Practical Asymmetric Synthesis of the Herbicide (*S*)-Indanofan via Lipase-Catalyzed Kinetic Resolution of a Diol and Stereoselective Acid-Catalyzed Hydrolysis of a Chiral Epoxide

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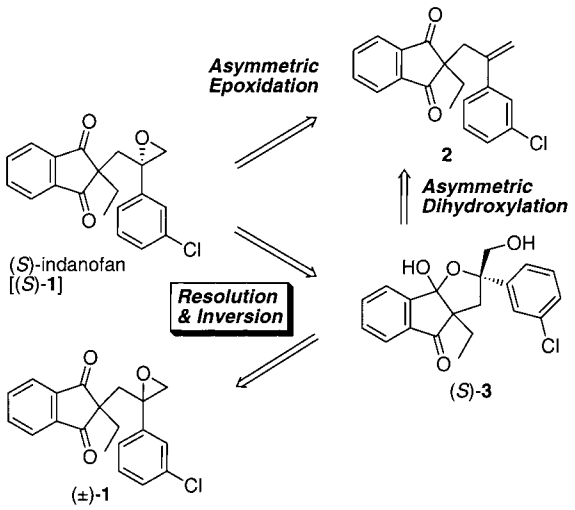
Abstract: Racemic indanofan [(±)-**1**] was efficiently converted to enantiopure (*S*)-indanofan [(*S*)-**1**] by a combination of enzymatic resolution and chemical inversion techniques. An additional important technique is the use of an *o*-xylene complex of a hemiketal (*S*)-**3c** as a precursor, which can be quantitatively converted to (*S*)-indanofan and easily purified by recrystallization from *o*-xylene.

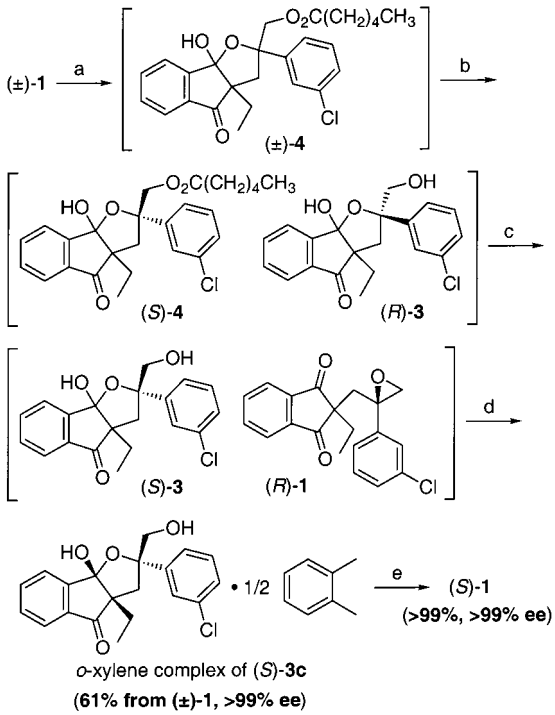
Indanofan [(±)-**1**] is a novel herbicide used for grass weeds in paddy fields, especially barnyardgrass (*Echinochloa oryzicola*).[2,3] It was commercialized as a racemic mixture in 1999; however, examination of the herbicidal activity of each enantiomer revealed that the active ingredient is only the (*S*)-enantiomer.[4] Therefore, an efficient and large-scale synthesis of (*S*)-indanofan [(*S*)-**1**] was required to develop this important compound. We describe herein the practical synthesis of (*S*)-**1** via lipase-catalyzed kinetic resolution of a diol and acid-catalyzed stereoselective hydrolysis of a chiral epoxide.[5]

The retrosynthetic plan for (*S*)-**1** is shown in Scheme 1. Our initial attempt was focused on asymmetric epoxidation, using the Jacobsen's salen manganese catalyst,[6] and asymmetric dihydroxylation using the Sharpless osmium catalyst,[7] starting from an olefin **2**. However, these reactions gave only low to modest ee's, and it was difficult to purify (*S*)-**1** without chromatography due to the use of transition metal catalysts and sluggish crystallization of (*S*)-**1**. While pursuing other synthetic routes, we established that diol (*S*)-**3** is an efficient precursor that can be quantitatively converted to (*S*)-**1** and easily purified by the formation of a unique solvent complex with *o*-xylene. In addition, (*S*)-**3** was easily prepared from

Scheme 1



Scheme 2[a]



[a] Key: (a) aqueous HCO_2H, then aqueous NaOH, and then *n*-hexanoyl chloride, pyridine, chlorobenzene; (b) lipase R, *i*-Pr_2O−phosphate buffer (pH 7.2); (c) MsCl, Et_3N, then aqueous NaOH, chlorobenzene; (d) 65% aqueous H_2SO_4 (5 equiv of H_2O), di(ethylene glycol) diethyl ether, then recrystallization from *o*-xylene/heptane (**61%** from (±)-**1**, >**99% ee**); (e) TsCl, aqueous NaOH, toluene (>**99%**).

(±)-**1** via lipase-catalyzed kinetic resolution of the diol followed by acid-catalyzed stereoselective hydrolysis of a chiral epoxide.

The synthesis of (*S*)-**1** is outlined in Scheme 2. A chlorobenzene solution of (±)-**1** was treated continuously with aqueous formic acid, aqueous NaOH, and *n*-hexanoyl chloride/pyridine to give crude *n*-hexanoate ester (±)-**4**. The crude ester was dissolved in *i*-Pr_2O and treated with a phosphate buffer (pH 7.2) solution of lipase R

(1) Correspondence concerning the X-ray crystal structure should be directed to C.S. and Y.T.O.

(2) For the herbicidal activity of (±)-**1**, see: Jikihara, T.; Shike, T.; Katsurada, M.; Watanabe, H.; Ikeda, O. (Mitsubishi Kasei Corporation), EP 398258 A1, 1990.

(3) For the synthesis of (±)-**1**, see: (a) Tanaka, K.; Hosokawa, A.; Yoshida, K. *Synthesis* **1999**, 249−253. (b) Tanaka, K.; Tanigawa, Y.; Hosokawa, A. *Synth. Commun.* **1999**, *29*, 211−218. (c) Tanaka, K.; Hosokawa, A.; Yasuda, M.; Yoshida, K. Presented at the 75th Symposium on Organic Synthesis, Tokyo, Japan, June 1999; Abstract 1-8.

(4) Tanaka, K.; Yoshida, K.; Hosokawa, A.; Katagiri, N.; Ikeda, O. (Mitsubishi Chemical Corporation). JP 10-285042, 1998.

(5) For biocatalytic deracemization techniques, see: Stecher, H.; Faber, K. *Synthesis* **1997**, 1−16 and references therein.

(6) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189−214 and references therein.

(7) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547 and references therein.

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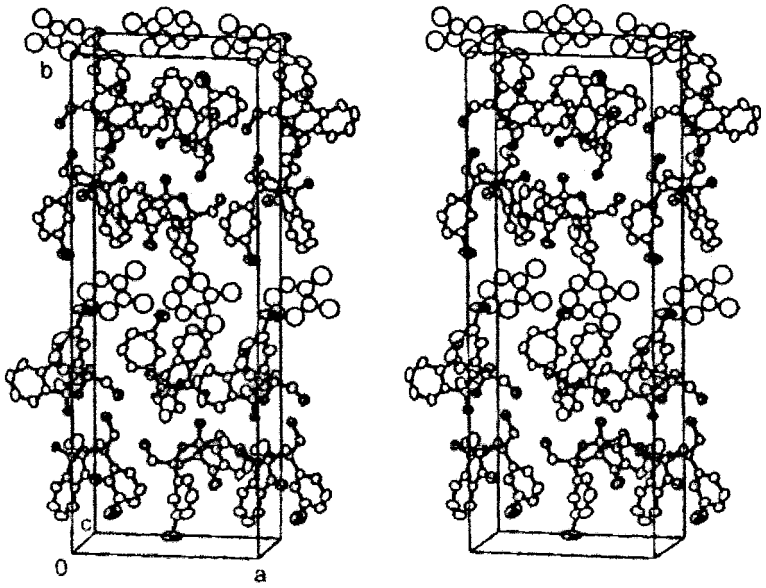
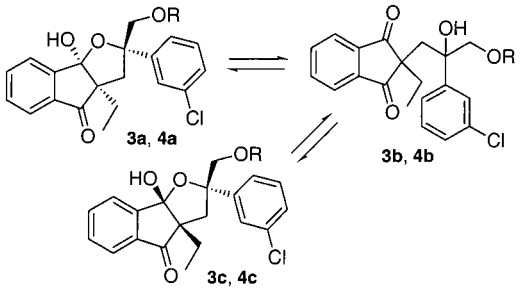


Figure 1. Stereo diagram of the crystal structure of the *o*-xylene complex of (*S*)-**3c** (>99% ee).

Scheme 3



R = H, **3a** : **3b** : **3c** = 81 : 6 : 13 (CD_3OD)
R = $CO(CH_2)_4CH_3$, **4a** : **4b** : **4c** = 61 : 8 : 31 (CD_3OD)

(*Penicillium roqueforti*) to give a mixture of (*R*)-**3** (83% ee) and (*S*)-**4** at 50% conversion (E = 28).[8,9] The use of an isobutyrate ester gave excellent selectivity [(*R*)-**3** (96% ee) at 46% conversion, E = 125]; however, its sluggish reaction rendered the hydrolysis impractical.[10] It is noteworthy that although the ester **4** exists in solution as a mixture of hemiketals **4a** and **4c**, and the 1,2-diol ester **4b** (Scheme 3),[11] good enantioselectivity was obtained. The mixture of (*R*)-**3** and (*S*)-**4** was dissolved in chlorobenzene and then treated with methanesulfonyl chloride and triethylamine followed by treatment with aqueous NaOH to give a mixture of (*R*)-**1** and (*S*)-**3**. The mixture was then dissolved in di(ethylene glycol) diethyl ether and treated with 65% aqueous H_2SO_4 (containing 5 equiv of H_2O with respect to (*R*)-**1**) to generate as the sole product the crude diol (*S*)-**3** with 76% ee. Independent experiments revealed that (*R*)-**1** (>99% ee) was hydrolyzed to give (*S*)-**3** with inversion of the chiral center in 82% yield and 83% ee under the same reaction conditions.[12] H_2SO_4 was employed as the acid catalyst because of high yield, enantioselectivity, and economics. The choice of solvent and the amount of H_2O are crucial for this reaction. The use of other solvents (DMF, EtOAc, acetone, THF, dioxane, DME, etc.) or different amounts of H_2O lowered the yield and the enantioselectivity of the hydrolysis.

The crude diol (*S*)-**3** was purified by recrystallization from *o*-xylene/heptane to give an *o*-xylene complex of (*S*)-**3** in 81% isolated yield from (±)-**1** with 81% ee, which could be raised to >99% ee in 61% isolated yield from (±)-**1** by recrystallization two more times. In addition, all the impurities could be removed during these crystallizations. Like the ester **4**, the diol **3** exists as a mixture of hemiketals **3a** and **3c**, and the 1,2-diol **3b** exists in solution with the hemiketal **3a** as the major isomer (Scheme 3).[11] Interestingly, in the presence of *o*-xylene, the crystallization of a solvent complex of the hemiketal (*S*)-**3c** (minor isomer in solution) preceded the crystallization of (±)-**3a** (major isomer in solution), increasing the ee of (*S*)-**3**. On the other hand, when the crystallization was carried out in the absence of aromatic solvents such as EtOAc/heptane and MeOH/heptane, crystallization of the hemiketal (±)-**3a** preceded crystallization of (*S*)-**3a**, decreasing the ee of (*S*)-**3**. Although comparable results were obtained with the use of *m*-xylene, the use of *p*-xylene did not give a solvent complex at all.[13]

The crystal structure of the *o*-xylene complex of (*S*)-**3c** (>99% ee) was determined by X-ray analysis (Figure 1). The crystal belongs to the space group $P2_12_12_1$, and each asymmetric unit contains two molecules of (*S*)-**3c** and one

(8) For the *E* value, see: Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294−7299.

(9) For recent examples of lipase-catalyzed kinetic resolution of 1,2-diols, see: (a) Hof, R. P.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 565−568. (b) Lovey, R. G.; Saksena, A. K.; Girijavallabhan, V. M. *Tetrahedron Lett.* **1994**, *35*, 6047−6050. (c) Jiménez, O.; Bosch, M. P.; Guerrero, A. *J. Org. Chem.* **1997**, *62*, 3496−3499. (d) Henegar, K. E.; Ashfold, S. W.; Baughman, T. A.; Sih, J. C.; Gu, R.-L. *J. Org. Chem.* **1997**, *62*, 6588−6597.

(10) The hydrolysis of *n*-hexanoate using 10% (w/w) of lipase R at 25 °C for 24 h gave 36% conversion, but that of isobutyrate gave only 8% conversion.

(11) Although the hemiketals/1,2-diol equilibration of **3** and **4** was investigated in various solvents such as CD_3OD, $CDCl_3$, acetone-d_6, DMSO-d_6, THF-d_8, and toluene-d_8 by ^1H NMR, the equilibrium composition did not change widely.

(12) To the best of our knowledge, only one example has been reported for acid-catalyzed hydrolysis of chiral styrene oxide derivatives [(*S*)-4-nitrostyrene oxide (large exess of 18 N H_2SO_4, DMF, 80% ee)]; see: Pedragosa-Moreau, P.; Morisseau, C.; Baratti, J.; Zylber, J.; Archelas, A.; Furstoss, R. *Tetrahedron* **1997**, *53*, 9707−9714.

(13) Although the use of some other aromatic solvents such as benzene, toluene, ethylbenzene, and chlorobenzene also gave the solvent complexes partially, the ee of (*S*)-**3** was not increased remarkably.

molecule of *o*-xylene.[14] In the crystal, there are two columns: one hydrophilic and one hydrophobic. Two molecules of (*S*)-**3c** orient themselves toward each other for hydrogen bonding. Due to this hydrogen bonding, the aromatic portions of the molecules form hydrophobic columns through *o*-xylene. The presence of the aromatic solvent enables the formation of this unique crystal structure and results in increasing the enantiomeric purity of **3**. In addition, the absolute configuration of (−)-**3** was determined to be *S* by the anomalous dispersion method.

Finally, the *o*-xylene complex of (*S*)-**3c** was treated with *p*-toluenesulfonyl chloride and aqueous NaOH to give (*S*)-**1** in >99% yield with >99% chemical and optical purity. The quantitative transformation from (*S*)-**3** to (*S*)-**1** could eliminate further purification.

In conclusion, racemic indanofan [(±)-**1**] was efficiently converted to enantiopure (*S*)-indanofan [(*S*)-**1**] in 61% overall yield by the combination of enzymatic resolution and chemical inversion techniques. The present synthesis employs only one isolated compound and no chromatographic purification. These features are suitable for a large-scale synthesis, and this process enabled the multikilogram-scale synthesis of (*S*)-indanofan.

Experimental Section

General Methods. Melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were collected at 300 MHz. Specific rotations were recorded on a JASCO DIP-370 polarimeter. Reactions were monitored by HPLC (column, Inertsil ODS-2; column temp, 40 °C; eluent, CH_3CN/H_2O (60/40); 1.0 mL/min; detect, 254 nm). The optical purity of **1** was determined by HPLC (column, CHIRALCEL OJ; column temp, rt; eluent, *n*-hexane/EtOH/MeOH (91/3/6); 1.0 mL/min; detect, 254 nm). The optical purity of **3** was determined by cyclization to **1** (TsCl/aqueous NaOH). All reagents and solvents were plant grade and used without further purification. Lipase R (*P. roqueforti*) was purchased from Amano Pharmaceutical Co., Ltd. Indanofan [(±)-**1**] was prepared according to the literature.[3a]

Preparation of the *o*-Xylene Complex of Diol (*S*)-3c. A mixture of (±)-**1** (25.0 g, 73.4 mmol), chlorobenzene (130 mL), H_2O (20.0 g, 1.11 mol), and formic acid (51.0 g, 1.11 mol) was stirred at 50 °C for 1.5 h followed by addition of 25% aqueous NaOH (190 g, 1.19 mol) and stirring at 50 °C for 0.5 h. The organic layer was separated and washed with aqueous NaCl and H_2O, and then a 30% portion of chlorobenzene was removed by distillation. To the solution was added pyridine (9.5 g, 0.120 mol) and subsequently *n*-hexanoyl chloride (11.5 g, 85.4 mmol) dropwise at <50 °C; then, the resulting mixture was stirred at 40−50 °C for 15 min. The reaction mixture was washed with aqueous HCl/NaCl and H_2O, and concentrated to give a crude (±)-**4**. An analytically pure sample of (±)-**4** was obtained by silica gel column chromatography: pale-yellow oil; IR (neat) 3421, 2958, 2933, 1716, 1704, 1217, 1159, 768 cm^{-1}; ^{1}H NMR (**4a**:**4b**:**4c** = 62:7:31, CD_3OD) δ 0.47 (t, J = 7.5 Hz, 3H, **4b**), 0.67−0.89 (m, 3H, **4a**; m, 3H, **4c**), 1.03−2.21 (m, 8H), 2.27 (d, J = 13.5 Hz, 1H, **4c**), 2.27 (d, J = 12.9 Hz, 1H, **4a**), 2.48 (s, 2H, **4b**), 2.84 (d, J = 12.9 Hz, 1H, **4a**), 3.02 (d, J = 13.5 Hz, 1H, **4c**), 3.69 (d, J = 11.4 Hz, 1H, **4c**), 3.80 (d, J = 11.4 Hz, 1H, **4c**), 3.97 (d, J = 11.4 Hz, 1H, **4b**), 4.06 (d, J = 11.4 Hz, 1H, **4a**), 4.13 (d, J = 11.4 Hz, 1H, **4b**), 4.29 (d, J = 11.4 Hz, 1H, **4a**), 6.73−7.92 (m, 8H). Anal. Calcd for $C_{26}H_{29}ClO_5$; C, 68.34; H, 6.40. Found: C, 68.08; H, 6.47.

(14) The ratio of (*S*)-**3**:*o*-xylene in the crystals of the *o*-xylene complex of (*S*)-**3** (>99% ee), determined by HPLC, was also 2:1.

The crude (±)-**4** was dissolved in *i*-Pr_2O (65 mL), and then a phosphate buffer (pH 7.2, 220 mL) solution of lipase R (10.0 g) was added. After stirring at 25 °C for 15 h (50% conversion), the mixture was diluted with chlorobenzene (150 mL). The organic layer was separated and filtered through Celite. The filtrate was washed with aqueous Na_2CO_3/NaCl and aqueous NaCl, and then *i*-Pr_2O was removed by distillation. To the solution was added triethylamine (10.0 g, 98.8 mmol) and subsequently methanesulfonyl chloride (10.0 g, 87.3 mmol) dropwise at <25 °C. After the addition was completed, 25% aqueous NaOH (50.0 g, 0.313 mol) was added and the resulting mixture was stirred at 70 °C for 2 h. EtOAc (100 mL) and aqueous NaCl were added to the mixture, and then the organic layer was separated, washed with aqueous NaCl, and concentrated. The residue was dissolved in di(ethylene glycol) diethyl ether (125 mL). To the solution was added dropwise 65% sulfuric acid (8.5 g, 0.165 mol-H_2O) at <25 °C, and the resulting solution was stirred at 20−25 °C for 0.5 h. The solution was neutralized (pH 7) with 10% aqueous NaOH, and the organic layer was separated and concentrated. The residue was dissolved in *o*-xylene (15 mL), and heptane (45 mL) was added dropwise at 0 °C. The resulting slurry was filtered, and the product was dried in vacuo to give an *o*-xylene complex of (*S*)-**3** (24.0 g, 59.4 mmol of (*S*)-**3**, 81% from (±)-**1**, 81% ee). The portion of this *o*-xylene complex of (*S*)-**3** (10.0 g, 24.8 mmol of (*S*)-**3**, 81% ee) was recrystallized from *o*-xylene two more times to give the *o*-xylene complex of (*S*)-**3c** (7.7 g, 18.7 mmol of (*S*)-**3c**, 61% from (±)-**1**, >99% ee). A solvent-free sample of (*S*)-**3** (>99% ee) was prepared from the *o*-xylene complex of (*S*)-**3c** (>99% ee) by silica gel column chromatography: colorless crystals; mp 98−99 °C; $[\alpha]_D^{25}$ −58.8 (*c* 0.507, $CHCl_3$); IR (neat) 3470, 3320, 1720, 1700 cm^{-1}; ^{1}H NMR (**3a**:**3b**:**3c** = 81:6:13, CD_3OD) δ 0.46 (t, J = 7.5 Hz, 3H, **3c**), 0.70 (t, J = 7.5 Hz, 3H, **3b**), 0.72 (t, J = 7.5 Hz, 3H, **3a**), 1.49−1.90 (m, 2H), 2.17 (d, J = 13.2 Hz, 1H, **3c**), 2.40 (d, J = 14.7 Hz, 1H, **3b**), 2.43 (d, J = 12.9 Hz, 1H, **3a**), 2.53 (d, J = 14.7 Hz, 1H, **3b**), 2.69 (d, J = 12.9 Hz, 1H, **3a**), 2.97 (d, J = 13.2 Hz, 1H, **3c**), 3.11 (d, J = 11.7 Hz, 1H, **3c**), 3.17 (d, J = 11.7 Hz, 1H, **3c**), 3.33 (d, J = 11.4 Hz, 1H, **3b**), 3.44 (s, 2H, **3a**), 3.46 (d, J = 11.4 Hz, 1H, **3b**), 6.74−7.90 (m, 8H). Anal. Calcd for $C_{20}H_{19}ClO_4$; C, 66.95; H, 5.34. Found: C, 66.90; H, 5.25.

Preparation of (*S*)-Indanofan [(*S*)-1]. To a solution of the *o*-xylene complex of (*S*)-**3c** (5.0 g, 12.1 mmol, >99% ee), *p*-toluenesulfonyl chloride (2.7 g, 14 mmol), and toluene (25 mL) was added 25% aqueous NaOH (7.5 g, 47 mmol), and the resulting mixture was stirred at 50 °C for 4 h and at 60 °C for 1 h. The mixture was diluted with H_2O, and the organic layer was separated, washed with H_2O and aqueous Na_2SO_4, and concentrated to give (*S*)-**1** (4.1 g, 12.0 mmol, >99%, >99% *ee*) as a colorless oil. After standing at room temperature for a long period of time, the oil was gradually crystallized to give colorless crystals: mp 41−42 °C; $[\alpha]_D^{25}$ −59.5 (*c* 0.556, $CHCl_3$); IR (neat) 1740, 1710, 1272, 1242, 722 cm^{-1}; ^{1}H NMR δ 0.65 (t, J = 7.5 Hz, 3H), 1.80 (q, J = 7.5 Hz, 2H), 2.48 (d, J = 5.4 Hz, 1H), 2.58 (d, J = 14.4 Hz, 1H), 2.76 (d, J = 14.4 Hz, 1H), 2.83 (d, J = 5.4 Hz, 1H), 6.81−6.82 (m, 1H), 6.97−7.01 (m, 1H), 7.09−7.11 (m, 2H), 7.71−7.84 (m, 3H), 7.89−7.93 (m, 1H). Anal. Calcd for $C_{20}H_{17}ClO_3$; C, 70.49; H, 5.03. Found: C, 70.57; H, 5.07.

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Supporting Information Available: Crystal data for the *o*-xylene complex of (*S*)-**3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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