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STUDIES ON THE IDENTIFICATION AND SYNTHESES OF INSECT PHEROMONES XXI

STEREOSELECTIVE SYNTHESIS OF ALL THE POSSIBLE OPTICAL ISOMERS OF THE MOSQUITO OVIPOSITION ATTRACTANT PHEROMONE**

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Abstract: All the four optical isomers of the oviposition attractant pheromone of the mosquito Culex pipiens fatigans were synthesized via Sharpless asymmetric epoxidation.

With the increasing number of identified chiral insect pheromone compounds, more attention has been payed on the topic of stereochemistry-activity relationship among pheromones. The oviposition attractant pheromone of the mosquito Culex pipiens fatigans was identified by Laurence and Pickett[1] from the apical droplet of the mosquito eggs as erythro-6-acetoxy-5-hexadecanolide in 1982. The synthetic racemate (1a + 1b) was reportedly as active as the natural pheromone, the absolute configuration, however, remains unclear[2]. We now wish to describe the stereoselective synthesis of all the possible optical isomers 1a-d. 1 could be regarded as the ring-opened product derived from 5,6-epoxyhexadecanoic acid and therefore Sharpless asymmetric epoxidation[3] appears to be a good method. During the progress of this synthesis, Mori'S publication[4] on the synthesis of both enantiomers of 1a and 1b was seen, which was based on a kinetic resolution of Sharpless epoxidation. Our method presents an alternative approach to synthesize all the optical isomers of 1.

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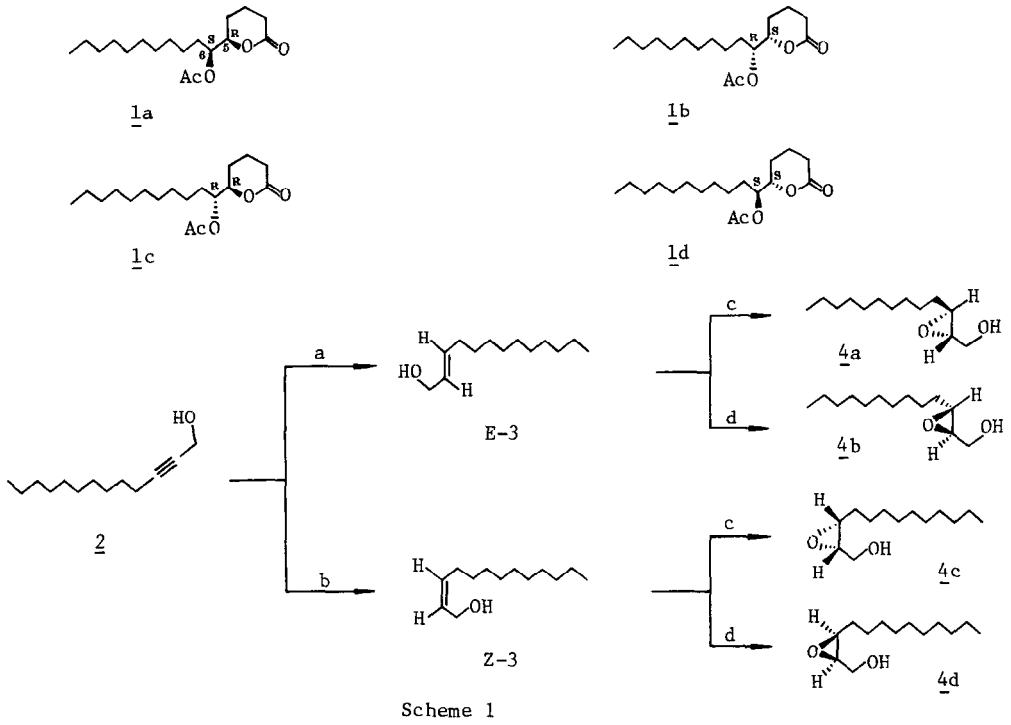
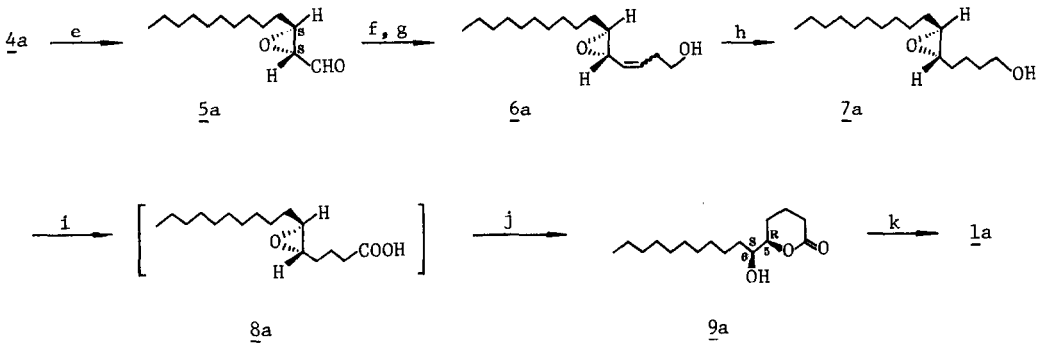


Scheme 1



Scheme 2

Conditions for Scheme 1 and 2:

a. P-2 Ni, H_2, b. LAH-diglyme, c. L(+)-DET-Ti(OPr^i)$_4$-t-BuOOH,

d. D(-)-DET-Ti(OPr^i)$_4$-t-BuOOH, e. CrO_3-Py-CH_2Cl_2,

f. $(C_6H_5)_3\overset{+}{P}CH_2CH_2CH_2OC(CH_3)_2OCH_3Br^-$, NaH-THF-DMSO,

g. HOAc-H_2O-CH_3CN (0.006 : 1 : 4), h. $(C_6H_5)_3PRhCl$, H_2,

i. $RuCl_3$ + $NaIO_4$, CH_3CN-CCl_4-H_2O (2 : 2 : 3), j. (+)-CSA-CH_2Cl_2, k. Ac_2O-Py.

The cis-allylic alcohol Z-3a or its E-3b isomer, prepared from propargylic alcohol 2[5] by partial hydrogenation over P-2Ni or LAH reduction in the usual manner, was exposed over Sharpless conditions [(+) or (-)-DET-Ti(OPr^i)$_4$-t-BuOOH (1 : 1.2 : 1), -45°C, 3 days for E-3 or 6-7 days for Z-3, based on the natural or unnatural tartarate used], gave all the 4 optically active epoxy alcohols 4a-d in a yield of 80%. The e.e. of 4a-d was shown to be 96-97%, estimated by ^{19}F-NMR and HPLC analysis[6] of the corresponding (S)-α-methoxy--α-(trifluoromethyl)phenyl acetate (MTPA ester) of 4a-d. 4a-b were entirely free of its erythro isomer and 4c-d were free of its threo isomer as judged by GC[7]. Starting from 4, the enantiomers of the erythro lactones 1a-b and the threo forms 1c-d were prepared in 7 steps as illustrated by preparation of 1a from 4a shown in Scheme 2.

(2S, 3S)-4a was treated with Collins reagent[8] (CrO_3-Py-CH_2Cl_2 at r.t., 0.5 hr, worked-up by filtering the crude product over an Al_2O_3 column) to give quantitative epoxy aldehyde 5a. Direct addition of the rest with functionalized three carbon atoms by Wittig reaction using the phosphonium salt bearing carboxyethyl or its ester failed owing to elimination of the phosphonium salt.[9] Thus the Wittig reagent with protected hydroxypropyl group according to Corey's recent publication[10] was employed with a slight modification. Treatment of 5a with the ylide prepared from 2-methoxy-2-propyl ether of (3-hydroxy propyl)triphenylphosphonium bromide and NaH (a DMSO-THP solution of 5a and 1.2 eq. of the Wittig reagent was added into NaH-THP at -10°C-0°C, 1 hr) followed by weak acidic hydrolysis (HOAc-CH_3CN-H_2O, 0.006 : 4 : 1, 30°C, 2 hr) gave 6a in a yield of 60-65% over 2 steps. Wilkinson homogeneous hydrogenation[11] of 6a yielded in addition to 7a (45% yield) a ketone by-product (15%) obtained from the catalytic rearrangment of the α,β-unsaturated epoxide[12], which could be removed from 7a by $NaBH_4$ reduction. The free OH of 7a was oxidized quantitatively to an (5S, 6S)-acid-8a by the catalytic RuO_4 oxidation[13] without affeting the chiral epoxy moeity. 8a was lactonized in acidic conditions to form 6S-hydroxy-5R-hexadecanolide 9a with inversion of the configuration at C_5. ^{19}F-NMR analysis of (S)-MTPA ester of 9a confirmed again the 97% e.e., indicating that there was no loss of optical activity from 4a to 9a. Acetylation of 9a gave the erythro 1a, $[\alpha]_D$ -37.4° (C 2.2, $CHCl_3$), (Lit.[4] -38.5°) in an overall yield of 15-20% from 2 in 9 steps. 1a: ^{1}H-NMR ($CDCl_3$) δ 0.86(t, J=7, 3H), 1.26(br, 18H), 1.76(m, 4H), 2.00(s, 3H), 2.40(m, 2H), 4.35(m, H), 4.80(m, 1H); IR (film) 1745, 1710, 1230 cm^{-1}; MS m/e 313 (2.15), 271(0.31), 253(0.48), 1.60(1.67), 142(2.9), 99(33.11), 100(8.09), 43(100%). The three other optical isomers were prepared in the similar manner. Comparison of the $[\alpha]_D$, ^{1}H-NMR, IR and MS of our synthetic pheromones 1a-b and two other threo isomers 1c-d with those of the Lit.[1,4] comfirmed the identity of 1a-d. The optical rotations of some intermediats and the products are summulized in Table 1[14].

Table 1

entry \ comp. $[\alpha]_D$	1	11	9
a	-37.4	-11.8	-18.9
b	+37.2	+11.9	+18.8
c	+14.6	-7.6	-1.8
d	-14.1	+7.7	+1.7

References and Notes

1. B.R.Laurence and J.A.Pickett, J.Chem.Soc.Chem.Commun. 59 (1982).
2. One of the authors was recently informed by Prof. K.Mori of Tokyo University that the absolute configuration of the natural pheromone was shown to be 5R, 6S.
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6. ^{19}F-NMR was performed on Varian XL-200 MHz using CF_3COOH as internal, chemical shift of the (S)-MTPA ester of 4a-d were 3.761, 3.836, 3.698, 3.629 ppm respectively, in an e.e. of 96-97%. HPLC: column, 250×5 mm YWG-80 (5μ), solvent: n-hexane-$ClCH_2CH_2Cl$ (2 : 1), 1.5 ml/min, detection at 217 nm.
7. GC was carried on Varian 3700, H_2 flaming detector. Column: FFAP 15 m×0.2 mm programmed from 100 to 230°C, 8°C/min, t_R: 19.09 min for 1a and 1b, 19.34 min for 1c and 1d.
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14. The optical rotation was measured on a Rodoliph Research Autopol Polarimeter with c in the range of 1.2-6 and $CHCl_3$ as solvent in all cases. All the compounds have been fully characterized by ^{1}H-NMR, IR(film) and Mass spectra.

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