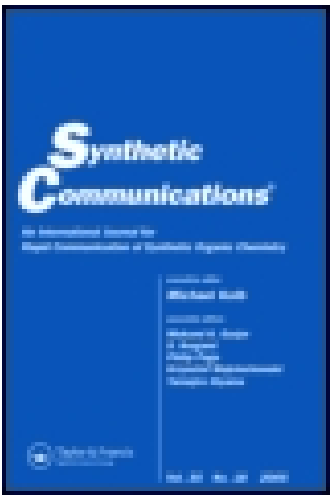

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Formal Synthesis of (-)-Serricornin

Hyun-Joon Ha [a] & Yoon-Gil Yim [a]
[a] Department of Chemistry , Hankuk University of Foreign Studies Yongin , Kyunggi-Do, 449--791, Korea
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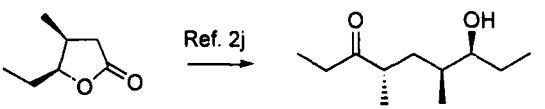
FORMAL SYNTHESIS OF (–)-SERRICORNIN

Hyun-Joon Ha*, and Yoon-Gil Yim

Department of Chemistry, Hankuk University of Foreign Studies
Yongin, Kyunggi-Do 449-791, Korea

Abstract: A formal synthesis of sex pheromone (–)-serricornin was achieved via (4*S*,5*S*)-5-ethyl-4-methyltetrahydrofuran-2-one prepared from lipase PS-resolved (4*S*,5*R*)-4-methyl-5-acetyloxymethyltetrahydrofuran-2-one.

The sex pheromone (–)-serricornin isolated from the female cigarette beetle (*Lasioderma, serricorne* F) is (4*S*,6*S*,7*S*)-7-hydroxy-4,6-dimethylnonan-3-one (**1**).[1] Due to the commercial importance of serricornin, ample examples of stereoselective synthesis were reported in last few years.[2] One of them is based on the formation of (4*S*,5*S*)-5-ethyl-4-methyltetrahydrofuran-2-one (**2**) followed by reduction and one carbon homologation to (4*S*,5*S*)-5-ethyl-4-methyl δ-valerolactone which was further elaborated toward (–)-serricornin.[2j] After our success obtaining optically active β-substituted γ-acetyloxymethyl-γ-butyrolactones[3] we have developed the simple access of the molecule **2** for the stereoselective synthesis of (–)-serricornin.

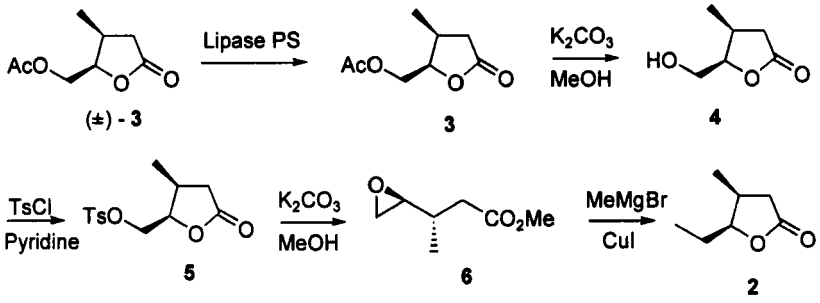


2 **1**

(4*S*,5*R*)-4-Methyl-5-acetyloxymethyltetrahydrofuran-2-one (**3**) was obtained as an unreacted substrate after lipase PS (*Pseudomonas cepacia*) mediated hydrolysis of

* To whom correspondence should be addressed.

racemate ((±)-**3**) at 60% conversion based on the consumption of NaOH. The enantioselectivity measured by GLC with the chiral column was ≥ 98% ee. Simple hydrolysis of acetate by Na_2CO_3 in MeOH gave free alcohol (4*S*,5*R*)-4-methyl-5-hydroxymethyltetrahydrofuran-2-one (**4**).



Scheme

The target molecule would be expected by reductive methylation of this alcohol activated properly toward the nucleophilic methyl anion. We decided to tosylate this alcohol using *p*-tolenesulfonyl chloride in pyridine to yield (4*S*,5*R*)-4-methyl-5-tosyloxymethyltetrahydrofuran-2-one (**5**) in 93% yield. The initial attempts of the direct methylation of this tolylate with MeMgBr or MeLi with cuprous compounds such as CuI, CuBr and CuCN were not satisfactory to get (4*S*,5*S*)-5-ethyl-4-methyltetrahydrofuran-2-one (**2**). From all reactions we tried the expected product was obtained in less then 10% yield with the recovery of unreacted starting material and unidentified byproducts. It was considered as a reason that there is possible steric hindrance by β-methyl substituent while a direct butylation was successful on the same γ-lactone bearing a *trans*-methyl substituent at β-position.[4] Therefore we decided to make an epoxide[5] (**6**) by the treatment of tosylate (**5**) with K_2CO_3 in 85% yield. Then it was methylated[6] by MeMgBr with catalytic amount of CuI to yield the expected target molecule (4*S*,5*S*)-5-ethyl-4-methyltetrahydrofuran-2-one (**2**) for the stereoselective synthesis of (–)-serricornin in 75% yield.

In conclusion a formal synthesis of the sex pheromone (–)-serricornin was achieved via (4*S*,5*S*)-5-ethyl-4-methyltetrahydrofuran-2-one prepared from lipase-resolved (4*S*,5*R*)-4-methyl-5-acetyloxymethyltetrahydrofuran-2-one in 40% overall yield.

Experimental

General Procedure: ^{1}H NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C). Chemical shifts were given in ppm using TMS as internal standard. Mass spectra were obtained using a Hewlett Packard Model 5985B spectrometer or a Kratos Concept 1-S double focusing mass spectrometer. Elemental analysis was taken on a Perkin-Elmer 240 DS elemental analyzer. Optical rotation was measured with Rudolph Research Autopole 3 polarimeter. Melting point was measured by Mel-II capillary melting point apparatus. The silica gel used for column chromatography was Merck 200-230 mesh. TLC was carried out with Merck 60F-254 plates with 0.25 mm thickness. E.e. values were determined by capillary GC analysis using Rt-βDEXsa (ϕ 0.25 mm x 30 M, He_2, 150 °C for 5min, 4 °C/min, 210 °C) purchased from Altech Co., Ltd.

(4*S*,5*R*)-4-Methyl-5-acetyloxymethyltetrahydrofuran-2-one (3): Enzyme lipase PS (10.3 g) obtained from Amano Pharmaceutical Co., Ltd. was added to a stirred solution of racemic *trans*-4-methyl-5-acetyloxymethyltetrahydrofuran-2-one (3.44 g, 20.0 mmol) in the mixed solvent of 1N phosphate buffer at pH 7.2 (232 ml) and acetone (8 ml). The resulting solution was stirred well at 35 °C while pH of the solution was maintained to 7.2 by adding 0.5 N NaOH solution. After 2.6 h for the reaction to be reached at 60 % conversion according to NaOH consumption, the reaction was quenched by adding celite and ice. The cake was filtered through Celite with water and EtOAc. The combined organic layer was washed with water twice, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. This crude oily product was purified by flash chromatography on silica gel to give 1.11 g of unreacted substrate (4*S*,5*R*)-4-methyl-5-acetyloxymethyltetrahydrofuran-2-one with ≥ 98% ee.. $[\alpha]_D$ –59.7 (c 3.1, CH_2Cl_2). ^{1}H NMR δ 1.08 (3H, d, J = 7.0 Hz), 2.07 (3H, s), 2.26 (1H, dd, J = 16.4, 6.4 Hz), 2.59 - 2.81 (2H, m), 4.16 (1H, dd, J = 12.2, 6.0 Hz), 4.32 (1H, dd, J = 12.2, 3.6 Hz), 4.60 - 4.68 (1H, m); ^{13}C NMR δ 13.5, 20.4, 31.6, 36.2, 62.7, 79.4, 170.3, 176.1.

(4*S*,5*R*)-4-Methyl-5-hydroxymethyltetrahydrofuran-2-one (4): (4*S*,5*R*)-4-Methyl-5-acetyloxymethyltetrahydrofuran-2-one (**3**, 845 mg, 4.91 mmol) was stirred in aqueous methanol solution (15 ml) containg Na_2CO_3 (1.56 g, 14.7 mmol) for 14 h. After completion of the reaction on TLC the solution was filtered over celite with MeOH (2 x 20 ml) and dried under reduced pressure to give oily product with white solid coated in

the flask. This was dissolved in EtOAc and filtered again over celite. The filterate was concentrated under reduced pressure. This was purified by flash column chromatography to yield 509 mg of the expected product in 80% yield. $[\alpha]_D$ –53.6 (c 2.1, CH_2Cl_2). ^1H NMR δ 1.07 (3H, d, J = 6.8 Hz), 2.79 (1H, dd, J = 16.8, 8.0 Hz), 2.55 (1H, dd, J = 17.0, 8.4 Hz), 2.91 (1H, q, J = 7.4 Hz), 3.44 (1H, bs), 3.75 (2H, d, J = 4.6 Hz), 4.43 - 4.51 (1H, m); ^{13}C NMR δ 13.6, 32.0, 36.6, 61.5, 83.2, 177.8.

(4*S*,5*R*)-4-Methyl-5-tosyloxymethyltetrahydrofuran-2-one (5): *p*-Toluenesufonyl chloride (1.41 g, 7.39 mmol) was added to hydroxymethyltetrahydrofuran-2-one **4** (480 mg, 3.69 mmol) in pyridine (5 ml) at 0 °C. After the addition was completed the ice bath was removed. The resultant solution was stirred at the ambient temperature for 48 h and neutralized with 10% HCl solution with ice bath. The reaction product was extracted with 50 ml of EtOAc three times. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. This crude oily product was purified by flash chromatography on silica gel to give 976 mg of white solid (4*S*,5*R*)-4-methyl-5-tosyloxymethyltetrahydrofuran-2-one with the mixed solvent of *n*-hexane and EtOAc (1:1, v/v) in 93 % yield. $[\alpha]_D^{20}$ –51.6 (c 3.0, CH_2Cl_2). mp 46-48 °C; ^1H-NMR ($CDCl_3$) δ: 1.04 (3H, d J = 7.0 Hz), 2.21 (1H, dd, J = 17.2, 8.0 Hz), 2.39 (3H, s), 2.49 (dd, 1H, J = 17.0, 8.8 Hz), 2.69 (1H, six, J = 7.2 Hz), 4.12 (2H, d, J = 4.2 Hz), 4.53 (1H, dt, J = 8.6, 4.2 Hz), 7.32 (2H, dd, J = 8.6, 2.6 Hz), 7.83 (2H, dd, J = 8.6, 2.0 Hz); ^{13}C-NMR ($CDCl_3$) δ: 13.4, 21.5, 31.8, 36.0, 67.7, 78.7, 128.0, 130.1, 132.0, 145.5, 175.7; m/z 284 (M+, 8%), 220 (23), 155 (21), 113 (18), 99 (100)., 91(37). Anal. Calcd for $C_{13}H_{16}O_5S$: C, 54.9; H, 5.67. Found: C, 55.2; H, 5.83.

Methyl (4*S*,5*R*)-4,5-epoxy-3-methylpentanoate (6): (4*S*,5*R*)-4-Methyl-5-tosyloxymethyltetrahydrofuran-2-one (**5**) (320 mg, 1.13 mmol) was treated with K_2CO_3 (187 mg, 1.35 mmol) in 5 ml MeOH at room temperature under N_2 atmosphere for 16h. After completion of the reaction on TLC the solution was filtered over celite with MeOH (2 x 20 ml) and dried under reduced pressure to give oily product with white solid coated in the flask. This was dissolved in EtOAc and filtered again over celite. The filterate was concentrated under reduced pressure. This was purified by flash column chromatography to yield the expected product **6** (115 mg) in 71% yield. $[\alpha]_D^{20}$ +1.2 (c 3.04, CH_2Cl_2). ^1H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J = 7.0 Hz), 1.78 (1H, six, J = 6.8 Hz), 2.10 (1H, dd, J = 15.2, 7.0 Hz), 2.26 (1H, dd, J = 15.2, 7.0 Hz), 2.41 (1H, dd, J = 5.2, 4.8 Hz), 2.57 (1H, t, J = 4.8 Hz), 2.63-2.70 (1H, m), 3.53 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 16.2,

32.4, 37.3, 45.7, 51.1, 55.3, 172.2. Anal. Calcd for $C_7H_{12}O_3$: C, 58.3; H, 8.39. Found: C, 58.1; H, 8.14.

(4*S*,5*S*)-5-Ethyl-4-methyltetrahydrofuran-2-one (2): A solution of MeMgBr (0.55 ml of 3 M soln, 1.66 mmol) dissolved in THF (6 ml) was added dropwise to a suspension of CuI (32 mg, 0.11 mmol) in dry THF (2 ml) at –30 °C. This mixture was stirred for 10 min at –30 °C. This solution was added dropwise into epoxide (**6**, 160 mg, 1.11 mmol) dissolved in THF (3 ml) –30 °C under N_2 atmosphere. After the addition was completed the resultant solution was stirred at –30 °C for 5 h. The reaction was quenched by pouring sat. $(NH_4)_2SO_4$ solution. The reaction product was extracted with 40 ml of EtOAc twice. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. This crude product was purified by flash chromatography on silica gel to give 106 mg solid (4*S*,5*S*)-4-methyl-5-ethyltetrahydrofuran-2-one (**3**) in 75 % yield. $[\alpha]_D$ –31.2 (c 0.2, CH_2Cl_2) lit,[2i] $[\alpha]_D$ –34.4 (c 2.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, d, J = 7.0 Hz), 0.91 (3H, t, J = 7.2 Hz), 1.37-1.58 (2H, m), 2.04 (1H, dd, J = 16.2, 3.0 Hz), 2.40-2.60 (1H, m), 2.61 (1H, dd, J = 14.6, 7.6 Hz), 4.23 (1H, dt, J = 8.4, 3.2 Hz) ; ^{13}C-NMR ($CDCl_3$) δ: 9.9, 13.3, 22.6, 32.4, 37.1, 84.7, 176.6; m/z 128 (M+, 4%), 100 (11), 99 (100), 71 (38), 59 (58).

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