1 C–C Bond formation

Introduction

C–C Bond formations are essential for the construction of the backbone of any organic compound in this book. Their mechanistic description is used as a general tool for their classification. Thus, in chapters **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.

Chapter **1.1** deals with *nucleophilic addition to the carbonyl group of aldehydes, ketones, and derivatives of carboxylic acids (esters, anhydrides, etc.), addition to acceptor-substituted olefins (Michael addition)*, and *carbonyl olefination*.

Examples are

- the classical addition of organometallics to aldehydes or ketones, such as the addition of Grignard compounds (**1.1.1**), allylsilanes (**1.1.2**, conducted according to the Tietze protocol in enantioselective fashion), and the Ti-induced geminal dimethylation of C=O groups (**1.1.6**);
- the desymmetrization of achiral anhydrides by Grignard compounds in the presence of a chiral catalyst (**1.1.3**);
- conjugate addition to auxiliary-substituted α,ß-unsaturated carbonyl systems (**1.1.4**) and trapping of an enolate formed by 1,4-addition to an acceptor-substituted olefin according to the Baylis–Hillman concept (**1.1.5**);
- carbonyl olefination, such as by the Wittig reaction (**1.1.6**) and the Lombardo reaction (**1.1.7**).

Chapter **1.2** deals with *alkylation reactions of aldehydes/ketones or carboxylic acids and ß-dicarbonyl compounds* at their α- and γ-positions, respectively.

Examples are

- the auxiliary-based stereoselective α-alkylation of ketones according to the SAMP method of Enders (**1.2.1**);
- the auxiliary-based stereoselective α-alkylation of chiral oxazolidinones according to the Evans methodology (**1.2.2**);
- the γ-alkylation of acetoacetate (**1.2.3**).

Reactions and Syntheses in the Organic Chemistry Laboratory. L. F. Tietze, Th. Eicher, U. Diederichsen, A. Speicher

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Chapter **1.3** deals with *reactions of the aldol and Mannich type*.

Examples are

- the synthesis of olivetol (**1.3.1**), involving aldol addition/condensation, Michael addition/Claisen condensation (cf. **1.4**), and a domino process for aromatization;
- the synthesis of the Wiechert–Hajos ketone (**1.3.2**) by Michael addition and (*S*)-proline-catalyzed enantioselective aldol addition/condensation (organocatalytic Robinson annelation);
- the diastereoselective aminoalkylation of an enamine via an *N*-acyl imino ester (**1.3.3**);
- the enantioselective Mukaiyama aldol reaction (**1.3.4**) of an aldehyde with a silylenol ether catalyzed by a chiral (acyloxy)borane, as well as the synthesis of the required chiral CAB ligand from (*S*,*S*)-tartaric acid;
- the enantioselective synthesis of an oxocyclohexane carboxylic ester (**1.3.5**) by a domino-Michael-aldol process using Jørgensen's catalyst as well as its synthesis from *L*-phenylalanine.

Chapter **1.4** deals with *electrophilic and nucleophilic acylation* reactions.

Examples are

- the synthesis of a chiral 1-alkylated 2-oxocyclopentane-1-carboxylate (**1.4.1**) by Dieckmann cyclization of an adipate, chemoenzymatic enantioselective reduction of a β-ketoester, α-alkylation of a chiral β-hydroxyester, and re-oxidation;
- the synthesis of both enantiomers of an α-hydroxyester (**1.4.2**) by an ECP protocol starting with succinylation of an arene by *O*-acetylated (*S*)-malic anhydride;
- the synthesis of (*S*)-naproxene (**1.4.3**) starting with a thermodynamically controlled Friedel–Crafts acylation of a naphthalene derivative and an enzymatic hydrolysis of an ester moiety;
- addition of an α-metalated (*O*-silyl)cyanohydrin as an acyl anion equivalent to an enone (**1.4.4**) according to the Hünig protocol.

Chapter **1.5** deals with *reactions of alkenes* proceeding *via carbenium ions*.

Examples are

- the synthesis of piperine (**1.5.1**) by a Lewis acid-catalyzed reaction of acetals with ethyl vinyl ether;
- the synthesis of cicloxilic acid (**1.5.2**) by way of a stereoselective Prins reaction;
- the synthesis of β-ionone (**1.5.3**) with formation of the cyclohexene ring by a cationic cyclization.

Chapter **1.6** deals with *transition-metal-catalyzed reactions* and is focused on some representative transformations using Pd and Cu as catalysts, such as:

- the Heck reaction, applied for a novel ligand-free stilbene synthesis (**1.6.1**);
- the Suzuki–Miyaura cross-coupling reaction for the synthesis of a functionalized biaryl (**1.6.2**);
- the Sonogashira cross-coupling reaction, used for diarylalkyne formation (**1.6.3**);
- a domino cuprate reaction of a β-mesyloxy alkenone, applied for the synthesis of 3,3-dimethylcyclohexanone (**1.6.4**).

Other transition-metal-mediated reactions are described in **1.1.6**/**1.1.7**/**2.1.1** (Ti), **2.1.2** (Mn), **3.3.2** (Ru), **4.2.2** (Rh).

Chapter **1.7** deals with *pericyclic reactions* (cycloadditions, electrocyclic transformations, sigmatropic reactions).

Examples are

- the synthesis of tranylcypromine (**1.7.1**) with cyclopropane formation by [1+2]-addition of carbenes to alkenes;
- the synthesis of [10]annulene (**1.7.2**) using a [1+2]-cycloaddition and an electrocyclic ring-opening (norcaradiene–cycloheptatriene rearrangement);
- the synthesis of a heptalene derivative (**1.7.3**) by [2+2]-cycloaddition of ADE to azulene followed by electrocyclic ring-opening;
- the synthesis of bishomocubane (**1.7.4**) by [4+2]-cycloaddition of 1,3-cyclohexadiene to a 1,4-quinone followed by intramolecular photochemical [2+2]-cycloaddition;
- the synthesis of α-terpineol (**1.7.5**) by the use of a Diels–Alder reaction as the key step, which is performed (a) for *rac*-α-terpineol and (b) for (+)-α-terpineol by an auxiliary-assisted Evans process (cf. **1.2.2**);
- generation of a bicyclo[2.2.2]octene derivative (**1.7.6**) by oxidation of an arene with a hypervalent iodine compound and trapping of the intermediate cyclohexadienone by [4+2]-cycloaddition.

The hetero-Diels–Alder reaction of α,β-unsaturated carbonyl compounds to electron-rich olefins ([4+2]-cycloaddition with inverse electron demand) is another type of pericyclic reaction and is described in **4.1.1**.

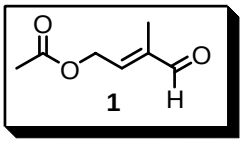
Chapter **1.8** deals with some basic *radical reactions*.

Examples are

- the radical addition of CCl_4 to an olefin (telomerization) combined with a Claisen [3,3]-sigmatropic rearrangement (**1.8.1**);
- the radical addition of arenes to activated olefins (Meerwein arylation) and the photochemical cyclization of *cis*-stilbenes to phenanthrenes (**1.8.2**).

1.1 Nucleophilic addition to aldehydes, ketones, carboxylic acid derivatives (esters, anhydrides, α,β-unsaturated carbonyl compounds)

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

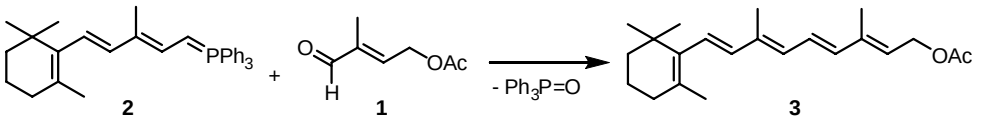


Topics:

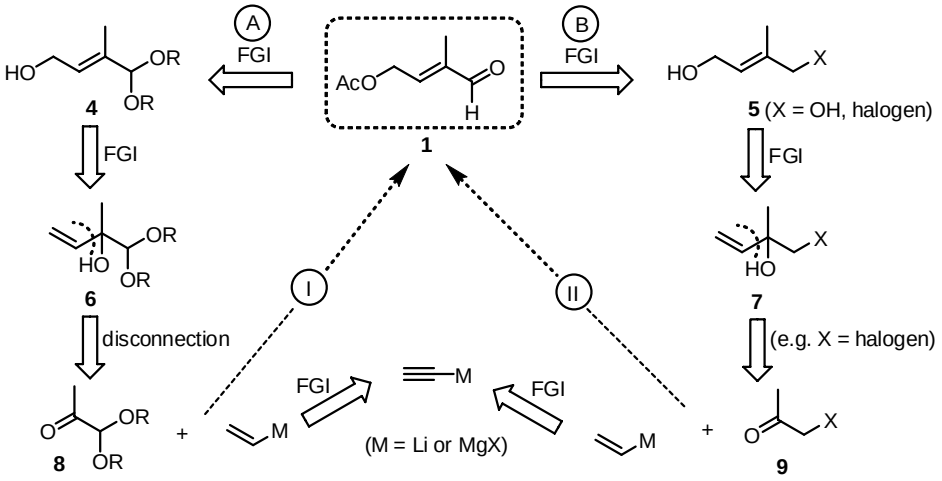
- Preparation of a C_5-building block for vitamin A synthesis
- Allylic alcohols from ketones and vinyl Grignard compounds
- Acetylation of an allyl alcohol with allylic inversion
- Kornblum oxidation R–CH_2–X → R–CH=O

(a) General

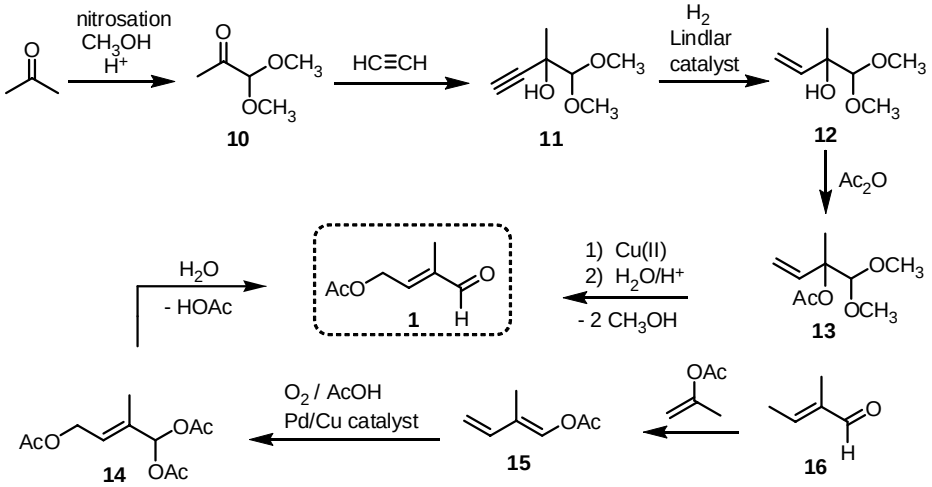
(*E*)-2-Methyl-2-butenal bearing an acetoxy group at the 4-position can be regarded as a functional isoprene unit and is used as a C_5-building block for the synthesis of terpenes by carbonyl olefination [1]. Thus, in the classical industrial vitamin A synthesis of BASF (cf. **4.2.6**), (*E*)-4-acetoxy-2-methyl-2-butenal (**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/II** have been described in the literature.

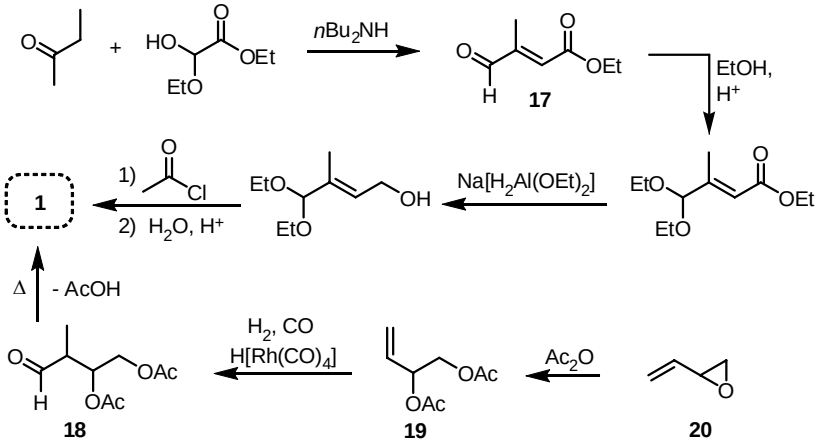


Approach **I** corresponds to a former industrial synthesis of **1** by BASF [2] starting with oxidation (nitrosation in the presence of methanol) of acetone to give methylglyoxal dimethyl acetal (**10**). This is followed by ethynylation with acetylene, partial hydrogenation, and acetylation (**10** → **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** [3, 4]; **15** can be obtained from the readily available tiglic aldehyde (**16**) and isopropenyl acetate:

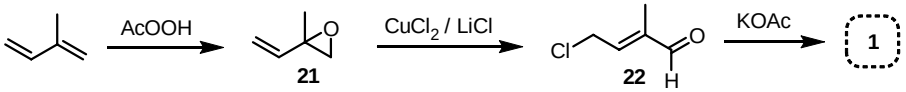


Approach **II** is the basis of a laboratory synthesis of **1** [5], which is described in detail in section (b).

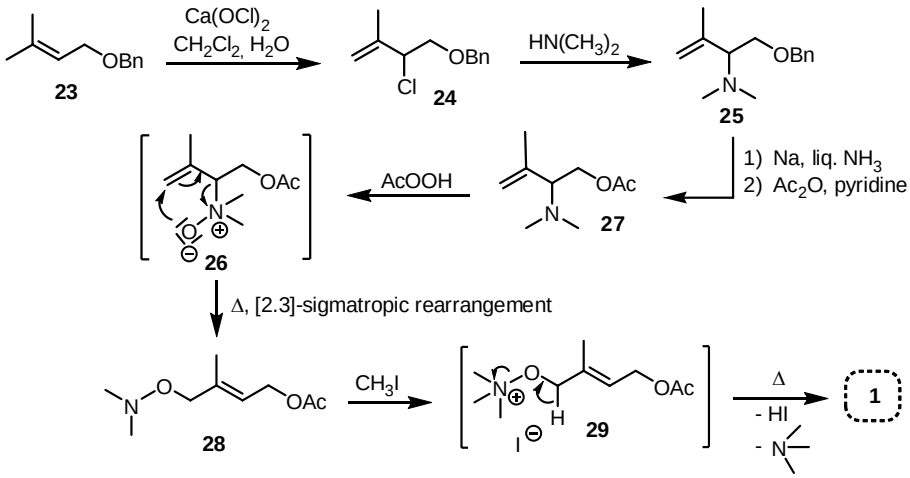
More recently, two other processes have been introduced for industrial syntheses of **1** [6] starting from (a) 3-formyl crotonate **17** and (b) 3,4-epoxy-1-butene (**20**), respectively. In (b), the key step is a regioselective Rh-catalyzed hydrocarbonylation (→ **18**) of the diacetate **19**, obtained 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 thermal Hofmann-like elimination of $(CH_3)_3N$ finally provides **1** via **29**:

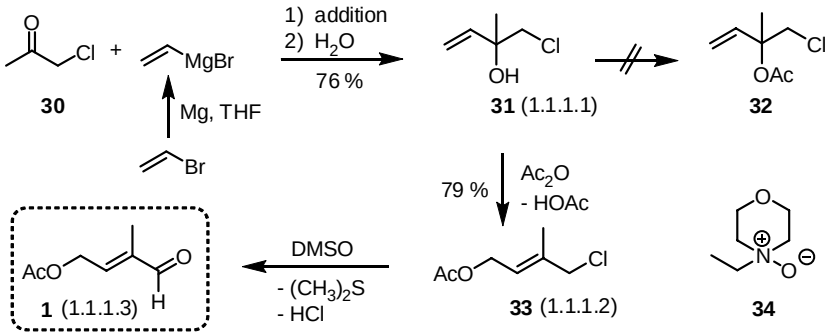


(b) Synthesis of 1

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 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**.

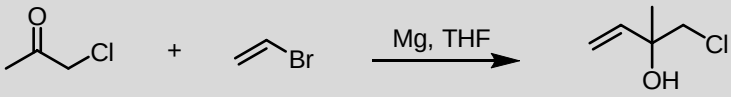
For the final step of the synthesis, the primary chloride in **33** is converted into the aldehyde group of **1** by means of Kornblum oxidation with dimethyl sulfoxide. The disadvantage of the Kornblum oxidation (in particular, odor of $(CH_3)_2S$!) can be avoided by the use of *N*-ethylmorpholine *N*-oxide (**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) [5]



Magnesium turnings (7.30 g, 0.30 mol) are added to anhydrous THF (70 mL) under N_2 and a small amount of ethyl bromide (1 g) is added to start the reaction. Vinyl bromide (32.0 g, 0.30 mol) in THF (90 mL) is then added dropwise with stirring at such a rate that the temperature never exceeds 40 °C (ca. 90 min). Stirring is continued for 30 min, the dark-grey solution is cooled to 0 °C, and a solution of chloroacetone (18.5 g, 0.20 mol) (note) in THF is added dropwise over 45 min. Stirring is continued at room temperature for 1 h.

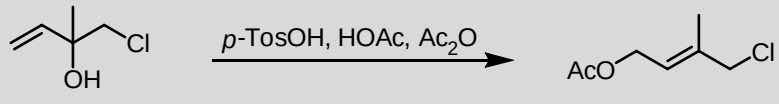
The adduct is hydrolyzed by the dropwise addition of ice-cold saturated aqueous NH_4Cl solution (100 mL) at 0 °C. The phases are separated and the aqueous phase is extracted with Et_2O (2 × 100 mL). The combined organic phases are washed with 2% $NaHCO_3$ solution (100 mL) and H_2O (100 mL), and dried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

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

^{1}H NMR ($CDCl_3$): δ (ppm) = 6.20–5.05 (12 lines of H_2C=CH system; 5.55–5.05 AB part; 6.20–5.75 X-part, J_{AB} = 1.8 Hz, J_{AX} = 16.2 Hz, J_{BX} = 10.3 Hz), 3.54 (s, 2 H, CH_2), 2.60 (s, 1 H, OH; exchangeable)], 1.41 (s, 3 H, 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 [5]



120.6 | *p*-TosOH x H_2O: 190.2 | 162.9

A solution of *p*-toluenesulfonic acid monohydrate (2.54 g, 13.4 mmol) in glacial acetic acid (60 mL) is added dropwise to a stirred solution of isoprene chlorohydrin (**1.1.1.1**, 15.3 g, 127 mmol) in acetic anhydride (20 mL) and glacial acetic acid (60 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.

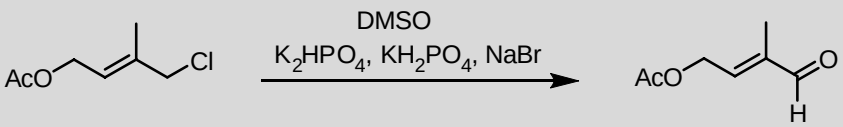
The solution is cooled and carefully poured into a mixture of 10% NaOH (800 mL) and ice (200 g). The resulting mixture is extracted with Et_2O (3 × 100 mL), and the combined ethereal phases are dried over Na_2SO_4 and concentrated *in vacuo*. The residue is fractionally distilled to give the product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

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1740 (C=O), 1235, 1025, 685.

^{1}H NMR (CCl_4): δ (ppm) = 5.68 (t_{br}, *J* = 7 Hz, 1 H, =CH), 4.57 (d, *J* = 7 Hz, 2 H, OCH_2), 4.09, 3.99 (s, total 2 H, ratio 1:6, *Z*-CH_2Cl/*E*-CH_2Cl), 2.02 (s, 3 H, $OCOCH_3$), 1.85 (s_{br}, 3 H, =C–CH_3).

Note: The ^{1}H NMR spectrum indicates a 6:1 mixture of the *E*/*Z* stereoisomers of the product.

1.1.1.3 * (*E*)-Acetoxy-2-methyl-2-butenal [5]



162.9 | 174.2 / 136.1 / 102.9 | 142.2

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, 99.5 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 CCl_4 (200 mL) (Caution!). The phases are separated, the aqueous phase is extracted with CCl_4 (100 mL), and the combined organic layers are dried over Na_2SO_4. The solvent is evaporated *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_D^{20} = 1.4647 (note).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2720 (aldehyde CH), 1735 (C=O acetoxy), 1690 (C=O), 1645.

^{1}H NMR ($CDCl_3$): δ (ppm) = 9.55 (s, 1 H, aldehyde CH; *Z*-isomer: δ = 10.23), 6.52 (tq, *J* = 6.0, 1.0 Hz, 1 H, =CH), 4.93 (dq, *J* = 6.0, 1.0 Hz, 2 H, OCH_2), 2.12 (s, 3 H, $OCOCH_3$), 1.81 (dt, *J* = 1.0, 1.0 Hz, 3 H, = C–CH_3).

Note: If smaller amounts of starting material are used, column chromatography (silica gel, 0.06–0.2 mm, eluent *n*-hexane/Et_2O, 9:1) is recommended as the purification procedure.

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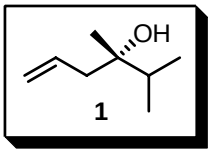
[10] H. Normant, *Adv. Org. Chem.* **1960**, *2*, 1.

[11] S. Suzuki, T. Onishi, Y. Fujita, M. Misawa, J. Otera, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3287; for **1**, a yield of 88% is reported.

[12] Sulfoxides anchored on ionic liquids are reported to represent non-volatile and odorless reagents for Swern oxidation: X. Me, T. H. Chan, *Tetrahedron* **2006**, *62*, 3389.

1.1.2 (*S*)-2,3-Dimethyl-hex-5-en-3-ol

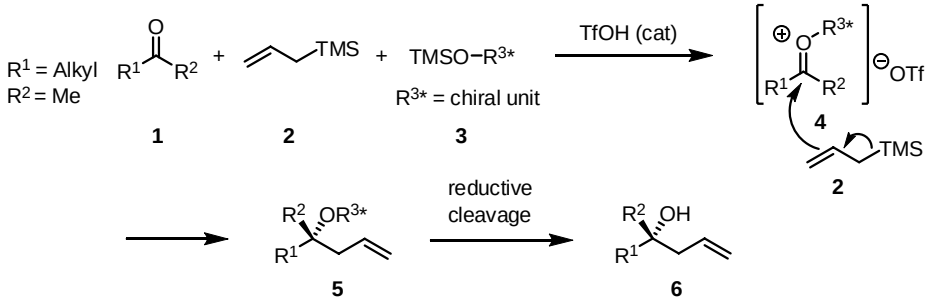


Topics:
- Stereoselective allylation of ketones
- Synthesis of enantiopure tertiary allyl alcohols
- Domino reactions

(a) General

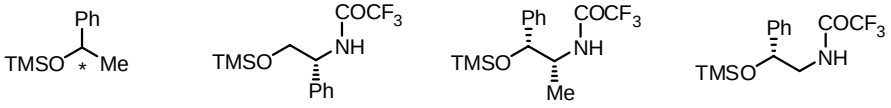
Allylations of aldehydes and ketones using allyl silanes, allyl stannanes, or allyl boronates are very important methods for the preparation of homoallylic alcohols [1]. The reactions can also be performed in an enantioselective way, with high asymmetric induction if aldehydes are used as substrates. Otherwise, the stereoselective allylation of ketones such as alkyl methyl ketones is much more difficult and so far only one method exists for this transformation, which was developed by Tietze and co-workers [2, 3].

The following asymmetric allylation of alkyl methyl ketones can be regarded as a three-component domino reaction, in which a ketone **1**, allyl trimethylsilane (**2**) as allylating reagent, and a chiral silyl ether **3** as *O*-alkylating component react to give the homoallylic ether **5**. A catalytic amount of triflic acid is needed for the initiation of this multicomponent process.



The allylation proceeds via an intermediate carboxenium ion **4**, which is attacked by the allyl silane **2**. If a benzyl trimethylsilyl ether **3** is used, the formed product **5** can be cleaved reductively to give the corresponding homoallylic tertiary alcohol **6**.

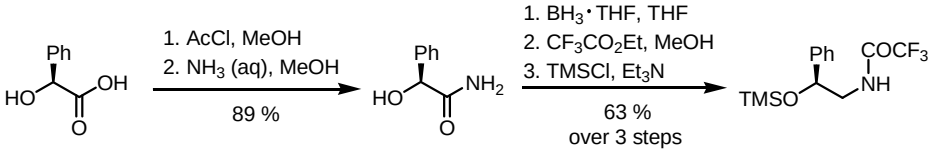
Chiral silyl ethers such as **3a** [4, 5] and **3b** [6] give only a very low selectivity of 1.8:1, whereas an excellent facial differentiation could be achieved with the norpseudoephedrine and mandelic acid derivatives **3c** [2] and **3d** [3], respectively.



3a **3b** **3c** **3d**

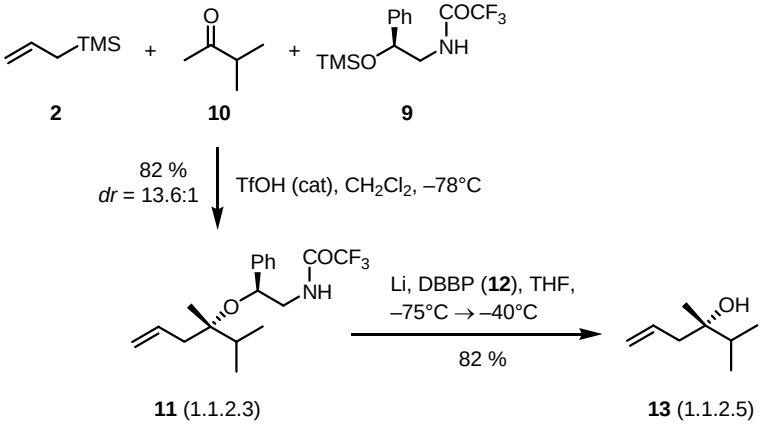
(b) Synthesis of 1

First, the chiral silyl ether **9** is synthesized, which is derived from mandelic acid (**7**) and used in the asymmetric allylation of 3-methyl-2-butanone (**10**) [3]. Mandelic acid (**7**) is activated using acetyl chloride and reacted with ammonia to give the mandelic acid amide (**8**). This is reduced with borane-tetrahydrofuran complex to afford the corresponding amine. Formation of the trifluoroacetamide by employing ethyl trifluoroacetate and silylation of the free hydroxy group with chlorotrimethylsilane in the presence of triethylamine leads to the chiral silyl ether **9**.



7 **8** (1.1.2.1) **9** (1.1.2.2)

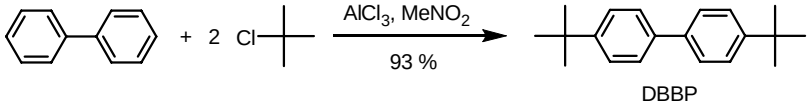
Second, 3-methyl-2-butanone (**10**) is allylated with allyl trimethylsilane (**2**) in the presence of **9** and a catalytic amount of triflic acid in CH_2Cl_2 at –78 °C. The formed benzyl ether **11** is reductively cleaved employing lithium and 4,4'-di-(*tert*-butyl)-1,1'-biphenyl (DBBP) (**12**) to give (*S*)-2,3-dimethyl-hex-5-en-3-ol (**13**). Recent computational investigations employing the B3LYP/G–31+G(d) level of theory in dichloromethane solution indicate that the reaction proceeds via an S_N1-type mechanism with an open transition state for the addition of the allyl silane [7].



2 **10** **9**

11 (1.1.2.3) **13** (1.1.2.5)

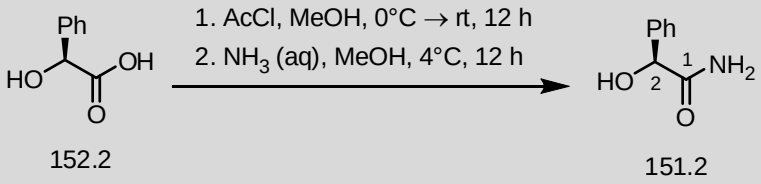
DBBP (**12**) can be easily prepared from biphenyl (**14**) by Friedels–Crafts alkylation using 2-chloro-2-methylpropane (**15**) and aluminum trichloride.



14 **15** **12** (1.1.2.4)

(c) Experimental procedures for the synthesis of 1

1.1.2.1 * (*S*)-Mandelic acid amide [3]



152.2 151.2

A 1 L oven-dried two-necked round-bottomed flask, equipped with a magnetic stirring bar and a three-way stopcock attached to an argon balloon, is charged with (*S*)-mandelic acid (25.0 g, 164 mmol) and anhydrous MeOH (670 mL). After cooling the mixture to 0 °C with an ice-water bath, acetyl chloride (31.5 mL, 443 mmol) is added dropwise from a dropping funnel at 0 °C with stirring. Stirring is continued for 12 h at room temperature.

Thereafter, the solvent is evaporated under reduced pressure (T < 40 °C), the residue is redissolved in MeOH (125 mL), and ice-cold saturated aqueous NH_3 solution (310 mL) is added with stirring. The flask is stored in a refrigerator (4 °C) overnight.

After evaporation of the solvent, the residue is recrystallized (EtOH/EtOAc) to afford colorless crystals; 22.0 g (89%), mp 120–121 °C, $[\alpha]_D^{20}$ = +78.0 (c = 1.7, acetone).

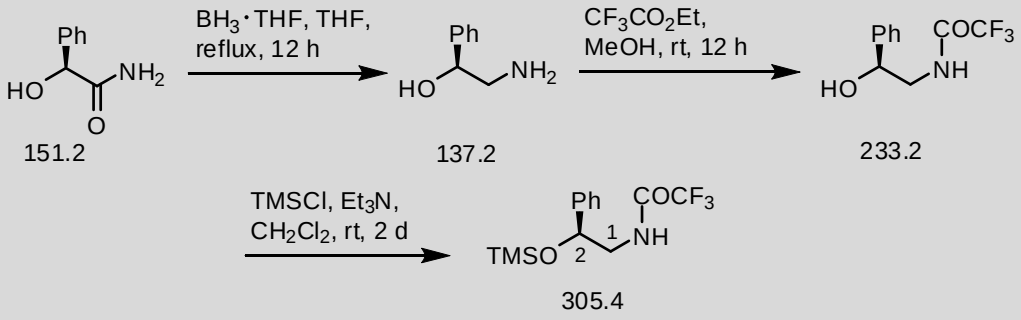
IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3357, 3187, 2927, 1681, 1495, 1452, 1422, 1295, 1190, 1102, 1056, 928, 895, 859, 763, 710.

^{1}H NMR (300 MHz, [D$_6$]DMSO): δ (ppm) = 7.43–7.22 (m, 6 H, Ph-H, NH), 7.13 (s, 1 H, NH), 5.95 (d, 1 H, J = 4.7 Hz, 2-H), 4.83 (d, 1 H, J = 4.7 Hz, OH).

^{13}C NMR (50 MHz, [D$_6$]DMSO): δ (ppm) = 174.5 (C-1), 141.3 (Ph-C), 127.8 (2 × Ph-CH), 127.2 (Ph-CH), 126.4 (2 × Ph-CH), 73.4 (C-2).

MS (EI, 70 eV): m/z (%) = 151 (10) $[M]^+$, 107 (100) $[M - CONH_2]^+$.

1.1.2.2 ** (*S*)-2,2,2-Trifluoro-*N*-(2-phenyl-2-trimethylsilanyloxyethyl)acetamide [3]



151.2 137.2 233.2 305.4

An oven-dried 500 mL three-necked round-bottomed flask, equipped with a magnetic stirring bar, an addition funnel, a stopper, and a reflux condenser with a three-way stopcock attached to an argon balloon, is charged with the amide **1.1.2.1** (21.6 g, 143 mmol). A solution of borane-tetrahydrofuran complex in THF (1 M, 300 mL, 300 mmol) is added by means of the addition funnel (Caution: gas formation!). The mixture is heated to reflux for 12 h and then cooled to room temperature, whereupon MeOH (60 mL) is carefully added (Caution: gas formation!) through the addition funnel. After evaporation of the solvent under reduced pressure, the crude product is dissolved in anhydrous MeOH (185 mL). Ethyl trifluoroacetate (14.4 mL, 143 mmol) is added dropwise and the mixture is stirred for 12 h at room temperature. The solvent is then removed under reduced pressure and the residue is taken up in CH_2Cl_2 (230 mL). NEt_3 (37.9 mL, 274 mmol) is then added with stirring, the mixture is cooled to 0 °C in an ice-water bath, chlorotrimethylsilane (17.4 mL, 143 mmol) is added, and stirring is continued for 2 d at room temperature.

The reaction is quenched with H_2O (150 mL), and the crude product is extracted with CH_2Cl_2 (3 × 250 mL). The combined organic layers are washed with brine (200 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue is purified by column chromatography on silica gel using *n*-pentane/*tert*-butyl methyl ether (5:1) as eluent to afford the acetamide as a colorless oil; 27.5 g (63 % over three steps), $[\alpha]_D^{20}$ = +53.5 (*c* = 1.0, $CHCl_3$).

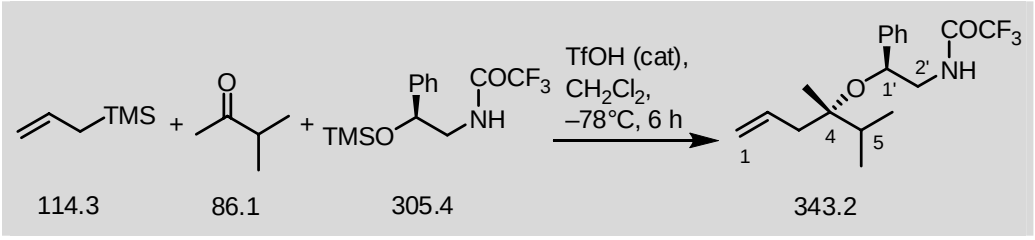
IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3317, 3090, 3032, 2959, 1708, 1556, 1494, 1454, 1366, 1254, 1166, 1027, 963, 842, 756.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.31–7.18 (m, 5 H, Ph-H), 6.60 (s, 1 H, NH), 4.74 (dd, 1 H, *J* = 8.4, 3.8 Hz, 1-H), 3.66 (ddd, 1 H, *J* = 13.5, 7.5, 3.8 Hz, 2-H_a), 3.19 (ddd, 1 H, *J* = 13.5, 8.4, 4.5 Hz, 2-H_b), –0.02 (s, 9 H, $Si(CH_3)_3$).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 140.9 (Ph-C), 128.5 (2 × Ph-CH), 128.1 (Ph-CH), 125.8 (2 × Ph-CH), 72.7 (C-1), 47.4 (C-2).

MS (DCI, NH_3, 200 eV): *m*/*z* (%) = 629 (2) $[2M + NH_4]^+$, 340 (50) $[M + 2NH_4]^+$, 323 (100) $[M + NH_4]^+$.

1.1.2.3 *** (4*S*,1'*S*)-4,5-Dimethyl-4-(1'-phenyl-2'-trifluoroacetamido-1'-ethoxy)-1-hexene [3]



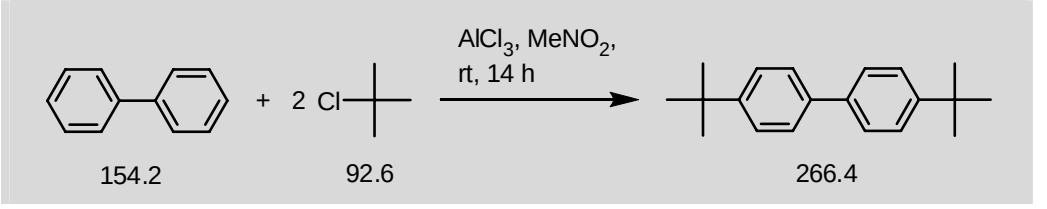
An oven-dried 500 mL two-necked round-bottomed flask, equipped with a magnetic stirring bar, a stopper, and a three-way stopcock attached to an argon balloon, is charged with **1.1.2.2** (13.8 g, 40.2 mmol), 3-methyl-2-butanone (6.92 g, 80.4 mmol), and CH_2Cl_2 (250 mL). After cooling to –78 °C, allyltrimethylsilane (12.8 mL, 80.4 mmol) is added by means of a syringe at –78 °C, and then precooled trifluoromethanesulfonic acid (750 μL, 8.40 mmol) is added. The reaction mixture is stirred for 6 h at –78 °C.

The reaction is then quenched with NEt_3 (18 mL) and MeOH (200 mL). The product is extracted with CH_2Cl_2 (4 × 250 mL), and the combined extracts are dried over Na_2SO_4 and concentrated. The residue is purified by column chromatography on silica gel using *n*-pentane/Et_2O (9:1) as eluent to afford a 13.6:1 mixture of the diastereomeric homoallylic ethers as a colorless oil; 11.3 g (82%), R_f = 0.77 (*n*-pentane/Et_2O, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.39–7.21 (m, 5 H, Ph-H), 6.69 (s_{br}, 1 H, N-H), 5.84 (ddt, *J* = 17.0, 10.2, 7.2 Hz, 1 H, 2-H), 5.13 (d, *J* = 17.0 Hz, 3 H, 1-H_Z), 5.12 (d, *J* = 10.2 Hz, 1 H, 1-H_E), 4.66 (dd, *J* = 8.2, 4.3 Hz, 1 H, 1'-H), 3.60 (ddd, *J* = 13.6, 7.2, 4.3 Hz, 1 H, 2'-H_b), 3.29 (ddd, *J* = 13.6, 8.2, 4.5 Hz, 1 H, 2'-H_a), 2.32 (m_c, 2 H, 3-H_2), 1.74 (sept, *J* = 6.9 Hz, 1 H, 5-H), 0.91 (d, *J* = 6.9 Hz, 3 H, 6-$H_{3/b}$), 0.84 (s, 3 H, 4-CH_3), 0.80 (d, *J* = 6.9 Hz, 3 H, 6-$H_{3/a}$).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ (ppm) = 156.95 (q, $^2J_{CF}$ = 38 Hz, C=O), 141.95 (Ph-C), 133.89 (C-2), 128.48, 127.88, 126.30 (Ph-C), 118.08 (C-1), 115.84 (q, $^1J_{CF}$ = 288 Hz, CF_3), 80.99 (C-4), 71.61 (C-1'), 46.87 (C-2'), 40.25 (C-3), 35.04 (C-5), 21.10 (4-CH_3), 17.15 (C-6).

1.1.2.4 ** 4,4'-Di-(*tert*-butyl)-1,1'-biphenyl (DBBP) [3]



A dry 250 mL three-necked round-bottomed flask, equipped with a magnetic stirring bar, a reflux condenser, an addition funnel, and a stopper, is first charged with nitromethane (75 mL) and biphenyl (13.2 g, 85.0 mmol) under an argon atmosphere. Anhydrous aluminum trichloride (3.00 g, 22.5 mmol) is then added, whereupon the color of the solution changes to deep violet. A solution of 2-chloro-2-methylpropane (17.4 g, 190 mmol) in nitromethane (20 mL) is then added dropwise to the stirred mixture over 30 min. At the end of the addition, the reaction starts with a vigorous evolution of HCl gas (Caution!) and stirring is continued for 14 h.

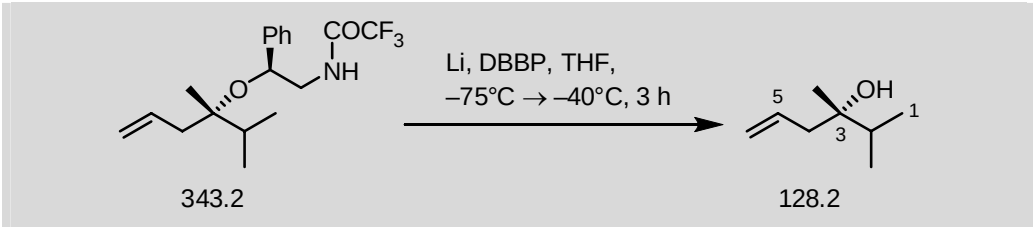
The reaction mixture is then poured onto crushed ice in a 500 mL beaker and allowed to warm to room temperature. It is extracted with nitromethane/*n*-pentane (1:1; 3 × 50 mL), and the combined organic phases are washed with brine (50 mL), dried over $MgSO_4$, and filtered. The yellowish filtrate is treated with silica gel (100 g) to provide a colorless solution, which is concentrated. The resulting white powder is recrystallized from nitromethane to give white needles of the biphenyl; 21.0 g (93%), mp 128–129 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.55–7.44 (m, 8 H, Ar-H), 1.37 (s, 18 H, 2 × $C(CH_3)_3$).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ (ppm) = 139 (Ar-C), 150 (Ar-C), 127 (Ar-CH), 126 (Ar-CH), 34.5 (2 × $\underline{C}(CH_3)_3$), 31.4 (2 × $C(\underline{C}H_3)_3$).

MS (EI, 70 eV): *m*/*z* (%) = 266 (41) $[M]^+$, 251 (100) $[M - CH_3]^+$.

1.1.2.5 *** (*S*)-2,3-Dimethyl-hex-5-en-3-ol [3]



343.2 128.2

An oven-dried 1 L two-necked round-bottomed flask, equipped with a magnetic stirring bar, a stopper, and a three-way stopcock attached to a balloon filled with argon, is charged with degassed THF (220 mL). **1.1.2.4** (6.88 g, 25.8 mmol) and lithium granules (max. Ø 1 mm) are added and the mixture is vigorously stirred at room temperature until the solution shows a deep-blue colour. The mixture is stirred for an additional 2 h at 0 °C and then cooled to –78 °C. A solution of the homoallylic ether **1.1.2.3** (11.1 g, 32.3 mmol) in anhydrous THF (50 mL) is then added dropwise. After stirring for 1 h at –78 °C, the mixture is allowed to warm to –45 °C and stirred for an additional 2 h. The reaction is then quenched by adding solid NH_4Cl at –45 °C (until the black solution turns yellow) and the mixture is allowed to warm to room temperature. The solid residue is filtered off and then a half-saturated NH_4Cl solution (120 mL) is added. The aqueous layer is extracted with Et_2O (3 × 100 mL) and the combined organic layers are washed with brine (60 mL), dried over Na_2SO_4, and concentrated. The residue is purified by column chromatography on silica gel using *n*-pentane to elute DBBP; then, a gradient of *n*-pentane/Et_2O from 15:1 to 3:1 as eluent affords the tertiary alcohol as a colorless oil; 3.40 g (82%), $[\alpha]_D^{20}$ = +14.2 (*c* = 1.0, $CHCl_3$), R_f = 0.43 (*n*-pentane/Et_2O, 5:1).

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3380, 3314, 3082, 2976, 2936, 2882, 1448, 1418, 1380, 1276, 1192, 1088, 1052, 912, 882.

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 5.89 (m_c, 1 H, 5-H), 5.22–5.07 (m, 2 H, 6-H_2), 2.23 (d, *J* = 7.0 Hz, 2 H, 4-H_2), 1.69 (sept, *J* = 7.0 Hz, 1 H, 2-H), 1.40 (s_{br}, 1 H, OH), 1.08 (s, 3 H, 3-CH_3), 0.94, 0.90 (2 × d, *J* = 7.0 Hz, 6 H, 1-H_3, 2-CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 134.1 (C-5), 118.6 (C-6), 74.25 (C-3), 44.12 (C-4), 36.84 (C-2), 22.83 (3-CH_3), 17.53, 16.90 (C-1, 2-CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 87 (84) $[M - C_3H_5]^+$, 69 (34) $[C_5H_9]^+$, 43 (100) $[C_3H_7]^+$.

[1] a) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763; b) I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, *97*, 2063; c) J. A. Marshall, *Chem. Rev.* **1996**, *96*, 31; d) C. E. Masse, J. S. Panek, *Chem. Rev.* **1995**, *95*, 1293; e) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207; f) I. Fleming, *Org. React.* **1989**, *37*, 57.

[2] a) L. F. Tietze, L. Völkel, C. Wulff, B. Weigand, C. Bittner, P. McGrath, K. Johnson, M. Schäfer, *Chem. Eur. J.* **2001**, *7*, 1304; b) L. F. Tietze, B. Weigand, L. Völkel, C. Wulff, C. Bittner, *Chem. Eur. J.* **2001**, *7*, 161; c) L. F. Tietze, K. Schiemann, C. Wegner, C. Wulff, *Chem. Eur. J.* **1998**, *4*, 1862; d) L. F. Tietze, C. Wegner, C. Wulff, *Eur. J. Org. Chem.* **1998**, 1639; e) L. F. Tietze, K. Schiemann, C. Wegner, *J. Am. Chem. Soc.* **1995**, *117*, 5851.

[3] L. F. Tietze, S. Hölsken, J. Adrio, T. Kinzel, C. Wegner, *Synthesis* **2004**, *13*, 2236.

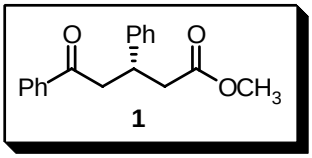
[4] a) T. Mukaiyama, M. Ohshima, N. Miyoshi, *Chem. Lett.* **1987**, 1121; b) T. Mukaiyama, H. Nagaoka, M. Murakami, M. Ohshima, *Chem. Lett.* **1985**, 977; c) J. Kato, N. Iwasawa, T. Mukaiyama, *Chem. Lett.* **1985**, 743.

[5] A. Mekhalfia, I. E. Markó, *Tetrahedron Lett.* **1991**, *32*, 4779.

[6] L. F. Tietze, C. Wegner, C. Wulff, *Synlett* **1996**, 471.

[7] L. F. Tietze, T. Kinzel, S. Schmatz, *J. Am. Chem. Soc.* **2006**, *128*, 11483.

1.1.3 (*S*)-5-Oxo-3,5-diphenylpentanoic acid methyl ester



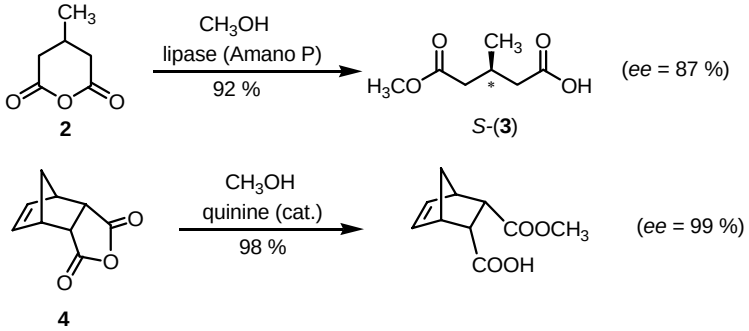
1

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 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 (1) by chiral alcohols or amines, (2) 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 [3], e.g.:

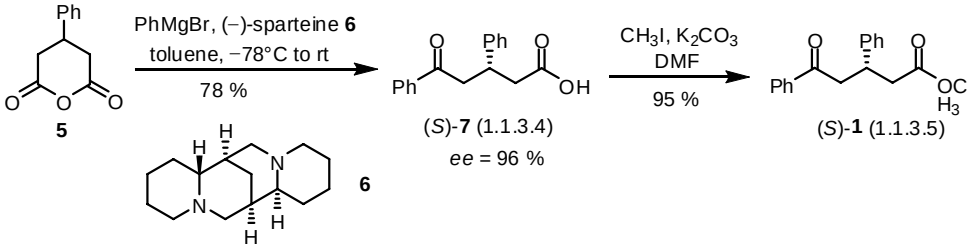


Only a few examples of the desymmetrization of cyclic anhydrides with carbon nucleophiles have been described [2]. Recently, asymmetric ring-opening reactions of 3-substituted glutaric anhydrides (like **2**) were found [4] to occur with Grignard compounds in the presence of (–)-sparteine as a chiral complexing ligand system, which has been shown [5] to be a very versatile organocatalyst [8] for asymmetric stereocontrol in reactions of organolithium compounds.

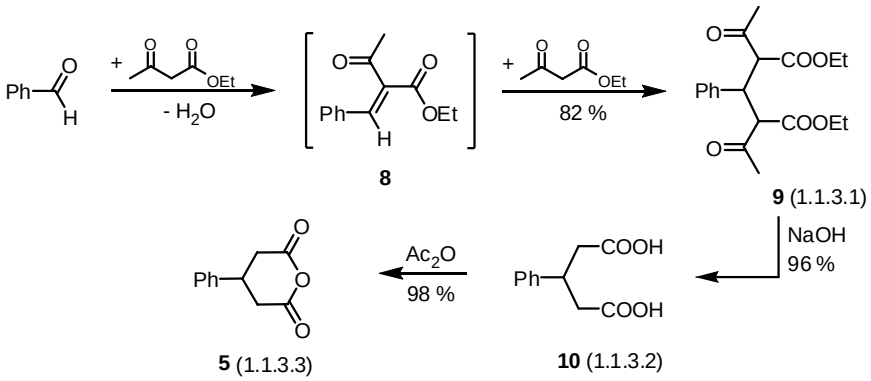
As described in section (b), a simple synthesis of the chiral target molecule **1** [6] can be achieved by application of the above protocol.

(b) Synthesis of 1

3-Phenylglutaric anhydride (**5**) is reacted with phenylmagnesium bromide in toluene at –78 °C in the presence of 1.3 equivalents of (–)-sparteine (**6**) as a stereocontrolling agent to give the δ-keto acid **7** in 78% yield and with high enantioselectivity (*ee* = 96%) [4]. 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 two moles 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:

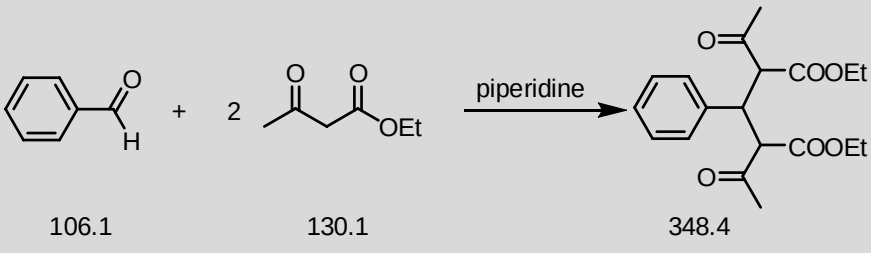


The diester **9** undergoes a two-fold "acid cleavage" of the acetoacetate moieties upon treatment with NaOH in EtOH, which results in the loss of two molecules of acetate and saponification of the carboxylic acid ester moieties to give 3-phenylglutaric acid (**10**). Finally, the diacid **10** is transformed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

1.1.3.1 * 2,4-Diacetyl-3-phenyl-pentanedioic acid diethyl ester [7]



Ethyl acetoacetate (75.5 g, 0.58 mol, note 1) and benzaldehyde (28.5 g, 0.27 mol) are dissolved in anhydrous EtOH (160 mL). Piperidine (4 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, washed with EtOH (–20 °C) until the washings remain colorless, and dried in vacuo. One obtains 77.2 g (82%) of colorless crystals; mp 150–152 °C (note 3).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3515 (enol OH), 2980 (C–H), 1740/1720 (C=O), 1500, 1470, 1380, 1190, 830.

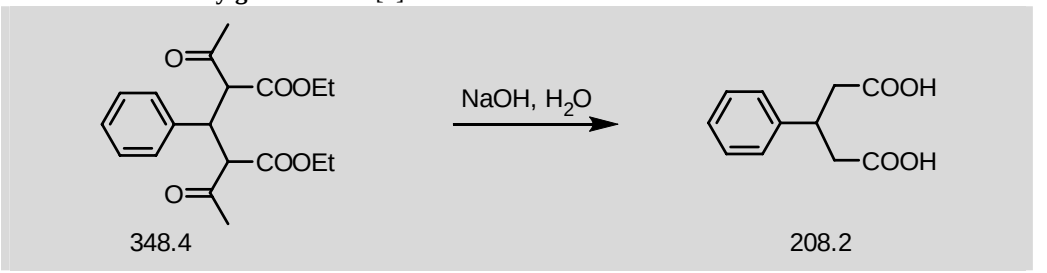
^{1}H NMR ($CDCl_3$): very complex because of enolization and different *E/Z* geometries.

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 TLC (SiO_2/Et_2O). It may be recrystallized from EtOH, which increases the mp to 154–155 °C.

1.1.3.2 * 3-Phenylglutaric acid [7]



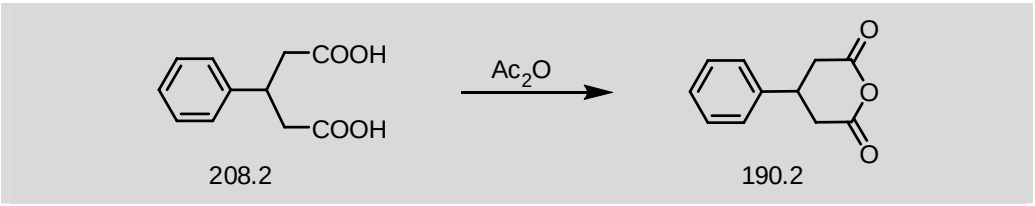
The diester **1.1.3.1** (69.7 g, 0.20 mol) is added to a mixture of 50% aqueous NaOH (200 mL) and EtOH (200 mL) and the resulting mixture is heated to reflux for 3 h.

The slurry obtained 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 (Na_2SO_4) 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 Et_2O (–20 °C), and dried. The yield is 40.0 g (96%) as colorless crystals, mp 145–147 °C; the product is sufficiently pure for further use.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3200–2500 (OH, associated), 1720/1705 (C=O), 1495, 1450, 1420, 820.

^{1}H NMR ([D_6]acetone): δ (ppm) = 10.88 (s_{br}, 2 H, COOH), 7.25 (m_c, 5 H), 3.66 (quintet, *J* = 6.7 Hz, 1 H), 2.72 (d, *J* = 6.7 Hz, 4 H).

1.1.3.3 * 3-Phenylglutaric anhydride [7]



The dicarboxylic acid **1.1.3.2** (26.0 g, 0.125 mol) in acetic anhydride (140 mL) is heated under reflux for 2 h.

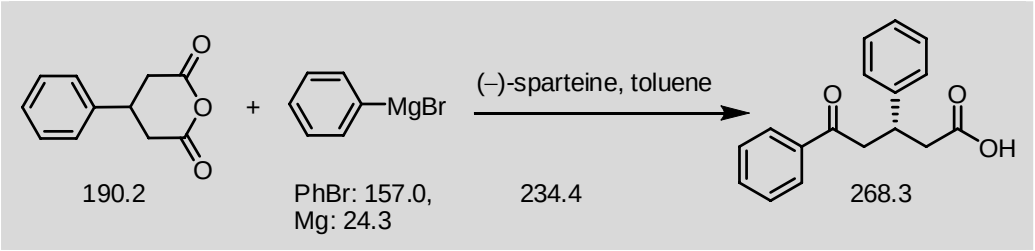
The reaction mixture is then concentrated to dryness. The residue is suspended in Et_2O (100 mL), filtered off, washed with Et_2O, and dried in vacuo. The yield is 23.3 g (98%) as colorless crystals, mp 103–105 °C; the product is sufficiently pure for further use.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3034, 2980, 1809, 1751, 1243, 1172, 1066, 953, 763, 702, 605, 591.

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.40 (t, *J* = 7.4 Hz, 2 H), 7.34 (t, *J* = 7.6 Hz, 1 H), 7.20 (d, *J* = 7.25 Hz, 2 H, Ar–H), 3.42 (m_c, 1 H, PhC–H), 3.11 (dd, *J* = 17.3/4.4 Hz, 2 H) and 2.89 (dd, *J* = 17.3/11.4 Hz, 2 H, CO–CH_2).

^{13}C NMR ($CDCl_3$): δ (ppm) = 165.84, 139.10, 129.40, 128.17, 126.25, 37.15, 34.11.

1.1.3.4 *** (*S*)-5-Oxo-3,5-diphenylpentanoic acid [4]



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 nitrogen. Once the Grignard reaction has started, the remainder of the 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 a nitrogen atmosphere. The solution is stirred for 3 h and then cooled to –78 °C. A solution of 3-phenylglutaric anhydride **1.1.3.3** (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.

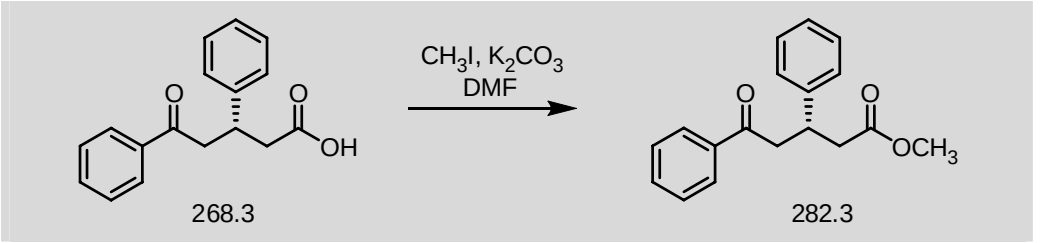
The solution is quenched with 2 M NaOH (50 mL), stirred thoroughly, and extracted with Et_2O (3 × 20 mL). The aqueous layer is separated and acidified with concentrated HCl under ice-cooling. The carboxylic acid precipitates and is collected by suction filtration, washed with H_2O (2 × 20 mL), and air-dried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

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3030 (Ph-H), 1734 (C=O, acid), 1698 (C=O, ketone), 1682, 1595, 1578.

^{1}H NMR ([D_6]DMSO): δ (ppm) = 12.06 (s_{br}, 1 H, COOH), 7.91 (d, *J* = 7.3 Hz, 2 H, ArH), 7.60 (t, *J* = 7.6 Hz, 1 H, ArH), 7.48 (t, *J* = 7.6 Hz, 2 H, ArH), 7.26 (d, *J* = 7.0 Hz, 2 H, ArH), 7.23 (t, *J* = 7.6 Hz, 2 H, ArH), 7.13 (t, *J* = 7.3 Hz, 1 H, ArH), 3.66 (quintet, *J* = 7.9 Hz, 1 H, PhCH), 3.44 (dd, *J* = 17.1, 7.9 Hz, 1 H) and 3.37 (dd, *J* = 17.1, 6.3 Hz, 1 H, C<u>H</u>$_2$CO$_2$H), 2.69 (dd, *J* = 15.8, 6.3 Hz, 1 H) and 2.56 (dd, *J* = 15.8, 8.5 Hz, 1 H, PhCOC<u>H</u>$_2$).

^{13}C NMR ([D_6]DMSO): δ (ppm) = 198.40, 172.85, 143.83, 136.68, 133.07, 128.61, 128.10, 127.84, 127.48, 126.20, 43.96, 40.37, 37.21.

1.1.3.5 * (*S*)-5-Oxo-3,5-diphenylpentanoic acid methyl ester [4]



Methyl iodide (2.84 g, 20.0 mmol) is added dropwise with stirring to a solution of the carboxylic acid **1.1.3.4** (268 mg, 1.00 mmol), anhydrous K_2CO_3 (207 mg, 1.50 mmol), and DMF (5 mL). The resulting mixture is stirred overnight at room temperature.

It is then quenched with 10% 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) and dried over Na_2SO_4. The solvent is removed *in vacuo* and the product is allowed to crystallize; one obtains 268 mg (96%) as colorless crystals, mp 82 °C.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 2970, 2870, 1735 (C=O, ester), 1680 (C=O, ketone), 1596, 1578, 1496.

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.91 (d, *J* = 6.9 Hz, 2 H, ArH), 7.53 (t, *J* = 7.6 Hz, 1 H, ArH), 7.43 (t, *J* = 7.9 Hz, 2 H, ArH), 7.26 (m, 3 H, ArH), 7.19 (m, 2 H, ArH), 3.88 (quintet, *J* = 7.3 Hz, 1 H, PhC<u>H</u>), 3.58 (s, 3 H, OCH_3), 3.39 (dd, *J* = 16.7, 6.9 Hz, 1 H) and 3.33 (dd, *J* = 16.7, 6.9 Hz, 1 H, C<u>H</u>$_2$CO$_2$Me), 2.82 (dd, *J* = 15.3, 7.3 Hz, 1 H) and 2.69 (dd, *J* = 15.3, 7.3 Hz, 1 H, PhCOC<u>H</u>$_2$).

^{13}C NMR ($CDCl_3$): 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*) may be 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 **1.1.3.4** in the absence of sparteine and then generating the methyl ester according to the procedure described above.

[1] S. R. Magnuson, *Tetrahedron* **1995**, *51*, 2167.

[2] A. C. Spivey, B. J. Andrews, *Angew. Chem*. **2001**, *113*, 3227; *Angew. Chem. Int. Ed*. **2001**, *40*, 3131.

[3] 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]).

[4] R. Shintani, G. C. Fu, *Angew. Chem*. **2002**, *114*, 1099; *Angew. Chem. Int. Ed*. **2002**, *41*, 1057.

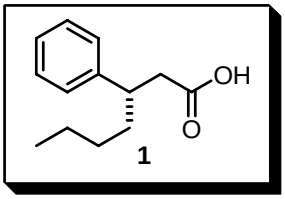
[5] a) D. Hoppe, T. Hense, *Angew. Chem*. **1997**, *109*, 2376; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 2282; b) P. A. Beak et al., *Acc. Chem. Res*. **2000**, *33*, 715.

[6] For comparison, see: A. Diaz-Ortiz, E. Diez-Barra, A. de la Hoz, P. Prieto, A. Moreno, *J. Chem. Soc. Perkin Trans. 1* **1996**, *259*.

[7] In analogy to Th. Eicher, H. J. Roth, *Synthese, Gewinnung und Charakterisierung von Arzneistoffen*, p. 80, Georg Thieme Verlag, Stuttgart, **1986**.

[8] A. Berkessel, H. Kröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**.

1.1.4 (*S*)-3-Phenylheptanoic acid

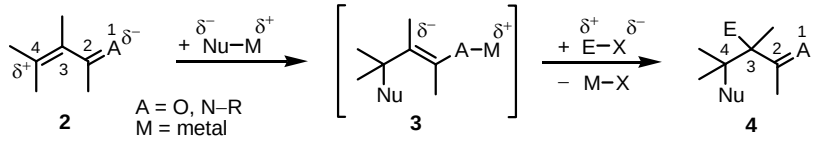


Topics:

- (–)-Ephedrine as a chiral auxiliary
- Chemoselective *N*-acylation of (–)-ephedrine
- Enantioselective conjugate addition of a Grignard compound to an α,β-unsaturated carboxamide
- Hydrolytic cleavage of a carboxamide, regeneration of the chiral auxiliary

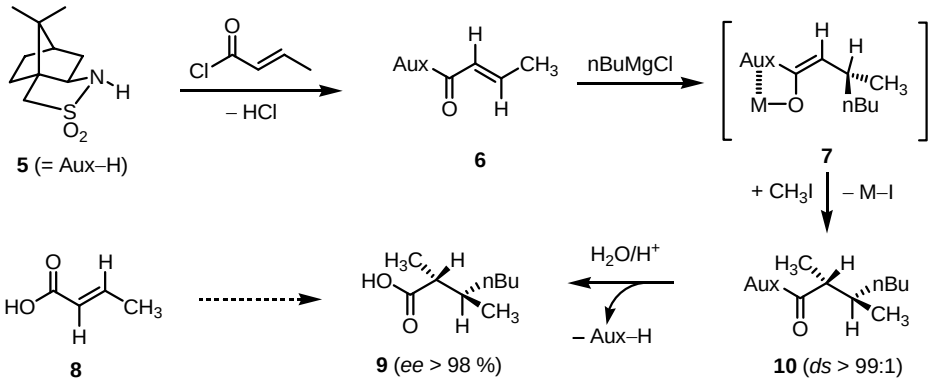
(a) General

Nucleophilic addition to a C=C double bond bearing an electron-withdrawing functionality (such as COR, COOR, $CONR_2$, C≡N, etc.) is often referred to as conjugate addition (Michael addition, 1,4-addition). Generally, Michael addition follows a two-step scheme,



in which a nucleophilic reagent (mainly an organometallic) adds to a conjugated system **2** in a 1,4-mode to give an enolate-like intermediate **3**, which is "trapped" by attack of an electrophilic reagent (proton acid, alkylating reagent, etc.) thus creating two new stereogenic sp^3 centers (positions 3/4) in the final addition product **4** [1].

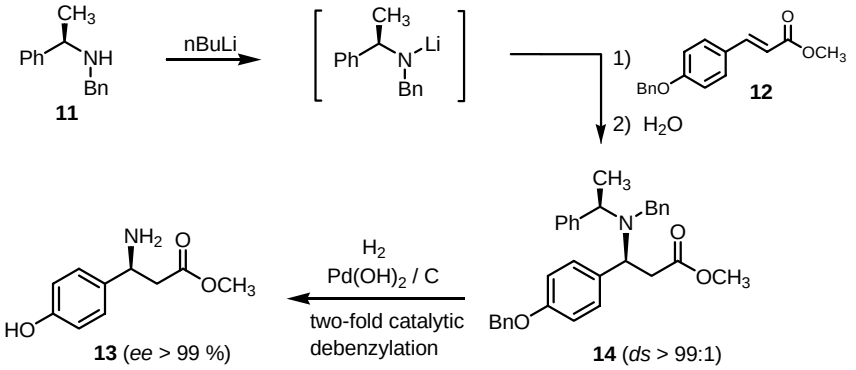
Michael addition can be conducted in an asymmetric fashion in three ways, namely (1) by attachment of the conjugated system to a chiral auxiliary, (2) by the use of a chiral nucleophilic reagent, and (3) by performing the reaction in the presence of a chiral catalyst or with a chiral ligand on the Nu-M system. All of these types of asymmetric Michael addition are covered by literature examples.



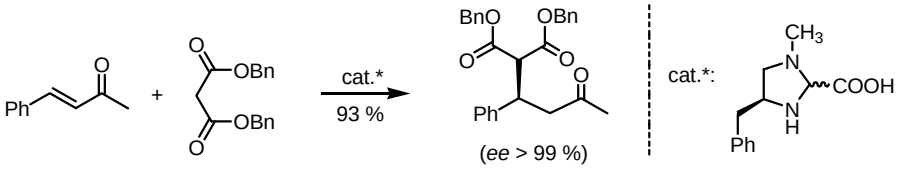
(1): The camphor-derived sultam auxiliary **5** (Oppolzer auxiliary [2]) can be used in Michael additions of the crotonic acid system [3] (**8** → **9**) to control both conjugate addition of an organometallic (**6** → **7**) and *in situ* trapping by subsequent alkylation of the primary adduct (**7** → **10**). The observed high stereoselectivity is due to coordination of the metal by the donor groups CO and SO_2 in the substrate **6**.

Representative of this category is the synthesis of the target molecule **1**, which is discussed in section (b).

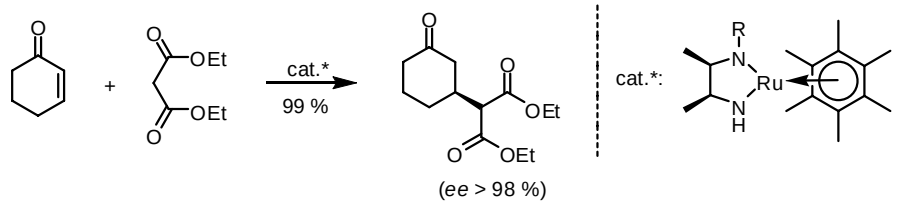
(2): The lithium amide of the readily available chiral secondary amine **11** (representing a chiral ammonia synthon) can undergo a highly diastereoselective 1,4-addition to α,β-unsaturated esters. This procedure is used for the synthesis of almost enantiopure (*S*)-β-amino esters, e.g. β-tyrosine methyl ester **13** from (4-benzyloxy)cinnamic ester **12** (**12** → **14** → **13**) ([4], cf. **4.4.2**):



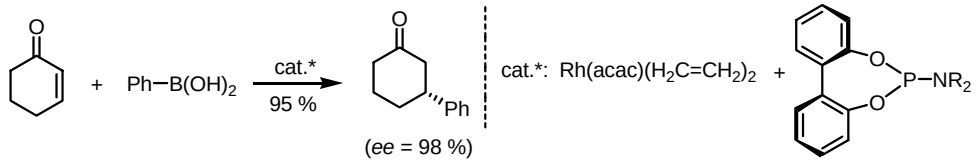
(3): Malonates undergo enantioselective conjugate addition to a variety of acyclic enones in the presence of a chiral phenylalanine-based imidazolidine organocatalyst [5] (cf. **1.3.5**), e.g.:



Malonates also add highly stereoselectively to cyclic enones under catalysis by chiral Ru amido complexes [6], e.g.:

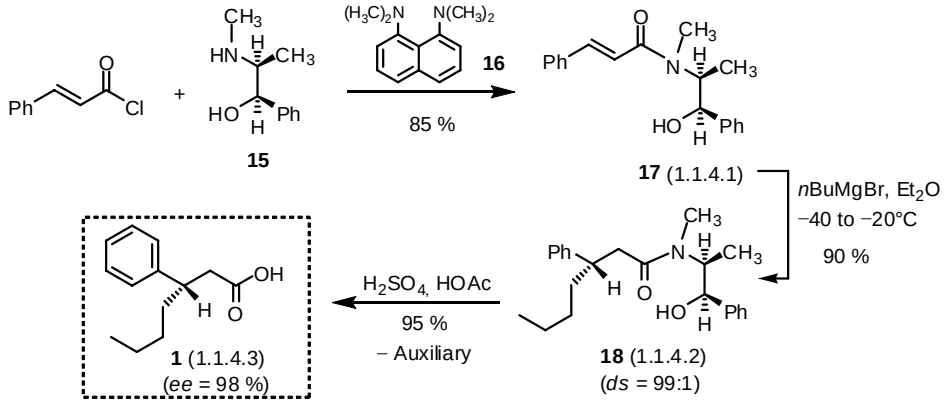


Interestingly, arylboronic acids are effective as nucleophilic partners in asymmetric Michael additions to cyclic [7] and acyclic enone systems [8], which are catalyzed by Rh complexes bearing axial chiral phosphoramidite ligands and which proceed with high enantioselectivities, e.g.:



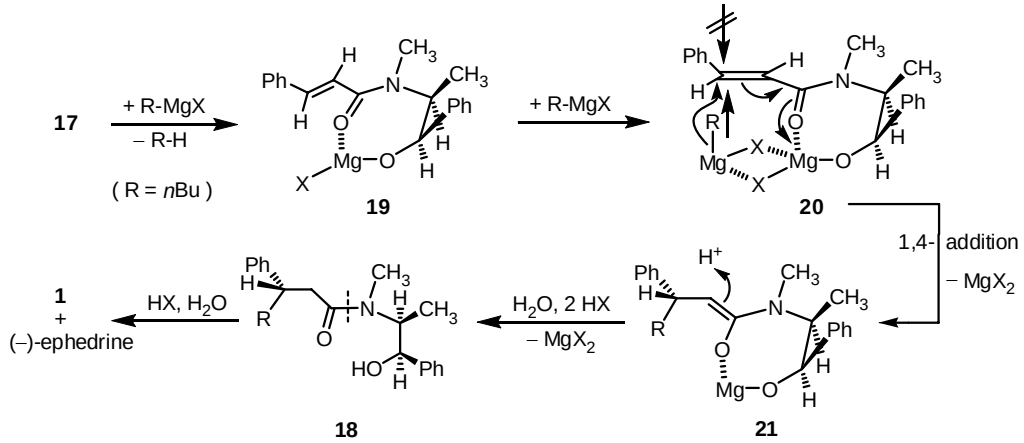
(b) Synthesis of 1

First, a cinnamic acid unit has to be connected to (–)-ephedrine (**15**) as chiral auxiliary. With cinnamoyl chloride in the presence of "proton sponge" (**16**) as a base, *N*-acylation of the auxiliary occurs chemoselectively to give the desired product **17**. Then, *n*-butyl magnesium bromide (in an excess of six equivalents) is reacted with the α,β-unsaturated amide **17** at –40 to –20 °C in diethyl ether to yield the Michael adduct **18** with a diastereoselectivity of 99:1 (ref. [9]: >99:1):



Finally, the auxiliary is removed by acid hydrolysis of the adduct **18** to provide the chiral acid **1** in nearly enantiopure (*S*)-form (*ee* ≈ 98%) together with (–)-ephedrine in quantitative yield ("regenerative" use of a chiral auxiliary, cf. **1.7.5**).

The high diastereoselectivity of the described Michael reaction is probably due to initial formation of the rigid Mg-chelate complex **19**:

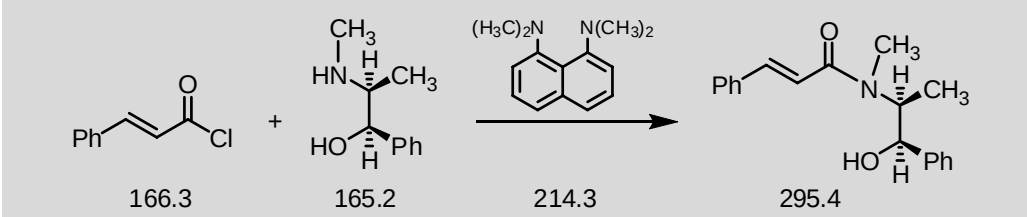


A second molecule of the Grignard reagent then coordinates to the Mg of the chelate complex, inducing attack on the enone system from the sterically less hindered (lower) side of the chelate (opposite to the methyl and phenyl groups at the stereogenic centers of the chiral auxiliary) as depicted in **20**. Protonation of the resulting enolate **21** and removal of the Mg complement the Michael addition to yield amide **18**, which is cleaved upon acidic hydrolysis to give the chiral acid **1** and the auxiliary **15**.

In this way, the target molecule **1** is formed in a three-step sequence with an overall yield of 53% (based on cinnamoyl chloride).

(c) Experimental procedures for the synthesis of 1

1.1.4.1 * (*E*)-*N*-((1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-3-phenylacrylamide [9]



166.3 165.2 214.3 295.4

A solution of cinnamoyl chloride (1.67 g, 10.0 mmol) in anhydrous THF (10 mL) is added dropwise to a stirred solution of (–)-ephedrine (1.65 g, 10.0 mmol) and proton sponge (2.14 g, 10.0 mmol) in anhydrous THF (15 mL) under a nitrogen atmosphere. The reaction mixture is stirred for 1 h at room temperature.

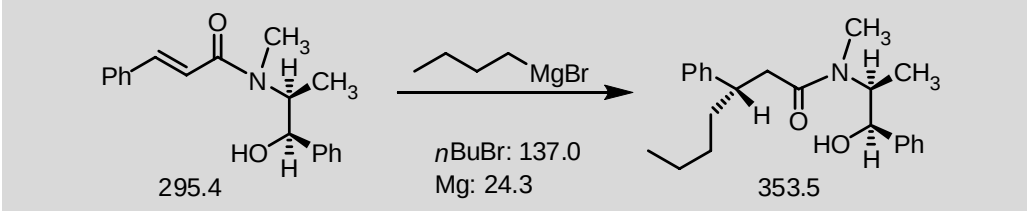
The precipitate formed is then removed by vacuum filtration and washed with Et_2O. The filtrate is washed with HCl (1 N, 2 × 10 mL) and brine (3 × 10 mL). The organic layer is dried ($MgSO_4$) and the solvents are removed under vacuum to give 2.50 g (85%) of a light-yellow resin-like solid, sufficiently pure according to TLC (SiO_2/Et_2O: R_f = 0.42); $[\alpha]_D^{20}$ = –150 (*c* = 1.00, $CHCl_3$).

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3334 (OH), 3059, 3026, 2977, 1642 (amide C=O), 1578.

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.71 (d, *J* = 15.5 Hz, 1 H, PhC<u>H</u>=CHCO), 7.52 (d, *J* = 2.5 Hz, 2 H, Ar–H), 7.31–7.40 (m, 8 H, Ar–H), 6.79 (d, *J* = 15.5 Hz, 1 H, PhCH=C<u>H</u>CO), 4.94 (d, not resolved, 1 H, HOC<u>H</u>Ph), 4.55 (m_c, 1 H, NCH), 4.51 (s_{br}, 1 H, OH), 2.85 (s, 3 H, NCH_3), 1.26 (d, *J* = 6.9 Hz, 3 H, NCHC<u>H</u>$_3$).

^{13}C NMR ($CDCl_3$): δ (ppm) = 168.43, 143.27, 141.80, 135.20, 129.78, 128.83, 128.21, 127.89, 127.53, 126.36, 117.91, 67.96, 58.76, 33.46, 12.11.

1.1.4.2 *** (*S*)-3-Phenyl-heptanoic acid ((1*S*,2*R*)-2-hydroxy-1-methyl-2-phenyl-ethyl) methyl amide [9]



295.4 *n*BuBr: 137.0 Mg: 24.3 353.5

A solution of *n*BuMgBr in anhydrous Et_2O (30 mL), prepared from *n*-butyl bromide (4.11 g, 30.0 mmol) and magnesium turnings (730 mg, 30.0 mmol), is added at –78 °C to a solution of

N-cinnamoylephedrine **1.1.4.1** (1.48 g, 5.00 mmol) in Et_2O (70 mL) under a nitrogen atmosphere. The solution is then stirred at –40 to –20 °C with monitoring by TLC (SiO_2/Et_2O) until the reaction is complete (~48 h).

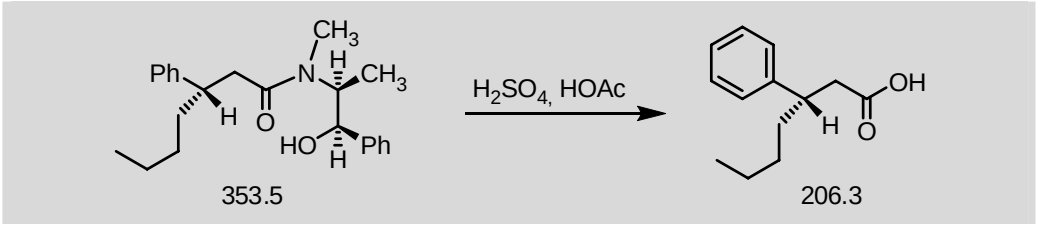
A phosphate buffer solution (50 mL, pH 7) is added to the reaction mixture, which is then allowed to warm to room temperature. The insoluble material is filtered off through Celite and washed with EtOAc (30 mL). The layers are separated and the aqueous layer is extracted with EtOAc (30 mL). The combined extracts are dried ($MgSO_4$) and concentrated in vacuo. The resulting crude Michael adduct is purified by chromatography (SiO_2/Et_2O; R_f = 0.60); yield 1.60 g (90%) as a light-yellow resin-like solid.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3365 (O–H), 3027, 2955, 2928, 2858, 1611 (amide C=O).

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.60–7.35 (m, 10 H, ArH), 4.73 (d, not resolved, 1 H, PhC<u>H</u>OH), 4.41 (m_c, 1 H, NCH), 4.08 (s_{br}, 1 H, OH), 3.15 (m_c, 1 H, PhCH), 2.49 (s, 3 H, NCH_3), 2.57 and 2.48 (dd, *J* = 14.6, 7.6 Hz, 2 H, PhCHC<u>H</u>$_2$CO), 1.75–1.60 (m, 2 H, CH_2), 1.11–1.31 (m, 4 H, CH_2–CH_2), 1.08 (d, *J* = 7.0 Hz, 3 H, NCHC<u>H</u>$_3$), 0.83 (t, *J* = 7.3 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ (ppm) = 174.00, 144.62, 141.54, 128.42, 128.05, 127.68, 127.33, 126.39, 126.25, 77.17, 58.05, 42.61, 41.45, 35.69, 33.36, 29.70, 22.64, 13.97, 12.00.

1.1.4.3 * (*S*)-3-Phenylheptanoic acid [9]



The Michael adduct **1.1.4.2** (1.41 g, 4.00 mmol) is dissolved in acetic acid (10 mL) and sulfuric acid (6 N, 20 mL) and then refluxed for 3 h.

The mixture is extracted with Et_2O (3 × 20 mL) and the combined extracts are washed with brine (2 × 20 mL). The carboxylic acid is extracted with NaOH (1 M, 2 × 10 mL). The aqueous phase is washed with Et_2O (20 mL), then acidified with concentrated HCl and extracted with Et_2O (3 × 10 mL). The combined organic phases are dried ($MgSO_4$) and concentrated *in vacuo* to yield 785 mg (95%) of a colorless oil; $[\alpha]_D^{20}$ = +33.6 (*c* = 4.0, benzene). The enantiopurity is 98% based on the optical rotation [9].

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3029, 2957, 2927, 2858, 1706 (C=O).

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.31–7.24 (m, 2 H, ArH), 7.22–7.14 (m, 3 H, ArH), 3.06 (m_c, 1 H, PhCH), 2.65 (dd, *J* = 15.5, 7.1 Hz, 1 H, $COCH_2$), 2.59 (dd, *J* = 15.5, 7.9 Hz, 1 H, $COCH_2$), 1.57–1.67 (m, 2 H, CH_2), 1.08–1.30 (m, 4 H, CH_3–C<u>H</u>$_2$–C<u>H</u>$_2$), 0.82 (t, *J* = 7.3 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ (ppm) = 178.28, 143.97, 128.45, 127.43, 126.47, 41.84, 41.49, 35.93, 29.46, 22.55, 13.90.

[1] For an instructive introduction to asymmetric conjugate addition, see G. Procter, *Asymmetric Synthesis*, p. 127, Oxford University Press, **1999**.

[2] W. Oppolzer, R. J. Mills, W. Pachinger, T. Stevenson, *Helv. Chim. Acta* **1986**, *69*, 154; see also ref. [1].

[3] W. Oppolzer, G. Poli, *Tetrahedron Lett*. **1986**, *27*, 4717.

[4] S. G. Davies, O. Ichihara, *Tetrahedron: Asymmetry* **1991**, *2*, 183. This work was extended: S. G. Davies, S. W. Epstein, O. Ishihara, A. Smith, *Synlett* **2001**, 1599; in addition, the intermediately formed enolates were subjected to electrophilic oxygenation with (–)-CSO (camphor-sultam oxaziridine) to give α-hydroxy-β-amino esters.

[5] N. Halland, P. S. Aburel, K. A. Joergensen, *Angew. Chem*. **2003**, *115*, 685; *Angew. Chem. Int. Ed.* **2003**, *42*, 661; compare: a) F.-Y. Zhang, E. J. Corey, *Org. Lett*. **2000**, *2*, 1097; b) H. Ito, T. Nagahara, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem*. **2004**, *116*, 1012; *Angew. Chem. Int. Ed.* **2004**, *43*, 994; c) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc*. **2006**, *128*, 7170 (enantioselective conjugate addition to nitroalkenes).

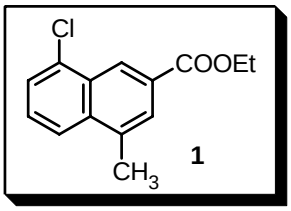
[6] M. Watanabe, K. Murata, T. Ikarya, *J. Am. Chem. Soc*. **2003**, *125*, 7508; see also: a) Y. Xu, K. Ohori, T. Ohshima, M. Shibasaki, *Tetrahedron* **2002**, *58*, 2585; b) J. G. Boiteau, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2003**, *68*, 9481.

[7] Y. Iguchi, R. Itooka, N. Miyaura, *Synlett* **2003**, 1040.

[8] O. Meyer, J.-M. Becht, G. Helmchen, *Synlett* **2003**, 1539; *Synthesis* **2003**, 2805.

[9] T. Mukaiyama, N. Iwasawa, *Chem. Lett*. **1981**, 913.

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

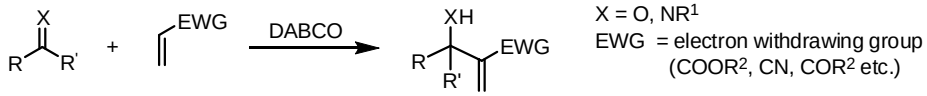


Topics:

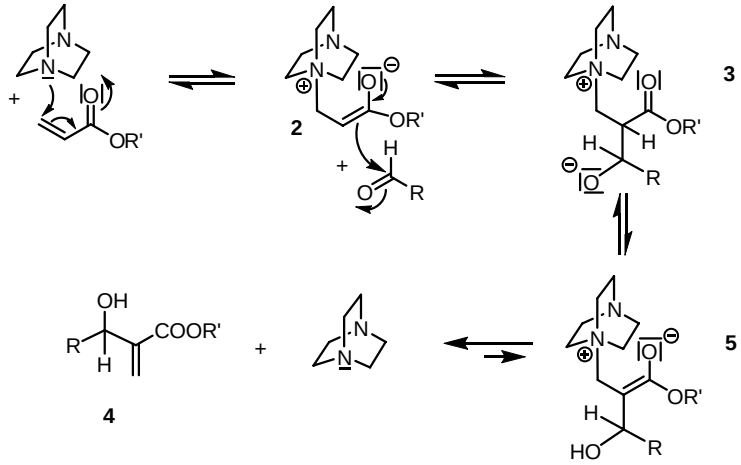
- Baylis–Hillman reaction of an aryl aldehyde with an acrylate in the presence of DABCO
- Acetylation of an OH function
- Transformation of an acetylated Baylis–Hillman adduct to a functionalized naphthalene system by reaction with nitroalkane/base (domino process)

(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 DABCO, is known as the Baylis–Hillman reaction [1, 2]:

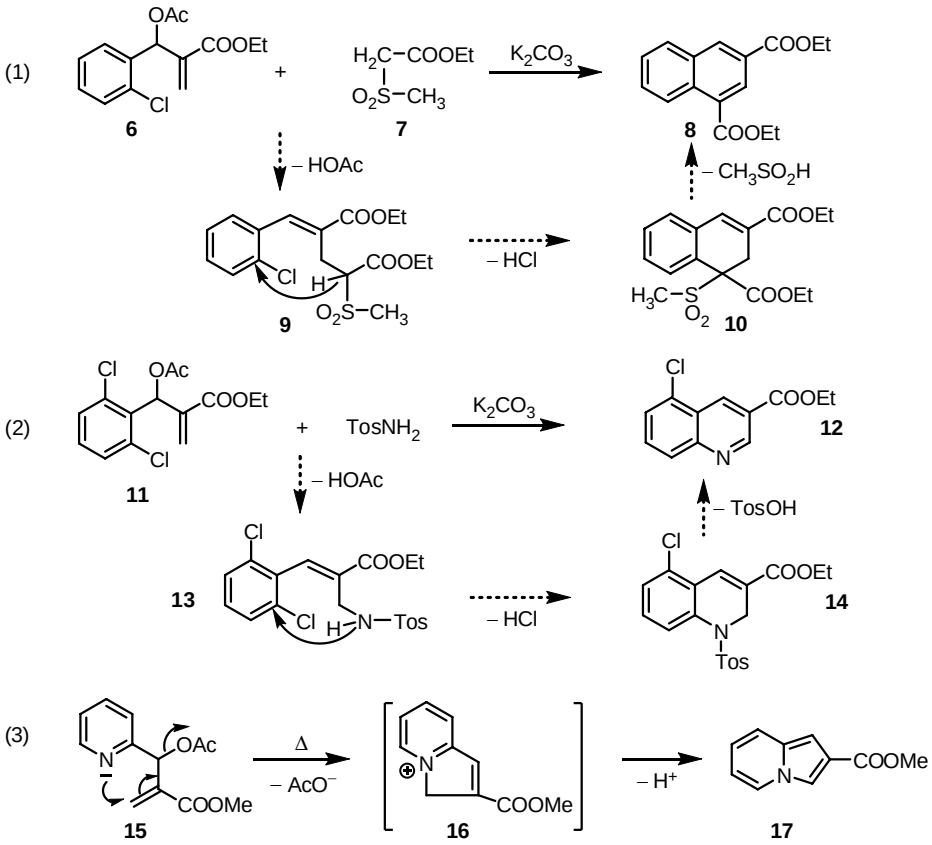


The generally accepted mechanism for the Baylis–Hillman process is illustrated by the reaction of an aldehyde with acrylate under the catalytic influence of DABCO:



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 fashion 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].

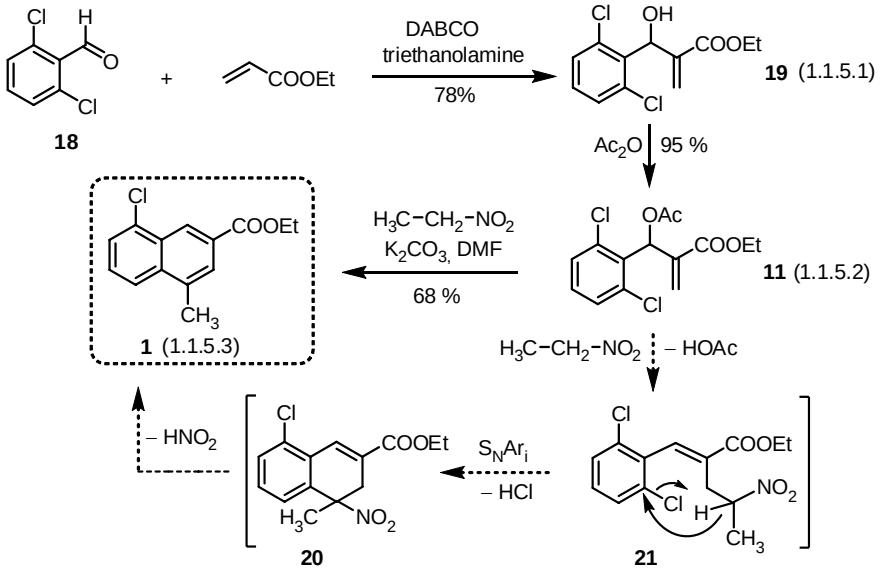
In (3), the acetylated Baylis–Hillman adduct **15** (obtained from pyridine-2-aldehyde and methyl acrylate with subsequent acetylation) is transformed into **17** by thermolysis. The process involves an S_N' substitution of the allylic acetate moiety in **15** to give the indolizinium ion **16** followed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

As a further example, the synthesis of **1** is described in detail in (b) [8, 9].

(b) Synthesis of 1

The synthesis of **1** [9] 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 requires a long reaction time of 5 d 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 ca. 12 h by the use of a catalytic system consisting of DABCO, triethanolamine, and the Lewis acid $La(OTf)_3$ [10]. 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 [10c]. In the next step, the adduct **19** is acetylated using acetic anhydride to give the acetate **11**:

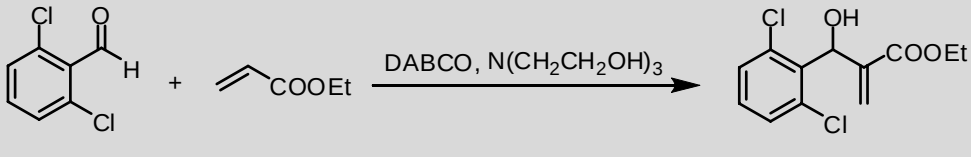


The acetate **11** reacts smoothly with nitroethane in *N*,*N*-dimethylformamide in the presence of K_2CO_3 as a base to provide the target molecule **1** in good yield (68%). Again, the functionalized naphthalene system is formed by way of a three-step domino process. First, the nitronate anion from nitroethane displaces acetate in **11** in an S_N'-like fashion 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

1.1.5.1 * 2-[(2,6-Dichlorophenyl)hydroxymethyl]-acrylic acid ethyl ester [10]



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).

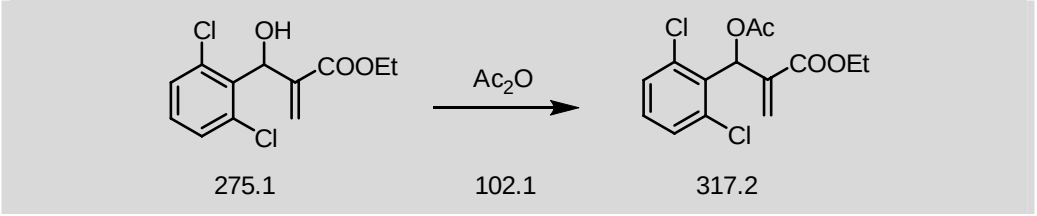
After 5-7 days, the reaction is stopped by dilution with Et_2O (150 mL) and the mixture is washed sequentially with 2% HCl (100 mL) and H_2O (100 mL). After drying over $MgSO_4$, filtration, and evaporation of the solvent, the crude product is purified by column chromatography (silica gel, petroleum ether/Et_2O, 2:1); yield 6.44 g (78%), colorless crystalline solid, mp 67–68 °C.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3492 (OH), 1694 (C=O), 1288, 1191, 1047, 964, 762.

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.31 (d, *J* = 7.8 Hz, 2 H, Ar-H), 7.17 (t, *J* = 7.8 Hz, 1 H, Ar-H), 6.41 (d, *J* = 1.6 Hz, 1 H, =CH_2), 6.34 (t, *J* = 1.9 Hz, 1 H, C<u>H</u>OH), 5.79 (d, *J* = 1.9 Hz, 1 H, =CH_2), 4.18 (m, 2 H, CH_2), 1.23 (t, *J* = 7.3 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ (ppm) = 166.04, 139.76, 135.58, 135.53, 129.46, 129.36, 126.10, 70.05, 61.00, 14.01.

1.1.5.2 * 2-[Acetoxy-(2,6-dichlorophenyl)methyl]acrylic acid ethyl ester [11]



To a mixture of the benzyl alcohol **1.1.5.1** (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 ($MgSO_4$), and concentrated *in vacuo* to give 4.54 g (95%) of a colorless, viscous oil.

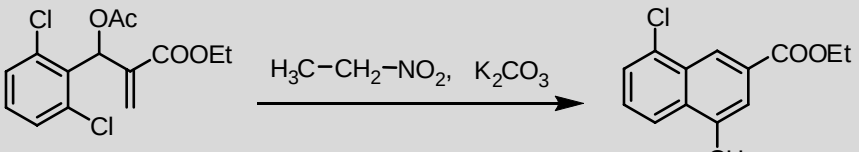
IR (liquid): $\tilde{\nu}$ (cm^{-1}) = 1747 (C=O), 1436, 1370, 1228, 1027.

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.33 (t, *J* = 1.89 Hz, 1 H, CHOAc), 7.31 (d, *J* = 8.20 Hz, 2 H, 2 Ar-H), 7.17 (t, *J* = 7.56 Hz, 1 H, Ar-H), 6.48 (d, *J* = 1.26 Hz, 1 H, =CH_2), 5.69 (d, *J* = 1.89 Hz, 1 H, =CH_2), 4.20 (m, 2 H, CH_2), 2.12 (s, 3 H, $COOCH_3$), 1.24 (t, *J* = 7.25 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ (ppm) = 169.38, 166.04, 136.23, 136.08, 132.49, 129.85, 129.38, 127.89, 70.30, 61.05, 20.67, 14.04.

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

1.1.5.3 * Ethyl 8-chloro-4-methylnaphthalene-2-carboxylate [9]



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 **1.1.5.2** (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, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product as a brown oil. It is purified by column chromatography on silica gel (*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 (C=O), 1269, 1236, 1186, 765.

^{1}H NMR ($CDCl_3$): δ (ppm) = 8.88 (s, 1 H, Ar-H), 7.95 (s, 1 H, Ar-H), 7.92–7.48 (m, 3 H, Ar-H, Cl part), 4.46 (q, *J* = 7.1 Hz, 2 H, $COOC\underline{H}_2CH_3$), 2.72 (s, 3 H, Ar-CH_3), 1.46 (t, *J* = 7.1 Hz, 3 H, $COOCH_2C\underline{H}_3$).

^{13}C NMR ($CDCl_3$): δ (ppm) = 166.62, 135.93, 135.28, 134.00, 130.38, 128.33, 127.69, 126.67, 125.72, 123.25, 61.25, 19.68, 14.41.

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

[1] S. Ciganek, *Organic Reactions* (Ed.: L. A. Paquette), Vol. 51, p. 201, John Wiley & Sons, Inc., New York, **1997**.

[2] a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811. b) For a new, highly active and selective catalytic system for the Baylis–Hillman reaction, see: J. You, J. Xu, J. G. Verkade, *Angew. Chem.* **2003**, *115*, 5208; *Angew. Chem. Int. Ed.* **2003**, *42*, 5054.

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[4] J. N. Kim, K. Y. Lee, *Curr. Org. Chem.* **2002**, *6*, 627.

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[6] Y. M. Chung, H. J. Lee, K.Y. Lee, J. N. Kim, *Bull. Korean Chem. Soc.* **2001**, *22*, 799.

[7] a) M. L. Bode, P. T. Kaye, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1809. b) For the synthesis of indolizines by a Baylis–Hillman reaction, see also: D. Basavaiah, A. J. Rao, *Chem. Commun.* **2003**, 604. c) In addition, Baylis–Hillman adducts have been transformed into 2-benzazepines: D. Basavaiah, T. Satyanarayana, *Chem. Commun.* **2004**, 32.

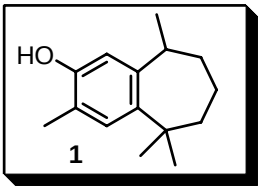
[8] To date, a conventional synthesis of the target molecule **1** has not been reported in the literature.

[9] J. N. Kim, Y. J. Im, J. H. Gong, K. Y. Lee, *Tetrahedron Lett.* **2001**, *42*, 4195.

[10] a) V. K. Aggarwal et al., *Chem. Commun.* **1996**, 2713; *J. Org. Chem.* **1998**, *63*, 7183. b) The DABCO-promoted Baylis–Hillman reaction may be accelerated by using a recoverable H-bonding organocatalyst: D. J. Maher, S. J. Connon, *Tetrahedron Lett.* **2004**, *45*, 1301; c) K. S. Park, J. Kim, H. Choo, Y. Chong, *Synlett* **2007**, 395.

[11] P. H. Mason, N. D. Emslie, *Tetrahedron* **1994**, *50*, 12001.

1.1.6 (±)-4-Hydroxy-*ar*-himachalan

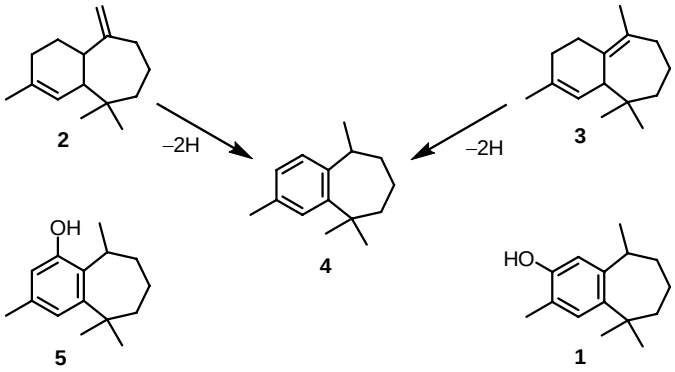


Topics:

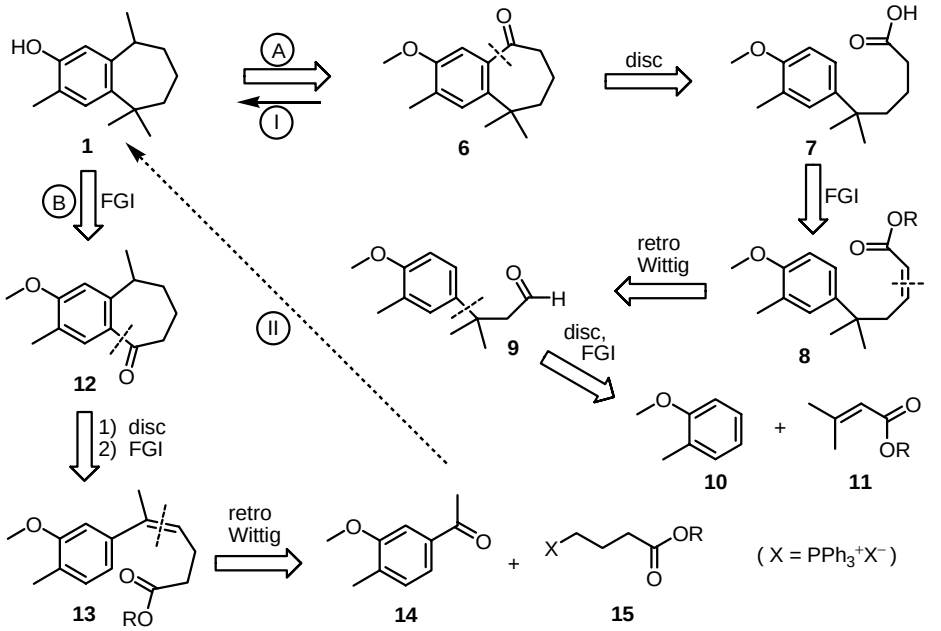
- Synthesis of a phenolic sesquiterpene
- Intramolecular Friedel–Crafts acylation
- Wittig reaction
- Transformation $Ar–NO_2$ → $Ar–NH_2$ → Ar–OH
- Demethylation of $Ar–O–CH_3$
- Ti-induced geminal dialkylation of a ketone

(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.

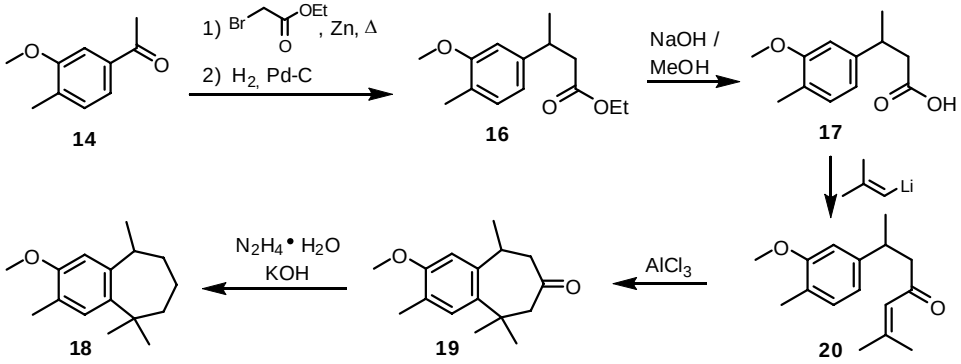


Two retrosynthetic pathways (**A** and **B**) can be considered for **1**. The first one leads to the benzosuberone **6**, which is further cleaved to the substrate *o*-methylanisole **10** and the 3-methyl-2-butenoic acid derivative **11** via **7**, **8**, and **9**. The second one leads to the differently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



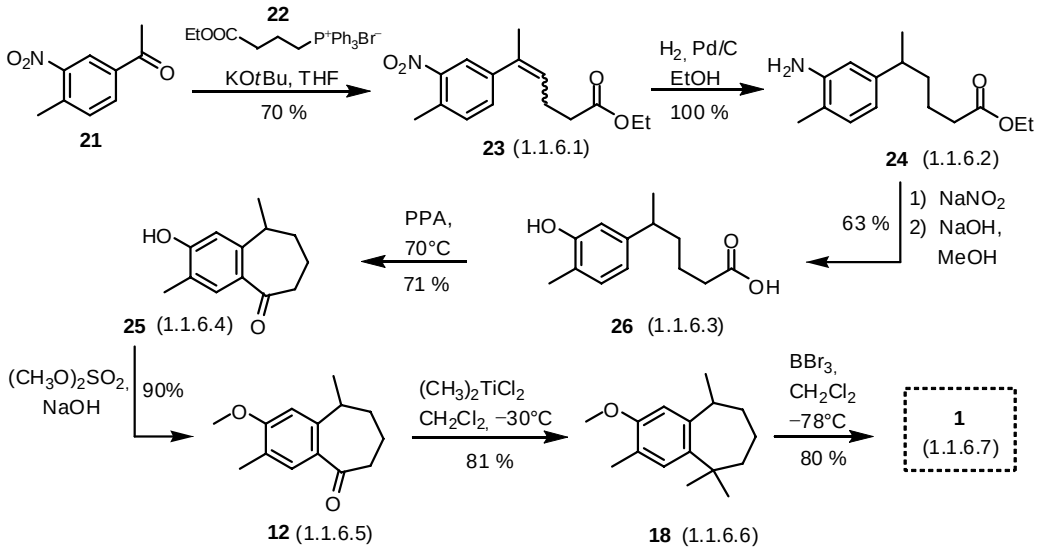
(b) Synthesis of 1

The synthesis of the methyl ether of **1** (**18**) has been reported in the literature [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 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**).

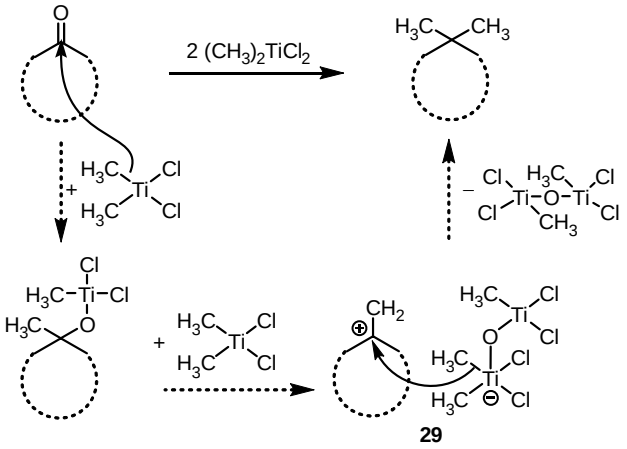


In contrast, the synthesis of **1** according to approach II (from retrosynthesis according to **B**) was found to be superior to all other alternatives [5] and is described in the following section with experimental details. This access via benzosuberone **12** requires the construction of the *gem*-dimethyl 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**).

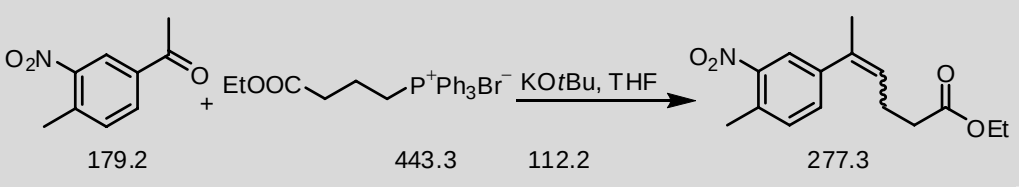


For the geminal dimethylation of **12**, two equivalents of $(CH_3)_2TiCl_2$ per carbonyl group are required. This leads to the following mechanism: (1) methyl transfer from titanium to the carbonyl carbon atom by nucleophilic addition of Ti-CH_3 to C=O, (2) methyl migration within the ion-pair ate-complex **29**. 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

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



(3-Carbethoxypropyl)triphenylphosphonium bromide (42.8 g, 94.0 mmol) 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 THF (100 mL) is then added dropwise with stirring. When the addition is complete, the dark mixture is heated to reflux for 12 h.

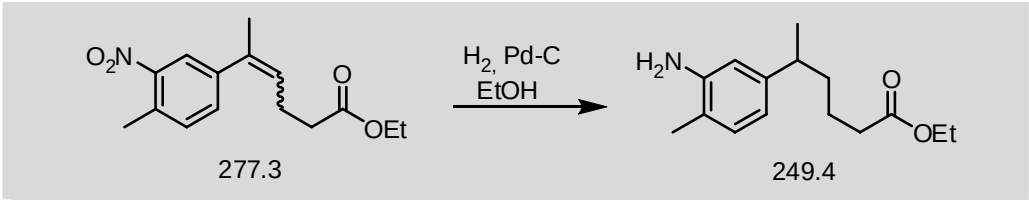
The reaction mixture is cooled to room temperature, poured into H_2O (500 mL), and extracted with Et_2O (4 × 250 mL). The combined ethereal phases are washed with H_2O (5 × 200 mL) and dried over $MgSO_4$. The solvent is removed, and the crude oily product is dissolved in the minimum volume of CH_2Cl_2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

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1770 (C=O), 1655 (C=C).

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.95 (d, *J* = 1.8 Hz, 1 H, Ar-H, *Z*), 7.79 (d, *J* = 1.3 Hz, 1 H, Ar-H, *E*), 7.50 (dd, *J* = 8.0/1.8 Hz, 1 H, Ar-H, *Z*), 7.35–7.29 (m, 2 H, Ar-H, *E*), 7.26 (d, *J* = 8.0 Hz, 1 H, Ar-H, *Z*), 5.82 (m_c, 1 H, =CH, *Z*), 5.52 (m_c, 1 H, =CH, *E*), 4.15 (q, *J* = 7.1 Hz, 2 H, OCH_2, *Z*), 4.10 (q, *J* = 7.1 Hz, 2 H, OCH_2, *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, 4 H, CH_2–CH_2, *E* and *Z*), 2.06 (d, *J* = 1.3 Hz, 3 H, =C–CH_3, *Z*), 2.03 (d, *J* = 1.3 Hz, 3 H, =C–CH_3, *E*), 1.28 (t, *J* = 7.1 Hz, 3H, *Z*), 1.23 (t, *J* = 7.1 Hz, 3 H, *E*).

MS (CI, CH_4, 120 eV): *m*/*z* (%) = 277 (76) $[M]^+$.

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



5% Pd/C catalyst (ca. 0.5 g) is added to a solution of the unsaturated ester **1.1.6.1** (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.

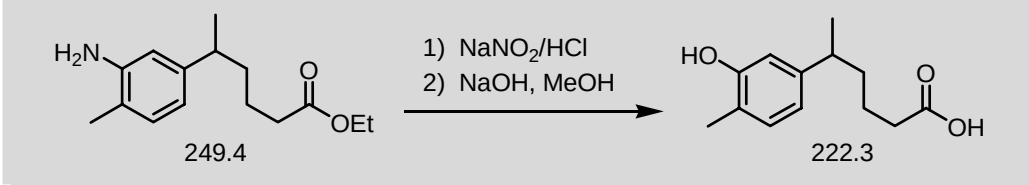
The catalyst is then filtered off and rinsed with EtOH. The EtOH solution is concentrated *in vacuo*. The product (9.00 g, 100%) is obtained as a faintly yellow oil, which is homogeneous according to TLC and is used in the next step without further purification.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3455, 3370 (NH_2), 1740 (C=O).

^{1}H NMR ($CDCl_3$): δ (ppm) = 6.95 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.52 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.49 (s_{br}, 1 H, Ar-H), 4.09 (q, *J* = 7.1 Hz, 2 H, OCH_2), 3.57 (s_{br}, 2 H, NH_2), 2.59–2.54 (m, 1 H, C<u>H</u>–CH_3), 2.26–2.22 (m, 2 H, CH_2), 2.12 (s, 3 H, Ar-CH_3), 1.59–1.48 (m, 4 H, $(CH_2)_2$), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3), 1.19 (d, *J* = 6.6 Hz, 3 H, CH–C<u>H</u>$_3$).

MS (CI, CH_4, 120 eV): *m*/*z* (%) = 249 (3) $[M]^+$.

1.1.6.3 * 5-(3-Hydroxy-4-methylphenyl)hexanoic acid [5]



The amino ester **1.1.6.2** (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 (ca. 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 (water bath) until the -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 the solvent is removed *in vacuo*. The residue (ester of **1.1.6.3**) 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, 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 ($MgSO_4$), the solvent is removed, and the residue is purified

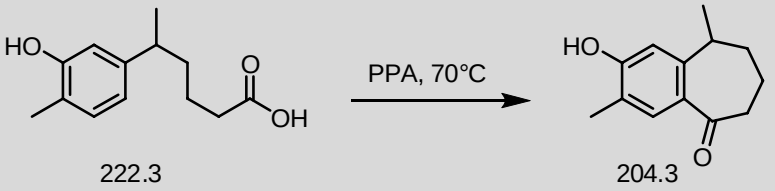
by chromatography on SiO_2 (eluent: Et_2O/petroleum ether, 3:2). The product is obtained as an orange solid, 4.50 g (63%), mp 96–97 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3450 (OH), 1720 (C=O).

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.01 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.65 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.58 (s, 1 H, Ar-H), 2.61–2.56 (m, 1 H, C<u>H</u>–CH_3), 2.31–2.28 (m, 2 H, CH_2), 2.19 (s, 3 H, Ar-CH_3), 1.57–1.49 (m, 4 H, $(CH_2)_2$), 1.19 (d, *J* = 6.6 Hz, 3 H, CH–C<u>H</u>$_3$).

MS (CI, CH_4, 120 eV): *m*/*z* (%) = 222 (76) $[M]^+$.

1.1.6.4 * 2-Hydroxy-3,9-dimethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one [5]



The finely powdered carboxylic acid **1.1.6.3** (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.

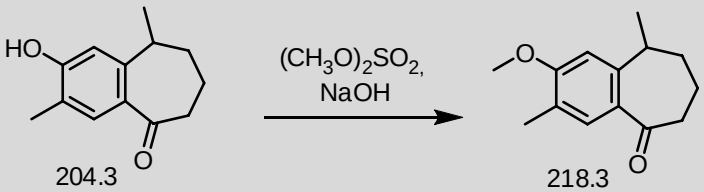
The dark-red reaction mixture is then poured into H_2O (50 mL) and extracted with Et_2O (3 × 25 mL). The combined ethereal extracts are dried ($MgSO_4$), the solvent is removed *in vacuo*, and the residue is purified by column chromatography (SiO_2, eluent: Et_2O/petroleum ether, 1:2). The product is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

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3115 (OH), 1670 (C=O).

^{1}H NMR ([D_6]DMSO): δ (ppm) = 9.90 (s, 1 H, OH), 7.29, 6.74 (s, each 1 H, Ar-H), 3.09–3.02 (m_c, 1 H, C<u>H</u>–CH_3), 2.58–2.51 (m, 2 H, CH_2), 2.11 (s, 3 H, Ar-CH_3), 1.92–1.76 (m, 2 H, CH_2), 1.48–1.34 (m, 2 H, CH_2), 1.28 (d, *J* = 6.6 Hz, 3 H, CH–C<u>H</u>$_3$).

MS (EI, 70 eV): *m*/*z* (%) = 204 $[M]^+$.

1.1.6.5 * 2-Methoxy-3,9-dimethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one [5]



The hydroxybenzosuberone **1.1.6.4** (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) is then added and stirring is continued for 30 min at room temperature; more $(CH_3O)_2SO_2$ (same amount as before) is then added and stirring is continued for 1 h at room temperature and for 30 min at 100 °C (water bath).

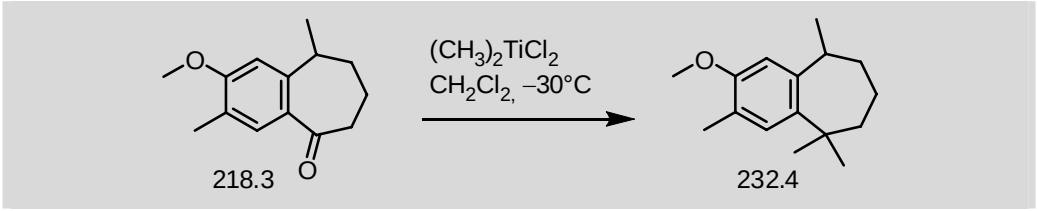
The reaction mixture is then cooled to room temperature, diluted with H_2O (10 mL), and extracted with Et_2O (3 × 20 mL). The combined extracts are dried ($MgSO_4$), the solvent is removed *in vacuo*, and the oily residue is purified by chromatography on SiO_2 (eluent: CH_2Cl_2). The product is obtained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

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1690 (C=O).

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.44, 6.69 (s, each 1 H, Ar-H), 3.88 (s, 3 H, OCH_3), 3.13 (m_c, 1 H, C<u>H</u>–CH_3), 2.74–2.68, 2.61–2.53 (m, each 1 H, CH_2), 2.19 (s, 3 H, Ar-CH_3), 1.98–1.83, 1.66–1.49 (m, each 2 H, CH_2), 1.39 (d, *J* = 7.0 Hz, 3 H, CH–C<u>H</u>$_3$).

MS (EI, 70 eV): *m*/*z* (%) = 218 (77) $[M]^+$.

1.1.6.6 ** 2-Methoxy-3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene [5]



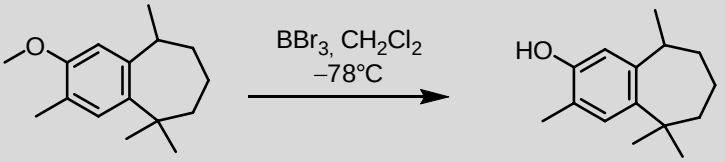
Under an N_2 atmosphere, a solution of dimethylzinc in toluene (2 M, 2.5 mL, 5.00 mmol) is added dropwise to a stirred solution of titanium tetrachloride (0.96 g, 5.00 mmol) in anhydrous CH_2Cl_2 (25 mL) at such a rate that an internal temperature of –30 °C is maintained. After 15 min, a solution of the ketone **1.1.6.5** (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 $NaHCO_3$ solution (100 mL), and dried over $MgSO_4$. The solvent is removed and the residue is purified by rapid filtration through silica gel (eluent: CH_2Cl_2). The product is obtained as a colorless oil, which is homogeneous according to TLC; 0.43 g (81%).

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.12, 6.71 (s, each 1 H, Ar-H), 3.81 (s, 3 H, OCH_3), 3.27 (m_c, 1 H, C<u>H</u>–CH_3), 2.18 (s, 3 H, Ar-CH_3), 1.79–1.74, 1.65–1.52 (m, each 3 H, aliph. H), 1.39, 1.31 [s, each 3 H, $C(CH_3)_2$], 1.36 (d, *J* = 7.1 Hz, 3 H, CH–C<u>H</u>$_3$).

MS (CI, CH_4, 120 eV): *m*/*z* (%) = 232 (66) $[M]^+$.

1.1.6.7 * 2-Hydroxy-3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene [5]



232.4 218.3

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 **1.1.6.6** (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 ($MgSO_4$). The solvent is removed and the crude product is purified by column chromatography (SiO_2, eluent: 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 (OH).

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.10, 6.65 (s, each 1 H, Ar-H), 4.57 (s_{br}, 1 H, OH), 3.22 (m_c, 1 H, C<u>H</u>–CH_3), 2.21 (s, 3 H, Ar-CH_3), 1.83–1.49 (m, 6 H, $(CH_2)_3$), 1.39 and 1.30 (s, each 3 H, $C(CH_3)_2$), 1.29 (d, *J* = 7.1 Hz, 3 H, CH–C<u>H</u>$_3$).

MS (CI, CH_4, 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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