SYNTHESIS OF THREE STEREOISOMERIC FORMS OF 2,8-DIMETHYL-1,7-DIOXASPIRO[5.5]UNDECANE, THE MAIN COMPONENT OF THE CEPHALIC SECRETION OF ANDRENA WILKELLA†

Kenji Mori* and Kaichi Tanida

Department of Agricultural Chemistry, The University of Tokyo,
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

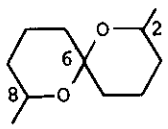
Abstract - Three stereoisomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane with defined stereochemistry at C-2 and C-8 were synthesized utilizing yeast reduction and dianion alkylation of ethyl acetoacetate.

The mandibular gland secretion of Andrena bees plays an important role in the communication between the sexes. Very recently Francke et al. identified 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane 1 as the main component in Andrena wilkella caught in Öland, Sweden, by mass spectral comparison with a racemic reference compound.[1] In continuation of our work on the synthesis of chiral spiroketal pheromones,[2] we here report a synthesis of 1 in three stereoisomeric forms, (2S, 6R, 8S), (2R, 6S, 8R) and (2R, 6RS, 8S)-isomers.

The chiral starting material in our synthesis was ethyl (S)-3-hydroxy-butanoate 2, $[\alpha]_D^{24}$ + 37.6° (c=1.57, $CHCl_3$), which was readily obtainable in 92% optical purity by the reduction of ethyl acetoacetate with baker's yeast.[3] Conversion of 2 into (S)-3b was carried out as described previously.[3] The key iodide (S)-4 was obtained in 80.4% yield by treating (S)-3b with NaI in acetone in the presence of a small amount of $NaHCO_3$.

The antipodal iodide (R)-4 was obtained in the following manner. The alcohol

† This paper is dedicated to Professor Tetsuji Kametani on the occasion of his retirement from Tohoku University.



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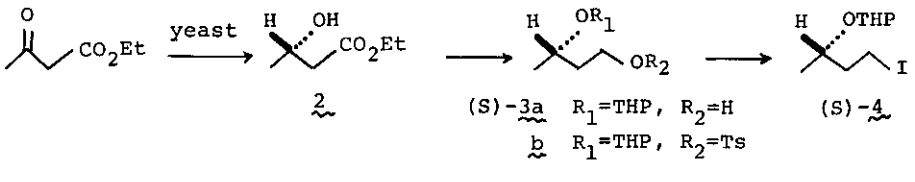
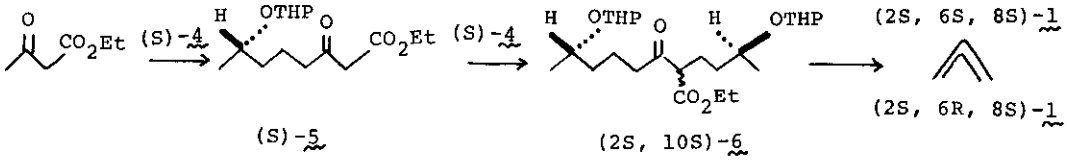


(S)-3a R_1=THP, R_2=H
b R_1=THP, R_2=Ts

(S)-3c R=THP
d R=H

(R)-3a R_1=THP, R_2=H
b R_1=THP, R_2=Ts
c R_1=THP, R_2=CH_2Ph
d R_1=H, R_2=CH_2Ph
e R_1=COPh, R_2=CH_2Ph

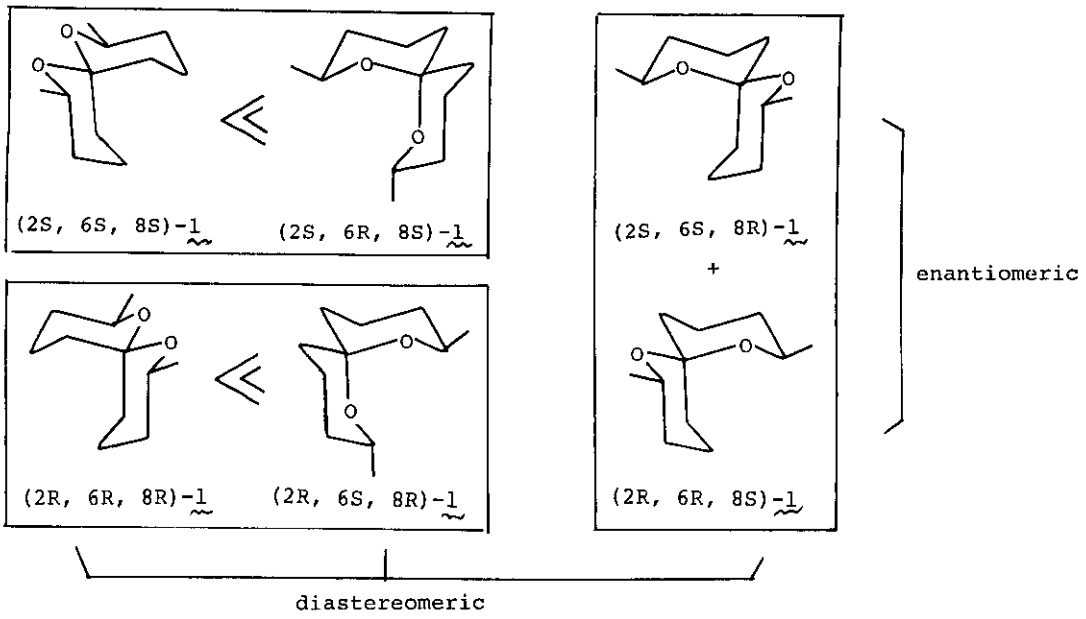


(S)-5

(2S, 10S)-6

(2S, 6S, 8S)-1

(2S, 6R, 8S)-1



(2S, 6S, 8S)-1

(2S, 6R, 8S)-1

(2S, 6S, 8R)-1

+

(2R, 6R, 8S)-1

(2R, 6R, 8R)-1

(2R, 6S, 8R)-1

enantiomeric

diastereomeric

(S)-3a was converted to the corresponding benzyl ether (S)-3c(90.5% yield) by treatment with $PhCH_2Cl$-NaH/THF. Removal of the tetrahydropyranyl (THP)protective group with dil HCl-MeOH yielded (S)-3d, bp 98-102°/1.5mm; n_D^{24} 1.5025; $[\alpha]_D^{24}$ -2.12° (c=1.13, $CHCl_3$), in 88% yield. Then the configuration of the OH group of (S)-3d was inverted by Mitsunobu's method[4,5] Thus (S)-3d was treated with $PhCO_2H$-Ph_3P-$EtO_2CN{=}NCO_2Et$ in THF to give crude (R)-3e. This was hydrolyzed with KOH-MeOH-H_2O to give the desired diol monobenzyl ether (R)-3d (72.7% yield from (S)-3d), bp99-102°/1.5mm; n_D^{24} 1.5027; $[\alpha]_D^{24}$ + 2.08°(c=1.11, $CHCl_3$). After protecting the OH group as a THP ether (R)-3c, the benzyl group was removed by hydrogenolysis (H_2/Pd-C/EtOH) to give (R)-3a, bp83-88°/1.5mm; n_D^{24}1.4513; $[\alpha]_D^{24}$-24.5° (c=1.32, $CHCl_3$), in 82% yield from (R)-3d. This gave (R)-4 via (R)-3b.

Connection of the chiral iodide 4 with $-CH_2COCH_2-$ unit was carried out in two steps. Firstly a dianion derived from ethyl acetoacetate (NaH, n-BuLi/THF)[6] was alkylated with 1 eq of either (S)-4 or (R)-4. By employing (S)-4, a new β-keto ester (S)-5 was obtained in 75% yield. This was further alkylated with (S)-4 in the presence of K_2CO_3/THF-DMF to give (2S,10S)-6. In the same manner (2R, 10R)-6 was obtained by employing (R)-4 for alkylation. For the synthesis of (2S, 10R)-6 the first alkylation was carried out with (S)-4 and the second was done with(R)-4.

Finally, the keto ester 6 was converted to 2,8-dimethyl-1,7-dioxaspiro[5.5] undecane 1 by hydrolysis and decarboxylation (KOH/MeOH-H_2O) followed by deprotection and ketalization (dilHCl/MeOH). Starting from (2S,10S)-6, we obtained (2S, 8S)-1 with unknown stereochemistry at C-6 (200mg from 1.8g of 6), bp 150-160°; n_D^{23} 1.4465; $[\alpha]_D^{23}$ -51.6° (c=1.27, n-pentane).[7] We first thought this to be a mixture of (2S,6S,8S)-1 and (2S,6R,8S)-1, both of which possesses a C_2-axis of symmetry. (We assumed two Me groups of 1 to prefer the equatorial position which should be energetically more favorable.) However, the glc and nmr data of our (2S,8S)-1 indicated it to be homogeneous: glc (column, CF-96-CR19, 40mx0.28mm at 70-220° (3°/min), carrier gas, N_2, 1.0kg/cm^2): Rt 26.22 min (98% purity); ^{1}H-nmr: δ(60MHz, $CDCl_3$) 1.10 (6H,d,J=6Hz), 1.2-2.0 (12H,br), ~3.4-~3.9 (2H,m); ^{13}C-nmr (25.05 MHz, $CDCl_3$) 19.7, 22.6, 33.7, 36.0, 66.0 (C-C-O), 97.1 (O-C-O). The six-line ^{13}C-nmr spectrum was in accord with the structures with a C_2-axis of symmetry. In connection with their synthetic works on the antibiotic A23187, Evans et al.[8] and Cresp et al.[9] synthesized crystalline 2,8-dialkyl-1,7-dioxaspiro[5.5]undecanes and found them to possess structures similar to (2S,6R,8S)-1 by X-ray crystallographic analyses.[8,10] We therefore tentatively assign R-configuration to C-6 of our (2S,8S)-

1. The oxygen anomeric effect seems to be operating to make (2S,6S,8S)-1 less stable than (2S,6R,8S)-1. In the same manner (2R,10R)-6 yielded (2R,6S,8R)-1, n_D^{24} 1.4463; $[\alpha]_D^{24}$ +51.7° (c=1.72, n-pentane). Its chromatographic and spectral data coincided with those of (2S,6R,8S)-1.

The third stereoisomer was prepared from (2S,10R)-6. In this case we obtained a racemic mixture of (2S,6S,8R)-1 and (2R,6R,8S)-1, n_D^{24} 1.4555; $[\alpha]_D^{24}$ ±0.00° (c=1.87, n-pentane); ^{1}H-nmr: δ(60MHz, $CDCl_3$) 1.08 (3H,d,J=6Hz), 1.09 (3H,d,J=6Hz), 1.3-2.0 (12H,br), ~3.3-~3.8 (1H,m), ~3.8-~4.3 (1H,m); ^{13}C-nmr: δ(25.05 MHz, $CDCl_3$) 18.9, 20.2, 22.3, 22.6, 29.7, 33.1, 34.0, 36.9, 66.9 (C-C-O), 69.4 (C-C-O), 98.3 (O-C-O); glc (column, CF96-CR19, 40mx0.28mm at 70-220° (3°/min); carrier gas, N_2, 1.0kg/cm^2):Rt 29.66min (100% purity).[11] The lack of a C_2-axis of symmetry in this isomer was clearly shown by its eleven-line ^{13}C-nmr spectrum.

In conclusion all the energetically possible stereoisomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane were synthesized. The optical resolution of the racemic mixture of (2S,6S,8R)-1 and (2R,6R,8S)-1 remains to be achieved.[cf.12] The biological activity of these spiroketal stereoisomers will be tested later by our European colleagues.

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11. ν_{max} 2950(s), 2870(m), 1440(m), 1385(m), 1370(m), 1350(w), 1330(w), 1275(w), 1260(w), 1230(s), 1210(m), 1195(w), 1180(w), 1160(w), 1140(m). 1120(w), 1085(s), 1060(w), 1050(m), 1030(m), 1005(s), 990(m), 970(m), 945(w), 915(w), 895(w), 870(w), 850(w), 840(w), 830(w), 810(w), 780(w)cm^{-1}; ms : m/e 69(56%), 97 (60%), 112(55%), 114(37%), 115(100%,base peak), 125(12%), 140(8%), 169(7%), 184(15%=M$^+$).
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