REGIOSPECIFIC FUNCTIONALIZATION OF INDOLE-2-CARBOXYLATES AND DIASTEREOSELECTIVE PREPARATION OF THE CORRESPONDING INDOLINES

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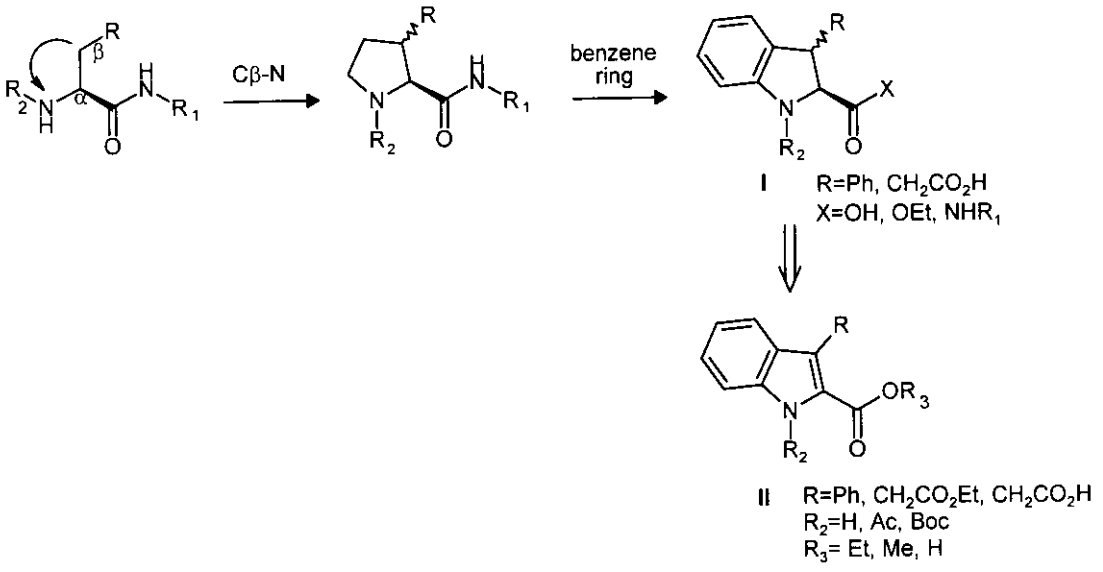
Abstract - The *N*-acyl derivatives of 3-substituted indole-2-carboxylates prepared through several routes were submitted to catalytic hydrogenation affording either *cis*- or *trans*-indoline diastereomers after quantitative C-2 epimerization.

Indole-2-carboxylates are efficient tools in alkaloid synthesis, or more recently for the preparation of enzyme inhibitors[1-3] and receptor ligands,[4,5] particularly peptidomimetics.[6] Among these compounds, indoline-2-carboxamides substituted or functionalized in position 3 may help to better characterize the active conformation of a specific α-amino acid, and then to design new nonpeptidic ligands, or enzyme inhibitors[1,5,7] with significantly increased *in vivo* stability towards proteases and peptidases (see Scheme 1). Formally they result from linkage between the β-carbon atom and nitrogen from a given α-amino acid, and can be regarded as proline derivatives, to which a benzene ring has been added. The aromatic ring in the indoline structure led to an increased lipophilicity combined with stabilization of the chiral pyrrolidine ring. We focused recently our interest on two typical representatives (I, R=Ph or R=CH_2CO_2H) as semi-rigid analogues of phenylalanine[8] and glutamic acid (Scheme 1).

The *N*-acylindole-2-carboxylates **(II)** constitute valuable precursors for the preparation of indolines **(I)** through regioselective hydrogenation of the pyrrole ring.



Scheme 1

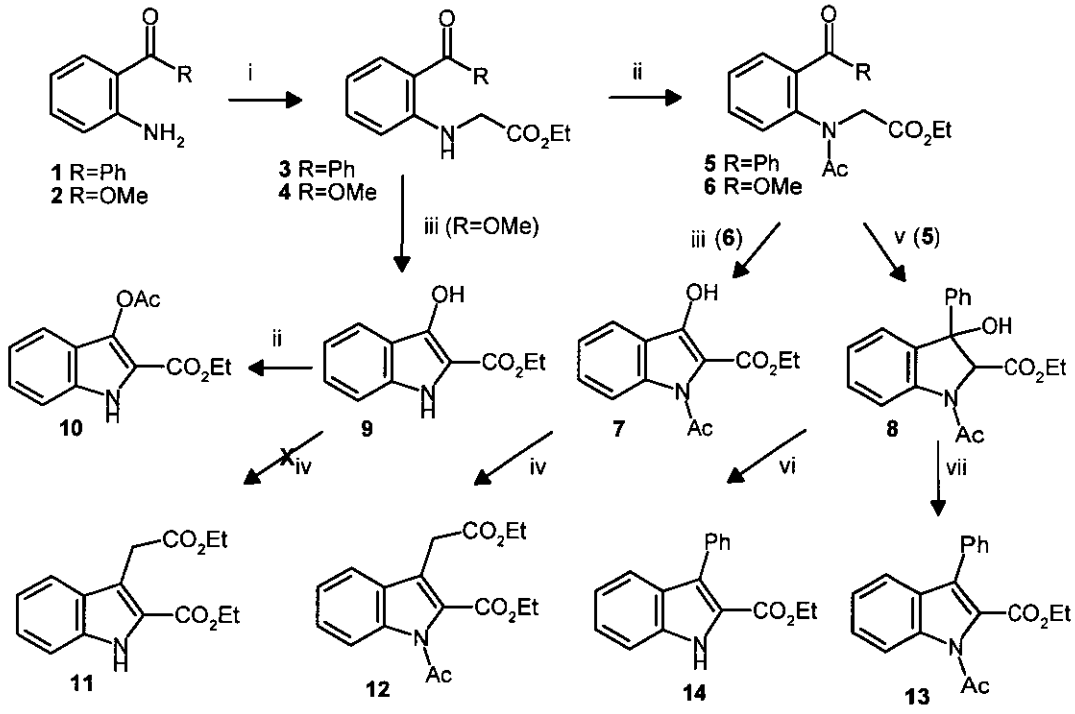
The aim of this work deals with the different modes of preparation of 3-substituted indole-2-carboxylate precursors **(II)**. In addition several aspects of their reactivities highlighted their potentialities as synthetic intermediates.

The Japp-Klingemann reaction has been used first to access to 3-substituted indole-2-carboxylates intermediates **(11)** and **(14)**, but low yields were generally obtained.[9-11]

Thus two other different strategies were developed here for the preparation of these compounds. They involved either anthranilic acid and derivatives (**1** or **2**, method a, Scheme 2) or a direct functionalization of indole-2-carboxylate (**15**, method b, Scheme 3).

The method depicted in Scheme 2 using the 2-aminobenzophenone **(1)** or the anthranilate derivative **(2)** results from a modified literature procedure.[12] The cyclization of **5** under alkaline conditions afforded the hydroxyindoline **(8)** which could be dehydrated in *N*-acetylindole **(13)** or indole **(14)** depending upon experimental conditions. The enol **(9)** did not react directly in the presence of a Wittig reagent. Its reactivity through double bond conjugation is rather close to an amide than to a carbonyl of ketone. The *N*-acylation of the pyrrole ring could restore satisfactory electrophilic character of the carbonyl in

position 3. However, the acylation of the enol **(9)** in the presence of acetic anhydride led only to the *O*-acetylated compound **(10)**. Thus, acylation was performed before cyclization step (compound **(6)**). Reacting indole **(7)** with ethyl triphenylphosphoranylideneacetate afforded the expected diester **(12)** in 84% yield.



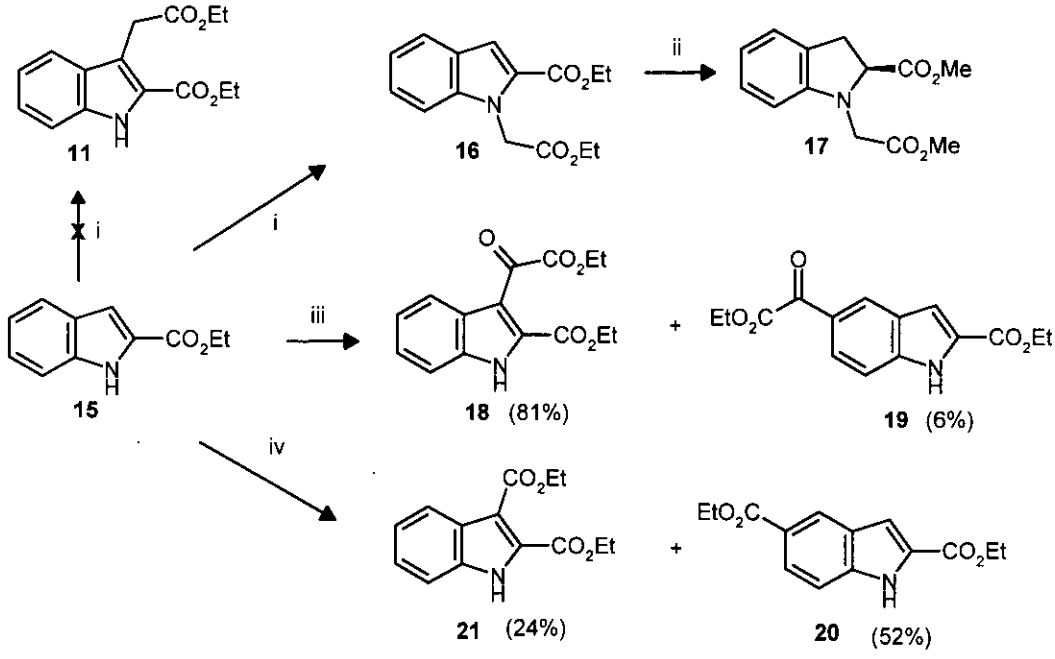
i: $BrCH_2CO_2Et$, DMF, 70°C ; ii: Ac_2O, Δ ; iii: *t*-BuOK, THF, 0°C ; iv: $PPh_3{=}CHCO_2Et$, toluene, Δ ; v: K_2CO_3, DMF, Δ ; vi: *p*-TsOH, benzene, Δ ; vii: gas HCl, Et_2O, 0°C.

Scheme 2 (method a)

Indole is an ambident nucleophile and is known to react with electrophiles at both nitrogen and at C-3.[13-15] When considering literature data dealing with substitution of indole-2-carboxylates, the nature of the substituted regioisomer strongly depends upon the nature of the electrophilic reagent and experimental conditions.

Particularly, the preparation of diester **(11)** has been recently described as the result of alkylation of ethyl indole-2-carboxylate **(15)** with ethyl bromoacetate in the presence of potassium carbonate[16] (Scheme 3). However, NMR spectral data showed that substitution occurred at the ring nitrogen instead of the

position 3 leading to **16**. The CH_2 signal in α position of nitrogen appears at 5.30 ppm for **16**, whereas CH_2 in α position of C-3 was found at 4.10 ppm for **11** prepared elsewhere (see Scheme 4). In addition, reduction of **16** with magnesium in methanol afforded the indoline **(17)** characterized by an ABX system in ^{1}H-NMR, and by only one methine signal in its ^{13}C NMR spectrum. This behaviour can be rationalized, when applying the hard-soft-acids-bases theory (HSAB).[17-19] In addition, considering both N and C-3 nucleophilic centers, the C-3 would behave as the hard base and react with acyl reagents, that behave as carbonium ions (hard electrophiles).[18]



i: $BrCH_2CO_2Et$, K_2CO_3, MeCN, Δ ; ii: Mg, MeOH ; iii: $ClCOCO_2Et$, $AlCl_3$, $ClCH_2CH_2Cl$, rt; iv: 1) $(COCl)_2$, $ClCH_2CH_2Cl$, $AlCl_3$, 0°C then rt ; 2) EtOH, Δ.

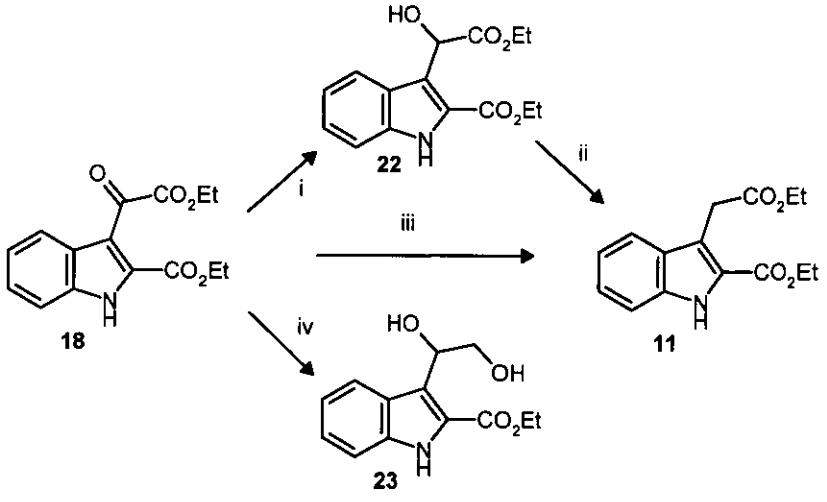
Scheme 3 (method b)

We chose oxalyl chloride and ethoxalyl chloride for acylation reaction, as they may yield in one step a precursor **(18)** of the expected indoleacetate **(11)** after reduction of α-keto ester **(18)**. Whereas reaction of ethoxalyl chloride with unsubstituted indole afforded easily the 3-acyl derivative[20] at 0°C, the same experimental conditions applied to indole-2-carboxylate **(15)** afforded the reagent unchanged. Acylation

performed in Friedel-Crafts conditions with aluminium chloride in 1,2-dichloroethane led to a mixture of two acyl derivatives which contained the expected 3-acyl derivative **(18)** as the major compound (see Scheme 3).

Surprisingly, when replacing ethoxalyl chloride by oxalyl chloride, and after a final short period refluxing in ethanol, decarbonylation occurred and the ethoxycarbonyl isomers **(20)** and **(21)** were recovered, but in a different *ratio,* when compared with those obtained earlier with ethoxalyl chloride (3-carbethoxy derivative **(21)** as the minor compound).

Acylation of indole-2-carboxylates using Friedel-Crafts conditions was already described in detail using different experimental conditions.[21] They obtained mixtures of 3-, 5- and 7-acyl derivatives depending upon the nature of the Lewis catalyst, the solvent and the electrophilic character of the acyl chloride. The reaction took place mainly ($AlCl_3$) or exclusively ($FeCl_3$) at the 3-position. Moreover, with the highly reactive chloroacetyl chloride, acylation occurred only on the benzene ring, and afforded both the 5-isomer (major) and the 7-isomer. It is interesting to notice that using these experimental conditions,[21] the 7-isomer was never isolated from the mixture with either ethoxalyl or oxalyl chloride.



i: $NaBH_4$ (1 eq), EtOH, rt ; ii: P_2I_4, CH_2Cl_2, rt ; iii: 1) *p*-toluenesulfonyl hydrazide, MeOH, Δ ; 2) $NaBH_4$, THF, Δ ; iv: $NaBH_4$ (2 eq), EtOH, rt.

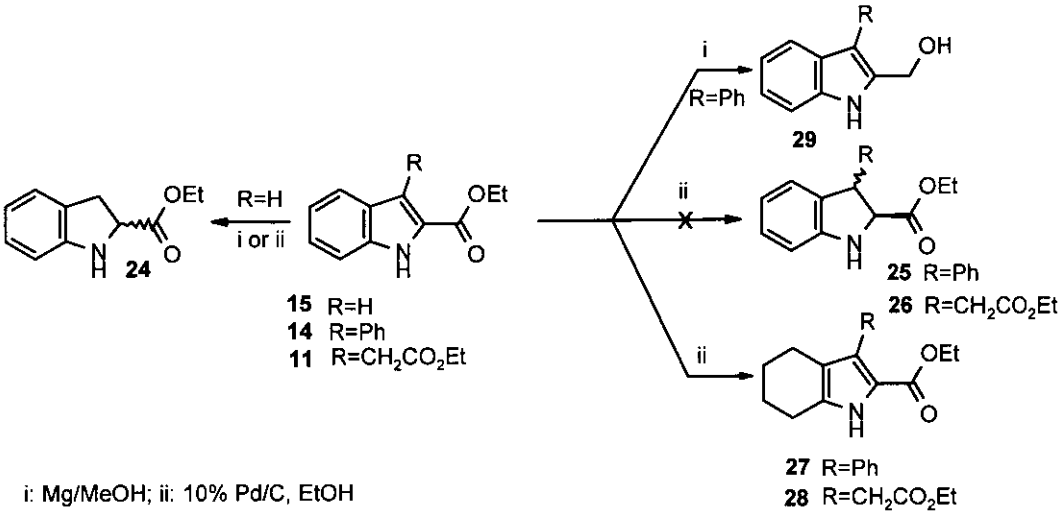
Scheme 4

The α-keto ester **(18)** was then submitted to different reduction conditions in order to prepare the acetate **(11)** (Scheme 4). The α-hydroxy derivative **(22)** was easily obtained with one equivalent of sodium borohydride. The same reaction in the presence of two equivalents of hydride led to the diol **(23)**. Diphosphorus tetraiodide has been described as a potent dehydrating agent particularly for reduction of benzyl alcohols.[22] This reactant was efficient in reducing the alcohol **(22)** into the acetate **(11)**. In addition, a modified Wolff-Kishner reduction[23] of the *p*-toluenesulfonylhydrazone intermediate with sodium borohydride afforded also the diester **(11)** in a good overall yield (61%).

Finally we performed partial catalytic hydrogenation of the pyrrole ring of indole-2-carboxylates **(11)** and **(14)** in order to obtain enantiomeric mixtures of *cis*-indolines (**25** and **26**). However, when compared with literature data,[24] unexpected results were obtained depending upon the reduction conditions and the nature of substituent R (Scheme 5). We selected two modes of hydrogenation already described for the 3-unsubstituted indole-2-carboxylate **(15)**, catalytic hydrogenation and reduction using magnesium in methanol. In both experimental conditions the 3-unsubstituted indoline **(24)** was obtained in good yield. However, when submitting the 3-phenyl **(14)** or 3-carboxymethyl derivative **(11)** to catalytic hydrogenation, the benzene ring instead of the pyrrole was quantitatively reduced affording respectively the tetrahydro derivatives **(27)** and **(28)**. Thus a clear-cut effect of the substituent in position 3 was highlighted with an aromatic **(14)** or an aliphatic **(11)** group on the regioselectivity of hydrogenation of these compounds, and to our knowledge it was not reported in the literature.

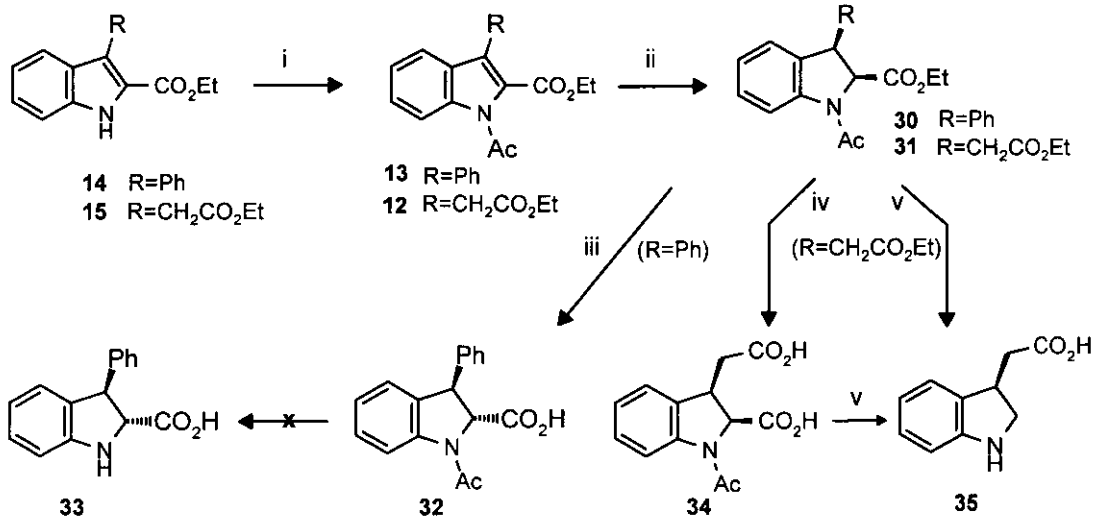
Another unexpected route of reduction was observed when reducing the indole **(14)** (R=Ph) with magnesium in methanol. Reduction took place at the 2-carboxylate function and the hydroxymethyl derivative **(29)** was obtained exclusively. These results emphasized the relatively high electron density of the pyrrole ring in compounds **(11)** and **(14)**, when compared with the benzene ring.

Thus we decided to deplete the electron density of the pyrrole ring of indoles **(14)** and **(11)** by *N*-acylation.



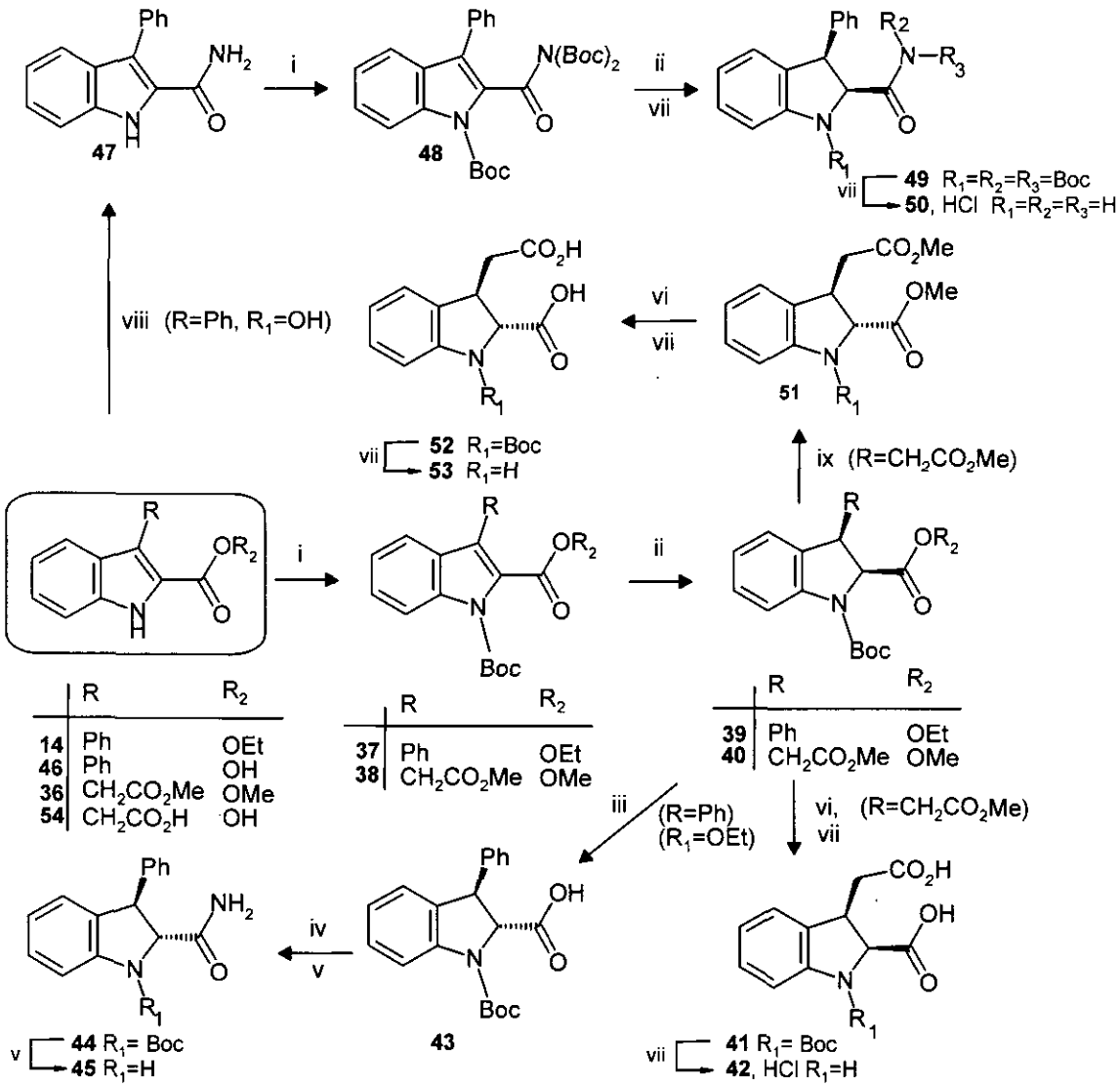
Scheme 5

Using magnesium in methanol, a mixture of *cis*- and *trans*-isomers was recovered, the *cis*/*trans* ratio depending upon the nature of the *N*-acyl substituent. Finally *N*-acetyl derivatives **(12)** and **(13)** were submitted to catalytic hydrogenation. As expected, the *cis*-indolines **(30)** and **(31)** were obtained (Scheme 6).



Scheme 6

However, even in very mild hydrolysis conditions of **30** (LiOH, DME), epimerization took place at *C*-2 and the *trans*-isomer **(32)** was recovered quantitatively. This was confirmed by X-Ray crystallography after resolution of the racemate using (+) - quinidine.[8]



i: $(Boc)_2O$, TEA, DMAP, THF, rt ; ii: H_2, 10% Pd/C, 60 psi, EtOH ; iii: LiOH, DME/H_2O, Δ ; iv: 1) $ClCO_2i$-Bu, TEA, CH_2Cl_2, 0°C ; 2) gas NH_3 ; v: TFA, CH_2Cl_2, -10°C ; vi: 1N NaOH, 0°C then rt ; vii: gas HCl, AcOEt ; viii: 1) $(COCl)_2$, DMF ; 2) gas NH_3 ; ix: 1N *t*BuOK /THF.

Scheme 7

Attempts to remove the acyl group from the acids **(32)** and **(34)** in acidic or basis medium at different

temperatures failed and the acid **(32)** remains unchanged, or decarboxylation occurred simultaneously with deacetylation **(35)**.[25]

In order to avoid these side reactions, the more labile *N*-Boc derivatives **(37)** and **(38)** were prepared starting from **14**, or from the easy-to-hydrolyze dimethyl ester **(36)**.

In these conditions, catalytic hydrogenation afforded the corresponding *cis*-indolines **(39)** and **(40)**. The mild alkaline hydrolysis of the methyl diester **(40)** in the presence of NaOH followed by deprotection of the *N*-Boc derivative **(41)** led to the *cis*-indoline 2-carboxylic acid **(42)** (J_{cis}=8.9 Hz). As observed earlier, smooth alkaline hydrolysis of **39** in the presence of LiOH in aqueous dimethoxyethane yielded nearly quantitatively the *trans*-acid **(43)** which was resolved into optically pure enantiomers with(-) - ephedrine. Activation of the acid **(43)** by means of isobutyl chloroformate and ammonolysis with ammonia gas followed by facile deprotection of the *N*-Boc derivative **(44)** led to the awaited *trans*-indoline-2-carboxamide **(45)**.

In order to avoid epimerization in **39**, the amide function was introduced at the beginning (compound **47**). Thus the indole-2-carboxamide **(47)** reacted with di-*tert*-butyl dicarbonate. However, different attempts to prepare the indoline *N*-Boc derivative led to a mixture of mono-, di- and tri-Boc compounds. Thus the tri-Boc derivative **(48)** was efficiently prepared by means of three equivalents of di-*tert*-butyl dicarbonate and submitted to catalytic hydrogenation leading to yield the *cis*-indoline **(49)**. The latter compound **(49)** afforded easily the awaited *cis*-indolinecarboxamide **(50)** in acidic medium. In order to access to the *trans*-diacid **(53)** (J_{trans}=5.5 Hz, mp149-150°C), the indoline **(40)** was reacted with potassium *tert*-butoxide to achieve complete epimerization (compound **51,** nonoptimized yield). This method is efficient as both couples of *cis* and *trans* diastereomers could be obtained through two different pathways.

Some of the chemical behaviours described in this paper result from specific electronic delocalizations, which more or less involve the lone pair of the pyrrole nitrogen. In compound **(14)** the favorable conjugation in the *N*-styryl system results in increased electron-density of the pyrrole ring rendering it

less sensitive to reduction. Thus the 3-phenyl derivative **(14)** presented a reactive ester, which was easily reduced into alcohol by sodium borohydride. Thus *N*-acylation of these systems restored reasonable electron densities of the 2,3 double bond. Moreover catalytic hydrogenation combined with controlled epimerization in basic medium and optical resolution of pairs of diastereomers constitute a versatile method of preparation of *cis*-or *trans*-3-subsituted indoline-2-carboxylates. These compounds will be useful for preparing short peptides containing 3-substituted indolines.

We developed here efficient methods of preparation of *N*-acylindole-2-carboxylate bearing an acetic or a phenyl group in position 3. They constitute valuable intermediates for further syntheses of various conformationally constrained α-amino acids and corresponding peptidomimetics. This approach can be generalized to other aromatic amino acids including Tyr and Trp, or other aromatic amino acids bearing functionalized alkyl side chains (Glu, Orn).

EXPERIMENTAL SECTION

Melting points were determined on a Mettler FP62 and are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz on a Brucker 200 AC spectrometer with Me_4Si as the internal standard (δ(ppm)). ^{13}C NMR spectra were recorded at 50 MHz on the same instrument using the $CDCl_3$ solvent peak at δ 77.0 ppm as the reference. Elemental analyses (CHN) were performed by the analytical group (Department of Chemistry, University Louis Pasteur-Strasbourg I). Flash chromatography was run on Gerdura SI 60 ((0.040-0.063 mm) Merck).

N-(Ethoxycarbonylmethyl)-2-aminobenzophenone (3).

To a solution of 2-aminobenzophenone **(1)** (6.0 g, 30.4 mmol) in dry DMF (50 mL) was added dropwise ethyl bromoacetate (3.4 mL, 30.4 mmol). The reaction mixture was stirred and heated at 80°C during 18 h. The solvent was removed under reduce pressure. The residue was dissolved in CH_2Cl_2 (60 mL).

The organic layer was washed twice with 5% aqueous $NaHCO_3$ (2x40 mL) and brine (50 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2) to afford **3** (6.90 g, 80%) as a yellow oil[26]; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J=7.2), 4.04 (d, 2H, J=5.2), 4.30 (q, 2H, J=7.2), 6.50-6.66 (m, 2H), 7.30-7.62 (m, 7H), 8.90 (br t, 1H).

Methyl *N*-(ethoxycarbonylmethyl)anthranilate (4).

To a solution of methyl anthranilate **(2)** (4.5 g, 30.0 mmol) in dry DMF (30 mL) was added dropwise ethyl bromoacetate (3.4 mL, 30.4 mmol). The reaction mixture was stirred and heated at 80°C during 10 h and after standard work-up reported for the preparation of **3**, the residue was crystallized from Et_2O/petroleum ether to give **4**[27] (5 g, 75%); ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, J=7.2), 3.80 (s, 3H), 4.01 (d, 2H, J=5.2), 4.29 (q, 2H, J=7.2), 6.54 (d, 1H, J=8.4), 6.67 (t, 1H, J=8.6), 7.37 (dt, 1H, J=8.6 and 1.6), 7.94 (dd, 1H, J=8.6 and 1.6), 8.19 (br s, 1H).

***N*-Acetyl-*N*-(ethoxycarbonylmethyl)-2-aminobenzophenone (5).**

To a solution of **3** (3 g, 9.2 mmol) in acetic anhydride (40 mL) was added a drop of H_2SO_4. The mixture was heated at 100°C for 2 h, cooled and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (60 mL). The organic layer was washed twice with saturated aqueous $NaHCO_3$ (2x30 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc-hexane, 85:15) to afford **5** (75%) as a red brown oil used without further purification; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, J=7.2), 1.85 (s, 3H), 4.13 (AB system, 2H, Δδ=1.00, J_{AB}=17.5), 4.07-4.16 (m, 2H), 7.41-7.62 (m, 6H), 7.69-7.72 (m, 3H).

Methyl *N*-acetyl-*N*-(ethoxycarbonylmethyl)anthranilate (6).

Compound (**6**) was synthesized from **4** following the same procedure previously described for the preparation of **5**. The organic layer was washed twice with saturated aqueous $NaHCO_3$ (2x30 mL), dried (Na_2SO_4), filtered and evaporated to afford **6** (3.2 g, 94%) as a yellow oil used without further purification; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J=7.2), 1.82 (s, 3H), 4.31 (AB system, 2H, Δδ=1.00,

J_{AB}=17.4), 3.92 (s, 3H), 4.07-4.16 (m, 2H), 7.41-7.80 (m, 3H), 8.05 (dd, 1H, J= 8.6 and 1.6).

Ethyl 1-acetyl-3-hydroxyindole-2-carboxylate (7).

6 (2.70 g, 11.85 mmol) was dissolved in dry THF (40 mL), cooled at 0°C and treated dropwise with a solution of 1N *t*-BuOK in THF (12 mL, 12.0 mmol). After the addition was completed (0.5 h), the resulting mixture was stirred one more 0.5 h at 0°C. Most of THF was then distillated under reduce pressure. To the residue was added 30 mL of a mixture H_2O/AcOH (5:1) with rapid stirring and extraction with CH_2Cl_2 (3x30 mL) was performed. The combined extracts were washed with brine (40 mL) and dried (Na_2SO_4), filtered and evaporated. The residue was crystallized from Et_2O/petroleum ether (3:1) to give **7** (2.1 g, 72%) as a white solid: mp 102°C; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3H, J=7.2), 2.23 (br s, 3H), 4.34 (q, 2H, J=7.2), 4.99 (br s, 1H), 7.25 (m, 1H), 7.74 (m, 2H), 8.61 (m, 1H).

Ethyl 1-acetyl-3-hydroxy-3-phenylindoline-2-carboxylate (8).

A solution of **5** (5.5 g, 17.0 mmol) in DMF (15 mL) was added to K_2CO_3 (5.5 g, 39.70 mmol) in DMF (10 mL). The reaction mixture was heated 3 h at 50°C, then poured into ice water and acidified with 6N HCl until pH 1. The resulting precipitate was filtered and redissolved in EtOAc. The aqueous layer was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), filtered and evaporated. The residue was triturated with Et_2O to afford **8** (4.9 g, 90%) as a white solid; mp 170-172°C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 0.76 (t, 3H, J=6.9), 2.07 (s, 3H), 3.45 (qd, 2H , J=6.9, J=3.6), 4.38 (br s, 1H), 4.91 (s, 1H), 7.09-7.40 (m, 8H), 8.33 (d, 1H, J=8.4). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.12; H, 5.99; N, 4.52.

Ethyl 3-hydroxyindole-2-carboxylate (9).

Compound **(9)** was synthesized from **4** following the same procedure previously described for the preparation of **7**. The residue was crystallized from Et_2O/petroleum ether (3:1) to give **9** (53%) as a white solid; mp 155°C (acetone)[27]; ^{1}H NMR ($CDCl_3$) δ 1.43 (t, 3H, J=7.3), 4.48 (q, 2H, J=7.3), 7.07-7.14 (m, 1H), 7.25-7.39 (m, 2H), 7.55-7.82 (m, 2H).

Ethyl 3-acetoxyindole-2-carboxylate (10).

To a solution of **9** (1 g, 4.87 mmol) in acetic anhydride (30 mL) was added a catalytic amount of conc. H_2SO_4. The mixture was heated at 100°C overnight, cooled and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (60 mL). The organic layer was washed twice with saturated aqueous $NaHCO_3$ (2x30 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc-hexane, 35:65) to afford **10** (1.05 g, 85%) as a white solid; mp 132°C (EtOH) (lit. 135°C)[28]; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H J=7.2), 2.43 (s, 3H), 4.38 (q, 2H J=7.2), 7.15 (m, 1H), 7.35 (m, 2H), 7.55 (d, 1H, J=7.4), 8.90 (s, 1H).

Ethyl 1-acetyl-3-ethoxycarbonylmethylindole-2-carboxylate (12).

A solution of **7** (2 g, 8.0 mmol) and ethoxycarbonylmethylenetriphenylphosphorane (4.17 g, 12.0 mmol) in toluene (40 mL) was heated to reflux for 4 h. The mixture was evaporated under reduce pressure. The residue was purified by flash chromatography on silica gel (EtOAc-hexane, 1:2) to afford **12** (2.1 g, 84%) as a yellow oil used without further purification; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, J=7.2), 1.41 (t, 3H, J=7.2), 2.60 (s, 3H), 4.00 (s, 2H), 4.15 (q, 2H, J=7.2), 4.45 (q, 2H, J=7.2), 7.31 (t, 1H, J=7.2), 7.46 (t, 1H, J=7.2), 7.61 (d, 1H, J=7.8), 8.07 (d, 1H, J=8.2).

Ethyl 1-acetyl-3-phenylindole-2-carboxylate (13).

8 (0.65 g, 2.0 mmol) was treated with a solution of 30% HCl in Et_2O (20 mL) at 0°C. The reaction mixture was stirred for 2 h at 0°C and evaporated under reduce pressure. The residue was dissolved in CH_2Cl_2 (60 mL), washed with saturated aqueous $NaHCO_3$ (40 mL) and H_2O (40 mL), dried (Na_2SO_4), filtered and evaporated to afford **13** (0.58 g, 95%); mp 92°C (EtOH);^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H, J=7.2), 2.70 (s, 3H), 4.26 (q, 2H, J=7.2), 7.28-7.58 (m, 8H). 8.08 (d, 1H, J=8.2).

Ethyl 3-phenylindole-2-carboxylate (14).

To a solution of **8** (4.9 g, 15.0 mmol) in benzene (100 mL) was added *p*-TsOH (2.86 g, 15,0 mmol). The mixture was heated for 12 h at 80°C, washed with H_2O (100 mL), then with saturated aqueous $NaHCO_3$

(100 mL), dried (Na_2SO_4), filtered and evaporated to afford **14** (3.83 g, 95%) as a beige solid; mp 140°C (EtOH) (lit. 137-138°C)[29]; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H , J=7.3), 4.31 (q, 2H, J=7.3), 7.10-7.67 (m, 9H), 9.04 (br s, 1H).

Ethyl 1-ethoxycarbonylmethylindole-2-carboxylate (16).

Ethyl indole-2-carboxylate **(15)** (0.50 g, 2.65 mmol), ethyl bromoacetate (1.80 g, 5.30 mmol), K_2CO_3 (1.10 g, 7.95 mmol) and MeCN (30 mL) were combined and heated to reflux for 48 h. The mixture was poured into H_2O (50 mL) and the aqueous mixture was extracted with Et_2O (2x30 mL). The combined ether solutions were washed with H_2O (2x30 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc-hexane, 1:4) to afford **16** (0.58 g, 80%) as a light yellow solid: mp 105°C[30]; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3H, J=7.3), 1.43 (t, 3H, J=7.3), 4.24 (q, 2H, J=7.3), 4.38 (q, 2H, J=7.3), 5.40 (s, 2H), 7.14-7.40 (m, 3H), 7.70 (d, 2H, J=8.1).

Methyl 1-methoxycarbonylmethylindoline-2-carboxylate (17).

16 (0.28 g, 1.0 mmol) was dissolved in anhydrous MeOH (10 mL). The solution was cooled at 10°C and magnesium (0.08 g, 3.2 mmol) was added. The solution was stirred at rt overnight, poured into a cooled solution of 3N HCl and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and evaporated under reduce pressure to obtain **17** as a yellow oil (0.20 g, 80%); ^{1}H NMR ($CDCl_3$) δ 3.35 (ABX system, AB part, 2H, $\Delta\delta$=0.2, J_{AB}=16.0, J_{AX}=8.7, J_{BX}=10.5), 3.71 (s, 3H), 3.78 (s, 3H), 4.09 (d, 2H, J=11.5), 4.58 (ABX system, X part, 1H, J_{AX}+J_{BX} =19.2), 6.37-7.42 (m, 1H), 6.67-6.74 (m, 1H), 7.04-7.10 (m, 2H) ; ^{13}C NMR ($CDCl_3$) δ 31.5, 48.2, 51.7, 52.1, 64.7, 106.5, 118.7, 124.2, 126.5, 127.6, 150.0, 170.4, 172.8.

Ethyl 3-ethoxycarbonylcarbonylindole-2-carboxylate (18) and ethyl 5-ethoxycarbonylcarbonyl-indole-2-carboxylate (19).

The ester **(15)** (1 g, 5.30 mmol) was dissolved in 1,2-dichloroethane (30 mL). Ethoxalyl chloride (1.30 mL, 11.20 mmol) was added dropwise followed by addition of $AlCl_3$ (1.54 g, 11.20 mmol) in one portion. The resulting mixture was stirring at rt for 12 h. Saturated aqueous $NaHCO_3$ (30 mL) was added. The

aqueous layer was extracted with EtOAc (2x50 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc-hexane, 1:4 then 1:1) to afford **18** (1.32 g, 81%) as yellow solid: mp 98°C (petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 6H, J=7.2), 4.43 (q, 4H, J=7.2), 7.33-7.50 (m, 3H), 8.25 (d, 1H, J=8.2), 9.43 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 14.7, 62.7, 62.9, 112.7, 116.1, 123.4, 124.5, 127.2, 127.7, 130.8, 135.6, 160.4, 164.4, 184.1. Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.27; H, 5.22; N, 4.84. Found: C, 62.22; H, 5.26; N, 4.86.

Compound **(19)** (92 mg, 6%), yellow solid: mp 132°C (petroleum ether); ^{1}H-NMR ($CDCl_3$) δ 1.45 (t, 6H, J=7.2), 4.47 (q, 4H, J=7.2), 7.35 (s, 1H), 7.52 (dd, 1H, J=8.6, J=1.5), 8.03 (dd, 1H, J=8.6, J=1.5), 8.44 (s, 1H), 9,50 (br s, 1H). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.27; H, 5.22; N, 4.84. Found: C, 62.32; H, 5.31; N, 4.81.

Ethyl indole-2-3-dicarboxylate (21) and ethyl 2,5-indoledicarboxylate (20).

$AlCl_3$ (0.59 g, 4.4 mmol) was suspended in CH_2Cl_2 (40 mL). The solution was cooled at 0°C then oxalyl chloride (0.35 mL, 4.4 mmol) was added dropwise. The reaction mixture was stirred for 0.5 h at 0°C before addition of ethyl indole-2-carboxylate **(1)** (0.38 g, 2.0 mmol) dissolved in CH_2Cl_2 (10 mL) and then at rt for 2 h. Ice water was added and the reaction mixture extracted with CH_2Cl_2 (2x50 mL), and the extract was dried (Na_2SO_4), filtered and evaporated. The residue was dissolved in boiling EtOH (20 mL) until dissolution and then stirred for 4 h at rt. After concentration under reduced pressure the residue was purified by flash chromatography on silica gel (EtOAc-hexane 1:8 then 1:1) to afford **21** (0.13 g, 24%) as a white solid : mp 85°C (benzene) (lit., 84-86°C)[31]; ^{1}H-NMR ($CDCl_3$) δ 1.32-1.48 (m, 6H), 4.29-4.51 (m, 4H), 7.14-7.26 (m, 2H), 7.88 (dd, 1H, J=7.8 , J=1.1), 8.01 (dd, 1H, J=7.8 , J=1.1), 10.24 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ 14.5, 61.1, 61.2, 108.7, 113.9, 120.2, 127.7, 128.3, 128.6, 128.8, 136.4, 161.5, 166.9.

Compound **(20)** : yellow solid (0.27g, 52%), mp 142°C (EtOH) (lit., 145-146°C)[32]; ^{1}H-NMR ($CDCl_3$) δ 1.38-1.47 (m, 6H), 4.36-4.50 (m, 4H), 7.31 (s, 1H), 7.45 (d, 1H, J=8.8), 8.02 (d, 1H, J=8.8), 8.48 (s, 1H), 9.78 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ 14.5, 14.6, 60.9, 61.4, 109.9, 111.8, 123.5, 125.8, 126.3, 127.1,

129.1, 139.2, 161.9, 167.3.

(2-Ethoxycarbonylindol-3-yl)ethyl-2-hydroxyacetate (22).

To a solution of **18** (0.15 g, 0.52 mmol) in EtOH (8 mL) was added $NaBH_4$ (0.02 g, 0.55 mmol). The resulting mixture was stirred for 4 h at rt. The solvent was removed under reduce pressure. The residue was dissolved in EtOAc (40 mL). The organic layer was washed with brine (40 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc-hexane, 1:1) to afford **22** (0.11 g, 63%) as a light yellow solid: mp 74°C (hexane); ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3H, J=7.2), 1.46 (t, 3H, J=7.2), 4.11-4.29 (m, 2H), 4.46-4.50 (m, 2H), 4.56 (d, 1H, J=7.1), 6.07 (d, 1H, J=6.8), 7.16-7.22 (m, 1H), 7.33-7.43 (m, 2H), 7.78 (d, 1H, J=8.3), 8.90 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.5, 61.8, 62.1, 66.2, 112.1, 120.5, 121.2, 121.3, 124.2, 126.1, 126.3, 135.7, 162.0, 173.5. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.92; H, 5.71; N, 4.85.

Ethyl 3-(1,2-dihydroxyethyl)indole-2-carboxylate (23).

To a solution of **18** (0.20 g, 0.69 mmol) in EtOH (8 mL) was added $NaBH_4$ (0.05 g, 1.38 mmol). The resulting mixture was stirred for 4 h at rt and after standard work-up reported for the preparation of **22**, **23** (0.10 g, 59%) was afforded as a light yellow solid: mp 154°C (petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 3H, J=7.1), 2.88 (br s, 1H), 3.73-3.88 (m, 2H), 4.39 (q, 2H, J=7.1), 4.98 (d, 1H, J=8.6), 5.44-5.51 (m, 1H), 7.11 (t, 1H, J=7.4), 7.14-7.38 (m, 2H), 7.80 (d, 2H, J=8.3), 9.23 (br s, 1H). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.76; H, 6.07; N, 5.69.

Ethyl 3-ethoxycarbonylmethylindole-2-carboxylate (11).

method a: To a solution of **22** (0.15 g, 0.52 mmol) in CH_2Cl_2 (5 mL) under argon was added in one portion P_2I_4 (0.58 g, 1.04 mmol). The resulting mixture was stirred for 12 h at rt. The mixture was poured into satured aqueous $NaHSO_3$ (10 mL). CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ were added. The organic layer was washed with brine (30 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc-hexane, 1:2) to afford **11** (0.11 g, 78%) as a light

yellow solid.

method b: To a solution of **18** (0.18 g, 0.65 mmol) in MeOH (12 mL) under argon was added *p*-toluene-sulfonylhydrazide (0.58 g, 1.04 mmol) and the resulting mixture was heated 8 h at reflux. The solvent was removed under reduce pressure. The residue was dissolved in THF (12 mL) and $NaBH_4$ (0.54 g, 14.0 mmol) was added. The reaction mixture was heated for 6 h at reflux and after standard work-up reported for the preparation of **22**, the residue was purified by flash chromatography on silica gel (EtOAc-hexane, 1:1) to afford **11** (0.11 g, 60%) as a light yellow solid: mp 78°C (EtOH); ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, J=7.2), 1.43 (t, 3H, J=7.2), 4.15-4.22 (m, 4H), 4.31 (q, 2H, J=7.2), 7.17 (t, 1H, J=7.5), 7.31-7.41 (m, 2H), 7.67 (d, 1H, J=7.9), 8.94 (br s, 1H).

Ethyl 3-phenyl-4,5,6,7-tetrahydroindole-2-carboxylate (27).

A solution of ester **(14)** (0.30 g, 1.13 mmol) in EtOH (20 mL) was hydrogenated at rt at 50 psi in the presence of 10% Pd/C (0.075 g) for 24 h. The catalyst was removed by filtration through a pad of celite and upon removal of solvent *in vacuo*, **27** was isolated as a white solid (0.18 g, 58%): mp 192°C ($CHCl_3$) (lit., 194-196°C)[33]; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3H, J=7.3), 1.60-1.90 (m, 4H), 2.42 (t, 2H, J=6.2), 2.65 (t, 2H, J=6.2), 4.16 (q, 2H, J=7.3), 7.24-7.40 (m, 5H), 8.78 (br s, 1H).

MS : M+ 269

(3-Phenylindol-2-yl)methanol (29).

To a solution of **14** (0.26 g, 1.0 mmol) in MeOH (10 mL) was added at 0°C magnesium (0.10 g, 4.1 mmol). After stirring at rt for 24 h, MeOH was distilled under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with H_2O (40 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc-hexane, 1:3) to afford **29** (0.12 g, 54%) as a white solid: mp 98-100°C (petroleum ether); ^{1}H NMR ($CDCl_3$) δ 4.90 (s, 2H), 7.12-7.18 (m, 8H), 7.73 (d, 1H, J=7.6), 8.60 (br s, 1H). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.72; H, 5.81; N, 6.22.

Methyl 3-methoxycarbonylmethylindole-2-carboxylate (36).

The diacid **(54)** (0.60 g, 2.73 mmol) was esterified by dissolving in MeOH (30 mL) and treating with concentrated H_2SO_4 (1.5 mL). The solution was heated to reflux for 20 h, the solvent removed *in vacuo*, the residue diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (2x25 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (25 mL) and H_2O (25 mL), dried (Na_2SO_4), filtered and evaporated to afford **36** (0.62 g, 89%) as a white solid: mp 128-130°C (EtOH); ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H), 3.92 (s, 3H), 4.20 (s, 2H), 7.10-7.40 (m, 3H), 7.66 (d, 1H, J=8.1), 8.98 (br s, 1H).

Methyl 1-(*tert*-butyloxycarbonyl)-3-(methoxycarbonylmethyl)indole-2-carboxylate (38).

To a stirred solution of diester **(36)** (2.47 g, 10.0 mmol) in THF (40 mL) was added at 0°C DMAP (2.44 g, 20.0 mmol), TEA (1.35 mL, 10 mmol) and di-*tert*-butyl dicarbonate (4.36 g, 20.0 mmol). The reaction mixture was stirred at rt for 0.5 h. The solvent was removed under reduced pressure. The residue was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (2x25 mL). The residue was purified by flash chromatography on silica gel (EtOAc-hexane, 1:6) to afford **38** (3.3 g, 95%) as a white solid: mp 88-90°C (petroleum ether-Et_2O); ^1H NMR ($CDCl_3$) δ 1.62 (s, 9H), 3.69 (s, 2H), 3.92 (s, 3H), 3.94 (s, 3H), 7.29 (t, 1H, J=8.4), 7.43 (t, 1H, J=8.4), 7.58 (d, 1H, J=8.4), 8.09 (d, 1H, J=8.4). Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.02; H, 6.11; N, 3.97.

Ethyl 1-(*tert*-butyloxycarbonyl)-3-phenylindole-2-carboxylate (37).

Compound **(37)** was synthesized from **14** following the same procedure previously reported for the preparation of **38**. The residue was purified by flash chromatography on silica gel (CH_2Cl_2-hexane, 3:7) to afford **37** (76%) as a light yellow solid: mp 96-98°C (petroleum ether). The compound was chromatographically and spectroscopically pure and was used without further analysis for the preparation of **39**; ^1H NMR ($CDCl_3$) δ 1.18 (t, 3H, J=7.3), 1.67 (s, 9H), 4.29 (q, 2H, J=7.3), 7.26-7.61 (m, 8H), 8.18 (d, 1H, J=8.4).

Methyl *cis*-1-(*tert*-butyloxycarbonyl)-3-(methoxycarbonylmethyl)indoline-2-carboxylate (40).

A solution of *N*-protected diester **(38)** (2.77 g, 7.97 mmol) in EtOH (40 mL) and EtOAc (10 mL) was hydrogenated at rt at 65 psi in the presence of 10% Pd/C (0.27 g) for 48 h. The catalyst was removed by filtration through a pad of celite and upon removal of solvent *in vacuo*, **(40)** was isolated as a white solid (2.5 g, 90%): mp 90-92°C (petroleum ether- Et_2O); ^1H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.67 (AB from ABX system, 2H, $\Delta\delta$=0.3, J_{AB}=17.0, J_{AX}=5.5, J_{BX}=9.5), 3.70 (s, 3H), 3.77 (s, 3H), 4.23 (X from ABX system, 1H, $J_{AX}+J_{BX}$=22.5), 5.02 (d, 1H, J=10.2), 6.92-7.05 (m, 2H), 7.18-7.27 (m, 1H), 7.90 (br s, 1H). Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.63; N, 4.01. Found: C, 62.24; H, 6.55; N, 4.06.

Ethyl *cis*-1-(*tert*-butyloxycarbonyl)-3-phenylindoline-2-carboxylate (39).

Compound **(39)** was synthesized from **37** following the same procedure previously described for the preparation of **40** to afford **39** as a white solid (84%); mp 104-106°C (petroleum ether- Et_2O); ^1H NMR ($CDCl_3$) δ 0.81 (t, 3H, J=7.2), 1.47 (s, 9H), 3.62 (qd, 2H, J=6.9, J=3.6), 4.96-5.07 (m, 2H), 6.91-6.97 (m, 2H), 7.14-7.30 (m, 6H), 8.00 (d, 1H, J=7.8). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.87; H, 6.68; N, 3.94.

***cis*-1-(*tert*-Butyloxycarbonyl)-3-(carboxymethyl)indoline-2-carboxylic acid (41).**

To a solution of diester **(40)** (0.2 g, 5.72 mmol) in EtOH (8 mL) was added 1N NaOH (8 mL, 8.0 mmol) at 0°C. After stirring at rt for 20 h most of EtOH was distilled under reduced pressure. To the residue was added CH_2Cl_2 (10 mL) and the resulting solution was acidified with 2N HCl at 0°C until pH 1. The organic layer was dried (Na_2SO_4), filtered and evaporated to afford **41** (0.15 g, 71%) as a white chromatographically pure solid: mp 162°C (acetone). The compound was used without further recrystallization for the preparation of **42**; ^1H NMR ($CDCl_3$) δ 1.50 (s, 9H), 2.80 (AB from ABX system, 2H, $\Delta\delta$=0.2, J_{AB}=17.9, J_{AX}=10.6, J_{BX}=3.8), 4.08-4.22 (m, 1H), 4.83 (d, 1H, J=10.2), 6.85-7.05 (m, 2H), 7.09-7.27 (m, 2H).

Hydrochloride of *cis*-3-(carboxymethyl)indoline-2-carboxylic acid (42).

41 (0.20 g, 6.22 mmol) was dissolved in EtOAc (10 mL), cooled and treated with gas HCl for 20 min.

The resulting precipitate was washed with dry Et_2O (2x25 mL) to obtain **42** (0.15 g, 94%) as a white solid: mp 200°C (Et_2O); ^1H NMR (DMSO-d_6) δ 2.63 (AB from ABX system, 2H, Δδ=0.3, J_{AB}=16.8, J_{AX}=6.9, J_{BX}=7.6), 3.93 (X from ABX system, 1H, $J_{AX}+J_{BX}$=14.5), 4.70 (d, 1H, J=8.9), 7.04-7.24 (m, 4H), 10.32 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 38.4, 42.1, 66.8, 119.1, 128.2, 128.5, 132.0, 137.7, 145.3, 173.6, 175.9; Anal. Calcd for $C_{11}H_{11}NO_4$, HCl: C, 51.27; H, 4.69; N, 5.43. Found: C, 51.03; H, 4.64; N, 5.32.

***trans*-1-(*tert*-Butyloxycarbonyl)-3-phenylindoline-2-carboxylic acid (43).**

To a solution of **39** (2.90 g, 79.8 mmol) in DME (75 mL) was added dropwise a solution of LiOH (3.35 g, 79.80 mmol) in H_2O (75 mL). The reaction mixture was heated for 72 h to reflux and then evaporated. The residue was dissolved in H_2O (50 mL). The cooled solution wad acidified with 1N HCl until pH 2.The aqueous layer was extracted with EtOAc (3x100 mL). After washing with H_2O (100 mL) the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford **43** (2.58 g, 96%) as a white solid; mp 82°C (petroleum ether); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 4.50-4.60 (br m, 2H), 7.0-7.30 (m, 9H). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.75; H, 6.46; N, 3.68.

***trans*-1-(*tert*-Butyloxycarbonyl)-3-phenylindoline-2-carboxamide (44).**

To a solution of **43** (1.50 g, 4.42 mmol) in CH_2Cl_2 (40 mL) under argon cooled at -15°C was added *N*-methylmorpholine (0.53 mL, 4.86 mmol). After 5 min stirring, isobutyl chloroformate (0.65 mL, 4.86 mmol) was added. The reaction mixture was stirred for 0.5 h at -15°C, cooled at -40°C and treated with gas NH_3 for 10 min. Stirring overnight at rt and evaporation of the solvent a residue which was dissolved in CH_2Cl_2 (100 mL). The organic layer was washed with H_2O (100 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc-hexane, 6:4) to afford **44** (1.27 g, 85%) as a white solid: mp 148°C (petroleum ether); ^1H NMR ($CDCl_3$) δ 1.57 (s, 9H), 4.62-4.71 (m, 2H), 6.20 (br s, 2H), 7.0-7.20 (m, 9H). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 70.79; H, 6.51; N, 8.44.

***trans*-3-Phenylindoline-2-carboxamide (45).**

To a solution of **44** (1.26 g, 3.72 mmol) dissolved in CH_2Cl_2 (10 mL) cooled at -20°C was added trifluoroacetic acid (10 mL, 130 mmol) and the reaction mixture was stirring for 4 h at -20°C. H_2O (30 mL) was added and the solution was evaporated. The residue was dissolved in CH_2Cl_2 (30 mL), washed with 5% aqueous $NaHCO_3$ (30 mL) and H_2O (30 mL), dried (Na_2SO_4), and filtered. Removal of the solvent afforded a solid (0.44 g, 71%); mp 198-200°C (Et_2O); ^1H NMR ($CDCl_3$) δ 4.45 (d, 1H, J=8.2), 6.70 (d, 1H, J=8.2), 6.90 (br s, 2H), 7.00-7.30 (m, 9H); Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.75. Found: C, 75.40; H, 5.96; N, 11.69.

3-Phenylindole-2-carboxylic acid (46).

To a solution of **14** (0.95 g, 3.58 mmol) in EtOH (30 mL) was added dropwise a solution of NaOH (0.50 g in EtOH/H_2O, 2:1, 20 mL) and the mixture was stirred for 12 h at rt and then evaporated. The residue was dissolved in H_2O (50 mL). The solution wad acidified with 1N HCl until pH 3. The aqueous layer was extracted with EtOAc (2x100 mL). After washing with H_2O (100 mL) the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford **46** (0.81 g, 95%) as a white solid; mp 184°C (benzene) (lit. 182-184°C)[10]; ^1H NMR ($CDCl_3$)δ 7.13-7,68 (m, 9H), 9.06 (br s, 1H).

3-Phenylindole-2-carboxamide (47).

To **46** (0.20 g, 0.84 mmol) was added under argon oxalyl chloride (2 mL, 22.9 mmol) and one drop of dry DMF. The reaction mixture was stirred for 12 h at rt and then evaporated. The residue was washed twice with benzene to remove excess of oxalyl chloride. The residue was dissolved in THF (20 mL), cooled at 0°C and treated with gas NH_3. The resulting solution was stirred for 2 h at rt, evaporated and after standard work-up, **47** (0.18 g, 90%) was obtained as a yellow solid: mp 193°C (petroleum ether). The compound was used in the next step without further characterization; ^1H NMR (DMSO-d_6) δ 6.57 (s broad, 2H), 7.02-7.51 (m, 9H), 11.57 (br s, 1H).

1-(*tert*-Butyloxycarbonyl)-3-phenylindole-2-(*N,N* bis-*tert*-butyloxycarbonyl)carboxamide (48).

Compound **(48)** was synthesized from **47** following the same procedure previously reported for the preparation of **40** in the presence of 3 eq of di-*tert*-butyl dicarbonate. The residue was purified by flash chromatography on silica gel (EtOAc-hexane, 1:6) to afford **48** (60%) as a white solid: mp 142°C (petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 18H), 1.66 (s, 9H), 7,24-7.65 (m, 8H), 8.30 (d, 1H, J=8.4). Anal. Calcd for $C_{30}H_{38}N_2O_7$, 1 H_2O: C, 64.73; H, 7.24; N, 5.03. Found: C, 64.37; H, 7.14; N, 5.08.

1-(*tert*-Butyloxycarbonyl)-3-phenylindoline-2-(*N,N* bis-*tert*-butyloxycarbonyl) carboxamide (49).

Compound **(49)** was synthesized from **48** following the same procedure previously described for the preparation of **40** to afford **49** (88%) as a white solid after trituration with a mixture of petroleum ether-Et_2O: mp 158°C; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 18H), 1.49 (s, 9H), 5.06 (d, 1H, J=11.3), 6.29 (d, 1H, J=11.3), 6.81-6.96 (m, 2H), 7.14-7.26 (m, 6H), 7.98 (d, 1H, J=8,1). The compound was spectroscopically and chromatographically pure, and was used in the next step without further characterization.

Hydrochloride of *trans*-3-phenylindoline-2-carboxamide (50).

Compound (**50**) was synthesized from **49** following the same procedure previously described for the preparation of **42**, and crystallized as a white solid (71%): mp 190°C (AcOEt); ^{1}H NMR (DMSO-d_6) δ 4.79 (d, 2H, J=6.2), 7.00-7.24 (m, 9H).

Methyl *trans*-1-(*tert*-butyloxycarbonyl)-3-methoxycarbonylmethylindoline-2-carboxylate (51).

Diester (**40**) (0.11 g, 0.33 mmol) was dissolved in dry THF (5 mL). To the resulting solution cooled at 0°C was added a solution of 1N *t*-BuOK in THF (0.4 mL, 0.4 mmol). The resulting mixture was stirred for 2 h at 0°C, 1 h at rt. A mixture of H_2O/AcOH (5:1) (30 mL) was added under vigorous stirring followed by extraction with CH_2Cl_2 (3x30 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), filtered and evaporated to afford **51** (0.05 g, 45%) as a light yellow solid used in the next step without further purification.

***trans*-1-(*tert*-Butyloxycarbonyl)-3-carboxymethylindoline-2-carboxylic acid (52).**

Compound **(52)** was synthesized from **51** following the same procedure previously reported for the preparation of **40**, (71%).

Hydrochloride of *trans*-3-(carboxymethyl)indoline-2-carboxylic acid (53).

Compound **(53)** was synthesized from **52** following the same procedure previously described for the preparation of **42**, (71%): mp 149°C (Et_2O); ^1H NMR (DMSO-d_6) δ 2.65 (AB from ABX system, 2H, $\Delta\delta$=0.3, J_{AB}=16.4, J_{AX}=7.3, J_{BX}=6.6), 3.76 (X from ABX system, 1H, $J_{AX}+J_{BX}$=13.9), 4.26 (d, 1H, J=5.5), 6.86-6.93 (m, 2H), 7.08-7.17 (m, 2H), 9.41 (s broad, 2H); ^{13}C NMR (DMSO-d_6) δ 39.1, 42.1, 64.2, 113.7, 122.8, 124.4, 128.3, 132.8, 144.0, 172.3, 172.6. Anal. Calcd for $C_{11}H_{11}NO_4$, HCl, 1/4H_2O: C, 50.39; H, 4.80; N, 5.34. Found: C, 50.30; H, 4.53; N, 5.22.

3-Carboxymethylindole-2-carboxylic acid (54).

To a solution of diester **(15)** (1.1 g, 3.8 mmol) in EtOH (20 mL) was added 1N NaOH (25 mL) at 0°C. After stirring at rt for 20 h, the medium xas concentrated under reduced pressure. To the residue was added a solution of 2N HCl (15 mL) at 0°C until pH 1 and the resulting precipitate filtered (0.6 g, 72%): mp 227°C (lit. 225-227°C)[16]; ^1H NMR (DMSO-d_6) δ 4.03 (s, 2H), 7.27 (t, 1H, J=8.1), 7.27 (t, 1H, J=8.1), 7.43 (d, 1H, J=8.1), 7.66 (d, 1H, J=8.2), 11.57 (br s, 1H), 12,62 (br s, 2H).

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Received, 31st July, 1998