COMMUNICATIONS TO THE EDITOR

An Enantiospecific Synthesis of 4-Hexanolide (γ-Caprolactone), the Sex Pheromone of the Female Dermestid Beetle Trogoderma glabrum (Herbst)

Suk-Ku Kang* and Dong-Soo Shin

Department of Chemistry, Sung Kyun Kwan University, Natural Science Campus, Suwon 170
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The (R)-enantiomeric form of (R)-(+)-4-hexanolide (**1**), γ-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.[1] 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.

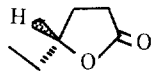

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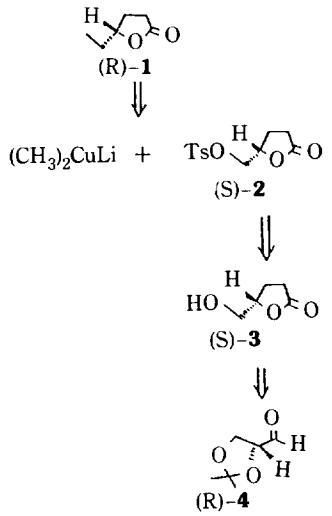
Figure 1

Several synthesis have been reported in the literature. Silvestein[2] have synthesized the (R)-form from (S)-glutamic acid. D-Ribolactone was used as a chiral starting material in the J. Font's[3] synthesis. Two synthesis[4,5] have been reported by asymmetric reduction of acethylenic ketone or acetylenic keto ester. R. Bernardi[6] 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-isopropylideneglyceraldehyde (**4**)[7] as a chiral starting material.

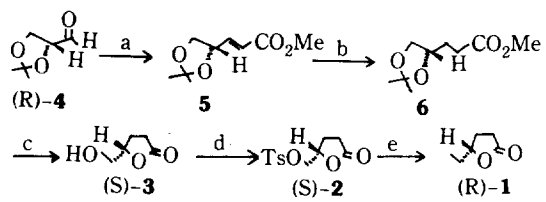
Bond formation between C-6 and C-7 can be accomplished with tosylate and dialkylcuprate. A simple retrosynthetic analysis (Scheme 1) reveals that (S)-(+)-5-hydroxymethyl-2-oxotetrahydrofuran (**3**)[2] is the key intermediate. We have prepared (S)-(+)-5-hydroxymethyl-2-oxotetrahydrofuran(**3**), the key intermediate. We have prepard (S)-(+)-5-hydroxymethyl-2-oxotetrahydrofuran (**3**), the key intermediate from (R)-2,3-O-isopropylideneglyceraldehyde (**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**)[7] 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**.[8] Wittig-Emmons olefination[9] 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 atomospheric pressure at room temperature to yield the saturated ester **6**[8] in good yield. Esterhydrolysis[10] with LiOH in THF-H_2O (3:1) for 3hr followed by deprotection of the acetonide with aqueous AcOH at 75-80°C for 2hr provided (S)-(+)-2-oxotetrahydrofuran **3**[8]. On treatment of (S)-(+)-2-oxotetrahydrofuran **3** with tosyl chloride in dichloromethane in the presence of pyridine, the corresponding crystalline tosylate **2**[8] was obtained in 96% yield. Addition of a benzene solution of the (S)-tosylate **2** to an ether solution of lithium dimethylcuprate[2] gave (R)-(+)-**1**[8] in 66% yield (Scheme 2). The compound synthesized was identical in all respects (TLC, IR, NMR, MS) with the compound reported in the

literature.



[a](a) $(MeO)_2POCH_2CO_2Me$. NaH. DME, rt → 60°C (b) H_2, Pd/C, EtOH (c) (i) 1.5 eqiv. LiOH, THF-H_2O (3:1), (ii) aq. AcOH (d) TsCl, pyr., CH_2Cl_2 (e) 2.0 eqiv. $(CH_3)_2$ CuLi, -70°C 2hr, -30°C 0.5 hr, 0°C 0.5 hr

Scheme 2. Synthesis of (R)-**1**[a]

References

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8. Satisfactory physical properties and spectroscopic data (^{1}H-NMR, IR, MS) were obtained for the compounds: (R)-2,3-O-isopropylideneglyceraldehyde (**4**); bp 39°C/15 mmHg; IR(NaCl, neat) 2850, 2750, 1725, 1180 cm^{-1}; ^{1}H-NMR (80MHz, $CDCl_3$) δ1.35(3H, s, CH_3), 1.46 (3H, s, CH_3), 4.01-4.18 (2H, d, OCH_2), 4.24-4.39 (1H, m, CH_2CHO), 9.85 (1H, s, CHCHO). Methyl (4S, 2E)-4,5-isopropylidenedioxypent-2-enoate (**5**); hexane: ethylacetate (9:1); $[\alpha]_D^{20}$ + 37.5° (c = 0.29, $CHCl_3$); IR (neat) 1700, 1650 cm^{-1}; ^{1}H-NMR δ1.42 (3H, s, CH_3), 1.45 (3H, s, CH_3), 3.63 (1H, m, CHHCHO), 3.75 (3H, s, OCH_3), 4.1 (1H, m, OCHHCHO), 4.65 (1H, m, CH_2CHO), 6.04 (1H, dd, J15 and 1.5Hz, CH = CH-CO), and 6.87 (1H, dd, J15 and 6Hz). Methyl(4S)-4,5-isopropylidenedioxypentanoate (**6**); bp 67-75°C/8 mmHg; IR(neat) 1700, 1650 cm^{-1}; ^{1}H-NMR δ1.42 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.9 (2H, m, CH_2), 2.5 (2H, m, $CH_2CO_2CH_3$), 3.63 (1H, m, CH-O), 3,75 (3H, s, OCH_3), 4.1 (2H, m, CH_2-O). (S)-(+)-5-hydroxymethyl-2-oxotetrahydrofuran (**3**); chloroform: methanol (98:2); $[\alpha]^{20}$ + 33.1° (c = 3.17, EtOH); IR (neat) 3400, 1765 cm^{-1}; ^{1}H-NMR δ 2.0-2.8 (4H, m, CH_2CH_2), 3.1 (1H, br.s, OH), 3.5-4.1 (2H, m, CH_2O), 4.6 (1H, m, -CH-O). (S)-(+)-p-toluenesulfonyloxymethyl-2-oxotetrahydrofuran (**2**); mp 85-7°C (ether; dichloromethane); $[\alpha]_D^{20}$ + 46.3° (c = 1.33, $CHCl_3$); IR (KBr, pellet) 1765 cm^{-1}; ^{1}H-NMR δ1.8-2.7 (4H, m, CH_2CH_2), 2.45 (3H, s, CH_3), 4.18 (2H, d, CH_2-O), 4.70 (1H, m, CH-O), 7.42 (2H, d, J = 10Hz), 7.85 (2H, d, J = 10Hz); MS 270 (M^+), 85 (base). (R)-(+)-hexan-4-olide (**1**); ether: hexane (3:2); $[\alpha]_D^{20}$ + 30.4° (c = 1.0, MeOH) [lit.,[2] $[\alpha]_D^{20}$ + 42.7° (c = 1, MeOH)]; IR (neat) 1770, 1170 cm^{-1}; ^{1}H-NMR δ 1.01 (3H, t, CH_3), 1.6-2.7 (6H, m, -$(CH_2)_2$-, -CH_2-), 4.6(1H, m, CH-O).
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Facile Cleavage of Tetrahydrofuran Derivatives with S-2-Pyridyl Thioates / $CuBr_2$ / CH_3CN†

Sunggak Kim* and Young Kwan Ko

Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 131

Jae In Lee

Department of Chemistry, Duksung Women's College, Seoul 132. *Received February 2, 1987*

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.[1] We wish to report that S-2-pyridyl thioates/cupric bromide rapidly and cleanly cleaves tetrahydrofuran derivatives in acetonitrile at room temperature,[2-8] although S-2-pyridyl thioates/cupric bromide was inert to tetrahydrofuran derivatives at room temperature for a long period of time.[9] 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

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