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# A NOVEL SUBSTITUTION REACTION OF TETRAHYDROPYRANO[3,4-*b*]INDOLE DERIVATIVE - CHAIN EXTENSION AND STRUCTURAL CORRELATION STUDY

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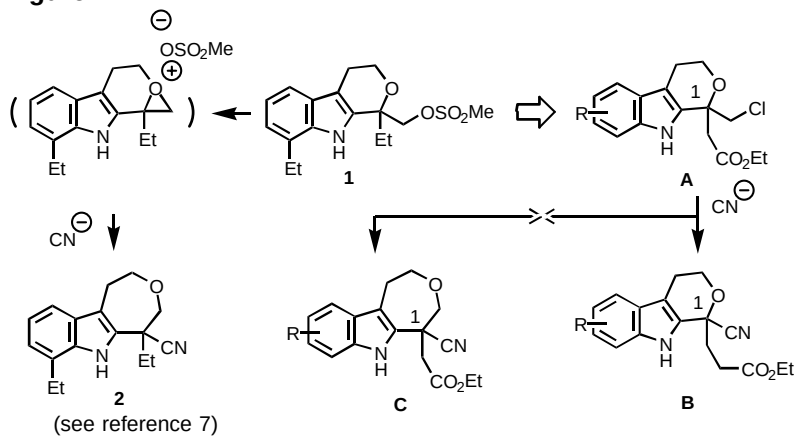
**Abstract** - An unusual cyanation with rearrangement of a 1-chloromethyl-tetrahydropyrano[3,4-*b*]indole-1-acetic acid ester derivative is reported. The resulting C-1 chain extension product is identified by correlation studies and spectral method.

Fused indoles are of general interest because they have a wide variety of medicinal interest, including their reported anti-inflammatory and analgesic properties.[1,2] A versatile method for synthesizing pyranoindole ring systems has been reported, including the preparation of 1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-alkanoic acids and their derivatives.[2] The exploration led to the discovery of an anti-inflammatorydrug, etodolac (**15**) (brand name: Lodine). Recently, research in the field of cyclooxygenase-2 (COX-2) inhibitors stimulated the reinvestigation of pyranoindoles.[3-5] More recently, it was reported that COX-2 may play an important role during premalignant hyperproliferating.[6] Therefore, exploring synthetic methods for preparing fused indoles is valuable.

During the study of chiral etodolac synthesis,[7] a novel ring-expansion reaction was discovered in an

**Figure 1**

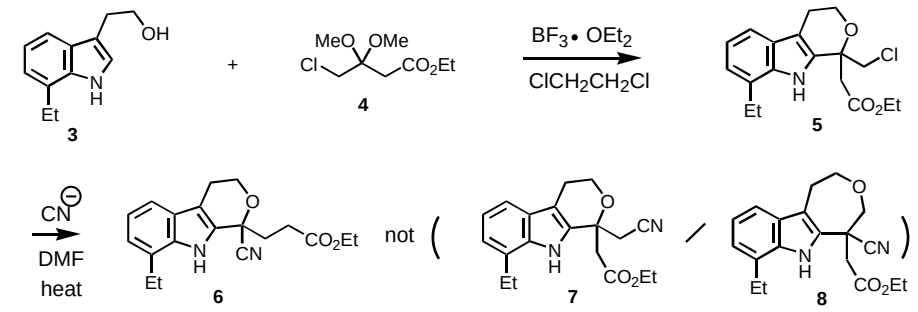



attempt of a cyanide substitution on the C-1 methanesulfonyloxymethyl side chain of a

tetrahydropyrano[3,4-*b*]indole derivative (**1**) (**1**-**2**, Figure 1). Further extension of this work has led to a series of tetrahydropyrano[3,4-*b*]indoles with a chloromethyl side chain and an ester side chain at the C-1 position as characterized generically by structure (**A**), wherein the chloro group of **A** mimics the methanesulfonyloxy group of **1**. This article describes an unusual cyanide displacement with C-1 chain extension executed by a linear chain rearrangement on derivative (**A**) (**A**-**B**, Figure 1), rather than by the expected ring expansion (**A**-**C**, Figure 1).

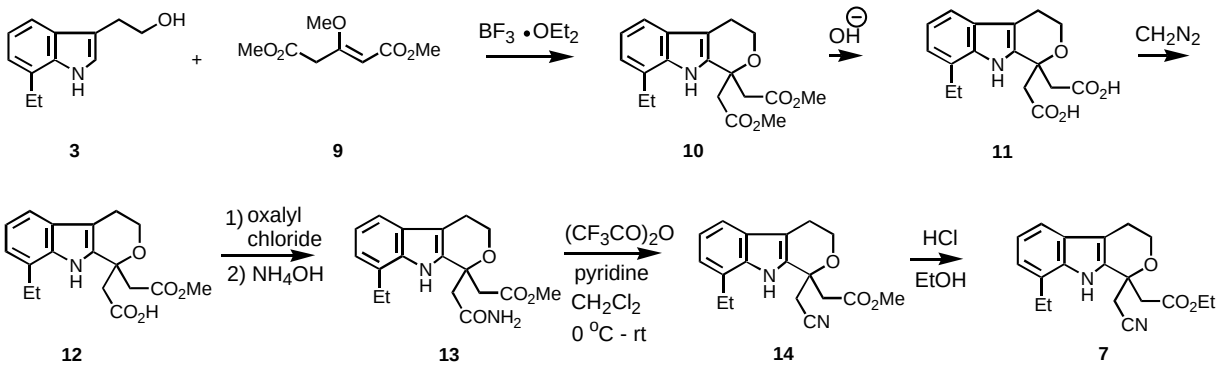
As shown in Scheme 1, cyclocondensation of 7-ethyltryptophol (**3**) with the ketal ester (**4**) gave pyranoindole (**5**). Heating of **5** with excessive amount of sodium cyanide in DMF led to a nitrile ester (**6**). During the early stages of this study, **6** was proposed to be a skeletal rearrangement product (**8**) formed through the ring expansion pathway (Figure 1).[8] However, as revealed by the NMR spectrum, beside methyleneoxy protons of ester (δ 4.08 (q), J = 7.2 Hz), only one pair of protons appeared at ~ δ 4.0, and

Scheme 1




could not support structure (**8**) for the existence of three pairs of methyleneoxy protons in **8**. The preparation of an authentic simple displacement product (**7**) and its comparison with **6** are desirable to

Scheme 2 - Correlation synthesis : an unambiguous synthesis of an envisaged simple displacement product of **5** (nitrile ester (**7**))

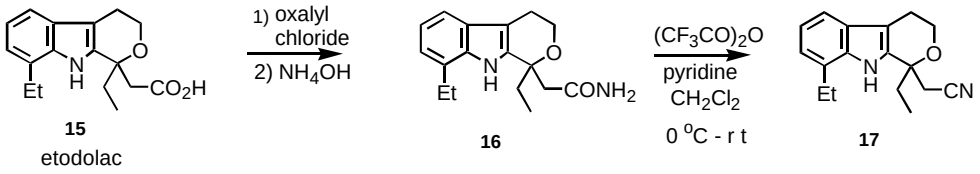



resolve this issue. Scheme 2 illustrates an unambiguous synthetic pathway of **7**. Cyclization of

7-ethyltryptophol (**3**) with 3-methoxypent-2-enedioic acid dimethyl ester (**9**) gave **10**, which was hydrolyzed to the diacid (**11**). Methylation of **11** using diazomethane led to the half ester (**12**), which was converted to the amide (**13**), and followed by dehydration of **13** to the nitrile (**14**) by conventional means. Finally, alcoholysis of **14** afforded the nitrile ester (**7**). Compounds (**7**) and (**6**) are not identical as shown by NMR spectra and TLC comparisons, thus the envisaged simple displacement pathway is excluded.

Having excluded the regioisomer (**7**), there remains lack evidence to ensure ring expansion occurs during cyanation of **5**. If the envisaged skeletal rearrangement product (**8**) were the resulting nitrile ester rather than **6**, then transforming its C-1 ethoxycarbonylmethyl side chain to ethyl by successive reduction, bromination and hydrogenolysis would lead to the known nitrile (**2**) (Figure 1). To author's surprise, starting from **6**, after these transformations, the end product (see **22**, Scheme 5) is not identical to the nitrile (**2**) as revealed by NMR spectra and TLC comparisons. To clarify suspicions concerning the initial assignment of **2** and for purposes of comparison, an unambiguous synthesis of the regioisomer (**17**) was performed by conventional means (Scheme 3). Compounds (**17**) and (**2**) are not identical as shown by

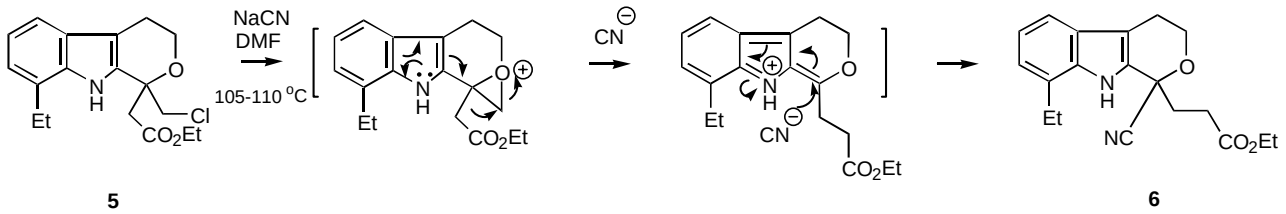
Scheme 3 - Correlation synthesis : an unambiguous synthesis of an envisaged simple displacement product of **1** ( nitrile **17**)




NMR spectra and TLC comparisons,[7] therefore the structure of **2** is reconfirmed and the skeletal rearrangement (**8**) is also excluded. Accordingly, the third possible structure, a linear chain rearrangement product (**6**), is proposed. As shown in Scheme 4, the reaction is envisaged as involving first intramolecular nucleophilic attack of the chloride by the pyrano oxygen to form a three-membered oxonium ion, which is subsequently fragmented through an indole ring assisted C-1 chain migration to the electrophilic carbon center. Cyanide ion is then collapsed onto the electrophilic C-1 position to afford tetrahydropyrano[3,4-*b*]indole-1-cyano-1-propionic acid ethyl ester (**6**), a C-1 chain extension product. A comparison with the ring-expansion pathway (Figure 1) enables the C-(1) chain migration to be explained by the electron withdrawing property of its ester group, which stabilizes partial negative charge generated during C-1 chain migration.

Consequently, the conversion of **6** to the chain extension nitrile (**22**) would be illustrated in Scheme 5. The regiochemistry of the chain extension product (**6**) is supported by a HMBC spectrum (Figure 2),

Scheme 4 - Proposed synthetic pathway for nitrile ester (**6**)




wherein the correlations between the carbonyl carbon and its α-/β- methylene protons firmly establish regiochemistry, since the nitrile ester (**8**) would not show comparable correlations.[9]

Scheme 5 - Correlation synthesis : synthesis of the chain-extended nitrile **22**

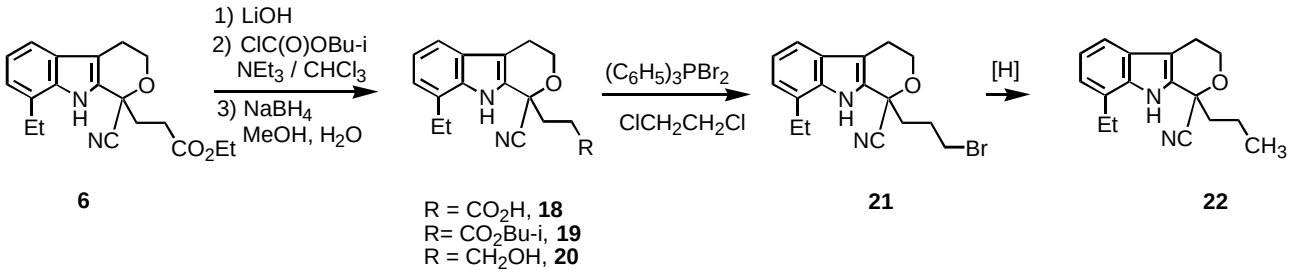
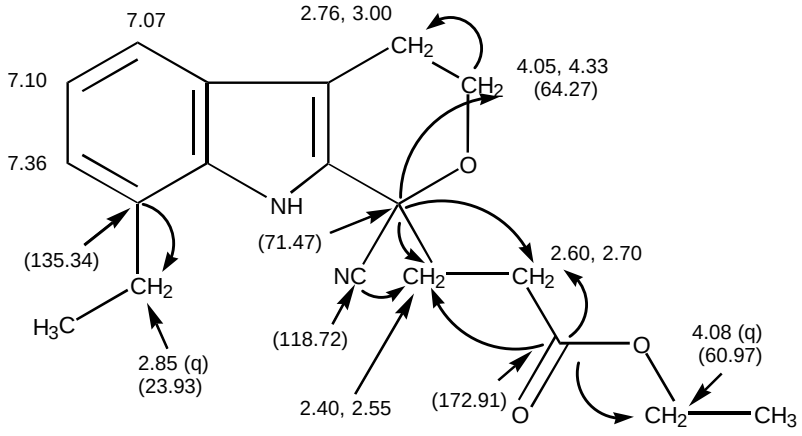



Figure 2 - HMBC correlation of **6**

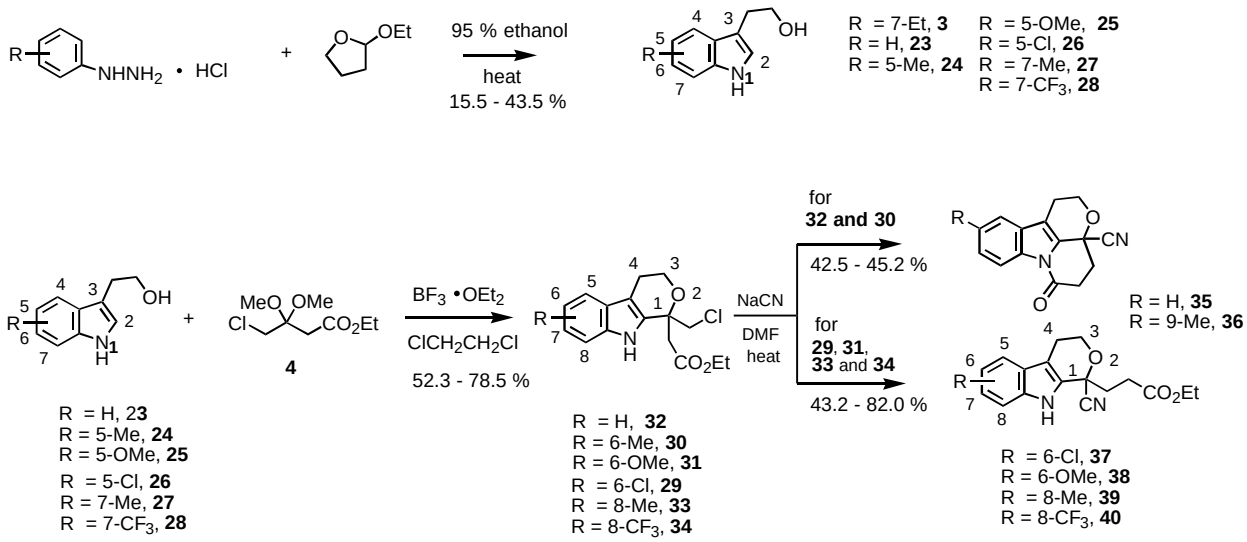



Next, several pyranoindoles (**29**-**34**) that differ only in the substituents in benzene rings were prepared from corresponding tryptophols,[10] their reaction with sodium cyanide in DMF was examined. As shown in Scheme 6, substituents R = 6-Cl (**29**), 6-OMe (**31**), 8-Me (**33**) and 8-$CF_3$ (**34**), react with sodium cyanide in DMF to afford the expected rearranged displacement products (**37**-**40**). Their NMR spectra are comparable with that of **6**. Instead of pyranoindoles (**30**) (R = 6-Me) and (**32**) (R = H), give fused

lactams (**35**) and (**36**) respectively, which are in fact formed by the condensation of indolyl NH and C-1 ester. These nitrile esters might be difficult to prepare by other methods.

In conclusion, this study has demonstrated a novel chain extension of tetrahydropyrano[3,4-*b*]indole derivative and verified the structure by rigorous correlation studies.

Scheme 6




## EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer FT-IR (Spectrum GX) spectrophotometers, NMR spectra were recorded on a Bruker-AC 500 (500 MHz) spectrometer, $CDCl_3$ and DMSO-$d_6$ were 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 analysis were determined by a Perkin-Elmer 2400. MS spectra were measured on JEOL-JMS-D100 instrument. Melting points were measured in open capillary tubes using Büchi immersion apparatus, and are uncorrected. Separations by flash chromatography were performed on silica gel (230-400 mesh). All reagents were of commercial quality and were used as received.

**4-Chloro-3,3-dimethoxy-butylic acid ethyl ester** (**4**). A mixture of ethyl 4-chloroacetoacetate (66.4 g, 0.40 mol), trimethyl orthoformate (60.0 g, 0.57 mol) and *p*-TSA·$H_2O$ (3.0 g, 15.9 mmol) was stirred at 25 $^oC$ for 72 h. The resulting mixture was evaporated at a water pump and then distilled under vacuum, the fraction boiled at 95-100 $^oC$ (11.8 mmHg) was collected to provide **4** (58.0 g, 68.1 %) as a colorless oil. IR (film) $\nu_{max}$:1738, 1714, 1636, 1141 $cm^{-1}$. $^1H$-NMR ($CDCl_3$): 4.16 (q, J = 7.1 Hz, 2H), 3.79 (s, 2H), 3.27 (s,

6H), 2.86 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H). MS (EI) *m/z* (%) : 178 ($M^+$-MeOH, 56), 133 (100), 91 (21). As revealed by $^1$H NMR spectrum, **4** contains ~11 mole % of the corresponding enol ether ester as co-distillate. An analytical sample of the enol ether was isolated by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/20). $^1$H-NMR ($CDCl_3$) : 5.14 (s, 1H), 4.66 (s, 2H), 4.20 (q, J = 7.0 Hz, 2H), 3.72 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). MS (EI) *m/z* (%) : 178 ($M^+$, 65), 133 (100).

**Typical procedure for synthesizing tryptophols - 7-Ethyltrtptophol** (**3**). To a suspension of 2-ethylphenylhydrazine hydrochloride (26.6 g, 0.15 mol) in 95 % ethanol (272 mL) was added 2-ethoxytetrahydrofuran (25.0 g, 0.22 mol). After being refluxed for 12 h, the reaction mixture was filtered through Celite and then evaporated. The reaction mixture was diluted with water and extracted with 1,2-dichloroethane. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated. Purification by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/6) provided **3** as a dark brown oil (12.5 g, 43.0 %). The spectral data are identical to those of an authentic sample.[10]

Each of the following tryptophols was prepared following the typical procedure from the starting phenylhydrazine in the same reaction scale.

**Tryptophol 23**. 21.5 % yield. The spectral data are identical to those of commercially available sample.

**5-Methyltryptophol** (**24**). Yellow oil, 32.0 % yield. IR (film) $\nu_{max}$: 3403, 1457, 1212 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) : 8.01 (br s, 1H), 7.39 (s, 1H), 7.23 (d, J = 8.2 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 7.00 (m, 1H), 3.88 (t, J = 6.5 Hz, 2H), 2.99 (t, J = 6.5 Hz, 2H), 2.45 (s, 3H). MS (EI) *m/z* (%) : 175 ($M^+$, 30), 144 (100), 115 (40). Anal. Calcd for $C_{11}H_{13}NO$ : C, 75.40; H, 7.48; N, 7.99. Found : C, 75.73; H, 7.78; N, 8.05.

**5-Methoxytryptophol** (**25**). Yellow oil, 33.5 % yield. IR (film) $\nu_{max}$: 3408, 1487, 1215 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) : 8.09 (br s, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 6.98 (s, 1H), 6.84 (m, 1H), 3.82 (s, 3H), 3.76 (t, J = 6.4 Hz, 2H), 2.97 (t, J = 6.4 Hz, 2H). MS (EI) *m/z* (%) : 191 ($M^+$, 35), 160 (100), 145 (40), 117 (62). Anal. Calcd for $C_{11}H_{13}NO_2$ : C, 69.09; H, 6.85; N, 7.32. Found : C, 69.23; H, 6.98; N, 7.08.

**5-Chlorotryptophol** (**26**). Yellow oil, 42.3 % yield. IR (film) $\nu_{max}$: 3414, 1458, 1019 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) : 8.19 (br s, 1H), 7.56 (s, 1H), 7.25 (m, 1H), 7.15 (m, 1H), 7.05 (m, 1H), 3.88 (t, J = 6.4 Hz, 2H), 2.97 (t, J = 6.4 Hz, 2H). MS (EI) *m/z* (%) : 195 ($M^+$, 30), 144 (100), 115 (10). Anal. Calcd for

$C_{10}H_{10}NOCl$ : C, 61.39; H, 5.15; N, 7.16. Found : C, 61.25; H, 5.38; N, 7.03.

**7-Methyltryptophol** (**27**). Yellow oil, 43.5 % yield. IR (film) $\nu_{max}$: 3397, 1433, 1043 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) : 8.03 (br s, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.06 (m, 2H), 7.01 (d, J = 7.0 Hz, 1H), 3.89 (t, J = 6.4 Hz, 2H), 3.02 (t, J = 6.4 Hz, 2H), 2.48 (s, 3H). MS (EI) *m/z* (%) : 175 ($M^+$, 30), 144 (100), 115 (10). Anal. Calcd for $C_{11}H_{13}NO$ : C, 75.40; H, 7.48; N, 7.99. Found : C, 75.37; H, 7.87; N, 7.84.

**7-Trifluoromethyltryptophol** (**28**). Yellow oil, 15.5 % yield. IR (film) $\nu_{max}$: 3348, 1448, 1317, 1046 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) : 8.50 (br s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.20 (m, 1H), 7.17 (m, 1H), 3.91 (t, J = 6.8 Hz, 2H), 3.04 (t, J = 6.8 Hz, 2H). MS (EI) *m/z* (%) : 229 ($M^+$, 50), 198 (100), 178 (100), 51 (10). Anal. Calcd for $C_{11}H_{10}NOF_3$ : C, 57.64; H, 4.40; N, 6.11. Found : C, 57.75; H, 4.56; N, 6.34.

**Typical procedure for cyclocondensation – (1-Chloromethyl -6-chloro- 1,3,4,9- tetrahydropyrano-[3,4-*b*]indol-1-yl)acetic acid ethyl ester** (**29**). 5-Chlorotryptophol (**26**) (5.7 g, 29.1 mmol) in 1,2-dichloroethane (163 mL) was stirred to homogeneous, then the ketal ester (**4**) (7.7 g, ~36.5 mmol) and $BF_3{\cdot}OEt_2$ (2.0 mL, 15.8 mmol) were added successively with stirring. After being stirred at rt for 63 h, the resulting dark mixture was diluted with ice water and 1,2-dichloroethane (60 mL) and adjusted to pH = 7 with saturated $NaHCO_3$. The separated organic layer was washed twice with water, dried ($MgSO_4$), and evaporated. The residue was diluted with 25 mL of isopropyl ether and stirred at rt overnight. The precipitate was collected and washed with isopropyl ether to give **29** (6.7 g) as a white powder. The filtrate was evaporated and diluted with isopropyl ether (5 mL) and left to stand at 0 $^oC$ overnight. The precipitate was collected and washed with isopropyl ether to give **29** (0.3 g) as a second crop. The yield was 7.0 g (70.2 %), mp 110-112 $^oC$ (1/4 ethyl acetate-hexane). IR (KBr) $\nu_{max}$ : 3269, 1695, 1213 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) : 9.27 (br s, 1H, NH), 7.50 (s, 1H), 7.29 (d, J = 9.0 Hz, 1H), 7.10 (d, J = 9.0 Hz, 1H), 4.22 (q, J = 7.0 Hz, 2H), 4.25, 3.97 (ABq, J = 11.9 Hz, 2H, $CH_2Cl$), 4.06 (m, 2H, $ArCH_2C\underline{H_2}O$), 3.30, 2.97 (ABq, J = 17.4 Hz, 2H, $CH_2C(O)$), 2.81 (m, 2H, $ArC\underline{H_2}CH_2O$), 1.32 (t, J = 7.0 Hz, 3H). MS (EI) *m/z* (%): 341 ($M^+$, 30), 292 (100), 254 (35), 204 (30). Anal. Calcd for $C_{16}H_{17}NO_3Cl_2$ : C, 56.15; H, 5.01; N, 4.09. Found : C, 56.23; H, 4.98; N, 4.05.

Each of the following solid pyranoindoles (**5**, **32**-**34**) was prepared following the typical procedure starting from the starting tryptophol and **4** in the same reaction scale. Liquid pyranoindole (**30**, **31**), was isolated by extraction and purified by column chromatography.

**(1-Chloromethyl-8-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid ethyl ester** (**5**). 58.6 % yield. White powder, mp 106-107 $^{o}$C (1/4 ethyl acetate-hexane). IR (KBr) $\nu_{max}$ : 3328, 1700, 1192 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 9.19 (br s, 1H, NH), 7.38 (d, J = 7.5 Hz, 1H), 7.09 (d, J = 7.3 Hz,1H), 7.03 (m, 1H), 4.29, 3.97 (ABq, J = 11.9 Hz, 2H), 4.22 (q, J = 7.0 Hz, 2H), 4.04 (m, 2H), 3.30, 2.95 (ABq, J = 6.9 Hz, 2H), 2.86 (q, J = 7.5 Hz, 2H), 2.83 (m, 2H), 1.37 (t, J = 7.5 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H). MS (EI) *m/z* (%): 335 ($M^+$, 26), 286 (100), 248 (22), 198 (16). Anal. Calcd for $C_{18}H_{22}NO_3Cl$ : C, 64.38; H, 6.60; N, 4.17. Found : C, 64.28; H, 6.58; N, 4.35.

**3-(1-Chloromethyl-6-methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid ethyl ester** (**30**). 52.3 % yield. Yellow oil. IR (film) $\nu_{max}$ : 3300, 1694, 1215, 1036 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 9.00 (br s, 1H, NH), 7.30 (s, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 4.25, 3.94 (ABq, J = 11.9 Hz, 2H), 4.18 (q, J = 7.0 Hz, 2H), 4.03 (m, 2H), 3.27, 2.94 (ABq, J = 17.3 Hz, 2H), 2.80 (q, J = 7.0 Hz, 2H), 2.44 (s, 3H), 1.28 (t, J=7.0 Hz, 3H). MS (EI) *m/z* (%): 321($M^+$, 18), 272 (100), 234 (27), 199 (37). Anal. Calcd for $C_{17}H_{20}NO_3Cl$ : C, 63.45; H, 6.26; N, 4.35. Found : C, 63.56; H, 6.22; N, 4.36.

**(1-Chloromethyl-6-methoxy-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid ethyl ester** (**31**). 55.5 % yield. Yellow oil. IR (film) $\nu_{max}$ : 3396, 1715, 1488, 1217 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 9.00 (br s, 1H, N$\underline{H}$), 7.26 (d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.25, 3.95 (ABq, J = 11.9 Hz, 2H, C$\underline{H}_2$Cl), 4.20 (q, J = 7.0 Hz, 2H), 4.04 (m, 2H, ArCH$_2$C$\underline{H}_2$O), 3.86 (s, 3H), 3.27, 2.97 (ABq, J = 17.3 Hz, 2H, C$\underline{H}_2$C(O)), 2.79 (m, 2H, ArC$\underline{H}_2$CH$_2$O), 1.29 (t, J = 7.0 Hz, 3H). MS (EI) *m/z* (%): 337 ($M^+$, 65), 288 (100), 250 (68), 200 (70). Anal. Calcd for $C_{17}H_{20}NO_4Cl$ : C, 60.45; H, 5.97; N, 4.15. Found : C, 60.29; H, 5.83; N, 4.08.

**(1-Chloromethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid ethyl ester** (**32**). 52.5 % yield. White powder, mp 68-69 $^{o}$C (1/4 ethyl acetate-hexane). IR (KBr) $\nu_{max}$ : 3378, 1731, 1699, 1078 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 9.13 (br s, 1H, NH), 7.51 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.19 (m, 1H), 7.11 (m,1H), 4.22 (q, J = 7.0 Hz, 2H), 4.03 (m, 2H, ArCH$_2$C$\underline{H}_2$O), 3.95, 3.78 (ABq, J = 11.9 Hz, 2H), 3.27 (m, 2H, ArC$\underline{H}_2$CH$_2$O), 2.97, 2.86 (ABq, J = 17.1 Hz, 2H), 1.30 (t, J = 7.0 Hz, 3H). MS (EI) *m/z* (%): 307 ($M^+$, 30), 258 (100), 220 (30), 170 (30). Anal. Calcd for $C_{16}H_{18}NO_3Cl$ : C, 62.44; H, 5.89; N, 4.55. Found : C, 62.32; H, 5.98; N, 4.36.

**(1-Chloromethyl-8-methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid ethyl ester** (**33**). 68.5

% yield. White powder, mp 130-131 $^{o}$C (1/4 ethyl acetate-hexane). IR (KBr) $\nu_{max}$ : 3309, 1700, 1193 cm$^{-1}$.$^{1}$H-NMR ($CDCl_3$) : 9.13 (br s, 1H, NH), 7.37 (d, J = 7.7 Hz, 1H), 7.04 (m, 1H), 7.00 (d, J = 7.1 Hz, 1H), 4.28, 3.96 (ABq, J = 11.9 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 4.04 (m, 2H), 3.30, 2.95 (ABq, J = 17.3 Hz, 2H), 2.83 (m, 2H), 2.49 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H). MS (EI) *m/z* (%): 321($M^+$, 29), 272 (100), 234 (38), 184 (70). Anal. Calcd for $C_{17}H_{20}NO_3Cl$ : C, 63.45; H, 6.26; N, 4.35. Found : C, 63.28; H, 6.56; N, 4.56.

**(1-Chloromethyl-8-trifluoromethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid ethyl ester** (**34**). 78.5 % yield. White powder, mp 108-110 $^{o}$C (1/4 ethyl acetate-hexane). IR (KBr) $\nu_{max}$ : 3299, 1707, 1040 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 9.71 (br s, 1H, NH), 7.68 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.18 (m, 1H), 4.27, 3.98 (ABq, J = 12.0 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 4.06 (m, 2H), 3.30, 2.97 (ABq, J = 17.3 Hz, 2H), 2.87 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H). MS (EI) *m/z* (%) : 375 ($M^+$, 29), 326 (100), 288 (40), 238 (26). Anal. Calcd for $C_{17}H_{17}NO_3ClF_3$: C, 54.34; H, 4.56; N, 3.73. Found : C, 54.15; H, 4.58; N, 3.36.

**Typical procedure for nitrile ester formation with C-1 side chain extension-3-(1-Cyano-8-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)propionic acid ethyl ester** (**6**). To a solution of the chloride (**5**) (3.1 g, 9.3 mmol) in DMF (43 mL) was added powdered sodium cyanide (9.3 g, 188.8 mmol). After being heated under nitrogen at 105-110 $^{o}$C for 22 h, the reaction mixture was filtered and the filtrate distilled at below 50 $^{o}$C to remove DMF. The residue was diluted with chloroform (80 mL) and washed with water (40 mL x 2). The separated organic solution was dried ($MgSO_4$) and evaporated. Purification by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/6) provided pyranoindole (**6**) (1.8 g, 60.0 %) as a yellow oil. IR (film) $\nu_{max}$: 3371, 1719, 1288, 1081 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 8.62 (br s, 1H), 7.36 (m, 1H), 7.10 (m, 1H), 7.07 (m, 1H) 4.33 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 4.05 (m, 1H), 3.00 (m, 1H), 2.85 (q, J = 7.5 Hz, 2H), 2.76 (m, 1H), 2.70 (m, 1H), 2.60 (m, 1H), 2.55 (m, 1H), 2.40 (m, 1H), 1.34 (t, J = 7.5 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H). $^{13}$C-NMR ($CDCl_3$) : 172.92 (0), 135.54 (0), 127.29 (0), 127.11 (0), 125.89 (0), 121.97 (1), 120.53 (1), 118.72 (0), 116.47 (1), 111.39 (0), 71.47 (0), 64.27 (2), 60.97 (2), 34.20 (2), 28.24 (2), 23.93 (2), 21.59 (2), 14.05 (3), 13.81 (3). MS (EI) *m/z* (%) : 326 ($M^+$, 31), 299 (9), 281 (8), 225 (100). Anal. Calcd for $C_{19}H_{22}N_2O_3$ : C, 69.92; H, 6.79; N, 8.58. Found : C, 69.68; H, 6.76; N, 8.77.

**6-Oxo-1,2,5,6-tetrahydro-4*H*-3-oxa-6a-azafluoranthene-3a-carbonitrile** (**35**)**.** Compound (**35**) was prepared following the typical procedure starting from the chloride (**32**) (1.4 g, 4.6 mmol) in DMF (22 mL) using sodium cyanide (4.6 g, 93.8 mmol) at 105-110 $^{o}$C to provide 0.5 g (45.2 %) of the product as a

brown plate crystals, mp 66-68 $^{o}$C (1/4 ethyl acetate-hexane). IR (KBr) $\nu_{max}$ : 2917, 1702, 1312, 1083 cm$^{-1}$.$^{1}$H-NMR ($CDCl_3$): 8.39 (d, J = 8.2 Hz, 1H), 7.51(d, J = 7.8 Hz, 1H), 7.43 (m, 1H), 7.36 (m, 1H), 4.49, 4.43 (each m, 2H, $ArCH_2C\underline{H_2}O$), 3.18, 3.02 (each m, 2H, $ArC\underline{H_2}CH_2O$), 3.00, 2.80 (each m, 2H, $CH_2C\underline{H_2}C(O)$), 2.65, 2.25 (each m, 2H, $C\underline{H_2}CH_2C(O)$). MS (EI) *m/z* (%): 252 ($M^+$, 75), 197 (100), 170 (25). Anal. Calcd for $C_{15}H_{12}N_2O_2$ : C, 71.42; H, 4.79; N, 11.10. Found : C, 71.28; H, 4.66; N, 10.78.

**9-Methyl-6-oxo-1,2,5,6-tetrahydro-4*H*-3-oxa-6a-azafluoranthene-3a-carbonitrile** (**36**). Compound (**36**) was prepared following the typical procedure starting from the chloride (**30**) (1.5 g, 4.6 mmol) in DMF (22 mL) using sodium cyanide (4.6 g, 93.8 mmol) at 105-110 $^{o}$C to provide 0.5 g (42.5 %) of the product as a yellow oil. IR (film) $\nu_{max}$ : 2924, 1702, 1018 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 8.24 (d, J = 8.4 Hz, 1H), 7.29 (s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 4.48 (m, 1H), 4.43 (dd, J = 11.5, 4.4 Hz, 1H), 3.18 (m, 1H), 2.98 (m, 1H), 2.78 (m, 1H), 2.65 (m, 1H), 2.46 (m, 1H), 2.44 (s, 3H), 2.26 (m, 1H). MS (EI) *m/z* (%): 266 ($M^+$, 80), 240 (16), 211 (100), 184 (18). Anal. Calcd for $C_{16}H_{14}N_2O_2$ : C, 72.16; H, 5.30; N, 10.52. Found : C, 72.18; H, 5.36; N, 10.77.

**3-(6-Chloro-1-cyano-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)propionic acid ethyl ester** (**37**). Compound (**37**) was prepared following the typical procedure starting from the chloride (**29**) (3.2 g, 9.3 mmol) in DMF (43 mL) using sodium cyanide (9.3 g, 188.8 mmol) at 75-80 $^{o}$C to provide 1.3 g (43.2 %) of the product as a brown oil. IR (film) $\nu_{max}$ : 3256, 1708, 1041 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 8.63 (br s, 1H, NH), 7.50 (s, 1H), 7.27 (d, J = 9.0 Hz, 1H), 7.19 (d, J = 9.0 Hz, 1H), 4.34 (dd, J = 11.7, 5.6 Hz, 1H), 4.10 (m, 1H), 4.06 (q, J = 7.0 Hz, 2H), 2.98 (m, 1H), 2.73, 2.69 (ABq, J = 32.0 Hz, 1H), 2.63 (m, 1H), 2.56 (m, 1H), 2.48, 2.40 (each m, 2H), 1.19 (t, J = 7.0 Hz, 3H). MS (EI) *m/z* (%): 332 ($M^+$, 60), 286 (40), 231 (100), 204 (40). Anal. Calcd for $C_{17}H_{17}N_2O_3Cl$ : C, 61.36; H, 5.15; N, 8.42. Found : C, 61.29; H, 5.34; N, 8.51.

**3-(1-Cyano-6-methoxy-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)propionic acid ethyl ester** (**38**). Compound (**38**) was prepared following the typical procedure starting from the chloride (**31**) (3.1 g, 9.3 mmol) in DMF (43 mL) using sodium cyanide (9.3 g, 188.8 mmol) at 75-80 $^{o}$C to provide 1.4 g (45.7 %) of the product as a brown oil. IR (film) $\nu_{max}$ : 3370, 1702, 1211 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 8.20 (br s, 1H, NH), 7.26 (d, J = 7.5 Hz, 1H), 6.95 (s, 1H), 6.90 (d, J = 7.5 Hz, 1H), 4.40, 4.33 (each m, 2H,), 4.08 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 2.98 (m, 2H), 2.73, 2.69 (ABq, J = 32.0 Hz, 2H), 2.63, 2.58 (each m, 1H), 2.48, 2.42 (each m, 1H), 1.19 (t, J = 7.2 Hz, 3H). MS (EI) *m/z* (%): 328 ($M^+$, 30), 301 (35), 228 (100). Anal. Calcd for $C_{18}H_{20}N_2O_4$ : C, 65.84; H, 6.14; N, 8.53. Found : C, 65.78; H, 6.35; N, 8.34.

**3-(1-Cyano-8-methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)propionic acid ethyl ester** (**39**). Compound (**39**) was prepared following the typical procedure starting from the chloride (**33**) (3.0 g, 9.3 mmol) in DMF (43 mL) using sodium cyanide (9.3 g, 188.8 mmol) at 105-110 $^{o}$C to provide 1.4 g (48.5 %) of the product as a brown oil. IR (film) $\nu_{max}$ : 3364, 1732, 1171 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 8.17 (br s, 1H, NH), 7.37 (d, J = 7.4 Hz, 1H), 7.08 (m, 1H), 7.05 (d, J = 8.4 Hz, 1H), 4.34 (dd, J = 11.6, 5.6 Hz, 1H), 4.09 (q, J = 7.3 Hz, 2H), 4.06 (m, 1H), 3.03 (dd, J = 11.5, 5.8 Hz, 0.5H), 3.00 (dd, J=11.5, 5.8 Hz, 0.5 H), 2.75 (dd, J=15.8, 3.1 Hz, 1H), 2.67 (m, 1H), 2.62 (m, 1H), 2.55 (m, 1H), 2.54 (s, 3H), 2.46 (m, 1H), 1.18 (t, J = 7.3 Hz, 3H). $^{13}$C-NMR ($CDCl_3$) : 172.75 (0), 136.22 (0), 127.16 (0), 125.75 (0), 124.08 (1), 120.98 (0), 120.52 (1), 118.61 (0), 116.51 (1), 111.58 (0), 71.40 (0), 64.25 (2), 60.94 (2), 34.25 (2), 28.22 (2), 21.58 (2), 16.70 (3), 14.06 (3). MS (EI) *m/z* (%): 312 ($M^+$, 61), 285 (6), 267 (15), 211 (100), 184 (33). Anal. Calcd for $C_{18}H_{20}N_2O_3$ : C, 69.21; H, 6.45; N, 8.97. Found : C, 69.15; H, 6.62; N, 8.76.

**3-(1-Cyano-8-trifluoromethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)propionic acid ethyl ester** (**40**). Compound (**40**) was prepared following the typical procedure starting from the chloride (**34**) (3.5 g, 9.3 mmol) in DMF (43 mL) using sodium cyanide (9.3 g, 188.8 mmol) at 105-110 $^{o}$C to provide 2.8 g (82.0 %) of the product as a white powder, mp 153-154 $^{o}$C (1/4 ethyl acetate-hexane). IR (KBr) $\nu_{max}$ : 3346, 1708, 1296, 1159 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 8.88 (br s, 1H, NH), 7.70 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.22 (m, 1H), 4.37 (dd, J = 11.5, 5.0 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 4.07 (m, 1H), 3.00 (m, 1H), 2.79 (m, 1H), 2.72 (m, 1H), 2.60 (m, 1H), 2.53 (m, 1H), 2.47 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H). $^{13}$C-NMR ($CDCl_3$) : 172.81 (0), 132.20 (0), 129.37 (0), 127.95 (0), 125.92 (0), 123.10 (1), 121.19 (1), 119.91 (1), 118.25 (0), 111.54 (0), 71.42 (0), 64.19 (2), 61.26 (2), 52.27 (0), 34.19 (2), 28.52 (2), 21.50 (2), 14.24 (3). MS (EI) *m/z* (%) : 366 ($M^+$, 32), 321 (22), 265 (100), 238 (14). Anal. Calcd for $C_{18}H_{17}N_2O_3F_3$: C, 59.02; H, 4.68; N, 7.65. Found : C, 58.83; H, 4.58; N, 7.36.

**(8-Ethyl-1-methoxycarbonylmethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid methyl ester** (**10**). To a solution of **3** (5.0 g, 26.4 mmol) and 3-methoxypent-2-enedioic acid dimethyl ester (**9**) (11.3 g, 60 mmol) in dichloromethane (100 mL) was added $BF_3{\cdot}OEt_2$ (1.2 mL, 9.5 mmol) and the mixture was stirred at rt for 12 h. The reaction mixture was washed with 1 % $Na_2CO_3$ and water. The separated organic layer was dried ($MgSO_4$) and evaporated. Purification by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/10) provided **10** as a white powder (2.4 g, 25.7 %), mp 92-94 $^{o}$C (ethyl acetate). IR (KBr) $\nu_{max}$ : 3380, 1736, 1698, 1207 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 9.25 (br s, 1H), 7.35 (d, J = 7.0 Hz, 1H), 7.06 (m, 2H), 4.04 (m, 2H, $ArCH_2C\underline{H}_2O$), 3.74 (s, 6H), 3.19 (s, 4H), 2.86 (q, J = 7.0 Hz, 2H), 2.78 (m, 2H), 1.37 (t, J = 7.0 Hz, 3H). MS (EI) *m/z* (%): 345 ($M^+$, 45), 330 (100). Anal. Calcd for

$C_{19}H_{23}NO_5$ : C, 66.07; H, 6.71; N, 4.06. Found : C, 66.02; H, 6.59; N, 4.15.

**(1-Carboxymethyl-8-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid** (**11**). To a solution of diester (**10**) (2.0 g, 2.8 mmol) in methanol (40 mL) was added lithium hydroxide monohydrate (0.4 g, 9.6 mmol), and stirring was continued for 13 h. The reaction mixture was then diluted with 5 % HCl solution, and extracted with chloroform. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated to give **11** as a brown powder (1.6 g, 87.4 %), mp 180-182 $^oC$ (ethyl acetate). IR (KBr) $\nu_{max}$ : 3420, 1699, 1078 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) : 9.20 (br s, 1H), 7.26 (d, J=7.0 Hz, 1H), 7.05 (m, 2H), 4.12 (m, 2H, $ArCH_2C\underline{H_2}O$), 3.24 (s, 4H), 2.98, 3.04 (each m, 2H), 2.84 (q, J = 7.0 Hz, 2H), 1.37 (t, J=7.0 Hz, 3H). MS (EI) *m/z* (%): 318 ($M^+$+1, 50), 252 (20), 158 (70), 113 (100). Anal. Calcd for $C_{17}H_{19}NO_5$ : C, 4.34; H, 6.03; N, 4.41. Found : C, 64.02; H, 5.98; N, 4.25.

**(8-Ethyl-1-methoxycarbonylmethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid** (**12**). To a solution of the diacid (**11**) (0.75 g, 2.36 mmol) in 1,2-dichloroethane (10 mL) was added dropwise a 0.6 M diazomethane ether solution (~ 4.0 mL) for 2 h. The resulting solution was then evaporated. Purification by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/2) provided **12** as a dark brown oil (0.3 g, 38.5 %). IR (film) $\nu_{max}$ : 3397, 1732 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) : 9.19 (br s, 1H, NH), 7.36 (d, J = 7.5 Hz, 1H), 7.05 (m, 2H), 4.07 (m, 2H, $ArCH_2C\underline{H_2}O$), 3.74 (s, 3H), 3.27, 3.16 (each m, 4H), 2.85 (q, J = 7.5 Hz, 2H), 2.81 (m, 2H), 1.37 (t, J = 7.5 Hz, 3H). MS (EI) *m/z* (%) : 332 ($M^+$+1, 100), 172 (70). Anal. Calcd for $C_{18}H_{21}NO_5$ : C, 65.24; H, 6.39; N, 4.23. Found : C, 65.12; H, 6.25; N, 4.03.

**(1-Carbamoylmethyl-8-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid methyl ester** (**13**). To a solution of the half ester (**12**) (0.3 g, 0.91 mmol) in toluene (3 mL) was added oxalyl chloride (1 mL) and stirred at rt for 1 h. After evaporation of the reaction mixture, the residue was poured into ice-cooled 28 % ammonia (10 mL), and then the mixture was extracted with ethyl acetate (20 mL x 2). The combined extracts were filtered through Celite and evaporated. Purification by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) provided **13** as a white powder (0.2 g, 67.0 %), mp 166-168 $^oC$ (ethyl acetate). IR (KBr) $\nu_{max}$ : 3296, 1729, 1668, 1193 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) : 9.67 (br s, 1H, NH), 7.36 (d, J = 7.5 Hz, 1H), 7.05 (m, 2H), 6.24 (br s, 1H, NH), 5.49 (br s, 1H, NH), 4.07 (m, 2H, $ArCH_2C\underline{H_2}O$), 3.73 (s, 3H), 3.16 (m, 2H), 3.03, 3.00 (ABq, J = 6.3 Hz, 2H), 2.87 (q, J=7.5 Hz, 2H), 2.85, 2.79 (each m, 2H), 1.36 (t, J = 7.5 Hz, 3H). MS (EI) *m/z* (%) : 331 ($M^+$+1, 100), 314 (25), 272 (30). Anal. Calcd for $C_{18}H_{22}N_2O_4$ : C, 65.44; H, 6.71; N, 8.48. Found : C, 65.32; H, 6.53; N, 8.51.

**(1-Cyanomethyl-8-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid methyl ester** (**14**). To a suspension of the amide (**13**) (0.12 g, 0.36 mmol) in dry dichloromethane (3 mL) were successively added pyridine (0.06 g, 0.76 mmol) and trifluoroacetic anhydride (0.09 g, 0.42 mmol). The internal temperature was maintained at < 30 $^{o}$C. After being stirred at rt overnight, the reaction mixture was washed with 1 % $H_2SO_4$ and water. The separated organic layer was dried ($MgSO_4$) and evaporated. Purification by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/5) provided **14** as a white powder (0.10 g, 88.1 %), mp 112-113 $^{o}$C (benzene). IR (KBr) $\nu_{max}$ : 3300, 1713, 1205 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 8.88 (br s, 1H, NH), 7.38 (d, J = 7.5 Hz, 1H), 7.09 (m, 2H), 4.05 (m, 2H, $ArCH_2C\underline{H_2}O$), 3.77 (s, 3H), 3.36, 3.23 (ABq, J = 17.2 Hz, 2H), 3.13 (dd, J = 18.0, 17.0 Hz, 2H), 2.88 (q, J = 7.5 Hz, 2H), 2.82 (m, 2H), 1.36 (t, J = 7.5 Hz, 3H). MS (EI) *m/z* (%) : 313 ($M^{+}$+1, 90), 295 (100). Anal. Calcd for $C_{18}H_{20}N_2O_3$ : C, 69.21; H, 6.45; N, 8.97. Found : C, 68.87; H, 6.47; N, 8.66.

**(1-Cyanomethyl-8-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid ethy ester** (**7**). The nitrile ester (**14**) (0.1 g, 0.32 mmol) was dissolved in anhydrous ethanol (5 mL) and cooled to 0 $^{o}$C. To the mixture was added dropwise acetyl chloride (0.66 g) and the mixture was stirred at rt for 44 h. After evaporation of solvent, the residue was diluted with dichloromethane (10 mL) and washed in successively with water, 5 % $Na_2CO_3$ and water. The separated organic layer was dried ($MgSO_4$) and evaporated to give **7** (0.06 g, 60.4 %) as a white powder, mp 100-102 $^{o}$C (benzene). IR (KBr) $\nu_{max}$ : 3329, 1704, 1087 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 8.92 (br s, 1H, NH), 7.37 (d, J = 7.5 Hz, 1H), 7.07 (m, 2H), 4.23 (q, J = 7.5 Hz, 2H), 4.05 (m, 2H, $ArCH_2C\underline{H_2}O$), 3.39, 3.22 (ABq, J = 17.1 Hz, 2H), 3.12 (dd, J = 18.0, 16.0 Hz, 2H), 2.86 (q, J = 7.0 Hz, 2H), 2.82 (m, 2H), 1.35 (t, J = 7.5 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H). MS (EI) *m/z* (%) : 327 ($M^{+}$+1, 100), 309 (95). Anal. Calcd for $C_{19}H_{22}N_2O_3$ : C, 69.92; H, 6.79; N, 8.58. Found : C, 69.78; H, 6.84; N, 8.63.

**2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetamide** (**16**). Compound (**16**) (0.19 g, 82.5 %) was prepared from etodolac (**15**) (0.23 g), by a similar procedure as that described for the amide ester (**13**) as a white powder, mp 174-175 $^{o}$C (1/4 ethyl acetate-hexane). IR (KBr) $\nu_{max}$ : 3259, 1673, 1040 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 9.39 (br s, 1H, NH), 7.35 (d, J = 7.8 Hz, 1H), 7.05 (m, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.45 (br s, 1H), 5.58 (br s, 1H), 4.08, 4.04 (each m, 2H), 2.93 (m, 2H), 2.84 (q, J = 7.5 Hz, 2H), 2.79 (m, 2H), 2.13, 2.02 (each m, 2H), 1.30 (t, J=7.5 Hz, 3H),, 0.87 (t, J = 7.5 Hz, 3H). MS (EI) *m/z* (%): 287 ($M^{+}$+1, 100), 172 (33). Anal. Calcd for $C_{17}H_{22}N_2O_2$ : C, 71.30; H, 7.74; N, 9.78. Found : C, 71.29; H, 7.75; N, 9.87.

**(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetonitrile** (**17**). Compound (**17**) (0.14 g, 93.4 %) was prepared from the amide (**16**) (0.16 g), by a similar procedure as that described for the nitrile ester **14** as a yellow granular crystals, mp 126-128 $^{o}$C (1/4 ethyl acetate-hexane). IR (KBr) $\nu_{max}$ : 3317, 2259, 1077 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 7.89 (br s, 1H, NH), 7.31 (d, J = 7.6 Hz, 1H), 7.05 (m, 1H), 6.98 (d, J = 7.6 Hz, 1H), 4.03, 3.86 (each m, 2H), 2.82 (q, J = 7.5 Hz, 2H), 2.76 (m, 2H), 2.73, 2.70 (each m, 2H), 2.05 (m, 2H), 1.30 (t, J = 7.5 Hz, 3H), 0.81 (t, J = 7.5 Hz, 3H). MS (EI) *m/z* (%): 269 ($M^{+}$+1, 95), 228 (90), 172 (100). Anal. Calcd for $C_{17}H_{20}N_2O_2$ : C, 76.09; H, 7.51; N, 10.44. Found : C, 76.27; H, 7.55; N, 10.67.

**3-(1-Cyano-8-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)propionic acid** (**18**). To a solution of **6** (1.0 g, 3.1 mmol) in methanol (20 mL) was added lithium hydroxide monohydrate (0.2 g, 4.8 mmol), and stirring was continued for 12 h. The reaction mixture was diluted with 5 % HCl solution, and extracted with ethyl acetate. The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated. Purification by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/1) provided **18** as a yellow oil (0.85 g, 93.0 %). IR (film) $\nu_{max}$ : 3364, 1703, 1310 cm$^{-1}$. $^{1}$H-NMR ($CDCl_3$) : 7.28 (m, 1H), 7.31 (d, J = 7.6 Hz, 1H), 6.98 (m, 2H), 4.26, 3.98 (each m, 2H), 2.92, 2.70 (each m, 2H), 2.85 (q, J = 7.5 Hz, 2H), 2.65, 2.51 (each m, 2H), 2.43, 2.30 (each m, 2H), 1.28 (t, J = 7.5 Hz, 3H). $^{13}$C-NMR ($CDCl_3$) : 174.38 (0), 135.56 (0), 128.01 (0), 127.68 (0), 125.73 (0), 121.34 (1), 119.80 (1), 119.13 (0), 116.10 (1), 109.80 (0), 71.92 (0), 64.07 (2), 33.76 (2), 28.18 (2), 24.02 (2), 21.57 (2), 19.19 (2), 14.25 (3). MS (EI) *m/z* (%): 299 ($M^{+}$+1, 100). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found : C, 68.21; H, 6.26; N, 9.12.

**8-Ethyl-1-(3-hydroxypropyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-carbonitrile** (**20**). To a solution of **18** (0.94 g, 3.2 mmol) in dichloromethane (20 mL) containing triethylamine (0.4 g, 4.0 mmol) was added at 0 $^{o}$C a solution of isobutyl chloroformate (0.43 g, 3.2 mmol) in dichloromethane (5 mL). After being stirred at 0 $^{o}$C for 1 h and at rt for 3 h, the reaction mixture was washed with water. The separated rganic layer was dried ($MgSO_4$) and evaporated to give the crude mixed anhydride (**19**) as an oil (0.74 g). To an ice-cooled solution of the crude **19** (0.74 g, ~1.8 mmol) in dry THF (15 mL) was added sodium borohydride (0.4 g, 10.6 mmol) with stirring. To the mixture was added water (5 mL) for a 1 h period. After the mixture was stirred at 0 $^{o}$C for 2 h, an additional amount of sodium borohydride (0.2 g, 5.3 mmol) was introduced and the resulting mixture was stirred for 2 h at rt. The reaction mixture was diluted with 5 % HCl solution, evaporated off methanol, and then extracted twice with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated. Purification by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/6) provided **20** as a white plate crystals (0.27 g, 30.0 %).

mp 132-134 °C, (1/4 ethyl acetate-hexane). IR (KBr) $\nu_{max}$ : 3480, 2239, 1049 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) : 8.36 (br s, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.10 (m, 2H), 4.35, 4.10 (each m, 2H, $ArCH_2C\underline{H_2}O$), 3.74, 3.67 (each m, 2H), 3.00, 2.77 (each m, 2H, $ArC\underline{H_2}CH_2O$), 2.86 (q, J = 7.5 Hz, 2H), 2.50, 2.24 (each m, 2H), 1.85, 1.75 (each m, 2H), 1.36 (t, J = 7.5 Hz, 3H). MS (EI) *m/z* (%): 284 ($M^+$, 65), 257 (20), 225 (100). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found : C, 71.79; H, 7.26; N, 9.68.

**1-(3-Bromopropyl)-8-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-carbonitrile** (**21**). To a solution of **20** (0.17 g, 0.60 mmol) in dry 1,2-dichlorethane (5 mL) was added triphenylphosphine dibromide (0.26 g, 0.61 mmol) at 0 °C, and the resulting solution was stirred for 2 h. The reaction mixture was washed with water, dried ($MgSO_4$), and evaporated. Purification by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/10) provided **21** as a yellow oil (0.08 g, 38.3 %). IR (film) $\nu_{max}$ : 3335, 2246, 1174, 1081, 1033 $cm^{-1}$. $^1$H-NMR ($CDCl_3$): 8.00 (br s, 1H, NH), 7.31(d, J = 7.0 Hz, 1H), 7.04 (m, 2H), 4.28, 4.02 (each m, 2H, $ArCH_2C\underline{H_2}O$), 3.33 (m, 2H, $CH_2Br$), 2.92, 2.68 (each m, 2H, $ArC\underline{H_2}CH_2$), 2.80 (q, J = 7.5 Hz, 2H), 2.39, 2.25 (each m, 2H), 2.03, 1.87 (each m, 2H), 1.30 (t, J = 7.5 Hz, 3H), $^{13}$C-NMR ($CDCl_3$): 135.38 (0), 127.40 (0), 127.16 (0), 125.92 (0), 122.07 (1), 120.70 (1), 118.93 (0), 116.54 (1), 111.39 (0), 71.66 (0), 64.30 (2), 37.71(2), 33.15 (2), 26.33 (2), 23.94 (2), 21.59 (2), 13.79 (3). MS (EI) *m/z* (%) : 348 ($M^+$, 20), 225 (100). Anal. Calcd for $C_{17}H_{19}N_2OBr$ : C, 58.80; H, 5.51; N, 8.07. Found : C, 58.76; H, 5.26; N, 8.46.

**8-Ethyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-carbonitrile** (**22**). To a solution of **21** (0.08 g, 0.23 mmol) in methanol (6 mL) were added catalytical amounts of 10 % Pd-C and triethylamine (0.023 g, 0.23 mmol). After being stirred under hydrogen for 15 h (hydrogen balloon), the reaction mixture was filtered through Celite and evaporated. Purification by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/15) provided **22** as a white powder (0.04 g, 65.0 %), mp 136-138 °C (1/4 ethyl acetate-hexane). IR (KBr) $\nu_{max}$ : 3344, 2235, 1695, 1042 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) : 8.00 (br s, 1H, NH), 7.30 (d, J = 7.4 Hz, 1H), 7.02 (m, 2H), 4.28, 4.00 (each m, 2H, $ArCH_2C\underline{H_2}O$), 2.90, 2.69 (each m, 2H, $ArC\underline{H_2}CH_2$), 2.78 (q, J = 7.5 Hz, 2H), 2.18, 1.98 (each m, 2H), 1.53, 1.42 (each m, 2H), 1.28 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). $^{13}$C-NMR ($CDCl_3$) : 135.27 (0), 128.32 (0), 127.02 (0), 125.97 (0), 121.83 (1), 120.55 (1), 119.29 (0), 116.49 (1), 110.89 (0), 72.20 (0), 64.21 (2), 41.58 (2), 23.92 (2), 21.66 (2), 16.73 (2), 13.37 (3, overlapping $\underline{C}H_3$). Ms (EI) *m/z* (%) : 268 ($M^+$, 26), 225 (100). Anal. Calcd for $C_{17}H_{20}N_2O$ : C, 76.09; H, 7.51; N, 9.92. Found : C, 76.26; H, 7.26; N, 9.66.

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