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A Formal and Enantioselective Synthesis of (–)-Serricornin, the Sex Pheromone of the Cigarette Beetle (*Lasioderma serricorne* F.)

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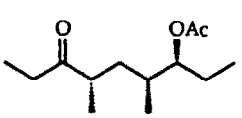
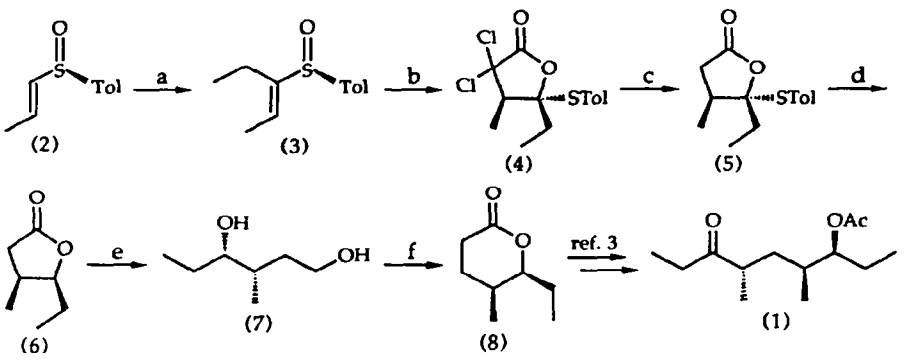
Abstract: A synthesis of (–)-Serricornin is described. The (4*S*,5*S*)-4-methyl-5-ethyl δ-valerolactone **8** has been synthesized with a high degree of enantioselectivity starting from (*R*)-(+)-(*E*)-1-propenyl *p*-tolylsulfoxide **2**, having the enantioselective Marino's lactonization as the key step.

A number of stereoselective syntheses of serricornin, the sex pheromone of the cigarette beetle (*Lasioderma serricorne* F.), have been reported in the last few years.[1] The most active stereoisomer of this class of pheromones has been shown to be the (4*S*,6*S*,7*S*)-isomer[2] (1) through a series of structure-activity studies.



(1)

In this paper we report the synthesis of (4*S*,5*S*)-4-methyl-5-ethyl δ-valerolactone **8**, with a high degree of enantioselectivity. Lactone **8** has already been transformed into Serricornin by Sato and coworkers.[3] The critical step in our synthesis for installing the chiral centers involves an enantioselective lactonization reaction of optically active vinyl sulfoxides, discovered by one of us.[4] The overall synthetic plan is outlined in Scheme 1.



reagents: (a) i. LDA, THF, HMPA, –78°C, ii. EtI, –78°C, 63%; (b) Cl_3CCOCl, Zn(Cu), THF, –40°C, 96%; (c) Al(Hg), THF, MeOH, H_2O, r.t., 84%; (d) RaNi, EtOH, 0°C, 66%; (e) LAH, Et_2O, 0°C-r.t., 98%; (f) i. *p*-TsCl, Py, $CHCl_3$, 0°C, ii. NaCN, DMSO, NaI, 90-95°C, 67%, iii. KOH, EtOH, H_2O, reflux, H_3O^+ then benzene, *p*-TsOH, 89%.

Scheme 1

Our synthesis begins with the readily available (*E*)-1-propenyl-(*R*)-*p*-tolylsulfoxide **2** prepared by a Horner-Emmons reaction of optically pure (*R*)-(+)-dimethylphosphorylmethyl *p*-tolylsulfoxide.[5] Deprotonation of vinyl sulfoxide **2** to generate the vinyl anion is effected with LDA, and subsequent quenching with ethyl iodide produces the requisite *E*-disubstituted vinyl sulfoxide **3** in good yield.[6] The key lactonization process is carried out on the sulfoxide **3** with a large excess of dichloroketene which is generated *in situ* from trichloroacetyl chloride and zinc-copper couple. This reaction produces a single diastereomer and enantiomer of the dialkyl butyrolactone **4** in 95% yield. Subsequent removal of the chlorine atoms with aluminum amalgam[7] in aqueous THF proceeds well and the stage is set for the stereoselective desulfurization of lactone **5**. While desulfurizations in general, and Raney/nickel desulfurizations[8] specifically are not known to proceed with high stereoselectivity, we have found that our butyrolactone systems do in fact, desulfurize with Raney/nickel with retention of configuration. Thus, treatment of lactone **5** with W-2 Raney/nickel[9] in ethanol led to the desired *cis*-dialkyl butyrolactone **6** in 66% yield. Previous studies[4] in our laboratory on desulfurizations of substituted butyrolactones have consistently given products with retention of configuration at the carbon bearing the sulfur atom.

Simple reduction of the lactone **6** with lithium aluminum hydride yields the optically pure diol **7** with two of the chiral centers of Serricornin in place. Conversion of the diol **7** into the valerolactone **8** required homologation of the diol through selective tosylation[10] of the primary alcohol and subsequent displacement of the

tosylate with sodium cyanide.[11] This was followed by hydrolysis and lactonization to the relay compound **8**, which was identical spectroscopically to the compound reported by Sato.[3]

The high enantioselectivity of the lactonization process for the preparation of optically pure butyrolactone provides an efficient and predictable method for the construction of chiral centers in acyclic natural products.

Experimental

All operations were carried out under an nitrogen atmosphere with oven-dried glassware. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR Spectrophotomer. ^{1}H-NMR spectra and ^{13}C-NMR spectrum were obtained on a Brüker WM-360 FT NMR or at Brüker AM-300 FT NMR using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. High resolution mass spectra (HRMS) were determined on a VG 70-250S instrument. Column chromatography was performed using Merck Silica Gel 60 (230-400 mesh).

(*R*)-(*E*)-1-propenyl *p*-tolylsulfoxide (2)

To a solution of (*R*)-(+)-dimethylphosphorylmethyl *p*-tolylsulfoxide[5] (25.0 g; 95.34 mmol) in anhydrous THF (300 mL) was added a solution of freshly prepared KHMDS (143.01 mmol) in anhydrous THF (250 mL) at –78°C under a nitrogen atmosphere. After 2.5 h, an excess of freshly distilled acetaldehyde (12.6 g; 286.02 mmols) was added dropwise at –78°C and stirring was continued at this temperature for 1.5 h. The mixture was then warmed slowly to room temperature, stirred for 2 h, and then quenched by addition of water. The reaction mixture was stirred for 10 minutes and transferred to a separatory funnel. After the layers were separated, the aqueous layer was extracted with diethyl ether (2x100 mL). The combined organic phases were washed with a saturated sodium chloride solution, water and dried over anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure gave a crude product which consisted of a 3/1 mixture of the isomeric vinyl sulfoxides *E*/*Z*, respectively. The crude product was chromatographed on silica gel (petroleum ether: ethyl acetate, 6:4) to afford 12.5 g of the desired E-vinyl sulfoxide **2** as an pale yellow oil: yield (73 %); $[\alpha]_D$= +143 (c= 2.0; $CHCl_3$).
IR (neat): ν 1038, 1442, 1490, 1634, 2937, 3030 cm^{-1}.
^{1}H-NMR ($CDCl_3$): δ = 1.87 (d, 3H, J=6.4 Hz); 2.37 (s, 3H); 6.19 (dq, 1H, J=15; 1.6 Hz); 6.40 (dq, 1H, J=15 Hz; 6.8 Hz); 7.27 (d, 2H, J=9.2 Hz); 7.53 (d, 2H, J=9.2 Hz).
^{13}C-NMR ($CDCl_3$): δ = 17.45; 21.04; 124.17; 129.65; 135.87; 136.02; 140.56; 141.00.
MS (70 eV): m/e = 181 (M+1), 180 (M^+), 132 (100%), 123, 117, 91, 65.
HRMS: m/e = calc. for $C_{10}H_{12}SO$: 180.0609; found: 180.0622.

(*R*)-(*E*)-1-ethyl-1-(*p*-tolylsulfinyl)-1-propene (3)

n-Butyl lithium (66.65 mmols; 25.5 mL of 2.61 M solution in hexanes) was added under a nitrogen atmosphere to a cold (0°C) solution of dry diisopropylamine (7.30 g; 72.20 mmols) in anhydrous THF (300 mL). After 30 minutes, the solution of LDA was cooled to –78°C and a cold (–78°C) solution of (*R*)-(*E*)-1-propenyl *p*-tolylsulfoxide 2 (10 g; 55.54 mmols) in anhydrous THF (50 mL) was added dropwise *via* a transfer needle under nitrogen. After 30 minutes at –78°C, HMPA (9.95 g; 55.54 mmols; 9.66 mL) was added, the reaction was stirred for 10 minutes at –78°C and then ethyl iodide (14.73 g; 94.42 mmols; 7.55 mL) was added. The reaction mixture was then stirred for an additional hour at –78°C, and was then quenched with a saturated ammonium chloride solution at that temperature. The organic layer was separated and the aqueous layer was extracted with ether (2x50 mL). The combined organic extracts were washed with a saturated sodium chloride solution and dried over anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure gave a crude product which was chromatographed on silica gel (petroleum ether/ethyl acetate, 7:3) to give 7.28 g of the desired sulfoxide 3 as an pale yellow oil: yield (63%); $[\alpha]_D$ = +43.3 (c= 2.0; $CHCl_3$).
IR (neat): ν 1053, 1451, 1645, 2970, 3053 cm^{-1}.
^{1}H-NMR ($CDCl_3$): δ = 0.82 (t, 3H, J=7.3 Hz); 1.85 (d, 3H, J=6.5 Hz); 2.15 (q, 2H, 9.2 Hz); 2.43 (s, 3H); 6.50 (q, 1 H, J=4.6 Hz); 7.29 (d, 2H, J=10.5 Hz); 7.48 (d, 2H, J=10.5 Hz).
^{13}C-NMR ($CDCl_3$): δ = 13.86; 13.92; 17.62; 21.66; 125.37; 129.86; 130.25; 140.17; 141.34; 147.12.
MS (70 eV): m/e = 209 (M^++1), 208 (M^+), 151, 140, 92, 65, 41 (100%).
HRMS: m/e = calc. for $C_{12}H_{16}SO$: 208.0922; found: 208.0917.

(3*R*,4*R*)-2,2-dichloro-4-ethyl-3-methyl-4-*p*-tolylthio γ-butyrolactone (4)

A solution of trichloroacetyl chloride (56.82 g; 312.5 mmols; 34.6 mL) in anhydrous THF (100 mL) was added during 30 min to a suspension of the vinyl sulfoxide 3 (13 g; 62.5 mmols) and zinc-copper couple[12] (1250 mmols; 81.7 g) in anhydrous THF (250 mL) at –40°C. The reaction mixture was then stirred vigorously at –40°C for an additional hour and then filtered through a pad of Celite® into an ice-cold saturated sodium bicarbonate solution. The zinc residue was washed with anhydrous ethyl ether (3x50 mL) and the combined filtrate and washings were placed in a separatory funnel. The aqueous layer was extracted with ether (3x50 mL), and the combined organic extracts were washed with a saturated sodium chloride solution, and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel

(petroleum ether/ethyl acetate, 9:1) to afford 19.0 g of the dichloro lactone **4** as a colorless solid: yield (96%); m.p. 108-110°C $[\alpha]_D$ = +2.96 (c= 3.0; $CHCl_3$)..
IR ($CHCl_3$): ν 745, 1166, 1250, 1582, 1802, 2950, 3061 cm^{-1}.
^{1}H-NMR ($CDCl_3$): δ = 1.12 (t, 3 H, J=7.5 Hz); 1.24 (d, 3 H, J=7.2 Hz); 1.72 (dq, 2 H, J=7.5 Hz); 2.21 (s, 3 H); 2.74 (q, 1 H, J=7.5 Hz); 7.07 (d, 2 H, J=9.5 Hz); 7.25 (d, 2 H, J=9.5 Hz).
^{13}C-NMR ($CDCl_3$): δ = 8.45; 8.87; 21.45; 28.08; 52.82; 81.64; 99.77; 124.64; 130.67; 136.96; 141.03; 166.90.
MS (70 eV): m/e = 320 (M+2), 319 (M+1), 318 (M^+), 239, 195, 124 (100%), 91, 57
HRMS: m/e = calc. for $C_{14}H_{16}SO_2Cl_2$: 318.0248; found: 318.0249.

(3*S*,4*R*)-4-ethyl-3-methyl-4-*p*-tolylthio γ-butyrolactone (5)

A solution of the dichlorolactone **4** (18.50 g; 58.17 mmols) in THF (50 mL) was added to a stirred suspension of aluminum amalgam (prepared from 23.5 g of aluminum pellets according to the procedure given in ref. 7) in THF (100 mL), followed by a 1:1 mixture of methanol/distilled water (100 mL). The suspension was stirred at room temperature for 24 h, and then filtered through a pad of Celite®. The amalgam was washed with anhydrous ethyl ether (2x50 mL) and the combined filtrate and washings were dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure, and the crude product was chromatographed on silica gel (petroleum ether/ethyl acetate, 9:1) to afford 12.22 g of the desired dechlorinated lactone **5** as a colorless oil: yield (84%); $[\alpha]_D$ = +66.5 (c= 2.3; $CHCl_3$).
IR (neat): ν 752, 1454, 1578, 1782, 2959, 3062 cm^{-1}.
^{1}H-NMR ($CDCl_3$): δ = 1.07-1.15 (m, 6 H); 1.73-1.81 (m, 2 H); 2.22 (dd, 1H, J=17.6; 5.8 Hz); 2.33 (s, 3H); 2.49-2.55 (m, 1 H); 2.75 (dd, 1H, J=17.6; 8.8 Hz); 7.12 (d, 2H, J=9.5 Hz); 7.42 (d, 2H, J=9.5 Hz).
^{13}C-NMR ($CDCl_3$): δ = 8.96; 14.56; 21.28; 27.10; 37.72; 37.87; 100.65; 126.06; 129.87; 136.41; 139.60; 175.19.
MS (70 eV): m/e = 251 (M+1), 250 (M^+), 161, 127 (100%), 109, 91, 84, 57.
HRMS: m/e = calc. for $C_{14}H_{18}SO_2$: 250.1028; found: 250.1018.

(3*S*,4*S*)-4-ethyl-3-methyl γ-butyrolactone (6)

A solution of lactone **5** (11.8 g; 47.2 mmols) in absolute ethanol (50 mL) was added to a stirred suspension of freshly prepared Raney nickel (ca. 35 g activated W-2 according to procedure given in ref. 9) in absolute ethanol (100 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes and then at room temperature until TLC indicated complete consumption of the starting material (ca. 12 h). The ethanolic solution was then decanted and the Raney nickel was washed with ether (2x30 mL). The combined organic extracts were filtered through a glass fritted funnel. The

solvents were removed under reduced pressure and the crude product was chromatographed on silica gel (petroleum ether/ethyl acetate, 9:1) to give 3.98 g of the desired product 6 as an colorless oil: yield (66%); $[\alpha]_D = -34.4$ (c=2.0; $CHCl_3$).
IR (neat): ν 811, 930 ,1128, 1223, 1466, 1777 cm^{-1}.
^{1}H-NMR ($CDCl_3$): δ = 0.92 (t, 3H, J=7.5 Hz); 1.12 (d, 3H, J=7.5 Hz); 1.85-2.00 (m, 2H); 2.2, (dd, 1H, J=16.8; 3.0 Hz); 2.40-2.60 (m,1H); 2.70 (dd, 1H, J=16.8; 7.6 Hz); 3.55-3.64 (m, 1H).
^{13}C-NMR ($CDCl_3$): δ = 13.53; 14.31; 26.57; 34.47; 37.53; 111.74; 176.28.
MS (70 eV): m/e = 128 (M^+), 99, 71, 59. 42 (100%).

(3*R*,4*R*)-3-methyl-1,4-hexanediol (7)

To a suspension of lithium aluminum hydride (1.26 g; 33.32 mmols) in anhydrous ethyl ether (100 mL) cooled (0°C) under nitrogen was added dropwise a solution of the lactone 6 (3.80 g; 29.65 mmols) in anhydrous ethyl ether (20 mL). The reaction mixture was stirred for 30 minutes at 0°C and then for 3 h at room temperature. The reaction mixture was cooled (0°C) and quenched with water (1.3 mL), 10% sodium hydroxide solution (1.3 mL) and water (5.2 mL) and was then stirred for an additional 30 minutes. The reaction mixture was filtered through a glass fritted funnel, the salts were washed with ethyl ether (2x50 mL) and the combined filtrate and washings were dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure to afford 3.84 g of the diol 7 as a viscous colorless oil which was used in the next step without further purification: yield (98%); $[\alpha]_D = +12.5$ (c= 1.0; $CHCl_3$).
IR (neat): ν 1010, 1132, 1237, 2943, 3406 (br) cm^{-1}.
^{1}H-NMR ($CDCl_3$): δ = 0.82 (t, 3H, J=7.2 Hz); 0.95 (d, 3H, J=7.2 Hz); 1.15-1.25 (m, 5H); 3.40 (s, 1H, OH), 4.05-4.30 (m, 3H).
^{13}C-NMR ($CDCl_3$): δ = 10.13; 14.93; 24.34; 31.79; 32.55; 77.30; 77.65.

(4*S*,5*S*)-5-ethyl-4-methyl δ-valerolactone (8)

Pyridine (4.55 g; 57.48 mmols; 4.6 mL) was added to a cold (0°C) solution of the diol 7 (3.8 g; 28.74 mmols) in chloroform (30 mL) followed by the addition of *p*-toluenesulfonyl chloride (5.48 g; 28.74 mmols) in small portions. The reaction mixture was stirred at 0°C, and was monitored by TLC until the starting material was consumed (ca. 14 h). After filtration through a pad of Celite® the solvent was evaporated under reduced pressure and the excess pyridine was removed in vacuo (0.5 mmHg). To a solution of the crude tosylate in DMSO (30 mL) was added sodium cyanide (1.28 g; 26.19 mmols) and sodium iodide (0.52 g; 3.5 mmols). The reaction mixture was heated at 90-95°C for 48 h, cooled to room temperature, and poured into

water. The reaction mixture was extracted with ethyl ether (2x50mL); the combined extracts were dried over anhydrous magnesium sulphate and the solvent was evaporated under reduced pressure. The crude product was chromatographed on silica gel (petroleum ether/ethyl acetate, 9:1) to afford 1.63 g (67%) of the hydroxynitrile as an oil: ^{1}H-NMR ($CDCl_3$): δ = 0.71-1.00 (m, 6H); 1.17-1.32 (m, 5H); 2.41 (t, 2H, J=6.8 Hz); 3.36 (s, 1H, OH), 4.0-4.25 (m, 2H).

A mixture of the hydroxynitrile (1.15 g; 8.16 mmols), water (3 mL) and sodium hydroxide (6.20 g; 155.04 mmols) was then refluxed for 48 h and then cooled to room temperature and diluted with water. The reaction mixture was neutralized with concentrated HCl, extracted with dichloromethane (3x30 mL), dried over anhydrous magnesium sulphate and then concentrated under reduced pressure. To the residue was added benzene (25 mL) and a catalytic amount of p-toluenesulfonic acid (ca. 0.15 g). The reaction mixture was then refluxed for 24 h using an Dean-Stark apparatus, cooled to room temperature and diluted with ethyl ether. The aqueous layer was extracted with ethyl ether (2x20 mL) and the combined organic extracts were washed with a sodium bicarbonate solution, a sodium chloride solution, water and finally dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure and the product was chromatographed on silica gel (hexane/ethyl acetate, 9: 1) to give 1.03 g of the lactone **8** as an colorless oil: yield (89%); $[\alpha]_D$ = –63.90 (c= 1.0; $CHCl_3$) [lit. $[\alpha]_D$ = –65.82 (c= 1.0; $CHCl_3$)].[1d]
IR (neat): ν 1721 cm^{-1}.
^{1}H-NMR ($CDCl_3$): δ = 0.92 (d, 3 H, J=7.6Hz)); 1.20 (t, 3 H, J=7.6Hz); 1.67-1.91 (m, 5 H); 2.36 (m, 2H); 4.18 (ddd, 1 H, J=6.2; 7.8Hz).
^{13}C-NMR ($CDCl_3$): δ = 10.60; 12.35; 23.86; 25.67; 26.58; 28.66; 84.90; 171.32.
MS (70 eV): m/e = 143 [(M+H)$^+$], 113, 84, 56 (100%)
HRMS: m/e = calc. for $C_8H_{14}O_2H$: 143.1072; found: 143.1075.

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