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Resolution of (1,1'-Binaphthalene)-2,2'-dithiol by Enzyme Catalysed Hydrolysis of a Racemic Diacyl Derivative#

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Abstract: Both enantiomers of (1,1'-binaphthalene)-2,2'-dithiol (**1**) can be obtained with 98 % ee by enzymatic (cholesterol esterase) resolution of the corresponding *S,S'*-dipentanoate. Absolute configuration and enantiomeric purity were determined by crystal structure and ^{1}H NMR analysis, respectively, of a diastereomeric derivative of **1**.

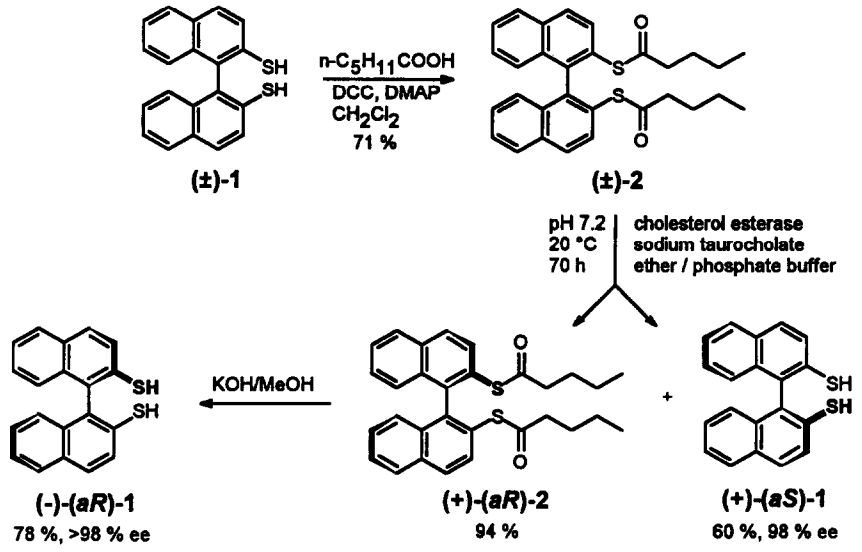
Enantiomerically pure C_2-symmetric binaphthalene derivatives are of interest as chiral ligands or building blocks for crown ethers[1], host molecules[2], liquid crystals[3], chiral phases for chromatography[4] and chiral auxiliaries[5]. Recently, we became interested in (1,1'-binaphthalene)-2,2'-dithiol, which has so far been employed as crown ether[6a] and chiral auxiliary[6b-j].

A convenient method for the preparation of enantiomerically pure (1,1'-binaphthalene)-2,2'-dithiol on a gram scale was elusive until recently. Di Furia *et al.*[7] have worked out a kinetic resolution of a corresponding thioether under Sharpless conditions. However, this method appears unsuitable for large scale preparation because it yields a complex mixture of products (diastereoisomers, mono- and di-oxidised species) which have to be separated by medium pressure chromatography. Three additional steps are necessary to get to the target molecule. Fabbri *et al.*[8] have recently developed a new procedure which uses the Newman-Kwart rearrangement of a thiocarbamoyl derivative of enantiomerically pure (1,1'-binaphthalene)-2,2'-diol as key step. The reaction has to be carried out under carefully controlled reaction conditions (5 g quantities, 285 °C, 22 min). Higher temperatures or longer reaction times result in variable losses of enantiomeric purity.

We now found that the enzymatic resolution of binaphthol as described by Kazlauskas[9] can also be applied to the corresponding thiol (Scheme 1). Racemic (1,1'-binaphthalene)-2,2'-dithiol (**1**) was prepared as described by Di Furia *et al.*[7b] Esterification with valeric acid/DCC gave the corresponding dipentanoate **2** in 71 % yield. This racemic ester was partially hydrolysed by cholesterol esterase in an ether/phosphate buffer (pH 7.20) mixture at 20 °C. Bovine pancreas acetone powder, which is commercially available, in conjunction with sodium taurocholate sufficed as cheap source for cholesterol esterase. Readjustment of the pH (7.20 ± 0.01) with 1 N aqueous sodium hydroxide using an autotitrator allowed to monitor the reaction which

Dedicated to Professor Léon Ghosez on the occasion of his 60th birthday.

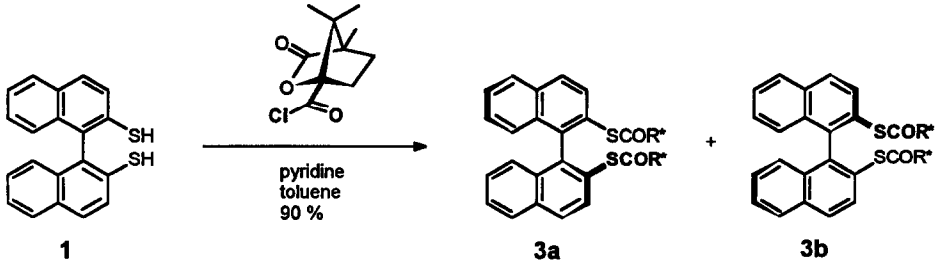
Scheme 1



stopped at a conversion of *ca.* 44 % after 70 hours, even when more enzyme was added to the reaction mixture at this time. The resultant (*aS*)-(1,1'-binaphthalene)-2,2'-dithiol [(+)-**1**], valeric acid and residual (*aR*)-pentanethioic acid *S,S'*-[(1,1'-binaphthalene)-2,2'-diyl] ester [(+)-**2**] were separated by liquid/liquid extraction. The thiolester was hydrolysed with potassium hydroxide in methanol to give the dithiol (-)-(*aR*)-**1** in 78 % yield.

Determination of the enantiomeric purity was carried out by ^{1}H NMR analysis of the diastereomeric camphanic thiolesters **3a** and **b** (Scheme 2) by integration of the CH_3 resonances[10]. The diastereomers showed quite remarkable differences in chemical shifts for the methyl resonances (0.89, 0.50 and -0.23 ppm for **3a**, 1.00, 0.85 and 0.70 ppm for **3b**). The diastereomeric excess for **3a** prepared from (+)-**1** was 98 %, for **3b** from (-)-**1** > 98 % de.

Scheme 2



Expectedly, optical rotation was found to be not reliable for determination of enantiomeric purity as the dithiol is easily oxidised to the corresponding disulphide[8] having $[\alpha]_{546}^{25}$ = -777 (c 0.5, $CHCl_3$) for the (*aR*)-enantiomer[7b]. A fast test for the enantiomeric purity of the reaction products was high pressure liquid chromatography of the dipentanoate **2** on a cellulose triacetate column (Merck) with methanol as eluent, since

the enantiomers of the thiolester displayed a separation factor of $\alpha = 2.02$ (*cf.* Figure 1). This adsorbent has generally been useful for the separation of binaphthalene derivatives lacking proton donating functional groups (*i.e.*, OH, NH_2). In accordance with the general rule, the thiol was not resolved on cellulose triacetate. The triacetate column was also quite inaccurate for ee-values > 95 % due to peak broadening. Similar results were obtained with a Chiralcel OD-H phase (Daicel).

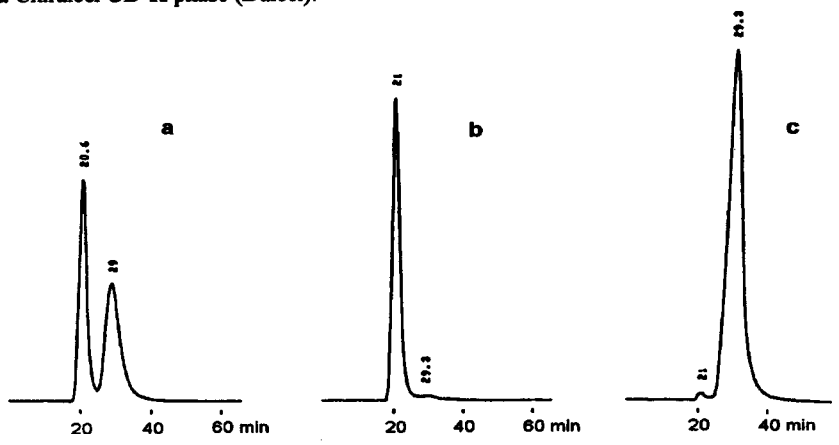


Figure 1. HPLC separation of the enantiomeric pentanethioic acid *S,S'*-[(1,1'-binaphthalene)-2,2'-diyl] esters (+)- and (-)-2. Chromatographic conditions: cellulose triacetate column (Merck), eluent MeOH, flow 1.0 mL/min, V_{inj} = 5 µl, c(sample) = 2 mg/mL, UV-Det. 254 nm. For determination of t_0 1,3,5-tri-*t*-butylbenzene was used. **a.** (±)-2. **b.** Residual (+)-2 after hydrolysis catalysed by cholesterol esterase. **c.** Ester (-)-2, obtained by enzyme catalysed hydrolysis and reesterification of (+)-1.

The configuration of the camphanic thiolester **3a** was determined by crystal structure analysis (Figure 2). The (*aS*)-configuration is in accordance with the result of Kazlauskas[9], who found that cholesterol esterase hydrolyses the (*aS*)-enantiomer of pentanoic acid (1,1'-binaphthalene)-2,2'-diyl ester. The crystal structure likely resembles the conformation in solution because it explains the unusual high field shift of -0.23 ppm for one of the CH_3 resonances (*cf.* above). It is apparent from Figure 2 that the CH_3-group group 7-$(CH_3)_{syn}$ indeed is directly located above the aromatic ring.

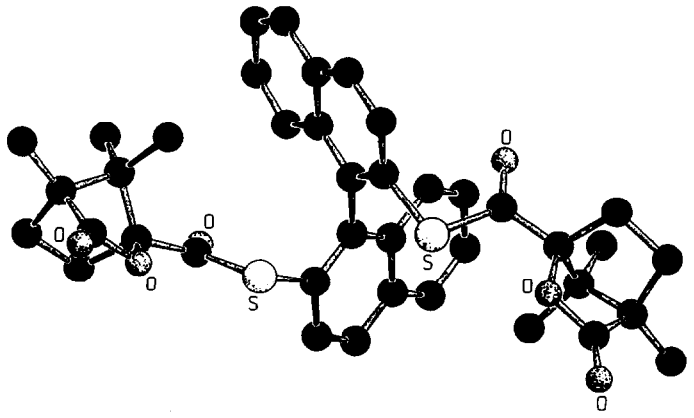


Figure 2. X-ray crystal structure of the diester **3a**.

EXPERIMENTAL SECTION

General. Melting points: Büchi apparatus according to Dr. Tottoli. - NMR: [300 MHz (^{1}H), 75.46 MHz (^{13}C)] Bruker WH 300. - Optical rotations: Perkin Elmer 241; $[\alpha]_D$ was extrapolated from $[\alpha]_{578}$ and $[\alpha]_{546}$ with the Drude equation. pH-Stat titration: Metrohm pH-Meter 654, Impulsomat 614 and Labograph E586; pH-electrode: Metrohm 6.0219.100; standard buffer solutions pH 7.0 and pH 9.0 (Merck) were employed for calibration. Crude bovine acetone powder was purchased from Sigma Chemicals Co; its activity was assessed by enzymatic hydrolysis of binaphthalene dipentanoate according to the procedure of Kazlauskas[9]: A solution of racemic pentanoic acid (1,1'-binaphthalene)-2,2'-diyl ester (1.23 g) in ether (15 mL) was vigorously stirred with 100 mM phosphate buffer (pH 7.0, 15 ml) in a round-bottomed flask at a constant temperature of 25 °C. After addition of crude sodium taurocholate (226 mg) and bovine acetone powder (603 mg) the pH was maintained at 7.0 by addition of aqueous 0.1 M sodium hydroxide. From the plot of volume of NaOH consumed *vs.* time an initial rate of 2.4 µmol/min was found, corresponding to an activity of 3.9 units/g.

Pentanethioic acid *S,S'*-[(1,1'-binaphthalene)-2,2'-diyl] ester (2). A solution of (1,1'-binaphthalene)-2,2'-dithiol (**1**) (6.35 g, 20.0 mmol), valeric acid (4.09 g, 40.0 mmol) and 4-dimethylaminopyridine (0.49 g, 4.0 mmol) in dry dichloromethane (140 mL) under argon atmosphere was cooled to -10 °C. *N,N*-Dicyclohexylcarbodiimide (9.10 g, 44.0 mmol) was added. A colourless precipitate formed within a few minutes. The mixture was warmed to room temperature and stirred overnight. Precipitated dicyclohexylurea was filtered off and washed with dichloromethane. The filtrate was extracted with 0.25 N HCl, twice with sodium hydrogen carbonate solution and once with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product which was purified by flash chromatography with light petroleum/ether 85:15 as eluent yielding 6.91 g (71 %) of a slightly yellowish oil, which solidified upon storage, mp 46-47 °C. ^{1}H NMR ($CDCl_3$): δ 0.74 (t, J = 7.2 Hz, 6H), 1.10 (m, 4H), 1.36 (m, 4H), 2.34 (dt, J = 7.2 Hz, 1.3 Hz, 4H), 7.07 (d, J = 8.1 Hz, 2H), 7.20-7.29 (m, 2H), 7.49 (m, 2H), 7.66 (d, J = 8.6 Hz, 2H), 7.93 (d, J = 8.1 Hz, 2H), 8.02 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 13.59 (q), 21.74 (t), 27.59 (t), 43.34 (t), 126.66 (d), 126.70 (d), 126.94 (d), 127.17 (s), 127.95 (d), 128.65 (d), 132.11 (d), 133.22 (s), 133.40 (s), 140.32 (s), 196.99 (s). Anal. Calcd for $C_{30}H_{30}O_2S_2$: C, 74.04; H, 6.21; S, 13.17. Found: C, 74.22; H, 6.27; S, 13.13.

Enzyme-catalysed kinetic resolution of 2. A 250 mL three-necked flask was charged with pancreas acetone powder (0.79 g, 3.1 units), sodium taurocholate (0.31 g), ether (25 mL) and 100 mM phosphate buffer (pH 7.0, 50 mL). The mixture was degassed by three times evacuating and flushing the flask with argon. A solution of thiolester **2** (1.90 g, 3.90 mmol) in ether (25 mL) was degassed and thermostated at 20 °C. This solution was then added to the thermostated (20 °C) stirred enzyme suspension and the pH adjusted to a value of 7.20 (± 0.01) by titration with 1 N sodium hydroxide solution. After 70 hours the consumption of sodium hydroxide solution had stopped at a conversion of 44 %. Stirring was continued for another day, then the pH was adjusted to a value of *ca.* 4.0 by addition of 1 N hydrochloric acid. The main part of the organic phase was separated. A considerable amount remained in an emulsion which was split by addition of magnesium sulphate. The aqueous layer was subsequently extracted with ether; the combined ethereal solutions were concentrated without drying to a volume of approximately 500 mL and then extracted three times with 300 mL of 1 N sodium hydroxide solution. The remaining ether phase containing the unhydrolysed ester was washed with

brine, dried with sodium sulphate and concentrated under reduced pressure. The resultant crude product was purified by flash chromatography with light petroleum/ether 85:15 as eluent to give 0.89 g of the ester (+)-2 (94 %) as viscous oil which solidified upon storage after two days, mp 46 - 47° C, $[\alpha]_D^{20} = +88.1$ (c 2.08, $CHCl_3$). The aqueous layer containing the sodium salts of (+)-1 and valeric acid was cooled in an ice bath and acidified with concentrated hydrochloric acid. The resulting suspension was extracted three times with 100 mL of dichloromethane. The organic layer was washed with sodium carbonate solution to remove valeric acid and with brine, dried with sodium sulphate and concentrated under reduced pressure yielding 0.37 g of thiol (+)-1 (60 %), mp 149-151 °C. Note: It is of crucial importance to remove traces of oxygen from any solvent used, because the dithiol is easily oxidised to the disulphide, especially under basic conditions.

(-)-(*aR*)-(1,1'-binaphthalene)-2,2'-dithiol [(-)-1]. A solution of thiolester (+)-2 (1.05 g, 2.1 mmol) and potassium hydroxide (2.00 g, 36 mmol) in methanol (20 mL) under an argon atmosphere was stirred for five hours at 40 °C until complete consumption of the starting material (tlc). The mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was dissolved in 200 mL of degassed 2 N sodium hydroxide and the solution extracted three times with dichloromethane. The organic phases were discarded, the aequeos phase was cooled to 0 °C, acidified with concentrated hydrochloric acid and extracted with dichloromethane. The organic layer was washed with sodium carbonate solution and with brine, dried with sodium sulphate and concentrated under reduced pressure to give 0.52 g (78 %) of (-)-1.

4,7,7-Trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carbothioic acid *S,S'*-[(1,1'-binaphthalene) 2,2'-diyl] ester (3). A solution of thiol 1 (413 mg, 1.30 mmol) and (-)-(1*S*)-camphanic chloride (700 mg, 3.20 mmol) in dry toluene (10 mL) under an argon atmosphere was cooled to 0 °C and dry pyridine (0.6 mL) was added dropwise. A colourless precipitate formed. The mixture was allowed to warm to room temperature and stirred overnight. Water (2 mL) was added and the resulting mixture stirred for an additional hour. After addition of more water (10 mL) the mixture was extracted three times with ether. The organic layer was washed with 2 N hydrochloric acid, sodium hydrogen carbonate solution and water, dried with sodium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography with light petroleum/ethyl acetate 2:1 as eluent (R_f = 0.28) to give 797 mg (90 %) of thiolester 3. The ratio of the diastereomers was determined by ^{1}H NMR. Signals at -0.23 ppm for **3a** and 0.70 ppm for **3b** were used for integration.

3a from (+)-1: mp 224-226 °C; $[\alpha]_D^{20}$ = + 50.9 (c 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ -0.23 (s, 6H), 0.50 (s, 6H), 0.89 (s, 6H), 1.51-1.95 (m, 6H), 2.20-2.34 (m, 2H), 7.11 (d, J = 7.9 Hz, 2H), 7.21 (m, 2H), 7.45 (m, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.88 (d, J = 8.2 Hz, 2H), 7.96 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 9.48 (q), 14.92 (q), 15.62 (q), 28.50 (t), 30.74 (t), 54.20 (s), 55.29 (s), 95.85 (s), 125.58 (s), 126.58 (d), 127.18 (d), 127.46 (d), 127.96 (d), 128.91 (d), 132.48 (d), 133.20 (s), 133.84 (s), 141.67 (s), 177.67 (s), 194.44 (s).

3b from (-)-1: mp 209-211 °C; $[\alpha]_D^{20}$ = - 63.3 (c 1.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.70 (s, 6H), 0.85 (s, 6H), 1.00 (s, 6H), 1.38-1.55 (m, 4H), 1.68-1.79 (m, 2H), 1.97-2.04 (m, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.23 (m, 2H), 7.49 (m, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.93 (d, J = 8.2 Hz, 2H), 8.00 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 9.57 (q), 16.35 (q), 16.37 (q), 28.77 (t), 30.86 (t), 54.43 (s), 55.37 (s), 95.88 (s), 125.66 (s), 126.83 (two carbons, d), 127.27 (d), 128.11 (d), 129.08 (d), 132.28 (d), 133.34 (s), 133.77 (s),

141.16 (s), 177.57 (s), 193.93 (s). Anal. Calcd for $C_{40}H_{38}O_6S_2$: C, 70.77; H, 5.64; S 9.45. Found: C, 71.02; H, 5.92; S, 9.23.

X-ray crystal structure analysis of 3a. Clear single crystals were obtained by crystallisation from dichloromethane/hexane. Formula: $C_{40}H_{38}O_6S_2$; molecular weight: 678.86; unit cell parameters: a = 8.243(5), b = 11.28(1), c = 19.14(1); V = 1779.7 Å^3; Z = 2; ρ(calc.) = 1.27 g/cm^3; crystal system: rhombic. - Data collection SYNTEX R3, MoK$_\alpha$ radiation (λ = 0.71073 Å), crystal size [mm^3]: 0.15 x 0.3 x 0.12; data collection mode: ω-scan, range 3.0° < 2Θ < 55°; numbers of reflections measured: 4288; number of symmetry-independent reflections observed with I > 2.5σ(I): 2998; linear absorption coefficient: 1.9 cm^{-1}; absorption correction: emperical; transmission factors: 0.93 (min), 1.00 (max). - The structure was solved by using direct methods. The known structure of the camphanic part allowed the determination of the absolute configuration; R = 4.7 %, R_w = 3.9 %; calculator: Microvax II, program used: SHELXTL PLUS.

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10. Control experiments with racemic **1** gave **3a** and **3b** in a 50:50 ratio, i.e. kinetic resolution can be excluded.

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