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An Efficient Asymmetric Synthesis of the Higher Dipteran Juvenile Hormone III Bisepoxide

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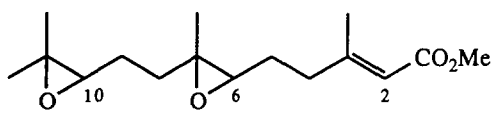
Abstract: (2*E*,6*S*,7*S*,10*R*) - Juvenile hormone III bisepoxide, the putative characteristic juvenile hormone of higher dipteran insects, has been synthesised efficiently and in high stereochemical purity from geraniol by application of Sharpless asymmetric epoxidation and dihydroxylation procedures.

Richard *et al.*[1] in 1989 identified methyl (2*E*)-6,7,10,11-bisepoxyfarnesate (**1**) as the principal biosynthetic product formed when larval ring glands of *Drosophila melanogaster* ("fruit" fly) are cultured *in vitro*. This novel metabolite, originally named juvenile hormone bisepoxide (JHB_3) and subsequently also referred to by other authors as juvenile hormone III bisepoxide,[2] was suggested[1] to be the predominant and characteristic juvenile hormone of higher dipteran insects. *Corpora allata* dissected from adult *D. melanogaster* ring glands,[3] and *corpora allata* or ring glands from larval and adult stages of related insects including *Musca domestica* (house fly),[1] *Sarcophaga bullata* (flesh fly),[1] *Calliphora vicina*[1] and *C. vomitoria*[4] (blowflies) and *Lucilia cuprina* (Australian sheep blowfly)[5,6] produce the same metabolite. A variety of biochemical and physiological studies[1,3,4,7] support the hormonal significance of JHB_3 (**1**). Its recognition has added a new dimension to our knowledge of the juvenile hormones of the farnesate group which mediate the neurohormonal control of development and reproduction of many insect species.[8]



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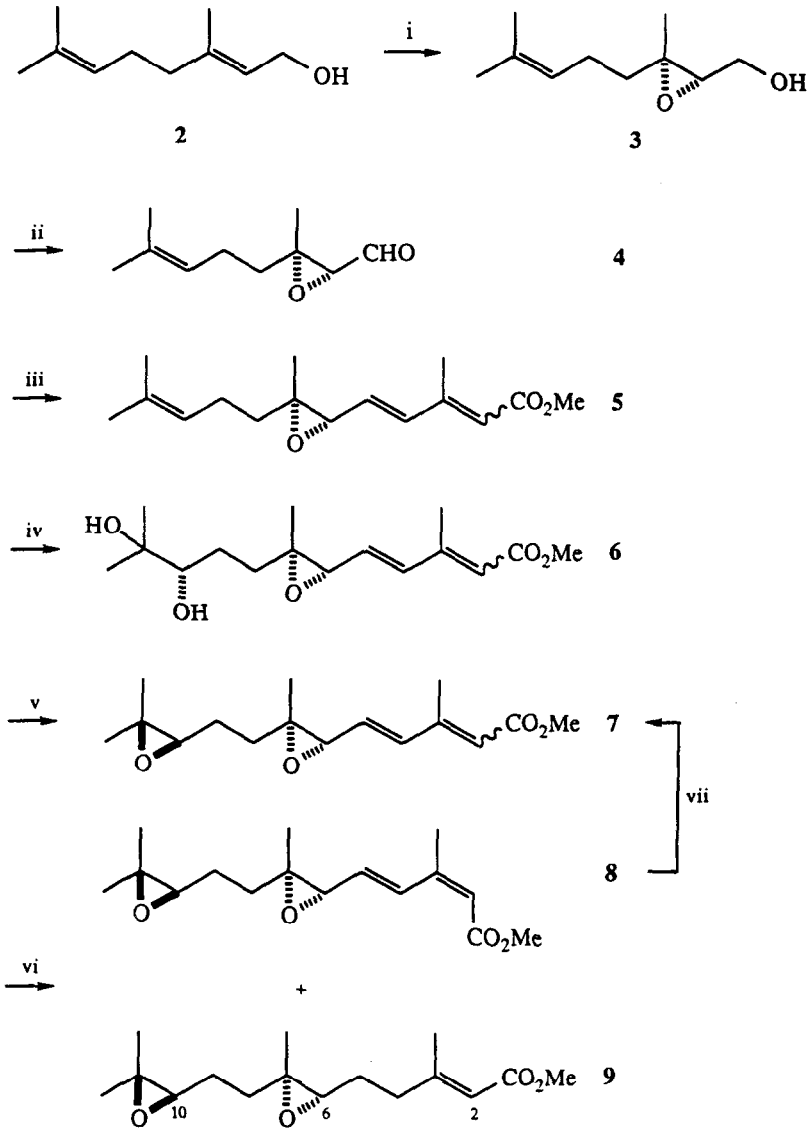
We have recently reported the synthesis of the (2*E*,6*S*,7*S*,10*R*)-, (2*E*,6*S*,7*S*,10*S*)-, (2*E*,6*R*,7*R*,10*S*)- and (2*E*,6*R*,7*R*,10*R*)-stereoisomers of JHB_3 (**1**) in high stereoisomeric purity.[9] Comparison of these stereoisomers with biosynthetically-labelled [*methoxy*-^{3}H]JHB_3 from *L. cuprina* then defined the absolute configuration of natural JHB_3 as (2*E*,6*S*,7*S*,10*R*), *i.e.* stereoisomer (**9**).[10] Whilst our original synthetic route[9] to the various stereoisomers provided access to the required reference compounds, the deliberately stereo-random introduction of the 10,11-epoxide function necessitated preparative HPLC separation of diastereoisomeric intermediates and consequent diversion of material if the natural isomer only is required. We describe here a convenient, efficient synthesis of natural (2*E*,6*S*,7*S*,10*R*)-JHB_3 (**9**) in high stereochemical purity from geraniol. The route employs as its key steps the Sharpless asymmetric epoxidation and dihydroxylation procedures to introduce the 6,7- and 10,11-epoxide functions.

Sharpless epoxidation of geraniol (**2**) in the presence of a catalytic quantity of (+)-diethyl tartrate[11] afforded the (2*S*,3*S*)–epoxyalcohol (**3**) in excellent 97% yield and with an enantiomer ratio of 93:7 (as determined by ^{1}H NMR shift analysis[11,12] of the derived acetate).[13] We initially attempted to introduce the second epoxide into the epoxyalcohol (**3**) *via* the related vicinal diol, in order then to utilise our previous synthetic route[9] to natural JHB_3 (**9**). Sharpless asymmetric dihydroxylation,[14] however, gave severe mixtures of products. Accordingly the epoxyalcohol (**3**) was oxidised under Swern conditions[15] to the epoxyaldehyde



Scheme 1. (i) cat. L-(+)-DET, TBHP, $Ti(O^iPr)_4$, 97%, enantiomer ratio 93:7; (ii) DMSO, $(COCl)_2$, NEt_3; (iii) $(EtO)_2OPCH_2C(Me)=CHCO_2Me$, $LiNH_2$, 67% from **3**; (iv) "AD-mix-α", 82%, C-10 epimer ratio 94:6; (v) $MeSO_2Cl$, NEt_3 then K_2CO_3, MeOH, 70% from **6**; (vi) H_2, $RhCl(PPh_3)_3$, 57% **9**, 8% diastereoisomers of **9**, and 16% **8**; (vii) cat. AIBN, PhSH.

(4), which was subjected without purification to a Horner-Wittig condensation with diethyl 3-methoxycarbonyl-2-methylprop-2-enylphosphonate[16] to form in 67% overall yield the triene-esters (5) as an inseparable 3.0:1 mixture of the (2*E*,4*E*)– and (2*Z*,4*E*)-isomers. The latter isomer appears unavoidable with this particular phosphonate,[16] and is best carried through until the final purification stage. Sharpless asymmetric dihydroxylation[14] of these triene-esters (5) with "AD-mix-α" now occurred smoothly and regiospecifically at the isolated 10,11-olefinic bond to yield primarily the (10*S*)-10,11-diols (6) in 82% yield with an epimer ratio of 94:6 at the newly created stereogenic centre. The (10*S*)-configuration of these diols (6) is that expected,[14] and was confirmed by the correct configuration of the ultimate JHB_3 (9) produced. The epimer ratio created at C-10 was calculated from the measured ratios of the initial epoxyalcohol enantiomers (3:*ent*–3, 93:7 by NMR analysis) and of the resulting JHB_3 enantiomeric pairs (9 + *ent*-9: their diastereoisomers, 88:12 by analytical HPLC[6,10]).[17]

Development of the 10,11-epoxide function with inversion of configuration at C-10 was then completed by mesylation of the secondary hydroxyl group followed by displacement of the mesylate with the anion of the vicinal tertiary alcohol.[19] This afforded in 70% yield a 3.0:1 mixture of (2*E*,4*E*)- and (2*Z*,4*E*)-diene-esters in which the major components (7) corresponded to the two olefinic isomers present at the penultimate stage of our previous synthesis of (2*E*,6*S*,7*S*.10*R*)-JHB_3 (9).[9] Hydrogenation of this diene-ester mixture with Wilkinson's catalyst[20] as before reduced only the disubstituted olefin in the (2*E*,4*E*)-esters, leaving the (2*Z*,4*E*)-esters (mainly 8) unaffected.[9] The latter esters were readily separated at this stage from their reduced counterparts by silica gel chromatography. Preparative HPLC[6] of the reduced esters then removed the unwanted (2*E*,6*S*,7*S*,10*S*)- and (2*E*,6*R*,7*R*,10*R*)-enantiomers produced in 8% yield as the result of the incomplete stereoselectivity of the two olefin oxidation processes. The desired (2*E*,6*S*,7*S*,10*R*)–JHB_3 (9) was obtained in 57% yield from the diene-ester mixture (7). It is free from diastereoisomers, and has an enantiomer ratio of *ca.* 99.5:0.5 resulting from the 93:7 and 94:6 stereoselectivities of the two asymmetric oxidations.[17]

If desired, the separated (2*Z*,4*E*)-diene-esters can be recycled by radical isomerisation catalysed by thiophenol and 2,2'-azobis(2-methylpropanenitrile),[21] regenerating a mixture of (2*E*,4*E*)- and (2*Z*,4*E*)-diene-esters (mainly 7) in an equilibrium ratio of 2.3:1 which can be again reduced.

This convenient synthesis provides JHB_3 (9) with the natural (2*E*,6*S*,7*S*,10*R*)-configuration in >99.5% stereochemical purity. Formation of the trace of the unnatural enantiomer (*ent*-9) could be avoided by crystallization of an appropriate derivative of the epoxyalcohol (3).[11] The route lends itself to the preparation of [4,5-$^3H_2$]JHB_3 for biological studies, by the use of tritium gas in the final hydrogenation step. Finally, the choice of alternative Sharpless asymmetric oxidation catalysts[11,12,14] would lead with equal facility to unnatural isomers of the hormone.

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13. In agreement with literature[11,12] this catalytic epoxidation is more convenient for larger scale reactions than the stoichiometric process which we used previously,[9] and gives a higher yield (97% v. 82%) albeit with a somewhat lower enantiomer ratio (93:7 v. 97:3). The higher stereoselectivity is not essential in the present synthesis since even 7% of the minor enantiomer (*ent*–**3**) yields only *ca.* 0.5% of the wrong enantiomer (*ent*–**9**) of JHB_3 (**9**) (see later).
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17. The C-10 epimer ratio could not be obtained from analysis of the diols, which are a mixture of 8 stereoisomers with the two olefinic isomers (**6**) predominant. The calculation assumes that the stereoselectivity of the olefin dihydroxylation process is effectively independent of the configuration of the 6,7-epoxide. This assumption seems reasonable given that previous reports[18] of double diastereoselection in asymmetric dihydroxylation have involved a stereogenic centre allylic to the reacting olefin, not three carbons removed as here. The calculated ratios of the stereoisomers of JHB_3 produced are (2*E*,6*S*,7*S*,10*R*)-(**9**): (2*E*,6*R*,7*R*,10*S*)-(*ent*-**9**): (2*E*,6*S*,7*S*,10*S*): (2*E*,6*R*,7*R*,10*R*) 87.4: 0.4: 5.6: 6.6.
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