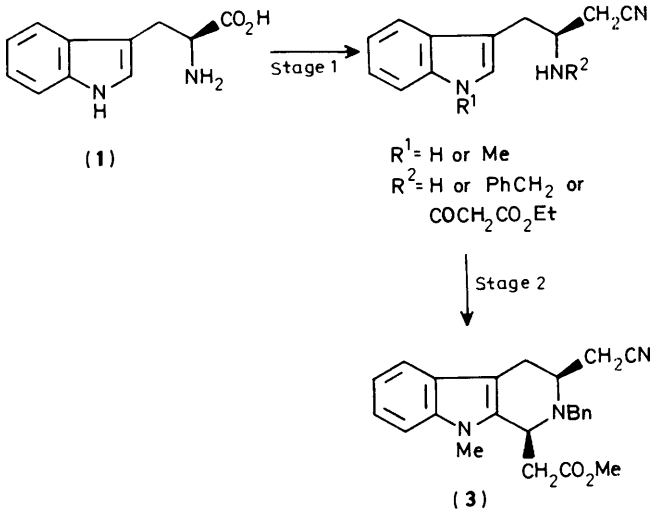
Application of a Modified Pictet–Spengler Reaction to the Synthesis of Optically Active Tetrahydro-β-carbolines, Key Intermediates in the Preparation of Many Indole Alkaloids

Patrick D. Bailey* and Sean P. Hollinshead
Department of Chemistry, University of York, Heslington, York YO1 5DD, U.K.

A recent modification of the Pictet–Spengler reaction has been applied to the synthesis of optically active tetrahydro-β-carbolines. The method was initially investigated by treating various N^{in},N^{α}-substituted tryptophan methyl esters (**10**) with methyl propynoate or dimethyl butynedioate; cyclisation of the resulting enamines (**13**) was achieved by the addition of trifluoroacetic acid, to give the desired tetrahydro-β-carbolines as mixtures of diastereoisomers (**11**) and (**12**). Single crystal *X*-ray structure determinations were carried out on two of the isolated diastereoisomers (**12b**) and (**11e**); chemical modification of these compounds allowed an unambiguous assignment of stereochemistry to all of the products from the modified Pictet–Spengler reaction. It was thereby ascertained that N^{in}-methylation and/or N^{α}-benzylation of the tryptophan methyl esters led to an increase in the proportion of *trans* products after condensation/cyclisation with methyl propynoate. This observation was applied to the preparation of the *cis*-cyano ester (**3**), which was required as a key intermediate in the synthesis of alkaloids of the ajmaline group.

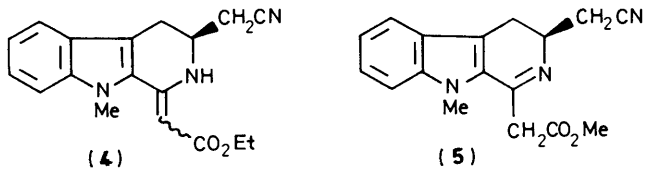
Virtually all the syntheses of alkaloids that contain the tetrahydro-β-carboline unit involve the use of the Pictet–Spengler[1] or Bischler–Napieralski[2] reactions in the formation of the C-ring. As part of work aimed at the synthesis of bridged alkaloids of the ajmaline series, we were interested in preparing the optically active cyano ester (**3**), as outlined in Scheme 1.



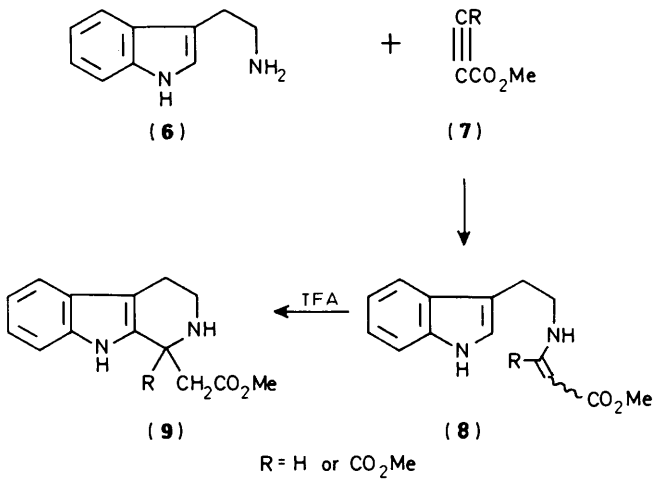
R^1 = H or Me
R^2 = H or $PhCH_2$ or $COCH_2CO_2Et$

Scheme 1.

The most obvious method of accomplishing stage 2 [(**2**) ⟶ (**3**)] would have been to have used methyl 3-oxopropanoate in a simple Pictet–Spengler reaction, but the reactivity of the aldehyde prohibited its use in this way. We therefore investigated the use of the Bischler–Napieralski reaction; ethyl malonyl chloride was treated with (**2b**; R^1 = Me, R^2 = H) to give amide (**2c**; R^1 = Me, R^2 = $COCH_2CO_2Et$) in 70% yield; cyclisation of this was effected with $POCl_3$ at room temperature, from which the cyano ester (**4**) was isolated in 22% yield after flash chromatography, instead of the expected 3,4-dihydro-β-carboline (**5**). In view of the overall low conversion of (**2b**; R^1 = Me, R^2 = H) to (**4**), reduction of the latter was not attempted, and we decided to investigate an alternative approach.



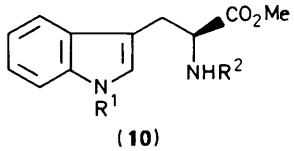
In 1984, Massiot *et al.*[3] published a modification of the Pictet–Spengler reaction, involving the addition of tryptamine (**6**) to conjugated alkynoates (**7**); cyclisation of the resulting enamines (**8**) was accomplished by the addition of trifluoroacetic acid (TFA)—see Scheme 2.



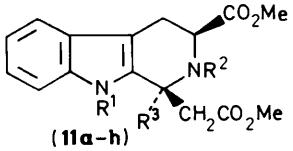
Scheme 2. R = H or CO_2Me

By using methyl propynoate as the Michael acceptor, we were hoping that direct reaction with the cyanoamine (**2d**; R^1 = Me, R^2 = CH_2Ph) might lead to the formation of the desired cyano

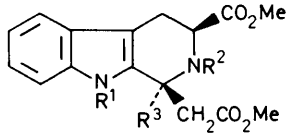
ester (**3**). We decided initially to investigate the applicability of the method to the synthesis of optically active tetrahydro-β-carbolines; various tryptophan methyl esters (**10**) were treated with methyl propynoate or dimethyl butynedioate, and the yield and stereochemistry of the cyclised di- and tri-esters (**11**)/(**12**) were investigated.



(**10**)
R^1 = H or Me
R^2 = H or $PhCH_2$



(**11a–h**)

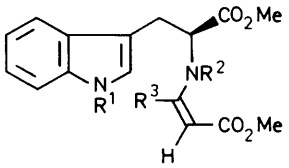


(**12a–h**)

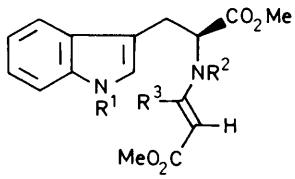
	R^1	R^2	R^3
a	H	H	H
b	H	$PhCH_2$	H
c	Me	H	H
d	Me	$PhCH_2$	H
e	H	H	CO_2Me
f	H	$PhCH_2$	CO_2Me
g	Me	H	CO_2Me
h	Me	$PhCH_2$	CO_2Me

Results and Discussion

We found that it was important to carry out the modified Pictet–Spengler reactions in two distinct steps, in which formation of the intermediate enamine (**13**) was carefully monitored. Thus, dimethyl butynedioate was treated with tryptophan methyl esters (**10**), and enamine formation was found to be complete in less than 15 min. In contrast, the less electrophilic methyl propynoate reacted very slowly (enamine formation requiring 1—10 days), whilst methyl but-2-ynoate failed to react at all. The resulting enamines gave distinctive ^1H n.m.r. spectra, in which the vinylic signals were indicative of the presence of *cis*- and *trans*-enamines (**13a**) and (**13b**) respectively.[4]



(**13a**)



(**13b**)

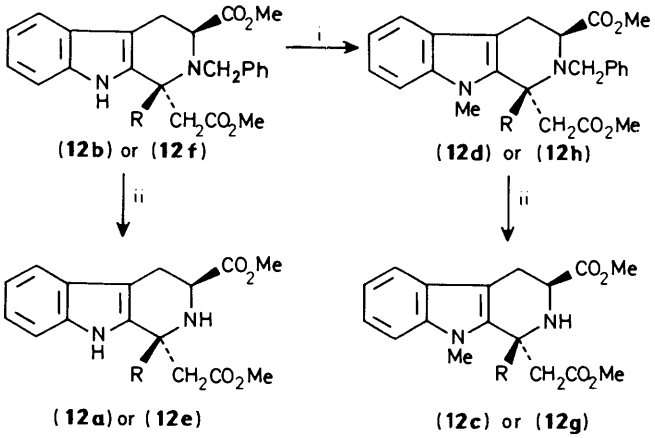
R^1 = H or Me
R^2 = H or $PhCH_2$
R^3 = H or CO_2Me

These enamines were not isolated, but acidification with TFA *in situ* led to the formation of the tetrahydro-β-carbolines (**11**)/(**12**), as mixtures of pairs of diastereoisomers; disappearance of the indole-2*H* proton at δ 7.1 in the ^1H n.m.r. spectrum of the crude product was indicative that the reaction had proceeded smoothly. Although ethoxyethane and benzene were also investigated as possible solvents, it was found that the overall reaction proceeded much more rapidly in chloroform, and this conveniently allowed ^1H n.m.r. spectra to be recorded during reaction in $CDCl_3$. It is noteworthy that the yields of isolated products varied considerably, and depended upon the N^{in}- and N^{α}-substitution of tryptophan methyl ester, as well as upon the Michael acceptor.

For most of our tetrahydro-β-carbolines, separation of the diastereoisomers could be accomplished by recrystallisation or flash chromatography.[5] Whilst ^{13}C n.m.r. could have been used to predict the stereochemistry of two of the methyl propynoate adducts [(**11a**)/(**12a**) and (**11c**)/(**12c**)],[6,7] the dimethyl butynedioate adducts could not be analysed in this way; we therefore chose to use *X*-ray crystallography to determine unambiguously the relative stereochemistry of two key diastereomerically pure products, (**12b**) and (**11e**),[8] from which the stereochemistry of all the products could be unambiguously assigned.

Having determined the relative stereochemistry at C-1 and C-3 for (**12b**) and (**11e**), we carried out simple chemical modifications, in order to determine the stereochemistry of the other tetrahydro-β-carbolines. Thus, hydrogenolysis of (**11f**) had yielded (**11e**), the stereochemistry of which was now known. Therefore, the C-1 epimer of (**11f**) must have had the (1*R*,3*S*)-configuration (**12f**). Chemical modifications of (**12b**) and (**12f**) were then performed, as outlined in Scheme 3, and single diastereoisomers were obtained from all the reactions.

Furthermore, when (**11a**) was treated with the tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorato] derivative of europium(III) in $CDCl_3$, the chiral shift reagent caused one of the methyl peaks at δ 3.75 in the ^1H n.m.r. spectrum to be shifted markedly downfield without any splitting of the singlet, suggesting that little or no racemisation had occurred. It was thus apparent that the product of the modified Pictet–Spengler reaction had been formed with high optical purity.

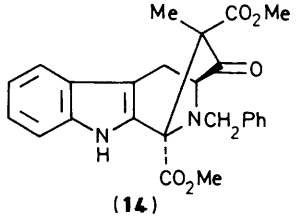


(**12b**) or (**12f**) (**12d**) or (**12h**)

(**12a**) or (**12e**) (**12c**) or (**12g**)

Scheme 3. *Reagents:* i, MeI/NaH; ii, H_2/Pd-C. R = H for (**12a—d**), and R = CO_2Me for (**12e—h**)

Confirmation that compound (**11f**) was indeed the (1*S*,3*S*)-isomer was obtained when N^{in}-methylation was attempted; treatment of (**11f**) with sodium hydride, followed by the addition of iodomethane, led to the formation of diastereomerically pure ketone (**14**), instead of the expected tri-ester (**11g**). However, it was subsequently ascertained that N^{in}-methylation could be accomplished cleanly by the addition of sodium hydride to a mixture of the N^{b}-benzyltetrahydro-β-carboline and iodomethane in DMF.



(**14**)

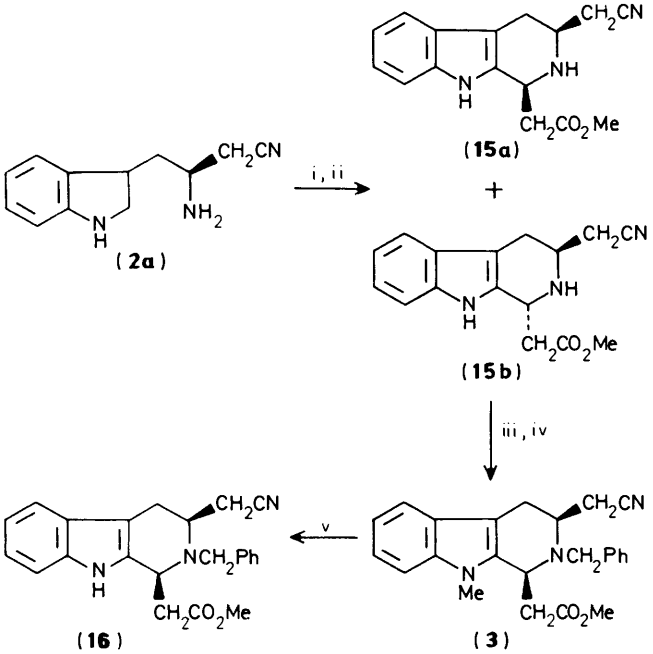
Thus, we were able to prepare unambiguously the (1*R*,3*S*)-diastereoisomers (**12a—h**) of all the tetrahydro-β-carbolines that had been prepared by the modified Pictet–Spengler reactions. By comparison of the ^{13}C n.m.r. spectra from these pure diastereoisomers with those from the modified Pictet–

Table.

Compound	R^1	R^2	R^3	Yield (%) of (1*S*,3*S*) + (1*R*,3*S*)*	Ratio of (1*S*,3*S*): (1*R*,3*S*)*
(11)/(12) **a**	H	H	H	50%	71:29
(11)/(12) **b**	H	CH_2Ph	H	45%	27:73
(11)/(12) **c**	Me	H	H	44%	37:63
(11)/(12) **d**	Me	CH_2Ph	H	25%	28:72
(11)/(12) **e**	H	H	CO_2Me	91%	68:32
(11)/(12) **f**	H	CH_2Ph	CO_2Me	51%	59:41
(11)/(12) **g**	Me	H	CO_2Me	99%	55:45
(11)/(12) **h**	Me	CH_2Me	CO_2Me	—	—
(3) + C-1 epimer†	H	H	H	49%	77:23

* Compounds (**11a**—**h**) are (1*S*,3*S*); (**12a**—**h**) are (1*R*,3*S*). † Compound (**3**) is (1*S*,3*S*), *cis*-isomer.

Spengler [which were a mixture of C-1 epimers], it was possible to assign and quantify the stereochemical outcome of the addition/cyclisation sequence, as reported in a preliminary communication.[8] As expected, the reactions with dimethyl butynedioate showed very little stereoselectivity, almost certainly due to the similarity in size of the two C-1 substituents. For the methyl propynoate adducts, the *cis*/*trans* ratio showed some stereoselectivity, with the *trans* being favoured in all cases except (**11a**)/(**12a**), in which unsubstituted tryptophan methyl ester was used. Particularly noticeable was that N^{in}-methylation and/or N^{a}-benzylation of the tryptophan methyl ester resulted in an increased proportion of *trans* product, and this generalisation has also been observed for the standard Pictet–Spengler reaction (*e.g.* ref. 9).



Scheme 4. *Reagents*: i, $CH{\equiv}CCO_2Me$; ii, TFA; iii, $PhCH_2Br$–$NaHCO_3$–CH_2Cl_2; iv, separate diastereoisomers; v, MeI–DMF then NaH

At this point, we felt that we were in a good position to apply the modified Pictet–Spengler reaction to the synthesis of the key cyano ester (**3**). In order to maximise the proportion of *cis*-diastereoisomer, we chose to N^{b}-benzylate and N^{in}-methylate after the formation of the tetrahydro-β-carboline. This tactic proved to be successful, and the addition/cyclisation reaction of methyl propynate with the tryptophan homologue (**2a**)[10] led to a 49% yield of isolated tetrahydro-β-carboline, in which the *cis*-isomer (**15a**) predominated over the C-1 epimer (**15b**) by a ratio of *ca.* 3:1. These diastereoisomers were N^{b}-benzylated, and then separated by flash chromatography. The optical activity of the C-1 epimer of (**16**) {$[\alpha]_D^{25}$ +97.4° (*c* 0.01 in MeOH)} indicated that chirality had been retained throughout the synthetic sequence; the high optical purity was confirmed by ^{1}H n.m.r. of the debenzylated product (H_2/Pd–C), which failed to reveal any splitting of the methyl ester singlet at δ 3.75 when Eu^{III} chiral shift reagent was added. Finally, N^{in}-methylation of the *cis*-isomer (**16**) yielded the desired cyano ester (**3**), as outlined in Scheme 4.

In conclusion, we have shown that the modified Pictet–Spengler reaction can be extended to the formation of optically active tetrahydro-β-carbolines, and leads to the formation of tricyclic products with specific functionality that is difficult to obtain by other methods. Furthermore, whilst the reactions do not proceed with high stereospecificity, some stereoselectivity can be induced by a judicious choice of the N^{in} and N^{b} substituents. With these observations in mind, we have shown that this method can be applied to the synthesis of cyano ester (**3**), a key intermediate in the synthesis of several alkaloids of the ajmaline group.

Experimental

M.p.s were determined on a Reichert microscope hot-stage apparatus, and are uncorrected. I.r. spectra were recorded on a Pye-Unicam SP3-200 spectrophotometer. N.m.r. spectra were recorded on a JEOL FX90Q spectrometer at 90 MHz (^{1}H) or 22.5 MHz (^{13}C), unless otherwise stated; chemical shifts are quoted in p.p.m. downfield from Me_4Si as internal standard. Mass spectra were obtained by electron impact at 70 eV on an A.E.I. MS3074 spectrometer. All solvents were purified and dried by standard methods. Flash chromatography[5] was carried out using silica as the stationary phase.

Bischler–Napieralski Reaction.—(S)-2-[2-(*Ethoxycarbonyl*)-*acetamido*]-4-(1-*methylindol*-3-*yl*)*butyronitrile* (**2c**).—Ethyl malonyl chloride (222 mg, 1.47 mmol) was added dropwise to a solution of compound (**2b**) in dichloromethane stirred over solid $NaHCO_3$ at 0 °C. After 15 min the reaction was quenched by the addition of water, which was made alkaline with 6M-NaOH(aq). The organic layer was dried ($MgSO_4$), and evaporated to yield the crude amide (**2c**), which was purified by flash chromatography (chloroform) as a light yellow oil (297 mg, 68%); $\nu_{max.}$(CH_2Cl_2) 3 460, 3 430, 2 240, 1 730, and 1 680 cm^{-1}; δ_H($CDCl_3$) 1.25 (3 H, t, *J* 7.1 Hz, CH_2CH_3), 2.32—2.85 (2 H, *ABX*, J_{AB} 16.9, J_{AX} 4.8, and J_{BX} 5.4 Hz, $ArCH_2CH$), 2.92—3.35 (4 H, m), 3.71 (3 H, s, NCH_3), 4.15 (2 H, q, *J* 7.1 Hz, CH_2CH_3), 4.32—4.55 (1 H, m, $ArCH_2CH$), 6.97 (1 H, s, indole 2-H), and 7.02—7.58 (4 H, m, ArH); δ_C($CDCl_3$) 14.02 (q), 22.04 (t), 28.82 (t), 32.66 (q), 41.36 (t), 46.90 (d), 61.65 (t), 108.54 (s), 109.45 (d), 117.38 (s), 118.71 (d), 118.94 (s), 119.43 (d), 122.05 (d), 127.71 (s), 127.86 (d), 137.23 (s), 165.26 (s), and 168.93 (s); *m*/*z* 327 (M^+), 196.

(3S)-3-*Cyanomethyl*-1-*ethoxycarbonylmethylene*-9-*methyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole* (**4**).—Phosphoryl chloride (1.40 g, 9.10 mmol), and compound (**2c**) (285 mg, 0.91 mmol) were stirred in anhydrous benzene for 24 h. The mixture was then diluted with water, basified with 10M-ammonia solution and the organic layer separated, dried ($MgSO_4$), and evaporated. Flash chromatography (chloroform) of the residue yielded unchanged starting material (**2c**) (70 mg, 25%) and the *title compound* (**4**) (62 mg, 22%) as a white crystalline solid, m.p. 145.5—147 °C (from MeOH) (Found C, 69.65; H, 6.15; N, 13.4%; M^+, 309.1481. $C_{18}H_{19}N_3O_2$ requires C, 69.88; H, 6.19;

N, 13.58%; M^+, 309.1477); $\nu_{max.}(CH_2Cl_2)$ 3 380, 2 219, and 1 640 cm^{-1}; $\delta_H(CDCl_3)$ 1.31 (3 H, t, *J* 7.1 Hz, CH_2CH_3), 2.68 (2 H, d, *J* 6.8 Hz), 2.81—3.43 (2 H, *AB*X, J_{AB} 11.3, J_{AX} 6.8, and J_{BX} 5.3 Hz, $ArCH_2CH$), 3.92 (3 H, s, NCH_3), 4.19 (3 H, distorted q, *J* 7.1 Hz, CH_2CH_3 and $ArCH_2CH$), 5.18 (1 H, s, C=CH), 7.10—7.63 (4 H, m, ArH), and 8.98 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 14.59 (q), 23.31 (t), 25.91 (t), 32.79 (q), 47.03 (d), 59.11 (t), 81.81 (d), 110.04 (d), 113.67 (s), 117.03 (s), 119.2 (d), 120.28 (d), 124.72 (d + s), 128.08 (s), 140.00 (s), 148.66 (s), and 170.55 (s); *m/z* 309 (M^+), 269, 237, 223, and 144.

Modified Pictet–Spengler Reaction.—(1S,3S)- *and* (1R,3S)-3-*Methoxycarbonyl*-1-*methoxycarbonylmethyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indoles* (**11a**)/(**12a**).—(*S*)-Tryptophan methyl ester (449 mg, 2.05 mmol) and methyl propynoate (173 mg, 2.05 mmol) were stirred together in trichloromethane for 60 h, after which time t.l.c. analysis indicated the absence of starting material. Trifluoroacetic acid (563 mg, 4.94 mmol, 2.4 mol equiv.) was then added in two equal portions, with a 5 min interval, and stirring was continued for a further 10 min. The reaction mixture was then poured into water and basified with 6M-NaOH (aq); the organic layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography (ethoxyethane–trichloromethane, 2:1) of this crude product yielded a mixture of the title compounds (**11a**)/(**12a**) (310 mg, 50%) in a ratio of 7:3; $\nu_{max.}(CH_2Cl_2)$ 3 415 and 1 730 cm^{-1}; $\delta_H(CDCl_3)$ 2.75—3.28 (4 H, m, $ArCH_2$ and CH_2CO_2Me), 3.71—3.73 (6 H, comprising 3 resolved singlets, CO_2Me), 4.51—4.73 (1 H, m, $ArCH_2CH$), 7.02—7.48 (4 H, m, ArH), and 8.78—8.89 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 25.20 (t), 25.79 (t), 40.31 (t), 40.90 (t), 46.86 (d), 49.41 (d), 52.01 (q), 52.17 (q), 52.71 (d), 56.40 (d), 107.05 (s), 108.19 (s), 111.11 (d), 118.05 (d), 119.51 (d), 121.95 (s), 126.82 (s), 134.24 (s), 135.98 (s), 173.36 (s), and 173.95 (s); *m/z* 302 (M^+), 243 and 229. Crystallisation from ethanol–ethoxyethane afforded the diastereoisomerically pure *title compound* (**11a**) as a white crystalline solid, m.p. 54—56 °C (Found: M^+, 302.1260. $C_{16}H_{18}N_2O_4$ requires M^+, 302.1266); $\nu_{max.}(CH_2Cl_2)$ 3 420 and 1 725 cm^{-1}; $\delta_H(CDCl_3)$ 2.60 (1 H, br, aliphatic NH) 2.81 (2 H, d, *J* 6.6 Hz), 2.88—3.25 (2 H, m), 3.72 (3 H, s), 3.79 (3 H, s), 4.50 (1 H, m), 4.61—4.72 (1 H, m), 7.01—7.50 (4 H, m), and 8.80 (1 H, br); $\delta_C(CDCl_3)$ 25.68 (t), 39.93 (t), 49.46 (d), 52.12 (q), 52.22 (q), 56.34 (d), 108.02 (s), 111.11 (d), 117.99 (d), 119.40 (d), 121.84 (d), 126.82 (s), 134.08 (s), 136.03 (s), 173.14 (s), and 173.36 (s); *m/z* 302 (M^+), 243, and 229.

(1S,3S)- *and* (1R,3S)-2-*Benzyl*-3-*methoxycarbonyl*-1-*methoxycarbonylmethyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indoles* (**11b**)/(**12b**).—(*S*)-N^{α}-Benzyltryptophan methyl ester (253 mg, 0.82 mmol) and methyl propynoate (69 mg, 0.82 mmol) were allowed to react in trichloromethane for 120 h after which the mixture was acidified with TFA and worked up as for (**11a**)/(**12a**). Flash chromatography (trichloromethane) yielded a mixture of the title compounds (**11b**)/(**12b**) (145 mg, 45%), in a ratio of 27:73; $\nu_{max.}(CH_2Cl_2)$ 3 435 and 1 725 cm^{-1}; $\delta_H(CDCl_3)$ 2.52—3.32 (4 H, m, $ArCH_2$ and CH_2CO_2Me), 3.60—3.72 (6 H, comprising 4 resolved singlets, CO_2CH_3), 3.74—4.41 (4 H, m, CH_2Ph, $ArCH_2CH$ and $CHCH_2CO_2Me$), 7.05—7.55 (9 H, m, ArH), 8.55—8.72 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 21.13 (t), 21.45 (t), 37.92 (t), 40.52 (t), 51.90 (q), 52.22 (d), 52.80 (d), 53.52 (t), 57.10 (d), 57.53 (d), 57.91 (t), 105.80 (s), 106.83 (s), 111.00 (d), 118.10 (d), 119.35 (d), 121.84 (d), 126.61 (s), 127.10 (d), 127.31 (m), 128.29 (d), 128.50 (d), 133.76 (s), 135.92 (s), 138.80 (s), 139.23 (s), 172.98 (s), 173.47 (s), 174.28 (s); *m/z* 392 (M^+), 333, 319, 301, and 91. Crystallisation from ethanol afforded the *title compound* (**12b**) as a white crystalline solid, which was subjected to single crystal *X*-ray structure determination, m.p. 138—139.5 °C (Found: M^+, 392.1737. $C_{23}H_{24}N_2O_4$ requires M^+, 392.1736); $\nu_{max.}(CH_2Cl_2)$ 3 430 and 1 725 cm^{-1}; $\delta_H(CDCl_3$; 400 MHz) 2.79 (1 H, dd, *J* 10.1, 17.1 Hz, $CHHCO_2Me$), 2.95 (1 H, dd, *J* 4.0, 17.1 Hz, $CHHCO_2Me$), 3.04 (1 H, dd, *J* 5.0, 16.0 Hz, $ArCHH$), 3.17 (1 H, ddd, *J* 1.0, 9.5, 16.1 Hz, $ArCHH$), 3.65 (3 H, s, CO_2CH_3), 3.68—3.89 (2 H, AB quartet centred on 3.79, *J* 14.1 Hz, CH_2Ph), 3.74 (3 H, s, CO_2CH_3), 3.98 (1 H, dd, *J* 5.0, 9.5 Hz, $ArCH_2CH$), 4.32 (1 H, dd, *J* 4.0, 10.1 Hz, $CHCH_2CO_2Me$), 7.05—7.55 (9 H, m, ArH), and 8.60 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 21.32 (t), 40.70 (t), 51.90 (q), 52.42 (d), 53.70 (t), 57.73 (d), 107.00 (s), 111.09 (d), 118.20 (d), 119.46 (d), 121.93 (d), 126.82 (s), 127.17 (d), 128.39 (d), 128.57 (d), 133.93 (s), 136.08 (s), 139.34 (s), 173.07 (s), and 173.60 (s); *m/z* 392 (M^+), 333, 319, 301, and 91.

(1S,3S)- *and* (1R,3S)-3-*Methoxycarbonyl*-1-*methoxycarbonylmethyl*-9-*methyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indoles* (**11c**)/(**12c**).—(*S*)-N^{in}-Methyltryptophan methyl ester (350 mg 1.51 mmol) and methyl propynoate (127 mg, 1.51 mmol) were allowed to react in trichloromethane for 24 h after which the mixture was acidified with TFA, and worked up as for (**11a**)/(**12a**). Flash chromatography (trichloromethane–ethoxyethane, 2:1) yielded a mixture of the title compounds (**11c**)/(**12c**) (210 mg, 44%), in a ratio of 37:63; $\delta_H(CDCl_3)$ 2.50—3.38 (4 H, m, $ArCH_2$ and CH_2CO_2Me), 3.53—3.78 (9 H, comprising 6 resolved singlets, CO_2CH_3, and NCH_3), 3.80—4.11 (1 H, m), 4.61—4.78 (1 H, m), and 6.98—7.52 (4 H, m, ArH); $\delta_C(CDCl_3)$ 25.42 (t), 25.85 (t), 29.70 (q), 30.89 (q), 38.85 (t), 40.48 (t), 47.20 (d), 48.88 (d), 50.99 (d), 51.85 (q), 52.07 (q), 55.65 (d), 106.84 (s), 108.85 (d + s), 118.00 (d), 119.19 (d), 121.63 (d), 126.34 (s), 134.25 (s), 134.90 (s), 137.23 (s), 138.00 (s), 171.53 (s), 171.74 (s), and 173.04 (s), 173.84 (s). Crystallisation from ethanol afforded the *title compound* (**12c**) as colourless needles, m.p. 143—144.5 °C (Found: M^+, 316.1427. $C_{17}H_{20}N_2O_4$ requires M^+, 316.1423); $\nu_{max.}(CH_2Cl_2)$ 1 745 cm^{-1}; $\delta_H(CDCl_3)$ 2.56 (1 H, br, NH), 2.73 (2 H, m), 2.65—3.26 (2 H, *AB*X, J_{AB} 15.5, J_{AX} 9.4 and J_{BX} 5.0 Hz), 3.63 (3 H, s), 3.76 (3 H, s), 3.79 (3 H, s), 3.93 (1 H, dd, *J* 4.8 and 9.8 Hz), 4.75 (1 H, dd, *J* 4.9 and 8.6 Hz), and 7.01—7.52 (4 H, m, ArH); $\delta_C(CDCl_3)$ 25.58 (t), 29.86 (q), 39.07 (t), 47.30 (d), 51.15 (d), 51.96 (q), 52.18 (q), 107.06 (s), 108.90 (d), 118.16 (d), 119.36 (d), 121.74 (d), 126.51 (2), 135.07 (s), 137.40 (s), 171.69 (s), and 173.69 (s); *m/z* 316 (M^+), 257, and 243.

(1S,3S)- *and* (1R,3S)-2-*Benzyl*-3-*methoxycarbonyl*-1-*methoxycarbonylmethyl*-9-*methyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indoles* (**11d**)/(**12d**).—(*S*)-N^{α}-Benzyl-N^{in}-methyltryptophan methyl ester (188 mg, 0.58 mmol) and methyl propynoate (49 mg, 0.58 mmol) were allowed to react in trichloromethane for 240 h after which the mixture was acidified with TFA, and worked up as for (**11a**)/(**12a**). Flash chromatography (trichloromethane) yielded a mixture of the title compounds (**11d**)/(**12d**) (60 mg, 25%) in a ratio of 28:72 (Found: M^+, 406.1894. $C_{24}H_{26}N_2O_4$ requires M^+, 406.1892); $\nu_{max.}(CH_2Cl_2)$ 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 2.61—290 (2 H, m), 2.92—3.17 (2 H, m), 3.32—3.78 (11 H, comprising 6 resolved singlets due to CO_2CH_3 and NCH_3, and a multiplet due to CH_2Ph), 3.92—4.09 (1 H, m, $ArCH_2CH$), 4.15—4.36 (1 H, m, $CHCH_2CO_2Me$), and 7.08—7.62 (9 H, m, ArH); $\delta_C(CDCl_3)$ 19.12 (t), 20.26 (t), 29.71 (q), 29.87 (q), 39.43 (t), 40.30 (t), 51.67 (q), 52.01 (q), 52.73 (d), 53.01 (t), 53.88 (d), 55.29 (d), 56.27 (d), 60.50 (t), 106.1 (s), 107.15 (s), 109.00 (d), 118.41 (d), 119.21 (d), 119.43 (d), 121.81 (d), 126.64 (s), 127.17 (d), 127.39 (d), 128.07 (d), 128.38 (d), 128.80 (d), 129.14 (d), 134.00 (s), 134.27 (s), 137.63 (s), 138.95 (s), 170.63 (s), 172.96 (s), and 174.50 (s); *m/z* 406 (M^+), 347, 333, 315, and 91. Attempts to separate these diastereoisomers were unsuccessful.

(1S,3S)- *and* (1R,3S)-1,3-*Dimethoxycarbonyl*-1-*methoxycarbonylmethyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indoles* (**11e**)/(**12e**).—(*S*)-Tryptophan methyl ester (240 mg, 1.1 mmol)

and dimethyl butynedioate (157 mg, 1.1 mmol) were allowed to react in trichloromethane for 5 min, after which the mixture was acidified with TFA, and worked up as for (**11a**)/(**12a**). This yielded a mixture of the title compounds (**11e**)/(**12e**) (360 mg, 91%), in a ratio of 68:32, and homogeneous by t.l.c. (Found: C, 59.5; H, 5.65; N, 7.9%; M^+, 360.1325. $C_{18}H_{20}N_2O_6$ requires C, 59.99, H, 5.59; N, 7.77%; M^+, 360.1321); $\nu_{max.}(CH_2Cl_2)$ 3 438 and 1 735 cm^{-1}; $\delta_H(CDCl_3)$ 2.70—3.55 (4 H, m, $ArCH_2$ and CH_2CO_2Me), 3.64—3.79 (9 H, comprising 4 resolved singlets, CO_2CH_3), 4.15—4.32 (1 H, m, $ArCH_2CH$), 7.02—7.56 (4 H, m, ArH), and 8.80—8.89 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 24.71 (t), 25.31 (t), 42.86 (t), 45.14 (t), 51.58 (q), 51.69 (q), 51.91 (q), 52.23 (d), 52.61 (q), 52.99 (q), 53.16 (q), 53.43 (d), 59.82 (s), 108.00 (s), 109.82 (s), 111.07 (d), 118.16 (d), 119.36 (d), 122.28 (d), 126.07 (s), 126.24(s), 129.70 (s), 130.08 (s), 135.98 (s), 136.37 (s), 170.28 (s), 171.09 (s), 172.17 (s), 172.72 (s), and 173.37 (s); *m/z* 360 (M^+), 301, and 287. Attempts to separate these diastereoisomers were unsuccessful.

(1S,3S)- *and* (1R,3S)-2-*Benzyl*-1,3-*dimethoxycarbonyl*-1-*methoxycarbonylmethyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indoles* (**11f**)/(**12f**).—(*S*)-N^{α}-Benzyltryptophan methyl ester (1.26 g, 4.1 mmol) and dimethyl butynedioate (581 mg, 4.1 mmol) were allowed to react in trichloromethane for 10 min after which the mixture was acidified with TFA and worked up as for (**11a**)/(**12a**). Flash chromatography (trichloromethane) yielded (**11f**) and (**12f**) (0.94 g, 51% total yield), both as white foams, in a ratio of 59:41. The first eluted component was the *title compound* (**11f**), m.p. 61—63 °C [from Et_2O–light petroleum (b.p. 40—60 °C)] (Found: M^+, 450.1798. $C_{25}H_{26}N_2O_6$ requires M^+, 450.1791); $\nu_{max.}(CH_2Cl_2)$ 3 400 and 1 730 cm^{-1}; $\delta_H(CDCl_3)$ 2.89—3.60 (4 H, m, $ArCH_2$ and CH_2CO_2Me), 3.61 (3 H, s, CO_2CH_3), 3.75 (3 H, s, CO_2CH_3), 3.77 (3 H, s, CO_2CH_3), 4.00 (1 H, m, $ArCH_2CH$), 4.00—4.43 (2 H, AB quartet CH_2Ph), 7.05—7.56 (9 H, m, ArH), and 9.91 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 25.20 (t), 41.02 (t), 52.78 (q), 53.37 (q), 53.97 (t), 54.51 (q), 57.27 (d), 65.72 (s), 108.63 (s), 112.64 (d), 119.63 (d), 120.39 (d), 123.42 (d), 127.32 (s), 128.40 (d), 128.84 (d), 129.70 (d), 133.72 (s), 137.45 (s), 140.70 (s), 173.53 (s), 175.21 (s), and 175.75 (s); *m/z* 450 (M^+), 391, 377, 359, and 91. The lower R_F component was the title compound (**12f**), m.p. 159.5—161.5 °C (from EtOH) (Found: M^+, 450.1798. $C_{25}H_{26}N_2O_6$ requires M^+, 450.1791); $\nu_{max.}(CH_2Cl_2)$ 3 420 and 1 725 cm^{-1}; $\delta_H(CDCl_3)$ 2.82—3.42 (2 H, *AB*X, J_{AB} 14.4, J_{AX} 5.6 and J_{BX} 2.3 Hz, $ArCH_2CH$), 2.76—3.76 (2 H, AB quartet, *J* 15.7 Hz, CH_2CO_2Me), 3.53 (3 H, s, CO_2CH_3), 3.62 (3 H, s, CO_2CH_3), 3.66 (3 H, s, CO_2CH_3), 3.78 (1 H, dd, *J* 2.2 and 5.5 Hz, $ArCH_2CH$), 4.02—4.87 (2 H, AB quartet, *J* 15.5 Hz, CH_2Ph), 7.01—7.58 (9 H, m, ArH), and 8.92 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 23.65 (t), 44.53 (t), 51.61 (q), 51.73 (t), 52.00 (q), 56.39 (d), 62.20 (s), 108.00 (s), 111.24 (d), 118.54 (d), 119.25 (d), 122.33 (d), 126.17 (s), 127.10 (d), 127.65 (d), 128.51 (d), 132.16 (s), 136.43 (s), 140.06 (s), 171.09 (s), and 173.05 (s); *m/z* 450 (M^+), 391, 377, 359, and 91.

(1S,3S)- *and* (1R,3S)-1,3-*Dimethoxycarbonyl*-1-*methoxycarbonylmethyl*-9-*methyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]-*indoles* (**11g**)/(**12g**).—(*S*)-N^{in}-Methyltryptophan methyl ester (0.80 g, 3.44 mmol) and dimethyl butynedioate (0.49 g, 3.44 mmol) were allowed to react in trichloromethane for 10 min after which the mixture was acidified with TFA, and worked up as for (**11a**)/(**12a**). This yielded a mixture of the title compounds (**11g**)/(**12g**) (1.28 g, 99%), in a ratio of 55:45; t.l.c. indicated an absence of impurities. Flash chromatography (toluene–ethoxyethane, 3:1) yielded (**11g**) and (**12g**) as white foams, which were recrystallised from ethanol. Compound (**11g**), R_F 0.35, m.p. 82—84 °C (Found: M^+, 374.1490. $C_{19}H_{22}N_2O_6$ requires M^+, 374.1478); $\nu_{max.}(CH_2Cl_2)$ 1 725 cm^{-1}; $\delta_H(CDCl_3)$ 2.35 (1 H, br, NH), 2.68—3.34 (2 H, *AB*X, J_{AB} 15.1, J_{AX} 11.2, and J_{BX} 4.2 Hz, $ArCH_2CH$), 2.87—3.70 (2 H, AB quartet, *J* 16.3 Hz, CH_2CO_2Me), 3.65 (3 H, s), 3.75 (3 H, s), 3.82 (3 H, s), 3.83 (3 H, s), 4.34 (1 H, dd, *J* 4.3 and 11.1 Hz, $ArCH_2CH$), and 7.01—7.59 (4 H, m, ArH); $\delta_C(CDCl_3)$ 25.54 (t), 31.46 (q), 43.10 (t), 51.96 (q), 52.19 (q), 52.80 (q), 53.48 (d), 60.82 (s), 109.28 (d), 111.20 (s), 118.61 (d), 119.60 (d), 122.64 (d), 126.00 (s), 130.67 (s), 138.48 (s), 170.86 (s), 173.19 (s), and 173.48 (s); *m/z* 374 (M^+), 315, and 301. Compound (**12g**), R_F (0.26), m.p. 128—129 °C (Found: M^+, 374.1480. $C_{19}H_{22}N_2O_6$ requires M^+, 374.1478); $\nu_{max.}(CH_2Cl_2)$ 1 725 cm^{-1}; $\delta_H(CDCl_3)$ 2.76—3.35 (2 H, AB quartet, *J* 13.6 Hz, CH_2CO_2Me), 2.76—3.30 (2 H, *AB*X, J_{AB} 15.3, J_{AX} 10.9, and J_{BX} 4.6 Hz, $ArCH_2CH$), 3.63 (3 H, s), 3.70 (3 H, s), 3.74 (3 H, s), 3.76 (3 H, s), and 7.01—7.54 (4 H, m, ArH); $\delta_C(CDCl_3)$ 24.43 (t), 29.80 (q), 38.30 (t), 50.82 (q), 51.09 (q), 51.19 (q), 52.28 (q), 60.78 (s), 108.13 d), 108.67 (s), 117.50 (d), 118.53 (d), 121.51 (d), 124.82 (s), 130.83 (s), 137.01 (s), 169.62 (s), 171.19 (s), and 171.57 (s); *m/z* 374 (M^+), 315, and 301.

(1S,3S)- *and* (1R,3S)-2-*Benzyl*-1,3-*dimethoxycarbonyl*-1-*methoxycarbonylmethyl*-9-*methyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indoles* (**11h**)/(**12h**).—(*S*)-N^{α}-Benzyl-N^{in}-methyltryptophan methyl ester and dimethyl butynedioate were allowed to react as in the preparation of (**11a**)/(**12a**), and yielded a complex mixture from which the desired products, (**11h**)/(**12h**), could not be isolated.

Interconversion of Pictet–Spengler Products.—Hydrogenolysis of (**11f**). The benzyl derivative (**11f**) (137 mg, 0.304 mmol) was dissolved in ethanol and subjected to catalytic hydrogenolysis over 5% Pd–C for 40 min at atmospheric pressure. The catalyst was filtered off and the solvent evaporated to give (1S,3S)-1,3-*dimethoxycarbonyl*-1-*methoxycarbonylmethyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole* (**11e**) (102 mg, 92%) as a white foam; this crystallised from ethanol as colourless prisms and was subjected to a single-crystal *X*-ray structure determination; m.p. 165—166.5 °C (Found: M^+, 360.1322. $C_{18}H_{20}N_2O_6$ requires 360.1321); $\nu_{max.}(CH_2Cl_2)$ 3 450 and 1 735 cm^{-1}; $\delta_H(CDCl_3)$ 2.68—3.31 (2 H, *AB*X, J_{AB} 15.1, J_{AX} 11.3, and J_{BX} 4.2 Hz, $ArCH_2CH$), 2.81—3.55 (2 H, AB quartet, *J* 16.8 Hz, CH_2CO_2Me), 3.72 (3 H, s, CO_2CH_3), 3.77 (3 H, s, CO_2CH_3), 3.83 (3 H, s, CO_2CH_3), 4.15 (1 H, dd, *J* 4.2 and 10.9 Hz, CH_2CHCO_2Me), 7.01—7.58 (4 H, m, ArH), and 8.49 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 25.03 (t), 45.67 (t), 52.12 (q), 52.33 (q), 52.98 (q), 53.74 (d), 60.08 (s), 110.41 (s), 111.33 (d), 118.59 (d), 119.83 (d), 122.71 (d), 126.44 (s), 130.02 (s), 136.63 (s), 171.41 (s), 172.87 (s), and 173.74 (s); *m/z* 360 (M^+), 301, and 287.

Hydrogenolysis of (**12b**). The benzyl derivative (**12b**) (100 mg, 0.255 mmol) was hydrogenolysed for 30 min as for (**11f**) to give (1R,1S)-3-*methoxycarbonyl*-1-*methoxycarbonylmethyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole* (**12a**) (74 mg, 96%) as a white foam which could not be crystallised (Found: M^+, 302.1260. $C_{16}H_{18}N_2O_4$ requires M^+, 302.1266); $\nu_{max.}(CH_2Cl_2)$ 3 455 and 1 735 cm^{-1}; $\delta_H(CDCl_3)$ 2.89 (2 H, d, *J* 7.0 Hz), 3.07 (2 H, d, *J* 5.5 Hz), 3.71 (3 H, s, CO_2CH_3), 3.73 (3 H, s, CO_2CH_3), 3.98 (1 H, dd, *J* 5.3 and 7.7 Hz), 4.50 (1 H, br, NH), 4.77 (1 H, br t, *J* 6.9 Hz), 7.01—7.48 (4 H, ArH), and 8.80 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 24.70 (t), 40.20 (t), 46.97 (d), 52.12 (q), 52.33 (q), 52.66 (d), 106.72 (s), 111.17 (d), 118.10 (d), 119.45 (d), 122.06 (d), 126.55 (s), 133.27 (s), 135.87 (s), and 173.19 (s); *m/z* 302 (M^+), 243, and 229.

Hydrogenolysis of (**12d**). The benzyl derivative (**12d**) (150 mg, 0.368 mmol) was hydrogenolysed for 30 min as for (**11f**) to give (**12c**) (110 mg, 94%), which was identical in all respects with (**12c**) that had been prepared directly by the modified Pictet–Spengler reaction.

Hydrogenolysis of (**12f**). The benzyl derivative (**12f**) (105 mg, 0.23 mmol) was hydrogenolysed as for (**11f**) to give (1R,3S)-1,3-

dimethoxycarbonyl-1-*methoxycarbonylmethyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole* (**12e**) (82 mg, 98%) as a white foam, which could be recrystallised from ethanol; m.p. 142—143 °C (Found: M^+, 360.1325. $C_{18}H_{20}N_2O_6$ requires M^+, 360.1321); $\nu_{max.}(CH_2Cl_2)$ 3 450 and 1 735 cm^{-1}; $\delta_H(CDCl_3)$ 2.68—3.24 (2 H, *AB*X, J_{AB} 15.2, J_{AX} 10.4, and J_{BX} 4.6 Hz, ArCH_2CH), 2.91—3.43 (2 H, AB quartet, J 16.1 Hz, CH_2-CO_2Me), 3.70 (3 H, s, CO_2CH_3), 3.81 (3 H, s, CO_2CH_3), 3.85 (3 H, s, CO_2CH_3), 3.85 (1 H, m, ArCH$_2$CH), 7.01—7.53 (4 H, m, ArH), 8.45 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 25.46 (t), 43.34 (t), 52.01 (q), 52.28 (q), 52.55 (d), 53.36 (q), 60.13 (s), 109.32 (s), 111.33 (d), 118.53 (d), 119.78 (d), 122.81 (d), 126.55 (s), 130.34 (s), 136.19 (s), 170.54 (s), 172.44 (s), and 172.87 (s); *m/z* 360 (M^+), 301, and 287.

Hydrogenolysis of (**12h**). The benzyl derivative (**12h**) (50 mg, 0.018 mmol) was hydrogenolysed for 50 min, as for (**11f**), giving (**12g**) (38 mg, 94%), which was identical in all respects with (**12g**) that had been prepared directly by the modified Pictet–Spengler reaction.

N^{in}-*Methylation of* (**12b**).—Sodium hydride (80% dispersion in oil; 11 mg, 0.44 mmol, 1.5 equiv.) was added to a stirred solution of (**12b**) (116 mg, 0.30 mmol) in dimethylformamide (3 ml) at 0 °C. After 15 min, the reaction mixture was allowed to warm to room temperature when iodomethane (46 mg, 0.33 mmol, 1.05 equiv.) was added, and stirring continued for 30 min. The mixture was then evaporated under reduced pressure and the residue taken up in trichloromethane; this solution was washed with water, dried ($MgSO_4$), and evaporated to yield the single diastereoisomer (1R,3S)-2-*benzyl*-3-*methoxycarbonyl*-1-*methoxycarbonylmethyl*-9-*methyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole* (**12d**) (80 mg, 67%) as a white foam which could not be crystallised (Found: M^+, 406.1892. $C_{24}H_{26}N_2O_4$ requires 406.1892); $\nu_{max.}(CH_2Cl_2)$ 1 735 cm^{-1}; $\delta_H(CDCl_3$; 400 MHz) 2.62 (1 H, dd, J 3.9, 14.2 Hz, CHHCO$_2$Me), 2.73 (1 H, dd, J 10.4, 14.1 Hz, CHHCO$_2$Me), 3.07 (1 H, dd, J 5.0, 15.8 Hz, ArCHH), 3.16 (1 H, ddd, J 1.0, 11.0, 15.7 Hz, ArCHH), 3.40—3.85 (2 H, AB quartet centred on 3.62, J 13.6 Hz, CH_2Ph), 3.55 (3 H, s), 3.58 (3 H, s), 3.79 (3 H, s), 4.18 (1 H, dd, J 5.0, 10.9 Hz, ArCH$_2$CH), 4.28 (1 H, dd, J 3.9, 10.4 Hz, CHCH$_2$CO$_2$Me), and 7.09—7.59 (9 H, m, ArH); $\delta_C(CDCl_3)$ 20.22 (t), 29.75 (q), 40.26 (t), 51.75 (q), 52.13 (q), 52.67 (t), 52.99 (d), 56.24 (d), 107.11 (s), 109.01 (d), 118.38 (d), 119.46 (d), 121.79 (d), 126.56 (s), 127.16 (d), 128.08 (d), 129.16 (d), 134.15 (s), 137.56 (s), 138.91 (s), 170.61 (s), and 173.00 (s); *m/z* 406 (M^+), 347, 333, 315, and 91.

N^{in}-*Methylation of* (**12f**). This reaction was carried out as described for the N^{in}-methylation of (**12b**), using (**12f**) (100 mg, 0.22 mmol). Anion formation took place at 0 °C for 30 min, and then at room temperature for 30 min; quenching with iodomethane, and subsequent work-up, yielded (1R,3S)-2-*benzyl*-1,3-*dimethoxycarbonyl*-1-*methoxycarbonylmethyl*-9-*methyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole* (**12h**) (60 mg, 58%) as a white foam which could not be crystallised (Found: M^+, 464.1952. $C_{26}H_{28}N_2O_6$ requires M^+, 464.1947); $\nu_{max.}(CH_2Cl_2)$ 1 735 cm^{-1}; $\delta_H(CDCl_3)$ 2.69—3.37 (2 H, *AB*X, J_{AB} 15.1, J_{AX} 5.7, and J_{BX} 2.0 Hz, ArCH_2), 2.97—3.82 (2 H, AB quartet, J 14.8 Hz, CH_2CO$_2$Me), 3.28 (3 H, s), 3.50 (3 H, s), 3.58 (3 H, s), 3.70 (3 H, s), 3.82 (1 H, m, ArCH$_2$CH), 4.11—4.64 (2 H, AB quartet, J 14.1 Hz, CH_2Ph), and 7.01—7.59 (9 H, m, ArH); $\delta_C(CDCl_3)$ 23.13 (t), 30.88 (q), 39.93 (t), 51.19 (t + q), 51.41 (q), 52.06 (q), 54.07 (d), 63.55 (s), 108.84 (d), 110.03 (s), 118.64 (d), 118.97 (d), 121.95 (d), 125.74 (s), 127.26 (d), 128.45 (d), 128.66 (d), 138.31 (s), 138.80 (s), 169.08 (s), 170.81 (s), and 172.82 (s); *m/z* 464 (M^+), 405, 391, 373, 144, and 91.

N^{in}-*Methylation of* (**11f**).—Sodium hydride (1.05 equiv.) was added to a stirred solution of (**11f**) (129 mg, 0.29 mmol) and iodomethane (1.05 equiv.) in dimethylformamide (3 ml) after which the mixture was stirred first at 0 °C for 60 min, and then at room temperature for 30 min. Work-up was carried out as for the N^{in}-methylation of (**12b**), and yielded (1S,3S)-2-*benzyl*-1,3-*dimethoxycarbonyl*-1-*methoxycarbonylmethyl*-9-*methyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole* (**11h**) (77 mg, 58%) as a white foam which could not be crystallised (Found: M^+, 464.1947. $C_{26}H_{28}N_2O_6$ requires M^+, 464.1947); $\nu_{max.}(CH_2Cl_2)$ 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 2.83—3.50 (2 H, *AB*X, J_{AB} 15.1, J_{AX} 7.4, and J_{BX} 4.8 Hz, ArCH_2CH), 3.19 (3 H, s), 3.45 (3 H, s), 3.16—3.78 (2 H, AB quartet, J 16.4 Hz, CH_2CO$_2$Me), 3.67 (3 H, s), 3.74 (3 H, s), 3.80—4.30 (2 H, AB quartet, J 15.8 Hz, CH_2Ph), 4.09 (1 H, dd, J 4.7 and 7.6 Hz, ArCH$_2$CH), and 7.01—7.55 (9 H, m, ArH); $\delta_C(CDCl_3)$ 24.71 (t), 30.67 (q), 39.29 (t), 51.37 (q), 52.67 (q), 54.08 (t), 59.11 (q), 66.81 (s), 109.01 (d), 109.23 (s), 118.44 (d), 119.25 (d), 122.12 (d), 125.48 (s), 126.94 (d), 127.92 (d), 128.08 (d), 130.95 (s), 138.21 (s), 139.13 (s), 169.63 (s), 172.66 (s), and 172.93 (s); *m/z* 464 (M^+), 405, 391 373, 144, and 91.

Cyclisation of (**11f**).—When (**11f**) (121 mg, 0.27 mmol) was treated with sodium hydride, and quenched with iodomethane as in the N^{in}-methylation of (**12b**), the *tetracyclic ketone* (**14**) (67 mg, 58%) was obtained as a white foam after work-up; m.p. 95.5—98 °C (from Et_2O) (Found: M^+, 432.1688. $C_{25}H_{24}N_2O_5$ requires M, 432.1686); $\nu_{max.}(CH_2Cl_2)$ 3 460, 1 770, and 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 1.68 (3 H, s, $COCH_3$), 2.65—3.39 (2 H, AB quartet, J 16.6 Hz, ArCH_2), 3.13 (3 H, s, CO_2CH_3), 3.65 (1 H, m, ArCH$_2$CH), 3.53—4.02 (2 H, AB quartet, J 13.9 Hz, CH_2Ph), 3.98 (3 H, s, CO_2CH_3), 7.01—7.54 (9 H, m, aromatic), and 9.14 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 19.08 (q), 20.16 (t), 48.93 (t), 52.40 (q), 52.72 (q), 61.39 (d), 68.76 (s), 72.28 (s), 107.33 (s), 111.23 (d), 118.60 (d), 119.74 (d), 122.17 (d), 122.61 (d), 126.34 (s), 127.48 (d), 128.40 (d), 129.60 (s), 135.53 (s), 137.88 (s), 168.76 (s), 168.93 (s), and 2 J9.61 (s); *m/z* 432 (M^+), 404, 341, 317, and 91.

Preparation of Tetrahydro-β-*carboline* (**3**).—(1S,3S)- *and* (1R,3S)-3-(*Cyanomethyl*)-1-*methoxycarbonylmethyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indoles* (**15a**)/(**15b**). Compound (**2a**) (1.0 g, 5.02 mmol) and methyl propynoate (0.46 g, 5.52 mmol) were allowed to react in trichloromethane for 96 h, after which the mixture was acidified with TFA and worked up as for the modified Pictet–Spengler preparation of (**11a**)/(**12a**). Flash chromatography (trichloromethane–ether, 9:1) yielded an inseparable mixture of the title compounds (**15a**)/(**15b**) (0.69 g, 49%), in a ratio of 77:23 as a white foam (Found: M^+, 283.1327. $C_{16}H_{17}N_3O_2$ requires M^+, 283.1321); $\nu_{max.}(CH_2Cl_2)$ 3 455, 2 240, and 1 735 cm^{-1}; $\delta_H(CDCl_3)$ 1.82 (1 H, br, NH), 2.40—2.98 (6 H, m, CH_2s), 3.02—3.34 (1 H, m), 3.70 (3 H, s, CO_2CH_3), 4.38 (1 H, m), 6.95—7.48 (4 H, m, ArH), and 8.51—8.71 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 24.09 (t), 24.83 (t), 27.81 (t), 28.30 (t), 40.28 (t), 40.79 (t), 46.98 (d), 47.38 (d), 49.96 (d), 50.88 (d), 52.22 (q), 107.19 (s), 108.17 (s), 111.21 (d), 117.77 (s), 118.08 (d), 119.63 (d), 122.09 (d), 126.79 (s), 134.30 (s), 136.09 (s), 173.22 (s), and 173.39 (s); *m/z* 283 (M^+), 210.

(1S,3S)-2-*Benzyl*-3-*cyanomethyl*-1-*methoxycarbonylmethyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole* (**16**).—The isomeric mixture (**15a**)/(**15b**) (0.85 g, 3.0 mmol total) and benzyl bromide (0.77 g, 4.5 mmol) were heated under reflux in dichloromethane over solid $NaHCO_3$ for 96 h. The solution was then filtered and evaporated and the N^b-benzylated diastereoisomers were separated by flash chromatography (chloroform) to give the *cis*-isomer (1S,3S)-2-*benzyl*-3-*cyanomethyl*-1-*methoxycarbonylmethyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole* (**16**) [0.40 g, 39% from (**15a**)] as the first component, and then its C-1 epimer [0.12 g, 12% from (**15b**)], both as white foams. *Compound* (**16**) failed to crystallise (Found: M^+, 373.1789. $C_{23}H_{23}N_3O_2$ requires M^+, 373.1790); $\nu_{max.}(CH_2Cl_2)$ 3 435, 2 245, and 1 728 cm^{-1}; δ_H ($CDCl_3$) 2.25—3.28 (6 H, m, ArCH_2CHCH_2CN and

CH_2CO_2Me), 3.52—3.68 (1 H, m, $ArCH_2CH$), 3.73 (3 H, s, CO_2CH_3), 3.95 (2 H, s, CH_2Ph), 4.24—4.45 (1 H, m, $CHCH_2CO_2Me$), 7.03—7.55 (9 H, m, ArH), 8.75 (1 H, br, indole NH); $\delta_C(CDCl_3)$ 21.78 (t), 23.46 (t), 41.28 (t), 51.95 (q), 52.12 (d), 53.04 (d), 59.59 (t), 104.34 (s), 111.11 (d), 118.10 (d), 118.54 (s), 119.51 (d), 122.16 (d), 126.88 (s), 127.47 (d), 128.34 (d), 128.61 (d), 132.19 (s), 136.03 (s), 138.69 (s), and 174.01 (s); *m/z* 373 (M^+), 333, 300, 282, and 91. C-1 *Epimer of* (**16**); m.p. 143.5—145 °C (from Et_2O–light petroleum (b.p. 40—60 °C); $[\alpha]_D^{25}$ +97.4° (*c* 0.01 in MeOH) (Found: M^+, 373.1789. $C_{23}H_{23}N_3O_2$ requires M^+, 373.1789); $\nu_{max.}(CH_2Cl_2)$ 3 470, 2 250, and 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 2.59—2.88 (6 H, m, $ArCH_2CHCH_2CN$ and CH_2CO_2Me), 3.24—3.83 (2 H, AB quartet, *J* 14.1 Hz, CH_2Ph), *ca.* 3.45—3.60 (1 H, m, $ArCH_2CH$), 3.62 (3 H, s, CO_2CH_3), 4.15 (1 H, dd, *J* 6.1, 8.3 Hz, $CHCH_2CO_2Me$), 7.02—7.55 (9 H, m, ArH), 8.53 (1H, br, indole NH); $\delta_C(CDCl_3)$ 21.73 (t), 23.13 (t), 40.25 (t), 49.76 (t), 51.45 (d), 51.90 (q), 52.76 (d), 107.07 (s), 111.21 (d), 118.06 (s + d), 119.56 (d), 122.06 (d), 126.57 (s), 127.33 (d), 128.54 (d), 133.29 (s), 136.09 (s), 138.57 (s), and 173.19 (s); *m/z* 373 (M^+), 333, 300, 282, and 91.

(1S,3S)-2-*Benzyl*-3-*cyanomethyl*-1-*methoxycarbonylmethyl*-9-*methyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole* (**3**).—Sodium hydride (1.05 equiv.) was added to a stirred solution of (**16**) (377 mg, 1.00 mmol) and iodomethane (1.05 equiv.) in dimethylformamide and the mixture was stirred first at 0 °C for 30 min and then at room temperature for 60 min. Work-up was carried out as in the N^{in}-methylation of (**12b**), and afforded the title compound (**3**) (370 mg, 94%) as a white foam which could not be crystallised (Found: M^+, 387.1943. $C_{24}H_{25}N_3O_2$ requires 387.1947); $\nu_{max.}(CH_2Cl_2)$ 2 240 and 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 2.45—3.05 (6 H, m, $ArCH_2CHCH_2CN$ and CH_2CO_2Me), 3.38—3.55 (1 H, m, $ArCH_2CH$), 3.63 (3 H, s), 3.71 (3 H, s), 3.86 (2 H, s, CH_2Ph), 4.52 (1 H, dd, *J* 6.2 and 8.4 Hz, $CHCH_2CO_2Me$), and 7.02—7.56 (9 H, m, ArH); $\delta_C(CDCl_3)$ 20.60 (t), 24.17 (t), 30.35 (q), 41.51 (t), 51.26 (d), 51.91 (q), 53.26 (d), 61.07 (t), 104.35 (s), 109.01 (d), 118.27 (d), 118.65 (s), 119.46 (d), 122.06 (d), 126.67 (s), 127.54 (d), 128.51 (d), 128.62 (d), 132.95 (s), 137.83 (s), 138.59 (s), and 171.36 (s); *m/z* 387 (M^+), 347, 314, and 91.

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