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Stereoselective Synthesis of (-)-(5R,6S)-6-Acetoxy-5-Hexadecanolide, The Mosquito Oviposition Attractant Pheromone

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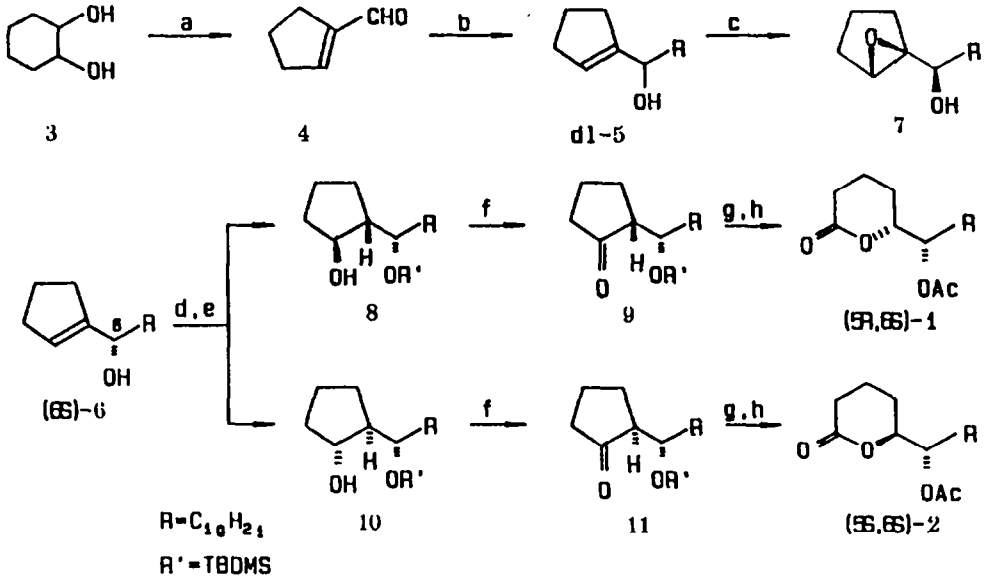
Abstract: The natural mosquito oviposition attractant pheromone, (-)-(5R,6S)-6-acetoxy-5-hexadecanolide (1) was synthesized from readily available 1,2-cyclohexanediol, using kinetic resolution of cyclic allylic alcohol by modified Sharpless asymmetric epoxidation reagent as the key step.

The mosquito Culex pipiens fatigans Wiedemann is found everywhere, but particularly in tropic zones where it is a vector for filarial diseases and possibly malaria. The major component of the oviposition attractant pheromone of this mosquito was isolated from apical droplet of its eggs and identified as (dl)-erythro-6-acetoxy-5-hexadecanolide[1]. The active natural pheromone was proved [2] to be (-)-(5R,6S)-6-acetoxy-5-hexadecanolide (1). Though a great number of synthetic routes to the mosquito oviposition attractant pheromone have been published[3], a short and efficient route to it still needs to be explored. We now wish to report a new stereoselective synthesis of 1, using kinetic resolution of cyclic allylic alcohol by modified Sharpless asymmetric epoxidation reagent.



Reagents: a. 1. $NaIO_4$, pH=4; 2. KOH-H_2O. b. $C_{10}H_{21}MgBr$, THF. c. $Ti(OiPr)_4$, D-(-)-DIPT, CaH_2, SiO_2, TBHP. d. TBDMSCl, imidazole. e.9-BBN then H_2O_2, NaOH. f. PDC, CH_2Cl_2. g. CF_3CO_3H. h. Ac_2O, Py.

Scheme

Cyclopentene aldehyde 4, prepared from the mixture of trans- and cis-1,2-cyclohexanediol 3[4], was reacted with decyl Grignard reagent($C_{10}H_{21}MgBr$) to give the (dl)-cyclic allylic alcohol 5[3b] in 78%. In order to obtain the (6S)-cyclic allylic alcohol 6, (dl)-5 was exposed over modified Sharpless reagent[5], using D-(-)-DET as ligand to give a mixture of (-)-(6S)-6(45%) and (6R)-4,5-epoxy alcohol (7) (55%) in 97% yield. The e.e of 6 was shown to be 96%, estimated by ^{19}F-NMR analysis of the corresponding (S)-α-methoxyl-α-(trifluoromethyl)phenylacetate (MTPA ester)[6] of 6 . The alcohol 6 was converted to the silyl ether by reacting with TBDMSCl in the presence of imidazole in quantitative yield. Hydroboration[7] of the silyl ether of 6 with 9-BBN followed by alkaline hydrogen peroxide work-up, yielded a mixture of the alcohol 8(66%) and its diastereoisomer 10 (32%) in 98% yield in a ratio of 2:1. The structure assignment of 8 was made based on an example

similar to this case[8]. The lower selectivity of hydroboration in this case might be attributed to the lack of preferential conformation of 6. Oxidation of 8 with PDC gave ketone 9 in 95% yield. Compound 9 was submitted to Beayer-Villige or oxidation with trifluoroperacetic acid followed by acetylation with acetic anhydride afforded the target erythro lactone 1, $[\alpha]_D^{26}$ -37.4° (c 0.805, $CHCl_3$) [lit[3f] $[\alpha]_D$ -37.4° (c 2.2, $CHCl_3$)] in 76% overall yield in two steps. Starting from 10, the threo lactone 2, $[\alpha]_D^{26}$ -15.9° (c 0.71, $CHCl_3$) [lit[3f] $[\alpha]_D$-14.6°], was prepared in eight steps as illustrated by the preparation of 1 from 3, shown in the Scheme.

In conclusion, a short and efficient stereoselective total synthesis of the natural mosquito oviposition attractant pheromone, (-)-(5R,6S)-1 was accomplished in eight steps from 1,2-cyclohexanediol 3 in 22.8% overall yield. Its stereoisomer (-)-(5S,6S)-2 was also prepared in similar way from the diastereoisomer 10 obtained from the hydroboration of (6S)-6.

Experimental

All m.ps. were uncorrected. The silica gel in epoxidation and for flash chromatography was silica gel H (10-40 μ) which was produced by Qingdao Chemical Plant, China. IR spectra were measured on a Shimadzu 440 spectrometer. ^{1}H-NMR spectra were recorded on Varian EM-360A (60 MHz) and FX-90Q (90 MHz) spectrometers, using TMS as internal standard. Mass spectra were conducted on a Shimadzu HP-5880A GC-MS instrument. The optical rotations were measured on a Rudolph Research Utopol III/WZZ-1 automatic polarimeter. Elemental analysis were performed by Analytical Department of this Institute. Dichloromethane(A.R.) was distilled from calcium hydride.Diethyl tartrate (DET) was prepared from tartaric acid and diisopropyl tartrate (DIPT) was obtained from Aldrich Chemical Co.. Titanium (IV) isopropoxide was distilled under reduced pressure and stored under inert atmosphere. 85% tert-butyl hydroperoxide (TBHP) was obtained from Merck-Schuchardt Co., which was further purified according to the literature[9]. Calcium hydride was obtained from Fluka-Garantie Co.. 1,2-cyclohexanediol was obtained

from Tokyo Kasei Chemical Co..

1-(1'-Hydroxyundecyl)-cyclopentene (5)

To an acid solution of 28.3g of sodium periodate in 250mL water (the pH of this solution was adjusted to 4 with nitric acid and sodium hydroxide). was added the solution of 12 g of 1,2-cyclohexanediol 3 in 150mL ether. The mixture was stirred vigorously for 0.5 h at room temp. After addition of 38.4 mL of 20% aq.KOH solution, the reaction mixture was stirred for an additional 1 h.The mixture was extracted with ether followed by usual work-up to give a residue,which was submitted to the following Grignard reaction.

A solution of 25.8mL (0.125mmol) of 1-bromodecane in 15mL of anhydrous THF was added dropwise to a stirred suspension of 3g (0.125mmol) of Mg turnings in 15mL of anhydrous THF at reflux temp.The mixture was then stirred for an additional 0.5 h under reflux. After cooling to the R.T., 6.1g (0.063mmol) of cyclopentene aldehyde 4 in THF was added and the mixture was stirred for 0.5 h. The reaction mixture was then poured into a cooled solution of aq. 5% HCl and extracted with ethyl acetate. The organic layer was washed successively with aq. $NaHCO_3$ and brine, and dried. The crude product was purified by flash chromatography on silica gel (petroleum ether-ethyl acetate 98:2 as eluent) to give a light yellow liquid 5 in 77.6% yield. IR (film) νmax: 3350(OH), 3050(=CH), 1650(C=C) cm^{-1}; ^{1}H-NMR (CCl_4): 5.37 (1H, br-s, OH), 4.04(1H, m, HC-OH), 3.07(1H, s, OH), 1.26[20H,br, $(CH_2)_9$, CH_2], 2.01(4H, m, CH_2-C=C), 0.85(3H, t, $-CH_3$) ppm; MS m/z: 238(M^+), 221 (M^+-OH), 169($C_{10}H_{21}CO^+$), 112($C_8H_{16}^+$), 97($C_6H_9O^+$, 100%), 69(M^+-$C_{10}H_{21}CO$), 67($C_5H_7^+$, 51)

1-[1'-(S)-Hydroxyundecyl]-cyclopentane (6)

To a mixture of 5.8mL (19.4mmol) of $Ti(O^iPr)_4$, 80mg (2mmol) of CaH_2 and 120mg of silica gel in 150mL of dry CH_2Cl_2 was injected 3.89mL (23.3 mmol) D-(-)-diethyl tartrate (DET) via syringe under N_2 at -40°C. After 10 min., (±)-5 was injected. To the stirred reaction mixture 2.02mL (12mmol) of anhydrous TBHP (5.92M) was injected at -40°C and then stirred for an additional 1h. After the reaction mixture being stored overnight at -20°C, it was added 70mL of 10% aqueous tartaric acid solution. Stirring was continued for 1.5 hrs at room temp. until the aqueous layer became clear. After being separated, the organic layer was dried over anhydrous Na_2SO_4 The residue was purified by flash chromatography (petroleum ether-ethyl acetate 95:5 as eluent) to afford 2.13g of 6 (45%) and 2.79g of 7 (55%).

6: $[\alpha]_D^{16}$ -5.49° (c 0.91, EtOH); IR (thin film) νmax: 3350(OH), 3050 (=CH), 1650(C=C) cm^{-1}; ^{1}H-NMR (CCl_4): 5.37(1H, br, =CH), 4.04(1H, m, HC-O), 3.07(1H, s, OH), 2.10(4H, m, CH_2-C=C), 1.26[20H, br, $(CH_2)_9$, CH_2]. 0.85(3H,

t, CH_3) ppm; MS m/z: 238(M^+), 221(M^+-OH), 169($C_{10}H_{21}CO^+$), 112($C_8H_{16}^+$), 97 ($C_6H_9O^+$, 100%), 69(M^+-$C_{10}H_{21}CO$), 67($C_5H_7^+$, 51.0).

7: $[\alpha]_D^{16}$ +11.57° (c, 2.10, EtOH); IR (thin film) νmax: 3400(OH), 1250(epoxy) cm^{-1}; ^{1}H-NMR (CCl_4): 3.60(1H, m, epoxy), 3.16(1H, s, OH), 1.20 [24H, br, $(CH_2)_9$, $(CH_2)_3$], 0.85(3H, t, CH_3) ppm; MS m/z: 254(M^+, 0.1%), 207 (M^+-H_2O-CH_3O, 0.2), 197(M^+-nBu, 0.1), 169($C_{10}H_{21}CO^+$, 0.2), 85($C_5H_{10}O^+$, 36) 83($C_5H_7O^+$, 15.4), 67($C_5H_7^+$, 40.4), 43($C_3H_7^+$, 78.0), 41($CH_3CH{=}CH^+$, 100).

(1S,2S)-2-Hydroxy-1-[1'-(S)-t-butyldimethylsilyloxylundecyl]-cyclopentanol (8)

To a solution of 1.1g of imidazole and 1g(4.2mmol) of 6 in 34ml of DMF was added a solution of 0.95g (6.3mmol) of TBDMSCl in 5mL of DMF. The reaction mixture was stirred at room temp. overnight and extracted with petroleum ether. The organic layer was washed with water and dried over anhydrous Na_2SO_4. After removal of solvent, the residue was purified by flash chromatography (petroleum-ethyl acetate 97:3 as eluent) to afford the pure silyl product in quantitative yield. $[\alpha]_D^{21}$ -28.2°(c, 0.63, EtOH); IR(film) ν max: 3030(=CH), 1720(C=C), 1250(Si-C) cm^{-1}; ^{1}H-NMR (CCl_4): 5.43(1H, br, =CH), 4.20(1H, m, HC-O), 2.10(4H, m, CH_2-CH=), 1.26 [20H, br,$(CH_2)_9$, CH_2], 0.84(12H, br, t-Bu, CH_3), 0.03[6H, s, $Si(CH_3)_2$] ppm; MS m/z: 352(M^+, 0.2%), 337(M^+-Me, 0.6), 295(M^+-t-Bu, 35.7), 219(M^+-t-Bu-Me-C_5H_8, 4.0),75(Me_2SiOH^+, 100], 67($C_5H_9^+$, 6.8).

To a solution of 0.42g (3.4mmol) of 9-BBN in 20ml of dry THF was added a solution of 517mg (1.47mmol) of above silyl product in 1mL of THF at 0°C under nitrogen,then the reaction temperature was raised to room temp. After standing at room temp. for 60 h, the reaction solution was stirred at 40°C for 5 h. After adjusting the pH of this solution to 8-9 with aq. 20% NaOH solution, the excess H_2O_2 was added. The reaction mixture was further stirred for 2 h and extracted with ether. The ether layer was washed successively with aq. sodium bisulfite, water and brine, and dried over anhydrous Na_2SO_4. After removing the solvent, the crude product was purified by flash chromatography (petroleum ether-ethyl acetate 98:2 as eluent) to afford 358mg of 8 (66%) and 173mg of 10 (32%) in 98% overall yield.

8: $[\alpha]_D^{21}$ -5.08° (c, 0.59, EtOH); IR(thin film): νmax: 3400(OH), 1260 (Si-C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90MHz): 4.07(1H, m, HC-OSi), 3.48(1H, m, HC-O), 1.85(3H, m, CH_2CH), 1.26[22H, br, $(CH_2)_9$, $(CH_2)_2$], 0.98(9H, s, t-Bu), 0.92 (3H,t, J=4Hz, Me), 0.04(6H, s, $SiMe_2$) ppm; MS m/z: 355(M^+-Me, 0.4%), 313 (M^+-nBu, 7.3), 312(313-H$^+$, 6.7), 285(M^+-C_6H_{13}, 2.1), 229(M^+-C_5H_8OH-tBu, 4), 114(tBu-Me_2Si^+, 3), 75($HOSiMe_2^+$, 100), 73($OSiMe_2^+$-1, 47.5), 57(tBu^+, 31). Found: C, 69.53, H, 12.46. Calc. for $C_{22}H_{46}O_2Si$: C, 69.65, H, 12.40.

10: $[\alpha]_D^{23}$ +41.34° (c, 1.49, EtOH); IR νmax: 3300(OH), 1250(silyl)cm^{-1}

^{1}H-NMR ($CDCl_3$, 90MHz): 3.85(1H, m, CH-OSi), 3.40(1H, m, CH-O), 1.70(3H, m, CH_2CH), 1.26[22H, br,$(CH_2)_9(CH_2)_2$], 0.98(9H, s, t-Bu), 0.85(3H, t, J=5Hz, Me), 0.04(6H, s, $SiMe_2$) ppm; MS m/z: 355(m^+-Me, 0.4%), 313 (M^+-t-Bu, 22.5), 285(M^+-C_6H_{13}, 6), 115(TBDMS$^+$-1, 8), 75($HOSiMe_2^+$, 100),57(t-Bu^+, 48).

(1S)-2-Keto-1-[1'-(S)-t-Butyldimethysilyloxylundecyl]-cyclopentanone 9

To a mixture of 500mg (1.33mmol) of PDC and 10mL of dried CH_2Cl_2 was injected a solution of 222mg(0.6 mmol) of 8 in 5mL dried CH_2Cl_2.After stirring for 5min, 59mg of PPTS was added to the reaction mixture. The reaction mixture was stirred for an additional 15 h and filtered through an alumina column.Work-up in usual way gave the pure oil 9 in 95% yield.$[\alpha]_D^{22}$ -50.82° (c, 0.76, EtOH); IR (thin film) νmax: 1740(C=O), 1250(TBDMS) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.80(1H, m, HC-OSi), 2.0(3H, m, CH_2COCH), 1.2(22H, br, C_9H_{18}, C_2H_4), 0.82 (12H, br, tBu, CH_3), 0.0(6H, s, $SiMe_2$) ppm; MS m/z: 367(M^+-1, 0.1%), 353(M^+-Me, 3.4), 311(M^+-tBu, 100), 285(M^+-C_5H_7O, 6.2), 227(M^+-$C_{10}H_{21}$, 11), 171(M^+-tBu-$C_{10}H_{21}$, 18), 141($C_{10}H_{21}^+$,19), 115(TBDMS$^+$-1,9.5), 83($C_5H_7O^+$, 23), 75($HO{=}SiMe_2^+$, 85).

(1R)-2-Keto-1-[1'-(S)-t-Butyldimethysilyloxylundecyl]-cyclopentanone 11

The oxidation of 10 was performed by using 200mg (0.54mmol) of 10, 500mg of PDC, and 60mg of PPTS. After working up as described for 9, 197mg of 11 were obtained in 99% yield. IR (film) max: 1740(C=O), 1250(TBDMS) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.80(1H, m, HC-OSi), 2.0(3H, m, CH_2COCH), 1.2(22H, br, C_9H_{18}, C_2H_4), 0.82 (12H, br, ^{t}Bu, CH_3), 0.0(6H, s, $SiMe_2$) ppm; MS m/z: 367(M^+-1, 0.1%), 353(M^+-Me, 12.1), 311(M^+-^{t}Bu, 100), 285(M^+-C_5H_7O, 3.45), 227(M^+-$C_{10}H_{21}$, 15.1), 141($C_{10}H_{21}^+$, 8), 115(TBDMS$^+$, 17.3), 83($C_5H_7O^+$, 22.8), 75($HO{=}SiMe_2^+$, 85).

(-)-(5R,6S)-6-Acetoxy-5-hexadecanolide 1

To a solution of 1mL of trifluoro acetic anhydride and 200mg (0.54mmol) of 9 in 8mL of CH_2Cl_2 was added 0.5mL of hydrogen peroxide(50-80%) in 2mL of CH_2Cl_2, and Na_2HPO_4 used as buffer, stirring for 4 h at room temp. The mixture was extracted with CH_2Cl_2. The organic layer was washed successively with sodium bisulfite and brine, and dried. After removal of solvent, the crude product was purified by flash chromatography (petroleum ether-ethyl acetate 98:2 as eluent) to afford 120mg of oxidation product in 82% yield. mp. 66-68°C. $[\alpha]_D^{30}$ -11.8° (c, 0.70, $CHCl_3$); IR (KCl): νmax 3400(OH), 1720 (lactone), 1270 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 4.10(1H, m, CH-O-CO), 3.8(1H, m, HC-OH), 3.6(1H, m, OH), 2.5(2H, m, CH_2-CO),1.9 [4H, m, $(CH_2$-$CO)_2$],1.26[18H,br, $(CH_2)_9$], 0.82(3H, t, J=4Hz, Me) ppm; MS m/z: 271 (M^++1, 0.1%), 253(M^+-OH, 0.9),235(M^+-$2H_2O$, 0.6), 169(M^+-$C_5H_7O_2$, 0.8),155(169$^+$-14, 0.1), 141($C_{10}H_{21}^+$,

0.2), 129(M^+-141, 4), 100($C_5H_8O_2^+$, 100), 57(tBu^+, 34), 71($C_5H_{11}^+$, 33).

The mixture of 80mg (0.3mmol) of the oxidation product, 0.5mL of acetic anhydride, 1mL of pyridine and 10mg of DMAP was stored at room temp. for 36 h. Work-up provided the crude product which was purified by flash chromatography (petroleum ether-acetate 95:5 as eluent) to give 86mg of a colourless oil 1 in 92% yield. $[\alpha]_D^{30}$ +37.4° (c, 0.805, $CHCl_3$); IR (thin film) νmax:1740(C=O), 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 4.95(1H, m), 4.34(m, 1H, m), 2.50(2H,m), 2.08(3H, s), 1.53-1.9(4H, m), 1.26(18H, br), 0.85(3H, t); MS m/z: 313 (M^++1, 8.6%), 253(M^+-1-60, 1), 142($C_7H_{10}O_3^+$, 22), 100($C_5H_8O_2^+$, 50.7), 99 ($C_5H_7O_2^+$, 90.6), 55($CHCH_2CO^+$, 35.5),43($C_3H_7^+$, 100).

(-)-(5S,6S)-6-Acetoxy-5-hexadecanolide (2)

Oxidation of 11 with trifluoroperacetic acid was carried out by using 200mg of 11, mL of trifluoroacetic anhydride, 0.5mL of hydrogen peroxide. After working up as described for 9, 124mg of the oxidative product was obtained in 85% yield. $[\alpha]_D^{30}$ +7.80° (c, 0.63, $CHCl_3$); IR(KCl): νmax 3400(OH), 1720(lactone), 1270 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 4.10(1H, m, CH-O-CO), 3.8(1H, m, HC-OH), 3.6(1H, m, OH), 2.5(2H, m, CH_2-CO), 1.9 [4H, m, $(CH_2$-$CO)_2$], 1.26 [18H,br,$(CH_2)_9$], 0.82(3H, t, J=4Hz, Me) ppm; MS m/z: 271 (M^++1, 0.1), 253 (0.9), 235(0.1), 169(6.8), 155(0.1), 141($C_{10}H_{21}^+$, 0.2), 100($C_5H_8O_2^+$, 100).

90mg (0.30mmol) of the oxidative product of 11 was acetylated as described above. Work-up provided 94mg of a colourless oil 2 in 90.4%. $[\alpha]_D^{26}$ -15.9° (c 0.71,$CHCl_3$). IR νmax: 1740(ester),1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 90MHz) 5.01(1H, m), 4.33(1H, m), 2.52(2H, m), 2.08(3H,s), 1.78(4H, m), 1.26(18H, br), 0.87(3H, t, J=5Hz). MS m/z: 313(M^++1, 9), 142($C_7H_{10}O_3^+$, 22), 100 ($C_5H_8O_2^+$, 51), 99($C_5H_7O_2^+$,91), 71($C_4H_7O^+$,29), 57($C_3H_5O^+$,10), 43($C_3H_7^+$,100).

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