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Synthesis of Enantiomerically Pure Juvenile Hormone II

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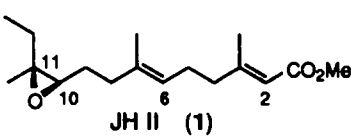
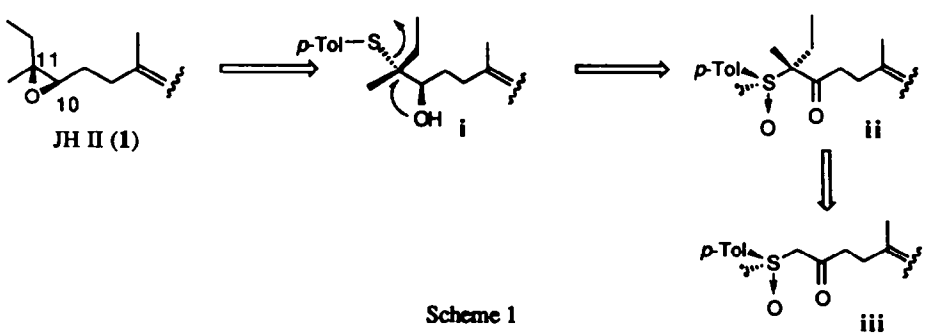
Abstract: An efficient preparative method for the enantiomerically pure juvenile hormone II has been developed by applying the diastereoselective alkylation and carbonyl reduction of an optically pure β-keto sulfoxide as the key steps.

Juvenile hormones of farnesoate and its homologous group are well known to play major roles in regulating the development and reproduction of many insect species and are still the constant subject of enormous interest in the field of synthetic organic chemistry as well as biology and biochemistry.[1] The success of enantiomerically pure JH's syntheses and the evaluation of their biological activities by Mori and his coworkers show it to be important to employ the enantiomerically pure specimen for the study of such biological activities.[2,3] Here we report a novel asymmetric synthesis of JH II (**1**) in optically pure form, based on the diastereoselective alkylation and carbonyl reduction of an optically pure β-keto sulfoxide as the key steps.



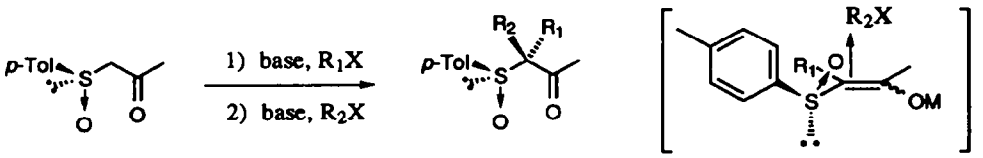
JH II (**1**)



JH II (**1**)

Scheme 1

Scheme 1 shows our synthetic strategy, in which the final stage to JH II via epoxy ring formation requires to set the stereocenters 10*R*,11*R* in the hydroxy sulfide **i**; the C-10 stereogenic center of **i** would be derived from the dialkylated keto sulfoxide **ii** under the chelation-controlled reduction conditions.[4] The requisite 11*R*, S_S keto sulfoxide **ii** would be derived from the keto sulfoxide **iii** via stepwise dialkylation. The problem associated with this route is the stereochemistry of the second alkylation stage, that is, the desired C-11 stereochemistry in **ii** should be derived from **iii** first by methylation and then ethylation, or by the reverse order. At the outset of the project, no reports on this stereochemical problem had appeared. However, Ogura and coworkers recently reported on the diastereoselective alkylation of β-keto sulfoxides in which the second alkylation occurs mainly from the tolyl side when the transition state is depicted in Scheme 2.[5] According to their results, the sulfoxide **ii** could be obtained from **iii** first by ethylation and then methylation in order.



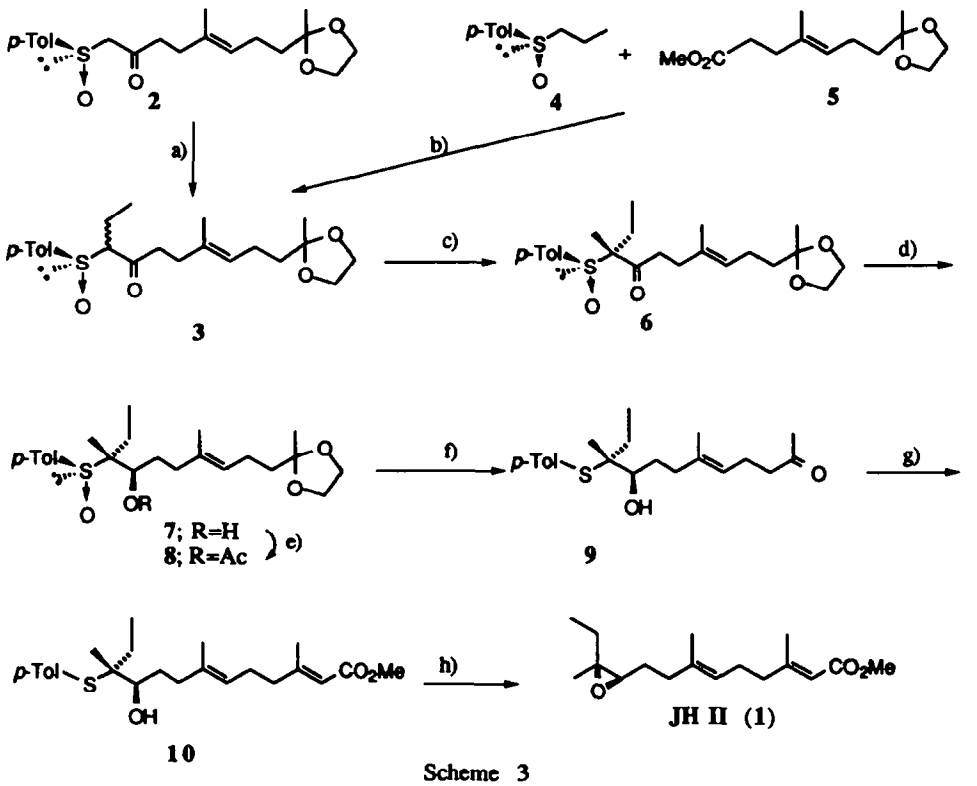
Scheme 2

When the keto sulfoxide **2**[6] was initially alkylated with EtI under the usual conditions (NaH, DMF), the yield of the mono-alkylated product **3** was extremely low (~30%) due to the formation of the di- and triethylation products as well as the *O*-alkylation products. Attempts to improve the yield under a variety of conditions were unsuccessful. Next, we examined an alternative route involving the condensation of the lithium carbanion of (*R*)-propyl tolyl sulfoxide (**4**)[7] with an ester (Scheme 3). Thus, the lithium carbanion of **4**, generated with LDA, was treated with the ester **5**[8] furnishing quantitatively a diastereomeric mixture (ca. 1:1) of the ethylated product **3**. The second alkylation of **3** with MeI in the presence of NaH in DMF afforded the dialkylated keto sulfoxide **6** (diastereoselectivity,9:1).[9] At this stage, it was impossible to determine rigorously the stereostructures of the dialkylated products by means of the NMR techniques including COSY and NOESY experiments. Accordingly, the major alkylated product was tentatively assigned to be **6**, based on the results by Ogura[5], as depicted in Scheme 3.

The carbonyl reduction of **6** with DIBAL-H in the presence of $ZnCl_2$ in THF at -90 °C[4] took place highly diastereoselectively to give a 96:4 separable diastereomeric mixture of a hydroxy sulfoxide **7** (66% overall yield from **3**). In order to avoid the rearrangement occurring between the hydroxy group and the sulfide moiety in **7**, the hydroxy group in **7** was protected as an acetate **8** (Ac_2O, DMAP). The acetate **8** was subjected to sulfinyl reduction by using NaI and $(CF_3CO)_2O$ in acetone, followed by removal of the protecting groups to afford a hydroxy sulfide **9** in 77% overall yield from **8**. Usual Horner-Emmons-Wardsworth reaction of **9** with trimethyl phosphonoacetate (NaH in THF) furnished an *E*-olefinic ester **10** (64% yield) together with its *Z*-isomer (27% yield).

Completion of the sequence requires only the epoxy ring formation. The formation of the sulfonium salt from **10** under the standard conditions ($Me_3O^+ \cdot BF_4^-$ in CH_2Cl_2) was quite slow probably due to the sterical reason. However, the reaction of **10** with $Me_3O^+ \cdot BF_4^-$ in nitromethane as the solvent proceeded smoothly at 0 °C for 0.5 h to give the sulfonium salt, which, after evaporation of the solvent, was treated with sodium methoxide in methanol, furnishing enantiomerically pure JH II (**1**) in 55% yield ($[\alpha]_D^{23}$ +15.1 (*c* 1.47, MeOH),

lit.[2] {$[\alpha]_D^{24}$ +17.6 (*c* 0.59, MeOH)}. The ^{1}H NMR spectrum of the material obtained here is accord with the reported values for JH II and shows to be diastereomerically pure.[10] Consequently, the stereostructure of the dialkylated keto sulfoxide **6** is determined as shown in Scheme 3.



Scheme 3

a) NaH, EtI, DMF, rt. b) LDA, THF and then **5**. c) NaH, MeI, DMF, rt. d) DIBAL-H, $ZnCl_2$, THF, -90 °C. e) Ac_2O, DMAP, CH_2Cl_2. f) (i) NaI, $(CF_3CO)_2O$, acetone; (ii) LAH; (iii) pyridinium *p*-toluenesulfonate, acetone. g) $(MeO)_2POCH_2CO_2Me$, NaH, THF, rt.. h) (i) $Me_3O^+ \cdot BF_4^- \cdot MeNO_2$, 0 °C; (ii) MeONa, MeOH.

In order to determine directly the optical purity of JH II, we examined several methods including NMR technique as well as chiral stationary phase HPLC using (±)-JH II.[11] We found that only the NMR technique (600 MHz) using the Pirkle's chiral solvating reagent,[12] 2,2,2-trifluoro-1-(9-anthryl)-ethanol, could be applied to the case of JH II.[13,14] In the presence of the chiral (*S*)-(-)-reagent, two sets of the epoxy ring proton signals (dd, *J*=6.87, 5.60 Hz) were perfectly separated each other ($\Delta\delta$=0.034 ppm). By using this method, the optical purity of the material synthesized here could be determined to be 100% e.e.

In summary, it has been demonstrated that the diastereoselective alkylation and carbonyl reduction of a chiral β-keto sulfoxide and the subsequent elaboration of the resulting chiral β-hydroxy sulfoxide offer an easy access to enantiomerically pure JH II.

References and Notes

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6. Enantiomerically pure (*R*)-β-keto sulfoxide **2** was prepared from the dianion of (*R*)-1-*p*-tolylsulfinyl-2-propanone and (*E*)-7-bromo-6-methyl-7-hepten-2-one ethylene ketal (Secrist III, J. A.; Hickey, C. J.; Norris, R. E. *J .Org. Chem.*, **1977**, *42*, 525) as reported for similar compounds. Kosugi, H.; Hoshino, K.; Uda, H. *J. Chem. Soc., Chem. Commun.*, **1991**, 1173.
7. $[\alpha]_D^{23}$ +221(*c*=0.781, $CHCl_3$). The optical purity was determined to be 100% e.e. from the HPLC analysis using DAICEL CHIRALCEL OD column (1:9 2-propanol-hexanes). Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.*, **1968**, *90*, 4869.
8. The ester **5** was prepared from the sequential reactions of (*E*)-7-bromo-6-methyl-7-hepten-2-one ethylene ketal[6] with the lithium enolate of *t*-butyl acetate, alkaline hydrolysis (20% NaOH, DMSO), followed by esterification with diazomethane (overall yield 98%). The deprotected ketone compound, (*E*)-methyl 4-methyl-8-oxo-4-nonenoate was known, see for one of the examples; Miles, D. H.; Lowey, D.; Johnson, W. S.; Kluge. A. F.; Meinwald, J. *Tetrahedron Lett.*, **1972**, 3019.
9. The diastereomerers were separable by silica gel chromatography, but gradually decomposed on standing even in a refrigerator to give the desulfenylation products. Accordingly, the dialkylated products were immediately used without purification. The ^1H NMR spectra of the diastereomers are partly different from each other.

   6; ^1H NMR (400 MHz; $CDCl_3$) δ 0.93 (3H, t, *J*=7.2), 1.25 (3H, s), 1.33 (3H, s), 1.61 (3H, br. s), 1.6-1.8 (m, 4H), 2.0-2.3 (m, 4H), 2.40 (3H, s), 2.55 (1H, ddd, *J*=18.5, 10.5, and 5.5 Hz), 2.80 (1H, ddd, *J*=18.5, 10.5, and 5.3 Hz), 3.9-4.0 (4H, m), 5.14 (1H, br t, *J*=7.0), 7.28 (2H, d, *J*=8.0), 7.39 (2H, d, *J*=8.0).

   The diastereomer of **6**; ^1H NMR (400 MHz; $CDCl_3$) δ 0.93 (3H, t, *J*=7.4), 1.31 (3H, s), 1.35 (3H, s), 1.52 (3H, br s), 1.6-1.8 (m, 4H), 1.78 (1H, m), 1.95-2.3 (4H, m), 2.39 (3H, s), 2.42 (1H, m), 3.9-4.0 (4H, m), 5.06 (1H, br t, *J*=7.0), 7.27 (2H, d, *J*=8.0), 7.37 (2H, d, *J*=8.0).
10. ^1H NMR (250 MHz; $CDCl_3$) δ 1.00 (3H, t, *J*=7.5Hz), 1.27 (3H, s), 1.35-1.71 (4H, m), 1.62 (3H, s), 2.05-2.25 (6H, m), 2.17 (3H, d, *J*=1.3Hz), 2.70 (1H, dd, *J*=6.7, 5.7Hz), 3.68 (3H, s), 5.14 (1H, br t), 5.67(1H, br s). For the comparison of the reported values of the authentic JH II,[2] the ^1H NMR spectrum (250 MHz) was also taken in CCl_4 (locked externally using $CDCl_3$) with TMS as internal standard. ^1H NMR (250MHz; CCl_4) δ 0.98 (3H, t, *J*=7.5Hz), 1.33 (3H, s), 1.30-1.70 (4H, m), 1.62 (3H, s), 1.95-2.25 (6H, m), 2.14 (3H, d, *J*=1.1Hz), 2.49 (1H, dd, *J*=7.9, 4.9.Hz), 3.61 (3H, s), 5.11 (1H, br t), 5.56 (1H, br s).
11. (±)-JH II could be synthesized from racemic **4** as the starting material by the identical pathway.
12. Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.*, **1977**, *42*, 384.
13. This method was successfully applied to determine the enantiomerical purity of JH III, see: (a) Mori, K.; Mori, H. *Tetrahedron*, **1987**, *43*, 4097,
14. Recently König and coworkers have succeeded the direct separation of enantiomeric JH I-III using a capillary GLC with a cyclodextrin derivative as the chiral phase. König, W. A.; Gehrcke, B.; Peter, M. G.; Preswich, G. D. *Tetrahedron: Asymmetry*, **1993**, *4*, 165.

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