Exploration of an Efficient Method for Optical Resolution of Etodolac

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The exploration of an efficient method for resolving etodolac using either *L*-cinchonidinium salt or chiral isopinocamphenol diastereomeric esters is described herein. Furthermore, racemization mechanism of chiral etodolac is rationalized in terms of an isotope labeling experiment.

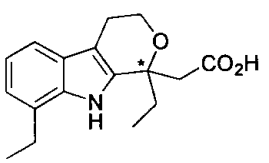
INTRODUCTION

Etodolac (brand name: Lodine) is an antiarthritic drug with anti-inflammatory and analgesic properties.[1,2] The structure of etodolac belongs to monoacids with a stereogenic carbon center, thus it is suitable for chemical resolution *via* either diastereomeric amine salts or esters. An *in vitro* pharmacological experiment reveals that the inhibition activity of arachidonic acid utilization of (+)-etodolac, **1**, is better than that of (±)-etodolac or (-)-etodolac, **2**,[3] which was confirmed in a clinical trial.[4] The potential clinical benefits of (+)-etodolac prompted the development of an efficient resolution method. Although several routes have been reported for resolution of etodolac,[4-8] none of them described optical purity optimization, recovery and/or racemization. Moreover, only one method described the resolution that diastereomeric esters produced. However, owing to their inferior crystalline properties, chiral esters separation requires a HPLC.[3] To our knowledge, the resolution of numerous organic acids is unpredictable. Attempts to resolve etodolac have been plagued with various obstacles: for example, inaccurate enantiomer crystallization, the need for an appropriate base to form diastereomeric salt, low yields, multiple crystallization as well as time consumption. Herein, our resolution using *L*-cinchonidine **3** avoids the aforementioned problems and both the (+)- and (-)-enantiomer are obtained in reasonable yields and with high optical purity. In addition, (+)-etodolac racemization was re-investigated and its mechanism is explained as an isotope labeling experiment. Moreover, using the diastereomeric esters of (1*R*,2*R*,3*R*,5*S*)-(-)-isopinocamphenol **4**, a new approach of resolving etodolac is described.

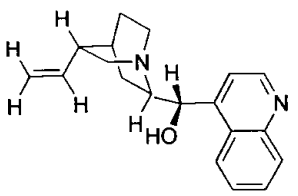
RESULTS AND DISCUSSION

Our initial goal was to ascertain suitable diastereomeric esters to resolve etodolac. (1*R*,2*R*,3*R*,5*S*)-(-)-isopinocamphenol, **4**, a chiral alcohol, which is available commercially or readily prepared from (+)-α-pinene,[9] can be employed to prepare diastereomeric esters due to its good crystalline property. The diastereomers were prepared through an acid-catalyzed cyclization of 7-ethyltryptophol, **9**, with an enol ether ester **8** in 1:1.05 diastereoisomeric ratio (Scheme I).[10,11] Notably, this low diastereoselectivity was confirmed by a recent study.[12] The enol ether ester **8** was prepared from methyl 3-ketovalerate **5** by three typical transformations.[13] Unfortunately, the isolated yield from a variety of solvents of the resolved etodolac was only moderate (~ 60%$_{max}$), although the e.e. value of the recovered (+)-etodolac **1** that was obtained had more than 95% optical purity. This prompted the search for an alternative resolving method. Notably, the invaluable diastereomeric esters were prepared efficiently, rather than by etodolac esterification with chiral alcohol **4**.

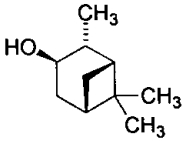
Table 1 lists the experimental results and the conditions through which *L*-cinchodinium salt was employed for optical



* : (S)-form
(+)-etodolac, 1
* : (R)-form
(-)-etodolac, 2

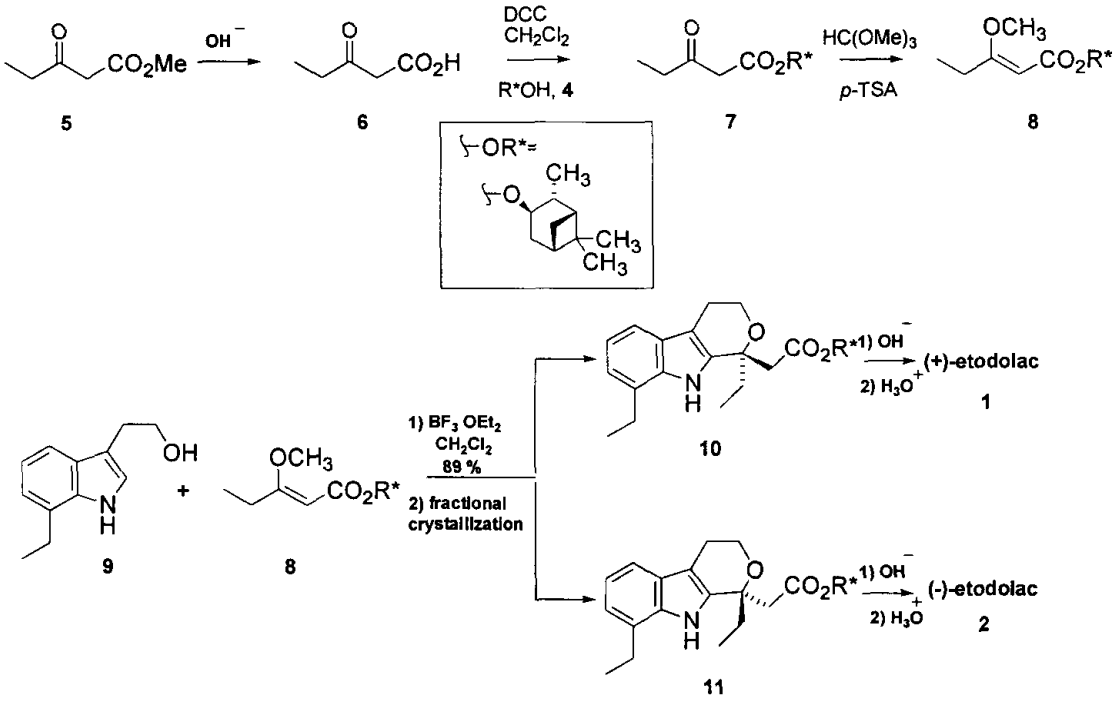


(-)-L-cinchonidine, 3



(1R, 2R, 3R, 5S)-(-)-
isopinocamphenol
4

Scheme I



resolution of etodolac. Several conclusions were ascertained from the test results. Firstly, the optical purity is low (see entries 1 and 6) during resolution, which was conducted at room temperature (25 °C) and in the absence of seed. This indicated that diastereomer crystallized randomly. Secondary, optical purity decreased drastically irrespective of the presence of seed (comparing entries 7, 8 and 9) during high concentration (> 0.17 g/mL) resolution. This indicated that the deposit rate of both diastereomeric salts was accelerated due to high concentration. Thirdly, the period required for cinchonidium salts deposits decreased significantly in the presence of seed (comparing entries 3, 4 and 6, 7); Finally, during

Table 1. Optimization of the Optical Resolution of Etodolac Using *L*-Cinchonidine

Entry	Conc. [a] (g/mL)	Temp (°C)	Seed [b] (mg)	Sonication (min)	Standing (hour)	Yield [c] (%)	$[\alpha]_D^{25}$ (C=3.0, EtOH)	Optical purity [d] (%)
1	20/200	25	-	-	24	ND	<10°	ND
2	20/200	25	100	-	4	50	+24.95°	99.0
3	20/200	0	-	-	12	50	+24.95°	99.0
4	20/200	0	100	-	1	50	+24.95°	99.0
5	20/140	0	100	-	1	80	+24.95°	99.0
6	20/140	25	-	5	0.5	80	<10°	ND
7	20/140	25	100	5	0.1	80	+24.95°	99.0
8	20/120	25	100	5	0.1	ND	+18°	71.4
9	20/100	25	100	5	0.1	ND	<10°	ND
10	20/200	0	100	-	1	80	-24.95°	99.0

ND: not determined

[a] It refers to the amount of *L*-cinchonidinium salt employed (in gram, prepared *in situ*) divided by the volume (in mL) of solvent employed for the resolution.

[b] It refers to the amount of respective optically pure *L*-cinchonidinium salt that was employed as seed.

[c] It refers to the yield of respective optically pure *L*-cinchonidinium salt, which is based on the theoretical amount of the respective chiral form.

[d] It refers to the optical purity of the resolved etodolac recovered from respective *L*-cinchonidinium salt.

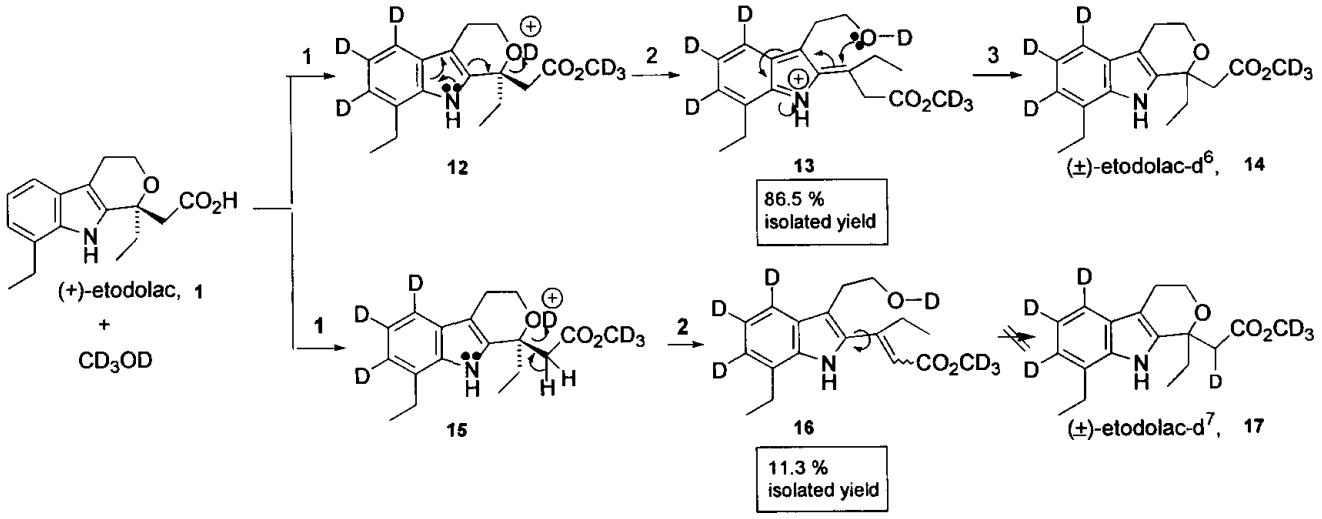
resolution under ultrasonic oscillation (entry 7), the period required for cinchonidium salt deposits decreased significantly in the presence of seed. Table 1 shows that the optimal condition for resolution appeared in entry 7, in which a highly optically pure (+)-etodolac **1** was isolated in good yield within a short period (~ 6 minutes) at room temperature. Furthermore, optical resolution was performed on scales as large as up to 50 g without affecting optical purity and isolated yield.

Racemization with concomitant esterification of chirally enriched etodolac was performed initially by refluxing the chirally enriched etodolac in methanol for 72 hours, using sulfuric acid as the catalyst.[4] However, TLC detected a major side product, thus the isolated yield (by column chromatography) of racemized etodolac methyl ester never exceeded 40%. It is proposed that the tetrahydropyran ring is unstable during the refluxing period. Therefore, the mechanistic racemization pathway was studied and the refluxing period was minimized. By refluxing (+)-etodolac in ^{4}d-methanol a labeling study was executed and the extent of esterification/racemization was monitored by a polarimeter and TLC. Surprisingly, only 1.5 hours were required for complete esterification/racemization. Furthermore, mass and ^{1}H NMR spectra verified, that in addition to the isolation of a ring-opening product **16** (11.3%, 3:1 E/Z mixture),[14,15] no deuterium labeling at the α-position of the ^{3}d ester moiety of the resulting labeled ester **14** (i.e. **17**) was observed. Although in both **14** and **16** (Scheme II) a large proportion of aryl protons were interchanged by deuterium atoms (~70-80%, determined by ^{1}H NMR) and a small proportion of indolyl NH protons were interchanged by deuterium atoms (~20-30%). This indicated that during refluxing the ring-opening product **16** is not re-cyclized easily to form a tetrahydropyran ring. Compared to that of the planner cationic intermediate **13**, during the free rotation of the side chain around the indole ring the enviroment for re-cyclization of **16** was more crowded and the entropy barrier was stronger.

Interestingly, the favored pathway, 6-*Endo-Tet* (i.e. **13-14**), violates the empirical rule of ring closure.[16] The course of racemization could be explained by the indole ring-assisted opening of the tetrahydropyrano C-O bond, which was followed by re-cyclization from either α- or β face of the planner cationic intermediate **13**.

In summary, etodolac was successfully resolved using *L*-cinchonidium salt. Several prominent factors, including seeding effect, critical concentration and acceleration of crystallization *via* sonication as well as a few combined factors, were established. Also demonstrated herein is that although the isolated yield of fractional crystallization remains to be optimized, diastereomeric esters (**10**, **11**) can be prepared efficiently. Furthermore, an isotope labeling study has rationalized a mechanistic explanation of racemization of chiral etodolac and it has been a basis for process research.

Scheme II



1. ^{4}d-MeOH/H_2SO_4(cat.), reflux 1.5 h, racemization/esterification; 2. indole ring - assisted ring-opening; 3. ring closure

EXPERIMENTAL SECTION

Infrared spectra were recorded on a Perkin-Elmer 577 spectrophotometer; NMR spectra were recorded on a DRX-500 (500 MHz) spectrometer. Elemental analyses were determined by a Perkin-Elmer 2400. Mass spectra and high resolution mass spectra were measured on JEOL-JMS-D100 and JEOL-JMSD-HX100 instruments, respectively. Specific rotations $[\alpha]_D$ were determined at the sodium D line (589 nm) at a specified temperature (T) and concentration (C in g/100 mL, solvent) using a digital polarimeter (JASCO DIP-360). Ultrasonic experiments were carried out in an ultrasonic cleaning bath (ELMA, HF-Frequ. 31 KHz). Melting points were measured in open capillary tubes using a Buchi immersion apparatus and are uncorrected. HPLC was carried out with a Nova-Pak C_{18} (4.0 mm × 10 cm) column, eluent, A:B = 80:20 isocratic @ 0.9 mL/min, A = MeOH, B = H_2O, detector, UV at 225 nm; room temperature.

L-Cinchonidium salt formation and fractional crystallization

typical procedure:

To a solution of (±)-etodolac (10.0 g, 34.7 mmole) in absolute ethanol (140 mL) was added *L*-cinchonidine (10.2 g, 34.6 mmole) at 45 °C. After 10 minutes of stirring, the mixture cleared. Then 100 mg of seed (prepared from optical pure (+)-etodolac **1** and *L*-cinchonidine **3** in methanol) was added to the re-cooled solution (25 °C) and allowed to stand at 0 °C for 4 hours. Alternatively, the re-cooled solution containing the seed was vibrated ultrasonically for 5 minutes. Then, by filtration, the cinchonidium salt of (+)-etodolac (i.e. *L*-cinchonidine-(+)-etodolac) was isolated (8.1 g, 80%). mp 114-116 °C, $[\alpha]_D^{25}$ = -46° (c = 1.0, ethanol). Subsequently, 100 mg of seed (prepared from optical pure (-)-etodolac **2** and *L*-cinchonidine **3** in methanol) was added to the mother liquid and allowed to stand at 0 °C for 1 hour. Filtration was again employed to isolate the cinchonidium salt of (-)-etodolac (i.e. *L*-cinchonidine-(-)-etodolac) (7.6 g, 75%). mp 112-113 °C, $[\alpha]_D^{25}$ = 90° (c = 1.0, ethanol). Anal. Calcd for $C_{36}H_{43}N_3O_4$: C, 74.32; H, 7.44; N, 7.22; found C, 73.90; H, 7.42; N, 7.16. By repeated manipulation, *L*-cinchonidine-(-)-etodolac was isolated in 80-82% yield.

Resolved chiral etodolac and *L*-cinchonidine recovery

To a vigorously stirred 1 N NaOH (480 mL) was added the resolved *L*-cinchonidine-(+)-etodolac (8.1 g, 14 mmole) and stirred for 10 minutes. The mixture was filtered to yield the recovered *L*-cinchonidine (3.8 g, 93%). The aqueous layer was extracted with dichloromethane, dried ($MgSO_4$) and evaporated to give a second crop of recovered *L*-cinchonidine (~ 5%). It was then acidified with conc. HCl and extracted twice with dichloromethane. The combined extracts were dried and evaporated to yield (+)-etodolac **1** (3.6 g, 90%), $[\alpha]_D^{25}$ = +24.95° (c = 3.0, ethanol), literature value: $[\alpha]_D^{23}$ = +25.2° (c = 3.0, ethanol),[3] optical purity ~ 99.0%. Similarly, (-)-etodolac **2** (3.7 g, 93%) was isolated from the resolved cinchonidium salt (8.1 g, 14 mmole), $[\alpha]_D^{25}$ = -24.95° (c = 3.0, ethanol), literature value: $[\alpha]_D^{23}$ = -25.6° (c = 3.0, ethanol),[3] optical purity ~ 97.5%. Each of the optically enriched isomers was recrystallized from benzene-petroleum ether to yield (+)-etodolac **2** (mp 138-140 °C) and (-)-etodolac **1** (mp 139-140 °C), respectively. Notably, both refined crystals displayed 100% optical purity.

The chiral ester 7

This compound (15.9 g, 90.0%) was prepared from 3-keto-valeric acid **6** (8.1 g, 70 mmole) and (1*R*,2*R*,3*R*,5*S*)-(-)-isopinocamphenol **4** (12.9 g, 83.6 mmole) using DCC (1 eq) in dichloromethane (400 mL). **7**, yellow oil, IR (film) ν_{max} 1725 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.11 (m, 1H), 3.46 (s, 2H), 2.59 (q, *J* = 7.5 Hz , 2H), 2.40 (m, 1H), 2.15 (m, 1H), 1.96 (m, 1H), 1.84 (m, 1H), 1.75 (m, 1H), 1.68 (m, 1H), 1.25 (s, 3H), 1.13 (t, *J* = 7.4 Hz, 3H), 1.09 (d, *J* = 7.4 Hz, 3H), 1.06 (d, *J* = 10.0 Hz, 1H), 0.98 (s, 3H); MS (EI) *m/z* (rel intensity) 252 (M^+, 35), 237 (45), 165 (100); Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59; found C, 71.58; H, 9.65.

The chiral enol ether ester 8

To a solution of the chiral ester **7** (6.2 g, 25 mmol) in trimethylorthoformate (200 mL) was added *p*-TSA.H_2O (1.0 g) and refluxed for 10 hours. The mixture was then evaporated and diluted with dichloromethane (120 mL) and washed successively with 10% sodium bicarbonate and water and dried ($MgSO_4$). The separated organic layer was evaporated and the residual solid was recrystallized from 1/5 (v/v) ethyl acetate/hexane (100 mL) to give **8** (5.7 g, 86%) as a white powder. mp 48-49 °C; IR (KBr) ν_{max} 1725 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ 5.11 (m, 1H), 4.99 (s, 1H), 3.65 (s, 3H), 2.79 (q, *J* = 7.5 Hz, 2H), 2.60 (m, 1H), 2.40 (m, 1H), 2.15 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.73 (m, 1H), 1.24 (s, 3H), 1.15 (t, *J* = 7.5Hz, 3H), 1.13 (d, *J* = 7.4 Hz, 3H), 1.11 (d, *J* = 9.8 Hz, 1H), 1.00 (s, 3H); MS (EI) *m/z* (rel intensity) 266 (M^+, 43), 251 (65), 113 (100); Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84; found C, 72.05; H, 9.78.

Diastereomeric ester formation from the cyclization of the chiral ether ester 8 and 7-ethyltryptophol 9

To a mixture of 7-ethyltryptophol (**9**) (29.2 g, 150

mmole) and the chiral enol ester (41.0 g, 150 mmole) in dry dichloromethane (2500 mL) was added boron trifluoride etherate (0.60 mL, 4.8 mmol). After 2 hours of stirring, the resulting mixture was diluted with ice-water and washed successively with 10% sodium carbonate and water. The separated organic layer was dried ($MgSO_4$) and evaporated. The residue was triturated with 1/5 (v/v) ethyl acetate/hexane, which yielded a diastereomeric mixture (**10**, **11**) (58.0 g, 91.0%) as an oil.

Fractional crystallization of the diastereomeric mixture (10, 11)

A solution of the diastereomers (**10**, **11**) (58.0 g, 140 mmole) in absolute ethanol (410 mL) was refluxed for 20 minutes. To the re-cooled solution was then added 50 mg of seed (prepared from optically pure (+)-etodolac and (1*R*,2*R*,3*R*,5*S*)-(-)-isopinocamphenol **4** using the standard method (DCC/CH_2Cl_2, DMAP)). The solution was then allowed to stand at 0 °C for 4 hours. After which the deposited needle crystal **10** was collected (17.4 g, 60.0%). mp 115-117 °C (1:5 ethyl acetate/hexane), $[\alpha]_D^{25}$ = -72° (c = 1.0, ethanol); IR (KBr) ν_{max} 1735 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.14 (br s, 1H), 7.35 (d, *J* = 7.0 Hz, 1H), 7.05 (m, 1H), 7.00 (d, *J* = 7.0 Hz, 1H), 5.10 (m, C(O)OC<u>H</u>, 1H), 4.03 (m, OC<u>H</u>CH_2, 1H), 3.95 (m, OC<u>H</u>CH_2,1H), 2.80-3.00 (m, 4H), 2.70-2.80 (m, 2H), 2.50-2.60 (m, 1H), 2.30 (br s, 1H), 2.15 (m, 1H), 2.03 (m, 1H), 1.90 (m, 1H), 1.80 (m, 1H), 1.70 (m, 1H), 1.60 (m, 1H), 1.37 (t, *J* = 7.0 Hz, C<u>H</u>$_3$, 3H), 1.25 (m, 1H), 1.22 (s, C<u>H</u>$_3$, 3H), 1.12 (d, *J* = 7.5 Hz, 1H), 1.05 (d, *J* = 7.5 Hz, 1H), 1.00 (m, 1H), 0.98 (s, C<u>H</u>$_3$, 3H), 0.87 (t, *J* = 7.0 Hz, C<u>H</u>$_3$, 3H); MS (EI) *m/z* (rel intensity) 423 (M^+, 35), 394 (28), 258 (42), 228 100); Anal. Calcd for $C_{27}H_{37}NO_3$: C, 76.56; H, 8.80; found C, 76.48; H, 8.68. Notably, using DCC as the condensation agent compound **10** obtained herein was identical to an authentic sample prepared from (+)-etodolac **1** and (-)-isopinocamphenol **4** in dichloromethane.

(+)-Etodolac 1 and (1*R*,2*R*,3*R*,5*S*)-(-)-isopinocamphenol (4) recovery

The chiral ester **10** (17.4 g, 41.1 mmol) was dissolved in a mixture of methanol (290 mL) and water (75 mL), then potassium hydroxide (10.0 g, 0.18 mol) was added and the mixture was heated under reflux for 2 hours. After evaporation, the residue was partitioned between dichloromethane and water. The separated aqueous layer was extracted twice with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to give the recovered (1*R*,2*R*,3*R*,5*S*)-(-)-isopinocamphenol **4** (6.2 g, 98%), which, in every aspect, is identical to that of a commercial sample. The aqueous layer was acidified to pH = 1 with conc. HCl and extracted into dichloromethane. The separated organic layer was dried and evaporated to yield (+)-etodolac **1** (11.6 g, 98%), $[\alpha]_D^{25}$ = +24° (c = 3.0, ethanol), with an optical purity of 95.2%, which was recrystallized from benzene-petroleum ether and yielded optically pure (+)-etodolac **2**, mp 138-140 °C, literature value 138-140 °C.[3]

Racemization with concomitant esterification of (+)-etodolac 1 in ^{4}d-methanol

A solution of optically active (+)-etodolac **1** (0.50 g, 1.74 mmol) in 10 mL of ^{4}d-methanol was stirred for 15 minutes and then treated with one drop (~32 mg) of conc. sulfuric acid. The mixture was refluxed for 1.5 hours under nitrogen and evaporated under vacuum after cooling. The oily residue was diluted with ethyl acetate and washed twice with water. The separated organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified on silica gel using 1:5 ethyl acetate to give successively **14** (0.46 g, 86.5%) and **16** (0.06 g, 11.3%), which are both optically inactive compounds. **14**, white powder, mp 126-128 °C (1:5 ethyl acetate/hexane); IR (KBr) ν_{max} 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.05 (br s, 0.77H), 7.36 (m, 0.18H), 7.00-7.06 (m, 0.36H), 4.05 (m, 1H), 3.94 (m, 1H), 3.02, 2.92 (ABq, *J* = 16.6 Hz, 2H), 2.88 (q, *J* = 7.6 Hz, 2H), 2.83 (m, 1H), 2.76 (m, 1H), 2.16 (m, 1H), 2.01 (m, 1H), 1.37 (t, *J* = 7.6 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); MS (EI) *m/z* (rel intensity) 307 (M^+, 50), 278 (100), 230 (100), 200 (30); HRMS, Calcd for $C_{18}H_{17}D_6NO_3$ 307.2054, found 307.2053. **16**, white powder, mp 129-131 °C (1:5 ethyl acetate/hexane), IR (KBr) ν_{max}1720, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.97 (br s, 0.67 H), 7.47 (m, 0.27 H), 7.05-7.10 (m, 0.54 H), 6.16, 6.07 (each s, 3:1 E/Z mixture, 1H), 3.93, 3.92 (each m, 3:1 E/Z mixture, 2H), 3.13, 3.04 (each m, 3:1 E/Z mixture, 4H), 2.87, 2.64 (each m, 3:1 E/Z mixture, 2H), 1.37 (t, *J* = 7.6 Hz, 3H), 1.11 (t, *J* = 7.4 Hz, 3H); MS (EI) *m/z* (rel intensity) 307 (M^+, 50), 306 (65), 275 (100), 226 (20), 212 (73), 183 (30); HRMS, Calcd for $C_{18}H_{17}D_6NO_3$ 307.2054, found 307.2063.

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Key Words

Optical resolution; Chiral etodolac; *L*-Cinchonidine; (-)-Isopinocamphenol.

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