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Modified Pictet–Spengler reaction. A highly diastereoselective approach to 1,2,3-trisubstituted-1,2,3,4-tetrahydro-β-carbolines using perhydro-1,3-heterocycles

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Dedicated to the loving memory of (the late) Maninder Kaur Chawla

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Abstract—A flexible variant of the Pictet–Spengler reaction employing oxazinanes as synthetic equivalents of several carbonyl compounds has been developed. Using acid catalyzed one pot condensation of perhydro-1,3-heterocycles various 1,3-disubstituted and 1,2,3-trisubstituted-1,2,3,4-tetrahydro-β-carbolines (THBCs) have been synthesized diastereoselectively.

1. Introduction

The interest in the synthesis of indole alkaloids stems from their intricate cyclic frame-work and diverse medicinal properties such as anti-tumor[1] and cardiovascular effects.[2] Many 1,2,3-trisubstituted-1,2,3,4-tetrahydro-β-carbolines (THBC) alkaloids[2,3] in their skeleton embody L-tryptophan unit pointing to its use in their synthesis as an enantiomerically pure starting material for control of the stereochemistry at C-1 and C-3 in the Pictet–Spengler reaction with aldehydes, which has long been in use for the synthesis of THBCs and other related systems.[4] Out of a variety of reaction conditions employed, the use of non-acidic aprotic media becomes more obvious when acid-labile aldehydes are used,[5] and aqueous-acidic conditions[6] result in considerably lower yields of the THBCs in comparison to non-acidic or acidic–aprotic reaction conditions.[7–10] A few variant approaches involving combinatorial chemistry,[11] solid phase synthesis,[12] and alternatives for aldehydes such as conjugated alkynoates,[13] azalactones,[14] Δ^1-piperidines,[15] acetals,[16] active methylene compounds[17] etc. have also appeared. Most of these methods exhibit good to excellent asymmetric control[10b,18] and several elegant routes leading to enantioselective and/or diastereoselective preparation of the title compounds using chiral auxiliaries such as carbohydrates,[19] amino acid esters,[20] (*R*) and (*S*)- glyceraldehydes,[21] (−)-8-phenylmethylcarbamates,[22] chiral acetylenic sulfoxides[23] or chemoselective and asymmetric reductions of corresponding dihydro β-carbolines[24] etc have also been developed.

We have for quite some time been engaged in developing an alternate synthetic strategy using the 'Folate model approach',[25] wherein variously C-2 substituted perhydro 1,3-heterocycles have been convincingly employed[26] as carbonyl equivalents for obtaining a variety of useful synthetic targets through a single pot, acid catalyzed C-2 unit transfer reaction of these reagents to various nucleophiles, thus avoiding the direct use of aldehydes. Owing to the ease in synthesis, proven carbonyl resource and efficacious elaboration at C-2 of oxazinanes[27] and oxazolidines,[28] a conspicuous merit of these reactions has been diversification of the transferred carbon unit—an attribute of potential utility in the synthesis of lead compounds for a variety of pharmacologically interesting[26d,e] events. Herein we report on the synthetic usefulness of this modified Pictet–Spengler reaction,[26a] wherein stable oxazinanes and oxazolidines are reacted with L-tryptophan derivatives to obtain the title compounds diastereoselectively as in the conventional Pictet–Spengler reaction.[4,5a,10,29]

2. Results and discussion

2.1. Synthesis of oxazinanes and oxazolidines

Oxazinanes **1a–e** and **g** used in this study are obtained by condensing γ-hydroxypropyl amine with aldehydes and **1f**, **h–m** were synthesized through borohydride reductions of correspondingly 2-substituted-4,4,6-trimethyl-5,6-dihydro-(4*H*)-1,3-oxazines **2a–f** obtained by condensation of

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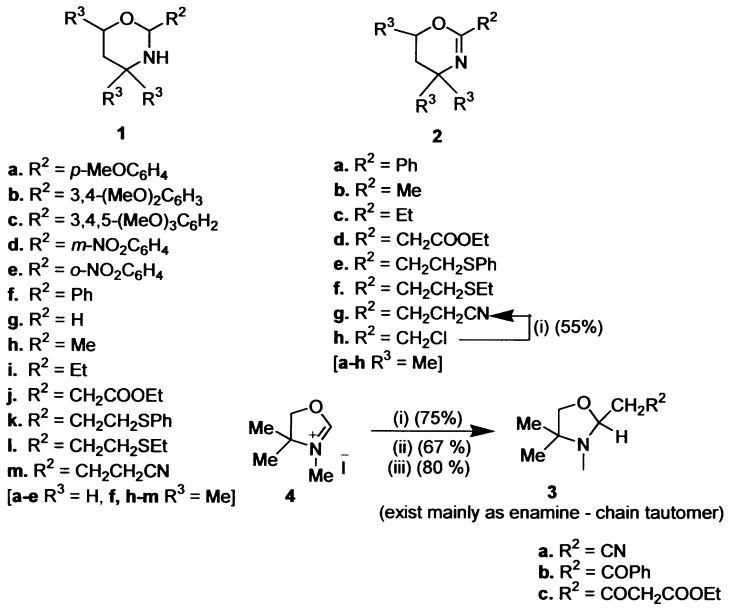


Scheme 1. *Reagents*: (i) Acetonitrile (anhyd.), LDA/THF, −78°C. (ii) Acetophenone, LDA/THF, −78°C. (iii) Ethyl acetoacetate, (a) NaH/THF/0°C, (b) *n*-BuLi, 0°C.

appropriate nitriles (R^2CN) with 2-methyl-2,4-pentanediol in the presence of concentrated sulphuric acid following the method of Meyers et al.[27] 2-Cyanoethyl-4,4,6-trimethyl-5,6-dihydro-(4*H*)-1,3-oxazine **2g** was obtained by reacting carbanion of acetonitrile with corresponding 2-chloromethyl oxazine **2h** obtained from chloroacetonitrile. For the synthesis of oxazolidines **3a–c** stabilized carbanions of acetonitrile, acetophenone and ethyl acetoacetate, respectively were reacted with 3,4,4,-trimethyl-Δ^2-oxazolinium iodide **4**[30] at low temperature following a method developed[31] by us (Scheme 1).

2.2. Diastereo-control in the synthesis of THBCs

To study the influence of reaction conditions on the stereoselection in the alternative Pictet–Spengler reaction involving perhydro 1,3-heterocycles **1** and **3** and the stereogenic amino acid esters viz. N_b-H L-tryptophan methyl ester (L-TrpOMe) **5a**, N_b-H L-tryptophan isopropyl ester (L-TrpOPr^i) **5b**, N_b-benzyl L-tryptophan methyl ester (N_b-benzyl-L-TrpOMe) **5c** and N_b-*p*-methoxybenzyl L-tryptophan isopropyl ester (N_b-*p*-MeObenzyl-L-TrpOPr^i) **5d** were chosen. Reactions of **1** or **3** with **5a–d** were conducted in anhydrous acetonitrile using trifluoroacetic acid (MeCN/TFA 10:0.1) or acetic acid (MeCN/AcOH 10:1.0) as catalysts at room temperature using stirring or ultrasonication (kinetic control) or alternatively at reflux temperature (thermodynamic control). Various C-1 substituted title THBCs have been obtained in these reactions in varying diastereomeric ratios. Under the conditions of thermodynamic control 1,2,3-trisubstituted THBCs are formed mainly/exclusively as *trans*-isomers.

2-*p*-Methoxyphenyl oxazinane **1a** and L-TrpOMe **5a** (1:1) upon refluxing in acidified anhydrous acetonitrile (MeCN/TFA 10:0.1) furnished *trans*-methyl 1-*p*-methoxyphenyl-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]-indole-3-carboxylate **6a** (R_f 0.7, ethyl acetate/hexane 3:7) and the corresponding *cis* isomer (R_f 0.8), albeit in poor diastereoselectivity ratio (Table 1, entry 1). However, **1a** cleanly reacts with **5a** under acid catalyzed conditions to furnish **6a** in which >CHAr unit (C-2) of **1a** gets incorporated as a new chiral center as C-1 of THBC **6a**. To monitor the influence of bulkiness of R^2 appended as C-2 of **1** (C-1 in THBCs **6**) on the distereoselectivity of this reaction, differently substituted oxazinanes **1b–f** have been reacted with **5a** (Scheme 2).

Reactions of oxazinanes **1b–f** with L-TrpOMe in anhydrous acetonitrile/TFA (10:0.1) solution at reflux furnished the corresponding THBC derivatives **6b–f**, respectively in 74–78% yield but with very similar diastereomeric ratios (Table 1, entries 2–6). However, when the reactions were performed at ambient temperature or by using ultrasonicator as energy transfer medium (ambient temperature), an increase in *cis* selectivity ranging from 71:29 to 91:9 (*cis*:*trans*) was observed. This is consistent with the reported[29c,d] observation of enhanced *cis* stereoselectivity in conventional Pictet–Spengler reaction under kinetically controlled reaction conditions and considering the bulkiness of R^2 at C-1, there seems to be a marginal increase in *cis* selectivity which in fact disappears when the reactions are conducted at reflux.

To monitor the effect of steric bulk of the ester function in **5**, L-TrpOPr^i **5b** was reacted with oxazinanes **1a–f** (Scheme 2). These reactions point to the incorporation of >CHR^2 unit in between indolyl C-2 and $-NH_2$ of **5b** and formation of *cis* and *trans* 2-methylethyl 1-substituted-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]-indole-3-carboxylates **6g–l**, but switching from **5a** to **5b** has only a modest effect on the diastereoselectivity with no clear-cut trend becoming apparent (Table 1, entries 7–12). However this method offers a variant route and demonstrates that oxazinanes can be employed in place of aldehydes in this key reaction.

In the conventional enantiosepecific Pictet–Spengler reaction, it has been demonstrated[5a] that the presence of a benzyl function at the N_b-nitrogen moiety permitted control of the

Table 1. *Cis*:*trans* ratios of THBCs [**6**, R^2=aryl (entries 1–22); **9**, R^2=alkyl (entries 23–36)]

Sr. no.	THBCs **6/9**			Acid	de (%)	Time (h)	**6/9** diastereomeric ratio[a] *cis*:*trans*	Yield (%)
	R^1	R^2	R^4					
1.	Me	*p*-$MeOC_6H_4$	H	TFA	2	6	49(71):51(29)	77
2.	Me	3,4-$(MeO)_2C_6H_3$	H	TFA	10	3.5	55(91):45(9)	78
3.	Me	3,4,5-$(MeO)_3C_6H_2$	H	TFA	12	2	56:44	74
4.	Me	*m*-$NO_2C_6H_4$	H	TFA	4	12	53:48	75
5.	Me	*o*-$NO_2C_6H_4$	H	TFA	0	12	50:50	78
6.	Me	Ph	H	TFA	10	12	55:45	75
7.	Pr^i	*p*-$MeOC_6H_4$	H	TFA	20	10	60:40	68
8.	Pr^i	3,4-$(MeO)_2C_6H_3$	H	TFA	18	18	59:41	74
9.	Pr^i	3,4,5-$(MeO)_3C_6H_2$	H	TFA	10	18	55:45	80
10.	Pr^i	*m*-$NO_2C_6H_4$	H	TFA	10	14	55:45	78
11.	Pr^i	*o*-$NO_2C_6H_4$	H	TFA	0	12	50:50	72
12.	Pr^i	Ph	H	TFA	20	12	60:40	84
13.	Me	*p*-$MeOC_6H_4$	CH_2Ph	TFA	96	13	02[b]:98	91
14.	Me	3,4-$(MeO)_2C_6H_3$	CH_2Ph	TFA	98	28	01[b]:99	82
15.	Me	3,4,5-$(MeO)_3C_6H_2$	CH_2Ph	TFA	98	28	01[b]:99	90
16.	Me	*m*-$NO_2C_6H_4$	CH_2Ph	TFA	96	15	02[b]:98	78
17.	Me	Ph	CH_2Ph	TFA	98	9	01[b]:99	88
18.	Pr^i	Ph	*p*-$MeOC_6H_4CH_2$	TFA	94	7	03[b]:97	86
19.	Pr^i	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4CH_2$	TFA	96	10	02[b]:98	88
20.	Pr^i	3,4-$(MeO)_2C_6H_3$	*p*-$MeOC_6H_4CH_2$	TFA	94	14	03[b]:97	78
21.	Pr^i	3,4,5-$(MeO)_3C_6H_2$	*p*-$MeOC_6H_4CH_2$	TFA	98	18	01[b]:99	92
22.	Pr^i	*m*-$NO_2C_6H_4$	*p*-$MeOC_6H_4CH_2$	TFA	96	16	02[b]:98	78
23.	Me	H	H	TFA	–	10	–	72
24.	Me	Me	H	TFA	10	12	55:45	68
25.	Me	Et	H	TFA	10	16	55:45	71
26.	Me	CH_2COOEt	H	TFA	20	10	60:40	74
27.	Me	CH_2CN	H	AcOH	20	12	60:40	61
28.	Me	Me	CH_2Ph	TFA	74	8	13:87	80
29.	Me	Et	CH_2Ph	TFA	76	24	12:88	74
30.	Me	CH_2COOEt	CH_2Ph	TFA	86	24	7:93	68
31.	Me	CH_2CH_2SPh	CH_2Ph	AcOH	90	12	5:95	72
32.	Me	CH_2CH_2SEt	CH_2Ph	AcOH	84	24	8:92	78
33.	Me	CH_2CH_2CN	CH_2Ph	TFA	86	30	7:93	61
34.	Me	CH_2CN	CH_2Ph	TFA	76	12	12:88	78
35.[c]	Me	CH_2COPh	CH_2Ph	TFA	90	36	5[b]:95	54
36.[d]	Me	CH_2COCH_2COOEt	CH_2Ph	AcOH	92	40	4[b]:96	56

± 3% As determined from the integration of the C-3 ester signal in the ^1H NMR spectrum.[32]

[a] The values in the parenthesis show the diastereomeric ratios of the reactions conducted using ultrasonicator (Julabo USR 05).[33]

[b] Minor *cis* compounds were only detected in the ^1H NMR spectra and could not be isolated.

[c] Obtained from **10a**.

[d] Obtained from corresponding enaminoketone **10b**.

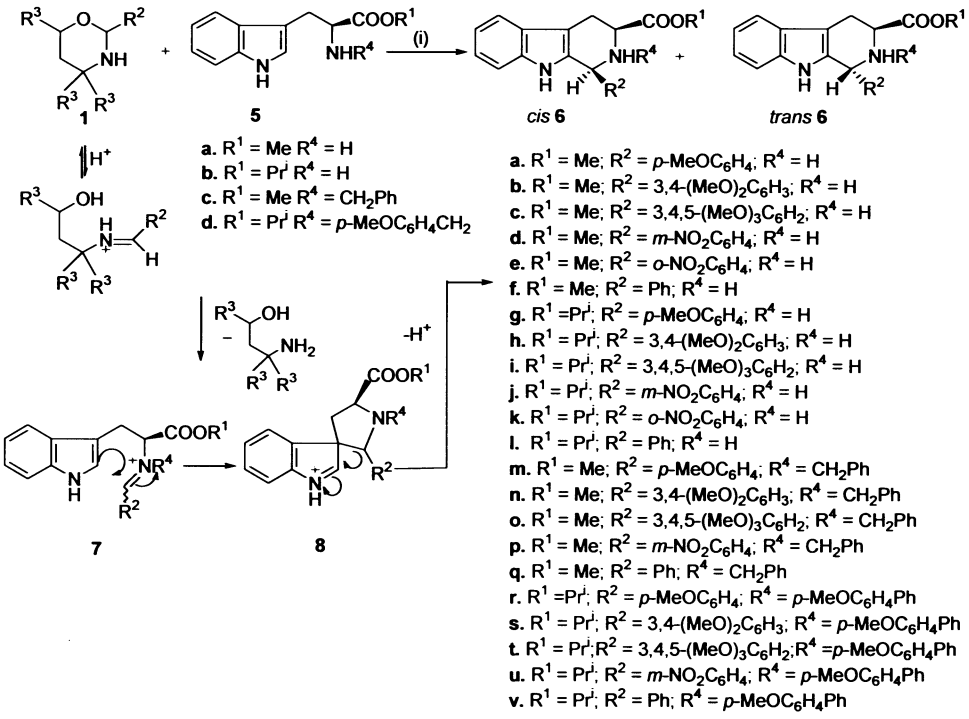
stereochemical outcome in favor of *trans* selectivity. We further envisaged, that the reactions of N_b-benzyl tryptophan esters with oxazinanes might furnish 1,2,3-trisubstituted THBCs with *trans* selectivity as was observed with aldehydes.

Thus N_b-benzyl-L-TrpOMe **5c** or N_b-*p*-MeObenzyl-L-TrpO-Pr^i **5d** in anhydrous acetonitrile/TFA (10:0.1) solution reacts under reflux with various oxazinanes **1** to furnish corresponding methyl N_b-benzyl-1-substituted 1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]-indole-3-carboxylates **6** (Scheme 2) mainly as *trans* isomers in good to excellent yield (Table 1, entries 13–22). The *trans*-N_b- substituted diastereomers are thermodynamically more stable than their *cis*-congeners. Evidence for this observation has already been furnished and proved by equilibration studies in acidic media.[4] Also the origin of diastereoselectivity[10b,34,36] in the reactions depicted herein is similar to the corresponding aldehyde approach.

All these reactions of **1** (existing as ring-chain tautomers),[37] can be visualized to proceed through the formation of an iminium intermediate **7** (Scheme 2) formed in situ, through the loss of appropriate aminopropanol, cyclises spontaneously by intramolecular electrophilic attack of the iminium carbon at C-2 or at C-3 of the indole moiety to form a spiroindolenine **8** which rearranges and subsequently deprotonates to yield corresponding THBCs **6**.

From these results, as expected, it is evident that on switching from a methyl to isopropyl ester, no appreciable effect on the stereoselectivity of the products was observed. In all the reactions in Scheme 2, in consonance with the aldehyde approach, high order of *trans* diastereoselectivity has been observed. Also there is no effect of variation of the steric bulk at C-2 of **1**, on the diastereoselectivity of the products, in contrast to the observation in the reactions of aldehydes in the conventional Pictet–Spengler approach.[36]

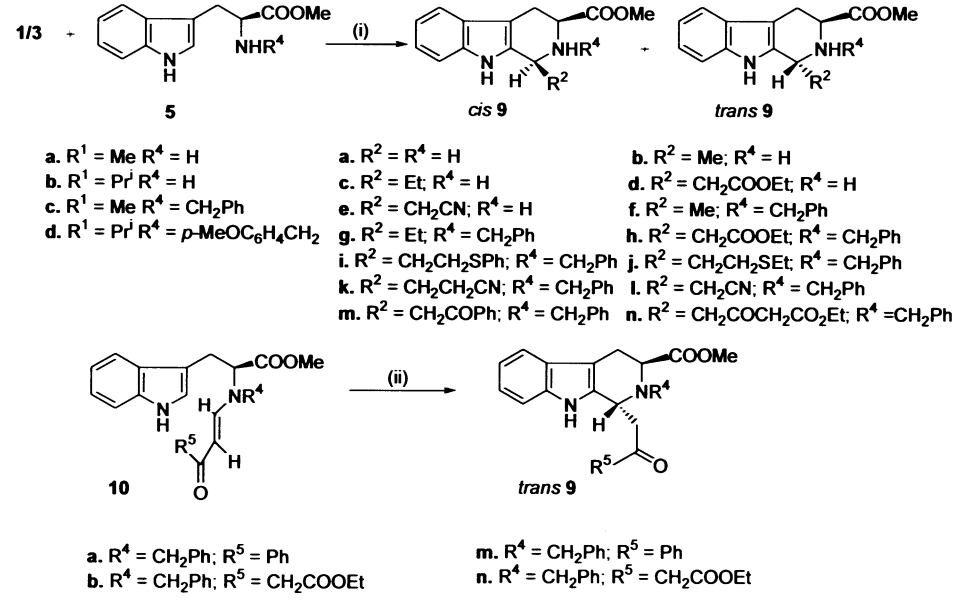
Further it has been realized that if benzaldehyde derivatives are employed, the desired THBCs are formed in satisfactory yields,[9,38] whereas with aliphatic counterparts, the THBCs in a majority of cases, are formed in much lower yield or as minor products. Furthermore the instability of relatively vulnerable aliphatic aldehydes necessitates their use in considerable molar excess,[5a,36,38] when implemented under



Scheme 2. *Reagents*: (i) MeCN, TFA.

acid catalysed reaction conditions, to drive the reaction to completion. We have recently demonstrated[26a] that N_b-benzyl THBCs bearing various C-1 aryl substituents can be easily accessed through the use of oxazinanes in a synthetically useful manner and with very high *trans* diastereoselectivity. In this vein, we have performed some reactions of perhydro 1,3-heterocycles with **5** to obtain various THBCs bearing C-1 aliphatic substituents including a pivotal indole alkaloidal intermediate.

Using our standard reaction conditions of thermodynamic control, initially a few reactions of **5a** lacking N_b-benzyl substituent with oxazinanes **1g–j** (Scheme 3) and oxazolidine **3a**, in 1:1 stoichiometric proportion were conducted (Table 1, entries 23–27), to monitor the *cis*/*trans* selectivity and the progress of formation of the products. However, although the corresponding C-1 substituted THBCs **9a–e** were obtained as equilibrated mixtures, the chemical yield was good to excellent, establishing thereby that **1/3** supporting C-2 alkyl substituents could be employed with clear-cut advantage in terms of the yield of **9** and cleanliness of the reaction as formation of the by-products was not detected, in comparison to the conventional approach employing aldehydes. The diastereoselectivity of THBCs is influenced



Scheme 3. *Reagents*: (i) MeCN, TFA; (ii) C_6H_6 or MeOH, dry HCl.

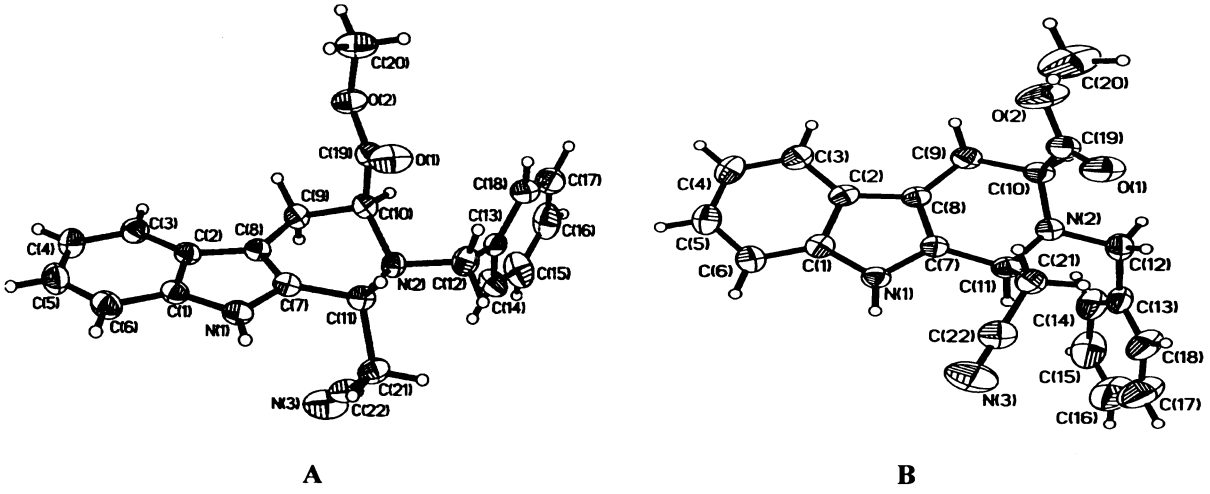


Figure 1. ORTEP presentation of X-ray structure of *trans* (A) and *cis* (B) **9l** showing the crystallographic numbering of the atoms (see Section 4 for details).[40]

only marginally (compare entries 26 and 27 with 24 and 25) by increasing the size of the C-1 substituent. Further the reactions could not be conducted at ambient temperature (kinetic control) owing to the lower reactivity of **1/3**.

To gain access to *trans* 1,2,3-trisubstituted THBCs and to extend the usefulness of the methodology to a variety of substitutional variations at C-1, reactions of **5c** with **1h–m** were conducted under similar conditions. The corresponding products **9f–k** (Table 1, entries 28–33) were obtained in high yield and excellent *trans* selectivity in consonance with the results reported for aldehydes (Scheme 3). Wherever possible the minor *cis* isomers were also isolated (vide Section 4) along with the major *trans* isomers and their structures established. The diastereomers were identified by ^{1}H- and ^{13}C NMR spectroscopy and by comparison with the literature data.[34,39]

The reaction of **3a** with **5c** under similar reaction conditions furnished 2-cyanomethyl substituted THBC **9l** as a mixture of *cis* and *trans* isomers (22:88). The overall transformation of **5c** to **9l** depicts a straightforward incorporation of the $-CH_2CN$ moiety at C-1, to furnish an analog of a pivotal intermediate used in the synthesis of corynantheidol and dihydrocorynantheol and related *seco*-alkaloids.[41]

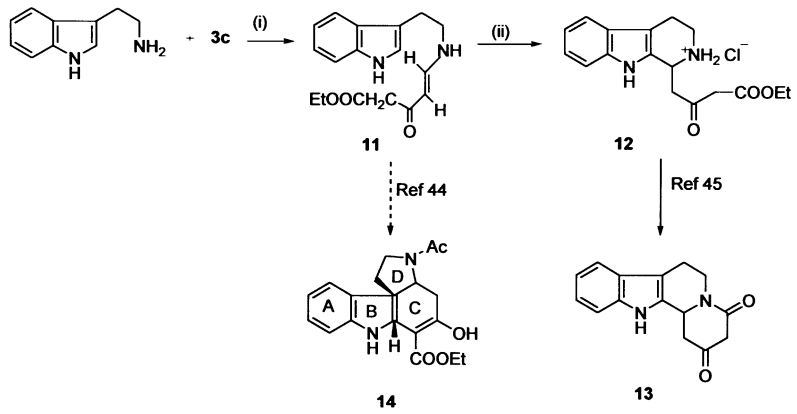
Although a large number of crystal structures of variously substituted THBCs have been reported,[10b,29c,34] to substantiate the stereochemical assignments to the new THBCs and to unambiguously correlate the stereochemistries of the other THBCs synthesized herein, the investigations in the X-ray structures of both *cis* and *trans* isomers of **9l** have been undertaken[40] (see Fig. 1 and Section 4 for details). The results obtained are very similar to the earlier reported structures.[10b] Thus it has been found that in both *cis* and *trans* **9l**, the didehydropiperidine ring adopts half-chair conformation with the substituents at C-1, N_b- and C-3 occupying axial/pseudoaxial, equatorial/pseudoequatorial and axial positions, respectively. For the *cis* **9l** the 1,3-diaxial conformation is adopted, whilst for the *trans* **9l** the $1_{pseudoaxial}$, 3_{axial} arrangement is observed.

Reaction of **3b** with **5c** under a similar set of conditions furnished an acyclic product N_b-benzyl-N_b-(2-benzoylethylene)-L-tryptophanate **10a** [*trans* enamine, δ 5.93, J=12.7 Hz (vinylic signals)], which upon treatment with a saturated benzene solution of hydrogen chloride at 0°C furnished *trans* THBC **9m**. The ^{1}H NMR monitoring of the crude cyclization reaction mixture through the disappearance of the indole-2*H* at ca. δ 6.96 was indicative of smooth cyclization leading to **9m**. Likewise oxazolidine **3c** furnished *trans* THBC **9n** through **10b**. Thus in all the reactions of **5c** with **1/3** the C-1 elaborated THBCs **9** were formed with high diastereoselectivity and chemical yield.

The use of N_b-benzyl or related substituents in L-tryptophan esters not only guarantee *trans* selectivity of the Pictet–Spengler products, but are also formed with very high enantioselectivity, although the product ratios are determined by thermodynamic control.[29b] On the other hand, examples of racemisation of especially the *trans* 1,3-disubstituted THBCs are known.[9c,29a] The THBCs of high optical purity have been isolated either at or below room temperature or by using excess of acid during reaction. To this end, in an attempt to investigate if this is also the case in the methodology described above, the ees of the *trans* and *cis* **6f**, synthesized under the conditions of thermodynamic control were determined by ^{1}H NMR spectroscopy[42] using chiral shift reagent, tris[3-heptafluoropropylhydroxymethylene-(+)-camphorato]europium (III) as well as specific optical rotation correlation with authentic *trans* and *cis* **6f**, prepared using racemisation-free conditions of Bailey[10b] et al. The products showed fair degree of enantioselectivity [86% for *trans* **6f** and >95% for *cis* **6f**].

2.3. Synthesis of congeners to naturally occurring alkaloids

2,4-Dioxo-1,2,3,4,6,7,12,12b-octahydroindolo [2,3-*a*] quinolizine **13**, a ketolactam, is of interest in connection with the total synthesis of indole alkaloids and their analogs. The known synthesis[43] of **13** proceeds in low yield and requires the use of sensitive 4-ethoxycarbonyl-3,3-ethylenedioxybutanal. The reaction of tryptamine with **3c**



Scheme 4. *Reagents*: (i) MeCN, AcOH; (ii) EtOH, dry HCl.

(anhydrous MeCN/AcOH, 10:1, reflux) furnished enaminone ester **11** [*Z* configuration, δ 4.93, J=7.2 Hz (vinylic protons)]. The enaminone ester **11** was cyclized (Scheme 4) to THBC **12**[44] in the presence of dry hydrogen chloride. The THBC **12** serves as an important intermediate for **13**[45] as well as the dihydroindole derivative **14**—a vindoline alkaloid.[44]

3. Conclusions

These few reactions demonstrate a facile incorporation of both aromatic and aliphatic substituents at C-1 of the THBC system in a synthetically useful manner through a single pot C-2 unit transfer reaction of **1/3** and the methodology is amenable to a variety of substitutional variations at C-1 of substituted THBCs. The chemical yield, simplicity of the methodology and ease in synthesis of a variety of oxazinanes makes this approach quite attractive. Although the diastereocontrol of the reactions described herein is of an order similar to the conventional Pictet–Spengler approach employing aldehydes, the method will be most suited for those cases where the desired aldehydes are unstable or difficult to handle.

4. Experimental

4.1. General

All melting points are uncorrected. IR spectra were recorded on Pye UNICAM SP 3-300 spectrophotometer. ^{1}H- and ^{13}C NMR spectra were run on Bruker AC 200 instrument using TMS as the internal standard. Mass (70 eV) spectra and elemental analyses were performed on Shimadzu QP 2000A spectrometer and Perkin–Elmer 2400 CHN elemental analyzer, respectively. TLC was performed on microplates coated with silica gel-G and the spots were developed in iodine chamber. Optical rotations were measured using a Jasco DIP-360 digital polarimeter. Column chromatography was performed on silica gel (60–120 mesh).

The reagents **1a**,[26a] **1d** and **e**,[26e] **1f**,[27] **1g**,[46] **1h–j**,[27] **2a–d**[27] and L-TrpOMe, L-TrpOPr^i, N_b-benzyl L-TrpOMe and N_b-*p*-MeObenzyl-L-TrpOPr^i were prepared in analogy with the reported[5a] procedures. L-Tryptophan was purchased from Sigma–Aldrich Co., USA.

Spectral data for compounds **6f**,[9a,34] **9a**,[47] **9b**,[5a,34] **9c**,[34] **9f**,[48] **9g**,[36] **11**,[44] **12**,[44] and **13**[45] were identical to those reported. Spectral data for compounds **6b–f**, **6h–l**, **6n–q** and **6s–v** are available as supporting information.

4.1.1. 2-(3,4-Dimethoxy)phenyltetrahydro-(2*H*)-1,3-oxazine (1b). A solution of 3,4-dimethoxy benzaldehyde (0.1 mol), 3-amino-1-propanol (0.1 mol), and *p*-toluenesulfonic acid (catalytic) in anhydrous benzene (30 mL) was refluxed for azeotropic removal of water using Dean–Stark apparatus till the reaction completed (TLC) (2–3 h). The solution was then filtered and the organic phase washed with cold aqueous sodium bicarbonate solution (5% w/v) and water, in succession. It was then dried (anhydrous Na_2SO_4) and the solvent was removed under reduced pressure. The thick residue solidified when refrigerated overnight and was pure enough for further use. Yield: quantitative, pale yellow solid, mp 66–68°C. ν_{max} (KBr): 3450, 1639, 1267 cm^{-1}. [Found: C, 64.51; H, 7.68; N 6.21. $C_{12}H_{17}NO_3$ requires C, 64.57; H, 7.62; N, 6.27%]. δ_H (200 MHz, $CDCl_3$): (oxazinane/imine=36.5:63.5%), 1.94 (quintet, J=6.2 Hz, 2H, C(5)H$_2$), 2.61 (br, 1H, D_2O exchangeable, NH), 3.78 (t, J=6.2 Hz, 2H, C(4)H$_2$), 3.90 (m, 8H, 2×OMe and C(6)H$_2$), 5.13 (s, 1H, C(2)H), 7.20 (m, 3H, ArH), 8.18 (s, 1H, –N=C*H*–)†. δ_C‡ (50.6 MHz, $CDCl_3$): 27.0, 33.3, 44.4, 55.8, 56.0, 59.5, 62.2, 67.8, 88.5, 108.7, 110.8, 126.6, 130.0, 151.4, 160.7. *m/z* 223 (M^+). Likewise 3,4,5-trimethoxy benzaldehyde furnished *2-(3,4,5-Trimethoxy)phenyltetrahydro-(2H)-1,3-oxazine (1c)*: yield: quantative, pale yellow solid, mp 47°C. ν_{max} (KBr): ν 3390, 1645, 1238 cm^{-1}. [Found: C, 61.64; H, 7.56; N, 5.49. $C_{13}H_{19}NO_4$ requires C, 61.66; H, 7.50; N, 5.53%]. δ_H (200 MHz, $CDCl_3$): (oxazinane/imine=30.5:69.5%), 1.93 (quintet, J=6.2 Hz, 2H, C(5)H$_2$), 2.65 (br, 1H, D_2O exchangeable, NH), 3.85 (m, 13H, 3×OMe, C(4)H$_2$ and C(6)H$_2$), 5.10 (s, 1H, C(2)H), 6.74 (s, 2H, ArH), 6.94 (s, 2H, ArH)†, 8.16 (s, 1H, –N=C*H*–)†. δ_C‡ (50.6 MHz, $CDCl_3$): 26.8, 33.3, 44.2, 55.9, 58.9, 60.6, 61.4, 67.7, 88.5, 105.0, 131.1, 153.2, 160.8. *m/z* 253 (M^+).

† Signals due to ring chain tautomerism.
‡ Extra signals appear due to ring-chain tautomerism.

Following dihydrooxazines were synthesized from corresponding nitriles (R^2CN) following Meyer's[27] method.

4.1.2. 2-(2-Thiophenyl)ethyl-4,4,6-trimethyl-5,6-dihydro-(4*H*)-1,3-oxazine (2e). Yield: 84%. Colorless free flowing oil. ν_{max} ($CHCl_3$): 2950, 1640, 1250 cm^{-1}. [Found: C, 68.39; H, 8.02; N, 5.28. $C_{15}H_{21}NOS$ requires C, 68.44; H, 7.98; N, 5.32%]. δ_H (200 MHz, $CDCl_3$): 1.09 (s, 3H, Me), 1.13 (s, 3H, Me), 1.20 (d, *J*=6.2 Hz, 3H, Me), 1.26 (m, overlapped by d of Me, 1H, C(5)*H*H), 1.70 (dd, *J*=13.5, 2.6 Hz, 1H, C(5)H*H*), 2.45 (t, *J*=7.5 Hz, 2H, $-CH_2CH_2S-$), 3.13 (t, *J*=7.5 Hz, 2H, $-CH_2CH_2S$), 4.10 (m, 1H, CH), 7.26 (m, 5H, ArH). δ_C (50.6 MHz, $CDCl_3$): 21.3, 29.5, 30.9, 31.7, 35.4, 41.8, 49.7, 67.7, 125.9, 128.7, 129.6, 136.1, 156.3. *m/z* 263 (M^+).

4.1.3. 2-(2-Thioethyl)ethyl-4,4,6-trimethyl-5,6-dihydro-(4*H*)-1,3-oxazine (2f). Yield: 62%. Colorless free flowing oil. ν_{max} ($CHCl_3$): 2950, 1640, 1250 cm^{-1}. [Found: C, 61.35; H, 9.69; N, 6.49. $C_{11}H_{21}NOS$ requires C, 61.39; H, 9.76; N, 6.51%]. δ_H (200 MHz, $CDCl_3$): 1.15 (s, 3H, Me), 1.17 (s, 3H, Me), 1.20 (t, *J*=7.5 Hz, 3H, $-SCH_2Me$), 1.22 (d, *J*=6.0 Hz, 3H, Me), 1.25 (m, overlapped by d of Me, 1H C(5)*H*H), 1.76 (dd, *J*=13.4, 2.3 Hz, 1H, C(5)H*H*), 2.38 (t, *J*=7.6 Hz, 2H, $-CH_2CH_2SEt$), 2.53 (q, *J*=7.5 Hz, 2H, $-SCH_2Me$), 2.75 (t, *J*=7.6 Hz, 2H, $-CH_2CH_2SEt$), 4.12 (m, 1H, CH). δ_C (50.6 MHz, $CDCl_3$): 14.6, 21.3, 25.5, 28.2, 29.5, 30.8, 35.8, 41.8, 49.9, 67.7, 156.4. *m/z* 215 (M^+).

4.1.4. 2-Chloromethyl-4,4,6-trimethyl-5,6-dihydro-(4*H*)-1,3-oxazine (2h). Yield: 74%. Colorless free flowing oil. ν_{max} ($CHCl_3$): 2925, 1660, 1255 cm^{-1}. [Found: C, 54.72; H, 7.85; N, 7.95. $C_8H_{14}NOCl$ requires C, 54.70; H, 7.97; N, 7.97%]. δ_H (200 MHz, $CDCl_3$): 1.18 (s, 3H, Me), 1.21 (s, 3H, Me), 1.32 (d, *J*=6.2 Hz, 3H, Me), 1.34 (m, overlapped by d of Me, 1H, C(5)*H*H), 1.72 (dd, *J*=13.7, 2.6 Hz, 1H, C(5)H*H*), 3.91 (s, 2H, $-CH_2Cl$), 4.20 (m, 1H, CH). δ_C (50.6 MHz, $CDCl_3$): 20.3, 28.4, 30.6, 40.8, 42.8, 49.4, 67.8, 152.7. *m/z* 175 (M^+).

4.1.5. 2-(β-Cyanoethyl)-4,4,6-trimethyl-5,6-dihydro-(4*H*)-1,3-oxazine (2g). To a solution of diisopropylamine (1.34 mL, 0.986 g, 9.5 mmol) in anhydrous THF (2 mL), *n*-BuLi (6.13 mL, 1.5N solution in hexanes) was added dropwise at −78°C under nitrogen atmosphere. The solution was allowed to warm to 0°C and stirred for additional 10 min. It was then cooled to −78°C and addition of pre-cooled THF (25 mL) was made whilst stirring under nitrogen. Anhydrous MeCN (dried over P_2O_5) (0.5 mL, 0.393 g, 9.5 mmol) was introduced, dropwise, with the help of a hypodermic syringe through septum cap (Aldrich). The solution was stirred for additional 10 min, and a solution of **2h** (1.67 g, 9.5 mmol) in THF (10 mL) was added over a period of 15 min. The reaction mixture was stirred for an additional hour at the same low temperature (−78°C), treated with saturated aqueous solution of ammonium chloride (25 mL), and extracted with ethyl acetate (2×25 mL). The combined extract was dried (anhydrous Na_2SO_4). Solvent was removed under reduced pressure and the residue was chromatographed using ethyl acetate/hexane mixtures (3:7 v/v).

Yield: 54%. Pale yellow oil. ν_{max} ($CHCl_3$): 2260, 1255 cm^{-1}. [Found: C, 66.62; H, 8.92; N, 15.49. $C_{10}H_{16}N_2O$ requires C, 66.66; H, 8.88; N, 15.55%]. δ_H (200 MHz, $CDCl_3$): 1.16 (s, 3H, Me), 1.19 (s, 3H, Me), 1.25 (d, *J*=6.5 Hz, 3H, Me), 1.38 (m, 1H, C(5)*H*H), 1.75 (dd, *J*=13.5, 2.7 Hz, 1H, C(5)H*H*), 2.43 (distorted t, 2H, $-CH_2CH_2CN$), 2.60 (distorted t, 2H, $-CH_2CH_2CN$), 4.16 (m, 1H, CH). δ_C (50.6 MHz, $CDCl_3$): 14.1, 21.1, 29.3, 30.2, 31.5, 41.8, 49.8, 68.2, 119.0, 154.5. *m/z* 180 (M^+).

Following tetrahydrooxazines were synthesized by the reduction[27] of their corresponding dihydrooxazines **2e**, **2f** and **2g**.

4.1.6. 2-(2-Thiophenyl) ethyl-4,4,6-trimethyl tetrahydro-(2*H*)-1,3-oxazine (1k). Yield: quantitative. Colorless viscous oil. ν_{max} ($CHCl_3$): 3350, 1245 cm^{-1}. [Found: C, 67.98; H, 8.71; N, 5.25. $C_{15}H_{23}NOS$ requires C, 67.92; H, 8.67; N, 5.28%]. δ_H (200 MHz, $CDCl_3$): 1.14 (m, 10H, 3×Me, C(5)*H*H), 1.44 (m, 1H, C(5)H*H*), 1.53 (br, 1H, D_2O exchangeable, NH), 1.85 (m, 2H, $-CHCH_2CH_2Ph$), 3.07 (t, *J*=7.3 Hz, 2H, $-CHCH_2CH_2Ph$), 3.65 (m, 1H, CH), 4.35 (t, *J*=6.0 Hz, 1H, $-CHCH_2CH_2Ph$), 7.36 (m, 5H, ArH). δ_C (50.6 MHz, $CDCl_3$): 22.1, 23.7, 29.3, 32.6, 35.8, 45.4, 48.9, 68.4, 81.6, 125.6, 128.6, 129.0, 136.0. *m/z* 265 (M^+).

4.1.7. 2-(2-Thioethyl) ethyl-4,4,6-trimethyl tetrahydro-(2*H*)-1,3-oxazine (1l). Yield: quantitative. Colorless viscous oil. ν_{max} ($CHCl_3$): 3380, 1260 cm^{-1}. [Found: C, 60.84; H, 10.64; N, 6.51. $C_{11}H_{23}NOS$ requires C, 60.82; H, 10.59; N, 6.45%]. δ_H (200 MHz, $CDCl_3$): 1.15 (m, 10H, 3×Me, C(5)*H*H), 1.24 (t, *J*=7.2 Hz, 3H, SCH_2Me), 1.44 (m, 1H, C(5)H*H*), 1.64 (br, 1H, D_2O exchangeable, NH), 1.80 (q, *J*=6.2 Hz, 2H, $-CHCH_2CH_2SEt$), 2.53 (q, *J*=7.2 Hz, 2H, $-SCH_2Me$), 2.64 (t, *J*=6.2 Hz, 2H, $-CHCH_2CH_2SEt$), 3.73 (m, 1H, CH), 4.34 (t, *J*=6.2 Hz, 1H, $-CHCH_2CH_2SEt$). δ_C (50.6 MHz, $CDCl_3$): 14.7, 22.3, 23.9, 25.8, 27.2, 32.8, 36.3, 45.7, 48.9, 63.6, 82.0. *m/z* 217 (M^+).

4.1.8. 2-(β-Cyanoethyl)-4,4,6-trimethyl tetrahydro-(2*H*)-1,3-oxazine (1m). Yield: quantative. Colorless viscous oil. ν_{max} ($CHCl_3$): 3385, 2255, 1265 cm^{-1}. [Found: C, 66.02; H, 9.94; N, 15.35. $C_{10}H_{18}N_2O$ requires C, 65.93; H, 9.89; N, 15.38%]. δ_H (200 MHz, $CDCl_3$): 1.12 (m, 9H, 3×Me), 1.22 (m, 1H, C(5)*H*H), 1.31 (m, 1H, C(5)H*H*), 1.65 (br, 1H, D_2O exchangeable, NH), 1.80 (m, 2H, $CHCH_2CH_2CN$), 2.48 (t, *J*=7.4 Hz, 2H, $CHCH_2CH_2CN$), 3.71 (m, 1H, CH), 4.31(t, *J*=5.7 Hz, 1H, $CHCH_2CH_2CN$). δ_C (50.6 MHz, $CDCl_3$): 12.8, 21.7, 23.3, 30.9, 32.2, 44.9, 48.5, 68.3, 80.7, 119.1. *m/z* 182 (M^+).

4.2. General procedure for the reaction of oxazinanes 1 or oxazolidines 3 with L-tryptophan esters

Oxazinanes **1** or oxazolidines **3** (1.0 mmol), appropriate tryptophan ester **5a**–**d** (1.0 mmol) and acetic acid (3 mL)/TFA (0.3 mL) in anhydrous acetonitrile (30 mL) were stirred/sonicated at rt or refluxed at 80°C till the reaction completed (TLC). The reaction was basified with cold aqueous sodium carbonate (5% w/v) solution and extracted with ethyl acetate (3×50 mL). The extract was washed once with cold water (2×50 mL) and dried (anhydrous Na_2SO_4).

Solvent was removed in vacuo and the residue was chromatographed on silica gel (60–120 mesh) using hexanes, ethyl acetate or their mixtures as eluents.

Using the above procedure the following products were synthesized.

4.2.1. *cis*-Methyl 1-(*p*-methoxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]-indole-3-carboxylate (6a). Yield: 38%. White solid, mp 215°C. ν_{max} (KBr): 3464, 1736 cm^{-1}. [Found: C, 71.38; H, 5.89; N, 8.42. $C_{20}H_{20}N_2O_3$ requires C, 71.42; H, 5.95; N, 8.33%]. δ_H (200 MHz, $CDCl_3$): 2.01 (br, 1H, D_2O exchangeable, NH), 2.95 (m, 2H, C(4)H_2), 3.79 (s, 6H, 2×OMe), 3.94 (dd, *J*=11.0, 4.3 Hz, 1H, C(3)H), 5.15 (s, 1H, C(1)H), 7.10 (AA′BB′ system, *J*=8.5, 8.5 Hz, 4H, ArH), 7.15 (m, 4H, ArH), 7.76 (br, 1H, D_2O exchangeable, NH). δ_C (50.6 MHz, $CDCl_3$): 25.6, 52.1, 55.3, 56.8, 57.8, 108.6, 110.8, 114.2, 114., 118.1, 119.5, 121.8, 129.7, 132.6, 134.8, 135.9, 159.7, 173.2. *m/z* 336 (M^+). trans-*Methyl 1-(*p-*methoxyphenyl)-1,2,3,4-tetrahydro-9*H-*pyrido [3,4-*b*]-indole-3-carboxylate* (**6a**): Yield: 39%. White solid. Mp 205°C. ν_{max} (KBr): 3380, 1741. [Found: C, 71.42; H, 5.95; N, 8.29. $C_{20}H_{20}N_2O_3$ requires C, 71.42; H, 5.95; N, 8.33%]. δ_H (200 MHz, $CDCl_3$): 1.89 (br, 1H, D_2O exchangeable, NH), 3.14 (ABX system, *J*=15.2, 5.6, 6.8 Hz, 2H, C(4)H_2), 3.71 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.97 (dd, *J*=6.8, 5.5 Hz, 1H, C(3)H), 5.37 (s, 1H, C(1)H), 6.84 (AA′BB′ system, *J*=8.5, 8.5 Hz, 4H, ArH), 7.16 (m, 3H, ArH), 7.52 (m, 1H, ArH), 7.59 (br, 1H, D_2O exchangeable, NH). δ_C (50.6 MHz, $CDCl_3$): 24.5, 52.0, 52.4, 54.2, 55.3, 109.1, 110.8, 114.6, 118.2, 119.4, 121.8, 129.5, 132.1, 151.4, 174.1. *m/z* 336 (M^+).

4.2.2. *cis*-2-Methylethyl 1-(*p*-methoxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]-indole-3-carboxylate (6g). Yield: 41%. Yellow viscous oil. ν_{max} ($CHCl_3$): 3310, 1734 cm^{-1}. [Found: C, 72.48; H, 6.59; N, 7.75. $C_{22}H_{24}N_2O_3$ requires C, 72.52; H, 6.59; N, 7.69%]. δ_H (200 MHz, $CDCl_3$): 1.27 (d, *J*=6.0 Hz, 3H, Me), 1.29 (d, *J*=6.0 Hz, 3H, Me), 2.34 (br, 1H, D_2O exchangeable, NH), 2.96 (m, 1H, C(4)*H*H), 3.18 (m, 1H, C(4)H*H*), 3.75 (s, 3H, OMe), 3.84 (dd, *J*=10.9, 4.1 Hz, 1H, C(3)H), 5.10 (m, 2H, C*H*(Me)$_2$ and C(1)H), 7.05 (AA′BB′ system, *J*=8.4, 8.4 Hz, 4H, ArH), 7.17 (m, 3H, ArH), 7.54 (m, 2H, ArH and D_2O exchangeable NH). δ_C (50.6 MHz, $CDCl_3$): 21.8, 25.7, 55.2, 57.1, 57.9, 68.7, 108.8, 110.9, 116.1, 119.4, 121.7, 127.2, 129.8, 132.9, 135.1, 136.2, 159.7, 172.4. *m/z* 364 (M^+). trans-*2-Methylethyl 1-(*p-*methoxyphenyl)-1,2,3,4-tetrahydro-9*H-*pyrido [3,4-*b*]-indole-3-carboxylate* (**6g**): Yield: 27%. White Solid. Mp 185°C. ν_{max} (KBr): 3365, 1730 cm^{-1}. [Found: C, 72.45; H, 6.65; N, 7.70. $C_{22}H_{24}N_2O_3$ requires C, 72.52; H, 6.59; N, 7.69%]. δ_H (200 MHz, $CDCl_3$): 1.21 (d, *J*=6.2 Hz, 3H, Me), 1.25 (d, *J*=6.2 Hz, 3H, Me), 1.89 (br, 1H, D_2O exchangeable, NH), 3.18 (ABX system, *J*=15.3, 5.2, 7.2 Hz, 2H, C(4)H_2), 3.78 (s, 3H, OMe), 3.86 (dd, *J*=12.3, 5.6 Hz, 1H, C(3)H), 5.03 (heptet, *J*=6.2 Hz, 1H, C*H*(Me)$_2$), 5.35 (s, 1H, C(1)H), 7.12 (AA′BB′ system, *J*=8.5, 8.5 Hz, 4H, ArH), 7.13 (m, 3H, ArH), 7.57 (m, 2H, ArH and D_2O exchangeable NH). δ_C (50.6 MHz, $CDCl_3$): 21.7, 24.7, 52.3, 54.3, 55.2, 66.4, 108.4, 110.8, 114.0, 116.1, 119.3, 121.7, 127.7, 129.5, 133.5, 134.5, 136.2, 159.4, 173.1. *m/z* 364 (M^+).

4.2.3. *trans*-Methyl N_b-benzyl-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]-indole-3-carboxylate (6m). Yield: 91%. White solid. Mp 192°C. ν_{max} (KBr): 3337, 1722cm^{-1}. [Found: C, 76.01; H, 6.15; N, 6.62. $C_{27}H_{26}N_2O_3$ requires C, 76.05; H, 6.10; N, 6.57%]. δ_H (200 MHz, $CDCl_3$): 3.20 (m, 2H, C(4)H_2), 3.61 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.85 (s, 2H, CH_2Ph), 3.90 (m, 1H, C(3)H), 5.40 (s, 1H, C(1)H), 6.85 (m, 2H, ArH), 7.28 (m, 12H, ArH and D_2O exchangeable NH). δ_C (50.6 MHz, $CDCl_3$): 24.3, 51.2, 54.1, 55.1, 56.0, 60.0, 106.3, 110.7, 114.0, 118.1, 119.2, 121.4, 127.0, 128.2, 128.5, 129.9, 134.0, 135.1, 136.4, 139.5, 159.9, 173.5. δ_C ($CDCl_3$, DEPT-135): 24.3(−ve), 51.2, 54.1 (−ve), 55.1, 56.0, 60.0, 110.7, 114.0, 118.1, 119.2, 121.4, 127.0, 128.2, 128.5, 129.9. *m/z* 426 (M^+).

4.2.4. *trans*-2-Methylethyl N_b-(4-methoxybenzyl)-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]-indole-3-carboxylate (6r). Yield: 88%. Yellow viscous oil. ν_{max} ($CHCl_3$): 3400, 1730 cm^{-1}. [Found: C, 74.42; H, 6.70; N, 5.73. $C_{30}H_{32}N_2O_4$ requires C, 74.38; H, 6.61; N, 5.78%]. δ_H (200 MHz, $CDCl_3$): 1.10 (d, *J*=6.2 Hz, 3H, Me), 1.20 (d, *J*=6.2 Hz, 3H, Me), 3.13 (m, 2H, C(4)H_2), 3.78 (s, 8H, 2×OMe and CH_2Ph), 3.85 (t, *J*=6.0 Hz, 1H, C(3)H), 4.98 (heptet, *J*=6.2 Hz, 1H, C*H*(Me)$_2$), 5.37 (s, 1H, C(1)H), 6.84 (m, 4H, ArH), 7.12 (m, 6H, ArH), 7.42 (m, 3H, ArH and D_2O exchangeable NH). δ_C (50.6 MHz, $CDCl_3$): 21.8, 21.9, 24.3, 53.5, 55.2, 55.9, 60.2, 67.6, 106.4, 110.7, 112.0, 113.7, 114.0, 118.1, 119.2, 121.4, 127.2, 129.7, 129.9, 131.6, 134.3, 135.2, 136.5, 158.7, 159.3, 172.7. *m/z* 484 (M^+).

4.2.5. *cis*- and *trans*-Methyl 1-carbethoxymethyl-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]indole-3-carboxylate (9d). Yield: 74%. Yellow viscous oil, ν_{max} ($CHCl_3$): 3684, 1740 cm^{-1}. [Found: C, 64.58; H, 6.28; N, 8. 87. $C_{17}H_{20}N_2O_4$ requires C, 64.55; H, 6.32; N, 8.86%]. δ_H (200 MHz, $CDCl_3$): 1.28 (m, 6H, CH_2*Me-cis* and *trans*), 2.09 (br, 2H, D_2O exchangeable, NH-*cis* and *trans*), 2.81 (m, 8H, CH_2COOEt and C(4)H_2-*cis* and *trans*), 3.75 (s, 3H, OMe-*trans*), 3.82 (s, 3H, OMe-*cis*), 3.86 (m, 2H, C(3)H-*cis* and *trans*), 4.20 (m, 4H, CH_2-*cis* and *trans*), 4.50 (m, 1H, C(1)H-*cis*), 4.55 (m, 1H, C(1)H-*trans*), 7.12 (m, 4H, ArH-*cis* and *trans*), 7.31 (m, 2H, ArH-*cis* and *trans*), 7.48 (d, *J*=7.2 Hz, 2H, ArH-*cis* and *trans*), 8.50 (br, 1H, D_2O exchangeable, NH-*trans*), 8.82 (br, 1H, D_2O exchangeable, NH-*cis*). δ_C (50.6 MHz, $CDCl_3$): 14.0 (*cis*), 14.2 (*trans*), 25.0 (*trans*), 25.6 (*cis*), 40.3 (*cis*), 40.9 (*trans*), 46.7, 49.3, 52.1 (*trans*), 52.5, 56.2, 60.9 (*trans*), 61.1 (*cis*), 106.8, 107.9, 110.9, 111.0, 117.9, 119.2, 119.3, 119.5, 121.8, 122.1, 126.6, 126.7, 134.1, 135.6, 135.6, 135.8, 172.7 (*cis*), 172.9 (*trans*), 173.2 (*cis*), 173.8 (*trans*). δ_C (50.6 MHz, $CDCl_3$, DEPT-135): 14.0 (*cis*), 14.2 (*trans*), 25.0 (−ve) (*trans*), 25.6 (−ve) (*cis*), 40.3 (−ve) (*cis*), 40.9 (−ve) (*trans*), 46.7, 49.3, 52.1 (*trans*), 52.5, 56.2, 60.9 (−ve) (*trans*), 61.1 (−ve) (*cis*), 110.9, 111.0, 117.9, 119.2, 119.3, 119.5, 121.8, 122.1. *m/z* 316 (M^+).

4.2.6. *cis*- and *trans*-Methyl 1-cyanomethyl-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]indole-3-carboxylate (9e). Yield: 61%. Yellow viscous oil. ν_{max} ($CHCl_3$): 3395, 2170, 1720 cm^{-1}. [Found: C, 66.95; H, 5.58; N, 15.64. $C_{15}H_{15}N_3O_2$ requires C, 66.91; H, 5.57; N, 15.61%]. δ_H

(200 MHz, $CDCl_3$): 2.05 (br, 2H, D_2O exchangeable, NH-*cis* and *trans*), 2.76 (m, 8H, C*H*$_2$CN and C(4)H$_2$-*cis* and *trans*), 3.75 (s, 3H, OMe-*trans*), 3.82 (m, 1H, C(3)H-*cis*), 3.84 (s, 3H, OMe-*cis*), 3.97 (dd, *J*=7.2, 5.2 Hz, 1H, C(3)H-*trans*), 4.61 (br t, *J*=6.7 Hz, 1H, C(1)H-*cis*), 4.70 (t, *J*=6.7 Hz, 1H, C(1)H-*trans*), 7.15 (m, 4H, ArH-*cis* and *trans*), 7.36 (d, *J*=7.5 Hz, 2H, ArH-*cis* and *trans*), 7.50 (d, *J*=7.5 Hz, 2H, ArH-*cis* and *trans*), 8.15 (br, 1H, D_2O exchangeable, NH-*trans*), 8.25 (br, 1H, D_2O exchangeable, NH-*cis*). δ_C (50.6 MHz, $CDCl_3$): 22.8 (*cis*), 23.8 (*trans*), 23.9 (*trans*), 24.5 (*cis*), 46.4, 48.9, 51.1 (*cis*), 51.2 (*trans*), 51.7, 55.2, 106.5 (*trans*), 107.6 (*cis*), 110.4, 117.0, 117.1, 117.6, 118.1, 118.2, 120.8, 125.7, 125.8, 131.3 (*trans*), 131.6 (*cis*), 135.5 (*trans*), 135.7 (*cis*), 172.0 (*cis*), 173.0 (*trans*). *m*/*z* 269 (M^+).

4.2.7. *cis*- and *trans*-Methyl 1-carbethoxymethyl-N_b-benzyl-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]indole-3-carboxylate (9h). Yield: 86%. Yellow viscous oil. ν_{max} ($CHCl_3$): 3420, 1715 cm^{-1}. [Found: C, 71.01; H, 6.45; N, 6.95. $C_{24}H_{26}N_2O_4$ requires C, 70.93; C, 6.40; N, 6.89%]. δ_H (200 MHz, $CDCl_3$): 1.20 (t, *J*=6.9 Hz, 3H, Me-*trans*), 1.24 (t, *J*=6.9 Hz, 3H, Me-*cis*), 2.98 (m, 8H, C*H*$_2$COOEt and C(4)H$_2$-*cis* and *trans*), 3.65 (m, 4H, C*H*$_2$Ph-*cis* and *trans*), 3.74 (s, 3H, OMe-*trans*), 3.85 (s, 3H, OMe-*cis*), 3.98 (m, 2H, C(3)H-*cis* and *trans*), 4.08 (q, *J*=6.9 Hz, 4H, CH_2-*cis* and *trans*), 4.34 (dd, *J*=10.0, 3.8 Hz, 1H, C(1)H-*trans*), 4.49 (m, 1H, C(1)H-*cis*), 7.15 (m, 4H, ArH-*cis* and *trans*), 7.34 (m, 12H, ArH-*cis* and *trans*), 7.54 (m, 2H, ArH-*cis* and *trans*), 8.63 (br, 1H, D_2O exchangeable, NH-*trans*), 8.81 (br, 1H, D_2O exchangeable, NH-*cis*). δ_C (50.6 MHz, $CDCl_3$): 13.8 (*trans*), 13.9 (*cis*), 21.0 (*trans*), 21.3 (*cis*), 38.1 (*cis*), 40.6 (*trans*), 51.5 (*trans*), 51.7 (*trans*), 52.3 (*trans*), 52.7 (*cis*), 53.6 (*trans*), 54.2 (*cis*), 56.9 (*trans*), 57.2 (*trans*), 57.2 (*trans*), 57.4 (*trans*), 60.7 (*trans*), 105.6 (*cis*), 106.6 (*trans*), 110.9 (*trans*), 117.9 (*trans*), 119.0 (*cis*), 119.1 (*trans*), 121.5 (*cis*), 121.6 (*trans*), 126.5 (*trans*), 126.9 (*trans*), 127.1 (*cis*), 128.1 (*trans*), 128.4 (*trans*), 133.7 (*trans*), 135.7 (*trans*), 135.8 (*cis*), 138.7 (*cis*), 139.1 (*trans*), 172.8 (*trans*), 172.9 (*trans*), 174.1 (*cis*), 174.2 (*cis*). *m*/*z* 406 (M^+).

4.2.8. *trans*-Methyl 1-(β-mercaptophenyl)ethyl-N_b-benzyl-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]indole-3-carboxylate (9i). Yield: 72%. White solid, mp 98°C. ν_{max} (KBr): 3405, 1720 cm^{-1}. [Found: C, 73.72; H, 6.15; N, 6.20. $C_{28}H_{28}N_2O_2S$ requires C, 73.68; N, 6.14; N, 6.14%]. δ_H (200 MHz, $CDCl_3$): 1.98 (m, 2H, CHC*H*$_2$CH$_2$S), 2.94 (m, 4H, CHCH$_2$C*H*$_2$S and C(4)H$_2$), 3.64 (m, 2H, C*H*$_2$Ph), 3.74 (s, 3H, OMe), 4.00 (m, 2H, C(3)H and C(1)H), 7.36 (m, 13H, ArH), 7.54 (m, 1H, ArH), 7.68 (br, 1H, D_2O exchangeable, NH). δ_C (50.6 MHz, $CDCl_3$): 21.1, 29.3, 33.6, 51.8, 53.4, 54.6, 56.8, 110.8, 118.1, 119.5, 121.8, 125.7, 126.9, 127.2, 128.3, 128.8, 128.9, 129.0, 133.7, 136.1, 139.1, 173.3. *m*/*z* 456 (M^+).

4.2.9. *trans*-Methyl 1-(β-mercaptoethyl)ethyl-N_b-benzyl-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]indole-3-carboxylate (9j). Yield: 78%. White solid, mp 85°C. ν_{max} (KBr): 3365, 1742 cm^{-1}. [Found: C, 70.63; H, 6.90; N, 6.85. $C_{24}H_{28}N_2O_2S$ requires C, 70.58; H, 6.86; N 6.86%]. δ_H (200 MHz, $CDCl_3$): 1.16 (t, *J*=7.3 Hz, 3H, SCH_2Me), 1.98 (m, 2H, CHC*H*$_2$CH$_2$S–), 2.40 (q, *J*=7.3 Hz, 2H, S*CH*$_2$CH$_3$), 2.57 (m, 2H, CHCH$_2$C*H*$_2$S), 3.13 (ABX system, *J*=15.8, 8.9, 5.3 Hz, 2H, C(4)H$_2$), 3.70 (ABq, *J*=13.7 Hz, 2H, C*H*$_2$Ph), 3.77 (s, 3H, OMe), 4.03 (m, 2H, C(3)H and C(1)H), 7.14 (m, 2H, ArH), 7.32 (m, 6H, ArH), 7.55 (m, 1H, ArH), 7.91 (br, 1H, D_2O exchangeable, NH). δ_C (50.6 MHz, $CDCl_3$): 14.6, 21.1, 25.7, 27.9, 34.2, 51.9, 53.4, 54.7, 56.9, 107.5, 110.8, 118.1, 119.5, 121.7, 121.7, 127.1, 128.2, 128.9, 134.1, 136.1, 139.3. 173.3. *m*/*z* 408 (M^+).

4.2.10. *trans*-Methyl 1-(β-cyanoethyl)-N_b-benzyl-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]indole-3-carboxylate (9k). Yield: 61%. Yellow viscous oil. ν_{max} ($CHCl_3$): 3360, 2260, 1735 cm^{-1}. [Found: C, 74.05; H, 6.21; N, 11.25. $C_{23}H_{23}N_3O_2$ requires C, 73.99; H, 6.16; N, 11.26%]. δ_H (100 MHz, $CDCl_3$): 2.10 (m, 2H, C*H*$_2$CH$_2$CN), 2.33 (t, *J*=7.4 Hz, 2H, CHCH$_2$C*H*$_2$CN), 3.12 (ABX system, *J*=16.0, 8.3, 5.8 Hz, 2H, C(4)H$_2$), 3.63 (m, 2H, C*H*$_2$Ph), 3.77 (s, 3H, OMe), 3.94 (m, 1H, C(3)H), 4.05 (dd, *J*=8.1, 3.7 Hz, 1H, C(1)H), 7.20 (m, 2H, ArH), 7.31 (m, 6H, ArH), 7.54 (d, *J*=7.0 Hz, 1H, ArH), 7.86 (br, 1H, D_2O exchangeable, NH). δ_H (50.6 MHz, $CDCl_3$): 13.0, 21.4, 28.6, 51,9, 53.2, 53.6, 56.8, 107.9, 111.0, 118.1, 119.2, 122.0, 127.1, 127.5, 128.4, 132.5, 136.4, 138.6, 173.0. *m*/*z* 373 (M^+).

4.2.11. *trans*-Methyl 1-cyanomethyl-N_b-benzyl-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]indole-3-carboxylate (9l). Yield: 61%. Colorless needles, mp 205°C. ν_{max} (KBr): 3325, 2270, 1740 cm^{-1}. [Found: C, 73.55; H, 5.90; N, 11.73. $C_{22}H_{21}N_3O_2$ requires C, 73.53; H, 5.84; N, 11.69%]. δ_H (200 MHz, $CDCl_3$): 2.87 (ABX system, *J*=16.6, 4.9, 7.8 Hz, 2H, C*H*$_2$CN), 3.14 (ABX system, *J*=15.9, 6.4, 5.6 Hz, 2H, C(4)H$_2$), 3.69 (s, 3H, OMe), 3.85 (ABq, *J*=14.4 Hz, 2H, C*H*$_2$Ph), 3.95 (m, 1H, C(3)H), 4.44 (dd, *J*=7.5, 5.1 Hz, 1H, C(1)H), 7.19 (m, 2H, ArH), 7.38 (m, 6H, ArH), 7.53 (d, *J*=7.7 Hz, 1H, ArH), 8.05 (br, 1H, D_2O exchangeable, NH). δ_C (50.6 MHz, $CDCl_3$): 22.3, 24.2, 51.9, 53.2, 54.4, 57.4, 108.5, 111.2, 118.0, 118.4, 119.8, 122.6, 126.4, 127.5, 128.3, 128.6, 131.2, 136.5, 138.4, 172.7. *m*/*z* 360 (M^++1), 319 (M^+−CH_2CN). cis-*Methyl 1-cyanomethyl*-N-*benzyl-1,2,3,4-tetrahydro-9*H-*pyrido [3,4-*b*]*indole-3-carboxylate* (**9l**): Yield: 9%. Colorless flakes, mp 157–58°C. ν_{max} (KBr): 3312, 2270, 1738 cm^{-1}. [Found: C, 73.55; H, 5.85; N, 11.72. $C_{22}H_{21}N_3O_2$ requires C, 73.53; H, 5.84; N, 11.69%]. δ_H (200 MHz, $CDCl_3$): 3.00 (ABX system, *J*=16.7, 9.8, 4.1 Hz, 2H, C*H*$_2$CN), 3.15 (ABX system, *J*=17.7, 2.0, 2.0 Hz, 2H, C(4)H$_2$), 3.65 (s, 3H, OMe), 3.95 (dd, *J*=6.8, 2.0 Hz, 1H, C(3)H), 4.17 (s, 2H, C*H*$_2$Ph), 4.50 (m, 1H, C(1)H), 7.15 (m, 2H, ArH), 7.38 (m, 6H, ArH), 7.54 (d, *J*=7.3 Hz, 1H ArH), 8.28 (br, 1H, D_2O exchangeable, NH). δ_C (50.6 MHz, $CDCl_3$): 21.8, 22.4, 51.9, 53.4, 57.2, 58.1, 107.2, 111.2, 118.4, 119.8, 120.0, 122.6, 126.2, 127.7, 128.4, 128.7, 131.6, 136.3, 137.8, 173.3. *m*/*z* 359 (M^+).

Crystal data for trans and cis **9l**: Single crystal diffraction measurement of crystals of *trans* and *cis* **9l** were carried out in a Siemens P4 single crystal diffractometer equipped with molybdenum sealed tube (λ=0.71073 Å) and highly oriented graphite monochromator.

Data for trans **9l**. $C_{22}H_{21}N_3O_2$, *M*=359.42, crystal in orthorhombic space group $P2_12_12_1$, *Z*=4, *a*=9.386(1), *b*=9.974(1), *c*=20.191(2) Å^3, *V*=1890.2(3) Å^3, D_c=1.263 Mg m^{-3},

μ=0.083 mm^{-1}, F(000)=760. A total of 1815 reflections were measured and the structure was solved by direct methods and refined on F^2 using SHELX97[49] software. Final $wR2$=0.0910, with a conventional $R1$=0.0368 [1536 reflections with $I > 2\sigma(I)$] and a goodness of fit=1.041 for 245 refined parameters.

Data for cis **9l**. $C_{22}H_{21}N_3O_2$, M=359.42, crystal in orthorhombic space group $P2_12_12_1$, Z=4, a=8.250(1), b=10.658(1), c=21.457(2) Å^3, V=1886.7(3) Å^3, D_c=1.265 Mg m^{-3}, μ=0.083 mm^{-1}, F(000)=760. A total of 1730 reflections were measured, and the structure was solved by direct methods and refined on F^2 using SHELX97[49] software. Final $wR2$=0.1042, with a conventional $R1$=0.0399 [1449 reflections with $I > 2\sigma(I)$] and a goodness of fit=1.046 for 245 refined parameters.

4.2.12. Methyl N_b-benzyl-N_b-(2-benzoylethylene)-L-tryptophanate (10a). Yield: 60%. Viscous oil. ν_{max} ($CHCl_3$): 3450, 1740, 1680 cm^{-1}. [Found: C, 76.72; H, 5.95; N, 6.36. $C_{28}H_{26}N_2O_3$ requires C, 76.71; H, 5.93; N, 6.39%]. δ_H (200 MHz, $CDCl_3$): 3.42 (ABX system, J=15.0, 8.8, 6.6 Hz, 2H, C(4)H_2), 3.62 (s, 3H, OMe), 4.40 (br, 3H, C(3)H and CH_2Ph), 5.93 (d, J=12.6 Hz, 1H, NCH=CHCO), 6.96 (br, 1H, indolyl C(2)H), 7.21 (m, 12H, ArH), 7.77 (d, J=6.9 Hz, 2H, ArH), 8.20 (br d, J=12.6 Hz, NCH=CHCO), 8.32 (br, 1H, D_2O exchangeable, NH). δ_C (50.6 MHz, $CDCl_3$): 29.7, 52.4, 54.3, 64.5, 95.1, 109.7, 111.5, 118.1, 119.6, 122.1, 123.6, 126.9, 127.5, 127.6, 128.2, 128.6, 131.6, 131.6, 135.2, 136.3, 140.0, 152.1, 170.8, 189.4. m/z 438 (M^+).

4.2.13. *trans*-Methyl 1-benzoylmethyl-N_b-benzyl-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]indole-3-carboxylate (9m). **10a** (10 mmol) was dissolved in anhydrous benzene (10 mL) and saturated with dry hydrogen chloride at 0°C. The reaction was stirred at ambient temperature to completion (10 min), basified (aq. $NaHCO_3$) and extracted with dichloromethane (2×50 mL). After drying (anhydrous Na_2SO_4) and evaporation the residue was chromatographed to obtain **9m**. Yield: 54%; viscous yellow oil. ν_{max} ($CHCl_3$): 3470, 1725, 1690 cm^{-1}. [Found: C, 76.75; H, 5.98; N, 6.42. $C_{28}H_{26}N_2O_3$ requires C, 76.71; H, 5.93; N, 6.39%]. δ_H (200 MHz, $CDCl_3$): 3.16 (m, 2H, C(4)H_2), 3.68 (m, 2H, CH_2COC$_6$H$_5$), 3.80 (s, 3H, OMe), 3.89 (m, 2H, CH_2Ph), 4.12 (dd, J=9.6, 5.09 Hz, 1H, C(3)H), 4.53 (dd, J=9.7, 2.6 Hz, 1H, C(1)H), 7.30 (m, 13H, ArH), 7.92 (d, J=7.1 Hz, 1H, ArH), 8.72 (br, 1H, D_2O exchangeable, NH). δ_C (50.6 MHz, $CDCl_3$): 22.3, 46.3, 51.7, 52.0, 53.5, 58.2, 111.0, 118.0, 119.2, 121.7, 127.1, 128.0, 128.3, 128.6, 129.2, 133.6, 134.8, 172.7, 196.2. m/z 438 (M^+).

4.2.14. Methyl (2*S*)-3-(3-indolyl)-2([1-(4-ethoxycarbonyl-3-oxo-1-butene)]-2-benzyl) aminopropanoate (10b). Yield: 60%. Yellow viscous oil. ν_{max} ($CHCl_3$): 3459, 1720, 1660 cm^{-1}. [Found: C, 60.69; H, 6.31; N, 6.21. $C_{26}H_{28}N_2O_5$ requires C, 69.64; H, 6.25; N, 6.25%]. δ_H (200 MHz, $CDCl_3$): 1.18 (t, J=7.0 Hz, 3H, Me), 3.40 (m, 4H, C(4)H_2 and COCH_2COO), 3.60 (s, 3H, OMe), 4.00–4.24 (m, 5H, CH_2Me, CH_2Ph and C(3)H), 5.25 (d, J=12.9 Hz, 1H, NCH=CHCO), 7.13 (m, 10H, NHCH=CHCO, indolyl C(2)H and ArH), 7.33 (m, 1H, ArH), 8.24 (br, 1H, D_2O exchangeable, NH). δ_C (50.6 MHz, $CDCl_3$): 14.0, 24.1, 48.1, 52.3, 60.9, 67.4, 97.5, 109.1, 111.5, 117.8, 119.3, 121.9, 123.7, 126.6, 127.0, 127.2, 127.6, 127.8, 128.5, 134.7, 136.2, 151.5, 168.6, 170.6, 189.5. m/z 389 (M^+−COOMe), 361 (−CH_2COOEt).

4.2.15. *trans*-Methyl 1-(3-ethoxycarbonyl-2-oxo)propyl-N_b-benzyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (9n). **9n** was synthesized from **10b** following a procedure similar to the cyclization of **9m** employing anhydrous MeOH as solvent. Yield: 54%. Yellow viscous oil. ν_{max} ($CHCl_3$): 3405, 1740, 1710 cm^{-1}. [Found: C, 69.65; H, 6.23; H, 6.25. $C_{26}H_{28}N_2O_5$ requires C, 69.64; H, 6.25; N, 6.25%]. δ_H (200 MHz, $CDCl_3$): 1.98 (t, J=7.3 Hz, 3H, Me), 3.16 (m, 4H, CH_2 and C(4)H_2), 3.39 (s, 2H, COCH_2COO), 3.76 (s, 3H, OMe), 3.81 (m, 2H CH_2Ph), 3.98 (m, 1H, C(3)H), 4.12 (q, J=7.3 Hz, 2H, CH_2Me), 4.35 (m, 1H, C(1)H), 7.25 (m, 8H, ArH), 7.53 (d, J=7.8 Hz, 1H, ArH), 8.40 (br, 1H, D_2O exchangeable, NH). δ_C (50.6 MHz, $CDCl_3$): 14.0, 20.9, 49.5, 49.8, 51.7, 52.0, 53.5, 57.8, 61.5, 106.9, 111.1, 118.1, 119.4, 21.9, 127.2, 128.4, 128.6, 133.0, 136.0, 139.0, 166.7, 173.0, 203.4. m/z 448 (M^+).

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