*Short Communication*

# Preparation of the Four Stereoisomers of Chalcogran, Pheromone Components of *Pityogenes chalcographus* and of Both Enantiomers of γ-Caprolactone, Pheromone Component of *Trogoderma granarium*

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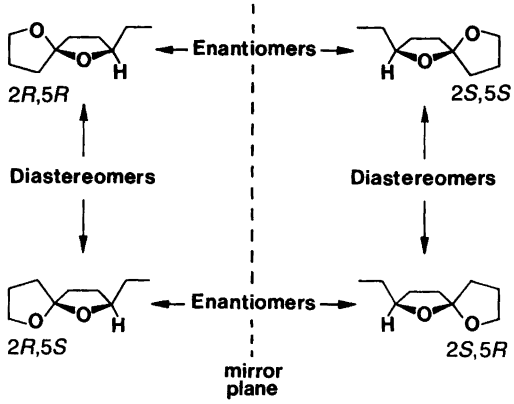
The spiroketal chalcogran (**1**) is a pheromone component[1] of the bark beetle *Pityogenes chalcographus (L.)* which is a pest on Norway spruce (*Picea abies, L.*). The diastereomeric (2*S*, 5*R*/*S*)-**1** mixture has been isolated from the beetle.[2]




Chalcogran (**1**)

For complete elucidation of the biological effects of chalcogran it is important to have access to all four possible stereoisomers in pure form. Syntheses of mixtures of the racemic diastereomers have been reported,[3] as well as syntheses of optically active mixtures of the diastereomers (2*S*,5*R*/*S*)-**1** or (2*R*,5*S*/*R*)-**1**.[4] There is one report of the synthesis of (2*R*,5*S*)-**1** and (2*R*, 5*R*)-**1** in reasonable diastereomeric purities (90/10 and 79/21) using preparative GLC to separate the diastereomeric mixture, (2*R*,5*S*/*R*)-**1**, initially formed.[4a]

Assignment of the stereochemistry at the 5-position (spiroketal linkage) has been made on the basis of NMR spectra of the racemic diastereomers separated by GLC.[4a,5]

The spiroketal linkage in the chalcogran diastereomers undergoes facile epimerisation in relatively non-polar solvents such as benzene, chloroform or ether.[4a,5] The lack of preparative procedures for obtaining the individual diastereomers can probably be ascribed to this fact. This problem also accounts for the uncertainty as to whether or not only one isomer is produced by the beetle.

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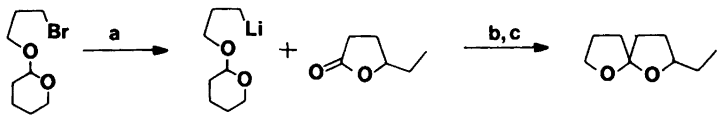


3 2 1

*Scheme 1.* (a) $Li/Et_2O$ −30 °C; (b) $Et_2O$, −80 °C, (c) $H_3O^+$.

The purpose of this work was to prepare the stereoisomers of chalcogran in purities high enough to evaluate the biological activity of each isomer.

The synthetic pathway we used (see Scheme 1) was similar to that of Smith *et al.*[3d] Two diastereomers of chalcogran (**1**) should thus be available from the alkyllithium formed from **3** and each of the enantiomers of γ-caprolactone (**2**). (*R*)-(+)-γ-caprolactone has been identified as a pheromone component of the beetle *Trogoderma granarium*,[6a] and both (*R*)- and (*S*)-γ-caprolactone have therefore been synthesized by several multistep routes.[6] A simple alternative would be direct resolution of the racemic lactone; to the best of our knowledge, no method for this has been reported. Our choice was liquid chromatography on a chiral stationary phase, triacetylcellulose (TAC), which has been used for the preparative resolution of various classes of racemic compounds.[7] The chromatography system has previously been described by one of us.[7d] Using this we were able to separate the racemic lactone into its enantiomers (*S*)-**2** (97 % ee) and (*R*)-**2** (90 % ee). Further purification of the latter enantiomer on TAC gave optically pure (*R*)-**2** [>99 % ee; $[\alpha]_D$ +53.2° (lit. +53.2°)[6a]].

Reacting according to Scheme 1, (*S*)- or (*R*)-γ-caprolactone (**2**) gave (2*S*,5*R*/*S*)- or (2*R*,5*R*/*S*)-chalcogran (**1**), respectively. The separation of the mixtures of diastereomers was achieved by repeated chromatography on silica gel using a gradient elution technique. All the isomers were prepared in the purities given in Table 1, as determined by capillary chromatography on a chiral stationary phase {Ni(II) bis[3-heptafluorobutyryl-1-(*R*)-camphorate][2,8] in SE-54}.

*Table 1.* Composition of the purified chalcogran isomers obtained from (*R*)- or (*S*)-γ-caprolactone (**2**) as judged by complexation gas chromatography.

| Compound | Composition/% | | | |
|---|---|---|---|---|
| | *SS* | *SR* | *RR* | *RS* |
| (2*S*,5*S*)-**1** | 97.0 | 1.0 | 2.0 | 0 |
| (2*S*,5*R*)-**1** | 2.1 | 96.2 | 0 | 1.7 |
| (2*R*,5*R*)-**1** | 3.8 | 0 | 95.3 | 0.9 |
| (2*R*,5*S*)-**1** | 0.3 | 5.2 | 3.2 | 91.3 |

Epimerisation could be prevented by storing the pure isomers in alkali-washed bottles in hexane or pentane solutions. After 1 year at −20 °C no epimerisation was observed.

The results of biological tests with the individual stereoisomers of chalcogran will be published elsewhere.

## Experimental

*(R)-4,5-dihydro-5-ethylfuran-2(3H)-one or (R)-(+)-γ-caprolactone* [(*R*)-**2**]. Methods for the preparation of the TAC and the columns, as well as the instrumental details, have been described elsewhere.[7d] *rac*-γ-Caprolactone was prepared according to the literature[9] and distilled (spinning band, b.p. 112.0 − 112.5 °C; GLC purity >99 %). The latter (0.1 g) was first dissolved in ethanol (95 %, 3 ml), the eluent, prior to injection on the columns. Owing to poor separation ($\alpha \approx 1.1$), a recycling technique was used. To avoid extreme band-broadening, the first part of the first eluted band (negative polarimeter response) and the last part of the second band (positive response) were collected after each cycle. After the fifth and last cycle the intermediate part of the overlapping bands was discarded. This procedure was repeated 9 times with 0.1 g of lactone in each run. The combined fractions with positive rotation were carefully concentrated to give an oil, which was distilled (bulb to bulb) to give (*R*)-**2** (350 mg); $[\alpha]_D^{20}$ +45.8° (neat), $[\alpha]_D^{20}$

+47.4° (*c* 1, MeOH) {lit.[6a] $[\alpha]_D^{20}$+53.2° (*c* 1, MeOH)}. From the optical rotation and the GLC behaviour of the chalcogran isomers produced from this lactone it is evident that its optical purity is 90±1 % (Table 1). Repeated chromatography of a small amount of (*R*)-**2** (90 % ee, 100 mg) furnished optically pure (*R*)-**2** (80 mg), $[\alpha]_D^{20}$ +53.2° (*c* 1.0, MeOH).

*(S)-4,5-dihydro-5-ethylfuran-2(3H)-one, or (S)-(-)-γ-caprolactone* [(*S*)-**2**]. The fractions with negative rotation from the 10 runs above were treated as above to give the (*S*)-lactone (290 mg); $[\alpha]_D^{20}$ −49.5° (neat), $[\alpha]_D^{20}$ −52.9° (*c* 1, MeOH) {lit. $[\alpha]_D^{20}$ −53.2° (*c* 1, MeOH)}. From the optical rotation this lactone should have a purity of >99 % ee. However, GLC (Table 1) of the chalcogran produced from this lactone indicated its optical purity to be 96.3±0.5 %.

*3-Lithio-1-propyl tetrahydropyranyl ether.* A mixture of 3-bromo-1-propanol (15.37 g, 0.11 mol), dihydropyran (11.3 g, 0.135 mol) and $POCl_3$ (1 drop) was stirred at 0 °C under argon for 1 h, after which the mixture was distilled to give **3** as a colourless oil (19.4 g, 79 %); b.p. 70–75 °C/1 mmHg. $^1$H NMR (60 MHz): δ 1.3–1.9 (6H, m), 2.17 (2H, quintet, *J*=7 Hz), 3.3–4.2 (4H, m), 3.53 (2H, t, *J*=7 Hz), 4.5–4.7 (1H, m) ppm. Anal. $C_8H_{15}O_2$ Br: C, H. To this bromoether (**3**) (2.10 g, 10 mmol) in dry ether (25 ml) under argon at −30 °C was added finely cut lithium (100 mg, 5 % Na) and the mixture was stirred at −30 °C until the lithium had reacted (2–3 h). The alkyllithium solution (40 % yield, 0.16 M by titration at −20 °C with 1-pentanol and a trace of 2,2′-bipyridyl in ether) was kept cool and used immediately in the next step.

*(2R,5R)- and (2R,5S)-2-Ethyl-1,6-dioxaspiro[4.4]nonane* [(2*R*,5*R*)- and (2*R*,5*S*)-**1**]. The alkyllithium from above (1.4 mmol) in ether at −50 °C was added to a stirred solution of (*R*)-(+)-γ-caprolactone (**2**; 155 mg, 1.36 mmol) in dry ether (5 ml) at −80 °C under argon. After 1 h at −80 °C the mixture was quenched at −50 °C by adding water (1 ml in 10 ml of THF). Hydrochloric acid (6M, 15 ml) was added at room temperature and the mixture stirred vigorously for 2 h. Work-up with ether gave an oil (0.3 g) which was chromatographed on silica gel (30 g) and eluted with pentane (200 ml) followed by pentane/dichloromethane [the latter freshly stirred with $Na_2CO_3$ (s) and distilled] (4:1) containing a gradually increasing concentration of ethyl acetate (from 0 % to 3 %) (total 1 l). 1–2 % ethyl acetate eluted first pure (2*R*,5*R*)-**1** (30 mg) {$[\alpha]_D^{25}$ −98 ± 4° (*c* 0.7, hexane); lit.[4a] $[\alpha]_D$ −76° (benzene)}, then (2*R*,5*R*/*S*)-**1** (30 mg) followed by slightly impure (2*R*,5*S*)-**1** (120 mg, 10/90 5*R*/*S*-ratio) (total yield of chalcogran 180 mg, 85 %). The latter fractions (120 mg) were rechromatographed as above to give mixed fractions (60 mg) and (2*R*,5*S*)-**1** (50 mg, 5*R*/*S* ratio 6/94) as well as some (2*R*,5*S*)-**1** of higher purity (10 mg, 5*R*/*S* ratio 3/97) {$[\alpha]_D^{25}$ +98 ± 7° (*c* 0.7, hexane); lit.[4a] $[\alpha]_D^{25}$ +62° (benzene)}. The separation of the diastereomers by LC was conveniently followed by capillary GLC: Fused silica column (25 m × 0.5 mm i.d.) coated with cross-linked SE-54, $d_f$ = 0.52 μm; Carrier gas $N_2$, μ = 10 cm/s; split 15/1; Temp. progr.: 70 °C, 8′, 8 °C $min^{-1}$ to 150 °C; retention time: (2*R*,5*R*)-**1**, 14.4 min; (2*R*,5*S*)-**1**, 14.6 min.

*(2S,5R)- and (2S,5S)-2-Ethyl-1,6-dioxaspiro[4.4]nonane* [(2*S*,5*R*)- and (2*S*,5*S*)-**1**]. In a similar manner, (*S*)-2-caprolactone [(*S*)-**2**] gave chalcogran (**1**) (150 mg, 71 %). After the first chromatographic separation (2*S*,5*S*)-**1** was obtained (25 mg, diastereomeric ratio 99/1) {$[\alpha]_D^{25}$ +96 ± 2° (*c* 1, hexane)} and after the second (2*S*,5*R*)-**1** was obtained (20 mg, diastereomeric ratio 98/2) {$[\alpha]_D^{25}$ −100 ± 3° (*c* 0.3, hexane)}.

*Determination of the purity of each of the four isomers of chalcogran.* Analysis was performed on a fused silica column (25 m × 0.25 mm i.d.) coated with Chirametal Ni(II) bis[3-heptafluorobutyryl-1(*R*)-camphorate] in SE-54 (purchased from CC and CC, Postfach 14 D, Kirchentellinsfurt, Tübingen, BRD). 90 °C isothermal, carrier gas $N_2$, 7 psi, μ = 14 cm $s^{-1}$, split 40/1. α-values: (2*S*,5*S*)-**1**, 1; (2*R*,5*R*)-**1**, 1.06; (2*R*,5*S*)-**1**, 1.52; (2*S*,5*R*)-**1**, 1.77. Base-line separation between all the peaks was observed. The results are given in Table 1.

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