α-ALKYLTRYPTOPHANS

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Abstract- A study of three direct methods for the synthesis of α-alkyl α-amino acids has been applied to the preparation of α-alkyltryptophan esters. Reaction of N_b-benzylidene-L-tryptophan methyl esters 3 with tetrabutylammonium hydrogen sulfate and methyl or ethyl iodide (phase-transfer method) gives α-methyl and α-ethyltryptophan methyl esters 6a,b in poor yield with complete racemization. Reaction of L-tryptophan 1 with dimethylformamide dimethyl or diethyl acetal followed by treatment of 8a,b with LDA and methyl iodide (Fitt and Gschwend method) gives rise to the formation of α,N_a-dimethyl-N_b-dimethylaminomethylenetryptophan methyl or ethyl esters hydriodide 9 a,b . Treatment of 9a or 9b with aqueous acid, under mild conditions, fails to hydrolyze the imine functionality. Reaction of 3 with LDA and methyl or ethyl iodide (Bey and Vevert method) followed by hydrolysis provides α-methyl and α-ethyltryptophan methyl esters 6a,b. By carrying out this procedure with isopropyl, benzyl and allyl iodide or bromide the corresponding α-alkyl esters are not obtained.

In the course of a continuing study of the biological effects of various types of tryptophan derivatives we undertook the preparation of some α-alkyltryptophans, which could conceivably act as serotonin antagonists[1] or as competitive inhibitors of monoamine oxidase[1] by acting as precursors capable of crossing the blood-brain barrier.

The only derivative of α-alkyltryptophans reported to date is α-methyltryptophan. Although several techniques to synthesize this amino acid have been described[1-3], all of these methods start from either difficult to obtain or expensive chemical raw materials, such as gramines or other 3-indole derivatives. Recently, Schöllkopf et al.[4] have reported on the asymmetric synthesis of the methyl (R)-α-mehtyltryptophanate via lithiated bislactim ethers. By this procedure these authors have described

the asymmetric synthesis of several non-proteinogenic amino acid[5].

On the other hand, Seebach et al.[6,7] have developed a stereoselectived method of α-alkylations of amino acids through heterocyclic enolates.

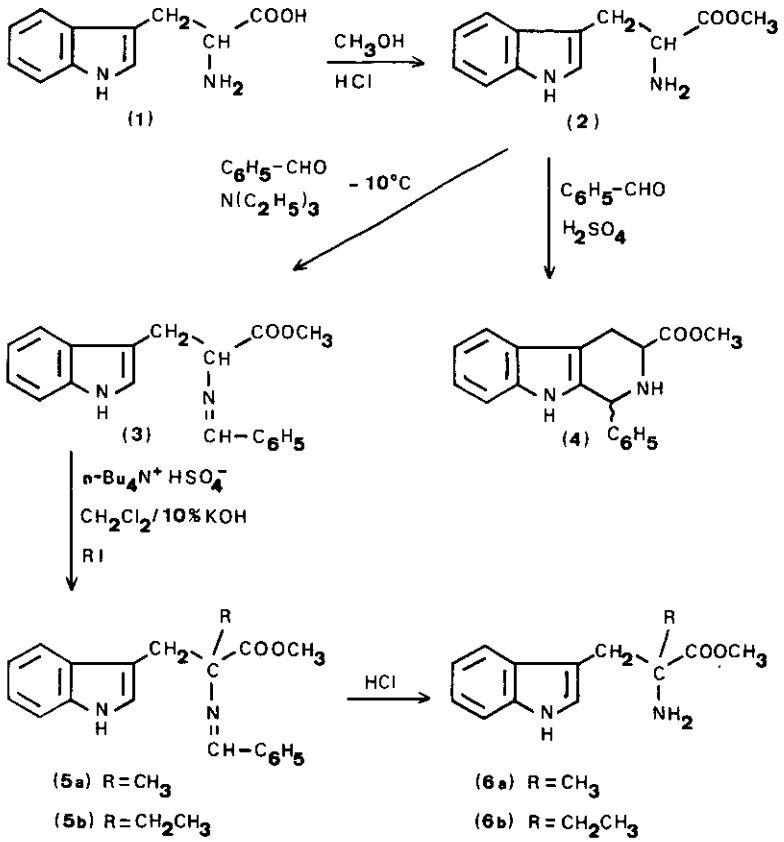
There are three direct methods for the synthesis of α-alkyl α-amino acids in the literature. The procedure reported by Bey and Vevert[8] is based on the direct alkylation of the benzalimine methyl ester of the amino acid. The Fitt and Gschwend[9] method consists of the reaction between the amino acid and N,N-dimethylformamide dimethyl acetal, followed by alkylation, via carbanion of the methyl ester of the newly formed formamide and imine hydrolysis. The Fitt procedure, described by O'Donnell and coworkers[10], is based on the alkylation of a stable Schiff base of α-amino acid esters by phase transfer reactions. Nevertheless, none of the above mentioned authors utilize their methods to synthesize α-alkyltryptophans.

In a previous work we reported[11] on the direct methylation of the lithium derivative of N-benzylidenetryptophan methyl ester. In this work we made the mistake of expecting that the reaction would take place within change of configuration at the chiral center-α-methyltryptophanate, $[\alpha]_D^{30} = -3.8º$ (c 0.7, $CHCl_3$). However, several authors[4,6,12] have carried out our method and in their hands our procedure gave essentially racemic material. Due to this discrepancy we have repeated the reaction and we have found erratic values of α which evidence that the reaction proceeds with 95% of racemization. In spite of the fact that the synthesis of α-methyltryptophan methyl ester by using the Bey and Vevert method[8] is not stereoespecific, it is interesting due to the simplicity of the procedure.

We present in this paper a comparative study of the above mentioned methods in order to ascertain which of them could give the most satisfactory results for the preparation of α-alkyltryptophans.

We first considered the utilization of the phase-transfer method[10]. The synthesis (Scheme 1) commenced with the preparation of L-tryptophan methyl ester 2 from L-tryptophan 1 by esterification in methanolic HCl. Treatment of 2 with benzaldehyde in a basic medium provides the N_b-benzylidene-L-tryptophan methyl ester 3[11,14]. In this way, no formation of the SS and RS diastereomers of methyl 1-phenyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate 4[14,15] can be chromatographically detected as a byproduct. Only 4 is formed in an acidic medium. The alkylation of 3 is accomplished in a two-phase solvent system (CH_2Cl_2/10% aqueous KOH) with tetrabutylammonium hydrogen sulfate as the phase-transfer reagent and methyl or ethyl iodide as the alkylating agents. The alkylated Schiff base products 5a,b are not isolated

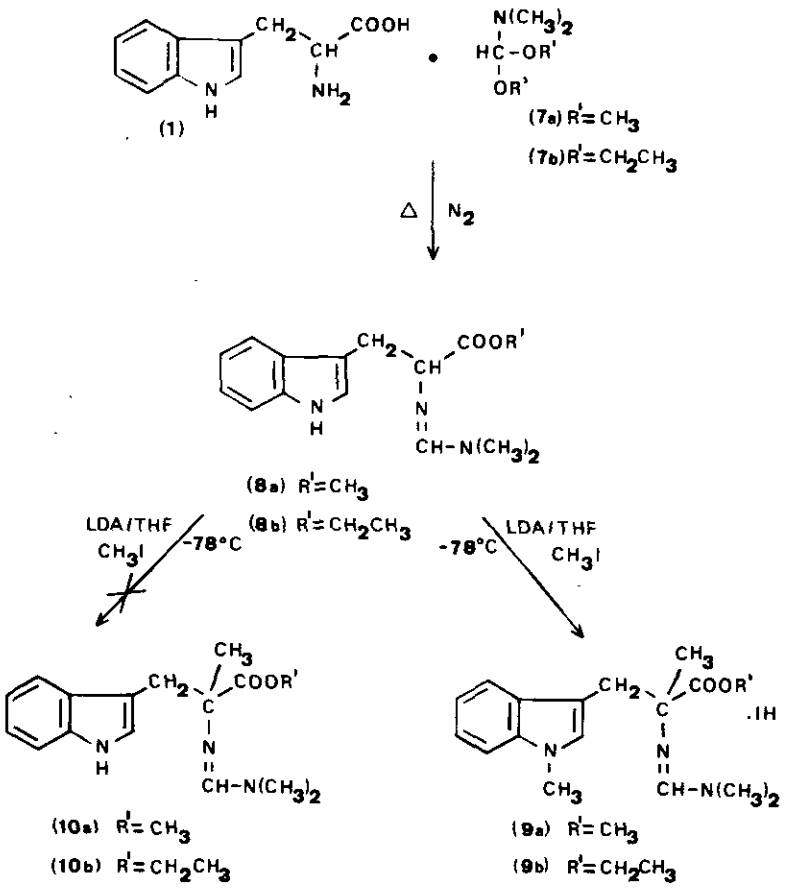
but are hydrolyzed under mild conditions to the α-methyl and α-ethyltryptophan methyl esters 6a,b in poor yield (procedure A).



Scheme 1

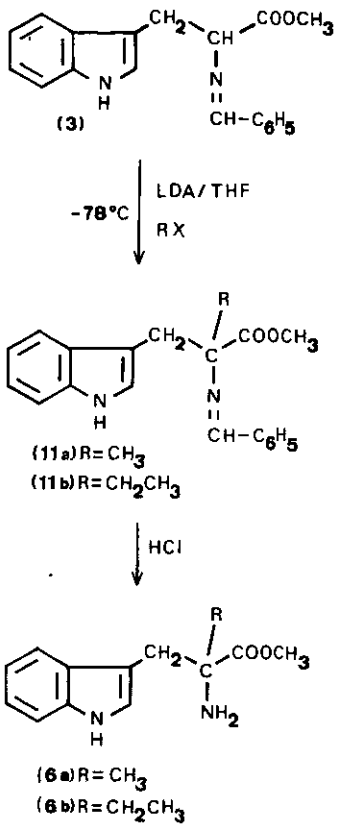
We then considered the Fitt and Gschwend procedure[9] which permits α-alkylation of the α-amino acid in three steps: (a) simultaneous protection of acid and amine groups with dimethylformamide dialkyl acetal, (b) α-alkylation, and (c) acidic hydrolysis.

Reaction of L-tryptophan 1 with dimethylformamide dimethyl or diethyl acetal 7a,b leads to the formation of N_b-dimethylaminomethylene-L-tryptophan methyl or ethyl esters 8a,b. The treatment of this intermediates with lithium diisopropylamide (LDA) and methyl iodide gives rise to the formation of α,N_a-dimethyl-N_b-dimethylaminomethylenetryptophan methyl or ethyl esters hydrogen iodides 9a,b. No α-methyl-N_b-dimethylaminomethylenetryptophans esters 10a,b are formed (Scheme 2). Mild acidic hydrolysis of 9a,b does not lead cleavage of the imine to release the amine functionality.



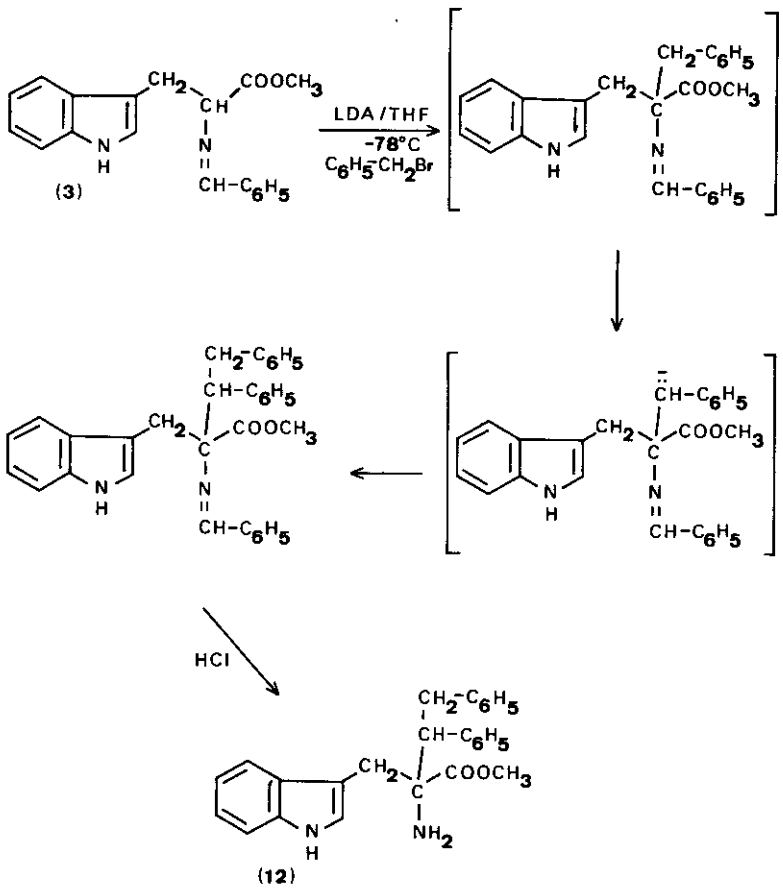
Scheme 2

Finally, we have carried out the method described by Bey and Vevert[8] (Scheme 3). The reactions of N_b-benzylidene-L-tryptophan methyl ester 3 which LDA in THF and methyl or ethyl iodide as alkylating agents provide the intermediates 11a,b. The α-methyl and α-ethyltryptophan methyl esters 6a,b are obtained in good yield from 11a,b via mild acidic hydrolysis (procedure B).



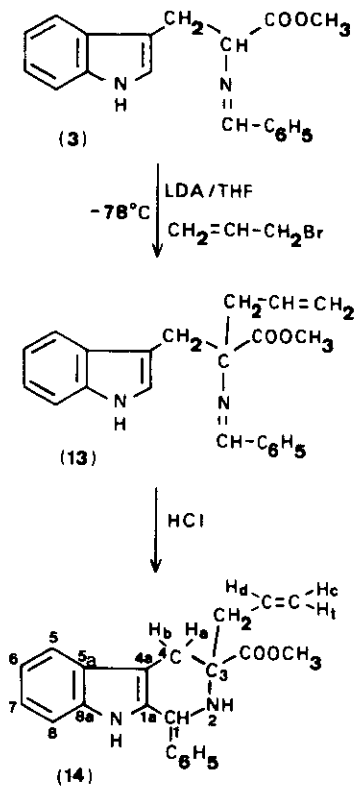
Scheme 3

Because of the promising results obtained in the synthesis of 6a,b by using the Bey Vevert method, other reactions have been carried out in order to prepare the α-isopropyl, α-benzyl and α-allyltryptophan methyl esters. However, in the reaction of 3 with LDA and isopropyl iodide or bromide, the L-tryptophan methyl ester 2 is recovered after treatment with aqueous hydrochloric acid. This is presumably due to the tendency of the isopropyl iodide or bromide to undergo elimination products[16]. Treatment of 3 with LDA and benzyl bromide provides α-(1,2-diphenylethyl)tryptophan methyl ester (48%). No α-benzyltryptophan methyl ester is formed (Scheme 4). The formation of 12 could be explained considering the large difference in pKa values between the indolic and benzylic hydrogens (∿16[17] for acidic NH and ∿35[18] for methylene). Bases such as LDA with high pK_b values act under kinetic control, without discrimination of relative acidities.



Scheme 4

Treatment of 3 with LDA and allyl bromide affords 3-allyl-3-metoxycarbonyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline 14 via intramolecular cyclization of the intermediate 13 in the acidic medium of hydrolysis (Scheme 5). None of the expected α-allyltryptophan methyl ester is formed in this reaction.



Scheme 5

EXPERIMENTAL

Melting points were determined or a Büchi apparatus in open capillaries and are uncorrected. Ir spectra were measured on a Perkin-Elmer 781 spectrophotometer. ^{1}H nmr spectra were recorded on a Varian T-60A (60 MHz) and Varian XL-300 (300 MHz) spectrometers using Me_4Si as an internal standard. ^{13}C nmr spectra were obtained on a Varian FT-80A spectrometer. Mass spectra were determined on a Varian MAT-711 spectrometer. The elemental analyses were performed by "Centro Nacional de Química Orgánica", Madrid.

L-Tryptophan Methyl Ester[13] 2 and N_b-Benzylidene-L-tryptophan Methyl Ester[11,14] 3

Both compounds (2,3) were obtained according to literature methods.

Methyl 1-Phenyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate 4

This compound was obtained in 33% yield according to the reported method[15]. mp 190-192 ºC (ethanol-water).

General Procedures for the Preparation of α-Alkyltryptophans

Procedure A

A mixture of 3 (3g, 0.01 mol), tetrabutylammonium hydrogen sulfate (3.99g, 0.012 mol), alkyl iodide (0.04 mol) in methylene chloride (25 ml) and 10% aqueous potassium hydroxide (25 ml) was stirred at 50 ºC for 4 h. The layers were separated and the organic layer was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed under reduced pressure and the resulting oil was treated with 1N-hydrochloric acid (25 ml) for 1 h at room temperature. The reaction mixture was washed with ethyl ether, and the aqueous phase was made basic with $NaHCO_3$, extracted with chloroform and dried ($MgSO_4$). The solvent was evaporated under reduced pressure providing an oil. Trituration with ethyl ether gave the compounds.

Procedure B

A mixture of diisopropylamine (1.3g, 0.013 mol) in dry THF (20 ml) was cooled to -78 ºC in a nitrogen atmosphere. Methyl lithium (6.5 ml, 0.013 mol) in THF (20 ml) was added and the mixture was stirred for 0.5 h. A solution of 3 (4g, 0.013 mol) in THF (30 ml) was added and stirred for an additional 0.5 h. Alkyl iodide (0.013 mol) was then added and the mixture was left overnight at room temperature. The lithium iodide was filtered and the solvent was evaporated under reduced pressure. The resulting oil was treated with 1N-hydrochloric acid (25 ml) for 1 h at room temperature. The reaction mixture was washed with ethyl ether, and the aqueous phase was made basic with $NaHCO_3$, extracted with chloroform and dried ($MgSO_4$). The solvent was evaporated under reduced pressure providing an oil. Trituration with ethyl ether gave the compounds.

α-Methyltryptophan Methyl Ester 6a

Procedure A. (0.5g, 16%). Procedure B. (2g, 66%); mp 135-137 ºC (cyclohexane); ir (ν, cm^{-1}) (KBr): 3340, 3290 (NH_2), 3140 (NH), 1720 (C=O), 1590 (ArC=C); ^1H nmr ($CDCl_3$) (δ, ppm): 1.4 (s, 3H, CH_3), 1.9 (s, 2H, NH_2), 2.7 (part A, AB system, J_{AB}= 14 Hz, 1H, CH_2), 3.1 (part B, AB system, J_{AB}= 14 Hz, 1H, CH_2), 3.5 (s, 3H, OCH_3), 6.7-7.2 (m, 5H, ArH), 7.9 (s, 1H, NH); ^{13}C nmr ($CDCl_3$) (δ, ppm): 26.8 (CH_2), 36.5 (α-CH_3), 52.1 (OCH_3), 59.2 (C_α), 110.8, 111.1, 119.2, 119.5, 122.0, 123.3, 128.2, 136.1 (indole), 178.0 (C=O); MS m/z (rel. intensity %): 232 (M^+, 0.2), 230 ($M^+ -H_2$, 7), 173 ($M^+ -C_2H_3O_2$, 5), 130 ($M^+ -C_4H_8NO_2$, 100), 102 ($M^+ -C_9H_8N$, 17); Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.21; H, 6.94; N, 12.06. Found: C, 66.93; H, 6.72; N, 11.99.

α-Ethyltryptophan Methyl Ester 6b

Procedure A. (0.45g, 14%). Procedure B. (1.45g, 45%); mp 105-106 ºC (cyclohexane); ir (ν, cm^{-1}) (KBr): 3340, 3300 (NH_2), 3160 (NH), 1720 (C=O), 1600 (ArC=C); ^1H nmr ($CDCl_3$) (δ,ppm): 0.9 (t, 3H, CH_3), 1.4-2.3 (m, 4H, CH_2, NH_2), 2.9 (part A, AB system, J_{AB}= 14 Hz, 1H, CH_2), 3.3 (part B, AB system, J_{AB}= 14 Hz, 1H, CH_2), 3.7 (s, 3H, OCH_3), 6.9-7.5 (m, 5H, ArH), 8.5 (s, 1H, NH); ^{13}C nmr ($CDCl_3$)(δ, pmm): 8.6 (CH_3), 33.2 (CH_2), 35.4 (α-CH_2), 52.0 (OCH_3), 63.0 (C_α), 110.2, 111.2, 119.0, 119.4, 121.9, 123.4, 128.1, 136.1 (indole), 177.5 (C=O); Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.26; H, 7.36; N, 11.37. Found: C, 67.97; H, 7.53; N, 11.12.

N_b-Dimethylaminomethylene-L-tryptophan Methyl Ester 8a

A suspension of L-tryptophan 1 (4g, 0.02 mol) in dimethylformamide dimethyl acetal 7a (30 ml) was refluxed under N_2 for 6 h. Methanol was removed by distillation and the reflux continued for an additional 1 h. Excess reagent was distilled and the residue was evaporated under reduced pressure to dryness. Column chromatography (ethyl ether) afforded 8a (4.2g, 78%); mp 112-115 ºC (ethyl ether); ir (ν, cm^{-1}) (KBr): 3340 (NH), 1730 (C=O), 1640 (C=N); ^1H nmr ($CDCl_3$)(δ, pmm): 2.6 (s, 6H, $N(CH_3)_2$), 2.9-3.3 (m, 2H, CH_2), 3.5 (s, 3H, OCH_3), 3.7-4.0 (m, 1H, CH), 6.7-7.5 (m, 6H, 5ArH, N=CH), 8.2 (s, 1H, NH); ^{13}C nmr ($CDCl_3$)(δ, ppm): 30.8 (CH_2), 37,1 (NCH_3), 51.7 (OCH_3), 69.3 (CH), 111.3, 111.8, 118.8, 118.9, 121.4, 123.4, 127.6, 136.3 (indole), 156.5 (CH=N), 174.7 (C=O); Anal. Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 66.04; H, 7.14; N, 15.43.

N_b-Dimethylaminomethylene-L-tryptophan Ethyl Ester 8b

A suspension of L-tryptophan 1 (4g, 0.02 mol) in dimethylformamide diethyl acetal 7b (30 ml) was refluxed under N_2 for 6 h. Ethanol was removed by distillation and the reflux continued for an additional 1 h. Excess reagent was distilled and the residue was evaporated under reduced pressure to dryness. Column chromatography (ethyl ether) afforded 8b (4.7g, 84%); mp 112-114 ºC (ethyl acetate); ir (ν, cm^{-1}) (KBr): 3140 (NH), 1720 (C=O), 1640 (C=N); ^1H nmr ($CDCl_3$)(δ, ppm): 1.2 (t, 3H, CH_3), 2.7 (s, 6H, $N(CH_3)_2$), 3.1-3.4 (m, 2H, CH_2), 3.9-4.4 (m, 3H, OCH_2, CH), 6.9-7.7 (m, 7H, 5ArH, N=CH, NH); ^{13}C nmr ($CDCl_3$)(δ, pmm): 14.1 (CH_3), 30.8 (CH_2), 37.0 (NCH_3), 60.5 (OCH_2), 69.3 (CH), 111.3, 111.8, 118.7, 118.9, 121.3, 123.4, 127.7, 136.3 (indole), 156.4 (CH=N), 174.3 (C=O); Anal. Calcd. for $C_{16}H_{21}N_3O_2$: C, 66.87; H, 7.31; N, 14.26. Found: C, 66.67; H, 7.56; N, 14.44.

α,N_a-Dimethyl-N_b-dimethylaminomethylenetryptophan Methyl Ester Hydriodide 9a

A mixture of diisopropylamine (1.3g, 0.013 mol) in dry THF (20 ml) was cooled to -78 ºC under N_2. Methyl lithium (6.5 ml, 0.013 mol) in THF (20 ml) was added and stirred for 0.5 h. A solution of 8a (3.15g, 0.013 mol) in THF (30 ml) was added and stirred for an additional 0.5 h. Methyl iodide (1.8g, 0.013 mol) was then added and the mixture was left overnight at room temperature. The lithium iodide was removed by filtration and the solvent was evaporated under reduced pressure. The resulting oil was treated with 1N-hydrochloric acid (25 ml) for 1 h at room temperature. The mixture was neutralized with $NaHCO_3$, extracted with chloroform and dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing an oil. Trituration with chloroform gave 9a (0.89g, 18%); mp 150-151 ºC (methanol-ethyl ether); ir (ν, cm^{-1})(KBr): 1730 (C=O), 1690 (C=N), 1610 (ArC=C); ^1H nmr ($CDCl_3$)(δ, ppm): 2.0 (s, 3H, α-CH_3), 2.8 (s, 3H, NCH_3), 3.1 (s, 3H, NCH_3), 3.5 (s, 2H, CH_2), 3.7 (s, 3H, NCH_3-indole), 3.8 (s, 3H, OCH_3), 6.8-7.9 (m, 6H, 5ArH, N=CH); ^{13}C nmr ($CDCl_3$)(δ, ppm): 24.9 (CH_2), 33.3, 35.2, 38.8 ($N(CH_3)_2$ and α-CH_3), 44.1 (NCH_3-indole), 53.7 (OCH_3), 65.7 (C_α), 106.8, 109.7, 119.0, 119.7, 122.1, 128.2, 128.9, 136.7 (indole), 154.1 (CH=N), 172.8 (C=O); MS m/z (rel. intensity %) : 301 (M^+ -IH, 2), 242 (M^+ - $C_2H_4O_2I$, 15), 157 (M^+ - $C_{10}H_{11}NI$, 43), 144 (M^+ - $C_7H_{14}N_2O_2I$, 100), 130 (M^+ - $C_8H_{16}N_2O_2I$, 28); Anal. Calcd. for $C_{17}H_{24}N_3O_2I$: C, 47.55; H, 5.59; N, 9.79. Found: C, 47.75; H, 5.81; N, 9.81.

α,N_a-Dimethyl-N_b-dimethylaminomethylenetryptophan Ethyl Ester Hydriodide 9b

A mixture of diisopropylamine (1.3g, 0.013 mol) in dry THF (20 ml) was cooled to -78 ºC under N_2. Methyl lithium (6.5 ml, 0.013 mol) in THF (20 ml) was added and stirred for 0.5 h. A solution of 8b (3.7g, 0.013 mol) in THF (30 ml) was added and stirred for an additional 0.5 h. Methyl iodide (1.8g, 0.013 mol) was then added and the mixture was left overnight at room temperature. The lithium iodide was removed by filtration and the solvent was evaporated under reduced pressure. The resulting oil was treated with 1N-hydrochloric acid (25 ml) for 1h at room temperature. The mixture was neutralized with $NaHCO_3$, extracted with chloroform and dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing 9b (2.1g, 37%); mp 156-158 ºC (methanol-ethyl acetate); ir (ν, cm^{-1})(KBr): 1740 (C=O), 1700 (C=N), 1600 (ArC=C); ^1H nmr (Me_2SO-d_6)(δ, ppm): 1.2 (t, 3H, CH_3), 1.9 (s, 3H, α-CH_3), 3.0 (s, 3H, NCH_3), 3.1 (s , 3H, NCH_3), 3.3-3.5 (m, 2H, CH_2), 3.7 (s, 3H, NCH_3-indole), 4.2 (q, 2H, OCH_2), 7.0-8.1 (m, 6H, 5ArH, N=CH); ^{13}C nmr (Me_2SO-d_6)(δ, ppm): 13.8 (CH_3),

27.4 (CH_2), 36.4, 41.6, 42.8 ($N(CH_3)_2$ and α-CH_3), 44.8 (NCH_3-indole), 60.1 (OCH_2), 61.4 (C_α), 108.3, 111.4, 118.0, 118.5, 121.1, 124.1, 126.9, 136.0 (indole), 156.3 (CH=N), 170.0 (C=O); MS m/z (rel. intensity %): 315 (M^+ -IH, 2), 156 (M^+ -$C_{11}H_{14}NI$, 100), 144 (M^+ -$C_8H_{16}N_2O_2I$, 3), 130 (M^+ -$C_9H_{18}N_2O_2I$, 14); Anal. Calcd. for $C_{18}H_{26}N_3O_2I$: C, 48.76; H, 5.91; N, 9.47. Found: C, 48.55; H, 5.65; N, 9.73.

α-(1,2-Diphenylethyl)tryptophan Methyl Ester 12

A mixture of diisopropylamine (1.3g, 0.013 mol) in dry THF (20 ml) was cooled to -78 ºC under N_2. Methyl lithium (6.5 ml, 0.013 mol) in THF (20 ml) was added and stirred for 0.5 h. A solution of 3 (4g, 0.013 mol) in THF (30 ml) was added and stirred for an additional 0.5 h. Benzyl bromide (2.23g, 0.013 mol) was then added and the mixture was left overnight at room temperature. The mixture was evaporated under reduced pressure and the residue was dissolved in chloroform, washed with H_2O twice, dried over $MgSO_4$, and evaporated to yield an oil which, was treated with 1N-hydrochloric acid (25 ml) for 1 h at room temperature. The reaction mixture was washed with ethyl ether, and the aqueous phase was neutralized with $NaHCO_3$, extracted with chloroform and dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing an oil. Trituration with ethyl acetate-carbon tetrachloride gave 12 (2.5g, 48%); mp 176-178 ºC (ethyl acetate); ir (ν, cm^{-1})(KBr): 3400, 3320 (NH_2), 1720 (C=O), 1590 (ArC=C); ^1H nmr ($CDCl_3$)(δ, ppm): 2.4 (s, 2H, NH_2), 2.8-3.3 (m, 4H, $2CH_2$), 3.4 (s, 3H, OCH_3), 5.3 (m, 1H, CH), 6.8-7.7 (m, 16H, 15ArH, NH). ^{13}C nmr ($CDCl_3$)(δ, ppm): 29.8 (t, CH_2), 47.2 (t, CH_2-C_6H_5), 51.5 (q, CH_3), 55.4 (d, CH), 64.0 (s, C_α), 107.3 (s), 110.6 (d), 118.1 (d), 119.0 (d), 121.4 (d), 126.8 (d), 126.9 (d), 127.9 (d), 128.2 (d), 128.4 (d), 128.5 (d), 129.7 (d), 134.1 (s), 135.5 (s), 136.2 (s), 142.3 (s)(aromatics), 175.2 (s, C=O); MS m/z (rel. intensity %): 398 (M^+, 40), 339 (M^+-$C_2H_3O_2$, 18), 307 (M^+-C_7H_7, 100), 247 (M^+-$C_9H_{11}O_2$, 29), 218 (M^+-$C_{14}H_{12}$, 48), 169 (M^+-$C_{11}H_7NO$, 34), 91 (M^+-$C_{19}H_{19}N_2O_2$, 24); Anal. Cacld. for $C_{26}H_{26}N_2O_2$: C, 78.30; H, 6.58; N, 7.03. Found: C, 78.29; H, 6.25; N, 7.05.

3-Allyl-3-methoxycarbonyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline 14

A mixture of diisopropylamine (1.3g, 0.013 mol) in dry THF (20 ml) was cooled to -78 ºC under N_2. Methyl lithium (6.5 ml, 0.013 mol) in THF (20 ml) was added and stirred for 0.5 h. A solution of 3 (4g, 0.013 mol) in THF (30 ml) was added and stirred for an additional 0.5 h. Allyl bromide (1.07g, 0.013 mol) was then added and the mixture was left overnight at room temperature. The mixture was evaporated under reduced pressure and the residue was dissolved in chloroform, washed with

H_2O twice, dried over $MgSO_4$, and evaporated to yield an oil which, was treated with 1N-hydrochloric acid (25 ml) for 1 h at room temperature. The reaction mixture was washed with ethyl ether, and the aqueous phase was neutralized with $NaHCO_3$, extracted with chloroform and dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing an oil. Trituration with ethyl acetate-petroleum ether gave **14** (1g, 22%); mp 135-137 ºC (ethyl acetate); ir (ν, cm^{-1})(KBr): 3220, 3160 (NH), 1700 (C=O), 1670 (C=C), 1590, 1550, 1520, 1480 (ArC=C); ^1H nmr ($CDCl_3$, 300 MHz)(δ, ppm): 2.45 (m, 1H, NH, overlaped with the signal at 2.47), 2.47 (q, 1H, allylic CH, J= 13.6 and 6.5 Hz), 2.67 (q, 1H, allylic CH, J= 13.6 and 6.5 Hz), 2.88 (q, 1H, H_a, J= 15.2 and 2.5 Hz), 3.49 (q, 1H, H_b, J= 15.2 and 1.6 Hz), 3.57 (s, 3H, CH_3), 5.13 (d, 1H, H_c, J= 11.4 Hz), 5.14 (d, 1H, H_t, overlaped with the signal at 5.13, J= 15.7 Hz), 5.36 (s, 1H, CH-C_6H_5), 5.77 (m, 1H, H_d), 7.02-7.53 (m, 10H, ArH, NH-indole); ^{13}C nmr ($CDCl_3$)(δ, ppm): 29.3 (t, C_4), 45.0 (t, allylic CH_2), 51.7 (q, CH_3), 55.4 (d, C_1), 62.7 (s, C_3), 107.4 (s, C_{4a}), 110.6 (d, C_8), 118.0 (d, C_5), 119.0 (t, $=CH_2$), 119.3 (d, C_6), 121.4 (d, C_7), 126.8 (s, C_{5a}), 127.9 (d, C_p-phenyl), 128.4 (d), and 128.5 (d)(C_o and C_m-phenyl), 131.9 (d, =CH), 134.1 (s, C_{1a}), 136.2 (s, C_{8a}), 142.2 (s, C_1-phenyl), 175.5 (s, C=O); MS m/z (rel. intensity %): 346 (M^+, 78), 305 (M^+-C_3H_5, 94), 246 (M^+-$C_5H_8O_2$, 53), 219 (M^+-$C_6H_9NO_2$, 64), 218 (M^+-$C_6H_{10}NO_2$, 100), 169 (M^+-$C_{11}H_{15}NO$, 72); Anal. Calcd. for $C_{22}H_{22}N_2O_2$: C, 76.27; H, 6.70; N, 8.08. Found: C, 76.46; H, 6.54; N, 7.96.

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