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SYNTHESIS OF RACEMIC SIRENIN, A PLANT SEX HORMONE

Kenji Mori and Masanao Matsui

Department of Agricultural Chemistry, University of Tokyo

Bunkyo-ku, Tokyo 113, Japan

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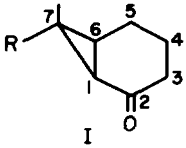
We recently reported the synthesis of some caran-2-ones (I) by the intramolecular α-ketocarbene-olefin addition (1). Its application to the synthesis of racemic sesquicarene (IIa) has also been reported (2,3). Herein is described another application. Sirenin (IIb) (4, 5a, 5b) is the sperm attractant produced by the female gametes of the water mold Allomyces. This unique sesquiterpene has been synthesized in the following manner.

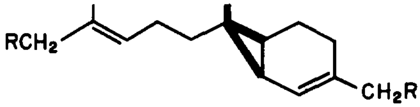
4,8-Dimethylnona-3,7-dienyl bromide (III)(6) was condensed with $CH_2(CO_2Et)_2$ to give IV, b.p. 135-138°/3mm; n_D^{14} 1.4630 (7). This was hydrolyzed and decarboxylated to give Va, b.p. 146-148°/0.6mm; n_D^{17} 1.4732, which consisted of Δ^5-trans and cis isomers (2.5 : 1) judging from the GLC analysis of the corresponding Me ester (Vb), b.p. 113-115°/4mm; n_D^{18} 1.4630.

The acid (Va) in C_6H_6 was treated with $SOCl_2$ to give an unstable acyl chloride (Vc), b.p. 105-115°/0.2mm, which was converted to VI by treatment with CH_2N_2-Et_2O. A cyclohexane solution of VI was heated under reflux in the presence of powdered Cu and $CuSO_4$ to give a crude product (VII + VII') in 84% yield from Vc. This was chromatographed over SiO_2-$AgNO_3$ (8) to give an analytically pure product (VII + VII'), b.p. 117-118°/5mm; n_D^{19} 1.4948; ν (film) 1680cm^{-1}; δ (CCl_4) 1.14 (3H, s), 1.59 (3H, s), 1.65 (3H, s), 4.99 (1H, t) ppm. The ratio of VII and VII' was 2:1 by GLC analysis.

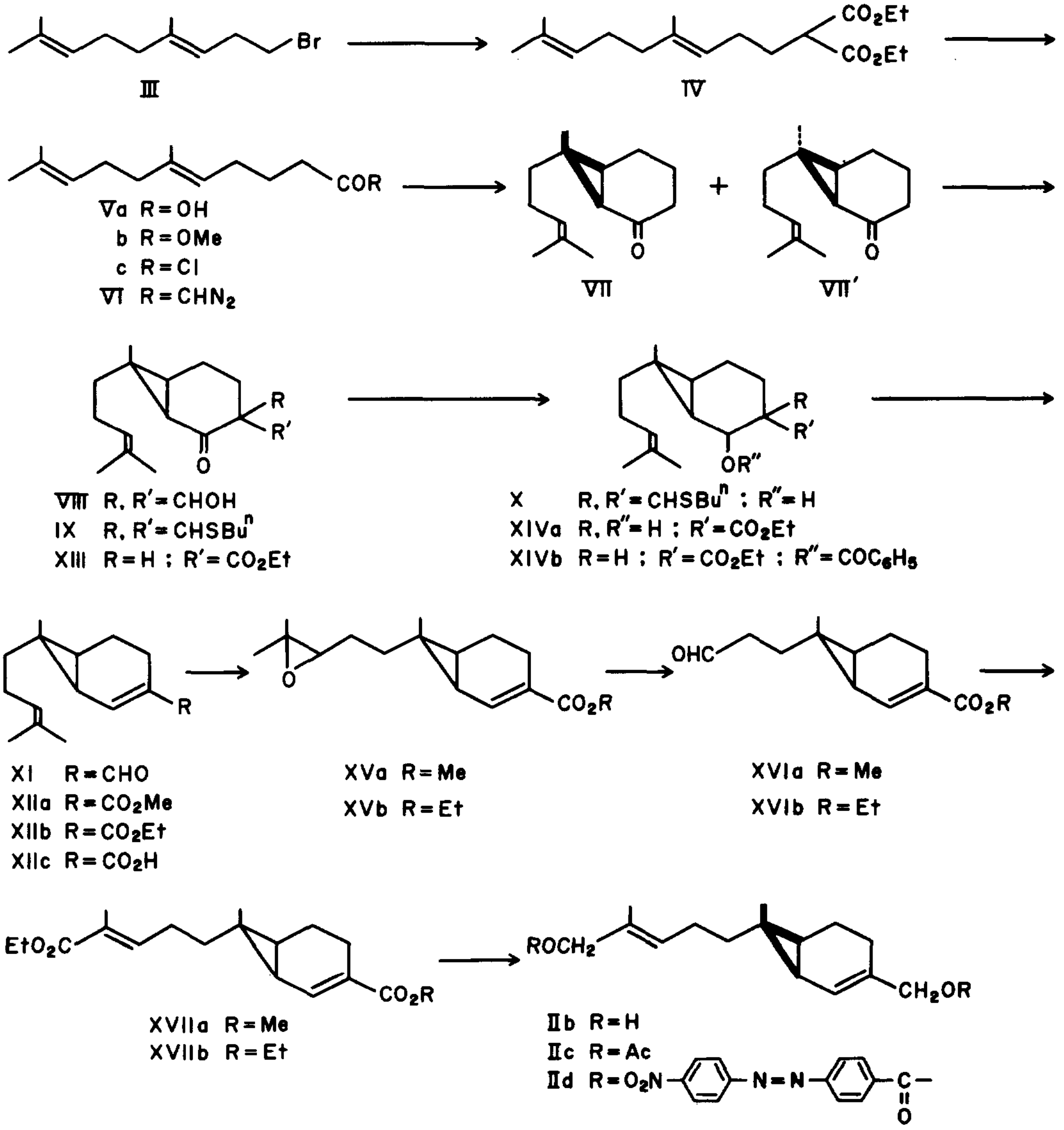
The bicyclic ketone (VII + VII') was formylated with HCO_2Et and NaH to give VIII, b.p. 117-119°/0.2mm; n_D^{26} 1.5250. This yielded the n-bytylthiomethylene derivative (IX), b.p. 195-198°/0.1mm; n_D^{24} 1.4526, by treatment with p-TsCl-C_5H_5N-$\overset{n}{\text{Bu}}$SH (9). Its reduction with



I



IIa R=H ; IIb R=OH



III

IV

Va R=OH
b R=OMe
c R=Cl
VI R=CHN$_2$

VII

VII'

VIII R, R'=CHOH
IX R, R'=CHSBu^n
XIII R=H ; R'=CO$_2$Et

X R, R'=CHSBu^n ; R"=H
XIVa R, R"=H ; R'=CO$_2$Et
XIVb R=H ; R'=CO$_2$Et ; R"=COC$_6$H$_5$

XI R=CHO
XIIa R=CO$_2$Me
XIIb R=CO$_2$Et
XIIc R=CO$_2$H

XVa R=Me
XVb R=Et

XVIa R=Me
XVIb R=Et

XVIIa R=Me
XVIIb R=Et

IIb R=H
IIc R=Ac
IId R=O$_2$N–C$_6$H$_4$–N=N–C$_6$H$_4$–C(=O)–

$NaBH_4$ in EtOH afforded crude X, which,without purification, was treated with $HgCl_2$ and $CdCO_3$ in EtOH to give impure XI, b.p. 118-126°/0.2mm. This was converted into the key intermediate (XIIa), b.p. 125-128°/1mm; n_D^{30} 1.4958; ν (film) 1700, 1630 cm^{-1}; δ (CCl_4) 0.92 (3H, s), 1.61 (3H, s), 1.67 (3H, s), 3.66 (3H, s), 5.05 (1H, t), 7.16 (1H, d) ppm, by the method of Corey et al. (10) followed by an extensive chromatography over SiO_2-$AgNO_3$ (8, 11). However, the recently described alternate preparation of the key intermediate (XIIb) was more convenient. Thus the ketone (VII + VII') was carbethoxylated with $CO(OEt)_2$ and NaH in C_6H_6 to give XIII, b.p. 142-143°/0.8mm; n_D^{29} 1.4978, which was reduced with $NaBH_4$ to give XIVa, b.p. 150-152°/1mm; n_D^{28} 1.4868. The corresponding benzoate (XIVb) was treated with $KOBu^t$ in Bu^tOH-C_6H_6 to yield XIIb, b.p. 145-148°/2.0mm; n_D^{31} 1.4962; ν (film) 1708, 1635 cm^{-1}; δ (CCl_4) 0.93 (3H, s), 1.29 (3H, t), 1.60 (3H, s), 1.67 (3H, s), 4.12 (2H, q), 5.05 (1H, t), 7.16 (1H, d) ppm (12). Its alkaline hydrolysis gave XIIc which was methylated to give XIIa, identical with the one prepared by the above described route.

Treatment of the esters (XIIa and b) with m-$ClC_6H_4CO_3H$ in CH_2Cl_2 gave epoxy esters XVa, b.p. 134-136°/0.8mm; n_D^{30} 1.4890 and XVb, b.p. 147-148°/1.2mm; n_D^{31} 1.4864, respectively. The epoxides were cleaved with H_5IO_6 in Et_2O (13) to yield aldehydes XVIa, b.p. 123-125°/1.0mm; n_D^{29} 1.5014; ν (film) 2720, 1710, 1690, 1630 cm^{-1}; δ (CCl_4) 0.90 (3H, s), 3.66 (3H, s), 7.14 (1H, d), 9.03 (1H, s) ppm; 2,4-dinitrophenylhydrazone, m.p. 186-187.5° (14) and XVIb, b.p. 131-133°/1.0mm; n_D^{30} 1.4960; 2,4-DNP, m.p. 164-165° (14), respectively. The aldehydes were subjected to the modified Wittig reaction (15) with $(EtO)_2P(O)CHMeCO_2Et$ and NaH in $MeOCH_2CH_2OMe$ to give diesters XVIIa (16), b.p. 180-190° (bath temp)/0.5mm; n_D^{31} 1.5006 and XVIIb, b.p. 190° (bath temp)/0.5mm; n_D^{31} 1.4978, ν (film) 1690, 1630 cm^{-1}; δ (CCl_4) 0.95 (3H, s), 1.30 (6H, t), 1.82 (3H, s), 4.12 (4H, q), 6.68 (1H, t), 7.14 (1H, d) ppm, after chromatographic purification over Al_2O_3. Reduction of the diesters with $LiAlH_4$ gave crude product which was chromatographed over Al_2O_3 (4) to afford pure racemic sirenin (IIb) as a viscous oil, ν ($CHCl_3$) 3680, ~3400, 2995, 2925, 2860, 1660, 1445, 1378, ~1220, 1160, 1113, 1057, 1030, ~980, 906, 864, 823 cm^{-1}; δ ($CDCl_3$) 0.87 (3H, s), 1.66 (3H, s), 1.69 (2H, s, 2-O<u>H</u>), 3.96 (4H, s), 5.40 (1H, t), 5.85 (1H, br. s) ppm. Its acetylation with Ac_2O-C_5H_5N gave dl-sirenin diacetate (IIc), b.p. 190° (bath temp)/0.3mm; n_D^{29} 1.4870; ν (film) 1725 cm^{-1}; δ (CCl_4) 0.89 (3H, s), 1.65 (3H, s), 2.00 (6H, s), 4.39 (4H, s), 5.44

(1H, t), 5.86 (1H, br. s) ppm. The bis-p-(p-nitrophenylazo)benzoate ester (bis-NABS-dl-sirenin, IId) crystallized as orange-red prisms, m.p. 168-170°, after chromatographic purification over Al_2O_3 (4), ν ($CHCl_3$) 3040, 2930, 2870, 1730, (sh.), 1725, 1605, 1590, 1580 (w), 1520, 1460, 1410, 1346, 1270, 1105, 1092 (sh.), 1010, 955 (w), 865, 855, 695 cm^{-1}; δ ($CDCl_3$) 0.98 (3H, s), 1.82 (3H, s), 4.80 (4H, s), 5.65 (1H, t), 6.10 (1H, br. s), 8.02-8.51 (16H, m) ppm. The NMR data of IIb and IId were in good accord with the published values (5b, 17).

It is interesting to note that juvabione (18) and dehydrojuvabione (19), sesquiterpenes with insect juvenile hormone activity, possess the carbon skeleton similar to that of sirenin. The biological activity of the racemic sirenin and the juvenile hormone activity of the intermediates XIIa and XVa will be described later.

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11. The crude product before chromatographic separation was a mixture of XIIa and bisabolene-type esters without the cyclopropane ring. XIIa was obtained as a mixture of the C-7 β-Me and α-Me isomers (2:1 by GLC analysis).
12. This was also a mixture of isomers at C-7 (β-Me isomer : α-Me = 2.6 : 1) which could not be separated by chromatography over SiO_2-$AgNO_3$.
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16. This was contaminated with XVIIb formed by ester-exchange with the excess reactant.
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Note Added After the submission of this paper we have been informed that the two successful syntheses of dl-sirenin have appeared in J. Am. Chem. Soc. [91, 4318 (July 1969); 91, 4933 (August 1969)].