THE FORMAL SYNTHESIS OF CHIRAL ETODOLAC USING CHIRAL 1,2-DI(ALKYLCARBONYL)OXYPENTAN-3-ONE AS CHIRAL BUILDING BLOCK

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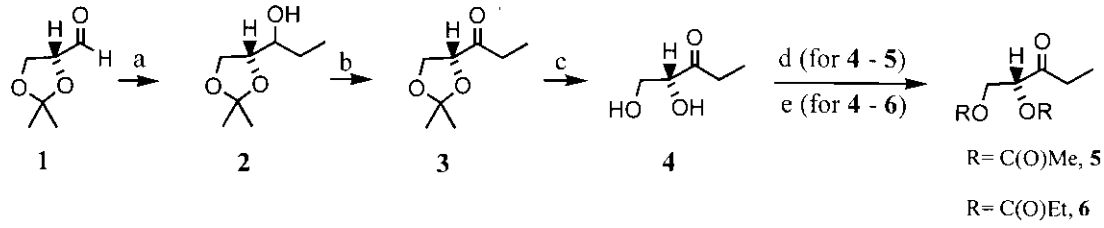
Abstract- A stereoselective synthesis of (+)- and (–)-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)-1-ethanols (**31**) and (**32**), the key intermediates for chiral etodolac was executed in seven steps starting from the asymmetric cyclization of (2*R*)-1,2-di(acetyloxypentan)-3-one (**5**) or (2*R*)-1,2-di(propionyloxypentan)-3-one (**6**) and 7-ethyltryptophol (**7**). Some unexpected transformations are also described.

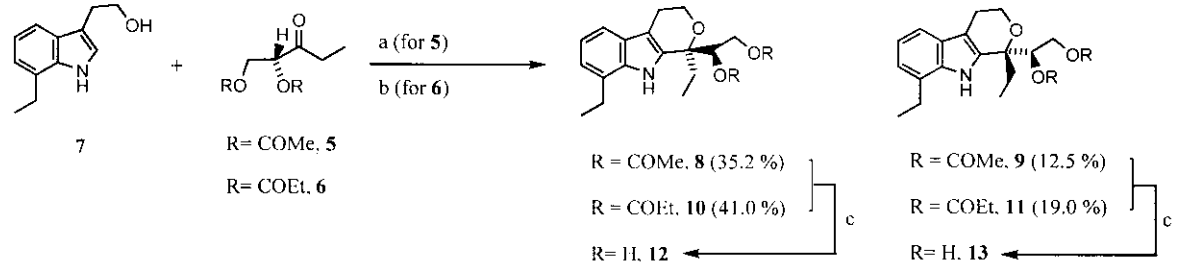
Etodolac (brand name: lodine) is an antiarthritic drug with antiinflammatory and analgestic properties.[1,2] The structure of etodolac belongs to mono acids with a stereogenic carbon center. Owing to the chiral environment of the biological system, its enantiomers might show different receptor affinities. The assumption has been confirmed by an *in vitro* test,[3] those results indicating that the inhibition (IC_{50}) of arachidonic acid utilization by (±)-etodolac, (+)-etodolac (**33**)[4] and (–)-etodolac (**34**) is 240 μM, 120 μM and more than 400 μM respectively. The results of this test were also confirmed by a clinical trial.[5] Therefore, the promising clinical benefits of (+)-etodolac prompted the development of an asymmetric synthesis of (+)-etodolac. Previous studies include an asymmetric synthesis of an etodolac analogue but with low enantioselectivity,[6] and a chemoenzymatic synthesis of (–)-etodolac in order to determine its (*R*) configuration.[7] We report herein our approach for an asymmetric synthesis of (+)- and (–)-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)-1-ethanols (**31**) and (**32**),[7] the key intermediates for chiral etodolac. The study started by using several chiral β-ketovaleric esters (or their enol ether forms)[8] and 7-ethyltryptophol (**7**)[1] for the acid-catalyzed formation of tetrahydropyran ring.[9] However, the de maximum value is only 11 %. This low selectivity might be attributed to the reason that the two chiral centers in the chiral keto ester and in the newly generated tetrahydropyran ring are far apart.[6] Two promising chiral ketones, (2*R*)-1,2-di(acetyloxypentan)-3-one (**5**) and (2*R*)-1,2-di(propionyloxypentan)-3-one (**6**), were employed to test the influence of the distance, although several steps are required to reach chiral etodolac. As shown in Scheme 1, each chiral ketone was prepared from (*R*)-2,3-isopropylideneglyceraldehyde (**1**)[10] using a four-step sequence. A stereoselective cyclization of **7** and **5** using BF_3·OEt_2 in toluene, as shown in Scheme 2, afforded diastereomeric products (**8**) and (**9**), in a ratio of 2.8:1. However, the yield is only 48 %. Similarly, cyclization of **7** and **6** using BF_3·OEt_2 in tetrahydrofuran at 45 °C, afforded diastereomeric products (**10**) and (**11**). Although this cyclization increased the yield to 60 %, the ratio decreased to 2.2:1. Cram's open-chain model leads to the

Scheme 1



a. EtMgBr, THF, 93 % crude; b. $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, 78 %; c. HOAc, H_2O, 93 % crude; d. MeC(O)Cl, Py, 94 % ; e. EtC(O)Cl, NEt_3, CH_2Cl_2, 82 %.

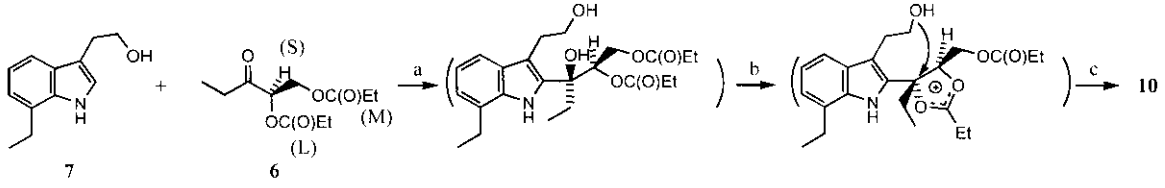
Scheme 2



a. $BF_3.OEt_2$, toluene, 48 % ; b. $BF_3.OEt_2$, THF, 45 °C, 60 % crude; c. NaOH, MeOH, H_2O, 85-86 %.

predication of diastereo-selectivity (Scheme 3). Lack of diastereo-selectivity could be explained by the low selectivity of nucleophilic attack of indole skeleton to ketone (**6**). The ethylcarbonyloxy group assisted dehydration may explain the stereochemistry of the ring-closure. Subsequently, this assumption was confirmed by a synthetic pathway leading to **31** from **12**, a key intermediate of known configuation.[7] The major cyclization products (**8**, **10**) were treated with a basic aqueous solution, to afford the diol (**12**). Alternatively, the minor cyclization products (**9**, **11**) undergo the same treatment to afford the diol (**13**). The diol (**12**) is oxidized with sodium periodate and the resulting aldehyde (**14**) is reduced to alcohol (**15**). Mesylation of **15** yielded mesylate (**16**). Cyanide substitution of the mesylate

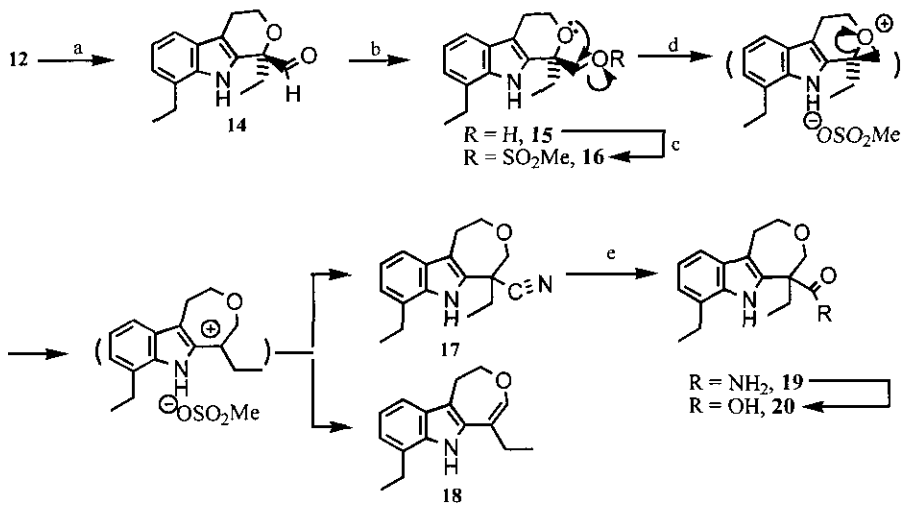
Scheme 3



a. nucleophilic attack from the α face of **6**, (Cram's model), b. neighboring group assisted dehydration, c. ring closure.

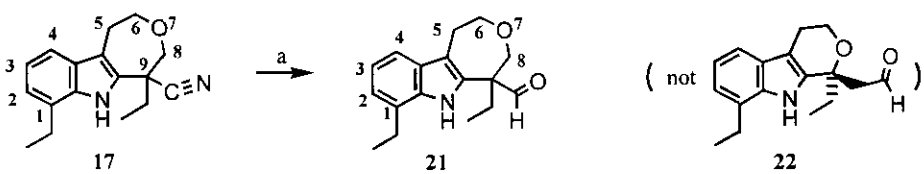
group of **16** followed by hydrolysis of the nitrile group of the substitution product might provide chiral etodolac. However, under vigorous cyanide formation and hydrolysis conditions, the unexpected chiral amide (**19**) and chiral acid (**20**) were obtained in succession (Scheme 4). Compound (**20**) is a regioisomer of etodolac.[12] The unique formation of **20** from **16** can be interpreted as the nucleophilic attack of the tetrahydropyrano oxygen to the electrophilic carbon center of the methanesulfonyloxy methyl side chain to form an oxonium ion intermediate, which undergoes rearrangement to a highly stabilized carbonium ion intermediate, followed by cyanide interception to yield **17** or deprotonation to yield **18**.[13] Compound (**18**) is an optical inactive product. Hydrolysis of **17** afforded the amide (**19**) and acid (**20**) in succession.

Scheme 4



a.$NaIO_4$, $NaHCO_3$(aq), CH_2Cl_2, 57.5 % ; b. $NaBH_4$, THF, CH_3OH, 74.4 %; c. $MeSO_2Cl$, NEt_3, , CH_2Cl_2, 90 % ; d.NaCN, DMF, 48.4 % (for **17**), 10.4 % (for **18**); e.NaOH, EtOH, 74.7 %.

Scheme 5

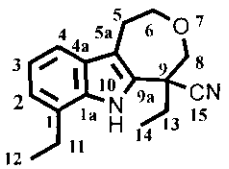


a. DIBALH, THF, -78 °C, 59.3 %.

For comparison purpose, aldehyde (**21**) was prepared from **17** by DIBALH reduction (Scheme 5). The characteristic ^{1}H-NMR peak of **21** appeared at the C-8 (δ 3.30 and δ 3.16, J=15.9 Hz, ABq). This peak differs from that of the desired aldehyde (**22**),[7] in which the corresponding α-CH_2 of the formyl appeared at δ 2.09 (m).[14] Distinctly, the comparable chemical shifts and splitting at the C-8 (δ 3.41 and δ

3.23, J=15.8 Hz, ABq) in **17** and the C-8 in **21** suggest that ring-expansion probably appeared at the nitrile formation step. The structure of **17** was confirmed on the basis of a HMBC spectral data (Table 1). Interestingly, **17** and **19** are optically active compounds.[15] The rapid cyanide interception of the carbonium intermediate during ring-expansion may have led to the chiral cyanide (**17**). The facial selectivity of the cyanide interception remains to be explored. To our knowledge, this type of rearrangement was not previously reported.[16]

Table 1 Selected long range ^{1}H-^{13}C coupling correlation of **17**

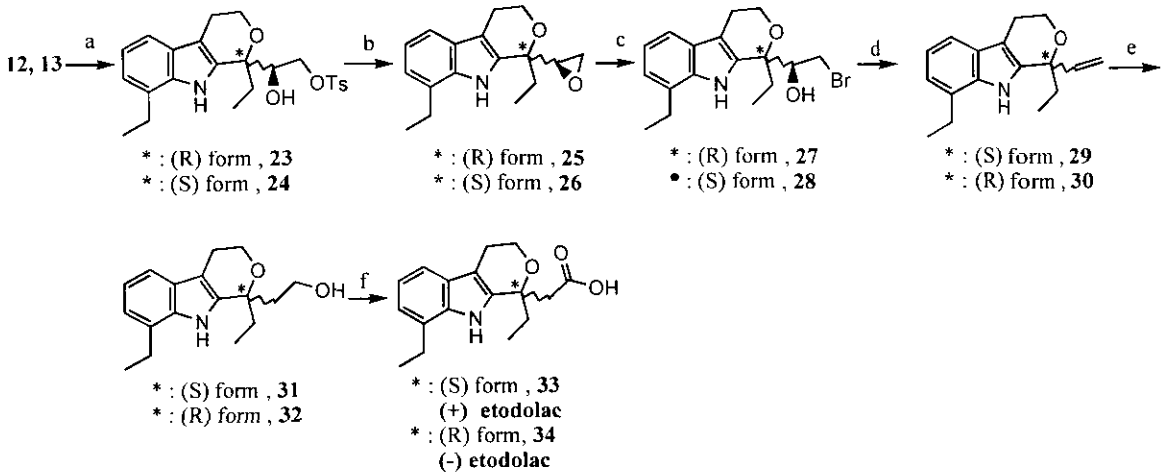


$C^{\#}$	δ/ppm	$H^{\#}$	δ/ppm	long range correlation
C-15	118.65	H-13	1.99, 2.05	$^{3}J_{C\text{-}H(H\text{-}13)}$
		H-8	3.23, 3.41	$^{3}J_{C\text{-}H(H\text{-}8)}$
C-13	26.66	H-8	3.23, 3.41	$^{3}J_{C\text{-}H(H\text{-}8)}$
		H-14	1.24	$^{2}J_{C\text{-}H(H\text{-}14)}$
C-9	77.60	H-13	1.99, 2.05	$^{2}J_{C\text{-}H(H\text{-}13)}$
		H-14	1.24	$^{3}J_{C\text{-}H(H\text{-}14)}$
		H-8	3.23, 3.41	$^{2}J_{C\text{-}H(H\text{-}8)}$
C-8	39.91	H-13	1.99, 2.05	$^{3}J_{C\text{-}H(H\text{-}13)}$
C-6	68.83	H-8	3.23, 3.41	$^{3}J_{C\text{-}H(H\text{-}8)}$
		H-5	3.06	$^{2}J_{C\text{-}H(H\text{-}5)}$
C-11	23.92	H-2	7.06	$^{3}J_{C\text{-}H(H\text{-}2)}$
		H-12	1.40	$^{2}J_{C\text{-}H(H\text{-}12)}$

As the diol (**12**) might be converted to chiral etodolac *via* a series of modifications without C-C bond cleavage. An alternative reaction pathway was carried out (Scheme 6). The diol (**12**) was tosylated and subsequently treated with base to give the epoxide (**25**) in a good yield. The neopentyl environment of the secondary alcohol may account for the regiospecificity of the tosylation reaction. An attempt to isomerize the epoxide (**25**) using $MgBr_2$·OEt_2 gave the bromohydrine (**27**) as the only isolated product. The expected aldehyde (**22**) (see Scheme 5) was not obtained, although many articles have reported the precedented methodology for acid-catalyzed rearrangement of epoxides to aldehydes.[17-19] Interestingly, treatment of **25** with an excessive amount of BF_3·OEt_2 in benzene leads to a deformylative ring-expanded product of good yield (Scheme 7), its spectral data are identical with those of **18**. It is suggested that the epoxide (**25**) underwent deformylation and migration of the C-C bond to the highly stabilized quaternary carbonium ion center,[20] which is formed by the cleavage of the tetrahydropyran C-O bond. Refluxing of **27** with metallic zinc in ethanol gave the elimination product (**29**), which, after

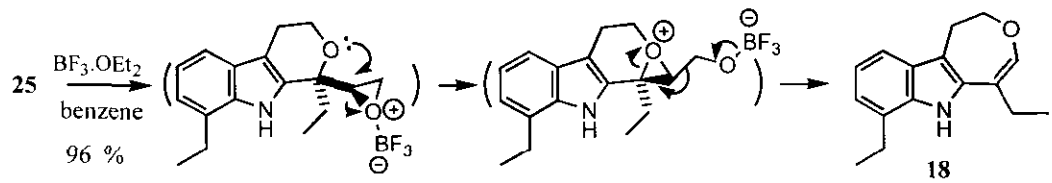
undergoing hydroboration-oxidation afforded the desired alcohol (**31**) in 93.3 % ee.[21] The optical antipode (**32**) was prepared from **13** by a similar sequence. Since the transformation of the (*S*)-(−)-alcohol (**31**) to (*S*)-(+)-etodolac (**33**) using a two-stage oxidation sequence has been described,[7] this work constitutes a formal synthesis of chiral etodolac.

Scheme 6



a. TsCl, pyridine, 93 %; b. NaH, THF, 95 %; c. $MgBr_2.OEt_2$, *i*-Pr_2O, 69-72 %; d. Zn, EtOH, 64 % (**27-29**) 46 % (**28-30**); e. $(BH_3)_2$, H_2O_2, 43-45 %; f. see reference 7.

Scheme 7



In conclusion, our results demonstrated that enantiomerically pure synthetic intermediates (**31** and **32**) can be prepared from chiral ketones (**5**, **6**) in moderate diastereo-selectivity. Moreover, some interesting transformations, such as a ring-expansion of a tetrahydropyran-fused indole derivative (**16**) during cyanide substitution and an unexpected deformylative ring expansion of a tetrahydropyran-fused indole derivative (**25**) are also clarified or reasonably explained.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 577 spectrophotometers, NMR spectra were recorded on a DRX-500 (500 MHZ) spectrometer, $CDCl_3$ was used as solvents, and TMS was added as an internal standard. If determined, the type of carbon in ^{13}C NMR spectra is indicated in parentheses after the

chemical shift: 0, quaternary, 1, methine, 2, methylene, and 3, methyl. Elemental analyses were determined by a Perkin-Elmer 2400. MS spectra and high-resolution MS 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). Melting points were measured in open capillary tubes using 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. All reagents were of commercial quality and were used as received.

(4*R*)-1-(2,2-Dimethyl)-(1,3)dioxolan-4-ylpropan-1-ol (2). A 1 M solution of ethylmagnesium bromide in dry THF (355 mL) was added to **1** (42 g, 0.323 mol) over 0.5 h at 0 °C. After another 1 h of stirring, the mixture was quenched with 10 % NH_4Cl and was then evaporated. The residue was partitioned between dichloromethane and water, and the phases were separated. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give **2** (48 g, 93 % crude) , which was used in the next step without purification. A small amount of sample was purified on silica gel using 1:5 ethyl acetate/hexane to give a yellow oil. IR (film) ν_{max}: 3450, 1380, 1220, 1070 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.90-4.01 (m, 3H), 3.70 (m, 1H), 1.50 (m, 2H), 1.43 (s, 3H), 1.37 (s, 3H), 1.01 (t, J=7.4 Hz, 3H); MS (70 eV) m/z (%): 159 (M^+-1, 1), 145 (56), 101 (100); $[\alpha]^{23}_D$ +14° (c 1.0, $MeCO_2Et$).

(4*R*)-1-(2,2-Dimethyl)-(1,3)dioxolan-4-ylpropan-1-one (3). A solution of dried dimethyl sulfoxide (52.2 mL) in dichloromethane (147 mL) and a solution of **2** (47 g, 0.29 mol) in CH_2Cl_2 (372 mL) were added sequentially, in 5 min intervals, to a solution of oxalyl chloride (29.8 mL, 0.35 mol) in dichloromethane (745 mL) cooled at –78 °C. After stirring for 20 min, triethylamine (205 mL) was added. The cooling bath was removed and stirring was continued for 30 min. The separated organic layer was washed three times with water, then was dried ($MgSO_4$) and evaporated. The residue was purified on silica gel using 1:5 ethyl acetate/hexane as eluent to give **3** (36.2 g, 78 %) as a brown oil. IR (film) ν_{max}: 1720, 1480, 1210, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.43, 4.46 (ABq, J=5.6 Hz, 1H), 4.18, 4.22 (ABq, J=7.7 Hz, 1H), 3.85, 3.99 (ABq, J=5.7 Hz, 1H), 2.64 (q, J=7.2 Hz, 2H), 1.49 (s, 3H), 1.40 (s, 3H), 1.06 (t, J=7.2 Hz, 3H); MS (70 eV) m/z (%): 157 (M^+-1, 2), 100 (8), 57 (100); $[\alpha]^{23}_D$ +71° (c 1.0, $MeCO_2Et$); Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.37; H, 8.61.

(2*R*)-1,2-Dihydroxypentan-3-one (4). A mixture of **3** (33 g, 0.21 mol), acetic acid (174 mL) and H_2O (64 mL) was heated at 65-70 °C for 1.5 h. The mixture was then evaporated to leave a residue, which was partitioned between dichloromethane and water. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to give **4** (23 g, 93 % crude) as a brown oil, which was used in next step without purification. Finally, a small amount of pure sample was prepared by silica gel purification using 1:5 ethyl acetate/hexane as eluent. IR (film) ν_{max}: 3400, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.25 (m, 1H), 3.95 (m, 2H), 2.54 (m, 2H), 1.15 (t, J=7.2 Hz, 3H); MS (70 eV) m/z (%): 119 (M^++1, 4), 100 (32), 88 (52), 75 (64), 73 (48), 61 (62), 57 (100); HR-EIMS Found: 119.0702, Calcd for $C_5H_{11}O_3$: 119.0708 (M^++1); $[\alpha]^{23}_D$ -60° (c 1.0, CH_2Cl_2).

(2*R*)-1,2-Di(acetyloxy)pentan-3-one (5). Acetyl chloride (20.5 g, 0.26 mmol) was added dropwise to an ice-cooled of **4** (14 g, 0.12 mmol) in pyridine (210 mL); the resulting solution was then allowed to stir at 0 °C for 2 h. After evaporation of pyridine under a vacuum at 25 °C, the residue was diluted with dichloromethane and water. The separated organic layer was washed with saturated ammonium chloride and water, and was then dried ($MgSO_4$) and evaporated. The residue was purified on silica gel using 1:10 ethyl acetate/hexane as eluent to give **5** (22.8 g, 94 %) as a brown oil. IR (film) ν_{max}: 1748, 1220 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.29 (*m*, 1H), 4.42 (*m*, 2H), 2.56 (q, J=7.2 Hz, 2H), 2.19 (s, 3 H), 2.07 (s, 3H), 1.09 (t, J=7.2 Hz, 3H); MS (70 eV) m/z (%): 203 (M^++1, 2), 159 (100), 143 (40), 117 (46), 103 (72), 57 (92); $[\alpha]^{23}_D$ +14° (c 1.0, CH_2Cl_2); Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.79; H, 7.31.

(2*R*)-1,2-Di(propionyloxy)pentan-3-one (6). Propionyl chloride (9.5 mL, 101.7 mmol) was added dropwise to an ice-cooled solution of **4** (5 g, 42.4 mmol) in dichloromethane (100 mL) and triethylamine (23 mL, 169 mmol). The resulting solution was allowed to stir at 0 °C for 15 min and then at rt for 1.5 h. The mixture was diluted with dichloromethane and water, and the phases were separated. The separated organic layer was washed with water, and then dried ($MgSO_4$) and evaporated. The residue was purified on silica gel using 1:5 ethyl acetate/hexane as eluent to give **6** (8 g, 82 %) as a brown oil. IR (film) ν_{max}: 1740, 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.28 (m, 1H), 4.40 (m, 2H), 2.50-2.66 (m, 4H), 2.32 (q, J=7.5 Hz, 2H) 1.00-1.20 (m, 9H); MS (70 eV) m/z (%): 230 (M^+, 5), 173 (100); $[\alpha]^{23}_D$ -15° (c 1.0, CH_2Cl_2); Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.95; H, 7.51.

(1*R*,1′*R*)-1,8-Diethyl-1-(1′,2′-diacetyloxy)ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (8) and **(1*S*,1′*R*)-1,8-Diethyl-1-(1′,2′-diacetyloxy)ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (9)**. A solution of **7** (10.0 g, 52.9 mmol) and **5** (10.0 g, 49.5 mmol) in dry toluene (250 mL) was stirred under nitrogen. BF_3·OEt_2 (10 mL, 7.9 mmol) was added dropwise to the above solution over a period of 15 min. After the addition, the mixture was stirred at 25 °C for 3 days. The solution was washed with saturated sodium bicarbonate and water, and then dried ($MgSO_4$) and evaporated. The crude product was purified on silica gel using 1:10 ethyl acetate/hexane as eluent to give in successively **8** (6.55 g, 35.2 %) and **9** (2.3 g, 12.5 %) as brown oils. **8**, IR (film) ν_{max}: 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.90 (br s, 1H), 7.37 (d, J=7.7 Hz, 1H), 7.09 (m, 1H), 7.04 (d, J=7.3 Hz, 1H), 5.50 (m, 1H), 4.52, 4.14 (ABq, J=12.1 Hz, 2H), 3.98 (m, 2H), 2.87 (q, J=7.6 Hz, 2H), 2.84 (m, 1H), 2.76 (m, 1H), 2.10 (s, 3H), 1.94 (m, 2H), 1.85 (s, 3H), 1.38 (t, J=7.6 Hz, 3H), 0.89 (t, J=7.3 Hz, 3H); MS (70 eV) m/z (%): 373 (M^+, 76), 308 (24), 284 (32), 249 (80), 228 (100); HR-EIMS Found: 373.1890 (M^+); Calcd for $C_{21}H_{27}NO_5$: 373.1889; $[\alpha]^{23}_D$ +34° (c 1.0, C_2H_5OH); Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H; 7.29, N, 3.75. Found: C, 67.19; H, 6.88; N, 3.43. **9**, IR (film) ν_{max}: 1742 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.91 (br s, 1H), 7.38 (d, J=7.2 Hz, 1H), 7.10 (m, 1H), 7.06 (d, J=7.1 Hz, 1H), 5.66 (m, 1H), 4.27 (m, 1H), 4.17 (m, 1H), 4.10 (m, 2H), 2.87 (q, J=7.6 Hz, 2H), 2.82 (m, 2H), 2.19 (s, 3H), 1.98 (m, 2H), 1.93 (s, 3H), 1.38 (t, J=7.6 Hz, 3H), 0.81 (t, J=7.4 Hz, 3H); MS (70 eV) m/z (%): 373 (M^+, 12), 308 (14), 263 (46), 249 (76), 228 (100); HR-EIMS Found: 373.1892, Calcd for $C_{21}H_{27}NO_5$: 373.1889; $[\alpha]^{23}_D$ +17° (c 1.0, C_2H_5OH); Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H; 7.29, N, 3.75. Found: C, 67.24; H, 6.91; N, 3.53.

(1*R*,1′*R*)-1,8-Diethyl-1-(1′,2′-dipropionyloxy)ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (10) and

(1*S*,1′*R*)-1,8-Diethyl-1-(1′,2′-dipropionyloxy)ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (11).[22] A solution of **7** (21.7 g, 114.8 mmol) and **6** (26.4 g, 123.3 mmol) in dry THF (108 mL) was stirred at rt under nitrogen. $BF_3{\cdot}OEt_2$ (65 mL, 513 mmol) was added dropwise to the above solution over a period of 10 min. After the addition, the mixture was stirred at 45-50 °C for 2.5 days. The solution was evaporated and the residue partitioned between dichloromethane and water. The separated organic layer was washed with saturated sodium bicarbonate and water, and then dried ($MgSO_4$) and evaporated to give the crude product. HPLC reading showed the ratio of two diastereomers was 2.2:1. The crude product was purified on silica gel using 1:8 ethyl acetate/hexane as eluent to give in successively **10** (19.0 g, 41.3 %) and **11** (9.6 g, 20.9 %) as brown oils. **10**, IR (film) ν_{max}: 1700, 1460, 1360, 1260 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.88 (br s, 1H), 7.35 (d, J=7.7 Hz, 1H), 7.07 (m, 1H), 7.01 (d, J=7.1 Hz, 1H), 5.53 (dd, J=4.1, 2.45 Hz, 1H), 4.53 (dd, J=6.1, 2.45 Hz, 1H), 4.12 (m, 1H), 3.98 (m, 2H), 2.85 (q, J=7.5 Hz, 2H), 2.83 (m, 1H), 2.73 (m, 1H), 2.33 (q, J=7.6 Hz, 2H), 2.12 (q, J=7.6 Hz, 2H), 1.91 (m, 2H), 1.37 (t, J=7.6 Hz, 3H), 1.08 (t, J=7.6 Hz, 3H), 1.01 (t, J=7.6 Hz, 3H), 0.88 (t, J=7.5 Hz, 3H); MS (70 eV) (m/z) (%): 402 (M^++1, 5), 311 (10), 291 (50), 276 (100); $[\alpha]^{23}_D$ +33° (c 1.0, CH_2Cl_2).

(1*R*,1′*R*)-1-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)ethane-1,2-diol (12). A mixture of **10** (10 g, 24.9 mmol), methanol (100 mL) and 1 M sodium hydroxide (200 mL) was heated to 80 °C and stirred for 1 h. The solution was cooled and neutralized with 3 N HCl and was then evaporated. The residue was partitioned between dichloromethane and water. The organic layer was washed with water, and then dried ($MgSO_4$) and evaporated. The residue was purified on silica gel using 1:2 ethyl acetate/hexane as eluent to give **12** as a yellow foam (6.1 g, 85 %). In a similar manner, the title compound (5.5 g, 86 %) was also prepared by the hydrolysis of the acetate **8** (8.3 g). IR (film) ν_{max}: 3400, 1460, 1090 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.34 (br s, 1H), 7.35 (d, J=7.8 Hz, 1H), 7.06 (m, 1H), 7.00 (d, J=7.1 Hz, 1H), 4.04 (m, 2H), 3.92 (m, 1H), 3.80 (m, 1H), 3.23 (m, 1H), 3.02 (br s, 1H), 2.84 (q, J=7.6 Hz, 2H), 2.81 (m, 1H), 2.70 (m, 1H), 2.10 (m, 2H), 1.35 (t, J=7.6 Hz, 3H), 1.00 (t, J=7.6 Hz, 3H); MS (70 eV) m/z (%): 289 (M^+, 8), 241 (28), 228 (52), 184 (20); HR-EIMS Found: 289.1694 (M^+), Calcd for $C_{17}H_{23}NO_3$: 289.1678; $[\alpha]^{23}_D$ -16° (c 1.0, CH_2Cl_2); Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.25; H, 7.63; N, 4.47.

(1*S*,1′*R*)-1-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)ethane-1,2-diol (13). The title compound (5.9 g, ~85 %) was prepared from **11** (9.6 g, ~23.9 mmol) using a similar procedure as that described for the preparation of **12**. In a similar manner, the title compound (3.4 g, 86 %) was also prepared by the hydrolysis of the acetate **9** (5.1 g). IR (film) ν_{max}: 3400, 1460, 1090 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.38 (br s, 1H), 7.35 (d, J=7.8 Hz, 1H), 7.07 (m, 1H), 7.00 (d, J=7.10 Hz, 1H), 4.00 (m, 2H), 3.97 (m, 1H), 3.80 (m, 1H), 3.72 (m, 1H), 2.91 (br s, 1H), 2.84 (q, J=7.6 Hz, 2H), 2.77 (m, 2H), 1.85 (m, 2H), 1.34 (t, J=7.6 Hz, 3H), 0.99 (t, J=7.4 Hz, 3H); MS (70 eV) m/z (%): 289 (M^+, 8), 255 (12), 241 (16), 228 (100), 212 (16), 184 (16); HR-EIMS Found: 289.1684 (M^+), Calcd for $C_{17}H_{23}NO_3$: 289.1678; $[\alpha]^{25}_D$ -6° (c 1.0, CH_2Cl_2). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.34; H, 7.85; N, 4.69.

(1*R*)-1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-carbaldehyde (14). Saturated sodium bicarbonate (1.5 mL) was added dropwise to a solution of **12** (4.5 g, 15.6 mmol) in dichloromethane (35

mL); the resulting solution was stirred for 5 min. Sodium periodate (6.3 g, 29.4 mmol) was added to this solution, and the mixture was stirred for 1 h. The organic phase was washed with water, and then dried ($MgSO_4$) and evaporated to leave a residue, which was purified on silica gel using 1:10 ethyl acetate/hexane as eluent to give **14** (2.3 g, 57.5 %) as a brown oil. IR ($CHCl_3$) ν_{max}: 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.93 (s, 1H), 8.05 (br s, 1H), 7.42 (d, J=7.70 Hz, 1H), 7.08-7.15 (m, 2H), 4.30 (m, 1H), 4.12 (m, 1H), 2.86-2.93 (m, 4H), 2.11 (m, 1H), 2.03 (m, 1H), 1.40 (t, J=7.40 Hz, 3H), 0.94 (t, J=7.40 Hz, 3H); MS (70 eV) m/z (%): 257 (M^+, 16), 228 (100); HR-EIMS Found: 257.1408 (M^+), Calcd for $C_{16}H_{19}NO_2$: 257.1416; $[\alpha]^{23}_D$ +70° (c 1.0, C_2H_5OH).

(1*R*)-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)methanol (15). Sodium borohydride (0.69 g, 15.8 mmol) was added in one lot to a solution of **14** (2 g, 7.78 mmol) in THF (29 mL), while being stirred under nitrogen at 25 °C. Methanol (2.9 mL) was added dropwise to the above mixture over a period of 20 min. The solution was stirred for 1 h and then evaporated. The residue was partitioned between dichloromethane and water. The separated organic layer was washed with water, and then dried ($MgSO_4$) and evaporated to leave a residue, which was purified on silica gel using 1:5 ethyl acetate/hexane as eluent to give **15** (1.5 g, 74.4 %) as a brown oil. IR (film) ν_{max}: 3450, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.96 (br s, 1H), 7.37 (d, J=7.4 Hz, 1H), 7.05 (m, 2H), 4.04 (m, 2H), 3.75-3.87 (m, 2H), 2.81 (m, 2H), 2.77 (q, J=7.5 Hz), 2.00 (q, J=7.4 Hz, 2H), 1.36 (t, J=7.5 Hz, 3H), 0.86 (t, J=7.4 Hz, 3H); MS (70 eV) (m/z) (%): 259 (M^+, 20), 230 (100); HR-EIMS Found: 259.1568 (M^+), Calcd for $C_{16}H_{21}NO_2$: 259.1572; $[\alpha]^{23}_D$ +12° (c 1.0, C_2H_5OH).

(1*R*)-1,8-Diethyl-1-(methanesulfonyloxy)methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (16). Methanesulfonyl chloride (1.75 g, 15.4 mmol) was added dropwise to an ice-cooled solution of **15** (1.4 g, 5.40 mmol) in dichloromethane (40 mL) and triethylamine (7.8 mL). After 1 h, the reaction mixture was neutralized with 1 N HCl and was then washed with water. The organic phase was then dried ($MgSO_4$) and evaporated to leave a residue, which was purified on silica gel using 1:5 ethyl acetate/hexane as eluent to give **16** (1.64 g, 90 %) as a brown oil. IR ($CHCl_3$) ν_{max}: 1200 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.96 (br s, 1H), 7.38 (d, J=7.2 Hz, 1H), 7.08 (m, 1H), 7.04 (m, 1H), 4.53 (d, J=10.0 Hz, 1H), 4.35 (d, J=10.0 Hz, 1H), 4.06 (m, 2H), 2.98 (s, 3H), 2.86 (q, J=7.5 Hz, 2H), 2.82 (m, 2H), 1.99 (q, J=7.5 Hz, 2H), 1.35 (t, J=7.5 Hz, 3H), 0.83 (t, J=7.5 Hz, 3H); MS (70 eV) (m/z) (%): 337 (M^+, 16), 308 (20), 241 (100), 228 (100), 212 (40), 184 (96); HR-EIMS Found: 337.1339 (M^+), Calcd for $C_{17}H_{23}NO_4S$: 337.1348; $[\alpha]^{23}_D$ +25.5° (c 1.0, CH_2Cl_2).

1,9-Diethyl-6,8,9,10-tetrahydro-5*H*-7-oxa-10-azabenzo[*a*]azulene-9-carbonitrile (17) and **1,9-Diethyl-6,10-dihydro-5*H*-7-oxa-10-azabenzo[*a*]azulene (18).**

run A: A mixture of **16** (0.7 g, 2.08 mmol) and sodium cyanide (2.0 g, 40.8 mmol) in DMF (9 mL) was heated to 90 °C over a period of 0.5 h and stirred for 12 h at 85-90 °C. The solution was concentrated under a vacuum to remove DMF, and then the residue was partitioned between dichloromethane and water. The separated organic phase was washed with water, and then dried ($MgSO_4$) and evaporated. The residue was purified on silica gel column chromatography using 1:10 ethyl acetate/hexane as eluent to give in successively **18** (0.052 g, 10.4 %) as a white powder and **17** (0.27 g, 48.4 %) as a brown oil. **17**, IR (film) ν_{max}: 2255 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.83 (br s, 1H), 7.37 (d, J=7.9 Hz, 1H), 7.14 (m, 1H),

7.06 (d, J=7.5 Hz, 1H), 4.33 (m, 1H), 4.19 (m, 1H), 3.41, 3.23 (ABq, J=15.8 Hz, 2H), 3.06 (m, 2H), 2.85 (m, 2H), 2.05 (m, 1H), 1.99 (m, 1H), 1.40 (t, J=7.5 Hz, 3H), 1.24 (t, J=7.5 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 133.84(0), 129.53(0), 128.18(0), 126.25(0), 120.41(1), 119.99(1), 118.65(0), 115.63(1), 113.65(0), 77.60(0), 68.83(2), 39.91(2), 34.33(2), 26.66(2), 23.92(2), 13.79(3), 8.84(3); MS (70 eV) (m/z) (%): 268 (M^+, 100), 238 (30), 185 (100), 170 (80), 156 (40); HR-EIMS Found: 268.1571 (M^+), Calcd for $C_{17}H_{20}N_2O$: 268.1576; $[\alpha]^{25}_D$ -12° (c 1.0, C_2H_5OH); Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.84; H, 7.28; N, 10.09. **18**, white powder, mp 109-110 °C (isopropylether). IR (KBr) ν_{max}: 3380, 1660, 1460, 1120 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.60 (br s, 1H), 7.32 (d, J=7.8 Hz, 1H), 7.08 (m, 1H), 6.99 (d, J=7.1 Hz, 1H), 5.50 (s, 1H), 4.42 (t, J=4.5 Hz, 2H), 3.21 (t, J=4.5 Hz, 2H), 2.87 (q, J=7.6 Hz, 2H), 2.31 (q, J=7.3 Hz, 2H), 1.40 (t, J=7.6 Hz, 3H), 1.20 (t, J=7.3 Hz, 3H); Ms (70 eV) m/z (%): 241 (M^+, 100), 226 (76), 212 (28), 184 (92); HR-EIMS Found: 241.1477 (M^+), Calcd for $C_{16}H_{19}NO$: 241.1466; Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.58; H, 7.79; N, 5.78.

run B: A mixture of **16** (0.5 g, 1.48 mmol) and potassium cyanide (1.93 g, 0.03 mol) in DMF (7.5 mL) was heated at 150 °C for 30 min with stirring. After a similar worked-up and purification as described in run A, **17** (0.06 g, 15.1 %) and **18** (0.11 g, 27.7 %) were obtained.

1,9-Diethyl-6,10-dihydro-5*H*-7-oxa-10-azabenzo[*a*]azulene (18). BF_3·OEt_2 (0.1 mL, 0.79 mmol) was added to a solution of **25** (0.084 g, 0.31mmol) in dry benzene (0.5 mL). The mixture was stirred for 5 min. It was then diluted with 50 mL of benzene and washed three times with 10 % sodium bicarbonate. The separated organic layer was washed with water, dried ($MgSO_4$) and evaporated. The residue was filtered from a short pad of silica gel using 1:5 ethyl acetate/hexane as eluent to give **18** (0.081 g, 96 %). Its spectral data are the same as those of an authentic sample prepared from **16**.

1,9-Diethyl-6,8,9,10-tetrahydro-5*H*-7-oxa-10-azabenzo[*a*]azulene-9-carboxylic acid amide (19) and **1,9-Diethyl-6,8,9,10-tetrahydro-5*H*-7-oxa-10-azabenzo[*a*]azulene-9-carboxylic acid (20)**. A mixture of **17** (0.1 g, 0.374 mmol), 1 M NaOH (1 mL) and ethanol (0.2 mL) was heated under refluxed for 4 h. At this stage, a small amount of the solution was concentrated, and then the residue was purified by silica gel column chromatography using 1:5 ethyl acetate/hexane as eluent, the partially hydrolyzed intermediate (**19**) was obtained as a brown oil. Refluxing was continued for another 12 h after which the mixture was evaporated. The residue was acidified with 3 N HCl and was then partitioned between dichloromethane and water. The organic phase was washed with water, and then dried ($MgSO_4$) and evaporated, the residue was purified on silica gel using 1:1 ethyl acetate/hexane as eluent to give **20** (0.08 g, 74.7 %) as a brown oil. **19**, IR ($CHCl_3$) ν_{max}: 3450, 1680 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.44 (br s, 1H), 7.26 (d, J=7.5 Hz, 1H), 7.08 (m, 1H), 7.01 (m, 1H), 6.94 (br s, 1H), 5.72 (br s, 1H), 4.16 (m, 2H), 3.38 (br s, 2H), 3.03 (m, 2H), 2.82 (q, J=7.7 Hz, 2H), 1.83 (q, J=7.3 Hz, 2H), 1.33 (t, J=7.7 Hz, 3H), 0.88 (t, J=7.3 Hz, 3H); MS (70 eV) m/z (%): 286 (M^+, 100), 238 (96), 184 (92); HR-EIMS Found: 286.1679 (M^+), Calcd for $C_{17}H_{22}N_2O_2$: 286.1681; $[\alpha]^{23}_D$ +13° (c 1.0, C_2H_5OH). **20**, IR (film) ν_{max}: 3000 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.24 (br s, 1H), 7.27 (m, 1H), 6.90-7.10 (m, 2H), 4.26 (m, 2H), 3.41 (br s, 2H), 3.05 (m, 2H), 2.85 (q, J=7.6 Hz, 2H), 1.88 (q, J=7.6 Hz, 2H), 1.32 (t, J=7.6 Hz, 3H), 0.91 (t, J=7.6 Hz, 3H); MS (70 eV) m/z (%): 287 (M^+, 100), 241 (96); HR-EIMS Found: 287.1515 (M^+), Calcd for $C_{17}H_{21}NO_3$: 287.1521.

1,9-Diethyl-6,8,9,10-tetrahydro-5*H*-7-oxa-10-azabenzo[*a*]azulene-9-carbaldehyde (21). A solution of **17** (0.1 g, 0.37 mmol) in dry hexane (15 mL) was cooled under nitrogen to –78 °C. DIBALH (1.5 mL, 1 M in hexane, 1.5 mmol) was added dropwise to the above solution , after stirring for 30 min at –78 °C, the excess of the reagent was destroyed with 1 mL of ethyl acetate. The mixture was then stirred with 1.5 g of 5 % aqueous silica at –78 °C for 30 min and then 3 h at 25 °C. The resulting mixture was then filtered through Celite followed by extraction with dichloromethane. The separated organic layer was washed with water, and then dried ($MgSO_4$) and evaporated. The residue was purified on silica gel using 1:10 ethyl acetate/hexane as eluent to afford **21** (0.06 g, 59.3 %) as a brown oil. IR ($CHCl_3$) ν_{max}: 1730, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.71 (s, 1H), 7.87 (br s, 1H), 7.33 (d, J=7.8 Hz, 1H), 7.10 (m, 1H), 7.01 (d, J=7.1 Hz, 1H), 4.29 (m, 1H), 4.21 (m, 1H) 3.30, 3.16 (ABq, J=15.9 Hz, 2H), 3.05 (m, 2H), 2.86 (q, J=7.6 Hz, 2H), 1.78 (q, J=7.7 Hz, 2H), 1.38 (t, J=7.7 Hz, 3H), 0.95 (t, J=7.6 Hz, 3H); MS (70 eV) (m/z) (%) 271 (M^+, 63), 242 (100), 185 (80); HR-EIMS Found: 271.1569 (M^+), Calcd for $C_{17}H_{21}NO_2$: 271.1572; $[\alpha]^{23}_D$ -34° (c 1.0, CH_2Cl_2); Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C 74.94; H, 7.82; N, 5.06.

(1*R*,1′*R*)-1,8-Diethyl-1-(1′-hydroxy-2′-tosyloxy)ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (23). *p*-Toluenesulfonyl chloride (0.72 g, 3.78 mmol) was added to a solution of **12** (0.84 g, 2.91 mmol) in pyridine (9 mL). The mixture was stirred for 10 min and was then placed in a refrigerator overnight to precipitate the pyridine hydrochloride. The mixture was then poured into ice water and acidified with 10 % sulfuric acid and was then extracted twice with dichloromethane. The combined extracts were washed with water, and then dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography using 1:5 ethyl acetate/hexane as eluent to give **23** (1.2 g, 93 %) as a foam. IR ($CHCl_3$) ν_{max}: 3450, 1360, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.31 (br s, 1H), 7.70 (d, J=7.5 Hz, 2H), 7.37 (d, J=7.7 Hz, 1H), 7.29 (d, J=7.5 Hz, 2H), 7.11 (m, 1H), 7.06 (d, J=7.1 Hz, 1H), 4.40 (d, J=10.7 Hz, 1H), 4.27 (d, J=8.9 Hz, 1H), 4.05 (m, 1H), 3.90 (m, 1H), 3.59 (m, 1H), 3.00 (br s, 1H), 2.86 (q, J=7.6 Hz, 2H), 2.82 (m, 1H), 2.69 (m, 1H), 2.44 (s, 3H), 2.15 (m, 1H), 2.03 (m, 1H), 1.38 (t, J=7.6 Hz, 3H), 1.02 (t, J=7.4 Hz, 3H); MS (70 eV) (m/z) (%): 443 (M^+, 12), 271 (32), 228 (100), 184 (20), 172 (24); HR-EIMS Found: 443.1740 (M^+), Calcd for $C_{24}H_{29}NO_5S$: 443.1767; $[\alpha]^{23}_D$ -78° (c 1.0, CH_2Cl_2); Anal. Calcd for $C_{24}H_{29}NO_5S$: C, 64.99; H, 6.59; N, 3.16. Found: C 64.62; H, 6.21; N, 3.38.

(1*S*,1′*R*)-1,8-Diethyl-1-(1′-hydroxy-2′-tosyloxy)ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (24). The title compound (**24**) (1.2 g, 93 %) was prepared from **13** (0.84 g) using a similar procedure as that described for the preparation of **23**, which was obtained as a foam. IR ($CHCl_3$) ν_{max}: 3450, 1360, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.27 (br s, 1H), 7.78 (d, J=8.3 Hz, 2H), 7.40 (d, J=7.7 Hz, 1H) , 7.34 (d, J=8.3 Hz, 2H), 7.12 (m, 1H), 7.07 (d, J=7.0 Hz, 1H), 4.40 (d, J=10.4 Hz, 1H), 4.35 (m, 1H), 4.24 (m, 1H), 4.04 (m, 1H), 3.86 (m, 1H) , 3.01 (br s, 1H), 2.90 (q, J=7.7 Hz, 2H), 2.86 (m, 1H), 2.72 (m, 1H) , 2.48 (s, 3H), 2.12 (m, 1H), 1.70 (m, 1H), 1.40 (t, J=7.7 Hz, 3H), 0.73 (t, J=7.4 Hz, 3H); MS (70 eV) (m/z) (%): 443 (M^+, 2), 271 (16), 241 (60), 228 (100), 184 (48); HR-EIMS Found: 443.1745 (M^+), Calcd for $C_{24}H_{29}NO_5S$: 443.1767; $[\alpha]^{23}_D$ +25° (c 1.0, CH_2Cl_2); Anal. Calcd for $C_{24}H_{29}NO_5S$: C, 64.99; H, 6.59; N, 3.16. Found: C 64.82; H, 6.45; N, 3.37.

(1*R*,1′*R*)-1,8-Diethyl-1-oxiran-2-yl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (25). Sodium hydride (0.4

g of 60 % in mineral oil, 10 mmol) was added to a solution of **23** (1.2 g, 2.7 mmol) in dry THF (12 mL) at 0 °C. After stirring for 1 hour at 0 °C, the mixture was allowed to stir at rt for 2 h and was then poured into ice water. The mixture was extracted with dichloromethane, and the organic layer was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified on silica gel using 1:10 ethyl acetate/hexane and then recrystallized from benzene to give **25** (0.7 g, 95 %) as a white powder, mp 109-110 °C. IR (KBr) ν_{max}: 3340, 1460, 1300, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.85 (br s, 1H), 7.36 (d, J=7.6 Hz, 1H), 7.06 (m, 1H), 7.01 (d, J=7.2 Hz, 1H), 4.10 (m, 1H), 3.95 (m, 1H), 3.23 (m, 1H), 2.81-2.86 (m, 4H), 2.74 (m, 1H), 2.70 (m, 1H), 2.04 (m, 2H), 1.34 (t, J=7.6 Hz, 3H), 0.86 (t, J=7.4 Hz, 3H); MS (70 eV) (m/z) (%): 271 (M^+, 36), 242 (100), 228 (92), 184 (40); HR-EIMS Found: 271.1614 (M^+), Calcd for $C_{17}H_{21}NO_2$: 271.1572; $[\alpha]^{23}_D$ +118° (c 1.0, CH_2Cl_2); Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C 75.03; H, 7.53; N, 5.08.

(1*S*,1′*R*)-1,8-Diethyl-1-oxiran-2-yl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (**26**). The title compound (**26**) (0.7 g, 95 %) was prepared from **24** (1.2 g) by a similar procedure to that described for the preparation of **25**, this compound was obtained as a white powder, mp 151-153 °C (benzene). IR (KBr) ν_{max}: 3340, 1460, 1300, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.81 (br s, 1H), 7.43 (d, J=7.7 Hz, 1H), 7.14 (m, 1H), 7.08 (d, J=7.2 Hz, 1H), 4.17 (m, 2H), 3.36 (m, 1H), 2.98 (m, 2H), 2.91 (q, J=7.6 Hz, 2H), 2.83 (m, 2H), 1.82 (m, 2H), 1.41 (t, J=7.6 Hz, 3H), 0.81 (t, J=7.3 Hz, 3H); MS (70 eV) m/z (%): 271 (M^+, 8), 241 (100), 226 (52), 184 (64); HR-EIMS Found: 271.1537 (M^+), Calcd for $C_{17}H_{21}NO_2$: 271.1572; $[\alpha]^{23}_D$ -75° (c 1.0, CH_2Cl_2); Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C 75.14; H, 7.49; N, 5.03.

(1*R*,1′*S*)-2-Bromo-1-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)ethanol (**27**).
Magnesium bromide etherate powder (1.89 g, 7.32 mmol) was added to a solution of **25** (1.00 g, 3.69 mmol) in isopropyl ether (20 mL) in one portion. The mixture was stirred at rt overnight. It was then diluted with 100 mL of dichloromethane and was then washed with water, dried ($MgSO_4$) and evaporated. The residue was purified on silica gel column chromatography using 1:5 ethyl acetate/hexane as eluent to give **27** as a white powder (0.93 g, 71.6 %). mp 107-108 °C (1:5 ethyl acetate/hexane). IR (KBr) ν_{max}: 3450, 1470, 1300 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.36 (br s, 1H), 7.42 (d, J=7.7 Hz, 1H), 7.14 (m, 1H), 7.10 (m, 1H), 4.18 (d, J=10.7 Hz, 1H), 4.15 (m, 1H), 3.97 (m, 1H), 3.86 (d, J=10.7 Hz, 1H), 2.83-5.00 (m, 5H), 2.77 (m, 1H), 2.23 (m, 1H), 2.14 (m, 1H), 1.43 (t, J=7.6 Hz, 3H), 1.08 (t, J=7.4 Hz, 3H); MS (70 eV) m/z (%): 353, 351 (M^+, 9), 271 (100), 228 (100); HR-EIMS Found: 351.0821 (M^+), Calcd for $C_{17}H_{22}NO_2Br$: 351.0834; $[\alpha]^{23}_D$ −16.4° (c 1.0, CH_3OH); Anal. Calcd for $C_{17}H_{22}NO_2Br$: C, 57.96; H, 6.29; N, 3.98. Found: C 57.57; H, 6.04; N, 3.60.

(1*S*,1′*S*)-2-Bromo-1-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)ethanol (**28**). The title compound (**28**) (1.35 g, 69 %) was prepared from **26** (1.5 g) using a similar procedure as that described for the preparation of **27**, which was obtained as a brown oil. IR ($CHCl_3$) ν_{max}: 3440, 1420 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.23 (br s, 1H), 7.43 (d, J=7.7 Hz, 1H), 7.13 (m, 1H), 7.08 (d, J=7.0 Hz, 1H), 4.30 (m, 1H), 4.13 (m, 1H), 3.93 (m, 1H), 3.91 (d, J=10.4 Hz, 1H), 3.62 (t, J=10.5 Hz, 1H), 2.92 (m, 3H), 2.78 (m, 2H), 2.12 (m, 1H), 1.81 (m, 1H), 1.41 (t, J=7.5 Hz, 3H), 0.74 (t, J=7.3 Hz, 3H); MS (70 eV) m/z (%): 353, 351 (M^+, 8), 228 (100); HR-EIMS Found: 351.0821 (M^+), Calcd for $C_{17}H_{22}NO_2Br$: 351.0834; $[\alpha]^{23}_D$

+14.5° (c 1.0, CH_3OH); Anal. Calcd for $C_{17}H_{22}NO_2Br$: C, 57.96; H, 6.29; N, 3.98. Found: C 57.58; H, 6.03; N, 3.58.

(1*S*)-1,8-Diethyl-1-vinyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (**29**). Activated zinc powder (4 g, 61.2 mmol) was added to a solution of **27** (1.3 g, 3.69 mmol) in absolute ethanol (4 mL); the resulting solution was then refluxed under N_2 for 12 h. It was then diluted with dichloromethane and was washed with water. The separated organic layer was dried ($MgSO_4$) and evaporated. The residue was purified on silica gel by column chromatography using 1:10 ethyl acetate/hexane as eluent to give **29** (0.6 g, 64 %) as a brown oil. IR (film) ν_{max}: 3440, 1420 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.56 (br s, 1H), 7.40 (d, J=7.8 Hz, 1H), 7.12 (m, 1H), 7.04 (d, J=7.2 Hz, 1H), 6.00 (dd, J=17.4, 10.5 Hz, 1H), 5.27 (d, J=10.5 Hz, 1H), 5.02 (d, J=17.5 Hz, 1H), 4.07 (m, 1H), 3.91 (m, 1H), 2.95 (m, 1H), 2.88 (q, J=7.7 Hz, 2H), 2.68 (m, 1H), 1.95 (m, 2H), 1.38 (t, J=7.6 Hz, 3H), 0.88 (t, J=7.5 Hz, 3H); MS (70 eV) m/z (%): 255 (M^+, 24). 226 (100); HR-EIMS Found: 255.1621 (M^+), Calcd for $C_{17}H_{21}NO$: 255.1624; $[\alpha]^{23}_D$ +12.4° (c 1.0, CH_2Cl_2); Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C 79.57; H, 8.01; N, 5.18.

(1*R*)-1,8-Diethyl-1-vinyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (**30**). The title compound (**30**) (0.5 g, 46 %) was prepared from **28** (1.5 g) using a similar procedure as that described for the preparation of **29**. IR (film) ν_{max}: 3360, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.62 (br s, 1H), 7.51 (d, J=7.7 Hz, 1H), 7.22 (m, 1H), 7.10 (d, J=7.2 Hz, 1H), 6.12 (dd, J=17.3, 10.5 Hz, 1H), 5.40 (m, 1H). 5.14 (d, J=17.3 Hz, 1H), 4.19 (m, 1H), 4.04 (m, 1H), 3.06 (m, 1H), 3.00 (q, J=7.6 Hz, 2H), 2,80 (m, 1H), 2.07 (m, 2H), 1.50 (t, J=7.6 Hz, 3H), 0.99 (t, J=7.4 Hz, 3H); MS (70 eV) m/z (%): 255 (M^+, 16), 226 (100); HR-EIMS Found: 255.1629 (M^+), Calcd for $C_{17}H_{21}NO$: 255.1624; $[\alpha]^{23}_D$ -13° (c 1.0, CH_2Cl_2); Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C 79.63; H, 8.11; N, 5.22.

(1*S*)-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)-1-ethanol (**31**). The olefin (**29**) (0.09 g, 0.353 mmol) in dry THF (5 mL) and 9-BBN (1 M of 2.5 mL, 2.5 mmol) was treated at 25 °C, under nitrogen, with diborane generated from sodium borohydride (0.5 g, 13.2 mmol) and $BF_3{\cdot}OEt_2$ (3 mL). The generator was heated on a water bath at 70 °C, and a gentle flow of nitrogen was maintained to ensure complete transfer of diborane to the reaction flask. The resulting solution was cooled to 0 °C and was then treated with 3 N NaOH (0.8 mL) and was stirred for 10 min. A 30 % solution H_2O_2 (0.8 mL) was added and the solution was stirred for another 10 min. The mixture was then stirred for 3 min at 50 °C and was then extracted with dichloromethane. The extract was washed with 1 N HCl and dried ($MgSO_4$) and then evaporated. Then, the residue was purified on silica gel using 1:2 ethyl acetate/hexane as eluent to give **31** (0.043 g, 45 %) as a foam. $[\alpha]^{23}_D$ –39° (c 1.0, $CHCl_3$), lit.,[7]: $[\alpha]^{23}_D$ – 41.8° (c 1.0, $CHCl_3$). **31** was identified by comparing its MS spectra data and retention time in HPLC with those of racemic form and the ^{1}H NMR data with those of chiral form.[7]

(1*R*)-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)-1-ethanol (**32**). The title compound (**32**) (0.041 g, 43 %) was prepared from **30** (0.09 g) using a similar procedure as that described for the preparation of **31**, which was obtained as a foam. IR (film) ν_{max}: 3350 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.95 (br s, 1H), 7.40 (d, J=7.7 Hz, 1H), 7.13 (m, 1H), 7.05 (d, J=7.3 Hz, 1H), 4.08 (m, 1H), 4.01 (m, 1H), 3.72 (m, 2H), 2.75-2,89 (m, 4H), 2.22 (m, 1H), 2.08 (m, 1H), 2.00 (m, 1H), 1.92 (m, 1H), 1.36 (t, J=7.5 Hz,

3H), 0.95 (t, J=7.5 Hz, 3H); MS (70 eV) m/z (%): 273 (M^+, 24), 244 (100), 228 (64); $[\alpha]^{23}_D$ +39° (c 1.0, $CHCl_3$); Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C 74.32; H, 8.29; N, 5.01.

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12. There are three apparent differences in ^{1}H-NMR signals: 1) the methylene CH_2 at C-8, δ 3.41 (br s, 2H) in **20**, *vs* δ 3.05 (br s, 2H) in α-CH_2 of CO_2H in (±)-etodolac;[1] 2) methylene CH_2 at C-5, δ 3.05 (m, 2H) in **20**, *vs* methylene CH_2 at C-4, δ 2.80 (m, 2H) in (±)-etodolac; and 3) quternary ethyl CH_2, δ 1.88 (q, J=7.6 Hz, 2H) in **20**, *vs* quaternary ethyl CH_2, δ 2.08 (m, 2H) in (±)-etodolac.
13. Another batch of experiments was carried out for optimization the yield of **18** (see EXPREIMENTAL).
14. Reduction of the aldehyde (**21**) using $NaBH_4$ in ethanol afforded the corresponding alcohol. The specific rotary value of this alcohol ($[\alpha]^{23}_D$ −11° (c 1.0, $CHCl_3$)) differs from that of the desired alcohol (**31**) ($[\alpha]^{20}_D$ -41.8° (c 1.0, $CHCl_3$)).[7] Furthermore, the HPLC retention time reading is also different from those of the alcohol (**31**) and a racemic form of **31** prepared by reduction ($LiAlH_4$/THF) of (±)–etodolac.
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22. Since the polarities of **11** and **6** are very close, the purification step is skipped. No analytical data of **11** are collected, although the subsequent hydrolysis gives the corresponding diol (**13**) with satisfactory spectral data.

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