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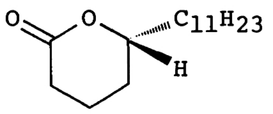
SYNTHESIS OF OPTICALLY PURE (R)- AND (S)-5-n-HEXADECANOLIDE. A PROPOSED PHEROMONE COMPONENT FROM ORIENTAL HORNET

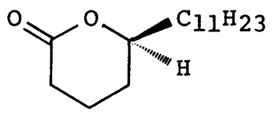
Tadashi KIKUKAWA and Akira TAI*
Institute for Protein Research, Osaka University, Yamada-oka, Suita, Osaka 565

Optically pure (R)- and (S)-5-n-hexadecanolide have been easily prepared by the reaction between optically active 1-bromo-3-tetrahydropyranyloxytetradecane (**5**) and lithium α-lithioacetate and the following lactonization. **5** was derived from optically pure 3-hydroxytetradecanoic acid obtained by the method reported before.

Since 5-n-hexadecanolide (**1**) was proposed to be the pheromone responsible for the social behavior of the oriental hornet, *Vespa orientalis*,1) various attempts to synthesize optically active **1** were carried out.2-6) Most recently, the preparation of highly optically pure (R)- and (S)-**1** has been achieved by S. Servi.7) However, the method would not be suitable for the practical preparation of the pheromone, because the preparation of the chiral key intermediate relied on the chromatoghraphic separation of diastereomers. This situation made up us to develop the simple and straightforward method for the preparation of optically pure (R)-and (S)-**1**.



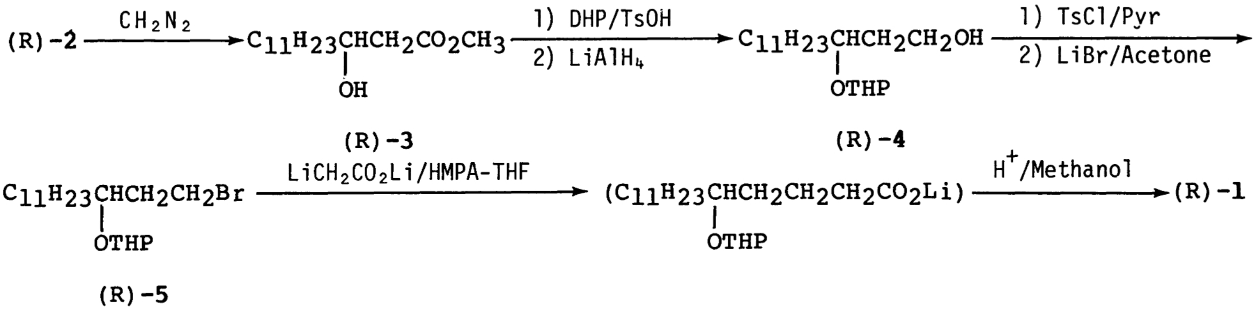
(R)-(+)-**1**



(S)-(-)-**1**

The key compounds of our process, (R)- and (S)-3-hydroxytetradecanoic acid (**2**), can easily be prepared by the method reported before.8) Thus, (R)-**2**, mp 70.0-71.5 °C, $[\alpha]_D^{20}$ -16.2° (c 1, $CHCl_3$) (lit,8) $[\alpha]_D^{20}$ -16.0° (c 1, $CHCl_3$)) and (S)-**2**, mp 71.0-72.0 °C, $[\alpha]_D^{20}$ +16.2° (c 1, $CHCl_3$), were obtained.

(R)- and (S)-**2** were easily converted to (R)- and (S)-**1**, respectively, by elongating two carbon unit at the carboxyl terminal of **2** as shown in Scheme 1.9)



$$\text{(R)-2} \xrightarrow{CH_2N_2} \underset{\text{(R)-3}}{C_{11}H_{23}\underset{OH}{C}HCH_2CO_2CH_3} \xrightarrow[\text{2) LiAlH}_4]{\text{1) DHP/TsOH}} \underset{\text{(R)-4}}{C_{11}H_{23}\underset{OTHP}{C}HCH_2CH_2OH} \xrightarrow[\text{2) LiBr/Acetone}]{\text{1) TsCl/Pyr}}$$

$$\underset{\text{(R)-5}}{C_{11}H_{23}\underset{OTHP}{C}HCH_2CH_2Br} \xrightarrow{LiCH_2CO_2Li/HMPA\text{-}THF} (C_{11}H_{23}\underset{OTHP}{C}HCH_2CH_2CH_2CO_2Li) \xrightarrow{H^+/\text{Methanol}} \text{(R)-1}$$

Scheme 1.

By the treatment with CH_2N_2, (R)-**2** was converted to methyl ester (**3**), mp 39.5-40.0 °C, $[\alpha]_D^{20}$ -14.2° (c 3.8, hexane). The sample was proved to be optically pure by the NMR taken in the presence of a chiral shift reagent.(10) The treatment of (R)-**3** with 3,4-dihydoropyran gave methyl (R)-3-tetrahydropyranyloxytetradecanoate, which was reduced to (R)-3-tetrahydropyranyloxy-1-tetradecanol (**4**) with $LiAlH_4$. The yield of the process from **2** to **4** was more than 95%. The alcohol, **4** was converted to a tosylate, which when reacted with LiBr in acetone to give (R)-1-bromo-3-tetrahydropyranyloxytetradecane (**5**). The yield of the process from **4** to **5** was 81%. The reaction of **5** with lithium α-lithioacetate in HMPA-THF gave 5-tetrahydropyranyloxyhexadecanoic acid as an intermediate, which was treated with p-toluensulfonic acid in a large amount of methanol to give (R)-5-n-hexadecanolide (**1**), bp 135-140 °C/mmHg, mp 36.5-37 °C (lit.(7) mp 40-41 °C), $[\alpha]_D^{20}$ +39.8° (c 4.2, THF), (lit.(7) $[\alpha]_D^{20}$ +39.97° (c 1, THF)). The yield of **1** was 50% based on **5**.

The series of reactions as Scheme 1 were submitted for the preparation of (S)-**1** from (S)-**2**. The physical and analytical data of (S)-**1** are as follows; bp 134-138 °C/0.5-1 mmHg, mp 38 °C, $[\alpha]_D^{20}$ -41.0° (c 1.5, THF) (lit.(7) $[\alpha]_D^{20}$ -39.2° (c 1, THF)).

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9) All new compounds reported here gave satisfactory NMR date and elemental analyses.
10) In the NMR, methyl protons (singlet) of the ester group of (R)- and (S)-3 showed different chemical shift in the presence of chiral shift reagent. The difference of chemical shifts was 0.12 ppm when NMR spectra were measured with the solution of the sample(15 mg), a mixture of (R)- and (S)-3, and $Eu(hfmc)_3$(15 mg) in $CDCl_3$(0.4 ml). As for the sample of (R)-3 or (S)-3, no detectable signal of the antipode was observed.

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