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SYNTHESIS OF THE ENANTIOMERS OF 1,7-DIOXASPIRO[5.5]UNDECANE AND 4-HYDROXY 1,7-DIOXASPIRO[5.5]UNDECANE, THE COMPONENTS OF THE OLIVE FLY PHEROMONE

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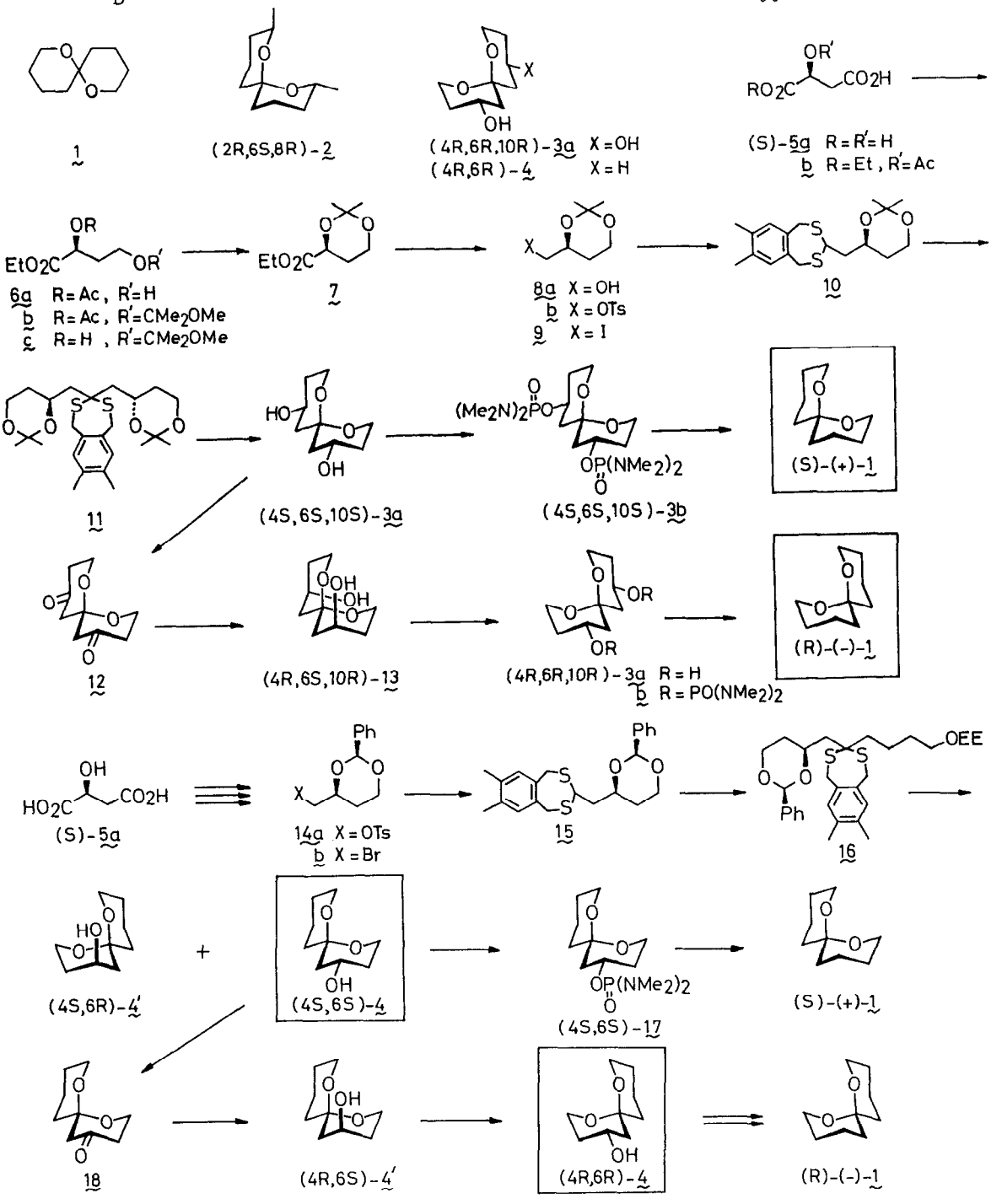
Summary: The enantiomers of the olive fly pheromone (1 and 4) were synthesized from (S)-malic acid in amounts sufficient for the biological test.

The major component of the sex pheromone of the olive fly (Dacus oleae Gmelin) was shown to be 1,7-dioxaspiro[5.5]undecane 1 by Baker, Francke and their co-workers.[2,3] The proposed structure 1 was confirmed by the synthesis of its racemate.[2,4] Nothing was known, however, concerning the absolute configuration of the pheromone. We therefore became interested in synthesizing both the enantiomers of 1 so as to provide reference samples for the determination of the stereochemistry of the natural pheromone.[5]

1,7-Dioxaspiro[5.5]undecane 1 is the proto-type of several spiroacetals isolated as natural products. In the case of the synthesis of substituted spiroacetals such as 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane 2,[6] its stable conformation is that which is depicted in the formula 2 with two equatorial Me groups. The absolute configuration of the spiro carbon atom is fixed due to the oxygen anomeric effect.[7] It therefore should be possible to synthesize the enantiomers of 1, if we can temporarily attach substituents on the tetrahydropyranyl rings to control the stereochemistry at the spiro center. The substituents must be removable in a later stage without any damage on the enantiomeric purity at the spiro center. As such a substituent, we chose an OH group, whose reductive removal is a well-established process. Consequently 3a or 4 was the key-intermediate in the present two syntheses. The latter, 4-hydroxy-1,7-dioxaspiro[5.5]undecane 4, is a minor component of the olive fly pheromone.[8] Three syntheses of (±)-4 were already reported.[8-10]

The known (S)-5b,[11] prepared from (S)-(-)-malic acid 5a, was reduced with B_2H_6 to afford 6a (84%), $[\alpha]_D^{20.8}$ -52.3° (c=2.3, EtOH). Protection of the primary OH group was effected with methoxypropene and PPTS to give 6b (90%). Treatment of 6b with NaOEt/EtOH gave 6c (94%), which was isomerized to 7 by the addition of a small amount of $BF_3 \cdot OEt_2$ in ether. Reduction of 7 with LAH in ether yielded 8a (82%), whose tosylation gave crystalline 8b (93%), mp 57.5-59°; $[\alpha]_D^{22}$ +1.7° (c=1.2, $CHCl_3$). This gave an iodide 9 (92%) upon treatment with NaI in acetone in the presence of $NaHCO_3$. Alkylation of 7,8-

dimethyl-1,5-dihydro-2,4-benzodithiepin[12] with 9 using n-BuLi as the base gave 10 (60%). Further alkylation of 10 with 9 (n-BuLi/THF) gave 11 (55%). Treatment of 11 with $CuCl_2 \cdot 2H_2O$ and CuO in Me_2CO-H_2O (99:1) under reflux[13] gave, as a single product, the key-intermediate (4S,6S,10S)-3a (87%), mp 153-154°; $[\alpha]_D^{21.5}$ +121.4° (c=0.5, acetone). The depicted strucure 3a was confirmed



by an X-ray analysis. The structure was solved by MULTAN 11/82 with final agreement values of R=0.033 and R_w=0.051.[14] The ORTEP computer drawing[14] of (4S,6S,10S)-3a and the known (S)-configuration at C-4 and C-10 enabled us to assign (S)-configuration to C-6. In order to remove the two OH groups, (4S,6S,10S)-3a was first treated with n-BuLi and $(Me_2N)_2POCl$(THF-TMEDA)[15] to give (4S,6S,10S)-3b (81%). Reduction of 3b with Li/$EtNH_2$-t-BuOH-THF[15] gave (S)-1 (74mg, 73%), $[\alpha]_D^{23}$+109.3° (c=0.28, n-pentane).

For the synthesis of (R)-1, we took advantage of the acid-catalyzed isomerization of (4R,6S,10R)-13 to (4R,6R,10R)-3a as described below. Oxidation of (4S,6S,10S)-3a with pyridinium chlorochromate[16] gave 12 (86%), mp 146.5°; $[\alpha]_D^{22}$+203.4° (c=1.0, $CHCl_3$). This was reduced with LiB(sec-Bu)$_3$H and worked up under alkaline condition to give (4R.6S,10R)-13 (58%), mp 57-61°; $[\alpha]_D^{23}$+ 111.1° (c=0.38, $CHCl_3$). The depicted structure 13 with two axial OH groups was supported by an X-ray analysis.[14] When 13 was treated with dil HCl in THF or when the reaction mixture after reduction of 12 with LiB(sec-Bu)$_3$H was worked up under acid condition (pH 3), (4R,6R,10R)-3a, mp 150-151° $[\alpha]_D^{23}$-121.7° (c=0.5, acetone), was obtained in 60% yield. Under the acid condition, the unstable 13 isomerized to the more stable[7] 3a. We are thus able to prepare both the enantiomers of 3a starting from the natural and more abundant enantiomer of malic acid. Deoxygenation of (4R,6R,10R)-3a proceeded via (4R,6R,10R)-3b (79.5 %) to give (R)-1 (47mg, 51%), $[\alpha]_D^{21}$-121.6° (c=0.1, n-pentane). The ^{1}H- and ^{13}C-NMR data of both (R)- and (S)-1 were in good accord with the published data.[2] The MS of (R)- and (S)-1 coincided with the authentic spectrum kindly provided by Dr. T.E. Bellas.[3]

In our second synthesis of 1, we employed 4 as the key-intermediate. The known 14a[17] was treated with LiBr/DMF to give 14b (97% yield). Alkylation of 7,8-dimethyl-1,5-dihydro-2,4-benzodithiepin[12] with 14b (n-BuLi/THF) gave 15 (83%), mp 146-147°; $[\alpha]_D^{20}$+69.2° (c=0.64, $CHCl_3$). Further alkylation of 15 with tetramethylene iodohydrin EE ether (n-BuLi/THF) yielded 16 (83%). Treatment of 16 with $CuCl_2 \cdot 2H_2O$ and CuO in Me_2CO-H_2O (10:1) gave a mixture of (4S,6S)-4 and (4S,6R)-4'. Complete separation of the mixture was effected by SiO_2 chromatography to give (4S,6S)-4 (79.3%), bp 82-84°/0.35mm; n_D^{20} 1.4830; $[\alpha]_D^{20}$+120° (c=2.61, n-pentane), and (4S,6R)-4' (7.1%), $[\alpha]_D^{20}$-120° (c=4.26, n-pentane).[18] Phosphorylation of (4S,6S)-4 with n-BuLi and $(Me_2N)_2POCl$ in DME-TMEDA gave (4S, 6S)-17 (88%). This was reduced with Li and $EtNH_2$-t-BuOH-THF to give (S)-1 (392mg, 64%), bp 76-80°/30mm; n_D^{21} 1.4592; $[\alpha]_D^{21}$+119° (c=1.41, n-pentane).[18]

Conversion of (4S,6S)-4 to (R)-1 was executed as follows. Oxidation of (4S,6S)-4 with pyridinium chlorochromate and NaOAc in CH_2Cl_2 gave 18 (82%), mp 69.0-70.0°; $[\alpha]_D^{18}$+140° (c=1.24, MeOH). This was reduced with LiB(sec-Bu)$_3$H in THF to (4R, 6S)-4' (71%), $[\alpha]_D^{20}$+121° (c=4.44, n-pentane). Treatment of (4R, 6S)-4' with a trace amount of p-TsOH in MeOH caused equilibration, and besides 7.3% of the recovered (4R,6S)-4', (4R,6R)-4 (88%), bp 79-81°/0.25mm; n_D^{20}1.4822; $[\alpha]_D^{20}$-116° (c=2.41, n-pentane), was obtained. Reductive removal of the OH group of (4R,6R)-4 was carried out as described for its antipode to give (R)-

1 [40lmg, 61.5% from (4R,6R)-4], bp 74-83°/33mm; n_D^{21}1.4589; $[\alpha]_D^{21}$-121° (c= 1.84, n-pentane)[19]

The bioassay of the enantiomers of 1 is now under way by Dr.G. Haniotakis, Greek Atomic Energy Commission.

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19) The optical purities of (R)-1 and (S)-1 obtained by the second route were kindly estimated by Prof. V. Schurig (Universität Tübingen) using his complexation glc technique and shown to be >99.5 and 92%, respectively.

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