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ABSOLUTE STEREOCHEMISTRY OF SERRICORNIN, THE SEX PHEROMONE OF CIGARETTE BEETLE, AS DETERMINED BY THE SYNTHESIS OF ITS (4S,6R,7R)-ISOMER

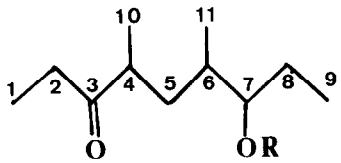
Masataka MORI*, Tatsuji CHUMAN, Masahiro KOHNO, Kunio KATO and Masao NOGUCHI
Central Research Institute, The Japan Tobacco Public Corporation
Umegaoka 6-2, Midori-ku, Yokohama 227, Japan

Hiroko NOMI and Kenji MORI
Department of Agricultural Chemistry, The University of Tokyo
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

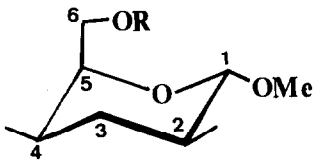
Summary: The absolute stereochemistry of serricornin was determined to be (4S,6S,7S) by the synthesis of its (4S,6R,7R)-isomer using a carbohydrate synthon.

Serricornin (1a)[4,6-dimethyl-7-hydroxynonan-3-one] is the sex pheromone of the female cigarette beetle, *Lasioderma serricorne (F.)*[1]. We have investigated the absolute stereochemistry of the molecule, which possesses three chiral carbon atoms at C-4, C-6 and C-7. By synthesizing its (4RS,6R,7S) and (4RS,6R,7R)-isomers, it was assigned that the stereochemistry of the adjacent carbon atoms having CH_3- and HO- at 6 and 7 positions are (6S,7S)[2]. We report here the determination of the remaining unknown configuration at C-4 by the synthesis of (4S,6R, 7R)-isomer using a carbohydrate synthon.

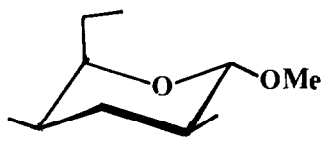
The starting material (2a)was derived stereoselectively from glucose in ten steps, m.p. 140° -143°, $[\alpha]_D^{23}$+30.9° (c=1.0,$CHCl_3$) [Lit.[3]m.p. 140°-142°, $[\alpha]_D$+27.0°; Lit.[4]m.p. 143°-143.5°, $[\alpha]_D$ +30.4°]. The absolute stereochemistry was unambiguously established to be (1S,2S,4R,5R) by X-ray crystallography[5]. Reductive deprotection of trityl group (Na/liq.NH_3, THF, NH_4Cl) gave 2b, m.p. 46.5°-47.0°, $[\alpha]_D^{23}$+112.0° (c=1.1,$CHCl_3$) [Lit[4]m.p. 45.0°-46.5°, $[\alpha]_D$+101.7°]. The corresponding tosylate (2c), $[\alpha]_D^{23}$+49.8° (c=5.3,Et_2O) [Lit.[4]$[\alpha]_D$+57.0°], was prepared by the usual method (TsCl, C_5H_5N, 0°, 4h) almost quantitatively from 2a. Treatment of 2c with Me_2CuLi (2 mol.eq.) in Et_2O (-40°→room temp.,overnight) yielded a methyl substitution product (3)[6] as an odoriferous liquid, $[\alpha]_D^{23}$+130.3° (c=0.2,CH_2Cl_2), δ_H 0.90(d,J=7Hz,3H),1.00(d,J=7Hz,3H),1.04(t,J=6Hz,3H),1.1



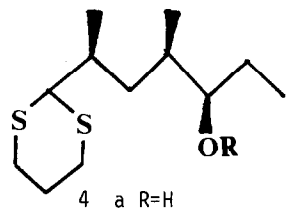
1 a R=H
b R=Ac



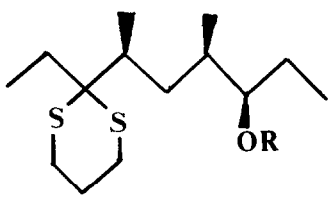
2 a R=Tr
b R=H
c R=Ts



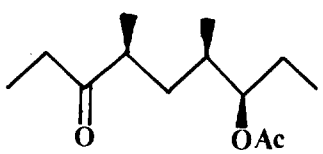
3



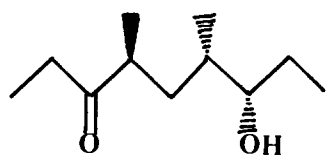
4 a R=H
b R=EE



5 a R=EE
b R=H
c R=Ac



6 (4S,6R,7R)



7 (4S,6S,7S)

-2.2(m,4H),3.45(s,3H),3.76(d,1H),4.18(d,J=5.6Hz,1H). The compound 3, without purification, was treated with propanedithiol and $BF_3.Et_2O$ (CH_2Cl_2, -20°→room temp., 2h)[7] to give 4a, $[\alpha]_D^{23}$+3.8° (c=2.3,$CHCl_3$), ν_{max} 3450 cm^{-1}, δ_H 0.88(d,J=6Hz,3H),0.96(t,J=7Hz,3H),1.08(d,J=7Hz,3H),1-2.2(m,4H), 2.85(m,4H),3.84(dt,1H),4.16(d,J=3Hz,1H),(70% yield from 2c). The hydroxyl group of the resulting dithiane (4a) was protected as ethoxyethyl ether (ethyl vinyl ether/PPTS, CH_2Cl_2, room temp., 1h) to afford 4b, $[\alpha]_D^{23}$+11.2° (c=1.16,CH_2Cl_2), MS m/z 45(83%),73(100),119(81),274(3%,M^+-EtO),(89% yield). The lithiation of 1,3-dithiane (4b) at C-2 with n-BuLi in THF was facilitated in co-existence of tetramethylethylenediamine[8] (-40°→-10°, 4h). The subsequent alkylation with ethyl iodide (-60°→room temp., overnight) proceeded in 94% yield to produce 5a, $[\alpha]_D^{23}$-27.16° (c=1.36, CH_2Cl_2), MS m/z 45(40%),73(53),147(100),348(0.3%,M^+). The characterization of the synthetic material was performed with its acetate, since the corresponding hydroxy ketone form was unstable during the purification procedures. The ethoxyethyl group in 5a was removed with 1% PPTS/EtOH (40°, 1h) to give 5b, $[\alpha]_D^{23}$-50.47° (c=1.61,CH_2Cl_2), MS m/z 147(100%),177(4),276(1.5%,M^+),(86% yield). The acetylation in the usual manner (Ac_2O, C_5H_5N, room temp., overnight) gave an acetate (5c), $[\alpha]_D^{23}$-18.65° (c=1.55,CH_2Cl_2), δ_H 0.8-1.2(m,12H),1.4-2.2(m,10H),2.8(m,4H),4.84(dt,1H), MS

m/z 43(85%),73(47),147(100),318(2%,M^+),(85% yield). The hydrolysis of dithiane (5c) under neutral conditions ($HgCl_2/CaCO_3$, 80% aq.MeCN, under reflux, 1h) afforded 6 as a sole product, (10.1 mg after purification by preparative GLC), $[\alpha]_D^{23}$+36.75° (c=0.39,hexane), $[\alpha]_{365}$+93.10°, $[\alpha]_{435}$ +72.38°, $[\alpha]_{546}$+44.54°, $[\alpha]_{577}$+40.35°, ν_{max} 2950(s),2925(s),2860(m),1730(s),1708(s),1455(m),1375 (m),1240(s),1100(m),1015(m),955(m), δ_H 0.8-1.1(m,12H),1.3-1.8(m,5H),2.06(s,3H),2.2-2.8(m,3H),4.74 (dt,1H), MS m/z 43(100%),57(85),86(61),111(21),139(18),157(18),168(9%,M^+-AcOH).

Table. ^{13}C-Nmr Data of Serricornin Acetate Isomers (δ_{TMS}, $CDCl_3$, ppm).

Carbon No.	Natural 1b[2]	Natural 1b after racemization at C-4[2]	(4RS,6R,7R)-isomers[2]	6 (4S,6R,7R)
1	7.84	7.84	7.84	7.84
2	34.22	34.28	34.28	34.28
3	214.88	214.88	215.00	215.00
4	43.53	43.53 43.35	43.53 43.35	43.35
5	24.22	24.22	24.22	24.22
6	33.70	33.70	33.70	33.58
7	78.04	78.04 77.75	78.10 77.80	77.81
8	35.98	35.98 36.39	35.92 36.39	36.39
9	10.18	10.18	10.18	10.18
10	16.67	16.67 17.32	16.61 17.32	17.38
11	14.45	14.45 14.63	14.45 14.63	14.63

The synthetic 6 (4S,6R,7R) should correspond to the antipode or the C-4 epimer of the antipode of natural 1b, since the absolute configuration at C-6 and C-7 of natural 1b was (6S,7S)[2]. Capillary GLC analysis of 6, under the conditions which separate the diastereomers (3% OV-101, 50 m, 80°-(+2°)-200°), showed a single peak, of which the Rt was not identical with that of natural 1b, but was identical with that of the C-4 epimer. As shown in Table, the ^{13}C-nmr spectroscopic data of 6 were not in agreement with those of the natural 1b, but was identical with those of the C-4 epimer. Considering the above results, it was concluded that the synthetic (4S,6R,7R)-isomer

corresponds to the C-4 epimer of the antipode of the natural pheromone, and, therefore, the absolute stereochemistry of serricornin was assigned to be (4S,6S,7S) (7).

References and Notes

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5 M.Mori, T.Chuman, T.Fujimori, K.Kato, A.Okubo and S.Toda, will be published elsewhere. 400 MHz ^{1}H-nmr analysis indicates that the pyranoid ring of 2a has $^1C_4$ conformation in $CDCl_3$ solution. Compounds 2b, 2c and 3 may exist in the same conformation.

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