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(1R, 2R)-2-Phenoxycyclohexan-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-phenoxycyclohexan-1-ol as chiral auxiliary has been described.

Key words: Frontalin, pheromone, (1R, 2R)-2-phenoxycyclohexan-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 Conte[1]. Several synthetic strategies have been reported for the preparation of chiral frontalin using a variety of chiral auxiliaries such as 8-phenylmenthol[2], 1,3-oxathiane[3] and (S)-2-(anilinomethyl)pyrrolidine[4].

2. Results and discussion

Recently, we demonstrated the applicability of (1R, 2R)-2-phenoxycyclohexan-1-ol (**1**) as a chiral auxiliary for the synthesis of α-hydroxy acids in high optical purities[5,6]. It appeared to us that (1R, 2R)-2-phenoxycyclohexan-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-phenoxycyclohex-1-yl pyruvate (**2**) was prepared by the action of pyruvic acid on (1R, 2R)-2-phenoxycyclohexan-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 procedure[7]. We carried out the addition of alkylzinc chloride **3** (obtained by the action of $ZnCl_2$ with the corresponding Grignard reagent) with (1R, 2R)-2-phenoxycyclohex-1-yl pyruvate (**2**) to afford the α-hydroxy ester **4**. Reduction of **4** with LAH furnished 2-[4-(hyd-

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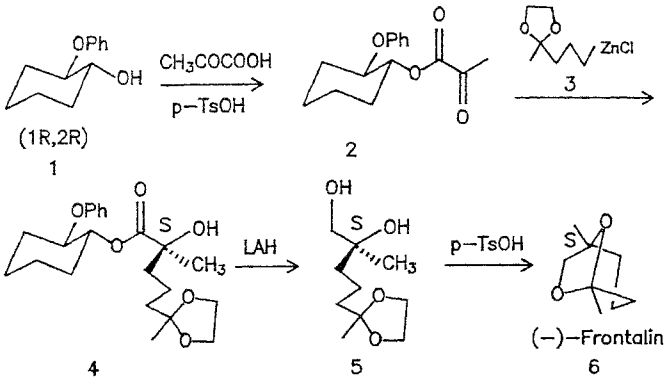

SCHEME 1.

roxymethyl)-4-hydroxypent-1-yl]-2-methyl-1,3-dioxolane (**5**). This diol on treatment with catalytic amount of *p*-TsOH[8] 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}CNMR 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_2CO_3 solution and water. The organic layer was dried over anhyd. Na_2SO_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; $[\alpha]_D^{24}$: −29.03 (c 3.27, MeOH), IR (neat): 1730 cm^{-1}; ^{1}HNMR: δ 1.20–2.32(m, 11H), 4.24(m, 1H), 5.08(m, 1H), 6.80–7.38(m, 5H), ^{13}CNMR: 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 $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; Found: C, 68.60; H, 6.90.

2-{4-[(2-Phenoxycyclohex-1-yloxy)carboxy]-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. $ZnCl_2$ (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. NH_4Cl solution was added and extracted with ether (3×20 ml). The ethereal solution was dried over anhyd. Na_2SO_4 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}; ^{1}HNMR: 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. Na_2SO_4 solution. The salts were filtered and the residue was washed with THF. The organic layer was dried over anhyd. Na_2SO_4 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%), IR (neat): 3500 cm^{-1}; ^{1}HNMR: δ 1.18(s, 3H), 1.32(s, 3H), 1.40–1.74(m, 6H), 2.40(b, 2H, 2 –OH, D_2O exchangeable), 3.42(s, 2H), 3.92(s, 4H); ^{13}CNMR: δ 18.06, 22.82, 23.53, 38.41, 39.41, 64.41, 69.41, 72.82, 110.00.

(−)-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 $NaHCO_3$ and washed with water. The organic layer was dried over anhyd. Na_2SO_4 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.[9] bp 99–100°C/120 mm]; $[\alpha]_D^{24}$: −36.52(c 2.57, ether), ee 70% [lit.[9] $[\alpha]_D^{25}$ −52(c 2, ether), ee>99%]; IR (neat): 2960, 1380, 1445, 1270, 1030 cm^{-1}; ^{1}HNMR: δ 1.34(s, 3H), 1.44(s, 3H), 1.48–1.81(m, 6H), 3.48(d, 1H, J=6Hz), 3.88(d, 1H, J=6Hz); ^{13}C NMR: δ 17.58, 22.63, 24.17, 33.47, 34.12, 73.77, 79.53, 107.65.

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References

1. KINZER, G.W., FENTIMAN, A.F., PAGE, T.F., FOLTZ, R.L., VITE, J.P. AND PITMAN, G.B. — *Nature*, 1969, **221**, 477–478.
2. WHITESELL, J.K. AND BUCHANAN, C.M. — *J. Org. Chem.*, 1986, **51**, 5443–5445.
3. OHWA, M. AND ELIEL, E.L. — *Chem. Lett.*, 1987, 41–44.
4. SAKITO, Y. AND MUKAIYAMA, T. — *Chem. Lett.*, 1979, 1027–1028.
5. BASAVAIAH, D. RAMA KRISHNA, P. AND BHARATHI, T.K. — *Tetrahedron Lett.*, 1990, **31**, 4347–4348.
6. BASAVAIAH, D., BHARATHI, T.K. AND RAMA KRISHNA, P. — *Synth. Commun.*, 1992, **22**, 941–947.
7. BELLAS, T.E., BROWNLEE, R.G. AND SILVERSTEIN, R.M. — *Tetrahedron*, 1969, **25**, 5149–5153.
8. YADAV, J.S., JOSHI, B.V. AND SAHASRABUDHE, A.B. — *Synth. Commun.*, 1985, **15**, 797–805.
9. MORI, K. — *Tetrahedron*, 1975, **31**, 1381–1384.