

## COMMUNICATIONS TO THE EDITOR

## An Enantiospecific Synthesis of 4-Hexanolide ( $\gamma$ -Caprolactone), the Sex Pheromone of the Female Dermestid Beetle *Trogoderma glabrum* (Herbst)

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The (R)-enantiomeric form of (R)-(+)-4-hexanolide (**1**),  $\gamma$ -caprolactone (Figure 1), is the sex pheromone of the dermestid beetle *Trogoderma glabrum* (Herbst), an economically important insect pest that infest nearly all forms of stored products, including grain, meat, dairy products, carpets and clothing.<sup>1</sup> Although (R)-(+)-4-hexanolide (**1**) have a simple structure, synthesis is difficult for the reason that (R)-**1** contain an asymmetric carbon center in the molecule.

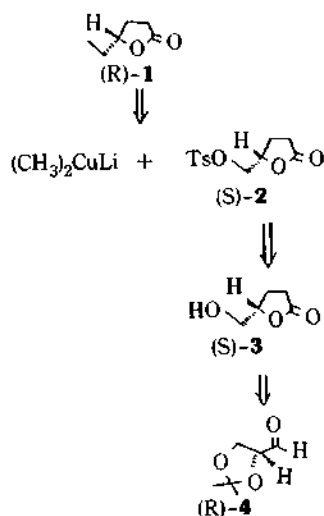
**1**

Figure 1

Several synthesis have been reported in the literature. Silvestein<sup>2</sup> have synthesized the (R)-form from (S)-glutamic acid. D-Ribolactone was used as a chiral starting material in the J. Font's<sup>3</sup> synthesis. Two synthesis<sup>4,5</sup> have been reported by asymmetric reduction of acetylenic ketone or acetylenic keto ester. R. Bernardi<sup>6</sup> also reported the synthesis of (R)-**1** from (2S, 3R)-5-phenyl-4-pentene-2,3-diol, which was obtained by microbial transformation of cinnamaldehyde with baker's yeast.

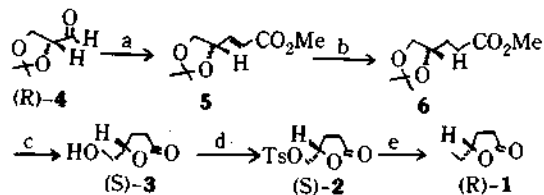
Since the absolute stereochemistry of pheromones is important in pheromone activity, this fact demands a highly efficient chiral synthesis on a large scale and in high optical purity. Here, we wish to report an enantiospecific synthesis of (R)-**1** using (R)-2,3-O-isopropylidenglyceraldehyde (**4**)<sup>7</sup> as a chiral starting material.

Bond formation between C-6 and C-7 can be accomplished with tosylate and dialkylcuprate. A simple retrosynthetic analysis (Scheme 1) reveals that (S)-(+)-5-hydroxymethyl-2-oxotetrahydrofuran (**3**)<sup>8</sup> is the key intermediate. We have prepared (S)-(+)-5-hydroxymethyl-2-oxotetrahydrofuran(**3**), the key intermediate. We have prepared (S)-(+)-5-hydroxymethyl-2-oxotetrahydrofuran (**3**), the key intermediate from (R)-2,3-O-isopropylidenglyceraldehyde (**4**) and synthesized (R)-**1** by C-C coupling reaction of (S)-5-p-toluenesulfonyloxymethyl-2-oxotetrahydrofuran (**2**) with dimethylcuprate.

Scheme 1. Retrosynthetic analysis of (R)-**1**

Optically active (R)-2,3-O-isopropylidene-D-glyceraldehyde (**4**)<sup>7</sup> was readily available from naturally occurring inexpensive carbohydrate, D-mannitol. The bis-acetonide of D-mannitol was prepared in a moderate yield and the resulting diol acetonide was cleaved with lead tetraacetate to yield (R)-glyceraldehyde acetonide **4**.<sup>8</sup> Wittig-Emmons olefination<sup>9</sup> of the aldehyde **4** with the anion of dimethyl methoxycarbonylmethylphosphonate furnished the unsaturated ester **5** as a mixture of (E):(Z) = 85:15 in 82% yield. Without separation of the mixture, the unsaturated ester **5** was subjected to hydrogenation at atmospheric pressure at room temperature to yield the saturated ester **6**<sup>8</sup> in good yield. Esterhydrolysis<sup>10</sup> with LiOH in THF-H<sub>2</sub>O (3:1) for 3hr followed by deprotection of the acetonide with aqueous AcOH at 75-80°C for 2hr provided (S)-(+)-2-oxotetrahydrofuran **3**.<sup>8</sup> On treatment of (S)-(+)-2-oxotetrahydrofuran **3** with tosyl chloride in dichloromethane in the presence of pyridine, the corresponding crystalline tosylate **2**<sup>8</sup> was obtained in 96% yield. Addition of a benzene solution of the (S)-tosylate **2** to an ether solution of lithium dimethylcuprate<sup>2</sup> gave (R)-(+)-**1**<sup>8</sup> in 66% yield (Scheme 2). The compound synthesized was identical in all respects (TLC, IR, NMR, MS) with the compound reported in the

literature.



<sup>a</sup>(a) (MeO)<sub>2</sub>POCH<sub>2</sub>CO<sub>2</sub>Me, NaH, DME, rt → 60°C (b) H<sub>2</sub>, Pd/C, EtOH (c) (i) 1.5 equiv. LiOH, THF-H<sub>2</sub>O (3:1), (ii) aq. AcOH (d) TsCl, pyr., CH<sub>2</sub>Cl<sub>2</sub> (e) 2.0 equiv. (CH<sub>3</sub>)<sub>2</sub>CuLi, -70°C 2hr, -30°C 0.5 hr, 0°C 0.5 hr

Scheme 2. Synthesis of (R)-1<sup>a</sup>

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- Satisfactory physical properties and spectroscopic data (<sup>1</sup>H-NMR, IR, MS) were obtained for the compounds: (R)-2,3-O-isopropylidene-glyceraldehyde (**4**); bp 39°C/15 mmHg; IR(NaCl, neat) 2850, 2750, 1725, 1180 cm<sup>-1</sup>; <sup>1</sup>H-NMR (80MHz, CDCl<sub>3</sub>) δ 1.35(3H, s, CH<sub>3</sub>), 1.46 (3H, s, CH<sub>3</sub>), 4.01-4.18 (2H, d, OCH<sub>2</sub>), 4.24-4.39 (1H, m, CH<sub>2</sub>CHO), 9.85 (1H, s, CHCHO). Methyl (4S, 2E)-4,5-isopropylidenedioxy-pent-2-enoate (**5**); hexane: ethyl-acetate (9:1); [α]<sub>D</sub><sup>20</sup> + 37.5° (c = 0.29, CHCl<sub>3</sub>); IR (neat) 1700, 1650 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ 1.42 (3H, s, CH<sub>3</sub>), 1.45 (3H, s, CH<sub>3</sub>), 3.63 (1H, m, CHHCHO), 3.75 (3H, s, OCH<sub>3</sub>), 4.1 (1H, m, OCHHCHO), 4.65 (1H, m, CH<sub>2</sub>CHO), 6.04 (1H, dd, J<sub>15</sub> and 1.5Hz, CH = CH-CO), and 6.87 (1H, dd, J<sub>15</sub> and 6Hz). Methyl(4S)-4,5-isopropylidenedioxy-pentanoate (**6**); bp 67-75°C/8 mmHg; IR(neat) 1700, 1650 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ 1.42 (3H, s, CH<sub>3</sub>), 1.45 (3H, s, CH<sub>3</sub>), 1.9 (2H, m, CH<sub>2</sub>), 2.5 (2H, m, CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 3.63 (1H, m, CH-O), 3.75 (3H, s, OCH<sub>3</sub>), 4.1 (2H, m, CH<sub>2</sub>-O). (S)-(+)-5-hydroxymethyl-2-oxotetrahydrofuran (**3**); chloroform: methanol (98:2); [α]<sub>D</sub><sup>20</sup> + 33.1° (c = 3.17, EtOH); IR (neat) 3400, 1765 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ 2.0-2.8 (4H, m, CH<sub>2</sub>CH<sub>2</sub>), 3.1 (1H, br.s, OH), 3.5-4.1 (2H, m, CH<sub>2</sub>O), 4.6 (1H, m, -CH-O). (S)-(+)-p-toluenesulfonyloxymethyl-2-oxotetrahydrofuran (**2**); mp 85-7°C (ether: dichloro-methane); [α]<sub>D</sub><sup>20</sup> + 46.3° (c = 1.33, CHCl<sub>3</sub>); IR (KBr, pellet) 1765 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ 1.8-2.7 (4H, m, CH<sub>2</sub>CH<sub>2</sub>), 2.45 (3H, s, CH<sub>3</sub>), 4.18 (2H, d, CH<sub>2</sub>-O), 4.70 (1H, m, CH-O), 7.42 (2H, d, J = 10Hz), 7.85 (2H, d, J = 10Hz); MS 270 (M<sup>+</sup>), 85 (base). (R)-(+)-hexan-4-olide (**1**); ether: hexane (3:2); [α]<sub>D</sub><sup>20</sup> + 30.4° (c = 1.0, MeOH) [lit.,<sup>2</sup> [α]<sub>D</sub><sup>20</sup> + 42.7° (c = 1, MeOH)]; IR (neat) 1770, 1170 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ 1.01 (3H, t, CH<sub>3</sub>), 1.6-2.7 (6H, m, -(CH<sub>2</sub>)<sub>2</sub>-, -CH<sub>2</sub>-), 4.6(1H, m, CH-O).
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## Facile Cleavage of Tetrahydrofuran Derivatives with S-2-Pyridyl Thioates / CuBr<sub>2</sub> / CH<sub>3</sub>CN<sup>†</sup>

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Previously we have reported a rapid and convenient preparation of sterically hindered carboxylic esters by the reaction of S-2-pyridyl thioates with alcohols in the presence of cupric bromide in acetonitrile.<sup>1</sup> We wish to report that S-2-pyridyl thioates/cupric bromide rapidly and cleanly

cleaves tetrahydrofuran derivatives in acetonitrile at room temperature,<sup>2-8</sup> although S-2-pyridyl thioates/cupric bromide was inert to tetrahydrofuran derivatives at room temperature for a long period of time.<sup>9</sup> Thus, the success of the reaction depends crucially on the use of acetonitrile as a solvent, although the reason for this observation is rather unclear.

The reaction was carried out with equimolar amounts of S-2-pyridyl methanethioate and cupric bromide using a slight

<sup>†</sup>This paper is dedicated to Professor Sae-Hee Chang on the occasion of his 60th birthday.