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DETERMINATION OF THE ABSOLUTE CONFIGURATION AT C-6 AND C-7 OF SERRICORNIN (4,6-DIMETHYL-7-HYDROXY-3-NONANONE), THE SEX PHEROMONE OF THE CIGARETTE BEETLE

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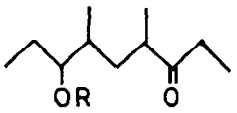
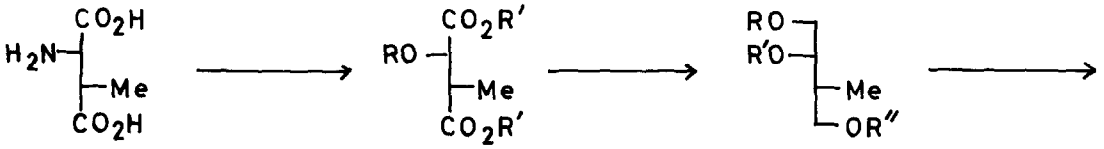
Summary : The absolute configuration at C-6 and C-7 of serricornin was established as (6S, 7S) by synthesizing its (6R, 7S)-erythro and (6R, 7R)-threo isomers.

The sex pheromone produced by the female cigarette beetle, Lasioderma serricorne, was recently isolated and named as serricornin.[1,2] The proposed structure, 4,6-dimethyl-7-hydroxy-3-nonanone 1a, was proved by its synthesis as a diastereomeric mixture.[2,3] The absolute stereochemistry at three chiral centers in 1a, however, remained unknown. We have now synthesized (4RS, 6R, 7R)-1a and (4RS, 6R, 7S)-1a and established the (6S, 6S)-stereochemistry of the natural product.

As the chiral starting material we employed (2S, 3S)-threo-β-methylmalic acid (2S, 3S)-3a[4] and diethyl (2R, 3S)-erythro-β-methylmalate (2R, 3S)-3d.[5] Our synthetic route from (2S, 3S)-3a is detailed in the Scheme. (2S, 3S)-(+)-β-Methylaspartic acid 2, $[\alpha]_D^{21}$ + 13.0° (5N-HCl), was prepared by resolving the racemate[6] with (S)-(-)-α-phenethylamine.[7] The amino acid 2 was deaminated (HNO_2) to give (2S, 3S)-3a, $[\alpha]_D^{24}$ + 5.3° (H_2O) (lit.[4] +5.2°). This was converted (CH_2N_2) to the corresponding ester 3b, bp 117~119°/12mm, $[\alpha]_D^{23}$ + 0.24° (Et_2O). The OH group in 3b was protected (dihydropyran-TsOH-ether) to give a THP ether 3c. Reduction (LAH) of 3c followed by hydrolysis (TsOH-MeOH) gave a triol 4b via 4a. A soln of 4b (+ trace TsOH) in acetone yielded 4c, bp 71~73°/3mm, $[\alpha]_D^{24}$ -7.3° (PhH), after work-up. This was converted ($PhCH_2Cl$-NaH-DMSO) to a benzyl ether



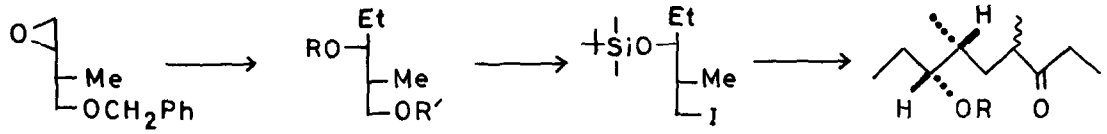
1a R=H
b R=Ac



2

(2S, 3S)-3a R=R'=H
b R=H, R'=Me
c R=THP, R'=Me

4a R=R"=H, R'=THP
b R=R'=R"=H
c R,R'=Me_2C= , R"=H
d R,R'=Me_2C= , R"=CH_2Ph
e R=R'=H. R"=CH_2Ph
f R=Ts. R'=H. R"=CH_2Ph

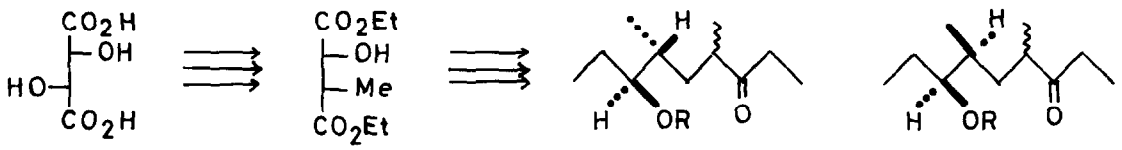


5

6a R=H, R'=CH_2Ph
b R=$SiMe_2Bu^t$, R'=CH_2Ph
c R=$SiMe_2Bu^t$, R'=H
d R=$SiMe_2Bu^t$, R'=Ts

7

(6R, 7R)-1a R=H
b R=Ac
c R=$SiMe_2Bu^t$



8

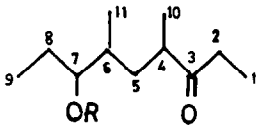
(2R, 3S)-3d

(6R, 7S)-1a R=H
b R=Ac

(6S, 7S)-1a

4d. The acetonide protecting group was removed (dil HCl-MeOH) and the resulting 4e, bp 140~142°/0.3mm, $[\alpha]_D^{24}$ -4.04° (PhH), was tosylated (TsCl-C_5H_5N) to give 4f. This was converted (KOH-MeOH) to an epoxide 5, bp 92~94°/0.35mm, $[\alpha]_D^{24}$ -8.28° (PhH). Treatment of 5 with Me_2CuLi (ether,-55→-20° after 4 hr) gave 6a (87% yield), bp 125~126°/0.5 mm, $[\alpha]_D^{24}$ -2.30° (PhH). The OH group in 6a was protected as a silyl ether (t-$BuMe_2SiCl$-imidazole-DMF) to give 6b. Hydrogenolysis of 6b on Pd-C removed the benzyl protecting group to afford 6c, whose tosylation (TsCl-C_5H_5N) yielded 6d. This was converted to 7 by the Finkelstein reaction (NaI-Acetone). Alkylation of diethyl ketone with 7 (LDA-

TABLE ^{13}C-NMR DATA OF SERRICORNIN ACETATE ISOMERS (δ, ppm)



Carbon No.	Natural 1b*	Natural 1b after racemization at C-4	(6R,7S)-1bα	(6R,7S)-1bβ	(6R,7R)-1b
1	7.84	7.84	7.78	7.84	7.84
2	34.22	34.28	34.11	34.34	34.28
3	214.88	214.88	214.88	214.94	215.00
4	43.53	43.53 43.35	43.88	43.58	43.53 43.35
5	24.22	24.22	23.34	23.28	24.22
6	33.70	33.70	34.11	33.81	33.70
7	78.04	78.04 77.75	78.92	79.09	78.10 77.80
8	35.98	35.98 36.39	35.51	35.01	35.92 36.39
9	10.18	10.18	10.00	10.06	10.18
10	16.67	16.67 17.32	18.08	16.21	16.61 17.32
11	14.45	14.45 14.63	15.85	15.33	14.45 14.63

* For the assignments of the signals see ref. 1. (Measured as $CDCl_3$ solns.)

THF-HMPA) gave (4RS, 6R, 7R)-1c. Deprotection of the silyl ether in 1c (10% aq. HF-MeCN, room temp)[8] yielded (4RS, 6R, 7R)-serricornin 1a, ν_{max} 3400 (m), 1710 (m) cm^{-1}. For the purpose of chromatographic and spectral comparisons with the natural product, (4RS, 6R, 7R)-1a was acetylated (Ac_2O-C_5H_5N) to give the corresponding acetate (4RS, 6R, 7R)-1b (2.4mg after purification by prep GLC), $[\alpha]_D^{23}$ + 16.6° (MeOH), ν_{max} 1735 (s), 1710 (s), 1240 (s) cm^{-1}, MS : m/z 168 (M^+-AcOH).

In the same manner, diethyl (2R, 3S)-β-methylmalate 3d (prepared from L-(+)-tartaric acid 8[5]) was converted to (4RS, 6R, 7S)-1b. In this case the mixture was separable into two pure diastereomers, (6R, 7S)-1bα (12.4 mg). $[\alpha]_D^{23}$ -13.2° (n-C_6H_{14}), MS : m/z 168, GLC (OV-101 column, 30m x 0.25 mm at 60~200° (+2°/min); He, 1 ml/min) : Rt 46.8 min, and (6R, 7S)-1bβ (5.8 mg), $[\alpha]_D^{23}$ -18.8° (n-C_6H_{14}), MS : m/z 168, GLC (same condition as for the α-isomer) : R_t 47.5 min. The stereochemistry at C-4 of these diastereomers could not be clarified. Neither of them were identical with the acetate derived from natural serricornin on the basis of GLC and NMR comparisons.

Synthetic (4RS, 6R, 7R)-1b was therefore carefully compared with the acetate 1b derived from natural serricornin. Upon GLC analysis (4RS, 6R, 7R)-1b showed two peaks, one at R_t 33.5 min and the other at R_t 33.8 min (OV-101 column, 30m x 0.25mm at 70~200° (+2°/min); He, 1 ml/min), the former of which coincided with that of the acetate 1b derived from natural pheromone. Since the separation of the synthetic diastereomeric mixture (4RS, 6R, 7R)-1b was unsuccessful in preparative scale, the naturally derived acetate 1b was racemized at C-4 by having been left to stand its $CDCl_3$ soln for 4 days at ca.20° Subsequent comparison (GLC and ^{13}C-NMR) of the synthetic acetate (4RS, 6R, 7R)-1b with the racemized acetate 1b proved their identity. The ^{13}C-NMR data of the natural and synthetic acetoxy ketones 1b are listed in the Table. The identity of (4RS, 6R, 7R)-1b with the natural 1b after racemization at C-4 can clearly be seen from the Table. However, they were different in their chiroptical properties : the synthetic (4RS, 6R, 7R)-1b was dextrorotatory, $[\alpha]_D^{23}$ + 16.6° (c=0.12, MeOH), while the equilibrated acetoxy ketone 1b derived from the natural pheromone was levoratatory, $[\alpha]_D^{23}$ -13.8° (c=0.08, MeOH). The absolute stereochemistry at C-6 and C-7 in serricornin 1a was therefore assigned to be 6S, 7S. The elucidation of the stereochemistry at C-4 is now in progress.

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RERERENCES AND FOOTNOTES

1. T. Chuman, M. Kohno, K. Kato and M. Noguchi, Tetrahedron Lett., 2361 (1979).
2. T. Chuman, K. Kato and M. Noguchi, Agric. Biol. Chem., 43, 2005 (1979).
3. M. Ono, I. Onishi, T. Chuman, M. Kohno and K. Kato, ibid., 44, 2259 (1980).
4. S. Tatsumi, M. Imaida and Y. Izumi, Bull. Chem. Soc. Japan, 39, 1818 (1966). These authors prepared this diacid by resolving the racemate prepared in three steps from ethyl propionate and diethyl oxalate.
5. K. Mori and H. Iwasawa, Tetrahedron, 36, 87 (1980).
6. H.D. Dakin, J. Biol. Chem., 141, 945 (1941).
7. Enzymatic resolution of the racemic N-acetate with Aspergillus aminoacylase was less successful, although the resolution with hog kidney acylase II had been reported to be satisfactory : cf. L. Benoiton, S.M. Birnbaum, M. Winitz, J.P. Greenstein, Arch. Biochem. Biophys. 81, 434 (1959).
8. R.F. Newton, D.P. Reynolds, M.A.W. Finch, D.R.Kelly and S.M. Roberts,Tetrahedron Lett., 3981 (1979).

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