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Asymmetric synthesis of a sex pheromone (3*S*,5*R*,6*S*)-3,5-dimethyl-6-isopropyl-3,4,5,6-tetrahydropyran-2-one

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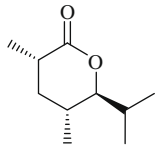
ABSTRACT

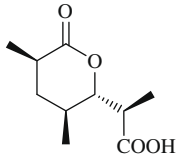
An Oppolzer anti-aldol approach for the synthesis of the sex pheromone (3*S*,5*R*,6*S*)-3,5-dimethyl-6-isopropyl-3,4,5,6-tetrahydropyran-2-one is reported.

1. Introduction

The insect sex pheromone (3*S*,5*R*,6*S*)-3,5-dimethyl-6-isopropyl-3,4,5,6-tetrahydropyran-2-one secreted by *Macrocentrus grandii*,[1] controls the population of the European corn borer *Ostrinia nubilalis*, in an environmentally friendly way to solve agricultural problems. Compound **1** is one of the three components of the pheromone mixture which was first isolated in 1992 from larval parasitoid *M. grandii*.[2] Lactone rings are an important structural feature of many natural products and are very important core moiety in many biologically important macrolide molecules such as methynolide, neomethymycin, methymycin, narbomycin, picromycin and a number of microbial macrolide antibiotics.[3] Our particular interest is to synthesize the pheromone (3*S*,5*R*,6*S*)-3,5-dimethyl-6-isopropyl-3,4,5,6-tetrahydropyran-2-one **1**, which has a similar structure to Prelog-Djerassi lactone **2**. With this in mind, we explored an Oppolzer anti-aldol reaction for the synthesis of this molecule as it offers better diastereomeric excess and high yield. Although some synthetic methods have been reported,[4] a more convergent and stereoselective synthesis of **1** is desirable. As a result, we report an efficient synthesis of **1**.



1



2

Herein, we report an efficient and practical synthesis of the pheromone from commercially available isobutyraldehyde. From the retrosynthetic analysis of compound **1** (Scheme 1), we envisaged that compound **5** is a key intermediate, which can be derived from isobutyraldehyde and *N*-propionylbornane-10,2-sultam **3**.[5] Oppolzer *anti*-aldol condensation products such as **4** are valuable building blocks as illustrated by the total synthesis of (3*S*,5*R*,6*S*)-3,5-dimethyl-6-isopropyl-3,4,5,6-tetrahydropyran-2-one **1**.

2. Results and discussion

The stereoselective synthesis of **1** was carried out, as shown in Scheme 2. Thus, the *N*-propionylbornane-10,2-sultam **3** was subjected to an asymmetric aldol reaction[6] with isobutyraldehyde at −78 °C to afford the *anti*-aldol product **4** in 75.3% yield (de = 84%) and confirmed by the ^{1}H NMR and specific rotation.[7] Reductive cleavage of *anti*-aldol product **4** with LAH gave 1,3-diol **5** in 92% yield.[8] The primary hydroxyl group in **5** was selectively tosylated by using TsCl, Bu_2SnO and triethylamine in dichloromethane to afford tosylated compound **6** in 90% yield.[9] The tosyl group in **6** was replaced by iodine by reaction with NaI in acetone to yield iodo alcohol **7** in 92% yield.[10] Next, the compound 7 was propionylated with propionyl chloride in the presence of triethylamine and a catalytic amount of DMAP in dry dichloromethane to afford ester **8** in 90% yield.[11] The cyclization of ester **8** using LHMDS in the presence of HMPA in dry THF gave the desired lactone **1** in 76% yield after column chromatography.[12]

The analytical and spectroscopic data of pheromone **1**, as well as the specific rotation values were in agreement with the literature.[2] All the compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, mass and IR spectroscopic data.

3. Conclusion

In conclusion a simple and highly efficient Oppolzer *anti*-aldol condensation approach for total synthesis of pheromone **1** was developed with an overall yield of 39.2%.

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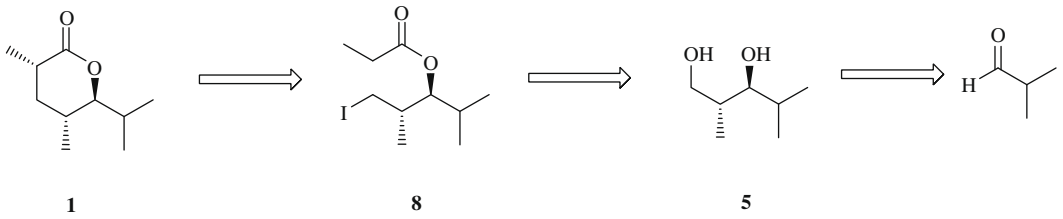
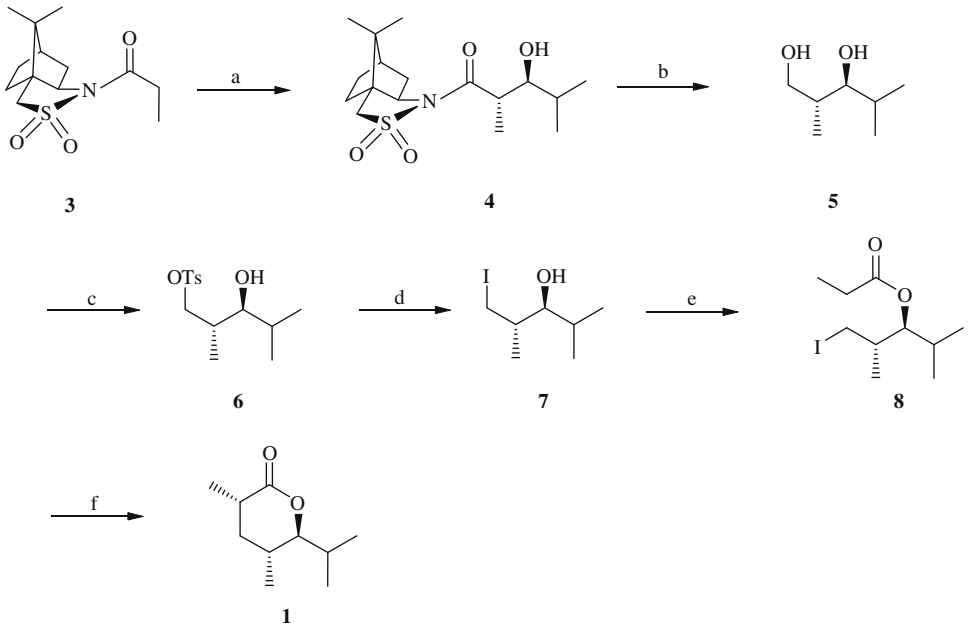


Scheme 1. Retrosynthesis of pheromone.



Scheme 2. Reagents and conditions: (a) Isobutyraldehyde, $TiCl_4$, $^iPr_2EtN$, dry DCM, 3 h, 75%; (b) LAH, dry ether, 2 h, 92%; (c) TsCl, TEA, Bu_2SnO, DMAP, dry DCM, 5 h, 90%; (d) NaI, dry acetone, reflux, 2 h, 92%; (e) propionyl chloride, TEA, DMAP, dry DCM, 3 h, 90%; (f) LHMDS (1.5 M solution in THF), HMPA, dry THF, 5 h, 76%.

4. Experimental

4.1. General methods

Solvents were dried over standard drying agents and were freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. ^1H NMR (200 MHz and 300 MHz) and ^{13}C NMR (50 MHz and 75 MHz) spectra were measured on a Varian Gemini FT-200 MHz spectrometer and Bruker Avance 300 MHz with tetramethylsilane as an internal standard for solutions in deuteriochloroform. *J* values are given in hertz. The IR spectra were recorded on a Perkin-Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C. Mass spectra were recorded on CEC-21-11013 or Fannigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system or LC/MSD Trap SL (Agilent Technologies).

4.1.1. (2*R*)-*N*-[2*S*,3*S*)-2,4-Dimethyl-3-hydroxypentan-1-oyl]bornane-10,2-sultam 4

To a stirred solution of compound **3** (1.0 g, 3.69 mmol) in dichloromethane (10 mL) was added $TiCl_4$ (1.2 mL), and diisopropylethylamine (2.0 mL) slowly at −78 °C for 90 min, and then isobutyraldehyde (0.8 g, 11.08 mmol) was added at the same temperature and stirred for another 90 min. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl (10 mL) solution and extracted into dichloromethane (3 × 20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, 60–120 mesh; hexane/ethyl acetate = 9:1) to afford compound **4** (R_f : 0.6, hexane/EtOAc 80:20) as a white solid (0.95 g, 75.3% yield): $[\alpha]_D^{25} = -70.5$ (*c* 1.0, $CHCl_3$); IR (film): 3541, 2963, 1691, 1326, 1212, 772, 537 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, 3H, *J* = 6.6 Hz), 0.98 (s, 1H), 1.01 (d, 3H, *J* = 6.6 Hz), 1.16 (s, 3H), 1.19 (d, 3H, *J* = 6.7 Hz), 1.29–1.47 (m, 2H), 1.61–1.74 (m, 1H), 1.84–1.97 (m, 3H), 2.06 (td, 2H, *J* = 6.4 Hz), 2.32 (br s, 1H), 3.29–3.38 (m, 1H), 3.48 (d, 2H, *J* = 7.5 Hz), 3.49–3.55 (dd, 1H, *J* = 5, 9 Hz), 3.87–3.93 (t, 1H, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 15.6, 19.8, 19.9, 20.7, 26.2, 31.1, 33.2, 38.7, 42.9, 44.6, 48.1, 48.5, 53.1, 65.6, 80.4, 176.1; ESI-MS: *m/z* 344 $[M+1]^+$.

4.1.2. (2*R*,3*S*)-2,4-Dimethylpentane-1,3-diol 5

To a cooled (0 °C) stirred suspension of lithium aluminium hydride (166 mg, 4.36 mmol) in dry ether (10 mL) was added compound **4** (1.0 g, 2.91 mmol) over a period of 2 h. After completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated Na_2SO_4 solution, filtered and extracted into ethyl acetate (5 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude compound **5**. The crude **5** was purified by silica gel column chromatography (sil-

ica gel, 60–120 mesh; hexane/ethyl acetate = 9:1) to obtain pure compound **5** (R_f : 0.3, hexane/EtOAc 70:30) in 92 % yield as white crystalline solid (350 mg). $[\alpha]_D^{25} = +8$ (*c* 1.0, $CHCl_3$); IR (KBr): 3313, 2968, 2928, 2874, 1228, 1038, 989, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.85(d, 3H, *J* = 6.7 Hz), 0.92 (d, 3H, *J* = 6.9 Hz), 1.00(d, 3H, *J* = 6.6 Hz), 1.60–1.74 (m, 1H), 1.75–1.87 (m, 1H), 2.82 (br s, 1H), 3.02 (br s, 1H), 3.38 (dd, 1H, *J* = 1.2, 9.0 Hz), 3.56–3.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.10, 19.21, 19.67, 31.49, 36.23, 67.83, 79.75; ESI-MS: *m/z* 131$[M+1]^+$.

4.1.3. (2*R*,3*S*)-3-Hydroxy-2,4-dimethylpentyl 4-methylbenzenesulfonate 6

To a stirred solution of diol **5** (100 mg, 0.76 mmol) in dry dichloromethane (5 mL) were added dry triethylamine (3.0 equiv) and catalytic amounts of DMAP and Bu_2SnO at 0 °C for half an hour, after which tosyl chloride (137 mg, 0.72 mmol) was added to the reaction mixture and the reaction was stirred for 5 h. After completion of the reaction as determined by TLC, water was added to the reaction mixture and it was extracted into dichloromethane, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and was purified by silica gel column chromatography (silica gel, 60–120 mesh) using hexane/ethyl acetate (9:1) to obtain compound **6** (R_f: 0.7, hexane/EtOAc 70:30) (195 mg, 90% yield) as a colourless liquid; $[\alpha]_D^{25} = +21$ (*c* 1.0, $CHCl_3$); IR (neat): 3558, 2965, 1354, 1177, 960 and 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.81 (d, 3H, *J* = 6.7 Hz), 0.84 (d, 3H, *J* = 6.7 Hz), 0.97 (d, 3H, *J* = 6.7 Hz), 1.26 (t, 1H, *J* = 7.5 Hz), 1.57–1.70 (m, 1H), 1.73 (d, 1H, *J* = 3.7 Hz), 2.46 (s, 3H), 3.18–3.28 (m, 1H), 4.00–4.12 (m, 1H), 7.33 (d, 2H, *J* = 7.5 Hz), 7.77 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR(75 MHz, $CDCl_3$): δ 8.97, 18.96, 19.51, 21.73, 31.02, 35.02, 72.88, 75.48, 128.01, 129.79, 133.57, 144.38; ESI-MS: *m/z* 287 [M+1].

4.1.4. (2*S*,3*S*)-1-Iodo-2,4-dimethylpentan-3-ol 7

To a solution of tosylated compound **6** (100 mg, 0.35 mmol) in dry acetone (5 ml), NaI (105 mg, 0.70 mmol) was added and stirred at 70 °C for 2 h. After completion of the reaction as determined by TLC, acetone was removed, and water was added to the reaction mixture and it was extracted into ethyl acetate (4 × 20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product **7** which was purified by silica gel column chromatography (silica gel, 60–120 mesh) using hexane/ethyl acetate (9:1) to obtain pure compound **7** (R_f : 0.6, hexane/EtOAc 90:10) (78 mg, 92%yield) as a colourless liquid. $[\alpha]_D^{25} = -32.5$ (*c* 2.0, $CHCl_3$); IR (neat): 3427, 2963, 1461, 1381, 1192 and 977 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (d, 3H, *J* = 6.6 Hz), 0.99 (d, 3H, *J* = 6.6 Hz), 1.01 (d, 3H, *J* = 6.6 Hz), 1.23–1.34 (m, 1H), 1.62–1.77 (m, 1H), 1.78–1.91 (m, 1H), 3.11–3.20 (dd, 1H, *J* = 6.0 Hz), 3.23–3.31 (dd, 1H, *J* = 7.3, 9.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.42, 13.87, 18.77, 19.17, 31.27, 37.70, 78.71; ESI-MS: *m/z* 243 $[M+1]^+$.

4.1.5. (2*S*,3*S*)-1-Iodo-2,4-dimethylpentan-3-yl propionate 8

To a solution of iodo compound **7** (100 mg, 0.413 mmol) in dry dichloromethane dry triethylamine (3.0 equiv) and a catalytic amount of DMAP at 0 °C were added and stirred for 10 min, and then propionyl chloride (45.6 mg, 0.49 mmol) was added and stirred for 3 h. After completion of the reaction, the reaction mixture was quenched with saturated aq. ammonium chloride solution and extracted into dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the removal of solvent under reduced pressure gave crude product **8** as a pale yellow syrup which was purified by silica gel column chromatography using hexane/ethyl acetate (9.5:0.5) as eluent to obtain pure propionylated compound **8** (R_f : 0.7, hexane/EtOAc 90:10) (110 mg, 90% yield) as a pale yellow liquid. $[\alpha]_D^{25} = -7$ (*c* 1.0, $CHCl_3$); IR (neat): 2969, 2936, 2878, 1737, 1462, 1187 and 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (d, 3H, *J* = 6.7 Hz), 0.91 (d, 3H, *J* = 6.7 Hz), 1.02 (d, 3H, *J* = 6.7 Hz), 1.17 (d, 3H, *J* = 7.5 Hz), 1.84–1.97 (m, 1H), 2.08–2.20 (m, 1H), 2.31–2.41 (q, 2H, *J* = 7.5, 15.1 Hz), 3.27–3.35 (dd, 1H, *J* = 6.9, 10.7 Hz), 3.44–3.51 (dd, 1H, *J* = 5.6, 10.7 Hz), 4.83–4.89 (dd, 1H, *J* = 3.9, 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.38, 11.69, 14.97, 17.94, 19.19, 27.69, 29.90, 37.40, 80.00, 174.23; ESI-MS: *m/z* 299 $[M+1]^+$.

4.1.6. (3*S*,5*R*,6*S*)-3,5-Dimethyl-6-isopropyl-3,4,5,6-tetrahydropyran-2-one 1

To a solution of compound **8** (90 mg, 0.335 mmol) in dry tetrahydrofuran (3 ml) were added LHMDS (lithium hexamethyldisilazine) (48.62 mg, 0.30 mmol) and HMPA (hexamethyl phosphoramide) (108 mg, 0.6 mmol) and reaction mixture was stirred for 5 h at −78 °C. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl and extracted into ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford crude compound **1** as a pale yellow liquid. Purification of the crude product by silica gel column chromatography using hexane/ethyl acetate (9:1) as eluent gave **1** (R_f : 0.5, hexane/EtOAc 90:10) (38 mg, 76% yield) as a pale yellow liquid. $[\alpha]_D^{25} = -24.5$ (*c* 1.0, $CHCl_3$); IR (neat): 2926, 1728, 1459, 1212, 1058, 772, 537 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.90 (3H, d, *J* = 6.6 Hz), 0.96 (3H, d, *J* = 6.9 Hz), 1.09 (3H, d, *J* = 6.6 Hz), 1.25 (3H, d, *J* = 6.6 Hz), 1.29 (1H, m), 1.79–1.92 (1H, m), 1.93–2.20 (2H, m), 2.48 (1H, dt, *J* = 1.1, 6.6 Hz), 3.78 (1H, dd, *J* = 2.2, 9.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.9, 15.7, 18.0, 20.0, 27.7, 28.8, 32.0, 35.3, 85.3, 176.6; ESI-MS: *m/z* 170 $[M]^+$ and 127 $(M-C_3H_7^+)$.

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