Supporting Information
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Supporting Information

Stereoselective Total Syntheses of Insect Juvenile Hormones, JH 0 and JH I

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General Information

All reagents and solvents were purchased from Sigma-Aldrich, Nacalai Tesque or Tokyo Chemical Industry, and used without further purification unless otherwise indicated. Solvents of anhydrous grade were used without distillation. All reactions were generally monitored by thin layer chromatography using 0.25 mm E. Merck silica gel plates (60F-254). Visualization was accomplished by irradiation with a UV lamp (254 nm) and/or a charring solution of ethanoic phosphomolybdic acid or KMnO₄aq. Flash column chromatography was performed with the indicated solvents and silica gel, Daisogel IR-60 1002W (particle size 0.040-0.063 mm). Yields refer to chromatographically pure compounds and spectroscopically pure compounds, except as otherwise indicated. Optical rotations ([α]D) were taken using a JASCO P-1030 polarimeter with a sodium lamp (D line). The FTIR spectra were measured by a JASCO FT/IR-420 infrared spectrophotometer. ¹H NMR spectra were recorded by either a JEOL JNM-LA 300 (300 MHz), Brucker BioSpin AVANCE III Nanobay (300 MHz) or JEOL JNM-LA 400 (400 MHz). Chemical shifts of the ¹H NMR were reported in parts per million (ppm, δ) relative to the residual solvent peak in CDCl₃ (δ = 7.26). The ¹³C NMR spectra were recorded by a Brucker BioSpin AVANCE III Nanobay (75 MHz) or a JEOL JNM-LA 400 (100 MHz). The chemical shifts of the ¹³C NMR were reported in ppm (δ) relative to CDCl₃ (δ = 77.0). Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were obtained using a JEOL JMX-AX500 for fast atom bombardment ionization (FAB) and chemical ionization (CI).

[1] General Procedure for the synthesis of (Z)-vinyl tosylate:

To a mixture of a β-ketoester (1.0 equiv) in CH₂Cl₂ (0.1 M), LiCl (5.0 equiv) and TsCl (1.5 equiv), N-methylimidazole (1.5 equiv), and Et₃N (1.5 equiv) were successively added at 0 °C under argon. The mixture was stirred at 0 °C and warmed to room temperature for 3 h. sat. NH₄Cl was added to the mixture. The mixture was extracted with AcOEt (x2). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give the product.


To a suspension of LiAlH₄ (1.0 equiv) in Et₂O (0.5 M) was slowly added a solution of the ester (1.0 equiv) in Et₂O at -40 °C. The mixture was stirred for 2h and quenched with a small amount
of cool water, anhydrous MgSO₄, and filtered. The filtrate was concentrated in vacuo to give the crude allyl alcohol, which was subjected to the next reaction without further purification. To a mixture of the crude alcohol in CH₂Cl₂ (0.5 M), CBr₄ (1.3 equiv) and PPh₃ (1.5 equiv) were successively added at 0 °C. The mixture was stirred at 0 °C for 30 min. The insoluble material was filtered. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give the product.

[3] General Procedure for the alkylation of the allyl bromide derivatives

To a solution of sodium hydride (ca 60% oil suspension, 3.0 equiv) in THF (0.1 M), methyl acetoacetate (3.0 equiv) was added dropwise under argon at 0 °C. The mixture was stirred for 20 min. n-Butyl lithium (2.6 M hexane solution, 3.0 equiv) was added to the mixture at 0 °C. The mixture was stirred for 20 min. The allyl bromide (1.0 equiv) synthesized above was added to the mixture. The mixture was stirred at 0 °C for 1 h, quenched with sat. NH₄Cl, and extracted with AcOEt (x2). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give the product.


To a suspension of PdCl₂(PPh₃)₂ (5 mol%) and the tosylate (1.0 equiv) prepared above in THF (0.1 M) was added R₂Zn (R = Me or Et) in hexane (2.0 equiv) at 0 °C under argon. The mixture was stirred at room temperature for 3 h, quenched with sat. NH₄Cl, and extracted with AcOEt (x2). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give the product.

Synthetic procedure for the optically active JH 0 and JH 1

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\begin{align*}
\text{(Z)-4-bromobut-2-en-2-yl 4-methylbenzenesulfonate (15)}
\end{align*}
\]

According to the general procedure [2], enol tosylate 24 (2.7 g, 10 mmol) was reduced with LiAlH₄ (380 mg, 10 mmol). The resulting crude alcohol was brominated with CBr₄ (4.31 g, 13 mmol) and PPh₃ (3.93 g, 15 mmol) to afford 15 (1.8 g, 60%, 2 step) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, J = 8.8 Hz, 2 H), 7.38 (d, J = 8.8 Hz, 2 H), 5.36 (t, J = 8.0 Hz, 1 H), 3.77 (d, J = 8.0 Hz, 2 H), 2.46 (s, 3 H), 2.01 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.7, 145.5, 133.3, 129.9, 127.9, 116.5, 24.6, 21.7, 20.4; IR (neat) 1684, 1601, 1367, 1186, 1099, 923, 821, 733, 677
(E)-4-bromobut-2-en-2-yl 4-methylbenzenesulfonate (16)

According to the general procedure [2], 239 (22.6 g, 83.8 mmol) was reduced by LiAlH₄ (3.18 g, 83.8 mmol). The resulting crude alcohol was brominated using CBr₄ (22.2 g, 87.2 mmol) and PPh₃ (26.4 g, 101 mmol) to afford 16 (15.31 g, 60%, 2 step) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, J = 8.4 Hz, 2 H), 7.35 (d, J = 8.4 Hz, 2 H), 5.39 (t, J = 8.0 Hz, 1 H), 3.83 (d, J = 8.0 Hz, 2 H), 2.45 (s, 3 H), 1.90 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 150.2, 145.5, 132.7, 129.8, 128.3, 117.0, 25.9, 21.6, 16.2; IR (neat) 2360, 1735, 1454, 1371, 1090, 1001, 897, 829, 738, 662 cm⁻¹; HRMS (Cl) m/z calcd for C₁₁H₁₄BrO₃S (M+H)+ , 306.9827, found 306.9826.

 OTs

(Z)-methyl 3-oxo-7-(tosyloxy)oct-6-enoate (17)

According to the general procedure [3], 15 (1.79 g, 5.89 mmol) was subjected to the alkylation reaction using 14 (1.0 mL, 8.83 mmol), NaH (ca 60% oil suspension, 353 mg, 8.83 mmol), and n-butyllithium (2.6 M, 3.4 mL, 8.83 mmol) to afford 17 (1.56 g, 78%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, J = 8.4 Hz, 2 H), 7.35 (d, J = 8.4 Hz, 2 H), 5.04 (t, J = 7.2 Hz, 1 H), 3.73 (s, 3 H), 3.40 (s, 2 H), 2.49 (t, J = 7.2 Hz, 2 H), 2.46 (s, 3 H), 2.17 (q, J = 7.2 Hz, 2 H), 1.89 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 201.4, 167.3, 145.0, 144.9, 133.7, 129.7, 127.7, 118.2, 52.1, 48.5, 41.6, 21.4, 20.0, 19.5; IR (neat) 3041, 1787, 1709, 1572, 1454, 1371, 1305, 1248, 1165, 1099, 909, 739, 579 cm⁻¹; HRMS (Cl) m/z calcd for C₁₆H₂₁O₆S (M+H)+ 341.1059, found 341.1055.

(E)-methyl 3-oxo-7-(tosyloxy)oct-6-enoate (18)

According to the general procedure [3], 16 (15.2 g, 50.1 mmol) was subjected to the alkylation reaction using 14 (17.1 mL, 150 mmol), NaH (ca 60% oil suspension, 6 g, 150 mmol), and n-butyllithium (2.6 M, 57.8 mL, 150 mmol) to afford 18 (13.5 g, 79%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, J = 8.0 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 4.99 (t, J = 7.4 Hz, 1 H), 3.70 (s, 3 H), 3.38 (s, 2 H), 2.50 (t, J = 7.4 Hz, 2 H), 2.42 (s, 3 H), 2.17 (q, J = 7.4 Hz, 2 H), 1.79 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 201.1, 167.3, 146.3, 144.9, 133.2, 129.6, 128.2, 118.8, 52.3, 48.9, 41.8, 21.5, 20.1, 15.9; IR (neat) 2956, 2369, 2336, 1748, 1718, 1599, 1440, 1366, 1180, 1089, 753 cm⁻¹; HRMS (FAB) m/z calcd for C₁₆H₂₁O₆S (M+H)+ 341.1059, found 341.1057.
(2Z,6Z)-methyl 3,7-bis(tosyloxy)octa-2,6-dienoate (19)

According to the general procedure [1], 17 (1.56 g, 5 mmol) was reacted with LiCl (1.27 g, 25 mmol), TsCl (1.41 g, 7.5 mmol), N-methylimidazole (0.59 mL, 7.5 mmol), and Et$_3$N (1.05 mL, 7.5 mmol) to afford 19 (1.6 g, 65%) as yellow powder. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.89 (d, $J = 8.3$ Hz, 2 H), 7.82 (d, $J = 8.3$ Hz, 2 H), 7.35 (d, $J = 8.3$ Hz, 4 H), 5.41 (s, 1 H), 4.92 (t, $J = 7.3$ Hz, 1 H), 3.50 (s, 3 H), 2.45 (s, 6 H), 2.29 (t, $J = 7.3$ Hz, 2 H), 2.05 (q, $J = 7.3$ Hz, 2 H), 1.90 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.2, 158.6, 145.7, 145.5, 145.2, 133.8, 133.2, 129.8, 129.6, 129.5, 128.3, 117.4, 110.3, 51.4, 34.1, 22.3, 21.6, 21.5, 20.2; IR (neat) 2937, 2360, 1730, 1684, 1367, 1182, 901, 756 cm$^{-1}$; HRMS (FAB) $m/z$ calcd for C$_{23}$H$_{27}$O$_8$S$_2$ (M+H)$^+$ 495.1147, found 495.1152.

(2Z,6E)-methyl 3,7-bis(tosyloxy)octa-2,6-dienoate (20)

According to the general procedure [1], 18 (13.5 g, 39.7 mmol) was reacted with LiCl (8.4 g, 59.5 mmol), TsCl (11.4 g, 59.5 mmol), N-methylimidazole (4.72 mL, 59.5 mmol) and Et$_3$N (8.29 mL, 59.5 mmol) to afford 20 (13.8 g, 70%) as yellow powder. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.85 (d, $J = 8.3$ Hz, 2 H), 7.73 (d, $J = 8.3$ Hz, 2 H), 7.34 (d, $J = 8.3$ Hz, 2 H), 7.30 (d, $J = 8.3$ Hz, 2 H), 5.43 (s, 1 H), 4.95 (t, $J = 7.4$ Hz, 1 H), 3.55 (s, 3 H), 2.43 (s, 3 H), 2.42 (s, 3 H), 2.33 (t, $J = 7.4$ Hz, 2 H), 2.15 (q, $J = 7.4$ Hz, 2 H), 1.76 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.0, 158.0, 146.8, 145.6, 145.0, 133.1, 133.0, 129.6, 129.6, 128.3, 128.1, 118.0, 110.1, 51.3, 34.6, 23.4, 21.6, 21.5, 15.9; IR (neat) 2952, 2356, 1733, 1674, 1368, 1177, 761 cm$^{-1}$; HRMS (FAB) $m/z$ calcd for C$_{23}$H$_{27}$O$_8$S$_2$ (M+H)$^+$ 495.1147, found 495.1154.

(2E,6Z)-methyl 3-ethyl-7-methylnona-2,6-dienoate (29)

According to the general procedure [4], the Negishi coupling of 19 (500 mg, 1.01 mmol) was conducted using 1.0 M solution of Et$_2$Zn in hexane (4.05 mL, 4.05 mmol) in the presence of Pd$_2$(dba)$_3$ (31.5 mg, 0.03 mmol) and CyPF-t-Bu (67.3 mg, 0.06 mmol) in DMF (10 mL) under argon at 50 °C for 23 h. After the workup, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 100 : 1) to give 29 (179 mg, 84%) as yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.62 (s, 1 H), 5.06 (brs, 1 H), 3.69 (s, 3 H), 2.62 (q, $J = 7.6$ Hz, 2 H), 2.14-2.17 (m, 4 H), 2.02 (q, $J = 7.6$ Hz, 2 H), 1.68 (s, 3 H), 1.07 (t, $J = 7.6$ Hz, 3 H), 0.96 (t, $J = 7.6$ Hz, 3 H).
According to the general procedure [4], the Negishi coupling reaction of 20 (500 mg, 1.01 mmol) was conducted using 1.0 M solution of Et₂Zn in hexane (4.05 mL, 4.05 mmol) in the presence of Pd₂(db₃)(31.5 mg, 0.03 mmol) and CyPF-Bu (67.3 mg, 0.06 mmol) in DMF (10 mL) under argon at 50 °C for 23 h. After the work up, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 100 : 1) to give 30 (179 mg, 84%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.62 (s, 1 H), 5.09 (brs, 1 H), 3.68 (s, 3 H), 2.62 (q, J = 7.6 Hz, 2 H), 2.18-2.15 (m, 4 H), 1.98 (q, J = 7.6 Hz, 2 H), 1.60 (s, 3 H), 1.07 (t, J = 7.6 Hz, 3 H), 0.98 (t, J = 7.6 Hz, 3 H)

(E)-methyl 3-ethyl-5-((2R,3S)-3-ethyl-3-methyloxiran-2-yl)pent-2-enoate

The a solution of AD-mix-α (2.86 g), and MeSO₂NH₂ (195 mg, 2.05 mmol) in t-BuOH-H₂O (1 : 1, 20 mL) was vigorously stirred at 0 °C for 30 min. To the mixture was added 32 (438 mg, 2.05 mmol). The mixture was stirred at room temperature for 16 h, quenched with Na₂SO₃ (3.07 g), and extracted with AcOEt (x2). The combined organic layers were washed with 1N KOH, dried over anhydrous MgSO₄ and filtered. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 30 : 1) to give 31 (490 mg, 96%) as yellow oil. To a solution of 33 (484 mg, 1.98 mmol) and pyridine (3.21 mL, 39.6 mmol) in CH₂Cl₂ (19.8 mL) was added MsCl (1.15 mL, 14.87 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h, quenched with sat. NH₄Cl, and extracted with AcOEt (x2). The combined organic layers were washed with aq. CuSO₄, and sat. NaHCO₃, dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated in vacuo to give the corresponding mesylate, which was subjected to the next epoxidation reaction without further purification. To a solution of the crude mesylate in MeOH (20 mL) was added K₂CO₃ (2.74 g, 19.8 mmol). The mixture was stirred at room temperature for 1 h, diluted with water and AcOEt, and extracted. The organic layer was washed with brine, dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated in vacuo to give the titled compound (413 mg, 92%, 2 step) as colorless oil. [α]¹⁸D = + 14.4 (c = 1.0 in CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 5.65 (s, 1 H), 3.68 (s, 3 H), 2.73 (dd, J = 7.3, 6.6 Hz, 1 H), 2.65 (q, J = 7.3 Hz, 2 H), 2.38-2.33 (m, 2 H), 1.77-1.45 (m, 4 H), 1.09 (t, J = 7.3 Hz, 3 H), 1.00 (t, J = 7.6 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 166.7, 164.8, 114.8, 64.0, 61.9, 50.8, 34.7, 26.7, 25.8, 25.3, 21.5, 12.9, 9.6; IR (neat) 2974, 1718, 1645, 1461, 1434, 1312, 1210, 1150, 1029, 803, 757 cm⁻¹; HRMS (CI) m/z calc
for C$_{13}$H$_{22}$O$_3$ (M+H)$^+$ 226.1596, found 227.1646.

(10R)-JH 0 (1)

According to the homologation sequence procedure [1]--[4], the total synthesis of JH 0 (1) was achieved [pale yellow oil, 16.5 mg (27%) from 32]. The analytical data of synthetic 1 shown in ref. 14 was identical with those of authentic data. $^5c$

(10R)-JH 1 (2)

According to the homologation sequence procedure [1]--[4], the total synthesis of JH 1 (2) was achieved [yellow oil, 19 mg (27%) from 32]. The analytical data of 2 shown in ref. 15 was identical with those of the authentic data. $^5a,d$ Selected nOe data of 2 confirmed the stereochemical outcomes of the homologation sequence.

Selected NOE correlations of JH 1 (2)