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CHEMICO-MICROBIAL SYNTHESES OF JAPANESE BEETLE AND MOSQUITO OVIPOSITION PHEROMONES

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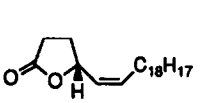
Abstract: *Japanese beetle and mosquito oviposition attractant pheromones have been synthesized from a common chiral precursor derived from baker's yeast reduction*

In this report we describe the chemico-microbial syntheses of two insect pheromones that possess chiral γ and δ lactones.[1] **(R)**-(-)-**(Z)**-5-tetradecenolide, **1**, the female produced sex pheromone of the economically important Japanese beetle, *Popilia japonica*,[2,3] is required to be nearly optically pure to exhibit full activity The presence of as little as 5% of the **(S,Z)** isomer lowers the attractancy of the **(R,Z)** isomer to 30% of the optically pure material [4a] There are a number of racemic and chiral syntheses of **1** reported.[4a-k]

6**(S)**-Acetoxy-5**(R)**-hexadecanolide, **2**, is the major component of the apical droplets that form on the eggs of the mosquito *Culex pipens fatigans*.[5] The substance acts as an oviposition pheromone attracting gravid females of the same mosquito species and inducing them to oviposit The natural material was shown to be the 5**(R)**,6**(S)** isomer by comparison with synthetic material [6] There are many chiral syntheses of this lactone starting from the chiral pool [7a-j]



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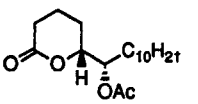

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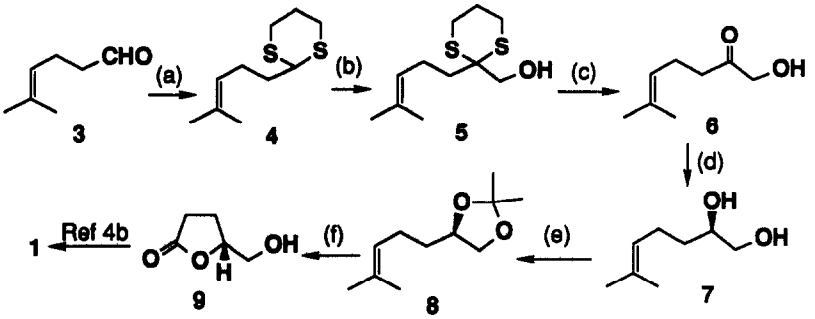
Scrutiny of these two molecules shows they share an **R**-configuration at the alkoxy center and an adjacent oxidized or unsaturated carbon. These common elements make it possible to develop syntheses from the same chiral precursor One obvious route to the chiral precursor is baker's yeast (*Saccharomyces cerevisiae)* reduction of appropriate ketones which follows Prelog's rule [8] Ketones containing adjacent primary hydroxyl groups undergo identical reduction[9] at substantially accelerated rates suggesting chelation involving the hydroxyl group at the active site Starting with an appropriately substituted ketol, it is possible to elaborate the yeast reduction-derived diol into either **1** or **2**..Initially, our synthesis of **1** started with the aldehyde **3** obtained by a

published procedure (Scheme 1).[10] Dithiane **4** was prepared in 81% yield by treatment of **3** with 1,3-propanedithiol in the presence of a catalytic amount of TsOH in refluxing benzene Deprotonation of **4** with n-BuLi followed by reaction with paraformaldehyde afforded the hydroxymethyldithiane **5** in 85% yield Alkylative hydrolysis of **5** with MeI in buffered aqueous acetonitrile[11] afforded the hydroxyketone **6** in 63% yield



(a) $HS(CH_2)_3SH$, TsOH, (b) n-BuLi, $(CH_2O)_n$, (c) CH_3I, CH_3CN-H_2O, $NaHCO_3$, (d) fermenting baker's yeast; (e) 2-methoxypropene, Amberlyst 15, (f) O_3 / DMS, Ag_2O / OH^-, H^+

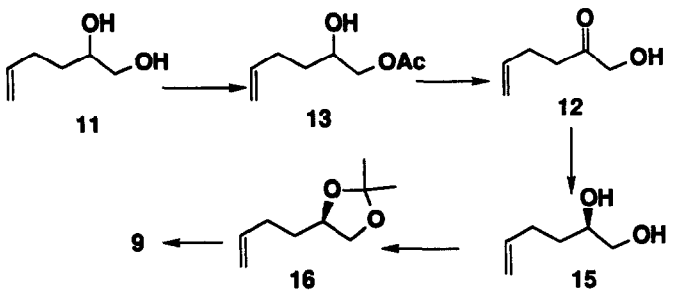
Scheme 1

Baker's yeast reduction of hydroxyketone **6** gave diol **7** in 68% yield and 97% optical purity as determined by chiral complexation GC analysis (Ni-4-PIN)[12] of the acetonide, **8**, prepared using 2-methoxypropene and catalytic amounts of Amberlyst 15.[13] The double bond of **8** was then ozonized and the resultant aldehyde oxidized with aqueous Ag_2O-NaOH to afford hydroxymethyl lactone **9** in 46% over-all yield (Scheme 1) Oxidation of **9** to aldehyde **10** and Wittig elaboration to the pheromone **1** are reported [4b]

Although the above conversion established the viability of the sequence, notable disadvantages are the lengthy route to hydroxyketone **6** and use of expensive and odoriferous dithiane reagent **5** Commercially available diol **11** is an inexpensive precursor of **12** (Scheme 2) Protection of the primary alcohol, oxidation of the secondary alcohol and regeneration of the primary alcohol would give **12** However, conventional procedures involving acetic anhydride - pyridine in dichloromethane to obtain **13** afforded substantial amounts of diacylated product **14** even at temperatures below 0°C Biphasic systems involving **11**, acetic anhydride and solid K_2CO_3 yielded somewhat reduced proportions of diacylated product, but left significant amounts of **11** Attempts to drive the reaction to completion by addition of excess anhydride resulted in increased proportions of diacylated product Separation of the mono and diacylated products by distillation was plagued by the codistillation of **14** and **13** Enzyme-mediated acylation using biphasic systems containing an acylation agent and enzyme in an organic solvent has been demonstrated to be regiospecific for primary hydroxyls of sugars [14, 15] When we applied this

technique to diol **11** using porcine pancreatic lipase (PPL) and acetic or butyric anhydride as the acylating agent,[16] high yields of the primary acylated products containing only traces of diesters were obtained

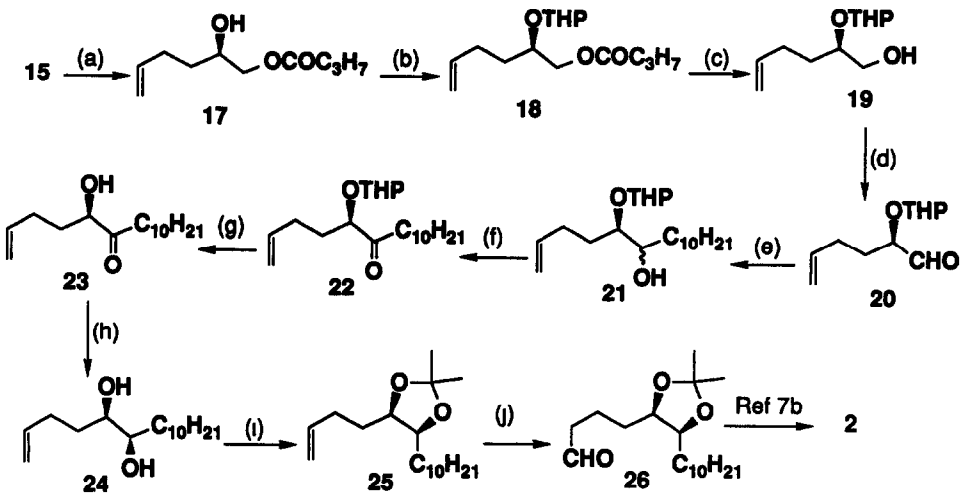
Although butyric anhydride gave faster and cleaner reaction than acetic anhydride, the ease of hydrolysis of the product following the oxidation of the secondary alcohol prompted us to use the acetate in preference to butyrate. Acetate **13** was prepared in 92% yield by the enzymatic method Jones oxidation followed by basic work up resulted in the cleavage of the acetate to afford the ketoalcohol **12** in 80% overall yield. Baker's yeast reduction of **12** afforded **15** in 47% yield and an optical purity of 98.5% [12] Acetonide **16** was prepared in nearly quantitative yield as in the case of **7**. Ozonolysis of the terminal olefin followed by transformation to **9** was conducted as before (Scheme 2).



(a) Ac_2O, PPL, (b) Jones oxidation, (c) aq NaOH, (d) fermenting baker's yeast, (e) 2-methoxypropene, Amberlyst 15, (f) O_3 / DMS, Ag_2O / OH^-, H^+

Scheme 2

Our approach to the synthesis of the mosquito oviposition pheromone **2** involved elaboration of chiral diol **15** (Scheme 3). The primary alcohol was converted enzymatically to butyrate **17** and the secondary alcohol protected as the THP ether, **18**, in nearly quantitative yield The primary alcohol was then regenerated with aqueous methanolic NaOH to give **19** and oxidized with Swern reagent[19] to aldehyde **20** also in nearly quantitative yield Addition of n-decylmagnesium bromide to **20** afforded an *erythro threo* mixture (45 55) of **21** [20] Conversion of this mixture into *erythro* diol was achieved through Swern oxidation of **21** to ketone **22** (83%), removal of the THP group (~100%) to give hydroxyketone **23** and $Zn(BH_4)_2$ reduction[21] of **23** to diol **24** (72%) The diol was protected as the acetonide using 2-methoxypropene and **25** hydroborated and oxidized *in situ* with pyridinium chlorochromate[22] to give aldehyde **26.** Oxidation of **26** to the carboxylic acid and its conversion to the mosquito oviposition attractant pheromone were carried out following reported methods [7b]



(a) $(C_3H_7CO)_2O$, PPL; (b) DHP, Amberlyst 15, (c) NaOH-H_2O-MeOH, (d) $(COCl)_2$, DMSO, Et_3N, (e) $C_{10}H_{21}MgBr$, (f) $(COCl)_2$, DMSO, Et_3N, (g) MeOH, Amberlyst 15, (h) $Zn(BH_4)_2$, (i) 2-methoxypropene, Amberlyst 15, (j) 9-BBN, PCC

Scheme 3

These syntheses exemplify the increasingly important role of baker's yeast as a chiral reagent

EXPERIMENTAL

Except a noted below experimental and intrumental conditions were as given in the accompanying paper. Complexation chromatography[12] was performed on a fused silica capillary column (25 m x 0.25 mm) coated with Ni-4-PIN (op), purchased from Capillary Columns and Complexation Chromatography, Kirchentellinsfurt, FRG, and a linear oven temperature program initiated at 85°C and increased at 0 1°C / min to 90°C. Optical rotations were measured on a Perkin Elmer P-22 or a Rudolph model 70 polarimeter Hexamethylphosphoric triamide (HMPA) was distilled from calcium hydride and stored over activated 4A molecular sieves

2-(4'-Methyl-3'-pentenyl)-1,3-dithiane, 4 A soln of 5 60 g (50 mmol) of 5-methyl-4-hexenal, **3**,[10] 5 60 g (55 mmol) of 1,3-propanedithiol and 50 mg of TsOH in 50 mL of benzene was refluxed with azeotropic removal of water for 2 h The reaction mixture was cooled to rm temp , the TsOH was destroyed by the addition of 0 2 g of triethylamine and the soln concentrated *in vacuo* Kugelrohr distillation of the residue, after allowing a forerun of ~1 g, afforded 8 18 g (81% yield) of **4** as an oil bp 120°C / 0 25 Torr IR 2295 cm^{-1}, ^1H NMR δ 1 62 (s, 3), 1 69 (s, 3), 1 84 (m, 2), 1 95 - 2 35 (m, 4), 2 83 (m, 4), 4 02 (t, 1, J = 7 0), 5 09 (tm, 1), Anal calcd for $C_{10}H_{18}S_2$ C 59 35, H 8 96, found C 59 62, H 8 73

2-(Hydroxymethyl)-2-(4'-methyl-3'-pentenyl)-1,3-dithiane, **5**. To 2-(4'-methyl-3'-pentenyl)-1,3-dithiane, **4**, 6.30 g (31 mmol) in 30 mL THF cooled to 0°C was added 13 mL of 2 5 M n-BuLi in hexane (32.5 mmol) and the reaction mixture was stirred for ~0.5 h Paraformaldehyde, 2 0 g, was added and the reaction mixture was warmed to rm. temp. over 1 h The reaction was diluted with 100 mL ethyl ether which was separated, washed with 3x10 mL of water, dried ($MgSO_4$) and concentrated *in vacuo* to afford an oil Chromatography on 200 g of basic activity (I) alumina using 20 - 40% ethyl acetate in hexanes (v/v) as the elution solvent afforded 1 45 g (7 mmol) of the unalkylated starting material and 4.75 g (20.5 mmol, 85% yield based on consumed starting material) of the hydroxymethyl dithiane, **5**, as a yellow oil IR 3460, 2295 cm^{-1}, ^1H NMR δ. 1 61 (s, 3), 1 68 (s, 3), 1 74 (m, 2), 1.85 (m, 2), 2 07 - 2 25 (m, 3), 2 58 (dt, 2, J = 13 0, 5 0), 2 94 (dd, 2, J = 13 0, 2 6), 3 75 (s, 2), 5.07 (tm, 1), Anal calcd. for $C_{11}H_{20}OS_2$ C 56 85, H 8 68; found C 57 07, H 8 71

1-Hydroxy-6-methyl-5-hepten-2-one, **6**· A mixture of 4 75 g (20 5 mmol) of 2-(hydroxymethyl)-2-(4'-methyl-3'-pentenyl)-1,3-dithiane, **5**, and 20 mL of iodomethane in 120 mL of a 1 5 mixture of aqueous acetonitrile buffered with 8.4 g of $NaHCO_3$ was vigorously stirred at rm temp for 48 h Acetonitrile was removed *in vacuo* and the residue partitioned between 100 mL ethyl ether and 20 mL water The ethyl ether layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford an oil which upon Kugelrohr distillation (60°C / 0 1 Torr) afforded 1 88 g (13 mmol, 63% yield) of **6** IR 3450, 2295, 1760 cm^{-1}, ^1H NMR δ. 1.61 (s, 3), 1 68 (s, 3), 2 31 (dt, 2, J = 7.4, 6 2), 2.42 (t, 2, J = 7 8), 2 78 (bs, 1), 4 23 (s, 2), 5 04 (tm, 1), Anal calcd for $C_8H_{14}O_2$ C 67 57, H 9 92, found C 67 43, H 10 14

6-Methyl-5-heptene-1,2(R)-diol, **7**: To a well stirred soln of 40 g of sucrose in 100 mL of tap water at 30°C was added 40 g of baker's yeast The mixture was stirred vigorously for 15 min at which time vigorous fermentation ensued and 1 56 g (11 mmol) of 1-hydroxy-6-methyl-5-hepten-2-one, **6**, was added and stirring continued in the open flask for 24 h at which point the starting material had been completely consumed The fermentation mixture was centrifuged and the aq soln was extracted with 3x30 mL of ethyl ether The centrifuged yeast was then stirred with 60 mL of acetone and the granular yeast precipitate was removed by filtration The precipitate was washed with 3x60 mL of acetone, the combined acetone layer was concentrated *in vacuo*, and the aqueous residue was extracted with 3x60 mL of ethyl ether The combined ethyl ether extracts were dried ($MgSO_4$) and the solvent concentrated *in vacuo* and residue upon Kugelrohr distillation (60°C / 0 1 Torr) afforded 1 08 g (7 5 mmol, 68%) of diol **7** as an oil $[\alpha]_D^{25}$ 17 8° (MeOH, c 7 0), lit [24] $[\alpha]_D^{25}$ 16 0°(EtOH, c 1.84) , IR 3375, 2995 cm^{-1} , ^1H NMR δ 1 46 (m,2), 1 62 (s, 3), 1 69 (s,3), 2 10 (m, 2), 2 76 (bs, 2), 3 42 (dd, 1, J = 10 5, 7 9), 3 61 - 3 77 (m, 2), 5 13 (tm,1)

1,2(R)-Isopropylidenedioxy-6-methyl-5-heptene, **8** A mixture of 0 72 g (5 mmol) of **7**, 0 5 mL of 2-methoxypropene and ~5 mg of Amberlyst 15 was stirred at rm temp for 0 5 h The liquid was decanted, the unreacted 2-methoxypropene was removed *in vacuo* and the residue distilled to afford 0 84 g (92% yield) of the acetonide **8**, bp 60°C /30 Torr (Kugelrohr) , $[\alpha]_D^{25}$ -15 91° ($CHCl_3$,

c 2 30), IR 2995 cm^{-1}, ^1H NMR δ 1 35 (s, 3), 1 41 (s, 3), 1 51 (m, 1), 1 61 (s, 3), 1 68 (m, 1), 1 68 (s, 3), 2 05 (m, 2), 3 50 (dd, 1, $J_1 = J_2 = 8$), 4.02 (dd, 1, J = 7 5, 6 5), 4.08 (m,1), 5 10 (m,1), Anal calcd for $C_{11}H_{20}O_2$ C 71 70, H 10 94, found. C 71.84, H 11 07.

(R)-(-)-5-Hydroxymethyl-2-oxotetrahydrofuran **9** from **8**· A soln of 0 184 g (1 mmol) of 1,2(R)-isopropylidenedioxy-6-methyl-5-heptene, **8**, in 5 mL of dichloromethane was ozonized at -78°C to the point of appearance of a blue color The ozonide was decomposed by the addition of 100 µL of dimethyl sulfide and the reaction mixture was warmed to rm temp CH_2Cl_2 and excess dimethylsulfide were removed *in vacuo*, the residue dissolved in 25 mL of a 1 1 mixture of ethyl ether and pentane and washed with 2x5 mL of water The solvents were removed *in vacuo*, the residue stirred with 1 mL of water to which 0 230 g (1 mmol) of Ag_2O and 1 mL of 2 M NaOH were added with vigorous stirring The reaction was stirred for an additional 0 5 h and filtered The silver salts were washed with ~5 mL water, the washings combined and acidified to pH 2 with conc HCl Concentration of the aq. soln *in vacuo* followed by extraction of the residue with EtOAc, afforded 0 054 g (46%) of (R)-(-)-5-hydroxymethyl-2-oxotetrahydro-furan, **9** $[\alpha]_D^{22}$ -37 80° ($CHCl_3$, c 2 00), (lit [25] $[\alpha]_D^{25}$ -53 5° ($CHCl_3$), IR 3400, 1765 cm^{-1}, ^1H NMR δ 2 15 (m, 2), 2 25 (m,1), 2 60 (m,2), 3 65 (dd, 1, J = 14 0, 7 0), 3 92 (dd, 1, J = 14 0, 3.5), 4 63 (m,1)

(R)-(-)-(Z)-5-Tetradecenolide,**1** This compound was prepared by the published procedure [4b] $[\alpha]_D^{22}$ -63 1° (MeOH, c 5 3), (lit [4b] $[\alpha]_D^{25}$ -70° ($CHCl_3$), IR 1785, 1715 cm^{-1}, ^1H NMR δ 0 87 (t, 3, J = 6), 1 22 - 1 35 (m, 10), 1 38 (m, 2), 1 88 - 2 00 (m, 2), 2 10 (m,2), 2 35 (m, 1), 2 55 (m, 1), 5 25 (dd, 1, $J_1 = J_2 = 8$ 0), 5 45 (dd, 1, J = 10 0, 5 0), 5 66 (dt, 1, 10 75, 7 75)

1-Acetoxy-5-hexen-2(R,S)-ol, **13** To a well stirred mixture of 23 2 g (200 mmol) of 5-hexene-1,2-diol and 30 g (300 mmol) of acetic anhydride in 400 mL ethyl ether were added 10 g of PPL The mixture was stirred for ca 36 h, then PPL was removed by filtration, the ethereal soln was washed with 4x30 mL 2M NaOH, the ethyl ether extract dried ($MgSO_4$) and the solvent evaporated *in vacuo* Upon distillation (50°C / 0 1 Torr) the residue gave 29 07 g (92%) of 1-acetoxy-5-hexen-2-(R,S)-ol, **13**, containing ~2% of the diacetate The product was used without further purification in the next step An analytical sample was obtained by flash chromatography on silica gel using 25% EtOAc in hexanes (v/v) as the elution solvent IR 3450, 1750 cm^{-1}, ^1H NMR δ 1 42 - 1 83 (m, 2), 2 10 (s, 3), 2 25 (m, 3), 3 60 - 4 17 (m, 3), 4 97 (d, 1, J = 9 5), 5 05 (d, 1, J = 18 5), 5 81 (ddt, 1, J = 18 5, 9 5, 6 5) Anal Calcd for $C_8H_{14}O_3$ C 60 74, H 8 92, found C 60 64, H 9 18

1-Hydroxy-5-hexen-2-one, **12** To a soln of 29 0 g (184 mmol) of 1-acetoxy-5-hexen-2-(R,S)-ol in 1L of chilled acetone, Jones reagent (6 M)[26] was added with vigorous stirring over ~0 5 h, while maintaining the temperature below 10°C When excess reagent color persisted for 10 min stirring was continued for an additional 0 5 h Excess oxidising agent was destroyed by addition of 2-propanol Acetone was decanted, the residual chromium salts were washed with 3x150 mL portions of acetone and the washings combined and concentrated *in vacuo* The residue was diluted with 500 mL of ethyl ether which was washed with 4x100 mL portions of 2 M NaOH, dried ($MgSO_4$) and concentrated *in vacuo* Upon distillation (45°C / 0 1torr) the residue afforded 16 87 g

(148 mmol, 80.5% yield) of **12** IR. 3450, 2995, 1760, 1650 cm^{-1}, ^1H NMR δ 2.19 - 2 65 (m, 4), 3 23 (bs,1), 4.25 (s, 2), 4 95 (d, 1, J = 9.7), 4 97 (d, 1, J = 17 6), 5.73 (ddt, 1, J = 17.6, 9 7, 5 9); Anal. calcd for $C_8H_{12}O_3$ (acetate): C 61.52, H 7 75 ; found: C 61.42, H 7.59.

5-Hexene-1,2(R)-diol, **15**· To a well stirred soln of 100 g of sucrose in 1L of warm (30°C) tap water was added 100 g of baker's yeast. Vigorous fermentation ensued in ~10-15 min at which time 11 4 g (100 mmol) of 1-hydroxy-5-hexen-2-one, **12**, was added which kept foaming under control Stirring was continued for an additional 12 h Work-up of the reaction mixture was carried out as for 6-methyl-5-heptene-1,2(R)-diol to afford 5 45 g (47%) of 5-hexene-1,2(R)-diol $[\alpha]_D^{22}$ -1 88° ($CHCl_3$, c 1 60), +4.0° (EtOH, c 1 60), bp 60°C /0 15 Torr Spectra of **15** were identical with those of the racemic material

1,2(R)-Isopropylidenedioxy-5-hexene, **16** A mixture of 2 9 g (25 mmol) of **15**, 2 0 mL of 2-methoxypropene and ~5 mg of Amberlyst 15 was stirred at 25°C for 0 5 h. The liquid was decanted, unreacted 2-methoxypropene was removed *in vacuo* and the residue distilled to afford 3 65 g (93% yield) of the acetonide **16** as a colorless liquid bp 50°C / 30 Torr (Kugelrohr) , $[\alpha]_D^{25}$ -13 77° (neat), IR· 2995, 1650 cm^{-1}; ^1H NMR δ. 1 34 (s, 3), 1 40 (s, 3), 1 58 (m, 1), 1 72 (m, 1), 2 10 (m, 2), 3 51 (dd, 1, $J_1 = J_2 = 7.4$), 4 03 (dd, 1, J = 7 5, 6 5), 4 07 (m, 1), 4 97 (d, 1, J = 9 5), 5 04 (d, 1, J = 18 7), 5 81 (ddt, 1, J = 18 7, 9 5, 6 5), Anal calcd for $C_9H_{16}O_2$ C 69 19, H 10 32, found C 68 91, H 10.47

(R)-(-)-5-Hydroxymethyl-2-oxotetrahydrofuran, **9** from **16** The procedure as outlined above for the preparation of **9** from **8** was used A soln. of 3 12 g (20 mmol) of **16** in 20 mL CH_2Cl_2 was ozonized and then oxidized with 4.6 g (20 mmol) of Ag_2O in 10 mL 2 M NaOH to afford 0 99 g (42%) of **9**, $[\alpha]_D^{22}$ -43 03° ($CHCl_3$, c 10 0), (lit [24] $[\alpha]_D^{25}$ -53 5° ($CHCl_3$)

1-Butyroxy-5-hexen-2(R)-ol, **17**. A mixture of 2.55 g (22 mmol) of 5-hexene-1,2(R)-diol, 5 28 g (33 mmol) of butyric anhydride and 2 5 g of PPL in 50 mL ethyl ether was stirred vigorously for 8 h Excess butyric anhydride was destroyed by stirring with 2 mL of methanol for 12 h, PPL was removed by filtration, the ethereal soln was washed with 2x15 mL of 2M NaOH, dried ($MgSO_4$) and concentrated *in vacuo* The product, 4 05 g (~98% yield), was sufficiently pure to be used in the next step An analytical sample was obtained by flash chromatography on silica gel using 30 - 60% ethyl acetate in hexanes (v/v) as the elution solvent bp 60°C / 0 25 Torr (Kugelrohr), $[\alpha]_D^{25}$ -7 8° ($CHCl_3$, c 1 08), IR 3450, 1750, 1650 cm^{-1}, ^1H NMR δ 0 96 (t, 3, J =7 5), 1 42 - 1 94 (m, 4), 2 20 (m, 2), 2 33 (t, 2, J =7 5), 3 60 - 4 17 (m, 3), 4 95 (bs, 1), 4 97 (d, 1, J = 9 5), 5 04 (d, 1, J = 18 7), 5 81 (ddt, 1, J = 18 7, 9 5, 6 5), Anal Calcd for $C_{10}H_{18}O_3$ C 64.49, H 9 74, found C 64 61, H 9 67

6-Butyroxy-5(R)-tetrahydropyranyloxy-1-hexene, **18** To a mixture of 4 05 g (22 mmol) of 1-butyroxy-5-hexen-2(R)-ol, **17**, 2 g (24 mmol) of dihydropyran stirred at 0°C were added 10 mg TsOH and the mixture was allowed to warm to rm temp and stirring was continued for 16 h Neutralization of TsOH with 2 drops of Et_3N, followed by removal of unreacted dihydropyran *in*

vacuo and filtration of the residual oil through a 5 g pad of neutral alumina using 20% ethyl ether in hexanes afforded 5 95 g (~100% yield) of **18** as a diastereoisomeric mixture appearing as two spots on tlc (silica) and two peaks on GC, 6-butyroxy-5(R)-tetrahydropyranyloxy-1-hexene, sufficiently pure to carry to the next step An analytical sample was obtained by flash chromatography on silica gel using 20% ethyl acetate in hexanes (v/v) as the elution solvent IR. 1743, 1650 cm^{-1}, ^1H NMR δ· 0.96 (t, 3, J = 7), 1.41 - 1 91 (m, 10), 2 15 (m, 2), 2 25 (m, 2), 3 48 (m, 2), 3.70 - 4.0 (m, 2), 4.15 (m,1), 4 70 (m,1), 4 97 (d, 1, J = 9.5), 5 04 (d, 1, J = 18 3), 5 80 (ddt, 1, J = 18 3, 9.5, 6 5); Anal calcd. for $C_{15}H_{26}O_4$· C 66 63, H 9 69; found. C 66.61, H 9.82

2(R)-Tetrahydropyranyloxy-5-hexen-1-ol, **19**: 1-Butyroxy-2(R)-tetrahydropyranyloxy-5-hexene, **18**, 5 95 g (22 mmol) was stirred with 2 g (50 mmol) of NaOH in 10 mL of methanol for 1 h, and concentrated *in vacuo* The residue was dissolved in 100 mL of ethyl ether, which washed with 10 mL water, the ethereal soln dried ($MgSO_4$) and concentrated *in vacuo* The residue was purified by flash chromatography on silica gel using 25% ethyl acetate in hexanes (v/v) as the elution solvent to afford 3.93 g (90% yield) of 2(R)-tetrahydropyranyloxy-5-hexen-1-ol, **19**, giving one peak by gc, but two spots on tlc (silica) IR: 3450, 1650 cm^{-1},^1H NMR δ 1 40 - 1 65 (m, 6), 1 65 - 1 90 (m, 2), 2 2 (m, 2), 2.35 (bs, 1), 3 32 - 4 15 (m, 5), 4 73 (m, 1), 4 95 (d, 1, J = 9 5), 5.04 (d, 1, J = 18 5), 5.81 (ddt, 1, J = 18.5, 9 5, 6 5), Anal Calcd for $C_{11}H_{20}O_3$· C 65 97, H 10 07, found C 65 66, H 9 90

2(R)-Tetrahydropyranyloxy-5-hexenal, **20**· To a soln of 0 727 g (5 75 mmol) of oxalyl chloride in 10 mL CH_2Cl_2 cooled to -78°C was added dropwise, a soln of 0.88 g (11.3 mmol) of DMSO in 2 mL CH_2Cl_2 The reacton mixture was stirred at -78°C for 5 min A soln. of 0 95 g (4.75 mmol) of 2(R)-tetrahydropyranyloxy-5-hexen-1-ol , **19**, in 1 mL CH_2Cl_2 was added over 2 min The reaction was stirred for ~0 5 h at -78°C and 2 mL triethylamine was added The cooling bath was then removed and the reaction mixture was warmed to rm temp The mixture was partitioned between ethyl ether and water and washed with 3x10 mL water The organic extract was dried ($MgSO_4$) and concentrated *in vacuo* to afford 0 95 g (~100% yield) of **20** as a diastereoisomeric mixture appearing as two spots on tlc (silica) and two peaks on GC This was used without further purification in the next step. IR. 1740, 1650 cm^{-1} , ^1H NMR δ 1 35 - 2 00 (m, 8), 2 20 (m, 2), 3 42 - 3 58 (m, 2), 3.90 (m, 1), 4 60 (m, 1), 4 97 (d, 1, J = 9 5), 5 04 (d, 1, J = 18 7), 5 81 (ddt, 1, J = 18 7, 9 5, 6 5), 9 67 (d, 1, J = 2 45)

5(R)-Tetrahydropyranyloxy-1-hexadecen-6(R,S)-ol, **21** A soln of **20** in 2 mL of THF was added to a soln. of 10 mL of 0.6M n-decylmagnesium bromide stirred in a water bath at 20°C Stirring was continued for an addl 2 h and the reaction was quenched by addn of 5 ml water The reaction mixture was extracted with 60 mL of ethyl ether and the ethereal soln was washed with 10 mL of water The organic extract was dried ($MgSO_4$) and concentrated *in vacuo* The product was purified by flash chromatography on 45 g of silica gel using 10 - 20% EtOAc in hexanes (v/v) as the elution solvent to afford 1 34 g (82% from **19**) of **21** as a mixture of diastereoisomers IR 3450, 1645 cm^{-1}, ^1H NMR δ 0 88 (t, 3), 1 14 - 1 40 (m, 18), 1 35 - 1 70 (m, 8), 2 15 (m, 2), 3 33 - 4 05

(m, 4), 4.16 (bs, 1), 4 50 (m, 1), 4 99 (d, 1, J = 10.7), 5 0 (d, 1, J = 16.1), 5.80 (ddt, 1, J = 16.1, 10 7, 6 7)· Anal. calcd. for $C_{21}H_{40}O_3$ C 74 07, H 11 84; found. C 74.25, H 12 09

5(R)-Tetrahydropyranyloxy-1-hexadecen-6-one, **22**: To well stirred soln of 0 635 g (5 mmol) of oxalyl chloride in 5 mL CH_2Cl_2 cooled to -78°C was added a soln. of 0 78 g (10 mmol) of DMSO in 3 mL CH_2Cl_2 over 5 min. and the reaction mixture was stirred for 10 min. A soln of 1 08 g (3 mmol) of 5(R)-tetrahydropyranyloxy-1-hexadecen-6(R,S)-ol in 2 mL of CH_2Cl_2 was added and the reaction stirred for an additional 0.5 h Triethylamine (1.5 mL, 10 mmol) was added at -78°C, the cooling bath was removed and the reaction mixture was warmed to rm temp. The reaction mixture was diluted with 60 ml of ethyl ether, washed with 3x10 mL water, dried ($MgSO_4$), and concentrated *in vacuo* to afford 0.847 g (83% yield) of **22** sufficiently pure for use in the next step An analytical sample was obtained by flash chromatography using 20% ethyl acetate in hexanes (v/v) as the elution solvent IR. 1722, 1650 cm^{-1}, ^1H NMR δ 0 88 (t, 3, J =7 0), 1 20 - 1 30 (m, 14), 1 45 - 1.88 (m, 10), 2.08 (m, 2), 2 52 (dt, 1, J = 17 5, 7 0), 2 68 (dt, 1, J = 17 5, 7 0), 3 40 (m,1), 3 82 (m, 1), 3 98 (m, 1), 4 49 (m, 1), 4 99 (d, 1, J = 10 7), 5 0 (d, 1, J = 16 1), 5 80 (ddt, 1, J = 16 1, 10 7, 6 7); Anal. calcd for $C_{21}H_{38}O_3$ C 74 51, H 11 31, found C 74 46, H 11 31

5(R)-Hydroxy-1-hexadecen-6-one, **23** A soln of 0 847 g (~2 5 mmol) of 5(R)-tetrahydropyranyloxy-1-hexadecen-6-one, **22**, in 5 mL of methanol was stirred with ~25 mg of Amberlyst 15 for 1h at rm. temp The soln was decanted and concentrated to afford 0 62 g (~100% yield) of **23** as an oil This compound was highly unstable and was used immediately in the next step IR. 3450, 1717, 1650 cm^{-1}, ^1H NMR δ 0 86 (t, 3, J = 7 0), 1 14-1 40 (m, 14), 1 40 - 1 94 (m, 4), 2.10 (m, 2), 2 44 (t, 2, J = 8 0), 3 47 (bs,1), 4 15 (dd, 1, J = 8 0, 2 0), 4 99 (d, 1, J = 10 7), 5 0 (d, 1, J = 16 1), 5 80 (ddt, 1, J = 16 1, 10 7, 6 7)

1-Hexadecen-5R,6S-diol, **24** A soln of 0 62 g (~2 5 mmol) of ketol **23** in 5 mL of ethyl ether was added to a stirred 0 16 M soln of $Zn(BH_4)_2$ in diethyl ether (25 mL) at 0°C and the reaction mixture was stirred for 0 5 h Unreacted hydride was destroyed with water (5 mL), the reaction mixture was diluted with an additional 20 mL of ethyl ether, the aqueous phase removed and the organic phase dried ($MgSO_4$) and solvent concentrated *in vacuo* to afford white crystals Recrystallization from hexanes afforded 0 46 g (72% yield) of the diastereoisomerically pure *erythro* diol, **24** mp 104-104 5°, $[\alpha]_D^{22}$ -4 00° ($CHCl_3$, c 1 1), IR (KBr) 3150, 1665 cm^{-1}, ^1H NMR ($CDCl_3$-acetone-d_6) δ 0.89 (t, 3, J = 7), 1 09 - 1 35 (m, 16), 1 35 (m, 2), 1 50 (m, 2), 2 04 (bs, 2), 2 19 (m, 2), 3 50 - 3.66 (m, 2), 4 98 (d, 1, J = 10 2), 5 05 (dt, 1, J = 17 0, 1 7), 5 80 (ddt, 1, J = 17 0, 10 2, 6 5), Anal calcd for $C_{16}H_{32}O_2$ C 74 93, H 12 59, found C 74 98, H 12 35

(5R,6S)-5,6-*O*-Isopropylidenedioxy-1-hexadecene, **25** A mixture of 0 38 g (1 5 mmol) of **24** and 0 5 mL of 2-methoxypropene and ~5 mg of Amberlyst 15 was stirred at rm temp for 1h Filtration of the soln , concentration *in vacuo* Distillation of the residue gave 0 412 g (93% yield) of **25** as an oil, bp 150°C /0 1Torr (Kugelrohr), $[\alpha]_D^{22}$ 9 66° ($CHCl_3$, c 2 73), IR 1650 cm^{-1}, ^1H NMR δ 0 89 (t, 3, J = 7 0), 1 12 - 1.67 (m, 20), 1 34 (s, 3), 1.44 (s, 3), 2 23 (m, 2), 4 04 (m, 2), 4 98 (d,

1, J = 10 2), 5.05 (dt ,1, J = 17.0, 1 7), 5 80 (ddt, 1, J = 17 0, 10 2, 6 5), Anal calcd for $C_{19}H_{36}O_2$· C 76 96, H 12 25; found C 76.69, H 12.47

(5R,6S)-5,6-*O*-Isopropylidenedioxy-1-hexadecanal, **26** To a soln of 0 30 g (1 mmol) of **25** in 1 mL THF stirred in an ice-bath was added 3 mL of 9-BBN (0 5M soln in THF) After the reaction mixture was stirred over night at rm temp , the soln was concentrated *in vacuo* The residue was dissolved in 5 mL of CH_2Cl_2, 1.0 g of PCC was added and the reaction was stirred for 2 h at rm temp and 1h at reflux temp The reaction mixture was cooled to rm temp , diluted with 30 mL of ethyl ether and filtered through a 10 g column of florisil Evaporation of the solvent followed by the removal of volatile impurities at 50°C under 0 1 Torr and flash chromatography of the residue on 25 g of silica gel using 20% ethyl ether in hexanes (v/v) as the elution solvent afforded 0 120 g (40% yield) of **26** as an oil whose spectral characteristics matched with those reported [7b] $[\alpha]_D^{22}$ 3 20° (MeOH, c 20 0), (lit[7b] $[\alpha]_D^{25}$ 5.35° ($CHCl_3$), IR· 1735 cm^{-1}, ^1H NMR δ 0 89 (t, 3, J = 7 0), 1 12 - 1 67 (m, 18), 1 34 (s, 3), 1 43 (s, 3), 1 85 (m, 4), 2 51 (t, 2, J = 7), 4 05 (m, 2), 9 78 (bs, 1)

6(S)-Acetoxy -5(R)-hexadecanolide, **2** Preparation of **2** from **26** was carried out following the literature[7b] procedure $[\alpha]_D^{22}$ -31 14° (MeOH, c 10 5), (lit[7b] $[\alpha]_D^{25}$ -39 02° ($CHCl_3$), IR 1750 cm^{-1}, ^1H NMR δ 0 88 (t,3, J = 7 0), 1 18 -1 37 (m, 16), 1 55 - 2 00 (m, 6), 2 05 (s, 3), 2 45 (ddd, 1, J = 10 0, 7 6, 6.4), 2 58 (m,1), 4 34 (ddd, 1, J = 11 2, 4 8, 4 8), 4 97 (dt,1, J = 8 0, 5 5))

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