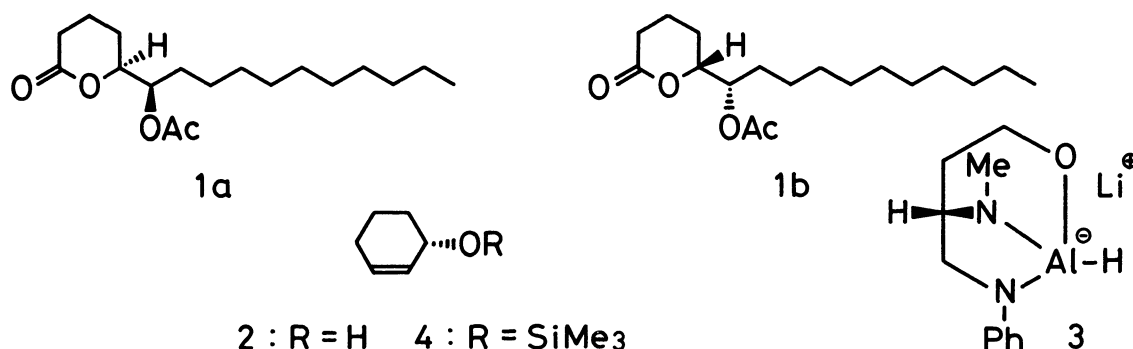


SYNTHESIS OF BOTH ENANTIOMERS OF ERYTHRO-6-ACETOXY-5-HEXADECANOLIDE,
THE MAJOR COMPONENT OF A MOSQUITO OVIPOSITION ATTRACTANT PHEROMONEToshio SATO, Makoto WATANABE, Naoki HONDA, and Tamotsu FUJISAWA*
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Stereoselective synthesis of both (5*S*,6*R*)-(+)- and (5*R*,6*S*)-(-)-6-acetoxy-5-hexadecanolides, the major component of a mosquito oviposition attractant pheromone, was achieved from (*S*)-2-cyclohexen-1-ol.

Erythro-6-acetoxy-5-hexadecanolide is the major component of the oviposition attractant pheromone from the apical droplet of eggs of the mosquito *Culex pipiens fatigans*.¹⁾ The racemic synthetic material has a biological activity, but the absolute configuration of the natural pheromone remained unknown. Although syntheses of the optically active pheromone were recently achieved,²⁾ we describe herein the stereoselective synthesis of both (5*S*,6*R*)-(+)- and (5*R*,6*S*)-(-)-6-acetoxy-5-hexadecanolides (1*a* and 1*b*) from easily obtainable (*S*)-2-cyclohexen-1-ol, in a simple method. Construction of two chiral centers at C₅ and C₆ was achieved by the regioselective S_N2 reaction of decyllithium to the key intermediate, (2*S*,3*S*)- or (2*R*,3*R*)-2,3-epoxycyclohexan-1-one (7 or 12).

The starting material, optically pure (*S*)-2-cyclohexen-1-ol (2) ($[\alpha]_D^{23} -112.5^\circ$ (c 1.06, CHCl₃)), was effectively synthesized from 2-cyclohexen-1-one in 95% yield using the chiral reducing reagent (3) of lithium aluminum hydride modified with (*S*)-4-anilino-3-methylamino-1-butanol, which was prepared easily from (*S*)-aspartic acid.³⁾ Procedure *via trans*-epoxidation or *cis*-epoxidation of 2 can lead to 1*a* or



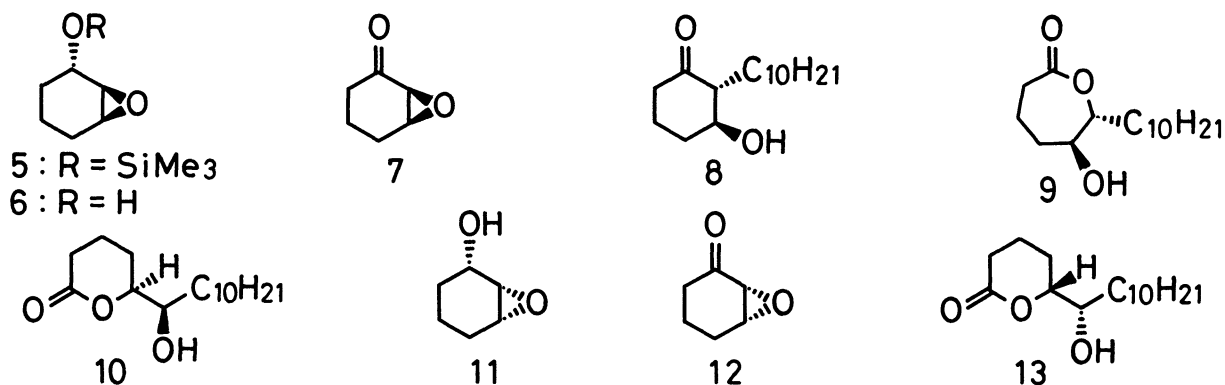
1*b*, respectively. Thus (*S*)-alcohol 2 was converted into trimethylsilyl ether 4 by treatment with trimethylsilyl chloride in the presence of triethylamine in 87% yield ($[\alpha]_D^{24} -96.9^\circ$ (c 1.24, CHCl₃)). Epoxidation of 4 with *m*-chloroperbenzoic acid by the method of Heathcock *et al.*⁴⁾ afforded (-)-epoxide 5 in 89% yield ($[\alpha]_D^{23} -11.2^\circ$ (c 1.00, CHCl₃)), which was contaminated with ca 10% of the *cis* isomer. Hydrolytic removal of the trimethylsilyl group gave epoxy alcohol 6 in 71% yield. The pure 6

($[\alpha]_D^{22} -8.72^\circ$ (c 1.03, CHCl_3)) could be obtained after purification on SiO_2 -TLC. Oxidation of the epoxy alcohol 5 with the Collins reagent⁵⁾ gave (2*S*,3*S*)-2,3-epoxycyclohexan-1-one 7 in 67% yield ($[\alpha]_D^{22} -159.1^\circ$ (c 0.916, CHCl_3)).

The introduction of the decyl group to 7 was accomplished by the regiospecific 1,2-addition of the alkyl lithium to lithium enolate epoxide.⁶⁾ Lithium enolate of 7 was treated with decyllithium to give only the desired 1,2-adduct ($\text{S}_\text{N}2$ product), (2*R*,3*S*)-2-decyl-3-hydroxycyclohexan-1-one (8) in 64% yield ($[\alpha]_D^{24} -4.93^\circ$ (c 0.568, CHCl_3)). Baeyer-Villiger oxidation of 8 with *m*-chloroperoxybenzoic acid⁷⁾ gave seven-membered lactone 9, which was essentially single product. The crude lactone 9 was treated with KOH-MeOH to give a dihydroxy acid,⁸⁾ which was heated at 130°C for 20 min^{2a)} to give hydroxylactone (5*S*,6*R*)-10 in 58% yield from 8 ($[\alpha]_D^{22} +12.4^\circ$ (c 0.390, CHCl_3)). Acetylation of the lactone 10 with $\text{Ac}_2\text{O-Py}$ gave the final product (5*S*,6*R*)-(+)-10 in 75% yield ($[\alpha]_D^{23} +39.1^\circ$ (c 0.202, CHCl_3); lit.^{2a)} $[\alpha]_D^{21.5} +38.8^\circ$ (CHCl_3)).

In the same manner mentioned above, (2*R*,3*R*)-2,3-epoxycyclohexan-1-one 12 (62%, $[\alpha]_D^{23} +153.8^\circ$ (c 0.690, CHCl_3)) was synthesized by oxidation of *cis*-2,3-epoxycyclohexan-1-ol (11),⁹⁾ obtained by *syn*-epoxidation¹⁰⁾ of (*S*)-alcohol 2. After introduction of the decyl group, (2*S*,3*R*)-2-decyl-3-hydroxycyclohexan-1-one (66%, $[\alpha]_D^{22} +4.35^\circ$ (c 0.323, CHCl_3)) was subjected to oxidation, followed by hydrolysis, and lactonization, to give the hydroxy lactone 13 (61%, $[\alpha]_D^{22} -12.5^\circ$ (c 1.29, CHCl_3)). Acetylation of the lactone yielded the (5*R*,6*S*)-(-)-10b (70%, $[\alpha]_D^{22} -39.2^\circ$ (c 0.610, CHCl_3); lit.^{2a)} $[\alpha]_D^{21.5} -38.5^\circ$ (CHCl_3)).

As mentioned above, stereoselective synthesis of both enantiomers of *erythro*-6-acetoxy-5-hexadecanolide with high optical purity was achieved using pure (*S*)-2-cyclohexen-1-ol as a starting material.



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