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RESEARCH ARTICLE
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SYNTHESIS OF (-)-(5R, 6S)-6-ACETOXY-5-HEXADECANOLIDE A PHEROMONE

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Abstract:
Synthetic methodology developed for (–)-(5R, 6S)-erythro-6-acetoxy-5-hexadecanolide,which is a D-ribose based synthetic pheromone used to promote mosquito oviposition. The important steps involved are Grignard reaction, oxidative cleavage of 1,2-diol followed by Wittig-Horner reaction, lactonization with magnesium and acetylation.

Keywords: Phermone, synthesis, Grignard reaction, Wittig-Horner reaction, Magnesium mediated electron transfer reduction, D-ribose

1. Introduction

Erythro-6-acetoxy-5-hexadecanolide **1** is a key component of the mosquito culex pipiens fatigans apical droplet of eggs, which Pickett and Laurence discovered in 1979 [1]. The west Nile virus can be spread by mosquitoes, which are primarily found in arid regions where they serve as a vector for filarial infections [2, 3]. The demand for safer pest control without the use of toxic insecticides or pesticides is what drives the majority of interest in this family of chemicals [4]. A few insect pheromones are being used commercially and others are undergoing field trials [5]. In keeping with our desire to investigate the potential applications of the Erythro-6-acetoxy-5-hexadecanolide, it has been hypothesized that the oviposition pheromone acts on *quinquefasciatus* as both an attractant and a stimulant [6]. The pheromone's absolute configuration was discovered to be (5*R*, 6*S*) by comparing the Mori's synthetic enantiomer [7]. The compound **1** is a δ-lactone which has two chiral centres and a decanyl side chain. The enantiomer of 1 was first synthesized by Fuganti et al in 1982 [8]. It was determined that (-)-(*5R, 6S*)-6-acetoxy-5-hexadecanolide **1** was the active natural pheromone and shown in figure 1.

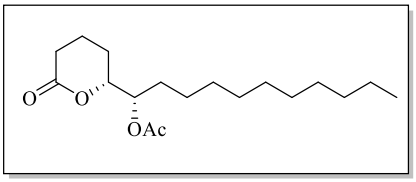


Figure 1: (–)-(5*R*, 6*S*)-Erythro-6-acetoxy-5-hexadecanolide **1**

The numerous synthetic approaches to the pheromone that attracts mosquito oviposition have been reported and synthesized [9-41]. Das et al. reported the facile total synthesis of (–)-(5*R, 6S*)-Erythro-6-acetoxy-5-hexadecanolide through epoxide opening by lithiated salt of ethylpropionate and acid catalysed lactonization [13]. Wang et al. reported the total synthesis of (–)-(5*R, 6S*)-Erythro-6-acetoxy-5-hexadecanolide by using 1,2-cyclohexanediol, using kinetic resolution of cyclic allylic alcohol by modified Sharpless asymmetric epoxidation reagent [25]. Couladouros and Mihou reported the synthesis of (–)-(5*R, 6S*)-Erythro-6-acetoxy-5-hexadecano lide via a carbonate ester, utilizing a novel lactonization with inversion of stereochemistry [18].

The reported synthetic routes to (–)-(5*R, 6S*)-Erythro-6-acetoxy-5-hexadecanolide mainly associated with the long reaction sequences, lower yields, and heavier workup procedures are some of the disadvantages in the earlier reported methods. To overcome the problems associated with earlier approaches, here in, we reported an alternative synthetic version of the easily accessible basic D-ribose. Here, we describe an effective synthesis of (–)-(5*R, 6S*)-Erythro-6-acetoxy-5-hexadecanolide in a highly stereo selective manner as part of our ongoing research on the entire synthesis of physiologically active natural compounds. An interim and methodical route to it still needs to be traversed. In this perception, we have reported a new stereoselective synthesis of compound **1** by using the Grignard reaction, followed by oxidative cleavage of 1, 2 diol, Wittig-Horner reaction and lactonization with magnesium mediated electron transfer reduction reactions in the sequence. Our reported synthetic methodology starting from commercially and cheaply available starting material, D-ribose with five synthetic steps and also involve simple reactions with easier experimental work with high purity are some advantages of this methodology compared with previous research methodologies.

2. Experimental Section

2.1. General

Th reaction was performed under inert atmosphere, in oven dried glassware. solvents such as THF and DCM were dried according to the standard procedures. With the use of 0.25 mm E. Merck pre-coated silica gel plates (60 F254), reactions were observed using TLC, and visualization was made possible by immersion in an ethnolic solution of the p-anisaldehyde stain after heating. On a Brucker, ^{1}H NMR spectra were captured at 400 or 500 MHZ, whereas ^{13}C NMR spectra were captured on a Brucker at either 100 or 125 MHz, respectively. coupling constants (*J*) are provided in Hertz (Hz) while chemical shifts (δ) were reported in ppm (parts per million). With a Brucker alpha spectrophotometer, FTIR spectra were captured and presented in cm^{-1}. Electrospray ionization time-off light technique was used to record HRMS data. Utilizing a polarimeter from PerkinElmer (model 341), optical rotations [D20] were observed.

2.1.1. (3aR,6R,6aR)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d] [1,3] dioxol-4-ol (4)

A stirred suspension of D-ribose **5** (10 g, 6.66 mol) in acetone (100 mL) was cooled to 0^{o}C, treated with 2,2-dimethoxypropane (16.4 mL, 13.3 mol) and *p*-toluenesulfonic acid (1.26 g, 0.66 mmol) and stirred while at room temperature for 1 h. The resulting clear reaction mass was neutralized with solid $NaHCO_3$ and filtered over a pad of celite. The filtrate was concentrated in vacuo and silica gel column chromatography purified (EtOAc:hexane = 1:2) to give compound 2 (11.5 g, 91%) as a colorless oil. $[\alpha]_D^{25}$-24.8 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.41 (s, 2H), 4.82 (d, *J* = 6.7 Hz, 1H), 4.58 (d, *J* = 5.7 Hz, 1H), 4.39 (s, 1H), 3.79-3.64 (m, 2H), 4.17-397 (brs, 1H), 1.49 (S, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.0, 102.6, 87.5, 86.6, 81.5, 63.4, 26.2, 24.6; IR (neat): ν 3345, 2923, 2854, 1726, 1461, 1376, 1055 cm^{-1}; MS (ESI): m/z 208 $[M+NH_4]^+$; HRMS: calcd for $C_8H_8O_5N$ $[M+NH_4]^+$ 208.1179; found: 208.1173.

2.1.2. 1-((4R,5S)-5-((R)-1-hydroxyundecyl)-2,2-dimethyl-1,3-dioxolan-4-yl) ethane-1,2-diol (3)

To a stirred solution of compound **4** (3 g, 15.7 mmol) in THF at 0 °C was slowly added decanyl magnesium bromide (56 mL, 55.2 mol (freshly prepared from magnesium (1.45 g, 60.5) and decanyl bromide (12.5 mL, 55.1 mmol) in THF 42.6 mL at 66 °C for 4 h) and stirring was continued for 6 h

at room temperature. With saturated NH_4Cl, the reaction mixture was quenched and concentrated. Three times 30 mL of ethyl acetate were used to extract the reaction mixture, which was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. To produce triol (1.8g, 61%) as a colourless liquid, the resulting residue was purified using column chromatography (EtOAc: Hexane, 17:3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.1-4.06 (m, 1H), 4.03-3.96(m, 1H), 3.89-3.78(m, 3H), 3.74-3.67 (m, 1H), 1.84-1.74 (m, 1H), 1.60-1.40 (m, 2H), 1.37 (s, 3H), 1.33 (s, 3H), 1.36-1.20 (m, 18H), 0.88 (t, *J* = 6.7, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 108.5, 80.2, 77.4(2), 69.5(2), 64.1, 34.0, 31.8, 29.6, 29.6(3), 29.3, 27.9, 25.4, 24.9, 22.6, 14.0; IR (neat): ν 3390, 2922, 2855, 1459, 1374, 1219, 1064 cm^{-1}; MS (ESI): m/z 335 $[M+Na]^+$; HRMS: calcd for $C_{18}H_{36}NaO_5$ $[M+Na]^+$ 335.2455; found: 335.2446.

2.1.3. Ethyl (Z)-3-((4R,5S)-5-((R)-1-hydroxyundecyl)-2,2-dimethyl-1,3-dioxolan-4-yl) acrylate (2)

To a stirred solution of compound **3** (1.0 g, 3.01 mmol) in DCM (10 mL) at 0 ^{o}C were added $NaIO_4$ (1.28 g, 6.02) and saturated $NaHCO_3$ (0.5mL) and stirring was continued for 6 h at room temperature. To the reaction mixture was added ethyl(triphenylphosphoranylidene)acetate (C2 ylide) at 0 ^{o}C and stirred for 4 h. The resulting mixture was filtered, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude residue was purified by column chromatography to give (746 mg, 67%) α,β unsaturated ester as a colorless liquid. $[\alpha]_D^{25}$- 128.8 (c 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.28 (dd, J =8.8, 11.5 Hz, 1H), 6.00 (d, J = 11.5 Hz, 1H), 5.54 (dd, *J* = 7.1, 7.9 Hz, 1H), 4.20 (q, *J* =7.1 Hz, 2H), 4.20-4.16 (m, 1H), 3.58 (dd, J = 7.7, 7.9 Hz, 1H), 3.01-2.94 (bs, 1H), 1.51 (s, 3H), 1.38 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.36-1.20 (m, 18H), 0.88 (t, J= 6.8Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 146.5, 121.8, 109.2, 81.8, 74.6, 70.1, 61.1, 33.5, 31.8, 29.6, 29.5(3), 29.2, 27.9, 25.4, 25.1, 22.6, 14.0(2); IR (neat): ν 3468, 3113, 2922, 2859, 1718, 1647, 1461, 1376, 1057 cm^{-1}; MS (ESI): m/z 371 $[M+H]^+$; HRMS: calcd for $C_{21}H_{39}O_5$ $[M+H]^+$ 371.2792; found: 371.2801.

2.1.4. (S)-6-((S)-1-hydroxyundecyl) tetrahydro-2H-pyran-2-one (6)

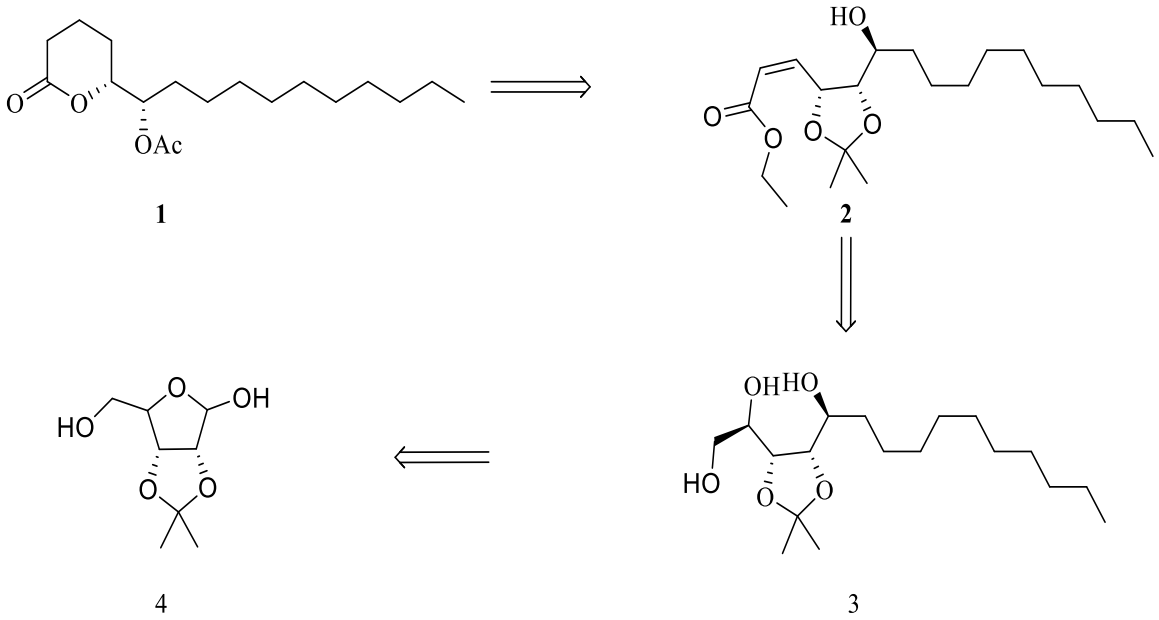
Mangnesium (64 mg, 2.70 mmol) was added to a stirred solution of compound **2** (100 mg, 0.270 mmol) in methanol (5 mL) and reflux for 4 h. Then the reaction mixture was filtered and concentrated under reduced pressure to obtain the residue which was purified by column chromatography (EtOAc: Hexane, 3:2) to afford lactone **6** (34.2 mg, 47%) along with diol **7** (11.1 mg, 13%) as colourless liquids. $[\alpha]_D^{25}$13.5 (c 0.3, CH_2Cl_2); [lit[17]. $[\alpha]_D^{20}$ 12.6 (c 1.05, CH_2Cl_2)]; IR (neat): ν 3279, 2921, 2853, 1715, 1458, 1283, 1071 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): d (ppm) 4.15–4.25 (m, 2H), 3.74–3.81 (m, 1H), 2.41–2.61 (m, 2H), 1.74–2.03 (m, 4H), 1.18–1.57 (m, 18H), 0.88 (t, 3H, J = 6.98 Hz). 13C NMR (CDCl3, 75 MHz): d (ppm) 171.7, 83.4, 72.3, 31.8, 31.6, 29.7, 29.5, 29.2, 25.8, 22.6, 21.0, 18.2, 14.0 ppm; MS (ESI): m/z 293 $[M+Na]^+$; (LC–MS): m/z = 293 $[M+Na]^+$. HRMS: calcd for $C_{16}H_{30}NaO_3$ $[M+Na]^+$ 293.2087; found: 293.2102.

2.1.5. (S)-1-((S)-6-oxotetrahydro-2H-pyran-2-yl)undecyl acetate (1)

To a stirred solution of compound **6** (20 mg, 0.074 mmol) in DCM (1 mL) at 0 ^{o}C were sequentially added triethyl amine (21 µL, 0.148 mmol), DMAP (1 mg, 0.007 mmol) and acetic anhydride (9 µL, 0.088 mmol). The reaction mixture was stirred for 4 h. Then the reaction mixture was concentrated under reduced pressured and purified by column chromatography (EtOAc:Hexane, 1:4) to give acetate (21 mg, 91%) as a colourless liquid. $[\alpha]_D^{20}$ -31.8 (c 0.4, $CHCl_3$); [lit.[5]] $[\alpha]_D^{20}$ 35.4 (c 0.85, $CHCl_3$)]; IR (neat): ν (cm^{-1}) 2924, 2853, 1737, 1373, 1240, 1073. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 4.93–5.03 (m, 1H), 4.35 (ddd, *J* = 3.0, 7.5, 10.5 Hz, 1H), 2.55–2.66 (m, 1H), 2.40–2.51 (m, 1H), 2.08 (s, 3H), 1.75–2.06 (m, 2H), 1.52–1.74 (m, 4H), 1.13–1.40 (m, 16H), 0.88 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.8, 170.4, 80.5, 74.3, 31.9, 29.6, 29.5, 29.4, 29.3, 25.2, 23.5, 22.7, 21.0, 18.2, 14.1; MS (ESI): m/z 335 $[M+Na]^+$; HRMS: calcd for $C_{18}H_{32}NaO_4$ $[M+Na]^+$ 335.2192; found: 335.2194.

3. Results and Discussions

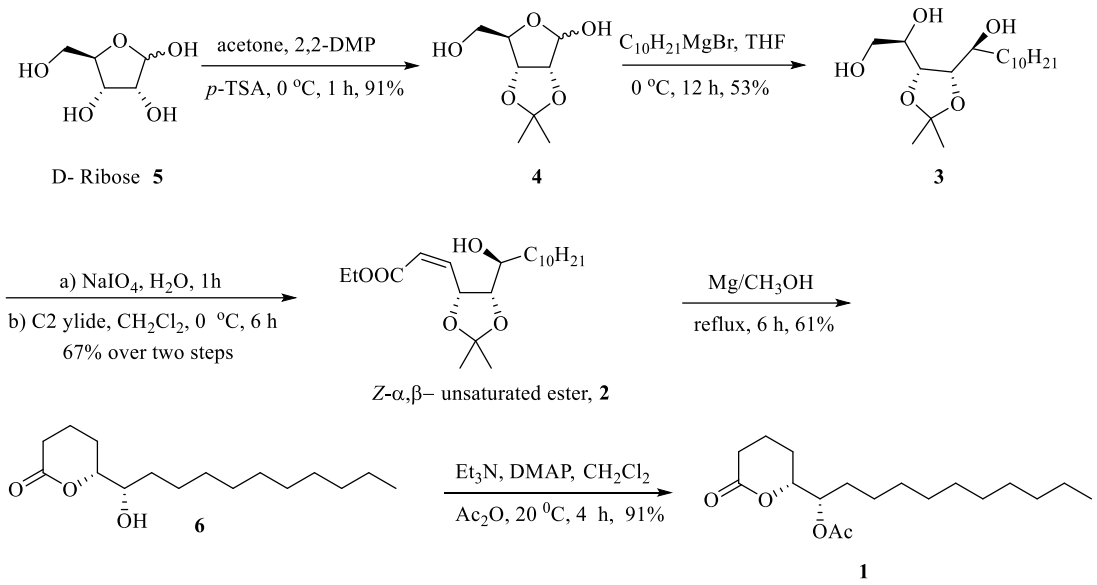
As per the retrosynthetic analysis, (–)-(5*R*, 6*S*)-erythro-6-acetoxy-5-hexadecanolide **1** (Scheme 1) should be derived from magnesium mediated electron transfer reduction followed by lactonisation of α,β-unsaturated ester **2**, which in turn would be obtained from oxidative cleavage and Horner-Wittig olefination of 1,2 diol **3**. The compound **3** can be accessed from alkylation of ribose acetonide **4** which was obtained from commercially available D-Ribose.



Scheme 1: Retrosynthetic analysis of (–)-(5*R*, 6*S*)-erythro-6-acetoxy-5-hexadecanolide **1**

The retrosynthetic analysis of our approach is shown in Scheme 1. It was envisioned that (–)-(5*R*, 6*S*)-erythro-6-acetoxy-5-hexadecanolide (**1**) could be obtained from (+)- D-ribose . The six-membered lactone could be constructed by the reductive elimination of α,β unsaturated ester and in-situ lactonization with magnesium. The α,β unsaturated ester **6** could be obtained from alcohol derivative **5**. The key intermediate **6** was synthesized from (+)-D-ribose **5**.

The total synthesis of (–)-(5*R*, 6*S*)-erythro-6-acetoxy-5-hexadecanolide **1** was shown in scheme 2. The synthesis of triol **3** commenced from D-ribose acetonide **4** (which was synthesized from commercially available D-ribose **5**, according to literature) [42], which was treated with excess of decanyl magnesium bromide in THF at -20 °C in 83% yield [43]. The oxidative cleavage of 1,2 diol in **3** proceeds with $NaIO_4$ in H_2O at rt for 1h [44]. This was followed by Horner Wittig olefination to give corresponding α,β-unsaturated ethyl carboxylate **2** with exclusive *Z*-selectivity in 81% yield [45]. δ-lactone **6** obtained by magnesium mediated electron transfer reduction of α,β-unsaturated ester and subsequent in situ lactonization in 78% yield [46]. The formation of six membered lactone ring would be produced from c2witting reagent and tartrate protected derivative. The mechanism in scheme **3** explained as follows. Mg in methanol system is extremely versatile, efficient and convenient reducing agent. The mechanism in scheme **3** involves Mg in methanol mediated reductive cyclization, reductive elimination, reductive cleavage and reduction of a conjugated double bond. Finally, acetate group was incorporated by using acetic anhydride, triethyl amine and DMAP in THF at 20 °C to furnish the target molecule (–)-(5*R*, 6*S*)-erythro-6-acetoxy-5-hexadecanolide **1** in 91% yield [47].



Scheme 2: Synthesis of (–)-(5*R*, 6*S*)-erythro-6-acetoxy-5-hexadecanolide **1**

4. Conclusion

A highly efficient and stereoselective D-ribose based synthesis of (–)-(5*R*,6*S*)-erythro-6-acetoxy-5-hexadecanolide was achieved in 6 steps with 17.9% overall yield through magnesium mediated reductive cleavage and lactonization.

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