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New Enzymatic and Chemical Approaches to Enantiopure Etodolac

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Abstract: (+)- and (-)-etodolac enantiomers were prepared both by classical resolution via crystallisation of diastereoisomeric salts with (+) and (-)- α -methylbenzylamine, and by suitable manipulation of derivatives (-)-3- and (+)-4, obtained by lipase-catalysed kinetic resolution of racemic 3. X-ray diffraction analysis of the 4-bromobenzoate derivative of (+)-3, obtained from enantiopure acetate (+)-4, allowed us to determine the absolute (R) configuration of (-)-etodolac. © 1997 Elsevier Science Ltd.

INTRODUCTION

Etodolac¹ (1) is a chiral drug with a stereogenic carbon atom and it is widely used for its antiinflammatory and analgesic properties as a racemic mixture. In recent years several attempts ^{2,3} have been made to find convenient synthetic approaches to enantiopure etodolac, as it has been shown² that the (+)-isomer is more active than the racemic mixture.



In 1983 Humber *et al.* reported on the HPLC preparative separation of etodolac diastereoisomeric esters with (-)-borneol.² Recently, an enantioselective Friedel-Crafts reaction between tryptophol and an optically active β -ketobutyrate, suitably functionalized with a "chiral auxiliary", has been described³ to give an etodolac analogue, but with only 40% ee. However, the high cost and the limited industrial applicability of the first procedure of racemate resolution, and the

low optical yield of the second stereoselective synthesis induced us to look for an alternative synthetic route to (+)- and (-)-1.

Thus, we successfully tried a more simple and direct approach, by using the classical fractional crystallisation of etodolac diastereoisomeric salts with (+)- and (-)- α -methylbenzylamine, and prepared both (+)- and (-)-1. Current scientific interest in enzymic reactions prompted us to search for a biocatalytic procedure, based either on the kinetic resolution of a racemic precursor of etodolac (such as ester 2a or alcohol 3), or on the lipase-mediated enantiodifferentiating hydrolysis or acetylation of a meso precursor (such as diester 5 or diol 6). These latter catalytic stereoselective reactions are reported in the literature⁴ to successfully dissymetrize structurally simple prochiral diesters or diols. Thus, it would have been interesting to try this kind of enzymic approach on our prochiral indole derivatives 5 and 6, in order to investigate the effects of structural environment on this enzymatic enantiotopically selective reactions, and to find out the limitations of the method.

We report herein on this search of the best synthetic approach to enantiopure etodolac.



RESULTS AND DISCUSSION

Enzymatic Approach

Preliminary studies of lipase-mediated hydrolysis were performed on racemic 2a in acetonitrile/water 1/9 solution (10 ml) at a constant pH value (pH=7), using *Candida cylindracea lipase* (CCL) and *Porcine pancreas lipase* (PPL) as catalysts. Both CCL (100 mg /100mg of substrate) and PPL (600 mg/ 100mg of substrate) left the ethyl ester unchanged, even after long reaction time. No transesterification was observed when substrate 2a was treated with CCL (100 mg /100mg of substrate) or PPL (600 mg /100mg of substrate) in cyclohexane solution (10 ml) in the presence of *n*-butanol (400 μ l). The same lack of reactivity towards lipase-catalysed hydrolysis or transesterification was observed for prochiral diester 5.

Thus, we prepared racemic 3 and meso 6 by lithium aluminium hydride reduction of derivatives 2a and 5.

The enzymatic acetylation of meso diol 6 (10 mg, 0.034 mol) was performed in acetonitrile solution (1 ml) using vinyl acetate (500 μ l) as an acyl donor, in the presence of CCL (5 mg), PPL (5 mg), or *Pseudomonas PS 30* (5 mg) as catalysts. CCL and PPL mediated acetylations afforded mono alcohol mono acetate derivative 7 with very high enantiomeric purity (ee = 0.99, HPLC), unfortunately proceeding at reaction rates of no practical use (5% conversion after 24h, HPLC). *Pseudomonas* PS30 Amano was found to be more reactive (10% conversion after 24h, HPLC), but significantly less selective than CCL and PPL towards substrate 6 (ee = 0.21, HPLC). No significant improvement was observed in doubling the amount of this enzyme.

We obtained better results in the kinetic resolution of racemic alcohol 3 (100 mg, 0.37 mmol) in the presence of vinyl acetate (1 ml) in various solvents (5 ml). In hydrocarbon solvents (hexane, cyclohexane) CCL gave rapid ($c^5 = 26$, 38 after 2h), but scarcely enantioselective reactions (ee acetate 4 = 0.67, 0.61; $E^5 = 6$). The use of acetonitrile and *t*-butyl methyl ether as solvents allowed us to obtain acetate 4 with high enantiomeric excess (ee = 0.89, 0.99; E = 17, 206), even if at low conversion (c = 0.48, 9.4 after 2h). Whatever solvent was chosen, PPL-mediated reactions were characterised by very modest conversions, and by a spread variety of ee values. *Pseudomonas* PS30-catalysed acetylations in acetonitrile solution afforded the other enantiomer, showing ee values not over 44%.

The best experimental conditions were used for a large scale enzymatic resolution (see Experimental), which provided a certain amount of derivative 4 (first eluted enantiomer, HPLC) with 59% ee after 24h. A long reaction time was preferred in order to have a higher conversion, in spite of a lower enantiomeric purity. However, this was not a limitation, because enantiomeric enriched derivative 4 could be successfully crystallised from hexane/ethyl acetate, to give a sample of enantiopure acetate 4 ($[\alpha]_D^{20} = +4.4^\circ$, c 1, CHCl₃). Basic hydrolysis in refluxing 10% NaOH solution afforded enantiopure alcohol 3 ($[a]_D^{20} = +42.4^\circ$ c=1, CHCl₃), which was converted into the corresponding 4-bromobenzoate ester. This latter derivative provided single crystals submitted to the X-ray diffraction study, in order to determine the absolute configuration of the stereocentre of the alcoholic fragment (figure 1). Thus, the (+)-enantiomers of alcohol 3 and of acetate 4 were found to have the R configuration.



Fig.1. An arbitrary perspective view of 4-bromobenzoate derivative of enantiopure alcohol (+)-3

(S)-Enriched alcohol 3 (33% ee), recovered from the previous large scale preparation (see Experimental), was stirred in *t*-butyl methyl ether solution in the presence of CCL and vinyl acetate for 12 h, to afford the left-handed isomer with 90% ee. Acetylation with acetic anhydride and pyridine, followed by crystallisation from hexane/ethyl acetate and basic hydrolysis, provided enantiopure (HPLC) (S)-3 ($[\alpha]_D^{20} = -41.8^\circ$, c 1, CHCl₃).

Several attempts were performed to convert both enantiopure alcohols (+)- and (-)-3 into the corresponding carboxylic acids, in order to complete the synthetic path towards the enantiopure forms of etodolac. Strong oxidative conditions (Jones' reagent, potassium permanganate) produced extensive degradation of the substrate. An oxidative procedure, based on the treatment of the alcoholic substrate with a dimethylsulfoxide/acetic anhydride mixture⁶ at room temperature, afforded aldehyde (S)-8 in 56% non-optimised yields. Further oxidation with nickel peroxide⁷ allowed us to isolate a sample of the carboxylic acid (S)-1, which was characterised as methyl ester (diazomethane), $[\alpha]_D^{20} = +110^\circ$ (c 1, CHCl₃). This latter was found to be enantiopure by HPLC analysis. Being (S)-(-)-3 precursor of the most useful (+)-1, our assignment of (R) absolute configuration to (+)-3 was found to be in perfect agreement with the (R) configuration of (-)-1, first attributed by Humber *et. al.*⁸. They analysed the relative configurations of the two stereocentres of an ester derivative of (-)-etodolac with (S)-(-)-borneol.

Thus, both (R)- and (S)-etodolac were found to be accessible by enantioselective CCL mediated acetylation of racemic derivative 3, followed by suitable manipulation of the resulting alcohol and acetate derivatives.

In order to fully investigate the effect of substrate chemical structure on the effectiveness of this biocatalytic kinetic resolution, we prepared racemic alcohol 9, showing less steric hindrance around the stereogenic carbon atom involved in the enzymatic reaction. However, both the enantiomers of acetate 10 could be obtained with very modest enantiomeric purities, using CCL, PPL, or *Pseudomonas PS 30* as catalysts.

Classical optical resolution

Eventually, the well established resolution via fractional crystallisation of diastereisomeric salts of 1 with an ancillary enantiomerically pure base, followed by recycling of the unwanted enantiomer by racemization, proved to be the most effective entry to the enantiopure forms of etodolac.

To this end, racemic acid 1 was treated with one equivalent of (R)-(+)- α -methylbenzylamine in acetone solution. Three subsequent crystallisations of the less soluble diastereoisomeric salt from acetone, followed by the usual acidic work-up, afforded enantiopure 1 ($[\alpha]_D^{20} = +66.8^\circ$, c 1 CHCl₃) in 30% yield. The enantiomeric excess was determined by HPLC analysis of the corresponding methyl ester 2b ($[\alpha]_D^{20} = +111.2^\circ$, c = 1 CHCl₃), prepared by treatment with diazomethane. This right-handed methyl ester derivative gave (S)-(-)-alcohol 3 upon lithium aluminium hydride reduction, thus allowing the assignment of the (S) configuration to the enantiomer here isolated.

The same procedure was repeated on racemic etodolac, using (S)-(-)- α -methylbenzylamine, to prepare (R)-etodolac (as methyl ester $[\alpha]_D^{20} = -111.9^\circ$, c = 1 CHCl₃)

A sample of (R)-2b was refluxed in toluene solution in the presence of a catalytic amount of p-toluenesulphonic acid: racemisation was found to be complete after two hours. Thus, we verified the possibility of a full conversion of the starting racemic etodolac into the most useful (S)-enantiomer.

CONCLUSIONS

In this work we have given a full account of the possible synthetic approaches to the enantiopure forms of 1, being the known procedure a time-consuming and expensive preparative HPLC separation of diastereoisomeric derivatives of etodolac.

We have clearly shown that classical resolution via crystallisation of diastereoisomeric salts is the most convenient route to (S)-1, as it happens for most part of enantiopure compounds⁹, which are currently viable on industrial scale. It is also possible to convert the starting racemic etodolac into one optical isomer completely, as the unwanted enantiomer can be usefully racemized in boiling toluene solution with acid catalysis.

We have also detected the limits of the enzyme-mediated dissymmetrization providing enantiomerically enriched products from achiral substrates. In fact, our experimental data have clearly shown the modest effectiveness of biocatalytic enantiotopically selective acetylation of meso derivatives, when the reacting groups are linked to a bulky moiety, as the three ring fused tetrahydropyranoindolyl unit is. The common unmodified lipases we have employed are reported⁴ to be active on substrates with a much simpler structure. On the contrary, the comparison between enzyme-mediated acetylation of derivatives 3 and 9 put into evidence the influence of "loca! steric hindrance" on the enantioselectivity values. Enantiomeric purities showed a dramatic drop when a less hindered stereogenic carbon atom brought the reacting hydroxyl group.

However, biocatalytic methods allowed us to prepare both (R)-4 and (S)-3, suitable precursors of the single enantiomers of etodolac. A sample of enantiopure 4 was converted into the corresponding 4-bromobenzoate derivative for the assignment of the absolute configuration *via* single crystal X-ray analysis.

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EXPERIMENTAL

The following enzymes were employed in this work: *Candida cylindracea lipase* (Sigma, Type VII, 900U/mg), *Porcine pancreas lipase* (Sigma, Type II), and *Pseudomonas* PS30 Amano. Enantiomeric excess of all chiral derivatives was determined by chiral HPLC analysis: Merck-Hitachi L-6200 apparatus, Chiralcel OD column, Daicel, 0.6 ml/min, UV 254 nm: hexane/isopropanol 9/1, (R)-3 R₁ = 9.39 min, (S)-3 R₁ = 19.84 min, (R)-4 R₁ = 8.06 min, (S)-4 R₁ =10.36 min, (R)-2b R₁ = 7.56 min, (S)-2b R₁ = 11.58 min; hexane/isopropanol 8/2, 6 R₁ = 12.30, 7 R₁ = 9.21, 14.50; hexane/isopropanol 93/7, 9 R₁ = 22.10, 52.23, 10 R₁ = 16.02, 18.12. ¹H NMR spectra were recorded in CDCl₃ solutions at room temperature unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz ¹H). The chemical shift scale was based on internal tetramethylsilane. J values are in Hz. Optical rotations were measured on a Jasco DIP 181 digital polarimeter. TLC analyses were performed on Merck Kieselgel 60 F₂₅₄ plates. All the chromatographic separations were carried out on silica gel columns.

X-ray Crystallography of 4-bromobenzoate derivative of enantiopure alcohol (+)-3

Crystal Data : $C_{24}H_{26}NO_3Br$, M = 456.4, monoclinic, space group P2₁, a = 12.545(2), b = 6.190(1), c = 14.337(2) A°, β = 104.66(1)°, V = 1077.1(3) A°³, Z = 2, D_c = 1.407 g cm⁻¹, F(000) = 472, μ (Cu K α) = 2.80 mm⁻¹. Colourless plate, 0.50 x 0.20 x 0.04 mm. Crystals were grown from hexane.

Data collection: Siemens P4 diffractometer, Cu-K α radiation. Cell parameters determined by leastsquares refinements of 38 accurately centred reflections in the range $10 < 2\vartheta < 70^{\circ}$. 3369 total reflections, of which 2911 independent, collected using $\vartheta/2\vartheta$ scan technique up to $2\vartheta_{max} = 116.4^{\circ}$. No crystal decay was observed.

Structure solution and refinement: the structure was solved by direct methods (SIR92 program)¹⁰ and refined on F^2 using SHELXL93¹¹. Full matrix least-squares refinement with anisotropic temperature factors for all non-H atoms (287 parameters refined) converged at R = 0.0553 for 2765 observed reflections (I < 2 σ (I)) and at 0.0573 for all data (wR2 = 0.1537). All H-atoms were found in the difference map and refined as riding on their host atoms. The largest peak in the $\Delta\rho$ map is 0.58 e A° -3 at 1.02 A° from bromine.

The absolute configuration was unambiguously assigned by the Flack parameter^{11,12} [F = -0.019 (32) for the (R) absolute configuration and F = 1.007(38) for the inverse one] and by an R-factor test [R = 0.0553 and R = 0.0645 for the (R) and (S) configurations, respectively].

Full data of the crystal structure have been deposited at Cambridge Crystallographic Data Centre.

Acid catalysed condensation of 7-ethyltryptophol with ethyl 3-oxopentanoate and methyl acetonedicarboxylate to provide derivatives 2a and 5

A mixture of 7-ethyltryptophol¹ (10.00 g, 0.053 mol), the suitable ketoester (0.063 mol), and p-toluenesulphonic acid (0.500 mg) in toluene (80 ml) was refluxed under a Dean-Stark trap for 5h. The reaction mixture was poured into water. The organic phase was washed with a saturated sodium hydrogen carbonate solution, dried over sodium sulphate, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column, eluting with hexane-ethyl acetate.

(\pm)-Ethyl 2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl) acetate (2a): 67%; Found: C, 72.57; H, 7.78; N, 4.21; C₁₉H₂₅NO₃ requires C, 72.35; H, 7.99; N, 4.44%; ¹H NMR δ 0.82 (3H, t, J = 7.4), 1.25 (3H, t, J = 7.4), 1.35 (3H, t, J = 7.4), 2.1 (2H, m), 2.85 (6H, m), 4.00 (2H, m), 4.18 (2H, m), 7.05 (2H, m), 7.35 (1H, d, J = 7.5), 9.11 (1H, broad s).

Methyl 2-[8-ethyl-1-(2-methoxy-2-oxoethyl)-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl]acetate (5): 82%; Found: C, 66.12; H, 6.80; N, 4.11; C₁₉H₂₃NO₅ requires C, 66.07; H, 6.71; N, 4.06%; ¹H NMR δ 1.38 (3H, t, J = 7.4), 2.81 (2H, t, J = 5.3) 2.86 (2H, q, J = 7.4), 3.15 (2H, d, J = 16), 3.25 (2H, d, J = 16), 3.75 (3H, s), 4.05 (2H, t, J = 5.3), 7.08 (2H, m), 7.28 (1H, d, J = 7.5), 9.31 (1H, broad s).

(±)- 2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)-1-ethanol (3)

To THF (100 ml), containing Lithium aluminium hydride (1.2 g, 0.032 mol), ethyl ester 2a (10 g,0.032 mol) dissolved in THF (10 ml) was added dropwise. The mixture was initially refluxed for 2h, then cooled and ethyl acetate (10 ml) was added carefully. Before the extraction with diethyl ether (three times 100 ml) the reaction mixture was diluted with water (50 ml) and washed with brine

(50 ml). The organic phase was dried on sodium sulphate, filtered and concentrated under reduced pressure giving racemic alcohol 3 (7.78 g, 89%) after purification by column chromatography (hexane-ethyl acetate) (Found: C, 74.71; H, 8.54; N, 5.07; $C_{17}H_{23}NO_2$ requires C, 74.69; H, 8.48; N, 5.12%). H¹ NMR: 0.95 (3H, t, J = 7.4), 1.36 (3H, t, J = 7.4), 1.98 (2H, m), 2.15 (2H, m), 2.85 (4H, m), 3.70 (2H, m), 4.05 (2H, m), 7.05 (2H, m), 7.38 (1H, d, J = 7.5), 7.75 (1H, broad s).

(R)-(+)-2(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)ethyl acetate (4) by kinetic resolution of racemic 3

A mixture of (±)-3 (4.01 g, 0.015mol), CCL (4.03 g), and vinyl acetate (40 ml) in *t*butylmethyl ether (400 ml) was stirred at room temperature for 24h. The residue obtained upon evaporation of the filtered reaction mixture was chromatographed on a silica gel column, eluting with hexane-ethyl acetate. The first eluted fractions provided enantiomeric enriched acetate 4 (1.65g, 35%, 59% ee). This latter was crystallised from hexane-ethyl acetate to afford an enantiopure sample (0.64 g, 14%) of (R)-4 ($[\alpha]_D^{20} = + 4.4^\circ c = 1$ CHCl₃) (Found: C, 72.41; H, 7.89; N, 4.34; C₁₉H₂₅NO₃ requires C, 72.35; H, 7.99; N, 4.44%). ¹H NMR: 0.96 (3H, t, J = 7.4), 1.42 (3H, t, J = 7.4), 1.93 (5H, s + m), 2.26 (2H, t, J = 7.4), 2.88 (4H, m), 4.05 (2H, t, J = 7.4), 4.18 (2H, m), 7.11 (2H, m), 7.42 (1H, d, J = 7.5), 7.79 (1H, broad s). The last eluted fractions gave (S)-enriched 5 (2.12 g, 52%, ee 33%).

(R)-(+)-2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)-1-ethanol (3)

(R)-4 (0.500 g, 1.59 mmol) in absolute ethanol (10 ml) was treated with a 10% solution of NaOH (3ml). The solution was stirred at room temperature until the TLC analysis indicated that the reaction was completed (30 min). The mixture was concentrated under reduced pressure then diluted with water (5 ml), extracted with diethyl ether (3 times, 20 ml). The organic phase was dried with sodium sulphate, filtered, and concentrated again to give after purification by column chromatography (hexane-ethyl acetate) enantiopure (R)-3 ($[\alpha]_D^{20} = +42.4^\circ$, c = 1, CHCl₃) (0.364 g, 84%).

(R)- 2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)-1-ethanol 4-bromo-benzoate ester

A solution of enantiopure (R)-3 (0.350 g, 1.28 mmol), 4-bromobenzoyl chloride (0.360 g, 1.65 mmol), and triethylamine (0.167 g, 1.65 mmol) in methylene chloride was stirred at room temperature for 1h. The reaction mixture was treated with water, washed with a saturated sodium hydrogen carbonate solution, and extracted with methylene chloride. The organic phase was dried on sodium sulphate, and the residue was chromatographed, eluting with hexane-ethyl acetate. The first eluted fractions gave the title compound (0.454 g, 78%) which was crystallised from hexane, to

provide crystals for X-ray diffraction study (Found: C, 63.20; H, 5.81; Br, 17.47; N, 3.11; $C_{24}H_{26}BrNO_3$ requires C, 63.16; H, 5.74; Br, 17.51; N, 3.07%). ¹H NMR: 0.95 (3H, t, J = 7.4), 1.33 (3H, t, J = 7.4), 1.95 (2H, m), 2.36 (2H, m), 2.80 (4H, m), 4.07 (2H, m), 4.44 (2H, m), 7.07 (2H, m), 7.38 (3H, m), 7.61 (2H, m), 7.66 (1H, broad s).

(S)-(-) 2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)-1-ethanol (3)

A solution of (S)-enriched alcohol **3** (2.00g, 0.733 mmol, 33% ee), CCL (2.00 g), and vinyl acetate (20 ml) in *t*-butylmethyl ether (200 ml) was stirred at room temperature for 12h. The residue, obtained upon evaporation of the filtered reaction mixture, was chromatographed on a silica gel column, eluting with hexane-hexane 1:ethyl acetate 1. The last eluted fractions provided enantiomerically enriched (S)-alcohol **3** (0.815 g, 41%, 90% ee). Its enantiomeric purity was improved by conversion into the acetate derivative upon reaction with acetic anhydride and pyridine, crystallisation from hexane-ethyl acetate, and basic hydrolysis. At the end of this sequence, alcohol (S)-**3** was recovered (0.487 g) with 99% ee (HPLC) ($[\alpha]_D^{20} = -41.8$, c 1, CHCl₃).

(S)-2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetaldehyde (8)

A solution of (S)-3 (0.273 g, 0.001 mol) in dimethylsulfoxide (3 ml) and acetic anhydride (2 ml) was allowed to stand at room temperature for 24h. The reaction mixture was poured into water, extracted with diethyl ether and washed with a saturated solution of sodium hydrogen carbonate. The organic phase was dried on sodium sulphate, and concentrated to dryness under reduced pressure. The residue was chromatographed on a silica gel column, using hexane-hexane 8 :ethyl acetate 2 as eluent. The first eluted fractions gave the methylthiomethyl ether derivative (0.080 g, 24%), a known possible by-product of this kind of oxidation (Found: C, 67.72; H, 7.94; N, 4.51; S, 10.10, C₁₈H₂₅NO₂S requires C, 67.68; H, 7.89; N, 4.38; S, 10.04%). ¹H NMR: 0.91 (3H, t, J = 7.4), 1.39 (3H, t, J = 7.4), 2.09 (7H, m + s), 2.79 (2H, t, J = 5.3), 2.86 (2H, q, J = 7.4), 3.54 (1H, m), 3.79 (1H, m), 4.01 (2H, t, J = 5.3), 4.62 (2H, s), 7.06 (2H, m), 7.37 (1H, d, J = 7.5), 8.26 (1H, broad s). EI-MS: m/z 333 (M⁺), 304, 228. The last eluted fractions gave aldehyde (S)-8 (0.152 g, 56 %). ¹H NMR: 0.87 (3H, t, J = 7.4), 1.36 (3H, t, J = 7.4), 2.09 (4H, m), 2.82 (2H, m), 2.86 (2H, q, J = 7.4), 4.00 (2H, m), 7.06 (2H, m), 7.36 (1H, d, j = 7.2), 8.43 (1H, broad s), 9.79 (1H, s); EI-MS: m/z 271 (M⁺), 242, 228.

(S)-Methyl-2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl) acetate (2b)

Nickel peroxide⁸ (0.400 g, 4.4 mmol) was added to a mixture of aldehyde (S)-8 (0.130 g, 0.48 mmol) and NaOH (0.030 g, 0.75 mmol) in water (20ml). The reaction mixture was stirred at room temperature for 12h. After removal of nickel peroxide, the filtrate was acidified with HCl 10% and

extracted with diethyl ether. The organic phase was dried on sodium sulphate, treated with a solution of diazomethane in diethyl ether, and the solvent removed under reduced pressure. The residue was chromatographed on a silica gel column, using hexane-hexane 7:ethyl acetate 3 as eluent, to afford methyl ester (S)-2b (0.083 g, 57%, 97% ee HPLC). $[\alpha]_D^{20} = .+110^\circ$, c 1, CHCl₃) (Found: C, 71.68; H, 7.61; N, 4.57; C₁₈H₂₃NO₃ requires C, 71.74; H, 7.69; N, 4.65%).; ¹H NMR: 0.84 (3H, t, J = 7.4), 1.38 (3H, t, J = 7.4), 2.09 (2H, m), 2.85 (6H, m), 3.71 (3H, s), 4.00 (2H, m), 7.05 (2H, m), 7.38 (1H, d, J = 7.5), 9.05 (1H, broad s). EI-MS: m/z 301 (M⁺), 272, 228.

(S)-2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl) acetic acid (1) - (S)-etodolac

(R)-(+)- α -Methylbenzylamine (8.47 g, 0.070 mol) was added to a solution of racemic 1 (20 g, 0.070 mol) in acetone (100 ml). After standing for 1h, the precipitate was filtered off and recrystallised thrice from acetone to afford the right-handed diastereoisomeric salt (m.p. 156°-161°C, $[\alpha]_D^{20} = +63.9^\circ$, c = 1, EtOH). A solution of this salt in water was acidified with HCl 10%, and extracted with ethyl acetate. The organic phase was dried on sodium sulphate, and concentrated under reduced pressure, to provide (+)-1 (6.02g, 30%, $[\alpha]_D^{20} = +65.6^\circ$, c = 1, CHCl₃) (99% ee as methyl ester) (Found: C, 71.12; H, 7.42; N, 4.81; C₁₇H₂₁NO₃ requires C, 71.06; H, 7.37; N, 4.87%). ¹H NMR: 0.85 (3H, t, J = 7.4), 1.30 (3H, t, J = 7.4), 2.12 (2H, m), 2.77 (2H, m), 2.84 (2H, m), 3.10 (2H, s), 4.10 (2H, m), 6.98 (1H, d, J = 7.5), 7.07 (1H, d, J = 7.5), 7.36 (1H, d, J = 7.5), 8.67 (1H, broad s).

(R)- -2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl) acetic acid (1) - (R)-etodolac

(S)-(-)- α -Methylbenzylamine (8.47 g, 0.070 mol) was added to a solution of racemic etodolac (20 g, 0.070 mol) in acetone (100 ml). After standing for 1h, the precipitate was filtered off and recrystallised thrice from acetone to afford the left-handed diastereoisomeric salt (m.p. 159°-163°C, $[\alpha]_D^{20} = -64.7^\circ$ c = 1, EtOH). A solution of this salt in water was acidified with HCl 10%, and extracted with ethyl acetate. The organic phase was dried on sodium sulphate, and concentrated under reduced pressure, to provide (+)-1 (5.63g, 28%, $[\alpha]_D^{20} = +66.8^\circ$, c = 1, CHCl₃) (99% ee as methyl ester). A sample of this acid was treated with diazomethane and reduced with lithium aluminium hydride in tetrahydrofuran, to afford enantiopure (R)-alcohol 5.

2-[8-Ethyl-1-(2-hydroxyethyl)-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl]-1-ethanol (6)

Lithium aluminium hydride reduction of diester 5 (7.00 g. 0.020 mol) gave diol 6 (4.45 g, 77%) after purification of the reaction residue by column chromatography (hexane-ethyl acetate) (Found: C, 70.48; H, 8.09; N, 4.79; $C_{17}H_{23}NO_3$ requires C, 70.56; H, 8.01; N, 4.84%). H¹ NMR: 1.32

(3H, t, J = 7.4), 2.25 (4H, t, J = 7), 2.85 (4H, m), 3.72 (4H, t, J = 7), 4.05 (2H, t, J = 5.3), 7.02 (2H, m), 7.38 (1H, d, J = 7.5), 8.40 (1H; broad s).

Ethyl 2-(1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate

A mixture of tryptophol (5.00 g, 0.031 mol), ethyl 2-oxobutanoate (4.84 g, mol), *p*-toluenesulphonic acid (0.400 g) in toluene (50 ml) was refluxed under a Dean-Stark trap for 5h. The reaction mixture was poured into water. The organic phase was washed with a saturated sodium hydrogen carbonate solution, dried over sodium sulphate, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column, using hexane-ethyl acetate as eluent, to afford the title compound (6.24 g, 74%) (Found: C, 69.71; H, 7.62; N, 5.01; $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09%). ¹H NMR: 1.28 (3H, t, J = 7.4), 1.67 (3H, s), 2.80 (2H, t, J = 5.3), 2.85 (1H, d, J = 16), 3.00 (1H, d, J = 16), 4.02 (2H, d, J = 5.3), 4.15 (4H, m), 7.06 (2H, m), 7.48 (1H, d, J = 7.5), 9.10 (1H, broad s).

2-(1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)-1-ethanol (8)

Lithium aluminium hydride reduction of ethyl 2-(1-methyl-1,3,4,9-tetrahydropyrano[3,4b]indol-1-yl)acetate (6.00 g. 0.022 mol) gave alcohol **8** (4.47 g, 83%) after purification of the reaction residue by column chromatography (hexane-ethyl acetate) (Found: C, 72.74; H, 7.49; N, 6.10; $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06%). H¹ NMR: 1.60 (3H, s), 2.14 (2H, m), 2.71 (2H, m), 2.95 (2H, m), 3.65 (2H, m), 4.05 (2H, m), 7.14 (2H, m), 7.30 (1H, d, J = 7.5), 7.50 (1H, d, J = 7.5), 8.12 (1H, broad s).

REFERENCES

- Demerson, C.A.; Humber, L.G.; Abraham, N.A.; Schilling, G.; Martel, R.R.; Pace-Asciak, C. J. Med. Chem. 1983, 36, 1778.
- 2. Demerson, C.A.; Humber, L.G.; Philipp, A.H. J. Med. Chem. 1976, 19, 391.
- Cabral, L.M.; Costa, P.R.R.; Vasconcellos, M.L.A.A.; Barreiro, E.J.; Castro, R.N. Synth.Commun. 1996, 26, 3671.
- 4. Poppe, L.; Novak, L. in Selective Biocatalysis, VCH, Weinheim, 1992, p.141-155
- For enzymatic kinetic resolutions the extent of conversion (c) and the enantiomeric ratio (E) were calculated according to Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C.J. J.Am.Chem.Soc., 1982, 104, 7294.
- 6. Albright, J.D.; Goldman, L. J.Am. Chem. Soc., 1965, 87, 4214.
- 7. Nakagawa, K.; Konaka, R.; Nakata, T. J.Org. Chem. 1962, 271, 1597

- 8. Humber, L.G.; Demerson, C.A.; Swaminathan, P.; Bird, P.H. J.Med.Chem., 1986, 29, 871.
- 9. R.A.Sheldon, in Chirotechnology, Marcel Dekker, Inc., New York, 1993, chapter 3, p.77.
- Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M.C.; Polidori, G., Camalli, M. J. Appl. Cryst. 1994, 27,435.
- 11. Sheldrick, G.M. SHELXL93. Program for the Refinement of Crystal Structures 1993, University of Gottingen, Germany.
- 12. Flack, H.D. Acta Cryst., 1983, A39, 876-881.

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