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

Atsushi Manabe, Yasufumi Ohfune,* Tetsuro Shinada*

Graduate School of Science, Osaka City University, Sugimoto, Sumiyoshi, Osaka 558-8585, Japan
Fax +81(6)66053153; E-mail: shinada@sci.osaka-cu.ac.jp; E-mail: ohfune@sci.osaka-cu.ac.jp

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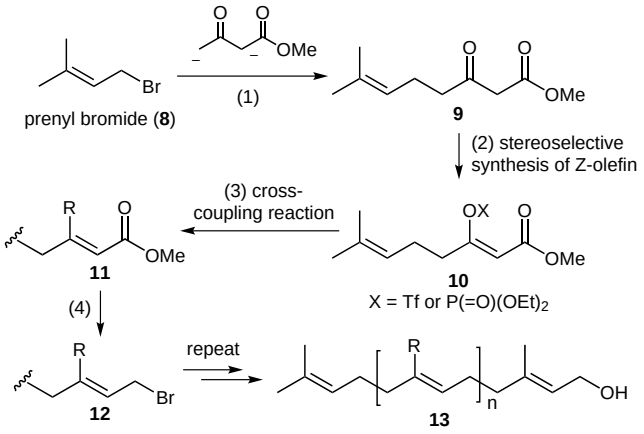
Abstract: Total syntheses of juvenile hormones JH 0 and JH I have been achieved by a new iterative enol tosylate homologation strategy.

Key words: juvenile hormone, acyclic terpenoid, enol tosylate, Negishi coupling reaction

Juvenile hormone (JH) is a key hormone that regulates an insect's life cycle.[1] The presence of JH in insects was first reported by Wigglesworth.[2] Since then, many efforts have been made for the structure determination of JH. The first structure determination was achieved by Röller and Trost in 1967.[3] The JH isolated from the robin moth, *Hyalophora cecropia*, was labeled as JH I. To date, several JH structures have been elucidated (Figure 1).[4] Among them, JH 0 (**1**), JH I (**2**), JH II (**3**), and 4-Me-JH I (**5**) are known to be unusual sesquiterpenoid congeners in which the methyl group(s) on the acyclic framework are substituted with ethyl group(s). These unusual structural features as well as their intriguing biological activities have received significant interests from the synthetic communities. Extensive synthetic reports have been documented for the total syntheses of these natural products focusing on the stereoselective construction of the unusual ethyl-group-containing terpene structure[5] as well as the chiral trisubstituted epoxide[5a–e,6] in which the 10*R*,11*S* stereocenters play a crucial role in the juvenilizing effects.[7] Although several total syntheses of **1**–**3** have been reported, the efficient total synthesis of the optically active **1**–**3** still remains a challenging synthetic task. We now report the total synthesis of JH 0 (**1**) and JH I (**2**) in an optically active form by the iterative enol tosylate homologation strategy.

Recently, the stereoselective syntheses of acyclic terpene derivatives by the vinyl triflate and vinyl phosphate mediated strategies have been reported (Scheme 1).[8] These approaches consisted of a series of the following sequential transformations: (1) alkylation of acetylacetate with a commercially available halide such as prenyl bromide (**8**) to give the β-keto ester **9**, (2) *Z*-selective conversion into vinyl triflate or vinyl phosphate **10**, (3) cross-coupling reaction of **10** to install the side chain, and (4) conversion of the resulting coupling product into an allyl bromide **12**. These synthetic methods are characterized by the stereocontrolled synthesis of the trisubstituted olefin via the stereochemically defined steps (2) and (3) under mild reaction conditions.



Scheme 1 Previous homologation sequence for the access to acyclic terpenoid analogues

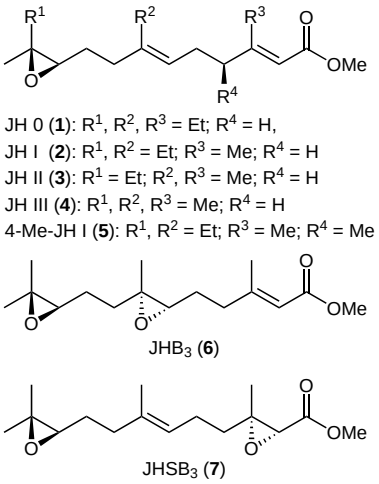


Figure 1 Structures of juvenile hormones

We assumed that JH 0 (**1**) and JH I (**2**) could be accessed by the above synthetic strategy starting from the known allyl bromide **A** or **B** (Scheme 2). However, these bromides are known to be volatile compounds and must be prepared in large quantities via rectification accompanying the separation of the olefin geometric mixture.[9] We postulated that these practical inconveniences could be solved by the outset of the unprecedented (*Z*)-1-bromo-3-tosyloxy-2-buten (**15**) and its *E*-isomer **16** as a surrogate of the allyl bromides. These tosylates would be much less volatile than **A** and **B**. Moreover, it is expected that **15** and

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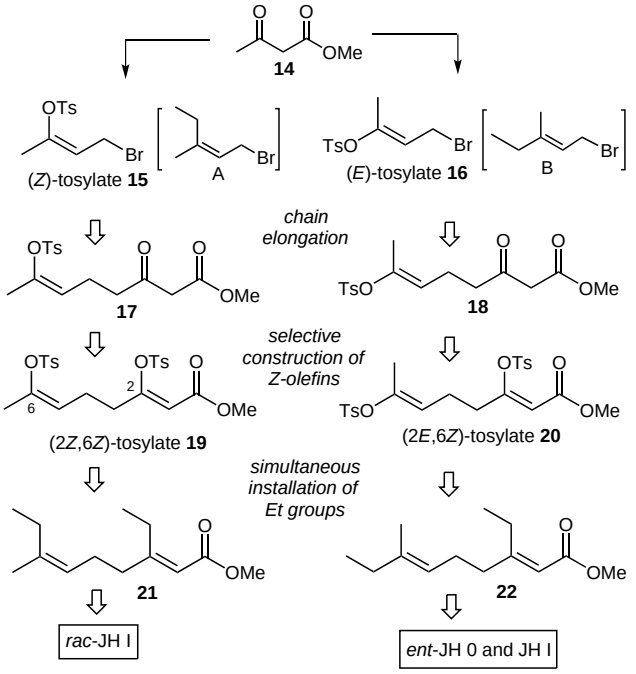
16 could be a versatile synthon in organic synthesis, while the syntheses and their synthetic potentials have not yet been examined. In this context, we planned a new homologation sequence using the allyl bromides **15** and **16** (Scheme 2). These bromides could be transformed into the bistosylates **19** and **20**, respectively, to test the double Negishi cross-coupling to access the common intermediates **21** and **22** of the racemic or optically active JH 0 (**1**) and JH I (**2**), respectively. The simultaneous side-chain installation to **19** is more efficient than the previous homologation methods in which the side chain was embedded one by one.

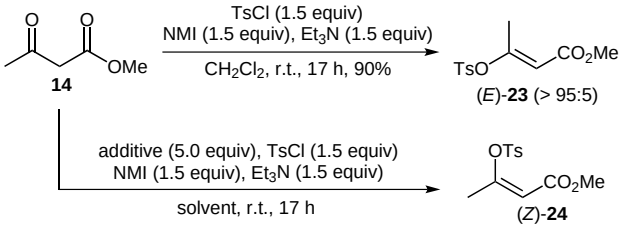


Scheme 2 New synthetic strategy for the stereoselective total syntheses of JH 0 and JH I

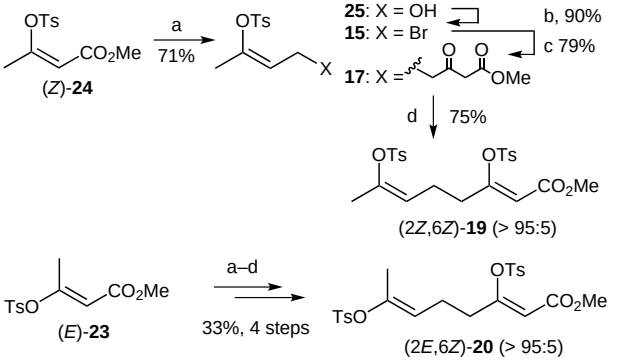
The syntheses of **15** and **16** were initially investigated. According to the previous reports on the stereoselective synthesis of the (*E*)- or (*Z*)-vinyl tosylate,[8a,10] triflate,[11] and phosphonate,[8b] (*Z*)-**24**[10] was synthesized from **14** on a 1 mmol scale in a stereoselective manner (Table 1, entry 1). On the other hand, the large-scale synthesis under the same conditions (LiOH, NMI, toluene) failed due to the provable insolubility of LiOH in toluene (Table 1, entry 2). The practical problem was solved by the adaptation of the modified reaction conditions using LiCl in CH_2Cl_2 to give (*Z*)-**24** with a satisfactory reproducibility and product yield (Table 1, entries 3 and 4). The geometrical isomer (*E*)-**23** was prepared in the absence of LiCl.[10]

The reduction of (*Z*)-**24** to **25** followed by the bromination reaction smoothly proceeded to give the nonvolatile **15** in 90% yield that was purified by silica gel column chromatography. The bromide **15** was subjected to the acyclic chain-elongation reaction using the corresponding enolate of **14** to provide **17** in 79% yield. The resulting β-keto ester **17** was iteratively subjected to the stereoselective tosylation reaction to provide the (2*Z*,6*Z*)-enol tosylate **19** (>95:5).[12] In a similar manner, the (2*Z*,6*E*)-enol tosylate **20** was prepared from (*E*)-**23** (Scheme 3)[11] These results confirmed that the enol tosylates **19** and **23** were compatible under the homologation reaction sequence.

Table 1 Synthesis of (*E*)- and (*Z*)-Enol Tosylates **23** and **24**



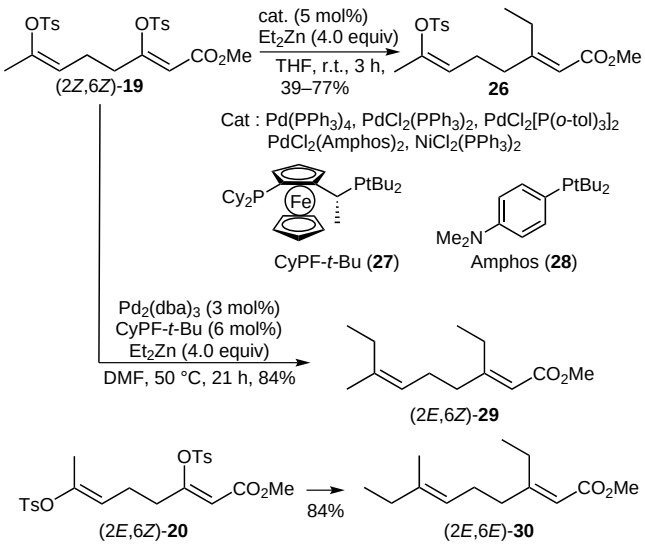
Entry	Additive	Solvent	Scale (mmol)	Yield (%)	*Z*/*E*
1	LiOH	toluene	1	84	94:6
2	LiOH	toluene	10	14	75:25
3	LiCl	CH_2Cl_2	10	95	>95:5
4	LiCl	CH_2Cl_2	100	93	>95:5



Scheme 3 Stereoselective synthesis of dienol tosylates **19** and **20**. *Reagents and conditions*: (a) $LiAlH_4$ (1.0 equiv), Et_2O, –40 °C to 0 °C, 2 h; (b) CBr_4 (1.3 equiv), Ph_3P (1.5 equiv), CH_2Cl_2, 0 °C, 30 min; (c) methyl acetylacetate (3.0 equiv), NaH (3.0 equiv), *n*-BuLi (3.0 equiv), THF, 0 °C, 1 h; (d) LiCl (5.0 equiv), TsCl (1.5 equiv), NMI (1.5 equiv), Et_3N (1.5 equiv), CH_2Cl_2, r.t., 3 h.

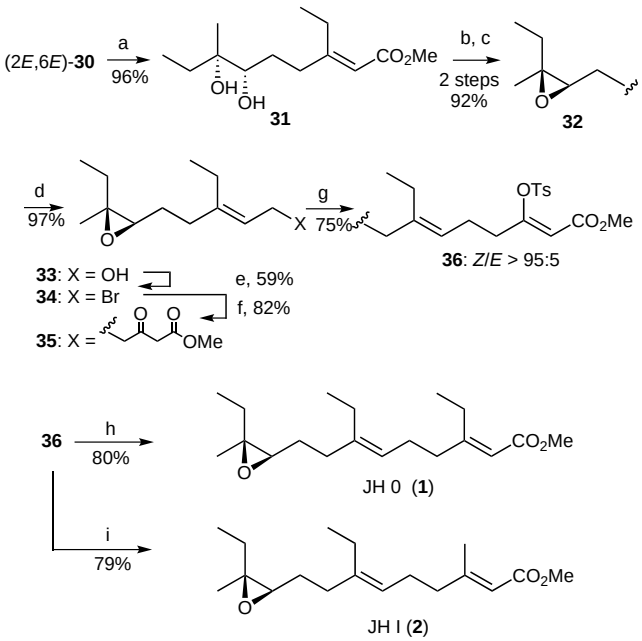
The installation of the ethyl groups by the Negishi cross-coupling reaction of **19** was attempted using 5 mol% of $Pd(PPh_3)_4$ and Et_2Zn to provide the monoethyl product **26** as a single stereoisomer. The coupling reactions using other catalysts and ligands resulted in recovery of the stating material or predominant formation of **26**. These results indicated that the simple enol tosylate is less reactive than that of the β-tosyloxy-α,β-unsaturated ester such as **24**.[13] Skrydstrup et al. showed that the ligand **27** accelerated the Negishi coupling reaction of the simple enol tosylate.[13a] Thus, the double cross-coupling reaction was attempted under the reported reaction conditions [1 mol% $Pd_2(dba)_3$, 2 mol% ligand **27**, THF] to give the desired **29** in 5% yield along with **26** as the major product. To improve the product yield, the solvents and catalyst loading

[the ratio of $Pd_2(dba)_3$/ligand **27**] were reinvestigated. As a result, this process was improved under the reaction conditions using twice the amount of the ligand **27** (6 mol%) to the $Pd_2(dba)_3$ (3 mol%) in DMF at 50 °C to furnish the double cross-coupling product (2*E*,6*Z*)-**29** in 84% yield. Under the same reaction conditions, **20** was converted into (2*E*,6*E*)-**30** in 84% yield (Scheme 4). Compounds (2*E*,6*Z*)-**29** and (2*E*,6*E*)-**30**, and the corresponding allyl alcohols are known to be the synthetic precursors of *rac*- and *ent*-JH 0 and JH I, respectively.[5a–h] These results imply that the total formal syntheses of *rac*- and *ent*-JH I have been established by the present homologation sequence.[13]



Scheme 4 Synthesis of key intermediates **29** and **30** for the synthesis of *rac*- and *ent*-JH I

We next attempted the total syntheses of the optically active JH 0 (**1**) and JH I (**2**) from (2*E*,6*E*)-**30** (Scheme 5). The key to these asymmetric syntheses relied on the construction of the chiral epoxide moiety. To this end, the Sharpless catalytic dihydroxylation reaction,[5a] the diastereoselective alkylation and carbonyl reduction of an optically pure β-keto sulfoxide,[5b] and the enantioselective reduction of 2-ethyl-2-methyl-1,3-cyclohexanedione by yeast as the key steps have been developed.[5c–e] Among them, we selected the Sharpless dihydroxylation reaction as the key reaction in this study.[5a,c–e] In the previous synthetic routes, the Sharpless dihydroxylation reaction was performed after the construction of the sesquiterpenoid skeletons of JH I and JH 0. In these cases, the dihydroxylation reaction competitively took place at both the C6,7 and C10,11 olefins to give a mixture of the corresponding diols.[4a,5a] We expected that this drawback could be overcome by taking advantage of the present homologation approach (Scheme 5). The chiral epoxide moiety was initially installed into (2*E*,6*E*)-**30** prior to the next homologation step. In this substrate, the high regioselectivity at C6,7 was expected due to its electronically richer property than that of the C2,3 olefin. In fact, the dihydroxylation proceeded in a highly regio- and stereoselective manner to provide the 6,7-diol **31**[14] that was converted into the chiral epoxide **32** via the S_N2 inversion reaction of the corresponding secondary mesylate. The chiral epoxide **32** was subjected to the homologation sequence to provide the (2*Z*)-enol tosylate **36** in four steps. The Negishi cross-coupling reaction using Et_2Zn or Me_2Zn smoothly proceeded to give JH 0 (**1**)[15] or JH I (**2**)[16] in their optically active forms. The analytical data of the synthetic JH 0 and JH I were identical to those of the authentic data (Supporting Information).[5a,d]



Scheme 5 Total synthesis of *ent*-JH 0 (**1**) and JHI (**2**). *Reagents and conditions*: (a) AD-mix α, $MeSO_2NH_2$ (1.0 equiv), *t*-BuOH–H_2O (1:1), 0 °C to r.t., 16 h, 96%; (b) 1) MsCl (7.5 equiv), pyridine (20 equiv), CH_2Cl_2, 0 °C to r.t., 4 h; 2) K_2CO_3 (10 equiv), MeOH, r.t., 1.5 h; (c) $LiAlH_4$ (1.0 equiv), Et_2O, –40 °C to 0 °C, 2 h; (d) CBr_4 (1.3 equiv), polymer-bound Ph_3P (1.5 equiv), imidazole (1.3 equiv), CH_2Cl_2, 0 °C, 30 min; (f) **14** (3.0 equiv), NaH (3.0 equiv), *n*-BuLi (3.0 equiv), THF, 0 °C, 1 h; (g) LiCl (5.0 equiv), TsCl (1.5 equiv), NMI (1.5 equiv), Et_3N (1.5 equiv), CH_2Cl_2, r.t., 3 h; (h) Et_2Zn (2 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), THF, r.t., 3 h, 80%; (i) Me_2Zn (2 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), THF, r.t., 3 h, 79%.

In this study, we have established an efficient and convergent synthetic route to access JH 0 and JH I. The new homologation reaction sequence is advantageous for not only the synthesis of natural JH but also for their analogues. Further applications of the new homologation strategy for the synthesis of various acyclic terpene derivatives are now in progress.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) (*Z*)-**24** was transformed into the corresponding bromide **A** by a series of sequential transformations: i) the Negishi cross-coupling reaction of with Et_2Zn in the presence of 10 mol% of $Pd(PPh_3)_4$, ii) reduction to the corresponding allylic alcohol, and iii) bromination to the allyl borimide **A**. However, it was found to be volatile and easily evaporated under the reduced pressure to lower the product yield (ca. 30%).

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(12) The olefin geometry was confirmed by NOE experiments of the synthetic JH 0 and JH I (see Supporting Information).

(13) The use of the unactivated enol tosylate in the cross-coupling reaction has been discussed, see: (a) Lindhardt, A. T.; Gøgsig, T. M.; Skrydstrup, T. *J. Org. Chem.* **2009**, *74*, 135. (b) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364. (c) Gelman, D.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2003**, *115*, 6175.

(14) The optical purity was confirmed by the total synthesis of JH 0 and JH I, and comparison of the optical rotations of the synthetic natural products with those of authentic data shown in below.

(15) **Analytical Data of JH 0 (1):** $[\alpha]_D^{18}$ +13.4 (*c* 0.8, MeOH) [lit.[5d] $[\alpha]_D$ + 13.8 (*c* 0.92, MeOH)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.61 (s, 1 H), 5.10 (br, 1 H), 3.68 (s, 3 H), 2.71 (dd, *J* = 6.6, 5.6 Hz, 1 H), 2.18–2.03 (m, 10 H), 1.63–1.48 (m, 4 H), 1.27 (s, 3 H), 1.07 (t, *J* = 7.6 Hz, 3 H), 1.00 (t, *J* = 7.6 Hz, 3 H), 0.96 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 165.7, 141.2, 123.1, 114.5, 64.6, 61.8, 50.7, 38.1, 33.3, 27.2, 25.8, 25.7, 25.3, 23.2, 21.6, 13.1, 12.9, 9.6. IR (neat): 2970, 2353, 1720, 1644, 1461, 1209, 1149, 761 cm^{-1}. HRMS–FAB: *m*/*z* calcd for $C_{19}H_{33}O_3$ $[M + H]^+$: 309.2430; found: 309.2421.

(16) **Analytical Data of JH I (2):** $[\alpha]_D^{18}$ +14.4 (*c* 0.98, MeOH) [lit.[5a,e] $[\alpha]_D^{22.5}$ +14.5 (*c* 0.78, MeOH)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.66 (d, *J* = 0.6 Hz 1 H), 5.08 (t, *J* = 6.3 Hz, 1 H), 3.68 (s, 3 H), 2.71 (dd, *J* = 7.2, 6.0 Hz, 1 H), 2.18–2.03 (m, 8 H), 2.16 (d, *J* = 0.6 Hz, 3 H), 1.63–1.48 (m, 4 H), 1.27 (s, 3 H), 0.99 (t, *J* = 7.2 Hz 3 H), 0.97 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 159.9, 141.3, 122.9, 115.3, 64.6, 61.8, 50.8, 41.1, 33.3, 27.2, 25.8, 25.6, 23.1, 21.6, 18.8, 13.1, 9.7. IR (neat): 2968, 2360, 1720, 1650, 1457, 1125, 1149, 770 cm^{-1}. HRMS–FAB: *m*/*z* calcd for $C_{18}H_{31}O_3$ $[M + H]^+$: 295.2273; found: 295.2270.

