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# A STEREOSELECTIVE SYNTHESIS OF "NATURAL" (4S,6S,7S)-SERRICORNIN, THE SEX PHEROMONE OF CIGARETTE BEETLE, FROM LEVOGLUCOSENONE

Masataka MORI*, Tatsuji CHUMAN and Kunio KATŌ

Central Research Institute, The Japan Tobacco Public Corporation

Umegaoka 6-2, Midori-ku, Yokohama 227, Japan

Kenji MORI

Department of Agricultural Chemistry, The University of Tokyo

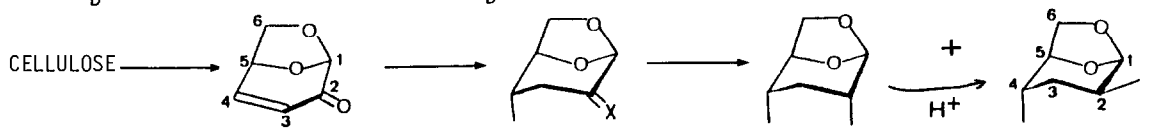
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

Summary: The natural stereoisomer of serricornin was synthesized stereoselectively from levoglucosenone. This firmly established the absolute stereochemistry of serricornin to be 4S,6S,7S. A short synthesis of (-)-δ-multistriatin was also reported.

In our course of the syntheses of the stereoisomers of serricornin 1a[1,2], the sex pheromone of cigarette beetle (*Lasioderma serricorne (F.)*), which is a serious pest of cured tobacco leaves, it was proposed that the absolute stereochemistry of the natural one is 4S,6S,7S[2]. To confirm the proposed stereochemistry of 1a, we attempted the stereoselective synthesis of the (4S,6S,7S)-isomer. A synthesis starting from an amino acid with a pivotal use of asymmetric alkylation has already been reported[3]. In the present study, as the starting material, we employed a carbohydrate enone "levoglucosenone" (2)[4](1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose), which is available on acid-catalysed pyrolysis of cellulose. The rigid 1,6-anhydro-D-sugar ring system was considered to be suitable to introduce the additional chiralities as described below.

Levoglucosenone (2) was prepared from cellulose powder by the method of Shafizadeh et al.[4c], and the fractional distillation gave almost pure sample[5](>98% purity);b.p.65°/0.7mm,$[\alpha]_D^{23}$-538° (c=1.1,$CHCl_3$)[Lit.[4c] $[\alpha]_D$-530°]. Treatment of 2 with $Me_2CuLi/Et_2O$ (-60°→-20°) gave a single C-4 methyl adduct (3a)[6] in 64% yield;b.p.63°/5mm,$[\alpha]_D^{23}$-299.4°(c=0.35,$Et_2O$);(DNPH deriv.,m.p.217°-219°,$[\alpha]_D^{23}$-179.3°(c=0.56,$CHCl_3$)[Lit.[4b] m.p.215°-216°,$[\alpha]_D$-150°]). The pmr analysis indicated that the methyl group now introduced has an *exo*-configuration[6]. The ketone 3a was converted into the compound 3b[7]($Ph_3PCH_2/Et_2O$),$[\alpha]_D^{23}$-227.7°(c=0.35,$Et_2O$),MS m/z 140($M^+$), and subsequent

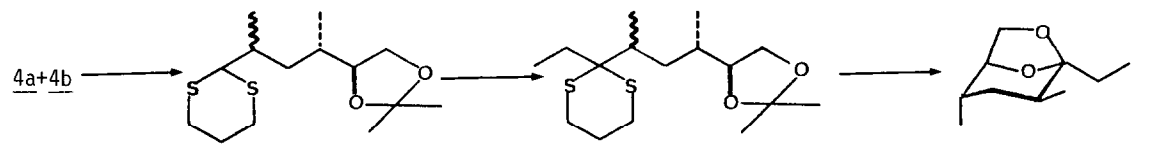
hydrogenation (Pd-C) of 3b gave two 2,4-di-C-methyl derivatives, 4a and 4b, in the ratio of ~4:1; 4a[8], $[\alpha]_D^{23}$-91.4°(c=0.4,pentane); 4b[8], $[\alpha]_D^{23}$-46.6°(c=0.125,pentane).




2 3a: X=O 3b: X=$CH_2$ 4a 4b

When the mixture of 4a and 4b was equilibrated in an acidic solution (catalytic p-TsOH/$CHCl_3$, under reflux,4h; then stood in a refrigerator,overnight), the ratio 4a:4b changed to 1.8:98.2. This fact indicated that the two methyl groups of 4a lies in unstable 1,3-diaxial relationship and the methyl group adjacent to enolizable acetal (at C-2) epimerized almost completely[9].

To prove the stereochemistries of 4a and 4b, we tried to convert them into an insect pheromone, multistriatin[10], according to the method of Weiler et al[11]. The mixture of 4a and 4b was treated with propanedithiol-$BF_3$.$Et_2O$/$CHCl_3$ (-20°→room temp.,2h), followed by protecting the freed glycol with 2,2-dimethoxypropane (PPTS/$CH_2Cl_2$) to give 5. The dithiane 5 was alkylated in the manner described previously (BuLi-TMEDA/THF,-60°→-10°,4h;EtI,-60°) to afford 6 in good yield. The hydrolysis of dithiane (6) in an acidic condition ($HgCl_2$/MeCN,reflux,1h) afforded 7 as almost a single product. After purification by preparative GLC, the chiroptical and spectroscopic data of 7, $[\alpha]_D^{23}$-84.7°[12](c=0.155,pentane), were identical with those of (-)-δ-multistriatin[13]. The successful conversion of 4a and 4b into (-)-δ-multistriatin established the absolute configurations at C-4 and C-5 of these compounds to be 4S,5S. The absolute stereochemistries of 4a and 4b were, therefore, assigned to be 1R,2R,4S,5S and 1R,2S,4S,5S, respectively.




5 6 7:(-)-δ-multistriatin

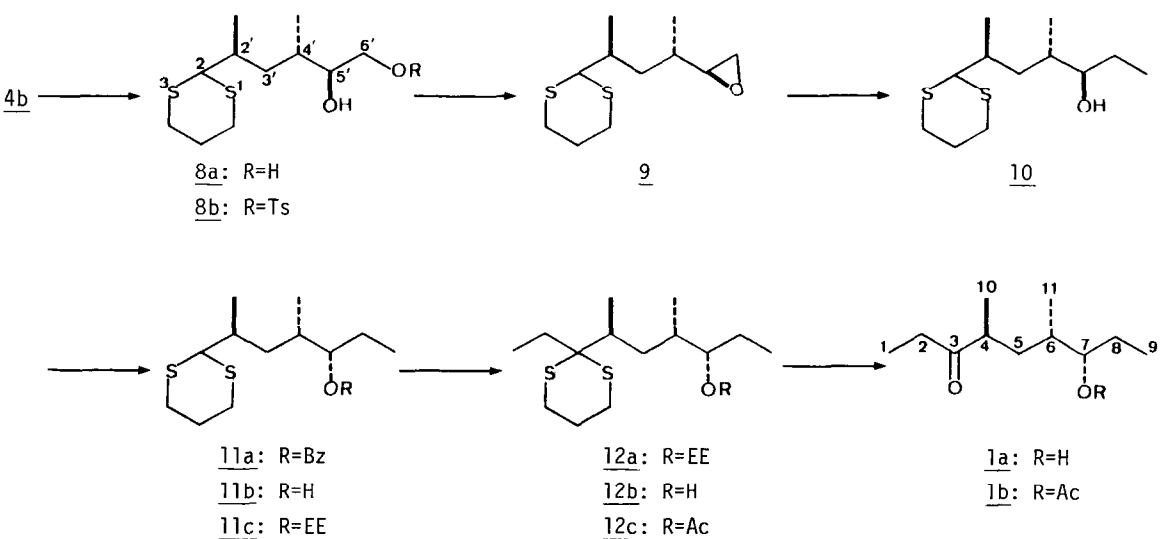
The compound 4b (~95% diastereometric purity), obtained by the method described above, was converted into dithiane (8a), $[\alpha]_D^{23}$-35.7°(c=0.83,MeOH), in 27.5% overall yield from 3a. The corresponding monotosylate (8b) (1 eq. of p-TsCl/$C_5H_5N$,0°,12h) was treated with KOH(1 eq.)/MeOH to afford an epoxide (9)[14], $[\alpha]_D^{23}$-29.3°(c=1.46,$CH_2Cl_2$), in 54% yield. The reaction of 9 with 5 eq. of $Me_2CuLi/Et_2O$ (-40°→room temp,8h) gave alcohol (10)[15], $[\alpha]_D^{23}$-19.63(c=1.15,$CH_2Cl_2$), in 77% yield. To obtain the alcohol having the desired configuration, we employed the method of Mitsunobu[16]

($Ph_3P$,BzOH/$Et_2O$,diethyl azodicarboxylate,0°,1h; then room temp.,overnight). The resulting benzoate (11a) (37% yield) was saponified (10% KOH/MeOH,room temp.,overnight) to give alcohol (11b),$[\alpha]_D^{23}$-32.76°(c=0.995,$CH_2Cl_2$). The GLC analysis revealed that the Walden inversion at C-5' proceeded completely[17].

The compound 11b was converted into acetyl serricornin (1b) as described previously[2]. The hydroxyl group of 11b was protected as α-ethoxyethyl ether (EVE-PPTS/$CH_2Cl_2$,room temp.,1h) to give 11c. The alkylation of dithiane 11c at C-2 in the condition described above (as 5→6) gave 12a. The protection of the hydroxyl group of 12a was exchanged to acetyl in the usual manner (PPTS/EtOH;$Ac_2O/C_5H_5N$), and hydrolysis of dithiane (12c) under the neutral condition ($HgCl_2$-$CaCO_3$,80% aq.MeCN,under reflux,1h) afforded 1b. The crude 1b was purified by prep. GLC; $[\alpha]_D^{23}$-19.67°(c=0.335,hexane),$[\alpha]_{577}$-17.75°,$[\alpha]_{546}$-20.37°,$[\alpha]_{435}$-38.42°,$[\alpha]_{365}$-75.32°. The spectroscopic data of 1b were analyzed by capillary GLC to give two peaks of the diastereomers corresponding to natural pheromone (4S,6S,7S) and its C-4 epimer (4R,6S,7S) in the ratio of 92:8. Based on the above data and the value of the (4S,6R,7R)-isomer[2]($[\alpha]_D$+36.75°), the $[\alpha]_D$ value of optically pure (100%) (4S,6S,7S)-serricornin acetate was calculated to be -18.2°.

The corresponding deacetylated product (1a) was biologically active toward male cigarette beetle[18].

In conclusion, the absolute stereochemistry of natural serricornin was firmly established to be 4S,6S,7S[19].



References and Notes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5 2: $\delta_H$ 3.7-3.9(m,2H),5.0(t,J=6Hz,1H),5.4(d,J=1Hz,1H),6.1(dd,1H),7.3(dd,1H).

6 3a: $\nu_{max}$ 1730 $cm^{-1}$; $\delta_H$ 1.2(d,J=7Hz,3H),2.05(brd,J=16Hz,<1Hz,1H),2.3(m,1H),2.85(dd,J=16Hz,8Hz,1H),~3.9(m,2H),4.4(m,1H),5.05(brs,1H). The small coupling (<1Hz) between H-3 axial (δ 2.05) and H-4 (δ 2.3) indicated the *cis*-disposition of these protons.

7 3b: $\delta_H$ 1.1(d,J=7Hz,3H),~1.9(m,2H),2.7(m,1H),~3.9(m,2H),4.83(d,1H),4.76(d,1H),5.5(brs,1H).

8 4a: $\delta_H$ 1.12(d,J=7Hz,3H),1.26(d,J=7Hz,3H),1-1.5(4H),~3.9(m,2H),4.2(m,1H),5.24(brs,1H).
4b: $\delta_H$ 0.81(d,J=7Hz,3H),1.17(d,J=7Hz,3H),1-1.5(4H),~3.9(m,2H),4.2(m,1H),5.16(brs,1H).

9 The similer phenomenone was observed in the case of the isomerization of β-multistriatin into the δ-isomer. (#10)

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12 The optical purity of 7 was calculated to be 95%, based on the literature (89°)(#10).

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14 9: $\nu_{max}$ 2950, 2900, 1275 $cm^{-1}$; $\delta_H$ 0.92(d,J=7Hz,3H),1.08(d,J=7Hz,3H),1-2.3(4H),2.5(m,1H),2.7(m,2H),2.75(m,4H),4.08(d,J=8Hz,1H).

15 10: $\nu_{max}$ 3400 $cm^{-1}$, $\delta_H$ 0.90(t,J=8Hz,3H),0.92(d,J=7Hz,3H),1.08(d,J=7Hz,3H),1.2-2.2(m,8H),2.8(m,4H),3.3(m,1H),4.1(d,J=8Hz,1H).

16 O.Mitsunobu and M.Eguchi, *Bull. Chem. Soc. Jpn.*, 44, 3427 (1971).

17 No preceding diastereomer (10)was detected on the GLC analysis of 11b (3% OV-101,50m,capillary,220°); 10: Rt. 10.0, 11b: Rt. 9.8.

18 The details of the bioassay on 1a will be reported elsewhere.

19 Quite recently, Hoffmann et al. reported a synthesis of (4RS,6S,7S)-serricornin employing yeast reduction as the key-step: R.W.Hoffmann, W.Helbig and W.Ladner, *Tetrahedron Lett.*, in the press. We thank Prof. R.W.Hoffmann for kindly sending to K.M. his manuscript prior to publication.


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