**Diastereoselective Synthesis of Chiral 1,3-Cyclohexadienals**

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**SUPPORTING INFORMATION 2**

**Experimental procedure for the synthesis of α,β-aldehyde intermediates**

|  |  |
| --- | --- |
| **Content** | **Page** |
| General Procedure of Synthesis of Aldehydes (**14-18**) | S2 |
| Synthesis of Aldehyde **19** | S6 |
| References | S7 |

**GENERAL PROCEDURE SYNTHESIS OF ALDEHYDES (14-18)**



Methyl Diethylphosphonoacetate (1.9 mL, 10.0 mmol) was added dropwise under argon atmosphere over a period of 5 min to a stirred suspension of NaH (60% on mineral oil; 500 mg, 10.0 mmol) in dry toluene (16.0 mL) at 0ºC, and the resulting mixture was stirred for 45 min at 0°C. A solution of ketone (10.0 mmol) in dry toluene (4.0 mL) was slowly added to the resulting mixture, and the reaction mixture was stirred at r.t. for 5h. After cooling to room temperature, the reaction was quenched with a saturated aqueous solution of NH4Cl and extracted with EtOAc (3x20 mL). The combined organic layer was washed with brine and dried over Na2SO4. After concentration under vacuum, the residue was purified by flash chromatography on silica gel (EtOAc:hexane) to afford (*E*)-oate and (*Z*)-oate as colorless oil.

DIBAL-H (4 equiv., 1.2 M in toluene) was added dropwise to a solution of ester in DCM (0.3 M) at −78°C. The reaction mixture was stirred at −78°C for 2h and the solution was allowed to reach 0°C. The solution was quenched with a saturated aqueous solution of potassium sodium tartrate at 0°C and stirred at room temperature for 3h. The resulting mixture was extracted with DCM (3x 30mL) and washed with brine. The resulting solution was dried over Na2SO4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc:hexane) to obtain alcohol as colorless oil.

MnO2 (5 equiv) was added to a solution of alcohol in DCM (0.5 M) at r.t. The reaction mixture was stirred at r.t. for 24h. The suspension was filtered through a pad of Celite and washed with EtOAc. The resulting solution was concentrated under vacuum, the residue was purified by column chromatography on silica gel (EtOAc:hexane) to afford aldehyde as a light yellow oil.

All characterization data are consistent with literature values.

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**Methyl (*Z,E*)-3-phenylbut-2-enoate, 14a.**[1]

**Yield:** 87% (1.5 g, 8.72 mmol).

**Z:E ratio:** 7:93.

**1H NMR** (300 MHz, CDCl3): δ=8.24-8.19 (2H, m, E isomer), 7.94-7-89 (2H, m, Z isomer), 7.62-7.57 (2H, m, E isomer), 7.21-7.16 (2H, m, Z isomer), 6.17 (1H, bs, E isomer), 3.76 (3H, s, E isomer), 3.54 (3H, s), 2.57 (3H, s, E isomer).



**(*Z,E*)-3-Phenyl-but-2-en-1-ol, 14b.**[2]

**Yield:** 88% (1.1 g, 7.63 mmol).

**Z:E ratio:** 2:98.

**1H NMR** (300 MHz, CDCl3): δ= 7.32-7.15 (10H, m), 5.96 (1H, td, *J* = 6.9, 1.5 Hz, E isomer), 5.70 (1H, td, *J* = 6.9, 1.2 Hz, Z isomer), 4.34 (2H, d, *J* = 6.9 Hz, E isomer), 4.05 (2H, d, *J* = 6.9 Hz, Z isomer), 2.07 (6H, bs, E isomer).



**(*Z,E*)-3-Phenyl-but-2-enal, 14.**[3]

**Yield:** 91% (1.0 g, 6.94 mmol).

**Z:E ratio:** 2:98.

**1H NMR** (300 MHz, CDCl3): δ= 10.18 (1H, d, *J* =7.5 Hz, E isomer), 9.47 (1H, d, *J* = 8.1 Hz, Z isomer), 7.55-7.29 (10H, m), 6.39 (1H, d, *J* = 7.5 Hz, E isomer), 6.13 (1H, d, *J* = 8.1 Hz, Z isomer), 2.56 (3H, s, E isomer), 2.30 (3H, s, Z isomer).

**HRMS** (ESI): Calculated for C10H11O ([M+H]+): 147.0804, found 147.0807.



**Methyl (*Z,E*)-3-(4-methylphenyl)but-2-enoate, 15a.**[4-6]

**Yield:** 63% (1.2 g, 6.30 mmol).

**Z:E ratio:** 15:85.

**1H NMR** (200 MHz, CDCl3): δ= 7.39 (2H, d, *J* = 8.4 Hz), 7.18 (2H, d, *J* = 8.4 Hz), 6.13 (1H, bs, E isomer), 5.89 (1H, bs, Z isomer), 3.74 (3H, s, E isomer), 3.57 (3H, s, Z isomer), 2.57 (3H, s), 2.36 (3H, s, E isomer), 2.17 (3H, s, Z isomer).

**HRMS** (ESI): Calculated for C12H14O2Na ([M+Na]+): 213.0886; found 213.0887.



**(*Z,E*)-3-(4-Methylphenyl)but-2-en-1-ol, 15b.**[2]

**Yield**:91% (930 mg, 5.73 mmol).

**Z:E ratio:** 15:85.

**1H NMR** (200 MHz, CDCl3): δ= 7.32 (2H, d, *J* = 8.2 Hz), 7.14 (2H, d, *J* = 8.2 Hz), 5.96 (1H, t, *J* = 6.7 Hz, E isomer), 5.69 (1H, t, *J* = 7.0 Hz, Z isomer), 4.35 (2H, d, *J* = 6.7 Hz, E isomer), 4.09 (2H, d, *J* = 7.0 Hz, Z isomer), 2.35 (3H, s), 2.07 (3H, s, E isomer), 2.05 (3H, s, Z isomer).



**(*Z,E*)-3-(4-Methylphenyl)but-2-enal, 15.**[7]

**Yield**:83% (762 mg, 4.76 mmol).

**Z:E ratio:** 2:98.

**1H NMR** (200 MHz, CDCl3): δ= 10.14 (1H, d, *J* = 7.9Hz, E isomer), 9.48 (1H, d, *J* = 8.2 Hz, Z isomer), 7.84 (2H, d, *J* = 8.2 Hz, Z isomer), 7.46 (2H, d, *J* = 8.3 Hz, E isomer), 7.22 (1H, d, *J* = 8.3 Hz, E isomer), 6.40 (1H, dd, *J* = 7.9, 1.4 Hz, E isomer), 2.55 (3H, s, E isomer), 2.39 (3H, s, E isomer).



**Methyl (*Z,E*)-3-(3-bromophenyl)but-2-enoate, 16a.** [8]

**Yield**:89 % (2.3 g, 8.90 mmol).

**Z:E ratio:** 12:88.

**1H NMR** (200 MHz, CDCl3): δ= 7.60-7.10 (8H, m), 6.07 (1H, bs, E isomer), 5.89 (1H, bs, Z isomer), 3.71 (3H, s, E isomer), 3.53 (3H, s, Z isomer), 2.54 (3H, s, Z isomer), 2.50 (3H, s, E isomer).

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**(*Z,E*)-3-(3-Bromophenyl)but-2-en-1-ol, 16b.** [9]

**Yield**:81% (1.6 g, 7.20 mmol).

**Z:E ratio:** 12:88.

**1H NMR** (200 MHz, CDCl3): δ= 7.52-7.12 (8H, m), 5.92 (1H, t, *J* = 6.5 Hz, E isomer), 5.68 (1H, t, *J* = 6.9 Hz, Z isomer), 4.31 (2H, t, *J* = 6.5 Hz, E isomer), 4.01 (2H, t, *J* = 6.9 Hz, Z isomer), 2.58 (1H, bs, OH), 2.32 (1H, bs, OH), 2.03 (3H, s, Z isomer), 2.00 (3H, s, E isomer).

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**(*Z,E*)-3-(3-Bromopheynyl)but-2-enal, 16.** [3]

**Yield**:61% (1.0 g, 4.42 mmol).

**Z:E ratio:** 5:95.

**1H NMR** (200 MHz, CDCl3): δ= 10.16 (1H, d, *J* = 7.7 Hz, E isomer), 9.45 (1H, d, *J* = 8.4 Hz, Z isomer), 7,66 (1H, bs), 7.49 (2H, dd, *J* = 16.5, 7.9 Hz), 7.30 (1H, d, *J* = 7.9 Hz), 7.26 (1H, d, *J* = 9.4 Hz), 6.34 (1H, d, *J* = 7.7 Hz, E isomer), 6.14 (1H, d, *J* = 8.4 Hz, Z isomer), 2.54 (3H, s, E isomer), 2.29 (3H, s, Z isomer).

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**Methyl (*Z,E*)-3-(4-bromophenyl)but-2-enoate, 17a.** [10]

**Yield**:64% (1.6 g, 6.40 mmol).

**Z:E ratio:** 22:78.

**1H NMR** (200 MHz, CDCl3): δ= 7.51 (2H, d, *J* = 8.8 Hz, E isomer), 7.34 (2H, d, *J* = 8.8 Hz, E isomer), 7.30-7.10 (4H, m, Z isomer), 6.14 (1H, bs, E isomer), 5.95 (1H, bs, Z isomer), 3.77 (3H, s, E isomer), 3.59 (3H, s, Z isomer), 2.58 (3H, s, E isomer), 2.37(3H, s, Z isomer).

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**(*Z,E*)-3-(4-Bromophenyl)but-2-en-1-ol, 17b.** [9]

**Yield**:90% (1.3 g, 5.76 mmol).

**Z:E ratio:** 16:84.

**1H NMR** (200 MHz, CDCl3): δ= 7.44 (2H, d, *J* = 8.5 Hz, E isomer), 7.26 (2H, d, *J* = 8.5 Hz, E isomer), 7.05 (2H, d, *J* = 8.4 Hz, Z isomer), 5.96 (1H, t, *J* = 6.5 Hz, E isomer), 5.72 (1H, t, *J* = 7.0 Hz, Z isomer), 4.35 (2H, d *J* = 6.5 Hz, E isomer), 4.04 (2H, d, *J* = 7.0 Hz, Z isomer), 2.04 (3H, s, E isomer), 2.01 (3H, s, Z isomer).

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**(*Z,E*)-3-(4-Bromophenyl)but-2-enal, 17.** [11]

**Yield**:69% (895 mg, 3.97 mmol).

**Z:E ratio:** 6:94.

**1H NMR** (200 MHz, CDCl3): δ= 10.15 (1H, d, *J* = 7.8 Hz, E isomer), 9.45 (1H, d *J* = 8.2 Hz, Z isomer), 7.53 (2H, d, *J* = 8.6 Hz, E isomer), 7.39 (2H, d, *J* = 8.6 Hz, E isomer), 7.16 (2H, d, *J* = 8.3 Hz, Z isomer), 6.35 (1H, d, *J* = 7.8 Hz, E isomer), 6.13 (1H, d, *J* = 8.2 Hz, Z isomer), 2.53 (3H, s, E isomer), 2.33 (3H, s, Z isomer).

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**Methyl (*E*)-3-(4-nitrophenyl)but-2-enoate, 18a.** [12]

**Yield**:69% (1.5 g, 6.90 mmol).

**1H NMR** (200 MHz, CDCl3): δ= 8.24 (2H, d, *J* = 8.7 Hz), 7.61 (2H, d, *J* = 8.7 Hz), 6.19 (1H, d, *J* = 1.4 Hz), 3.79 (3H, s), 2.60 (3H, d, *J* = 1.4 Hz).

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**(*E*)-3-(4-Nitrophenyl)but-2-en-1-ol, 18b.** [13]

**Yield**:99% (1.3 g, 6.83 mmol).

**1H NMR** (200 MHz, CDCl3): δ= 8.19 (2H, d, *J* = 8.9 Hz), 7.54 (2H, d, *J* = 8.9 Hz), 6.11 (1H, t, *J* = 6.5 Hz), 4.42 (2H, t, *J* = 5.1 Hz), 2.11 (3H, s).

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**(*E*)-3-(4-Nitrophenyl)but-2-enal, 18.** [14]

**Yield**:97% (1.3 g, 6.63 mmol).

**1H NMR** (200 MHz, CDCl3): δ= 9.42 (1H, d, *J* = 8.2 Hz), 8.29 (2H, d, *J* = 8.7 Hz), 7.49 (2H, d, *J* = 8.7 Hz), 6.21 (1H, dd, *J* = 8.2, 1.5 Hz), 2.34 (3H, d, *J* = 1.5 Hz).

**SYNTHESIS OF ALDEHYDE 19**



Methyl Diethylphosphonoacetate (5.8 mL, 29.4 mmol) was added dropwise under argon atmosphere over a period of 5 min to a stirred suspension of NaH (60% on mineral oil; 1130 mg, 29.4 mmol) in dry toluene (18 mL) at 0ºC, and the resulting mixture was stirred for 45 min at 0°C. A solution of cyclohexanone (2.6 mmol) in dry toluene (9.0 mL) was slowly added to the resulting mixture, and the reaction mixture was stirred at r.t. for 5h. After cooling to room temperature, the reaction was quenched with a saturated aqueous solution of NH4Cl and extracted with EtOAc (3x20 mL). The combined organic layer was washed with brine and dried over Na2SO4. After concentration under vacuum, the residue was purified by flash chromatography on silica gel (EtOAc:hexane) to afford **19a** (95%, 471 mg, 2.53mmol) as colorless oil.

**Methyl 2-cyclohexylideneacetate, 19a.** [15]

**1H NMR** (200 MHz, CDCl3): δ= 5.56 (1H, s), 3.63 (3H, s), 2.81-2.76 (2H, m), 2.18-2.12 (2H, m), 1.59 (6H, bs).

All characterization data are consistent with literature values.

DIBAL-H (3.7 mL, 1.5 M in toluene) was added dropwise to a solution of **19a** (451 mg, 2.53 mmol) in DCM (25.3 mL) at −78°C. The reaction mixture was stirred at −78°C for 2h and the solution was allowed to reach 0°C. The solution was quenched with a saturated aqueous solution of potassium sodium tartrate at 0°C and stirred at room temperature for 3h. The resulting mixture was extracted with EtOAc (3x50 mL) and washed with brine. The resulting solution was dried over Na2SO4 and concentrated under vacuum to obtain **19b** (67%, 266 mg, 1.70 mmol) as colorless oil.

**2-Cyclohexylideneethan-1-ol, 19b.** [2]

**1H NMR** (200 MHz, CDCl3): δ= 5.30 (1H, t, *J* = 7.2 Hz), 4.08 (2H, d, *J* = 7.2 Hz), 2.20-2.00 (4H, m), 1.51 (6H, bs).

All characterization data are consistent with literature values.

To a solution of **19b** (266mg, 1.70 mmol) in DCM (8.5 mL), PDC (770 mg, 2.04 mmol) and NaHCO3 (186mg, mmol) were added. The reaction mixture was stirred under Ar atmosphere at room temperature for 3h. Then, the resulting suspension was filtered through pad of Celite washing with DCM. The filtrate was evaporated under vacuum to obtain **19** (54%, 140 mg, 0.91 mmol) as a colourless oil.

**2-Cyclohexylideneacetaldehyde, 19.** [16]

**1H NMR** (200 MHz, CDCl3): δ= 9.97 (1H, d, *J* = 8.4 Hz), 5.79 (1H, d, *J* = 8.4 Hz), 2.67 (2H, bt, *J* = 5.4 Hz), 2.26 (2H, t, *J* = 5.4 Hz), 1.74-1.59 (6H, m).

**HRMS** (ESI): Calculated for C8H13O [(M+H)+]: 125.0961; found 125.0966.

All characterization data are consistent with literature values.

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