## Synthesis of the Enantiomeric Forms of 4-Hexanolide (γ-Caprolactone) from the Optically Active 5-Phenyl-4-pentene-2,3-diol Prepared from Cinnamaldehyde and Baker's Yeast

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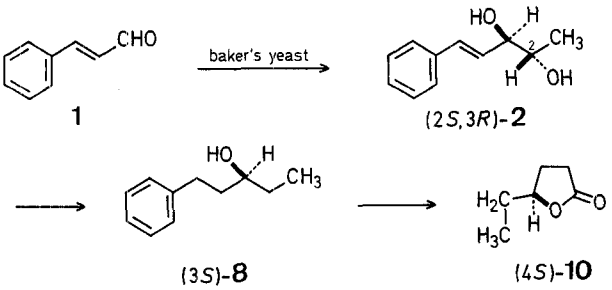
The preparation of the optically active forms of insect pheromone components by resolution of synthetic racemic mixtures is, in general, not feasible due to the nature of these compounds which usually are volatile oils and lack suitable functionalities[1]. Accordingly, several synthetic procedures have been worked out which lead from easily accessible chiral natural products to the optically active compounds[2]. The components of the "Chiral Pool"[3] used so far as starting materials include carbohydrates, amino acids, terpenes, and α-hydroxy acids[2].

The (*R*)-enantiomeric form of 4-hexanolide (**10**, γ-caprolactone) is the attractant pheromone of the *Trigoderma* species; both enantiomers have been prepared[4] from L- and D-glutamic acid. We report here the synthesis of the enantiomeric forms of **10** from (2*S*,3*R*)-5-phenyl-4-pentene-2,3-diol [(2*S*,3*R*)-**2**] which, in turn, is prepared[5] by fermentation of cinnamaldehyde (**1**) with baker's yeast.




The synthetic sequence leading from (2*S*,3*R*)-**2** to the lactone (4*S*)-**10** involves hydrogenation of **2** to the saturated diol (2*S*,3*R*-**3**) regioselective removal of the hydroxy group at C-2 of **3** to give (3*S*)-1-phenyl-3-pentanol [(3*S*)-**8**], and ozonolysis of this latter alcohol to give the $C_6$ lactone (4*S*)-**10** which at C-4 (ring atom 5) contains the chirality originally present at C-3 of the starting diol (2*S*,3*R*)-**2**.

In detail, diol (2*S*,3*R*)-**2** is hydrogenated to give the crystalline saturated diol (2*S*,3*R*)-**3** which is converted into an 8:2 mixture of the monotosylates (2*S*,3*R*)-**4** and (2*S*,3*R*)-**5** by treatment with 1 mol equiv tosyl chloride in pyridine/dichloromethane. The **4**:**5** ratio is increased to 9:1 by column chromatography of the product mixture on silica gel using ethyl acetate/hexane as eluent; preparative H.P.L.C. of the 8:2 product mixture affords pure (2*S*,3*R*)-**4** and a mixture of **4** and **5**. The structure **4** was assigned to the main product on the basis of its $^1$H-N.M.R. spectrum.

An attempt to remove the tosyloxy group at C-2 of **4** by treatment with sodium cyanoborohydride[7] in hexamethylphosphoric triamide gave the (2*R*,3*R*)-epoxide **7** as the sole product. However, reduction of **4** with lithium alanate in boiling ether affords a 65:35 mixture (by G.L.C. analysis) of the alcohols **8** and **9** in ~85% yield, thus supporting the intermediacy of epoxide **7** in the sequence. Compound (3*S*)-**8** is readily isolated from the mixture **8**+**9** by column chromatography on silica gel using ethyl acetate/hexane as eluent, and is submitted to ozonolysis to give, upon work-up of the ozonization mixture with hydrogen peroxide/formic acid, the desired lactone (4*S*)-**10**. Starting from a 9:1

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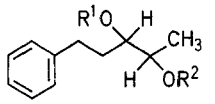
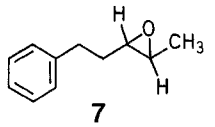
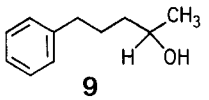
mixture of **4** and **5**, and conceivably proceeding through the 9:1 mixture of the (2*R*,3*R*) and (2*S*,3*S*) epoxides **7**, respectively, a sample of the 4-hexanolide was isolated by preparative G.L.C. and was shown on the basis of the optical rotation and comparison with the Ref. [5] value to contain ~90% of the (4*S*)-isomer of **10**.



**3** $R^1 = R^2 = H$
**4** $R^1 = H$ ; $R^2 = Tos$
**5** $R^1 = Tos$ ; $R^2 = H$
**6** $R^1 = R^2 = Tos$



**7**



**9**

The synthesis of (4*R*)-4-hexanolide [(4*R*)-**10**] should proceed analogous to that of (4*S*)-**10**, starting from the diol (2*R*,3*S*)-**3**. We prepared this latter diol from its enantiomer, (2*S*,3*R*)-**3**, by conversion into the ditosylate (2*S*,3*R*)-**6** which, upon benzoate displacement[8] followed by lithium alanate reduction gave (2*R*,3*S*)-**3**. This compound was identical in all respects with (2*S*,3*R*)-**3** but showed opposite optical rotation, its optical purity being 95%.

**(2*S*,3*R*)-5-Phenyl-4-pentene-2,3-diol [(2*S*,3*R*)-2]:**
To a stirred suspension of baker's yeast[9] (1 kg) in tap water (2000 ml) containing D-glucose (200 g), a solution of cinnamaldehyde (**1**; 30 g) in ethanol (50 ml) is added over 2 h at 20–30 °C. After a further hour, additional portions of yeast (500 g) and D-glucose (100 g) are added and stirring is continued overnight. The mixture is filtered through Celite® and the filtrate extracted with ethyl acetate/ethanol (9:1; 3 × 500 ml). The extract is dried with sodium sulfate, the solvent evaporated in vacuo, and the residue column-chromatographed on silica gel (150 g). Elution with hexane/ethyl acetate (9/1) gives cinnamyl alcohol and 3-phenylpropanol; subsequent elution with hexane/ethyl acetate (1/9) affords (2*S*,3*R*)-**2** as a thick oil which solidifies on standing; yield: 6–10 g (16–25%); m.p. 42–44 °C; $[\alpha]_D^{20}$: +16.4° (*c* 1.05, ethanol).

| | | | |
|---|---|---|---|
| $C_{11}H_{14}O_2$ | calc. | C 74.13 | H 7.92 |
| (178.2) | found | 74.38 | 7.73 |

**(2*S*,3*R*)-5-Phenylpentane-2,3-diol [(2*S*,3*R*)-3]:**
The diol (2*S*,3*R*)-**2** (9 g) is hydrogenated in ethanol (90 ml) in the presence of 10% palladium-on-carbon (300 mg) under 4 atm pressure for 4 h at room temperature; yield: 9.1 g (100%); m.p. 80–85 °C (from hexane/ethyl acetate); $[\alpha]_D^{20}$: +40° (*c* 0.85, ethanol).

| | | | |
|---|---|---|---|
| $C_{11}H_{16}O_2$ | calc. | C 73.30 | H 8.95 |
| (180.2) | found | 73.12 | 9.03 |

**(2*S*,3*R*)-5-Phenyl-2-tosyloxy-3-pentanol [(2*S*,3*R*)-4] and (2*S*,3*R*)-5-Phenyl-3-tosyloxy-2-pentanol [(2*S*,3*R*)-5]:**
Tosyl chloride (19 g, 0.1 mol) is added portionwise over 3 h to a stirred solution of the diol (2*S*,3*R*)-**3** (18 g, 0.1 mol) in dichloromethane (200 ml) + pyridine (50 ml) at 0 °C. Stirring is continued overnight at room temperature, and the solution then washed with cold 5% hydrochloric acid (4 × 150 ml). The organic layer is dried with sodium sulfate, the solvent evaporated, and the residue [30 g (80%), which on T.L.C. (silica gel; hexane/ethyl acetate/propanol, 70/30/1) shows two partly overlapping spots] is submitted to careful column chromatography on silica gel (200 g) using ethyl acetate/hexane (5/95–10/90) as eluent to give a 9:1 mixture of (2*S*,3*R*)-**4** and (2*S*,3*R*-**5** [as determined from the relative intensities of the signals at δ = 3.75 (3-H of **4**) and 3.95 ppm (2-H of **5**)]. The product mixture is a thick oil which slowly decomposes on standing.

The pure compound (2*S*,3*R*)-**4** can be obtained by H.P.L.C. of the product mixture before chromatography.

$^1$H-N.M.R. ($CDCl_3$/TMS, 90 MHz): δ = 7.9–7.0 (m, 9H); 4.6 (m, 1H); 3.75 (m, 1H); 3.0–2.4 (m, 2H); 2.4 (s, 3H); 1.9–1.5 (m, 2H); 1.2 ppm (d, 2H).

**(3*S*)-5-Phenyl-3-pentanol [(3*S*)-8] and (2*R*)-5-Phenyl-2-pentanol [(2*R*)-9]:**
A solution of the 9:1 mixture of (2*S*,3*R*)-**4** and (2*S*,3*R*)-**5** (22 g) in dry ether (100 ml) is added dropwise, with stirring, to lithium alanate (6 g) in ether (250 ml). The mixture is heated to boling for 5 h. Then, a saturated solution of sodium potassium tartrate (50 ml) is added, the organic phase is separated, dried with sodium sulfate, and evaporated. The mixture of the alcohols **8** and **9** thus obtained (7 g, 65%) is column-chromatographed on silica gel (250 g) using ethyl acetate/hexane (5/95) as eluent to give (3*S*)-**8**; yield: 3 g (28%); m.p. 36–38 °C; $[\alpha]_D^{20}$: +23° (*c* 1.04, ethanol). On the basis of the optical rotation of the final product (4*S*)-**10**, the product (3*S*)-**8** should contain 90% of the (3*S*)-isomer.

| | | | |
|---|---|---|---|
| $C_{11}H_{16}O$ | calc. | C 80.84 | H 9.83 |
| (164.2) | found | 80.68 | 9.95 |

Further elution of the column with ethyl acetate/hexane 10/90 affords (2*R*)-**9** as an oil; b.p. 110 °C (oven)/~40 torr; $[\alpha]_D^{20}$: −3.6° (*c* 1, ethanol). The product should contain 90% of the (2*R*)-isomer (cf. above).

| | | | |
|---|---|---|---|
| $C_{11}H_{16}O$ | calc. | C 80.84 | H 9.83 |
| (164.2) | found | 80.91 | 9.76 |

**(4*S*)-4-Hexanolide [(4*S*)-10]:**
A solution of (3*S*)-5-phenyl-3-pentanol [(3*S*)-**8**, 80% optical purity; 7 g) in dichloromethane/methanol (1/1; 50 ml) containing 70% formic acid (2 ml) is ozonized at 0 °C for 28 h, until on T.L.C. the spot of the starting material has disappeared; during ozonization, the solvent is replaced as required. The solution is evaporated in vacuo to a small volume and the residue is taken up in water (15 ml). This mixture is heated on a boiling water bath and a 1:1 mixture (2 ml) of 99% formic acid and 30% hydrogen peroxide is added. After 3 h, the excess oxidant is destroyed by adding a trace of 10% palladium on carbon, heating for 30 min, and filtering, and the resultant solution is continuously extracted with ether. The extract is washed with aqueous 10% sodium hydroxide (2 × 10 ml) and the alkaline extract is acidified with dilute sulfuric acid and again extracted continuously with ether. The organic extracts are combined and dried with sodium sulfate. The solvent is carefully evaporated and the residual product distilled at 70 °C (oven) at water-pump vacuum to give (4*S*)-**10**; yield: 1.2 g (25%).

M.S.: *m/e* = 114 ($M^+$, 10%), 85 (100).

I.R. (neat): $\nu = 1770\ cm^{-1}$.

A purified sample obtained by preparative G.L.C. (Varian 90 P-3, 2 m × 3 mm (i.d.) Pyrex column, 20% DEGS on Chromosorb W-AW, 60–80 mesh, column temperature 125 °C) showed $[\alpha]_D^{20}$: −42° (*c* 0.3, methanol) (Ref. [4], for the (4*R*)-isomer +53.2°), thus indicating ~80% optical purity.

**(2*R*,3*S*)-5-Phenylpentane-2,3-diol [(2*R*,3*S*)-3]:**
*(2S,3R)-2,3-Ditosyloxy-5-phenylpentane* [(2*S*,3*R*)-**6**]: Tosyl chloride (40 g, ~0.2 mol) is added portionwise to a stirred solution of (2*S*,3*R*)-5-phenylpentane-2,3-diol [(2*S*,3*R*)-**3**; 18 g, 0.1 mol) in dry pyridine (200 ml) at −10 °C. Stirring is continued for 16 h at 0 °C and the mixture then poured onto ice (600 g). The mixture is extracted with ethyl acetate (3 × 400 ml), the organic extract is washed with cold 5% hydrochloric acid (3 × 100 ml), dried with sodium sulfate, and evaporated in vacuo. The residue is crystallized from methanol; yield: 30 g (80%); needles, m.p. 64–66 °C $[\alpha]_D^{20}$: −4.2° (*c* 1.07, chloroform).

| | | | |
|---|---|---|---|
| $C_{25}H_{28}O_6S_2$ | calc. | C 61.47 | H 5.78 |
| (488.5) | found | 61.33 | 5.86 |

$^1$H-N.M.R. ($CDCl_3$/TMS): δ = 4.4–4.8 ppm (m, H-2, H-3).

*(2R,3S)-5-Phenylpentane-2,3-diol* [(2*R*,3*S*)-**3**]: To a stirred solution of the ditosylate (2*S*,3*R*)-**6** (20 g, 0.04 mol) in HMPT (100 ml) heated at 100 °C, sodium benzoate (72 g, 0.5 mol) is added portion-

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wise. The mixture is stirred at 100 °C for a total of 20 h and then poured into ice water (500 ml), whereupon an oil separates. The mixture is extracted with ether (3 × 200 ml), the organic extract is dried with sodium sulfate, and evaporated. The organic extract contains the dibenzoate and less polar products. The crude organic extract is added to lithium alanate (5 g) in ether (300 ml) and the mixture stirred at room temperature overnight. Then, saturated sodium potassium tartrate (60 ml) is added, the organic phase is separated, dried with sodium sulfate, and evaporated; yield: 5 g (55%); m.p. 79–81 °C; $[\alpha]_D^{20}$: −38° (*c* 1.13, ethanol). The product has an optical purity of 95%.

| | | | |
|---|---|---|---|
| $C_{11}H_{16}O_2$ | calc. | C 73.30 | H 8.95 |
| (180.2) | found | 73.20 | 9.10 |

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