STEREOSELECTIVE SYNTHESIS OF AN ALARM PHEROMONE OF GREMATOGASTER ANTS USING (4*S*)-4-BENZYLOXAZOLIDINONE AS CHIRAL AUXILIARY

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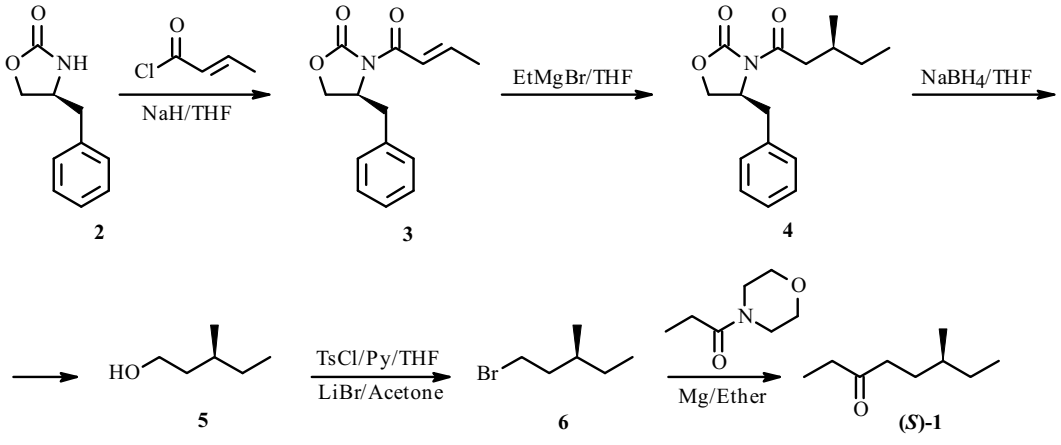
(S)-6-Methyl-3-octanone, a component of the alarm pheromone of Grematogaster ants, was synthesized through a key step of stereoselective Michael addition reaction using (4S)-4-benzyloxazolidinone as chiral auxiliary. The target product was obtained with an overall yield of 43.0% over six steps in high enantiomeric purity.

Keywords: (4*S*)-4-benzyloxazolidinone, chiral auxiliary, Michael addition, synthesis, (*S*)-6-methyl-3-octanone, pheromone.

Several insects show a remarkable ability to distinguish the stereoisomers of their chiral pheromone components [1]. For instance, specificity of response to the enantiomers of their alarm pheromones has been demonstrated for the leaf cutting ants, *Atta texana* and *Atta cephalotes*, and the myrmicine ant, *Pogonomyrmex barbatus*. 6-Methyl-3-octanone was isolated and identified as a component of the alarm pheromone of Grematogaster ants [2], a pest causing serious losses of croppers throughout the world. Since effective and cost-efficient control of Grematogaster ant populations can be foreseen with the aid of the alarm pheromone, several total syntheses of the racemate and the (*R*) enantiomer or (*S*) enantiomer have been published [2–5].

Recently, our group has undertaken a research program on preparation of chiral auxiliaries [6–8] and application of them to synthesize the insect pheromones [9, 10]. In this paper, we have developed an efficient procedure to stereoselectively synthesize (*S*)-6-methyl-3-octanone (**1**) via a key step of asymmetric Michael addition using optically pure (4*S*)-4-benzyloxazolidinone as chiral auxiliary (Scheme 1).



Scheme 1

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As shown in Scheme 1, (4*S*)-4-benzyloxazolidinone (**2**) was reacted with crotonoyl chloride to give compound **3** in 85.8% yield in the presence of NaH. Then **4** was obtained via asymmetric Michael addition of ethylmagnesium bromide to **3** in 98% diasteromeric excess and 87.3% yield, which was analyzed by HPLC and purified by flash column chromatography. Nondestructive removal of the auxiliary group of **4** gave (*S*)-3-methylpentan-1-ol (**5**) in 83.2% yield. The (*S*)-**5** was smoothly converted to tosylate in the presence of pyridine, and then converted to the corresponding bromide **6** in 81.6% yield by treating with lithium bromide. The bromide **6** was prepared as a Grignard reagent and then reacted with propionyl morpholine to get (*S*)-6-methyl-3-octanone (**1**) in 84.5% yield, and the overall yield of (*S*)-**1** was 43.0%. In these reactions, the stereocenter of the compounds was not touched, and the spectral data of (*S*)-**1** were in accord with the literature, as well as the specific rotation value [3].

EXPERIMENTAL

All organic solvents were dried by standard methods. TLCs were performed on precoated plates of silica gel HF254 (0.5 mm, Yantai, China). Flash column chromatography was performed on silica gel H (Yantai, China). Melting points were measured on a WRS-1A digital melting point apparatus and uncorrected. Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter. IR spectra were recorded on an IR spectrum One (PE) spectrometer, and ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Varian Unity INOVA 600 spectrometer in $CDCl_3$ using TMS as internal standard. The diastereoisomeric purity was determined by means of HPLC (Dionex, Ultimate3000 pump) using solid-phase extraction in reversed phase mode (C8 phase) (70:30 water–methanol, 1 mL/min, 254 nm).

(*S*)-3-((*E*)-But-2-enoyl)-4-benzyloxazolidinone (3). NaH (0.35 g, 31.04 mmol) was added portionwise to a solution of (*S*)-4-benzyloxazolidinone **2** (5.0 g, 28.22 mmol) in dry THF (70 mL) and the mixture was stirred for 30 min at room temperature. Crotonyl chloride (1.7 mL, 33.86 mmol) was added dropwise to the mixture and the solution was allowed to stand for 5 h. The reaction mixture was quenched with H_2O (50 mL) and then THF was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (50 mL × 3) and the organic layers were combined, washed with dilute HCl, aqueous saturated $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (*n*-hexane–EtOAc, 8:1, v/v) gave a white solid **3** (5.9 g, 85.8%). $[\alpha]_D^{20}$ +75.3°C (*c* 2.0, $CHCl_3$), lit. [11] $[\alpha]_D^{20}$ +77.9°C (*c* 2.0, $CHCl_3$). Mp 84.8–85.1°C, lit. [11] 85.0–86.0°C. IR (NaCl, cm^{-1}): 1769, 1677, 1630. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 1.99 (3H, t, J_1 = 0.6, J_2 = 5.4, CH_3), 2.80 (1H, dd, J_1 = 9.6, J_2 = 13.2, $PhCH_2$), 3.33 (1H, dd, J_1 = 3.0, J_2 = 13.2, $PhCH_2$), 4.19 (2H, m, OCH_2), 4.7 (1H, m, CH), 7.22–7.35 (m, 7H, Ar-H, CH=CH). ^{13}C NMR ($CDCl_3$, δ): 18.55, 37.78, 55.21, 66.03, 121.73, 127.24, 128.88 (2C), 129.41 (2C), 135.30, 147.01, 153.39, 164.89.

(*S*)-3-((*S*)-3-Methylpentanoyl)-4-benzyloxazolidinone (4). Bromoethane (3.43 mL, 40.78 mmol) was added dropwise under argon to a suspension of magnesium turnings (1.04 g, 42.8 mmol) in dry THF (20 mL). The mixture was stirred for 1 h under reflux. The resulting dark solution was cooled to 0°C and transferred via a cannula to a solution of **3** (5.0 g, 20.39 mmol) in THF (30 mL) at –78°C, and the mixture was stirred at –78° for 3 h. The reaction was quenched by saturated aqueous NH_4Cl (20 mL). After evaporation of the solvent, the aqueous layer was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous NH_4Cl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by flash column chromatography (*n*-hexane–EtOAc, 16:1, v/v) gave a colorless oil **4** (5.2 g, 87.3%). $[\alpha]_D^{20}$ +21.25°C (*c* 2.0, EtOAc). IR (NaCl, cm^{-1}): 1784, 1698. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.84–0.90 (6H, m, $2CH_3$), 0.90–0.96 (2H, m, CH_2), 1.24 (1H, m, CH), 1.40 (1H, t, J_1 = 1.2, J_2 = 6.0, $COCH_2$), 1.98 (1H, t, J_1 = 1.8, J_2 = 4.2, $COCH_2$), 2.95 (1H, dd, J_1 = 5.4, J_2 = 10.8, $PhCH_2$), 3.25 (1H, dd, J_1 = 9.0, J_2 = 10.2, $PhCH_2$), 4.11 (2H, m, OCH_2), 4.63 (1H, m, NCH), 7.17 (2H, d, J = 7.2, Ph), 7.19 (1H, d, J = 7.8, Ph), 7.28 (2H, t, J_1 = 7.8, J_2 = 6.6, Ph). ^{13}C NMR ($CDCl_3$, δ): 11.21, 19.13, 29.29, 30.98, 37.76, 41.98, 54.97, 65.89, 127.02, 128.65 (2C), 129.16 (2C), 135.17, 153.14, 172.53.

(*S*)-3-Methylpentan-1-ol (5). A solution of $NaBH_4$ (0.61 g, 30.3 mmol) in ethanol (10 mL) was added dropwise to a solution of **4** (3.0 g, 10.9 mmol) in THF (20 mL) at 0°C. The ice bath was removed and the mixture was stirred at room temperature for 2 h. The mixture was then recooled to 0°C, and dilute HCl was added carefully to quench the excess hydride reagent. After evaporation of the solvent, the aqueous layer was extracted with Et_2O, and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by flash column chromatography (*n*-hexane–EtOAc, 6:1, v/v) gave **5** as a colorless oil (0.93 g, 83.2 %). $[\alpha]_D^{20}$ + 8.58°C (neat), lit. [12] $[\alpha]_D^{20}$ +8.77°C (neat). IR (NaCl, cm^{-1}): 3300. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.84–0.95 (6H, m, $2CH_3$), 1.13–1.25 (2H, m, $2CH_2$), 1.36 (1H, m, CH), 2.34 (1H, s, OH), 2.92 (1H, m, OCH_2), 3.40 (1H, m, OCH_2). ^{13}C NMR ($CDCl_3$, δ): 11.42, 20.58, 30.43, 31.24, 39.52, 60.15.

(*S*)-1-Bromo-3-methylpentane (6). *p*-Toluenesulfonyl chloride (2.5 g, 13.2 mmol) and pyridine (2.0 mL, 24.0 mmol) were added to a solution of **5** (0.9 g, 8.8 mmol) in THF (20 mL) . After stirring at room temperature for 2 h, the mixture was poured into cold 1 M HCl. The resulting mixture was extracted with Et_2O. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under vacuum to provide the tosylate as a yellowish oil. The tosylate was dissolved in acetone (20 mL), and anhydrous LiBr (1.1 g, 20.0 mmol) was added at room temperature. The mixture was stirred for 2 h under reflux and filtered through a pad of silica gel, and the pad was further washed with Et_2O (50 mL). The filtrate was concentrated under vacuum to afford a yellowish oil, which was purified by flash column chromatography (*n*-hexane–EtOAc, 15:1, v/v) to give a colorless oil **6** (1.19 g, 81.6%). $[\alpha]_D^{20}$ +5.2°C (*c* 0.59, $CHCl_3$), lit. [13] $[\alpha]_D^{23}$ +5.3°C (*c* 0.59, $CHCl_3$). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.94 (6H, m), 1.10–1.90 (5H, m), 3.35 (2H, t). ^{13}C NMR ($CDCl_3$, δ): 11.42, 19.58, 29.65, 31.08, 33.69, 38.16.

(*S*)-6-Methyloctan-3-one (1). Compound **6** (0.51 g, 3.6 mmol) was added dropwise under argon to a suspension of magnesium turnings (0.13 g, 5.4 mmol) in dry Et_2O (10 mL). The mixture was stirred for 1 h under reflux. The resulting dark solution was cooled to 0°C and transferred via a cannula to a solution of 1-morpholinopropan-1-one (0.57 g, 4 mmol) in Et_2O (10 mL), and the mixture was stirred at 0°C for 12 h. The reaction was quenched by saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted by Et_2O, and the combined organic layer was washed with saturated aqueous NH_4Cl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by flash column chromatography (*n*-hexane) gave a yellowish oil **(*S*)-1** (0.45 g, 84.5%). $[\alpha]_D^{20}$ +11.6°C (*c* 1.0, $CHCl_3$), lit. [3] $[\alpha]_D^{20}$ +11.06°C (*c* 1.0, $CHCl_3$). IR (NaCl, cm^{-1}): 2980, 2860, 1720, 1460, 1375. ^{1}H NMR ($CDC1_3$, δ, ppm, J/Hz): 0.84 (3H, d, CH_3), 0.92 (6H, m, $2CH_3$), 1.00–1.80 (5H, br, CH_2-CH-CH_2), 1.93–2.4 (4H, m, CH_2-CO-CH_2). ^{13}C NMR ($CDCl_3$, δ): 7.78, 11.45, 20.35, 30.24, 30.89, 34.58, 36.95, 39.56, 210.65.

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