(1R, 2R)-2-Phenoxy-cyclohexan-1-ol as chiral auxiliary: Enantioselective synthesis of frontalin

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Abstract

Enantioselective synthesis of frontalin, an important pheromone, using (1R, 2R)-2-phenoxy-cyclohexan-1-ol as chiral auxiliary has been described.

Key words: Frontalin, pheromone, (1R, 2R)-2-phenoxy-cyclohexan-1-ol, pyruvate.

1. Introduction

Frontalin is a component of the aggregation pheromone of the southern pine beetle Dendroctonus frontalis Zimmerman and western pine beetle Dendroctonus brevicomis Le Conte1. Several synthetic strategies have been reported for the preparation of chiral frontalin using a variety of chiral auxiliaries such as 8-phenyl menthol2, 1,3-oxathiane3 and (S)-2-(anilinomethyl)pyrrolidine4.

2. Results and discussion

Recently, we demonstrated the applicability of (1R, 2R)-2-phenoxy-cyclohexan-1-ol (1) as a chiral auxiliary for the synthesis of α-hydroxy acids in high optical purities5,6. It appeared to us that (1R, 2R)-2-phenoxy-cyclohexan-1-ol would be a suitable chiral auxiliary for the synthesis of chiral frontalin. Accordingly, we have planned the synthesis of frontalin as shown in Scheme 1.

The required (1R, 2R)-2-phenoxy-cyclohex-1-yl pyruvate (2) was prepared by the action of pyruvic acid on (1R, 2R)-2-phenoxy-cyclohexan-1-ol (1) in the presence of catalytic amount of p-TsOH. The required alkyl bromide 2-(3-bromoprop-1-yl)-2-methyl-1,3-dioxolane was prepared following the literature procedure7. We carried out the addition of alkylzinc chloride 3 (obtained by the action of ZnCl2 with the corresponding Grignard reagent) with (1R, 2R)-2-phenoxy-cyclohex-1-yl pyruvate (2) to afford the α-hydroxy ester 4. Reduction of 4 with LAH furnished 2-[4-(hyd-
roxymethyl)-4-hydroxypent-1-yl]-2-methyl-1,3-dioxolane (5). This diol on treatment with catalytic amount of p-TsOH afforded (-)-frontalin (6) as a colourless liquid in 70% optical purity.

Though this methodology did not provide the frontalin in optically pure form this result demonstrates the applicability of (1R, 2R)-2-phenoxycyclohexan-1-ol as a chiral auxiliary. Now our studies are directed towards the development of a new 2-aryloxycyclohexan-1-ol to achieve higher enantiomeric purities.

3. Experimental

3.1. General

Elemental analyses were performed on a Perkin–Elmer 240C-CHN analyser. IR spectra were recorded on Perkin–Elmer model 1310 or 297 spectrophotometers. $^1$H NMR spectra (100 MHz) and $^{13}$C NMR spectra (25 MHz) were recorded on Jeol–FX–100 spectrometer, using chloroform-d as solvent and TMS as internal reference. Optical rotations were measured on Autopol II automatic polarimeter at the wavelength of the sodium D-line (589 nm).

(1R, 2R)-2-Phenoxycyclohex-1-yl pyruvate (2): To a stirred solution of (1R, 2R)-2-phenoxycyclohexan-1-ol (1) (20 mM, 3.84 g) in dry benzene (50 ml), pyruvic acid (50 mM, 3.47 ml) and p-toluenesulfonic acid (1.2 mM, 220 mg) were added and heated under reflux with azeotropic removal of water for 3 h. The reaction mixture was allowed to cool to room temperature, diluted with ether, washed with sat. K$_2$CO$_3$ solution and water. The organic layer was dried over anhyd. Na$_2$SO$_4$ and the solvent
was evaporated. The crude material was distilled under reduced pressure to furnish 2 as a colourless liquid. Yield: 4.45 g (85%); bp: 154-156°C/1.5 mm; [α]D29: -29.03 (c 3.27, MeOH), IR (neat): 1730 cm⁻¹; ¹H NMR: δ 1.20-2.32 (m, 11H), 4.24 (m, 1H), 5.08 (m, 1H), 6.80-7.38 (m, 5H), ¹³C NMR: δ 23.06, 23.23, 26.59, 29.59, 29.94, 77.00, 77.77, 116.59, 121.53, 129.65, 158.24, 160.36, 192.07. Analysis Calcd for C₁₉H₁₈O₄: C, 68.68; H, 6.92; Found: C, 68.60; H, 6.90.

2-{4-[2-Phenoxycyclohex-1-yl oxy]carbonyl-4-hydroxy}pent-1-yl-2-methyl-1,3-dioxolane (4): To a stirred solution of Grignard reagent (20 mM) prepared from 2-(3-bromoprop-1-yl)-2-methyl-1,3-dioxolane and magnesium in dry THF at 0°C, anhyd. ZnCl₂ (20 mM, 2.72 g) was added. After stirring for 2 h at 0°C, the reaction mixture was cooled to -78°C, and a precooled (at -78°C) solution of [(1R,2R)-2-phenoxycyclohex-1-yl] pyruvate (2) (10 mM, 2.62 g) in dry THF (5 ml) was added. After 3 h stirring at -78°C, the reaction mixture was allowed to warm to 0°C, sat. NH₄Cl solution was added and extracted with ether (3×20 ml). The ethereal solution was dried over anhyd. Na₂SO₄ and concentrated. The crude material 3.6 g (91%) was directly used in the next step without any purification. IR (neat): 3500, 1720 cm⁻¹; ¹H NMR: δ 1.00-2.20 (m, 20H), 3.21 (b, 1H, -OH), 3.96 (s, 4H), 4.22 (m, 1H), 5.00 (m, 1H), 6.60-7.20 (m, 5H).

2-[4-(Hydroxymethyl)-4-hydroxypent-1-yl]-2-methyl-1,3-dioxolane (5): A solution of α-hydroxy ester 4 (9.1 mM, 3.6 g) in dry THF was added dropwise to a stirred suspension of LAH (8.1 mM, 307 mg) in dry THF at room temperature. After 2 h stirring at room temperature, the reaction was quenched by adding sat. Na₂SO₄ solution. The salts were filtered and the residue was washed with THF. The organic layer was dried over anhyd. Na₂SO₄ and the solvent was evaporated. The crude material was purified by column chromatography (30% ethyl acetate in hexane) to obtain pure diol 5 as a colourless liquid. Yield: 968 mg (52%), ¹H NMR: δ 1.18 (s, 3H), 1.32 (s, 3H), 1.40-1.54 (m, 6H), 3.42 (s, 2H), 3.92 (s, 4H); ¹³C NMR: δ 18.06, 22.82, 23.53, 38.41, 39.41, 64.41, 69.55, 72.82, 60-70 (m, 5H).

(--)-Frontalin (6): To a stirred solution of diol 5 (408 mg, 2 mM) in 10 ml of dichloromethane, p-toluenesulfonic acid (40 mg) was added at 0°C and stirred for 2 h at the same temperature. The excess acid was neutralized by adding solid NaHCO₃ and washed with water. The organic layer was dried over anhyd. Na₂SO₄ and evaporated. Purification by column chromatography (using hexane), followed by distillation, gave frontalin as a colourless liquid. Yield: 173 mg (61%); bp: 90-92°C/100 mm [lit. bp 99-100°C/120 mm]; [α]D25: -36.52 (c 2.57, ether), ee 70% [lit. [α]D5: -52 (c 2, ether), ee>99%]; IR (neat): 2960, 1380, 1445, 1270, 1030 cm⁻¹; ¹H NMR: δ 1.18 (s, 3H), 1.32 (s, 3H), 1.40-1.74 (m, 6H), 2.40 (b, 2H, 2 -OH, D₂O exchangeable), 3.42 (s, 2H), 3.92 (s, 4H); ¹³C NMR: δ 17.58, 22.63, 24.17, 33.47, 34.12, 73.77, 79.53, 107.65.
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