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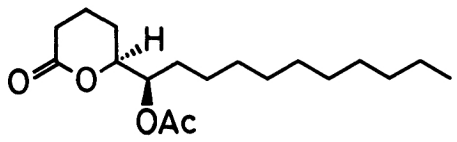
SYNTHESIS OF BOTH ENANTIOMERS OF ERYTHRO-6-ACETOXY-5-HEXADECANOLIDE, THE MAJOR COMPONENT OF A MOSQUITO OVIPOSITION ATTRACTANT PHEROMONE

Toshio SATO, Makoto WATANABE, Naoki HONDA, and Tamotsu FUJISAWA*
Chemistry Department of Resources, Mie University, Tsu, Mie 514

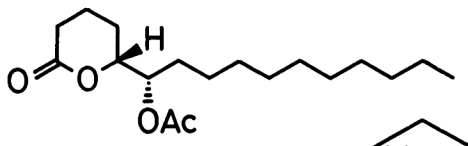
Stereoselective synthesis of both (5*S*,6*R*)-(+)- and (5*R*,6*S*)-(-)-6-acetoxy-5-hexadecanolides, the major component of a mosquito oviposition attractant pheromone, was achieved from (*S*)-2-cyclohexen-1-ol.

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 (1a and 1b) from easily obtainable (*S*)-2-cyclohexen-1-ol, in a simple method. Construction of two chiral centers at C_5 and C_6 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).

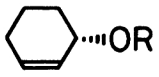
The starting material, optically pure (*S*)-2-cyclohexen-1-ol (2) ($[\alpha]_D^{23}$ -112.5° (c 1.06, $CHCl_3$)), was effectively synthesized from 2-cyclohexen-1-one in 95% yield using the chiral reducing reagent (3) of lithium aluminum hydride modified with (*S*)-4-anilino-3-methylamino-1-butanol, which was prepared easily from (*S*)-aspartic acid.[3] Procedure *via trans*-epoxidation or *cis*-epoxidation of 2 can lead to 1a or



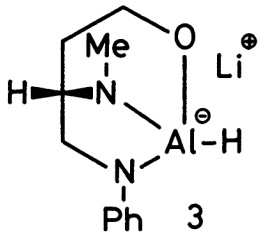
1a



1b



2 : R = H 4 : R = $SiMe_3$



3

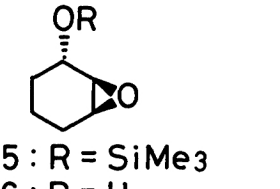
1b, respectively. Thus (*S*)-alcohol 2 was converted into trimethylsilyl ether 4 by treatment with trimethylsilyl chloride in the presence of triethylamine in 87% yield ($[\alpha]_D^{24}$ -96.9° (c 1.24, $CHCl_3$)). Epoxidation of 4 with *m*-chloroperbenzoic acid by the method of Heathcock *et al.*[4] afforded (-)-epoxide 5 in 89% yield ($[\alpha]_D^{23}$ -11.2° (c 1.00, $CHCl_3$)), 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

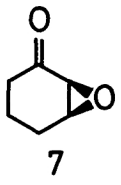
($[\alpha]_D^{22}$ -8.72° (c 1.03, $CHCl_3$)) could be obtained after purification on SiO_2-TLC. Oxidation of the epoxy alcohol 5 with the Collins reagent[5] gave (2*S*,3*S*)-2,3-epoxycyclohexan-1-one 7 in 67% yield ($[\alpha]_D^{22}$ -159.1° (c 0.916, $CHCl_3$)).

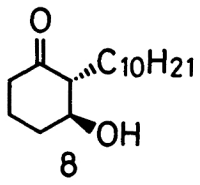
The introduction of the decyl group to 7 was accomplished by the regiospecific 1,2-addition of the alkyllithium to lithium enolate epoxide.[6] Lithium enolate of 7 was treated with decyllithium to give only the desired 1,2-adduct (S_N2 product), (2*R*,3*S*)-2-decyl-3-hydroxycyclohexan-1-one (8) in 64% yield ($[\alpha]_D^{24}$ -4.93° (c 0.568, $CHCl_3$)). Baeyer-Villiger oxidation of 8 with *m*-chloroperoxybenzoic acid[7] 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° (c 0.390, $CHCl_3$)). Acetylation of the lactone 10 with Ac_2O-Py gave the final product (5*S*,6*R*)-(+)-1a in 75% yield ($[\alpha]_D^{23}$ +39.1° (c 0.202, $CHCl_3$); lit.[2a] $[\alpha]_D^{21.5}$ +38.8° ($CHCl_3$)).

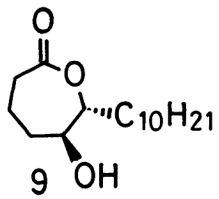
In the same manner mentioned above, (2*R*,3*R*)-2,3-epoxycyclohexane-1-one 12 (62%, $[\alpha]_D^{23}$ +153.8° (c 0.690, $CHCl_3$)) was synthesized by oxidation of *cis*-2,3-epoxycyclohexan-1-ol (11),[9] obtained by *syn*-epoxidation[10] of (*S*)-alcohol 2. After introduction of the decyl group, (2*S*,3*R*)-2-decyl-3-hydroxycyclohexan-1-one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

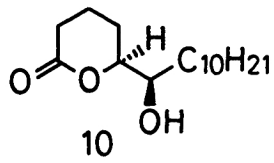
As mentioned above, stereoselective synthesis of both enantiomers of *erythro*-6-acetoxy-5-hexadecanolide with high optical purity was achieved using pure (*S*)-2-cyclohexen-1-ol as a starting material.

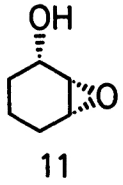


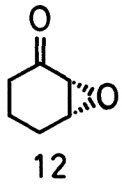


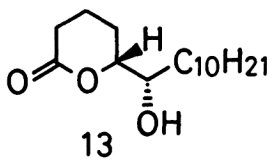












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