Efficient resolution of (±)-pantolactone by inclusion crystallization with the use of chiral 1,1,2-triphenylethane-1,2-diol

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Enantioselective formation of crystalline 1 : 1 host—guest complexes with (*R*)- or (*S*)-1,1,2-triphenylethane-1,2-diol as a host compound allows efficient preparative resolution of (±)-pantolactone. Optically active pantolactones (98% *ee*) were obtained in 65—67% yield.

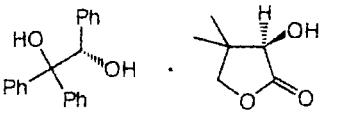
Key words: resolution of enantiomers, pantolactone, host—guest complexes, inclusion crystallization, (*R*)- and (*S*)-1,1,2-triphenylethane-1,2-diol.

Enantioselective inclusion crystallization is a promising method for the separation of racemic compounds,[1—3] first of all, such as alcohols, esters, lactones, and other neutral substrates, that cannot be resolved by usual techniques *via* diastereomeric salts. Pantolactone (PL), which is widely used in fine organic synthesis, is also among these substrates. Earlier, (±)-PL has been resolved by inclusion crystallization using (*R*,*R*)-(−)-2,3-bis(diphenylhydroxymethyl)-1,4-dioxaspiro[4.5]decane as a chiral host compound. The latter is prepared in several steps, and the yield of optically active PL does not exceed 30%.[4]

In this communication, inclusion crystallization of PL racemate with accessible chiral 1,1,2-triphenylethane-1,2-diol (TPED) is proposed as an efficient method for the preparation of optically active PL. Note that this diol has not been used before for the resolution of enantiomers; only its ability to form crystalline molecular complexes with simple achiral molecules such as MeOH, acetone, dioxane, *etc.* has been reported.[5]

We found that chiral TPED selectively forms crystalline 1 : 1 host—guest molecular complexes with one of the PL enantiomers (^{1}H NMR). (*S*)-TPED interacts predominantly with (*R*)-PL to give complex **1**, while (*R*)-TPED interacts with (*S*)-PL to produce complex **2**.

To find the optimum conditions for the resolution of (±)-PL, we studied crystallization of complexes **1** and **2** from different solvents such as ether—hexane, THF—hexane, ether—THF—hexane, benzene—hexane, and toluene—heptane. Component ratios and concentrations and the temperature regime were also varied. The best resolution of (±)-PL was achieved upon three-step crystallization of **1** and **2** from a benzene—hexane mixture to give optically active PL (98% *ee*) in 65—67% yield. The corresponding pantolactone is quantitatively extracted with water from an ethereal solution of complex **1** or **2**.



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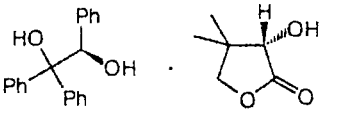

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Experimental

(±)-Pantolactone and (*R*)- and (*S*)-TPED were purchased from Fluka. The stoichiometry of complexes **1** and **2** and the configuration of optically active PL were determined by ^{1}H NMR spectroscopy on a Bruker AM-300 instrument in $CDCl_3$ in the presence of BINOL as a chiral solvating shift reagent.[6] The optical purity of chiral PL was determined by GLC on a Biokhrom-21 instrument (quartz capillary column 30 000 × 0.25 mm, β-DEX™ (Supelco) as stationary phase (0.25 μm), helium as carrier gas (1 mL min^{-1}), CH_4 as nonsorbable component, column temperature 135 °C). Retention times for CH_4, (*S*)-PL, and (*R*)-PL were 3.1, 20.7, and 21.2 min, respectively.

Isolation of (*R*)-(−)-PL from (±)-PL *via* complex 1. A mixture of (±)-PL (390 mg, 3 mmol) and (*S*)-(−)-TPED (436 mg, 1.5 mmol) was dissolved in 6 mL of benzene at 65 °C. Hexane (12 mL) was added with stirring at the same temperature, and the resulting solution was allowed to cool to ~20 °C. After one day, the crystals that formed were filtered off, washed with a benzene—hexane mixture (1 : 5, 3 mL), and dried *in vacuo* (1—2 Torr) at ~20 °C to give complex **1** (598 mg) enriched in (*R*)-PL enantiomer (60% *ee*). The crystals obtained were dissolved in 6 mL of benzene at 65 °C, and hexane (12 mL) was added with stirring at the same temperature. The

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mixture was kept at −20 °C for 1 day and at 0 °C for 3 h. The crystals that formed were filtered off and washed with cooled hexane (2.5 mL) to give complex **1** (476 mg) containing (*R*)-PL enantiomer (85% ee). The complex was recrystallized once again as described above from a mixture of benzene (4 mL) and hexane (8 mL). Crystallization at 0 °C and then at −20 °C for 3 h gave complex **1** (432 mg, 68.5%), m.p. 110—112 °C. Found (%): C, 74.26; H, 6.70. $C_{26}H_{28}O_5$. Calculated (%): C, 74.53; H, 6.72. ^{1}H NMR ($CDCl_3$), δ, signals for PL: 1.05, 1.2 (both s, each 3 H, CMe_2); 2.95 (br.s, 1 H, OH); 4.0 (m, 2 H, CH_2O); 4.1 (s, 1 H, CHO); signals for TPED: 2.6 (br.s, 1 H, C(2)OH); 3.2 (s, 1 H, C(1)OH); 5.62 (br.s, 1 H, CHO); 7.0—7.75 (m, 15 H, 3 Ph).

Complex **1** was dissolved in 10 mL of ether, and PL was extracted with water (5×5 mL). Concentration of the aqueous extract *in vacuo* gave (*R*)-(−)-PL (98% *ee*) (131 mg, 67%), m.p. 91 °C, $[\alpha]_D^{20}$ −50.5° (*c* 2, H_2O). These values agree very closely with the known literature data.[4,7] Pure (*S*)-(−)-TPED remaining in the ethereal solution upon extracting PL with water can be used repeatedly to separate (±)-PL.

Isolation of (*S*)-(+)-PL from (±)-PL *via* complex 2. Analogously, (*R*)-(+)-TPED was used to resolve (±)-PL *via* complex **2**, m.p. 111—112 °C. (*S*)-PL enantiomer (98% *ee*) was obtained in 65% yield, m.p. 90—91 °C, $[\alpha]_D^{20}$ +50.3° (*c* 2, H_2O).

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