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A NEW SYNTHESIS OF (-)-(5*R*,6*S*)-6-ACETOXY-5-HEXADECANOLIDE, THE MOSQUITO *CULEX PIPIENS FATIGANS* OVIPOSITION ATTRACTANT PHEROMONE

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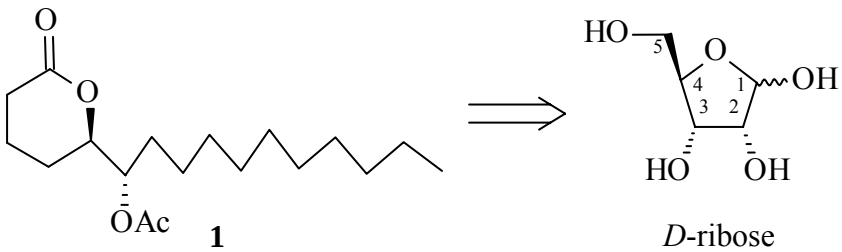
Abstract*- A new synthesis of (-)-(5R,6S)-6-acetoxy-5-hexadecanolide, the main component of the mosquito Culex pipiens fatigans oviposition attractant pheromone, from D-ribose is reported.*

Since its isolation and identification, (-)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide[1] (**1**, Figure 1) the main component of the mosquito *Culex pipiens fatigans* oviposition attractant pheromone, has become a popular synthetic target. Several syntheses have been reported in the literature, including *inter alia* Sharpless asymmetric epoxidation or dihydroxylation of a double bond as the key-step and enzymatic resolution of racemic diols.[2] Commercially available chiral compounds such as ascorbic acid and 2-desoxy-*D*-ribose have also been used as starting materials.[2] We now report a new and efficient synthesis of **1** starting from *D*-ribose.



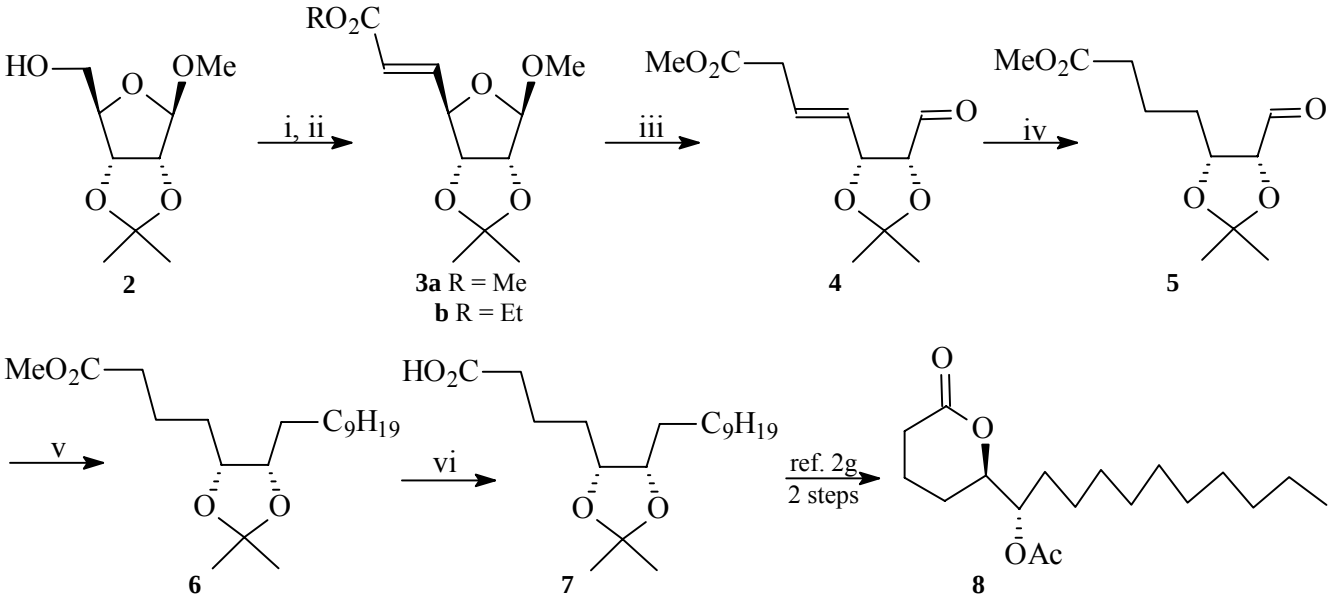
1 *D*-ribose

Figure 1

It becomes evident when comparing the structures of **1** and *D*-ribose, that the two chiral centres of the hexadecanolide have the configuration of the C-2 and C-3 carbons of the ribose molecule, from which **1** could be prepared by simple transformations: (i) introduction of the long chain at C-1 of *D*- ribose by a

Wittig reaction, (ii) deoxygenation of the C-4 carbon and (iii) elongation at C-5 position by oxidation and Wittig olefination.

The known compounds (**3**),[3] (Scheme 1) readily prepared from *D*-ribose in three steps, have already been lengthened at the C-5 carbon by the proper size and functionality. In our hands, compounds (**3**) were prepared from **2** as a *ca.* 10:1 inseparable mixture of *E*/*Z* isomers, by oxidation[4] followed by Wittig olefination with $Ph_3P{=}CHCO_2R$ (R = Me or Et).



Scheme 1 *Reagents and Conditions: i, CrO_3, dry pyridine, CH_2Cl_2, 20 ºC, 20 min; ii, $Ph_3P{=}CHCO_2R$ (R = Me or Et), $PhCO_2H$ (10%), CH_2Cl_2, 20 ºC, 12 h, 65-70% from **2**, E/Z ca. 10/1; iii, 0.15 M solution of **3** in MeOH, Mg (10 equiv.), 0 ºC, 1 h, 52% (40% recovered); iv, H_2, 10% Pd/C, MeOH, 20 ºC, 30 min 86%; v, (a) $Ph_3P^+(CH_2)_8MeBr^-$, 1.6 M n-Buli in pentane, –78 ºC, THF, (b) H_2, 10% Pd/C, MeOH, 20 ºC, 1 h, 42% overall; vi, 10% aqueous KOH, MeOH, 20 ºC, 2 h, 90%.*

It is known[5] that magnesium in methanol (Mg/MeOH) causes a reductive cleavage of γ-functionalized α,β-unsaturated esters. Since this is the case of compounds (**3**), it was expected that magnesium in methanol could deoxygenate the C-4 carbon, as desired. Indeed, when **3a** was allowed to react with Mg in methanol, aldehyde (**4**) was formed in a reaction reminiscent of the Vasella rearangement.[6] The reaction conditions were crucial at this step and we found that the best results were obtained when a *ca.* 0.15 M solution of **3a** in methanol was allowed to react with excess of Mg (10 equiv.) at 0 ºC for 1 h. At this point more than half of **3a** was consumed (recovered 40% of **3a**) and aldehyde (**4**) was isolated in 52% yield after chromatographic separation (87% yield based on the consumed compound (**3a**)). At longer reaction times - expected to achieve complete reaction of ester (**3a**) - aldehyde (**4**) started to decompose and several new undesired byproducts were formed, reducing the yield of **4**. Ester (**3b**) gave also aldehyde (**4**), evidently by transesterification during the reaction progress.

Attempted Wittig olefination of aldehyde (**4**), in order to indroduce the long chain, was unsuccessful. Thus, the double bond of **4** was selective hydrogenated over 10% Pd/C to aldehyde (**5**) before the Wittig

reaction with the appropriate phosphorus ylide, which proceeded smoothly. Both aldehydes (**4**) and (**5**) were found to be quite unstable and used further without complete characterisation. The Wittig product was again hydrogenated over 10% Pd/C to give the desired methyl ester (**6**), which has spectral data analogous to those reported for the respective ethyl ester.[7] Further basic hydrolysis of the ester (**6**) afforded the known acid (**7**),[2g] which can be easily transformed to the desired pheromone (**8**) by simple manipulations according to the literature.[2g]

In conclusion, we have achieved a new synthesis of (-)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide from *D*-ribose utilising cheap and easily available reagents and applying simple and convenient methods. The key-step involves a reductive elimination of the readily prepared unsaturated ester (**3**) by Mg in MeOH to aldehyde (**4**), which by further formal manipulations is transformed to the target molecule.

EXPERIMENTAL

Methyl (5R,6S)-(E)-7-Oxo-5,6-isopropylidenedioxyhept-3-enoate (**4**). To a solution of **3a** (0.590 g, 2.283 mmol) in dry MeOH (15 mL) was added magnesium turnings (0.555 g, 22.83 mmol) and the reaction mixture was stirred at 0 ºC for 1 h. H_2O (10 mL) was then added and the mixture was extracted with CH_2Cl_2 (2x10 mL). The organic layer was dried over $MgSO_4$, the solvent was then evaporated and the residue was chromatographed on silica gel with hexane/EtOAc 5:1 as the eluent to give first unchanged **3a** (0.236 g, 40%) followed by compound (**4**) as an oil (0.271 g, 52% or 87% based on the consumed **3a**), which was used in the next step without further purification; δ_H ($CDCl_3$, 300 MHz) 1.44 (s, 3 H), 1.62 (s, 3 H), 3.12 (t, *J* 6.8, 2 H), 3.69 (s, 3 H), 4.42 (dd, *J* 7.3, 3.3, 1 H), 4.87 (dd as t, *J* 7.3, 1 H), 5.52 (dd, *J* 15.6, 7.3, 1 H), 6.03 (dt, *J* 15.6, 6.8, 1 H) and 9.57 (d, *J* 3.3, 1 H); δ_C ($CDCl_3$, 75 MHz) 25.21, 27.28, 37.18, 51.90, 78.27, 82.15, 111.17, 126.92, 128.02, 171.14 and 200.54.

Methyl (5R,6S)-7-Oxo-5,6-isopropylidenedioxyheptanoate (**5**). To a solution of compound (**4**) obtained as above (0.228 g, 1 mmol) in MeOH (20 mL) was added 10% Pd/C (catalytic) and the mixture was stirred at rt under 1 atm H_2 for 30 min. The solids were filtered off, the solvent evaporated and the residue was chromatographed on silica gel using CH_2Cl_2 as the eluent to give compound (**5**) as an oil (0.199 g, 86%), which was used in the next step without further purification; δ_H ($CDCl_3$, 300 MHz) 1.41 (s, 3 H), 1.58 (s, 3 H), 1.72 (centered, m, 4 H), 2.36 (t, *J* 7.3, 2 H), 3.67 (s, 3 H), 4.27 (dd, *J* 7.2, 3.4, 1 H), 4.35 (ddd, *J* 7.3, 7.2, 3.9, 1 H), and 9.57 (d, *J* 3.4, 1 H); δ_C ($CDCl_3$, 75 MHz) 21.85, 25.21, 27.51, 29.03, 33.43, 51.48, 78.17, 81.86, 110.70, 173.47 and 202.10.

Methyl (5R,6S)-5,6-Isopropylidenedioxyhexadecanoate (**6**). To a stirred solution of $Ph_3P^+(CH_2)_8MeBr^-$ (0.482 g, 1.242 mmol) in THF (30 mL), 1.6 M of *n*-BuLi solution in pentane (0.8 mL, 1.28 mmol) was added dropwise at –78 ºC and the mixture was allowed to warm to 0 ºC. The solution was cooled again to

–78 ºC and was added to aldehyde (**5**) (0.130 g, 0.565 mmol) dissolved in THF (5 mL). The mixture was allowed overnight stirring to warm to rt, quenched by adding H_2O (100 mL) and extracted with Et_2O (50 mL). The organic layer was dried over $MgSO_4$, the solvent was then evaporated and the residue was chromatographed on silica gel with hexane/EtOAc 15:1 as the eluent to give the Wittig product as an oil, which was dissolved in MeOH (15 mL), 10% Pd/C (catalytic) was added and the mixture was stirred at rt under 1 atm H_2 for 1 h. The solids were filtered off, the solvent evaporated and the residue was chromatographed on silica gel using hexane/EtOAc 20:1 as the eluent to give compound (**6**) as an oil (0.081 g, 42%); $[\alpha]_D^{25}$ +4.6 º (c 0.6, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz) 0.86 (t, *J* 7.0, 3 H), 1.26 (br s, 18 H), 1.33 (s, 3 H), 1.42 (s, 3 H), 1.51 (m, 2 H), 1.69 (m, 1 H), 1.86 (m, 1 H), 2.38 (t, *J* 7.3, 2 H), 3.67 (s, 3 H), and 4.02 (m, 2 H); δ_C ($CDCl_3$, 75 MHz) 14.02, 21.65, 22.59, 25.89, 26.22, 28.51, 29.07, 29.26, 29.51, 29.61, 31.84, 33.79, 51.37, 77.55, 77.94, 107.35, and 173.79; *m/z* (%) 327 (40, M^+-15), 285 (9), 253 (23), 235 (15) 217 (9). Anal. Calcd for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18. Found: C, 70.33; H, 11.02.

(5R,6S)-5,6-Isopropylidenedioxyhexadecanoic Acid (**7**). A mixture of compound (**6**) (0.052 g, 0.152 mmol), MeOH (2.5 mL) and 10% aqueous KOH (2.5 mL) was stirred at rt for 2 h, then neutralised with AcOH and extracted with CH_2Cl_2 (30 mL). The organic layer was dried over $MgSO_4$, the solvent was then evaporated and the residue was chromatographed on silica gel with hexane/EtOAc 7:1 as the eluent to give acid **7** as a syrup (0.045 g, 90%); $[\alpha]_D^{25}$ +4.1 º (c 1.1, $CHCl_3$) [lit.,[2g] $[\alpha]_D^{22}$ +5.65 º (c 1.0, $CHCl_3$)]; δ_H ($CDCl_3$, 300 MHz) 0.88 (t, *J* 6.8, 3 H), 1.26 (br s, 18 H), 1.33 (s, 3 H), 1.43 (s, 3 H), 1.49 (m, 2 H), 1.68 (m, 1 H), 1.84 (m, 1 H), 2.42 (t, *J* 7.3, 2 H), 4.02 (m, 2 H) and 10.4 (br s, 1 H); δ_C ($CDCl_3$, 75 MHz) 14.08, 21.44, 22.66, 25.92, 26.26, 28.53, 29.04, 29.32, 29.58, 29.66, 31.87, 33.79, 51.37, 77.60, 78.00, 107.52, and 179.34; HRMS (MALDI-FTMS) Calcd for $C_{19}H_{36}O_4Na$ $[M+Na]^+$: 351.2506. Found: 351.2508; 0.6 ppm error. Anal. Calcd for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05. Found: C, 69.55; H, 10.98.

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7. While the ^{1}H-NMR spectrum of compound (**6**) is in excellent agreement with that of the respective ethyl ester reported in the literature,[2g] there are some differences in the ^{13}C-NMR spectra. We found only one peak –that of the terminal carbon – at δ<20, while Kang and Cho reported[2g] 4 peaks at the same region for the ethyl ester. It is apparent that these results are wrong, since the structure of this particular compound can not justify more than two peaks at δ 10-20 (the CH_3 of the ethyl group and the terminal methyl carbon). Furthermore, the ^{13}C-NMR spectrum of compound (**6**) is in accord with spectra of very similar compounds.[8]
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