Tetrahedron Letters, Vol.30, No.6, pp 743-746, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

AN ENANTIOSPECIFIC SYNTHESIS OF (-)-(5R,6S)-6-ACETOXY-5-HEXADECANOLIDE, THE MOSQUITO OVIPOSITION ATTRACTANT PHEROMONE

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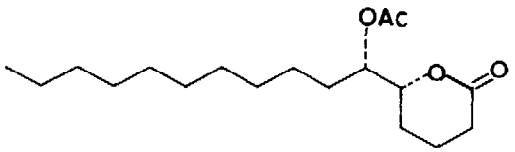
Summary: (-)-(5R,6S)-6-Acetoxy-5-hexadecanolide, (-)-**1**, the natural mosquito oviposition attractant pheromone was synthesized from readily available carbohydrate, (-)-2-deoxy-D-ribose, using radical carbon-carbon bond formation as the key step.

The major component of the oviposition attractant pheromone of the mosquito *Culex pipiens fatigans* was isolated from apical droplet of the mosquito eggs and identified as (±)- *erythro*-6-acetoxy-5-hexadecanolide, by Laurence and Pickett[1]. In 1985, the absolute configuration of the natural pheromone was shown[2] to be (-)-(5R,6S)-6-acetoxy-5-hexadecanolide **1**. Although several syntheses have been reported[3], short and efficient syntheses of **1** remain of interest. Herein, we wish to report a new and enantiospecific synthesis of **1** starting from (-)-2-deoxy-D-ribose.

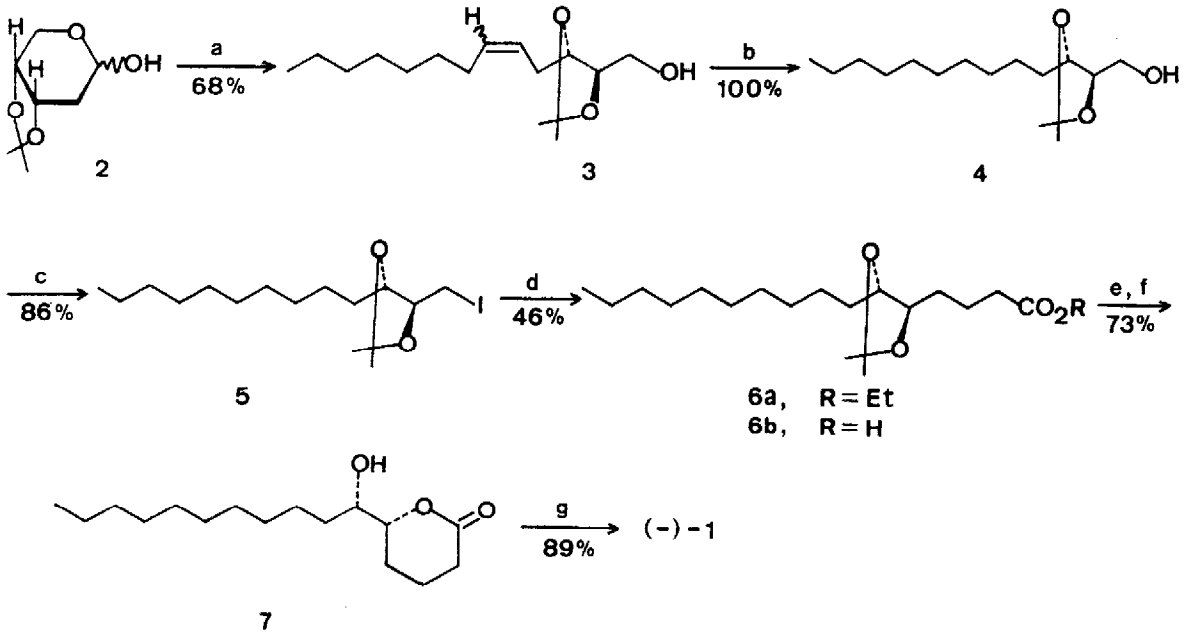


(-)-(5R,6S)-**1**

Acetonide **2**, prepared[4] as an anomeric mixture in ~60% yield from commercial (-)-2-deoxy-D-ribose(95%) was condensed with n-octyltriphenylphosphorane to give the unsaturated alcohol **3**[5] (TLC : SiO_2, EtOAc/hexanes(1:1), $R_f \sim 0.65$). The ratio of (Z)- and (E)-isomer was about 9:1 by ^{1}H-NMR spectrum. Without separation of the geometrical isomers, catalytic hydrogenation on Pd/C at atmospheric pressure of hydrogen provided the saturated alcohol **4**[5] (TLC : SiO_2, EtOAc/hexanes(1:4), $R_f \sim 0.20$), $[\alpha]_D^{22} = +19.9^\circ$ (c 1.0, $CHCl_3$). The alcohol **4** was directly converted[6] to the iodide **5**[5] (TLC : SiO_2, EtOAc/hexanes/pet ether(1:1:1), $R_f \sim 0.64$), $[\alpha]_D^{22} = +11.3^\circ$ (c 3.0, $CHCl_3$) by reacting with iodine and triphenyl-

phosphine in the presence of imidazole. Elongation of the appropriate three-carbon unit was achieved by a radical chain reaction[7] of the iodide 5 with ethyl acrylate (10 equiv) and tributylstannane (2.0 equiv) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) to afford the condensed product **6a**[5] (TLC : SiO_2, CH_2Cl_2, $R_f \sim 0.58$), $[\alpha]_D^{22}$ = +18.5° (c 1.0, $CHCl_3$). In our hands, the photo-induced radical chain reaction[8] of 5 with ethyl acrylate (10 equiv) in the presence of nBu_3SnCl and $NaBH_4$ under high-pressure Hg lamp (450 W) gave the condensed ester **6a**, $[\alpha]_D^{22}$ = +18.5° (c 1.0, $CHCl_3$) in a low yield (17%). Hydrolysis of the ester **6a** with potassium hydroxide gave the acid **6b** in 92% yield, TLC of **6b**[5] : SiO_2, EtOAc/hexanes(3:2), $R_f \sim 0.22$. Simultaneous deprotection of the acetonide and lactonization of the acid **6b** with p-toluenesulfonic acid furnished the semifinal hydroxylactone 7[5] (TLC : SiO_2, ether, $R_f \sim 0.51$), $[\alpha]_D^{22}$ = -12.4° (c 5.0, $CHCl_3$) lit.[3a] -12.5° (c 0.54, $CHCl_3$) , mp 66-68℃ (lit.[3b] 67-68℃). The spectral data (^{1}H-NMR, IR) of 7 were identical with the data of the synthetic compound provided by Professor K. Mori (The University of Tokyo). Acetylation of the semifinal hydroxylactone 7 afforded the target compound **1** (TLC : SiO_2, ether, $R_f \sim 0.70$), $[\alpha]_D^{26}$ = -37.4° (c 1.55, $CHCl_3$) lit.[3b] $[\alpha]_D^{21}$ = -36.2° (c 1.39, $CHCl_3$) (Scheme 1).

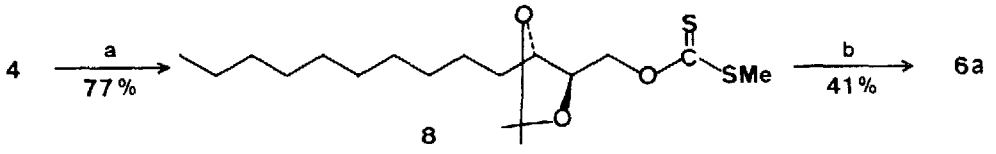
Scheme 1



(a) $(C_6H_5)_3P^+(CH_2)_7CH_3Br^-$, nBuLi, THF, 25℃, 12h (b) H_2, Pd/C, EtOAc, 1 atm, 25℃, 7h (c) I_2, $(C_6H_5)_3P$, imidazole, toluene, 60℃, 3h (d) ethyl acrylate, AIBN, nBu_3SnH, toluene, 110℃, 4h (e) KOH, $MeOH/H_2O$(1:1), 70℃, 2h (f) 50% HOAc, 80℃, 2h and then p-TsOH, benzene, 80℃, 1h (g) Ac_2O, pyridine, 25℃, 24h.

Alternatively, the xanthate **8**[5] (TLC : SiO_2, $CHCl_3$, $R_f \sim 0.81$), $[\alpha]_D^{22}$ = +24.0° (c 3.0, $CHCl_3$) was easily prepared from the corresponding alcohol **4** by treating with carbon disulfide and methyl iodide in the presence of sodium hydride. The nBu_3SnH-AIBN induced radical addition of the xanthate **8** to ethyl acrylate (10 equiv) gave the condensed ester **6a** (TLC : SiO_2, CH_2Cl_2, $R_f \sim 0.58$), $[\alpha]_D^{22}$ = +18.5° (c 1.0, $CHCl_3$) in 41% yield (Scheme 2).

Scheme 2



(a) NaH, CS_2, CH_3I, THF, 25 ℃, 1.5h (b) ethyl acrylate, AIBN, nBu_3SnH, toluene, 100 ℃, 2h.

In conclusion, we have completed an enantiospecific total synthesis of (-)-**1** in eight steps from (-)-2-deoxy-D-ribose in more than 10% overall yield.

Acknowledgement: We thank Professor K. Mori for the copies of the spectral data (^{1}H-NMR and IR) for the compounds **7** and (-)-**1**. We are indebted to Dr. Kyu-Wan Kim, Yung-Jin Pharm. Co., Ltd. for $[\alpha]_D$ measurements. Financial support from the Korea Science and Engineering Foundation is gratefully acknowledged.

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5. Satisfactory spectral and physical data were obtained for the new compounds in accord with the structure. Selected physical and spectral data are as follows. **3**: ^{1}H-NMR (80MHz, $CDCl_3$) δ 0.86(t, 3H), 1.28(bs, 10H), 1.34(s, 3H), 1.47(s, 3H), 1.99(m, 2H), 2.33(m, 2H), 3.61(d, 2H), 4.22(m, 2H), 5.46(m, 2H). IR(neat) 3450cm^{-1}(OH). $[\alpha]_D^{22}$ = +12.1° (c 1.0, $CHCl_3$). **4**: ^{1}H-NMR(80MHz, $CDCl_3$) δ 0.88(t,3H), 1.28(bs, 16H), 1.34(s, 3H), 1.47(s, 3H), 1.70(bs, 2H), 3.59(t, 2H), 4.14(m,2H). IR(neat) 3400(OH), 1040cm^{-1}. **5**: ^{1}H-NMR(80MHz, $CDCl_3$) δ 0.89(t, 3H), 1.29(bs, 18H), 1.34(s, 3H), 1.47(s, 3H), 3.17(d, 2H, J=7Hz), 4.22(m, 2H). MS(m/e) 382(M), 367(M-15, base peak). **6a**: ^{1}H-NMR(80MHz, $CDCl_3$) δ 0.85(t, 3H), 1.21(t, 3H), 1.25(bs, 18H), 1.29(s, 3H), 1.40(s, 3H), 1.50-2.21(m, 4H), 2.39(t, 2H, J=7Hz), 4.10(m, 4H). IR(neat) 1738cm^{-1}(C=O). MS(m/e) 356(M), 341(M-15, base peak),311, 299. ^{13}C-NMR(22.6MHz, $CDCl_3$) δ 173.36, 107.35, 78.39, 77.97, 60.28, 34.11, 31.83, 29.52, 29.24, 29.13, 28.52, 26.21, 25.90, 22.59, 21.71, 17.92, 15.26, 14.17, 13.98, **6b**: ^{1}H-NMR(80MHz, $CDCl_3$) δ 0.86(t, 3H), 1.26(s, 18H), 1.32(s, 3H), 1.42 (s, 3H), 1.51-2.10(m, 4H), 2.39(t, 2H, J=7Hz), 4.02(m, 2H), 10.40(bs, 1H). IR(neat) 2900, 2840, 1700, 1160cm^{-1}. MS(m/e) 328(M), 313(M-15, base peak), 299, 253, 241, 235, 158. $[\alpha]_D^{22}$ = +5.65° (c 1.0, $CHCl_3$). **7**: ^{1}H-NMR(80MHz, $CDCl_3$) δ 0.88(t, 3H), 1.26(bs, 16H), 1.35-1.60(m, 2H), 1.70-2.00(m, 4H), 2.05(bs, 1H), 2.40-2.66(m, 2H), 3.82(m, 1H), 4.10-4.40(m, 1H). IR(KBr)3400, 1715cm^{-1}, mp 66-68℃. MS(m/e) 270(M), 252(M-18), 100(base peak). **8**: ^{1}H-NMR(80MHz, $CDCl_3$) δ 0.89(t, 3H), 1.31(bs, 16H), 1.38(s, 3H), 1.49(s, 3H), 1.58(bs, 2H), 2.62 (s, 3H), 4.18-4.68(m, 4H). IR(neat) 1460, 1250, 1065cm^{-1}. MS(m/e) 362(M), 347(M-15), 254(base peak), 239, 179. **1**: ^{1}H-NMR(80MHz, $CDCl_3$) δ 0.89(t, 3H), 1.26(bs, 16H), 1.58-2.06(m, 6H), 2.10(s, 3H), 2.53(m, 2H), 4.34(m, 1H), 4.98 (m, 1H). IR(neat) 1740, 1360, 1220, 1050cm^{-1}. MS(m/e) 312(M), 269, 268, 252, 224, 192, 154, 142, 99(base peak), 55.

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(Received in Japan 12 December 1988)