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SYNTHESIS OF OPTICALLY ACTIVE 2S-, AND 7S-METHYL-1.6-DIOXA-SPIRO[4.5]DECANE, THE PHEROMONE COMPONENTS OF *PARAVESPULA VULGARIS* (*L.*), FROM *S*-ETHYL LACTATE.

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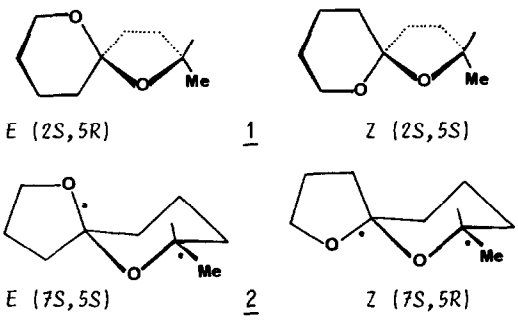
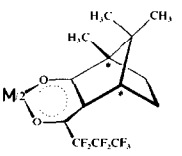
Summary *(-)-2S,5RS-1 and (-)-7S,5S-2 are obtained from S-ethyl lactate 4 and their absolute configuration is thus directly correlated. Accurate enantiomeric compositions of intermediates and products were measured by complexation gas chromatography on nickel-, and manganese-bis-3-heptafluorobutyryl-1R-camphorate, 3. It could be conclusively established that the syntheses proceed with a high degree of preservation of configuration.*

E,Z-Mixtures of the methyl-1.6-dioxaspiro[4.5]decanes 1 and 2 have been identified in the pheromone bouquet of workers of the common wasp *Paravespula vulgaris* (*L.*) by FRANCKE *et al.*[1]. The diastereomers of 1 and 2 are chiral. The importance of molecular configuration - including optical isomerism - in pheromone perception is now well appreciated [2]. We have recently carried out the first quantitative enantiomer resolution of the spiroketal pheromone 2-ethyl-1.6-dioxaspiro[4.4]nonane by complexation gas chromatography on an optically active metal chelate [3]. The method is well suited to determine exact enantiomeric compositions of natural and synthetic material since only minute amounts of unpurified and underivatized sample are required for analysis *via* head-space technique. Here we wish to report on the quantitative analytical enantiomer resolution of the diastereomers of 1 and 2 and on the synthesis and configurational composition of optically active 2S,5RS-1 and 7S,5S-2 obtained from the common precursor *S*-ethyl lactate 4.



E (2S,5R) 1 *Z* (2S,5S)

E (7S,5S) 2 *Z* (7S,5R)



3a M = Mn(II)

3b M = Ni(II)

We previously proved [3a] that alkylation [4] of α-acetyl-γ-butyrolactone dianion [5] with chiral oxiranes to yield 2-alkyl-1.6-dioxaspiro[4.4]nonanes *acc. to MORI et al.* [4] is not accompanied by racemization. Therefore, 2S-1 has been prepared by alkylation of α-acetyl-δ-valerolactone [6] dianion, 8, with *S*-methyl oxirane, 7, obtained from *S*-ethyl lactate, 4 (ee 97.6% [7]) (*Scheme 1*).

The enantiomeric pairs of racemic *E*- and *Z*-1 can be quantitatively resolved by complexation chromatography on manganese-*bis*-3-heptafluorobutyryl-1R-camphorate 3a in squalane (*Fig. 1, top*).

In the chromatogram of optically active 2S-labeled 1 (*Fig. 1, middle*) the central peaks have vanished to an extent of 2.4% (*Fig. 2*), thus establishing an enantiomeric purity of ee 95.2% for E,Z-2S-1. The enantiomeric purity of the intermediate S-methyl oxirane 7 has been determined on the chiral phase 1R-3b to ee 95.9%. Thus, the exact data (± 0.5%) obtained for enantiomeric compositions by glc clearly show that the overall synthesis starting from S-4 (ee 97.6% [7]) proceeds with a high degree of preservation of configuration.

For peak assignment the 2S-labeled E,Z-diastereomers of 1 were quantitatively separated by preparative glc [8]. The first fraction proved identical with that of the first eluting major isomer (65%) in *Fig. 1, middle*. From its ^{1}H-nmr it is assigned E configuration based on the observation of a greater downfield shift of the CH_3 resonances with the paramagnetic complexing agent $Eu(fod)_3$, as compared to that for the sterically more hindered minor isomer Z (35%). This conclusion is confirmed by a recent nmr assignment given by FRANCKE *et al.*[9]. Thus, the order of peak emergence of 1 on 1R-3a is E(2S,5R< 2R,5S) < Z(2R,5R < 2S,5S). The separated diastereomers E,Z-2S-1 undergo epimerization at 5°C (neat) within a few days. Monitoring the altering configurational composition of E(2S,5R)-1 by complexation chromatography on 1R-3a (*Fig. 1, bottom*) showed that racemization occured solely at the spiro center of chirality - as expected.

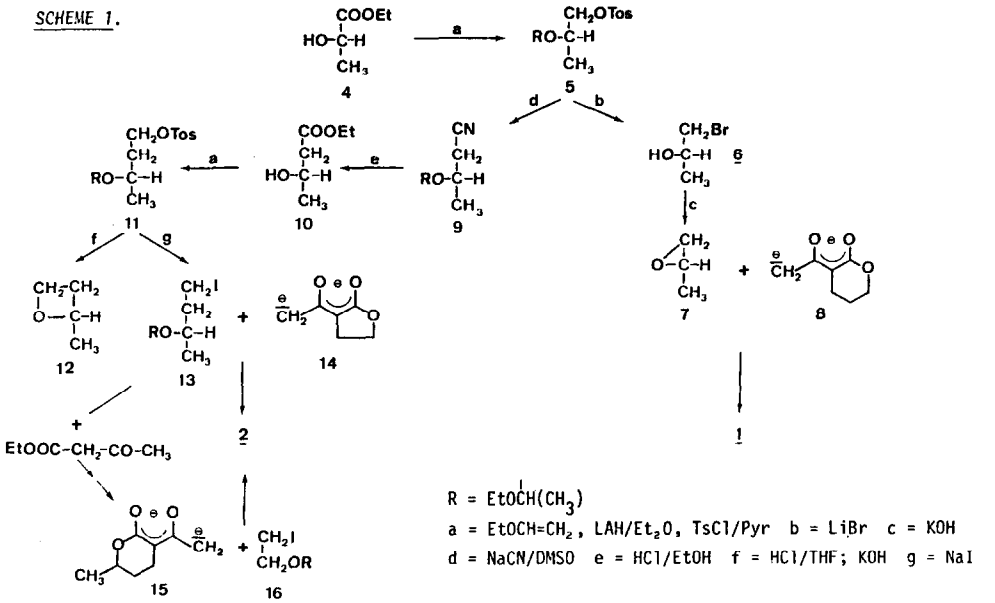
For the synthesis of 7S-2 it was considered useful to start from the same 'chiral pool', *i.e.* from S-ethyl lactate, 4. Acc. to *Scheme 1* 4 (ee 97.6% [7]) has been transferred *via* chain extension to ethyl S-3-hydroxybutanoate, 10 [10], which after protection, LAH reduction and tosylation was cyclisized to S-2-methyl oxetane, 12. From its enantiomeric purity, determined on 1R-3a, it can be concluded that the key-intermediate S-10 had at least the same purity, *i.e.*, ee 95.1% [11]. Only low chemical yields of 7S-2 were observed upon alkylation of α-acetyl-γ-butyrolactone [6] dianion [5] 14 with either S-methyl oxetane 12 or with the tosylate S-11, however, 34% of 7S-2 were obtained upon alkylation of 14 with R-protected S-1-iodo-3-hydroxybutane 13 (*Scheme 1*).

Racemic 2 may be resolved on the chiral phase 1R-3awith some difficulty in 65 h (*Fig.3, top*). Only one enantiomeric pair is observed. The same chromatogram is obtained for 2 prepared by the *inverse* route, *i.e.*, upon alkylation of α-acetyl-γ-methyl-δ-valerolactone [12] dianion [5], 15, with R-protected 1-hydroxy-2-iodoethane, 16 (*Scheme 1*). Obviously, only one diastereomer is formed during both reactions and/or is stable at ambient conditions. This observation may be rationalized by a strong conformational stabilization of the E configuration in which the methyl group attains an equatorial position whereas the oxygen atom of the neighboring ring occupies an axial site (*anomeric effect*). Very recently, FRANCKE *et al.* [9] using a different synthetic route for racemic 2 also observed the preferential formation of one diastereomer which was assigned E by nmr evidence. However, small amounts of Z isomer, detected by glc-ms, were also reported.

In the chromatogram of optically active 7S-2 (*Fig. 3, bottom*) again only one diastereomer is observed. Its absolute configuration is assigned E(7S,5S) and its enantiomeric purity is ee >95% (*Fig. 3, bottom*). By comparison with ee of the side-product S-2-methyl oxetane (ee 95.1%) and of the starting material S-ethyl lactate (ee 97.6% [7]) it can be concluded that alkylation of 14 by S-13 does not lead to racemization within experimental error (± 1.0%).

For the synthesis of the antipodes 2R-1 and 7R-2 the precursor R-7 may be conveniently obtained from S-alanine [13] and R-13 from 2R,3R-allothreonine [10], respectively.

SCHEME 1.



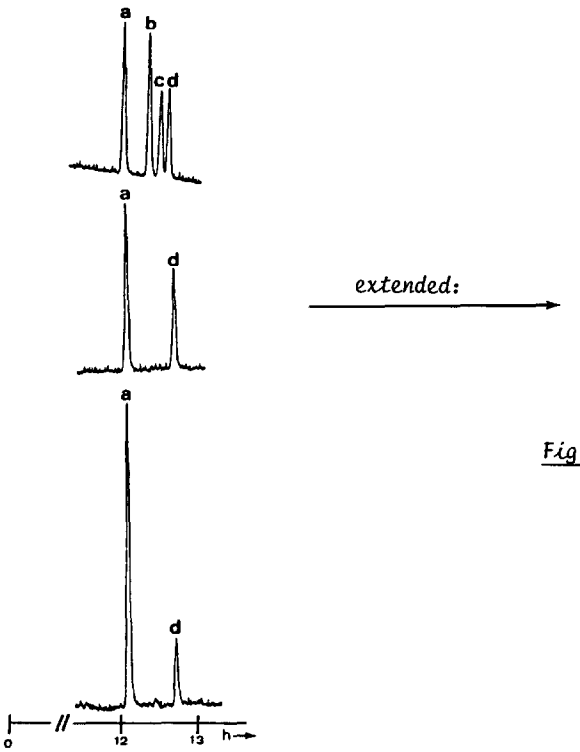


Fig. 1. Enantiomer resolution of 1 on 3 (0.13 *m* in squalane) at 50°C (160 m x 0.4 mm stainless steel capillary, split: 1:50, 1.7 cc N_2/min)
top : racemic mixture of E- and Z-1
middle: optically active E- and Z-2S-1
bottom: 2S,5R-1 (prep glc) after epimerization
Peak assignment: a 2S,5R b 2R,5S c 2R,5R d 2S,5S

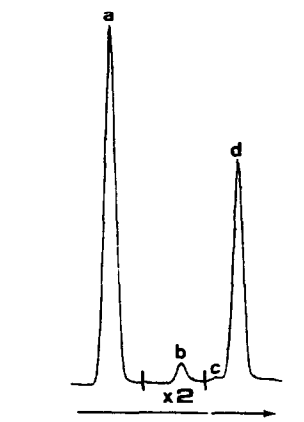


Fig. 2. Determination of ee of 2S,5R-1
(*Conditions see Fig. 1.*)

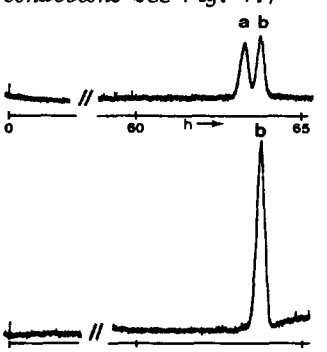


Fig. 3. Enantiomer resolution of 2 on 3 (0.13 *m* in squalane) at 30°C (*Column see Fig. 1.*)
top: racemic E-2 *bottom*: optically active E-7S-2. Peak assignment: a 7R,5R b 7S,5S

Experimental

Preparation of *2S,5RS*-1: 1.2g (20 mmol) *S*-methyl oxirane (ee 95.9%) prepared[13,14] from *S*-ethyl lactate (ee 97.6%[7]) was reacted[4] with the dianion of 3g (20 mmol) α-acetyl-δ-valerolactone[6] to yield 0.8g (26%) *2S,5RS*-1 (bp 100°C/60mm) ee 95.2% (*E* isomer) $[\alpha]_D^{20}$=-10.2° (*E*=65%,*Z*=35%), 1dm c=3, MeOH). MS[15]: M^+ 156(*15%*) 141(*6%*) 128(*7%*) 117(*17%*) 116(*14%*) 101(*100%*) 98(*50%*) 83(*42%*), ^{13}C-NMR (*$CHCl_3$*):105.2,105.1,76.1,73.8,61.4,38.8,37.6,34.1,31.3,25.3,25.2,23.6,21.1,20.2 *ppm*.

Preparation of *7S,5S*-2: 9.3g (70 mmol) ethyl *S*-3-hydroxybutanoate $[\alpha]_D^{20}$=41.7°(c=1, $CHCl_3$) α_D^{20}= 16.6°(neat)[11] prepared from *S*-ethyl lactate[10] (ee 97.6%[7]) was protected[14] with 30cc $EtOCH=CH_2$/ 2cc CF_3COOH (18h,-3°C) to give 13.3g (93%) acetal (bp 94°C/12mm). 12.5g (61 mmol) acetal was reduced with 2.7g LAH in 200cc Et_2O (5h,33°C) to yield 8.7g (88%) alcohol (bp 59°C,0.7mm) which was treated with 10.2g TsCl in 35cc Pyr/60cc CH_2Cl_2 (12h,-10° to 22°C) to give 14g (83%) *S*-11. This was converted in the dark with 14g NaI in acetone (18h, 40°C)[14] to 9.8g (81%) *S*-13 (bp 41° C, 0.05mm) $[\alpha]_D^{20}$=42.8° (c=1, $CHCl_3$) α_D^{20}=57.1°(neat). 9.8g (36 mmol) *S*-13 was reacted[4] with the dianion of 4.8g (38 mmol) α-acetyl-γ-butyrolactone[6]. The mixture was hydrolized (10cc HCl) and decarboxylated (80cc THF/20cc dil HCl) to give 2g (34%) *7S,5S*-2 (bp 60°C/13mm) ee>95% $[\alpha]_D^{20}$=-67.0° (c=3, 1dm, MeOH) α_D^{20}=-78.2°(neat). MS [15]: 156(*9%*) 115(*11%*) 112(*20%*) 97(*26%*) 87(*100%*) 84(*87%*), ^{13}C-NMR (*$CDCl_3$*): 105.8,66.5,37.8,32.5,23.6,21.8,20.3 *ppm*.

Acknowledgment

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References and Notes

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10 experimental data will be published elsewhere

11 Bakers yeast reduction of ethyl 3-oxobutanoate yielded *S*-10, $[\alpha]_D^{20}$=39.5° ($[\alpha]_D^{20}$=36.5°[14]) (c=1.2, $CHCl_3$) leading to *S*-12 with ee 89.2% as determined on *1R*-3a.

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