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Asymmetric synthesis of (2*R*,5*S*)-2-methyl-5-hexanolide, the sex pheromone of carpenter bee *Xylocopa hirutissima*

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ABSTRACT

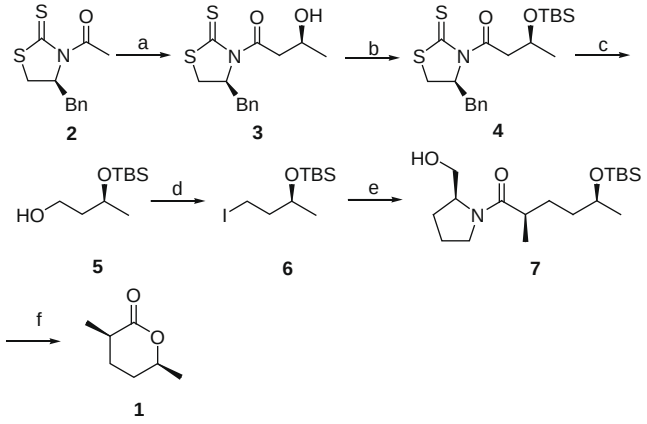
The stereoselective synthesis of the (2*R*,5*S*)-2-methyl-5-hexanolide, a sex pheromone of *Xylocopa hirutissima*, has been achieved in 6 steps and 33% overall yield. The synthesis relies on an asymmetric *N*-acetyl thiazolidinethione aldol reaction to establish the C5 stereogenic centers. The remaining stereogenic center at C2 was set through a *N*-propionylprolinol-mediated asymmetric alkylation reaction.

1. Introduction

(2*R*,5*S*)-2-Methyl-5-hexanolide was isolated and identified as a major component of the sex pheromone from the male *Xylocopa hirutissima* in 1976.[1] Due to its attractive biological activities, various methods for the synthesis of (2*R*,5*S*)-2-methyl-5-hexanolide have been described.[2] Wu et al.[3] reported a synthesis of this pheromone with 20% overall yield from (4*S*)-3-methacryloyl-4-phenyl-2-oxazolidinone involving an asymmetric conjugate addition as a key step. Sonoda et al.[4] described a one-step synthesis of the sex pheromone via the transition-metal-mediated carbonylation of saturated alcohols with CO. Very recently, via the intermolecular asymmetric alkylation of (4*S*)-iodobutan-2-ol with 2-ethyl-4,4-dimethyl-2-oxazoline, the synthesis of the sex pheromone has been reported.[5] However, there are currently only a few syntheses of the optically active pheromone.[6] Furthermore, these methods suffer from disadvantages such as low overall yields, low enantiometric purity and the use of expensive starting materials. In connection with our studies on the chiral auxiliary-mediated asymmetric synthesis of the pheromone of insects,[7] we were interested in developing a simple and feasible route to (2*R*,5*S*)-2-methyl-5-hexanolide. Herein, we report a novel method for the stereoselective synthesis of (2*R*,5*S*)-2-methyl-5-hexanolide employing an asymmetric aldol condensation and asymmetric alkylation reaction as the key steps (Scheme 1).

2. Results and discussion

The stereoselective synthesis of **1** was carried out, as shown in Scheme 1. Thus, starting with the *N*-acetyl thiazolidinethione **2**, the asymmetric aldol reaction[8] of its titanium enolate with acetaldehyde at 0 °C afforded the aldol product **3** in 56% yield after purification (de = 76% for the crude aldol products). The absolute configuration of compound **3** was demonstrated by X-ray analysis.[9] Protection of its secondary hydroxyl group with TBSCl afforded the silyl ether **4** in 97% yield. Cleavage of the chiral auxiliary moiety was accomplished following Wu's[10] procedure to obtain the protected alcohol **5** in 93% yield along with the recovery of the (*S*)-4-benzyl-1,3-thiazolidine-2-thione (95% yield). Conversion of this alcohol to alkyl iodide **6** by treatment with Ph_3P, imidazole and I_2 (93% yield) would serve as the electrophile for a diastereoselective alkylation reaction to install the C2 stereocenter of the target molecule. Due to the lower nucleophilicity exhibited by enolates



Scheme 1. Reagents and conditions: (a) $TiCl_4$, DIPEA, CH_2Cl_2, 0 °C, then acetaldehyde (55.8%); (b) TBSCl, 2,6-lutidine, DMF (97.4%); (c) $NaBH_4$, C_2H_5OH (93.1%); (d) Ph_3P, I_2, imidazole (93.2%); (e) (*S*)-prolinol propionamide, *n*-BuLi, diisopropylamine, THF, −78 °C to 0 °C (83.8%); (f) 1 M HCl, reflux (82.2%).

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derived from (*S*)-4-benzyl-1,3-thiazolidine-2-thione, the more reactive enolate derived from the prolinol propionamide was employed in the alkylation reaction.[11] Thus, the dianion of *N*-propionylprolinol was reacted with the alkyl iodide to give **7** in 84% yield (de = 92% for the crude alkylation products). Subsequent acid hydrolysis of **7** gave the desired lactone **1** in 82% yield (98% ee[12]) after column chromatography. The analytical and spectroscopic data of the pheromone, as well as the specific rotation value were in agreement with the literature.[2]

3. Conclusion

In conclusion, we have provided an effective procedure for the stereoselective synthesis of the sex pheromone of *X. hirutissima* (33% overall yield) from easily available starting materials. In this approach, the C2 stereocenter was established by employing an *N*-propionylprolinol-mediated asymmetric alkylation reaction, the C5 stereocenter was set through an asymmetric acyl-thiazolidinethione aldol reaction. Further application of this methodology to the syntheses of other biologically active compounds is currently underway in our laboratory.

4. Experimental

4.1. General

All solvents were obtained from commercial sources and dried or purified by standard procedures before use. Separations by flash chromatography were performed on 300–400 mesh silica gel. Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected. Optical rotations were measured using a sodium D line on WZZ-2B Automatic Polarimeter. HPLC analyses were carried out on a Dionex chromatograph (Ultimate3000 pump, C8 reversed-phase chromatographic column) equipped with a diode-array UV detector. Mass spectra were recorded on Finnigan LCQ DUO MS system. IR spectra were recorded on an IR-spectrum (PE) spectrometer. NMR spectra were recorded on Varian Unity Inova 600 spectrometer in $CDCl_3$ (^1H at 600 MHz and ^{13}C at 125 MHz) using TMS as the internal standard.

4.2. (3*S*)-1-[(*S*)-4-Benzyl-2-thioxothazolidin-3-yl]-3-hydroxybutan-1-one 3

A solution of *N*-acetyl (4*S*)-benzylthiazolidinethione (1.25 g, 4.98 mmol) in freshly distilled CH_2Cl_2 (30 mL) at 0 °C was treated dropwise with a solution of $TiCl_4$ (5.5 mL, 1 M solution in CH_2Cl_2, 5.48 mmol) under Ar, and the solution was allowed to stir for 20 min. To the yellow mixture was added diisopropylethylamine (4.98 mmol, 0.83 mL), and the solution was stirred for 40 min at 0 °C. A solution of acetaldehyde (5.5 mL, 1.36 M in CH_2Cl_2, 7.47 mmol) was transferred via cannula to the reaction mixture, which was then stirred for 1 h at 0 °C. The reaction was quenched with saturated ammonium chloride (30 mL), and the layers were separated. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed in vacuum to afford the crude aldol products as a mixture of diastereomers (88:12). Purification by flash chromatography (hexane/EtOAc, 5:1) afforded **3** (0.78 g, 56%) as a yellow solid, which was recrystallized from EtOAc–petroleum ether to give a yellow needle crystal. Mp 75.7–76.5 °C; $[\alpha]_D^{25} = +167.2$ (*c* 1.143, $CHCl_3$); IR (NaCl, cm^{-1}): ν_{max} 3426, 3026, 1693, 1603, 1496, 1166; ^1H NMR (600 MHz, $CDCl_3$): δ 1.28 (d, *J* = 6.6 Hz, 3H), 2.80 (d, *J* = 3.6 Hz, 1H), 2.91 (d, *J* = 12.0 Hz, 1H), 3.05 (dd, *J* = 10.8, 13.2 Hz, 1H), 3.12 (dd, *J* = 9.3, 17.7 Hz, 1H), 3.22 (dd, *J* = 3.6, 13.2 Hz, 1H), 3.41 (dd, *J* = 7.5, 11.1 Hz, 1H), 3.66 (dd, *J* = 2.4, 17.4 Hz, 1H), 4.32–4.35 (m, 1H), 5.39–5.42 (m, 1H), 7.29–7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.3, 32.0, 36.8, 47.3, 64.0, 68.2, 127.3, 128.9, 129.4, 136.3, 173.1, 201.4.

4.3. (3*S*)-1-[(*S*)-4-Benzyl-2-thioxothazolidin-3-yl]-3-(*tert*-butyldimethylsilyloxy)butan-1-one 4

To a solution of **3** (1.06 g, 3.6 mmol) in DMF (15 mL) were added TBSCl (2.16 g, 14.3 mmol) and 2,6-lutidine (2.1 mL, 17.9 mmol). The solution was stirred at room temperature for 5 h. Then ice water (60 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 40 mL). The organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 100:1) provided the silyl ether **4** (1.43 g, 97% yield). Mp 72.9–73.7 °C; $[\alpha]_D^{25} = +120.2$ (*c* 1.220, $CHCl_3$); IR (NaCl, cm^{-1}): ν_{max} 3027, 1700, 1602, 1168; ^1H NMR (600 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.09 (s, 3H), 0.85 (s, 9H), 1.24 (d, *J* = 5.4 Hz, 3H), 2.88 (d, *J* = 11.4 Hz, 1H), 3.04 (dd, *J* = 10.8, 13.2 Hz, 1H), 3.13 (dd, *J* = 4.2, 16.2 Hz, 1H), 3.26 (dd, *J* = 3.6, 13.2 Hz, 1H), 3.45 (dd, *J* = 6.6, 11.4 Hz, 1H), 3.57 (dd, *J* = 8.4, 16.2 Hz, 1H), 4.44–4.47 (m, 1H), 5.24–5.27 (m, 1H), 7.28–7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.8, −4.4, 17.9, 24.1, 25.8, 32.2, 36.6, 48.0, 65.8, 68.7, 127.2, 128.9, 129.4, 136.6, 172.2, 201.1.

4.4. (*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-butanol 5

$NaBH_4$ (1.78 g, 31.2 mmol) was added to a stirred solution of **4** (3.19 g, 7.79 mmol) in EtOH (45 mL). After stirring at room temperature for 3 h, the excess $NaBH_4$ was carefully destroyed by the dropwise addition of 1 M HCl. The solution was removed in vacuo, and the residue was extracted with EtOAc (3 × 30 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 20:1) provided **5** as a colorless oil (1.48 g, 93%). $[\alpha]_D^{25} = +24.6$ (*c* 0.906, *CHCl*$_3$) {lit.[13] $[\alpha]_D^{25} = +25$ (*c* 2.00, $CHCl_3$)}; IR (NaCl, cm^{-1}): ν_{max} 3368, 1472, 1376; ^1H NMR (600 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.61–1.66 (m, 1H), 1.76–1.81 (m, 1H), 2.56 (s, 1H), 3.70–3.74 (m, 1H), 3.82–3.86 (m, 1H), 4.09–4.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.0, −4.4, 17.9, 23.4, 25.8, 40.4, 60.4, 68.3.

4.5. (*S*)-3-(*tert*-Butyldimethylsilyloxy)butyl iodide 6

To a solution of **5** (1.07 g, 5.2 mmol) in CH_2Cl_2 (25 mL) were added imidazole (1.06 g, 15.6 mmol), Ph_3P (2.73 g, 10.4 mmol), and I_2 (2.64 g, 10.4 mmol). The solution was stirred at room temperature for 3 h and then washed with saturated aqueous sodium thiosulfate, saturated aqueous sodium bicarbonate, and brine. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 100:1) provided the alkyl iodide **6** (1.52 g, 93%). $[\alpha]_D^{25} = +50.2$ (*c* 0.833, $CHCl_3$) {lit.[14] $[\alpha]_D^{25} = +45.9$ (*c* 1.66, $CHCl_3$)}; IR (NaCl, cm^{-1}): ν_{max} 2956, 2929, 2892, 2857, 1472, 1375; ^1H NMR (600 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 1.15(d, *J* = 6.0 Hz, 3H), 1.86–1.96 (m, 2H), 3.18–3.26 (m, 2H), 3.86–3.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.6, −4.2, 3.5, 18.0, 23.5, 25.8, 43.2, 68.2.

4.6. (2*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-1-[(S)-2-(hydroxymethyl)pyrrolidin-1-yl]-2-methylhexan-1-one 7

A solution of LDA was prepared from diisopropylamine (0.47 mL, 3.31 mmol) and *n*-BuLi (3.31 mmol) in dry THF under Ar at 0 °C. The (*S*)-prolinol propionamide (0.26 g, 1.66 mmol) in THF (1 mL) was slowly added, and the mixture was stirred at room temperature for 30 min then cooled to −78 °C, and the iodide **6** (0.40 g, 1.27 mmol) was added. The resulting solution was slowly

warmed to room temperature over 4 h and then quenched with saturated aqueous ammonium chloride, and extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude alkylation products as a mixture of diastereomers (96:4). Flash chromatography (hexane/EtOAc, 2:1) provided the product **7** (0.37 g, 84%). $[\alpha]_D^{25} = +22.5$ (*c* 0.600, $CHCl_3$); IR (NaCl, cm^{-1}): ν_{max} 3401, 1621, 1463, 1373, 1057; ^1H NMR (600 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.92 (s, 9H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.36–1.45 (m, 2H), 1.49–1.54 (m, 1H), 1.63–1.71 (m, 2H), 1.88–1.94 (m, 1H), 1.97–2.02 (m, 1H), 2.04–2.08 (m, 1H), 2.57–2.60 (m, 1H), 3.51–3.54 (m, 1H), 3.60–3.66 (m, 2H), 3.79–3.82 (m, 1H), 4.24–4.27 (m, 1H), 5.20 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.8, −4.5, 17.7, 18.0, 23.7, 24.3, 25.7, 25.8, 28.0, 29.8, 37.3, 38.1, 47.7, 60.6, 66.9, 68.6, 177.8.

4.7. (2*R*,5*S*)-2-Methyl-5-hexanolide 1

A mixture of **7** (0.66 g, 0.360 mmol) and 1 N HCl (3 mL) was stirred under reflux for 2 h and extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 10:1) to give the product **1** (0.20 g, 82%). Mp 49–50 °C. $[\alpha]_D^{25} = -95.1$ (*c* 0.427, $CHCl_3$) [lit.[2q] $[\alpha]_D^{25} = -91.0$ (*c* 0.73, $CHCl_3$)]; IR (NaCl, cm^{-1}): ν_{max} 2971, 2939, 2879, 1738; ^1H NMR (600 MHz, $CDCl_3$): δ 1.20 (d, *J*=6.6 Hz, 3H), 1.36 (d, *J*=6.6 Hz, 3H), 1.52–1.64 (m, 2H), 1.90–1.94 (m, 1H), 2.06–2.10 (m, 1H), 2.58–2.59 (m, 1H), 4.44–4.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.4, 21.3, 25.8, 28.6, 33.2, 74.6, 176.5; MS (ESI): 129 (M^++1, 100).

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