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STEREOCONTROLLED SYNTHESIS OF ALL OF THE FOUR POSSIBLE STEREOISOMERS OF 3,11-DIMETHYL-2-NONACOSANONE, THE FEMALE SEX PHEROMONE OF THE GERMAN COCKROACH[1]

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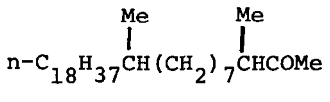
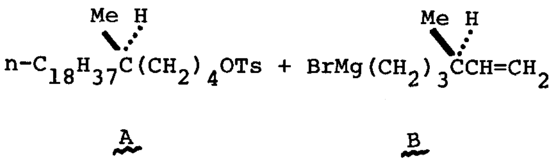
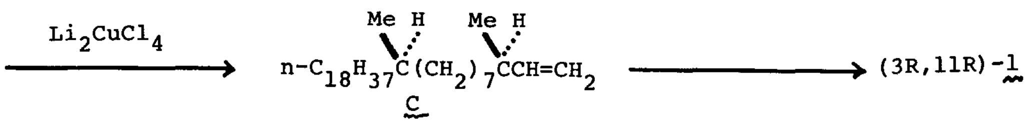
From the cuticular wax of sexually mature females of the German cockroach (Blattella germanica), Fukami and coworkers isolated 3,11-dimethyl-2-nonacosanone (1) as the sex pheromone which elicited typical courting behavior in males inclucing wing-raising.[2] A number of syntheses were reported yielding a diastereomeric mixture of 1.[2-6] However, no synthesis of optically pure 1 was reported except an unsuccessful attempt to that goal by Rossi *et al.*[7] We have now completed the synthesis of all of the four possible stereoisomers of 1 in optically pure forms and established the hitherto unknown absolute configuration of the natural pheromone to be 3*S*,11*S*.[8] The key step in our synthesis was the coupling of a chiral tosylate (A) with a chiral Grignard reagent (B) to give an olefin (C), which was converted to 1 in a standard manner.

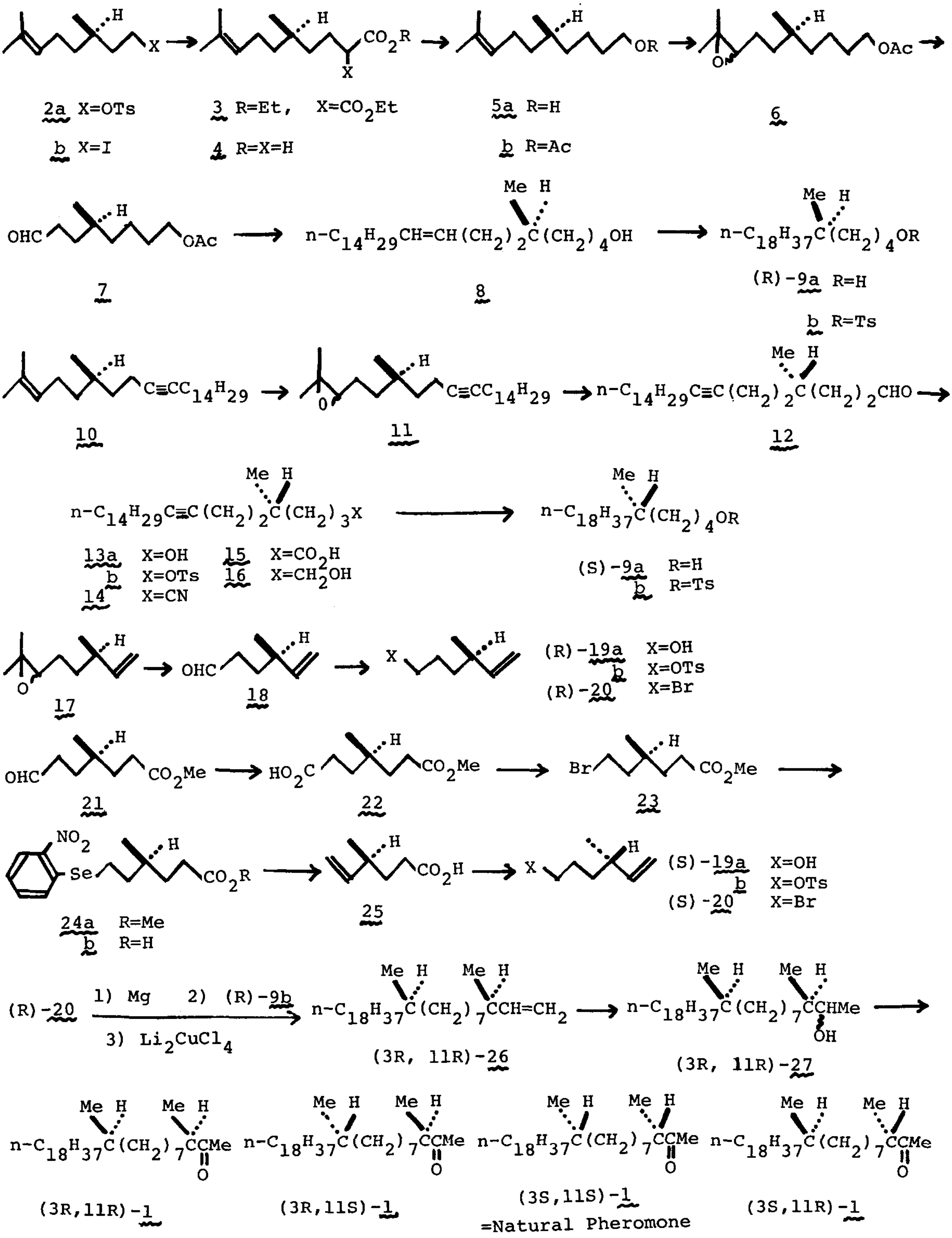


$n\text{-}C_{18}H_{37}\overset{Me}{CH}(CH_2)_7\overset{Me}{CH}COMe$

1






H
X
CO2R
X
OR
OAc
O
2a X=OTs
b X=I
3 R=Et, X=CO2Et
4 R=X=H
5a R=H
b R=Ac
6
OHC
OAc
n-C14H29CH=CH(CH2)2C(CH2)4OH
Me H
n-C18H37C(CH2)4OR
7
8
(R)-9a R=H
b R=Ts
C≡CC14H29
n-C14H29C≡C(CH2)2C(CH2)2CHO
10
11
12
n-C14H29C≡C(CH2)2C(CH2)3X
n-C18H37C(CH2)4OR
13a X=OH
b X=OTs
14 X=CN
15 X=CO2H
16 X=CH2OH
(S)-9a R=H
b R=Ts
17
OHC
18
(R)-19a X=OH
b X=OTs
(R)-20 X=Br
OHC
CO2Me
HO2C
Br
21
22
23
NO2
Se
CO2R
CO2H
24a R=Me
b R=H
25
(S)-19a X=OH
b X=OTs
(S)-20 X=Br
(R)-20
1) Mg 2) (R)-9b
3) Li2CuCl4
n-C18H37C(CH2)7CCH=CH2
(3R, 11R)-26
n-C18H37C(CH2)7CCHMe
OH
(3R, 11R)-27
n-C18H37C(CH2)7CCMe
(3R,11R)-1
(3R,11S)-1
(3S,11S)-1
=Natural Pheromone
(3S,11R)-1

The chiral components A and B were prepared from (R)-(+)-citronellol derived from highly optically pure (R)-(+)-citronellic acid.[9] (R)-(+)-Citronellyl tosylate (2a) was treated with NaI in acetone to give an iodide (2b). The standard malonic ester synthesis converted it to a carboxylic acid (4) via a malonate (3). This was reduced ($LiAlH_4$) and acetylated ($Ac_2O/C_5H_{15}N$) to give an acetate (5b). An epoxide (6)was obtained by oxidizing 5b with m-chloroperbenzoic acid, whose HIO_4 cleavage gave an aldehyde (7), $[\alpha]_D^{20}$ + 1.45° (neat). The Wittig reaction between 7 and a phosphorane generated from $n\text{-}C_{15}H_{31}P^+Ph_3Br^-$ (n-BuLi/THF) yielded an olefinic alcohol (8). This was hydrogenated over Pd-C to give a crystalline alcohol [(R)-9a], mp 47.0-47.5°, $[\alpha]_D^{20}$ + 1.01 ± 0.1°(c= 4.065, ether). The corresponding tosylate [(R)-9b] was obtained in the conventional manner. The antipodal alcohol [(S)-9a] was prepared as follows. Alkylation of hexadec-1-yne with citronellyl iodide (2b) gave an acetylene (10). This was epoxidized to 11. HIO_4 oxidation cleaved 11 to give 12. This was reduced ($LiAlH_4$) to an alcohol (13a). The corresponding tosylate (13b) was converted (NaCN/DMSO) to a nitrile (14). Hydrolysis ($NaOH/EtOH\text{-}H_2O$) of 14 gave an acid (15), which was reduced ($LiAlH_4$) to give an alcohol (16). This was hydrogenated (H_2/Pd-C) to afford the desired alcohol [(S)-9a], mp 47.0-47.5°,$[\alpha]_D^{20}$ -1.01± 0.08° (c=5.37, ether). The corresponding tosylate [(S)-9b] was prepared in the conventional manner.

In order to prepare the another half of the molecule, the known epoxide (17)[10] was cleaved (HIO_4) to give an aldehyde (18). This was reduced ($LiAlH_4$) to an alcohol [(R)-19a]. The corresponding tosylate (19b) was treated with LiBr in acetone to give a bromide [(R)-20], $[\alpha]_D^{19}$ -12.6° (neat). The preparation of (S)-20 was more complicated. The known aldo ester (21)[11] was oxidized (CrO_3) to a half ester (22). Its Ag salt was treated with Br_2 in CCl_4 to give a bromide (23). This was reacted with o-nitroselenophenol to yield a selenide (24a).[12] Its hydrolysis (NaOH) to 24b followed by oxidative elimination with H_2O_2 yielded an olefinic acid (25), $[\alpha]_D^{20.5}$ + 14.72° (neat). This was reduced ($LiAlH_4$) to give an alcohol [(S)-19a]. The corresponding tosylate [(S)-19b] was converted to (S)-20, $[\alpha]_D^{20.5}$ + 13.2° (neat).

The coupling of (R)-9b with the Grignard reagent derived from (R)-20 was successfully carried out in the presence of Li_2CuCl_4 in THF.[13] The Markownikoff hydration of the resulting olefin [(3*R*,11*R*)-**26**] with $Hg(OAc)_2/THF-H_2O$ and $NaBH_4-NaOH/H_2O$ gave an alcohol [(3*R*,11*R*)-**27**][14]. This was oxidized (Jones CrO_3) to give (3*R*,11*R*)-**1**, mp 42.0-42.5°, $[\alpha]_D^{21}$ -5.63±0.2°(c=4.1, n-hexane). In the same manner, (*S*)-**9a** and (*R*)-**20** gave (3*R*,11*S*)-**1**, mp 33.5-34.0°, $[\alpha]_D^{21}$ -5.68±0.2° (c=4.0, n-hexane); (*S*)-**9a** and (*S*)-**20** gave (3*S*,11*S*)-**1**, mp 43.5-45.0°, $[\alpha]_D^{21}$ +5.98 ±0.3°(c=0.9, n-hexane); (*R*)-**9a** and (*S*)-**20** gave (3*S*,11*R*)-**1**, mp 34.0-35.0°, $[\alpha]_D^{21}$ + 5.73 ±0.15° (c=2.04, n-hexane). The natural pheromone **1** melted at 44.0-45.5° with $[\alpha]_D^{22}$ +5.1° (c=3.54, n-hexane).[8] The IR and NMR spectra of the natural pheromone were entirely identical with those of (3*R*,11*R*)- and (3*S*,11*S*)-isomers, while they were very similar to those of (3*R*,11*S*)- and (3*S*,11*R*)-isomers. The natural pheromone was identified as (3*S*,11*S*)-**1** by the mixture mp determination showing no mp depression[15]. The natural and the synthetic four isomers showed the same range of pheromone activity when tested on the males of German cockroach at 50 μg/ml dose. Thus the pheromone receptor seems to be devoid of stereospecificity.

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REFERENCES AND FOOTNOTES

1 This work was presented by K.M. at the Symposium entitled "Stereochemical Aspects of Pesticide Chemistry" (the 175th ACS National Meeting) in Anaheim, Calif., on March 16, 1978.

2 R. Nishida, H. Fukami and S. Ishii, *Experientia*, **30**, 978 (1974); *Appl. Entomol. Zool.*, **10**, 10 (1975).

3 T. Sato, R. Nishida, Y. Kuwahara, H. Fukami and S. Ishii, *Agric. Biol. Chem.*, **40**, 391 (1976).

4 M. Schwarz, J.E. Oliver and P.E. Sonnet, *J. Org. Chem.*, **40**, 2410 (1975).

5 A.W. Burgstahler, L.O. Weigel, W.J. Bell and M.K. Rust, *ibid.*, **40**, 3456(1975).

6 L.D. Rosenblum, R.J. Anderson and C.A. Henrick, *Tetrahedron Letters*,419(1976).

7 C. Conti, A. Niccoli and R. Rossi, *Chim. e Ind.(Milano)*, **58**, 877 (1976).

8 Very recently Fukami *et al.* proposed the 3*S*-stereochemistry of **1**. (R. Nishida, H. Fukami and S. Ishii, *J. Chem. Ecol.*, in the press). We thank Prof. H. Fukami for this information.

9 K. Mori, *Tetrahedron*, **33**, 289 (1977).

10 G.J. Cernigliaro and P.J. Kocienski, *J. Org. Chem.*, **42**, 3622 (1977).

11 K. Mori, S. Tamada and M. Matsui, *Tetrahedron Letters*, 901 (1978).

12 K.B. Sharpless and M.W. Young, *J. Org. Chem.*, **40**, 947 (1975).

13 G. Fouquet and M. Schlosser, *Angew. Chem. intern. Ed.*, **13**, 83 (1974).

14 H.C. Brown and W.F. Hammar, *J. Am. Chem. Soc.*, **89**, 1522 (1967).

15 Prof. Fukami and Dr. Yamaoka kindly carried out the mp and mmp determinations. Their data were as follows: (3*R*,11*R*)-**1**, mp 44.5-45.0°; (3*R*,11*S*)-**1**, mp 37.5-38.0° ;.(3*S*,11*S*)-**1**, mp 44.0-45.5° ; (3*S*,11*R*)-**1**, mp 38.0-38.5°. (Natural + 3*S*,11*S*)-**1**, mmp 44.0-45.0°; (Natural + 3*S*,11*R*)-**1**, mmp 33.5-35.0°; (Natural + 3*R*,11*R*)-**1**, mmp 37.0-37.5°.

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