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A Convergent and Stereoselective Synthesis of the Sex Pheromone of *Macrocentrus grandii*

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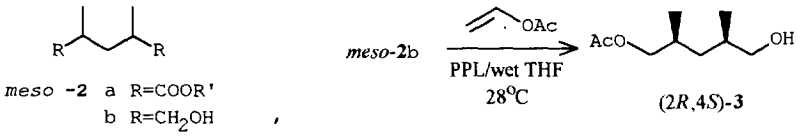
Abstract: The synthesis of (3*S*,5*R*,6*S*)-3,5-Dimethyl-6-isopropyl-3,4,5,6-tetrahydropyran-2-one (**1**), the sex pheromone of the larval parasitoid *M. grandii*, is described.

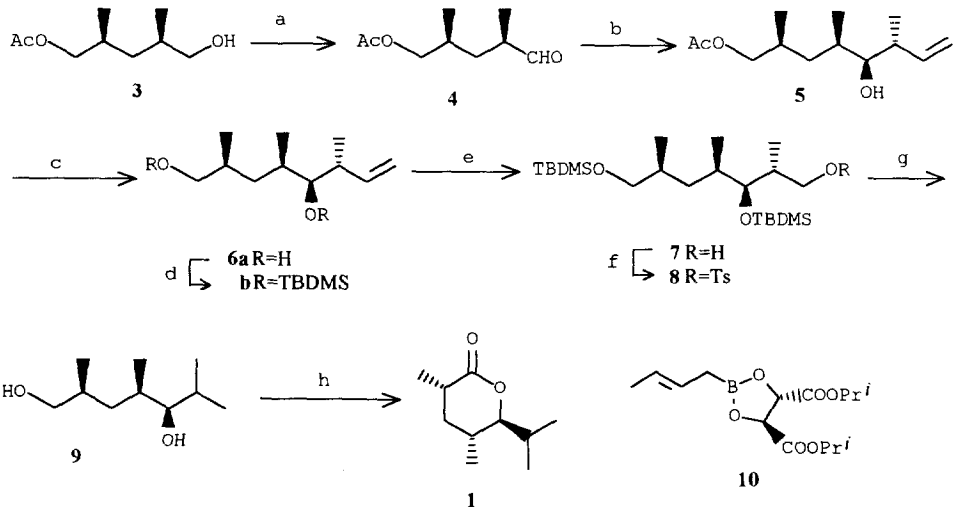
To control the population of European corn borer *Ostrinia nubilalis* Hübner, one of the valuable method is to deploy its natural enemy, the larval parasitoid *Macrocentrus grandii*[1]. Accordingly, the population of *M. grandii* is affected by its courtship behavior, which is related to the recently isolated and determined (3*S*,5*R*,6*S*)-3,5-dimethyl-6-isopropyl-3,4,5,6-tetrahydropyran-2-one (**1**)[2] as the third components of the sex pheromone of *M. grandii*. **1** acts synergistically with another sex pheromone components of female *M. grandii*, to increase the male response. Our particular interest lay in the structural similarity of **1** to the Prelog-Djerassi lactone, a well-known oxidative degradation product of neomethymycin, methymycin, narbomycin, picromycin and a number of microbial macrolide antibiotics[3]. Although some synthetic methods were reported[4], a more convergent and stereoselective synthesis of **1** is desirable. Here we report an efficient synthesis of **1**, in which the stereochemistry at C-3, C-5 and C-6 was controlled.

The retrosynthetic analysis of the target molecule led us to propose the use of the monoacetate **3** as the chiral building block which was anticipated to be accessible by enzymatic resolution. Several articles have been reported about the lipase catalyzed hydrolysis reaction of the C_2-symmetric diesters analogs of compound **2a**[5]. Unfortunately, we found that, in our hands, it is not always convenient to achieve the expected high e.e. of the hydrolyzed compound according to the reported procedures. This led us to turn to the lipase catalyzed acyl transformation of the *meso*-diol **(2b)**. Finally a better procedure was found in which the crude *porcine pancreatic lipase* (purchased from Sigma) was used to effect the enantioselective acetylation of *meso*-diol **(2b)** with vinyl acetate in wet THF. The monoacetate (2*R*,3*S*)-**(3)** was thus obtained in 50% yield and 98% ee[6] together with 20% of the diacetylated side product (Scheme 1).



Scheme 1

Oxidation of **3** with pyridinium dichromate (PDC) provided **4**, which was subjected to the asymmetric Aldol reaction with (*E*)-crotyl-(*S*,*S*)-boronate **(10)**[7] to afford (2*S*,4*R*,5*S*,6*R*)-**5** (d.e. 88%). Basic hydrolysis of **5** gave the diol **(6a)**. The hydroxyl groups of **6a** was protected as *tert*-butyldimethylsilyl ether **(6b)**. Ozonolysis of **6b** followed by reduction with sodium borohydride afforded **7**. The tosylate (**8**) derived from **7** was converted into **9** by the routine $LiAlH_4$ reduction, and by simultaneous deprotection of the silyl group. Oxidative lactonization of **9** with tris(triphenylphosphine) ruthenium(II) chloride and *N*-methylmorpholine *N*-oxide[8] furnished (3*S*,5*R*,6*S*)-**1** (91%, $[\alpha]_D$-24.0, Lit 4a $[\alpha]_D^{20}$-25.0).



Reaction conditions: a): PDC/CH_2Cl_2. b): **10**, toluene, 4Å Ms, -78°C, 75% (two steps). c): K_2CO_3, MeOH/H_2O=2:1, 92%. d): TBDMS-Cl, imidazole, quant. e): CH_2Cl_2/MeOH=5:1, -78°C, O_3, $NaBH_4$, 84%. f): p-TsCl/Py, 90%. g): $LiAlH_4$, Et_2O, ref. 5h, 85%. h): $(Ph_3P)_3RuCl_2$, NMO/acetone, 91%.

Scheme 2

In conclusion, we have developed a new synthetic route to the enantiomerically pure (3*S*,5*R*,6*S*)-**1**. The use of the building block (2*R*,4*S*)-**(3)** and the asymmetric Aldol reaction has been the key to our success.

Experimental Section

^1H NMR spectra were recorded in $CDCl_3$ solution with TMS as internal standard on Bruker AMX-300 spectrometers. Capillary gas chromatographic analysis were performed on a HP 5890 model instrument equipped with CYDEX-B (chiral) (50 m × 0.32 mm). Mass spectra were obtained with HP 5989A model

mass spectrometer with electron impact source. IR spectra were determined on IR-440 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 20°C in $CHCl_3$ unless mentioned else.

All reactions were conducted under dry N_2 atmosphere, using glassware dried at ca. 125°C. Ether, THF were distilled from sodium benzophenone ketyl; CH_2Cl_2, DMF were distillled from CaH_2; pyridine was distilled from NaOH. Other solvents and reagents were dried over 4Å molecular sieves before use. Removal of solvents was accomplished on a rotary evaporator at reduced pressure.

(2*R*, 4*S*)-5-Acetoxy-2, 4-dimethyl-pentanol (3):

To a solution of **2** (120 mg, 0.90 mmol) in 4 mL of THF was added H_2O (5 μl), PPL (350 mg), and vinyl acetate (0.8 mL, 0.75 g, 8.72 mmol). The mixture was stirred at 28°C for 8 h. After filteration and removal of the solvents, the residue was purified by flash column chromatography to gave 62 mg of **3** as a colorless oil. $[\alpha]_D^{20}$ +10.4 (c, 1.2). Lit., $[\alpha]_D$ +9.4 (ee 92%)[5e]. $[\alpha]_D$ +10.6 (the maximal rotation)[5b]. Mosher ester[9] of **3**: t_R=21.69 min. GC condition: The temperature was programmed from 150°C (maintained for 1 min.), then raised to 220°C at a rate of 5°C/min. ^{1}H NMR ($CDCl_3$): δ, 7.51 (m, 2H), 7.40 (m, 3H), 4.23 (dd, *J*=10.8, 5.3 Hz, 1H), 4.05 (dd, *J*=10.7, 6.2 Hz, 1H), 3.90 (dd, *J*=10.8, 5.7 Hz, 1H), 3.80 (dd, *J*=10.8, 6.3 Hz, 1H), 3.55 (s, 3H, OMe), 2.01 (s, 3H), 1.90-1.35 (m, 4H), 0.94 (d, *J*=6.7 Hz, 3H), 0.93 (d, *J*=6.7 Hz, 3H).

(2*R*, 4*S*)-5-Acetoxy-2, 4-dimethyl-pentanal (4):

To a solution of **3** (80 mg, 0.46 mmol) in 5 mL of anhydrous CH_2Cl_2 was added 400 mg of PDC. The mixture was stirred at room temperature for 3 h. Subsequent filtration, concentration and flash column chromatography afforded 70 mg of crude **4** which was used in the next reaction without purification.

(2*S*, 4*R*, 5*S*, 6*R*)-1-Acetoxy-2, 4, 6-trimethyl-oct-7-ene-5-ol (5):

The above crude aldehyde **4** (70 mg, 0.40 mmol) was dissolved in anhydrous toluene (1 mL). This solution was cooled to -78°C and then added dropwise via a cannula to a solution of **10**[10] (0.5 mL, 1.0 M in toluene, 0.5 mmol) in anhydrous toluene (2 mL) and 50 mg of 4Å molecular sieves at -78°C. The resulting mixture was maintained at -78°C for 3 h and then allowed to warm to room temperature gradually. Removal of the solvents afforded a crude residue which was subjected to column chromatography (petroleum ether-AcOEt, 10:1, SiO_2) to give 72 mg of **5** in 75% yield (from **3** over two steps). $[\alpha]_D$ +1.7 (*c* 0.6). t_R=21.14 min, (d.e. 88%). GC condition: The temperature was kept at 90°C for 3 min., then raised to 200°C at a rate of 3°C/min. ^{1}H NMR: δ, 5.70 (ddd, *J*= 17.0, 9.9, 8.0 Hz, 1H), 5.10 (m, 2H), 3.95 (dd, *J*=10.6, 5.4 Hz, 1H), 3.80 (dd, *J*=10.6, 6.9 Hz, 1H), 3.15 (dd, 8.4, 3.1 Hz, 1H), 2.25 (m, 1H), 2.02 (s, 3H), 1.90-1.65 (m, 4H), 0.97 (d, *J*=6.3 Hz, 3H), 0.95 (d, *J*=6.6 Hz, 3H), 0.89 (d, 3H, *J*=6.8 Hz). HRMS: Calcd for $C_{13}H_{24}O_3$: 228.1725; Found 228.1728. IR (film): ν, 3400 (br), 2950, 1710, 1380, 1250 cm^{-1}.

(2*S*, 4*R*, 5*S*, 6*R*)-2, 4, 6-Trimethyl-oct-7-ene-1, 5-diol (6a):

To a solution of **5** (60 mg, 0.26 mmol) in MeOH (1.5 mL) and H_2O (1.0 mL), K_2CO_3 (100 mg, 0.72 mmol) was added. The mixture was stirred at 40°C for 1.5 h. Upon removal of the solvent, the routine work-up gave 52 mg of **6a** in 92% yield. $[\alpha]_D$ -19.5 (*c* 0.2). ^{1}H NMR: δ, 5.70 (ddd, *J*=17.0, 10.0, 8.2 Hz, 1H), 5.12-5.07 (m, 2H), 3.48 (m, 2H), 3.20 (dd, *J*=8.5, 3.0 Hz, 1H), 2.28 (m, 1H), 1.72 (brs, 2H),1.75-1.50 (m, 4H), 0.98 (d, *J*=6.8 Hz, 3H), 0.94 (d, *J*=6.8 Hz, 3H), 0.89 (d, *J*=6.7 Hz, 3H). HRMS for (M+1-H_2O, $C_{11}H_{21}O$) calcd. 169.1592 found 169.1598. IR (film): ν, 3380 (br), 2900, 1460 cm^{-1}.

(2*S*,4*R*, 5*S*, 6*R*)-1, 5-Bis[(*tert*-butyldimethylsilyl)oxy]-2, 4, 6-trimethyl-oct-7-ene (6b):

A solution of the above diol **(6a)** (66 mg, 0.35 mmol) in dry DMF (5 mL) was treated with imidazole (100 mg, 1.47 mmol) and *tert*-butyldimethylsilyl chloride (130 mg, 0.86 mmol) at 0°C. After stirring for 2 h, the reaction mixture was partitioned between 1:1 hexane-Et_2O (15 mL) and brine (15 mL). The aqueous phase was then extracted with 1:1 hexane-Et_2O (3 × 20 mL). The organic extracts were combined and dried over $MgSO_4$. Concentration under reduced pressure furnished a colorless oil that was chromatographed to yield quantitative **6b** (146 mg). $[\alpha]_D^{20}$ +3.7 (*c* 0.3). ^{1}H NMR: δ, 5.70 (ddd, *J*=17.0, 10.0, 8.2 Hz, 1H), 5.10 (m, 2H), 3.48 (dd, *J*=9.7, 5.2 Hz, 1H), 3.38 (dd, *J*=9.6, 6.3 Hz, 1H), 3.18 (dd, *J*=8.4, 3.2 Hz, 1H), 2.30 (m, 1H), 1.85-1.45 (m, 4H), 1.04 (d, *J*=6.7 Hz, 3H), 0.94 (d, *J*=6.6 Hz, 3H), 0.91 (s, 18H), 0.88 (d, *J*=7.2 Hz, 3H), 0.01 (s, 12H). MS (EI): *m/z* (%) 414 (M^+, 0.6), 299 (14.2), 55 (100.0). HRMS: calc. for (M-TBDMS) $C_{17}H_{35}O_2Si$ 299.2406. Found: 299.2441. IR (film): ν, 3080, 2950, 2930, 1640, 1470, 1390, 1250, 1080, 1010 cm^{-1}.

(2*S*,4*R*,5*S*,6*R*)-1, 5-Bis[(*tert*-butyldimethylsilyl)oxy]-2, 4, 6-trimethyl-oct-7-ol (7):

Ozone was bubbled through a stirred and cooled solution of **6b** (70 mg, 0.17 mmol) in CH_2Cl_2-MeOH (5:1, 6 mL) at -78°C until saturation. After flashing off the excess ozone with nitrogen, $NaBH_4$ (30 mg, 0.79 mmol) was added slowly. Then the mixture was gradually raised to room temperature and stirred for 3 h. Water (5 mL) and ether (5 mL) was added. The phases were separated and the aqueous layer was extracted with ether (4 × 20 mL). The organic extracts were combined and washed with brine and dried over $MgSO_4$. The extracts were concentrated and chromatographed to offer 59 mg of 7 (84%). $[\alpha]_D^{20}$ -17.9 (*c* 0.3). ^{1}H NMR: δ, 3.65 (m, 2H), 3.50 (m, 1H), 3.40 (m, 2H), 1.90-1.40 (m, 5H), 1.25 (s, 1H, OH), 0.91 (s, 18H), 0.88 (d, *J*=6.8 Hz), 0.83 (d, *J*=6.6 Hz, 3H), 0.79 (d, *J*=6.9 Hz, 3H), 0.03 (s, 12H). MS(EI): *m/z* (%) 400 (M-H_2O, 0.8), 172 (4.6), 57 (100.0). IR (film): ν, 3450 (br), 2950, 1470, 1390, 1250, 1080, 1010, 990, 830, 775 cm^{-1}.

(2*S*,4*R*,5*S*,6*R*)-1, 5-Bis[(*tert*-butyldimethylsilyl)oxy]-2, 4, 6-trimethyl-oct-7-yl tosylate (8):

p-TsCl (120 mg, 0.63 mmol) was added to a stirred and cooled solution of 7 (90 mg, 0.22 mmol) in dry pyridine (2 mL). The mixture was stirred for 2h at 0-5°C. The mixture was poured into ice-water and extracted with ether (3 × 20 mL). The ethereal solution was subsequently washed with brine, saturated

$CuSO_4$ (aq.) and brine. The residue after routine work-up was chromatographed to give 110 mg of **8** (90%). $[\alpha]_D$ -9.8 (*c* 0.2). ^1H NMR: δ, 7.80 (d, *J*=6.6 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 4.18 (dd, *J*=9.7, 5.2 Hz, 1H), 4.10 (dd, *J*=9.6, 6.3 Hz, 1H), 3.35 (m, 3H), 2.45 (s, 3H), 1.80-1.40 (m, 5H), 0.93 (d, *J*=7.2 Hz, 3H), 0.91 (s, 18H), 0.86 (d, *J*=6.9 Hz, 3H), 0.78 (d, *J*=6.8 Hz, 3H), 0.02 (s, 12H). MS (EI): *m/z* (%) 572 (M+, 4.6), 457 (10.2), 43 (100.0). HRMS: calc. for $C_{29}H_{56}O_5SSi_2$ 572.3387, Found: 572.3362. IR (film): ν, 2980, 1600, 1470, 1360, 1250, 1180, 1090 cm^{-1}.

(2*S*,4*R*,5*R*)-2, 4, 6-Trimethylheptane-1, 5-diol (9):

A solution of **8** (30 mg, 0.05 mmol) in dry ether (2 mL) was added dropwise to a stirred and suspension of $LiAlH_4$ (38 mg, 1 mmol) in dry ether (8 mL) at 0-5°C. The mixture was heated and refluxed for 5 h and then poured into ice water. The ethereal layer was separated and the aqueous layer was saturated with NaCl and extracted with ether. The combined ethereal solution was washed with brine and dried over $MgSO_4$, After concentration, the residue was purified by flash chromatography to give 7.8 mg of **9** (85%). $[\alpha]_D$ -8.9 (*c* 0.3). ^1H NMR: δ, 3.53 (d, *J*=4.5 Hz, 2H), 3.08 (dd, *J*=7.2, 4.5 Hz, 1H), 1.79 (bs, 2H, OH), 1.90-1.60 (m, 5H), 1.26 (m, 1H), 0.97 (d, *J*=6.3 Hz, 3H), 0.93 (d, *J*=6.7 Hz, 3H), 0.89 (d, *J*=6.6 Hz, 3H). MS (EI): *m/z* (%) = 175 (M+1, 0.7), 157 (10.1), 43 (100.0). HRMS: calc. for (M-H_2O) $C_{10}H_{21}O$ 157.1592. Found: 157.1584. IR (film): ν, 3350, 1470, 1090, 990 cm^{-1}.

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

To a solution of the above diol-**9** (18 mg, 0.10 mmol) in dry acetone (2 mL) was added tris(triphenylphosphine) ruthenium (II) chloride (10 mg, 10 μmol) and of *N*-methylmorpholine *N*-oxide (50 mg, 0.43 mmol). The mixture was stirred at room temperature for 5 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (5 mL) and washed with 1 N HCl, water, dried over $MgSO_4$, The residue after concentration was chromatographed to give 16 mg (91%) of the (3*S*,5*R*,6*S*)-**1**. $[\alpha]_D$ -24.0 (*c* 0.2), Lit 4a: $[\alpha]_D^{20}$ -25.0 (*c* 0.2, $CHCl_3$). t_R=16.45 min. GC condition: The temperature was kept at 90°C for 3 min., then raised to 200°C at a rate of 3°C/min. ^1H NMR: δ, 3.84 (dd, *J*=10.2, 1.7 Hz, 1H), 2.48 (dq, *J*=11.5, 6.6, 6.0 Hz, 1H), 1.90 (ddd, *J*=7.0, 7.0, 1.9 Hz, 1H),1.92-1.80 (m, 2H), 1.31 (ddd, *J*=12.0, 11.0, 11.1Hz, 1H), 1.28 (d, *J*=7.1 Hz, 3H), 1.08 (d, *J*=7.0 Hz, 3H), 0.97 (d, *J*=6.8 Hz, 3H), 0.90 (d, *J*=6.8 Hz, 3H). MS (EI): *m/z* (%) = 170 (M^+, 0.3), 127 (64.2), 43 (100.0). HRMS: calc. for (M-$C_3H_7^+$) $C_7H_{11}O_2$ 127.0759. Found: 127.0743. IR (film): ν, 2950, 1725, 1010 cm^{-1}.

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