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Enantio and Stereoselective Synthesis of (5R,6S)-6-Acetoxy-hexadecanolide, a Mosquito Oviposition Attractant Pheromone

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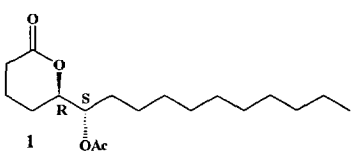
Abstract: The enantio and stereoselective synthesis of (5R, 6S)-6-acetoxy-hexadecanolide is described via chemo, regio and stereoselective opening with LiI of a chiral epoxy alcohol precursor.

The major component of the oviposition attractant pheromone isolated from the apical droplet of the eggs of the mosquito *Culex pipiens fatigans* is (5R,6S)-6-Acetoxy-hexadecanolide **1.**[1]



1

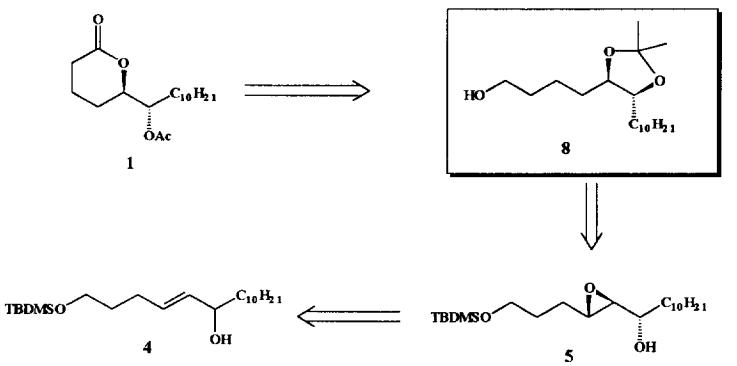
The substance attracts other gravid females of the same and some related mosquito species inducing them to oviposit in the same spot where the original eggs are found.

In the last years many syntheses of it appeared in the literature, [2] some of them employing Sharpless AE for the introduction of the correct chirality.

Generally Sharpless AE/KR was used on a small fragment of the carbon framework containing the hydroxyallylic function,[3] and subsequently the C_{15} chain was obtained by a regioselective coupling reaction on the epoxy ring.

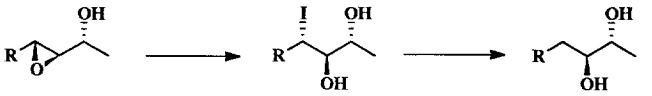
In an alternative retrosynthetic analysis (scheme 1), the AE/KR can be conveniently performed on the racemic alcohol **4** (which already contains the complete carbons framework), if the optically active epoxy alcohol **5** could be opened in regio and stereoselective fashion to the key diol **8**.

SCHEME 1



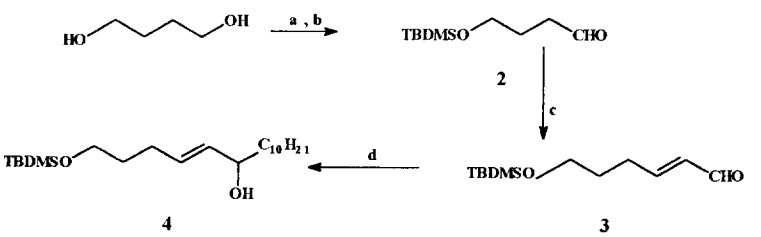
During our extensive studies on the opening of 2,3-epoxy alcohols, we found that metal halides like MgI_2 and LiX (X=I, Br, Cl) were able to give 3-halo-1,2-diols **B** from 2,3-epoxy alcohols **A** with high regio and stereoselectivity [4] (scheme 2). Furthermore the halohydrins obtained can be easily reduced to the corresponding *erythro* vicinal diols **C** by n-Bu_3SnH ("in situ" if MgI_2 is used), without need of any protection of hydroxyl group, necessary with the use of common reducing agent.[5]

SCHEME 2



Therefore we decided to utilize our methodologies for the regioselective opening of an appropriate epoxy alcohol like **5**. To this end racemic allylic alcohol **4** was firstly obtained from the commercially available 1,4-butandiol by the sequence shown in scheme 3.

SCHEME 3

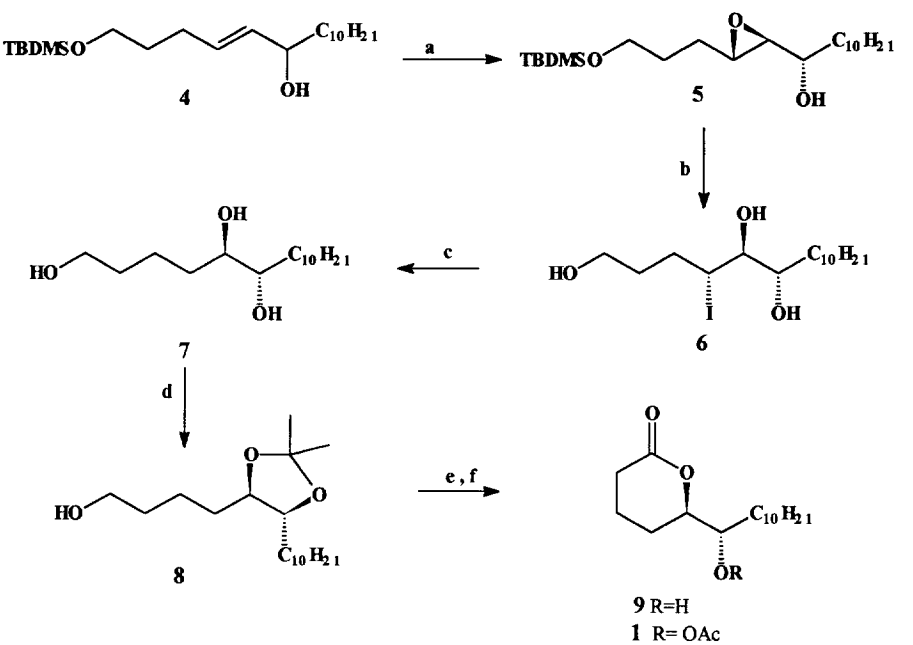


a: NaH, TBDMSCl in THF, rt, 90 min, 97% b: PCC, AcONa in CH_2Cl_2, rt, 2h, 95% c: formylmethylenetriphenylphosphorane in benzene, reflux, 24h, 70% d: $C_{10}H_{21}MgBr$ in Et_2O, 0°C to rt, 15 min, 75%

1,4-butandiol was monosilylated to known 4-[(t-Buyldimethylsilyl)oxy]-butan-1-ol [6] and oxidized with PCC affording the aldehyde **2**, which was then transformed into the α, β-unsaturated aldehyde **3** by Wittig reaction.[7] Addition of n-decylmagnesium bromide to **3** afforded the racemic alcohol **4**, which contains the complete C_{15} chain framework.

The allylic alcohol **4** (scheme 4) was then subjected to the Sharpless AE/KR, [8] with the obtaining of the optically active epoxy alcohol **5** in good yield and high ee (95 %).

SCHEME 4



a: L(+)-DIPT, $Ti(OiPr)_4$, molecular sieves in CH_2Cl_2, -20°C, 4 days, 45% b: LiI, Amberlyst 15 in CH_3CN, rt, 3 h, 90% c: n-Bu_3SnH, AIBN in toluene, 70°C, 2 h, 95% d: $(CH_3)_2C(OCH_3)_2$, pTsOH in $(CH_3)_2CO$, rt, 3 h, 99% e: $NaIO_4$, $RuCl_3$ in CCl_4/CH_3CN and phosphate buffer, rt, 4 h, then pTsOH, 1 h, 60% f: Ac_2O, Py, rt, 1 h, 99%

The epoxide ring opening of compound **5** was then performed with LiI/Amberlyst 15 in CH_3CN [4c]: in these conditions only the regioisomer **6** was obtained in high yield, without traces of the other regioisomer. Furthermore the use of an ion exchange resin like Amberlyst 15 gave contemporaneously the removal of the TBDMS protective group from primary hydroxy function.

Reduction of **6** with n-Bu_3SnH afforded the *erythro* diol **7**, which was then protected as acetonide **8**; oxidation with $RuCl_3 \cdot 3H_2O$ and subsequent lactonization with catalytic amount of pTsOH afforded the δ-lactone **9**.

Finally acetylation of **9** yielded quantitatively the lactone **1**, $[\alpha]_D$= -36.7 (c=1.8 in $CHCl_3$) in an overall yield of 23% from **4** (six steps) with ^1H and ^{13}C-NMR spectra completely in agreement with those reported in literature.[3,9]

In conclusion, this alternative route to the (5R,6S)-6-Acetoxy-hexadecanolide, not only demonstrates the usefulness of developed methodology for regio and stereoselective opening of epoxy ring, but also compares favourably with the already reported syntheses.

EXPERIMENTAL SECTION

General: Flash chromatography was carried out on silica gel Merck (70-230 mesh). TLC analysis were carried out on Merck Kieselgel 60 F-254 plates. All solvent used, except CH_3CN, were distilled and dried before use. ^{1}H-NMR spectra were recorded on a Varian Gemini (200 MHz) instrument in a $CDCl_3$ solution. ^{13}C-NMR spectra were determinated on the same instrument (50.3 MHz) in a $CDCl_3$ solution. Optical rotation were measured on a JASCO DIP-370 polarimeter.

4-[(t-Butyldimethylsilyl)oxy]-1-butanal 2. To a stirred suspension of PCC (323 mg,1.5 mmol) in CH_2Cl_2 (13 mL) and AcONa (15 mg, 0.3 mmol) 4-[(t-Butyldimethylsilyl)oxy]-1-butanol [6] (204 mg, 1 mmol) in CH_2Cl_2 (13 mL) was added. After 2 h (TLC monitoring) Et_2O was added and the mixture was passed through a short pad of florisil. The solvents were dried over Na_2SO_4 and evaporated under reduced pressure; the residue was purified by flash chromatography on silica gel (hexane: ether 7/3), affording **2** (192 mg, 95%). ^{1}H-NMR: 9.76 (t, J=2.6 Hz, 1H); 3.61 (t, J=5.9 Hz, 2H); 2.40-2.52 (m, 2H); 1.75-1.89 (m, 2H); 0.86 (s, 9H); 0.02 ppm (s, 6H). ^{13}C-NMR: 202.96; 62.01; 40.62; 25.71; 25.47; 25.33; 18.07; -5.70 ppm.

6-[(t-Butyldimethylsilyl)oxy]-2-hexenal 3. To a solution of formylmethylenetriphenylphosphorane (365 mg,1.2 mmol) in benzene (20 mL), **2** (202 mg,1 mmol) in benzene (3.4 mL) was added and the mixture was refluxed for 24 h. Then the solvent was removed under reduced pressure and the residue chromatographed on silica gel (petroleum ether:ether 9/1), affording pure **3** (160 mg, 70%).^{1}H-NMR: 9.47 (d, J=7.1 Hz, 1H); 6.77-6.95 (m, 1H); 6.02-6.18 (m, 1H); 3.61 (t, J=6.1 Hz, 2H); 2.31-2.47 (m, 2H); 1.60-1.77 (m, 2H); 0.86 (s, 9H); 0.02 ppm (s, 6H). ^{13}C-NMR: 194.36; 158.89; 133.14; 61.95; 30.71; 29.16; 25.69; 18.05; -5.65 ppm.

1-[(t-Butyldimethylsilyl)]oxy-4-hexadecen-6-ol 4. To a solution of the Grignard reagent, prepared from 1-bromodecane (309 mg, 1.4 mmol) and magnesium (34 mg) in ether (2.5 mL), **3** (228 mg, 1 mmol in 1.5 mL of ether) was added dropwise at 0°C. The reaction was stirred at room temperature for 15 min and then quenched with NH_4Cl sat. sol.(10 mL). The separated organic layer was dried (Na_2SO_4), concentrated in vacuo and chromatographed on silica gel (hexane:ether 7/3) to give **4** (277 mg, 75%). ^{1}H-NMR: 5.31-5.70 (m, 2H); 3.93-4.08 (m, 1H); 3.57 (t, J=6.5 Hz, 2H); 1.99-2.13 (m, 2H); 1.06-1.70 (m, 21H); 0.72-0.92 (m, 12H); 0.02 ppm (s, 6H). ^{13}C-NMR: 133.64; 131.32; 72.96; 62.33; 37.17; 32.08; 31.71; 29.41; 29.13; 28.25; 25.71; 25.28; 22.44; 18.04; 13.84; -5.63 ppm.

(4R,5S,6S)-1-[(t-Butyldimethylsilyil)oxy]-4,5-epoxy-hexadecan-6-ol 5. To solution of **4** (370 mg, 1 mmol), L(+)-DIPT (40 mg, 0.17 mmol) in CH_2Cl_2 (4 mL) and activated molecular sieves 3Å (100 mg) were added. The stirred mixture, under Argon, was cooled to -20°C, added of $Ti(OiPr)_4$ (28 mg, 0.1 mmol) and allowed to stir for 30 min at -20°C. Then TBHP (0.23 mL of 3 M sol. in isooctane, 0.7 meq) was added and the mixture was allowed to stand (TLC monitoring). After 3 days (~50% conversion) the reaction was quenched with an aqueous solution of $FeSO_4 \cdot 7\ H_2O$ (3.3 g) and tartaric acid (1 g) in 10 mL H_2O at -20°C and vigorously stirred at rt for 30 min until two clear phases appeared. The phases were

separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were concentrated and then stirred for 30 min at 0°C with 30% NaOH in brine (1 mL). After phase separation and extraction, the organic layer was washed with brine and dried (Na_2SO_4); the residue was purified by flash chromatography on silica gel (hexane:ether 7/3) affording **5** (174 mg, 45%). $[\alpha]_D$ = -5.6 (c = 1.8, $CHCl_3$). The ee could be estimated to be 95 % by ^{1}H-NMR analysis of the corresponding (S)-MPTA ester. ^{1}H-NMR: 3.70-3.82 (m, 1H); 3.55-3.70 (m, 2H); 2.94-3.08 (m, 1H); 2.70-2.80 (m, 1H); 1.88 (bs,OH); 1.10-1.70 (m, 22H); 0.75-1.00 (m, 12H); 0.02 ppm (s, 6H). ^{13}C-NMR: 68.55; 62.51; 60.95; 54.69; 33.42; 31.76; 29.53; 29.44; 29.39; 29.17; 29.04; 28.06; 25.77; 25.15; 22.50; 18.13; 13.91; -5.56 ppm.

(4R, 5S, 6S)-4-Iodo-1,5,6-trihydroxy-hexadecane 6. To a solution of **5** (386 mg, 1 mmol) in CH_3CN (10 mL) LiI (535 mg, 4 mmol) and Amberlyst 15 (543 mg, 2.5 mmol) were added. The mixture was stirred at rt and after the reaction was completed (TLC monitoring, ~2 h) the mixture was filtered. The filtrated solution, diluted with AcOEt, was washed with satd. $Na_2S_2O_3$ solution; the organic layer, dried over Na_2SO_4, was then evaporated in vacuo and chromatographed on silica gel (hexane:ethyl acetate 4/6) affording pure **6** (360 mg, 90%). ^{1}H-NMR: 4.32-4.44 (m, 1H); 3.75-3.90 (m, 2H); 3.67 (t, J=6.2 Hz, 2H); 3.04 (bs, OH); 2.69 (bs, 2 OH); 1.07-2.05 (m, 22H); 0.86 ppm (t, J=6.4 Hz, 3H). ^{13}C-NMR: 78.74; 72.77; 61.45; 41.30; 32.04; 31.94; 31.76; 30.03; 29.48; 29.18; 25.45; 22.52; 13.92 ppm.

(5R, 6S)-1,5,6-Trihydroxy-hexadecane 7. To a solution of **6** (400 mg, 1 mmol) in benzene (10 mL) n-Bu_3SnH (320 mg, 1.1 mmol) and AIBN (cat.) were added. The mixture was heated at 70°C for 2 h (TLC monitoring), then the solvent was removed in vacuo; the tin residues were removed according to Curran's procedure [10] and the crude mixture, purified by silica gel chromatography, afforded **7** (270 mg, 99%). ^{1}H-NMR: 3.55-3.71 (m, 4H); 3.41 (bs, OH); 1.15-1.70 (m, 26H); 0.86 ppm (t, J=6.4 Hz, 3H). ^{13}C-NMR: 74.72; 74.54; 62.72; 32.38; 31.76; 31.21; 30.60; 29.45; 29.18; 25.84; 22.51; 22.07; 13.91 ppm.

(5R, 6S)-5,6-O-Isopropylidenedioxy-1-hexadecanol 8. A solution of **7** (274 mg, 1 mmol), $(CH_3)_2C(OCH_3)_2$ (146 mg, 1.4 mmol) and pTsOH (cat.) in $(CH_3)_2CO$ (10 mL) was stirred at room temperature; after 3h (TLC monitoring) the mixture was filtered on basic alumina and the filtrate concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane:ethyl acetate 1/1) affording **8** (320 mg, 99%). ^{1}H-NMR: 3.9-4.05 (m, 2H); 3.57 (t, J=6.2 Hz, 2H); 1.10-1.62 (m, 30H); 0.83 ppm (t, J=6.5 Hz, 3H). ^{13}C-NMR: 78.01; 77.89; 62.37; 32.40; 31.69; 29.49; 29.38; 29.22; 29.11; 28.39; 26.02; 25.76; 22:43; 22.30; 13.82 ppm.

(5R, 6S)-6-Hydroxy-hexadecanolide 9. Compound **8** (326 mg, 1 mmol) was dissolved in CCl_4 (2 mL), CH_3CN (2 mL) and phosphate buffer 0.2 M (3 mL) with vigorous stirring. Then $NaIO_4$ (600 mg, 2.8 mmol) and $RuCl_3 \cdot H_2O$ (5 mg) were added. The reaction was stopped after 4 h (TLC monitoring), diluting with CH_2Cl_2 (30 mL) and the organic layer was separated. The aqueous layer was then extracted with CH_2Cl_2 and the organic layers, filtered on a celite pad, were collected and concentrated. Then catalytic pTSA was added with stirring; after 1 h at rt the solvent was evaporated and the crude mixture, chromatographed on silica gel (hexane: ethyl acetate 4/6), afforded **9** (162 mg, 60%). ^{1}H-NMR: 4.17-4.29 (m, 1H); 3.75-3.85 (m, 1H); 2.26-2.68 (m, 2H); 1.01-2.00 (m, 23H); 0.86 ppm (t, J=6.5 Hz, 3H) . ^{13}C-NMR: 171.94; 83.42; 72.42; 31.75; 31.60; 29.63; 29.53; 29.42; 29.28; 29.15; 29.08; 25.69; 22.49; 21.08; 18.16; 13.87 ppm. $[\alpha]_D$ = -10.8 (c = 1.4, $CHCl_3$).

(5R, 6S)-6-acetoxy-hexadecanolide 1. Compound **9** (135 mg, 0.5 mmol) was acetylated with standard procedure (acetic anhydride and pyridine) affording **1** (155 mg, 99%). Spectroscopical data of our synthetic pheromone are in agreement with those reported in literature. ^{1}H-NMR: 4.90-5.01 (m, 1H);

4.27-4.37 (m, 1H); 2.27-2.67 (m, 2H); 2.06 (s, 3H); 1.07-1.99 (m, 22H); 0.86 ppm (t, J=6.7 Hz, 3H). ^{13}C-NMR: 170.6; 170.2; 80.52; 74.35; 31.76; 29.41; 29.30; 29.16; 25.11; 23.40; 22.50; 20.84; 18.10; 13.87 ppm. $[\alpha]_D$ = -36.7 (c = 1.2, $CHCl_3$)(lit.-37.4[3a], -38.5[3d], -37.2[9]).

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