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A STEREOCONTROLLED SYNTHESIS OF (R,Z)- AND (R,E)-14-METHYL-8-HEXADECENALS (TROGODERMAL), THE SEX PHEROMONES OF TROGODERMA SPECIES

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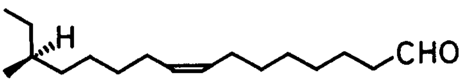
Summary: *A stereocontrolled synthesis of (R,Z)- and (R,E)-14-methyl-8-hexadecenals with high stereochemical purity in both absolute and geometrical configurations was achieved by the use of the S_N2 type ring-opening reaction of (S)-β-methyl-β-propiolactone for the construction of the (R)-configurations, and the cis-addition of diorganocuprate to acetylene and the S_N2' type ring-opening reaction of δ-vinyl-δ-valerolactone for the introduction of (Z)- and (E)-double bonds, respectively.*

(Z)-14-Methyl-8-hexadecenal and its (E)-isomer (trogodermal) were identified as the essential female-secreted sex pheromones of *Trogoderma* species of insects.[1] Although conflicting results have been reported on the pheromone activity of (R)- and (S)-trogodermals for male Khapra beetles *(Trogoderma granarium)*,[2,3] (R)-enantiomers of (Z)- and (E)-trogodermals were found to be more attractive to male *T. inclusum* and *T. variabile* and to *T. glabrum* than the corresponding (S)-enantiomers, respectively.[4,5]

The (R)- and (S)-trogodermals were synthesized by Mori *et al.*[4,6] and Rossi *et al.*[3,7] In their syntheses, (R)-[4,6] or (S)-citronellol,[3] or (S)-2-methyl-1-butanol[7] was used as a starting chiral material, and introduction of (Z)- or (E)-double bond was performed by the Lindlar reduction or lithium aluminum hydride reduction of carbon-carbon triple bond, respectively. We wish to describe here a shorter stereocontrolled route for the synthesis of (R,Z)- and (R,E)-trogodermals (1 and 2); asymmetric center of the C_{14} carbon was constructed by the S_N2 type ring-opening reaction of (S)-(-)-β-methyl-β-propiolactone (7) with a Grignard reagent in the presence of a copper catalyst, which proceeds with almost



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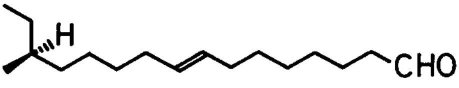

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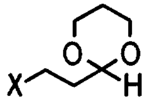
inversion.[8] The geometrical configuration of the double bond was controlled by the *cis*-addition of organocuprate to acetylene[9] for (Z)-configuration or S_N2' type ring-opening reaction of δ-vinyl-δ-valerolactone (12) with the Grignard reagent in the influence of a copper catalyst for (E)-configuration.[10] These processes, including carbon-carbon bond formation, make the present route more efficient.

One of the key-intermediates for the synthesis of 1, (Z)-13,13-trimethylenedioxytridec-5-enyl chloride (6) was prepared easily from 3,3-trimethylenedioxypropyl bromide (3) as a starting material. Bromide 3 was converted into the corresponding Grignard reagent in 90% yield,[11] which was treated with 1,4-dibromobutane in the presence of Li_2CuCl_4 (1 mol%) in THF at 0 °C for 1 h to give four-carbon homologated bromide (4)[12] in 86% yield; bp 130 ∿ 133 °C/1.8 mmHg. According to the modified procedure of Normant *et al.*,[9] (Z)-double bond of 6 was introduced by the *cis*-addition of diorganocuprate to acetylene, followed by alkylation. 7,7-Trimethylenedioxyheptylmagnesium bromide, prepared from 4 in 81% yield, was treated with a half equivalent of copper(I) iodide in THF-Me_2S (20:1) at -30 °C, followed by introduction of acetylene at -20 °C to give the diorganocuprate (5). Alkylation of 5 with 1-chloro-4-iodobutane in the presence of trimethyl phosphite at -30 °C for 2 h and at room temperature overnight afforded 6[12] (>99.9% pure) in 86% yield; bp 145 ∿ 146 °C/0.5 mmHg.

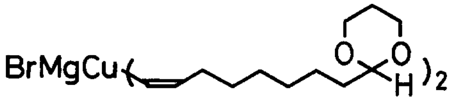
The chiral (S)-lactone 7 was easily prepared from (R)-(-)-3-bromobutyric acid (99% optically pure) ($[M]^{25}_{546}$ -115.3° (0.165M, 2M $HClO_4$), lit.[13] $[M]^{25}_{546}$ +116.5° (0.163M, 2M $HClO_4$) for the (S)-enantiomer), which was derived by the resolution of racemic 3-bromobutyric acid with (S)-(-)-α-(1-naphthyl)ethylamine, in a yield of 66%; $[\alpha]^{20}_{D}$ -27.8° (C 4.14, $CHCl_3$).[8]

Synthesis of the chiral intermediate (8) was easily achieved by the S_N2 type ring-opening reaction of lactone 7 with the Grignard reagent, prepared in 83% yield from 6 and magnesium under reflux in THF, in the presence of a copper(I) catalyst. Thus, treatment of 7 with the Grignard reagent in the presence of copper(I) iodide (3 mol%) in THF-Me_2S (20:1) at -15 °C for 2 h gave the (S)-acid



3 X = Br

4 X = $(CH_2)_4Br$



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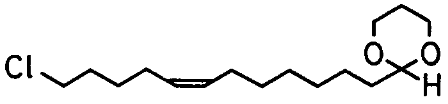

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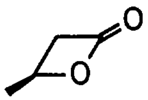

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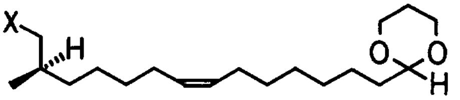
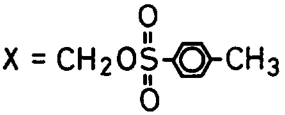


8 X = CO_2H

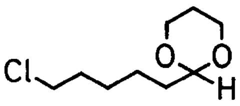
9 X = CH_2OH

10 

$X = CH_2O\overset{O}{\underset{O}{S}}-C_6H_4-CH_3$

8[12] in 80% yield; $[\alpha]_D^{22}$ -4.96° (C 7.86, $CHCl_3$). Esterification of 8 with diazomethane and subsequent reduction with lithium aluminum hydride gave the alcohol (9)[12] in 95% yield. Treatment of 9 with p-toluenesulfonyl chloride in pyridine gave the tosylate (10). Reduction of 10 with lithium aluminum hydride and deacetalization in acetone-aqHCl afforded (R,Z)-trogodermal (1)[12] in 70% yield (Z, >99.9%); $[\alpha]_D^{22}$ -5.96° (C 1.06, $CHCl_3$) [lit.[4] $[\alpha]_D^{21}$ -5.94° (C 1.06, $CHCl_3$), lit.[7] $[\alpha]_D^{25}$ -5.90° (C 4.570, ether)].[14] Thus, the highly optically and gemetrically pure 1 was obtained in an overall yield of 24% from 3.

A key intermediate for the synthesis of 2, (E)-13,13-trimethylenedioxytridec-5-enyl chloride (15) was synthesized *via* the acid (13), which was prepared by the use of the regio- and stereoselective ring-opening reaction of δ-vinyl-δ-valerolactone (12) with a Grignard reagent in the presence of copper(I) catalyst. Coupling of 1-bromo-3-chloropropane with the Grignard reagent of 3 in the presence of Li_2CuCl_4 gave three-carbon homologated chloride (11)[12] in 81% yield; bp 118 ∿ 120 °C/3.5 mmHg. The Grignard reagent, prepared from 11 and magnesium in 81% yield, was added into a solution of 12 and copper(I) iodide (5 mol%) in THF-Me_2S (20:1) at -45 °C. After stirring at -45 °C for 1 h, 13[12] was obtained in a yield of 95%. Esterification of 13 with diazomethane and reduction with lithium aluminum hydride gave an alcohol (14)[12] in 97% yield; bp 155 ∿ 156 °C/0.3 mmHg. Chlorination of 14 with triphenylphosphine in carbon tetrachloride under reflux for 12 h gave the chloride 15[12] in 81% yield (E:Z = 9:1); bp 162 ∿ 165 °C/0.8 mmHg. The chloride 15 was converted into the corresponding Grignard reagent in 80% yield. The copper-catalyzed reaction of the Grignard reagent with 7 afforded the (S)-acid (16)[12] in 77% yield. Reduction of 16 and deacetalization in the similar manner for the synthesis of 1 gave (R,E)-trogodermal (2)[12] in 60% yield (E:Z = 9:1); $[\alpha]_D^{22}$ -4,72° (C 2.33, Et_2O) [lit.[6] $[\alpha]_D^{21}$ -5.99° (C 5.08, $CHCl_3$), lit.[7] $[\alpha]_D^{25}$ -5.04° (C 4.776, Et_2O)].



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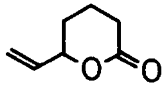

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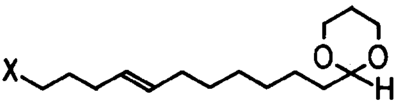
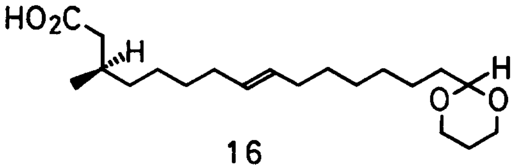


13 X = CO_2H
14 X = CH_2OH
15 X = CH_2Cl



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Thus, the stereocontrolled short-step synthesis of (R,Z)- and (R,E)-trogodermals was achieved by the use of the regio- and stereoselective ring-opening reactions of both (S)-β-methyl-β-propiolactone and δ-vinyl-δ-valerolactone with Grignard reagents in the presence of copper(I) catalyst.

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