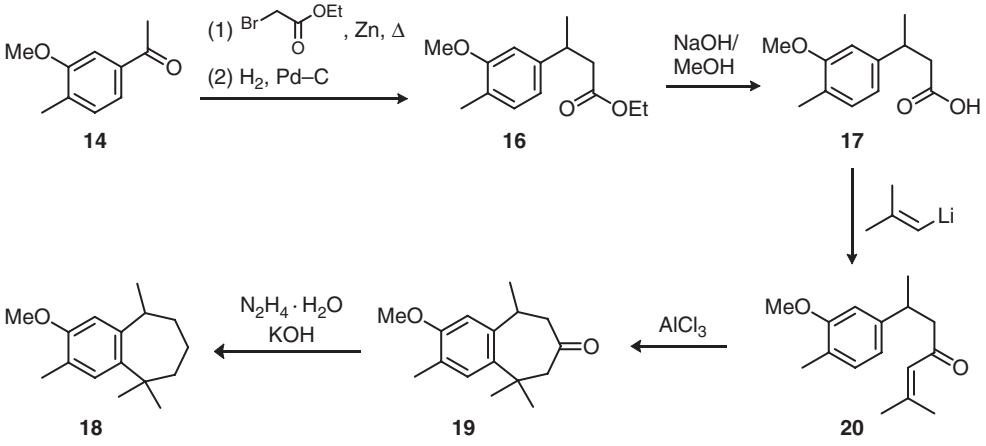
Two retrosynthetic pathways (**A** and **B**) can be considered for **1**. The first one leads to the benzosuberone **6**, which is further cleaved to the substrate *o*-methylanisole **10** and the 3-methyl-2-butenoic acid derivative **11** via **7**, **8**, and **9**. The second one leads to the differently substituted benzosuberone **12** and further on to **14** and **15** via **13**.



(b) **Synthesis of 1**

The synthesis of the methyl ether of **1** (**18**) has been reported in the Ref. [4]; the strategy deviates from approaches **I**/**II** suggested by the retrosynthesis

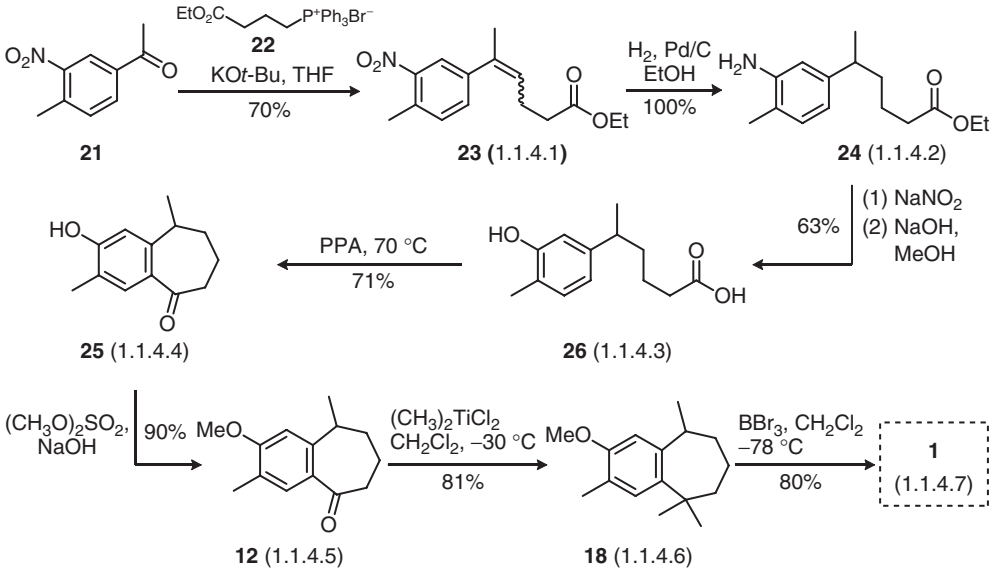
patterns **A**/**B**. This synthesis begins with a Reformatsky reaction of the acetophenone **14** and bromoacetate followed by catalytic hydrogenation to give the ester **16**. Reaction of the corresponding acid **17** with β,β-dimethylvinyllithium leads to the vinyl ketone **20**, which, after a Friedel–Crafts-analogous ring closure (→**19**) and removal of the keto function (in **19**) by a Huang–Minlon procedure, affords **18**. The moderate outcome of the final steps (**17** →→→ **18**) is responsible for the modest overall yield of 4% (based on **14**).



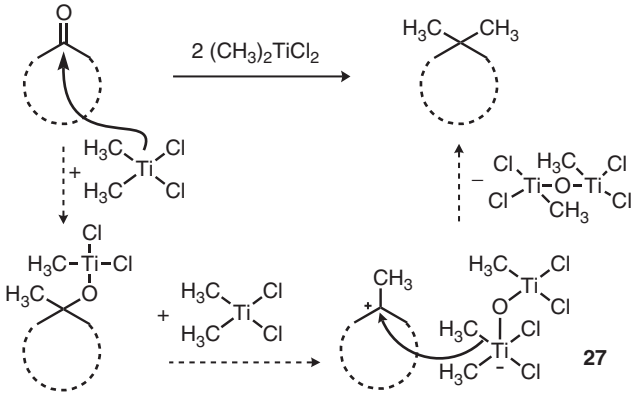
In contrast, the synthesis of **1** according to approach **II** (from retrosynthesis according to **B**) was found to be superior to all other alternatives [5] and is described in the following section with experimental details. This access via benzosuberone **12** requires the construction of the *gem*-dimethyl moiety from a carbonyl group, a transformation elegantly accomplished by use of the titanium reagent $(CH_3)_2TiCl_2$ [6].

4-Methyl-3-nitroacetophenone (**21**) is subjected to a Wittig reaction with the commercially available C_4-phosphonium salt **22** in the presence of KO*t*Bu as base. The carbonyl olefination results in the formation of the unsaturated ester **23** (obtained as a mixture of *E*/*Z* isomers). Hydrogenation of the C=C double bond and the nitro group in **23** using Pd/C in ethanol provides the amino ester **24**. The primary aromatic amine function in **24** is then transformed into a phenolic OH group by the classical two-step process of diazotization with aqueous HNO_2 and nucleophilic substitution of the diazonium group by hydroxide in methanol. In this process, the ester function is also hydrolyzed to give the carboxylic acid **26**. Ring closure to the benzosuberone **25** by intramolecular Friedel–Crafts acylation is then achieved by treatment with polyphosphoric acid. After methylation of the phenolic OH group using dimethyl sulfate/NaOH (**25** → **12**), geminal dimethylation at the C=O group of **12** is accomplished with $(CH_3)_2TiCl_2$ at −30 °C to give the benzocycloheptene **18**. Finally, the methyl ether function in **18**

is cleaved with BBr_3 to give the *ar*-himachalan **1** in a linear seven-step sequence with an overall yield of 18% (based on **21**).

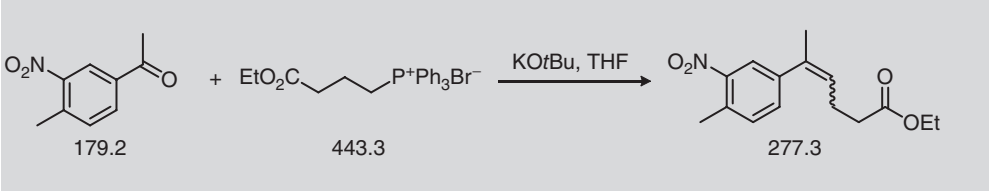


For the geminal dimethylation of **12**, 2 equiv of $(CH_3)_2TiCl_2$ per carbonyl group are required. This leads to the following mechanism: (i) methyl transfer from titanium to the carbonyl carbon atom by nucleophilic addition of $Ti-CH_3$ to C=O and (ii) methyl migration within the ion-pair ate-complex **27**. As the driving force, the large difference in Δ_H Ti–O versus Δ_H Ti–C (480 vs. 250 kJ mol^{-1}) can be assumed [6, 7].



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

1.1.4.1 * Ethyl 5-(4-methyl-3-nitrophenyl)-4-hexenoate [5]



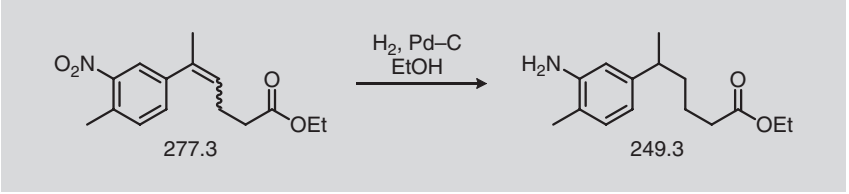
(3-Carbethoxypropyl)triphenylphosphonium bromide (42.8 g, 94.0 mmol) (note) is added to a stirred solution of KO*t*Bu (10.0 g, 90.0 mmol) in anhydrous THF (100 ml), and stirring is continued for 1.5 h. A solution of 4-methyl-3-nitroacetophenone (11.2 g, 72.0 mmol) in anhydrous THF (100 ml) is then added dropwise with stirring. When the addition is complete, the dark mixture is heated to reflux for 12 h (TLC control).

The reaction mixture is cooled to room temperature, poured into H_2O (500 ml), and extracted with Et_2O (4 × 250 ml). The combined ethereal phases are washed with H_2O (5 × 200 ml), dried over $MgSO_4$, and filtered. The solvent is removed *in vacuo*, the crude oily product is dissolved in the minimum volume of CH_2Cl_2, and purified (i) by rapid filtration through SiO_2 (CH_2Cl_2) and (ii) by chromatography on SiO_2 (Et_2O/petroleum ether, 1 : 6). The product (14.0 g, 70% 2 : 1 mixture of *E*/*Z* stereoisomers, $R_f = 0.28$ (Et_2O/petroleum ether 1 : 6)) is used directly in the next step.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1770, 1655.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.95 (d, *J* = 1.8 Hz, 1H, Ar–H, *Z*), 7.79 (d, *J* = 1.3 Hz, 1H, Ar–H, *E*), 7.50 (dd, *J* = 8.0, 1.8 Hz, 1H, Ar–H, *Z*), 7.35–7.29 (m, 2H, Ar–H, *E*), 7.26 (d, *J* = 8.0 Hz, 1H, Ar–H, *Z*), 5.82 (m_c, 1H, =CH, *Z*), 5.52 (m_c, 1H, = CH, *E*), 4.15 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$, *Z*), 4.10 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$, *E*), 2.59 (s, 3H, Ar–CH_3, *E*), 2.57 (s, 3H, Ar–CH_3, *Z*), 2.55–2.44 and 2.36–2.25 (m, 4H, CH_2–CH_2, *E* and *Z*), 2.06 (d, *J* = 1.3 Hz, 3H, =C–CH_3, *Z*), 2.03 (d, *J* = 1.3 Hz, 3H, =C–CH_3, *E*), 1.28 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$, *Z*), 1.23 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$, *E*).
MS (CI, 120 eV): *m*/*z* (%) = 277 (76) $[M]^+$.

Note: The phosphonium salt is commercially available but rather expensive. However, it can be prepared according to Ref. [8].

1.1.4.2 * Ethyl 5-(3-amino-4-methylphenyl)hexanoate [5]

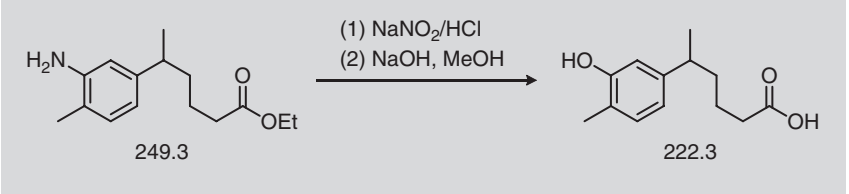


5% Pd/C catalyst (approximately 0.5 g) is added to a solution of the unsaturated ester **1.1.4.1** (10.0 g, 36.0 mmol) in EtOH (200 ml). Hydrogenation is carried out in a hydrogenation apparatus for 12 h under a hydrogen pressure of 2.5 bar (TLC control).

The catalyst is then filtered through Celite®, and the filter cake is rinsed with EtOH. The EtOH solution is concentrated *in vacuo*. The product (9.00 g, 100%) is obtained as a faintly yellow oil, which is homogeneous according to TLC and is used in the next step without further purification.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3455, 3370, 1740.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.95 (d, J = 7.5 Hz, 1H, Ar–H), 6.52 (d, J = 7.5 Hz, 1H, Ar–H), 6.49 (s_{br}, 1H, Ar–H), 4.09 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.57 (s_{br}, 2H, NH_2), 2.59–2.54 (m, 1H, C<u>H</u>–CH_3), 2.26–2.22 (m, 2H, CH_2), 2.12 (s, 3H, Ar–CH_3), 1.59–1.48 (m, 4H, $(CH_2)_2$), 1.24 (t, J = 7.1 Hz, 3H, CH_3), 1.19 (d, J = 6.6 Hz, 3H, CH–C<u>H</u>$_3$).
MS (CI, 120 eV): m/z (%) = 249 (3) $[M]^+$.

1.1.4.3 * 5-(3-Hydroxy-4-methylphenyl)hexanoic acid [5]



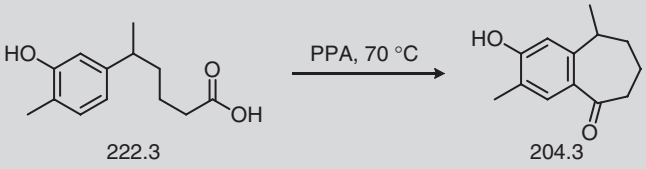
The amino ester **1.1.4.2** (8.00 g, 32.0 mmol) is stirred with HCl (5 M, 20 ml). When most of the ester has dissolved, the reaction mixture is cooled in an ice bath and a solution of $NaNO_2$ (2.5 M, 13 ml, 32.5 mmol) is added with stirring at such a rate that the internal temperature does not exceed 5 °C. More $NaNO_2$ solution is added until the I_2/starch test for free HNO_2 is positive (approximately 15 min after the last addition); the excess of HNO_2 is then destroyed by the addition of urea. The solution of the diazonium salt thus obtained is heated to 100 °C until evolution of N_2 ceases.

After cooling to room temperature, the resulting two-phase system is extracted with Et_2O (3 × 50 ml), the combined extracts are dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue (ester of **1.1.4.3**) is dissolved in a solution of NaOH (5.12 g, 128 mmol) in MeOH (100 ml) and stirred at room temperature for 12 h.

The solvent is then removed *in vacuo*, the residue is dissolved in H_2O (100 ml), and the (alkaline) solution is washed with Et_2O (3 × 50 ml). The organic extracts are discarded (check by TLC), and the aqueous phase is brought to pH 1 by the addition of concentrated HCl (stirring!) and extracted with Et_2O (3 × 50 ml). The combined ethereal extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is purified by chromatography (SiO_2, Et_2O/petroleum ether, 3 : 2). The product is obtained as orange solid; 4.50 g (63%), mp 96–97 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3450, 1720.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.01 (d, J = 7.5 Hz, 1H, Ar–H), 6.65 (d, J = 7.5 Hz, 1H, Ar–H), 6.58 (s, 1H, Ar–H), 2.61–2.56 (m, 1H, C<u>H</u>–CH_3), 2.31–2.28 (m, 2H, CH_2), 2.19 (s, 3H, Ar–CH_3), 1.57–1.49 (m, 4H, $(CH_2)_2$), 1.19 (d, J = 6.6 Hz, 3H, CH–C<u>H</u>$_3$).
MS (CI, 120 eV): m/z (%) = 222 (76) $[M]^+$.

1.1.4.4 * **2-Hydroxy-3,9-dimethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one** [5]



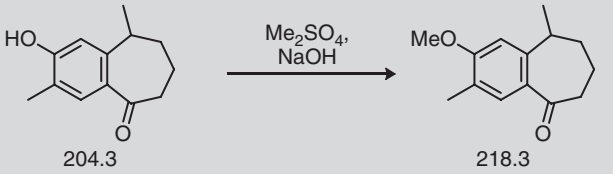
The finely powdered carboxylic acid **1.1.4.3** (2.00 g, 9.00 mmol) is suspended in polyphosphoric acid (20 ml, 85% P_4O_{10}). The resulting orange suspension is heated to 70 °C for 2 h with intense stirring.

The dark-red reaction mixture is then poured into H_2O (50 ml) and extracted with Et_2O (3 × 25 ml). The combined ethereal extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is purified by column chromatography (SiO_2; Et_2O/petroleum ether, 1 : 2). The product is obtained in the form of colorless crystals; 1.30 g (71%), mp 142–143 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3115, 1670.
^{1}H NMR (400 MHz, [D_6]DMSO): δ (ppm) = 9.90 (s, 1H, OH), 7.29, 6.74 (2 × s, 2 × 1H, 2 × Ar–H), 3.09–3.02 (m_c, 1H, C<u>H</u>–CH_3), 2.58–2.51 (m, 2H, CH_2),

2.11 (s, 3H, Ar–CH_3), 1.92–1.76 (m, 2H, CH_2), 1.48–1.34 (m, 2H, CH_2), 1.28 (d, $J = 6.6$ Hz, 3H, CH–C$\underline{H}_3$).
MS (EI, 70 eV): m/z (%) = 204 $[M]^+$.

1.1.4.5 * 2-Methoxy-3,9-dimethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one [5]

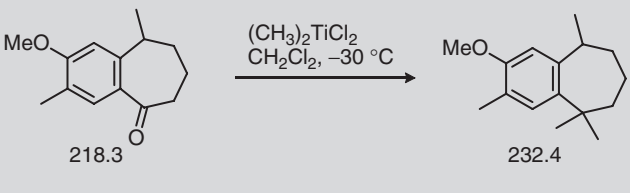


The hydroxybenzosuberone **1.1.4.4** (1.00 g, 5.0 mmol) is added over a period of 5 min to a stirred solution of NaOH (200 mg, 5.00 mmol) in H_2O (2.0 ml). Dimethyl sulfate (0.63 g, 5.0 mmol, 500 µl; Caution: carcinogenic!) is then added, and stirring is continued for 30 min at room temperature; more $(CH_3O)_2SO_2$ (0.63 g, 5.0 mmol, 500 µl) is then added, and stirring is continued for 1 h at room temperature and for 30 min at 100 °C (water bath).

The reaction mixture is then cooled to room temperature, diluted with H_2O (10 ml), and extracted with Et_2O (3 × 20 ml). The combined extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The oily residue is purified by chromatography (SiO_2; CH_2Cl_2). The product is obtained as a faintly yellow solid; 0.96 g (90%), mp 61–62 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1690.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.44, 6.69 (2 × s, 2 × 1H, Ar–H), 3.88 (s, 3H, OCH_3), 3.13 (m_c, 1H, C$\underline{H}$–CH_3), 2.74–2.68, 2.61–2.53 (2 × m, 2 × 1H, CH_2), 2.19 (s, 3H, Ar–CH_3), 1.98–1.83, 1.66–1.49 (2 × m, 2 × 2H, CH_2), 1.39 (d, $J = 7.0$ Hz, 3H, CH–C$\underline{H}_3$).
MS (EI, 70 eV): m/z (%) = 218 (77) $[M]^+$.

1.1.4.6 ** 2-Methoxy-3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene [5]

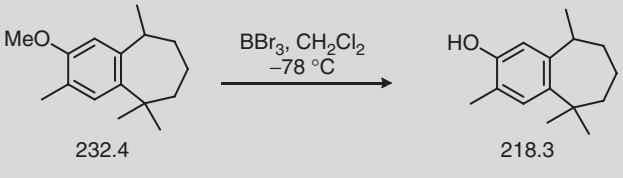


Under a nitrogen atmosphere, a solution of dimethylzinc in toluene (2 M, 2.5 ml, 5.00 mmol) is added dropwise to a stirred solution of titanium tetrachloride (0.96 g, 5.00 mmol) in anhydrous CH_2Cl_2 (25 ml) at such a rate that an internal temperature of −30 °C is maintained. After 15 min, a solution of the ketone **1.1.4.5** (0.50 g, 2.30 mmol) in CH_2Cl_2 (1.0 ml) is added dropwise at −30 °C. During the addition, the brown color of the reaction mixture changes to an intense dark brown. The mixture is allowed to warm to room temperature and is then heated under reflux for 12 h.

The reaction mixture is poured into H_2O (50 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The extracts are combined, washed successively with H_2O (100 ml) and saturated aqueous $NaHCO_3$ solution (100 ml), dried over $MgSO_4$, and filtered. The solvent is removed *in vacuo*, and the residue is purified by rapid filtration through silica gel (CH_2Cl_2). The product is obtained as a colorless oil; 0.43 g (81%), which is homogeneous according to TLC.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.12, 6.71 (2 × s, 2 × 1H, Ar–H), 3.81 (s, 3H, OCH_3), 3.27 (m_c, 1H, C<u>H</u>–CH_3), 2.18 (s, 3H, Ar–CH_3), 1.79–1.74, 1.65–1.52 (2 × m, 2 × 3H, 3 × CH_2), 1.39, 1.31 (2 × s, 2 × 3H, $C(CH_3)_2$), 1.36 (d, J = 7.1 Hz, 3H, CH–C<u>H</u>$_3$).
MS (CI, 120 eV): m/z (%) = 232 (66) $[M]^+$.

1.1.4.7 * 2-Hydroxy-3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene [5]



A 1.0 M solution of boron tribromide (4.0 ml, 8.0 mmol) in CH_2Cl_2 is added to a stirred solution of the methoxy compound **1.1.4.6** (0.42 g, 1.48 mmol) in anhydrous CH_2Cl_2 (40 ml) at −78 °C. The reaction mixture is allowed to warm to room temperature over 12 h.

H_2O (50 ml) is then added, the organic phase is separated, the aqueous phase is extracted with CH_2Cl_2 (3 × 20 ml), and the combined organic phases are dried over $MgSO_4$ and filtered. The solvent is removed *in vacuo*, and the crude product is purified by column chromatography (SiO_2; CH_2Cl_2) to give 0.25 g (80%) of the hydroxy-*ar*-himachalan as a yellowish oil, which is pure according to TLC.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3370.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.10, 6.65 (2 × s, 2 × 1H, Ar–H), 4.57 (s_{br}, 1H, OH), 3.22 (m_c, 1H, C<u>H</u>–CH_3), 2.21 (s, 3H, Ar–CH_3), 1.83–1.49 (m, 6H, $(CH_2)_3$), 1.39 and 1.30 (2 × s, 2 × 3H, $C(CH_3)_2$), 1.29 (d, J = 7.1 Hz, 3H, CH–C<u>H</u>$_3$).
MS (CI, 120 eV): m/z (%) = 218 (478) $[M]^+$.

Note: The ^{1}H NMR spectrum is identical to that of the natural product according to Ref. [4].

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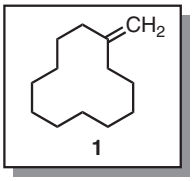
8. For synthesis of the phosphonium salt **22**, see: Perlmutter, P., Selajerem, W., and Vounatsos, F. (2004) *Org. Biomol. Chem.*, **2**, 2220–2228.

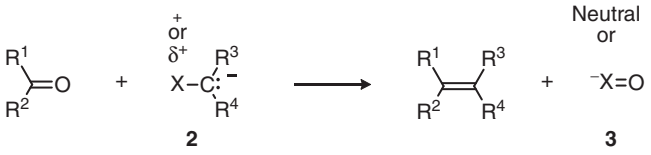
1.1.5
Methylenecyclododecane



Topics: • Carbonyl olefination by the Lombardo reaction

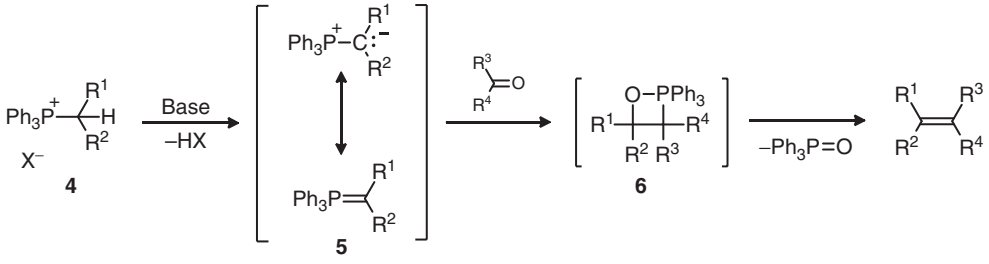
(a) General

The term *carbonyl olefination* covers a series of C–C bond-forming reactions, which allow the chemo- and stereoselective formation of an olefinic double bond at carbonyl groups of aldehydes, ketones, esters, amides, and so on, according to the following general scheme:



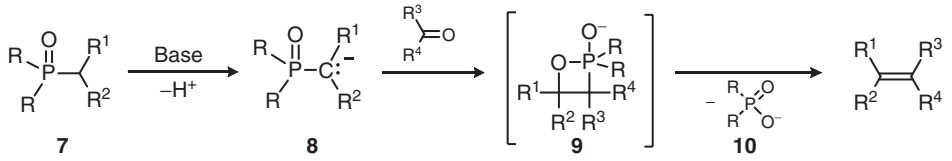
As reactants for carbonyl olefinations, α-carbanionic species of type **2** are required, which attack as nucleophiles at the carbonyl C atom. They also exhibit electrophilic properties at the structural unit X for attack at the carbonyl oxygen, which is removed as an X=O moiety **3** in the olefination process. If X carries a positive charge, **2** represents a betaine or ylide. Several types of reactants **2** containing P, Si, and metal centers in the X part have been developed as carbonyl olefinating reagents.

1) The classical procedure for carbonyl olefination is the Wittig reaction [1], using phosphoranes **5**. The phosphoranes **5** (easily obtainable by deprotonation of the corresponding α-CH phosphonium salts **4**) react with aldehydes or ketones to give alkenes and phosphine oxide:



The mechanism and stereochemistry of the Wittig reaction have been thoroughly investigated [2, 3]. The intermediates are the oxaphosphetanes **6** (from nonstabilized P-ylides), which collapse thermally by elimination of phosphine oxide. As a simplified rule, resonance-stabilized P-ylides give rise to (*E*)-alkenes, while nonstabilized P-ylides preferentially lead to (*Z*)-alkenes. The high value of the Wittig reaction is documented by a very large number of applications in the synthesis of alkenes (cf. Sections 1.1.4 and 4.1.6).

2) The Wittig–Horner reaction is a prominent example of the principle of "PO-activated olefination" [1], in which α-carbanions **8** (R = OR′) from phosphonates react with aldehydes and ketones; phosphonamides and phosphine oxides behave analogously:

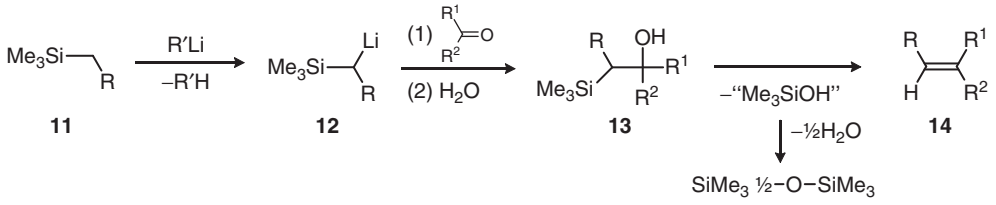


The mechanism of the Wittig–Horner reaction is comparable to that of the Wittig reaction [2, 3]. Oxaphosphetanes **9** can be assumed as primary intermediates, which are cleaved by olefin formation and elimination of phosphate **10** (R = OR′). The main advantages of the Wittig–Horner reaction lie in the facts that:

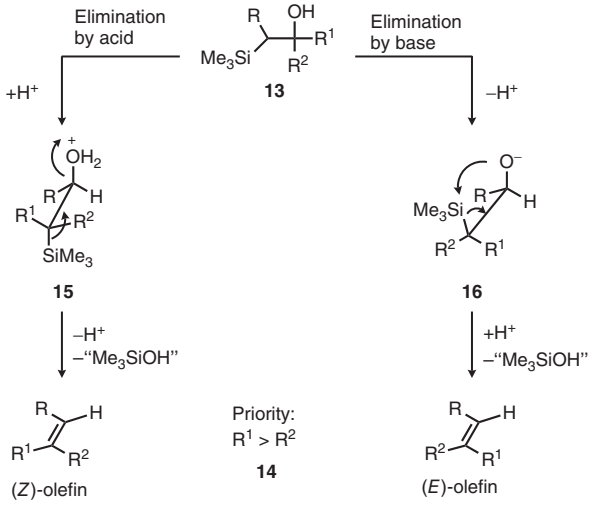
- the reactivity of the α-carbanions **8** often proves to be superior to that of the corresponding P-ylides **5**, thus allowing olefination of carbonyl substrates not or less susceptible to the Wittig method, for example, cyclohexanone, and
- the phosphates **10** (R = OR′) formed in the olefination process are water soluble, thus considerably improving the isolation and purification procedures for the olefinic products.

Phosphonates **7** (R = OR′) are obtained from phosphites and halogenoalkanes by the Arbusov reaction.

3) In the Peterson olefination (sometimes called the *sila-Wittig reaction*) [4], α-lithiated trialkylsilanes **12**, obtained from tetraalkylsilanes of type **11** by metallation with lithium diisopropylamide (LDA) or *n*BuLi, react with aldehydes or ketones:

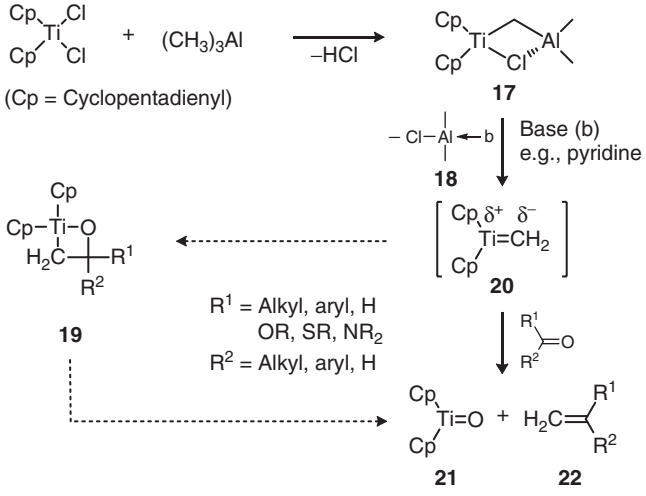


Initially, a β-hydroxysilane **13** is obtained, which is transformed into the olefin **14** by elimination of a silanol $Me_3Si–OH$ (finally appearing as $Me_3Si–O–SiMe_3$). The stereochemistry of olefin formation **13** → **14** can often be controlled by whether an acid or a base is used for the silanol elimination. Use of an acid generally leads to an anti-elimination (transition state **15**), whereas use of base leads to a syn-elimination (transition state **16**); in this way, the stereoselective formation of either (*Z*)- or (*E*)-alkenes **14** can be achieved.



4) Olefin formation using the Wittig, Horner, or Peterson procedures is, with only a few exceptions, restricted to aldehydes and ketones. However, by the application of a series of titanium-based reagents, a broad variety of carbonyl-containing substrates, not only aldehydes and ketones but also esters, lactones, amides, and so on, become amenable to olefination reactions, predominantly methylenations.

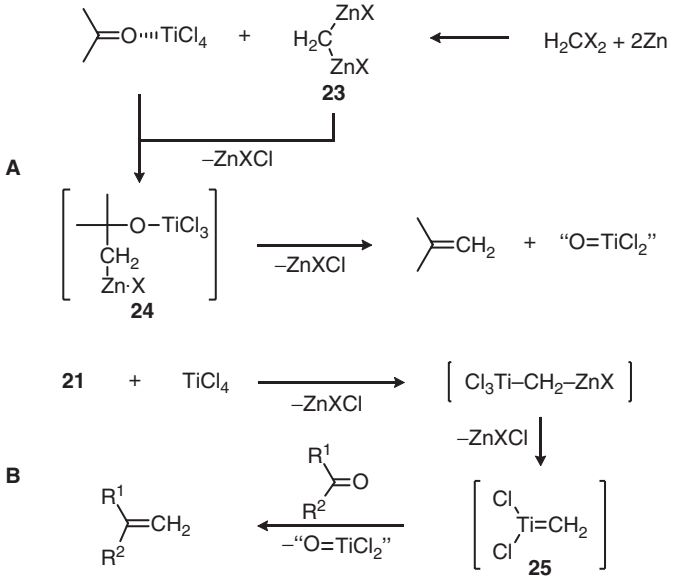
   a. The Tebbe reagent **17**, obtained from bis(cyclopentadienyl)titanium dichloride and trimethylaluminum, can react with practically all kinds of carbonyl-containing substrates [5, 6] in the presence of a Lewis base (e.g., pyridine) to give methylenation products **22** (alkenes, enol ethers, enamines, etc.):



The Tebbe reaction is likely to proceed via a titanium ylide **20** (generated from the bridged reagent **17** by a Lewis base-induced removal of the chlorodimethylaluminum moiety **18**), its (formal) [2 + 2]-cycloaddition to the carbonyl group, and eliminative cycloreversion of the intermediate **19** to give the methylenation product **22**. In addition, **21** is formed by an oxygen transfer to titanium.

b. Reagent combinations of dihalogenomethanes, zinc, and titanium tetrachloride (H_2CX_2/Zn/$TiCl_4$, Lombardo and Takai reagents), which are easier to handle and less expensive than the Tebbe reagent, may also allow the methylenation of aldehydes and ketones; in general, however, ester functionalities are not affected [5].

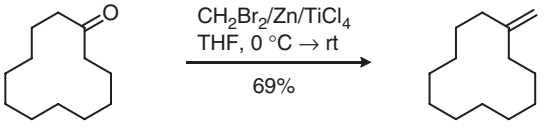
The structures of the titanium species responsible for the Lombardo/Takai olefination are unknown. It is assumed that a "dimetallic" Zn species **23** is formed initially, which can lead to methylenation products via two alternative routes: (i) by reaction with the carbonyl group activated by $TiCl_4$ as a Lewis acid (via **24**) or (ii) by transmetallation with $TiCl_4$ leading to a Ti ylide **25**, which reacts with the carbonyl group in analogy with the Tebbe reaction:



(b) **Synthesis of 1**

Methylenecyclododecane (**1**) is prepared from cyclododecanone (**26**) in a one-pot procedure [7] by means of methylenation using the Lombardo reagent prepared *in situ* from dibromomethane, titanium tetrachloride, and zinc dust (in the ratio

1.5 : 1.1 : 4.5). The reaction proceeds smoothly at 0 °C to room temperature in anhydrous THF to give the macrocycle **1** in 69% yield after the usual work-up and purification by chromatography on silica gel.

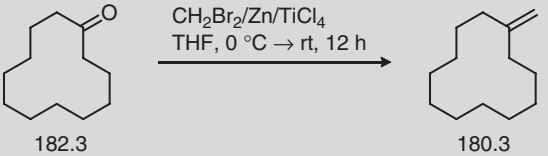


26 **1** (1.1.5.1)

It should be noted that **1** is also accessible by a Wittig reaction starting from ketone **26** [8].

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

1.1.5.1 ** **Methylenecyclododecane** [7]



182.3 180.3

Dibromomethane (13.0 g, 74.8 mmol, 5.94 ml) and titanium tetrachloride (10.4 g, 55.0 mmol, 6.07 ml) are added sequentially to a vigorously stirred suspension of zinc dust (14.8 g, 226 mmol) in anhydrous THF (250 ml). After stirring the mixture for 15 min at 0 °C, a solution of cyclododecanone (9.10 g, 49.9 mmol) in anhydrous THF (50 ml) is added dropwise, and stirring is continued for 12 h at room temperature.

The mixture is then diluted with Et_2O (200 ml) and filtered, and the filtrate is washed with 1 M aqueous HCl (250 ml) and brine (250 ml). The organic layer is dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is dissolved in *n*-pentane and purified by column chromatography (SiO_2, *n*-pentane) to give the product as a colorless liquid; 6.24 g (69%), $R_f = 0.76$ (*n*-pentane).

UV (CH_3CN): λ_{max} (nm) (log ε) = 192.0 (3.854).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2930, 1643, 887, 469.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.79 (m_c, 2H, 1-CH_2), 2.06 (m, 4H, 2-H_2, 12-H_2), 1.55 – 1.47 (m, 4H, 4-H_2, 10-H_2), 1.31 (m_c, 14H, 3-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 11-H_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 147.5 (C-1), 110.3 (1-CH_2), 33.04 (C-2, C-12), 24.43, 24.11, 23.69, 23.24 (C-3, C-4, C-5, C-6, C-8, C-9, C-10, C-11), 22.59 (C-7).
MS (EI, 70 eV): *m*/*z* (%) = 180 (46) $[M]^+$, 96 (100) $[M-C_6H_{12}]^+$.

Note: The product can be distilled *in vacuo*, $bp_{0.8}$ 76–77 °C.

References

1. (a) Smith, M.B. (2013) *March's Advanced Organic Chemistry*, 7th edn, John Wiley & Sons, Inc., New York, p. 1165; (b) For a review on olefination of carbonyl compounds, see: Korotchenko, V.N., Nenajdenko, V.G., Balenkova, E.S., and Shastin, A.V. (2004) *Russ. Chem. Rev. (Engl. Transl.)*, **73**, 957–989.
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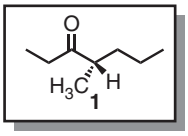
1.2
Alkylation of Aldehydes/Ketones, Carboxylic Acids, and β-Dicarbonyl Compounds

1.2.1
(+)-(*S*)-4-Methylheptan-3-one



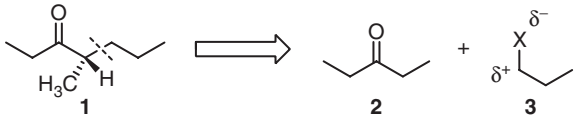
Topics:

- Synthesis of an enantiopure pheromone by application of the Enders SAMP method
- Formation of the SAMP hydrazone of a methylene ketone
- Diastereoselective α-alkylation of a SAMP hydrazone, hydrolytic cleavage of the alkylated SAMP hydrazone

(a) **General**

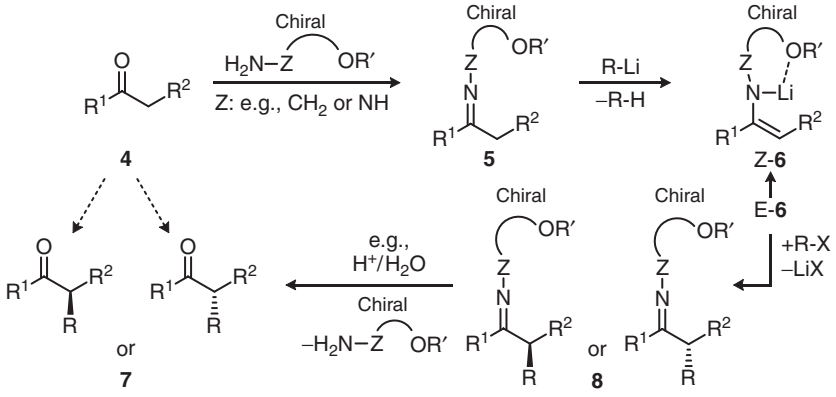
(+)-(*S*)-4-Methylheptan-3-one (**1**) is the main alarm pheromone of the leafcutter ant *Atta texana*; it is 400 times more active than its enantiomer.

Retrosynthetic analysis leads directly to pentan-2-one (**2**) and an alkylation reagent **3** representing the α-side chain.

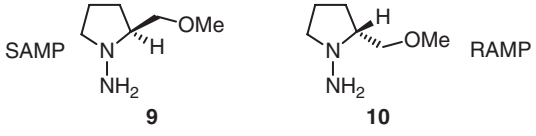


The main objective in the synthesis of **1** is therefore the stereoselective monoalkylation of a dialkyl ketone **4** possessing an α-CH_2 group. This requires the transformation of the C=O group into a C=N–R moiety carrying a chiral group R, which provides stereochemical control for the alkylation process. Since an additional binding, for example, by chelate formation, is necessary, β-alkoxyamines and alkoxyhydrazines are interesting candidates; they can be easily prepared from "chiral pool" amino acids.

For a stereoselective alkylation, the following steps have to be considered. Derivatization of the ketone (**4** → **5**), α-deprotonation at CH_2 and formation of a chelated azaenolate **6** with a rigid backbone, diastereoselective reaction of **6** with an electrophile (here: R–X, **6** → **8**), and finally removal of the auxiliary to give one pure enantiomer of the desired α-alkylated ketone (**8** → **7**):



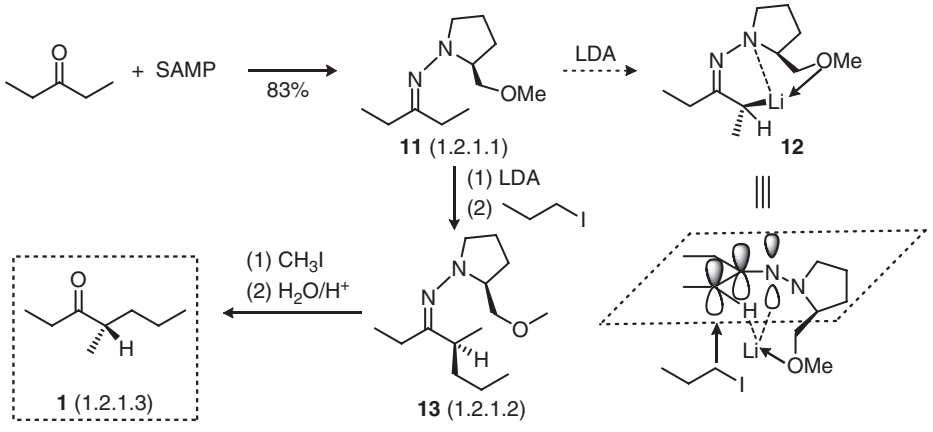
This concept has been verified in several modifications [1]. Particularly successful outcomes have been achieved with the enantiomers of the hydrazine derived from (*S*)- or (*R*)-prolinol methyl ether (SAMP/RAMP, **9**/**10**), both of which are readily available [2] and thus allow the preparation of both enantiomers of an α-alkyl ketone [3].



Here, the SAMP method (Enders method) is used to prepare the ketone **1** with high enantiopurity [4].[3)]

(b) **Synthesis of 1**

First, the SAMP auxiliary is condensed with diethyl ketone (**2**) to give the chiral hydrazone **11**:



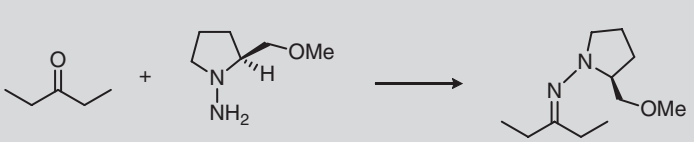
The hydrazone **11** is metallated with LDA, and the formed azaenolate **12** is reacted with *n*-propyl iodide to provide the α-alkylated hydrazone **13** as a single diastereomer. The alkylation process presumably follows an S_E2 mechanism with retention of configuration, as visualized in the transition state **12**. Li chelation of the methoxy group is obviously responsible for the high degree of diastereoselection observed.

The hydrazone **13** is cleaved by alkylation with CH_3I to give the corresponding hydrazonium salt, which is cleaved by acid hydrolysis in an aqueous two-phase system to give the α-alkylated ketone **1** with 99% ee. This mild method of hydrazone cleavage has the drawback that the chiral auxiliary cannot be recovered ("sacrificial" vs. "regenerative" use of a chiral auxiliary [5]).

Ozonolysis is another method that has been introduced for the cleavage of SAMP hydrazones; it leads directly to the α-alkylated carbonyl source and a SAMP-derived nitrosamine [6].

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

1.2.1.1 ** **Preparation of the Chiral Hydrazone** [4][3)]

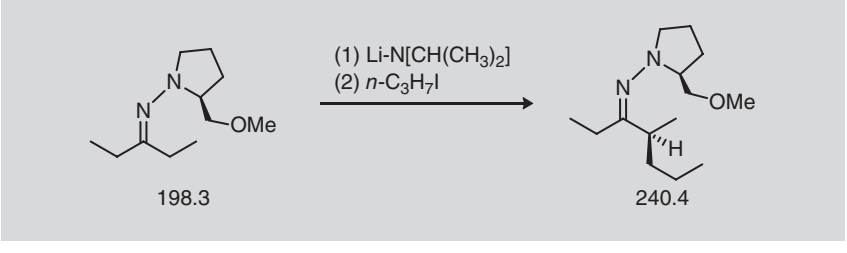


3) for a review on asymmetric synthesis with the RAMP/SAMP auxiliaries, see Ref. [3b].

(−)-(*S*)-1-Amino-2-(methoxymethyl)pyrrolidine [2] (2.60 g, 20.0 mmol) and 3-pentanone (distilled, bp_{760} 101 – 102 °C; 1.89 g, 22.0 mmol, ≈2.32 ml) are stirred at 60 °C for 20 h in a 25-ml single-necked flask.

The reaction mixture is then diluted with anhydrous CH_2Cl_2 (20 ml) and dried over Na_2SO_4. The solvent is evaporated, and the residue is distilled from a deactivated Kugelrohr (trimethylchlorosilane is distilled from the apparatus at atmospheric pressure). Any remaining solvent in the distillate is evaporated *in vacuo* to leave a colorless oil; 3.29 g (83%), $bp_{0.04}$ 46 °C (oven temperature 50 – 55 °C).

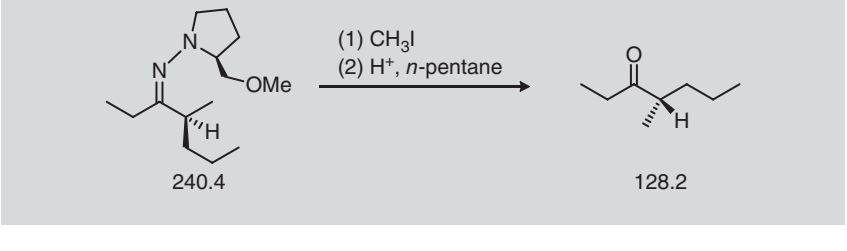
1.2.1.2 *** Diastereoselective Alkylation of the Chiral Hydrazone [4]



A solution of diisopropylamine (distilled from CaH_2, bp_{760} 84 °C; 0.84 g, 8.30 mmol, ≈1.17 ml) in anhydrous diethyl ether (40 ml) is prepared under nitrogen at −78 °C in an oven-dried, 100-ml, two-necked flask fitted with a septum. *n*-Butyllithium in *n*-hexane (1.6 M, 5.2 ml) is added by means of a syringe (cannula), and the solution is stirred for 10 min at −78 °C. The solution is then warmed to 0 °C over approximately 30 min, and the hydrazone prepared in **1.2.1.1** (1.52 g, 7.70 mmol) is slowly added dropwise from a syringe. Stirring is continued at 0 °C for 10 h. The solution is then cooled to −110 °C (petroleum ether/N_2), propyl iodide (distilled, bp_{760} 102 °C; 1.47 g, 8.65 mmol, ~0.84 ml) is added dropwise over 10 min through a cannula (the cannula is cooled during the addition), and stirring is continued for 1 h.

The mixture is warmed to room temperature, diluted with CH_2Cl_2 (40 ml), and filtered, and the solvent is evaporated. The residue is used immediately for the next step.

1.2.1.3 *** Cleavage of the alkylated hydrazone [4]



The crude product prepared in **1.2.1.2** and methyl iodide (3.54 g, 25.0 mmol, ~1.56 ml; Caution: carcinogenic!) are heated under reflux. Excess methyl iodide is evaporated *in vacuo*. The formed hydrazonium iodide (green-brown oil) is stirred vigorously with *n*-pentane (60 ml)/aqueous HCl (6 M, 40 ml) for 60 min.

The organic phase is separated, and the aqueous phase is extracted with *n*-pentane (2 × 50 ml). The combined organic layers are washed with brine, dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* and the green residue is distilled from a Kugelrohr (pretreated with trimethylchlorosilane). The ketone is obtained as colorless liquid; 475 mg (48% based on SAMP), bp_{110} 140 °C (oven temperature), $[\alpha]^{20}_D = +16.5$ ($c = 1.2$, *n*-hexane) (note).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1710, 740.
^{1}H NMR ($CDCl_3$): δ (ppm) = 2.45 (m, 3H, CH_2CO, CHCO), 1.84–0.71 (m, 13H, $CH_2 + CH_3$).

Note: Observed ee = 87% (*S*); reported [3]: $[\alpha]^{20}_D = +22.1$ ($c = 1.0$, *n*-hexane), ee = 99.5% (*S*).

References

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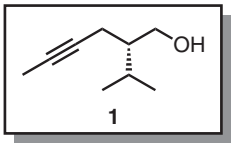
1.2.2

(*S*)-2-Isopropylhex-4-yn-1-ol

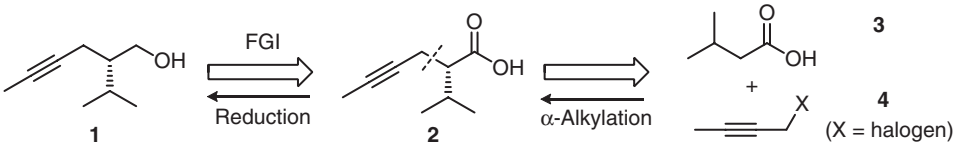


Topics:

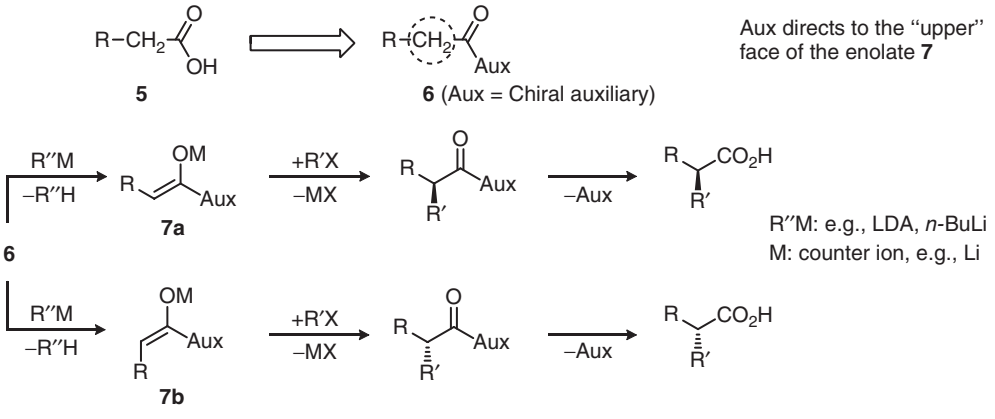
- Enantioselective α-alkylation of an alkanoic acid by application of the Evans methodology
- Synthesis of a chiral oxazolidinone (Evans auxiliary) from L-valine
- Synthesis of 1-bromobut-2-yne (alkylating reagent)
- N-Acylation and enantioselective α-alkylation of a chiral *N*-acyloxazolidinone
- Reductive removal of the Evans auxiliary, transformation of the *N*-acyl moiety into the corresponding primary alcohol

(a) **General**

The target molecule **1** was required as a building block in the context of a multistep natural product synthesis (L.F. Tietze *et al.*, unpublished results). Retrosynthesis of **1** leads to **2** and, furthermore, to isovaleric acid (**3**) and the propargylic halide **4** as substrates.

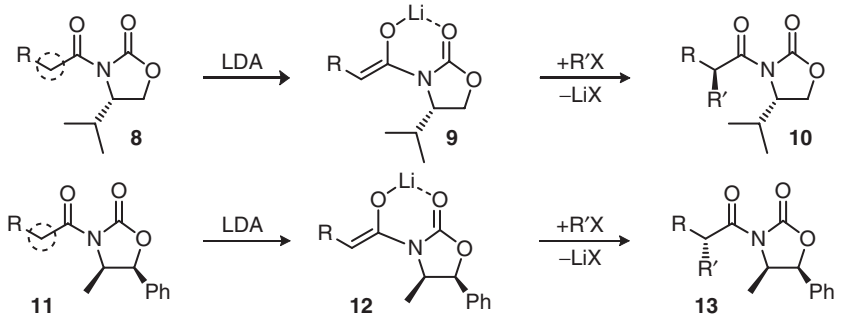


Accordingly, the synthesis consists of an α-alkylation of the acid **3** followed by reduction of the carboxyl group of the formed product **2** to provide the primary alcohol **1**. The main objective for a stereochemically concise synthesis of **1** is stereoselective α-alkylation of an alkanoic acid $R-CH_2-CO_2H$ (**5**). For stereodifferentiation in the alkylation process, carboxylic acid derivatives **6** can be employed, in which a chiral auxiliary is introduced at the acyl C-atom (cf. Section 1.2.1) [1]. The chiral auxiliary influences the configuration of the enolates **7a**/**7b** (*Z* or *E*, formed by deprotonation of **6**) and the facial selectivity of the alkylation (*re* or *si*) according to the following scheme:



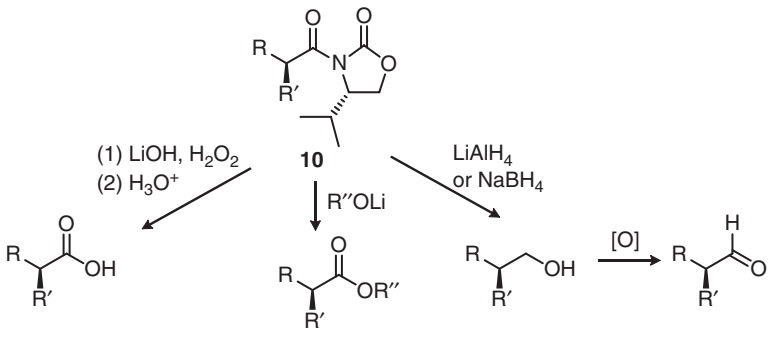
For high stereoselectivity in the enolate formation and the alkylation, formation of a chelate by coordination of the metal ion to an appropriate functionality of the chiral auxiliary is necessary. Widely used chiral carboxylic acid derivatives are **8** and **11**, containing an oxazolidinone as the chiral auxiliary (Evans auxiliaries) [2].

Deprotonation of **8** and **11** with LDA produces the chelated enolates **9** and **12**, respectively, with a *Z*-selectivity of >99 : 1, which can then be α-alkylated with alkyl halides (only reactive alkyl halides such as methyl, benzyl, allyl, and propargyl can be used) with very high levels of diastereoselectivity to give the products **10** and **13**:



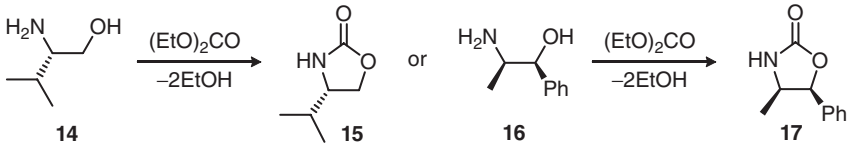
It should be noted that the enolates **9** and **12** can also be used in aldol reactions. In these transformations, using a (*Z*)-enolate, a syn product is obtained via a closed transition state, whereas with an (*E*)-enolate the anti product is formed predominately. By adding 1 mol of a Lewis acid, the stereochemical outcome is reversed, because under these conditions an open transition structure is preferred.

Removal of the chiral auxiliary from the α-alkylated *N*-acyl oxazolidinones **10** and **13** may be achieved by hydrolysis, alcoholysis, or reduction, as illustrated for **10**.



In this way, almost enantiopure α-alkylated carboxylic acids, esters, primary alcohols, and aldehydes can be obtained.

The chiral oxazolidinones **15** and **17**, as parts of the chiral *N*-acyl derivatives **8** and **11**, are prepared from readily available 1,2-amino alcohols such as L-valinol (**14**), formed from L-valine, and norephedrine (**16**) by reaction with diethyl carbonate. The acylation of **15** and **17** to give **8** and **11**, respectively, is accomplished by deprotonation with *n*-BuLi or LDA followed by reaction of the anion with an acid chloride:

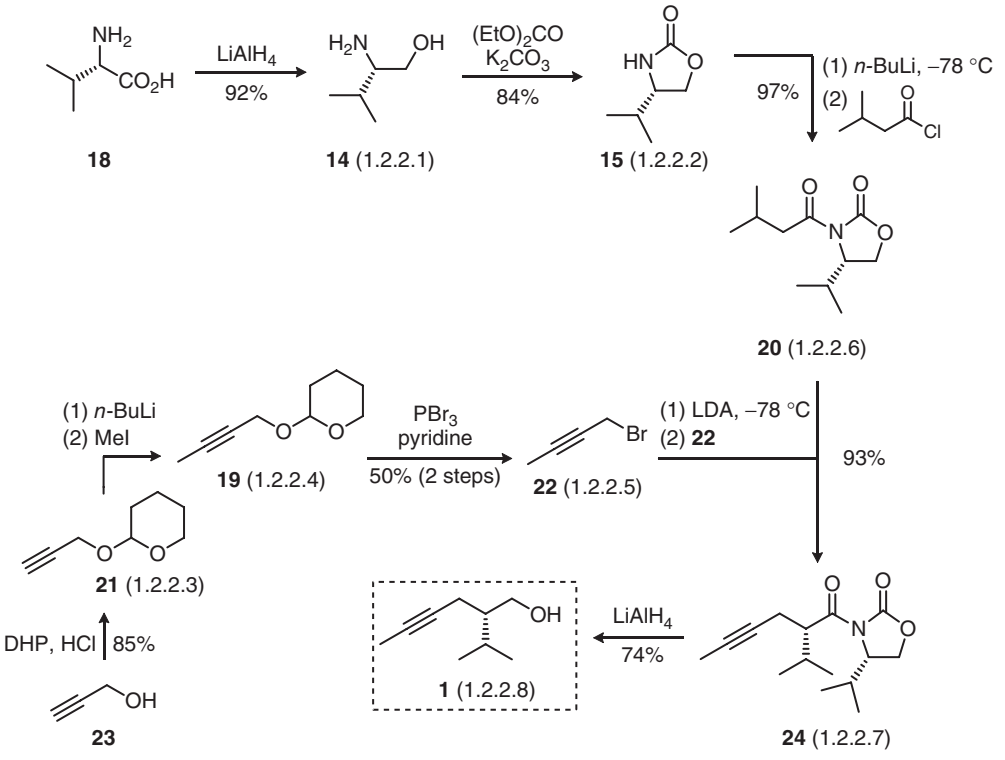


Because of the complementary outcomes of their α-alkylations, the systems **8** and **11** allow the preparation of both enantiomers of an (α-alkyl)alkanoic acid $R-CHR'-CO_2H$.

In Section (b), the synthesis of the target molecule **1** from a chiral α-alkylated isovaleric acid (**2**) is presented, which is accessible by application of the auxiliary **15** and the Evans methodology.

(b) **Synthesis of 1**

The synthesis of **1** is convergent and is divided into three parts. First, the auxiliary **15** is prepared from (*S*)-valine; second, the propargylic halide **22** is synthesized from propargyl alcohol (**23**); third, the auxiliary **15** is acylated, then the diastereoselective α-alkylation with **22** is performed, and finally the auxiliary is removed reductively.

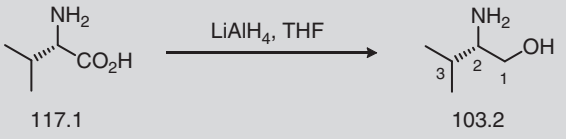


1) L-Valine (**18**) is reduced with $LiAlH_4$ in THF to give L-valinol (**14**), which is transformed into the chiral oxazolidinone **15** by cyclocondensation with diethyl carbonate in the presence of K_2CO_3 [3, 4].
2) Propargylic alcohol (**23**) is converted to its tetrahydropyranyl ether **21** by reaction with dihydropyran in the presence of concentrated HCl. The THP ether **21** is deprotonated at the terminal acetylene function, and the formed acetylide is methylated *in situ* with CH_3I to give **19**. The THP ether in **19** is cleaved by treatment with phosphorus tribromide in the presence of pyridine in diethyl ether, thereby generating 1-bromo-2-butyne (**22**) required as the alkylating agent [5, 6].
3) The oxazolidinone **15** is N-deprotonated using *n*-BuLi in THF and acylated with isovaleroyl chloride (both at −78 °C) to give the *N*-isovaleroyloxazolidinone **20** in almost quantitative yield. α-Alkylation of **20** is achieved in THF by deprotonation at the CH_2 group with LDA to yield the enolate **9** (R = $(CH_3)_2CH$), and subsequent reaction with the propargylic halide **22** in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) at −78 °C cleanly affords the alkylation product **24** as a single diastereomer (93% yield, ds = 150 : 1).

Finally, treatment of **24** with $LiAlH_4$ in THF at −78 °C leads to reductive removal of the auxiliary with the formation of the chiral acetylenic alcohol **1** [5, 6].

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

1.2.2.1 ** **(2*S*)-2-Amino-3-methylbutan-1-ol (L-valinol)** [4]



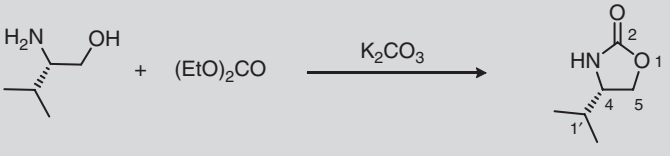
117.1 103.2

In a flame-dried, three-necked, round-bottomed flask equipped with a reflux condenser and a mechanical stirrer, $LiAlH_4$ (25.8 g, 0.68 mol) is suspended in anhydrous THF (300 ml) and cooled to 0 °C (nitrogen atmosphere). L-Valine (40.0 g, 0.34 mol) is carefully added in 1 g portions under vigorous stirring (Caution: reaction starts slowly!), and after addition the reaction mixture is heated to reflux for 15 h.

It is then cooled to 0 °C, and ice-cold water (40 ml) is carefully added (dropwise at the beginning). The gray-white aluminum salts are filtered off, suspended in a THF/H_2O mixture (4 : 1, 200 ml), stirred for 30 min, and then this mixture is also filtered. The process is repeated once more. The combined filtrates are concentrated *in vacuo*, the residue is dissolved in $CHCl_3$ (200 ml), and the mixture is refluxed in a Dean–Stark apparatus. The solvent is removed *in vacuo*, and the residue is distilled under reduced pressure to afford L-valinol as a colorless liquid; 32.2 g (92%), mp 55–56 °C, bp_{16} 85–86 °C, $[\alpha]^{20}_D = +25.7$ ($c = 1.0$, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.62 (dd, $J = 12.0$, 3.5 Hz, 1H, 1-H_b), 3.31 (dd, $J = 8.0$, 12.0 Hz, 1H, 1-H_a), 2.60 (ddd, $J = 8.0$, 6.5, 3.5 Hz, 1H, 2-H), 2.34 (s_{br}, 3H, NH_2, OH), 0.99 (dsept, $J = 7.0$, 6.5 Hz, 1H, 3-H), 0.92 (d, $J = 7.0$ Hz, 6H, $2 \times CH_3$).

1.2.2.2 ** **(4*S*)-Isopropyloxazolidin-2-one** [4]



103.2 118.1 129.2

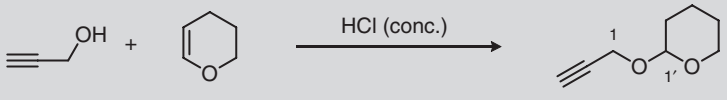
In a micro distillation apparatus equipped with a Vigreux column (30 cm) and an internal thermometer, a mixture of L-valinol **1.2.2.1** (31.0 g, 0.30 mol), diethyl carbonate (76.8 g, 0.65 mol), and anhydrous K_2CO_3 (4.13 g, 0.03 mol) is slowly heated to 130–140 °C. EtOH is distilled off in the course of the reaction (internal temperature should not exceed 100 °C, temperature at the top of the Vigreux column

should not exceed 85 °C). After EtOH formation has ceased, the mixture is heated for another 30 min.

It is then cooled to room temperature, diluted with CH_2Cl_2 (200 ml), and filtered. The filtrate is washed with saturated aqueous $NaHCO_3$ solution (2 × 50 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*, and the residue is crystallized from EtOAc/*n*-pentane to afford the oxazolidinone; 32.7 g (84%), mp 74–75 °C, $[\alpha]^{20}_D = -19.2$ ($c = 1.24$, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.14 (s_{br}, 1H, NH), 4.47 (dd, J = 9.0, 8.5 Hz, 1H, 5-H_b), 4.12 (dd, J = 9.0, 6.0 Hz, 1H, 5-H_a), 3.64 (ddd, J = 8.5, 6.5, 6.0 Hz, 1H, 4-H), 1.76 (dsept, J = 7.0, 6.5 Hz, 1H, 1′-H), 0.97 (d, J = 7.0 Hz, 3H, CH_3), 0.90 (d, J = 7.0 Hz, 3H, CH_3).

1.2.2.3 * **2-(2-Propynyloxy)tetrahydropyran** [5, 6]

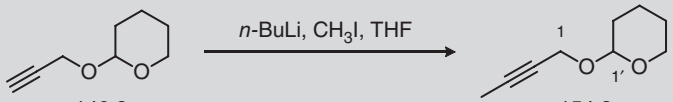


Concentrated HCl (1 µl) is added to a stirred mixture of propargyl alcohol (28.1 g, 500 mmol) and 3,4-dihydro-2*H*-pyran (DHP) (43.7 g, 520 mmol) at 0 °C. Stirring is continued for 24 h at room temperature.

KOH (900 mg) is then added and the mixture is stirred for another 15 min. Fractional distillation using a Vigreux column affords the tetrahydropyran as a colorless liquid; 59.6 g (85%), bp_{20} 72–80 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.78 (t, J = 3.2 Hz, 1H, 1′-H), 4.26 (dq, J = 15.2, 2.3 Hz, 1H, 1-H_b), 4.09 (dq, J = 15.2, 2.3 Hz, 1H, 1-H_a), 3.90–3.75 (m, 1H, 5′-H_b), 3.52–3.43 (m, 1H, 5′-H_a), 2.02 (t, J = 2.5 Hz, 1H, 3-H), 1.88–1.40 (m, 6H, 2′-H_2, 3′-H_2, 4′-H_2).

1.2.2.4 ** **2-(2-Butynyloxy)tetrahydropyran** [5, 6]



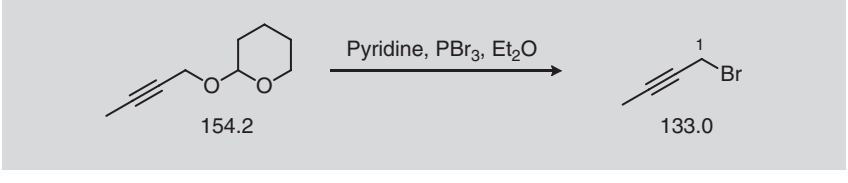
n-Butyllithium in *n*-hexane (2.5 M, 172 ml, 429 mmol) is added dropwise over 1 h to a stirred solution of the tetrahydropyran **1.2.2.3** (50.0 g, 357 mmol) in THF (600 ml) at −78 °C. Stirring is continued at −78 °C for 5 h; then methyl iodide

(152 g, 1.07 mol, 66.9 ml; Caution: carcinogenic!) is added and the solution is allowed to warm to room temperature over 14 h.

The reaction is quenched by the addition of H_2O (20 ml) and the solvent is removed *in vacuo*. The brown, oily crude product is dissolved in benzene (150 ml; Caution: carcinogenic!) and this solution is concentrated *in vacuo* to remove the remaining H_2O by azeotropic distillation. The residue is fractionally distilled to afford the product as a colorless oil; 50.4 g (91%), bp_{10} 75–80 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.76 (t, J = 3.2 Hz, 1H, 1′-H), 4.27 (dq, J = 15.2, 2.3 Hz, 1H, 1-H_b), 4.14 (dq, J = 15.2, 2.3 Hz, 1H, 1-H_a), 3.86–3.73 (m, 1H, 5′-H_b), 3.54–3.42 (m, 1H, 5′-H_a), 1.90–1.42 (m, 6H, 2′-H_2, 3′-H_2, 4′-H_2), 1.81 (t, J = 2.3 Hz, 3H, 4-H_3).

1.2.2.5 ** **1-Bromo-2-butyne** [5, 6]

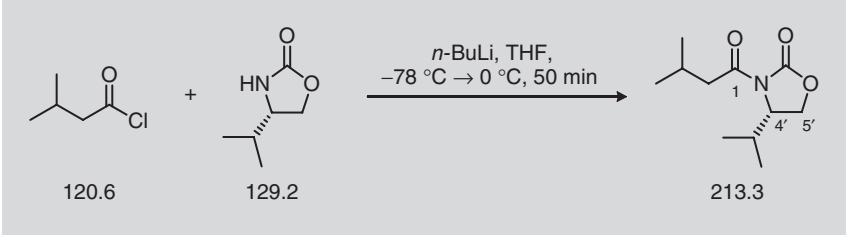


Phosphorus tribromide (37.6 g, 139 mmol, 13.1 ml) is added dropwise to a solution of the tetrahydropyran **1.2.2.4** (42.9 g, 278 mmol) and pyridine (0.2 ml) in Et_2O (25 ml), and the mixture is heated under reflux for 3 h.

The reaction is quenched with H_2O (50 ml), the organic layer is separated, and the aqueous layer is extracted with Et_2O (2 × 150 ml). The combined organic layers are washed with saturated $NaHCO_3$ solution (2 × 150 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is fractionally distilled with a Vigreux column to afford 1-bromo-2-butyne as a colorless liquid; 21.6 g (58%), bp_{43} 38–43 °C, R_f = 0.72 (*n*-pentane/MeO*t*Bu = 5 : 1).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.91 (q, J = 2.5 Hz, 2H, 1-H_2), 1.89 (t, J = 2.5 Hz, 3H, 4-H_3).
MS (EI): m/z (%) = 135 (60) $[M+2H]^+$, 133 (60) $[M]^+$.

1.2.2.6 ** **(*S*)-4-Isopropyl-3-isovaleroyl-oxazolidin-2-one** [5, 6]

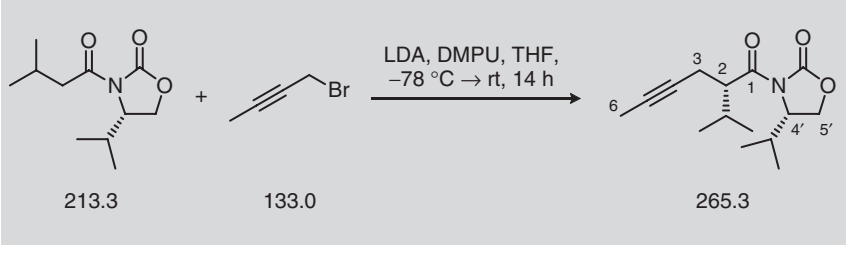


n-Butyllithium in *n*-hexane (2.6 M, 78.2 ml, 203 mmol) is added dropwise with stirring to a solution of the oxazolidinone **1.2.2.2** (25.0 g, 194 mmol) in anhydrous THF (800 ml) at −78 °C and stirring is continued for 30 min. Isovaleroyl chloride (25.7 g, 213 mmol, 26.2 ml) is then added dropwise and the reaction mixture is stirred at −78 °C for 20 min and at 0 °C for 30 min.

The reaction is quenched by the addition of K_2CO_3 solution (1 M, 150 ml), and the solvents are removed *in vacuo*. After the addition of H_2O (500 ml), the layers are separated and the aqueous layer is extracted with MeO*t*Bu (4 × 400 ml). The combined organic layers are washed with brine (2 × 100 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue is fractionally distilled to afford the product as a colorless liquid; 41.3 g (100%), $bp_{0.008}$ 70–85 °C, $R_f = 0.47$ (*n*-pentane/Et_2O, 1 : 1).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.38 (m_c, 1H, 4′-H), 4.26–4.08 (m, 2H, 5′-H_2), 2.88 (dd, J = 15.9, 7.2 Hz, 1H, 2-H_b), 2.64 (dd, J = 15.9, 7.2 Hz, 1H, 2-H_a), 2.32 (dsept, J = 7.3, 4.0 Hz, 1H, *i*Pr-CH), 2.13 (non, J = 7.2 Hz, 1H, 3-H), 1.00–0.76 (m, 12H, 4 × CH_3).

1.2.2.7 *** **(*S*,*S*)-4-Isopropyl-3-(2-isopropyl-hex-4-ynoyl)-oxazolidin-2-one** [5, 6]



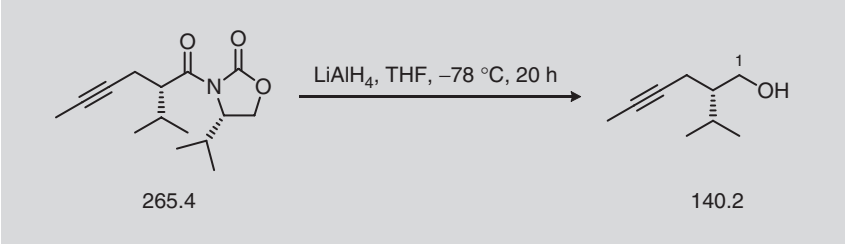
n-Butyllithium in *n*-hexane (2.8 M, 41.5 ml, 116 mmol) is added dropwise to a stirred solution of diisopropylamine (12.8 g, 126 mmol, 17.8 ml) in anhydrous THF (250 ml) at −78 °C. Stirring is continued at 0 °C for 45 min, and then the mixture is again cooled to −78 °C. A solution of the oxazolidinone **1.2.2.6** (22.5 g, 105 mmol) in THF (25 ml) is added dropwise with stirring over 1 h at −78 °C, and the resulting mixture is stirred for a further 2 h. DMPU (32 ml) and the freshly prepared bromide **1.2.2.5** (20.0 g, 150 mmol) are then added over 1 h. The reaction mixture is allowed to slowly warm to room temperature and stirred for a further 14 h.

Saturated aqueous NH_4Cl solution (100 ml) is then added, the organic layer is separated, and the aqueous layer is extracted with Et_2O (3 × 150 ml). The combined organic layers are successively washed with ice-cold aqueous HCl (1 M, 100 ml), saturated aqueous $NaHCO_3$ solution (100 ml), and brine (100 ml), dried over Na_2SO_4, and filtered. The solvents are removed *in vacuo*, and the residue is purified by column chromatography (SiO_2, *n*-pentane/MeO*t*Bu, 20 : 1 → *n*-

pentane/MeO*t*Bu, 3 : 1) to afford the alkylation product as a colorless oil; 26.0 g (93%), ds = 150 : 1, $[\alpha]^{20}_D = +63.6$ ($c = 0.5$, $CHCl_3$), $R_f = 0.41$ (*n*-pentane/MeO*t*Bu, 5 : 1).

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3376, 2964, 2924, 2876, 1780, 1698, 1468, 1432, 1388.
UV (CH_3CN): λ_{max} (nm) (log ϵ) = 206.0 (3.5222).
^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.52 (ddd, $J = 7.6$, 3.8, 3.8 Hz, 1H, 2-H), 4.34–4.16 (m, 2H, 5′-H_2), 3.93 (ddd, $J = 9.5$, 7.0, 5.0 Hz, 1H, 4′-H), 2.61–2.32 (m, 3H, 3-H_2, 2-C<u>H</u>Me_2), 1.98 (oct, $J = 7.0$ Hz, 1H, 4′-C<u>H</u>Me_2), 1.71 (t, $J = 2.8$ Hz, 3H, 6-H_3), 0.95 (d, $J = 6.8$ Hz, 3H, *i*Pr-CH_3), 0.94 (d, $J = 7.0$ Hz, 6H, 2 × *i*Pr-CH_3), 0.92 (d, $J = 7.0$ Hz, 3H, *i*Pr-CH_3).
^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 174.8 (C-1), 153.6 (C-2′), 76.4 (C-4), 76.2 (C-5), 62.9 (C-5′), 58.5 (C-4′), 48.2 (C-2), 29.8 (4′-*i*Pr-*C*H), 28.3 (2-*i*Pr-*C*H), 20.6 (2-*i*Pr-*C*H_3), 19.0 (C-3), 18.9 (2-*i*Pr-*C*H_3), 17.8 (4′-*i*Pr-*C*H_3), 14.4 (4′-*i*Pr-*C*H_3), 3.4 (C-6).
MS (DCI, 200 eV): *m*/*z* (%) = 549 (40) $[2M+NH_4]^+$, 283 (100) $[M+NH_4]^+$.

1.2.2.8 ** (*S*)-2-Isopropylhex-4-yn-1-ol [5, 6]



A suspension of $LiAlH_4$ (5.74 g, 151 mmol) in THF (66 ml) is added dropwise to a stirred solution of the oxazolidinone **1.2.2.7** (20.0 g, 75.4 mmol) in anhydrous THF (300 ml) at −78 °C, and stirring is continued for 20 h.

The reaction is then quenched by the dropwise addition of H_2O (6 ml), and the mixture is allowed to warm to room temperature, whereupon 15% NaOH solution (6 ml) and H_2O (20 ml) are added. The precipitate formed is filtered off, washed with THF, and extracted with Et_2O using a Soxhlet apparatus for 14 h. The solvent is then evaporated under reduced pressure, the residue is redissolved in benzene (Caution: carcinogenic!), and this solution is concentrated once more *in vacuo* to remove small amounts of H_2O by azeotropic distillation. The residue is fractionally distilled with a Vigreux column to afford the alcohol as a colorless liquid; 7.8 g (74%), $bp_{0.5}$ 48–49 °C, $[\alpha]^{20}_D = -3.0$ ($c = 0.5$, $CHCl_3$), $R_f = 0.27$ (*n*-pentane/MeO*t*Bu, 5 : 1).

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3346, 2960, 2922, 2876, 1388, 1368, 1072, 1040.
^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.79–3.59 (m, 2H, 1-H_2), 2.37–2.07 (m, 2H, 3-H_2), 1.89 (s, 1H, OH), 1.78 (m_c, 1H, C<u>H</u>Me_2), 1.75 (t, J = 2.6 Hz, 3H, 6-H_3), 1.45 (m_c, 1H, 2-H), 0.91 (d, J = 6.5 Hz, 3H, CH(C<u>H</u>$_3$)$_2$), 0.88 (d, J = 6.5 Hz, 3H, CH(C<u>H</u>$_3$)$_2$).
^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 77.7 (C-4), 76.8 (C-5), 63.8 (C-1), 46.1 (C-2), 27.8 (*i*Pr-*C*H), 19.9 (*i*Pr-*C*H_3), 19.7 (*i*Pr-*C*H_3), 18.2 (C-3), 3.4 (C-6).
MS (EI, 70 eV): m/z (%) = 140 (2) $[M]^+$, 125 (31) $[M-CH_3]^+$, 97 (100) $[M-i\text{Pr}]^+$, 53 (20) $[CH_3CCCH_2]^+$.

References

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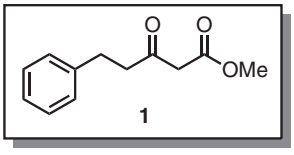
1.2.3

Methyl 3-oxo-5-phenylpentanoate



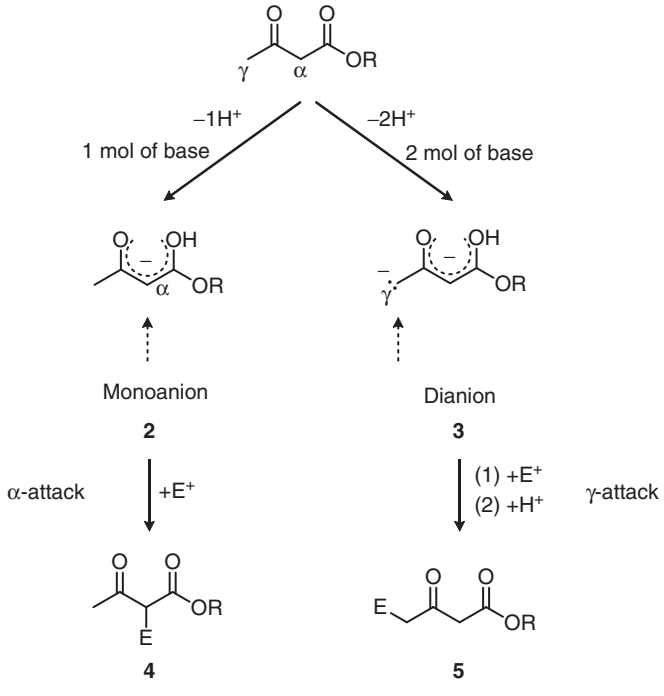
1

Topic: • γ-Alkylation of acetoacetate

(a) General

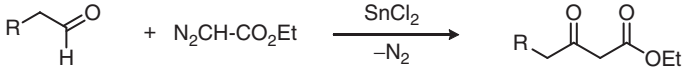
Among the numerous methods for the synthesis of β-ketoesters [1], the elongation of acetoacetate by γ-alkylation is the most relevant for β-ketoesters of structural type **1**.

In acetoacetate, the α-CH_2 group shows far stronger C–H acidity than the γ-CH_3 group (ΔpK_a (α vs. γ) approximately 10). As a consequence, attack of electrophiles can be regioselectively directed either to the α-position through formation of the monoanion **2** or to the γ-position through the formation of the (ambident) dianion **3**.



Accordingly, with an alkyl halide as attacking electrophile, acetoacetate is transformed to the product **4** of α-alkylation using 1 equiv of base, whereas with 2 equiv of a sufficiently strong base, product **5** is obtained, since the γ-CH_2 group in the dianion is of higher electron density than the (delocalized) α-CH group [2].

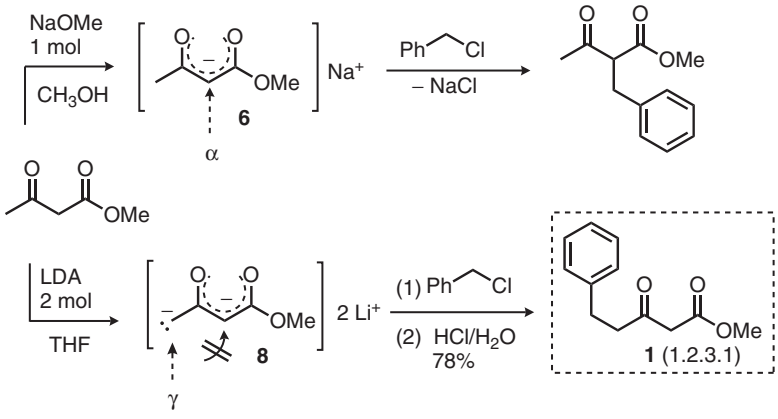
A useful and preparatively versatile alternative for the synthesis of γ-substituted acetoacetates such as **1** is the C_2-chain elongation of aldehydes with ethyl diazoacetate catalyzed by tin(II) chloride [3]:



(b) **Synthesis of 1**

If methyl acetoacetate is reacted with benzyl chloride in the presence of $NaOCH_3$ in anhydrous methanol, the "classical" α-alkylation of acetoacetate occurs via the formation of the α-monoanion **6** and its nucleophilic attack at the benzyl halide to give methyl 2-benzyl-3-oxobutanoate (**7**) in 80% yield [4]:

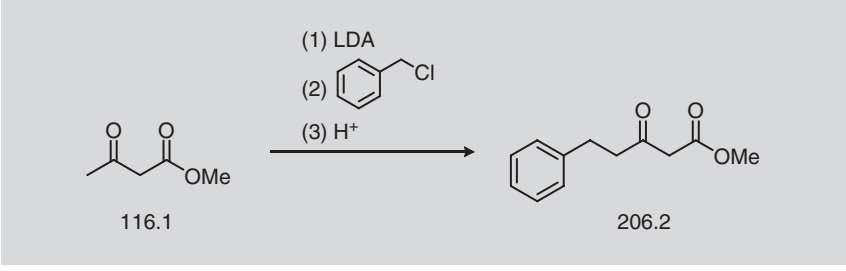
If methyl acetoacetate is reacted with 2 equiv of LDA in THF at 0 °C and subsequently with benzyl chloride, **1** is obtained after work-up with aqueous HCl in



78% yield. Initially, the acetoacetate dianion **8** is formed, which undergoes regioselective γ-alkylation with the benzyl halide in an S_N process [5].

(c) Experimental Procedure for the Synthesis of 1

1.2.3.1 ** **Methyl 3-oxo-5-phenylpentanoate** [5]



In a 250-ml two-necked flask, fitted with a septum, an inert gas attachment (N_2), and a magnetic stirrer, diisopropylamine (5.15 g, 50.0 mmol, approximately 7.13 ml) (note 1) is added by means of a syringe to anhydrous THF (100 ml). *n*-Butyllithium in *n*-hexane (1.6 M, 32.5 ml, 52.0 mmol) is slowly added dropwise with stirring at 0 °C. After 20 min, methyl acetoacetate (2.80 g, 24.0 mmol, approximately 2.60 ml) is added dropwise, and stirring is continued for 20 min at 0 °C (formation of the dianion). Finally, benzyl chloride (3.04 g, 24.0 mmol, approximately 2.76 ml) is added dropwise, and stirring is continued for an additional 20 min at 0 °C.

A mixture of concentrated HCl (10 ml), H_2O (25 ml), and Et_2O (75 ml) is added to the reaction mixture. The organic phase is separated, and the aqueous phase is extracted with Et_2O (2 × 50 ml). The combined organic phases are washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue is distilled *in vacuo* to give the product as a colorless oil; 3.67 g (78%), $bp_{0.2}$ 116–117 °C; $n^{20}{}_D = 1.5293$.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3080, 3060, 3030, 1745, 1715, 1600, 1495.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.22 (s, 5H, Ar–H), 3.67 (s, 3H, CO_2CH_3), 3.39 (s, 2H, 2-CH_2), 2.86 (s, 4H, 4- and 5-CH_2) (note 2).

Notes:

1) Diisopropylamine is distilled over CaH_2 before use; bp_{760} 83–84 °C.
2) In the ^{1}H NMR spectrum, the 4- and 5-CH_2 signals happen to coincide and thus appear as a singlet. In addition, small peaks due to the enol form of **1** are observed.

References

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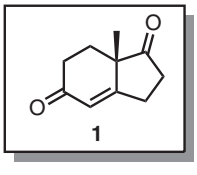
2. Smith, M.B. (2013) *March's Advanced Organic Chemistry*, 7th edn, John Wiley & Sons, Inc., New York, p. 541; see also ref. [1], p. 1539.
3. Holmquist, C.R. and Roskamp, E.J. (1989) *J. Org. Chem.*, **54**, 3258. By application of this method to hydrocinnamic aldehyde, the ethyl ester of **1** is formed in 86% yield; for the mechanism, see ref. [2], p. 1407.
4. In analogy to *Organikum* (2001), 21st edn, Wiley-VCH Verlag GmbH, Weinheim, p. 608.
5. (a) Harris, T.M. and Harris, C.M. (1969) *Org. React.*, **17**, 155; (b) Harris, T.M. and Harris, C.M. (1977) *Tetrahedron*, **33**, 2159–2185.

1.3
Reactions of the Aldol and Mannich Type

1.3.1
(+)-(7a*S*)-7,7a-Dihydro-7a-Methyl-1,5(6*H*)-Indanedione



1

Topics:

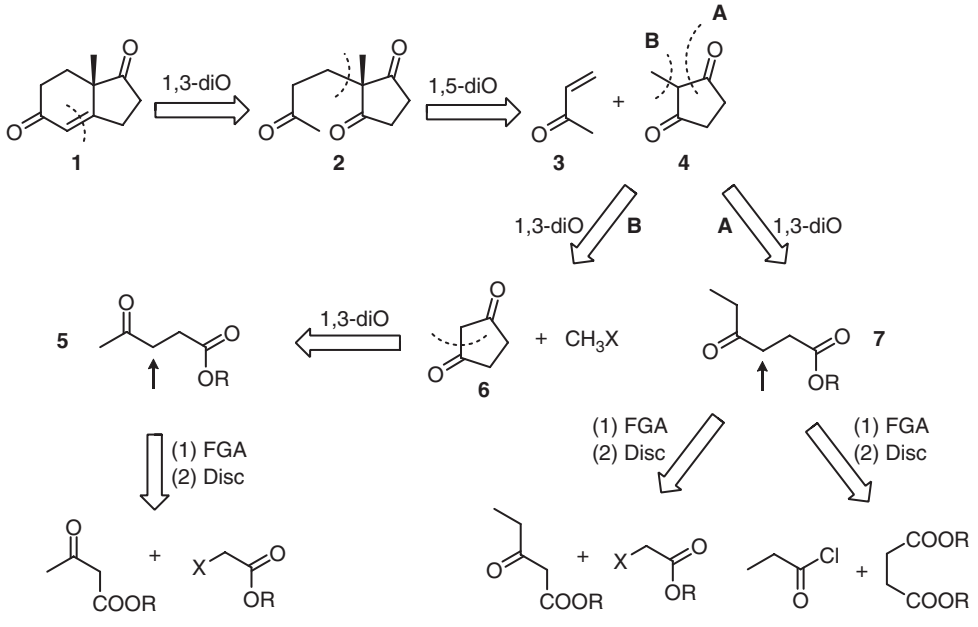
- Acylation of succinic acid
- Michael addition
- Asymmetric intramolecular aldol condensation with a chiral catalyst, enantioselective organocatalysis, Eder–Sauer–Wiechert–Hajos–Parrish reaction
- Asymmetric Robinson annulation

(a) **General**

The hydrindene **1** is an important building block in numerous syntheses of steroids and of other natural products [1]. Its preparation is one of the first outstanding

examples of the importance of enantioselective organocatalysis, which has gained general acceptance in recent years.

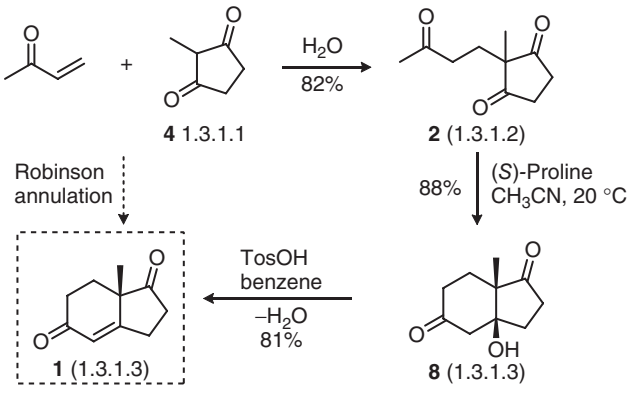
The retrosynthesis of **1** follows a retro-Robinson annulation, which consists of a retro-aldol reaction and a retro-Michael addition to give 2-methyl-cyclopentane-1,3-dione (**4**) and methyl vinyl ketone (**3**) as starting materials.



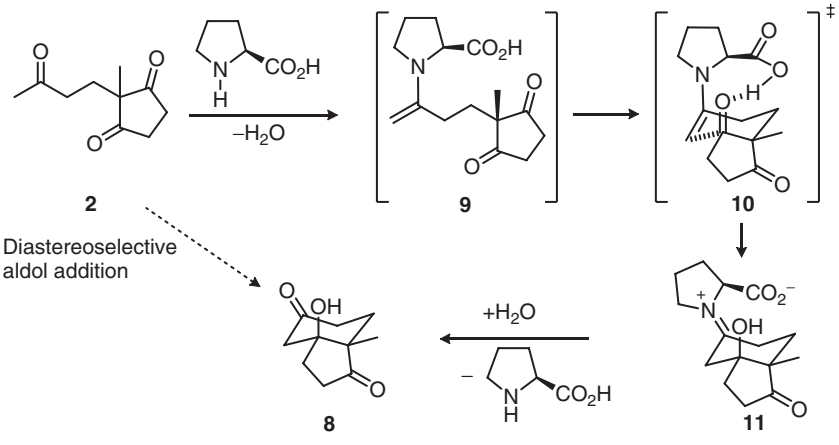
The dione **4** can be obtained either from acetoacetate and haloacetate via a γ-ketoester and cyclopenta-1,3-dione (**6**) according to pathway **B**, or from the γ-ketoester **7** according to pathway **A**. For the preparation of **7**, again two different approaches could be used. According to the proposed retrosynthetic analysis, the synthesis of **1** has been achieved in an enantioselective way by 1,4-addition of 2-methylcyclopentane-1,3-dione (**4**) to methyl vinyl ketone to give the Michael adduct **2** and subsequent asymmetric intramolecular aldol condensation of **2** in the presence of (*S*)-proline as organocatalyst to give **1** in high chemical yield and excellent enantiopurity [2].

(b) **Synthesis of 1**

The procedure presented here was developed by Eder *et al*. [3], as well as by Hajos and Parrish [4]. Cyclization of the Michael adduct **2** initially provides the *cis*-aldol adduct **8** as a single diastereomer in 88% yield and with 84% ee; subsequently, **8** is subjected to acid-catalyzed H_2O elimination with TosOH in benzene to give the desired product **1** in 81% yield:

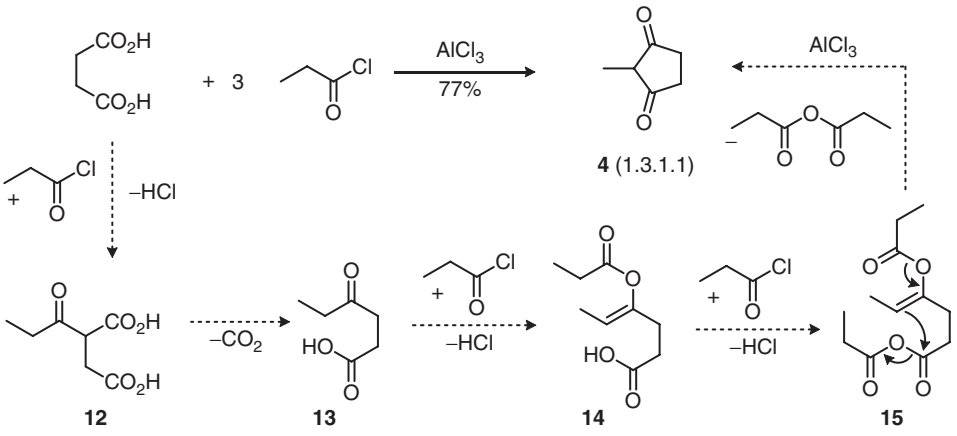


The role of proline as chiral organocatalyst can be interpreted in terms of a mechanism [5] based on initial enamine formation between (*S*)-proline and the carbonyl group in the side chain of **2**. Subsequent ring closure of the enamine **9** by addition to one of the remaining C=O groups leads to the iminium carboxylate betaine **11**. A transition state **10** with hydrogen-bond differentiation between the two diastereotopic C=O groups may account for the high stereoselectivity of the ring-closure reaction (**9** → **11**). The catalytic cycle is terminated by hydrolysis of **11** to yield the aldol adduct **8** with the regeneration of the catalyst:



(*S*)-Proline can also be used for other enantioselective intermolecular aldol and Mannich reactions [5, 6]. Moreover, analogs of proline have been used as organocatalysts for a multitude of different reactions [7].

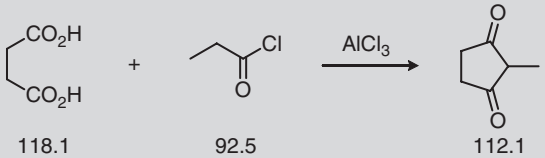
For the synthesis of 2-methyl-cyclopentane-1,3-dione (**4**), an efficient one-step procedure [8] is used, which consists of the acylation of succinic acid with propionyl chloride in the presence of $AlCl_3$ according to the retrosynthetic pathway **A** [9].



Since 3 equiv of the acid chloride are required, a domino process is likely to occur, which involves α-acylation of succinic acid (→**12**), decarboxylation of the β-keto acid **12** (→**13**), and acylation of its enol (→**14**); finally, activation of the remaining carboxyl function by formation of a mixed anhydride (or chloride) (→**15**) and Claisen-like cyclization of the acylenol functionality in **15** lead to the dione **4**.

(c) Experimental Procedures for the Synthesis of 1

1.3.1.1 * 2-Methylcyclopentane-1,3-dione [8]



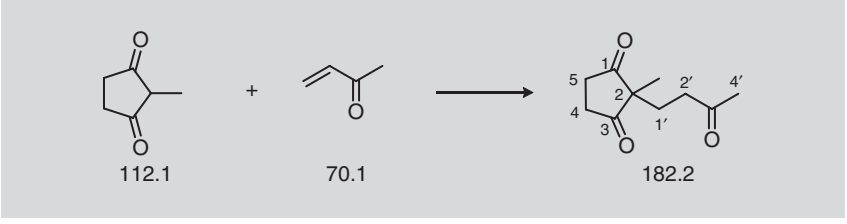
Finely powdered succinic acid (5.90 g, 0.50 mol) is added in small portions to a solution of anhydrous aluminum chloride (200 g, 1.50 mol) in anhydrous nitromethane (200 ml), causing vigorous gas evolution (HCl! Hood!). When HCl evolution has ceased, propionyl chloride (139 g, 1.50 mol) is added and the mixture is heated to 80 °C for 3 h. A red solution results.

The solution is cooled and poured onto ice (400 g). The mixture is maintained at −10 °C for 15 h, allowing the product to crystallize. The solid is collected by filtration, washed with a 10% aqueous NaCl solution (200 ml) and toluene (200 ml), and recrystallized from H_2O (heating with activated charcoal and filtration) to give colorless prisms; 43.0 g (77%), mp 214–216 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3200–2600, 1590.

^{1}H NMR (300 MHz, [D_4]MeOH): δ (ppm) = 4.84 (s, OH), 2.44 [s, CH_2-CH_2; keto form], 2.90–2.25 [m, CH_2-CH_2; enol form], 1.54 (s, CH_3); keto–enol tautomeric mixture.

1.3.1.2 * **2-Methyl-2-(3-oxobutyl)-cyclopentane-1,3-dione** [3, 4]

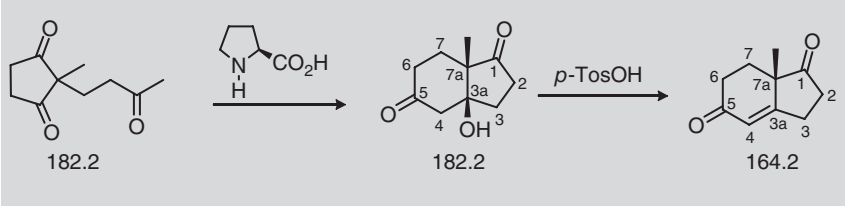


Methyl vinyl ketone (14.0 g, 200 mmol, ~16.2 ml) is added in one portion to a suspension of 2-methyl-1,3-cyclopentanedione **1.3.1.1** (11.2 g, 100 mmol) in H_2O (25 ml), and the mixture is stirred for 5 days at room temperature under a nitrogen atmosphere.

The clear, red-brown solution is then extracted with toluene (3 × 25 ml). The combined extracts are dried over $MgSO_4$, filtered, and stirred for 2 h at room temperature with activated charcoal. The charcoal is removed by filtration and washed with hot toluene (50 ml). The combined filtrates are concentrated, and the residue is fractionally distilled *in vacuo* to give a colorless oil; 15.0 g (82%), $bp_{0.1}$ 108–110 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2970, 2930, 2875, 1765, 1720, 1450, 1420, 1370, 1170.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.79 (s, 4H, 4-H_2, 5-H_2), 2.60–1.65 (m, 4H, 1′-H_2, 2′-H_2), 2.09 (s, 3H, 4′-H_3), 1.10 (s, 3H, CH_3).

1.3.1.3 * **(+)-(7a*S*)-7,7a-Dihydro-7a-methyl-1,5(6*H*)-indanedione** [3, 4]



1) **(+)-(3a*S*,7a*S*)-3a,4,7,7a-Tetrahydro-3a-hydroxy-7a-methyl-1,5(6*H*)-indanedione**

A solution of the triketone **1.3.1.2** (5.60 g, 30.7 mmol) and (−)-(*S*)-proline (3.54 g, 30.7 mmol) in acetonitrile (40 ml) is stirred at room temperature for 6 days under a nitrogen atmosphere (balloon). The initially light-yellow solution becomes dark brown to black.

Proline is collected by filtration and washed with a small amount of acetonitrile. The filtrate is concentrated *in vacuo*, the dark-brown residue is dissolved

in EtOAc (100 ml), and this solution is filtered through silica gel (10 g). The silica gel is rinsed with additional EtOAc (150 ml), and the combined filtrates are concentrated *in vacuo*. A light-brown residue is obtained, which solidifies after 14 h at −20 °C. Recrystallization from Et_2O gives light-yellow crystals. The yield is 4.90 g (88%), mp 119–120 °C, $[\alpha]^{20}_D = +60$ ($c = 0.5$, $CHCl_3$).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3470 (OH), 1740, 1710 (6-ring C=O), 1305, 1270, 1065.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.84 (s, 1H, OH), 2.63 (s, 2H, 4-H_2), 2.61–1.65 (m, 8H, 2-H_2, 3-H_2, 6-H_2, 7-H_2), 1.21 (s, 3H, CH_3).

2) **(+)-(7a*S*)-7,7a-Dihydro-7a-methyl-1,5(6*H*)-indanedione**
A mixture of the hydroxy ketone prepared in step (1) (3.64 g, 20.0 mmol), anhydrous *p*-toluene-sulfonic acid (25 mg, 0.15 mmol), and molecular sieves (4 Å, 5 g) in anhydrous benzene (30 ml; Caution: carcinogenic!) is heated under reflux for 30 min.
The mixture is then cooled, aqueous $NaHCO_3$ solution (1 M, 2 ml) is added, and the phases are separated. The organic phase is dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is a yellow oil, which solidifies in 14 h at −20 °C. The product is washed with ice-cold Et_2O and recrystallized from Et_2O/*n*-pentane; 2.66 g (81%), mp 64–65 °C, $[\alpha]^{20}_D = +362$ ($c = 0.1$, benzene). The compound is almost enantiopure with >98% ee.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3045, 1745, 1660, 1455, 1355, 1235, 1150, 1065.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.95 (m, 1H, 4-H), 2.95–1.75 (m, 8H, 2-H_2, 3-H_2, 6-H_2, 7-H_2), 1.30 (s, 3H, CH_3).

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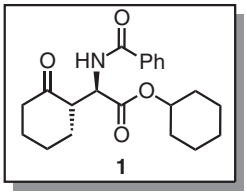
3. Eder, U., Sauer, G., and Wiechert, R. (1971) *Angew. Chem.*, **83**, 492–793; *Angew. Chem., Int. Ed. Engl.*, (1971), **10**, 496–497.
4. Hajos, Z.G. and Parrish, D.R. (1974) *J. Org. Chem.*, **39**, 1612–1615.
5. (a) Hoang, L., Bahmanyar, S., Houk, K.N., and List, B. (2003) *J. Am. Chem. Soc.*, **125**, 16–17; (b) Clemente, F.R. and Houk, K.N. (2004) *Angew. Chem.*, **116**, 5890–5892; *Angew. Chem. Int. Ed.*, (2004), **43**, 5766–5768.
6. (a) Dalko, P.J. and Moisan, L. (2004) *Angew. Chem.*, **116**, 5248–5286; *Angew. Chem. Int. Ed.*, (2004), **43**, 5138–5175; (b) Seayad, J. and List, B. (2005) *Org. Biomol. Chem.*, **3**, 719–724; (c) Amino acids as organocatalysts in carbohydrate synthesis: Kazmaier, U. (2005) *Angew. Chem.*, **117**, 2224–2226; *Angew. Chem. Int. Ed.* (2005), **44**, 2186–2188; (d) organo-catalyzed direct aldol reactions of aldehydes with ketones: Tang, Z., Yang, Z.-H., Chen, X.-H., Cun, L.-F., Mi, A.-Q., Jiang, Y.-Z., and Gong, L.-Z. (2005) *J. Am. Chem. Soc.*, **127**, 9285–9289; (e) Cordova, A., Zou, W., Ibrahem, I., Reyes, E., Engqvist, M.,

and Liao, W.-W. (2005) *Chem. Commun.*, 3586–3588.
7. (a) Westermann, B. (2003) *Nachr. Chem.*, **51**, 802–805; (b) Berkessel, A. and Gröger, H. (2005) *Asymmetric Organocatalysis*, Wiley-VCH Verlag GmbH, Weinheim.
8. Schick, H., Lehmann, G., and Hilgetag, G. (1969) *Chem. Ber.*, **102**, 3238–3240.
9. For comparison, see the multistep synthesis of **1** in *Org. Synth.*: John, J.P., Swaminathan, S., and Venkataraman, P.S. (1963) *Org. Synth. Coll.*, **4**, 840.

1.3.2

Cyclohexyl 2-benzoylamino-2-(2-oxocyclohexyl) acetate



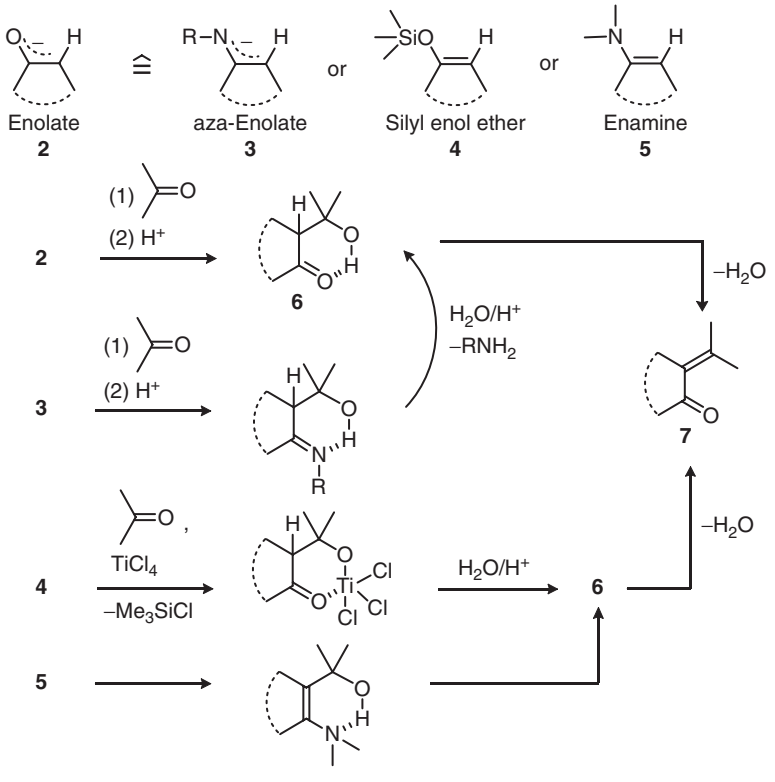
1

Topics:

- Diastereoselective aminoalkylation of an enamine by an *N*-acyl imino ester (modified aldol reaction)
- Esterification of an *N*-acyl-α-amino acid
- Formation of an *N*-acyl imino ester by α-halogenation/dehydrohalogenation

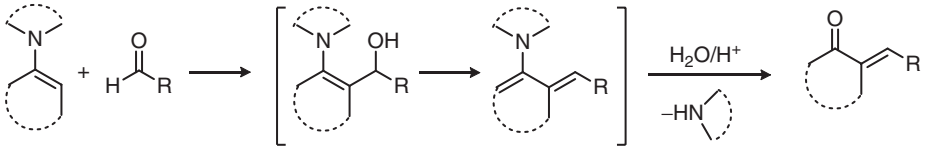
(a) **General**

In the directed aldol reaction [1], equivalents of enolates **2** for example, α-lithiated imines **3** (Wittig aldol reaction), silyl enol ethers **4** (Mukaiyama aldol reaction, cf.

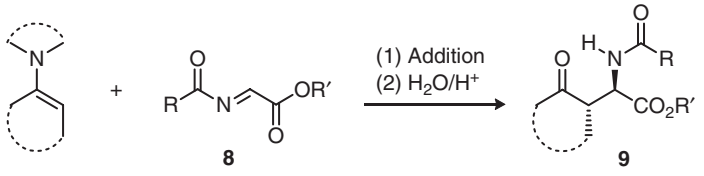


Section 1.3.4), or enamines **5** react with aldehydes or ketones to give the product **6** by an aldol addition and/or **7** by an aldol condensation:

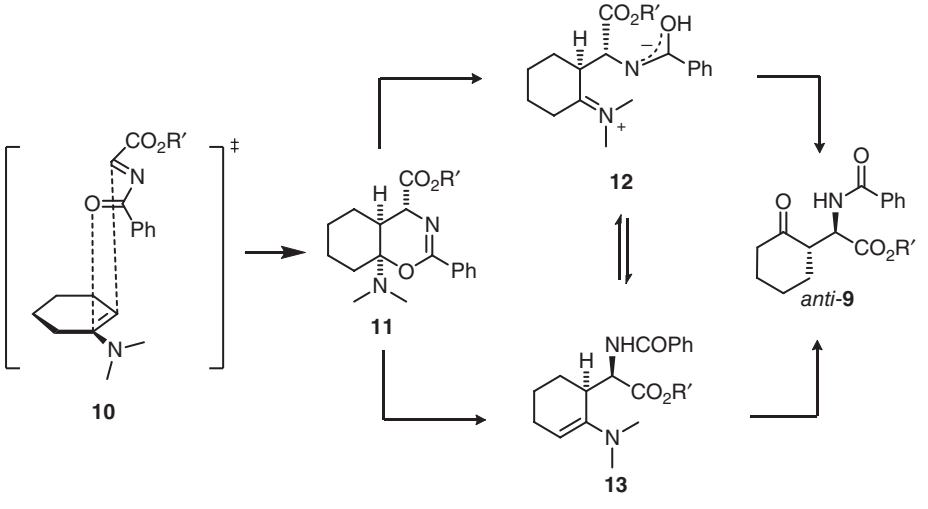
Enamines of cycloalkanones are easily accessible and can undergo aldol condensation with aldehydes under equilibrium conditions with azeotropic removal of H_2O and subsequent acid hydrolysis [2]:



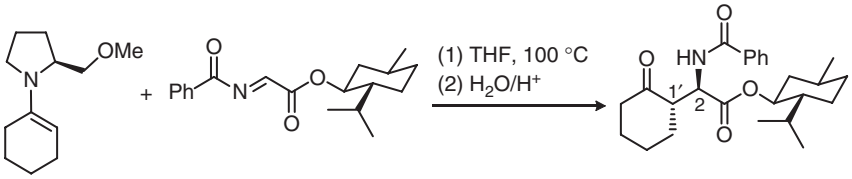
When enamines of this type are reacted with acyl iminoacetates **8** as electrophilic substrates, an aza-analogous aldol addition takes place to give *N*-acyl-γ-keto-α-aminoesters **9** [3], as exemplified in Section (b).



The relative configuration of the products **9** is anti (X-ray). The high diastereoselectivity (>96% de) in this aza-modified aldol process is consistent with a hetero-Diels–Alder-like transition state **10** for the formation of an intermediate **11**, which may undergo ring opening either to the zwitterion **12** or the enamine **13**. After acid hydrolysis, the anti product **9** is obtained [3]:

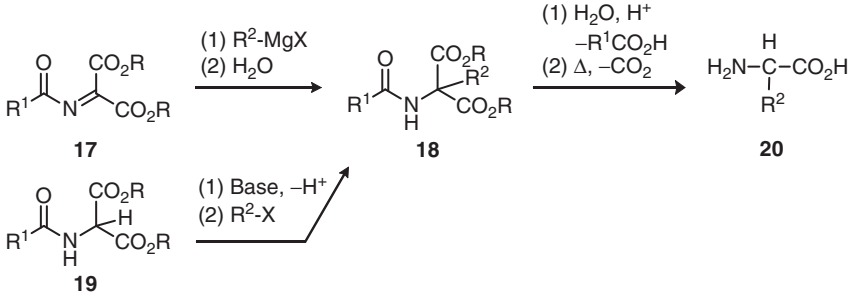


For the formation of enantioenriched products, chiral esters and chiral enamines can be used. Following the concept of double stereodifferentiation [4], the (+) and (−)-menthyl esters of **8** (R = Ph) are reacted with the chiral enamine **14** derived from (*S*)-proline. Using the (+)-menthyl ester **15**, reaction proceeds in quantitative yield and with complete diastereo and enantioselectivity (de = ee > 99%) and gives the pure compound **16** with (1′*S*,2*R*)-configuration at the newly formed stereogenic centers ("matched" case), while the (−)-menthyl ester (**8**, R = Ph) leads to a product of type **9** with de > 98% and ee = 45% ("mismatched" case [5]).



14 **15** **16**

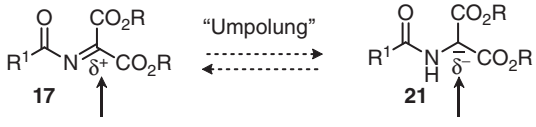
It should be noted that acyl iminomalonates **17** represent interesting electrophilic building blocks and can be used for the synthesis of α-amino acids [6] by reaction with Grignard compounds followed by hydrolysis and decarboxylation:



17 **18** **20**

19

This mode of formation of α-amino acids is an alternative to a method [7] in which acyl aminomalonates **19** are alkylated in the presence of a base to give **18**. Acyl iminomalonates **17** represent the "umpoled" version [8] of the acyl amidomalonate anion **21**:



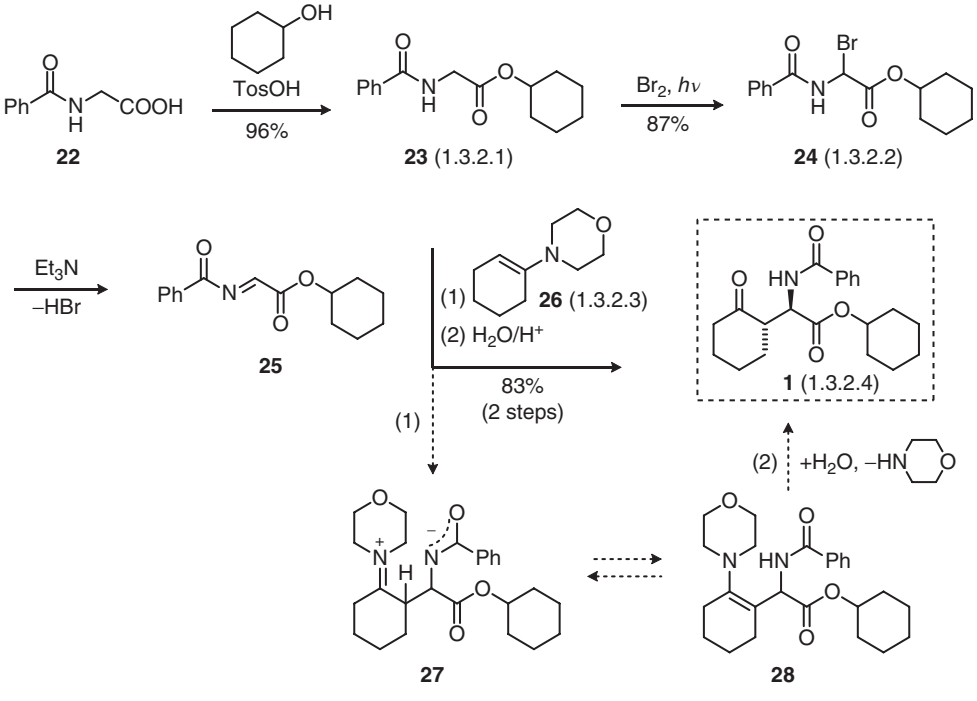
17 **21**

(b) **Synthesis of 1**

Commercially available hippuric acid (**22**) is subjected to azeotropic esterification with cyclohexanol in the presence of TosOH in toluene. Photobromination of the

cyclohexyl ester **23** with Br_2 in CCl_4 occurs at the α-position to the COOR group and affords the bromo ester **24**. In the concluding steps, the bromo ester **24** is transformed into the benzoyl iminoacetate **25**, which, without isolation, leads to **1** by reaction with the enamine **26** followed by hydrolysis. For this reaction, a solution of the bromo ester **24** in THF is treated at −78 °C first with triethylamine and then with the enamine morpholinocyclohexene (**26**) [9]. The reaction presumably proceeds via the intermediates **27** and **28**. After hydrolysis of the reaction mixture at pH 4–5, **1** is isolated in 79% yield and with ds > 98 : 2, thus documenting the high level of stereoselectivity of the aza-modified aldol process. In the described process, **1** is obtained as a racemic mixture because neither a chiral enamine nor a chiral ester is used.

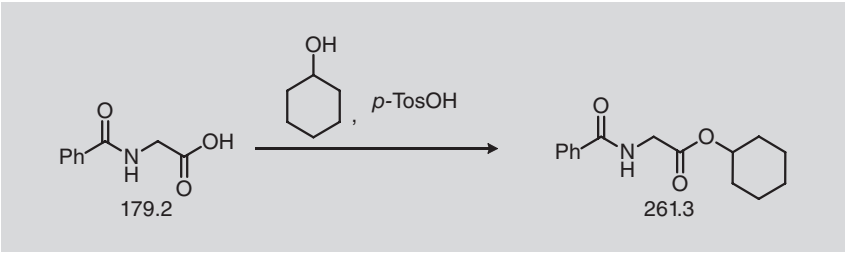
Interestingly, the diastereoselectivity seen with the corresponding methyl or ethyl esters is significantly more temperature-dependent compared to that with the larger cyclohexyl ester **23** used here. The methyl and ethyl esters give high diastereoselectivity in the reaction with the enamine **26** only at −100 °C (ds > 98 : 2), whereas only around 85 : 15 ds is achieved at −78 °C [3].



The target molecule **1** is obtained in a three-step sequence in an overall yield of 67% (based on hippuric acid (**22**)).

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

1.3.2.1 * **Cyclohexyl 2-benzoylaminoacetate** [3]

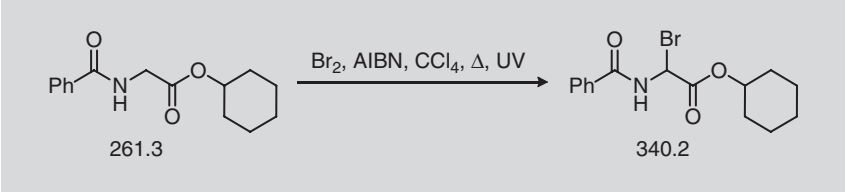


Hippuric acid (35.8 g, 0.20 mol) and cyclohexanol (20.0 g, 0.20 mol) are heated under reflux with *p*-toluenesulfonic acid (1.0 g) in toluene (200 ml) under azeotropic removal of H_2O in a Dean–Stark trap, until the theoretical amount of H_2O is formed.

After cooling to 35–40 °C and diluting with additional EtOAc (200 ml), the organic layer is washed twice with H_2O, dried over $MgSO_4$, and filtered. The solvent is removed *in vacuo*, and the crude product is recrystallized from EtOAc/*n*-hexane (1 : 1) to give a colorless solid; 50.3 g (96%); mp 102–103 °C; TLC (SiO_2, EtOAc/*n*-hexane, 1 : 2): $R_f = 0.57$.

UV: λ_{max} (nm) = 224, 194.
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3326, 2955, 2939, 2854, 1748, 1650, 1550, 1494, 1450, 1401, 1380, 1360, 1312, 1251, 1201, 1081, 1013, 949, 733, 692.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.82–7.79 (m, 2H, Ar–H), 7.54–7.42 (m, 3H, Ar–H), 6.70 (s, 1H, NH), 4.84 (m, 1H, hex-H_1), 4.20 (d, J = 3.3 Hz, 2H, α-H_2), 1.93–1.83 (m, 2H, c-hex-H_2), 1.79–1.68 (m, 2H, c-hex-H_2), 1.60–1.20 (m, 6H, c-hex-H_2).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 169.5, 167.3, 133.8, 131.7, 128.6, 127.0, 74.3, 42.1, 31.5, 25.2, 23.6.
EI HRMS: m/z = 261.1364 (calcd. 261.1365).

1.3.2.2 ** **Cyclohexyl 2-benzoylamino-2-bromoacetate** [9]



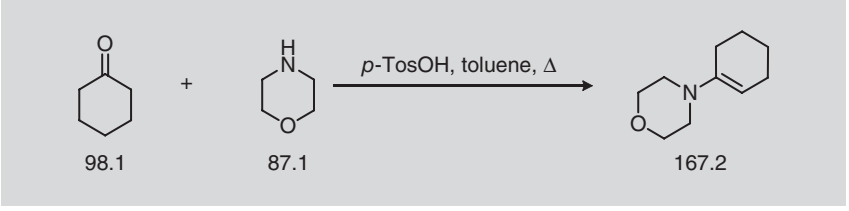
A solution of bromine (3.51 g, 22.0 mmol) in anhydrous carbon tetrachloride (30 ml; Caution: resorption through the skin!) is added dropwise over 2 h under UV irradiation (500 W) to a refluxing solution of the acetate **1.3.2.1** (5.22 g,

20.0 mmol) and azobisisobutyronitrile (50 mg) in carbon tetrachloride (40 ml) to give a light-brown solution. After completion of the addition of bromine, irradiation and refluxing are continued for 3 h.

The solvent is removed *in vacuo*, and the product is crystallized from EtOAc/petroleum ether (50–80 °C) (1 : 1). The water-sensitive product is kept under argon at 4 °C. The product is obtained as a colorless solid; 5.92 g (87%); mp 107–109 °C; TLC (SiO_2, EtOAc/*n*-hexane, 1 : 2): $R_f = 0.27$.

UV: λ_{max} (nm) = 231.5, 194.5.
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3298, 3038, 2940, 2861, 1733, 1660, 1602, 1581, 1519, 1490, 1453, 1379, 1358, 1340, 1285, 1240, 1194, 1133, 1009, 934, 719, 691, 530.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.80–7.40 (m, 6H, Ar–H, NH), 6.60 (d, J = 9.9 Hz, 1H, CH), 4.90 (m, 1H, c-hex-H), 1.20–1.90 (m, 10H, c-hex-H_2).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 166.3, 165.6, 132.8, 132.4, 128.8, 127.4, 75.9, 50.5, 31.1, 30.6, 25.1, 23.3, 23.2.

1.3.2.3 * 1-Morpholine-1-cyclohexene [10]

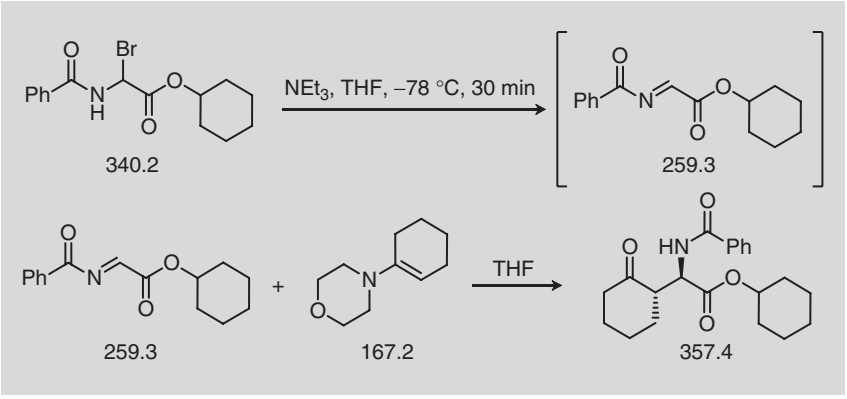


Cyclohexanone (11.8 g, 0.12 mol) and morpholine (12.5 g, 0.14 mol) are heated under reflux with *p*-toluenesulfonic acid (20 mg) in toluene (25 ml) for 10 h with azeotropic removal of H_2O in a Dean–Stark trap.

After cooling to room temperature, the organic layer is washed twice with H_2O until pH 7 is reached, then dried over $MgSO_4$, and filtered. The solvent is removed, and the residue is distilled *in vacuo* to give the enamine as a colorless liquid; 17.5 g (87%), bp_{93} 74–75 °C; TLC (SiO_2, EtOAc/*n*-hexane, 1 : 2): $R_f = 0.58$.

UV: λ_{max} (nm) = 220.
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2926, 2893, 1647, 1450, 1385, 1358, 1264, 1204, 1123, 899, 789.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.62 (t, J = 1.7 Hz, 1H, 12-H_1), 3.76–3.54 (m, 2H, 2-H_2, 6-H_2), 2.92–2.64 (m, 4H, 3-H_2, 5-H_2), 2.07–1.84 (m, 4H, 9-H_2, 12-H_2), 1.60 (m, 4H, 10-H_2, 11-H_2).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 145.4, 100.4, 66.9, 48.4, 26.8, 24.3, 23.3, 22.7.
EI-HRMS: m/z = 167.1306 (calcd. 167.1310).

1.3.2.4 ** Cyclohexyl 2-benzoylamino-2-(2-oxocyclohexyl) acetate [3]



Triethylamine (697 µl, 0.50 g, 5.0 mmol) is added to a solution of the bromoacetate **1.3.2.2** (5.0 mmol) in anhydrous THF (35 ml) under an argon atmosphere at −78 °C. After stirring for 30 min, the solution is cooled to −95 °C, and a precooled (−78 °C) solution of the enamine **1.3.2.3** (0.92 g, 5.5 mmol) in anhydrous THF (10 ml) is carefully added. The temperature is maintained at −95 °C for 6 h and at −78 °C for 6 h thereafter. After warming to room temperature, the mixture is hydrolyzed by the addition of a dilute citric acid solution until the pH reaches 4–5, and stirring is continued for 5 h.

The solvent is then removed *in vacuo*, the residue is extracted with EtOAc (3 × 35 ml), and the organic layer is washed with H_2O (20 ml), dried over $MgSO_4$, and filtered. After removal of the solvent, the product is purified by column chromatography (SiO_2, *n*-hexane/EtOAc, 2 : 1) and the resulting oil is dissolved in *n*-hexane and treated in a sonicator for 20 min. Recrystallization yields a colorless solid; 1.49 g (83%); mp 106–108 °C; TLC (EtOAc/*n*-hexane, 2 : 1): $R_f = 0.52$; de > 98% based on HPLC (RP C18, H_2O/0.1% TFA (trifluoroacetic acid), CH_3CN/H_2O, 8 : 2/0.1% TFA; 60–90% in 30 min, $t_R = 14.6$ min).

UV: λ_{max} (nm) = 224.0, 192.5.
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3320, 2936, 2860, 1712, 1654, 1546, 1517, 1488, 1447, 1316, 1281, 1268, 1240, 1208, 1011, 719, 693.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.78–7.40 (m, 5H, Ar–H), 7.00 (d, J = 9.65 Hz, 1H, NH), 4.90 (dd, J = 3.22, 9.59 Hz, 1H, α-H), 4.80 (td, 1H, c-hexane), 3.39–3.31 (m, 1H, c-hexanone), 2.42–2.34 (m, 4H, 2 CH_2, c-hexanone), 2.29–2.26 (m, 2H, CH_2, c-hexanone), 2.10 (m, 2H, CH_2, c-hexanone) 1.90–1.20 (m, 10H, c-hexane).
EI HRMS: m/z = 358.20131 (calcd. 358.20128).

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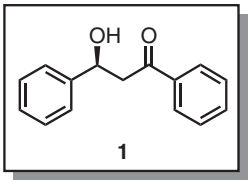
1.3.3

(*S*)-1-Hydroxy-1,3-diphenyl-3-propanone



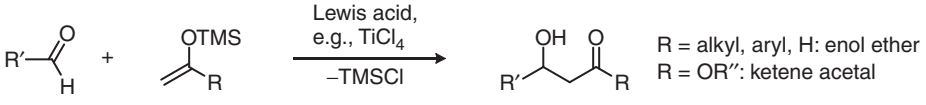
1

Topics:

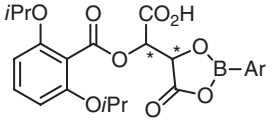
- Chiral (acyloxy)borane catalyzed asymmetric Mukaiyama aldol reaction
- Synthesis of chiral β-hydroxy ketones
- Preparation of the CAB ligand from 2,6-dihydroxybenzoic acid and (*S*,*S*)-(−)-tartaric acid
- Ester and aryl ether formation, cleavage of benzyl esters

(a) General

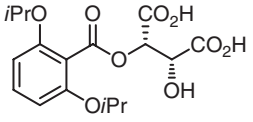
Aldol reactions are among the most powerful and efficient synthetic methods for the formation of carbon–carbon bonds [1]. In the Mukaiyama aldol reaction (cf. Section 1.3.3), silyl enol ethers or silyl ketene acetals are combined with aldehydes in the presence of a Lewis acid (e.g., $TiCl_4$) to give β-hydroxy ketones (aldols) or β-hydroxy esters, respectively:



By using a chiral Lewis acid, an asymmetric Mukaiyama aldol reaction can be performed. For this purpose, Ishihara and Yamamoto [2] developed the chiral (acyloxy)borane (CAB) complexes **2**, which are based on a chiral ligand derived from tartaric acid and aryl boronic acids. They proved to be efficient chiral catalysts for aldol reactions [3] and have also been successfully applied for a variety of other asymmetric transformations such as Diels–Alder reactions [4], hetero-Diels–Alder reactions [5], and allylations [6].



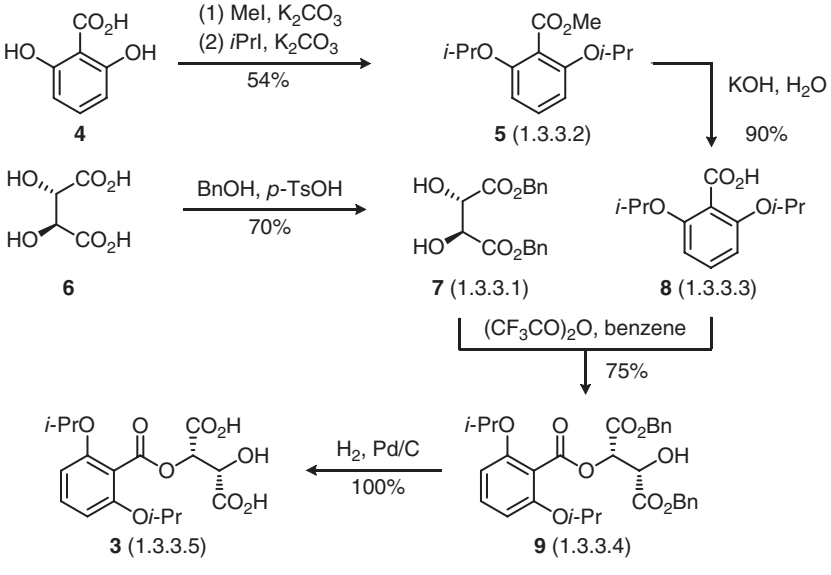
2



3

(b) **Synthesis of 1**

1) For the synthesis of the catalyst of type **2**, the chiral CAB ligand **3** is prepared in a five-step sequence starting from 2,6-dihydroxybenzoic acid (**4**) and (*S*,*S*)-(−)-tartaric acid (**6**). First, the O-alkylated carboxylic acid **8** is synthesized in a three-step sequence consisting of the formation of the methyl ester, its O-alkylation to give the bis-isopropyl ether **5**, and saponification of the methyl ester moiety (**5** → **8**) [5c]. Second, (*S*,*S*)-(−)-tartaric acid (**6**) is transformed into the dibenzyl ester **7** by reaction with benzyl alcohol in the presence of a catalytic amount of *p*-toluenesulfonic acid with azeotropic removal of H_2O [7]. Mono-esterification of the 1,2-diol functionality in the dibenzyl



4

5 (1.3.3.2)

6

7 (1.3.3.1)

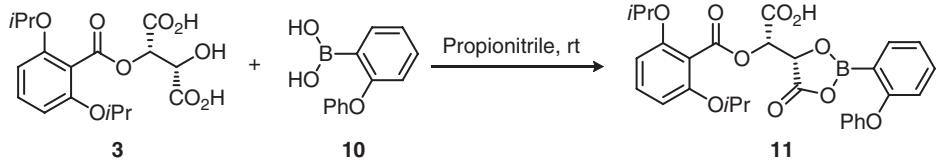
8 (1.3.3.3)

3 (1.3.3.5)

9 (1.3.3.4)

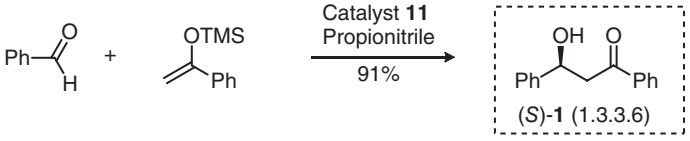
ester **7** with the carboxylic acid **8** is accomplished with trifluoroacetic anhydride, probably via the intermediate formation of a mixed anhydride. The final step of the synthesis is cleavage of the dibenzyl ester moieties in **9** by hydrogenation to give the desired CAB ligand **3** [6b].

The active CAB species **11** is prepared *in situ* from (2*S*,3*S*)-2-*O*-(2,6-diisopropoxybenzoyl)tartaric acid (**3**) and commercially available 2-phenoxyphenylboronic acid (**10**) in propionitrile [3c]:



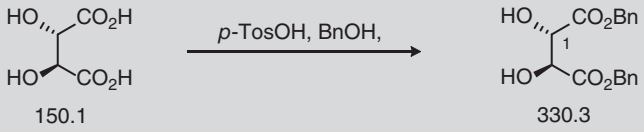
3 **10** **11**

2) The asymmetric Mukaiyama aldol reaction of benzaldehyde and 1-phenyl-1-(trimethylsilyloxy)ethylene is performed in propionitrile at −78 °C under promotion by 20 mol% of the catalyst **11** and leads to the (*S*)-enantiomer of 1-hydroxy-1,3-diphenyl-3-propanone (**1**) in 91% chemical yield and 90% ee.



(c) Experimental Procedures for the Syntheses of 3 and 1

1.3.3.1 * **(*S*,*S*)-Dibenzyl tartrate** [5]



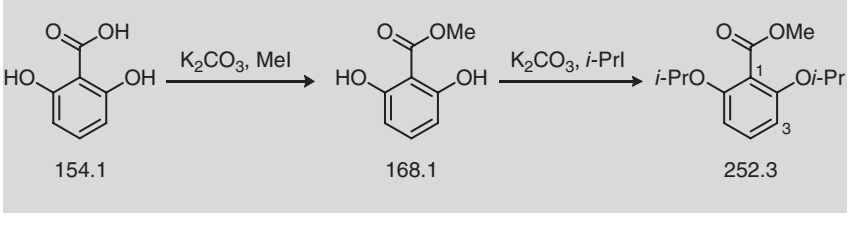
A stirred solution of (*S*,*S*)-(−)-tartaric acid (15.0 g, 100 mmol), benzyl alcohol (20.7 ml, 21.6 g, 200 mmol), and *p*-toluenesulfonic acid monohydrate (476 mg, 2.50 mmol, 2.5 mol%) in toluene (200 ml) is refluxed for 48 h in a 500-ml round-bottomed flask equipped with a Dean–Stark trap and an argon bubbler.

It is then cooled to room temperature, diluted with EtOAc (120 ml), and washed with saturated aqueous $NaHCO_3$ solution (2 × 30 ml) and brine (2 × 30 ml). The organic layer is dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue is dissolved in toluene (80 ml) and the desired product is obtained by

precipitation upon addition of isooctane (80 ml). After filtration and drying the residue under high vacuum, the tartrate is obtained as white fibers; 23.2 g (70%), mp 54–55 °C, $[\alpha]^{20}_{D} = +10.0$ ($c = 1.0$, $CHCl_3$).

UV (CH_3CN): λ_{max} (nm) (log ε) = 267.0 (2.200), 262.5 (2.439), 251.5 (2.376), 257.0 (2.515), 207.0 (4.207).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3464, 3280, 3034, 2946, 1747, 1498, 1455, 1378, 1275, 1218, 1192, 1126, 1093, 1029, 1003, 978, 736, 695, 608, 507, 457.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.34 (m_c, 10H, Ph–H), 5.25 (d, $J = 2.0$ Hz, 4H, $C\underline{H}_2Ph$), 4.59 (d, $J = 7.3$ Hz, 2H, 1-H), 3.17 (d, $J = 7.3$ Hz, 2H, OH).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 171.3 (CO_2Bn), 134.7 (Ph–C_{quart}), 128.7 (Ph–CH), 128.4 (Ph–CH), 72.1 (C-1), 68.1 (CH_2Ph).
MS (ESI): m/z (%) = 683 (100) $[2M+Na]^+$, 353 (22) $[M+Na]^+$.

1.3.3.2 ** Methyl 2,6-diisopropoxybenzoate [5]



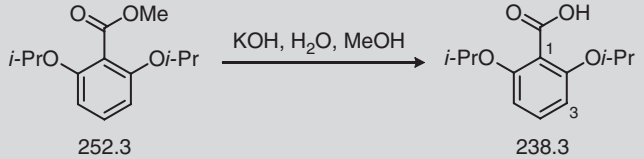
Iodomethane (Caution: carcinogenic!) (17.8 ml, 40.6 g, 286 mmol) is added to a mixture of 2,6-dihydroxybenzoic acid (20.0 g, 130 mmol), anhydrous K_2CO_3 (19.8 g, 143 mmol), and anhydrous DMF (300 ml) in a 1000-ml round-bottomed flask equipped with a dropping funnel. The mixture is stirred at room temperature for 20 h, then poured into ice-cold aqueous HCl (1 M, 300 ml), and extracted with Et_2O (3 × 250 ml). The combined organic layers are washed with brine (150 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

The oily residue (crude 2,6-dihydroxybenzoic acid methyl ester, max. 130 mmol) is dissolved in DMF (300 ml) in a 1000-ml round-bottomed flask equipped with a dropping funnel. First, anhydrous K_2CO_3 (44.9 g, 325 mmol) is added in one batch; then 2-iodopropane (36.4 ml, 61.9 g, 364 mmol) is added dropwise under continuous stirring at room temperature. Stirring is continued for 2 days, and then the mixture is poured into ice-cold aqueous HCl (1 M, 300 ml) and extracted with Et_2O (2 × 250 ml). The combined organic layers are washed with brine (3 × 150 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

Purification of the residue by column chromatography on silica gel (400 g, *n*-pentane/EtOAc, 20 : 1) leads to the methyl ester as colorless cuboids; 17.7 g (54% for two steps), mp 57–59 °C, $R_f = 0.30$ (*n*-pentane/EtOAc, 20 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 280.5 (3.353), 203.0 (4.585).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2981, 1735, 1595, 1467, 1386, 1295, 1255, 1112, 1071, 959, 902, 823, 783, 739, 665.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.18 (t, J = 8.4 Hz, 1H, H-4), 6.50 (d, J = 8.4 Hz, 2H, 2 × H-3), 4.49 (sept, J = 6.2 Hz, 2H, 2 × OC<u>H</u>$(CH_3)_2$), 3.86 (s, 3H, CO_2CH_3), 1.28 (d, J = 6.2 Hz, 12H, 2 × OCH(C<u>H</u>$_3)_2$).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 167.3 (CO_2CH_3), 155.9 (C-2), 130.5 (C-4), 116.2 (C-1), 106.5 (2 × C-3), 71.4 (2 × O*C*H$(CH_3)_2$), 52.1 (CO_2CH_3), 22.1 (2 × OCH($CH_3)_2$).
MS (EI, 70 eV): m/z (%) = 252 (15) $[M]^+$, 221 (10), 168 (39) $[M-2C_3H_6]^+$, 136 (100) $[M-2C_3H_6CH_3OH]^+$, 108 (12), 43 (9) $[C_3H_7]^+$.

1.3.3.3 ** 2,6-Diisopropoxybenzoic acid [5]



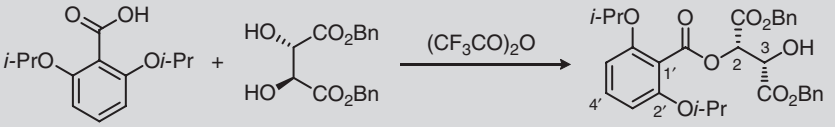
252.3 238.3

The benzoate **1.3.3.2** (15.6 g, 61.9 mmol) is added to a solution of KOH (28.2 g, 681 mmol) in MeOH (170 ml) and H_2O (19 ml). The mixture is heated to 80 °C and stirred for 15 h at this temperature.

After the addition of H_2O (200 ml), the MeOH is evaporated under reduced pressure. The aqueous solution is added dropwise to a stirred aqueous HCl solution (2 M, 400 ml) at 0 °C to give a white precipitate, which is collected by filtration, washed with ice-cold H_2O (3 × 30 ml), and dried *in vacuo*. The benzoic acid is isolated as a colorless amorphous solid; 13.3 g (90%), mp 106–107 °C, R_f = 0.05 (*n*-pentane/EtOAc, 10 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 280.5 (3.343), 204.0 (4.581).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2982, 2934, 2662, 1702, 1597, 1467, 1387, 1340, 1302, 1258, 1173, 1112, 1072, 904, 804, 782, 742, 655, 445.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.24 (t, J = 8.4 Hz, 1H, 4-H), 6.56 (d, J = 8.4 Hz, 2H, 3-H), 4.56 (sept, J = 5.9 Hz, 2H, OC<u>H</u>$(CH_3)_2$), 1.33 (d, J = 5.9 Hz, 12H, OCH(C<u>H</u>$_3)_2$).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 168.8 (CO_2H), 156.7 (C-2), 131.4 (C-4), 114.4 (C-1), 106.9 (2 × C-3), 72.0 (2 × O*C*H$(CH_3)_2$), 22.0 (2 × OCH($CH_3)_2$).
MS (EI, 70 eV): m/z (%) = 238 (8) $[M]^+$, 154 (27) $[M-2C_3H_6]^+$, 136 (100) $[M-OCH(CH_3)_2-C_3H_7]^+$, 108 (12), 43 (7) $[C_3H_7]^+$.

1.3.3.4 ** **Dibenzyl (2*S*,3*S*)-2-*O*-(2,6-diisopropoxybenzoyl) tartrate** [5]



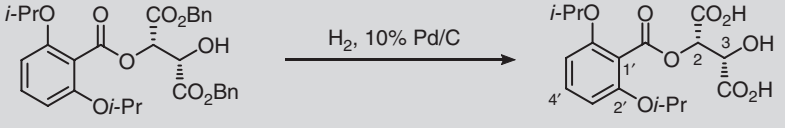
238.3 330.3 550.6

Trifluoroacetic anhydride (1.96 ml, 2.91 g, 13.9 mmol) is added by means of a syringe over a period of 20 min to a stirred suspension of the acid **1.3.3.3** (3.00 g, 12.6 mmol) and the tartrate **1.3.3.1** (4.16 g, 12.6 mmol) in anhydrous benzene (65 ml; Caution: carcinogenic!) at room temperature. Stirring is continued for 90 min.

The pale-yellow solution is then poured into saturated aqueous $NaHCO_3$ solution (100 ml), and the mixture is extracted with Et_2O (3 × 50 ml). The combined organic layers are dried over Na_2SO_4 and filtered. The solvent is removed *in vacuo*, and the residue is purified by column chromatography (SiO_2, CH_2Cl_2). The tartaric acid dibenzyl ester is obtained as a colorless sticky oil; 5.23 g (75%), $[\alpha]^{20}_D = +33.4$ ($c = 1.0$, $CHCl_3$), $R_f = 0.19$ (CH_2Cl_2).

UV (CH_3CN): λ_{max} (nm) (log ε) = 282.5 (3.382), 203.0 (4.711).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3522, 3034, 2979, 2935, 1748, 1595, 1499, 1465, 1385, 1334, 1255, 1114, 1071, 967, 905, 789, 736.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.38–7.31 (m, 10H, Ph–H), 7.25 (t, J = 8.3 Hz, 1H, 4′-H), 6.53 (d, J = 8.3 Hz, 2H, 3′-H), 5.85 (d, J = 2.4 Hz, 1H, 2-H), 5.33 (d, J = 12.0 Hz, 1H, C$\underline{H}_2$Ph), 5.26 (d, J = 1.8 Hz, 2H, C$\underline{H}_2$Ph), 5.10 (d, J = 12.0 Hz, 1H, C$\underline{H}_2$Ph), 4.82 (dd, J = 9.0, 2.4 Hz, 1H, 3-H), 4.55 (sept, J = 6.0 Hz, 2H, OC$\underline{H}$(CH_3)$_2$), 3.18 (d, J = 9.0 Hz, 1H, OH), 1.30 (d, J = 6.0 Hz, 6H, OCH(C$\underline{H}_3$)$_2$), 1.28 (d, J = 6.0 Hz, 6H, OCH(C$\underline{H}_3$)$_2$).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.2 (CO_2Bn), 166.4 (CO_2Bn), 165.1 (CO_2Ar), 156.4 (2 × C-2′), 135.2 (Ph–C_{quart}), 134.7 (Ph–C_{quart}), 131.2 (C-4′), 128.6, 128.5, 128.3, 128.2 (Ph–*C*H), 114.0 (C-1′), 105.9 (2 × C-3′), 73.0 (C-2), 71.1 (2 × O*C*H(CH_3)$_2$), 71.0 (C-3), 67.9 (*C*H_2Ph), 67.3 (*C*H_2Ph), 21.9 (OCH(*C*H_3)$_2$), 21.8 (OCH(*C*H_3)$_2$).
MS (ESI): m/z (%) = 1124 (100) $[2M+Na]^+$, 573 (25) $[M+Na]^+$.

1.3.3.5 ** **(2*S*,3*S*)-2-*O*-(2,6-Diisopropoxybenzoyl)tartaric acid** [5]



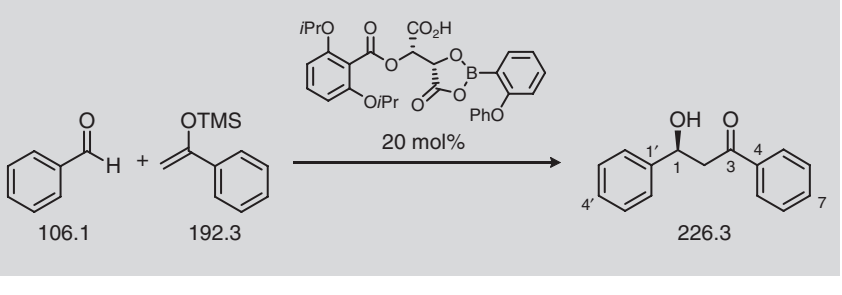
550.6 370.4

Palladium on charcoal (10%, 240 mg) is added to a solution of the dibenzyl ester **1.3.3.4** (3.00 g, 5.45 mmol) in EtOAc (25 ml) under an argon atmosphere. The balloon filled with argon is then replaced by a balloon filled with hydrogen, and the reaction mixture is stirred at room temperature for 14 h.

The mixture is then filtered through a Celite® pad, and the solvent is removed *in vacuo* to afford the monoacylated tartaric acid in quantitative yield, which is dried *in vacuo* to become a colorless crystalline solid; 2.02 g (100%), mp 76–78 °C, $[\alpha]^{20}_{D} = +27.8$ ($c = 1.0$, EtOH).

UV (CH_3CN): λ_{max} (nm) (log ε) = 282.0 (3.376), 202.5 (4.539).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3495, 2982, 1743, 1596, 1467, 1387, 1254, 1112, 903, 733, 662.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.25 (t, $J = 8.4$ Hz, 1H, 4′-H), 6.53 (d, $J = 8.4$ Hz, 2H, 3′-H), 5.84 (d, $J = 1.5$ Hz, 1H, 2-H), 4.87 (d, $J = 1.5$ Hz, 1H, 3-H), 4.54 (sept, $J = 6.1$ Hz, 2H, OC<u>H</u>$(CH_3)_2$), 1.30 (d, $J = 6.1$ Hz, 6H, OCH(C<u>H</u>$_3)_2$), 1.25 (d, $J = 6.1$ Hz, 6H, OCH(C<u>H</u>$_3)_2$).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 173.1 (CO_2H), 170.0 (CO_2H), 164.4 (CO_2Ar), 156.2 (2 × C-2′), 131.8 (C-4′), 114.0 (C-1′), 113.6 (2 × C-3′), 72.6 (C-2), 72.1 (2 × O*C*H$(CH_3)_2$), 70.5 (C-3), 21.9 (OCH(*C*H$_3)_2$), 21.8 (OCH(*C*H$_3)_2$).
MS (ESI): m/z (%) = 763 (87) $[2M+Na]^+$, 393 (100) $[M+Na]^+$.

1.3.3.6 ** **(*S*)-1-Hydroxy-1,3-diphenyl-3-propanone** [4]



The monoacylated tartaric acid **1.3.3.5** (74.1 mg, 0.20 mmol) and 2-phenoxyphenylboronic acid (42.8 mg, 0.20 mmol) are dissolved in anhydrous propionitrile (1.0 ml) and stirred at room temperature for 30 min. The reaction mixture is then cooled to −78 °C, and benzaldehyde (101 µl, 106 mg, 1.00 mmol) is added by means of a syringe, followed by 1-phenyl-1-(trimethylsiloxy)ethylene (349 µl, 327 mg, 1.70 mmol). The reaction mixture is stirred at −78 °C for 4 h, then an aqueous HCl solution (0.25 M, 4.0 ml) is added, and the mixture is allowed to warm to room temperature.

The mixture is poured into Et_2O (40 ml) and H_2O (20 ml), the phases are separated, and the aqueous layer is extracted with Et_2O (2 × 20 ml). The combined organic layers are washed with H_2O (20 ml) and saturated aqueous $NaHCO_3$ solution (20 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* and

purified by column chromatography on deactivated silica gel (30 g + 0.3 ml NEt_3, *n*-pentane/Et_2O, 5 : 1) to give the aldol adduct as a light-yellow sticky oil; 206 mg (91%), ee = 90%, $[\alpha]^{20}_D = -67.0$ ($c = 1.0$, $CHCl_3$), $R_f = 0.14$ (*n*-pentane/Et_2O, 5 : 1).

The enantiomeric excess value of the aldol **1.3.3.6** is determined by HPLC analysis of the corresponding (+)-MTPA ester, which is obtained by small-scale reaction of **1.3.3.6** with (+)-α-methoxy-α-trifluoromethylphenyl acetyl chloride and anhydrous pyridine in CCl_4 according to Mosher's method [8]. (*S*)-1-Hydroxy-1,3-diphenyl-3-propanone (25.0 mg, 0.11 mmol) and (+)-α-methoxy-α-trifluoromethylphenyl acetyl chloride (20.7 µl, 27.8 mg, 0.11 mmol) are mixed with CCl_4 (0.1 ml; Caution: resorption through the skin!) and pyridine (0.1 ml). The reaction mixture is stirred at room temperature for 12 h and poured into Et_2O (10 ml) and H_2O (10 ml), and after extraction the phases are separated. The organic layer is dried over Na_2SO_4, filtered, and concentrated, and the residue obtained is dissolved in EtOAc for HPLC analysis.

UV (CH_3CN): λ_{max} (nm) (log ε) = 279.0 (3.178), 241.0 (4.103).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3469, 3057, 1670, 1597, 1447, 1393, 1215, 1055, 1020, 916, 872, 747.
^{1}H NMR (300 MHz, [D_6]benzene): δ (ppm) = 7.61 (dd, J = 8.1, 1.5 Hz, 2H, 2 × 5-H), 7.35 (dd, J = 7.5, 1.8 Hz, 2H, 2 × 2′-H), 7.20 (t, J = 7.5 Hz, 2H, 2 × 3′-H), 7.13–7.05 (m, 2H, 7-H, 4′-H), 6.96 (t, J = 8.1 Hz, 2H, 2 × 6-H), 5.23 (dd, J = 9.3, 2.9 Hz, 1H, 1-H), 3.53 (s_{br}, 1H, OH), 2.94 (dd, J = 17.7, 9.3 Hz, 1H, 2-H_b), 2.80 (dd, J = 17.7, 2.9 Hz, 1H, 2-H_a).
^{13}C NMR (76 MHz, [D_6]benzene): δ (ppm) = 199.7 (C-3), 144.1 (C-1′), 137.0 (C-4), 133.2 (C-7), 128.5 (2 × C-5, 2 × C-6, C-4′), 127.5 (2 × C-3′), 126.1 (2 × C-2′), 70.0 (C-1), 48.0 (C-2).
MS (EI, 70 eV): m/z (%) = 226 (48) $[M]^+$, 208 (58) $[M-H_2O]^+$, 186 (47), 131 (11) $[M-H_2O-C_6H_5]^+$, 120 (48), 105 (100) $[C_6H_5CHCH_3]^+$, 77 (96) $[C_6H_5]^+$, 51 (33).
HPLC: Chiralcel OD (Daicel); 250 × 4.6 mm ID

eluent: *n*-hexane/EtOAc, 40 : 1; isocratic
retention time: t_{R1} = 12.8 min (*S*)-isomer; t_{R2} = 15.1 min (*R*)-isomer.

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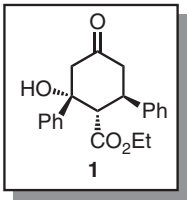
1.3.4

Ethyl (1*S*,2*R*,6*R*)-2-hydroxy-4-oxo-2,6-diphenylcyclohexane-1-carboxylate



1

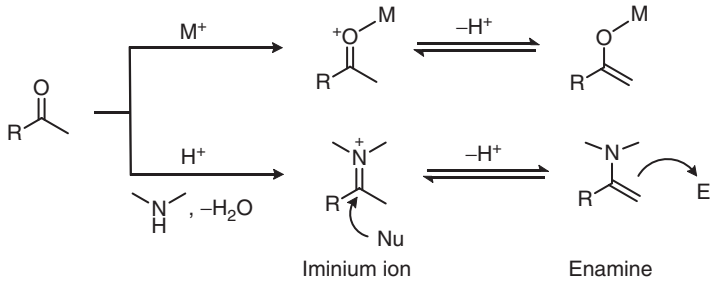
Topics:

- Organocatalysis
- Enantioselective synthesis of an oxocyclohexane carboxylic ester (Michael addition, intramolecular aldol reaction)
- Synthesis of Jørgensen's catalyst from L-phenylalanine (amide formation, amines by reduction of amides, imidazolidine formation)

(a) General

Enantioselective catalysis is an important topic in organic synthesis. In the past, this was mainly accomplished by the use of transition-metal catalysts containing metals such as Pd [1], Ru, or Rh in the presence of chiral ligands. However, on the basis of the enantioselective synthesis of hydrindens by Wiechert, Eder, Sauer, Hajos, and Parrish [2] over 30 years ago, using L-proline as chiral catalyst (cf. Section 1.3.1), it has been demonstrated that enantioselective catalysis can also be effected by a wide range of small, metal-free chiral molecules, such as amino acids and their derivatives.

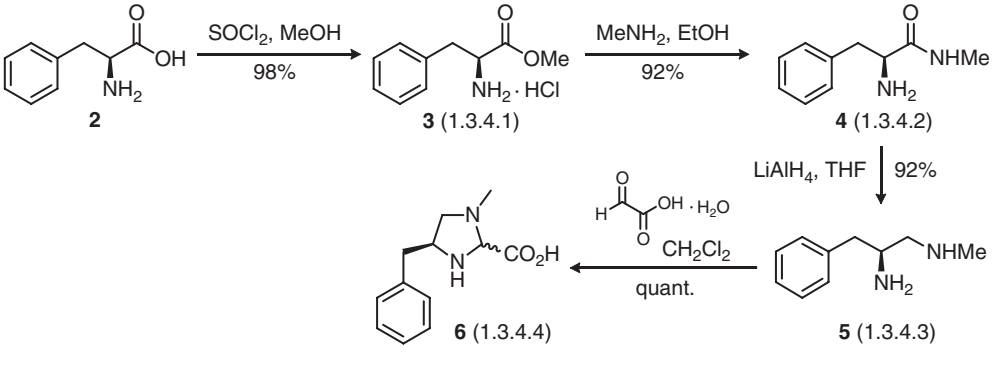
In the meantime, extensive studies have been carried out with regard to the use of such organocatalysts in various reactions [3], such as the aldol [4], Michael [5], Mannich [6], and Diels–Alder reactions [7], as well as hydrogenations [8], with high stereoselectivity. The concept of organocatalysis (or aminocatalysis) is mainly based on electronic similarities between a Lewis-acid-activated carbonyl group and an iminium ion. Thus, an iminium ion is more reactive than a carbonyl moiety because of a lower energy of its lowest unoccupied molecular orbital (LUMO), which is manifested in an increase of its electrophilicity and its α-C–H acidity. In this way, organocatalysis exploits both the higher reactivity of iminium ions and their easy deprotonation to give enamines, which can either react with electrophiles or be used in pericyclic processes.



Among the various asymmetric C–C bond-forming reactions that may be exploited for the formation of chiral building blocks, enantioselective domino reactions [9] are of particular importance as multiple stereogenic centers can be formed during a single transformation. Jørgensen and coworkers [10][4] recently published a highly diastereo and enantioselective domino-Michael–aldol reaction of acyclic β-keto esters and α,β-unsaturated ketones in the presence of a chiral organocatalyst easily accessible in a few steps from L-phenylalanine. An example of this organocatalyzed domino process, yielding cyclohexanone-4-carboxylates with several stereogenic centers, is presented in Section (b), together with the synthesis of the required organocatalyst.

(b) **Synthesis of 1**

1) Jørgensen's catalyst **6** is prepared in a four-step sequence, starting from L-phenylalanine (**2**), which is transformed into the methyl ester hydrochloride **3** by reaction with $SOCl_2$ in MeOH. Aminolysis of **3** leads to the corresponding methyl amide **4**, which is reduced with lithium aluminum hydride. The 1,2-diamine **5** thus obtained is subjected to cyclocondensation with glyoxylic acid monohydrate to give the desired organocatalyst imidazolidine-2-carboxylic acid **6**.

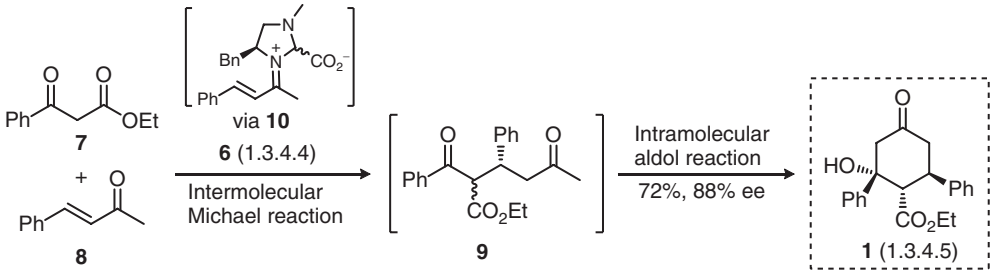


4) A comparable organocatalyzed three-component cyclization of aldehydes, α,β-unsaturated aldehydes, and nitroalkenes gives rise to highly functionalized cyclohexene derivatives, establishing four stereocenters in a one-pot reaction; see Ref. [9a].

2) The synthesis of the oxocyclohexanecarboxylic acid ethyl ester **1** in a single process is achieved by a highly diastereo and enantioselective domino-Michael–aldol reaction of ethyl benzoylacetate (**7**) and benzylidene acetone (**8**) in the presence of the organocatalyst **6**.

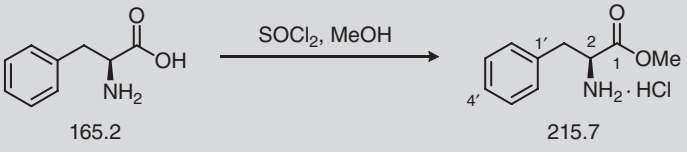
Initially, the β-keto ester (**7**) and the enone (**8**) undergo an intermolecular Michael reaction to form the adduct **9**, which subsequently undergoes an intramolecular aldol reaction to give the target molecule **1** with three defined stereogenic centers in a chemical yield of 72% and 88% ee.

The catalyst plays a threefold role in this domino process: (i) it activates the Michael acceptor by the formation of an iminium ion (**10**); (ii) it generates the active Michael donor by deprotonation of the β-keto ester (**7**); and (iii) it acts as a base in the intramolecular aldol reaction.



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

1.3.4.1 ** **Methyl (2*S*)-2-amino-3-phenylpropionate hydrochloride** [11]



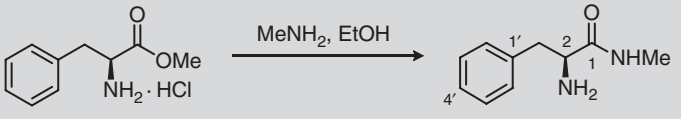
Thionyl chloride (18.8 g, 158 mmol, 11.5 ml) is slowly added to a stirred suspension of L-phenylalanine (20.1 g, 122 mmol) in MeOH (120 ml) under an argon atmosphere at 0 °C, and stirring is continued at room temperature for 22 h.

After removal of the solvent *in vacuo*, H_2O (30 ml) is added and evaporated *in vacuo*. This process is repeated three times. After drying *in vacuo*, the hydrochloride is obtained as a colorless solid; 25.7 g (98%), mp 160–161 °C.

UV (CH_3CN): λ_{max} (nm) (log ε) = 263.5 (2.197), 257.0 (2.298), 252.0 (2.214), 192.5 (4.435).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2845, 1747, 1584, 1496, 1242, 1146, 1084, 935, 741, 702.
^{1}H NMR (300 MHz, D_2O): δ (ppm) = 7.88–7.33 (m, 5H, Ph–H), 4.70 (s_{br}, NH_2), 4.50 (t, J = 5.9 Hz, 1H, 2-H), 3.91 (s, 3H, CO_2CH_3), 3.42 (dd, J = 14.6, 5.9 Hz, 1H, 3-H), 3.32 (dd, J = 14.3, 7.5 Hz, 1H, 3-H).
^{13}C NMR (76 MHz, D_2O): δ (ppm) = 171.0 (C-1), 134.7 (C-4′), 130.4 (C-2′, C-6′), 130.2 (C-3′, C-5′), 129.1 (C-1′), 55.1 (C-2), 54.6 (CO_2CH_3), 36.6 (C-3).
MS (EI, 70 eV): m/z (%) = 179 (2) $[M-HCl]^+$.

1.3.4.2 * (2*S*)-2-Amino-3-phenylpropionic acid methyl amide [7c]



215.7 178.2

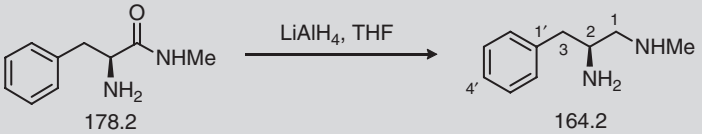
A solution of the hydrochloride **1.3.4.1** (25.6 g, 119 mmol) in EtOH (200 ml) is added to a stirred solution of methylamine (8 M, 59.4 ml, 475 mmol) in EtOH under an argon atmosphere at 0 °C, and stirring is continued for 20 h at room temperature.

The solvent is then removed *in vacuo*, the residue is suspended in Et_2O (30 ml), and the solvent is again evaporated to remove the excess methylamine. This procedure is repeated twice to give the hydrochloride of the desired product as a white solid. The amide is obtained from the hydrochloride by treating the residue with saturated aqueous $NaHCO_3$ solution (100 ml) and extracting with $CHCl_3$ (4 × 100 ml).

The combined organic layers are washed with brine, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo* to afford the amide as colorless crystals; 19.6 g (92%), mp 55–56 °C, $[\alpha]^{20}_D$ = −100.5 (c = 1.0, $CHCl_3$), R_f = 0.39 (EtOAc/MeOH, 1 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 268 (2.096), 264 (2.190), 258.0 (2.307), 253.0 (2.237), 248.0 (2.130), 192.5 (4.515).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3372, 2939, 1646, 1527, 1399, 1109, 927, 857, 747, 701, 482.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.35–7.17 (m, 5H, Ph–H), 3.60 (dd, J = 9.4, 3.8 Hz, 1H, 3-H_A), 3.28 (dd, 1H, J = 13.8, 4.0 Hz, 3-H_B), 2.81 (d, J = 4.9 Hz, 3H, CH_3), 2.67 (dd, J = 13.8, 9.6 Hz, 1H, 2-H), 1.33 (s_{br}, 2H, NH_2).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 174.7 (C-1), 137.9 (C-1′), 129.2 (C-2′,C-6′), 128.6 (C-3′, C-5′), 126.7 (C-4′), 56.4 (C-2), 40.9 (C-3), 25.7 ($NHCH_3$).
MS (DCI, 200 eV): m/z (%) = 179 (100) $[M+H]^+$, 196 (45) $[M+NH_4]^+$.

1.3.4.3 ** (2*S*)-1*N*-Methyl-3-phenylpropane-1,2-diamine



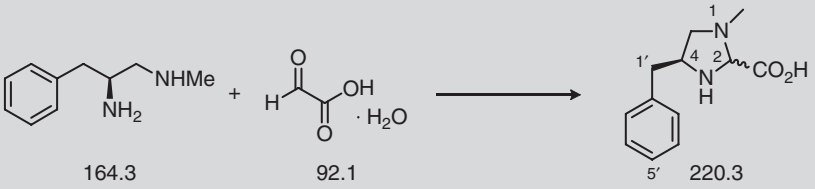
178.2 164.2

A solution of the amide **1.3.4.2** (3.79 g, 21.3 mmol) in THF (80 ml) is added dropwise to a stirred suspension of $LiAlH_4$ (2.96 g, 78.0 mmol) in THF (60 ml) under an argon atmosphere, and stirring is continued at reflux for 20 h.

After cooling to 0 °C, saturated Na_2SO_4 solution is added dropwise, and the mixture is stirred for 30 min. The white solid is then filtered off and washed with EtOAc. The filtrate is washed with brine, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. Finally, the residue is purified by distillation to yield the diamine as a colorless oil; 3.40 g (97%), $bp_{0.4}$ 120–121 °C, $n^{20}_D = 1.528$, $[\alpha]^{20}_D = -6.0$ ($c = 1.0$, $CHCl_3$), $R_f = 0.33$ ($CHCl_3$/MeOH, 1 : 1 + 10% NEt_3).

UV (CH_3CN): λ_{max} (nm) (log ε) = 268.0 (2.138), 261.0 (2.268), 192.0 (4.491).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3372, 2939, 1646, 1527, 1399, 1109, 928, 747, 701.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.30–7.13 (m, 5H, Ph–H), 2.75 (dd, $J = 15.5$, 5.0 Hz, 1H, 3-H_A), 2.62 (dd, 1H, $J = 11.4$, 3.8 Hz, 3-H_B), 2.51–2.41 (m, 2H, 1-H), 2.40 (s, 3H, NHC$\underline{H}_3$), 1.23 (s_{br}, 3H, NH_2, N*H*CH_3).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 139.1 (C-1′), 129.1 (C-2′, C-6′), 128.3 (C-3′, C-5′), 126.1 (C-4′), 58.3 (C-1), 52.2 (C-2), 42.7 (C-3), 36.5 ($NHCH_3$).
MS (DCI, 200 eV): *m*/*z* (%) = 165 (100) $[M+H]^+$.

1.3.4.4 * (4*S*,2*R*/*S*)-4-Benzyl-1-methylimidazolidine-2-carboxylic acid (Jørgensen's catalyst) [5b]



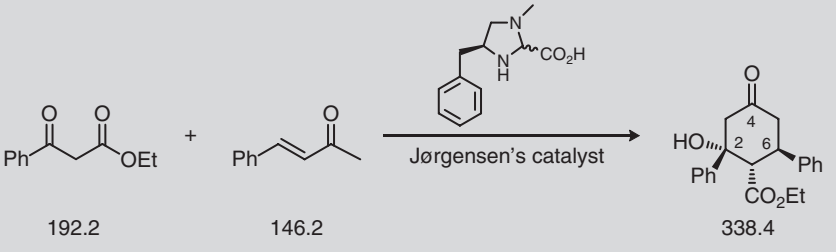
164.3 92.1 220.3

The diamine **1.3.4.3** (2.96 g, 18.05 mmol) is suspended in CH_2Cl_2 (180 ml) under an argon atmosphere. Glyoxylic acid monohydrate (1.66 g, 18.05 mmol) is added, and the resulting suspension is stirred at room temperature for 16 h.

Evaporation of the solvent under reduced pressure affords the carboxylic acid in quantitative yield as a colorless solid as a 2 : 1 mixture of diastereomers; mp 122–123 °C, $[\alpha]^{20}_D = +10.3$ ($c = 1.0$, MeOH), $R_f = 0.47$ ($CHCl_3$/MeOH, 1 : 1 [+10% NEt_3]).

UV (CH_3CN): λ_{max} (nm) (log ε) = 267.0 (2.104), 258.0 (2.359), 252.0 (2.330), 248.0 (2.270), 205.0 (3.949).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3483, 2951, 2786, 1664, 1629, 1573, 1435, 1301, 1205, 1176, 1025, 943, 781, 755, 704, 607.
^{1}H NMR (300 MHz, $CDCl_3$): major diastereomer: δ (ppm) = 8.10–7.40 (2 × s_{br}, 2H, CO_2H, NH), 7.32–7.20 (m, 5H, Ph–H), 4.19 (s, 1H, 2-H), 3.74 (quintet, $J = 6.8$ Hz, 1H, 4-H), 3.48–3.41 (m, 1H, 5-H_A), 3.21 (dd, $J = 13.4$, 5.8 Hz, 1H, 5-H_B), 2.93–2.52 (m, 2H, 1′-H), 2.89 (s, 3H, N–CH_3).
Minor diastereomer: δ (ppm) = 8.10–7.40 (2 × s_{br}, 2H, CO_2H, NH), 7.32–7.20 (m, 5H, Ph–H), 4.12 (s, 1H, 2-H), 4.01 (quintet, $J = 6.7$ Hz, 1H, 4-H), 3.71–3.64 (m, 1H, 5-H_A), 3.01 (dd, $J = 13.4$, 6.3 Hz, 1H, 5-H_B), 2.93–2.52 (m, 2H, 1′-H), 2.84 (s, 3H, NCH_3).
^{13}C NMR (76 MHz, $CDCl_3$): major diastereomer: δ (ppm) = 168.9 (CO_2H), 137.4 (C-2′), 128.8 (2 × C-3′), 128.7 (2 × C-4′), 126.8 (C-5′), 84.9 (C-2), 58.4 (C-4), 58.1 (C-5), 40.4 (N–CH_3), 38.3 (C-1′).
Minor diastereomer: δ (ppm) = 169.4 (CO_2H), 137.3 (C-2′), 129.1 (2 × C-3′), 128.6 (2 × C-4′), 126.7 (C-5′), 81.9 (C-2), 58.9 (C-5), 57.3 (C-4), 39.8 (C-1′), 39.2 (NCH_3).
MS (ESI): m/z (%) = 243 (40) $[M+Na]^+$.

1.3.4.5 ** Ethyl (1*S*,2*R*,6*R*)-2-hydroxy-4-oxo-2,6-diphenylcyclohexane-1-carboxylate [10][4]



192.2 146.2 338.4

To a stirred solution of benzylidene acetone (77.1 mg, 527 µmol) in CH_3CN (1 ml) are added ethyl benzoylacetate (203 mg, 1.06 mmol) and Jørgensen's catalyst **1.3.4.4** (11.6 mg, 52.7 µmol, 10 mol%), and the resulting solution is stirred for 93 h at room temperature.

The reaction mixture is then diluted with Et_2O (2 ml). After filtration and washing the filter cake with Et_2O (2 ml), the solvent is removed *in vacuo* to afford the ethyl ester as a colorless solid; 127 mg (72%), ee = 88%, $[\alpha]^{20}_D = -7.6$ ($c = 1.0$, $CHCl_3$).

UV (CH_3CN): λ_{max} (nm) (log ε) = 256.5 (0.074), 251.0 (0.022), 201.0 (1.340).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3348, 1713, 1374, 1225, 1145, 1029, 749, 698.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.55 (d, $J = 7.5$ Hz, 2H, Ph–H), 7.39–7.22 (m, 7H, Ph–H), 4.45 (d, $J = 2.5$ Hz, 1H, OH), 3.86–3.74 (m, 1H, 5-H), 3.61–3.49 (m, 3H, 1-H, OCH_2), 2.79–2.70 (m, 4H, 3-H, 5-H), 0.53 (t, $J = 7.2$ Hz, 3H, CH_3).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 206.0 (C-4), 174.2 (-CO_2R), 144.1 (Ph–C_{quat}), 140.2 (Ph–C_{quat}), 128.4 (2 × Ph–C), 127.6 (2 × Ph–C), 127.6 (2 × Ph–C), 127.5 (2 × Ph–C), 124.6 (2 × Ph–C), 60.6 (C-2), 56.6 (C-1), 54.0 (C-3), 47.4 (C-5), 43.3 (C-6), 13.2 (CH_3).
MS (EI, 70 eV): m/z (%) = 338 (12) $[M]^+$.

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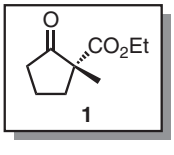
1.4
Electrophilic and Nucleophilic Acylation

1.4.1
(–)-Ethyl (1*R*)-1-methyl-2-oxocyclopentane-1-carboxylate



Topics:

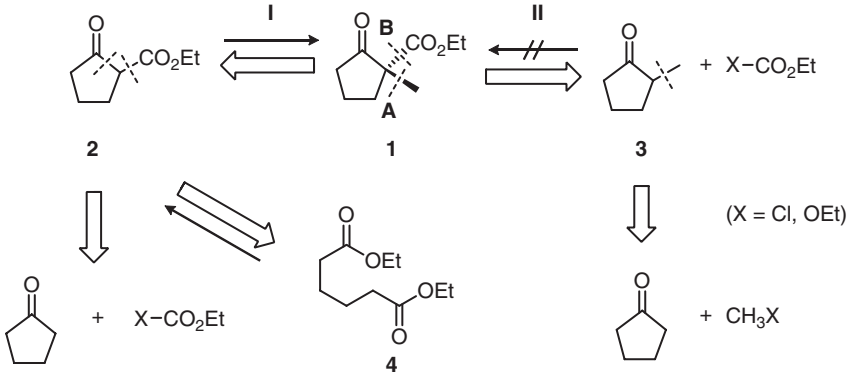
- Dieckmann cyclization
- Stereoselective enzymatic reduction of a β-keto ester to a β-hydroxy ester
- Stereoselective α-alkylation of a β-hydroxy ester (Frater–Seebach alkylation)
- Oxidation of a secondary hydroxy group to a keto group

(a) General

The chiral β-keto ester **1** is the starting material for a synthesis of the pheromone frontalin [1]. In general, cyclopentane derivatives are valuable building blocks in

the total synthesis of natural products, since many of them, for example, steroids and iridoids, contain a five-membered ring system.

Retrosynthesis of **1** according to **A** and **B** immediately leads to cyclopentanone or diethyl adipate and two routes **I**/**II** for the synthesis of **1**:

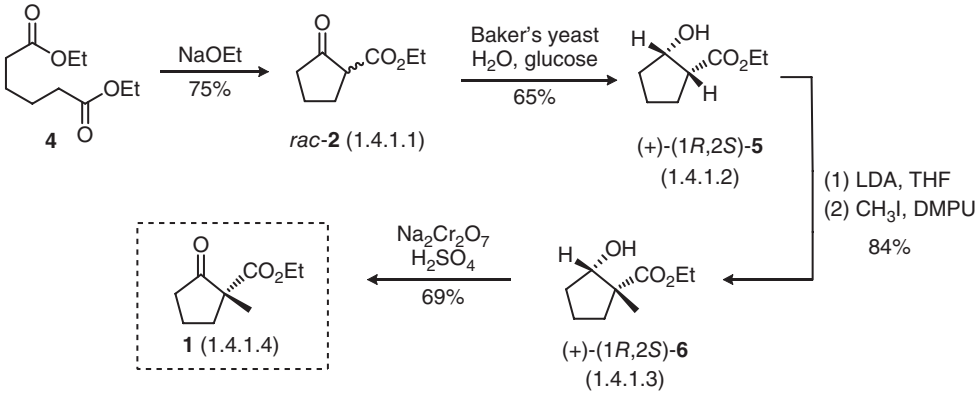


Route **I** represents a 2-methylation of cyclopentanone-2-carboxylate (**2**), which is easily accessible either from diethyl adipate or from α-acylation of cyclopentanone with dialkyl carbonate. Route **II** requires a 2-acylation of 2-methylcyclopentanone (**3**) with dialkyl carbonate; however, the disadvantage arises that Claisen condensations of **3** are reported to take place preferentially at the less hindered C-5 [2]. Therefore, route **I** is favorable and, as the central problem of the synthesis of **1**, there remains the enantioselective formation of its stereogenic center.

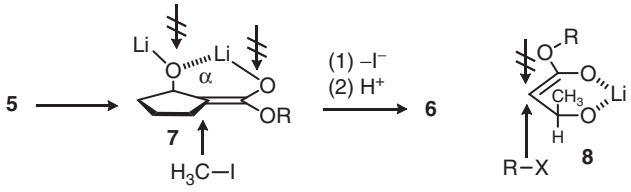
(b) **Synthesis of 1**

The starting material of choice for the synthesis of **1** is cyclopentanone carboxylate *rac*-**2**, which is readily prepared from diethyl adipate (**4**) by Dieckmann cyclization in the presence of NaOEt [3]. Since direct enantioselective methylation of *rac*-**2** at the 2-position by application of the SAMP methodology (cf. Section 1.2.1) proceeds only with modest stereoselection [4], an indirect approach to **1** is applied [5].

In the first step, the well-established [6] enzymatic reduction of the racemic β-keto ester **2** with Baker's yeast in fermenting aqueous glucose solution is performed, which produces the 2-cyclopentanol-1-carboxylate **5** with (1*R*,2*S*)-configuration in 99% ee as a single diastereomer. In the second step, the chiral β-hydroxy ester **5** is deprotonated with 2 equiv of LDA and then reacted with methyl iodide in the presence of DMPU. In this process, known as *Frater–Seebach alkylation* [7], exclusive α-C-alkylation of the β-hydroxy ester is observed to give the product **6** with high stereoselectivity (>98% de).



Intermediates in the Frater–Seebach alkylation are dianions (here: **7**), which exist as rigid Li-chelated structures. These are thought to be responsible for the stereodifferentiation in the alkylation **5** → **6**, as also described for analogous reactions of open-chain systems (e.g., **8**, "acyclic stereoselection") [8].

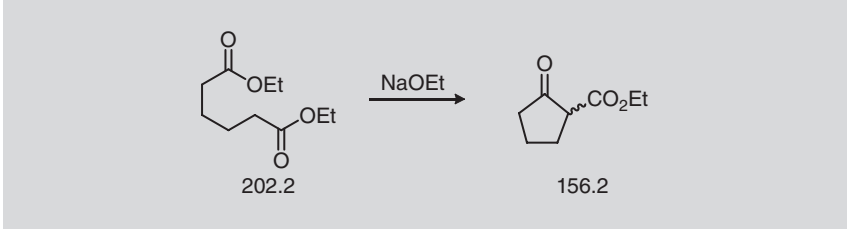


In the last step, the hydroxy ester **6** is oxidized using $Na_2Cr_2O_7/H_2SO_4$ to provide the chiral β-keto ester **1**.

Thus, the target molecule is obtained in practically enantiopure form (>98% ee) in a four-step procedure with an overall yield of 28% (based on **4**).

(c) Experimental Procedures for the Synthesis of 1

1.4.1.1 * Ethyl 2-oxo cyclopentane-1-carboxylate [3]



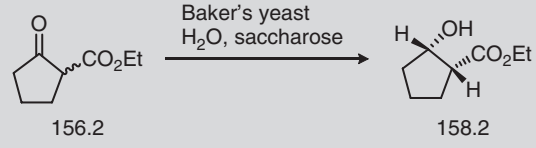
Sodium ethoxide is prepared by reacting metallic sodium (11.5 g, 0.50 mol) with anhydrous EtOH (150 ml) and distilling off the excess EtOH *in vacuo*. Anhydrous

toluene (100 ml) and diethyl adipate (101 g, 0.50 mol) are added, and the resulting suspension is heated under reflux with stirring for 8 h.

The mixture is then cooled to room temperature, aqueous HCl (2 M) is added until a clear two-phase system is obtained (approximately 250 ml), and the phases are separated. The organic phase is washed with saturated aqueous $NaHCO_3$ and brine (each 100 ml), dried over Na_2SO_4, and filtered. The solution is distilled *in vacuo* (20 mbar), and the fraction obtained in the range 100–140 °C is again distilled *in vacuo* (2 mbar, Vigreux column) to give a colorless oil; 58.2 g (75%), bp_2 88–89 °C, $n^{20}_D = 1.4519$.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1740, 1715.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.01 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.15 (dd, *J* = 9.3, 8.7 Hz, 1H, 1-H), 2.13–2.04 (m, 4H, CH_2), 1.98–1.88 (m, 1H, CH_2), 1.77–1.61 (m, 1H, CH_2), 1.08 (t, *J* = 7.1 Hz, 3H, CH_3).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 211.8 (C-2), 168.9 (CO_2Et), 60.5, 54.2, 37.5, 26.9, 20.5, 13.7.

1.4.1.2 * (+)-Ethyl (1*R*,2*S*)-2-hydroxycyclopentane-1-carboxylate [5]



156.2 158.2

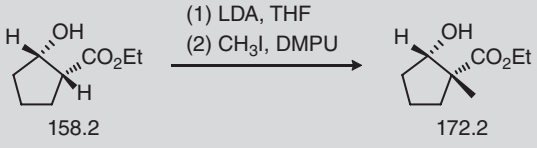
In a 3-l Erlenmeyer flask with a stirring or shaking apparatus, Baker's yeast (225 g; *Pleser*, *Darmstadt*) is suspended in H_2O (tap, 1.5 l), and saccharose (225 g) is added. After 0.5 h, ethyl 2-oxocyclopentane-1-carboxylate **1.4.1.1** (22.5 g, 143 mmol) and Triton® X 114 (450 mg, *Fluka*) are added, and the mixture is stirred for 48 h at room temperature.

Hyflow Super Cel® (80 g, Fluka) is added in portions with stirring, and then the mixture is filtered through a G2-frit, saturated with NaCl, and extracted with Et_2O (4 × 300 ml). The ethereal extracts are dried over $MgSO_4$ and filtered. The extracts of four such experiments are combined, the solvent is removed under normal pressure, and the residue is purified by distillation. The product is obtained as a colorless oil; 62.6 g (65%), bp_{10} 95–96 °C. $[\alpha]^{20}_D = +15.1$ (*c* = 2.25, $CHCl_3$), Ref. [9]: +14.7 (*c* = 2.08, $CHCl_3$).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3660, 3450, 2985, 1765.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.38 (dt, *J* = 4.3, 3.5 Hz, 1H, 2-H), 4.13 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.14 (s_{br}, 1H, OH), 2.62 (ddd, *J* = 9.9, 8.8, 4.4 Hz,

1H, 1-H), 2.00–1.80 (m, 3H, CH_2), 1.75–1.69 (m, 2H, CH_2), 1.63–1.54 (m, 1H, CH_2), 1.22 (t, J = 7.1 Hz, 3H, CH_3).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 174.5, 73.5, 60.3, 49.4, 33.8, 26.0, 21.8, 14.0.

1.4.1.3 ** (+)-Ethyl (1*R*,2*S*)-2-hydroxy-1-methylcyclopentane-1-carboxylate [5]



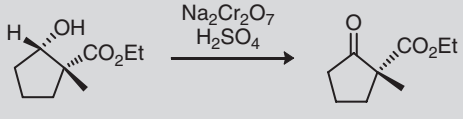
158.2 172.2

A solution of LDA is prepared by adding *n*-butyllithium (375 ml, 0.60 mol, 1.6 M in *n*-hexane) to *N*,*N*-diisopropylamine (60.7 g, 0.60 mol) in anhydrous THF (225 ml) at −78 °C, and then the mixture is kept at 0 °C for 1 h. A solution of the carboxylate **1.4.1.2** (40.1 g, 0.25 mol) in anhydrous THF (60 ml) is then added in one portion to this LDA solution at −50 °C. The temperature rises to −10 °C, and stirring is continued for 0.5 h at this temperature. Iodomethane (49.7 g, 0.35 mol; Caution: carcinogenic!) in DMPU (125 ml) is added, whereupon the temperature rises to 40 °C. Stirring is continued for 20 h at room temperature.

The mixture is then poured into saturated aqueous NH_4Cl solution (1000 ml) and extracted with Et_2O (4 × 200 ml). The combined organic layers are washed with brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The crude product is purified by distillation; 36.1 g (84%), colorless oil, bp_{10} 99–100 °C; $[\alpha]^{20}_D$ = +28.4 (c = 1.61, $CHCl_3$).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3455 (OH), 1730, 1720, 1705.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.09 (q, J = 7.3 Hz, 2H, OCH_2), 3.90 (dd, J = 5.6, 3.3 Hz, 1H, 2-H), 3.09 (s_{br}, 1H, OH), 2.19–2.09 (m, 1H, CH_2), 1.96–1.70 (m, 2H, CH_2), 1.66–1.43 (m, 3H, CH_2), 1.19 (t, J = 7.3 Hz, 3H, $CH_2\underline{CH_3}$), 1.09 (s, 3H, 1-CH_3).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 177.0 (C=O), 79.8 (C-2), 60.4 (O-CH_2), 53.9 (C-1), 33.0 (CH_2), 31.8 (CH_2), 22.2 (CH_2), 20.3 (CH_2), 17.1 (CH_3), 14.0 (CH_3).

1.4.1.4 * (−)-Ethyl (1*R*)-1-methyl-2-oxocyclopentane-1-carboxylate [5]



172.2 170.2

A chromic acid solution prepared from $Na_2Cr_2O_7 \cdot 2H_2O$ (89.4 g, 0.30 mol) and concentrated H_2SO_4 (75 g) in H_2O (200 ml) is added dropwise to a solution of (+)-(1*R*,2*S*)-**1.4.1.3** (34.4 g, 0.20 mol) in Et_2O (200 ml) at 0–5 °C, and stirring is continued for 20 h at room temperature (note).

H_2O (220 ml) is then added, and the mixture is extracted with Et_2O (4 × 200 ml). The combined organic layers are washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The crude product is purified by distillation; 23.5 g (69%), colorless oil, bp_{10} 96 °C; $[\alpha]^{20}_D = -13.3$ ($c = 1.09$, $CHCl_3$).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1750, 1735.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.10 (q, J = 7.1 Hz, 2H, OCH_2), 2.50–2.20 (m, 3H, CH_2), 2.07–1.76 (m, 3H, CH_2), 1.25 (s, 3H, 1-CH_3), 1.19 (t, J = 7.1 Hz, 3H, $CH_2C\underline{H}_3$).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 215.8 (C-2), 172.3 (CO_2Et), 61.2, 55.8, 37.6 (3 × CH_2), 36.1 (CH_2), 19.5 (CH_2), 19.3 (CH_3), 14.0 (CH_3).

Note: The alcohol can be also oxidized with Dess–Martin-periodinane (DMP) following the procedure described in **2.3.2.4**.

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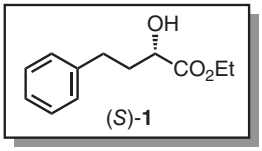
1.4.2

Ethyl (*S*)- and (*R*)-2-hydroxy-4-phenylbutanoate



Topics:

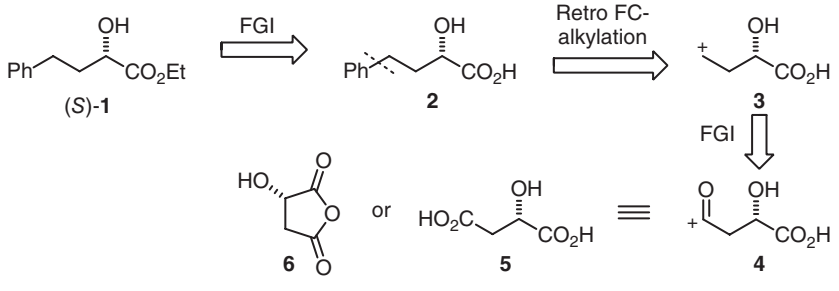
- Ex-chiral pool synthesis of both enantiomers of an α-hydroxy-alkanoic ester
- Friedel–Crafts acylation of an arene (succinoylation)
- Catalytic reduction Ph–C=O → Ph–CH_2
- Mesylation of an OH function
- Inversion of configuration of a secondary alcohol

(a) **General**

Syntheses of enantiopure compounds can be performed following two principal strategies:

1) The construction of the target molecule is conducted in a stereoselective manner with respect to the required operations, either in an enantioselective way using chiral catalysts or in a diastereoselective way using chiral auxiliaries, which are subsequently removed (*asymmetric synthesis*) [1].
2) The stereogenic elements required, for example, one (or several) stereogenic center(s), are introduced by using natural products or other readily available enantiopure compounds as chiral starting materials, which are transformed to the target molecule by stereocontrolled reactions (*ex-chiral pool synthesis*, *ECP synthesis*) [2].

ECP syntheses have been performed using a multitude of stereo-defined natural products, for example, hydroxy- and amino acids, terpenoids, and carbohydrates. For an appropriate choice of a suitable candidate from the chiral pool, the functionalities as well as the number of stereogenic elements and their absolute configuration in the natural product and in the target molecule should correspond. This is demonstrated by the synthesis [3] of (*S*)-**1** containing one stereogenic center.

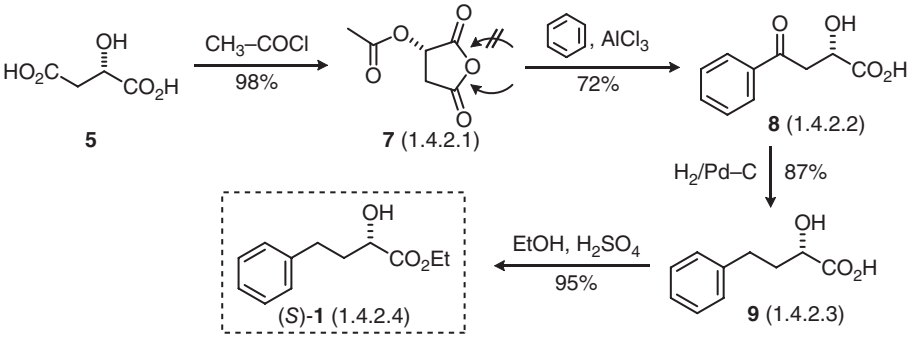


Functional group interconversion (FGI) and arene bond disconnection at the benzylic carbon (**1** → **2**) leads to a C_4-synthon **3**, which is represented by the acylium ion **4** derived from (*S*)-malic acid (**5**). This chiral (*S*)-configured

hydroxy-C_4-dicarboxylic acid is a readily available natural product (i.e., from the "chiral pool") that contains the complete carbon side chain of the target molecule together with the "correct" terminal functionalization and stereochemistry. Therefore, (*S*)-malic acid (**5**), or preferably its anhydride **6**, are excellent substrates for an ECP synthesis of (*S*)-**1** [4].[5)]

(b) **Synthesis of 1**

1) Reaction of (*S*)-malic acid (**5**) with acetyl chloride gives *O*-acetyl malic anhydride (**7**) by acetylation of the hydroxy group in **5** and elimination of H_2O. Chemoselective Friedel–Crafts acylation (succinoylation) of benzene with the unsymmetrical anhydride **7** in the presence of $AlCl_3$ at the more sterically accessible C=O group affords (*S*)-2-hydroxy-4-oxo-4-phenylbutanoic acid (**8**) in good yield [5]. The acetate in **7** is also cleaved in this process to give a free hydroxy group.



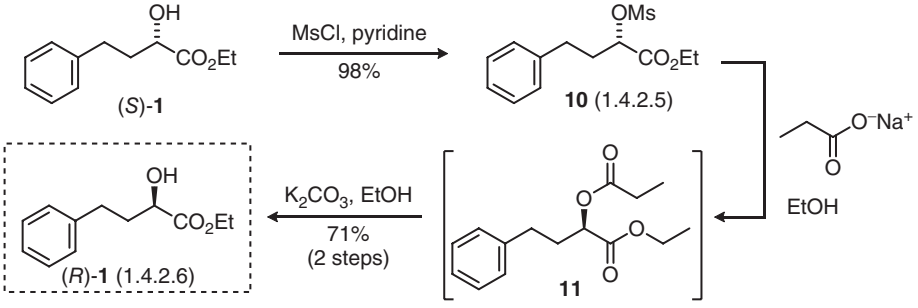
On hydrogenation of the α-oxo acid **8**, the benzylic carbonyl group is readily reduced to a CH_2 unit to yield the α-hydroxy acid **9** in almost quantitative yield and 99% ee. Esterification of the acid **9** according to the Fischer method ($EtOH/H_2SO_4$) yields the ethyl ester (*S*)-**1** in practically enantiopure form (ee = 99%).

2) The simplest way to obtain (*R*)-**1** would be direct inversion of the 2-OH group in the (*S*)-2-hydroxy ester prepared in (1). However, the Mitsunobu reaction (cf. Section 3.4.4) as the method of choice gives unsatisfactory results. Thus, even under modified conditions with $EtO_2C–N=N–CO_2Et/Ph_3P/ClCH_2CO_2H$, followed by hydrolysis with K_2CO_3/H_2O, the acid *ent*-**9** is obtained only in moderate yield [6].

Therefore, the OH group inversion of the stereogenic center in (*S*)-**1** is performed by converting the hydroxy group into a good leaving group by mesylation

5) Other retroanalytical approaches may lead to C_5- and C_6-carbohydrates as chiral starting materials for the synthesis of ethyl esters **1**. However, although readily available, carbohydrates are not considered as substrates for the synthesis of **1**, since transformations sacrificing several stereogenic centers in favor of one are regarded as ineffective with respect to atomic and stereochemical economy.

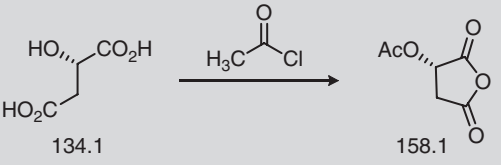
with CH_3SO_2Cl in pyridine. The mesylate **10**, which is obtained quantitatively, is subjected to an S_N2 displacement (Walden inversion) with sodium propionate in ethanol. The diester **11** is selectively cleaved by alcoholysis with K_2CO_3 in EtOH (due to equilibrium formation of ethanolate) to give the enantiomeric ethyl ester (*R*)-**1** in almost enantiopure form (ee = 97%).



Thus, the target molecule (*S*)-**1** is obtained in a four-step sequence from (*S*)-malic acid in an overall yield of 63%, and the target molecule (*R*)-**1** is obtained from (*S*)-**1** in a three-step sequence in an overall yield of 83% (or from **5** in a seven-step sequence in an overall yield of 52%).

(c) Experimental Procedures for the Synthesis of 1 (both enantiomers)

1.4.2.1 * (*S*)-α-Acetoxybutanedioic anhydride [7]



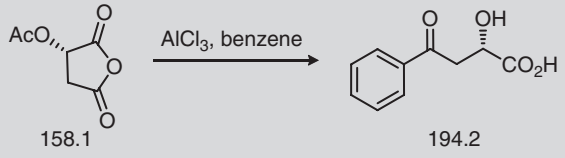
A solution of (*S*)-malic acid (10.0 g, 75.0 mmol) in acetyl chloride (350 ml) is heated to reflux with stirring for 5 h.

The solvent is then removed under reduced pressure and co-evaporated with toluene (2 × 30 ml) to yield (*S*)-α-acetoxybutanedioic anhydride as a light-yellow solid; 11.6 g (98%); mp 50–52 °C; $[\alpha]^{20}_D = -23.1$ ($c = 5.0$, $CHCl_3$); TLC (SiO_2, $CHCl_3$/MeOH/H_2O/AcOH = 50 : 50 : 3 : 0.3): $R_f = 0.88$.

UV (MeOH): λ_{max} (nm) = 209.
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3012, 2962, 1806, 1743, 1405, 1375, 1293, 1216, 1099, 1032, 966, 917, 722, 663, 572.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.51 (dd, J = 9.6, 6.3 Hz, 1H, CH), 3.36 (dd, J = 19.0, 9.4 Hz, 1H, CH_2), 3.01 (dd, J = 19.0, 6.3 Hz, 1H, CH_2), 2.18 (s, 3H, CH_3).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.5, 169.9, 169.5, 137.1, 68.4, 37.7.

1.4.2.2 * (*S*)-2-Hydroxy-4-oxo-4-phenylbutanoic acid [7]



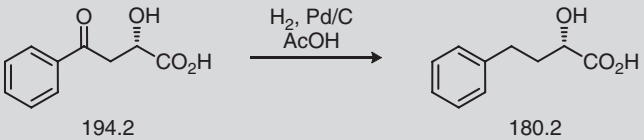
158.1 194.2

Anhydrous $AlCl_3$ (30.0 g, 225 mmol) is added in one portion to a solution of (*S*)-anhydride **1.4.2.1** (9.50 g, 60.1 mmol) in anhydrous benzene (100 ml; Caution: carcinogenic!) at 0 °C. The mixture is heated under reflux with vigorous stirring for 4 h.

It is then poured onto a mixture of crushed ice (100 g) and acidified with aqueous HCl (1 N, ~100 ml) to give a solution of pH ~ 1. The mixture is stirred for 2 h and extracted with EtOAc (3 × 100 ml). The combined organic phases are washed with brine, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The crude product is crystallized from EtOAc by the addition of petroleum ether to yield the (*S*)-2-hydroxy acid as a colorless powder; 8.4 g (72%); mp 136–138 °C; $[\alpha]^{20}_D = -8.75$ (c = 4.0, EtOH); TLC (SiO_2; $CHCl_3$/MeOH/H_2O/AcOH = 70 : 30 : 3 : 0.3): R_f = 0.58.

UV (CH_3OH): λ_{max} (nm) = 278, 241, 201.
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3476, 3083, 3061, 2928, 1734, 1677, 1595, 1451, 1364, 1222, 1194, 1105, 811, 761, 689, 580.
^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 12.0 (s_{br}, 1H, CO_2H), 7.95 (d, J = 7.2 Hz, 2H, Ar–H), 7.64 (dd, J = 7.5, 7.2 Hz, 1H, Ar–H), 7.53 (t, J = 7.5 Hz, 2H, Ar–H), 5.50 (s_{br}, 1H, OH), 4.50 (t, J = 6.0 Hz, 1H, CH), 3.32 (d, J = 6.0 Hz, 2H, CH_2).
^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 197.4, 174.8, 136.7, 128.5, 127.9, 66.6, 42.6.

1.4.2.3 ** (*S*)-2-Hydroxy-4-phenylbutanoic acid [3]



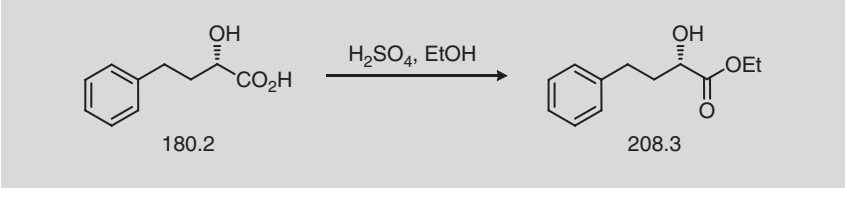
194.2 180.2

A solution of the hydroxy acid **1.4.2.2** (5.4 g, 0.028 mol) in AcOH (80 ml) is hydrogenated (1 bar) over 10% palladium on carbon (0.7 g) at room temperature for ~2 days.

After complete conversion, indicated by TLC, the solution is filtered and the solvent is removed *in vacuo*. The crude product is recrystallized from toluene to give (*S*)-2-hydroxy-4-phenylbutanoic acid as a colorless powder; 4.40 g (87%); mp 65–67 °C; $[\alpha]^{20}_D = +13.4$ ($c = 2.5$, EtOH); TLC (SiO_2; $CHCl_3$/MeOH/H_2O/AcOH = 70 : 30 : 3 : 0.3): $R_f = 0.65$.

UV (CH_3OH): λ_{max} (nm) = 267, 258, 242, 207.
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3461, 3027, 2957, 2926, 2861, 2589, 1733, 1497, 1454, 1290, 1270, 1242, 1175, 1097, 1077, 866, 767, 742, 696.
^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.27 (m, 2H, Ar–H), 7.17 (m, 3H, Ar–H), 3.93 (dd, J = 8.1, 4.5 Hz, 1H, CH), 2.67 (t, J = 7.8 Hz, 2H, CH_2), 1.86–1.99 (m, 1H, CH_2), 1.74–1.85 (m, 1H, CH_2).
^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 175.5, 141.5, 128.3 (2 Ar–C), 126.0, 69.0, 35.7, 30.6.

1.4.2.4 * **Ethyl (*S*)-2-hydroxy-4-phenylbutanoate** [3]

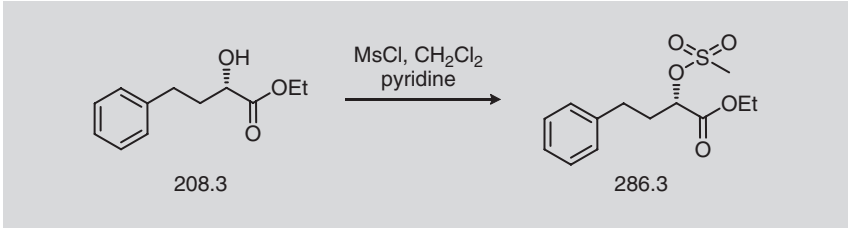


Concentrated H_2SO_4 (2 ml) is added to a solution of the hydroxy acid **1.4.2.3** (3.06 g, 0.017 mol) in anhydrous EtOH (200 ml). The mixture is heated under reflux with stirring for 2 h (TLC control).

The solvent is removed *in vacuo*, and a mixture of H_2O (50 ml) and EtOAc (200 ml) is added. The organic phase is separated, washed with saturated aqueous $NaHCO_3$ (80 ml) and brine (90 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* to provide the ester as a light-yellow oil; 3.36 g (95%); $[\alpha]^{20}_D = +19.8$ ($c = 2.5$, $CHCl_3$); TLC (SiO_2; $CHCl_3$, 0.1% AcOH): $R_f = 0.67$.

UV (CH_3OH): λ_{max} (nm) = 267, 247, 205.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.33–7.15 (m, 5H, Ar–H), 4.23–4.16 (m, 2H, $C\underline{H}_2$-CH_3, 1H, CH), 2.94 (s_{br}, 1H, OH), 2.84–2.69 (m, 2H, Ph–$C\underline{H}_2$–CH_2), 2.17–2.06 (m, 2H, Ph–CH_2–$C\underline{H}_2$), 2.01–1.88 (m, 2H, Ph–CH_2–$C\underline{H}_2$), 1.27 (t, J = 7.1 Hz, 3H, CH_3).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 175.1, 141.1, 128.5, 128.3, 125.9, 69.6, 61.6, 35.9, 30.9, 14.1.

1.4.2.5 * **Ethyl (*S*)-2-methanesulfonyloxy-4-phenylbutanoate** [3]



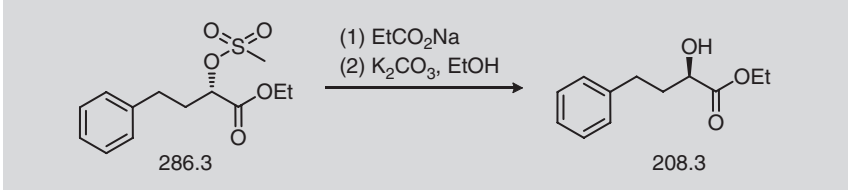
208.3 286.3

Methanesulfonyl chloride (3 ml) is added dropwise to a solution of the hydroxy ester **1.4.2.4** (3.13 g, 0.015 mol) in anhydrous CH_2Cl_2 (10 ml) and anhydrous pyridine (10 ml) at 0 °C. The resulting mixture is stirred at room temperature overnight.

The reaction mixture is then diluted with EtOAc (200 ml), the resulting solution is washed with ice-cold H_2O (3 × 200 ml), ice-cold 2 M aqueous HCl (200 ml), saturated aqueous $NaHCO_3$ (200 ml), and brine (200 ml), then dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* to give the mesylated hydroxy ester as a light-yellow oil; 4.21 g (98%), TLC (SiO_2; $CHCl_3$/MeOH/H_2O/AcOH = 50 : 50 : 3 : 0.3): $R_f = 0.88$.

UV (CH_3OH): λ_{max} (nm) = 267, 242, 202.
IR (film): $\tilde{\nu}$ (cm^{-1}) = 3062, 3029, 2983, 2939, 2869, 1751, 1497, 1455, 1362, 1300, 1252, 1211, 1174, 1039, 964, 864, 844, 820, 747, 701.
^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.30 (m, 2H, Ar–H), 7.18–7.24 (m, 3H, Ar–H), 5.08 (dd, J = 7.5, 5.1 Hz, 1H, CH), 4.17 (q, J = 7.2 Hz, 2H, CH_2CH_3), 3.27 (s, 3H, SCH_3), 2.71 (t, J = 7.5 Hz, 2H, CH_2), 2.07–2.17 (m, 2H, CH_2), 1.21 (t, J = 7.2 Hz, 3H, CH_3).
^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 168.5, 140.1, 128.3, 128.1, 126.1, 76.8, 61.34, 37.9, 33.2, 30.0, 13.8.

1.4.2.6 ** **Ethyl (*R*)-2-hydroxy-4-phenylbutanoate (*ent*-1)** [3]



286.3 208.3

Sodium propionate (4.57 g, 0.016 mol) is added to a solution of the mesylated hydroxy ester **1.4.2.5** (3.92 g, 0.013 mol) in EtOH (130 ml). The resulting mixture is heated under reflux with stirring for 48 h.

The reaction mixture is then cooled to room temperature and filtered; the filtrate is concentrated under reduced pressure. The residue is dissolved in EtOAc (100 ml), and the resulting solution is washed twice with brine, dried over anhydrous Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue (crude diester **11**) is dissolved in EtOH (250 ml), K_2CO_3 (5.88 g, 0.043 mol) is added, and the resulting mixture is stirred at room temperature overnight.

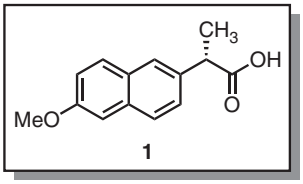
It is then filtered, and the filtrate is neutralized with aqueous HCl (6 M) and concentrated *in vacuo*. The product is dissolved in EtOAc (150 ml) and washed with H_2O (50 ml), and brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent is removed *in vacuo* to give the alcohol as an colorless oil; 1.92 g (71%), TLC (SiO_2; $CHCl_3$, 0.1% AcOH): $R_f = 0.67$, $[\alpha]^{20}_D = -18.8$ ($c = 2.4$ in $CHCl_3$).

UV (CH_3OH): λ_{max} (nm) = 267, 258, 242, 205.
IR (film): $\tilde{\nu}$ (cm^{-1}) = 3429, 3063, 3028, 2980, 2961, 2930, 2865, 1732, 1497, 1454, 1370, 1299, 1247, 1178, 1077, 864, 747, 701.
^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.28 (m, 2H, Ar–H), 7.14–7.20 (m, 3H, Ar–H), 5.41 (s_{br}, 1H, OH), 4.08 (q, $J = 7.4$ Hz, 2H, $C\underline{H_2}CH_3$), 4.00 (m_{br}, 1H, CH), 2.66 (t, $J = 8.1$ Hz, 2H, CH_2), 1.77–1.86 (m, 1H, $C\overline{H}_2$), 1.18 (t, $J = 7.4$ Hz, 3H, CH_3).
^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 174.0, 141.5, 128.3, 128.2, 126.8, 68.9, 59.7, 35.7, 30.6, 13.7.

References

1. For monographs, see: (a) Procter, G. (1999) *Asymmetric Synthesis*, Oxford University Press, Oxford; (b) Atkinson, R.S. (1997) *Stereoselective Synthesis*, John Wiley & Sons, Inc., New York; (c) Christmann, M. and Bräse, S. (eds) (2007) *Asymmetric Synthesis – The Essentials*, Wiley-VCH Verlag GmbH, Weinheim.
2. (a) For a monograph, see: Hanessian, S. (1983) *The Chiron Approach*, Pergamon Press, New York; (b) for chiral pool reagents ("chirons"), see: Fuhrhop, J.-H. and Li, G. (2003) *Organic Synthesis*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim; (c) for a compilation of commercially available enantiopure products, see: Breuer, M., Ditrich, K., Habicher, T., Hauer, B., Keßeler, M., Stürmer, R., and Zelinsky, T. (2004) *Angew. Chem.*, **116**, 806–843; *Angew. Chem. Int. Ed.*, (2004), **43**, 788–824.
3. Lin, W.-Q., He, Z., Jing, Y., Cui, X., Liu, H., and Mi, A.-Q. (2001) *Tetrahedron: Asymmetry*, **12**, 1583–1588.
4. Conventional retrosynthesis of the α-hydroxy acid **2** leads to hydrocinnammic aldehyde by retro-cyanohydrin transformation. For the problem of asymmetric cyanohydrin synthesis, see: Brunel, J.-M. and Holmes, I.P. (2004) *Angew. Chem.*, **116**, 2807–2810; *Angew. Chem. Int. Ed.*, (2004), **43**, 2752–2778.
5. Compound **9** has also been prepared by chemo and enantioselective enzymatic reduction of 4-phenyl-2,4-dioxobutanoic acid: Casy, G. (1992) *Tetrahedron Lett.*, **33**, 8159–8162.
6. Mitsunobu, O. (1981) *Synthesis*, 1–28.
7. Henrot, S., Larcheveque, M., and Petit, Y. (1986) *Synth. Commun.*, **16**, 183–190.

1.4.3
Naproxen



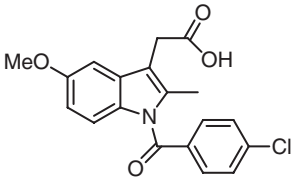
1

Topics:

- Enantioselective synthesis of a drug
- Friedel–Crafts acylation
- Chemoselective α-halogenation of an alkyl aryl ketone
- Acetalization using an orthoester
- Lewis acid-induced rearrangement of an α-halogeno acetal
- Kinetic resolution by enantioselective enzymatic ester hydrolysis
- Resolution by formation of diastereomeric salts

(a) **General**

Naproxen (**1**, (*S*)-(+)-2-(6′-methoxy-2-naphthyl)propionic acid) is a prominent member of the drugs derived from aryl- and hetaryl-substituted acetic and propionic acids, which exhibit anti-inflammatory, analgetic, and antirheumatic properties [1]. Other important examples are indomethacin (**2**), diclofenac (**3**), ibuprofen (**4**), and tiaprofenic acid (**5**).



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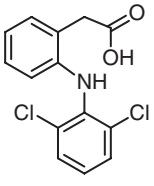
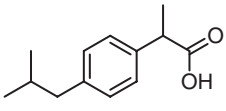


3

Derivatives of acetic acid



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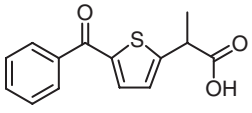


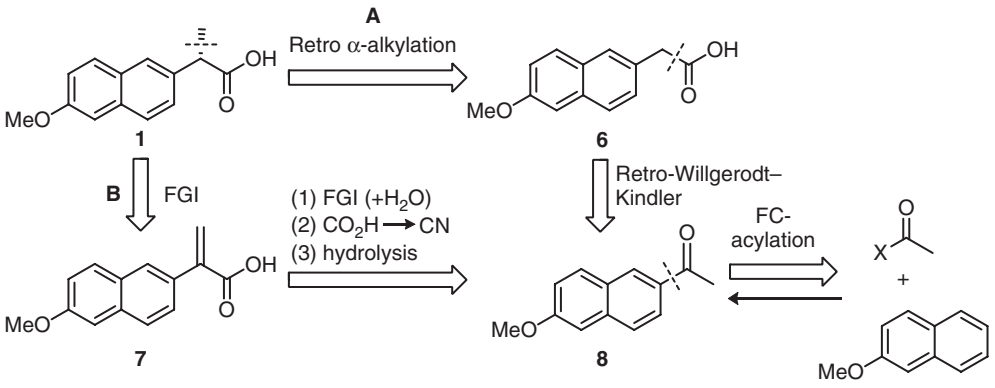
5

Derivatives of α-substituted propionic acid

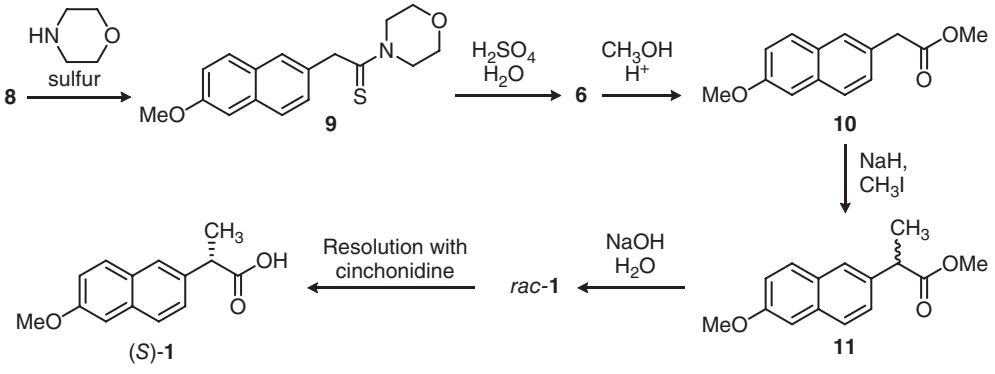
These nonsteroidal anti-inflammatory compounds act as effective inhibitors of prostaglandin biosynthesis [2].

The α-aryl and α-hetaryl propionic acids (e.g., **4** and **5**) are used therapeutically as racemic mixtures. An exception is naproxen, which is marketed and applied as the (+)-(*S*)-enantiomer.

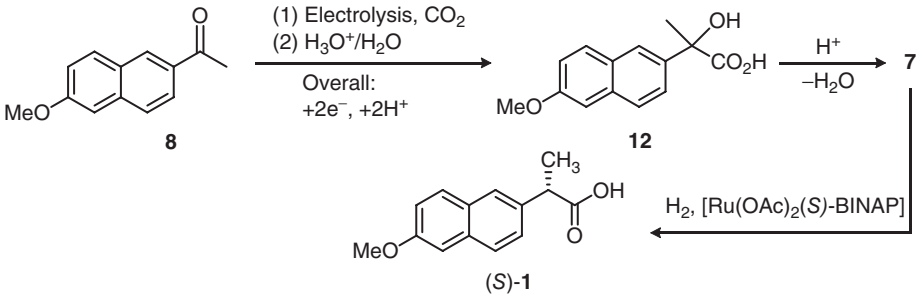
The retrosynthesis of **1** according to pathway **A** leads to 2-methoxynaphthalene via **6** and **8**. Similarly, according to pathway **B**, **1** can be traced back to **7**, which again would be accessible from 2-methoxynaphthalene via **8**. Selective formation of the stereogenic center in **1** could be achieved either by a facially selective alkylation of **6** using the Evans procedure or by enantioselective hydrogenation of **7**. Compounds **6** and **7** should be easily accessible from **8** by classical routes, such as Willgerodt–Kindler or Tl(III)-induced redox transformations (→**6**) or a cyanohydrin reaction/CN → CO_2H hydrolysis/H_2O elimination sequence (→**7**).



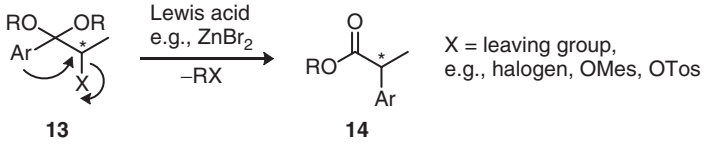
In fact, the first industrial synthesis of naproxen (Syntex) [3] used a Willgerodt–Kindler reaction of 2-acetyl-6-methoxynaphthalene (**8**) to give the morpholide **9**; subsequent hydrolysis led to the arylacetic acid **6**. Its methyl ester **10** was alkylated with CH_3I/NaH (**10** → **11**); saponification of the alkylated ester **11** provided the racemic acid (*rac*-**1**), which was resolved using cinchonidine or other chiral bases to give (*S*)-naproxen (**1**).



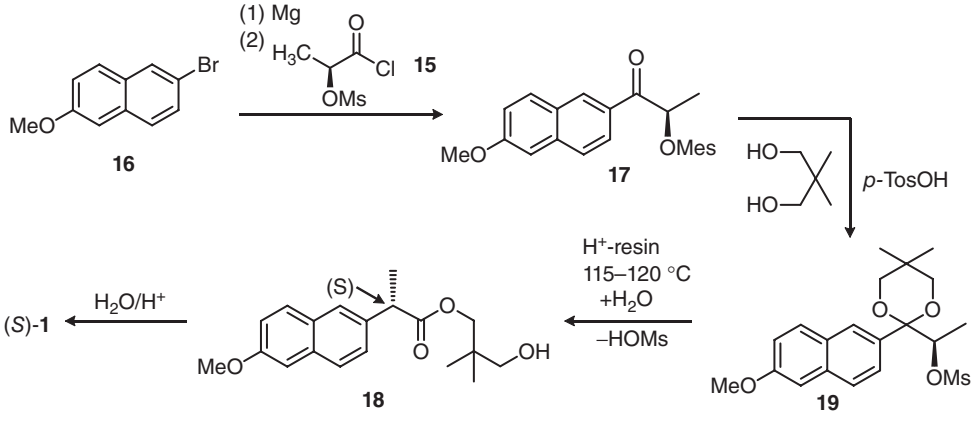
According to the retrosynthetic analysis, (β-naphthyl)acrylic acid **7** is a suitable substrate for the enantioselective formation of **1**, which is readily formed from **7** by homogeneous catalytic hydrogenation in the presence of a chiral Ru complex (Ru(II)-(*S*)-BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthalene)) [4]. The acrylic acid **7** may be obtained from 2-acetyl-6-methoxynaphthalene (**8**) via the already mentioned cyanohydrin route or more elegantly by an electrocarboxylation. Thus, $2e^-$ cathodic reduction of the carbonyl group in **8** in the presence of CO_2 gives the hydroxy acid **12**, whose subsequent acid-catalyzed dehydration leads to **7** [5].



In a strategy that differs from the above retroanalytical considerations, the α-arylpropionate side chain in **1** can also be established by Lewis acid-induced 1,2-migration of the aryl moiety in aryl ethyl ketals **13** bearing a leaving group at C-2. The reaction leads to esters **14** [6]:



If the leaving group X in **13** assumes a stereodefined position, the 1,2-aryl shift proceeds with preservation of the stereochemical information. This was accomplished in an ECP synthesis of naproxen (**1**) starting with the acid chloride **15** of (*S*)-*O*-mesyl lactic acid [3]:



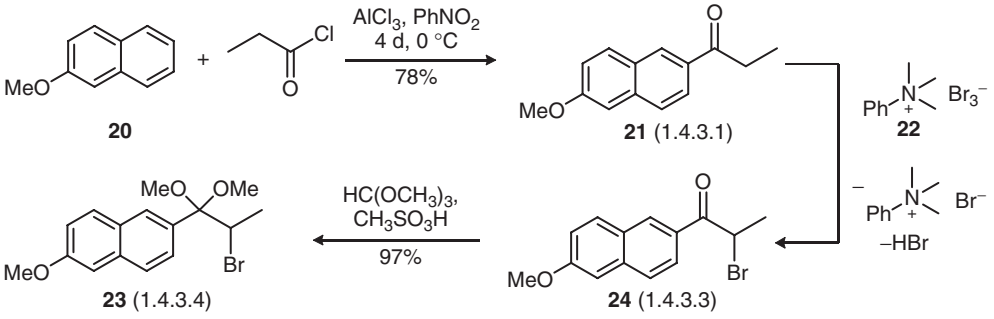
In the first step, the Grignard compound from 2-bromo-6-methoxynaphthalene (**16**) is acylated with the acid chloride **15** to give the naphthyl ketone **17**, the C=O group of which is protected as a 1,3-dioxane with the formation of **19**. On treatment with an acidic ion-exchange resin, the *O*-mesyl acetal moiety in **19** rearranges to give the ester **18**, acid hydrolysis of which provides (*S*)-naproxen (**1**) in

enantiomerically pure form and in 75% overall yield. Remarkably, in the rearrangement step **19** → **18**, migration of the β-naphthyl residue occurs stereoselectively with complete inversion of configuration at the propionate side chain [7].

For reasons of practicability in the laboratory, a synthesis is presented here that is based on the Lewis acid-promoted rearrangement of an α-bromo ketal to a racemic naproxen ester. This racemic ester is transformed to the chiral target molecule (i) by enantioselective enzymatic hydrolysis, and (ii) by saponification to give the racemic acid and its resolution by cinchonidine salt formation.

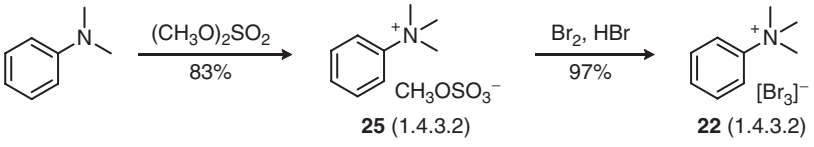
(b) **Synthesis of 1**

The synthesis starts with Friedel–Crafts acylation of 2-methoxynaphthalene (**20**) with propionyl chloride in the presence of $AlCl_3$. The reaction conditions (nitrobenzene as solvent, 4 days at 0 °C) favor thermodynamic product control in the S_EAr process and direct substitution at the desired β-(2)-position (**20** → **21**) [8]:



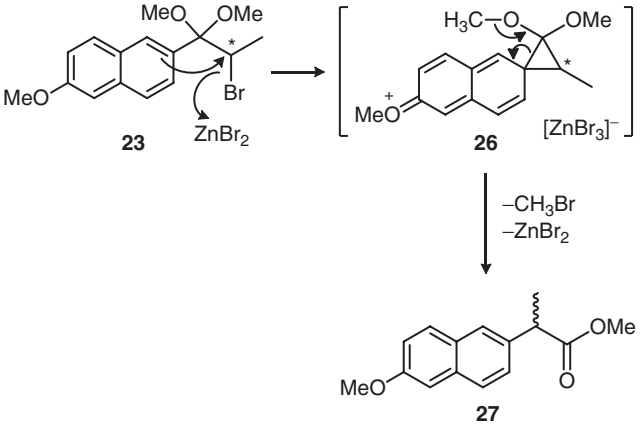
Next, 6-methoxy-2-propionylnaphthalene (**21**) has to be brominated chemoselectively at the aliphatic side chain. Since treatment with elemental bromine would lead to additional bromination at the 5-position of the aromatic nucleus [9], trimethylphenylammonium perbromide (**22**) is used as a specific reagent, which leads exclusively to the α-bromo ketone **24** [10].

The perbromide **22** is prepared in two steps from *N*,*N*-dimethylaniline via the methanesulfate **25** [11]:

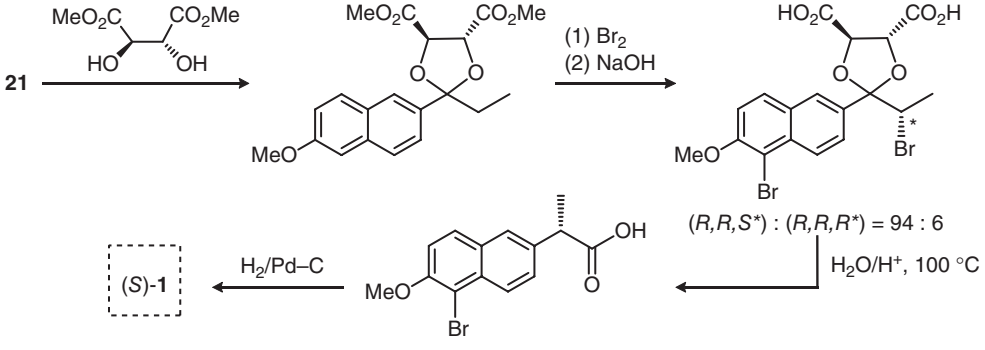


Bromo ketone **24** is transformed to the dimethyl ketal **23** by reaction with trimethyl orthoformate in the presence of CH_3SO_3H. On heating with anhydrous

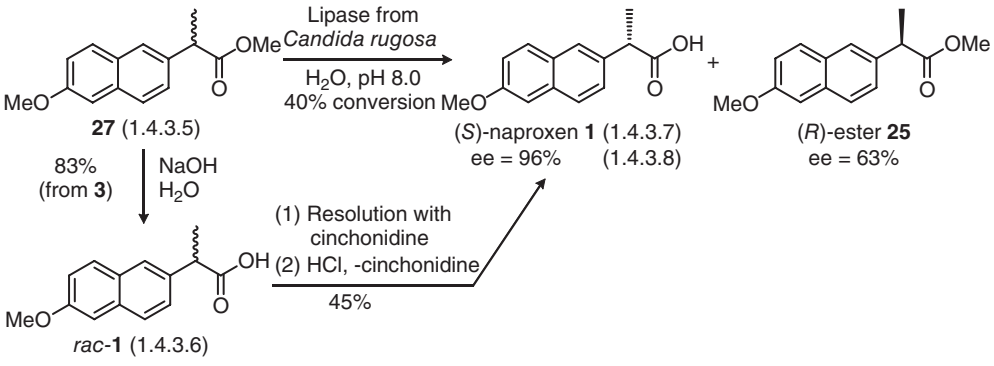
$ZnBr_2$ in toluene, the α-bromo acetal **23** rearranges to the methyl ester **27** of racemic naproxen. For the Lewis acid-induced 1,2-aryl shift, an arenium ion **26** [12] can be postulated as intermediate, which rearomatizes upon dealkylation with a bromide ion to give CH_3Br and the methyl ester **27** [10, 13].



It should be noted that the procedure can be slightly modified by first transforming the ketone **21** into its acetal, which is then brominated using bromine. If one uses a chiral alcohol such as dimethyl tartrate for the acetalization, the subsequent bromination and rearrangement proceed with high induced stereoselectivity [14].



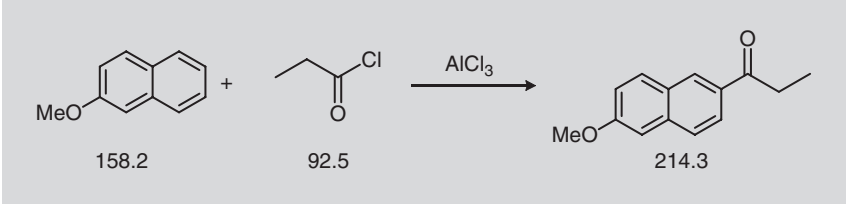
In the final step of the described synthesis of **1**, the racemic methyl ester **27** is subjected to kinetic resolution by enzymatic hydrolytic ester cleavage, using the lipase from *Candida rugosa.* This transformation is conducted up to 40% conversion and gives (*S*)-naproxen (**1**) with 96% ee and the (*R*)-ester with 63% ee [15]:



Alternatively, the racemic methyl ester **27** may be saponified with aqueous NaOH to give racemic naproxen (*rac*-**1**). This is resolved by the formation of diastereomeric salts with the chiral base cinchonidine, which are separated by fractional crystallization. The cinchonidine salt of the (+)-enantiomer is isolated, purified, and cleaved with aqueous HCl to give optically pure (+)-(*S*)-naproxen in 45% yield with $[\alpha]^{20}_{D} = +68$ ($c = 0.84$, CH_2Cl_2); for the isolation of the (−)-(*R*)-enantiomer, see Ref. [16].

(c) Experimental Procedures for the Synthesis of 1

1.4.3.1 * 6-Methoxy-2-propionylnaphthalene [8]



Anhydrous aluminum trichloride (112 g, 0.84 mol) is dissolved in anhydrous nitrobenzene (1300 ml), and the solution is cooled to 0 to −2 °C under an argon atmosphere. With vigorous stirring, a solution of 2-methoxynaphthalene (106 g, 0.67 mol) in anhydrous nitrobenzene (340 ml) is added dropwise over 2 h. After stirring for 1 h at 0 °C, propionyl chloride (71.6 g, 0.77 mol, note) is added at such a rate that the internal temperature is kept at −3 °C. When the addition is complete, the dark reaction mixture is stirred for 96 h at 0 °C.

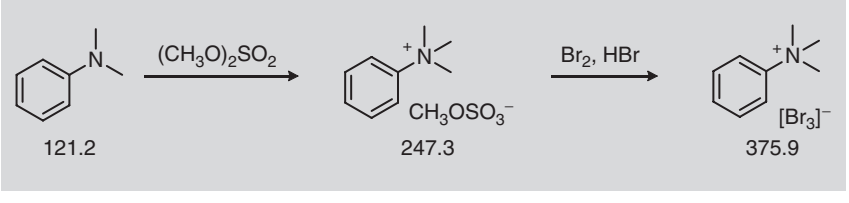
It is then poured onto a mixture of crushed ice (approximately 2 kg) and concentrated HCl (225 ml). CH_2Cl_2 is added to provide a clean phase separation, and the aqueous phase is extracted with CH_2Cl_2 (500 ml). The CH_2Cl_2 is distilled off from the combined organic phases, and the remaining solution is steam-distilled (to remove the nitrobenzene). The solid residue is dissolved in CH_2Cl_2, the solution is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The brownish residue is distilled *in vacuo* ($bp_{0.2}$ 154–156 °C), and the distillation product is

recrystallized from MeOH. The acylation product is obtained as colorless needles; 112 g (78%), mp 111–112 °C, TLC (SiO_2; benzene): $R_f = 0.55$.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1680, 1625, 1600.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.38 (d, J = 3.0 Hz, 1H, Ar–H), 7.99 (dd, J = 9.0, 3.0 Hz, 1H, Ar–H), 7.82 (d, J = 9.0 Hz, 1H, Ar–H), 7.74 (d, J = 9.0 Hz, 1H, Ar–H), 7.17 (d, J = 9.0, 3.0 Hz, 1H, Ar–H), 7.13 (d, J = 3.0 Hz, 1H, Ar–H), 3.92 (s, 3H, OCH_3), 3.05 (q, J = 8.0 Hz, 2H, $COCH_2$), 1.26 (t, J = 8.0 Hz, 3H, CH_3).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 200.1 (C=O), 159.4, 137.4, 131.3, 129.6, 128.1, 127.3, 124.9, 119.9, 55.6 (OCH_3), 31.9 (CH_2), 8.7 (CH_3).
MS (EI): m/z = 214.1 $[M]^+$, 185.0 $[M-C_2H_5]^+$, 158.0 $[M-C_3H_5O]^+$.

Note: It is recommended that the reaction is performed under N_2.

1.4.3.2 * Trimethylphenylammonium perbromide [11]



1) Dimethyl sulfate (63.0 g, 0.50 mol, ~48.0 ml; Caution: carcinogenic!) is added dropwise to a vigorously stirred solution of *N*,*N*-dimethylaniline (63.0 ml, 0.50 mol) in benzene (120 ml; Caution: carcinogenic!) at 5 °C. During the addition, the temperature of the reaction mixture rises to approximately 75 °C. After stirring for 1 h, the mixture is cooled to 3 °C; the crystalline salt is collected by suction filtration, washed with benzene, and air-dried (Hood!). Trimethylphenylammonium methanesulfate is obtained as colorless crystals; 103 g (83%), mp 108–110 °C.

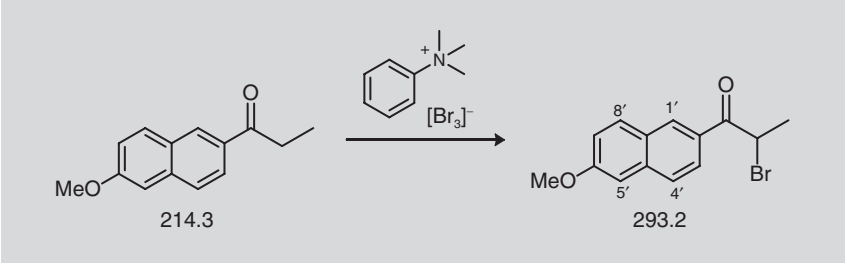
^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.86 (m, 2H, 2-H, 6-H), 7.59 (m, 3H, 3-H, 4-H, 5-H), 3.82 (s, 9H, $^+N(CH_3)_3$), 3.72 (s, 3H, $CH_3OSO_3^-$).

2) The methanesulfate from (1) (80.0 g, 0.32 mol) is dissolved in 24% aqueous HBr (320 ml, 1.41 mol), and bromine (74.9 g, 0.47 mol, ~24.0 ml) is added dropwise with intense stirring over 30 min. The precipitated perbromide is collected by suction filtration and recrystallized from acetic acid; yellow needles, 117 g (97%), mp 113–115 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1600, 1490, 1460, 960.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.96 (m, 2H, 2-H, 6-H), 7.61 (m, 3H, 3-H, 4-H, 5-H), 3.61 (s, 9H, $^+N(CH_3)_3$).
^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 147.1 (C-1), 129.9 (C-3, C-4, C-5), 120.2 (C-2, C-6) 56.3 (CH_3).

1.4.3.3 * 2-Bromo-1-(6-methoxy-2-naphthyl)propan-1-one [9]



The perbromide **1.4.3.2** (75.2 g, 0.20 mol) is added in one portion to a stirred solution of 6-methoxy-2-propionylnaphthalene (**1.4.3.1**) (42.8 g, 0.20 mol) in THF (420 ml). A clear orange-red solution results, from which a colorless salt precipitates (note 1) after some minutes; the supernatant solution becomes colorless. Stirring is continued for 30 min at room temperature.

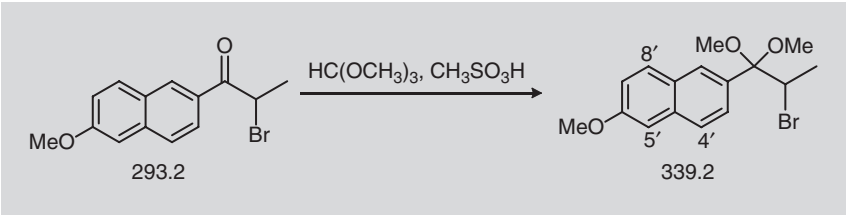
The reaction mixture is diluted with H_2O (1200 ml) and extracted with petroleum ether (2 × 150 ml), and the combined organic extracts are dried over Na_2SO_4 and filtered. The solvent is removed *in vacuo*, and the oily residue is triturated with EtOH (400 ml). The bromo ketone crystallizes in fine colorless needles (note 2), which is collected by suction filtration, washed with pre-cooled EtOH, and dried *in vacuo*; 56.0 g (96%), mp 78–79 °C, TLC (SiO_2; benzene): $R_f = 0.65$.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1685, 1620, 1600.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.46 (d, J = 1.7 Hz, 1H, 1′-H), 8.01 (dd, J = 8.7, 1.9 Hz, 1H, 3′-H), 7.84 (d, J = 9.0 Hz, 1H, 8′-H), 7.76 (d, J = 8.8 Hz, 1H, 4′-H), 7.19 (dd, J = 8.9, 2.5 Hz, 1H, 7′-H), 7.14 (d, J = 2.5 Hz, 1H, 5′-H), 5.42 (q, J = 6.7 Hz, 1H, 2-H), 3.93 (s, 3H, OCH_3), 1.93 (d, J = 6.7 Hz, 3H, 3-H_3).

Notes:

1) Trimethylphenylammonium bromide, mp 210–212 °C.
2) Crystallization is complete after 12 h in a refrigerator.

1.4.3.4 * 2-Bromo-1-(6-methoxy-2-naphthyl)propan-1-one dimethyl acetal [10]

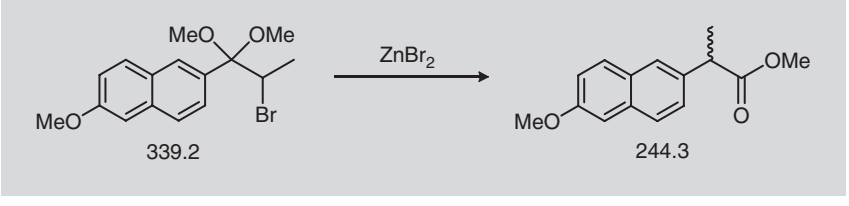


A suspension of the bromo ketone **1.4.3.3** (41.4 g, 0.14 mol), trimethyl orthoformate (43.5 g, 0.41 mol), and methanesulfonic acid (2.72 g) in anhydrous MeOH (150 ml) is heated to 45 °C for 24 h; a clear solution results.

The reaction mixture is then poured into 2% aqueous Na_2CO_3 solution (1000 ml) and is extracted with Et_2O (3 × 250 ml). The combined extracts are dried over Na_2CO_3 and filtered, and the solvent is removed *in vacuo*. The resulting almost colorless oil is dissolved in MeOH (300 ml), and the solution is cooled (refrigerator, 12 h). The crystallized dimethyl acetal is collected by suction filtration, washed with MeOH at −10 °C, and dried *in vacuo*; fine colorless needles, 46.0 g (97%), mp 87–88 °C, TLC (SiO_2; benzene): $R_f = 0.75$.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 2990, 2970, 2940, 2830 (CH), 1630, 1610.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.93 (d, J = 1.8 Hz, 1H, 1′-H), 7.76 (d, J = 9.8 Hz, 1H, 8′-H), 7.69 (d, J = 8.7 Hz, 1H, 4′-H), 7.57 (dd, J = 8.6, 1.8 Hz, 1H, 3′-H), 7.14 (m, 2H, 5′-H, 7′-H), 4.54 (q, J = 6.0 Hz, 1H, 2-H), 3.91, 3.39, 3.23 (3 × s, 9H, 3 × OCH_3), 1.54 (d, J = 6.3 Hz, 3H, 3-H_3).

1.4.3.5 * (*R,S*)-Methyl 2-(6-methoxy-2-naphthyl)propionate [13]



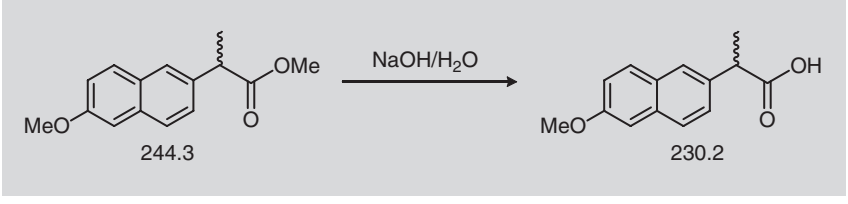
A suspension of the dimethyl acetal **1.4.3.4** (33.9 g, 0.10 mol) and anhydrous zinc bromide (2.25 g, 10.0 mmol) in anhydrous toluene (100 ml) is heated to reflux with stirring under a N_2 atmosphere for 1 h.

After cooling to room temperature, the reaction mixture is poured into H_2O (1000 ml) and extracted with Et_2O (3 × 300 ml). The combined extracts are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*.

For enzymatic resolution, a pure sample of the racemic methyl ester **1.4.3.5** is obtained by column chromatography (SiO_2; *n*-hexane/EtOAc, 85 : 15), mp 89 – 90 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3005, 2974, 2932, 1731, 1602.
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.70 (d, J = 8.5 Hz, 2H, 4′-H, 8′-H), 7.66 (d, J = 1.6 Hz, 1H, 1′-H), 7.40 (dd, J = 8.5, 1.9 Hz, 1H, 3′-H), 7.14 (dd, J = 8.8, 2.5 Hz, 1H, Ar – H), 7.11 (d, J = 2.2 Hz, 1H, Ar – H), 3.90 (s, 3H, $ArOCH_3$), 3.85 (q, J = 7.3 Hz, 1H, 2-H), 3.66 (s, 3H, CO_2CH_3), 1.57 (d, J = 7.3 Hz, 3H, 3-H_3).
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 175.1, 157.7, 135.7, 133.7, 129.3, 129.0, 127.2, 126.2, 126.0, 119.0, 105.7, 55.3, 52.0, 45.4, 18.6.

1.4.3.6 * (*R,S*)-2-(6-Methoxy-2-naphthyl)propionic acid (*rac*-naproxen) [13]



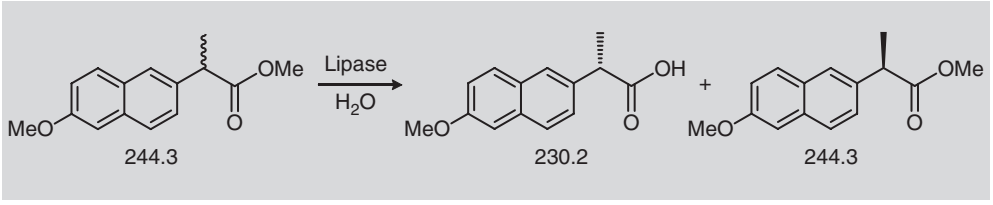
244.3 230.2

The crude methyl ester **1.4.3.5** is dissolved in MeOH (500 ml), 30% aqueous NaOH (150 ml) is added, and the mixture is heated to reflux for 4 h.

The MeOH is distilled off *in vacuo*, the residue is dissolved in H_2O (approximately 1200 ml), and the alkaline solution is extracted with Et_2O (2 × 400 ml). The organic phase is discarded. The aqueous phase is acidified with concentrated HCl (pH ~ 1), and the precipitated acid is extracted with Et_2O (2 × 400 ml). The combined extracts are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The remaining solid is recrystallized from acetic acid, and a second crop is obtained by (careful) dilution of the mother liquor with H_2O. The racemic acid is obtained as fine colorless needles; 19.0 g (83%), mp 152 – 153 °C, TLC (SiO_2; Et_2O): R_f = 0.80.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3200 – 2800, 1710, 1605.
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 10.6 (s_{br}, 1H, CO_2H), 7.75 – 7.65 (m, 3H, 1′-H, 4′-H, 8′-H), 7.40 (dd, J = 8.5, 1.8 Hz, 1H, 3′-H), 7.13 (d, J = 8.8 Hz, 1H, 7′-H), 7.10 (d, J = 2.4 Hz, 1H, 5′-H), 3.90 (s, 3H, OCH_3), 3.86 (q, J = 7.0 Hz, 1H, 2-H), 1.58 (d, J = 7.0 Hz, 3H, 3-H_3).
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 180.5, 157.7, 134.9, 133.8, 129.3, 128.9, 127.2, 126.2, 126.1, 119.0, 105.6, 55.3, 45.2, 18.1.

1.4.3.7 ** **(*S*)-2-(6-Methoxy-2-naphthyl)propionic acid** [(*S*)-**naproxen**]
(by kinetic enzymatic resolution, [15])

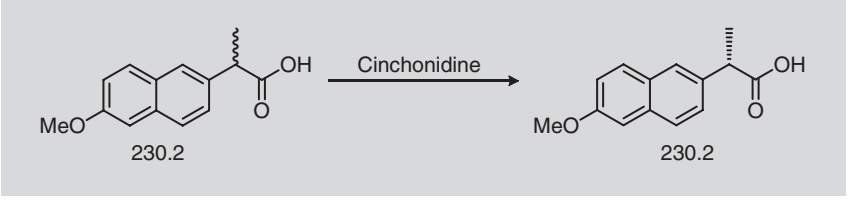


Finely powdered racemic naproxen methyl ester **1.4.3.5** (150 mg, 0.65 mmol), mercaptoethanol (1 drop), and polyvinyl alcohol (5 mg) are added to crude *C. rugosa* lipase (EC 3.1.1.3, Type VII, Sigma L-1754, 50 mg, 600 µg of protein) in a 0.2 M phosphate buffer solution at pH 8.0 (1 ml). The suspension is stirred at 30 °C for 120 h. Both the progress of the conversion and the enantiomeric purity can be monitored simultaneously by HPLC analysis (chiral HPLC Lichro Cart 250-4 (*S*,*S*)-Whelk-01, 5 µm; hexane/isopropanol/acetic acid, 90 : 9.5 : 0.5, 1.2 ml min^{-1}, 254 nm).

The pH of the reaction mixture is adjusted to 2–3 with concentrated HCl, and the mixture is extracted with Et_2O (5 × 10 ml). The combined ethereal extracts are extracted with saturated aqueous Na_2CO_3 solution (5 × 10 ml), and the combined aqueous layers are re-extracted with Et_2O (3 × 10 ml). The combined ethereal extracts are washed with brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo* to give the unreacted naproxen methyl ester as a white solid.

The Na_2CO_3 extracts are acidified with aqueous HCl (6 N), saturated with NaCl, and extracted with Et_2O (5 × 10 ml). The ethereal phase is washed with brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo* to give (*S*)-naproxen as a white solid; 53 mg (35% isolated yield); $[\alpha]^{20}_D = +65$ ($c = 1.00$, $CHCl_3$); ee = 96% [15].

1.4.3.8 ** **(*S*)-2-(6-Methoxy-2-naphthyl)propionic acid** [(*S*)-**naproxen**]
(by resolution with cinchonidine, [16])



Racemic naproxen **1.4.3.6** (11.5 g, 50.0 mmol) is dissolved in a hot mixture of MeOH (200 ml) and acetone (50 ml). A warm solution of cinchonidine (15.0 g, 51.0 mmol) in MeOH (150 ml)/acetone (100 ml) is added, and the mixture is allowed to cool and crystallize over 12 h. The precipitate is filtered off and

recrystallized twice from MeOH (350 ml)/acetone (150 ml), allowing a 12 h crystallization time; cinchonidine salt of (*S*)-naproxen, mp 178–179 °C.

The salt is suspended in benzene (160 ml; Caution: carcinogenic!)/6.5 N aqueous HCl (160 ml), and the stirred mixture is heated at 30–40 °C until two clear phases are formed (approximately 30 min). The organic layer is separated, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is recrystallized from acetone/petroleum ether (40–65 °C); yield 2.60 g (45%) of (*S*)-naproxen, colorless needles, mp 156–157 °C, $[\alpha]^{20}_D = +68$ ($c = 0.84$, $CHCl_3$).

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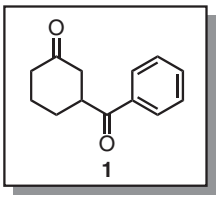
1.4.4

3-Benzoylcyclohexanone



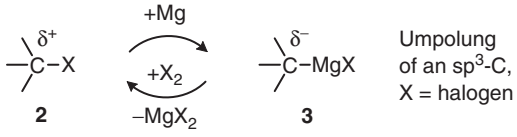
1

Topics:

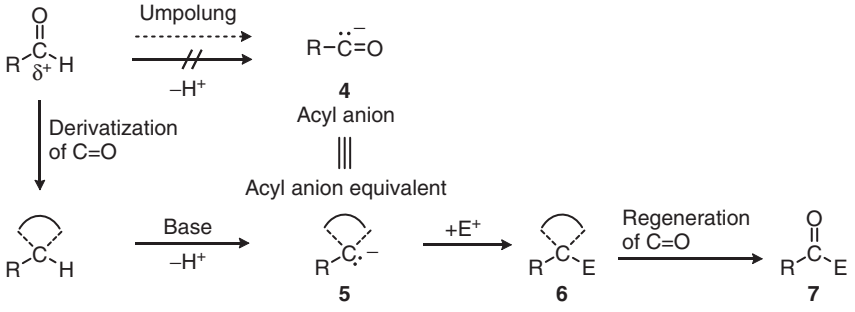
- (*O*-Trimethylsilyl)cyanohydrin anions as acyl anion equivalents, umpolung of carbonyl groups, nucleophilic acylation according to the Hünig methodology
- Formation of an (*O*-trimethylsilyl) cyanohydrin
- 1,4-Addition of an α-metallated (*O*-trimethylsilyl) cyanohydrin to an enone

(a) General

The concept of "umpolung" [1] has been developed on the basis of reactions in which the polarity of an atom (mainly carbon) in a functional group is reversed through chemical transformation. A simple example is provided by the formation of a Grignard compound from a halide R–X through insertion of Mg into the C–X bond (**2** → **3**). Another example is the reaction of a Grignard compound with an elemental halogen (**3** → **2**). In these two processes, an sp^3 C atom changes its polarity from δ^+ to δ^-, and vice versa:



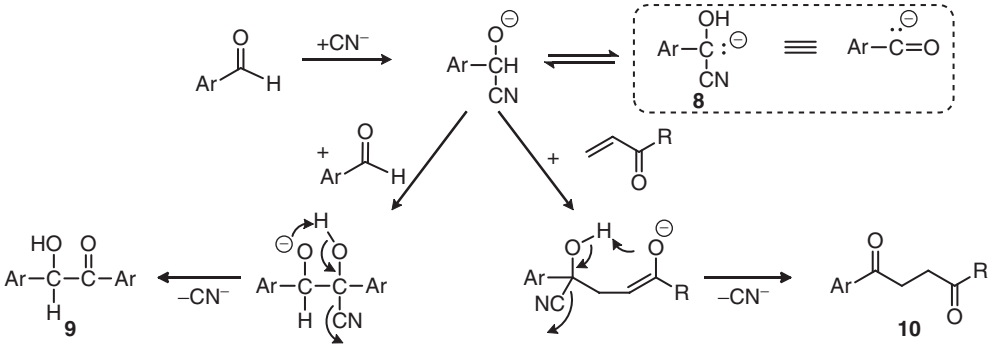
Attractive for synthesis are umpolung reactions at the carbonyl group of aldehydes, in which the polarity of the electrophilic carbon atom of the C=O group is switched to that of an acyl anion **4**:



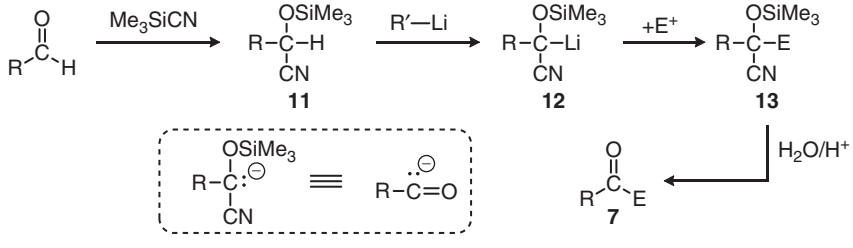
Direct deprotonation at the aldehyde CH=O group is not possible because the pK_a of the hydrogen is about 54. However, by derivatization of the C=O group, the acidity of the C–H can be increased to allow the generation of a carbanion **5** as an equivalent of the acyl anion **4**, which is capable of reacting with electrophiles (simplified as E^+, **5** → **6**). Regeneration of the carbonyl group (**6** → **7**) affords a product

of type **7** resulting from combination of E^+ with an aldehyde; thus, the process represents a (formal) nucleophilic acylation of an electrophilic system, as illustrated by the following examples.

1) The acyl anion equivalent **8** formed by the addition of cyanide to the carbonyl group of aryl aldehydes is the central intermediate in the combination of two aryl aldehydes to give benzoins **9** (benzoin reaction [2]) or the 1,4-addition of aryl aldehydes to α,β-unsaturated ketones to give 1,4-diones **10** (Stetter reaction [3]), both of which are catalyzed by cyanide:

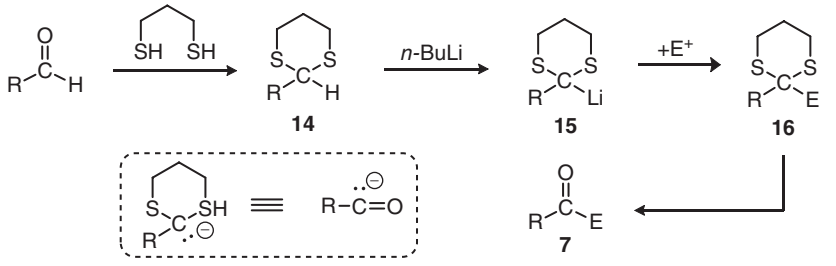


2) Similar acyl anion equivalents are represented by the α-lithiated *O*-silylcyanohydrins **12**, which result from metalation of *O*-silylcyanohydrins **11** (accessible by addition of trimethylsilyl cyanide to aldehydes) with R–Li (Hünig procedure for nucleophilic acylation [4]). Their reactions with electrophilic systems – for example, alkylation, addition to aldehydes or ketones, 1,4-addition to enones – lead to **13**, which can easily be transformed into products of type **7** by subsequent desilylation and loss of HCN, as exemplified in Section (b):



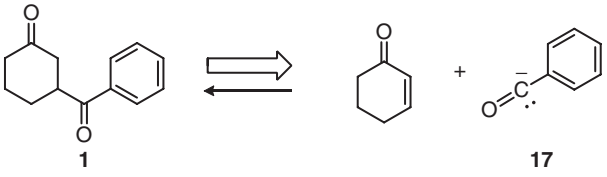
3) 2-Substituted 1,3-dithianes **14** (cyclic dithioacetals, accessible from aldehydes and propane-1,3-dithiol) can be deprotonated with *n*-BuLi to give 2-lithio-1,3-dithianes **15**, which also represent acyl anion equivalents (Corey–Seebach procedure for nucleophilic acylation [5]). As expected, the lithiodithianes **15** are again susceptible to reactions with electrophilic systems: for example, alkylation, addition to aldehydes or ketones, conjugate addition to enones, ring-opening addition to oxiranes. In the products

16 thus formed, the carbonyl moiety can be regenerated (**16** → **7**) by dethioacetalization, which is preferably carried out by means of an oxidative procedure:



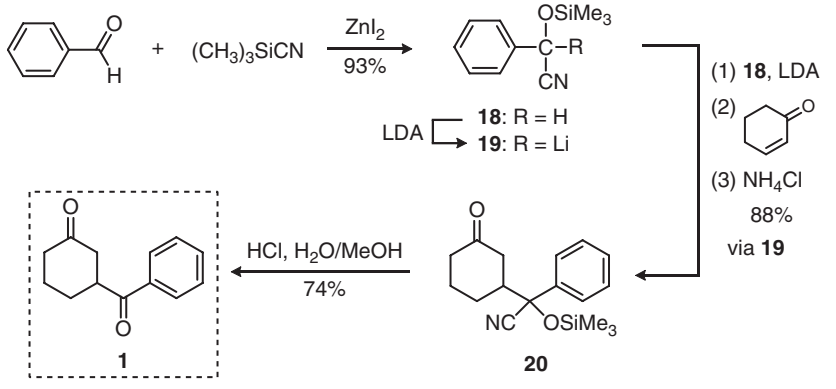
Since 1,3-dithiane chemistry often suffers from the disadvantages of unpleasant odor produced by the sulfur compounds involved and problems in cleaving the thioacetal moiety, the Hünig protocol is often preferred for nucleophilic acylations.

As the result of a simple retrosynthetic analysis, the target molecule **1** should be accessible from cyclohexenone by 1,4-addition of a benzoyl carbanion (**17**) or an equivalent thereof.



(b) **Synthesis of 1**

The requisite *O*-trimethylsilylated cyanohydrin **18** is prepared by Lewis acid-catalyzed addition (ZnI_2) of trimethylsilyl cyanide to benzaldehyde [6, 7]:



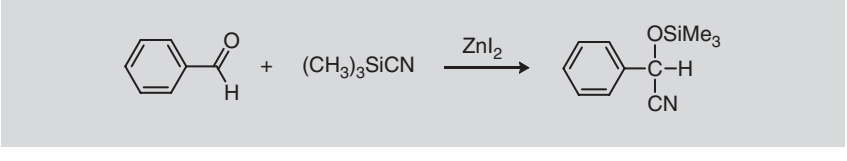
Compound **18** is then subjected to metalation with LDA in THF at −78 °C to give the lithiated cyanohydrin **19**, which is reacted *in situ* with cyclohexenone at −78 to −20 °C. 1,4-Addition of the benzoyl anion equivalent **19** to the enone occurs smoothly, leading to the product **20** after work-up with aqueous NH_4Cl solution.

On hydrolysis with a strong acid (HCl in H_2O/methanol), the cyanohydrin *O*-silyl ether functionality in **20** is cleaved with loss of cyanide to yield the 3-benzoylcyclohexanone (**1**).

Thus, the target molecule **1** is obtained in a three-step sequence in an overall yield of 61% (based on benzaldehyde).

(c) Experimental Procedures for the Synthesis of 1

1.4.4.1 *** Phenyl(trimethylsilyloxy)acetonitrile [8]



Under nitrogen and with exclusion of moisture, benzaldehyde (7.64 g, 72.0 mmol, note 1) is added dropwise over a period of 20 min to trimethylsilyl cyanide (7.94 g, 80.0 mmol, note 2) and a few milligrams of anhydrous zinc iodide (note 3) with stirring. The solution is then heated to 80–100 °C for 2 h; the progress of the reaction may be followed by IR.

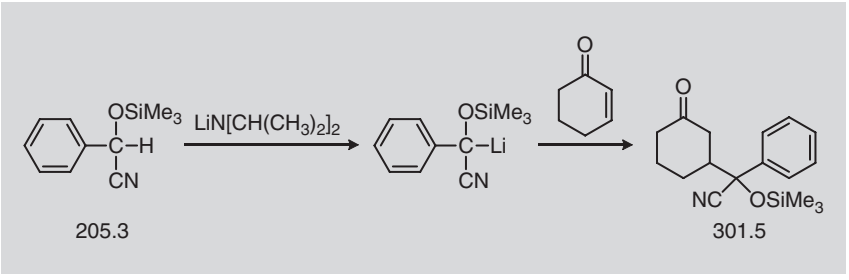
The product is isolated by fractionating distillation *in vacuo* and is obtained as a colorless oil; 13.7 g (93%), bp_1 62–63 °C, $n^{20}{}_D = 1.4840$ (note 4).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3070, 3040, 1260, 875, 850, 750.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.40–7.24 (m, 5H, Ph–H), 5.48 (s, 1H, C–H), 0.21 (s, 9H, $Si(CH_3)_3$).

Notes:

1) Benzaldehyde has to be freshly distilled, bp_{10} 62–63 °C.
2) Trimethylsilyl cyanide has to be distilled prior to use, bp 118–119 °C. *nicht kursiv* $(CH_3)_3SiCN$ is a toxic compound!
3) ZnI_2 should be dried *in vacuo* at 100 °C for 5 h before use.
4) The cyanohydrin is easily hydrolyzed to give HCN. Caution: Hood!

1.4.4.2 *** (3-Oxocyclohexyl)phenyl(trimethylsilyloxy)acetonitrile [9]



205.3 301.5

n-Butyllithium (1.6 M in *n*-hexane, 19.4 ml, 31.0 mmol) is added to a stirred solution of diisopropylamine (3.12 g, 31.0 mmol, note 1) in anhydrous THF (20 ml) at −78 °C under nitrogen and with exclusion of moisture, and the mixture is stirred for 15 min. The silylated cyanohydrin **1.4.4.1** (6.15 g, 30.0 mmol) is added dropwise at the same temperature, which leads to the deposition of a yellow precipitate. Finally, 2-cyclohexen-1-one (2.88 g, 30.0 mmol, note 2) is added dropwise, and the temperature of the reaction mixture is slowly increased to −20 °C over a period of 4 h (note 3).

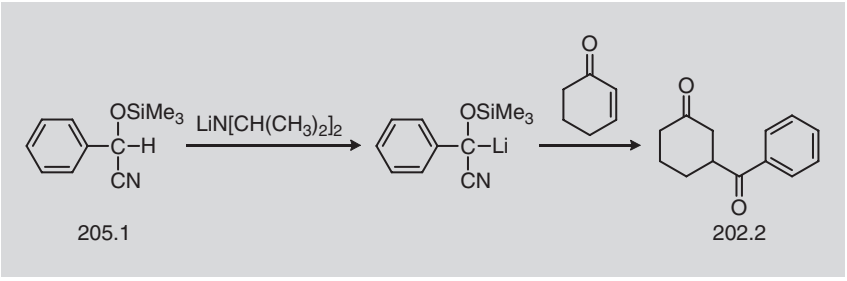
Saturated aqueous NH_4Cl solution (30 ml) is added, and the mixture is stirred for 3 min at room temperature. It is then extracted with Et_2O (3 × 30 ml), and the combined organic extracts are washed with saturated aqueous NH_4Cl (30 ml) solution and brine (30 ml), dried over Na_2SO_4, and filtered. The solvents are removed *in vacuo*, and the residue is distilled *in vacuo* in a Kugelrohr apparatus to give the product as a colorless liquid; 8.00 g (88%), $bp_{0.05}$ 140 °C (oven temperature 145 °C), $n^{20}_D = 1.5125$ (note 4).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3080, 3060, 3030, 2960, 2900, 2870, 1720, 1260.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.41–7.21 (m, 5H, Ph–H), 2.65–1.25 (m, 9H, c-hexane-H), 0.12 (s, 9H, $(CH_3)_3Si$).

Notes:

1) Diisopropylamine is distilled from CaH_2 before use, bp 84–85 °C.
2) Cyclohexenone is distilled before use, bp 168–169 °C.
3) For the preparation of 3-benzoylcyclohexanone, hydrolysis of the reaction mixture is conducted with HCl in H_2O/CH_3OH as described in the preparation of **1.4.4.3**.
4) The product is easily hydrolyzed forming HCN. Caution: Hood!

1.4.4.3 *** 3-Benzoylcyclohexanone [9]



205.1 202.2

Aqueous HCl (2 N, 30 ml) and MeOH (15 ml) are added to the reaction mixture (cf. **1.4.4.2**) and stirring is continued for 14 h at room temperature (note).

The mixture is then diluted with water (approximately 100 ml) and extracted with Et_2O (3 × 50 ml). The combined ethereal extracts are washed with aqueous NaOH (1 M, 50 ml) and brine, dried over Na_2SO_4, and filtered. The solvents are removed *in vacuo*, and the residue is fractionally distilled *in vacuo* to give the product as a colorless oil; 4.48 g (74%), $bp_{0.01}$ 130–131 °C, $n^{20}{}_D = 1.5574$.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3080, 3070, 3030, 2960, 2880, 1710, 1680.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.05–7.15 (m, 5H, Ph–H), 4.10–3.53 (m, 1H, CH–CO), 2.75–1.45 (m, 8H, CH_2).

Note: HCN is formed during the hydrolysis. Caution: Hood!

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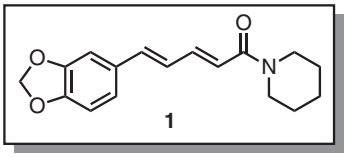
1.5
Reactions of Alkenes Via Carbenium Ions

1.5.1
Piperine



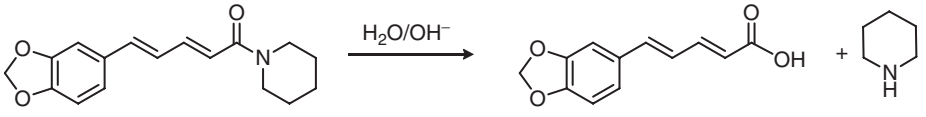
1

Topics:

- Synthesis of a natural product of the arylpolyene type
- Acetal formation by the orthoester method
- Lewis acid-induced C–C bond formation by addition of an acetal to an enol ether
- Acid-catalyzed ROH elimination; acetal hydrolysis
- Knoevenagel condensation/ decarboxylation
- Transformation of a carboxylic acid into a carboxylic acid amide

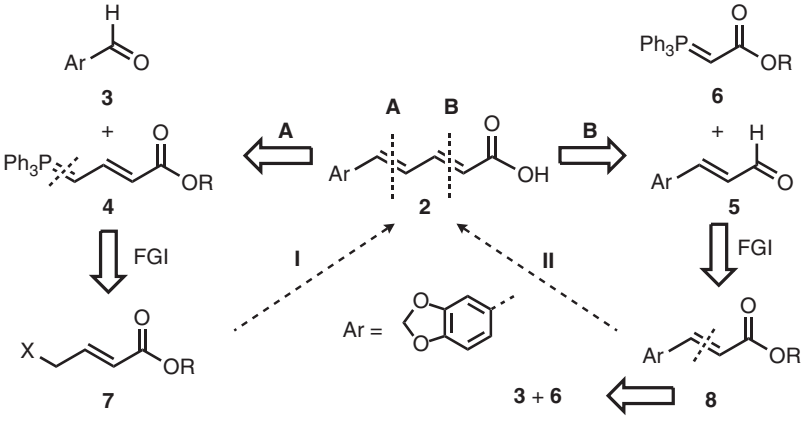
(a) **General**

Piperine (**1**, 4-(3,4-methylenedioxyphenyl)-1,3-butadiene-1-carboxypiperidide) is a constituent of several pepper species (piperaceae), especially of black pepper (*Piper nigrum* L.), as the pungent component. Like many piper alkaloids, piperine also exhibits antimicrobial properties [1]. Hydrolysis of **1** in a basic medium leads to piperinic acid (**2**) and piperidine, whose name is derived from its natural origin:



1 **2**

Piperinic acid (**2**) can be regarded as an intermediate for the synthesis of **1**. The retrosynthesis of **2** can be performed in two directions (**A**/**B**) by disconnections at the double bonds according to a retro-Wittig transformation:



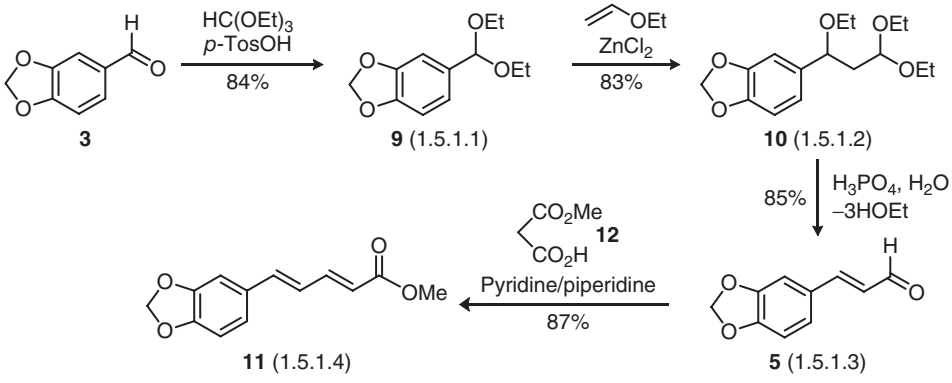
Retrosynthesis according to A leads to the aldehyde piperonal (**3**) and a C_4-ylide **4**, which is derived from γ-halogeno crotonate **7**, in turn available from crotonate by allylic halogenation (e.g., with NBS (*N*-bromosuccinimide)).

Retrosynthesis according to **B** leads to the C_2-ylide **6** (derived from haloacetate) and 3-arylacrolein **5**, which should be accessible from cinnamate **8** by reduction (e.g., with DIBAL (diisobutylaluminum hydride)).

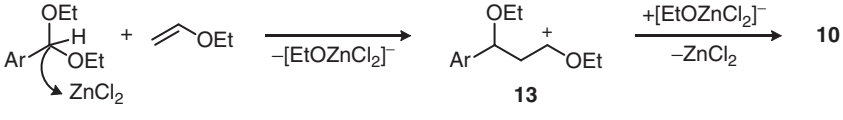
Both approaches toward **2** have been described in the literature. However, the carbonyl olefination of **3** and **4** to give **2** (route **I**) suffers from preparative disadvantages [2]; the same is true for the construction of **2** by two consecutive carbonyl olefinations via **5** (route **II**) (R. Pick and Th. Eicher, unpublished results). Therefore, an alternative method is used for the synthesis of **2** [3], which has been effectively applied in the synthesis of polyolefinic systems ([4], cf. Section 4.1.5) and which relies on carbenium ion-based C–C bond formation.

(b) **Synthesis of 1**

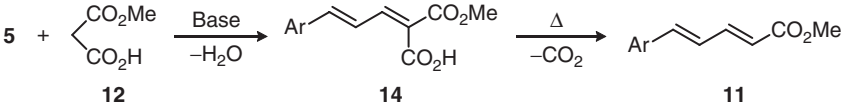
In the first part of the synthesis of **1**, piperonal (**3**) is transformed to its diethyl acetal **9** by reaction with triethyl orthoformate in the presence of TosOH. The acetal **9** adds to the C=C double bond of ethyl vinyl ether in the presence of a Lewis acid, for example, $ZnCl_2$, to give rise to the 3-aryl-1,1,3-triethoxypropane derivative **10**:



The transformation **9** → **10** can be rationalized by (i) the formation of a carbenium ion from the acetal **9** induced by the Lewis acid, (ii) its electrophilic Markownikov-oriented addition to the electron-rich C=C double bond of the vinyl ether, and (iii) termination by transfer of OEt to the cationic intermediate **13**:

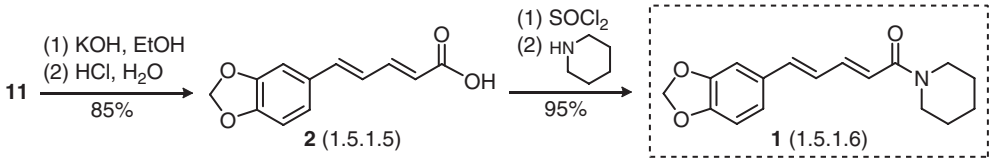


Compound **10** is transformed into the α,β-unsaturated aldehyde by acid-catalyzed hydrolysis of the acetal followed by elimination of EtOH. Finally, the C_5-1,3-diene side chain in **1** is completed by Knoevenagel condensation of **5** with monomethyl malonate (**12**) to give the methyl ester **11** as a result of concomitant decarboxylation of the initial condensation product **14** under the reaction conditions [5]:



12 **14** **11**

As the last step in the synthesis of **1**, the methyl ester **11** is saponified using KOH in ethanol to give piperinic acid (**2**), and the amide is formed in the conventional manner by reacting **2** with $SOCl_2$ followed by Schotten–Baumann reaction of the intermediate acid chloride with piperidine:

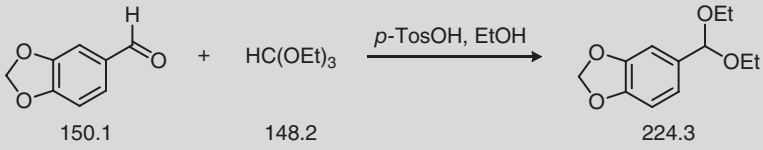


2 (1.5.1.5) **1** (1.5.1.6)

Thus, the target molecule **1** is obtained in a six-step sequence in an overall yield of 42% (based on piperonal).

(c) Experimental Procedures for the Synthesis of 1

1.5.1.1 * Piperonal diethyl acetal [3]



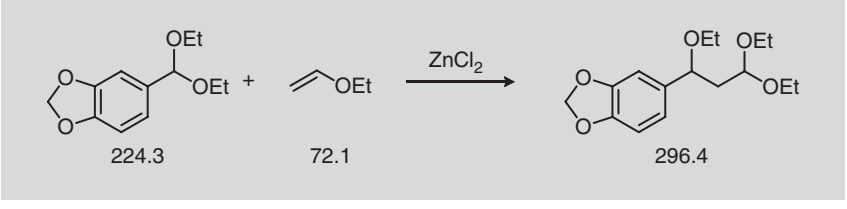
150.1 148.2 224.3

A stirred solution of piperonal (50.0 g, 0.33 mol), triethyl orthoformate (97.8 g, 0.66 mol), and TosOH·H_2O (10 mg) in anhydrous EtOH (330 ml) is heated to 80 °C for 1 h (TLC control) with exclusion of moisture.

The excess EtOH is then distilled off, the residue is dissolved in Et_2O (200 ml), and the solution is washed several times with H_2O (100 ml). The ethereal solution is dried over K_2CO_3 and filtered, and the solvent is removed *in vacuo*. The residue is fractionated *in vacuo* on a 20-cm Vigreux column. The acetal is obtained as a colorless oil; 62.1 g (84%), $bp_{0.1}$ 84–86 °C, $R_f = 0.55$ (*n*-pentane/Et_2O 1 : 1).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2974, 2880, 1504.
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.98 (d, *J* = 1.3 Hz, 1H, ArH), 6.93 (dd, *J* = 7.9, 1.3 Hz, 1H, ArH), 6.78 (d, *J* = 7.9 Hz, 1H, ArH), 5.94 (s, 2H, OCH_2O), 5.39 (s, 1H, OCHO), 3.60 (dq, *J* = 9.4, 6.9 Hz, 2H, $OC\underline{H}_2CH_3$), 3.50 (dq, *J* = 9.4, 6.9 Hz, 2H, $OC\underline{H}_2CH_3$), 1.24 (t, *J* = 6.9 Hz, 6H, $OCH_2C\underline{H}_3$).
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 147.7, 147.5, 133.4, 120.3, 107.8, 107.0, 101.4, 101.0, 61.1, 15.2.

1.5.1.2 * 1,1,3-Triethyl-3-(3,4-methylenedioxyphenyl)propane [3]



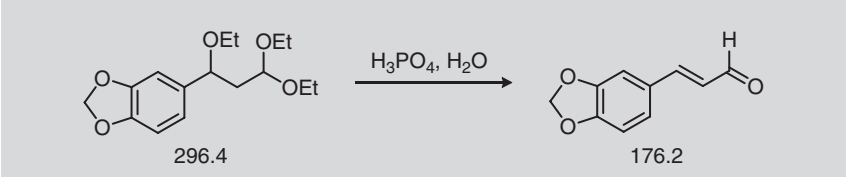
A suspension of anhydrous zinc chloride (0.70 g, note 1) in anhydrous EtOAc (5 ml) is added to the diethyl acetal **1.5.1.1** (56.0 g, 250 mmol) with stirring and under exclusion of moisture. The mixture is heated to 40 °C, and ethyl vinyl ether (19.5 g, 270 mmol) is added at such a rate that the temperature is maintained between 40 and 45 °C. When the addition is complete, stirring is continued at 40–45 °C for 1 h.

The reaction mixture is then allowed to cool to room temperature and is diluted with Et_2O (130 ml). The ethereal solution is washed with aqueous NaOH (2 N, 25 ml), dried over Na_2SO_4, and filtered. After removal of the solvent, the residue is fractionated *in vacuo* (20-cm Vigreux column). The product is obtained as a colorless oil; 62.7 g (83%), $bp_{0.1}$ 97–99 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2973, 2875, 1503.
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.83 (s_{br}, 1H, ArH), 6.75 (s_{br}, 2H, ArH), 5.95 (s, 2H, OCH_2O), 4.58 (dd, *J* = 6.9, 4.7 Hz, 1H, OCHO), 4.28 (dd, *J* = 8.8, 5.4 Hz, 1H, Ar–CH–O), 3.22–3.75 (m, 6H, 3 × OCH_2), 2.08 (ddd, *J* = 13.9, 6.9, 5.4 Hz, 1H, C–CH_2–C), 1.84 (ddd, *J* = 13.6, 8.8, 4.7 Hz, 1H, C–CH_2–C), 1.21, 1.20, 1.15 (3 × t, *J* = 6.9 Hz, 3 × 3H, $OCH_2C\underline{H}_3$).
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 147.9, 146.9, 136.7, 120.1, 108.0, 106.7, 100.9, 100.4, 78.3, 63.8, 61.3, 42.4, 18.5, 15.4.

Note: Commercially available anhydrous zinc chloride is dried *in vacuo* over P_4O_{10}.

1.5.1.3 * 3-(3,4-Methylenedioxyphenyl)acrolein [3]

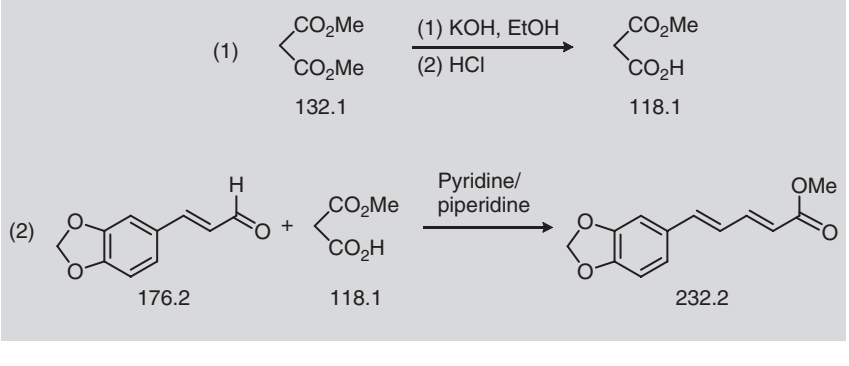


A stirred mixture of the triethoxypropane **1.5.1.2** (60.4 g, 204 mmol), 1,4-dioxane (400 ml), H_2O (140 ml), 90% phosphoric acid (20 ml), and hydroquinone (0.2 g) is heated under reflux for 8 h under a N_2 atmosphere.

After cooling to room temperature, the reaction mixture is poured into ice-cold H_2O (1000 ml). After stirring for 1 h, the precipitated product is collected by suction filtration, and washed with diluted aqueous $NaHCO_3$ solution and with H_2O until the washings are neutral. The crude aldehyde is recrystallized from EtOH; 30.0 g (83%), yellow crystals, mp 84–85 °C.

UV (EtOH): λ_{max} (log ε) = 338 nm (4.29), 297 (4.06), 248 (4.07), 220 (4.06).
IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3048, 2992, 2916, 2823, 2729, 2701, 1666, 1620, 1597.
^{1}H NMR (500 MHz, [D_6]DMSO): δ (ppm) = 9.59 (d, *J* = 7.9 Hz, 1H, CHO), 7.62 (d, *J* = 15.8 Hz, 1H, Ar–C<u>H</u>=CH), 7.42 (d, *J* = 1.6 Hz, 1H, ArH), 7.23 (dd, *J* = 7.9, 1.6 Hz, 1H, ArH), 7.00 (d, *J* = 7.9 Hz, 1H, ArH), 6.74 (dd, *J* = 15.8, 7.9 Hz, 1H, =C<u>H</u>CHO), 6.09 (s, 2H, OCH_2O).
^{13}C NMR (126 MHz, [D_6]DMSO): δ (ppm) = 194.0 (CHO), 153.1, 150.0, 148.1, 128.5, 126, 125.7, 108.6, 106.8, 101.7 (OCH_2O).

1.5.1.4 ** Methyl 4-(3,4-methylenedioxyphenyl)-1,3-butadiene-1-carboxylate [3]



1) Monomethyl malonate: A solution of KOH (16.8 g, 0.30 mol) in anhydrous MeOH (170 ml) is added dropwise to a stirred solution of dimethyl malonate

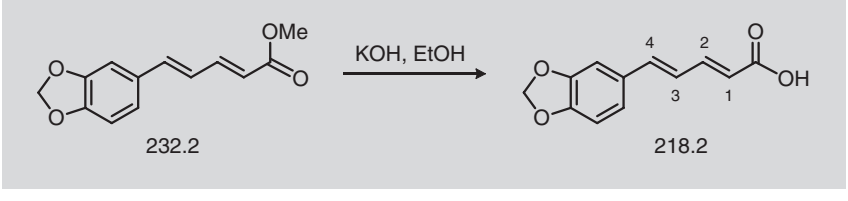
(40.0 g, 0.30 mol) in anhydrous MeOH (170 ml) at room temperature. Stirring is continued for 24 h, and the precipitated potassium salt is collected by suction filtration, washed with Et_2O (50 ml), and dried *in vacuo*.
The salt is dissolved in H_2O (30 ml), and concentrated HCl (58 ml) is added dropwise at 0 °C with stirring. The mixture is then extracted with Et_2O (4 × 50 ml), the combined ethereal extracts are dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is distilled *in vacuo*, and the product is obtained as a colorless oil; 33.6 g (95%), $bp_{0.18}$ 84–85 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.90 (s, 1H, CO_2H), 3.78 (s, 3H, CH_3), 3.46 (s, 2H, CH_2).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 171.8 (CO_2H), 167.1 (CO_2CH_3), 52.8 (CH_2), 40.7 (CH_3).

2) A mixture of the aldehyde **1.5.1.3** (17.6 g, 0.10 mol), monomethyl malonate (17.7 g, 0.10 mol), anhydrous piperidine (1 ml), and anhydrous pyridine (40 ml) is heated at 80 °C for 2 h and at 130 °C for 1 h.
The reaction mixture is then diluted with Et_2O (150 ml), and the ethereal solution is washed several times with H_2O (100 ml). Thereafter, it is washed with aqueous HCl (2 N, 100 ml), and then with further H_2O until the washings are neutral. The ethereal solution is dried over $MgSO_4$ and filtered, the solvent is removed *in vacuo*, and the residue is recrystallized from MeOH. The diene ester is obtained as yellow crystals; 20.1 g (87%), mp 142–143 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2947, 1706, 1616, 1607, 1505.
^{1}H NMR (500 MHz, [D_6]DMSO): δ (ppm) = 7.37 (ddd, J = 15.1, 8.5, 1.9 Hz, 1H, C<u>H</u>=CHCO$_2$), 7.22 (d, J = 1.3 Hz, 1H, ArH), 7.10–7.05 (combined signals, 3H, ArH, Ar–C<u>H</u>=C<u>H</u>), 6.92 (d, J = 7.9 Hz, 1H, ArH), 6.04 (s, 2H, OCH_2O), 6.00 (d, J = 15.1 Hz, 1H, =$CHCO_2$), 3.67 (s, 3H, OCH_3).
^{13}C NMR (126 MHz, [D_6]DMSO): δ (ppm) = 166.6, 148.2, 148.0, 145.2, 140.5, 130.4, 124.6, 123.2, 119.4, 108.5, 105.7, 101.3, 51.2.

1.5.1.5 * 4-(3,4-Methylenedioxyphenyl)-1,3-butadiene-1-carboxylic acid [3]



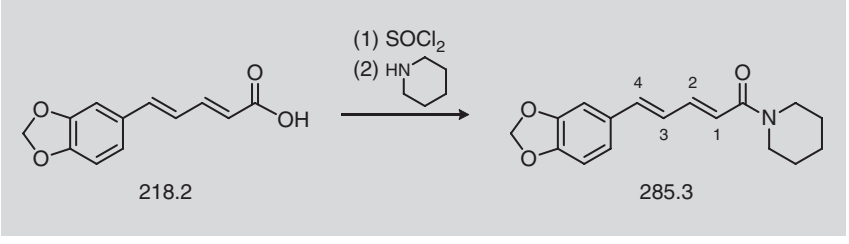
A solution of the methyl ester **1.5.1.4** (18.6 g, 80.0 mmol) in 20% KOH in EtOH (100 ml) is heated under reflux for 3 h.

The solvent is then removed *in vacuo*, and the residue is dissolved in the minimum amount of hot H_2O (approximately 50 ml). The solution is cooled to 0 °C and

acidified by the dropwise addition of concentrated HCl with stirring. The precipitated acid is collected by suction filtration, washed with ice-cold water, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue is recrystallized from EtOH; 14.5 g (83%), yellow crystals, mp 217–218 °C; TLC (SiO_2/Et_2O): $R_f = 0.60$.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3100–2400, 1680.
UV (EtOH): λ_{max} (log ε) = 343 nm (4.42), 308 (4.21), 262 (4.07).
^{1}H NMR ([D_6]DMSO): δ = 7.54–7.16 (m, 1H, vinyl-H-2), 7.21–6.68 (m, 5H, Ar–H, H-3, H-4), 6.01 (s, 2H, OCH_2), 5.93 (d, J = 14 Hz, 1H, vinyl-H-1).

1.5.1.6 * **4-(3,4-Methylenedioxyphenyl)-1,3-butadiene carboxypiperidide** (piperine), [2]



1) The acid **1.5.1.5** (8.72 g, 40.0 mmol) is suspended in anhydrous benzene (180 ml; Caution: "Leerzeichen einfügen" carcinogenic!), and then thionyl chloride (10 ml, distilled before use, bp_{760} 78–79 °C) and anhydrous DMF (1.2 ml) are added. The mixture is heated to reflux with stirring for 2 h (N_2 atmosphere, Hood, evolution of HCl and SO_2!). The solvents are removed *in vacuo*, and the solid residue (crude acid chloride) is used directly in the next step.
2) The acid chloride from the previous step is dissolved in anhydrous benzene (40 ml), and the solution is cooled to 0 °C. A solution of anhydrous piperidine (14.8 g, 0.17 mol, 16.0 ml) in benzene (40 ml) is then added dropwise with stirring over 20 min; when the addition is complete, stirring is continued for 2 h at room temperature.

H_2O (200 ml) is then added, the aqueous phase is extracted with benzene (3 × 50 ml; Caution: carcinogenic!), and the combined organic extracts are dried over Na_2SO_4 and filtered. The solvent is removed *in vacuo*, and the residue (dark oil) is dissolved in hot 4 : 1 cyclohexane/benzene (80 ml). On cooling to room temperature, the product crystallizes in well-shaped yellowish needles, which are collected by suction filtration, washed with cyclohexane, and dried; 11.0 g (95%), mp 130–132 °C, TLC (SiO_2; Et_2O): $R_f = 0.40$.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1640, 1615, 1590.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61–7.28 (m, 1H, vinyl-H-2), 6.98–6.64 (m, 5H, Ar–H, 3-H, 4-H), 6.46 (d, J = 13.9 Hz (trans coupling), 1H, H-1), 6.00 (s, 2H, OCH_2), 3.69–3.51 (m, 4H, NCH_2), 1.82–1.42 (m, 6H, β- and γ-piperidine-CH_2).

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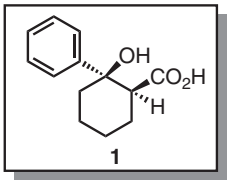
1.5.2
Cicloxilic Acid



1

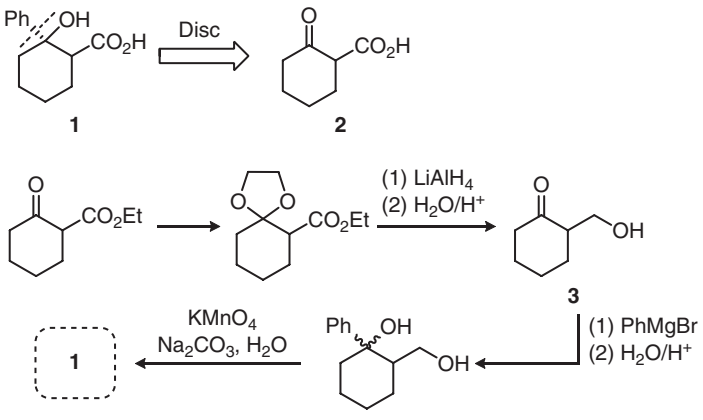
Topics:
- Synthesis of a drug
- Formation of a tertiary alcohol by addition of RMgX to a ketone
- Acid-catalyzed dehydration of a tertiary alcohol
- Stereoselective Prins reaction (acid-catalyzed addition of formaldehyde to an alkene)
- Oxidation of a primary alcohol to a carboxylic acid

(a) General

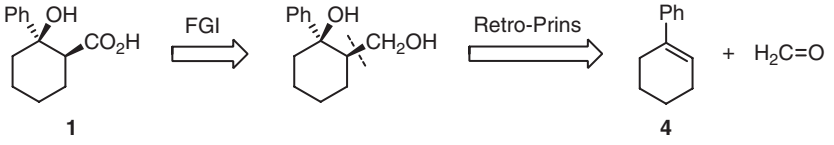
Cicloxilic acid (**1**, *rac-cis*-2-hydroxy-2-phenylcyclohexane-1-carboxylic acid) is used medicinally as a choleretic and hepatic protectant [1]. Its stereochemistry, with a cis relationship of the OH and CO_2H groups, was established by ^{1}H NMR spectroscopic investigation [2].

A straightforward retrosynthesis of **1** leads to cyclohexanone-2-carboxylic acid (**2**) as starting material, from which **1** might have been considered accessible by a

simple Grignard reaction with PhMgBr. However, since this did not work, a somewhat lengthy transformation of the keto ester into **3** was necessary [3], which was then transformed into **1** by Grignard reaction (PhMgBr) followed by oxidation. Further negative aspects of this synthesis are its low yield and its lack of stereoselectivity, giving a mixture of the cis and trans diastereomers.



A second, less conventional retrosynthetic analysis leads to 1-phenylcyclohexene and formaldehyde:

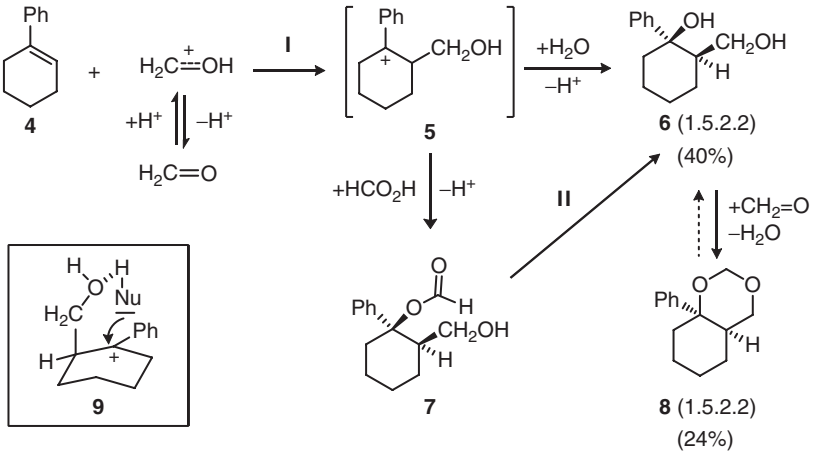


This approach was used in the described synthesis of **1**, with the advantage that it proceeds with high diastereoselectivity.

The acid-catalyzed addition of aldehydes, mainly formaldehyde, to alkenes is known as the *Prins reaction*. In this process, the carbenium ion derived from the addition of the protonated carbonyl source to the alkene C=C bond is the central intermediate; it is intercepted by addition of a nucleophile, preferentially the solvent used (H_2O, formic acid, etc.), to give as products a 1,3-diol and/or its monoester [4, 5].

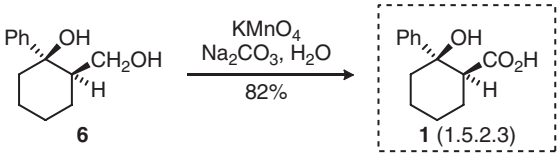
(b) **Synthesis of 1**

For the synthesis of **1**, 1-phenylcyclohex-1-ene (**4**) is reacted with formaldehyde in aqueous formic acid (5 : 95) to give **6** and **7** as the main products, accompanied by a side product **8**, which contains an acetal moiety formed by the reaction of **6** with a second molecule of formaldehyde. The formate **7** can easily be transformed into **6** by saponification with NaOH.

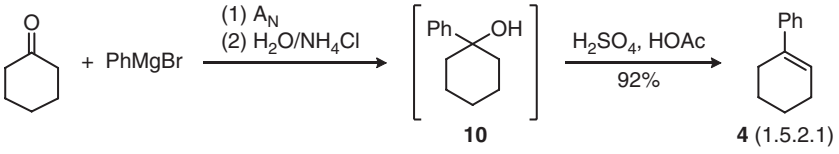


The high stereoselectivity of the Prins reaction, giving the cis diastereomers **6** and **7**, can be explained in terms of a pre-orientation through hydrogen bonding between the incoming nucleophile and the hydroxymethyl group in the cation **5** in the transition state [2].

In the final step of the synthesis, the diol **6** is oxidized with $KMnO_4$ in aqueous Na_2CO_3 solution to give cicloxilic acid **1**:



The required substrate, 1-phenylcyclohex-1-ene (**4**), is prepared from cyclohexanone by addition of phenylmagnesium bromide and subsequent acid-catalyzed elimination of H_2O (E1 process) from the formed tertiary benzyl alcohol [6]:

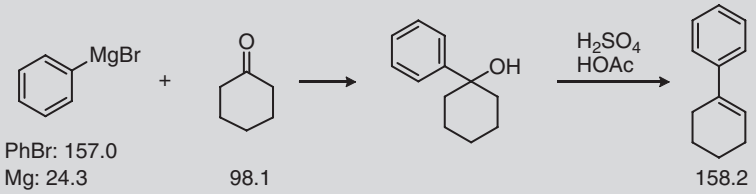


In this way, the target molecule **1** is obtained in a stereoselective three-step sequence in an overall yield of 47% (based on cyclohexanone).[6)]

6) With regard to maximizing the overall yield, it has been considered that the cyclic acetal **8** may be hydrolyzed ($CH_3OH/H_2O/HCl$) to give the diol **6** in practically quantitative yield.

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

1.5.2.1 * 1-Phenylcyclohex-1-ene [6]



The first 20 ml of a solution of bromobenzene (94.5 g, 0.50 mol; note 1) in anhydrous Et_2O (200 ml) and methyl iodide (4–6 drops; Caution: carcinogenic!) are added to magnesium turnings (14.5 g, 0.50 mol) in anhydrous Et_2O (20 ml). When the reaction has started, the rest of the bromobenzene solution is added dropwise with efficient stirring at such a rate that gentle boiling of the reaction mixture is maintained. When the addition is complete, heating under reflux is continued for 2 h.

A solution of cyclohexanone (49.1 g, 0.50 mol; note 2) in anhydrous Et_2O (40 ml) is then added dropwise with efficient stirring to the solution of phenylmagnesium bromide prepared as described above, again at such a rate that gentle boiling of the reaction mixture is maintained. When the addition is complete, heating at reflux is continued for 30 min.

The mixture is then cooled in an ice bath, and an ice-cold saturated aqueous NH_4Cl solution (400 ml) is added dropwise with vigorous stirring. The organic phase is separated, and the aqueous phase is extracted with Et_2O (150 ml). The ethereal phases are combined, dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the yellowish residue (note 3) is stirred for 30 s with a mixture of concentrated H_2SO_4 (20 ml) and acetic acid (80 ml) at 50 °C. The mixture is then poured into a two-phase system of H_2O (500 ml) and Et_2O (300 ml) and shaken. The ethereal phase is separated, washed repeatedly with saturated aqueous $NaHCO_3$ solution (4 × 100 ml), dried over Na_2SO_4, and filtered. The solvent is removed, and the residue is distilled *in vacuo*. The product is obtained as a colorless liquid; 72.5 g (92%), $bp_{4.5}$ 90–91 °C, $n^{20}_D = 1.5665$.

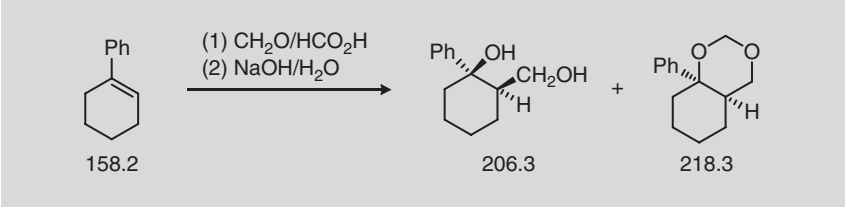
IR (film): $\tilde{\nu}$ (cm^{-1}) = 3010, 2910–2835, 1660, 1495, 1445.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.50–7.05 (m, 5H, Ph–H), 6.20–5.91 (m, 1H, vinyl-H), 2.61–2.00 (m, 4H, CH_2), 2.00–1.43 (m, 4H, CH_2).

Notes:

1) Bromobenzene is purified by distillation *in vacuo*, bp_{15} 48–49 °C.

2) Cyclohexanone has to be distilled before use; bp_{760} 155–156 °C, $[\alpha]^{20}_D = 1.4500$.
3) This residue consists of 1-phenylcyclohexan-1-ol as the crude product and is subjected *in situ* to acid-catalyzed dehydration.

1.5.2.2 ** *cis*-2-Hydroxymethyl-1-phenylcyclohexan-1-ol [4]



Phenylcyclohexene (**1.5.2.1**) (66.5 g, 0.42 mol) is suspended in a mixture of formic acid (420 ml) and H_2O (15 ml). A 40% formaldehyde solution (44.1 ml, 0.59 mol) is added dropwise over 30 min with stirring. When the addition is complete, the suspension is stirred for 3 h at room temperature.

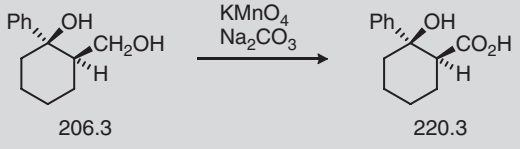
The solvent is then removed *in vacuo* at an external temperature of 30 °C. A colorless oil is obtained, which is treated with a solution of NaOH (28.0 g) in EtOH (210 ml) with efficient stirring for 12 h at room temperature. The reaction mixture is then diluted with an equal volume of H_2O (approximately 250 ml) and extracted with chloroform (2 × 150 ml); the combined extracts are dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The oily residue is dissolved in petroleum ether (300 ml) with heating, and the solution is cooled to room temperature and kept in a freezer for 24 h. The crystallized diol is filtered off, retaining also the filtrate (see below), and the purification procedure is repeated. The product is obtained as colorless crystals; 34.5 g (40%), mp 82–83 °C, TLC (SiO_2; Et_2O): $R_f = 0.80$.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3500–3180, 2930–2840.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.62–7.21 (m, 5H, phenyl-H), 3.73, 2.45 (s, 1H, OH; exchangeable with D_2O), 3.65–3.25 (m, 2H, OCH_2), 2.25–1.25 (m, 9H, cyclohexyl-H).

The solvent is removed *in vacuo* from the petroleum ether solution of the first crystallization of the diol, the residue is dissolved in the minimum amount of EtOH, and the solution is kept in a freezer for 12 h. The dioxane is obtained as colorless crystals; 22.5 g (24%), mp 62–63 °C, TLC (SiO_2; Et_2O): $R_f = 0.80$.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.41–7.25 (m, 5H, phenyl-H), 4.87–4.75 (m, 2H, OCH_2O), 3.85, 3.53 (d, J = 11.2 Hz, 2 × 1H, OCH_2), 2.54–1.08 (m, 9H, cyclohexyl-H).

1.5.2.3 * *cis*-2-Hydroxy-2-phenylcyclohexane carboxylic acid (cicloxilic acid) [4]



206.3 220.3

A solution of the diol **1.5.2.2** (29.0 g, 141 mmol) in H_2O (1500 ml) is heated to 85 °C (internal temperature). At this temperature, a mixture of finely powdered $KMnO_4$ (57.5 g, 364 mmol) and anhydrous Na_2CO_3 (29.0 g, 274 mmol) is added in small portions with vigorous stirring. When the addition is complete, stirring at 85 °C is continued for 30 min (note).

The MnO_2 formed is removed by suction filtration, and the filter cake is washed with H_2O (3 × 100 ml). Concentrated HCl is added dropwise to the filtrate with stirring until a pH of approximately 1 is reached. The colorless precipitate is collected by suction filtration, washed with a small amount of iced water, and dried over P_4O_{10} *in vacuo*. Recrystallization from cyclohexane yields 25.5 g (82%) of cicloxilic acid; mp 139–140 °C, TLC (SiO_2; Et_2O): R_f = 0.75.

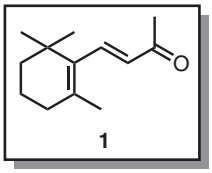
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3530, 3200–2600, 1680.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.57–7.15 (m, 5H, Ph–H), 3.10–2.91 (m, 1H, 1-H), 2.15–1.20 (m, 8H, 4 × CH_2).

Note: If the reaction mixture still contains an excess of permanganate, MeOH is added until decolorization occurs.

References

1. Kleemann, A. and Engel, J. (1999) *Pharmaceutical Substances*, 3rd edn, Thieme Verlag, Stuttgart, p. 434.
2. Turbanti, L., Cerbai, G., and Ceccarelli, G. (1978) *Arzneim.-Forsch./Drug Res.*, **87**, 1249.
3. Brit. (1969), GB 1167386 19691015.
4. Ger. Offen. (1977), DE 2607967 A1 19770526. *Chem. Abstr.*, (1977), **87**, 84688.
5. (a) Adams, D.R. and Bhatnagar, S.P. (1977) *Synthesis*, 661; (b) Thiem, J. (1980) *Houben-Weyl, Methoden der Organischen Chemie*, vol. 6/1a, p. 793; (c) For the use of Prins cyclizations in natural product synthesis, see: Overman, L.E. and Pennington, L.D. (2003) *Chem. Soc. Rev.*, **32**, 381–383.
6. Garbisch, E.W. Jr. (1961) *J. Org. Chem.*, **26**, 4165.

1.5.3
β-Ionone

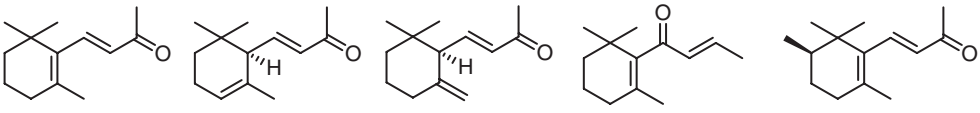


Topics:

- Synthesis of a terpene-derived C_{13}-dienone
- α-Alkylation of acetoacetate
- Ethynylation of a carbonyl compound
- Acetoacetylation of an alcohol with diketene
- Carroll reaction of allyl acetoacetates ([3,3]-sigmatropic rearrangement)
- Cationic cyclization of a 1,5-diene to a cyclohexene derivative

(a) General

Ionones are a group of natural fragrances, which are formed by oxidative degradation of tetraterpenoids (carotins) [1]. α-Ionone **2** is the main component of violet oil, while β- and γ-ionones (**1** and **3**) are found in several essential oils. Structurally related to the ionones are the damascones (e.g., β-damascone **4**, a constituent of rose oil) and irones (e.g., β-irone **5** (2-methyl-β-ionone), a fragrant compound from the oil of iris roots) [2].



β-Ionone **1** | (*R*)-(+)-α-Ionone **2** | (*R*)-(+)-γ-Ionone **3** | β-Damascone **4** | (*R*)-(+)-β-Irone **5**

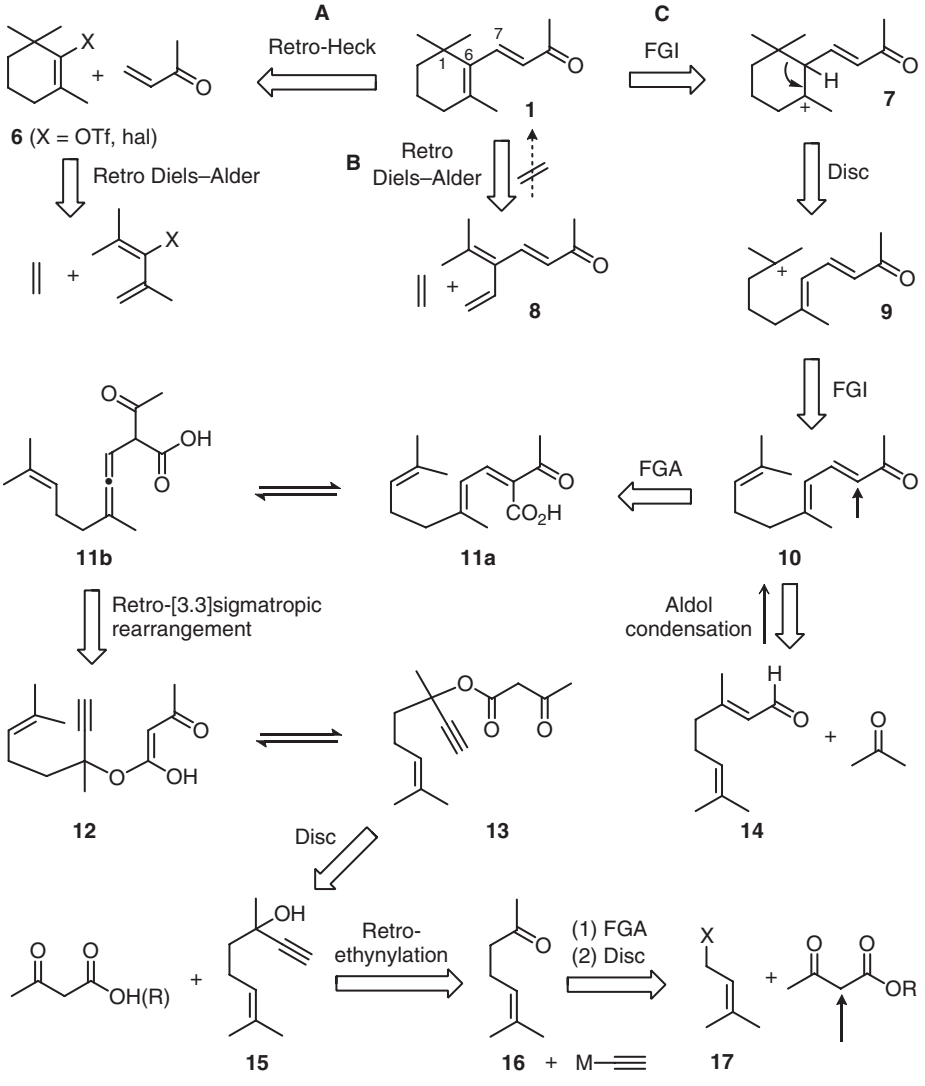
β-Ionone is one of the most potent odorous organic compounds (perceptible in concentrations <0.1 ppb); it is an important ingredient of perfumes and is used as a substrate in natural product syntheses, for example, of damascone [3] and of vitamin A (cf. Section 4.1.5).

Three retrosynthetic pathways for β-ionone (**1**) are discussed here.

In A, disconnection of the C-6/C-7 bond according to a retro-Heck transformation leads to the cyclohexene **6**, which could formally be obtained by a Diels–Alder reaction. However, this would be an electronically disfavored transformation.

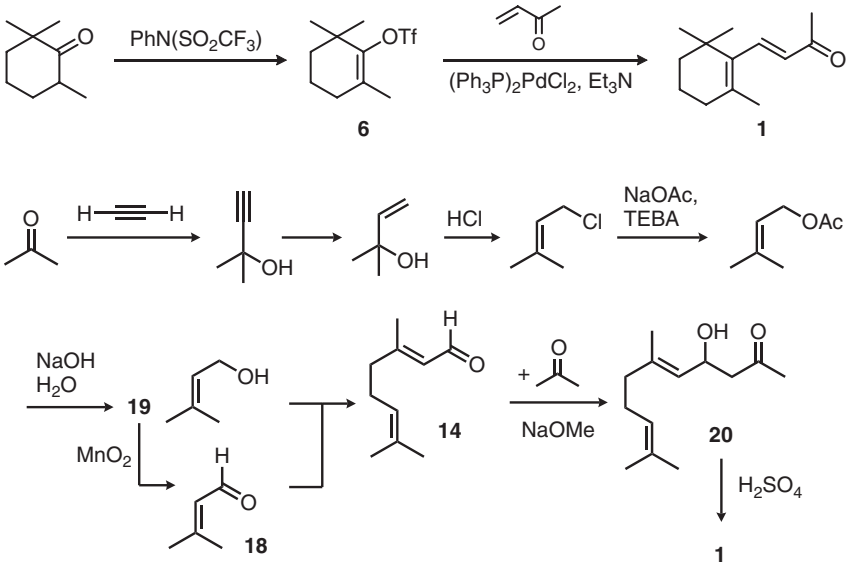
In B, the cyclohexene ring is disconnected by a retro-Diels–Alder reaction to give ethylene as dienophile and the 1,3-diene system **8**. However, as discussed before, their [4 + 2]-cycloaddition is not a favorable process, again because of electronic reasons (no activated dienophile) as well as a lack of regioselectivity (different 1,3-diene moieties exist in **8**).

In C, a protonation/deprotonation sequence initiates a ring opening (**1** → **7** → **9**) to pseudoionone (**10**), which could be obtained by an aldol condensation of geranial (**14**) with acetone. Another possible retrosynthesis of **10** includes a retro-Claisen protocol (**10** → **11a** → **11b**) leading to dehydrolinalool (**15**) and acetoacetate via dehydrolinalool acetoacetate (**12**/**13**). **15** may be obtained from methylheptenone **16**, which is accessible from **17** and acetoacetate.

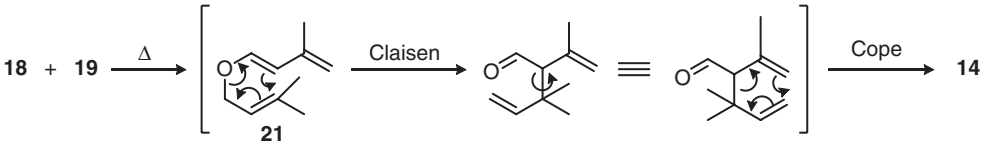


Realizations of the retroanalytical pathways A–C for the synthesis of **1** have been reported in the literature.

Thus, a short and efficient approach to **1** utilizes the Heck reaction of the trifluoromethanesulfonate **6** ($X = OSO_2CF_3$) of 2,6,6-trimethylcyclohexanone with methyl vinyl ketone [4]:



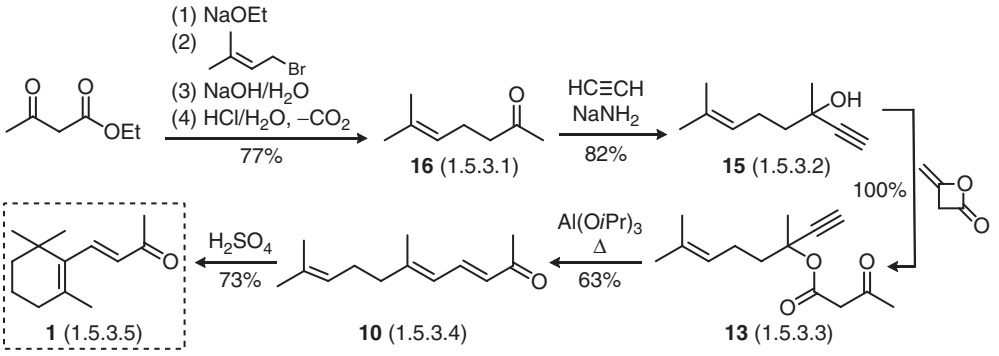
In the second approach toward **1**, acetone is condensed with geranial (**14**) [5], which is obtained by a pericyclic domino process of two [3,3]-sigmatropic reactions between the allylic alcohol **19** and the aldehyde **18** via the vinyl allyl ether **21**:



The third approach to the target molecule **1**, according to retrosynthesis C, uses elements of the industrial β-ionone synthesis of BASF and is described in detail [6].

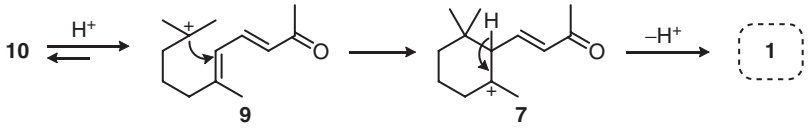
(b) **Synthesis of 1**

First, 6-methylhept-5-ene-2-one (**16**) is prepared from acetoacetate by α-alkylation with prenyl bromide (cf. Section 4.1.3), ester hydrolysis, and decarboxylation of the intermediately formed β-keto acid. Ethynylation of methylheptenone **16** with sodium acetylide [7] gives the tertiary alcohol dehydrolinalool (**15**), which is esterified with diketene.



The propargylic acetoacetate **13** is subjected to a thermal [3,3]-sigmatropic rearrangement in the presence of $Al(OiPr)_3$ with concomitant decarboxylation of the resulting β-allenic acid (**11b**) to give the unsaturated ketone **10** (pseudoionone). The Claisen (oxa-Cope) rearrangement of allylic or propargylic acetoacetates (Carroll reaction) is often used in terpene synthesis (also industrially [8]) as a C_3 chain elongation process (here: $C_{10} \rightarrow C_{13}$).

The final step of the synthesis of β-ionone (**1**) is the acid-catalyzed cycloisomerization of pseudoionone (**10**). Mechanistically, a cationic cyclization of the 1,5-diene through carbenium ion formation (by protonation of the terminal C=C double bond) and its addition to an internal olefinic C=C bond resulting in the formation of a cyclohexene can be assumed.

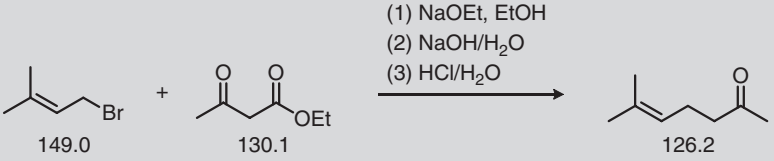


Cyclizations of this type occur with a high degree of stereoselectivity (stereoelectronic control in **9** → **7** as a result of a chair-like transition state) and are involved in the biosynthesis of steroids and other polycycles [9].

Using the described approach, the target molecule **1** is obtained in a five-step sequence with an overall yield of 29% (based on acetoacetate).

(c) Experimental Procedures for the Synthesis of 1

1.5.3.1 * **6-Methylhept-5-en-2-one** [10]

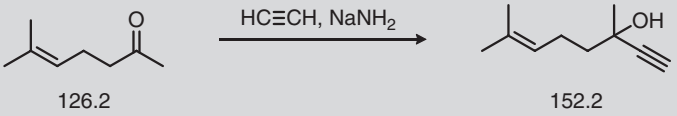


Sodium (12.6 g, 0.55 mol) is added to a stirred solution of ethyl acetoacetate (87.8 g, 0.67 mol) and anhydrous EtOH (150 ml) (formation of H_2). The mixture is cooled to 0 °C, and 1-bromo-3-methyl-2-butene (**4.2.2.2**) (74.5 g, 0.50 mol) is added dropwise over 20 min. Stirring is continued at room temperature for 3 h and at 60 °C for 4 h. During this time, a fine crystalline precipitate of sodium bromide is formed.

The mixture is then filtered, the filtrate is concentrated *in vacuo*, and the residue is treated with 10% aqueous NaOH solution (200 ml). The resulting mixture is stirred at room temperature for 2 h and at 60 °C for 3 h, cooled, and acidified to pH 4 with concentrated HCl. The solution is extracted with Et_2O (3 × 100 ml), and the combined organic phases are washed with saturated aqueous $NaHCO_3$ solution (150 ml) and H_2O, dried over $MgSO_4$, and filtered. The solvent is removed *in vacuo*, and the residue is fractionally distilled through a Vigreux column to give a colorless oil with a fruity odor; 51.7 g (77%), bp_{12} 64–65 °C, $n^{20}{}_D = 1.4404$.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1720, 1360, 1160.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.00 (m, 1H, 5-H), 2.4–2.1 (m, 4H, 3-H_2, 4-H_2), 2.04 (s, 3H, 1-H_3), 1.63 (m, 6H, 7-H_3, 6-CH_3).

1.5.3.2 ** **Dehydrolinalool (3,7-dimethyl-1-octyn-6-en-3-ol)** [11]



126.2 152.2

Finely powdered sodium amide (18.0 g, 0.46 mol, note 1) is added in portions to a stirred solution of methylheptenone **1.5.3.1** (30.0 g, 0.24 mol) in anhydrous Et_2O (150 ml) at −15 °C. After stirring the mixture for 3 h, a rapid stream of acetylene is passed through it for 4 h. The temperature is then held at −20 °C for 15 h. Thereafter, a rapid stream of acetylene is again passed through the mixture at −15 °C for 4 h.

The brown-yellow mixture is poured into well-stirred iced water (500 ml). The ethereal phase is separated, and the aqueous phase is extracted with Et_2O (150 ml). The combined organic phases are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The yellow residue is fractionally distilled *in vacuo* to give a colorless oil with an odor similar to that of geranial; 29.7 g (82%), bp_{10} 85–88 °C. $n^{20}{}_D = 1.4632$ (note 2).

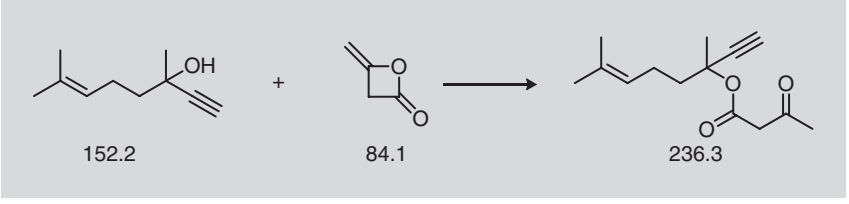
IR (film): $\tilde{\nu}$ (cm^{-1}) = 3400, 3300, 2970, 2920, 2860, 1450, 1120.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.15 (t, J = 6.5 Hz, 1H, 6-H), 2.52 [s, 1H, OH (exchangeable with D_2O)], 2.49 (s, 1H, 1-H), 2.35–1.9 (m, 2H, 5-H_2), 1.66 (s, 6H, 2 × 7-CH_2), 1.64 (t, J = 7 Hz, 2H, 4-H_2), 1.50 (s, 3H, 3-CH_3).

Notes:

1) $NaNH_2$ is obtained by filtering a suspension in toluene (sintered glass filter) and washing twice with Et_2O.
2) If the product still contains methylheptenone (determined by GC), it is shaken for 15 h with sodium bisulfite solution and redistilled.

1.5.3.3 ** Dehydrolinalool acetoacetate [12]

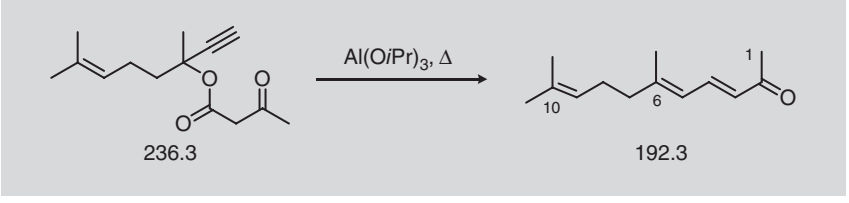


Sodium methoxide (0.20 g; freshly prepared and dried at 100 °C/0.1 mbar) is added to a solution of dehydrolinalool (**1.5.3.2**) (26.6 g, 175 mmol) in anhydrous toluene (40 ml). Diketene (16.4 g, 195 mmol) is added dropwise to the stirred solution over a period of 2 h, keeping the temperature under 30 °C with occasional cooling if necessary. Stirring is continued at 30 °C for 5 h and at room temperature for 15 h.

The light-brown mixture is then washed with aqueous H_2SO_4 (1 M, 50 ml), saturated aqueous $NaHCO_3$ solution (50 ml), and H_2O (2 × 50 ml). The organic phase is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The residual yellow oil is sufficiently pure for further use; yield 41.3 g (100%). Distillation *in vacuo* gives a colorless oil, $bp_{0.005}$ 43–44 °C, n^{20}_D = 1.4652.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3290, 2060, 1755, 1725.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.25–4.80 (m, vinyl-H + enol-H), 3.34 (s, including previous signal 3H, CO–CH_2), 2.56 (s, 1H, ≡CH), 2.22 (s, 3H, CO–CH_3), 2.1–1.8 (m, 2H, allyl-CH_2), 1.70 [s, 6H, =C(CH_3)$_2$], 1.60 (s, 3H, CH_3), 1.75–1.5 (m, 2H, CH_2).

1.5.3.4 ** Pseudoionone (6,10-dimethylundeca-3,5,9-trien-2-one) [12]

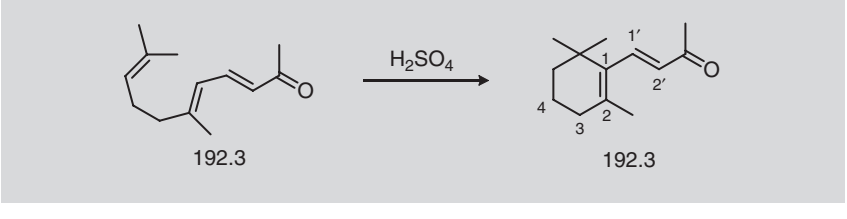


A stirred mixture of the crude dehydrolinalool acetoacetate (**1.5.3.3**) (41.3 g, 175 mmol), decalin (50 ml), glacial acetic acid (0.5 ml), and aluminum isopropoxide (40 mg) is heated to 175–190 °C for 2 h with evolution of CO_2 (bubble trap).

The mixture is then cooled, washed with aqueous H_2SO_4 (1 M, 50 ml), saturated aqueous $NaHCO_3$ solution (3 × 50 ml), and H_2O (2 × 50 ml), dried over $CaSO_4$, and filtered. The decalin is distilled off at 10 mbar (bp_{10} 70–71 °C). The yellow residue is fractionally distilled to give a pale-yellow oil; 21.2 g (63%), $bp_{0.5}$ 92–95 °C, $n^{20}{}_D = 1.5272$. The purity of the product is determined by GC.

UV (CH_3CN): λ_{max} (log ε) = 284 (4.51), 212 nm (4.14).
IR (film): $\tilde{\nu}$ (cm^{-1}) = 1685, 1665, 1630, 1590, 1250, 975.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.41 (dd, *J* = 11.0, 3.0 Hz, 1H, 4-H), 6.20–5.81 (m, 2H, 3-H, 5-H), 5.05 (m, 1H, 9-H), 2.40–2.05 (m, 4H, 7-H_2, 8-H_2), 2.27 (s, 3H, 1-H_3), 1.90 (s, 3H, 6-CH_3), 1.67, 1.61 (s, 6H, 2 × 10-CH_3).

1.5.3.5 ** **β-Ionone [4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-2-one]** [13]



192.3 192.3

Pseudoionone (**1.5.3.4**) (50.0 g, 0.26 mol) is added to a well-stirred mixture of concentrated sulfuric acid (175 g) and glacial acetic acid (75 g) at 5 °C over 40 min, keeping the temperature below 10 °C. Stirring is continued at 10–15 °C for 10 min.

The mixture is then poured into a well-stirred mixture of iced water (1000 ml) and Et_2O (250 ml). The organic phase is separated, and the aqueous phase is extracted with Et_2O (250 ml). The combined organic phases are washed with H_2O (250 ml), 1% aqueous Na_2CO_3 solution (250 ml), and further H_2O (250 ml). The solvent is evaporated *in vacuo* and the residue is steam-distilled. The β-ionone is taken up in Et_2O (2 × 250 ml), the ethereal solution is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The residue is distilled through a 20 cm packed column (Raschig–rings) to give a light-yellow oil with a characteristic, pleasant odor; 36.5 g (73%), $bp_{0.7}$ 91–93 °C, $n^{20}{}_D = 1.5198$.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1700, 1675, 1615, 1590, 1260.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.13, 5.99 (d, *J* = 16.1 Hz, 1H, 4-H, 3-CH), 2.19 (s, 3H, 4′-H_3), 2.07 (m, 2H, 3-H_2), 1.75 (s, 3H, 2-CH_3), 1.80–1.20 (m, 4H, 4-H_2, 5-H_2), 1.07 (s, 6H, 6-$(CH_3)_2$).

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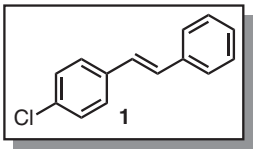
1.6
Transition-Metal-Catalyzed Reactions

1.6.1
(*E*)-4-Chlorostilbene

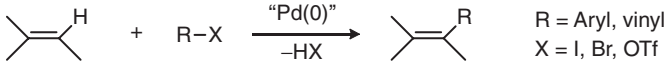


Topic:

- Pd-catalyzed arylation of an alkene by a Heck reaction

(a) **General**

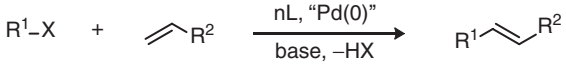
The palladium-catalyzed arylation and alkenylation of alkenes is known as the *Heck reaction* [1]:



This coupling reaction of two sp^2-hybridized carbon centers usually requires the presence of (i) a mono- or bidentate phosphine as complexing ligand, and (ii) a

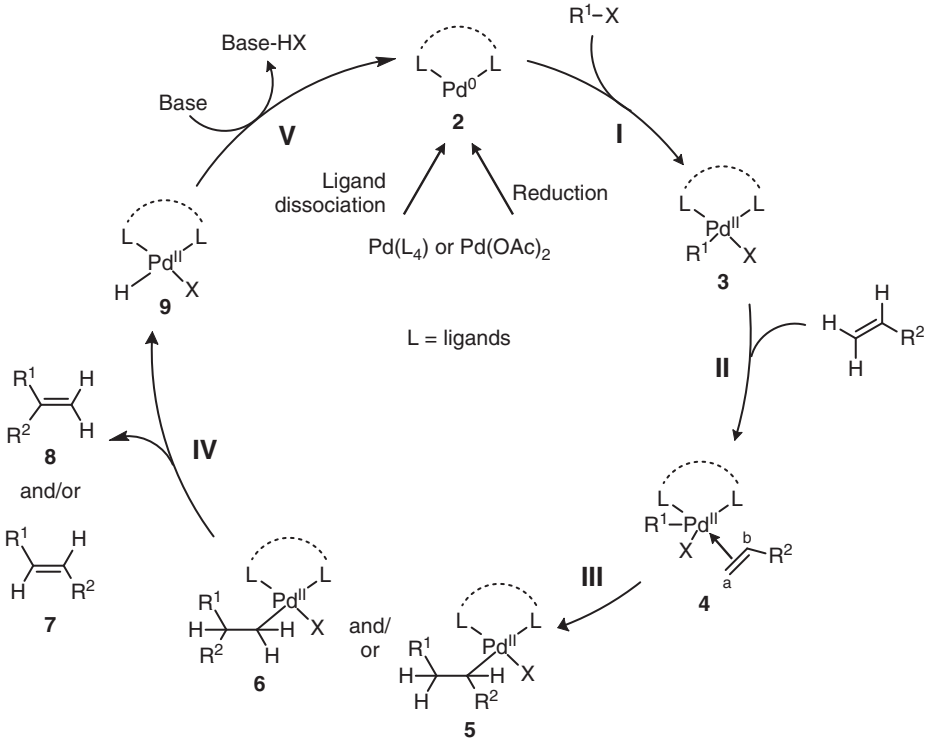
base, often a tertiary amine such as triethylamine or diisopropylethylamine (Hünig base) or an inorganic base such as K_2CO_3 and NaOAc.

The generally accepted mechanism for the Heck reaction [2] consists of a catalytic cycle of five consecutive partial steps **I**–**V**, as formulated for the reaction of a monosubstituted alkene $R^2-CH=CH_2$ with an aryl or alkenyl halide R^1-X:



In step **I**, an oxidative addition of a 14-electron complex, $Pd(0)L_2$ (**2**), takes place by insertion into the $C(sp^2)-X$ bond of R^1-X to give a tetracoordinated 16-electron Pd(II) complex **3**. Complex **2** is formed *in situ* either by reduction of a Pd(II) source such as $Pd(OAc)_2$ by, for example, a tertiary amine [1e, 2b] or a phosphine, or by dissociation of two ligands of a $Pd(0)L_4$ species such as $Pd(PPh_3)_4$.

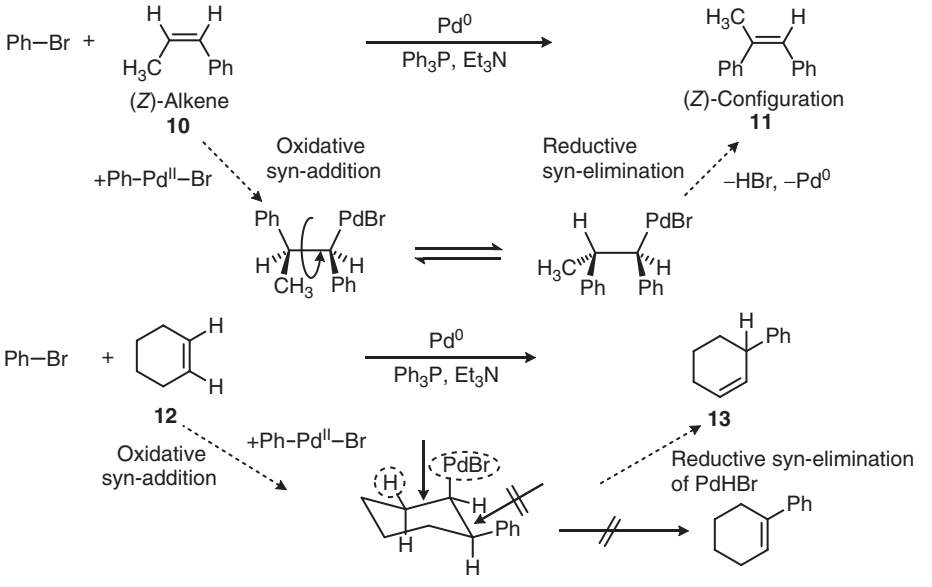
In steps **II** and **III**, the alkene coordinates to the Pd(II) species **3** (π-complex **4**) and is inserted into the $Pd(II)-R^1$ bond. The insertion process **III** is stereoselective and proceeds in a syn manner. Since the alkene $R^2-CH=CH_2$ is unsymmetrical, C_a or C_b may be involved in the insertion and two regioisomeric σ-alkyl-Pd(II) species **5** and/or **6** may be formed.



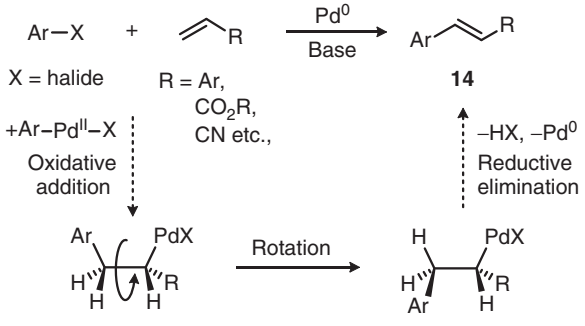
In step **IV**, a syn Pd-β-hydride elimination leads to the formation of the products **7**/**8** and the Pd(II) hydrido complex **9**.

In step **V**, the catalytic cycle is completed by regeneration of the catalytic $Pd(0)L_2$ species (**2**) from **9** by reaction with a base. Steps **IV** and **V** are regarded as reductive elimination.

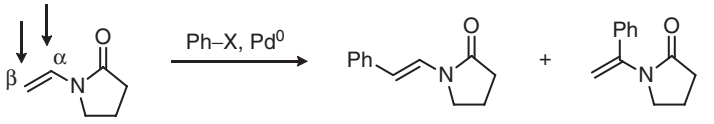
The syn-stereoselectivity of the insertion into the C=C double bond and the reductive elimination has been shown in Heck reactions of stereodefined alkenes such as **10** and **12**, from which the products **11** and **13** are obtained [3]:



The regioselectivity (steps (**III**)/(**IV**)) of Heck reactions of unsymmetrical alkenes $R-CH=CH_2$ with Ar–X [2a] has been investigated using acryl derivatives and styrenes. Substitution usually occurs practically exclusively at the β-CH_2 site of the olefinic substrate to give products **14**, which are predominantly of (*E*)-configuration:



However, in some cases, the regioselectivity has been shown to be influenced (*inter alia*) by the nature of the leaving group X in Ar–X. Thus, from the enamide **15** with X = halide, a mixture of regioisomers **16**/**17** is produced, in which the β-product **16** predominates (3 : 2). However, with X = *O*-triflate, the α-substitution product **17** is formed exclusively:



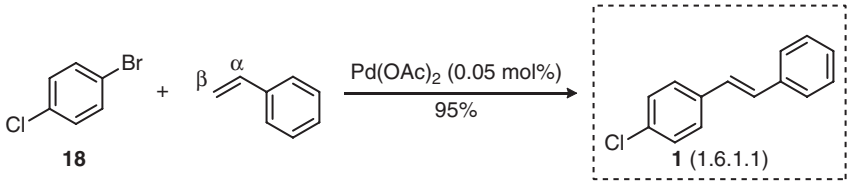
15 **16** **17**

A similar result is obtained if one performs the reaction of Ar–X (X = Hal) in the presence of Ag^+ salts. It is assumed that in this case, as well as using ArOTf, a Pd^+ intermediate is formed. It should be noted that acrylates react at the β-position under both conditions. The Heck reaction is of great synthetic value (cf. Section 3.3.5 and Ref. [4]). It can be performed in inter- and intramolecular modes [5]. Using chiral ligands, enantioselective transformations can be performed with >98% ee [6]. Increasingly, palladacycles are finding application as catalysts in phosphine-free Heck reactions [7, 8], even in polymer-supported form [9]. Likewise, as presented in Section (b), ligand-free Pd sources can be used [10]; for a conventional example, see Section 3.3.5.

Ligand-free Pd catalysts are effective for Heck reactions of aryl iodides [11], for Heck reactions in water [12], and for Heck reactions of substrates with less common leaving groups such as diazonium salts and carboxylic acid derivatives [13]. For the preparatively preferred aryl bromides, however, a convenient ligand-free method has only recently been devised [10].

(b) **Synthesis of 1**

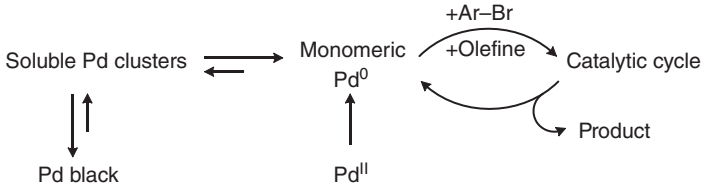
Heck reactions of donor- and acceptor-monosubstituted alkenes (preferentially acrylates and styrenes) can be performed with ligand-free palladium acetate as long as the amount of Pd catalyst is kept between 0.01 and 0.1 mol%. This is exemplified by the reaction of 4-(chloro)bromobenzene (**18**) with styrene in the presence of 0.05 mol% $Pd(OAc)_2$ in *N*-methyl-2-pyrrolidinone (NMP) at 135 °C, which proceeds chemoselectively to give the 4-chloro-substituted *trans*-stilbene **1** in a yield of 94%; the overall conversion is 99%, the trans selectivity is 99 : 1, and the regioselectivity (i.e., α-attack vs. β-attack, cf. Section (a)) is >95 : 5:



18 **1** (1.6.1.1)

At higher catalyst concentrations, palladium black precipitates and the reaction stops before full conversion is obtained.

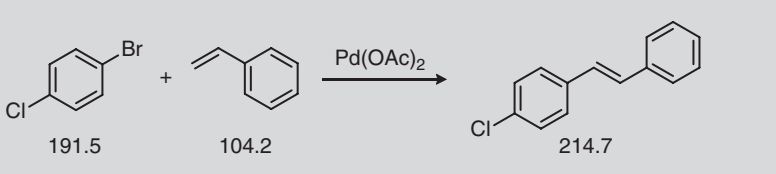
The following proposed mechanism for the arylation [10] explains the effect of low catalyst concentration:



With aryl bromides, the rate-determining step of a Heck reaction is usually the oxidative addition of a monomeric Pd(0) species to the sp^2C-Br bond.[7] Thus, if one uses a higher concentration of Pd(0), in a side reaction this can also aggregate to form soluble Pd clusters, which will turn into insoluble palladium black. Since the latter process is autocatalyzed, it rapidly leads to a lack of soluble Pd(0) species and thus to a termination of product formation.

(c) Experimental Procedure for the Synthesis of 1

1.6.1.1 ** **(*E*)-4-Chlorostilbene** [10]



Under an inert atmosphere, a two-necked flask is charged with NaOAc (0.90 g, 11.0 mmol), 1-bromo-4-chlorobenzene (1.91 g, 10.0 mmol) in NMP (14.0 ml). In a separate flask, $Pd(OAc)_2$ (5.0 mg) is dissolved in NMP (100 ml) to give a stock solution. An aliquot (9.00 ml) of this solution (0.02 mol% Pd with respect to 1-bromo-4-chlorobenzene) is added to the flask containing the bromochlorobenzene by means of a syringe. The stirred mixture is heated to 120 °C, styrene (1.46 g, 14.0 mmol) is added, and stirring is continued at 135 °C for 15 h.

The mixture is then cooled to room temperature, poured into H_2O (75 ml), and extracted with toluene (2 × 75 ml). The combined organic layers are washed with H_2O (3 × 50 ml) and brine (50 ml), dried over Na_2SO_4, and filtered. The solution is filtered through a small plug of Celite® to remove the catalyst, the Celite® is washed with toluene (50 ml), and the solvent is removed *in vacuo* to give a white solid; yield 2.01 g (94%, note), $R_f = 0.33$ (SiO_2; petroleum ether).

7) It should be noted that with aryl iodides the rate-determining step is presumably the insertion process ((3) in (a)) leaving most of the Pd sources in the form of (relatively) stable Pd(II) complexes.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.03 (d, J = 16.4 Hz, 1H, CH=CH) and 7.07 (d, J = 16.4 Hz, 1H, CH=CH), 7.20–7.53 (m, 9H, 9 × Ar–H).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 126.6, 127.4, 127.7, 127.9, 128.7, 128.9, 129.3, 133.2, 135.9, 137.0.

Note: The product contains 5% of 4-chloro-(1-phenylethenyl)benzene (determined by ^{1}H NMR), R_f = 0.49 (SiO_2; petroleum ether).

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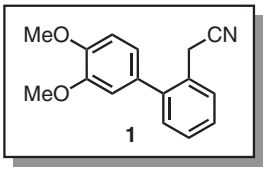
1.6.2

2-Cyanomethyl-3′,4′-dimethoxybiphenyl



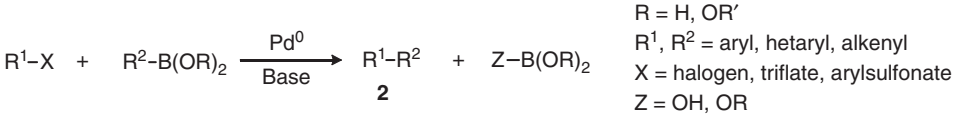
1

Topic:

- Synthesis of biaryls by Suzuki–Miyaura cross-coupling reaction of arylboronic acids with haloarenes

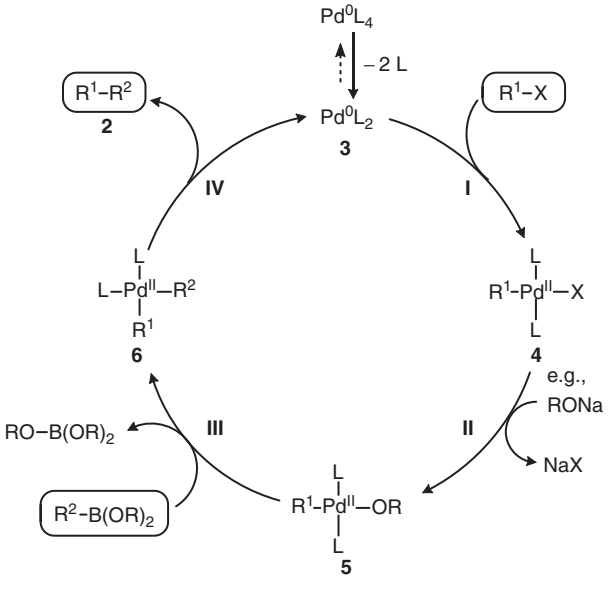
(a) **General**

The Suzuki–Miyaura cross-coupling reaction [1] allows C–C bond formation between aryl or alkenyl boronic acids/esters and arenes, hetarenes, or alkenes bearing a leaving group (halides, triflates, arylsulfonates) to afford products of type **2**:



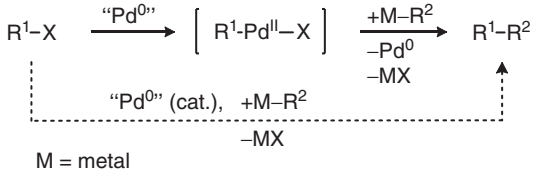
This $C(sp^2)–C(sp^2)$ bond-forming process [2] is catalyzed by Pd(0) complexes, mostly $Pd(PPh_3)_4$, and requires the presence of an inorganic base such as an alkali metal hydroxide, alcoholate, or carbonate to form an ate-complex as an intermediate.

The proposed mechanism of the Suzuki–Miyaura reaction [3] is represented by a catalytic cycle that, in principle, is similar to that operating in the Heck and Sonogashira reactions (cf. Sections 1.6.1 and 1.6.3):

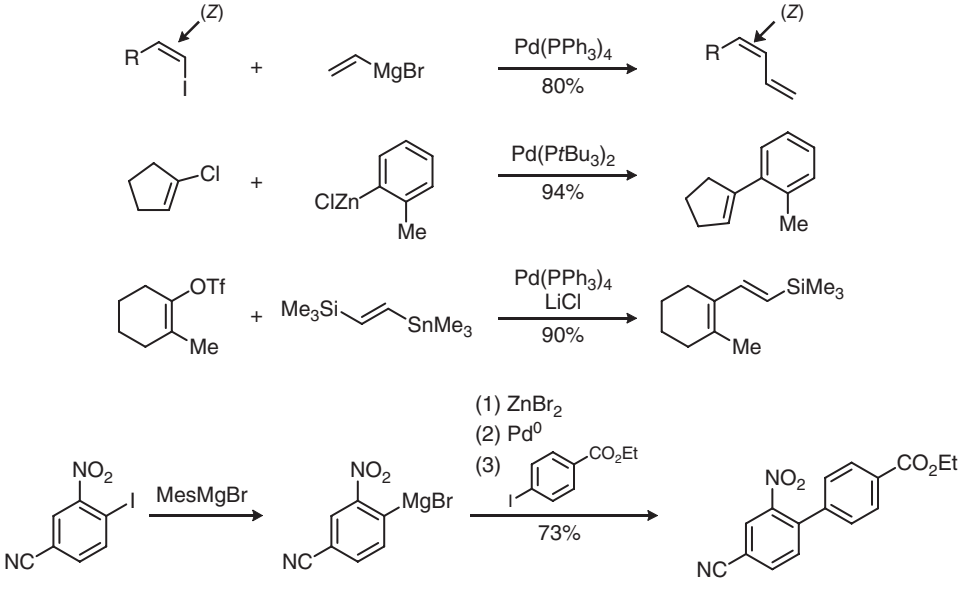


The catalytically active Pd species is again a 14 e $Pd(0)L_2$ complex (**3**) (produced from $Pd(0)L_4$ by ligand dissociation), which starts the catalytic cycle by oxidative addition to R^1-X (step **I**). The resulting tetracoordinated Pd(II) complex **4** is attacked by the base, for example, RONa, the ligand X is exchanged by alcoholate, and a new complex **5** is formed (step **II**). In a second exchange reaction, the boronic acid/ester substitutes the alkoxy ligand (**5** → **6**) by transfer of its organic residue R^2 to the Pd coordination sphere (presumably via ate-complex formation at boron, step **III**). Finally, the Pd(II) complex **6** undergoes a reductive elimination to afford the C–C coupled product **2** (most likely from a complex with a cis orientation of R^1 and R^2 in **6**) and the Pd(0) species **3**, which reenters the catalytic cycle (step **IV**).

Similarly, other organometallics $M-R^2$ can also be used in this Pd(0)-catalyzed "transmetallation" process:



Thus, Pd(0)-mediated transmetallation allows numerous synthetically useful $C(sp^2)-C(sp^2)$ coupling reactions of alkenes and arenes substituted with halogen or triflate. In this respect, Grignard compounds [4], organozinc halides (Negishi cross-coupling [5]), organotin compounds (Stille cross-coupling [6]), and organosilanes have been used, as shown by the following examples:



Besides the Suzuki cross-coupling reactions, the Stille reaction is also widely used, with the advantage that the addition of a base is not necessary. On the other hand, tin is highly toxic. The Negishi protocol also seems to be quite flexible, since the required organozinc halides can be generated by transmetallation from Grignard compounds [5]. Using the commercially available stable catalyst $HPd(PtBu_3)_3 \cdot BF_4$, even aryl and alkenyl chlorides undergo coupling reactions with aryl, vinyl, and alkyl zinc bromides [7]; numerous functional groups (NO_2, CO_2R, CN, COR) are tolerated.

The Suzuki reaction is widely used for the formation of 1,3-butadienes and unsymmetrical biaryls, which are challenging targets in natural product and pharmaceutical chemistry [8–12]:

$$Ar^1{-}X \quad + \quad Ar^2{-}B(OH)_2 \xrightarrow{Pd^0} Ar^1{-}Ar^2$$

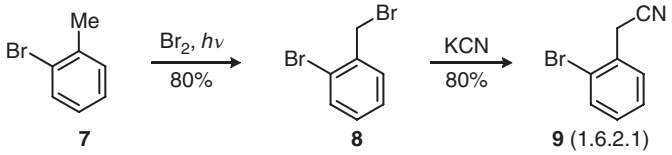
X = Br, I, triflate, arylsulfonate
Ar^1 = Functionalized aryl (CO_2R, CN, NO_2, etc.)
Ar^2 = Functionalized aryl (ether, acetal, etc.)

As Ar^1-X species, mainly bromides, iodides, triflates, and arylsulfonates [13] are used; chlorides can also be coupled in the presence of highly active Pd catalysts such as $HPd(PtBu_3)_3 \cdot BF_4$ [14]. Moreover, diazonium salts and aromatic carboxylic acids can also be employed [15]. Phosphine-free and palladacycle-based modifications of the Suzuki reaction have also been developed [16]. Generally, in Ar^1-X, functional groups such as NO_2, CN, and CO_2R, are tolerated, whereas the boronic acids $Ar^2-B(OH)_2$ may contain ether or acetal functions.

In Section (b), a Suzuki reaction is used for the preparation of **1**, which serves as a substrate for the synthesis of a simple alkaloid (cf. Section 5.2.3 Buflavine) containing an unsymmetrical functionalized biaryl unit [17].

(b) **Synthesis of 1**

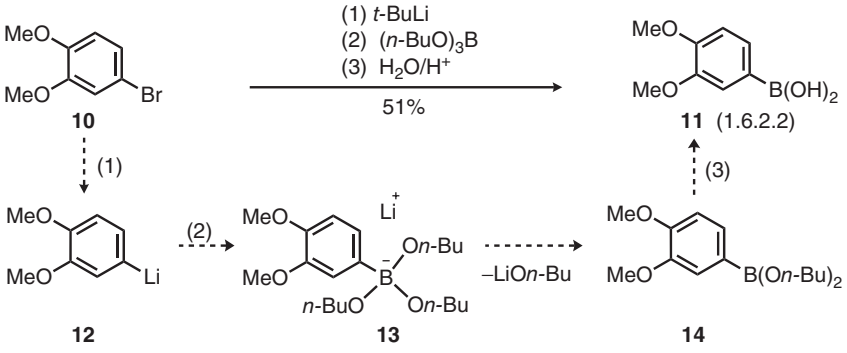
First, the substrate for the Suzuki reaction, (2-bromophenyl)acetonitrile (**9**) is prepared by way of a conventional two-step procedure [18] by photobromination of 2-bromotoluene (**7**) to give **8** and S_N displacement of the benzylic bromide by cyanide:



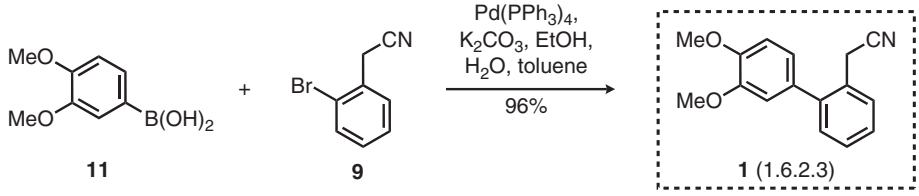
7 **8** **9** (1.6.2.1)

The second building block is (3,4-dimethoxyphenyl)boronic acid (**11**), which is obtained [19] from 4-bromoveratrole (**10**) by halogen–metal exchange with *t*-BuLi (**10** → **12**; with the usually employed *n*BuLi partial o-lithiation is observed).

Reaction of the formed lithio compound **12** with tri-*n*-butyl borate and subsequent acid hydrolysis of the thus obtained boronate **14** leads to **11**. The formation of **14** probably proceeds via the ate-complex **13** and cleavage thereof with loss of *n*-BuOLi:

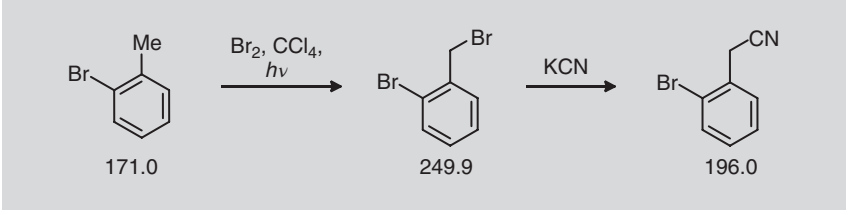


The building blocks **9** and **11** are combined in a Suzuki – Miyaura cross-coupling reaction using $Pd(PPh_3)_4$ as catalyst and K_2CO_3 as base in a solvent mixture. After standard work-up, the biaryl system **1** is isolated in almost quantitative yield.



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

1.6.2.1 ** **(2-Bromophenyl)acetonitrile** [18]



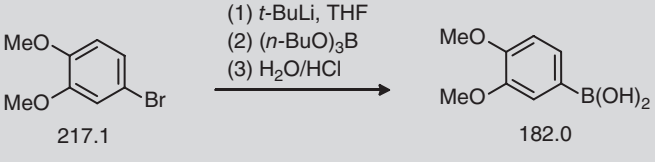
2-Bromotoluene (8.55 g, 50.0 mmol) is dissolved in CCl_4 (250 ml; Caution: resorption through the skin!), and the solution is stirred and heated to reflux under irradiation (daylight lamp 500 W). Bromine (8.19 g, 51.3 mmol) is slowly added from a dropping funnel at such a rate that the refluxing CCl_4 remains

almost colorless. After completion of the reaction, the irradiation is stopped and the solution is cooled to room temperature. The mixture is then rapidly washed with iced water (150 ml), ice-cold saturated aqueous $NaHCO_3$ solution (150 ml), and further iced water (150 ml). The organic layer is dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is distilled *in vacuo* (bp_{16} 130–131 °C) to yield the bromide as colorless liquid; yield 10.0 g (80%).

2-Bromobenzyl bromide (10.0 g, 40 mmol), sodium cyanide (2.45 g, 50.0 mmol, Caution!), and triethylene glycol (20 ml) are carefully heated to 100 °C with vigorous stirring. The mixture is stirred at this temperature for a further 30 min, then poured into water, and extracted with $CHCl_3$ (4 × 20 ml). The isocyanide (formed as a side-product) is removed from the combined organic layers by shaking with 5% aqueous H_2SO_4 (15 ml) for 5 min, and the organic layer is separated and washed sequentially with dilute aqueous $NaHCO_3$ solution (30 ml) and water. The organic layer is dried over $CaCl_2$ and filtered, and the solvent is removed *in vacuo*. The residue is purified by distillation (bp_{17} 146–147 °C) to yield a colorless liquid; yield 6.27 g (80%).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3060, 2260, 1565, 1475, 1020, 740.
^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 7.57 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar–H), 7.49 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar–H), 7.33 (dt, *J* = 7.8, 1.7 Hz, 1H, Ar–H), 7.18 (dt, *J* = 7.8, 1.7 Hz, 1H, Ar–H), 3.80 (s, 2H, CH_2).
^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 132.8, 129.7, 129.6, 129.5, 127.9, 123.3, 116.7, 24.60.
MS (EI, 70 eV): *m*/*z* (%) = 197 (34) $[M+H]^+$, 195 (35) $[M-H]^+$, 171 (8), 169 (9), 116 (100), 89 (36).

1.6.2.2 ** 3,4-Dimethoxyphenylboronic acid [19]



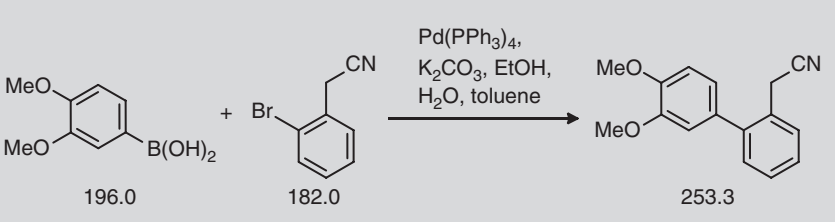
tert-Butyllithium (1.5 M in CH_2Cl_2, 13.5 ml, 20.2 mmol) is slowly added to a stirred solution of 4-bromoveratrole (4.00 g, 18.4 mmol) in THF (50 ml) at −78 °C over 4 h (the temperature must not exceed −70 °C), followed by trimethyl borate (2.87 g, 27.6 mmol). The mixture is then allowed to warm to room temperature overnight.

HCl (2 M, 25 ml) is added, and the aqueous phase is extracted with Et_2O (2 × 50 ml). The combined organic layers are extracted with aqueous NaOH (2 M, 2 × 50 ml), and then the combined aqueous extracts are acidified with concentrated HCl to pH 1. The aqueous layer is extracted with Et_2O (3 × 50 ml),

and the combined organic layers are dried over $MgSO_4$, filtered, and concentrated to give the boronic acid as colorless solid; 1.72 g (51%), mp 238–240 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.85 (dd, J = 8.2, 1.3 Hz, 1H, Ar–H), 7.68 (d, J = 1.3 Hz, 1H, Ar–H), 7.01 (d, J = 8.2 Hz, 1H, Ar–H), 4.01 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3).
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 153.0, 148.6, 129.9, 117.5, 110.8, 55.9, 55.9.

1.6.2.3 ** 2-Cyanomethyl-3′,4′-dimethoxybiphenyl [17]



A solution 3,4-dimethoxyphenylboronic acid **1.6.2.2** (2.00 g, 11.0 mmol) in EtOH (60 ml) is added to a mixture of (2-bromophenyl)acetonitrile **1.6.2.1** (1.96 g, 10.0 mmol), toluene (60 ml), $Pd(PPh_3)_4$ (348 mg, 0.30 mmol), K_2CO_3 (4.15 g, 30.0 mmol), and water (40 ml). The mixture is degassed and heated to reflux for 24 h under inert gas atmosphere.

After cooling to room temperature, water (50 ml) is added and the mixture is extracted with Et_2O (3 × 80 ml). The combined organic layers are dried over $MgSO_4$, filtered, and concentrated. The residue is purified by column chromatography (SiO_2; CH_2Cl_2) to give 2.43 g (96%) of a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.56–7.46 (m, 1H, Ar–H), 7.44–7.26 (comb. m, 3H, Ar–H), 6.95 (d, J = 8.5 Hz, 1H, Ar–H), 6.85 (s_{br}, 2H, Ar–H), 3.93 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.63 (s, 2H, CH_2–CN).
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 149.1, 148.7, 141.9, 132.6, 130.6, 129.1, 128.2, 128.1, 121.2, 118.5, 112.3, 111.4, 56.0, 56.0, 22.1.

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Tzschukke, C.C., Markert, C., Glatz, H., and Bannwarth, W. (2002) *Angew. Chem.*, **114**, 4678–4681; *Angew. Chem. Int. Ed.*, (2002), **41**, 4500–4503; for ligandless biaryl coupling, see: (d) Tao, X., Zhao, Y., and Shen, D. (2004) *Synlett*, 359–361; (e) Solodenko, W., Weu, H., Leue, S., Stuhlmann, F., Kunz, U., and Kirschning, A. (2004) *Eur. J. Org. Chem.*, 3601–3610.

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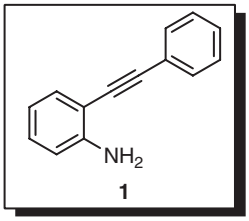
1.6.3
(2-Phenylethynyl)aniline

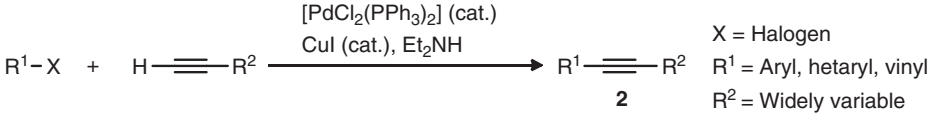


1

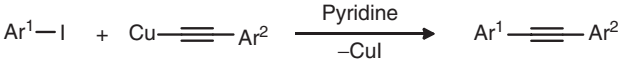
Topic: • Sonogashira cross-coupling reaction of terminal acetylenes with aryl and vinyl halides

(a) **General**

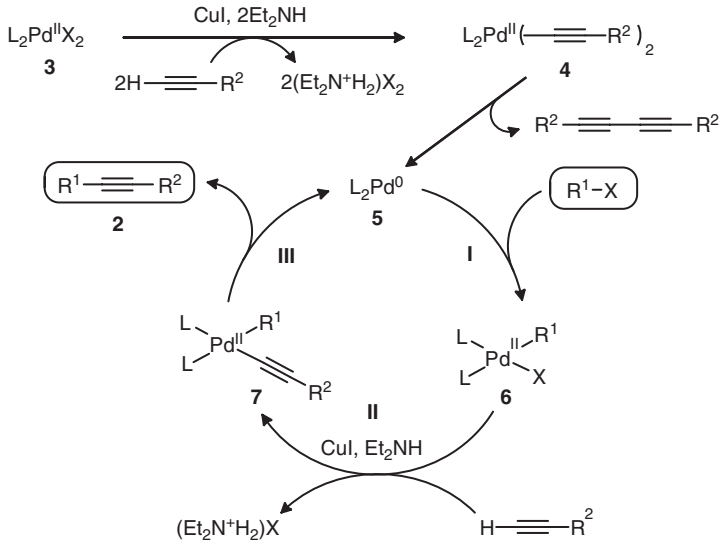
The Sonogashira cross-coupling reaction [1] allows C–C bond formation between C(sp) and C(sp^2) centers by a Pd(0)-catalyzed reaction of haloarenes, halohetarenes, and haloalkenes with alkynes to give the coupled products **2**. The reaction is co-catalyzed by Cu(I) iodide and requires the presence of a base, preferably diethylamine:



The Sonogashira coupling is related to the Stephens–Castro reaction [2], the coupling of iodoarenes with copper(I) aryl acetylides:

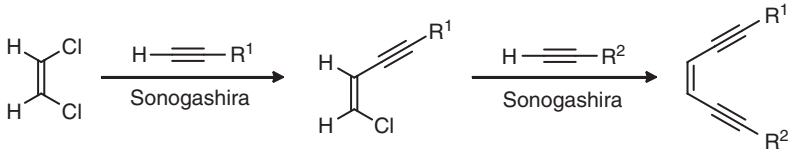


The mechanism of the Sonogashira cross-coupling reaction [2] resembles that of the Heck and Suzuki–Miyaura reactions by providing C–C bond formation in the coordination sphere of Pd complexes (L = ligand, e.g., Ph_3P).

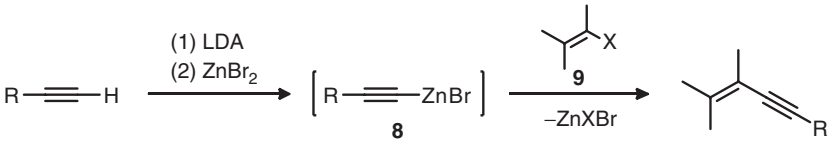


The catalytic cycle is initiated by a $Pd(0)L_2$ species **5**, which is generated, for example, in a preceding sequence from a Pd(II) complex **3** by base-induced exchange of the ligands X with acetylide and subsequent disproportionation of the acetylide Pd(II) complex **4** leading to the formation of $Pd(0)L_2$ (**5**) and, as a side product, a diyne. This can be avoided by using a Pd(0) complex such as $Pd(PPh_3)_4$ as catalyst. The Pd(0) species **5** undergoes an oxidative addition to R^1-X (step **I**), which is followed by base-induced substitution of X by acetylide in the Pd(II) complex **6** catalyzed by Cu(I) iodide (step **II**). Finally, a reductive elimination process of the formed Pd(II) complex **7**, most likely from a syn arrangement (step **III**), leads to the disubstituted acetylene **2** and $Pd(0)L_2$, which again enters into the catalytic cycle.

Usually, iodo compounds are used in the Sonogashira reaction because these are more reactive than the bromo and chloro compounds [3]. This allows the chemoselective reaction of haloarenes bearing different halogens as substituents. Moreover, the consecutive introduction of two different acetylenic moieties in dihaloalkenes is also possible, which is used in the syntheses of analogs of enediyne antibiotics [2]:



As an alternative to the Sonogashira reaction, alkynylation of haloalkenes **9** can be efficiently accomplished by Pd(0)-catalyzed reaction with *in situ* generated alkynyl zinc bromides **8**, which are easily accessible from acetylides and $ZnBr_2$ [4]:

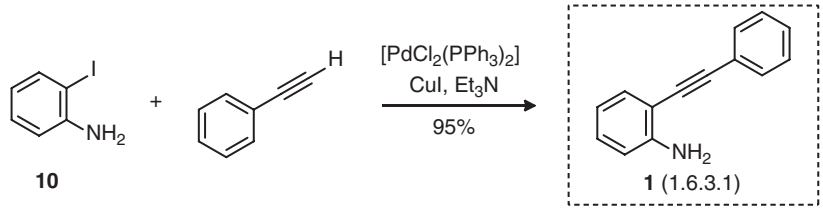


The great synthetic value of the Sonogashira reaction, above all, stems from the fact that further transformations of the alkyne moiety may be performed. This is documented, for example, in a series of syntheses of heterocyclic systems [5].

Thus, in Section (b), the preparation of substrate **1** for a Pd-catalyzed indole synthesis (cf. Section 3.2.4) by means of a Sonogashira cross-coupling [6] is described.

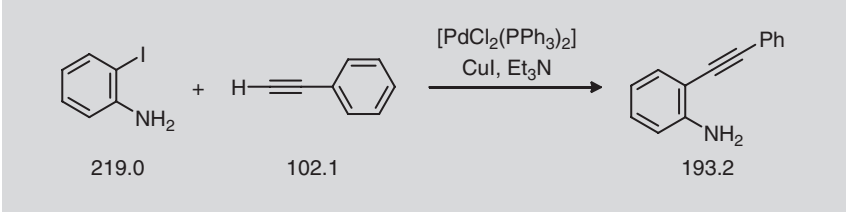
(b) **Synthesis of 1**

The synthesis of **1** starts from 2-iodoaniline (**10**), which is commercially available but can also be easily prepared by ortho-lithiation of aniline and subsequent quenching with iodine [7]. The Sonogashira cross-coupling reaction of **10** with phenylacetylene in the presence of $[PdCl_2(PPh_3)_2]$ as catalyst, Cu(I) iodide as co-catalyst, and triethylamine as base provides (2-phenylethynyl)aniline (**1**) in almost quantitative yield:



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

1.6.3.1 ** **2-(Phenylethynyl)aniline** [6]



A mixture of 2-iodoaniline (2.19 g, 10.0 mmol), phenylacetylene (1.12 g, 11.0 mmol), CuI (190 mg, 1.00 mmol), $[PdCl_2(PPh_3)_2]$ (210 mg, 0.30 mmol), and Et_3N (20 ml) is stirred for 1 h at 60 °C.

The reaction mixture is then diluted with H_2O (20 ml) and extracted with $CHCl_3$ (3 × 20 ml). The combined extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The crude product is purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 3 : 1) and recrystallized from

n-hexane/EtOAc (20 : 1) to give pale-yellow prisms; 1.84 g (95%); mp 86–87 °C; $R_f = 0.60$ (*n*-hexane/EtOAc, 3 : 1).

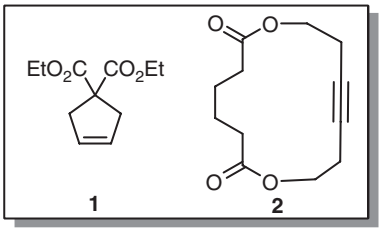
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3500, 2250, 1620.
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.56–7.51 (m, 2H, Ph–H), 7.39–7.32 (m, 4H, Ph–H), 7.14 (dt, J = 7.9, 1.4 Hz, 1H), 6.79 (t, J = 7.7 Hz, 2H), 4.29 (s_{br}, 2H, NH_2).

References

1. (a) Beller, M. and Bolm, C. (eds) (2004) *Transition Metals for Organic Synthesis*, **2** vols., Wiley-VCH Verlag GmbH, Weinheim; (b) de Meijere, A. and Diederich, F. (eds) (2004) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd edn, **2** vols., Wiley-VCH Verlag GmbH, Weinheim; Instead of Pd complexes, nanosized Pd(0) ((c) Li, P., Wang, L., and Li, H. (2005) *Tetrahedron*, **61**, 8633–8640), ultrafine Ni(0) (Wang, L., Li, P., and Zhang, Y. (2004) *Chem. Commun.*, 514–515), or Pd immobilized on organic–inorganic hybrid materials (Li, P.-M. and Wang, L. (2006) *Adv. Synth. Catal.*, **348** 681–685) has also been applied in the Sonogashira process.
2. Nicolaou, K.C. and Sorensen, E.J. (1996) *Classics in Total Synthesis*, Wiley-VCH Verlag GmbH, Weinheim, p. 582.
3. (a) Krause, N. (1996) *Metallorganische Chemie*, Spektrum Akademischer Verlag, Heidelberg, p. 216; Efficient catalysts have also been developed for the Sonogashira coupling of chloroarenes: (b) Köllhofer, A., Pullmann, T., and Plenio, H. (2003) *Angew. Chem.*, **115**, 1086–1088; *Angew. Chem. Int. Ed.*, (2001), **40**, 1056–1058.
4. (a) Negishi, E.-i., Qian, M., Zeng, F., Anastasia, L., and Babinski, D. (2003) *Org. Lett.*, **5**, 1597–1600; (b) Anastasia, L. and Negishi, E.-I. (2001) *Org. Lett.*, **3**, 3111–3113.
5. See: Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 83, 140.
6. Yasuhara, A., Kanamori, Y., Kaneko, M., Numata, A., Kondo, Y., and Sakamoto, T. (1999) *J. Chem. Soc., Perkin Trans. 1*, 529–534.
7. Snieckus, V. (1990) *Chem. Rev.*, **90**, 879–933.

1.6.4

Diethyl cyclopent-3-ene-1,1-dicarboxylate and 1,8-Dioxacyclotetradec-11-yne-2,7-dione



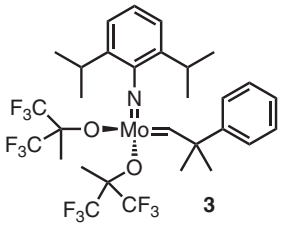
Topics:

- Ring-closing alkene metathesis
- Synthesis of Ru complexes
- Ligand exchange
- Ring-closing alkyne metathesis with an air-stable molybdenum alkylidene phenanthroline catalyst
- Synthesis of a cyclopentene
- Synthesis of an acyclic dialkyne
- Synthesis of a cyclic alkyne

(a) **General**

The alkene metathesis is a very important method for the formation of C=C-double bonds. The most useful procedures from the synthetic standpoint are the ring-closing metathesis (RCM), the ring-opening metathesis (ROM), and the cross metathesis (CM) of alkenes. Further important variants are the ring-opening metathesis polymerization (ROMP), the acyclic diene metathesis (ADMET), and the alkyne metathesis mostly in the ring-closing mode (RCAM (ring-closing alkene metathesis)) [1].

As catalysts for these transformations, organometallic compounds of the Schrock type **3** containing molybdenum or tungsten and of the Grubbs type **4**, **5**, and **6** containing ruthenium are used. Another useful catalyst for the alkene metathesis are the Ru-phenylindenylidene complexes **7a** and **7b**.



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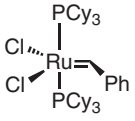

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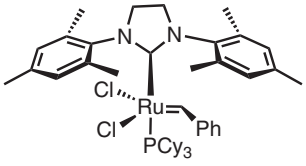

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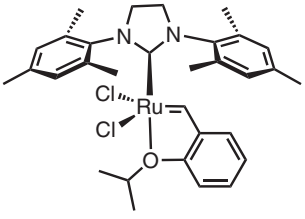
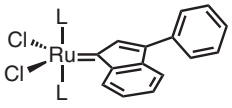


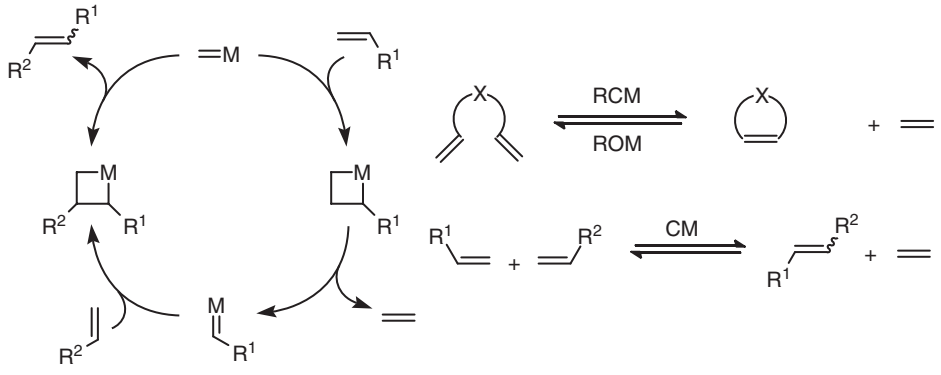
6



7a: L = PPh_3
7b: L = PCy_3

The alkene metathesis proceeds via a [2 + 2]-cycloaddition of an alkene and the alkylidene unit of the catalyst to form a metallacyclobutane. In a cycloreversion, the reaction could go backwards or form another alkylidene unit which reacts with another alkene to give the product and the catalyst. It is important to know that metatheses are thermodynamically controlled. In this respect, CMs and RCMs are favored by an entropic effect because of the formation of ethene or other gases.

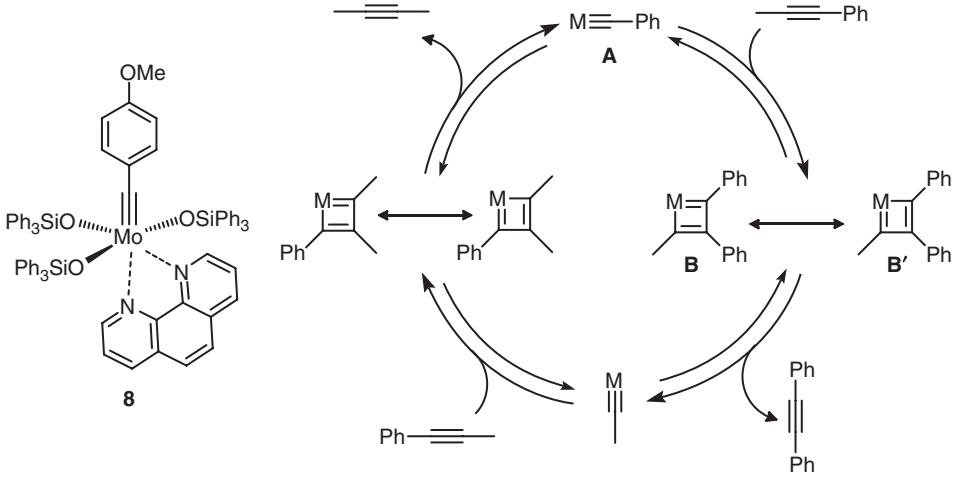
CMs are nowadays often used as a replacement for the Wittig reaction and the RCMs leading to cyclohexenes as a replacement for the Diels–Alder reaction.



However, one of the major drawbacks is the usually low *E/Z*-selectivity, though novel developments by Schrock *et al.* [2] seem to solve the problem. But another possibility to prepare selectively *E*- or *Z*-cycloalkenes of larger rings is the use of the alkyne RCM. Fürstner [3] has recently developed novel air-stable Mo complexes **8** which can be employed for this purpose.

The cyclic alkynes obtained can then be hydrogenated using a Lindlar-type catalyst to give (*Z*)-cycloalkenes. On the other hand, Birch reduction or some novel methods [4] lead to the corresponding (*E*)-compounds.

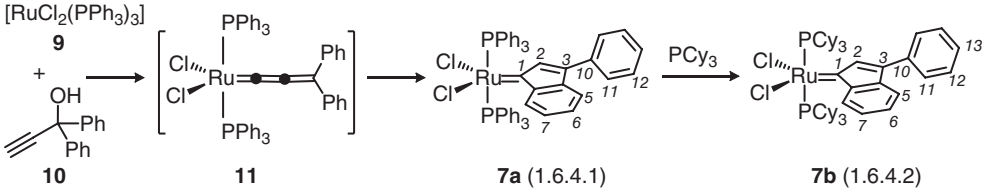
The alkyne metathesis follows a similar mechanism as the alkene metathesis with a metallayclobutadiene as an intermediate:



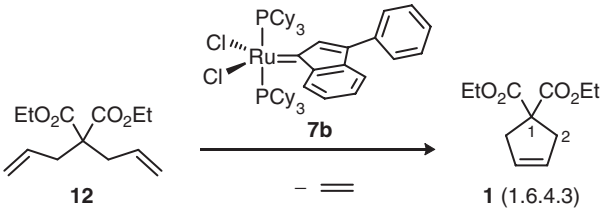
(b) **Synthesis of 1 and 2**

For the synthesis of the cyclopentene **1** by an RCM of the α,ω-diene **12**, the Ru-phenylindenylidene complex **7b** is used as catalyst [5]. Though catalysts **4** and **5** would also be suitable, the ruthenium-phenyliden complexes **7a** and **7b** developed

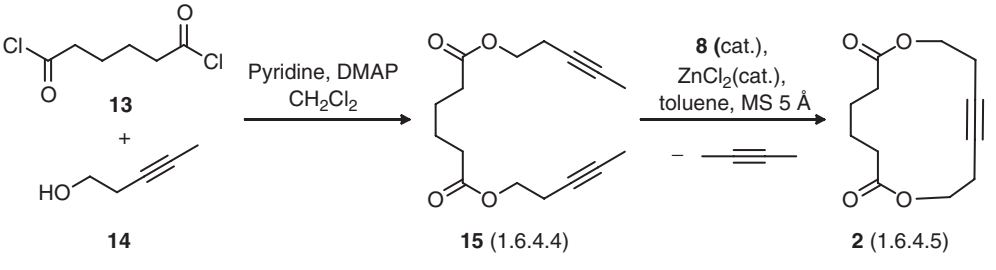
by Fürstner [3] are very good alternatives to the first-generation Grubbs catalyst **4**. The main advantage of these catalysts is their ease of preparation using the Ru complex **9** and the inexpensive and nontoxic diphenylpropargylic alcohol **10** as the carbene source. In contrast, for the synthesis of the Grubbs catalysts, phenyldiazomethane has to be employed. The preparation of **7a** proceeds via **11** by heating a mixture of **9** and **10** under reflux for 90 min in THF. The complex **7a** can then be transformed into the complex **7b** by heating **7a** in the presence of tricyclohexylphosphane.



For the synthesis of **1**, the commercially available 1,6-diene **12** is used in the presence of 1.5 mol% of **7b** in dichloromethane.

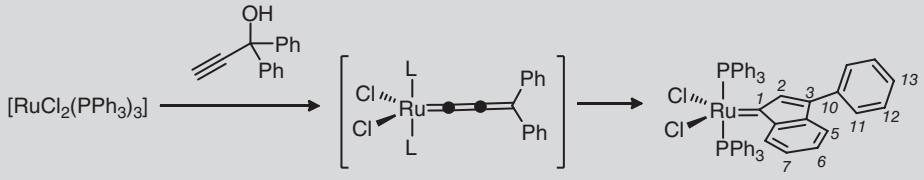


For the ring-closure alkyne metathesis, the novel air-stable Mo complex **8**, which is commercially available, can be employed [3], and as a substrate for the metathesis, the adipic ester **15** containing two alkyne moieties is used in the example described here. It can be obtained from adipyl dichloride **13** with 3-pentynol **14**.



(c) **Experimental Procedures for the Synthesis of 1 and 2**

1.6.4.1 *** **Ruthenium-phenylindenylidene complex 7a** [5]



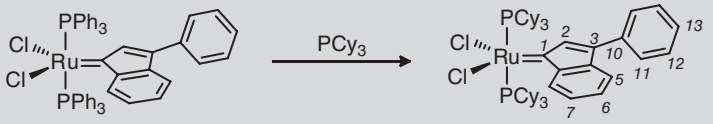
958.8 886.8

A two-necked flask equipped with a reflux condenser, a magnetic stirring bar, and an argon or nitrogen supply is evacuated, dried with a heat gun, and flushed with argon or nitrogen. The flask is charged with $[RuCl_2(PPh_3)_3]$ (10.4 g, 10.8 mmol), THF (600 ml), and 1,1-diphenylpropargyl alcohol (3.37 g, 16.2 mmol), and the resulting mixture is refluxed under inert gas for 2.5 h. During this period, the mixture turns dark-red.

For work-up, the solvent is evaporated *in vacuo* (12 mbar), the residue is suspended in *n*-hexane (400 ml), and the suspension is stirred for approximately 3 h until the solid is thoroughly ground and has a homogeneous appearance. The powdered solid is filtered off and dried *in vacuo* to give 9.60 g (quant.) of the complex **1.6.4.1** as an orange powder.

^{1}H NMR (600 MHz, CD_2Cl_2): δ (ppm) = 7.54 (1H, 13-H), 7.54 (12H, Ph), 7.50 (2H, 11-H, 12-H), 7.46 (6H, Ph), 7.34 (2H, 12-H), 7.33 (12H, Ph), 7.31 (td, J = 7.5, 1.5 Hz, 1H, 6-H), 7.25 (dd, J = 7.5, 1.5 Hz, 1H, 5-H), 7.08 (dd, J = 7.3, 1.0 Hz, 1H, 8-H), 6.67 (td, J = 7.4, 1.0 Hz, 1H, 7-H), 6.38 (s, 1H, 2-H).
^{13}C NMR (150 MHz, CD_2Cl_2): δ (ppm) = 301.0 (s, J = 12.9 Hz (t), C-1), 145.4 (s, C-3), 141.8 (s, J = 2.7 Hz (t), C-9), 139.8 (s, C-4), 139.4 (d, J = 5.2 Hz (t), 175.4 Hz, C-2), 135.6 (s, C-10), 130.1 (d, C-6), 130.1 (d, C-7), 129.41 (2C, d, C-12), 129.36 (d, C-13), 129.33 (d, 165 Hz, C-8), 127.1 (2C, d, C-11), 118.6 (d, 160 Hz, C-5). Phenyl signals: X part of ABX spin systems (A, B = ^{31}P, X = ^{13}C), δ = 135.2 (d, [J(P,C) + J(P′,C)] = 11.2 Hz, C-*ortho*), 131.2 (s, [J(P,C) + J(P′,C)] = 42.8 Hz, C-*ipso*) 130.6 (d, C-*para*), 128.4 (d, [J(P,C) + J(P′,C)] = 9.6 Hz, C-*meta*).
^{31}P NMR (243 MHz, CD_2Cl_2, rel. ext. H_3PO_4): δ (ppm) = 28.7.

1.6.4.2 *** Ruthenium-phenylindenylidene complex (7b) [5]



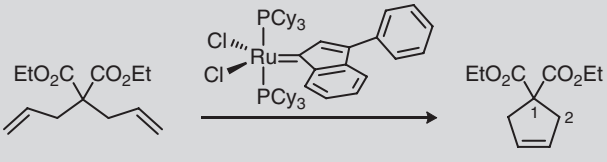
886.8 923.1

PCy_3 (9.39 g, 33.5 mmol) is added to a solution of the complex **1.6.4.1** in CH_2Cl_2 (250 ml), and the resulting mixture is stirred for 2 h at ambient temperature under argon.

The solvent is evaporated, and the crude product is suspended in *n*-hexane (400 ml) and stirred for approximately 3 h at ambient temperature. The thoroughly powdered complex is filtered off and is carefully washed with *n*-hexane (100 ml) in several portions. Drying of the product *in vacuo* affords 7.90 g (80%) of complex **1.6.4.2** as an analytically pure orange powder.

^{1}H NMR (600 MHz, CD_2Cl_2): δ (ppm) = 8.67 (dd, J = 7.5 Hz, 1H, 8-H), 7.75 (2H, 11-H), 7.52 (1H, 13-H), 7.40 (2H, 12-H), 7.39 (s, 1H, 2-H), 7.38 (td, 1H, J = 7.3 Hz, 6-H), 7.29 (td, J = 7.5 Hz, 1H, 7-H), 7.27 (dd, J = 7.3 Hz, 1H, 5-H). Cyclohexyl signals: δ = 2.60, 1.77, 1.73, 1.66, 1.65, 1.52, 1.50, 1.47, 1.21, 1.19, 1.18.
^{13}C NMR (150 MHz, CD_2Cl_2): δ (ppm) = 293.9 (s, J = 8.1 Hz (t), C-1), 145.0 (s, C-9), 141.4 (s, C-4), 139.8 (s, C-3), 139.1 (d, ^1J(C,H) = 175 Hz, C-2), 136.8 (s, C-10), 129.4 (d, ^1J(C,H) = 163 Hz, C-8), 129.4 (2C, d, C-12), 129.2 (d, C-7), 128.7 (d, C-6), 128.4 (d, C-13), 126.6 (2C, d, C-11), 117.6 (d, ^1J(C,H) = 157 Hz, C-5). Cyclohexyl signals: δ (ppm) = 33.1 (CH), 30.21, 30.16, 28.3, 28.1, 26.9 (all CH_2).
^{31}P NMR (243 MHz, CD_2Cl_2, rel. ext. H_3PO_4) δ (ppm) = 32.6.

1.6.4.3 ** Diethyl cyclopent-3-ene-1,1-dicarboxylate [5]



240.3 212.2

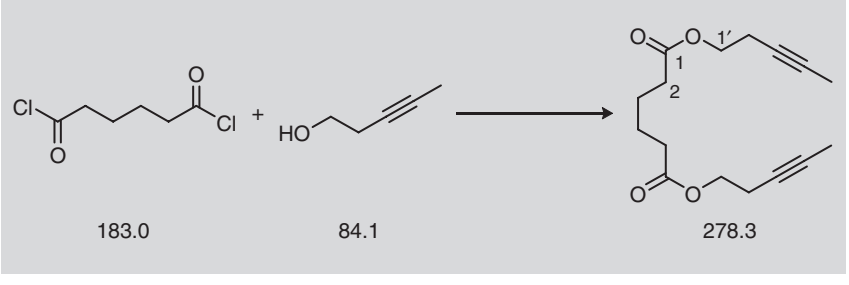
To a stirred solution of the ruthenium-indenyliden complex **1.6.4.2** (32.5 mg, 1.5 mol%) in dichloromethane (5.0 ml) in a dry two-neck round-bottom flask equipped with a gas inlet and a glass stopper, diethyl 2,2-diallylmalonate (577 mg, 2.40 mmol) is added under argon or nitrogen atmosphere (note) at room temperature, and stirring is continued for 90 min at this temperature.

The solvent is removed *in vacuo*, and the residue is purified by column chromatography on silica gel (*n*-pentane/diethyl ether = 20 : 1) to give 459 mg (90%) of the cyclopentene derivative **1.6.4.3** as a colorless oil.

IR (film) $\tilde{\nu}$ (cm^{-1}) = 3063, 2983, 1733, 1625, 1256, 1182, 1072, 697.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.62–5.60 (m, 2H, 2 × 3-H), 4.20 (q, J = 7.1 Hz, 4H, $C\underline{H}_2CH_3$), 3.01 (s, 4H, 2 × 2-H_2), 1.25 (t, J = 7.1 Hz, 6H,$CH_2C\underline{H}_3$).
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.2 ($COCH_2CH_3$), 127.7 (2 × C-3), 61.4 ($COCH_2CH_3$), 58.8 (C-1), 40.8 (C-2), 14.0 ($COCH_2CH_3$).
MS: *m*/*z* (rel. intensity): 212 (M^+, 23), 166 (52), 138 (89), 123 (2), 111 (52), 93 (44), 79 (63), 66 (84), 55 (8), 39 (20), 29 (100).

Note: Strict exclusion of oxygen is necessary for high yields.

1.6.4.4 * **Di(pent-3-yn-1-yl) adipate** [6, 7]



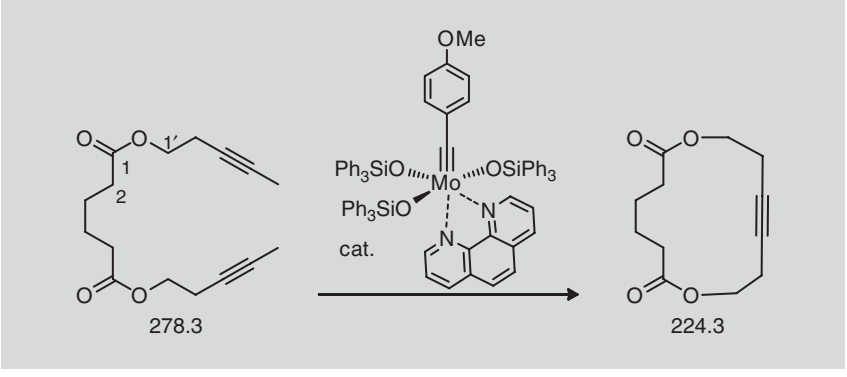
To a stirred solution of 3-pentnyl-1-ol (5.04 g, 59.9 mmol) and dimethylaminopyridine (DMAP) (cat., ~40 mg) in anhydrous pyridine (5.0 ml) and anhydrous dichloromethane (50 ml) in a dry two-neck round-bottom flask equipped with a dropping funnel and a glass stopper, a solution of adipyl dichloride (5.48 g, 29.9 mmol) in dichloromethane (20 ml) is added dropwise at 0 °C. Stirring is continued for 12 h at room temperature.

For work-up, aqueous HCl (1 M, 80 ml) is added slowly with stirring. The organic phase is separated and washed consecutively with aqueous HCl (1 M, 30 ml) and saturated aqueous $NaHCO_3$ solution (30 ml). The combined aqueous phases are extracted with ethyl acetate (50 ml), and the combined organic layers are washed with brine (50 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the residue is co-evaporated twice with a small amount of toluene (15 ml) to remove remaining pyridine by azeotropic distillation. After drying of

the residue *in vacuo,* the adipic acid dialkynylester **1.6.4.4** is obtained as a colorless solid, which is used in the next step without further purification; 7.49 g (90%); mp = 63–64 °C.

IR (film) $\tilde{\nu}$ (cm^{-1}) = 2962, 2918, 2856, 1735, 1698, 1468, 1453, 1427, 1412, 1394, 1371, 1302, 1250, 1136, 1070, 1051, 981, 924, 913, 750, 734, 707.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.11 (t, J = 7.0 Hz, 4H, 2 × 1′-H_2), 2.44 (tq, J = 7.0, 2.5 Hz, 4H, 2 × CH_2), 2.36–2.31 (m, 4H, 2 × CH_2), 1.76 (t, J = 2.5 Hz, 6H, 2 × CH_3), 1.69–1.63 (m, 4H, 2 × CH_2).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 173.0 (C-1), 77.2, 74.7 (C-3′, C-4′), 62.7 (C-1′), 33.8, 24.3, 19.2 (C-2, C-3, C-2′), 3.4 (C-5′).
MS: *m*/*z* (EI) (rel. intensity): 278 (2) $[M]^+$, 213 (22), 196 (11), 195 (92), 177 (12), 153 (12), 150 (16), 149 (26), 135 (27), 133 (10), 132 (76), 131 (22), 129 (35), 126 (13), 125 (12), 117 (78), 111 (64), 107 (20), 101 (17), 97 (13), 83 (19), 67 (100), 66 (76), 65 (21), 55 (24), 41 (19).
HRMS: (ESI+): *m*/*z*: calc. for $[C_{16}H_{22}O_4 + Na]^+$: 301.1410; found: 301.1409.

1.6.4.5 ** **1,8-Dioxacyclotetradec-11-yne-2,7-dione** [6, 7]



A two-necked flask with a magnetic stirring bar, an argon or nitrogen supply, and a glass stopper is evacuated, dried with a heat gun, and flushed with argon or nitrogen. Then it is charged with $ZnCl_2$ (12.7 mg, 5 mol%) and molecular sieves (5 Å, about 4 g, activated at 180 °C *in vacuo*). Anhydrous toluene (90 ml) is added, and the suspension is stirred for 1 h at room temperature. Afterwards, [Mo(≡CAr)($OSiPh_3$)$_3$(phen)] (Ar = 4-methoxyphenyl, phen = 1,10-phenanthroline) (114 mg, 5 mol%) and 1,6-bis(pent-3-yne-1-yl)hexanedioate **1.6.4.4** (519 mg, 1.87 mmol) are added in solid form and the mixture stirred for 18 h at room temperature.

For work-up, a frit (diameter about 4.5 cm) is filled with silica gel (~19 g) with the help of *n*-hexane/ethyl acetate (5 : 1). Then the reaction mixture is filtered through this pad of silica gel with *n*-hexane/ethyl acetate (5 : 1, ~140 ml) as eluent, and the filtrate is discarded (TLC control). Then the pad is eluted again with

n-hexane/ethyl acetate (5 : 1, ~120 ml), and the filtrate is collected and evaporated *in vacuo* to give analytically pure **1.6.4.5** as colorless solid; 350 mg (84%); mp = 109–110 °C.

IR (film) $\tilde{\nu}$ (cm^{-1}) = 2995, 2954, 2937, 2918, 2901, 2872, 1721, 1458, 1425, 1384, 1341, 1272, 1236, 1167, 1140, 1080, 1065, 1021, 981, 931, 843, 824, 699.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.13–4.06 (m, 4H, 2 × CH_2), 2.53–2.47 (m, 4H, 2 × CH_2), 2.39–2.30 (m, 4H, 2 × CH_2), 1.76–1.67 (m, 4H, 2 × CH_2).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 173.2 (2 × $CH_2CO_2CH_2$), 78.2 (2 × C≡C), 62.8 (2 × CH_2), 35.2 (2 × CH_2), 25.4 (2 × CH_2), 19.4 (2 × CH_2).
MS: *m*/*z* (EI) (rel. intensity): 129 (3), 111 (8), 78 (100), 66 (20), 55 (15), 41 (8).
HRMS: (ESI+): *m*/*z*: calc. for $[C_{12}H_{16}O_4 + Na]^+$: 247.0941; found: 247.0938.

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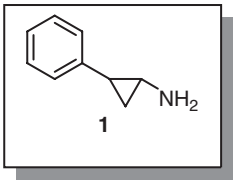
1.7
Pericyclic Reactions

1.7.1
Tranylcypromine

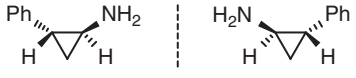


1

Topics:
- Synthesis of an aminocyclopropane-based drug
- [1 + 2]-Cycloaddition of carbethoxycarbene to styrene, cyclopropanation of an alkene
- Ester saponification
- Separation of stereoisomers by fractional crystallization
- Thermal Curtius degradation

(a) **General**

Tranylcypromine (**1**) is the racemic mixture of *trans*-(*E*)-2-phenylcyclopropyl-1-amine and is used pharmaceutically as a psychoanaleptic and antidepressant [1]. Tranylcypromine acts as an inhibitor of monoamine oxidase A, thus retarding the metabolic degradation of serotonin, noradrenaline, adrenaline, and other amines [2].



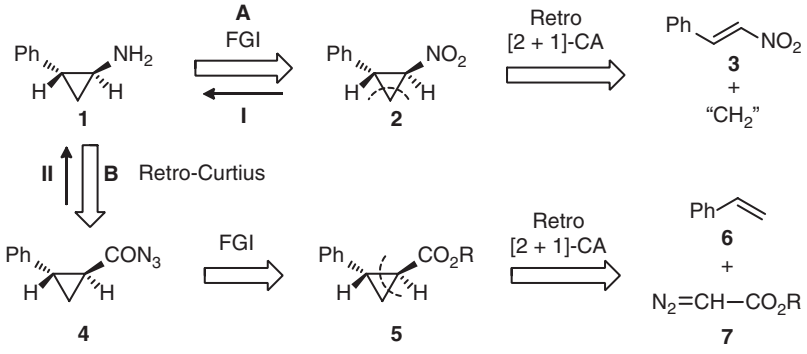
(+)-(*1S,2R*) **1** (–)-(*1R,2S*)

Both enantiomers of **1** are known, and their structure–activity relationships have been investigated; the (1*S*,2*R*)-compound shows a 10 times higher inhibitory activity than its enantiomer.

For the retrosynthesis of cyclopropanes, the most appropriate bond disconnections generally result from retro-[1 + 2]-cycloadditions. Thus, the target molecule **1** offers two retroanalytical pathways (**A**/**B**).

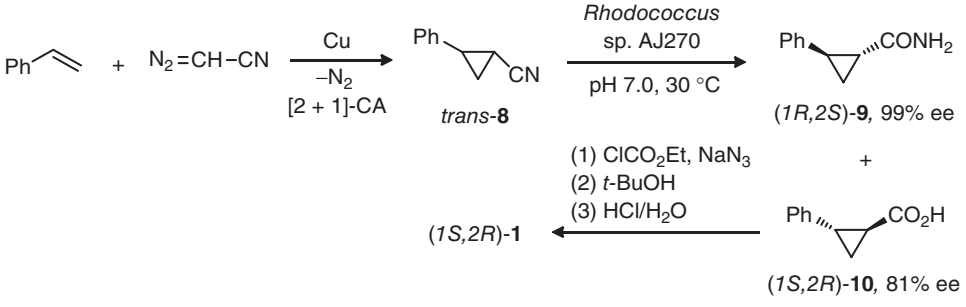
In **A**, after FGI ($NH_2 \rightarrow NO_2$), the resulting phenylnitrocyclopropane **2** should result from [1 + 2]-cycloaddition of a methylene (CH_2) source to (*E*)-2-phenyl-1-nitroethene (**3**), which is easily accessible by nitroaldol condensation (Henry reaction) of benzaldehyde and nitromethane.

In **B**, after FGI of the primary amine function to an acyl azide **4** (retro-Curtius rearrangement) and further on to (*E*)-2-phenylcyclopropane carboxylate **5**, retro-[1 + 2]-cycloaddition would lead to a carbalkoxycarbene (easily accessible from diazoacetate **7**) and styrene (**6**).



In fact, phenylnitrocyclopropane **2** can be prepared from phenylnitroethene **3** by cyclopropanation with trimethyloxosulfonium iodide/NaH according to the Corey–Chaykovsky method [3]. Unfortunately, its reduction to tranylcypromine is not described in the literature, thus eliminating this short and straightforward possibility (**I**) for the synthesis for **1**.

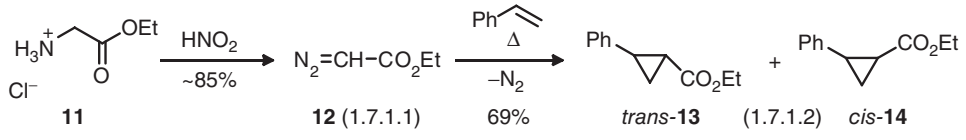
However, approach **II** based on retrosynthesis **B** is documented [4] and is described in detail in Section (b).



It should be noted that enantiopure (1*R*,2*S*)-**1** can be obtained by way of a chemoenzymatic transformation of (*E*)-2-phenylcyclopropanecarbonitrile (**8**) [5]. *Rhodococcus* sp. AJ 270, a versatile nitrile hydratase/amidase, catalyzes the enantioselective hydrolysis of **8** to afford the corresponding amide **9** and the acid **10** in high enantiomeric excess. The acid **10** is transformed to (+)-(1*S*,2*R*)-tranylcypromine by a modified Curtius rearrangement.

(b) **Synthesis of 1**

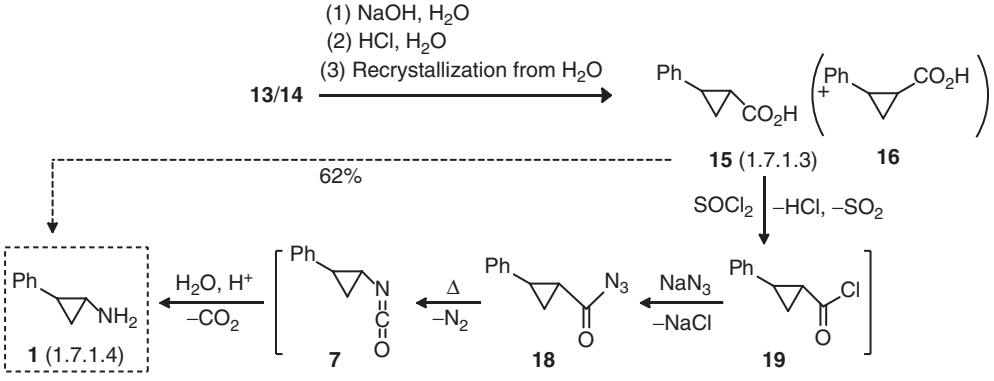
The synthesis of **1** [4] starts with cyclopropanation of styrene with carbethoxycarbene generated by thermolysis of ethyl diazoacetate (**12**). The diazoacetate **12** is prepared from glycine ethyl ester hydrochloride (**11**) by nitrosation with HNO_2 [6]:



The cyclopropanation leads to a mixture of the diastereomers of ethyl 1-phenylcyclopropane-1-carboxylate (**13** and **14**) as a racemic mixture with a trans/cis ratio of approximately 21. The cis/trans mixture **13**/**14** is saponified using aqueous NaOH, and the resulting isomeric acids **15**/**16** are separated by fractional crystallization from H_2O to obtain the pure *trans*-acid **15** required for the further synthesis.

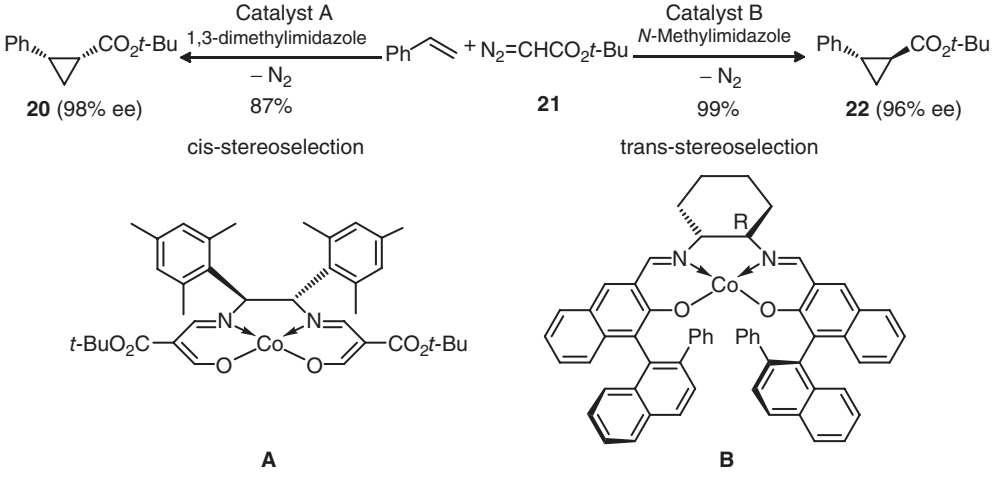
The *trans*-1-phenylcyclopropane-2-carboxylic acid (**15**) is transformed to **1** by Curtius degradation of the corresponding acyl azide. This is achieved by conversion of **15** to the acid chloride (**19**), reaction with NaN_3 to give the azide (**18**), and thermolysis of the azide to afford the isocyanate (**17**) via 1,2-*N*-sextet rearrangement. Finally, the isocyanate is transformed in acidic medium (via

the corresponding carbamic acid and decarboxylation thereof) to the primary amine **1**:



The four-step transformation **15** → **1** is executed in a one-pot procedure with spectroscopic detection of the intermediates **17**–**19**. Tranylcypromine is thus obtained in four separate steps with an overall yield of 19% (based on **11**).

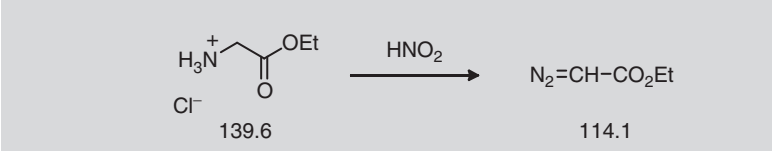
Another possibility is the enantio and diastereoselective cyclopropanation of styrene with diazoacetates in the presence chiral Co(II) chelate complexes:



Thus, reaction of styrene with *tert*-butyl diazoacetate (**21**) using the β-ketoimidato-Co(II) complex **A** leads to the cis-disubstituted cyclopropane **20** [7], whereas using the salen-type Co(II) complex **B** leads to the trans-disubstituted cyclopropane **22**, both with >96% ee [8].

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

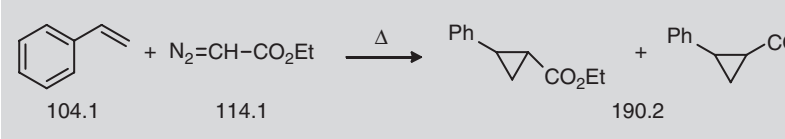
1.7.1.1 ** **Ethyl diazoacetate** [6]



A solution of sodium nitrite (32.8 g, 0.48 mol) in H_2O (100 ml) at −5 °C is added to a well-stirred mixture of glycine ethyl ester hydrochloride (56.0 g, 0.40 mol) in H_2O (100 ml) and CH_2Cl_2 (240 ml) also at −5 °C. The mixture is cooled to −9 °C, and 5% aqueous sulfuric acid (cold, 38.0 g) is added dropwise over approximately 3 min, keeping the reaction temperature below 1 °C; after the addition, stirring is continued for 15 min.

The mixture is transferred to a cold separatory funnel, the phases are separated, and the aqueous phase is extracted with CH_2Cl_2 (30 ml). The combined organic phases are neutralized with 5% aqueous $NaHCO_3$ solution (400 ml in total) until the gas formation (CO_2) ends. The organic layer is dried over $CaCl_2$, filtered, and used directly for the next step without further purification; approximately 280 ml containing 36.0–40.0 g (79–88%) of ethyl diazoacetate.

1.7.1.2 ** **Ethyl 2-phenylcyclopropane-1-carboxylate** [4]



In a three-necked flask fitted with a dropping funnel, a stirrer, a thermometer, and a distillation unit (note 1), styrene (17.7 g, 0.17 mol; note 2) and hydroquinone (0.4 g) are heated to 125 °C. Then, the solution of ethyl diazoacetate prepared in **1.7.1.1**, in which additional styrene (34.4 g, 0.33 mol) and hydroquinone (0.4 g) are dissolved, is added dropwise with vigorous stirring at such a rate that the internal temperature stays at 125–135 °C (external temperature approximately 160 °C). The addition is complete after approximately 3 h.

The CH_2Cl_2 solution (faintly yellow) which distilled off is concentrated *in vacuo* at room temperature to a volume of approximately 40 ml and added dropwise to the reaction mixture (same conditions as above).

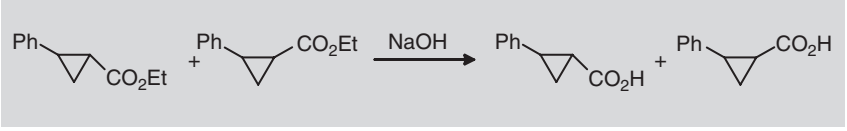
For work-up, the CH_2Cl_2 is removed at normal pressure, and the excess styrene is distilled off at 15 mbar (18.7 g, 0.18 mol). Distillation is continued at 1 mbar to yield 41.8 g (69% based on reacted styrene) of a colorless liquid, bp_1 106–108 °C, which consists of a mixture of the cis and trans products (as indicated by ^1H NMR).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1725, 760, 700.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.4–7.0 (m, 5H, Ph–H), 4.16, 3.86 (q, J = 7.0 Hz, together 2H, OCH_2), 2.7–2.4 (m, 1H, 2-H), 2.2–1.4 (m, 3H, 3-H_2, 1-H), 1.26, 0.96 (t, J = 7.0 Hz, 3H, CH_3; relative intensity 1 : 2, ratio of the cis/trans stereoisomers).

Notes:

1) A reaction flask of volume at least 500 ml should be used because (especially at the beginning) the production of N_2 during the thermolysis of the diazoacetate causes strong foaming.
2) Styrene has to be distilled over hydroquinone before use; bp_{12} 33–34 °C.

1.7.1.3 ** ***trans*-2-Phenylcyclopropane-1-carboxylic acid** [4]

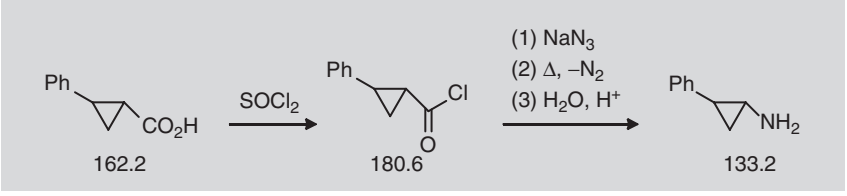


A solution of the *cis*/*trans*-ester mixture from **1.7.1.2** (38.0 g, 0.20 mol) and NaOH (11.8 g, 0.30 mol) in EtOH/H_2O (110 ml/15 ml) is heated under reflux for 9 h.

The reddish mixture is then concentrated *in vacuo*, the residue is dissolved in H_2O (50 ml), and the solution is cooled in an ice bath. With efficient stirring, concentrated HCl is added; the precipitated acid is collected by suction filtration, washed with H_2O, and recrystallized from H_2O (approximately 2.5 l) with the addition of charcoal. After a second recrystallization from H_2O, the pure *trans*-acid is obtained; 11.4 g (35%), colorless crystals, mp 92.5–93.5 °C. Concentration of the combined mother liquors from both recrystallizations to a volume of approximately 500 ml yields a second crop; 5.20 g (16%), mp 91–92 °C; total yield of the *trans*-acid 51%, TLC (SiO_2; Et_2O): $R_f \approx 0.75$.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3500–2300, 1695, 1245.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.4–6.9 (m, 5H, Ph–H), 2.7–2.4 (m, 1H, 2-H), 2.9–1.2 (m, 3H, 1-H, 3-H_2); CO_2H is not observed.

1.7.1.4 ** **(±)-*trans*-2-Phenylcyclopropyl-1-amine (tranylcypromine)** [4]



1) *trans*-2-Phenylcyclopropane-1-carboxylic chloride: A solution of the *trans*-acid **1.7.1.3** (13.0 g, 0.08 mol) and thionyl chloride (20.3 g, 0.17 mol) in anhydrous benzene (45 ml; Caution: carcinogenic!) is heated under reflux for 5 h (Caution: Hood! Evolution of HCl and SO_2!). The reaction mixture is then concentrated *in vacuo*, benzene (30 ml) is added, and distillation *in vacuo* is repeated to remove the excess $SOCl_2$. The yellowish crude acid chloride (IR (film): $\tilde{\nu} = 1780\ cm^{-1}$ (C=O), 13.5 g, (93%)) is used in the next step without further purification.
2) A solution of the acid chloride from (1) in toluene (70 ml) is added dropwise over 1 h to a well-stirred suspension of sodium azide (21.0 g, 0.32 mol, Caution: Hood! Shield!) in anhydrous toluene at 70 °C (external temperature). The temperature is then slowly increased, whereupon N_2 evolution occurs at 70–80 °C. When the addition is complete, the reaction mixture is heated to reflux until the evolution of N_2 ceases (approximately 4 h).

After cooling to room temperature, the inorganic salts are filtered off by suction and washed with toluene; the solvent is removed from the filtrate *in vacuo*, leaving the isocyanate as the residue (IR (film): $\nu = 2280\ cm^{-1}$ (N=C=O), 11.9 g). After cooling to 10 °C, concentrated HCl (135 ml) is added dropwise over 45 min and the solution is heated to reflux for 2 h. The mixture is then cooled to room temperature, and ice cold H_2O (50 ml) is added. After extraction with Et_2O (100 ml), the acidic aqueous phase is concentrated to dryness *in vacuo*. The residue is suspended in Et_2O (100 ml) and, with cooling in an ice bath, a 50% aqueous KOH solution (50 ml) is added. The liberated amine is taken up in Et_2O, the aqueous (alkaline) phase is washed twice with Et_2O (50 ml), and the ethereal extracts are combined and dried over $MgSO_4$ and filtered. The solvent is removed *in vacuo*, and the oily, faintly yellow residue is fractionated *in vacuo* (microdistillation apparatus). Tranylcypromine is obtained as a colorless liquid; 6.60 g (62% based on *trans*-acid **1.7.1.3**), $bp_{0.4}$ 43–45 °C.

IR (film): $\tilde{\nu}\ (cm^{-1}) = 3370, 3300, 1605, 1500, 1460, 745, 700.$
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.4–6.9 (m, 5H, Ph–H), 2.7–2.4 (m, 1H, 2-H), 2.1–1.7 (m, 1H, 1-H), 1.55 (s, 2H, NH_2), 1.2–0.7 (m, 2H, 3-H_2).

Derivatives:

1) Tranylcypromine hydrochloride: The hydrochloride is obtained by passing anhydrous HCl into a solution of the amine in anhydrous Et_2O; colorless crystals, mp 155–157 °C (from MeOH by addition of EtOAc/Et_2O, 1 : 1).
2) *N*-Benzoyl-2-phenyl-1-cyclopropylamine: Tranylcypromine benzoate is obtained by Schotten–Baumann acylation of the amine (1,4-dioxane as solvent, 1 h at +20 °C) with an equimolar amount of benzoyl chloride; colorless needles, mp 120–121 °C (from MeOH).

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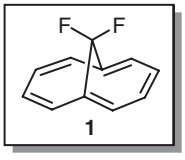
1.7.2
11,11-Difluoro-1,6-methano[10]annulene



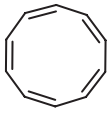
1

Topics:

- Vogel synthesis of a 1,6-methano-bridged [10]annulene
- Birch reduction of naphthalene
- Chemoselective cyclopropanation ([1 + 2]-cycloaddition) of a polyolefinic system
- Base-induced dehydrohalogenation
- Norcaradiene–cycloheptatriene rearrangement

(a) **General**

[10]Annulene is a problematic member of the family of aromatic [*n*]annulenes [1]. Containing 10π-electrons, it formally fulfills the criteria of the Hückel rule for aromatic compounds with $n = 2$. However, in all of its possible double-bond stereoisomers, either high sp^2-bond-angle deformations (as in **2**) or severe steric interactions of hydrogens (as in **4**) exist, which prohibit an approximately planar 10π perimeter geometry required for "aromatic" stabilization.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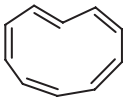
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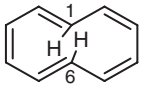

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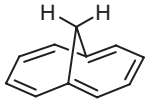


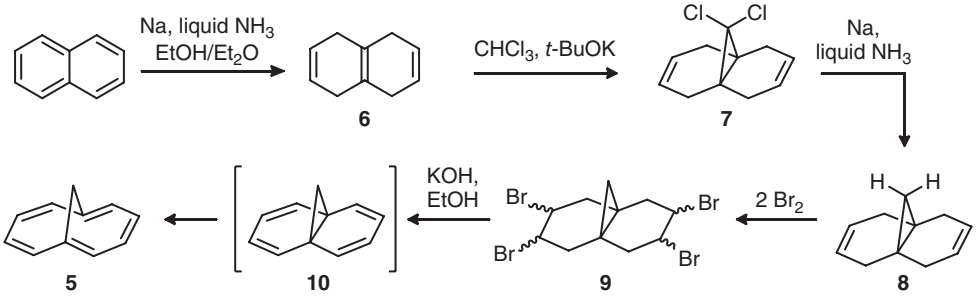
5

1,6-Methano-[10]annulene

In fact, the diastereomeric all-*cis*- and mono-*trans*-[10]annulenes (**2** and **3**) have been prepared and proved to be unstable, nonplanar, and therefore non-aromatic

polyenes. As conceived and realized by Vogel [2], removal of the hydrogen interference in the di-trans-form **4** by replacement of the inner hydrogens by a methylene group led to the 1,6-bridged [10]annulene **5**, the spectroscopic data of which correspond to an aromatic 10π-system.

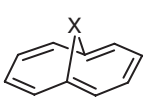
The ^{1}H NMR spectrum of **5** shows it to be a diatropic hydrocarbon (ring protons giving rise to an AA′BB′ multiplet at $\delta = 7.27$ and 6.95 ppm; CH_2 positioned above the π-plane and giving a signal at $\delta = -0.52$ ppm). According to X-ray structural analysis, the sp^2-C perimeter lacks overall planarity, but the average sp^2C-sp^2C distance is of the order seen in benzenoid compounds (137.3–141.9 pm vs. 139.8 pm in benzene) and indicates significant delocalization of the π-system. Chemically, **5** is stable toward oxygen and thermally stable up to 220 °C; it undergoes S_EAr reactions (e.g., bromination, nitration, acylation), as expected for a benzenoid aromatic.



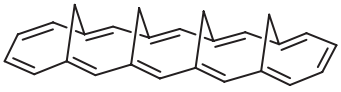
Vogel's synthesis [2] of 1,6-methano[10]annulene (**5**) starts with isotetralin **6**, which is readily available by Birch reduction of naphthalene. Reaction with dichlorocarbene, generated from $CHCl_3$ and *tert*-BuOK, takes place chemoselectively at the internal double bond of **6** to give **7** by cyclopropanation. Dehalogenation of **7** by treatment with Na/liquid NH_3 leads to the propellane **8**, which is converted to **5** either (i) by addition of bromine to the double bonds followed by dehydrohalogenation with KOH (via **9**) or (ii) by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). In both transformations (i) and (ii), the intermediate norcaradiene derivative **10** undergoes thermal electrocyclic ring opening to afford the [10]annulene system.

The Vogel concept has also been realized for [10]annulenes with other bridging groups (**11**, X = O, NH, CF_2) and – using a different synthetic strategy from that used to obtain **5** [3] – for a series of multibridged [14]-, [18]-, and [22]annulenes (e.g., **12**).[8] Other types of bridging in [10]annulene are present in the 1,5-methano species **13**, which shows strong structural similarity to the isoelectronic azulene (cf. Section 1.7.3), and in the tricyclic hydrocarbon **14**, a triply short-circuited derivative of tris-*trans*-di-*cis*-[10]annulene:

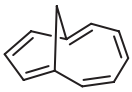
8) In addition, syn- and anti-bridging and oligomethylene-bridging in [14]annulene has been achieved, as well as the synthesis of a "10π pyridine"; see Ref. [1].



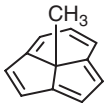
11 (X = CF_2, O, NH)



12



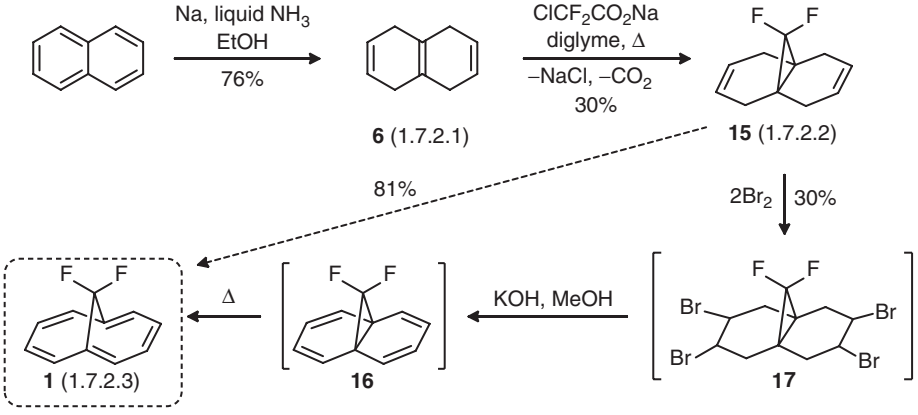
13



14

(b) **Synthesis of 1**

The synthesis of **1** follows the basic concept developed for the 1,6-methano species **5** [4]. First, naphthalene is subjected to Birch reduction using Na in liquid NH_3 (with EtOH as proton source). As already mentioned, a twofold 1,4-reduction of the condensed aromatic system takes place to give the 1,4,5,8-tetrahydronaphthalene (**6**, isotetralin). Compound **6** is then reacted in diglyme at 165 °C with sodium chlorodifluoroacetate, from which difluorocarbene is generated ($F_2ClCCO_2N \rightarrow CF_2 + CO_2 + NaCl$), which adds chemoselectively to the internal double bond (more electron-rich by virtue of its tetraalkyl substitution than the peripheral disubstituted C=C bonds) to yield the carbene monoadduct **15**:

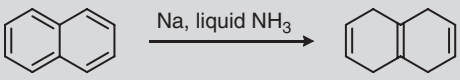


The transformation of the difluoropropellane **15** to 11,11-difluoro-1,6-methano[10]annulene (**1**) follows the already established protocol: addition of 2 mol of bromine to **15** gives the tetrabromide **17** (not isolated), which is followed by a fourfold dehydrobromination by KOH in MeOH to afford the norcaradiene system **16**. Under the reaction conditions, the central 1,6-bond in **16** is cleaved in a norcaradiene–cycloheptatriene rearrangement to provide the target molecule.

The [10]annulene **1** is thus synthesized in a three-step sequence with an overall yield of 18% (based on naphthalene).

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

1.7.2.1 ** **1,4,5,8-Tetrahydronaphthalene** [4]

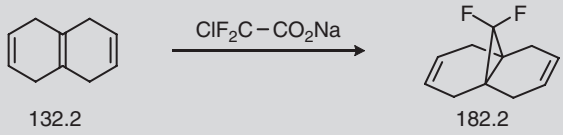


Ammonia (1.0 l) is condensed into a flask in a dry ice/acetone bath (Hood!). The drying tube is removed, and sodium (64.1 g, 1.80 mol) is added in small pieces with vigorous stirring over 1 h. A solution of naphthalene (64.1 g, 0.50 mol) in anhydrous diethyl ether (250 ml) and anhydrous ethanol (200 ml) is then added over a period of 3 h and stirring is continued for 6 h at −78 °C.

The cooling bath is removed, and the ammonia is allowed to evaporate over 12 h. The residue is then taken up in MeOH (40 ml) with stirring under nitrogen to destroy the excess sodium. Ice water (1.5 l) is added, and the mixture is extracted with Et_2O (3 × 100 ml). The combined organic phases are dried over Na_2SO_4 and concentrated under reduced pressure at 20 °C. The residue is washed several times with H_2O using a glass frit and is recrystallized from MeOH (approximately 530 ml). The yield is 60.5 g (76%), mp 52–53 °C (approximately 98% pure). Recrystallization from MeOH raises the mp to 57–58 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3020, 2870, 2840, 2810, 1660.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.67 (s, 4H, vinyl-H), 2.50 (s, 8H, allyl-H).

1.7.2.2 ** **11,11-Difluorotricyclo[4.4.1.0^{1,6}]undeca-2,8-diene** [4]



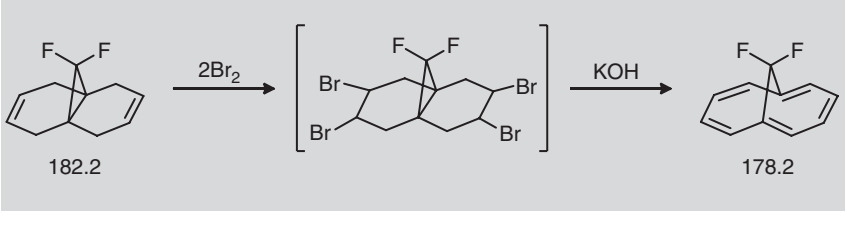
1) Sodium chlorodifluoroacetate: A solution of chlorodifluoroacetic acid (71.7 g, 0.55 mol) in methanol (110 ml) is added dropwise to a stirred solution of NaOH (22.0 g, 0.55 mol) in MeOH (250 ml). The temperature is held at 40 °C by occasional cooling with an ice bath. The solvent is evaporated *in vacuo* and the salt is dried over P_4O_{10} at 1 mbar. The yield is 83.7 g (100%).
2) A solution of sodium chlorodifluoroacetate prepared in (1) (76.1 g, 0.50 mol) in anhydrous diglyme (100 ml) is added to a refluxing, vigorously stirred solution of isotetralin **1.7.2.1** (46.2 g, 0.35 mol) in diglyme (140 ml) at such a rate that the temperature of the reaction mixture does not fall below 165 °C. After

the addition, stirring is continued for 15 min at 165 °C until carbon dioxide evolution ceases.

The solution is cooled to room temperature, poured into H_2O (1 l), and extracted with *n*-pentane (1 × 300 ml, 4 × 100 ml). The combined extracts are washed with H_2O (300 ml), dried over $MgSO_4$, and filtered. The solvent is removed *in vacuo* at room temperature, and the residue is distilled over a 30-cm packed column (Raschig rings). The column is heated during the distillation with a heating gun or infrared lamp to prevent solidification of the product in the column. The first fraction (bp_{12} 89–91 °C) is discarded. The next fractions (bp_{12} 91–103 °C) are collected and recrystallized from MeOH to give 19.0 g (29%) of colorless, square plates; mp 58–60 °C, 98% pure (GC).

IR (KBr): $\tilde{\nu} = 3040, 2980, 2890, 2830, 1670\ cm^{-1}$.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.59 (s, 4H, vinyl-H), 2.8–1.8 (m, 8H, allyl-H).

1.7.2.3 ** **11,11-Difluoro-1,6-methano[10]annulene** [4]



The carbene adduct **1.7.2.2** (10.9 g, 60.0 mmol) is dissolved in anhydrous dichloromethane (120 ml), and the solution is cooled to −60 °C. A solution of bromine (19.2 g, 0.12 mol) in CH_2Cl_2 (60 ml) is added with stirring at such a rate that no brown color from excess bromine remains (approximately 15 min).

The solvent is evaporated *in vacuo* at room temperature, and the colorless crystalline residue is dried under high vacuum (oil pump) for approximately 15 min and then dissolved in THF (60 ml). This solution is dropped into a stirred, refluxing solution of potassium hydroxide (28.0 g, 0.50 mol) in MeOH (160 ml) over a period of 20 min and refluxing is continued for 2 h. The solution is then cooled to 40 °C, aqueous HCl (6 N, 120 ml) is carefully added, and the mixture is heated under reflux for 1 h.

The reaction mixture is cooled to room temperature, poured into H_2O (800 ml), and extracted with *n*-pentane (5 × 150 ml). The combined organic extracts are washed with saturated aqueous $NaHCO_3$ solution (300 ml), dried over $MgSO_4$, and filtered. Al_2O_3 (20 g, basic, activity grade I) is added, and the solvent is evaporated *in vacuo*. The product is eluted from the alumina in a Soxhlet extractor with *n*-pentane, which crystallizes on cooling the extract to give long, pale-yellow needles, and are recrystallized from MeOH. The yield is 7.20 g, mp 116–118 °C.

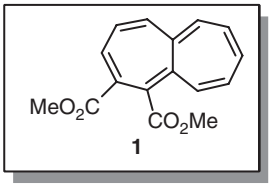
Concentration of the mother liquor gives an additional 1.20 g. Chromatography of the residue on silica gel (120 × 1.5 cm column; *n*-pentane) affords about 0.40 g of additional product. The total yield is 8.80 g (81%).

UV (cyclohexane): λ_{max} (log ε) = 409 (2.73), 398 (2.93), 389 (2.90), 380 (2.77), 293 (3.77), 253 nm (4.81).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3030, 1375, 1100, 790.
^{1}H NMR ($CDCl_3$): δ (ppm) = 7.4–6.8 (m, AA′BB′ system of eight aromatic protons [4]).

References

1. For an instructive and detailed discussion of the [10]annulene problem, see Hopf, H. (2000) *Classics in Hydrocarbon Chemistry*, Wiley-VCH Verlag GmbH, Weinheim, p. 218 and 227.
2. Vogel, E. and Roth, H.D. (1964) *Angew. Chem.*, **76**, 145.
3. Vogel, E., Deger, H.M., Sombroek, J., Palm, J., Wagner, A., and Lex, J. (1980) *Angew. Chem.*, **92**, 43–45; *Angew. Chem., Int. Ed. Engl.*, (1980), **19**, 41–43.
4. (a) Rautenstrauch, V., Scholl, H.-J., and Vogel, E. (1968) *Angew. Chem.*, **80**, 278–279; (b) Vogel, E., Klug, W., and Breuer, A. (1974) *Org. Synth.*, **54**, 11; original contribution from Vogel, E., 1981.

1.7.3
Dimethyl heptalene-1,2-dicarboxylate

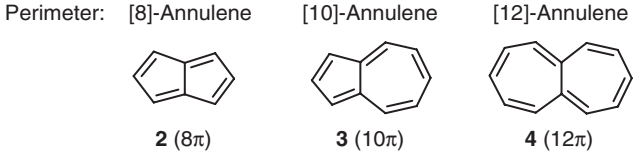


1

Topics:
- Hafner–Ziegler azulene synthesis
- S_NAr of activated haloarenes
- Zincke reaction (pentamethine cyanines from nucleophilic ring-opening of N-acceptor-substituted pyridinium ions)
- Formation of a vinylogous 6-aminofulvene and its electrocyclization to azulene
- Dipolar [2 + 2]-cycloaddition to azulene, ring expansion azulene → heptalene

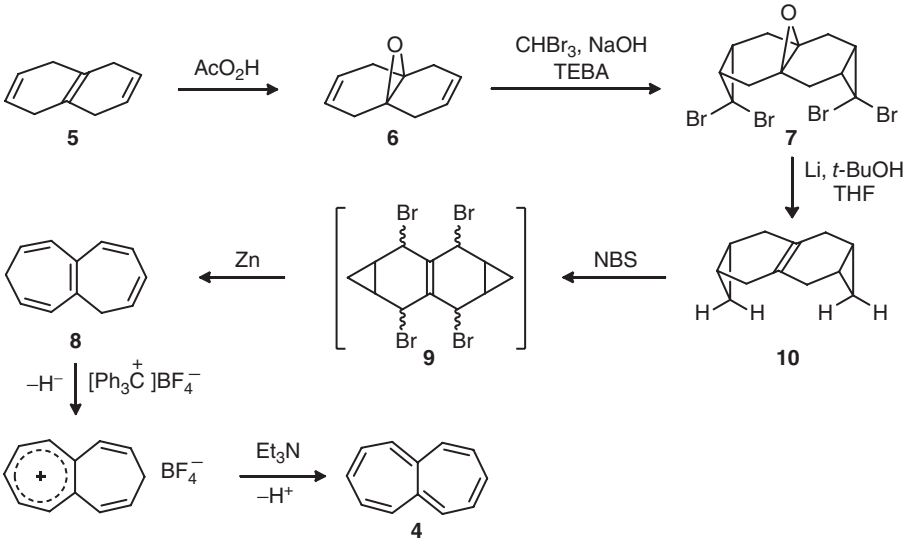
(a) **General**

Heptalene (**4**) belongs to the first members of the group of zero-bridged annulenes (cf. Section 1.7.2) [1], the π-electron systems of which formally contain a pentafulvene unit (as in pentalene (**2**) and azulene (**3**)) or a heptafulvene unit (as in heptalene (**4**)) [1]:



Heptalene (**4**) itself is a very reactive, oxygen-sensitive, nonplanar cyclopolyolefin, temperature-dependent ^{1}H NMR spectroscopic analysis of which is indicative of dynamic interconversions between different conformers. The nonplanar structure of the heptalene skeleton has been confirmed by X-ray analysis of stable derivatives such as the dicarboxylate **1**, the two rings of which preferentially adopt a boat-like structure in the crystalline state [2].

Most syntheses of **4** start from 1,4,5,8-tetrahydronaphthalene (**5**), the educt of Vogel's classical methano[10]annulene synthesis (cf. Section 1.7.2):

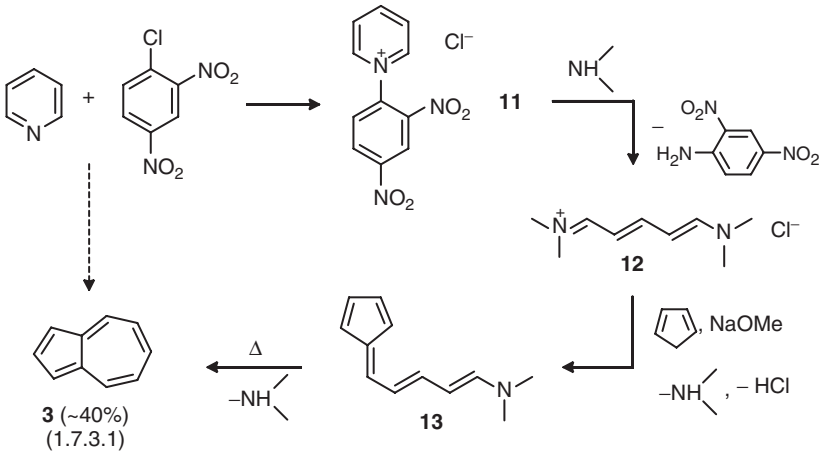


Isotetralin **5** can be epoxidized chemoselectively at the central double bond to give **6**, and subsequent dibromocarbene addition under phase-transfer conditions provides the anti-bis-adduct **7**, which is readily dehalogenated and deoxygenated by Li in *tert*-BuOH/THF (→**10**). NBS bromination of **10** furnishes a mixture of tetrabromides (**9**), reduction of which with zinc gives 3,8-dihydroheptalene (**8**). Dehydrogenation, first by hydride abstraction ($Ph_3C^+ \cdot BF_4^-$) and then by deprotonation (Et_3N) (**8** → **4**), completes the synthesis of **4** [3].

(b) **Synthesis of 1**

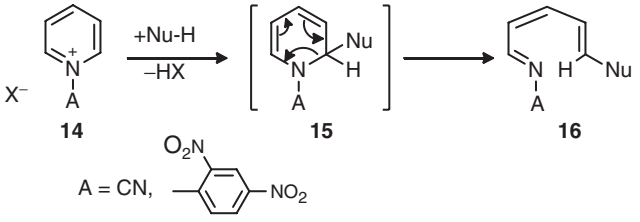
For the synthesis of the stable heptalene derivative **1**, a straightforward approach has been reported [4], which is based on the ring expansion of azulene (**3**) by a [2 + 2]-cycloaddition with dimethyl acetylene dicarboxylate.

Thus, first the synthesis of azulene (**3**) is described [5]. The method of choice is the one-pot, multistep procedure submitted by Hafner [6] starting from 1-(2,4-dinitrophenyl)pyridinium chloride (**11**), which is prepared *in situ* by S_NAr reaction of 2,4-dinitrochlorobenzene with pyridine.

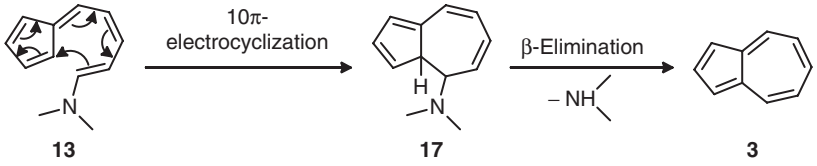


On reaction with dimethylamine, the salt **11** undergoes ring-opening of the pyridine nucleus with amine exchange, resulting in the formation of the (symmetrical) pentamethine cyanine **12** as the key intermediate. Condensation of **12** with cyclopentadiene in the presence of NaOMe leads to the bisvinylogous 6-aminofulvene **13**, which, on heating to 125 °C, cyclizes to afford azulene (**3**) with concomitant elimination of $HN(CH_3)_2$.

The ring-opening process **11** → **12** is an example of the Zincke reaction, which is generally observed when N-acceptor-substituted pyridinium salts **14** interact with *O*- or *N*-nucleophiles through initial attack at C-2 (→**15**) and opening of the N–C-2 bond to furnish 1-azatrienals **16** [7]:



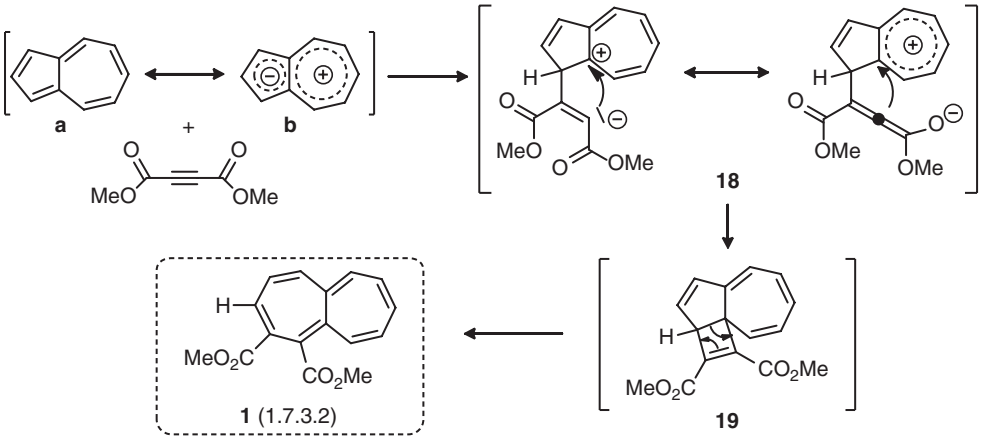
The cyclization of the bisvinylogous 6-aminofulvene **13** to azulene is mechanistically interpreted as an electrocyclic 10π process leading to **17**, which subsequently undergoes loss of the amine moiety in a (thermal) β-elimination (**17** → **3**) [5]:



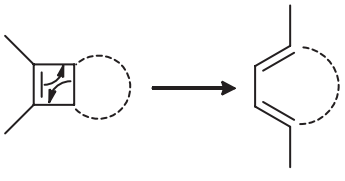
The ring expansion of azulene with dimethyl acetylene dicarboxylate proceeds as a thermal reaction in boiling tetralin. After purification by chromatography

(separation from unreacted azulene), the heptalene diester **1** is obtained as air-stable, brown-red crystals.

The formation of **1** from azulene (**3**) can be understood as a two-step dipolar [2 + 2]-cycloaddition [8], since the electron distribution (**b**) in azulene (**3**) leads to exclusive attack of electrophiles at the five-membered ring with formation of a stabilized tropylium ion in the dipolar intermediate **18**:

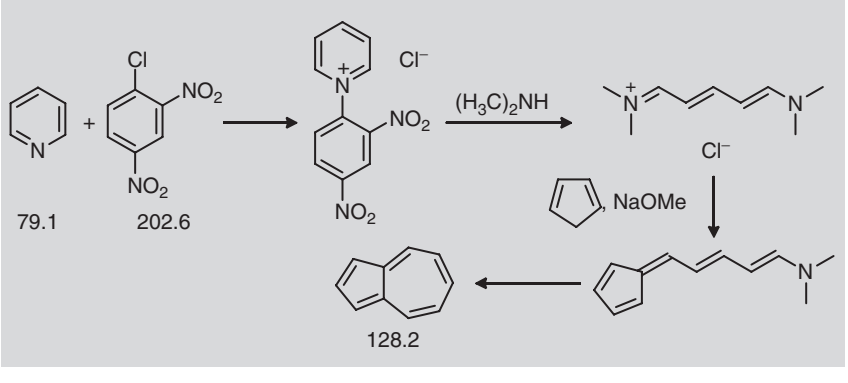


Finally, the formed [2 + 2]-cycloadduct **19** expands to the heptalene system by 4π-cycloreversion of the cyclobutene subunit to a 1,3-diene.



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

1.7.3.1 ** **Azulene** [6]



2,4-Dinitrochlorobenzene (40.5 g, 0.20 mol, Caution: Caustic!) and anhydrous pyridine (240 ml) are stirred and heated at 85–90 °C (steam bath) for 4 h. *N*-(2,4-Dinitrophenyl)pyridinium chloride begins to precipitate as a yellow-brown solid after approximately 30 min. The mixture is cooled to 0 °C in an ice–salt bath, and then a solution of dimethylamine (20.0 g, 0.44 mol, see note) in anhydrous pyridine (60 ml) is added dropwise over 30 min. The temperature of the reaction mixture rises to 4 °C. After the addition, the red-brown solution is slowly warmed to room temperature and stirred for 12 h. The drying tube is then replaced with a gas inlet tube and the system is flushed with nitrogen.

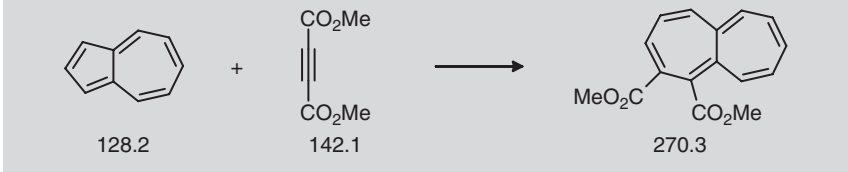
Cyclopentadiene (prepared by distillation of the dimer [9]; 14.0 g, 0.21 mol) is added under a nitrogen atmosphere. Sodium methoxide (2.5 M; sodium (4.60 g) in anhydrous MeOH (80 ml)) is added dropwise with stirring over a period of 30 min. The solution warms to 26 °C and is left at room temperature for 15 h. The dropping funnel is then replaced by a distillation head, and the reaction mixture is carefully heated (Hood! $(H_3C)_2NH$ is evolved!). Pyridine and MeOH are distilled off until the temperature reaches 105 °C (approximately 150 ml of distillate). The distillation head is removed, anhydrous pyridine (200 ml) is added, and the mixture is heated for 4 days at 125 °C under nitrogen.

The mixture is then cooled to 60 °C, and pyridine is distilled off under reduced pressure. The blue-black crystalline residue is extracted with *n*-hexane (400 ml) in a Soxhlet extractor for 4 h. Traces of pyridine are removed from the blue *n*-hexane solution by washing it with 10% aqueous HCl (3 × 30 ml) and H_2O (30 ml). The organic phase is dried over Na_2SO_4, and the volume is reduced by half by distillation using a 50 cm Vigreux column. The concentrated solution is filtered through a column (30 × 4 cm, 200 g of basic Al_2O_3, activity grade II, *n*-hexane as eluent). The solvent is evaporated from the eluate to give dark-blue leaflets, 9.10 g (36%, mp 97–98 °C). Further purification can be achieved by sublimation at 90 °C and 10 mbar (mp 99–100 °C).

UV (*n*-hexane): λ_{max} (log ε) = 580 (2.46), 352 (2.87), 339 (3.60), 326 (3.48), 315 (3.26), 294 (3.53), 279 (4.66), 274 (4.70), 269 (4.63), 238 (4.24), 222 nm (4.06).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1580, 1450, 1395, 1210, 960, 760.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.4–6.8 (m).

Note: The solution of dimethylamine in pyridine is prepared by adding dimethylamine gas (dried over KOH) to anhydrous pyridine under water-free conditions.

1.7.3.2 ** Dimethyl heptalene-1,2-dicarboxylate [6]



Azulene **1.7.3.1** (1.28 g, 10.0 mmol) and dimethyl acetylene dicarboxylate (2.13 g, 15.0 mmol) are heated under reflux in freshly distilled tetralin (20 ml) for 20 min. The solution is cooled, diluted with *n*-hexane (150 ml), and chromatographed on alumina (basic, activity grade IV, 100 g) with *n*-hexane as eluent (fraction 1). Absorbed material is eluted with CH_2Cl_2 until no more product appears in the eluate (TLC) (fraction 2).

The fractions are treated as follows:

Fraction 1: The blue eluate is concentrated *in vacuo*, and the residue is chromatographed on alumina (basic, activity grade I, 200 g) eluting with *n*-hexane. Tetralin elutes first, followed by a blue solution containing unreacted azulene. The azulene crystallizes on evaporating the solvent to give a recovered yield of 0.78 g (61%).

Fraction 2: The solvent is evaporated, and the residue is chromatographed on an alumina column (basic Al_2O_3, activity grade IV, 500 g) eluting with *n*-hexane/Et_2O (5 : 3). Purple (1), dark blue (2), blue-green (3), yellow-brown (4), violet (5), and blue (6) fractions are obtained. The product is isolated from fraction 4 by evaporating the solvents *in vacuo* and recrystallizing the residue from *n*-hexane/Et_2O. The yield is 0.26 g (9.6%; 25% based on recovered azulene), mp 112–113 °C.

UV (*n*-hexane): λ_{max} (log ε) = 337 (3.63), 266 (4.29), 204 nm (4.36).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1720, 1570, 1440, 1260, 1230.
^{1}H NMR (300 MHz, [D_6]acetone): δ (ppm) = 7.27 (d, J = 7.0 Hz, 1H, 3-H), 6.7–5.7 (m, 7H, vinyl-H), 3.71, 3.64 (s, 2 × 3H, 2 × OCH_3).

References

1. For a review, see: Hopf, H. (2000) *Classics in Hydrocarbon Chemistry*, Wiley-VCH Verlag GmbH, Weinheim, p. 285.
2. Hafner, K., Knaup, G.L., and Lindner, H.J. (1988) *Bull. Chem. Soc. Jpn.*, **61**, 155–163.
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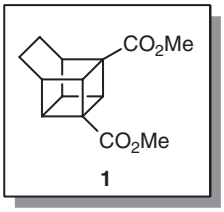
1.7.4

Dimethyl 1,8-bishomocubane-4,6-dicarboxylate



1

Topics:

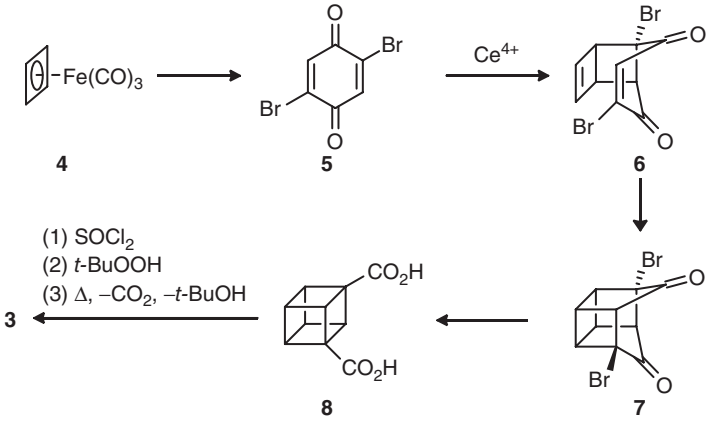
- Halogenation of a phenol (S_EAr)
- Dehydrogenation of a hydroquinone to a 1,4-benzoquinone
- Use of 1,4-quinones as electron-deficient dienophiles in a Diels–Alder reaction
- Photochemical intramolecular [2 + 2]-cycloaddition with cyclobutane formation
- Favorskii rearrangement
- Methyl esters from carboxylic acids and diazomethane

(a) **General**

1,8-Bishomocubane (**2**) is structurally derived from cubane (**3**) by replacement of one cube-edge C–C bond by an ethano ($CH_2–CH_2$) bridge. For this basket-shaped cage hydrocarbon, the trivial name "basketane" is used.


2 **3**

The synthesis of **2** is based on an elegant approach to cubane [1], developed by Pettit [2], as outlined in the following scheme:



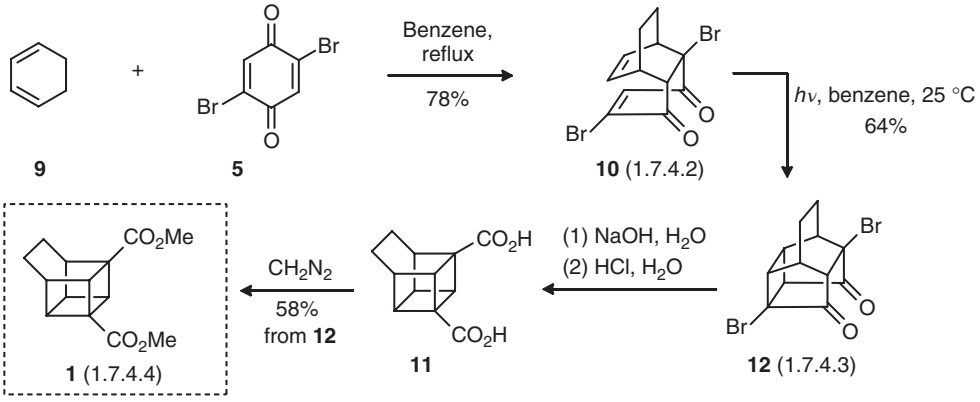
4 **5** **6** **7** **8** **3**

Cyclobutadiene (liberated from its iron complex **4** by oxidation with Ce(IV)) reacts with the dibromoquinone **5** to give the [2 + 2]-cycloadduct **6**. The two double bonds in **6** are in a syn-arrangement, making them suitably predisposed for an intramolecular [2 + 2]-cycloaddition, which occurs readily upon irradiation and provides the dibromodiketone **8**. This is converted to the cubane-1,3-diacid by ring contraction through twofold Favorskii rearrangement (→**7**) and further to cubane (**3**) by decarboxylation of its bis-*tert*-butyl perester.

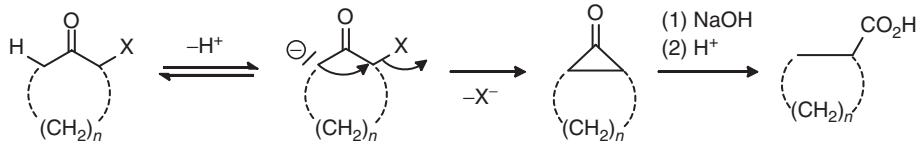
Consequently, the synthesis of **2** includes the essential features of the foregoing strategy, namely (i) an intramolecular [2 + 2]-photocyclization of an appropriate precursor containing the handle of the basketane system and (ii) Favorskii ring contraction to transform an α-bromocyclopentanone to a cyclobutane dicarboxylic acid.

(b) **Synthesis of 1**

The synthesis of **1** starts with the Diels–Alder reaction of cyclohexa-1,3-diene (**9**) with 2,5-dibromo-1,4-benzoquinone (**5**) utilizing the well-established ability of 1,4-quinones to act as electron-deficient dienophiles in [4 + 2]-cycloadditions [3] (**9** + **5** → **10**):

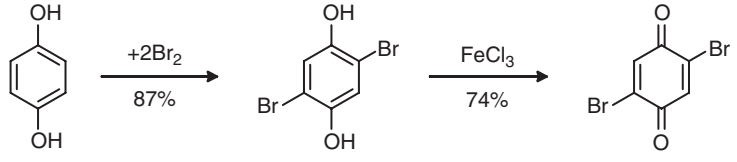


On irradiation of the Diels–Alder adduct **10** in benzene at 25 °C, a photochemically allowed intramolecular [2 + 2]-cycloaddition of the two syn-oriented C=C double bonds occurs with the formation of the dibromodione **12**. Treatment of **12** with NaOH leads to the bishomocubane 1,3-dicarboxylic acid **11** by ring contraction via a cyclopropanone [4].



Finally, the diacid **11** is esterified with diazomethane to give the dimethyl ester **1**. The sequence **12** → **11** → **1** is performed as a one-pot procedure.

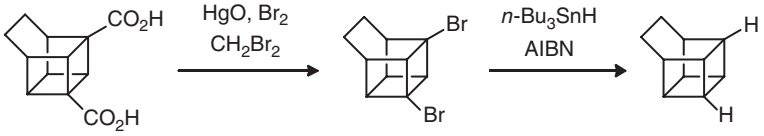
The requisite dibromo-1,4-benzoquinone **5** is prepared by bromination of hydroquinone, which as an activated arene undergoes symmetrical disubstitution to give **13**. This is oxidized using $FeCl_3$ to afford the dibromoquinone **5**.



13 (1.7.4.1) **5** (1.7.4.1)

Thus, the basketane diester **1** is obtained in a five-step sequence with an overall yield of 19% (based on hydroquinone).

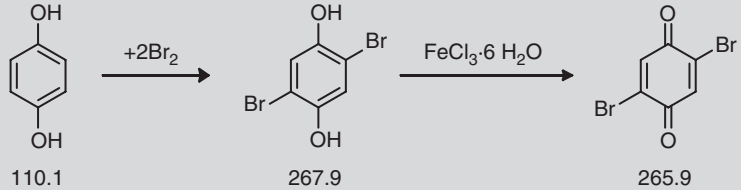
It should be noted that the hydrocarbon **2** may be obtained from the diacid **11** by a modified Hunsdiecker reaction to give the dibromide **14** followed by reductive debromination with nBu$_3$SnH (**14** → **2**) [5]. This two-step sequence corresponds to an overall decarboxylation of **11**:



11 **14** **2**

(c) Experimental Procedures for the Synthesis of 1

1.7.4.1 * **2,5-Dibromo-1,4-benzoquinone** [6]



110.1 267.9 265.9

1) A solution of bromine (64.0 g, 0.40 mol, ~20.5 ml) in glacial acetic acid (20 ml) is added dropwise to a stirred suspension of hydroquinone (22.0 g, 0.20 mol) in glacial acetic acid (200 ml) at room temperature. The temperature rises to about 30 °C, with the initial formation of a clear solution, followed, after

5–10 min, by the deposition of a colorless precipitate. Stirring is continued for 1 h.

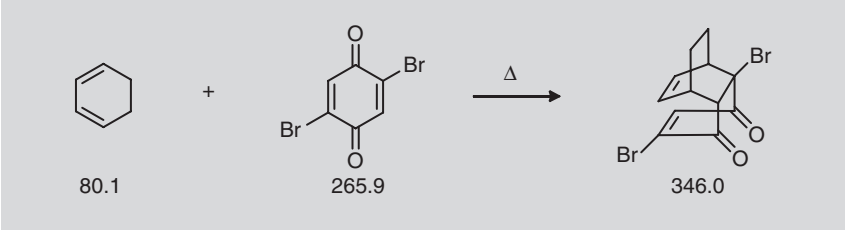
The mixture is then filtered, and the solid is washed with a small amount of glacial acetic acid. The mother liquor is concentrated *in vacuo* to around half of its original volume and is allowed to stand for 12 h. The formed crystals are collected, and the procedure is repeated to give a third crop. The total yield of crude product is 46.4 g (87%), mp 180–187 °C. Recrystallization from glacial acetic acid gives crystals with mp 188–189 °C. However, the crude product can be used without purification for the next step.

2) A solution of $FeCl_3 \cdot 6H_2O$ (65.4 g, 242 mmol) in H_2O (140 ml) is added dropwise to a stirred, refluxing solution of 2,5-dibromohydroquinone prepared in step (1) (27.4 g, 102 mmol) in H_2O (800 ml) over a period of 15 min. The desired *p*-quinone immediately crystallizes from the mixture.

It is collected by filtration after cooling to room temperature, washed with H_2O, and recrystallized from EtOH (800 ml) to give yellow needles; 20.0 g (74%), mp 188–190 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1770, 1760.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.12 (s, 2H, 3-H, 6-H).

1.7.4.2 * 2,5-Dibromotricyclo[6.2.2.0^{2,7}]dodeca-4,9-dien-3,6-dione [5]

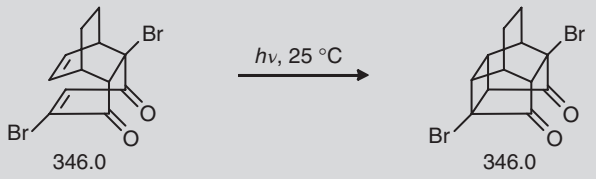


A solution of 2,5-dibromo-*p*-benzoquinone **1.7.4.1** (10.0 g, 37.5 mmol) and cyclohexa-1,3-diene (6.40 g, 80.0 mmol) in anhydrous benzene (20 ml, Caution: Carcinogenic!) is heated under reflux for 3 h.

The solvent and excess cyclohexa-1,3-diene are then distilled off to leave a thick oil, which crystallizes on scratching. The solid is treated with hot petroleum ether (40–60 °C, 2 × 100 ml). The filtrates are combined and cooled to −10 °C. The product crystallizes as colorless crystals. Concentration of the mother liquor gives a small second crop. The total yield is 10.3 g (78%), mp 116–118 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1690, 1670, 1600.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.39 (s, 1H, vinyl-H), 6.3–6.2 (m, 2H, vinyl-H), 3.7–3.1 (m, 3H, bridgehead-H and CO–CH), 2.6–1.2 (m, 4H, CH_2–CH_2).

1.7.4.3 ** **1,6-Dibromopentacyclo[6.4.0$^{3.6}$.0$^{4.12}$.0$^{5..9}$]dodeca-2,7-dione** [5]



Apparatus: Photolysis apparatus with quartz filter and high-pressure mercury vapor lamp (Philips HPK-125 W or Hanau TQ-150 W).

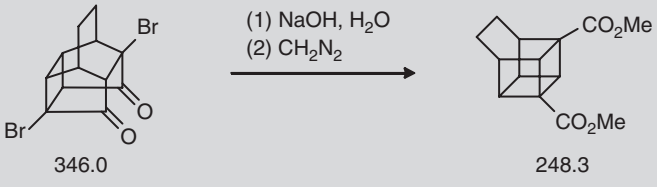
Dibromodione **1.7.4.2** (10.0 g, 29.9 mmol) in anhydrous benzene (260 ml; Caution: carcinogenic!) (note) is flushed with nitrogen for approximately 15 min and irradiated at room temperature for 5 h, during which partial crystallization of the product occurs.

The crystals are filtered off, and the mother liquor is concentrated *in vacuo* to a volume of approximately 30 ml, which leads to the deposition of a second crop of yellowish crystals; total yield 6.40 g (64%), mp 206–208 °C, pure by TLC (silica gel; CH_2Cl_2).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1780.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.41 (s_{br}, 3H), 3.15–3.0 (m, 1H, CH adjacent to CO and CBr; assignment unclear), 2.5–1.6 (m, 6H, CH + CH_2).

Note: Irradiation in toluene (under otherwise identical conditions) gives a lower yield (41%).

1.7.4.4 ** **Dimethyl 1,8-bishomocubane-4,6-dicarboxylate** [5]



A stirred mixture of product **1.7.4.3** (6.30 g, 18.2 mmol) and 25% aqueous sodium hydroxide (65 ml) is heated under reflux for 2 h. The cooled solution is acidified with concentrated hydrochloric acid, keeping the temperature below 5 °C. The colorless precipitate is collected by filtration, washed with H_2O, and dried *in vacuo*. The yield is 5.4 g.

The solid is added in small portions to an ethereal solution of diazomethane (prepared from 6.20 g, ~60.0 mmol of nitroso methyl urea [7] at 0 °C). Complete dissolution occurs with nitrogen evolution. The mixture is stirred for 5 min, and

excess diazomethane is destroyed by slow addition of 2 M acetic acid until N_2 evolution stops.

The organic layer is separated, washed with H_2O, saturated aqueous $NaHCO_3$, and brine (30 ml each), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The dark residue is chromatographed on silica gel (0.06–0.02 mm, 150 g) eluting with *n*-hexane/Et_2O (1 : 1). The first fraction contains the product, which is obtained as a colorless oil after evaporation of the solvents; it crystallizes from *n*-pentane on cooling to −15 °C. The yield is 2.60 g (58%), mp 54–56 °C (pure by TLC).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1725.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.73, 3.70 (s, 3H, CO_2Me), 3.5–2.85 (m, 6H, cyclobutane CH), 1.54 (s_{br}, 4H, CH_2-CH_2).

References

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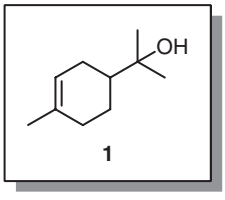
1.7.5
α-Terpineol



1

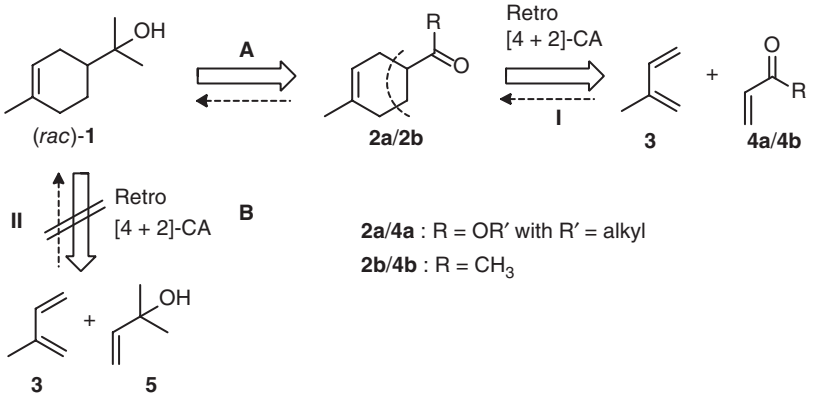
Topics:

- Synthesis of a cyclic monoterpene alcohol: (i) in racemic form, (ii) in enantiopure form
- Lewis acid-catalyzed regioselective Diels–Alder reaction
- Diastereoselective Diels–Alder reaction by use of a chiral auxiliary (Evans auxiliary)
- Tertiary alcohols from esters and Grignard compounds
- Synthesis and application of an (*S*)-phenylalanine-based Evans auxiliary

(a) **General**

α-Terpineol (**1**, *p*-menthenol) belongs to the class of cyclic monoterpenes, which are biogenetically derived from two isoprene units via the mevalonate pathway. α-Terpineol is widespread in Nature; its (+)- and (−)-enantiomers have been found in pine oil (etheric oil from *Pinus palustris* (Pinaceae)). Because of its odor, which is reminiscent of that of lavender, it is used in perfumery as a fragrance. α-Terpineol is obtained industrially from α-pinene [1].

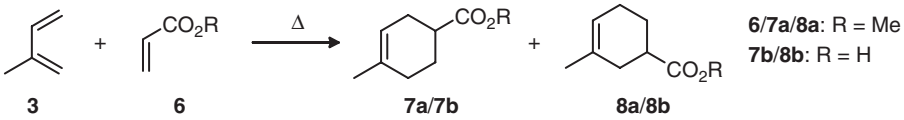
Retrosynthetic analysis of **1** according to pathway A leads to isoprene (**3**) and acrylate (**4a**) or methyl vinyl ketone (**4b**) via the cyclohexene **2**.



The formation of **2** from **3** and **4** by a Diels–Alder reaction is a favored process because of favorable electronic interaction (electron-rich diene and electron-poor dienophile). The tertiary alcohol function in **1** can be introduced by reaction of cycloadduct **2a** with 2 mol of CH_3MgX (see the synthesis in Section (b)) or by treating **2b** with 1 mol of CH_3MgX.

Retrosynthesis according to pathway **B** by direct retro-Diels–Alder disconnection of **1** leads to isoprene (**3**) and the allylic alcohol **5** as dienophile. However, their combination in a thermal [4 + 2]-cycloaddition (**II**) is a less favorable process according to frontier orbital interaction considerations since the highest occupied molecular orbital (HOMO) (diene)/LUMO (dienophile) energy difference is significantly higher in the case of **5** than it is with **4a** [2].

The [4 + 2]-cycloaddition of isoprene (**3**) to an acrylic ester **4a** has served as a model reaction in investigating the regioselectivity and stereoselectivity of Diels–Alder reactions.



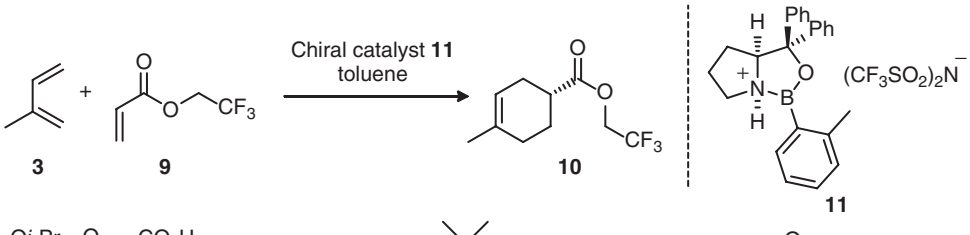
1) When isoprene (**3**) and methyl acrylate (**6**) are reacted thermally at 80 °C, a 70 : 30 mixture of the regioisomeric cycloadducts **7a** and **8a** is obtained in 80% yield. The regioselectivity is significantly improved by the addition of a Lewis

acid; thus, in the presence of $AlCl_3$, a 95 : 5 mixture of **7a** and **8a** (77% yield, see Section (b)) results [3, 4]. Separation is possible by fractional crystallization of the regioisomeric acids **7b** and **8b** after saponification; the ester **7a** may then be obtained free of its regioisomer by re-esterification of the purified acid **7b** with CH_2N_2.

2) Asymmetric Diels–Alder reactions have been performed (i) by use of a dienophile connected to a chiral auxiliary and (ii) by use of a chiral Lewis acid as catalyst [5].

Concerning (i), an example is presented in Section (b), in which an acrylic acid attached to an Evans auxiliary (cf. Section 1.2.2) is utilized for [4 + 2]-cycloaddition to isoprene [6]. After removal of the auxiliary, an enantiopure ester of type **7a** is produced, which allows the preparation of (*R*)-**1**.

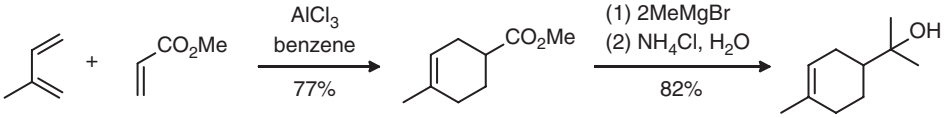
Concerning (ii), a catalytic asymmetric version of the Diels–Alder reaction of isoprene with acrylate has been developed [7], which involves the use of the trifluoroethyl ester **9** and a chiral proline-derived cationic oxazaborolidine derivative **11** (as its triflimide) and gives the cycloadduct **10** in excellent yield (99%) and with high enantioselectivity (ee = 98%). Ester **10** could also be used as a substrate for the synthesis of (*R*)-**1**.



Catalysts of type **11** have been shown to have a broad spectrum of applications in enantioselective [4 + 2]-cycloadditions [7, 8]. CAB [9] (**12**, cf. Section 1.3.3) and chiral bisoxazoline ligands [10] (BOX, **13**) have also proved to be successful catalysts for asymmetric Diels–Alder reactions [11] because they form rigid metal–substrate complexes and provide excellent stereoselectivities. Likewise, for hetero-Diels–Alder reactions with inverse electron demand, efficient catalysts based on Cr, Zr, or Sc complexes are known [12]. Furthermore, enantioselective Diels–Alder reactions [13] using α,β-unsaturated aldehydes as dienophiles and chiral amines as organo catalysts can be performed by employing, for example, imidazolidinone **14**. The formation of an iminium ion by reaction of the carbonyl moiety of the dienophile with the amine functionality of the organo catalyst lowers the LUMO energy of the dienophile, leading to an acceleration of the Diels–Alder reaction.

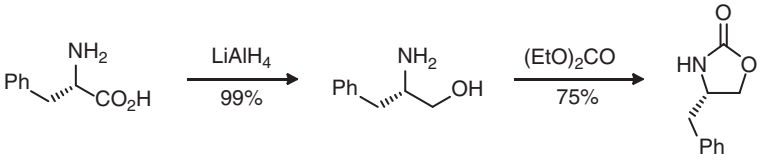
(b) **Synthesis of 1**

1) Synthesis of (*rac*)-α-terpineol [3, 14]
The Diels–Alder reaction of isoprene with methyl acrylate (**6**) is performed in benzene solution at room temperature in the presence of $AlCl_3$ as Lewis acid. The cycloadduct **7a** (containing a 5% impurity of the regioisomeric ester **8a**; for separation, see Section (a)) is reacted with 2 mol of methylmagnesium iodide. This classical transformation of an ester to a tertiary carbinol containing two equal α-substituents leads to the racemic α-terpineol (*rac*-**1**) after the usual work-up with NH_4Cl solution.



3 **6** **7a** (1.7.5.1) *rac*-**1** (1.7.5.2)

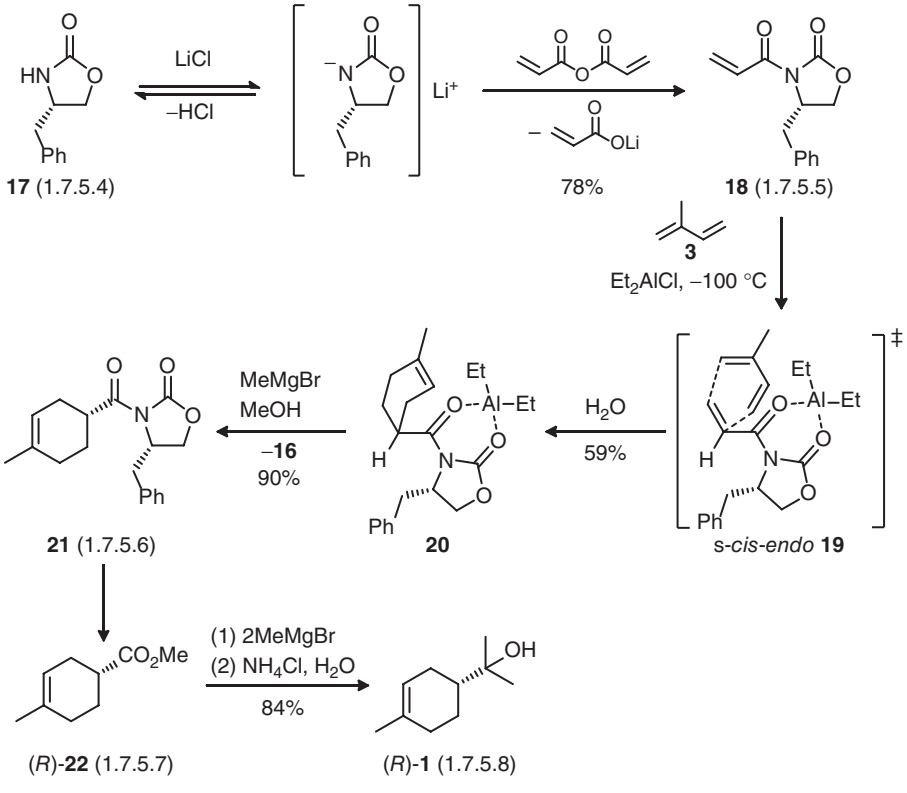
2) Synthesis of (+)-(*R*)-α-terpineol [6]
As chiral auxiliary, an oxazolidin-2-one **17** of the Evans type (cf. Section 1.2.2) is used. It is readily prepared from (*S*)-phenylalanine (**15**) by reduction with $LiAlH_4$ and cyclocondensation of the resulting (*S*)-phenylalaninol (**16**) with diethyl carbonate.



15 **16** (1.7.5.3) **17** (1.7.5.4)

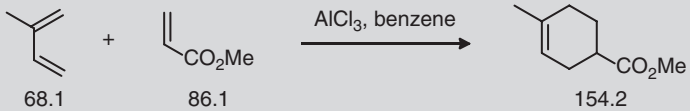
To introduce an acrylic moiety, the chiral auxiliary **17** is equilibrium-deprotonated using LiCl in THF and acylated with acryloyl anhydride prepared *in situ* from acryloyl chloride and acrylic acid in the presence of triethylamine [15] to give the chiral acrylic amide **18**.
Diels–Alder reaction of **18** with isoprene (**3**) proceeds readily at −100 °C in the presence of diethylaluminum chloride in CH_2Cl_2/toluene as solvent to give (after hydrolytic work-up) the cycloadduct **21** with a diastereoselectivity of de = 90% via an s-cis-endo transition state **19**. The efficient stereodiscrimination can be explained (i) by the Lewis acid Et_2AlCl, which provides for rigid chelation of the dienophile moiety by coordinative interaction with both C=O groups of the *N*-acyloxazolidin-2-one system **20**, and by (ii) π-stacking, which causes a stereoelectronic stabilization of the transition state [6]. Thus, improved diastereoselectivity is observed with the benzyl-substituted auxiliary **17** as compared to that seen with auxiliaries with aliphatic residues, for example, the valinol-derived analog.

The diastereomeric purity of the cycloadduct **21** can be raised up to >98% de by recrystallization. Compound **21** is cleaved by treatment with CH_3OMgBr (prepared *in situ* by reaction of CH_3MgBr with CH_3OH) to give the chiral methyl ester (*R*)-**22** with >99% ee. The chiral auxiliary **17** can be recovered from the reaction mixture, allowing its regenerative use. Finally, the methyl ester (*R*)-**22** is transformed into (+)-(*R*)-α-terpineol ((*R*)-**1**) by reaction with 2 mol of MeMgI; the chiral monoterpene alcohol (*R*)-**1** is obtained in almost enantiopure form with >98% ee.



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

1.7.5.1 ** **Methyl 4-methylcyclohex-3-ene-1-carboxylate** [14]



A solution of methyl acrylate (26.1 g, 303 mmol) (note 1) in anhydrous benzene (30 ml; Caution: carcinogenic!) is added dropwise to a well-stirred suspension of anhydrous $AlCl_3$ (4.30 g, 32.0 mmol) in anhydrous benzene (250 ml) over 15 min. The temperature rises to 25 °C and the $AlCl_3$ dissolves. A solution of isoprene (20.9 g, 307 mmol) in benzene (50 ml) is then added dropwise over a period of 60 min. The temperature is held at 15–20 °C with occasional cooling during this period. Stirring is continued at room temperature for 3 h.

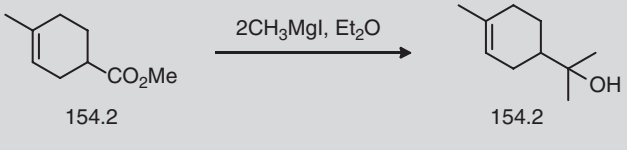
The solution is poured into aqueous HCl (2 M) saturated with NaCl (500 ml), the phases are separated, and the organic phase is washed with H_2O (250 ml), dried over Na_2SO_4, and filtered. The solvent is evaporated under slightly reduced pressure at 70 °C and the residue is fractionally distilled *in vacuo*. The product is obtained as a colorless oil; 35.7 g (77%), bp_{17} 80–82 °C, $n^{20}{}_D = 1.4630$ (note 2).

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 1745, 1440, 1175.
^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 5.28 (s_{br}, 1H, 3-H), 3.60 (s, 3H, CO_2CH_3), 2.70–1.65 (m, 7H, 1-H, 2-H_2, 5-H_2, 6-H_2), 1.63 (s, 3H, CH_3).

Notes:

1) Methyl acrylate should be freshly distilled over hydroquinone before use, bp_{760} 80–81 °C.
2) The product is a 95 : 5 mixture with the regioisomeric 3-methylcyclohex-3-ene-1-carboxylic methyl ester [4] (see Section (a)). This mixture is used in the next step.

1.7.5.2 * ***rac*-α-Terpineol** [3]



154.2 154.2

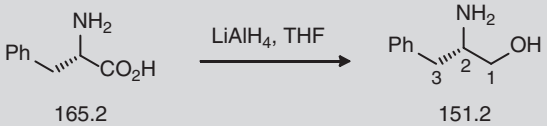
An iodine crystal is added to magnesium turnings (7.20 g, 300 mmol) covered with anhydrous Et_2O (30 ml), followed by a few milliliters of a solution of methyl iodide (42.6 g, 300 mmol; Caution: carcinogenic!) in anhydrous Et_2O (50 ml). The formation of the Grignard reagent starts immediately, and the remaining methyl iodide solution is added dropwise at such a rate that the Et_2O refluxes gently (approximately 1 h). After the addition is complete, the solution is heated under reflux for 30 min. Then, a solution of the ester **1.7.5.1** (20.0 g, 130 mmol) in Et_2O (50 ml) is added dropwise with stirring over 40 min. The mixture boils vigorously during the addition, and a gray precipitate forms. Heating under reflux is continued for 2 h.

The mixture is then cooled in an ice bath, and a pre-cooled solution of NH_4Cl (60 g) in H_2O (300 ml) is added. The organic layer is separated, and the aqueous

layer is extracted with Et_2O (2 × 50 ml). The combined organic layers are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The residue is fractionally distilled to give the product as a colorless oil with a turpentine-like odor; 16.4 g (82%), bp_{15} 94–95 °C, $n^{20}{}_D = 1.4790$.

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3600–3200, 2980, 2940, 2850, 1450, 1390, 1375.
^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 5.30 (s_{br}, 1H, 3-H), 2.41 (s, 1H, OH), 2.20–1.50 (m, 7H, 1-H, 2-H_2, 5-H_2, 6-H_2), 1.60 (s, 3H, 4-CH_3), 1.13 (s, 6H, $C(CH_3)_2$).

1.7.5.3 ** (2*S*)-2-Amino-3-phenylpropan-1-ol [15]



165.2 151.2

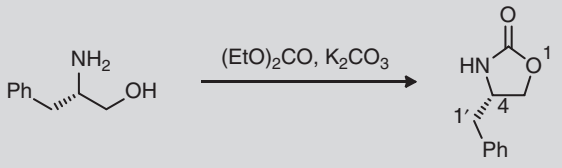
L-Phenylalanine (54.5 g, 330 mmol) is added with caution to a stirred suspension of $LiAlH_4$ (25.0 g, 660 mmol) in anhydrous THF (400 ml) over 30 min at 0 °C under a N_2 atmosphere (note). The mixture is warmed to room temperature and then heated under reflux with stirring for 15 h.

The solution is then cooled in an ice bath, and H_2O (135 ml) is carefully added dropwise. After filtration, the filtrate is concentrated under reduced pressure, and the residue is recrystallized from THF/H_2O (4 : 1, 200 ml) to yield the L-phenylalaninol as light-yellow needles; 49.2 g (99%), mp 91–92 °C, $[\alpha]^{20}{}_D = -17.4$ ($c = 1.0$, $CHCl_3$), $R_f = 0.14$ (EtOAc/MeOH, 10 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 268.0 (2.229), 258.5 (2.363), 254.0 (2.304), 192.5 (4.473).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3356, 2876, 1577, 1492, 1338, 1122, 1065, 754, 698, 621, 592.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.32–7.17 (m, 5H, Ph–H), 3.58 (dd, $J = 10.6$, 4.2 Hz, 1H, 1-H_b), 3.35 (dd, $J = 10.6$, 7.3 Hz, 1H, 1-H_a), 3.05 (m_c, 1H, 2-H), 2.75 (dd, $J = 13.5$, 5.4 Hz, 1H, 3-H_b), 2.48 (s_{br}, 3H, NH_2, OH), 2.46 (dd, $J = 13.5$, 8.8 Hz, 1H, 3-H_a).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 138.6, 129.1, 128.5, 126.3 (6 × Ph–C), 65.9 (C-1), 54.1 (C-2), 40.5 (C-3).
MS (DCI, 200 eV): *m*/*z* (%) = 152 (100) $[M+H]^+$, 169 (37) $[M+NH_4]^+$.

Note: The reaction starts with delay, but then vigorously.

1.7.5.4 ** **(4*S*)-4-Benzyloxazolidin-2-one** [15]



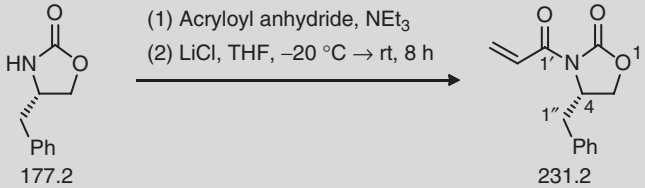
151.2 177.2

A dry, three-necked, round-bottomed flask equipped with a thermometer, a Vigreux column, and a magnetic stirring bar is charged with the amino alcohol **1.7.5.3** (15.1 g, 100 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and diethyl carbonate (29.5 g, 250 mmol). The mixture is carefully heated to 135–140 °C, and EtOH is allowed to distil as it is formed. After 2 h, 15 ml of distillate would have been collected.

The reaction mixture is then diluted with CH_2Cl_2 (250 ml) and filtered. The solution is washed with saturated aqueous $NaHCO_3$ solution (100 ml), dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. Recrystallization from EtOAc/*n*-pentane gives the oxazolidinone as colorless needles; 13.3 g (75%), mp 88–89 °C, $[\alpha]^{20}_D = -62.5$ ($c = 1.0$, $CHCl_3$), $R_f = 0.47$ (EtOAc).

UV (CH_3CN): λ_{max} (nm) (log ε) = 263.5 (2.191), 258.0 (2.302), 252.5 (2.218), 206.0 (3.939).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1751, 1404, 1244, 1096, 1021, 942, 757, 708.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.37–7.17 (m, 5H, Ph–H), 6.01 (s_{br}, 1H, NH), 4.43 (m_c, 1H, 5-H_b), 4.17–4.05 (m, 2H, 4-H, 5-H_a), 2.88 (m_{cr}, 2H, 1′-H_2).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 159.5 (C-2), 135.9, 129.0, 128.9 (6 × Ph–C), 69.52 (C-5), 53.72 (C-4), 41.33 (C-1′).
MS (EI, 70 eV): *m*/*z* (%) = 177 (7) $[M]^+$, 86 (86) $[M-C_7H_7]^+$.

1.7.5.5 ** **(4*S*)-3-(1-Acryloyl)-4-benzyl-oxazolidin-2-one** [6]



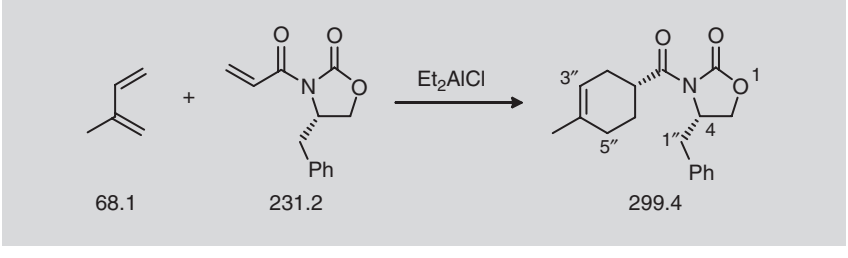
177.2 231.2

Triethylamine (13.4 g, 132 mmol, 18.4 ml) and acryloyl chloride (5.98 g, 66.0 mmol, 5.34 ml) are added to a stirred solution of acrylic acid (5.13 g, 71.2 mmol, 4.88 ml) in anhydrous THF (300 ml) at −20 °C under a N_2 atmosphere, and stirring is continued at this temperature for 2 h. LiCl (2.58 g, 61.0 mmol) is added, followed by the oxazolidinone **1.7.5.4** (9.00 g, 50.8 mmol). The mixture is allowed to warm to room temperature and then stirred for 8 h.

The reaction is quenched by the addition of aqueous HCl (0.2 M, 70 ml), and the THF is removed *in vacuo*. After addition of EtOAc (100 ml), the mixture is washed with half-saturated aqueous $NaHCO_3$ solution (80 ml) and brine (80 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. Column chromatography of the residue on silica gel (*n*-pentane/EtOAc, 4 : 1) yields the acryloyloxazolidinone as colorless crystals; 9.21 g (78%), mp 74–75 °C, $R_f = 0.42$ (*n*-pentane/EtOAc, 4 : 1), $[\alpha]^{20}_D = +79.0$ ($c = 1.0$, $CHCl_3$).

UV (CH_3CN): λ_{max} (nm) (log ε) = 207.5 (4.316), 191.5 (4.658).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1784, 1682, 1389, 1352, 1313, 1245, 1216, 989, 696.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.47 (dd, $J = 17.0$, 10.5 Hz, 1H, 2′-H), 7.37–7.21 (m, 5H, 5 × Ph–H), 6.58 (dd, $J = 17.0$, 1.7 Hz, 1H, 3′-H_b), 5.92 (dd, $J = 10.5$, 1.7 Hz, 1H, 3′-H_a), 4.70 (m_c, 1H, 4-H), 4.17 (m_c, 2H, 5-H_2), 3.33 (dd, $J = 13.3$, 3.3 Hz, 1H, 1″-H_b), 2.78 (dd, $J = 13.3$, 9.4 Hz, 1H, 1″-H_a).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 164.8 (C-1′), 153.3 (C-2), 135.2 (C-2″), 131.9 (C-3′), 129.4 (C-2′), 128.9, 127.3 (5 × Ph–C′), 66.20 (C-5), 55.22 (C-4), 37.70 (C-1″).
MS (EI, 70 eV): *m*/*z* (%) = 231 (27) $[M]^+$, 140 (18) $[M-CH_2Ph]^+$, 55 (100) $[M-C_{10}H_{10}NO_2]^+$.

1.7.5.6 *** **(4*S*,1″*R*)-4-Benzyl-3-(4-methylcyclohex-3-enecarbonyl)oxazolidin-2-one** [6]



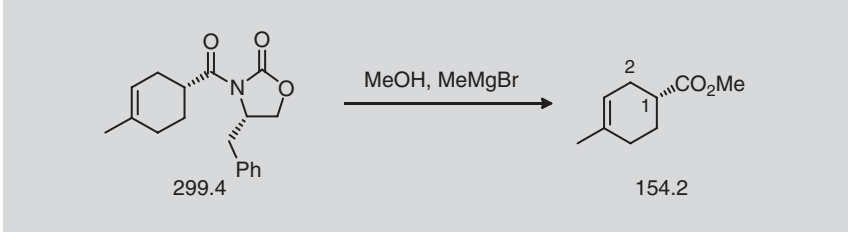
A solution of the acryloyloxazolidinone **1.7.5.5** (6.89 g, 29.8 mmol) and isoprene (70 ml) in anhydrous dichloromethane (70 ml) is cooled to −100 °C. Diethylaluminum chloride (41.7 ml, 1 M in *n*-hexane, 41.7 mmol), cooled to −78 °C, is added via a coolable dropping funnel over a period of 10 min, whereupon the mixture turns yellow. The mixture is stirred at −100 °C for 30 min.

It is then poured into aqueous HCl (1 M, 600 ml). After the addition of CH_2Cl_2 (100 ml), the layers are separated and the aqueous phase is extracted with CH_2Cl_2

(2 × 200 ml). The combined organic layers are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. Purification of the residue by column chromatography on silica gel (*n*-pentane/EtOAc, 4 : 1) gives the product as white needles; 5.30 g (59%), mp 87–88 °C, $[\alpha]^{20}_D = +92.8$ ($c = 1.0$, $CHCl_3$), $R_f = 0.39$ (*n*-pentane/EtOAc, 4 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 263.5 (2.239), 257.5 (2.392), 252.0 (2.392), 247.0 (2.367).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3026, 2963, 2835, 1700, 1387, 1238, 1219, 1202.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.36–7.15 (m, 5H, 5 × Ph–H), 5.40 (m, 1H, 3″-H), 4.66 (m, 1H, 4-H), 4.23–4.10 (m, 2H, 5-H_2), 3.72–3.59 (m, 1H, 1″-H), 3.24 (dd, J = 13.4, 3.2 Hz, 1H, 1′-H_b), 2.75 (dd, J = 13.4, 9.5 Hz, 1H, 1′-H_a), 2.35–1.68 (m, 6H, 2″-H_2, 5″-H_2, 6″-H_2), 1.65 (s, 3H, 4″-CH_3).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 176.5 (1″-(CO)N), 153.0 (C-2), 135.3, 133.7, 129.4, 128.9, 127.3 (5 × Ph–C, C-4″), 119.0 (C-3″), 66.00 (C-5), 55.24 (C-4), 38.41 (C-1″), 37.88 (Ph–CH_2), 29.42 (C-5″), 27.71 (C-2″), 25.68 (C-6″), 23.38 (4″-CH_3).
MS (ESI, 70 eV): m/z (%) = 622 (6) $[2M+Na]^+$, 354 (100) $[M-H+2Na]^+$, 322 (25) $[M+Na]^+$.

1.7.5.7 ** Methyl (*R*)-4-methylcyclohex-3-enecarboxylate [6]



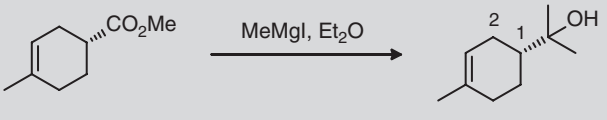
Methylmagnesium bromide (3 M in Et_2O, 2.3 ml, 4.68 mmol) is added dropwise to anhydrous methanol (20 ml) at 0 °C, and the solution is stirred at this temperature for 5 min. A solution of the Diels–Alder adduct **1.7.5.6** (0.70 g, 2.34 mmol) in MeOH (20 ml) is then added dropwise and the mixture is stirred for 90 min.

The reaction is quenched by the addition of aqueous pH 7 phosphate buffer solution (20 ml), and stirring is continued for a further 30 min at room temperature. The mixture is diluted with half-saturated aqueous NH_4Cl (40 ml) and brine (40 ml), and CH_2Cl_2 (40 ml) is added. The layers are separated and the aqueous layer is extracted with CH_2Cl_2 (3 × 40 ml). The combined organic layers are dried over $MgSO_4$ and filtered, and the solvent is removed at room temperature under reduced pressure. The crude product is purified by column chromatography on silica gel (*n*-pentane/Et_2O, 14 : 1) to give the methyl ester as

a colorless liquid; 324 mg (90%), $n^{20}_D = 1.4624$, $[\alpha]^{20}_D = +52.2$ ($c = 2.1$, CH_2Cl_2), $R_f = 0.46$ (*n*-pentane/EtOAc, 20 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 267.0 (1.934), 263.0 (2.159), 251.5 (2.155), 257.0 (2.269), 191.5 (4.576).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2961, 2928, 1734, 1455, 1442, 1163, 697.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.41–5.34 (2 × m, 1H, 3-H), 3.68 (s, 3H, OCH_3), 2.56–2.43 (m, 1H, 1-H), 1.62–1.78, 1.94–2.05, 2.17–2.26 (3 m, 9H, 2-H_2, 3-H_2, 4-CH_3, 5-H_2).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 23.43 (4-CH_3), 25.43 (C-6), 27.62 (C-2), 29.24 (C-5), 39.03 (C-1), 51.56 (O-CH_3), 119.15 (C-3), 133.69 (C-4), 176.47 (C=O).
MS (EI, 70 eV): *m*/*z* (%) = 154 (32) $[M]^+$, 95 (46) $[M-CH_3-CO_2]^+$, 94 (100) $[M-CH_3-CO_2-H]^+$.

1.7.5.8 ** (+)-(*R*)-α-Terpineol [6]



230.3 154.3

A solution of the methyl ester **1.7.5.7** (209 mg, 1.36 mmol) in anhydrous Et_2O (10 ml) is added dropwise to a solution of methylmagnesium iodide (3 M in Et_2O, 1.62 ml, 4.86 mmol) in Et_2O (15 ml) at room temperature. The mixture is stirred for 4.5 h at this temperature (TLC control).

The mixture is then poured into saturated aqueous NH_4Cl solution (30 ml). The layers are separated, and the aqueous layer is extracted with Et_2O (5 × 20 ml). The combined organic phases are washed with H_2O (20 ml) and brine (20 ml), dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue is purified by column chromatography on silica gel (*n*-pentane/Et_2O, 7 : 3) to give (+)-(*R*)-α-terpineol as a colorless oil, which crystallizes upon refrigeration; 177 mg (84%), ee = 90%, mp 25–26 °C, $[\alpha]^{20}_D = +91.1$ ($c = 1.0$, $CHCl_3$), $R_f = 0.27$ (*n*-pentane/Et_2O, 7 : 3).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3600–3100, 2970, 2924, 2889, 2836, 1438, 1377, 1366, 1158, 1133.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.42–5.36 (m, 1H, 3-H), 1.67–1.64 (m, 3H, 4-CH_3), 1.50 (m, 1H, 1-H), 2.13–1.72, 1.33–1.20 (2 × m, 7H, 2-H_2, 5-H_2, 6-H_2, OH), 1.91, 1.17 (2 × s, 2 × 3H, C(OH)($C\underline{H}_3$)$_2$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 133.99 (C-4), 120.51 (C-3), 72.71 (COH), 44.95 (C-1), 30.96 (C-5), 26.85 (C-2), 27.42*, 26.22* ($COH(CH_3)_2$), 23.93 (C-6), 23.33 (4-CH_3).
MS (EI, 70 eV): *m*/*z* (%) = 154 (14) $[M]^+$, 136 (69) $[M-CH_3]^+$, 121 (55) $[M-2CH_3]^+$.

GC: column: WCOT fused silica CP-Chiralsil-DEX CB (25 m × 0.25 mm)
carrier: H_2; temperature: 100 °C
retention time: t_{R1} = 9.14 min (minor enantiomer); t_{R2} = 9.34 min (major enantiomer).

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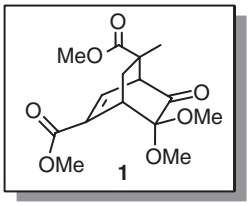
1.7.6

Bicyclo[2.2.2]octene Derivative



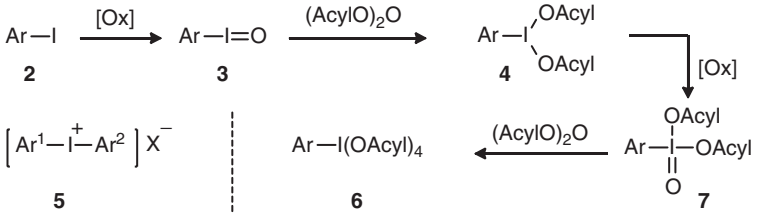
1

Topics:

- Oxidation of an *o*-methoxy-substituted phenol with a hypervalent iodine compound
- Diels–Alder reaction of a cyclohexa-1,3-dienone with methacrylate

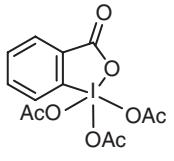
(a) **General**

In general, hypervalent organoiodine compounds [1–3] are derived from aryl iodides **2** (oxidation level of I: +1) by oxidation at the iodine atom. Thus, **2** can be oxidized to iodoxyarenes **3** and diacylated to give (diacyloxy)iodoarenes **4** (oxidation level of I: +3):



2 **3** **4** **5** **6** **7**

Hypervalent iodine(III) compounds such as **4** can be further oxidized to iodine(V) compounds of types **6**/**7** represented, for example, by Dess–Martin periodinane (**8**, DMP) and *ortho*-iodoxybenzoic acid (**9**, IBX), which are important reagents for the oxidation of primary and secondary alcohols to give aldehydes and ketones, respectively (cf. Section 2.3.2).



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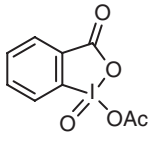
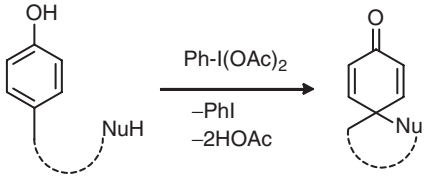


9

Diaryliodonium compounds **5** are another type of hypervalent iodine compounds used in synthetic chemistry [4].

The trivalent (diacyloxy)iodoarenes **4** (most frequently Ar = Ph, acyl = acetyl or trifluoroacetyl) are often applied for oxidative transformations of organic substrates, leading to the formation of C–C bonds or C–heteroatom bonds of various types [1].

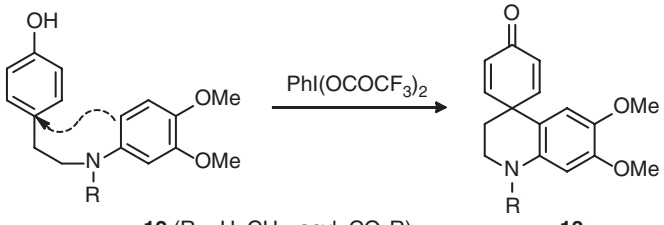
In particular, the oxidation of phenols with **4** leads to a variety of synthetically useful products [2]. Ortho-substituted phenols and *o*- or *p*-hydroquinones afford the corresponding benzoquinones, whereas para-substituted phenols **10** in the presence of an external or internal nucleophile lead to the corresponding 4,4-disubstituted cyclohexa-2,5-dienones (or spirodienones) **11**:



10 **11**

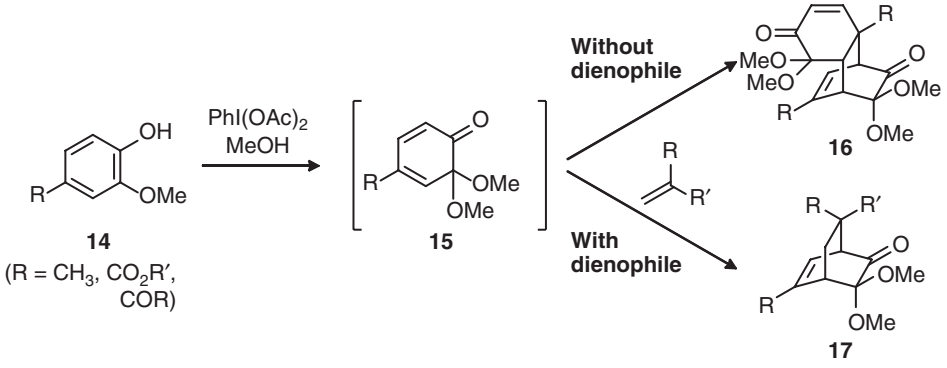
Nu = RO, halogenide anions, electron-rich arenes

Intramolecular phenol oxidations have been widely exploited for the construction of a spirodienone fragment in polycyclic systems [1], especially for the oxidative coupling of two phenolic arene units [5], as illustrated by the following example (**12** → **13**) [6]:



12 (R = H, CH_3, acyl, CO_2R) **13**

An analogous type of reaction is observed when phenols **14** with a methoxy substituent in an ortho-position to the OH function are oxidized with $PhI(OAc)_2$ in methanol as solvent [7, 8]:



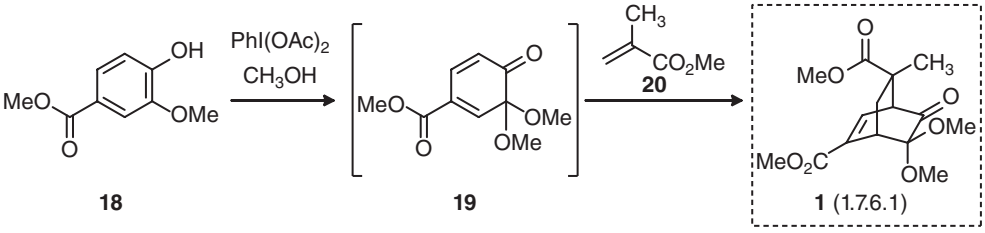
14
(R = CH_3, CO_2R', COR)

15

The initial products are the acetal-masked *o*-quinonoid systems **15**, which are of limited stability but, as potential cyclohexa-1,3-dienes, can be readily trapped by electron-deficient dienophiles in a Diels–Alder reaction to give cycloadducts **17** of the bicyclo[2.2.2]octenone type. In the absence of dienophiles, compounds **15** dimerize to polycycles **16**. As shown in Section (b), this remarkable phenol oxidation mediated by a hypervalent iodine source can be conducted as an efficient one-pot synthesis of highly functionalized bicyclo[2.2.2]octane derivatives [8] that are otherwise difficult to obtain.

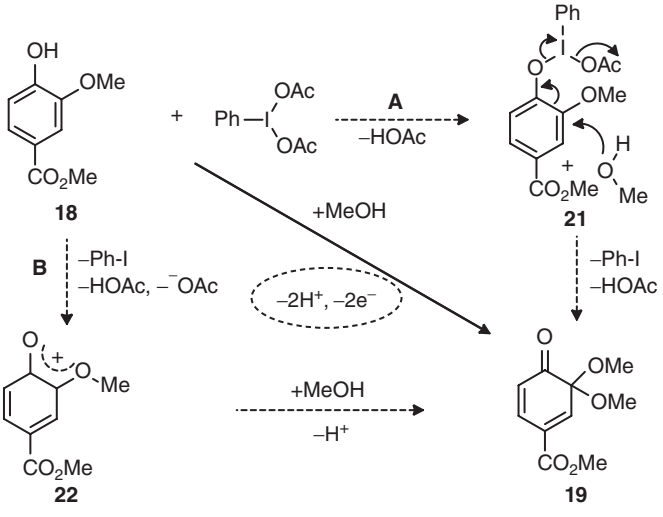
(b) **Synthesis of 1**

Methyl vanillate (**18**) is oxidized with (diacetoxy)iodobenzene in the presence of an excess of methyl methacrylate (**20**) in methanol at room temperature. The bicyclo[2.2.2]octen-2-one **1** is obtained (54% overall yield) in a clean, regio and stereoselective [4 + 2]-cycloaddition of the dienophile to cyclohexa-2,4-dienone **19** formed *in situ* by oxidation of the electron-rich phenolic substrate **18**.



The observed regio and stereoselectivity of the Diels–Alder reaction **19** + **20** → **1** can be explained in terms of frontier molecular orbital theory [8].

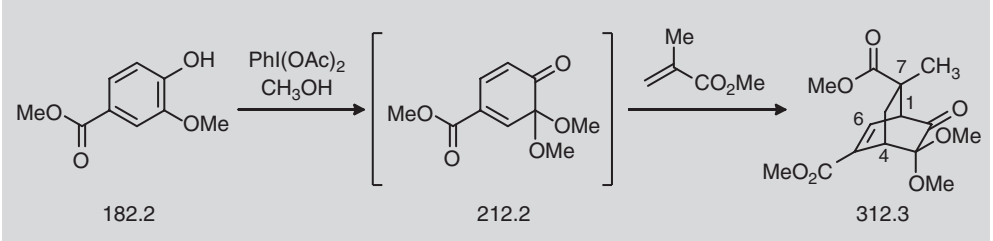
For the oxidative transformation **18** → **19**, two mechanistic alternatives are reasonable [2]. In mechanism A, the phenol **18** is attached to the iodine(III) of



$PhI(OAc)_2$ by ligand exchange with extrusion of HOAc to give an intermediate **21**. This undergoes redox disproportionation in an addition/elimination process by attack of CH_3OH, resulting in the formation of the cyclohexa-2,4-dienone **19**, iodobenzene, and HOAc. In mechanism **B**, the phenol **18** is oxidized in a two-electron/one-proton transfer – presumably via a phenoxy radical – to give the (resonance-stabilized) carboxenium ion **22**, which is trapped by addition of CH_3OH and loss of a second proton to afford the product **19**. Concomitantly, $PhI(OAc)_2$ is reduced to iodobenzene with formation of two molecules of acetate.

(c) Experimental Procedure for the Synthesis of 1

1.7.6.1 ** **(1*R**,4*S**,7*S**)-3,3-Dimethoxy-5,7-bis(methoxycarbonyl)-7-methylbicyclo[2.2.2]oct-5-en-2-one** [8]



182.2 212.2 312.3

A solution of methyl vanillate (1.00 g, 5.49 mmol) in anhydrous MeOH (70 ml) is added over a period of 8 h by means of a syringe pump to a solution of (diacetoxy)iodobenzene (2.12 g, 6.58 mmol) and methyl methacrylate (14.5 ml, 13.7 g, 137 mmol) in anhydrous MeOH (30 ml) at room temperature under nitrogen atmosphere. Stirring is continued for 2 h.

The solvent, excess dienophile, and other volatile products are removed *in vacuo*. Purification by flash chromatography (EtOAc/*n*-hexane, 9 : 1) gives the product as a colorless liquid; 918 mg (54%); $R_f = 0.57$ (EtOAc/*n*-hexane, 9 : 1).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2975, 1727.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.09 (dd, J = 6.5, 1.7 Hz, 1H, 6-H), 3.65–3.71 (m, 1H, 4-H), 3.74, 3.64 (2 × s, 6H, 2 × CO_2CH_3), 3.48 (d, J = 6.5 Hz, 1H, 1-H), 3.34, 3.26 (2 × s, 6H, 2 × OCH_3), 2.19 (dd, J = 18.1, 3.1 Hz, 1H, 8-H_A), 1.93 (dd, J = 18.1, 2.2 Hz, 1H, 8-H_B), 1.31 (s, 3H, 7-CH_3).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 201.0 (C-2), 175.7 (C=O), 164.3 (C=O), 137.4 (C-5), 137.4 (C-5), 93.4 (C-3), 57.3 (C-8), 52.4 (C-4), 51.9 (OCH_3), 50.0 (H-1), 49.8 (C3-OCH_3), 46.7 (C3-OCH_3), 38.4 (C-8), 25.4 (C-7).
MS (DCI, NH_3, 200 eV): 643 $[2M+NH_4]^+$, 330 $[2M+NH_4]^+$.

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6. Compound **13** is a central intermediate in a synthesis of the *Amaryllidacea* alkaloid maritidine: (a) Kita, Y., Takada, T., Gyoten, M., Tohma, H., Zenk, M.H., and Eichhorn, J. (1996) *J. Org. Chem.*, **61**, 5857–5864; A spirodienone of type **11** is a key intermediate in a synthesis of the anti-Alzheimer agent galanthamine: (b) Krikorian, D., Tarpanov, V., Parushev, S., and Mechkarova, P. (2000) *Synth. Commun.*, **30**, 2833–2846.
7. Chu, C.-S., Lee, T.-H., and Liao, C.-C. (1994) *Synlett*, 635–636.
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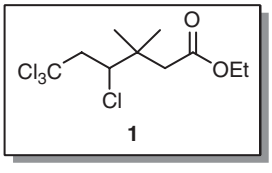
1.8 Radical Reactions

1.8.1 Ethyl 4,6,6,6-tetrachloro-3,3-dimethylhexanoate



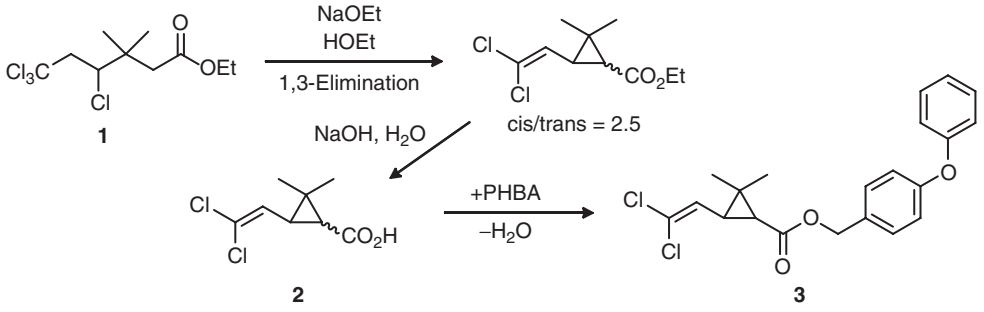
1

Topics:

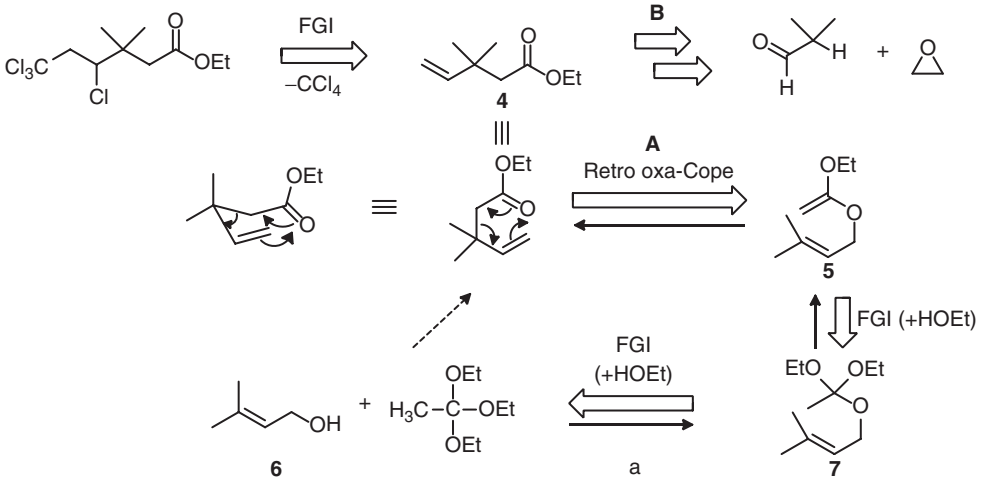
- Claisen orthoester reaction, [3,3]-sigmatropic rearrangement
- Telomerization by radical addition of CCl_4 to an alkene

(a) General

The target molecule **1** is the key intermediate in the synthesis of the (dichlorovinyl)cyclopropane carboxylic acid **2**. Esterification of **2** with (3-phenoxy)benzyl alcohol leads to **3**, which is an important insecticide (Permethrin, cf. Section 4.2.1). Compound **3** was developed as an analog of esters of chrysanthemic acid, a group of natural insecticides mainly isolated from the flowers of an aromatic plant of the genus *Tannacetum* (formerly *Chrysanthemum* or *Pyrethrum*).



For the retrosynthesis of **1**, two considerations must be taken into account: (i) the left-hand part of **1** may result from addition of CCl_4 to a C=C double bond, and (ii) in the resulting unsaturated ester **4**, the C=C and C=O functionalities are in a 1,5-arrangement and are therefore susceptible to a [3,3]-sigmatropic transformation according to a retro-oxa-Cope rearrangement (A):[9]

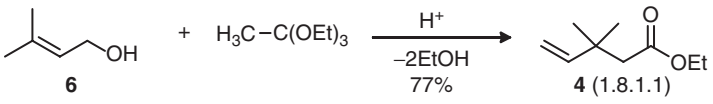


Thus, the retrosynthesis of **4** leads to the allylic alcohol **6** and triethyl orthoacetate via **7** and **5** as a simple approach to the γ,δ-unsaturated ester **4** based on a [3,3]-sigmatropic rearrangement. The synthesis of **1** along these lines is described in detail.

(b) **Synthesis of 1**

In the first step, the ester **4** is prepared by a Claisen orthoester reaction of 3-methyl-2-buten-1-ol (**6**) with triethyl orthoacetate in the presence of phenol [1]; (G. Künast, Bayer AG, private communication, 1981):

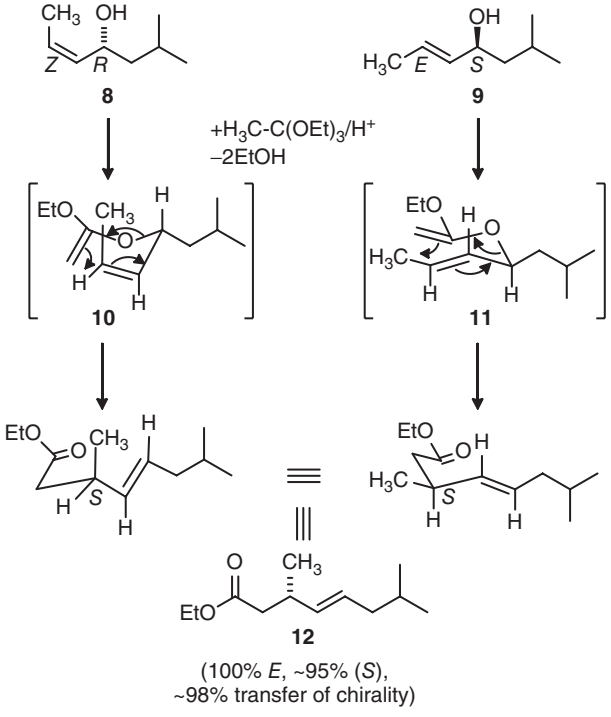
9) Other retrosynthetic pathways, for example, B leading to isobutanal and oxirane as educts of a possible synthesis of **1**, are less favorable (criterion of simplicity!).



6 4 (1.8.1.1)

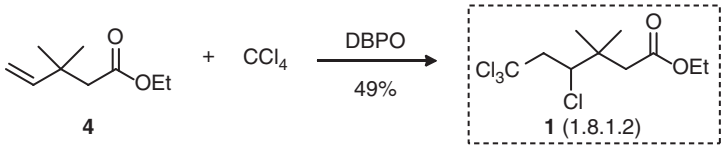
First, one molecule of EtOH in the orthoacetate is exchanged by the allylic alcohol **6** (→**7**), and then elimination of a second EtOH transforms the orthoester **7** to the ketene acetal **5** [2]; both reactions require H^+-catalysis. The allyl vinyl ether functionality in **5** is capable of a [3,3]-sigmatropic rearrangement (oxa-Cope reaction; a related rearrangement is the Carroll reaction in Section 1.5.3), leading directly to the γ,δ-unsaturated ester **4**.

It should be noted that, as a consequence of a highly ordered chair-like transition state, the oxa-Cope process (e.g., **5** → **4**) can be conducted with high stereoselectivity and transfer of stereogenic information from the substrates to the product. This is exemplified by an instructive example [3] describing the formation of the unsaturated ester **12** with (*S*)-*E*-stereochemistry from stereodifferent precursors, namely the (*R*)-*Z*-alcohol **8** and the (*S*)-*E*-alcohol **9**, by reaction with orthoacetate/propionic acid via the intermediates **10**/**11**.[10)]

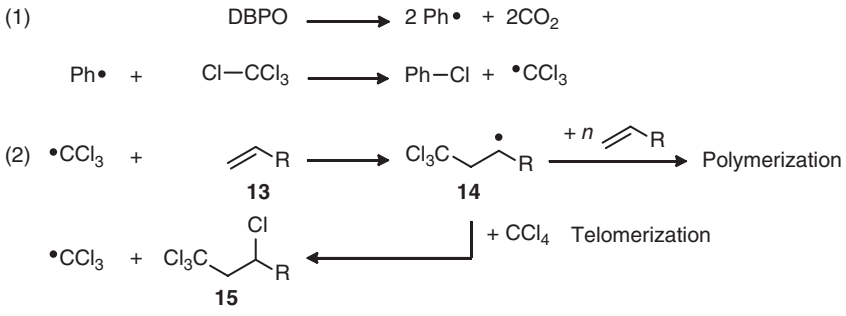


10) The chair-like transition states of the pericyclic transformations [(*R*)-*Z*-**10** → (*S*)-*E*-**12** ← (*S*)-*E*-**11**] should be favored by virtue of having the smallest number of nonbonding interactions, i.e. pseudoaxial substituents [3].

In the second step, CCl_4 is added to the unsaturated ester **4** in the presence of dibenzoyl peroxide (DBPO) to yield **1**:



The reaction proceeds by a radical chain process initiated by DBPO:

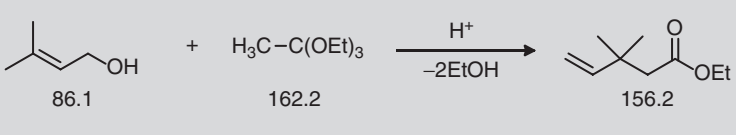


First, DBPO is cleaved thermally to give a phenyl radical, which generates a $\bullet CCl_3$ radical from CCl_4. In the chain propagation reaction (2), the $\bullet CCl_3$ radical adds to the terminal carbon atom of the olefinic substrate (**13**) to generate the secondary radical **14**. This radical may either lead to a polymerization of the olefinic substrate or abstract a chlorine atom from CCl_4, thus perpetuating chain propagation with formation of the addition product **15** (telomerization [4]). The competition between telomerization and polymerization is controlled by steric factors in the radical intermediate and the olefinic substrate. Increased steric hindrance favors telomerization.

Thus, the target molecule **1** is obtained in a two-step sequence with an overall yield of 38%.

(c) Experimental Procedures for the Synthesis of 1

1.8.1.1 ** Ethyl 3,3-dimethyl-4-pentenoate [1]



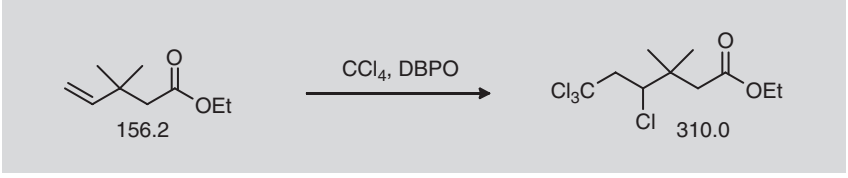
A mixture of 3-methyl-2-buten-1-ol (bp 140 °C; 43.1 g, 0.50 mol), ethyl orthoacetate (distilled, bp 144–146 °C; 97.3 g, 0.60 mol), and phenol (Caution: Irritant!

7.00 g, 74.4 mmol) is heated to 135–140 °C for 10 h with continuous removal of the EtOH formed.

The mixture is then cooled, diluted with Et_2O (200 ml), washed sequentially with aqueous HCl (1 N, 2 × 100 ml, to hydrolyze the excess of orthoacetate), saturated aqueous $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue is distilled over a short column. The yield is 60.4 g (77%), bp_{11} 57–60 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3090, 1740, 1640, 1370, 1240.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.90 (dd, J = 18.5, 10.0 Hz, 1H, 4-H), 5.15–4.7 (m, 2H, 5-H_2), 4.07 (q, J = 7.0 Hz, 2H, OCH_2), 2.25 (s, 2H, 2-H_2), 1.20 (t, J = 7.0 Hz, 3H, CH_3), 1.13 (s, 6H, 2 × 3-CH_3).

1.8.1.2 ** Ethyl 4,6,6,6-tetrachloro-3,3-dimethylhexanoate [1]



Ethyl 3,3-dimethyl-4-pentenoate **1.8.1.1** (23.4 g, 150 mmol) and DBPO (Caution: Explosive! 25% H_2O, 2.40 g) in tetrachloromethane (200 ml; Caution: resorption through the skin!) are heated under reflux for 8 h using a Dean–Stark trap. An additional 2.40 g of moist DBPO is added, and refluxing with removal of H_2O is continued for 8 h.

The solution is then cooled and washed twice with ice-cold aqueous NaOH (1 N, to remove benzoic acid) and thrice with brine. The organic phase is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The residue is distilled *in vacuo* over a short column. The yield is 22.8 g (49%), $bp_{0.2}$ 132–138 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2980, 1730, 1465, 1370, 720, 690.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.43 (dd, J = 8.0, 3.3 Hz, 1H, 4-H), 4.12 (q, J = 7.0 Hz, 2H, O–CH_2), 3.19 (d, J = 3.3 Hz, 1H, 5-H_A), 3.13 (d, J = 8.0 Hz, 1H, 5-H_B), 2.66 (d, J = 15.0 Hz, 1H, 2-H_A), 2.26 (d, J = 15.0 Hz, 1H, 2-H_B), 1.24 (t, J = 7.0 Hz, 3H, CH_3), 1.20 (s, 3H, 3-CH_3), 1.13 (s, 3H, 3-CH_3).

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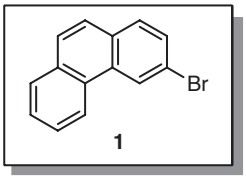
1.8.2

3-Bromophenanthrene



1

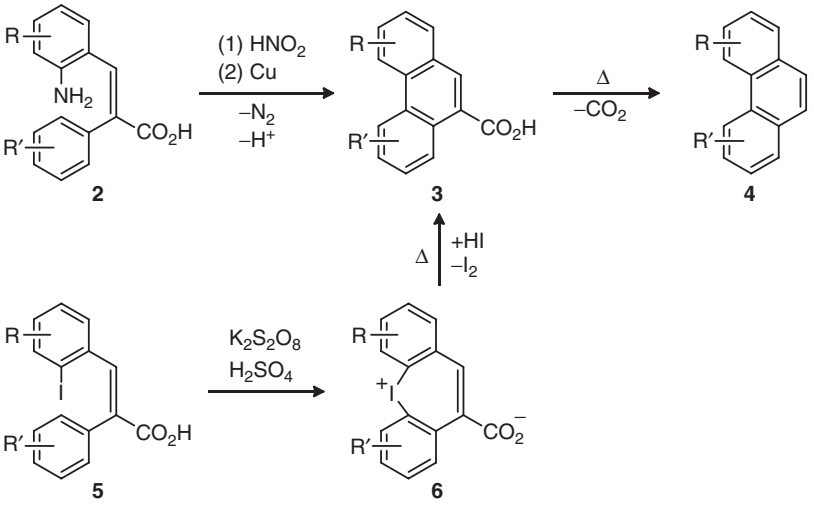
Topics:

- Meerwein arylation (radical addition of arenes to activated alkenes)
- 1,2-Elimination
- Photoisomerization of *trans*-stilbenes to *cis*-stilbenes, electrocyclization of *cis*-stilbenes to dihydrophenanthrenes, and their dehydrogenation to phenanthrenes

(a) **General**

For the synthesis of phenanthrenes, three methods are of preparative importance [1].

1) In the Pschorr phenanthrene synthesis [2], an *o*-amino-*cis*-stilbene carboxylic acid **2** is diazotized, and the resulting diazonium salt is reductively dediazoniated with Cu and cyclized to give a phenanthrene-9-carboxylic acid **3**, which is thermally decarboxylated to a phenanthrene **4**. For the cyclization step, a radical mechanism is likely, in analogy to the Gomberg–Bachmann arylation [2]. The Pschorr method cannot be used for the synthesis of **1** [3].

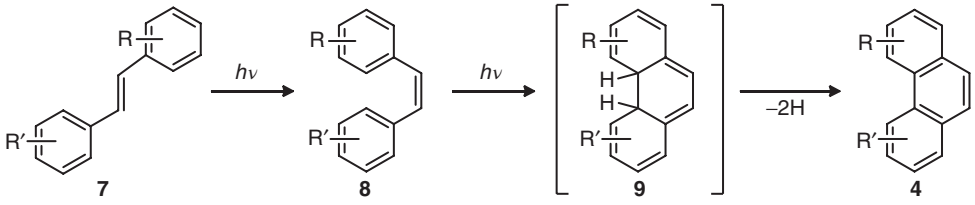


2 **3** **4**

5 **6**

2) In an oxidative cyclization [4], α-aryl-*o*-iodocinnamic acids **5** are converted to phenanthrenes by reaction with $K_2S_2O_8$. First, cyclic iodonium salts (iodepinium salts) **6** are formed, which on thermolysis lead to phenanthrene carboxylic acids **3**. These compounds can be decarboxylated to give phenanthrenes **4** as described above. The intermediacy of an iodoso arene species as the initial oxidation product of **5** and its S_EAr_i cyclization to **6** have been established, but the mechanism of the cyclization of **6** is not known.

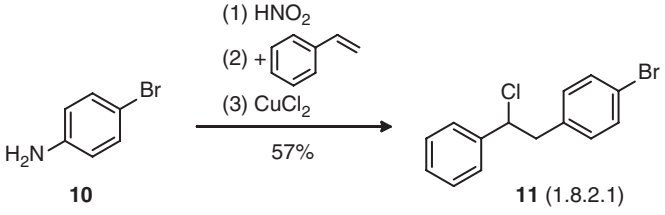
3) In a photochemical domino process [5], *trans*-stilbenes **7** are photoisomerized to give the corresponding *cis*-stilbenes **8**, which undergo 6π-electrocyclization to dihydrophenanthrenes **9** followed by *in situ* dehydrogenation to phenanthrenes **4**:



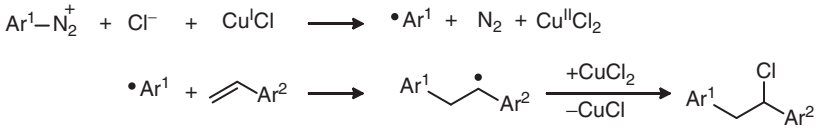
The target molecule **1** has been synthesized by application of methods (2) and (3). In Section (b), a synthesis based on the photochemical cyclization route [6] is described.

(b) **Synthesis of 1**

trans-4-Bromostilbene (**12**), the required starting material, is prepared in a two-step sequence from 4-bromoaniline (**10**) by diazotization with HNO_2 and reaction of the diazonium salt with styrene in the presence of Cu(II) chloride in aqueous acetone to afford the bibenzyl derivative **11**:

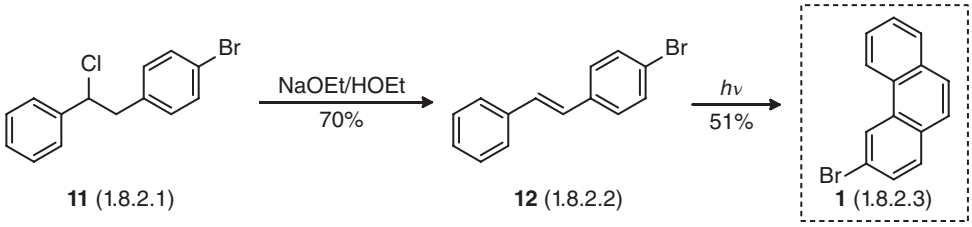


The addition of aryl diazonium salts to activated alkenes (besides styrene, acrylonitrile and acrylates are often used) proceeds with loss of N_2 and is catalyzed by Cu(I) (Meerwein arylation [7]). The Meerwein arylation follows a radical chain mechanism related to the Cu(I)-induced Sandmeyer reaction:



Dehydrochlorination of the bibenzyl **11** with NaOEt/HOEt leads to *trans*-4-bromostilbene (**12**). This is subjected to photolysis in cyclohexane solution in the presence of iodine, resulting in isomerization to the corresponding *cis*-stilbene,

electrocyclic ring closure to a dihydrophenanthrene, and subsequent dehydrogenation to give the desired 3-bromophenanthrene (**1**).

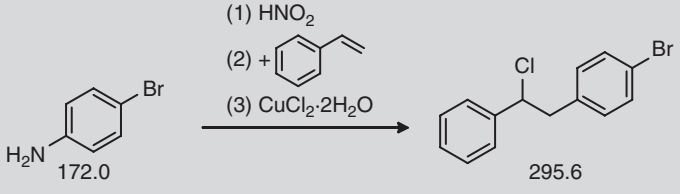


11 (1.8.2.1) **12** (1.8.2.2) **1** (1.8.2.3)

Using this procedure, the target molecule **1** is obtained in a three-step sequence in an overall yield of 20% (based on 4-bromoaniline).

(c) Experimental Procedure for the Synthesis of 1

1.8.2.1 * **2-(4-Bromophenyl)-1-chloro-1-phenylethane** [8]



Sodium nitrite (7.00 g, 0.10 mol) in water (35 ml) is added dropwise to a stirred solution of *p*-bromoaniline (17.2 g, 0.10 mol) in aqueous hydrochloric acid (5 M, 60 ml) with cooling in an ice–salt bath so as to maintain the reaction temperature below 5 °C (note 1). The solution is brought to pH 4–5 by the addition of solid $NaHCO_3$ (14.3 g) in portions. The solution is then added dropwise over 10 min to a solution of styrene (10.4 g, 0.10 mol; note 2) and $CuCl_2 \cdot 2H_2O$ (4.00 g, 25.0 mmol) in acetone (100 ml). Nitrogen evolution starts slowly, becomes vigorous after approximately 1 h, and ends after 15 h.

Et_2O (100 ml) is added, the dark organic phase is separated, and the aqueous phase is extracted with Et_2O (2 × 50 ml). The combined ethereal phases are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residual brown oil is crystallized by the addition of the minimum volume of petroleum ether (50–70 °C): 16.9 g (57%), mp 81–82 °C. Recrystallization from EtOH gives light-brown needles, mp 87–88 °C.

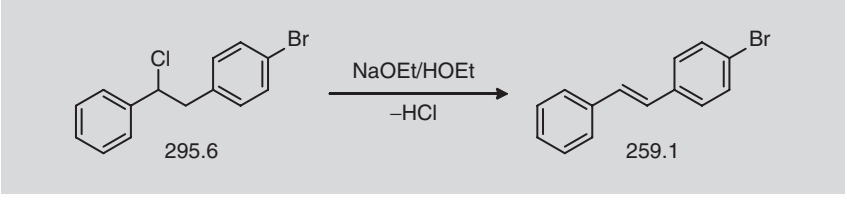
UV (CH_2Cl_2): λ_{max} (log ε) = 316 (3.57), 330 nm (sh).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1585, 800, 765, 690.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.30, 6.88 (2 × d, J = 8.0 Hz, 4H, 4-bromophenyl-H), 7.25 (s, 5H, Ar–H), 4.88 (t, J = 6.0 Hz, 1H, 1-H), 3.24 (d, J = 6.0 Hz, 2H, 2-H_2).

Notes:

1) Completeness of the reaction is tested with starch-iodide paper; the presence of HNO_2 results in a blue color.
2) Styrene is distilled from hydroquinone, bp_{12} 33–34 °C, and is stored with hydroquinone.

1.8.2.2 * *trans*-4-Bromostilbene [8]

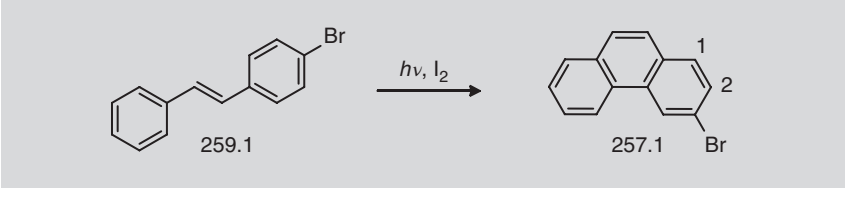


A sodium ethoxide solution is prepared by dissolving sodium (1.15 g, 0.05 mol) in anhydrous EtOH (50 ml), and then compound **1.8.2.1** (5.90 g, 20.0 mmol) is added with stirring. The suspension is warmed on a steam bath until dissolution is complete. After approximately 2 min, a fine precipitate of sodium chloride begins to form. After approximately 6 min, a voluminous precipitate of the product forms. The mixture is heated under reflux with vigorous stirring for 1 h.

H_2O (5 ml) is added to the hot solution, the mixture is cooled with stirring in an ice bath, and the precipitate is collected by filtration and washed with EtOH (10 ml). The crude product (approximately 5.5 g) is recrystallized from isopropanol (decolorizing with activated charcoal) to give colorless needles; 3.60 g (70%), mp 137–138 °C, TLC: single spot (silica gel; CH_2Cl_2).

UV (CH_2Cl_2): λ_{max} (log ε) = 314 (4.52), 427 nm (sh).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1580, 820, 750, 700, 690.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.50–7.26 (m, 9H, Ar–H), 7.14–7.00 (m, 2H, 1-H, 2-H).

1.8.2.3 ** 3-Bromophenanthrene [6]



Apparatus: Photolysis apparatus with quartz filter and high-pressure mercury vapor lamp (Philips HPK-125 W or Hanau TQ-150 W).

A solution of *trans*-4-bromostilbene **1.8.2.2** (2.60 g, 10.0 mmol) and iodine (0.13 g, 1.00 mmol) in anhydrous cyclohexane (1000 ml) is irradiated for 16 h while air is passed through it (note).

The solvent is evaporated *in vacuo*, the red residue is dissolved in cyclohexane (50 ml), and the solution is filtered through neutral Al_2O_3 (25 g, activity grade I). The colorless filtrate is concentrated, and the residue (1.35 g, mp 76–78 °C) is recrystallized from EtOH to give colorless needles; 1.30 g (51%), mp 83–84 °C, TLC: single spot (silica gel; CH_2Cl_2).

UV (CH_2Cl_2): λ_{max} (log ε) = 298 (4.17), 286 (4.05), 277 (4.18), 268 (sh), 254 nm (4.95).
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1580, 840, 820, 730.
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.80–8.20 (m, 2H, Ar–H), 7.90–7.20 (m, 7H, Ar–H).

Note: Passing oxygen instead of air through the reaction mixture and prolongation of the irradiation time do not improve the yield.

References

1. Another method often mentioned in textbooks, the Haworth synthesis, seems to be of limited scope and is only applicable to phenanthrene itself and some alkyl-substituted derivatives: Beyer, H. and Walter, W. (1998) *Lehrbuch der Organischen Chemie*, 23rd edn, S. Hirzel Verlag, Stuttgart, p. 686.
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