Tetrahedron Letters 52 (2011) 2302–2305

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Oxygen-containing analogues of juvenile hormone III

Katherine A. Davies, Kevin G. M. Kou, Jeremy E. Wulff *

Department of Chemistry, University of Victoria, Victoria, British Columbia, Canada V8W 3V6

ARTICLE INFO

Article history:
Received 8 November 2010
Accepted 25 January 2011
Available online 15 March 2011

Keywords:
Juvenile hormones
Structural analogues
Claisen rearrangement
Iterative synthesis
Vinyl ethers

ABSTRACT

Juvenile hormone III (JH-III) controls several aspects of insect development, and analogues of JH-III are widely used as insect control agents. Recent reports suggest that these compounds may also perturb the normal development of crustaceans, and perhaps other aquatic species. In an attempt to prepare more highly degradable (and thus less environmentally persistent) mimics of JH-III, we prepared a series of analogues incorporating vinyl ether functionality. The stability of these compounds in water or warm, moist air was evaluated, revealing two distinct decomposition pathways.

Juvenile hormone III (JH-III) is the most important of several structurally related insect hormones (JH-0 – JH-III, Fig. 1A), and the only member of the family found outside of Lepidoptera.[1] The juvenile hormones regulate insect development,[2] reproduction,[3] and caste differentiation.[4] During the insect growth cycle, the concentration of juvenile hormone dictates the progression from larva to pupa and eventually to adult.[5]

Many structural analogues of JH-III are known to be agonists of juvenile hormone activity. Because concentrations of juvenile hormone must be very low for the insect to reach the adult stage, the presence of these hormone mimics (e.g., methoprene, kinoprene, epofenonane and fenoxycarb, Fig. 1B) triggers impaired development, ultimately resulting in fatal morphological abnormalities.[5] As a result, many of these compounds are used as insect control agents. The most commercially important of these is the *S*-enantiomer of methoprene, which is widely used for the control of mosquitoes, flies (in agriculture), fire ants, fleas and other pests.[5]

Despite its potent activity against many insect species, methoprene is nontoxic to both mammals and birds.[6] At the same time, methoprene is known to be acutely toxic to certain species of fish, shrimp and crabs,[7] although it is not known to what extent this represents a legitimate threat to these species in the natural environment. A link between methoprene use and deformities in frogs has been postulated,[8] but this remains controversial.[9]

Of perhaps greater ecological concern, methoprene has been shown to have toxic effects on juvenile and adult crustaceans at very low concentrations, and anecdotal evidence suggests a possible link between methoprene use and fatal abortive moults in lobsters.[10] This may be due to mimicry by methoprene of methyl farnesoate (Fig. 1C), which appears to function as a hormone in crustaceans, and indeed is thought to play similar roles in crustaceans to the juvenile hormones in insects.[11]

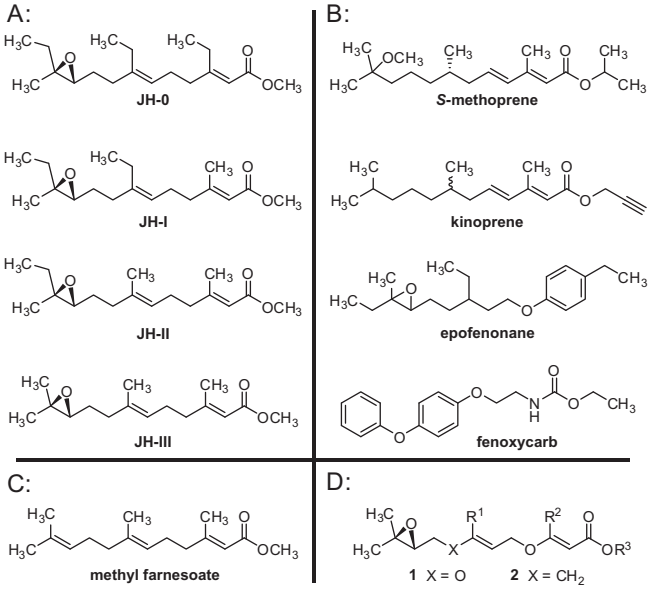


Figure 1. Structures of the juvenile hormones and related compounds; (A) insect juvenile hormones; (B) a selection of analogues known to have good activity against insect populations; (C) methyl farnesoate, a putative crustacean juvenile hormone; (D) compounds targeted in this work.

* Corresponding author. Tel.: +1 250 721 7179; fax: +1 250 721 7147.
E-mail address: wulff@uvic.ca (J.E. Wulff).

0040-4039/$ - see front matter Crown Copyright © 2011 Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.01.103

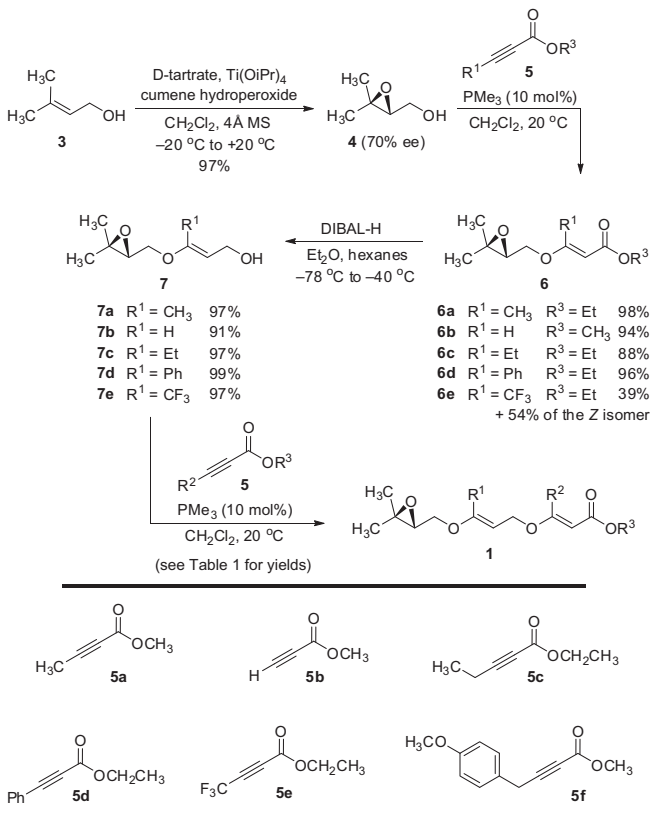
Methoprene can be degraded both microbially[12] and photochemically,[13] but it is chemically robust. Given recent concerns about unwanted effects in crustaceans (presumably following transport of methoprene from treated water supplies into the ocean), it seems that a more rapidly degradable analogue of the juvenile hormones might be useful for certain applications.

With this in mind, we targeted a series of vinyl ether-containing analogues of juvenile hormone III (Fig. 1D, **1** and **2**), hypothesizing that inclusion of the sensitive vinyl ether functions would make the target compounds prone to decomposition, either by hydrolysis or other means.

We first synthesized the bis-vinyl ether analogues **1**, through an iterative conjugate addition[14]/reduction/conjugate addition sequence from epoxy-alcohol **4**[15] and methyl or ethyl alkynoates **5** (Scheme 1). Alkynoates **5a–c** were available commercially;[16] **5d**,[17] **5e**[18] and **5f**[19] were prepared following published methods.

The yields for the individual conjugate addition and reduction steps were generally excellent, and in almost all cases, the target compounds were isolated as nearly single geometrical isomers (*E*, *E*). In the specific case of conjugate additions to ethyl 4,4,4-trifluoro-2-butynoate (leading to the formation of **6e** or **1h**), a mixture of geometrical isomers was formed,[20] but these could be separated chromatographically. With the exception of **1c** and **1d**, all of the bis-vinyl ethers were sufficiently stable to be purified by flash chromatography over triethylamine-treated silica gel.

Less-substituted bis-vinyl ethers have been reported previously,[21,22] but molecules of the type described here are unknown in the literature. It therefore seemed prudent to undertake a careful examination of their stability before planning any biological assays. In particular, since insect-control experiments are often conducted either in water (for water-breeding species like mosquitoes) or else in warm, humid growth chambers (mimicking a tropical environment), we sought to characterize the behaviour of these compounds under similar conditions.



Scheme 1. Synthesis of the bis-vinyl ether juvenile hormone mimics.

Table 1
Stabilities of bis-vinyl ether analogues of JH-III

Product	R^1	R^2	R^3	Yield (%)	$t_{1/2}$	
					Method A[a]	Method B[b]
1a	Me	Me	Me	99	17 h	<5 min
1b	Me	H	Me	94	3.5 h	<5 min
1c	Me	*p*-MeOBn	Me	<5%	—[f]	—[f]
1d	Me	CF_3	Et	<5%	—[f]	—[f]
1e	H	Me	Me	96	39 h	28 min
1f	H	H	Me	97	>24 h[d]	73 min[e]
1g	CF_3	Me	Me	93	>14 d	n. d.[g]
1h	CF_3	CF_3	Et	58[c]	>14 d	n. d.[g]
1i	Ph	Me	Me	98	>14 d	n. d.[g]
1j	Et	Et	Et	99	60 h	<5 min

[a] Method A: 37 °C, 5% CO_2, >90% relative humidity.
[b] Method B: 1:1 CD_3OD:D_2O, 20 °C.
[c] Isolated along with 42% of the corresponding Z isomer.
[d] Monitoring was complicated by volatility of the substrate.
[e] Decomposition occurred via hydrolysis.
[f] Sufficiently pure compound was not available for testing.
[g] The substrate was insoluble in 1:1 CD_3OD:D_2O.

To compare the stabilities of the synthesized compounds under humid nonsolution conditions (Table 1, method A), we deposited acetonic solutions of each substrate, together with 4,4′-dibromobiphenyl as an internal standard, onto several watch glasses. The solvent was allowed to evaporate over 1 h in a fume hood, after which the watch glasses were transferred to a cell-culture incubator (37 °C, 5% CO_2, >90% relative humidity[23]). Samples were periodically removed, and the composition was evaluated by NMR.

Fig. 2 shows the change in the proton NMR spectrum (normalized to the internal standard) for **1a** over time. The substrate smoothly underwent Claisen rearrangement[24] to afford ketone **8a**[25] (Scheme 2) with a half life of 17 h. Interestingly, continued monitoring of the reaction revealed that **8a** underwent further decomposition to volatile byproducts, such that the proton NMR spectrum showed essentially just the internal standard after 1 week of incubation. Simple evaporation of **8a** (MW = 270 g/mol) under these conditions was ruled out by the fact that **2a**

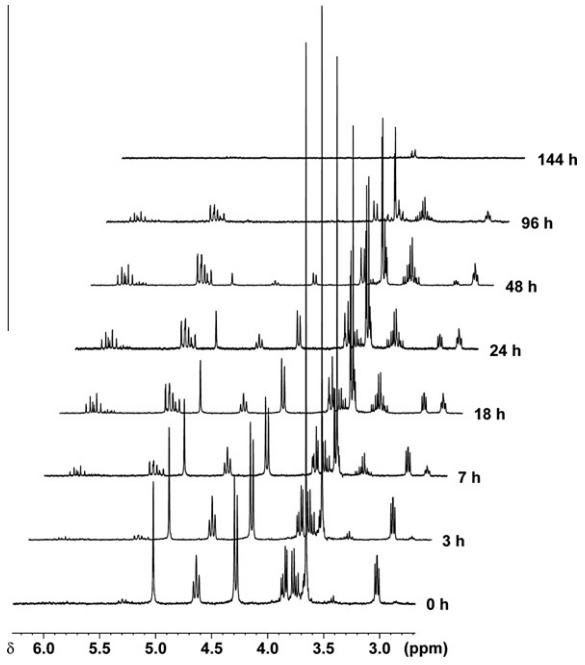
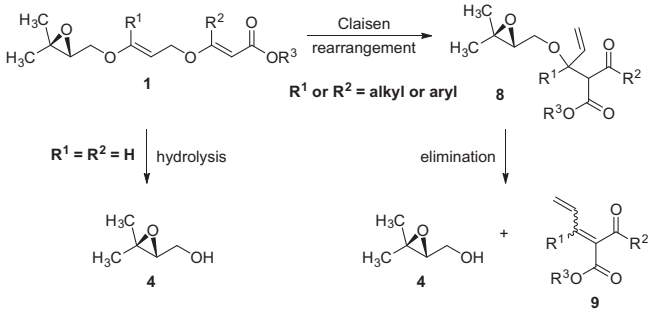


Figure 2. Decomposition of **1a** at 37 °C, 5% CO_2, >90% relative humidity.



Scheme 2. Decomposition pathways for the bis-vinyl ethers. Assignments of the elimination products are tentative.[26]

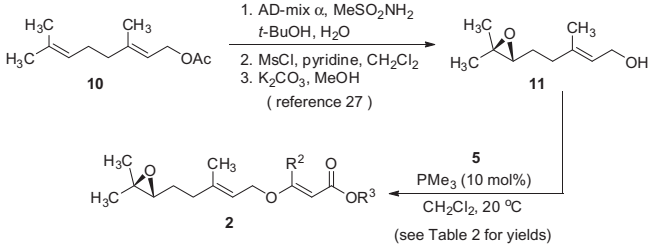
(MW = 268 g/mol) was not lost in an identical assay. Although the volatile byproducts could not be conclusively identified in this experiment, long-term incubation of **1a** in D_2O led to the tentative identification of **9a**[26] (Scheme 2), along with several other species, suggesting that the final decomposition step involves elimination of the starting material epoxy-alcohol.

Compounds **1b**, **1e** and **1j** decomposed similarly to **1a**, while **1g**, **1h** and **1i** were robust under these incubation conditions. In aqueous solution (1:1 CD_3OD:D_2O, method B), **1a**, **1b**, **1e** and **1j** again decomposed via Claisen rearrangement, but with greatly accelerated rates. Aqueous stabilities for **1g**, **1h** and **1i** could not be evaluated, since these compounds were insoluble in water. In fact, the immiscibility of **1g**, **1h** and **1i** with water may play a role in their stability under the conditions of method A.

Claisen rearrangement was not observed for the less-substituted analogue **1f** under either set of conditions. Instead, this compound underwent hydrolysis in aqueous solution to return compound **4**. The presumed aldehydic co-products from this hydrolysis reaction were not observed in large amounts, presumably due to further decomposition by aldol processes.

Since the synthesized bis-vinyl ethers proved either unstable or insoluble in water, we also pursued a series of mono-vinyl ethers (**2**) using a phosphine-mediated conjugate addition[14] of alkynes **5** to the known alcohol[27] **11** (Scheme 3). Once again, the yields were excellent for all synthesized compounds except for the very unstable trifluoromethyl-substituted analogue **2e**.

The mono-vinyl ethers were subjected to the same stability trials (Table 2, method A and method B) as those used for the bis-vinyl ethers. Under both conditions, **2c** decomposed slowly by Claisen rearrangement, while **2e** underwent more rapid decomposition. The other analogues were stable under the assay conditions. To further evaluate the relative stabilities of the different vinyl ether groups, we dissolved each compound in a mixture of 50% CD_3OD and 50% acidified (with H_2SO_4) D_2O. Under these forcing conditions, the epoxide opened rapidly ($t_{1/2}$ <5 min) to give a mixture of alcohols (**13**), but the vinyl ether groups hydrolysed with an analytically convenient range of rates (Table 2, method C). Small amounts of Claisen-rearranged products were also detected under

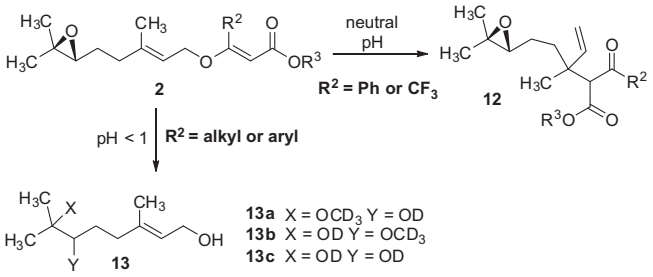


Scheme 3. Synthesis of the mono-vinyl ether juvenile hormone mimics.

Table 2
Stabilities of mono-vinyl ether analogues of JH-III

Product	R^2	R^3	Yield (%)	$t_{1/2}$		
				Method A[a]	Method B[b]	Method C[c]
2a	Me	Me	97	>14 d	>14 d	3 h[e]
2b	H	Me	99	>14 d	>14 d	>14 d
2c	Ph	Et	98	8.8 d[d]	21 h[d]	2.7 h[e]
2d	*p*-MeOBn	Me	96	>14 d	>14 d	21 h[e]
2e	CF_3	Et	27	14 h[d]	<5 min[d]	<5 min[d]
2f	Et	Et	99	>14 d	>14 d	2.5 h[e]

[a] Method A: 37 °C, 5% CO_2, >90% relative humidity.
[b] Method B: 1:1 CD_3OD:D_2O, room temperature.
[c] Method C: 1:1 CD_3OD:D_2O, pH <1, room temperature.
[d] Decomposition occurred mostly by Claisen rearrangement.
[e] Decomposition occurred mostly by vinyl ether hydrolysis.



Scheme 4. Decomposition pathways for the mono-vinyl ethers.

these conditions. The decomposition pathways observed for **2** are summarized in Scheme 4.

In summary, we have prepared and characterized two series of vinyl ether-containing analogues of juvenile hormone III. As intended, these compounds exhibit a range of stabilities under likely assay conditions, with half-lives ranging from minutes to weeks.

Depending upon the nature of the substituents and the assay conditions employed, the synthesized compounds decomposed by either Claisen rearrangement or vinyl ether hydrolysis. For the most part, the presence of an electron-rich 'Western' olefin (between C-6 and C-7) and an electron-poor 'Eastern' olefin (between C-2 and C-3) accelerated the rate of the Claisen rearrangement (e.g., **1a** reacts much faster than **2a**; **2e** reacts much faster than **2a**; **1d** decomposes during chromatography, while **1a** is stable on silica; **1g** is more stable than **1a**; etc.). To the best of our knowledge, these trends are not reported elsewhere, and will be a useful precedent for the synthetic exploitation of bis-vinyl ethers for other applications.

In cases where the synthesized compounds are not prone to Claisen rearrangements (e.g., **1f**, **2a**, **2b**, **2d** and **2f**) or in cases where the Claisen rearrangement is sufficiently slow (e.g., **2c**) decomposition can occur via vinyl ether hydrolysis. In these cases, more electron rich vinyl ethers generally hydrolyse faster (e.g., **2f** > **2a** > **2b**), but a lack of water solubility for more lipophilic substrates (e.g., **2c** and **2d**) probably also plays a role in reducing the rate of hydrolysis for some compounds.

With knowledge of the relative stabilities of our candidate JH-III mimics, we are currently planning a series of biological assays to test their function in insects. Results from this study will be reported in due course.

Acknowledgements

We are grateful to the University of Victoria for startup funds, and to the Canada Foundation for Innovation and the BC Knowledge Development Fund for providing equipment. Additional

operating funds were provided by the Natural Sciences and Engineering Research Council of Canada and the Merck Frosst Canadian Academic Development Program.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.103.

References and notes

1. Schooley, D. A.; Baker, F. C.; Tsai, L. W.; Millar, C. A.; Jamieson, G. C. In Hoffmann, J., Porchet, M., Eds.; Biosynthesis, metabolism and mode of action of invertebrate hormones; Springer: Berlin, 1984; pp 373–383.
2. Riddiford, L. M. In *Comprehensive Insect Physiology, Biochemistry, and Pharmacology*; Kerkut, G. A., Gilbert, L. I., Eds.; Permagon: Oxford, 1985; Vol. 8, pp 37–84.
3. Koeppe, J. K.; Fuchs, M.; Chen, T. T.; Hunt, L.-M.; Kovalick, G. E.; Briers, T. In *Comprehensive Insect Physiology, Biochemistry, and Pharmacology*; Kerkut, G. A., Gilbert, L. I., Eds.; Permagon: Oxford, 1985; Vol. 8, pp 165–203.
4. See: Hrdý, I.; Kuldová, J.; Hanus, R.; Wimmer, Z. *Pest Manag. Sci.* **2006**, *62*, 848–854. and references cited therein.
5. Henrick, C. A. *AMCA Bulletin No. 7* **2007**, 225–239.
6. Environmental Protection Agency Reregistration Eligibility Document, List A, Case 0030, 1991.
7. (a) McKenney, C. L., Jr.; Matthews, E. *Environ. Pollut.* **1990**, *64*, 169–178; (b) Christiansen, M. E.; Costlow, J. D.; Monroe, R. J. *Mar. Biol.* **1977**, *39*, 269–279; (c) Celestial, D. M.; McKenney, C. L., Jr. *Environ. Pollut.* **1994**, *85*, 169–173.
8. La Clair, J. J.; Bantle, J. A.; Dumont, J. *Environ. Sci. Technol.* **1998**, *32*, 1453–1461.
9. For a useful summary, see: Glare, T. R.; O'Callaghan, M. *Report for the New Zealand Ministry of Health: Environmental and Health Impacts of the Insect Control Juvenile Hormone Analogue, S-Methopriene.* Lincoln (New Zealand): Biocontrol & Biodiversity, Grasslands Division, AgResearch.
10. (a) Walker, A. N.; Bush, P.; Puritz, J.; Wilson, T.; Chang, E. S.; Miller, T.; Holloway, K.; Horst, M. N. *Integr. Comp. Biol.* **2005**, *45*, 118–126; (b) Horst, M. N.; Walker, A. N.; Bush, P.; Wilson, T.; Chang, E. S.; Miller, T.; Larkin, P. *Comp. Biochem. Physiol. D* **2007**, *2*, 44–52.
11. For leading references, see: Homola, E.; Chang, E. S. *Comp. Biochem. Physiol.* **1997**, *117B*, 347–356.
12. (a) Schooley, D. A.; Bergot, B. J.; Dunham, L. L.; Siddall, J. B. *J. Agric. Food. Chem.* **1975**, *23*, 293–298; (b) Schooley, D. A.; Creswell, K. M.; Staiger, L. E.; Quistad, G. B. *J. Agric. Food. Chem.* **1975**, *23*, 369–373.
13. Quistad, G. B.; Staiger, L. E.; Schooley, D. A. *J. Agric. Food. Chem.* **1975**, *23*, 299–303.
14. Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241–244.
15. Chandrasekhar, S.; Chandrashekar, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2209–2214.
16. Alkyne **5a** was purchased from Acros Organics; **5b** and **5c** were purchased from Sigma Aldrich.
17. Dieter, R. K.; Lu, K.; Velu, S. E. *J. Org. Chem.* **2000**, *65*, 8715–8724.
18. Hamper, B. C. *Org. Synth.* **1992**, *70*, 246–255.
19. Davies, K. A.; Abel, R. C.; Wulff, J. E. *J. Org. Chem.* **2009**, *74*, 3997–4000.
20. We have observed similar mixtures of isomers in conjugate additions of other alcohols to 4-methyl-2-pentynoates (i.e., R^1 = *i*-Pr), suggesting that the mixture of isomers in both cases is attributable to steric factors.
21. (a) Lubineau, A.; Augé, J.; Bellanger, N.; Caillebourdin, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1631–1636; (b) Lubineau, A.; Augé, J.; Bellanger, N.; Caillebourdin, S. *Tetrahedron Lett.* **1990**, *31*, 4147–4150.
22. Krompiec, S.; Kuźnik, N.; Urbala, M.; Rzepa, J. *J. Mol. Catal. A: Chem.* **2006**, *248*, 198–209.
23. Measured by the dry-bulb/wet-bulb method.
24. Claisen rearrangements of bis-vinyl ethers under aqueous conditions have been reported previously, and were attributed to hydrophobic effects. See Ref. 21.
25. The structure of **8a** ($R_1 = R_2 = R_3 = CH_3$) was confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS.
26. Incubation of **1a** for 1 week in 1:1 CD_3OD:D_2O led to the appearance of olefinic signals at 7.1 ppm (dd, *J* = 17, 11 Hz) and 6.6 ppm (dd, *J* = 17, 11 Hz), consistent with the formation two geometric isomers of conjugated diene **9**.
27. Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865–8869.