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SYNTHESIS OF OPTICALLY ACTIVE 2-ETHYL-1,6-DIOXASPIRO[4.4]NONANE (CHALCOGRAN), THE PRINCIPAL AGGREGATION PHEROMONE OF PITYOGENES CHALCOGRAPHUS (L.)+

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(2*R*, 5*RS*)- and (2*S*, 5*RS*)-ethyl-1,6-dioxaspiro[4.4]nonanes (chalcograns) were synthesized in a simple manner by applying the recent technique of dianion chemistry.

Recently a diastereomeric mixture (1 : 1) of an interesting spiro-ketal was isolated as the principal aggregation pheromone of "Kupferstecher," *Pityogenes chalcographus* (L.), a pest of Norway spruce.[1] The proposed structure, 2-ethyl-1,6-dioxaspiro

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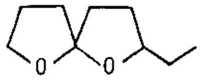
+ This paper is dedicated to Prof. Dr. A. Butenandt on the occasion of his 75th birthday.



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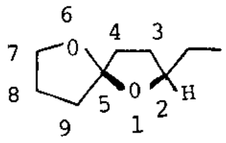
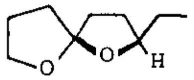


(2R, 5R)-1



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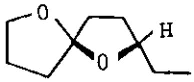
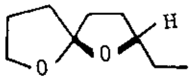
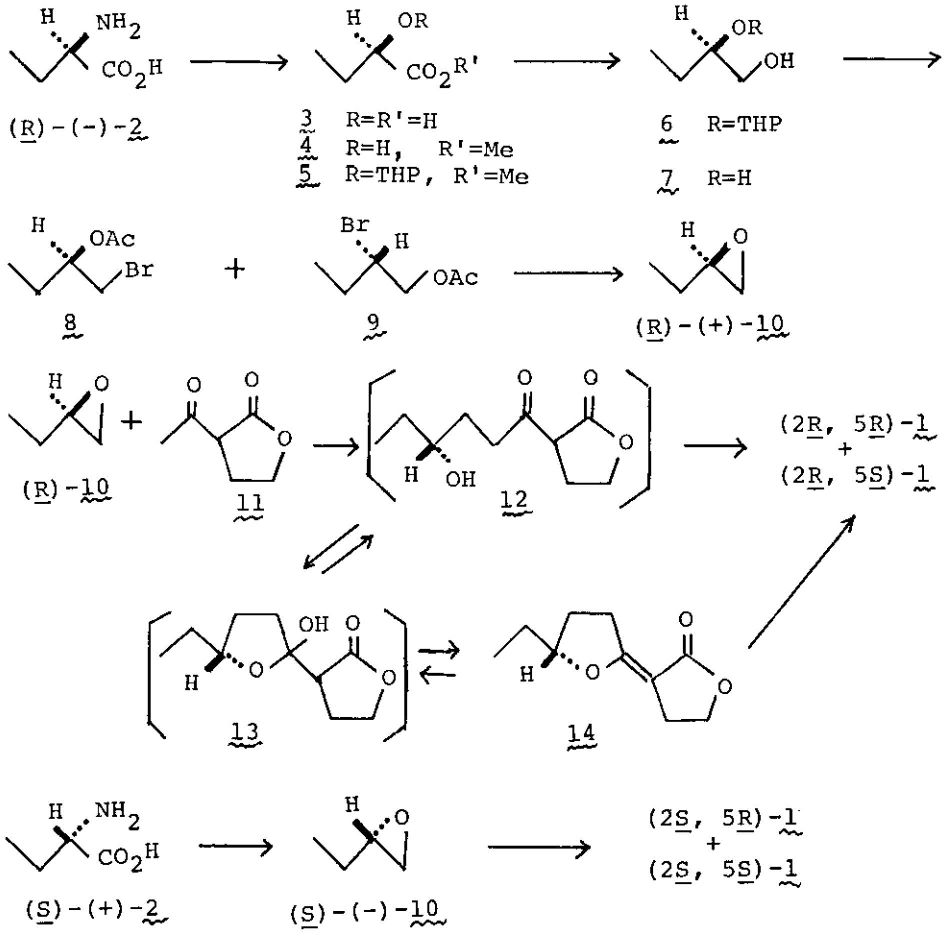


(2S, 5R)-1



(2S, 5S)-1



[4.4] nonane **1**, was confirmed by the synthesis of the racemic mixture of the two pairs of diastereomers.[1] Nothing is known about the absolute configuration at C-2 of the natural pheromone. Our results on other ketal pheromones such as *exo*-brevicomin[2] and frontalin[3] strongly suggest the importance of chirality in pheromone perception.[4] In both cases only one enantiomer was biologically active. We therefore attempted the synthesis of optically active chalcogran with fixed stereochemistry at C-2, and obtained the two pairs of optically active diastereomers, (2*R*, 5*R*)-**1**+(2*R*, 5*S*)-**1** and (2*S*, 5*R*)-**1**+(2*S*, 5*S*)-**1** as described below. The key step in the present synthesis was the alkylation of the dianion of α-acetyl-γ-butyrolactone **11** with a chiral epoxide, (*R*)-or (*S*)-**10**.

(*R*)-(-)-α-Amino-*n*-butyric acid **2** was treated with HNO_2 to give (*R*)-α-hydroxy-*n*-butyric acid **3** which was isolated after CH_2N_2 treatment as the methyl ester **4**, bp 73~75°C/33mm, n_D^{21} 1.4155; $[\alpha]_D^{21}$ + 5.12° (neat). The optical purity of **4** was estimated to be >98% by the MTPA ester method.[5] The corresponding tetrahydropyranyl (THP) ether **5**, bp 78~83°C/3 mm, n_D^{21} 1.4155; $[\alpha]_D^{21}$ + 77.1° (c=3.4, ether), was prepared in the usual manner. This was reduced with $LiAlH_4$ to give an alcohol **6**, whose methanolysis (MeOH-*p*-TsOH) gave (*R*)-(+)-1,2-butanediol **7**, bp 90~95°C/6mm, n_D^{21} 1.4320; $[\alpha]_D^{21}$ + 12.4° (c=2.1, EtOH) [lit.[6] $[\alpha]_D^{22}$ + 12.4° (c=16.1, EtOH)], in 50% overall yield from **4**. Conversion of **7** to the chiral epoxide **10** was carried out according to the general method of Golding *et al.*[7] Thus **7** was treated with HBr-AcOH to give a mixture of **8** and **9**, bp 85~86°C/25 mm, n_D^{21} 1.4476; $[\alpha]_D^{21}$ + 21.0°

(c=2, ether). This was heated with KOH aq soln to give (*R*)-(+)-1,2-epoxybutane **10**, bp 61~63°C, n_D^{21} 1.3865; $[\alpha]_D^{21}$ + 13.6° (c=1.1, ether); ν_{max} 905, 835 cm^{-1} ; δ(60MHz) 0.99 (3H, t, J=7Hz), 1.46 (2H, q, J=7Hz), 2.22~2.90 (3H, m).

The alkylation of the dianion of **11** generated by NaH and *n*-BuLi[8] was first studied with (±)-**10** and yielded (±)-**14** in 45% yield, bp 134~136°C/1 mm, n_D^{21} 1.5139; ν_{max} 1740, 1675 cm^{-1}; δ (60 MHz) 1.00 (3H, t, J=7Hz), 1.64 (2H, q, J=7Hz), 1.6~2.5 (2H, m), 2.55~3.6 (4H, m), 4.21 (2H, t, J=7Hz), ~4.5 (1H, m); MS: m/e 182 (M^+). This was presumably derived from **12** via **13**. The compounds **12**, **13** and **14** were thought to be in equilibrium under acidic condition, since the acid hydrolysis of **14** (conc HCl, 70°, 1 hr) afforded a racemic mixture of the two pairs of diastereomers of chalcogran **1** in 70% yield. In order to increase the yield of the final product, the following procedure was adopted for the synthesis of the optically active pheromone. The reaction of (*R*)-(+)-**10** with the dianion of **11** (0°, 1 hr; 25°, 1hr) generated by NaH and *n*-BuLi in THF-HMPA (3 : 1) gave **12** which was hydrolyzed and decarboxylated ($Ba(OH)_2$ aq soln, reflux, 16 hr). Acidification of the reaction mixture with conc HCl yielded crude **1**. This was distilled to give a diastereomeric mixture of (2*R*, 5*R*)-**1** and (2*R*, 5*S*)-**1** in 39.4% yield (615 mg), bp 176~182°C, n_D^{22} 1.4426; $[\alpha]_D^{22}$ + 16.74° (neat) ; ν_{max} 2960 (s), 2920 (sh), 2870 (s), 1460 (m), 1440 (w), 1380 (w), 1345 (m), 1295 (w), 1245 (w), 1210 (w), 1175 (m), 1155 (m), 1115 (m), 1080 (m), 1060 (m), 1045 (s), 1015 (s), 1000 (sh), 950 (m), 925 (m), 915 (m), 860 (m), 830 (w), 780 (w) cm^{-1} ; δ(100 MHz) 0.90 (3H, t, J=7Hz), 1.14~1.66 (~3H, m), 1.66~2.20 (~7H, m), 3.56~4.02 (3H, m); MS : m/e 156.1133 ($M^+= C_9H_{16}O_2$). Similarly (S)-10, n_D^{22} 1.3822; $[\alpha]_D^{22}$ -13.7° (c=1.48, ether), was prepared from (S)-(+)-2 and treated with the dianion of 11 to give, after subsequent manipulation, a diastereomeric mixture of (2S, 5R)-1 and (2S, 5S)-1 in 30.1% yield, (651 mg), n_D^{21} 1.4436; $[\alpha]_D^{22}$ -15.92° (neat).

The diastereomeric composition of our products was determined by GLC (column : PEG 20M, 50m x 0.25 mm at 60°; carrier gas : N_2, 1.2 kg/cm^2). The (2R)-mixture consisted of 40.1% of the minor (Rt 50.0 min) and 59.9% of the major (Rt 52.7 min) isomers, while the (2S)-mixture was of 41.3% of the minor and 58.7% of the major isomers. Since the natural pheromone itself was a diastereomeric mixture, no attempt was made to separate our mixture. It should be added that a very recent publication of Silverstein et al[9] enabled the assignment of the (2R, 5R)-or (2S, 5S)-stereochemistry to the major isomers.

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