Tetrahedron Letters,Vol.23,No.18,pp 1921-1924,1982 0040-4039/82/181921-04$03.00/0
Printed in Great Britain

SYNTHESIS AND ABSOLUTE CONFIGURATION OF (+)-LINEATIN, THE PHEROMONE OF *TRYPODENDRON LINEATUM*

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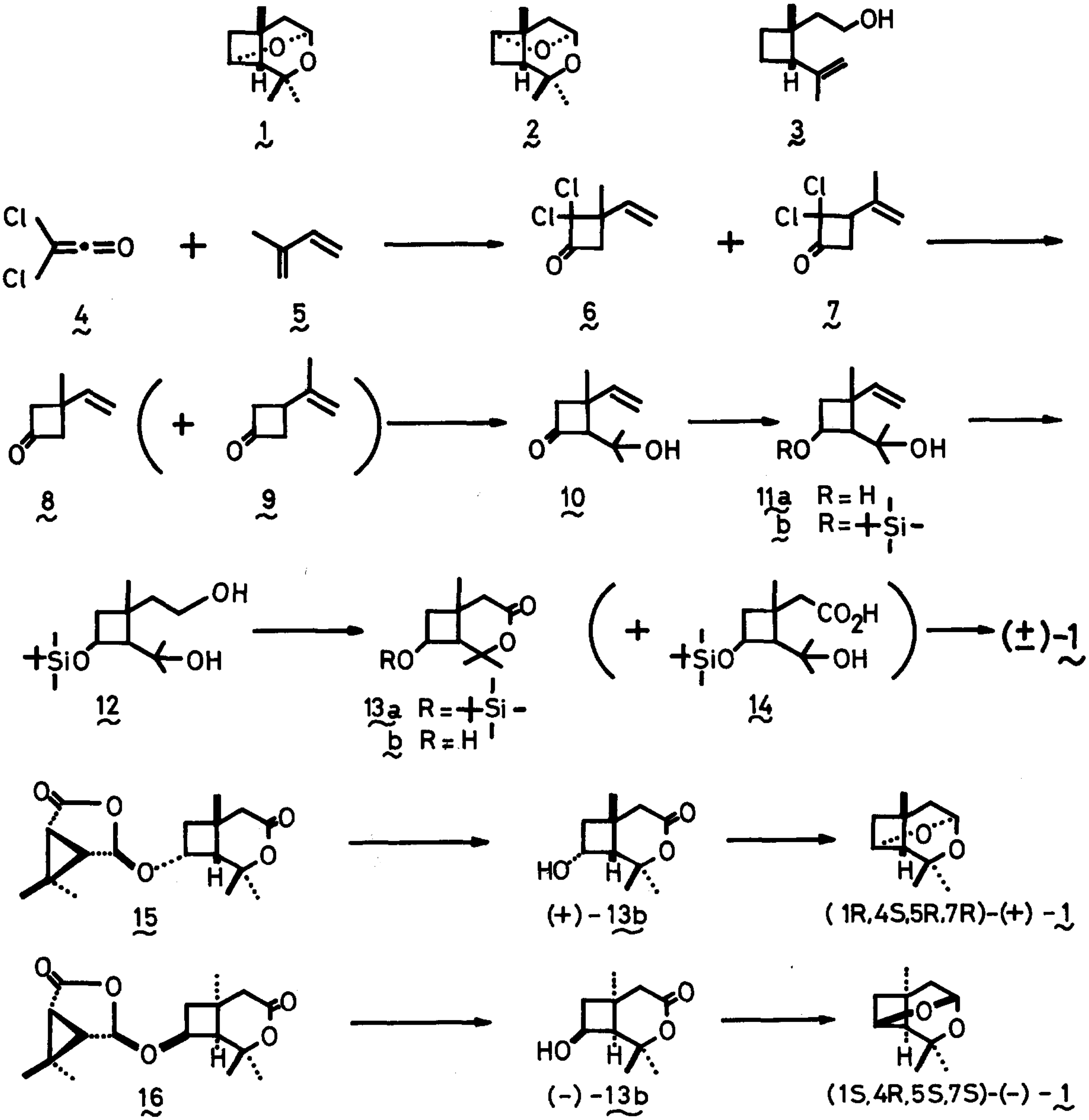
Summary : A new synthesis of (±), (+)- and (-)-lineatin (3,3,7-trimethyl-2, 9-dioxatricyclo[$3.3.1.0^{4,7}$] nonane, 1) was achieved. The stereochemistry of (+)-lineatin was established as 1*R*, 4*S*, 5*R*, 7*R* by an X-ray crystallographic analysis of an intermediate 15.

Lineatin is an aggregation pheromone produced by female beetles of *Trypodendron lineatum*, which is a severe pest in both European and North American forests. Its structure was first proposed by MacConnell *et al*. to be one of the two isomeric tricyclic acetals (1 or 2 without assignment of the absolute configuration).[2] The synthesis of (±)-1 and (±)-2 by us[3] and by others[4] established the structure of lineatin to be 1. Its absolute configuration, however, remained ambiguous in spite of the two low-yield syntheses of lineatin enantiomers by optical resolution of intermediates.[5,6] We have now completed a new and more efficient synthesis of lineatin and carried out a single-crystal X-ray analysis of an optically active intermediate 15. This enabled us to assign 1*R*, 4*S*, 5*R*, 7*R* stereochemistry to (+)-lineatin, the bioactive enantiomer. The present stereochemical assignment suggests a close biogenetical relationship between (+)-lineatin 1 and (+)-grandisol 3, the boll weevil pheromone.

Cycloaddition of dichloroketene 4 (generated from Cl_3CCOCl, Zn-Cu and $POCl_3$) to isoprene 5 employing Hassner's improved procedure[7] afforded in 81% yield an unstable mixture of 6 and 7 in which the desired regioisomer 6 was predominating (3.3 : 1). This was immediately reduced with Zn-AcOH to give a mixture of 8 and 9. These were separable by fractional distillation to give



the desired ketone **8**,[8] bp 86°/110 mm, in 39% yield from Cl_3CCOCl. The isomer **9**, bp 99°/110 mm, was also obtained in 15% yield. A carbanion derived from **8** (LDA/THF, -78°) was reacted with acetone to give **10** as a crude stereoisomeric mixture, which was reduced with Li(sec-Bu)$_3$BH in THF to give **11a**. Treatment of **11a** with t-BuMe$_2$SiCl and imidazole in DMF afforded **11b**, bp 98-102°/0.07-0.25mm, in 56% yield from **8**. Hydroboration-oxidation (B_2H_6/THF and H_2O_2-NaOH) of **11b** proceeded smoothly to give **12** as a stereoisomeric mixture in 93% yield. This was oxidized with pyridinium dichromate[9] in CH_2Cl_2 (room temp., 36 hr) to afford a δ-lactone 13a, mp 60.5-61.0°, in 53% yield together with 14 which could not be lactonized due to the *trans* nature of the two side-chains carrying CO_2H and OH groups, respectively. Removal of the silyl protective group of 13a with $(n\text{-}Bu)_4NF$ yielded 13b, mp 64-65°, in 61% yield. Reduction of 13b with DIBALH was followed by acidification (dil HCl) to give (±)-1 in 47% yield. The over-all yield of (±)-lineatin from Cl_3CCOCl by this 9-step synthesis was 3.0%.

For the synthesis of optically active lineatin, the racemic lactone 13b was resolved by converting it to a diastereomeric acetals 15 and 16. The resolving agent used was a chiral hemiacetal, 4-hydroxy-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one, which was prepared from (1*R*)-*cis*-chrysanthemic acid (93.6% e.e.) by ozonolysis.[10] This resolving agent (1.16g) was mixed with (±)-13b (1.5g) and p-TsOH (12 mg) in C_6H_6 (50 ml) and heated under reflux with continuous removal of water. The crude product was chromatographed over a Lobar column (Grosse C ; elution with CH_2Cl_2-acetone 50 : 1) to give less polar 15 (1.099g, 87.6%), mp 143-144°, $[\alpha]_D^{23}$ -108.0° (c=1.06, EtOH),[11] and more polar 16 (1.100g, 87.6%), mp 124-125°, $[\alpha]_D^{23}$ -65.1° (c=1.02, EtOH).[12]

The structure of the less polar diastereomer was determined as 15 by its single-crystal X-ray analysis. A crystal with dimensions 0.3 x 0.3 x 0.4 mm was used. The crystal data are : $C_{17}H_{24}O_5$, M=308.38, monoclinic, space group $P2_1$, a=12.981 (2), b=8.104 (2), c=7.742 (1)Å, β=91.00 (1)°, V=814.3 (4) Å^3. Of the 1999 reflections (1.5° < θ < 27.5°) collected on an Enraf Nonius CAD-4 diffractometer using graphite-monochromated Mo Kα radiation (0.71073Å), 1682 were judged observed ($|I_0| \geq 3\sigma(|I_0|)$) after correction for Lorenz effect. The structure was solved by MULTAN[13] with final R value of 0.035. The ORTEP computer drawing is shown in Figure 1. Details will be reported later in our full paper.

Conversion of 15 into 1 was straightforward. Upon acid treatment with HCl-MeOH, 15 gave (+)-13b, mp 90-91° $[\alpha]_D^{21}$ + 48.2° (c=1.0, CCl_4). This yielded (+)-lineatin 1 (873.8 mg

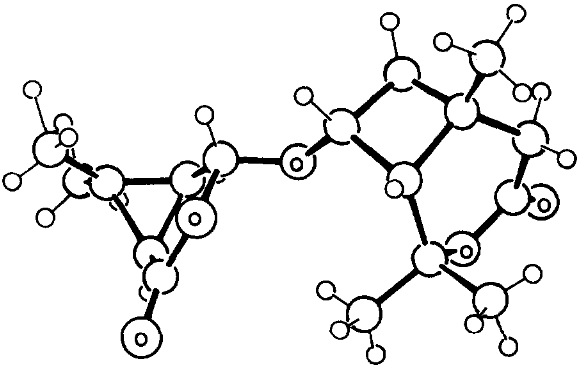


Figure 1. Computer-generated perspective drawing of the X-ray model of 15. The configuration shown is based on the known configuration of the resolving agent.

from 1.7016g of **15**), bp 110°/53 mm, n_D^{22} 1.4586, $[\alpha]_D^{21.5}$ + 85.8° (c=1.1, $CHCl_3$), $[\alpha]_D^{21.5}$+ 85.8° (c=1.0, n-pentane), after DIBALH reduction followed by acidification. The above-mentioned X-ray result allowed us to assign 1*R*, 4*S*, 5*R*, 7*R* stereochemistry to (+)-lineatin. This is in accord with Slessor's proposal[6] and necessitates reinterpretation of our ORD and CD data reported previously.[5,14] Similarly the more polar diastereomer **16** gave (-)-**13b**, mp 90-91°, $[\alpha]_D^{22}$ -47.2° (c=1.0, CCl_4), which yielded (1*S*, 4*R*, 5*S*, 7*S*)-(-)-lineatin **1** (834.2 mg from 1.5717g of **16**), bp 110°/53mm, n_D^{22} 1.4588, $[\alpha]_D^{22}$-87.7° (c=1.1, $CHCl_3$), $[\alpha]_D^{22}$ -87.6° (c=1.1, n-pentane). The spectral data of our synthetic **1** were identical with those reported earlier.[3,5]

In conclusion we established beyond doubt the 1*R*, 4*S*, 5*R*, 7*R* stereochemistry of (+)-lineatin and are now able to prepare gram-quantities of (±)-lineatin for practical field tests.[15]

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11 δ(60MHz, $CDCl_3$) 1.12 (6H, s), 1.30 (3H, s), 1.33 (3H, s), 1.48 (3H, s), ∿4.56 (1H, m), 4.92 (1H, s). Found: C, 66.24; H, 7.87%.

12 δ(60MHz, $CDCl_3$) 1.13 (6H, s), 1.28 (3H, s), 1.36 (3H, s), 1.51 (3H, s), ∿4.43 (1H, m), 5.06 (1H, s). Found: C, 66.31; H, 7.96%.

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14 The reinterpretation will be discussed in our full paper.

15 We are grateful to Dr. M. Sasaki, Sumitomo Chemical Co., for discussions. Financial support by Sumitomo Chemical Co. is acknowledged with thanks

(Received in Japan 30 January 1982)