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Synthesis of Four Stereoisomers of the Higher Dipteran Juvenile Hormone III Bisepoxide

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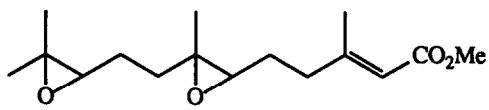
Abstract: The 6*S*,7*S*,10*R*-, 6*S*,7*S*,10*S*-, 6*R*,7*R*,10*S*-, and 6*R*,7*R*,10*R*-stereoisomers of the juvenile hormone III bisepoxide from higher Dipteran insects have been synthesised in high stereoisomeric purity. The route involves Sharpless epoxidation of geraniol to enantiomeric epoxyalcohols, which are each elaborated *via* separable diastereomeric bromohydrins.

Juvenile hormones of the farnesoate group play major roles in regulating the development and reproduction of many insect species.[1] The recent identification[2] of juvenile hormone III bisepoxide (JHB_3, **1**), a novel member of the farnesoate group, as a putative juvenile hormone in the higher Diptera has led to much interest in the biology and biochemistry of this compound.[2,3] Although JHB_3 is known[2] to have the 2*E*-geometry of the olefinic bond, neither the relative nor absolute configuration of its stereogenic centres has been defined. The difficulties involved are severe in view of the minute (pmol) levels of hormone produced by insect tissues themselves. In order to address the configuration of natural JHB_3, and to provide stereochemically pure compounds for biological studies, we have developed synthetic methodology leading to four stereoisomers of JHB_3 (**1**).



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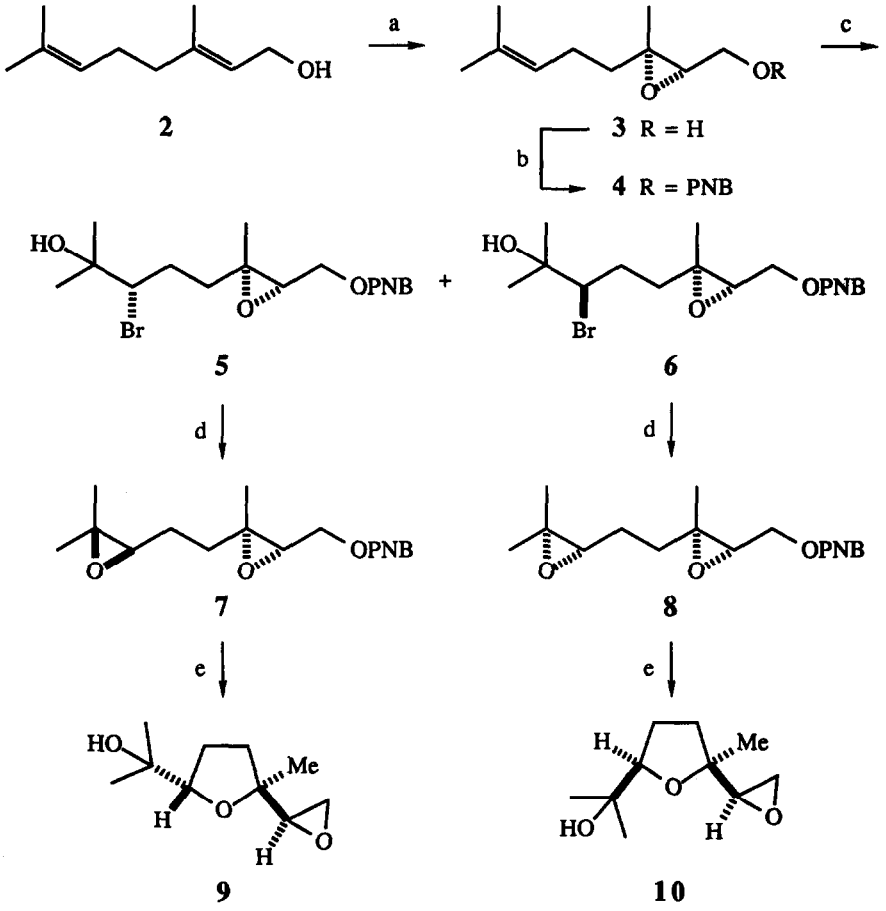
The choice of the four particular stereoisomers of the eight which are possible for structure (**1**) was based upon biosynthetic considerations. The addition of farnesoic acid to ring glands of *Drosophila melanogaster* dramatically increases JHB_3 biosynthesis, [2,3g,3h] indicating a probable precursor-product relationship. We assume that the olefinic configurations of farnesoic acid are conserved in the epoxidation processes, and that in particular the 6,7-epoxide function of JHB_3 carries *trans* carbon chains reflecting the *E*-olefin from which it is derived. The stereoisomers of interest are accordingly the 6*S*,7*S*,10*R*-(**14**) and 6*S*,7*S*,10*S*-diastereomers, and their respective 6*R*,7*R*,10*S*- and 6*R*,7*R*,10*R*-enantiomers. Of these possibilities, it is likely that JHB_3 has the 10*R* configuration corresponding to that of juvenile hormone III,[4] the analogous 10,11-monoepoxide of methyl farnesoate which also occurs in the higher Diptera. Our synthetic approach employed as its key step the introduction of chirality by Sharpless asymmetric epoxidation[5] of geraniol to afford the enantiomeric epoxyalcohols, which were elaborated *via* separable diastereomeric bromohydrins to the required JHB_3 stereoisomers (Schemes 1,2).

Thus Sharpless epoxidation of geraniol (**2**) in the presence of 1.2 equivalents of (+)-diethyl tartrate afforded the (2*S*,3*S*)-epoxyalcohol (**3**) in an enantiomeric excess of 94%.[5] Esterification to the *p*-nitrobenzoate (**4**)[5,6] provided protection for the alcohol function and introduced a rigid chromophoric substituent to assist chromatography and crystallisation at subsequent stages. Treatment with aqueous N-bromosuccinimide gave a mixture of diastereomeric bromohydrins which was separated by preparative high pressure liquid chromatography

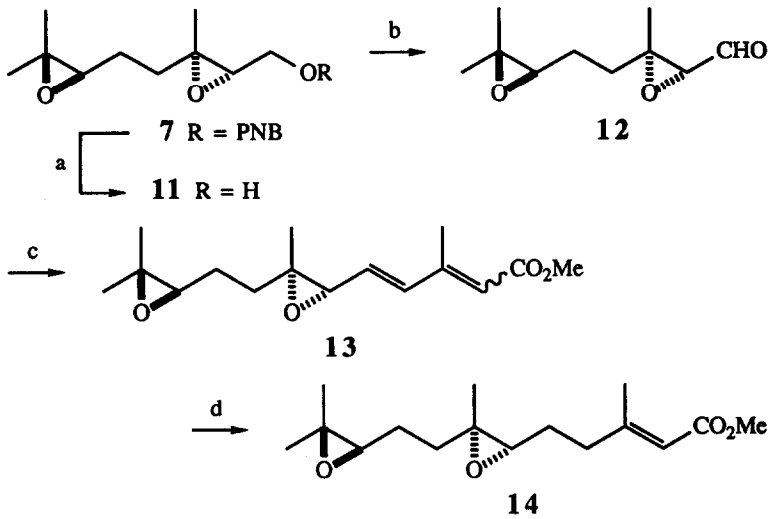
(HPLC) to afford the diastereomerically pure components (**5**) and (**6**). Cyclization of these bromohydrins (**5**) and (**6**) with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) yielded the diepoxides (**7**) and (**8**) respectively, which could be recrystallised to high enantiomeric purity.

The absolute configurations at C-6 of the diepoxides (**7**) and (**8**) were determined as indicated in Scheme 1. Prolonged treatment of each with sodium hydroxide effected initial hydrolysis of the ester followed by Payne rearrangement[7] of the resulting diepoxyalcohols and exclusive formation of the *trans*- and *cis*-tetrahydrofurans (**9**) and (**10**) respectively, as reported by Klein *et al.*[8] for the corresponding racemic diepoxyalcohols. The identity of the *trans*- and *cis*-tetrahydrofurans (**9**) and (**10**) was established by comparison of their ^{1}H NMR data with literature values,[9,10] by ^{1}H nuclear Overhauser effects, and by independent synthesis of the racemate of the *cis*-isomer (**10**) from neryl chloride.[9,11] The base-promoted conversions of the diepoxides (**7**) and (**8**) into the tetrahydrofurans (**9**) and (**10**) occur with complete stereospecificity and involve successive inversions of configuration at C-2 and C-6. The geometry of the products in conjunction with the 2*S*,3*S* configuration of the diepoxides (**7**) and (**8**) defines the C-6 configurations of the latter as *R* and *S* respectively.



Scheme 1 (a) (+)-DET, TBHP, Ti(O^{i}Pr)$_4$, 82%; (b) *p*-$O_2NC_6H_4COCl$, NEt_3, 72%; (c) NBS, H_2O, 55%; (d) DBU, 67% recryst. (**7**), 78% recryst. (**8**); (e) NaOH, 60% (**9**), 85% (**10**)

With the preparation of the diepoxides (**7**) and (**8**) of established absolute stereochemistry and high stereoisomeric purity achieved, the synthesis of the 6*S*,7*S*,10*R*-isomer of JHB_3 was completed as in Scheme 2. Mild hydrolysis of the *p*-nitrobenzoate (**7**) with sodium hydroxide gave the (2*S*,3*S*,6*R*)-diepoxyalcohol (**11**), of > 98% enantiomeric excess as determined by ^1H NMR analysis of the derived acetate with the chiral shift reagent $Eu(hfc)_3$.[5] Swern oxidation[12] gave the diepoxyaldehyde (**12**), which was isolated and subjected immediately to a Horner-Wittig condensation with diethyl 3-methoxycarbonyl-2-methylprop-2-enylphosphonate[13] to form the dehydro JHB_3 (**13**) as a 4:1 mixture of 2*E*,4*E*- and 2*Z*,4*E*-isomers. Hydrogenation of this mixture using Wilkinson's catalyst[14] reduced only the disubstituted olefinic bond in the former isomer, leaving the latter isomer unaffected. The desired 6*S*,7*S*,10*R*-isomer (**14**) of JHB_3 was readily separated by column chromatography. Its diastereomeric purity was confirmed by HPLC which showed only one of the two peaks present in non-stereospecifically epoxidised methyl farnesoate.[15]



Scheme 2 (a) NaOH; (b) DMSO, $(COCl)_2$;
(c) $(EtO)_2OPCH_2C(Me)=CHCO_2Me$, $LiNH_2$, 43% from (**7**);
(d) H_2, $RhCl(PPh_3)_3$, 49% with 18% recovered 2*Z*-(**13**)

Similar reaction sequences were used to synthesise the 6*S*,7*S*,10*S*-isomer of JHB_3 from the (2*S*,3*S*,6*S*)-diepoxide (**8**), and the 6*R*,7*R*,10*S*- and 6*R*,7*R*,10*R*-isomers of JHB_3 from (2*R*,3*R*)-epoxygeraniol, itself prepared by Sharpless epoxidation in the presence of (-)-diethyl tartrate.[5] The biological properties of these four isomers of JHB_3,[16] synthesised here for the first time, and their stereochemical relationship to the natural hormone, are under study.

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16. Characteristic physical properties of the isomers are as follows.
(6*S*,7*S*,10*R*)-JHB$_3$ (**14**): $[\alpha]^{21}_{365}$ + 2.2° (*c*. 0.11%, CH_2Cl_2); ^{13}C NMR (75.5 MH_z, $CDCl_3$) δ 167.01 (C-1), 158.84 (C-3), 115.64 (C-2), 63.95, 62.83 (C-6,10), 60.56, 58.31 (C-7,11), 50.87 (OMe), 37.57, 35.54, 26.65, 24.71 (C-4,5,8,9), 24.79 (3-Me), 18.76, 18.63, 16.42 (C-12, 7-Me, 11-Me).
(6*S*,7*S*,10*S*)-JHB$_3$: $[\alpha]^{21}_{D}$ - 20.0° (*c*. 0.085%, CH_2Cl_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.00 (C-1), 158.78 (C-3), 115.66 (C-2), 63.77, 62.29 (C-6,10), 60.43, 58.43 (C-7,11), 50.88 (OMe), 37.54, 35.11, 26.65, 24.52 (C-4,5,8,9), 24.80 (3-Me), 18.76, 18.60, 16.67 (C-12, 7-Me, 11-Me).
(6*R*,7*R*,10*S*)-JHB$_3$: $[\alpha]^{21}_{365}$ - 1.9° (*c*. 0.47%, CH_2Cl_2); ^{13}C NMR as for (6*S*,7*S*,10R)-JHB$_3$.
(6*R*,7*R*,10*R*)-JHB$_3$: $[\alpha]^{21}_{D}$ + 20.0° (*c*. 0.045%, CH_2Cl_2); ^{13}C NMR as for (6*S*,7*S*,10*S*)-JHB$_3$.

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