Diastereo- and Enantio-selectivity in the Pictet–Spengler Reaction

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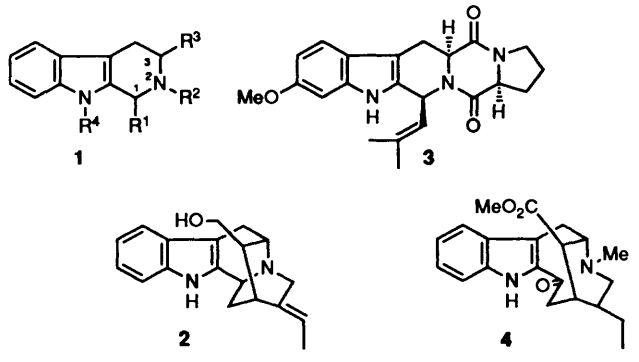
The factors that control the relative and absolute stereochemistry of 1,3-disubstituted and 1,2,3-trisubstituted tetrahydro-β-carbolines formed *via* the Pictet–Spengler reaction are discussed. In particular, the stereochemical factors that lead to the predominance of *cis*-1,3-disubstituted products under conditions of kinetic control are presented, with the aid of X-ray crystallographic data on a number of compounds; methods for assigning relative stereochemistry on the basis of NMR data are given; the mechanism by which racemisation can occur during the Pictet–Spengler reaction has also been studied, and procedures for eliminating this problem are given.

The Pictet–Spengler reaction[1] is the most direct method of forming the tetrahydro-β-carboline system **1**, which is the commonest structural unit of indole alkaloids. For members



of the family that possess substituents at both the C(1) and C(3) positions, the Pictet–Spengler reaction not only creates the key tricyclic ring system, but it can also be used to control the stereochemistry at the C(1) and C(3) chiral centres. A number of important factors have influenced the stereo-control that has been sought. (1) Natural products possessing the 1,3-disubstituted tetrahydro-β-carboline unit almost invariably possess a *cis* relationship between the C(1) and C(3) substituents, exemplified by bridged indole alkaloids (*e.g.* koumidine **2**) and some dipeptide mycotoxins (*e.g.* fumitremorgin C **3**); many ring-opened β-carboline alkaloids are also clearly derived from bridged precursors that also display the *cis* relationship (*e.g.* dregamine **4**).

(2) The absolute stereochemistry at C(3) is invariably consistent with L-tryptophan as a chiral building block. Although L-tryptophan is usually the biosynthetic precursor, it almost always suffers decarboxylation during subsequent biosynthesis, so its chiral centre is lost.[2] Nevertheless, it obviously offers an attractive starting material for asymmetric synthesis.

(3) The C(1) and C(3) chiral centres of 1,3-disubstituted tetrahydro-β-carbolines can sometimes be epimerised during synthetic sequences, so that the stereochemical outcome of the Pictet–Spengler reaction need not be permanent (*e.g.* ref. 3). The asymmetric synthesis of tetrahydro-β-carboline alkaloids lacking a C(3) substituent is also possible from L-tryptophan (*e.g.* ref. 4).

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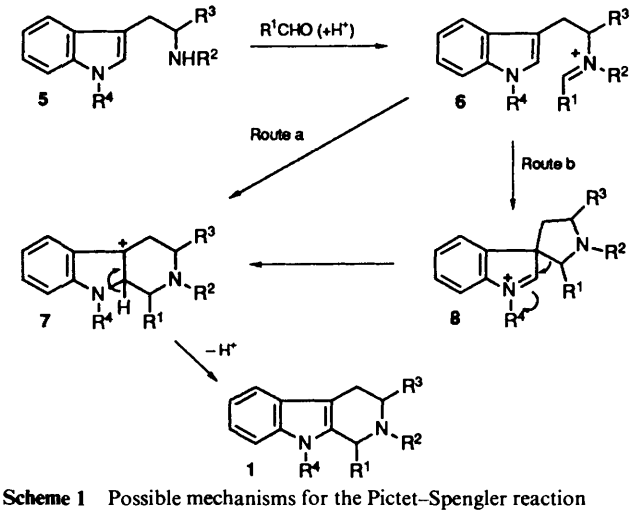
All of these factors mean that both *cis* and *trans* 1,3-disubstituted tetrahydro-β-carbolines can be used in the synthesis of indolic natural products. In this paper, we present a detailed analysis of the factors that control the diastereoselectivity of the Pictet–Spengler reaction; we consider how ^{13}C NMR can be used to determine the relative stereochemistry of tetrahydro-β-carbolines; and we analyse the mechanisms that might cause racemisation during Pictet–Spengler reactions involving D- or L-tryptophan derivatives, and indicate how such racemisation can be minimised for the asymmetric synthesis of indole alkaloids.

Results and Discussion

It is perhaps surprising that the presence or absence of an alkyl substituent on the N(2)-nitrogen of 1,3-disubstituted tetrahydro-β-carbolines should have such a dramatic effect on all aspects of their formation, conformation and structure determination. But, because of this, they will be clearly distinguished as 1,3-disubstituted or 1,2,3-trisubstituted tetrahydro-β-carbolines where appropriate.

Diastereo-control in the Pictet–Spengler Reaction.—In order to predict the diastereoselectivity in the Pictet–Spengler reaction, it is important that the mechanism should be clearly understood. Two likely pathways could operate in the reaction (Scheme 1), in which an iminium intermediate is attacked either directly at C(2) (route a), or at C(3) followed by a rearrangement of the spiroindolenine **8** (route b). Analogy



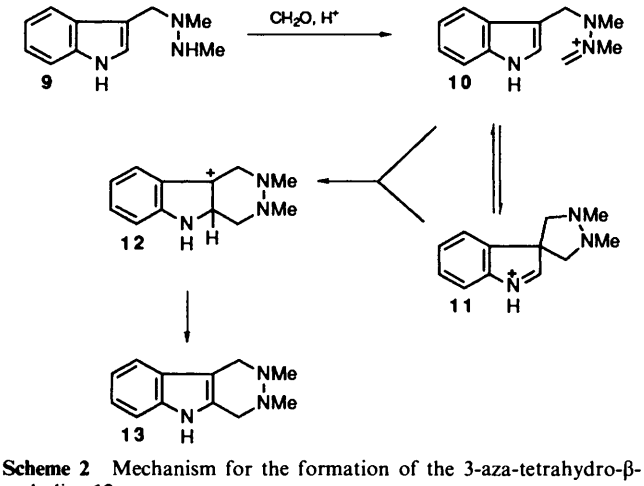
Scheme 1 Possible mechanisms for the Pictet–Spengler reaction

Table 1 The reaction of aldehydes with L-tryptophan methyl ester

Aldehyde	Temp. (°C)	Solvent	*cis*/*trans* Ratio[a]	Yield (%)[b]
PhCHO	110	PhMe	40:60	62
PhCHO	80	PhH	37:63	76 (ee 11%)[c]
PhCHO	40	CH_2Cl_2	45:55	72
PhCHO	RT	CH_2Cl_2	80:20	74
PhCHO	RT	PhH	78:22	65
PhCHO	0	CH_2Cl_2	82:18	74 (ee >95%)[c]
PhCHO	−70	CH_2Cl_2	83:17	62
$C_6H_{11}CHO$	0	CH_2Cl_2	71:29	71
$C_6H_{11}CHO$	80	PhH	59:41	85
$Me(CH_2)_2CHO$	0	CH_2Cl_2	80:20	72
$Me(CH_2)_2CHO$	80	PhH	47:53	88
$Ph(CH_2)_2CHO$	0	CH_2Cl_2	83:17	75
$Ph(CH_2)_2CHO$	80	PhH	51:49	83
Me_2CHCHO	0	CH_2Cl_2	83:17	82
Me_2CHCHO	80	PhH	43:57	76
$MeO_2C(CH_2)_2CHO$	0	CH_2Cl_2	80:20	60

[a] *cis* and *trans* Isomers were identified by ^{13}C NMR using the method of Cook *et al.*;[23] and *cis*:*trans* ratios were determined from ^1H NMR areas of the methyl ester peaks or from the relative heights of diastereotopic carbons (average of at least 5 peak ratios) in the ^{13}C spectra. [b] Yields are quoted for the pure isolated *cis*/*trans* mixture of diastereoisomers, obtained after purification by flash chromatography. Care was taken to avoid separation of the isomers, to ensure that NMR would give accurate values for the *cis*:*trans* ratios. [c] Enantiomeric excesses (ee) were estimated by the addition of the chiral shift reagent, tris[3-heptafluoropropylhydroxymethylene-(+)-camphorato]europium(III).

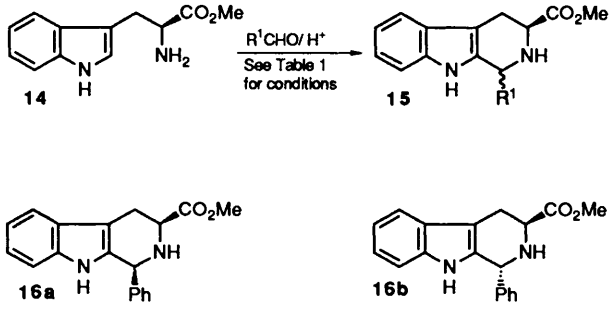
with tetrahydrocarbazole formation, which had been elegantly demonstrated to proceed *via* a spiro intermediate by Jackson *et al.*,[5] was questionable; the latter involves an irreversible 5-*exo*-*tet* cyclisation (favoured),[6] whilst the Pictet–Spengler reaction would have required 5-*endo*-*trig* cyclisation (disfavoured)[6] were a similar pathway followed. But clear evidence for the involvement of the spiro intermediate was obtained by us in 1987,[7] when we used an isotopic labelling experiment to demonstrate that the 3-aza-tetrahydro-β-carboline **13** was formed from the hydrazine **9** and methanal *via* the symmetrical spiro compound **11** (Scheme 2); however, it was our



Scheme 2 Mechanism for the formation of the 3-aza-tetrahydro-β-carboline **13**

discovery that the formation of the spiro intermediate was fast and reversible that considerably simplified the stereochemical arguments. Thus, for a standard Pictet–Spengler reaction (Scheme 1), the stereochemistry of the spiro intermediate would not be expected to influence the stereochemistry of the final product; instead, formation of the pentahydro-β-carboline carbonium ion **7** was inferred to be rate determining, and the energy of the associated *cis* and *trans* transition states should govern the stereochemical outcome under conditions of kinetic control. Interestingly, it is still unclear whether the carbonium ions (**7** in Scheme 1, and **12** in Scheme 2) are formed by rearrangement of the spiro intermediates **8** and **11**, or by selective removal of the iminium intermediates **6** and **10** from the initial equilibria by direct attack at the indole 2-position. But, in either case, it is reasonable to suppose that the transition states resemble the pentahydro-β-carboline carbonium ions **7** and **12**, and that the relative stability the stereoisomers of **7** should direct the stereoselectivity of the kinetically controlled Pictet–Spengler reaction. Importantly, the presence of only a single sp^2 centre in the piperidine ring should result in cyclohexane-like conformations.

For the kinetically controlled formation of 1,3-disubstituted tetrahydro-β-carbolines, it seems reasonable to suppose that the 1- and 3-substituents would both prefer to be equatorial (reducing 1,3-diaxial interactions), resulting in *cis*-selectivity in the final product. Using this argument, we were able to show that lowering the temperature in this type of Pictet–Spengler reaction gave the *cis* product selectively (see Table 1).[8] Until that time, very few examples of *cis*-selectivity had been reported,[9] and it was generally accepted that the reactions showed little diastereoselectivity.[10]



1,3-Disubstituted tetrahydro-β-carbolines are formed with poor stereo-control (roughly 50:50 *cis*:*trans* mixtures being typical) under the high yielding conditions developed by Cook *et al.* (refluxing benzene, catalytic acid);[11] this is not primarily due to the higher temperature reducing the kinetic selectivity, but to the fact that the reaction is reversible under these conditions. Thus, when we subjected the pure *cis*-isomer **16a** to these conditions, a 1:2 mixture of **16a** and **16b** was generated. From a series of reactions in acidified refluxing benzene, it became clear that the *cis* and *trans* isomers have very similar stabilities. How can this be explained on conformational grounds? In an attempt to clarify this, we have tried

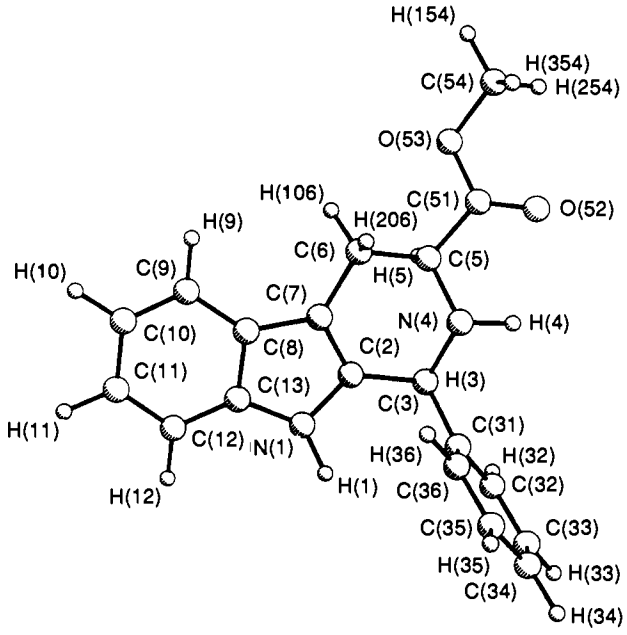


Fig. 1 X-Ray crystal structure for compound **16a** showing the crystallographic numbering of the atoms

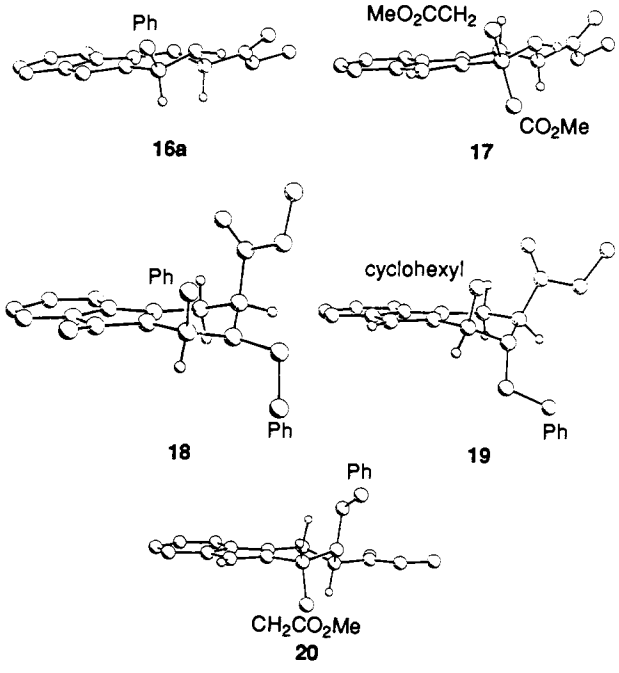
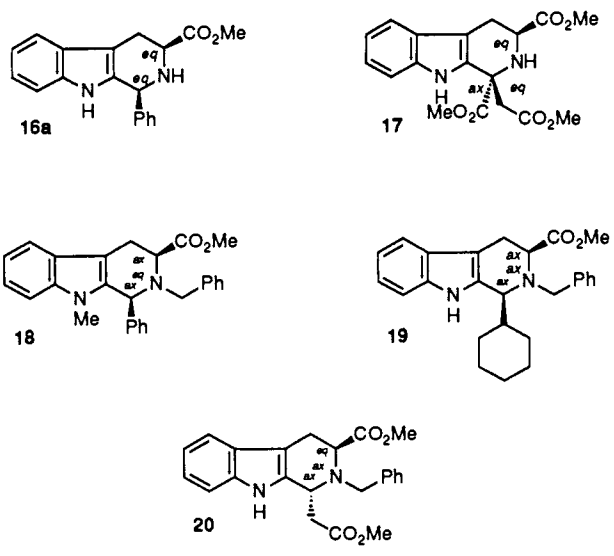


Fig. 2 X-Ray crystal structures of compounds **16a** and **17–20**

to crystallise as many tetrahydro-β-carbolines as possible, and several X-ray crystal structures have been published already.[12–15] We had not been successful, however, in crystallising any *cis*-1,3-disubstituted tetrahydro-β-carbolines until very recently; the X-ray crystal structure of compound **16a** is shown in Figs. 1 and 2, and it is noteworthy that the 1- and 3-substituents are both equatorial in the half-chair structure. This conformational preference has been observed in the only other X-ray crystal structure of a *cis*-1,3-disubstituted tetrahydro-β-carboline.[16] In Fig. 2, the crystal structures of **16a** and of four other tetrahydro-β-carbolines **17–20** that had been analysed by us[12–15] are shown, with the views chosen in such a way that the conformations of the crucial piperidine rings can be easily compared. From these X-ray crystal structures, as well as those determined by other groups,[17] we can make the



following observations. (a) The didehydropiperidine rings usually adopt half-chair conformations, allowing the substituents at C(1), N(2) and C(3) to occupy pseudo-axial or pseudo-equatorial positions. But it is important to note that a number of conformational features come into play with the didehydropiperidine, that were not factors for the carbonium ions **7**. In particular, reduction in 1,3-diaxial interactions by slight twisting has a much lower energy price in the didehydro system, whereas $A_{1,2}$ ring strain[18] does not apply to the carbonium ion intermediates.

(b) For those tetrahydro-β-carbolines lacking an N(2)-benzyl group (**16a** and **17**), the C(3)-ester has a dominant preference for the equatorial position, forcing the 1-substituents to be equatorial if *cis*, and axial if *trans*. This is consistent with $A_{1,2}$ ring strain disfavouring equatorial groups in the 1-position, as pointed out by Ungemach *et al.*[10] One might, therefore, expect that the *cis* and *trans* isomers would be of similar stability, as is indeed observed.

(c) For 1,2,3-trisubstituted tetrahydro-β-carbolines, it is striking that the 1-substituents are now driving the conformations, with an overpowering preference for being axial. Thus, for *cis*-isomers **18** and **19**, the 1,3-diaxial conformations are adopted, whilst for the *trans*-isomer **20** the $1_{ax},3_{eq}$ arrangement is seen. Systems of this type have a thermodynamic preference for the *trans* stereochemistry, in order to minimise 1,3-diaxial interactions.

The 1,2,3-trisubstituted tetrahydro-β-carbolines require further discussion, for they are formed with high *trans* stereoselectivity from the Pictet–Spengler reactions of N^{α}-benzyl tryptophan derivatives with aldehydes,[10] under conditions of either kinetic or thermodynamic control. The products possess an identical sub-structure to *N*-benzyl-3,4-didehydropiperidines (*e.g.* **21**[19] and **22**[20]); these compounds

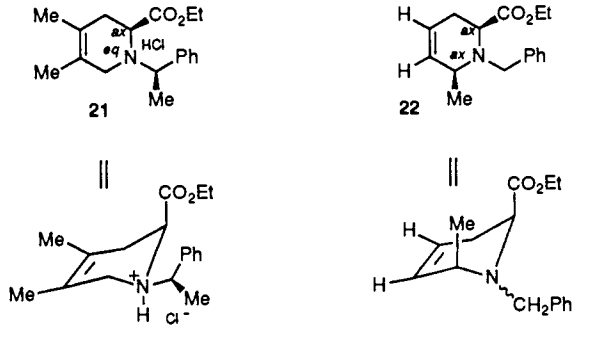


Table 2 Comparison of C(2)′ chemical shifts for *cis* and *trans* *N*(2)-benzyl substituted tetrahydro-β-carbolines **1** (R^2 = CH_2Ph). Data from ref. 27, except for final entry (see following paper)

Compound 1			Chemical shift of *cis*-isomer (ppm)	Chemical shift of *trans*-isomer (ppm)
R^4	R^1	R^3	C(2)′	C(2)′
H	Ph	CO_2Me	57.26	54.34
Me	Ph	CO_2Me	59.16	53.20
H	C_6H_{11}	CO_2Me	61.38	53.20
Me	C_6H_{11}	CO_2Me	63.01	52.98
H	Et	CO_2Me	58.41	53.53
Me	Et	CO_2Me	61.22	52.99
H	CH_2CO_2Me	CO_2Me	57.91	53.52
Me	CH_2CO_2Me	CO_2Me	60.50	53.01
H	CH_2CO_2Me	CH_2CN	59.59	49.76
Me	CH_2CO_2Me	CH_2CN	61.07	49.62
H	$CH_2CH_2CO_2Me$	CO_2Me	59.36	53.33

also adopt half-chair conformations, with 2/6-substituents showing a strong axial preference. If this applies to N(2)-benzyl tetrahydro-β-carbolines, then both the 1- and 3-substituents would prefer being axial for the *cis*-isomers, as is indeed observed. In view of the apparent absence of this effect when the N(2)-benzyl is replaced by hydrogen (*e.g.* **16a**), the argument in favour of an anomeric effect operating in such systems[21] is weakened; moreover, the observed 1,2,3-triaxial conformation for **19** could have no anomeric stabilisation, as the nitrogen lone pair is equatorial in this case. It is difficult to find a convincing argument to explain the dramatic effect of the benzyl substituent, particularly as it appears to have little axial/equatorial preference itself. Conformational analysis requires a comparison of the stability of 4 conformations/invertomers for each *cis* and *trans* isomer, even assuming that the half-chair form is adopted in all cases, and it is far from obvious which structures are likely to be of lowest energy. But the general rule is clear: an N(2)-benzyl substituent strongly favours the 1-substituent being axial, and 1,3-diaxial interactions favour 3-substituents being equatorial and thus *trans*.

Finally, why are *trans* 1,2,3-trisubstituted tetrahydro-β-carbolines favoured under conditions of kinetic control? A suggestion given by Cook,[10] and later expounded by us,[22] was that the *E*-iminium ions (presumably slightly favoured over the *Z*-isomers) were attacked directly by the indolic 2-position, with the nucleophile and developing electron pair displaying an *anti* relationship—this would have led to a clear preference for the *trans*-isomers. Alternatively, the stereochemistry of the spiroindolenine intermediates could have dictated the eventual stereochemistry of the 1,2,3-trisubstituted tetrahydro-β-carbolines, with their formation governed by similar factors. But, assuming the reversibility of formation of the spiro intermediate,[7] neither of these arguments seems sufficiently compelling to explain the excellent stereo-control discovered by Cook in the reaction of N^{α}-benzyl-tryptophan esters with aldehydes.[10] Perhaps some of the key steric factors that lead to a thermodynamic preference for *trans*-1,2,3-trisubstituted tetrahydro-β-carbolines also govern kinetic control *via* the carbonium ion precursors **7**.

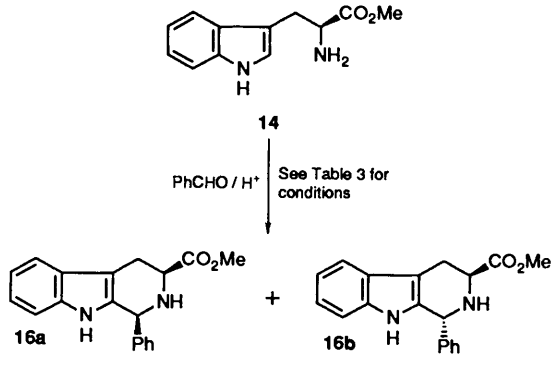
Stereochemical Assignment using ^{13}C *NMR*.—For 1,3-disubstituted tetrahydro-β-carbolines, the method developed by Cook has undoubtedly stood the test of time.[23] He reasoned that these β-carbolines would adopt a half-chair conformation, and that the *cis*-1,3-disubstituted derivatives would have both substituents equatorial. The *trans*-isomer would almost certainly have the 3-substituent equatorial, but the 1-substituent axial (in order to reduce $A_{1,2}$ ring strain); the greater 1,3-diaxial interactions for the *trans*-isomer would cause shielding of the C(1) and C(3) carbons by the compression effect.[24] These predictions were fully borne out by NMR observations,[23] and are totally consistent with the X-ray crystal structures reported herein.

In our early work on indole alkaloids, we were expecting that 1,2,3-trisubstituted tetrahydro-β-carbolines would follow a similar pattern, although Cook had already commented that analogous NMR analysis was not possible.[25] We published our own observations on the limitation of the NMR method, but pointed out that the ^{13}C chemical shift of C(1) did reliably indicate *cis* (downfield) or *trans* (upfield) stereochemistry for a series of 1,2,3-trisubstituted tetrahydro-β-carbolines.[26] We have, however, since found exceptions to this observation, although the correlation is valid in most cases.

In the event, a much simpler ^{13}C NMR analysis has proved totally reliable (as far as we know).[27] The benzylic carbon is easily identified (from DEPT or off-resonance spectra) at *ca* δ 70. For the *cis*-isomers, the X-ray crystal structures indicate no steric crowding of the benzyl group, as the 1- and 3-substituents are both axial. Despite the variation in the stereochemistry of the N(2)-nitrogen, the benzyl group clearly experiences greater crowding in the *trans*-isomers, and this should lead to shielding through the compression effect.[24] This is indeed observed, and the benzylic carbon for the *trans*-isomers always resonate upfield compared to those for the *cis*-isomers (Table 2).

Racemisation.—The use of N^{α}-benzyl-L-tryptophan methyl ester in the Pictet–Spengler reaction leads to optically pure 1,2,3-trisubstituted tetrahydro-β-carbolines.[3] In contrast, racemisation can be a serious problem during the formation of 1,3-disubstituted tetrahydro-β-carbolines, and several specific examples of racemisation are reported in the literature.[9b,c] What is the mechanism of this racemisation, and how can it be controlled?

It would seem that most of the problems of racemisation arise from carrying out Pictet–Spengler reactions at elevated temperatures, although the role of acid also turns out to be critical. The significance of these factors is clearly demonstrated in Table 3, which summarises a series of reactions conducted between L-tryptophan methyl ester and benzaldehyde (Scheme 3)—a condensation for which racemisation has been noted to be particularly troublesome.[8]



Scheme 3 Epimerisation studies on **14** (see Table 3)

In the presence of a trace of acid, virtually no racemisation occurs at room temperature, whilst about 35% racemisation occurs at reflux in benzene. These latter conditions lead to the thermodynamic *cis*:*trans* product ratio (*ca.* 1:2), but when the optically pure *cis*-product **16a** was subjected to these conditions, both the *cis*- and *trans*-isomers were formed with high optical purity; this indicates that racemisation occurs before the Pictet–Spengler reaction takes place. Moreover, it was shown (by chiral HPLC retention times) that epimerisation had occurred at C(1), indicating that the thermodynamic product is

Table 3 Racemisation studies on **16a/b**

	Substrate	[Acid]	Time (h)	Temp. (°C)	Solvent	*cis*/*trans* Ratio	Ee (%) *cis* **16a**	Ee (%) *trans* **16b**
		Trace	3	0	CH_2Cl_2	80:20	>95	>95
14 +	PhCHO	Trace	3	80	PhH	40:60	65	66
	PhCHO	0.14 equiv.	3	80	PhH	50:50	72	20
	PhCHO	1.0 equiv.	3	80	PhH	45:55	>95	38
	PhCHO	2.0 equiv.	3	80	PhH	40:60	>95	66
	PhCHO	9.5 equiv.	3	80	PhH	36:64	>95	>95
	16a	None	18	80	PhH	100:0	>95	
	16a	Excess	3	80	PhH	70:30	>95	>95
	16a	Excess	18	80	PhH	40:60	>95	>95

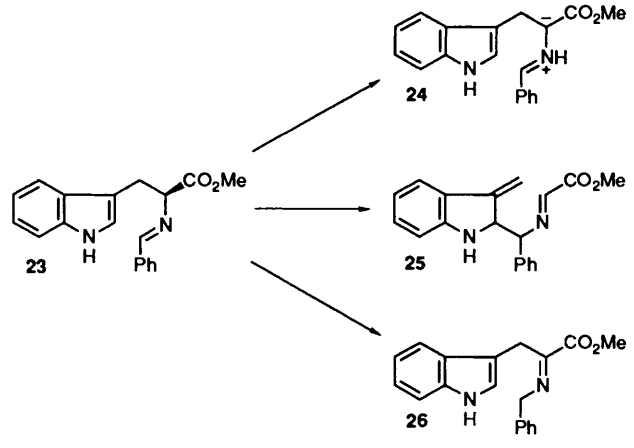
Table 4 The racemisation in benzene of the imine **28** derived from L-phenylalanine methyl ester and benzaldehyde

[Acid] (TFA)	Temp.	Isomer ratio **30a**:**30b** (*S*):(*R*)
No acid	Reflux	52.2:47.9
Cat H^+ (0.05 equiv.)	Reflux	50.9:49.1
Excess H^+ (5 equiv.)	Reflux	53.2:46.8
No acid	Room temp.	99.6:0.4
Cat H^+ (0.05 equiv.)	Room temp.	95.7:4.3
Excess H^+ (5 equiv.)	Room temp.	97.5:2.4

formed by the reversibility of the Pictet–Spengler reaction, rather than by a separate mechanism involving epimerisation (and partial racemisation) at C(3).

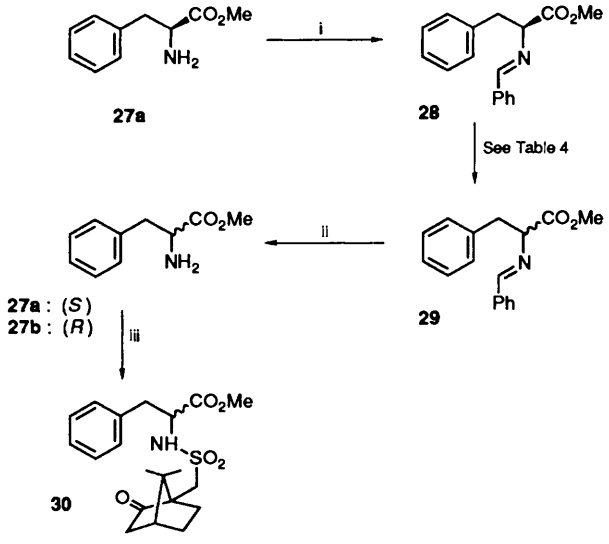
However, when the reaction between L-tryptophan methyl ester and benzaldehyde was conducted in the presence of a large excess of acid [TFA (10 equiv.)], no racemisation was observed, even in refluxing benzene. This is an extremely important result, for the use of excess acid should guarantee that virtually all Pictet–Spengler reactions yielding 1,3-disubstituted tetrahydro-β-carbolines can be conducted under racemisation-free conditions.

There are several acid-catalysed mechanisms that could account for the racemisation, and the most plausible intermediates for this process (structures **24**–**26**) are summarised in Scheme 4. The 1,3-dipole **24** was deemed unlikely, since



Scheme 4 Possible intermediates accounting for racemisation in the Pictet–Spengler reaction

attempts to trap it as the cyclo-adduct with maleic anhydride were totally unsuccessful. The 1-aza-Cope rearrangement mechanism (*via* **25**) was effectively disproven by carrying out a reaction between L-Trp-OMe and PhCHO in which all exchangeable protons were replaced by deuterium. The *trans* product had undergone 34% racemisation by HPLC, whilst 27% deuterium incorporation had occurred at C(3); thus (within experimental error) all racemisation takes place *via* loss of the C(3)-proton, and this is not consistent with the aza-Cope pathway. It therefore seems almost certain that racemisation occurs *via* imine (or iminium ion) tautomerism. Further evidence in favour of this pathway was obtained from experiments using the imine derived from L-phenylalanine methyl ester and benzaldehyde (which does not undergo Pictet–Spengler cyclisation under the conditions used); allowing this to react with acid under a variety of conditions (see Scheme 5) led to varying degrees of racemisation, as indicated in Table 4. As with our earlier Pictet–Spengler reactions, virtually no racemisation occurred at room temperature, irrespective of the amount of acid added. But in refluxing benzene, total racemisation occurred in all cases.



Scheme 5 *Reagents and conditions:* i, PhCHO, PhH, azeotrope, 15 min; ii, 1 mol dm^{-3} HCl; iii, (+)-camphor-10-sulfonyl chloride, 1 mol dm^{-3} NaOH, CH_2Cl_2, 15 min

Cook has proposed[3] that optically pure 1,2,3-trisubstituted tetrahydro-β-carbolines result from Pictet–Spengler reactions involving N^{α}-benzyl-L-tryptophan methyl ester because the iminium ion is removed so rapidly from the reaction; no neutral imine is ever available for tautomeric racemisation. This explanation seems reasonable, and our results concerning 1,3-disubstituted tetrahydro-β-carbolines are in full accord. Hence, in the presence of a large excess of acid, the imine intermediate is immediately protonated, and cyclisation of the resulting iminium ion is rapid.

Thus, racemisation-free Pictet–Spengler reactions can be virtually guaranteed by conducting the cyclisations at (or below) room temperature, or by ensuring that the free imine concentration is low; the latter can be achieved by using a secondary amine as the amino component, or by triggering the cyclisation using a large excess of acid.

In summary, *cis*-1,3-disubstituted tetrahydro-β-carbolines can be obtained with good diastereoselectivity by the kinetically controlled reaction of L-tryptophan esters with aldehydes under acidic conditions at (or below) room temperature. Methyl esters give about 4:1 *cis* selectivity at room temperature. No evidence for racemisation was found for reactions conducted at (or below) room temperature, but optical integrity can be further guaranteed by triggering the cyclisation with a large excess of acid—in practice, this is often conveniently achieved by preforming the imine under neutral conditions, prior to inducing cyclisation by the addition of acid. Higher temperatures in the initial Pictet–Spengler reaction lead to poor diastereoselectivity (thermodynamic control), and the risk of racemisation. The ^{13}C NMR chemical shift data for the C(1) and C(3) carbons is a reliable indicator of the stereochemistry of tetrahydro-β-carbolines lacking an *N*(2)-substituent. The *cis* products resulting from kinetic control possess the correct absolute stereochemistry for elaboration to virtually all indole alkaloids based on the tetrahydro-β-carboline skeleton.

The *trans* 1,3-disubstituted tetrahydro-β-carbolines can be obtained with excellent diastereo-control, and in high optical purity, by carrying out the Pictet–Spengler between N^{α}-benzyltryptophan esters and aldehydes, under conditions of kinetic or thermodynamic control. The ^{13}C NMR chemical shift data for the benzylic carbon is a reliable indicator of the stereochemistry for the 1,2,3-trisubstituted products. But using proteinogenic L-tryptophan, the absolute stereochemistry of the major *trans* product is the mirror image of that displayed by most indole alkaloids.

Finally, this combination of product studies, mechanistic studies, and structural analyses has given probably the most accurate insight into the reasons for the stereo-control observed in Pictet–Spengler reactions.

Experimental

Melting points were determined on a Reichert microscope hot-stage apparatus, and are uncorrected. NMR spectra were recorded on a JEOL FX90Q at 90 MHz (^1H) and 22.5 MHz (^{13}C), or a Bruker MSL300 spectrometer at 300 MHz (^1H) and 75 MHz (^{13}C), unless otherwise stated. Chemical shifts were measured in ppm on the δ scale downfield from tetramethylsilane as internal standard. All ^{13}C data are quoted with ^1H multiplicities (off resonance results in brackets), although this multiplicity was usually inferred from DEPT experiments. Where appropriate, NMR data in brackets refers to the minor diastereoisomer or minor rotamer. Infrared spectra were recorded on a Pye–Unicam SP3-200 or a Perkin-Elmer 1420 spectrophotometer. Mass spectra were obtained by electron impact at 70 eV on an AEI MS-3074 spectrometer, unless otherwise stated. Optical rotations were measured using a Perkin-Elmer 141 polarimeter. Analytical TLC was carried out on Merck aluminium sheet silica gel 60 F_{254} plates (thickness 0.2 mm). Spots were visualised with a UV hand lamp or iodine vapour. Flash chromatography[28] was performed using silica gel 60 (230–400 mesh) as the stationary phase, purchased from Camlab. HPLC was performed on a Bio-Rad 1330 HPLC with UV detector using a Spherisorb capped SiO_2 column, or a 5 mm DNBPG covalent chiral column.

Unless otherwise indicated all reactions were carried out under an atmosphere of dry nitrogen or argon.

General Procedures for the Preparation of Tetrahydro-β-carbolines: see Table 1.—These procedures are exemplified by the synthesis of (1*S*,3*S*)- and (1*R*,3*S*)-methyl 1-phenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylates **16a**/**16b**.

Method A: high temperatures (40–110 °C). In a typical reaction, L-tryptophan methyl ester (500 mg, 2.29 mmol) and benzaldehyde (267 mg, 2.52 mmol, 1.1 equiv.) in benzene (or toluene or dichloromethane) were brought to reflux over activated molecular sieves (4 Å), and a trace of TFA (<5 mole %) was then added. After 1 h an excess of TFA (522 mg, 4.58 mmol, 2 equiv.) was added, and refluxing was continued for a further 3 h when cyclisation was complete. The reaction mixture was then poured into water and made alkaline with an excess of aqueous NaOH (2 mol dm^{-3}). The organic layer was separated, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica eluted with ethoxyethane–trichloromethane (1:9) afforded **16a**/**16b**[11] as a white foam (533 mg, 76%) in the ratio 37:63.

Although spontaneous cyclisation in refluxing benzene was occasionally observed (*cf.* ref. 11), acid catalysis gave much more reliable results. However the amount of acid present did not affect the *cis*:*trans* ratio.

Method B: low temperatures (−78 °C for room temp.). In a typical reaction, L-tryptophan methyl ester (500 mg, 2.29 mmol) and benzaldehyde (267 mg, 2.52 mmol, 1.1 equiv.) were stirred at 0 °C in dichloromethane with a trace of TFA (<5 mole %) over activated molecular sieves (4 Å), until formation of the imine was complete (24 h). The reaction mixture was then cooled to the appropriate temperature and cyclisation was initiated by the addition of an excess of TFA (522 mg, 4.58 mmol, 2 equiv.). Stirring was maintained at this temperature until the reaction was complete by TLC (3–4 h). Work-up and purification were the same as in Method A to afford **16a**/**16b** (519 mg, 74%) in the ratio 82:18.

Data for *cis* isomer **16a**, m.p. 227–228 °C: R_f on silica 0.5 (methanol–trichloromethane, 1:9); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 3010, 1740, 1460, 1440 and 1270; δ_H(90 MHz; $CDCl_3$) 2.38 (1 H, br s, N_b-H), 2.91–3.23 (2 H, m, $ArCH_2$), 3.79 (3 H, s, CO_2CH_3), 3.96 (1 H, dd, *J* 10.5, 4.8 Hz, $ArCH_2CH$), 5.12–5.28 (1 H, m, PhC*H*) and 7.01–7.63 (10 H, m, ArH and indole N*H*); δ_C(22.5 MHz; $CDCl_3$) 25.68 (t), 52.22 (q), 56.88 (d), 58.69 (d), 108.89 (s), 110.90 (d), 118.21 (d), 119.62 (d), 121.95 (d), 127.09 (s), 128.61 (d), 128.94 (d), 134.62 (s), 136.14 (s), 140.69 (s) and 173.09 (s); *m*/*z* 306 (M^+, 100%), 247 (48), 218 (89) and 169 (16) (Found: M^+, 306.1368. $C_{19}H_{18}N_2O_2$ requires M^+, 306.1368).

Data for *trans* isomer **16b**: R_f on silica 0.22 (methanol–trichloromethane, 1:9); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 3010, 1735, 1460 and 1265; δ_H(90 MHz; $CDCl_3$) 2.37 (1 H, br s, N_bH), 3.06–3.29 (2 H, m, $ArCH_2$), 3.69 (3 H, s, CO_2CH_3), 3.84–4.03 (1 H, m, $ArCH_2CH$), 5.29–5.42 (1 H, m, PhC*H*), 7.00–7.72 (10 H, m, ArH and indole N*H*); δ_C(22.5 MHz; $CDCl_3$) 23.62 (t), 50.98 (q), 51.30 (d), 53.85 (d), 107.32 (s), 109.92 (d), 117.13 (d), 118.43 (d), 120.86 (d), 125.90 (s), 127.36 (d), 127.64 (d), 132.08 (s), 135.17 (s), 140.85 (s) and 172.98 (s); *m*/*z* 306 (M^+, 100%), 247 (43), 218 (63) and 169 (17) (Found: M^+, 306.1362. $C_{19}H_{18}N_2O_2$ requires M^+, 306.1368).

The reactions of the other aldehydes with L-tryptophan methyl ester (Table 1) were carried out using the following two sets of conditions: (i) refluxing benzene following the procedure of Method A above; (ii) dichloromethane at 0 °C following the procedure of Method B above.

Spectroscopic data for the other 1,3-disubstituted tetrahydro-β-carbolines are quoted as mixtures of *cis*/*trans* isomers (where the signals are resolved, the *trans* isomer has been identified in brackets). In all cases they were obtained as foams, yields 71–88% (Table 1).

(1S,3S)- *and* (1R,3S)-*Methyl* 1-*cyclohexyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole*-3-*carboxylates:*[11] R_f on silica 0.5 (methanol–trichloromethane, 1:9); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 3010, 2970, 1730, 1370 and 1100; δ_H(90 MHz; $CDCl_3$) 0.80–2.20 (12 H, m, cyclohexane ring H and N_bH), 2.62–3.21 (2 H, m, $ArCH_2$), 3.33–3.70 (1 H, m, $ArCH_2CH$), 3.81 (3.74) (3 H, s, CO_2CH_3), 3.90–4.12 (1 H, m, ArC*H*), 6.91–7.63 (4 H, m, ArH) and 8.12 (7.98) (1 H, br s, indole NH); δ_C(22.5 MHz; $CDCl_3$)

26.12 (25.08) (t), 26.88 (26.70) (t), 26.97 (26.81) (t), 29.81 (30.73) (t), 42.43 (43.31) (d), 52.11 (q), 56.71 (53.53) (d), 57.81 (55.53) (d), 109.10 (108.13) (s), 110.91 (110.85) (d), 117.82 (119.02) (d), 119.43 (119.54) (d), 121.61 (121.73) (d), 127.32 (s), 135.02 (134.80) (s), 136.24 (136.03) (s) and 174.01 (174.80) (s); *m/z* 312 (M^+, 10%), 229 (100), 169 (30) (Found: M^+, 312.1834. $C_{19}H_{24}N_2O_2$ requires M^+, 312.1838).

All attempts to separate this pair of diastereoisomers were unsuccessful.

(1S,3S)- *and* (1R,3S)-*Methyl* 1-*propyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indoles*-3-*carboxylates*: R_f on silica 0.35 (methanol–trichloromethane, 1:9); $\nu_{max}(CHCl_3)/cm^{-1}$ 3470, 3010, 2960, 1735, 1450, 1440, 1325, 1270 and 1175; δ_H(90 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 7.0, $CH_2CH_2CH_3$), 1.20–1.90 (4 H, m, $CH_2CH_2CH_3$), 2.23 (1 H, br s, N_bH), 2.71–3.17 (2 H, m, $ArCH_2$), 3.52–3.84 [4 H, m, comprising two resolved singlets at δ 3.76 (3.70) due to CO_2CH_3 and $ArCH_2CH$], 3.94 (1 H, dd, *J* 7.7, 5.1, ArC*H*—*trans* isomer), 4.00–4.20 (1 H, m, ArC*H*—*cis* isomer), 6.95–7.60 (4 H, m, ArH) and 8.18 (8.09) (1 H, br s, indole N*H*); δ_C(22.5 MHz; $CDCl_3$) 14.05 (14.18) (q), 18.49 (19.36) (t), 25.97 (25.06) (t), 36.82 (37.52) (t), 52.15 (52.08) (q), 52.47 (50.13) (d), 56.44 (52.39) (d), 107.66 (106.51) (s), 110.85 (110.77) (d), 117.85 (d), 119.35 (119.20) (d), 121.50 (121.43) (d), 127.11 (126.98) (s), 135.73 (s), 135.95 (135.87) (s) and 173.83 (174.37) (s); *m/z* 272 (M^+, 21%), 229 (100) and 169 (48) (Found: M^+, 272.1519. $C_{16}H_{20}N_2O_2$ requires M^+, 272.1525).

All attempts to separate this pair of diastereoisomers were unsuccessful.

(1S,3S)- *and* (1R,3S)-*Methyl* 1-(2-*phenylethyl*)-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole*-3-*carboxylate*: R_f on silica 0.53 (methanol–trichloromethane, 1:9); $\nu_{max}(CHCl_3)/cm^{-1}$ 3470, 3010, 2950, 1735, 1455, 1440, 1270 and 1175; δ_H(90 MHz; $CDCl_3$) 1.73–2.16 (2 H, m, CH_2CH_2Ph), 2.65 (1 H, br s, N_bH), 2.52–3.10 (5 H, m, comprising $ArCH_2$, CH_2Ph and $ArCH_2CH$), 3.70 (3.61) (3 H, s, CO_2CH_3), 3.85 (1 H, dd, *J* 7.7, 5.1, ArC*H*—*trans* isomer), 3.96–4.08 (1 H, m, ArC*H*—*cis* isomer), 6.92–7.51 (9 H, m, ArH) and 8.12 (7.92) (1 H, br s, indole N*H*); δ_C(22.5 MHz; $CDCl_3$) 25.73 (24.95) (t), 31.20 (32.00) (t), 36.09 (36.58) (t), 51.97 (51.87) (q), 52.17 (49.54) (d), 56.23 (52.17) (d), 107.66 (106.51) (s), 110.78 (110.70) (d), 117.72 (d), 119.18 (119.05) (d), 121.36 (d), 125.78 (d), 126.93 (126.78) (s), 128.26 (128.16) (d), 135.09 (135.18) (s), 135.85 (135.72) (s), 141.51 (141.59) (s) and 173.69 (174.23) (s); *m/z* 334 (M^+, 14%), 229 (100), 169 (28) (Found: M^+, 334.1683. $C_{21}H_{22}N_2O_2$ requires M^+, 334.1681).

All attempts to separate this pair of diastereoisomers were unsuccessful.

(1S,3S)- *and* (1R,3S)-*Methyl* 1-*isopropyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indoles*-3-*carboxylates*: R_f on silica 0.15 (ethoxyethane–trichloromethane, 1:9); $\nu_{max}(CHCl_3)/cm^{-1}$ 3440, 3310, 2910, 1730, 1335 and 1260; δ_H(90 MHz; $CDCl_3$) 0.82–1.40 [6 H, m, $CH(CH_3)_2$], 1.92–3.42 [4 H, m, due to $ArCH_2$, $CH(CH_3)_2$ and N_bH], 3.53–3.82 [4 H, m, comprising two resolved singlets at δ 3.79 and (δ 3.71) due to CO_2CH_3, and a multiplet due to $ArCH_2CH$], 4.01–4.52 (1 H, m, ArC*H*), 6.90–7.90 (4 H, m, ArH) and 8.21 (8.10) (1 H, br s, indole N*H*); δ_C(22.5 MHz; $CDCl_3$) 16.41 (17.82) (q), 18.80 (19.12) (q), 25.35 (23.73) (t), 31.31 (32.29) (d), 52.39 (q), 56.34 (53.47) (d), 58.18 (56.12) (d), 108.57 (106.94) (s), 111.00 (d), 117.88 (d), 119.45 (d), 121.73 (121.89) (d), 126.93 (126.61) (s), 133.81 (132.40) (s), 136.30 (s) and 174.66 (173.90) (s); *m/z* 272 (M^+, 4%), 229 (100), 211 (11), 169 (53) and 28 (57) (Found: M^+, 272.1514. $C_{18}H_{20}N_2O_2$ requires M^+, 272.1525).

Flash chromatography on silica eluted with ethoxyethane–trichloromethane (1:19) allowed separation of the *cis* isomer. Data for *cis* isomer: $\nu_{max}(CHCl_3)/cm^{-1}$ 3440, 3310, 2910, 1730, 1335 and 1260; δ_H(90 MHz; $CDCl_3$) 0.84 [3 H, d, *J* 6.8, $CH(CH_3)_2$], 1.13 [3 H, d, *J* 6.8, $CH(CH_3)_2$], 1.90–2.41 [1 H, m, $CH(CH_3)_2$], 2.50–3.26 (3 H, m, $ArCH_2$ and N_bH), 3.61–3.73 (1 H, m, $ArCH_2CH$), 3.79 (3 H, s, CO_2CH_3), 4.03–4.20 (1 H, m, ArC*H*), 6.95–7.64 (4 H, m, ArH), 8.05 (1 H, br s, indole N*H*); δ_C(22.5 MHz; $CDCl_3$) 16.25 (q), 19.12 (q), 26.06 (t), 31.48 (d), 52.12 (q), 56.40 (d), 57.91 (d), 108.89 (s), 110.90 (d), 117.83 (d), 119.35 (d), 121.51 (d), 127.20 (s), 135.11 (s), 136.11 (s) and 174.01 (s); *m/z* 272 (M^+, 4%), 229 (100), 211 (11), 169 (53) and 28 (57) (Found: M^+, 272.1520. $C_{16}H_{20}N_2O_2$ requires M^+, 272.1525).

General Procedure for the Preparation of **16a/16b** *using Different Acid Concentrations* (*see Table* 3).—L-Tryptophan methyl ester (500 mg, 2.29 mmol), benzaldehyde (267 mg, 2.52 mmol, 1.1 equiv.) and TFA (36.6 mg, 0.32 mmol, 0.14 equiv.) were allowed to react together in anhydrous benzene for 3 h under azeotropic conditions (or refluxed over activated molecular sieves). Work-up and purification were the same as in Method A to afford **16a/16b** (533 mg, 76%). The concentrations of acid used are given in Table 3.

Preparation of **16a/16b** *in the presence of deuterium oxide.* L-Tryptophan methyl ester (500 mg, 2.29 mmol), benzaldehyde (267 mg, 2.52 mmol, 1.1 equiv.). TFA (261 mg, 1 equiv.) and D_2O (1.2 g, 27 equiv.) were allowed to react in anhydrous benzene for 6 h under azeotropic conditions. Work-up and purification were the same as in Method A to afford **16a/16b** (515 mg, 73%).

Attempted racemisation of optically pure **16a**. The optically pure *cis* isomer **16a** obtained using Method B (dichloromethane at 0 °C) (200 mg, 0.65 mmol) was dissolved in anhydrous benzene and an excess of TFA (707 mg, 9.5 equiv.) was added. The reaction mixture was then refluxed for 18 h. Work-up and purification were the same as in Method A to give **16a/16b** (166 mg, 83%) in the ratio 2:3.

Racemisation Results using Phenylalanine Derivatives (*see Table* 4): *Preparation of* L-*Phenylalanine Methyl Ester* **27a**.—This compound was prepared by refluxing L-phenylalanine in saturated HCl–MeOH for 4 h. To free the HCl salt, 14% aqueous ammonia was added, and the free base was extracted with chloroform.

Imine formation. L-Phenylalanine methyl ester **27a** (2.0 g, 11.1 mmol) and benzaldehyde (1.24 g, 11.7 mmol, 1.05 equiv.) in anhydrous benzene were refluxed for 15 min in a Dean–Stark apparatus to remove water, a solution of the imine **28** in benzene being thus generated.

Racemisation. The solution of the above imine **28** was cooled and various amounts of TFA were then added (for conditions see Table 4). These conditions were maintained for *ca.* 24 h.

Hydrolysis of the imine **28**. On removal of the solvent under reduced pressure, hydrochloric acid (1 mol dm^{-3}) was added to the residue and this mixture was shaken for 5 min. The mixture was extracted with chloroform to remove the benzaldehyde. The aqueous phase was then basified with 14% aqueous ammonia and extracted with chloroform. The organic layer was separated, dried ($MgSO_4$) and evaporated to give phenylalanine methyl ester **27a/27b** (average recovery yield 82%), which was used without further purification.

Addition of chiral auxiliary. Phenylalanine methyl ester **27a/27b** (0.25 g, 1.4 mmol), (+)-camphor-10-sulfonyl chloride (0.35 g, 1.4 mmol, 1 equiv.) and aqueous NaOH (2 mol dm^{-3}; 1 cm^3) were vigorously stirred in dichloromethane at room temperature for 15 min. The reaction mixture was then neutralised with hydrochloric acid (2 mol dm^{-3}). The organic layer was separated, dried ($MgSO_4$) and evaporated to give **30** (0.44 g, 81%), which was analysed without purification.

Data for **30** derived from racemic phenylalanine methyl ester **27a/b**: $\nu_{max}(CHCl_3)/cm^{-1}$ 3020, 2400, 1740, 1520, 1420, 1335, 1220 and 930; δ_H(90 MHz; $CDCl_3$) 0.64–4.7 [21 H, complex multiplets including sharp singlets between δ 0.6–1.1, and 2 well resolved singlets of equal intensity (total 3 H) at δ 3.7 and 3.75

Table 5 Crystal data, data collection and refinement results for **16a**

Crystal size	0.76 × 0.32 × 0.28 mm^3
Morphology	Parallelapiped
Wavelength	0.710 69 Å
θ_{max}/°	23
Z	2
μ/cm^{-1}	0.79
M	306.4
Unit cell	
a	8.815(1) Å
b	5.850(1) Å
c	15.156(1) Å
$\alpha = \gamma$	90°
β	93.77(1)°
Space group	$P2_1$ monoclinic No. 4 International Tables, vol. IV
d_c	1.30(1) g cm^{-3}
F(000)	324 e
Number of unique data used in refinement	1579 ($I > 1.5 \times \sigma I$ cut off applied)
Merging R_1	6.5% (mean multiplicity 1.7)
Empirical formula (from refined structure)	$C_{11}N_2H_{10}(CO_2CH_3)(C_6H_5)$
Minimum and maximum electron density peaks from final difference Fourier map	maximum; 0.28 e/Å minimum: −0.26 e/Å
Final R_{CRYST}	3.9%

Table 6 Fractional coordinates of atoms with standard deviations for **16a**

Atom	x	y	z
N(1)	0.056 3(4)	−0.541 10(0)	0.131 94(19)
C(2)	0.07193(4)	−0.413 3(8)	0.209 04(20)
C(3)	−0.002 0(4)	−0.468 3(7)	0.292 99(20)
C(31)	−0.169 9(4)	−0.524 1(7)	0.280 89(20)
C(32)	−0.227 9(4)	−0.720 3(8)	0.315 09(24)
C(33)	−0.382 6(5)	−0.761 2(9)	0.308 2(3)
C(34)	−0.479 4(5)	−0.606 6(9)	0.266 8(3)
C(35)	−0.421 9(5)	−0.410 2(8)	0.231 40(23)
C(36)	−0.269 0(4)	−0.370 4(7)	0.238 59(22)
N(4)	0.016 3(3)	−0.261 2(7)	0.349 00(18)
C(5)	0.170 6(4)	−0.176 9(7)	0.358 23(21)
C(51)	0.181 2(4)	−0.005 7(7)	0.432 71(22)
O(52)	0.082 1(3)	0.039 2(8)	0.478 12(18)
O(53)	0.317 3(3)	0.092 5(7)	0.440 88(16)
C(54)	0.340 8(6)	0.258 0(9)	0.510 3(3)
C(6)	0.213 0(4)	−0.072 0(7)	0.270 95(21)
C(7)	0.167 3(4)	−0.235 7(7)	0.197 45(20)
C(8)	0.215 0(4)	−0.249 1(8)	0.109 92(21)
C(9)	0.312 7(4)	−0.117 4(8)	0.060 91(22)
C(10)	0.337 3(5)	−0.180 8(8)	−0.023 20(24)
C(11)	0.264 7(5)	−0.373 1(8)	−0.061 82(24)
C(12)	0.167 9(5)	−0.504 5(8)	−0.015 43(23)
C(13)	0.143 7(4)	−0.440 6(7)	0.069 97(20)

Table 7 Bond lengths (Å) with standard deviations for **16a**

N(1)–C(2)	1.387(4)	C(5)–C(51)	1.508(5)
N(1)–C(13)	1.385(4)	C(5)–C(6)	1.527(5)
C(2)–C(3)	1.502(5)	C(51)–O(52)	1.177(5)
C(2)–C(7)	1.355(5)	C(51)–O(53)	1.328(5)
C(3)–C(31)	1.515(5)	O(53)–C(54)	1.435(6)
C(3)–N(4)	1.482(5)	C(6)–C(7)	1.504(5)
C(31)–C(32)	1.372(5)	C(7)–C(8)	1.420(5)
C(31)–C(36)	1.382(5)	C(8)–C(9)	1.404(5)
C(32)–C(33)	1.382(6)	C(8)–C(13)	1.402(5)
C(33)–C(34)	1.367(6)	C(9)–C(10)	1.359(6)
C(34)–C(35)	1.379(6)	C(10)–C(11)	1.403(6)
C(35)–C(36)	1.365(6)	C(11)–C(12)	1.376(6)
N(4)–C(5)	1.445(5)	C(12)–C(13)	1.377(5)

Table 8 Bond angles (°) with standard deviations for **16a**

C(2)–N(1)–C(13)	108.3(3)	C(5)–C(51)–O(52)	125.0(4)
N(1)–C(2)–C(3)	125.0(3)	C(5)–C(51)–O(53)	111.6(3)
N(1)–C(2)–C(7)	109.4(3)	O(52)–C(51)–O(53)	123.4(4)
C(3)–C(2)–C(7)	125.6(3)	C(51)–O(53)–C(54)	116.5(3)
C(2)–C(3)–C(31)	114.7(3)	C(5)–C(6)–C(7)	108.5(3)
C(2)–C(3)–N(4)	105.8(3)	C(2)–C(7)–C(6)	122.0(3)
C(31)–C(3)–N(4)	108.3(3)	C(2)–C(7)–C(8)	107.7(3)
C(3)–C(31)–C(32)	121.3(3)	C(6)–C(7)–C(8)	130.2(3)
C(3)–C(31)–C(36)	119.9(3)	C(7)–C(8)–C(9)	133.9(3)
C(32)–C(31)–C(36)	118.7(3)	C(7)–C(8)–C(13)	107.2(3)
C(31)–C(32)–C(33)	120.4(4)	C(9)–C(8)–C(13)	118.9(3)
C(32)–C(33)–C(34)	120.2(4)	C(8)–C(9)–C(10)	119.2(4)
C(33)–C(34)–C(35)	119.7(4)	C(9)–C(10)–C(11)	120.9(4)
C(34)–C(35)–C(36)	119.8(4)	C(10)–C(11)–C(12)	121.1(4)
C(31)–C(36)–C(35)	121.1(4)	C(11)–C(12)–C(13)	117.9(4)
C(3)–N(4)–C(5)	113.6(3)	N(1)–C(13)–C(8)	107.4(3)
N(4)–C(5)–C(51)	108.1(3)	N(1)–C(13)–C(12)	130.5(3)
N(4)–C(5)–C(6)	109.6(3)	C(8)–C(13)–C(12)	122.0(3)
C(51)–C(5)–C(6)	112.0(3)		

(2 × CO_2CH_3)], 5.6 and 6.05 (1 H total, br doublets, 2 × NH) and 7.1–7.4 (m, 5 H, ArH); δ_C(22.5 MHz; $CDCl_3$) 19.30 (q), 19.40 (q), 19.62 (q), 25.36 (25.15) (t), 26.66 (26.12) (t), 39.29 (39.07), 42.48 (d), 42.59 (42.11) (t), 47.95 (s), 48.06 (s), 48.33 (s), 51.15 (50.77) (t), 52.23 (52.34) (q), 57.16 (57.33) (d), 58.79 (58.41) (s), 58.79 (59.49) (s), 64.15 (t), 126.94 (d), 128.35 (d), 129.32 (d), 135.77 (135.55) (s), 171.91 (171.80) (s) and 215.03 (215.62) (s); m/z 393 (M^+, 1%), 375 (2), 215 (11), 151 (52), 123 (55), 109 (100), 81 (76) and 67 (42) (Found: M^+, 393.1596. $C_{20}H_{27}NO_5S$ requires M^+, 393.1610).

X-Ray Crystallography.—A summary of the crystal data, data collection and refinement parameters for compound **16a** are given in Table 5. The structure, and the crystallographic numbering, are shown in Fig. 1. Intensity data were collected on a FAST area detector system. The structure solution of **16a** was accomplished by direct methods using the program SHELX86[29] and refined by full matrix least-squares using SHELX76.[30] No absorption correction was applied, but data were connected for Lorentz and polarisation effects. Non-hydrogen atoms were refined anisotropically. The hydrogen atoms attached to N(1) and N(4) were located and refined isotropically; all other hydrogen atoms in **16a** were included in calculated positions with fixed thermal parameters.

Neutral atom scattering factors were taken from the International Tables for X-Ray Crystallography.[31] Molecular

drawings were plotted using the PLUTO78 program.[32] All calculations were performed on a VAX8200 computer. The final atomic parameters are listed in Table 6, and selected bond lengths and bond angles are given in Tables 7 and 8. Additional material available from the Cambridge Crystallographic Data Centre comprises hydrogen atom coordinates, thermal parameters and torsional angles.*

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