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Stereochemistry of Methyl 2-Benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate

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The Pictet–Spengler reaction of N_a-methyl-N_b-benzyltryptophan methyl ester hydrochloride (**4a**) with methyl 3-formylpropionate was carried out in 50% aqueous MeOH under reflux to afford methyl *trans*-2-benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (**3a**) as a major product and *trans*-2-benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic acid (**5a**) as a minor product. In earlier work, the stereochemistry of the major product **3a** had been erroneously assigned as 1,3-*cis* (**3b**), while the minor product **5a** had been incorrectly assigned as the 1,3-*trans* compound **3a**. Compound **3b** was not formed in this reaction. The stereochemistry of the major product (**3a**) was confirmed by X-ray crystallographic analysis in the present work.

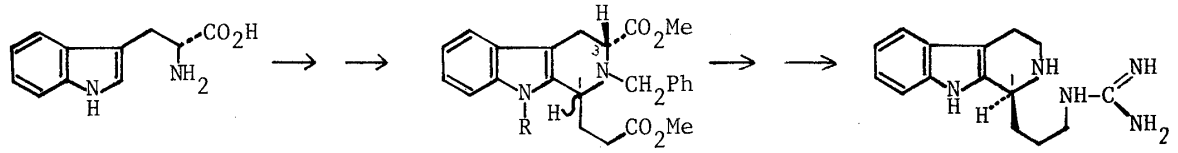
Keywords——stereochemistry; methyl 2-benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate; Pictet–Spengler reaction; X-ray crystallographic analysis; epimerization; Dieckmann cyclization; conformation

In a recent communication,[1] we reported the synthesis of (1*S*)-(−)-trypargine (**1a**), which has been isolated from the skin of African rhacophorid frogs, *Kassina senegalensis*, from (1*S*, 3*R*)-(−)-methyl 2-benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]-indole-1-propionate (**2a**). Compound (−)-**2a** was the main isomer obtained by the asymmetric Pictet–Spengler reaction of a (+)-N_b-benzyltryptophan methyl ester (derived from D-tryptophan) with α-ketoglutaric acid followed by methylation with diazomethane, and the stereochemistry of (−)-**2a** was unequivocally shown to be 1,3-*trans* by an X-ray crystallographic analysis.

For the chemical correlation of stereochemistry, the optically active N_a-methylated compound ((−)-**3**) was prepared by the N_a-methylation of *trans*-(−)-**2a**. Although (−)-**3** was considered to be the 1,3-*trans* isomer (**3a**) from the results of ^1H and ^{13}C nuclear magnetic resonance (NMR) spectral analysis, it was found to be identical with the 1,3-*cis* isomer (**3b**) whose stereochemistry had already been determined by one of the present authors.[2] These observations prompted us to re-examine the earlier assignments of stereochemistry for the N_a-methyl dimethyl esters (**3a** and **3b**).

In this report, we wish to describe the revision of the stereochemical and structural assignments for the 1,3-*trans* and 1,3-*cis* isomers (**3a** and **3b**) reported earlier.[2] In addition, studies on the conformational elucidation of **3a** and **3b** are reported on the basis of unambiguous evidence obtained by X-ray crystallographic analysis, as well as NMR spectral analysis.

Initially, syntheses of the *trans*- and *cis*-N_a-methyl dimethyl ester (**3a** and **3b**) were



(−)-**2a**: R=H, C_1-αH
(−)-**2b**: R=H, C_1-βH
(−)-**3**: R=Me, C_1-αH

(−)-**1a**

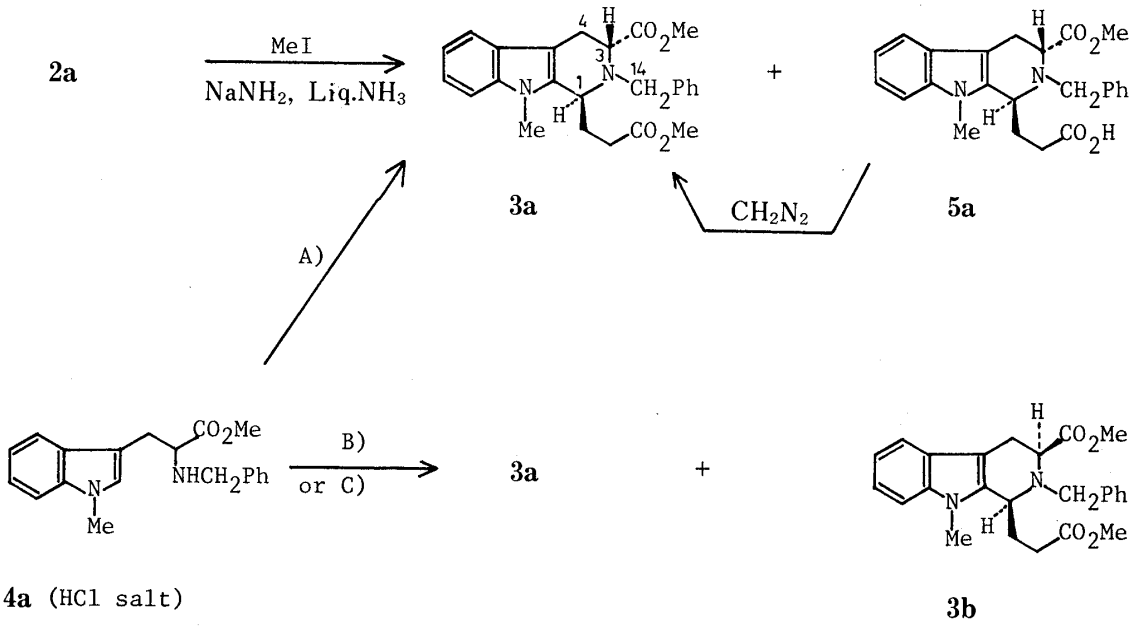
Chart 1

attempted by the procedure reported previously[2] and alternative methods. The Pictet–Spengler condensation of (±)-N_a-methyl-N_b-benzyltryptophan methyl ester (**4a**; hydrochloride) with methyl 3-formylpropionate in 50% aqueous MeOH gave two crystalline compounds, (±)-**3a** and (±)-**5a**, in 51.0 and 9.0% yields, respectively. Compounds (±)-**3a** and (±)-**5a** were identical with the so-called 1,3-*cis* isomer and the 1,3-*trans* isomer reported previously, respectively. However, the mass and ^{1}H-NMR spectra of (±)-**5a** showed the molecular ion (M^+) at *m/z* 406 and only one signal due to the methoxycarbonyl group at δ 3.83 as a singlet. Moreover, (±)-**5a** was methylated with ethereal diazomethane to provide the dimethyl ester ((±)-**3a**). Compound (±)-**5a** was independently obtained by condensation between (±)-**4b** (free base) and α-ketoglutaric acid according to the procedure of Cook *et al.*[3] From the above results, the structure of (±)-**5a** (which had previously been incorrectly assigned as the 1,3-*trans* isomer, (±)-**3a**), was clearly established as 2-benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic acid, having the same stereochemistry as the major product ((±)-**3a**).

The other stereoisomer ((±)-**3b**) of (±)-**3a** was obtained through two different synthetic routes since (±)-**3b** was actually not produced in the above condensation of (±)-**4a** with methyl 3-formylpropionate in aqueous media. In the first route, the Pictet–Spengler reaction of (±)-**4b** with α-ketoglutaric acid as mentioned above yielded a mixture of (±)-**5a** and its diastereoisomer ((±)-**5b**) in a ratio of *ca.* 5:4 (analyzed by high-performance liquid chromatography (HPLC)) in 89.1% total yield. The mixture of (±)-**5a** and (±)-**5b**, when reacted with ethereal diazomethane, afforded (±)-**3a** as a crystalline compound and its diastereoisomer ((±)-**3b**) as an amorphous substance after separation by column chromatography. In the second route, methyl 3-formylpropionate was reacted in refluxing benzene with (±)-**4b** to give (±)-**3a** and (±)-**3b** (*ca.* 3:1) in a yield of 78.4%.

The stereochemistry of (±)-**3a** and (±)-**3b** was determined as follows. In the ^{1}H-NMR spectrum of (±)-**3a** (Table I), coupling constants ($J_{3,4}$=5.3 and 10.5 Hz) between protons at the C-3 and C-4 positions reveal that the proton located at C-3 in (±)-**3a** occupies the axial position, as it does in the *trans* diastereoisomer, (−)-**2a** ($J_{3,4}$=5.3 and 8.8 Hz). Two signals at δ 3.47 and δ 3.83 due to the methoxycarbonyl groups have very different values of chemical shifts. The methylene protons of the N_b-benzyl functional group appeared as an AB system with chemical shifts δ 3.38 and δ 3.81, showing magnetically nonequivalent nature. These phenomena are common to *trans*-(−)-**2a**. Furthermore, the good agreement of the chemical shifts in the ^{13}C-NMR spectra (Table II) observed between (±)-**3a** [δ: 53.5 (C_1), 56.2 (C_3), 20.4 (C_4), 52.9 (C_{14})] and *trans*-(−)-**2a** [δ: 54.7 (C_1), 56.7 (C_3), 21.3 (C_4), 53.4 (C_{14})] reflect the same stereochemistry. A similar phenomenon was also observed in the case of (±)-**3b** [δ: 54.3 and 57.6 (C_1 and C_3), 18.1 (C_4), 61.3 (C_{14})] and *cis*-(−)-**2b** [δ: 56.2 and 58.7 (C_1 and C_3), 19.8 (C_4), 59.4 (C_{14})].

On the other hand, because of the possibility that epimerization might occur during N_a-methylation of *trans*-(−)-**2a**, the following reactions were performed using the racemic compound. The *trans* dimethyl ester ((±)-**2a**) was alkylated with MeI in liquid ammonia



A) $MeO_2CCH_2CH_2CHO$/50% aq. MeOH, reflux, 40 h
B) 1) $HO_2CCH_2CH_2COCO_2H$/benzene–dioxane, reflux, 10—20 h
2) CH_2N_2/MeOH–CH_2Cl_2, r.t.
C) $MeO_2CCH_2CH_2CHO$/benzene, reflux, 23 h

Chart 2

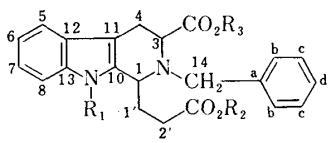
TABLE I. ^{1}H-NMR Data[a-c]

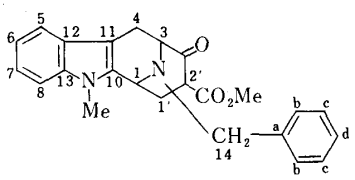
	(−)-**2a**	(−)-**2b**	(±)-**3a**	(±)-**3b**
H-1	3.87—3.94 m	3.76—3.94 m	3.76—3.88 m	3.82—3.94 m
H-3	3.98 dd	3.76—3.94 m	4.09 dd	3.82—3.94 m
	(5.3, 8.8)		(5.3, 10.5)	
H_a-4	3.03 dd	2.99 dd	3.06 dd	3.02 dd
	(5.3, 15.8)	(6.3, 15.8)	(5.3, 15.8)	(6.1, 16.2)
H_b-4	3.12 dd	3.22 dd	3.13 dd	3.32 dd
	(8.8, 15.8)	(3.6, 15.8)	(10.5, 15.8)	(2.0, 16.2)
H_2-14	3.58, 3.84 ABq	3.82, 3.89 ABq	3.38, 3.81 ABq	3.73, 3.87 ABq
	(13.6)	(14.0)	(13.2)	(13.4)
CO_2CH_3	3.50 s	3.55 s	3.47 s	3.52 s
	3.75 s	3.69 s	3.83 s	3.63 or 3.65 s[d]

a) The δ values are in ppm downfield from TMS.
b) In $CDCl_3$ solution.
c) Numbers in parentheses are the coupling constants J (Hz).
d) One of the signals is due to the N–CH_3 group.

containing $NaNH_2$ to yield (±)-**3a**, which was identical with (±)-**3a** obtained above. Furthermore, treatment of *trans*-(±)-**2a** with $NaNH_2$ in liquid ammonia in the presence of NH_4Cl as an anion-trapping agent resulted in recovery of the starting material ((±)-**2a**) in a yield of 73.5%. None of the diastereoisomer of (±)-**2a** or (±)-**3a** was observed. The results of the NMR spectral analysis and the above two experiments demonstrate that (±)-**3a** has the same 1,3-*trans* configuration as (±)-**2a**. To confirm this stereochemical assignment of (±)-**3a**,

TABLE II. Carbon-13 Chemical Shifts[a]





	(−)-**2a**[b]	(−)-**2b**[b]	(−)-**8a**[c]	(±)-**3a**[b]	(±)-**3b**[b]	(±)-**7a**[b]	(±)-**9**[b]
C(1)	54.7	56.2[e]	57.5[e]	53.5	54.3[e]	55.4	48.9
C(3)	56.7	58.7[e]	58.3[e]	56.2	57.6[e]	55.8	55.1
C(4)	21.3	19.8	20.7	20.4	18.1	20.1	22.3
C(5)	118.1	118.2	118.5	118.2	118.3	118.5	118.8
C(6)	119.5	119.4	119.7	119.2	119.0	119.4	119.1
C(7)	121.7	121.7	122.4	121.4	121.4	121.7	121.3
C(8)	110.9	110.9	111.6	108.9	108.8	108.9	108.8
C(10)	134.2	133.4	131.5	135.7	134.7	134.7	134.5
C(11)	107.4	106.3	107.0	106.4	104.9	107.0	105.6
C(12)	126.95	127.0	126.7	126.6	126.7	126.5	126.7
C(13)	136.3	136.2	135.2	137.6	137.6	137.5	137.0
C(14)	53.4	59.4	53.7	52.9	61.3	52.4	56.1
C(14a)	139.3	139.0	137.3	139.2	139.0	138.3	138.3
C(14b)	129.1[d]	129.0[d]	130.3[d]	129.3[d]	129.1[d]	129.9[d]	128.7[d]
C(14c)	128.2[d]	128.3[d]	129.0[d]	128.2[d]	128.4[d]	128.3[d]	128.4[d]
C(14d)	127.04	127.3	128.8	127.0	127.4	127.5	127.3
C(1′)	28.9	29.3	28.8	28.0	29.2[f]	27.3	28.1
C(2′)	29.8	30.4	31.8	29.68	29.8[f]	32.6	94.0
N-CH_3				29.74	29.8	29.7	29.3
$CO_2\underline{C}H_3$	51.4	51.5		51.3	51.3		51.4
	51.8	51.8		52.0	52.0		
C=O	173.3	173.9	170.3	173.3	174.1	179.4	171.9[e]
	174.3	174.6	177.4	173.9	174.3	180.0	172.5[e] (Enol form)

a) The δ values are in ppm downfield from TMS.
b) In $CDCl_3$ solution.
c) In $CDCl_3+CD_3OD$ solution.
d—*f*) Signals in any column may be reversed.

the X-ray crystallographic analysis of (±)-**3a** was carried out.

The N_a-methyl dimethyl ester ((±)-**3a**) crystallizes in the monoclinic space group $P2_1/c$ with four molecules per unit cell, and the dimensions are $a=12.156(2)$, $b=10.604(2)$, $c=16.801(3)$ Å and $\beta=91.77(1)°$. In all, 3278 unique and significant reflections having $F_o>3\sigma(F_o)$ were measured on a Rigaku AFC-5 diffractometer using graphite-monochromated Mo$K\alpha$ radiation. Scanning was done by the $\omega-2\theta$ scanning method at a rate of 2°/min in 2θ in the range up to $2\theta=55°$.

The structure was solved by the direct method using the structure determination program package based on MULTAN[4] provided with the diffractometer. The structure was refined by block-diagonal least-squares methods to an R value of 0.094.

This X-ray crystallographic analysis confirmed that (±)-**3a** has the 1,3-*trans* configuration shown in Figs. 1 and 2,[5] and consequently, (±)-**3b** was assigned as the 1,3-*cis* diastereoisomer. The conformation of *trans*-(±)-**3a** on the ring C is substantially consistent with that of *trans*-(−)-**2a**, with an axial substituent at C-1, an axial N_b-benzyl functional group and an equatorial methoxycarbonyl group, and the ^1H- and ^{13}C-NMR spectra indicate that the conformation of *trans*-(±)-**3a** is the same both in solution and in the crystalline state.

TABLE III. Final Atomic Parameters ($\times 10^4$) with Estimated Standard Deviations in Parentheses

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	1949 (5)	2165 (7)	5657 (4)	27 (4)	66 (7)	21 (2)	4 (4)	0 (3)	3 (3)
N(2)	1827 (4)	1386 (6)	6374 (3)	31 (4)	59 (6)	22 (2)	−2 (4)	−2 (2)	−3 (3)
C(3)	1007 (6)	363 (7)	6256 (6)	31 (5)	52 (7)	31 (3)	−7 (5)	−4 (3)	5 (4)
C(4)	−190 (6)	853 (8)	6131 (5)	32 (5)	75 (8)	38 (3)	−5 (5)	−5 (3)	12 (4)
C(5)	−2174 (6)	2283 (8)	5004 (5)	35 (5)	84 (9)	39 (3)	10 (5)	−10 (3)	−13 (5)
C(6)	−2764 (7)	3011 (10)	4447 (5)	47 (6)	119 (11)	39 (4)	17 (7)	−17 (4)	−11 (5)
C(7)	−2260 (7)	3884 (10)	3946 (5)	53 (6)	121 (11)	35 (4)	26 (7)	−15 (4)	−6 (5)
C(8)	−1111 (7)	4074 (9)	3968 (5)	68 (7)	96 (10)	28 (3)	24 (7)	−5 (4)	0 (5)
N(9)	615 (5)	3330 (6)	4701 (4)	41 (4)	71 (6)	24 (2)	3 (4)	−2 (2)	3 (3)
C(10)	823 (5)	2455 (7)	5290 (4)	33 (5)	63 (7)	22 (2)	2 (5)	−1 (3)	−3 (3)
C(11)	−141 (6)	1876 (7)	5512 (4)	33 (5)	61 (7)	28 (3)	0 (5)	−5 (3)	0 (4)
C(12)	−999 (6)	2454 (7)	5028 (5)	31 (5)	66 (7)	30 (3)	5 (5)	−7 (3)	−4 (4)
C(13)	−511 (6)	3334 (8)	4527 (4)	45 (5)	76 (8)	23 (3)	12 (5)	−5 (3)	−3 (4)
C(14)	1594 (6)	2152 (8)	7079 (4)	37 (5)	83 (8)	23 (3)	−1 (5)	−2 (3)	−10 (4)
C(14A)	2660 (6)	2668 (8)	7463 (4)	55 (6)	76 (8)	20 (3)	−17 (5)	−3 (3)	−1 (4)
C(14B)	3589 (7)	1869 (9)	7552 (5)	50 (6)	94 (9)	33 (3)	−10 (6)	−14 (3)	2 (5)
C(14C)	4558 (8)	2332 (11)	7922 (6)	63 (7)	155 (14)	35 (4)	−29 (8)	−16 (4)	8 (6)
C(14D)	4579 (9)	3606 (11)	8201 (6)	101 (9)	154 (14)	33 (4)	−64 (10)	−15 (5)	6 (6)
C(14E)	3671 (9)	4381 (10)	8115 (6)	126 (11)	99 (11)	34 (4)	−53 (9)	−6 (5)	−12 (5)
C(14F)	2690 (8)	3912 (8)	7744 (5)	95 (8)	77 (9)	25 (3)	−19 (7)	0 (4)	−5 (4)
C(1′)	2671 (6)	1493 (8)	5032 (5)	33 (5)	80 (8)	30 (3)	7 (5)	4 (3)	−8 (4)
C(2′)	3786 (7)	1065 (9)	5381 (6)	43 (6)	98 (10)	46 (4)	28 (6)	3 (4)	6 (5)
C(3′)	4587 (7)	2052 (11)	5647 (6)	57 (7)	152 (14)	45 (4)	44 (8)	19 (4)	33 (6)
C(4′)	5018 (9)	4176 (11)	5940 (7)	86 (9)	112 (12)	54 (5)	−13 (8)	−6 (5)	1 (6)
C(5′)	1420 (7)	4155 (8)	4311 (5)	59 (6)	80 (9)	28 (3)	−1 (6)	7 (3)	9 (4)
C(6′)	1058 (7)	−530 (8)	6950 (5)	52 (6)	69 (8)	38 (4)	2 (6)	−4 (4)	9 (4)
C(7′)	2217 (9)	−1824 (11)	7787 (6)	89 (9)	112 (12)	51 (5)	18 (8)	−8 (5)	35 (6)
O(1)	5484 (6)	1792 (9)	5926 (6)	55 (5)	186 (12)	111 (6)	11 (7)	−21 (4)	49 (7)
O(2)	4261 (5)	3220 (6)	5565 (4)	41 (4)	110 (7)	60 (3)	3 (4)	−4 (3)	6 (4)
O(3)	297 (5)	−886 (6)	7315 (5)	50 (5)	204 (12)	84 (5)	15 (6)	17 (4)	85 (6)
O(4)	2092 (4)	−907 (6)	7132 (4)	49 (4)	89 (6)	45 (3)	7 (4)	−6 (3)	22 (3)

Temperature factors are of the form $T=\exp[-(\beta_{12}h^2+\beta_{22}k^2+\beta_{33}l^2+2hk\beta_{12}+2kl\beta_{23}+2h(\beta_{13})]$.

In the case of the *cis* isomer ((±)-**3b**), a 1,3-diequatorial conformer A and a 1,3-diaxial conformer B exist, as shown in Chart 3. However, the ^{1}H-NMR spectrum of *cis*-(±)-**3b** shows an ABX pattern for H–C_3–C_4<H/H () ($J_{AB}=16.2$, $J_{AX}=2.0$ and $J_{BX}=6.1$ Hz) suggesting the equatorial nature of the proton at C-3. In the ^{13}C-NMR spectrum, the signal due to the carbon atom at the 4-position is approximately 7 ppm or more upfield from the corresponding carbon signal of the 1,3-disubstituted tetrahydro-β-carboline [*trans*-**6a**: 25.1 ppm (C_4); *cis*-**6b**: 26.0 ppm (C_4)][6] as a result of the γ-effect arising from the axial orientation of the N_b-benzyl group. The constancy of the ^{13}C-NMR chemical shifts at C-4 also supports the view that the N_b-benzyl group of the two compounds ((±)-**3a** and (±)-**3b**) has the same axial conformation. The benzylic carbon chemical shift (C_{14}: 52.9 ppm) in *trans*-(±)-**3a** is 8.4 ppm upfield relative to that in *cis*-(±)-**3b**, and it is considered that the steric interaction between the axial benzyl group and the equatorial substituent adjacent to the N_b-position causes the upfield shift in *trans*-(±)-**3a**. Thus, it suggests that *cis*-(±)-**3b** exists preferentially in the 1,2,3-triaxial conformation shown in conformer B because of the steric hindrance between the N_a-methyl group and the equatorial 1-substituent present in conformer A. Moreover, conformer A involves an unfavorable interaction between the axial benzyl group and the equatorial substituent at C-1 or C-3.

TABLE IV. Bond Lengths in Å Unit with Estimated Standard Deviations in Parentheses

Atom 1	Atom 2	Length (STD)	Atom 1	Atom 2	Length (STD)
C(1)	– N(2)	1.471 (10)	C(1′)	– C(2′)	1.529 (13)
N(2)	– C(3)	1.483 (9)	C(2′)	– C(3′)	1.489 (14)
C(3)	– C(4)	1.554 (10)	C(3′)	– O(1)	1.206 (13)
C(4)	– C(11)	1.504 (11)	C(3′)	– O(2)	1.306 (13)
C(11)	– C(10)	1.385 (11)	O(2)	– C(4′)	1.496 (13)
C(10)	– C(1)	1.514 (12)	N(2)	– C(14)	1.471 (10)
C(11)	– C(12)	1.439 (13)	C(14)	– C(14A)	1.530 (13)
C(12)	– C(13)	1.401 (12)	C(14A)	– C(14B)	1.416 (12)
C(13)	– N(9)	1.391 (10)	C(14B)	– C(14C)	1.403 (14)
N(9)	– C(10)	1.375 (10)	C(14C)	– C(14D)	1.431 (16)
N(9)	– C(5′)	1.480 (12)	C(14D)	– C(14E)	1.380 (16)
C(12)	– C(5)	1.439 (10)	C(14E)	– C(14F)	1.419 (16)
C(5)	– C(6)	1.393 (14)	C(14F)	– C(14A)	1.401 (12)
C(6)	– C(7)	1.403 (14)	C(3)	– C(6′)	1.502 (11)
C(7)	– C(8)	1.411 (12)	C(6′)	– O(3)	1.187 (13)
C(8)	– C(13)	1.409 (13)	C(6′)	– O(4)	1.345 (10)
C(1)	– C(1′)	1.560 (13)	O(4)	– C(7′)	1.472 (13)

TABLE V. Bond Angles in Degrees with Estimated Standard Deviations in Parentheses

Atom			Angle (STD)	Atom			Angle (STD)
1	2	3		1	2	3	
C(5′)	– N(9)	– C(10)	127.5 (6)	C(3)	– N(2)	– C(14)	111.4 (7)
C(5′)	– N(9)	– C(13)	124.4 (7)	N(2)	– C(3)	– C(4)	113.3 (6)
C(10)	– N(9)	– C(13)	108.2 (8)	N(2)	– C(3)	– C(6′)	110.3 (7)
N(9)	– C(10)	– C(1)	125.0 (7)	C(4)	– C(3)	– C(6′)	109.4 (8)
N(9)	– C(10)	– C(11)	110.8 (7)	C(11)	– C(4)	– C(3)	106.1 (8)
C(11)	– C(10)	– C(1)	124.2 (6)	C(1)	– C(1′)	– C(2′)	112.9 (7)
C(10)	– C(11)	– C(12)	105.3 (6)	C(1′)	– C(2′)	– C(3′)	118.0 (8)
C(10)	– C(11)	– C(4)	123.9 (7)	C(2′)	– C(3′)	– O(1)	112.0 (10)
C(12)	– C(11)	– C(4)	130.8 (7)	C(2′)	– C(3′)	– O(2)	116.2 (8)
C(11)	– C(12)	– C(13)	108.1 (6)	O(1)	– C(3′)	– O(2)	121.7 (10)
C(11)	– C(12)	– C(5)	131.6 (8)	C(3′)	– O(2)	– C(4′)	114.7 (8)
C(13)	– C(12)	– C(5)	120.3 (8)	N(2)	– C(14)	– C(14A)	110.8 (7)
N(9)	– C(13)	– C(12)	107.7 (7)	C(14)	– C(14A)	– C(14B)	119.6 (7)
N(9)	– C(13)	– C(8)	128.9 (8)	C(14)	– C(14A)	– C(14F)	119.4 (7)
C(12)	– C(13)	– C(8)	123.4 (7)	C(14B)	– C(14A)	– C(14F)	121.0 (8)
C(12)	– C(15)	– C(6)	115.9 (9)	C(14A)	– C(14B)	– C(14C)	119.6 (9)
C(5)	– C(6)	– C(7)	123.0 (8)	C(14B)	– C(14C)	– C(14D)	118.8 (9)
C(6)	– C(7)	– C(8)	121.8 (9)	C(14C)	– C(14D)	– C(14E)	121.5 (10)
C(13)	– C(8)	– C(7)	115.5 (9)	C(14D)	– C(14E)	– C(14F)	119.8 (10)
C(10)	– C(1)	– N(9)	109.6 (7)	C(14A)	– C(14F)	– C(14E)	119.4 (9)
C(10)	– C(1)	– C(1′)	109.9 (6)	C(3)	– C(6′)	– O(3)	125.9 (8)
N(2)	– C(1)	– C(1′)	111.5 (6)	C(3)	– C(6′)	– O(4)	112.3 (8)
C(1)	– N(2)	– C(3)	112.7 (7)	O(3)	– C(6′)	– O(4)	121.8 (8)
C(1)	– N(2)	– C(14)	112.1 (6)	C(6′)	– O(4)	– C(7′)	116.1 (8)

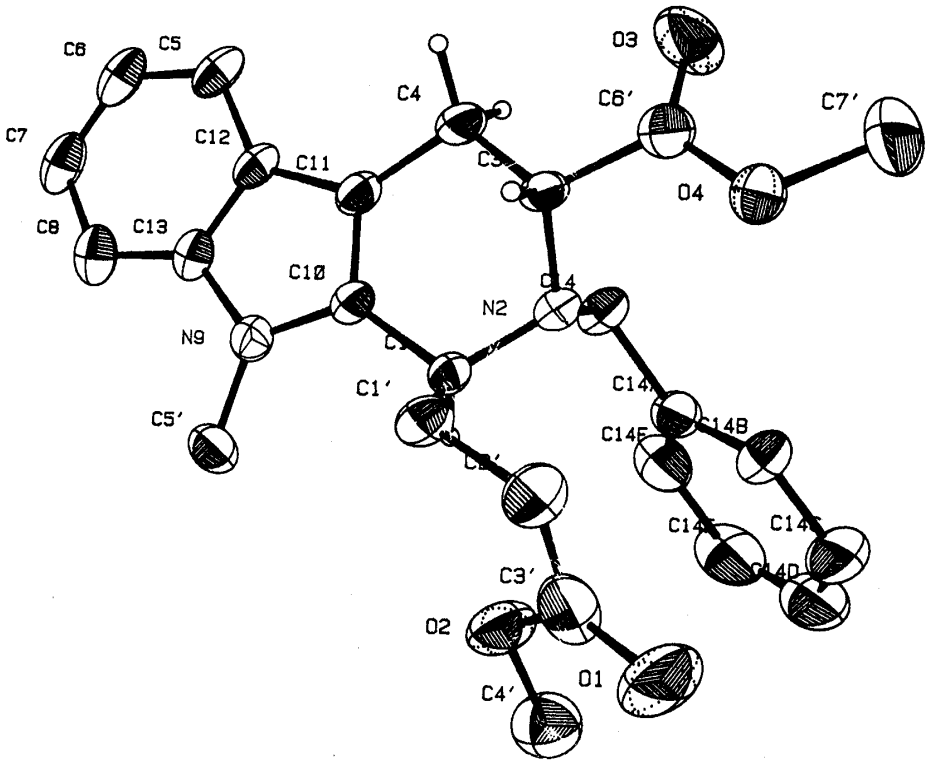


Fig. 1. An ORTEP Drawing of the Structure of **3a**

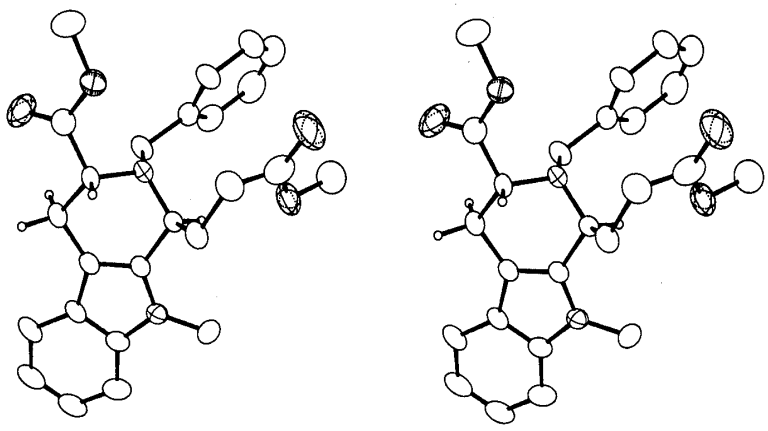
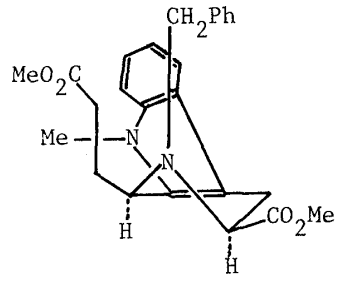


Fig. 2. Stereoscopic View of the Structure of **3a**

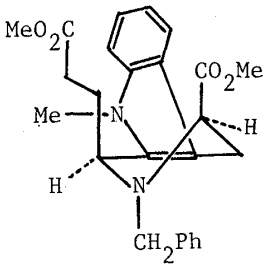
It is interesting to note that the bulky N_b-benzyl moiety and 1-substituent take the *trans* diaxial relationship in the predominant conformation in both *trans*-(±)-**3a** and *cis*-(±)-**3b**.

In conclusion, the Pictet–Spengler reaction of (±)-**4a** with methyl 3-formylpropionate in aqueous media yielded the *trans* dimethyl ester ((±)-**3a**) as a major product and the *trans* monomethyl ester ((±)-**5a**) as a minor product, while the *cis* dimethyl ester ((±)-**3b**) was not formed in the reaction. Therefore, the previous stereochemical and structural asignments for the so-called *trans* and *cis* diastereoisomers ((±)-**3a** and (±)-**3b**) must be corrected as described in this paper (Chart 2).

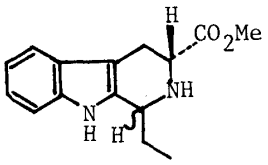
Hydolysis under alkaline conditions and the relative reactivity in the Dieckmann reaction were investigated to examine the differences in chemical properties between *trans*-(±)-**3a** and *cis*-(±)-**3b**.



conformer A



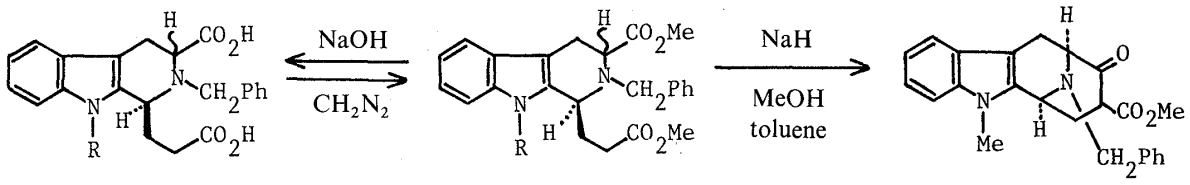
conformer B



trans-**6a**
cis-**6b**

Chart 3

The *trans* isomer ((±)-**3a**) was hydrolyzed with NaOH to afford the dicarboxylic acid ((±)-**7a**), which was converted back to the original *trans* isomer ((±)-**3a**) on treatment with ethereal diazomethane. The same sequence of reactions was also carried out using optically active *trans*-(−)-**2a** to yield *trans*-(−)-**2a** with retention of configuration, whereas *cis*-(±)-**3b** afforded a mixture of *trans* and *cis* diastereoisomers ((±)-**3a** and (±)-**3b**) in a ratio of 2.7 : 1 through partial epimerization under the same conditions. Thus, these results suggest that 1,3-*trans* configuration may be thermodynamically more stable than 1,3-*cis* configuration.



trans-**7a**: R=Me
cis-**7b**: R=Me
trans-**8a**: R=H

trans-**3a**: R=Me
cis-**3b**: R=Me
trans-**2a**: R=H

9

Chart 4

The Dieckmann reaction of *trans*-(±)-**3a** in boiling toluene in the presence of NaH and one equimolar amount of MeOH resulted in the formation of the β-ketoester ((±)-**9**) in 83.8% yield. The 1,3-diaxial conformation in *cis*-(±)-**3b** might be expected to be favorable for the Dieckmann cyclization, producing the β-ketoester. Contrary to expectation, however, the Dieckmann condensation of *cis*-(±)-**3b** under the same conditions was unsuccessful and *cis*-(±)-**3b** was completely epimerized into *trans*-(±)-**3a** in a yield of 80.1%. A further study on the cyclization of *cis*-(±)-**3b** was made under different conditions [NaH in toluene; NaH in tetrahydrofuran (THF, Hobson's method)[7]], but only 20—30% of epimerization into *trans*-(±)-**3a** was observed.

It seems to be difficult to explain the different reactivities observed between *trans*-(±)-**3a** and *cis*-(±)-**3b** in the Dieckmann reaction simply from the present results. However, one possible explanation is as follows. Enolate formation at the C-2′ position on *trans*-**3a** initially takes place and then the cyclization of the resultant enolate (A) to the β-ketoester (**9**) may proceed by epimerization at the C-3 position prior to cyclization *via* a transient dienolate (B) at the C-2′ and C-3 positions. In the case of *cis*-**3b**, initial abstraction of a proton by the base (probably sodium methoxide generated *in situ*) occurs at the C-3 equatorial proton (sterically less hindered than that of *trans*-**3a**) thus providing the stable enolate (D). This enolate

reversibly forms the unstable β-ketoester (**10**)[8] and resists cyclization into **9** under the above Dieckmann conditions, furnishing the thermodynamically more stable *trans*-**3a**.

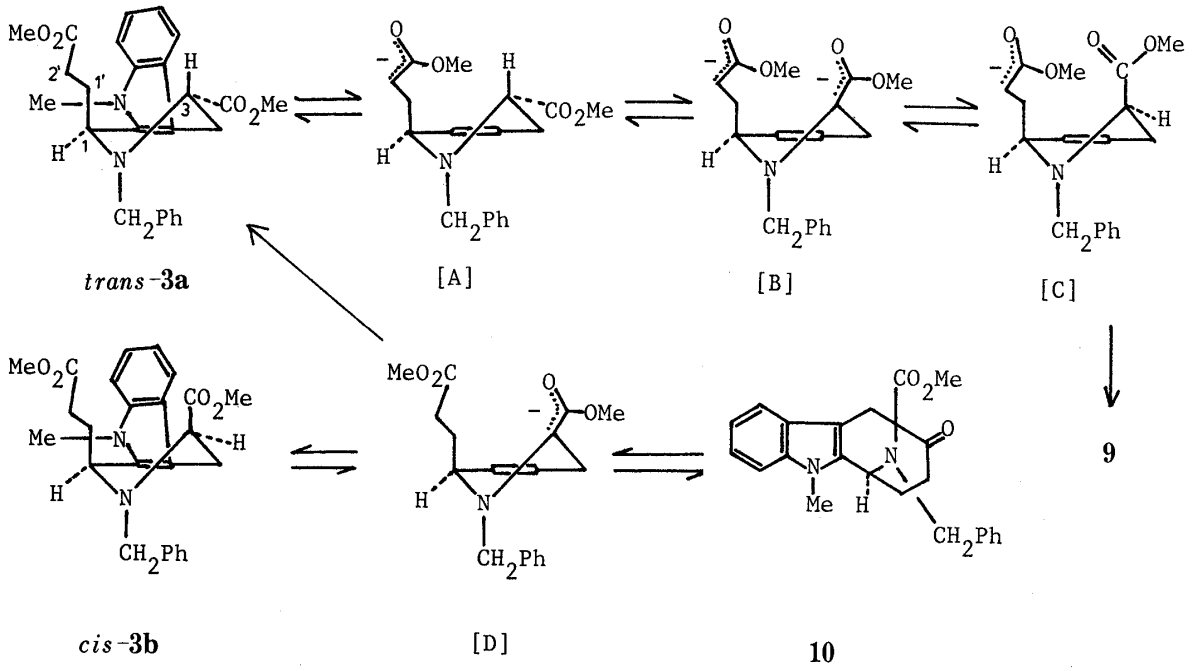


Chart 5

Experimental

All melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Ultraviolet (UV) spectra were recorded on a Hitachi 323 spectrophotometer. Infrared (IR) spectra were recorded on a Hitachi 285 spectrophotometer. Mass spectra (MS) were recorded with a JEOL JMS-D300 mass spectrometer. The ^1H and ^{13}C NMR spectra were obtained on a JEOL FX-270 spectrometer. Chemical shifts for the ^1H and ^{13}C-NMR spectra are reported as δ values (parts per million) from tetramethylsilane (TMS) as an internal standard. Abbreviations used are: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), aromatic (arom). Chromatography was performed on SiO_2 (Kieselgel 60, 35—70 mesh, Merck) unless otherwise indicated. High-performance liquid chromatography (HPLC) was carried out in the reverse phase [μ-Bondapak C_{18} (3.9 mm × 30 cm); Radial-PAK Cartridge C_{18} (5 mm × 10 cm); Waters Associates]. The eluting solvent was 60—90% CH_3CN–$AcONH_4$ (0.025—0.05 M, pH 4.00).

Methyl *trans*-2-Benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (3a) and *trans*-2-Benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (5a)—A mixture of N_a-methyl- N_b-benzyltryptophan methyl ester hydrochloride (**4a**: 3.585 g, 0.01 mol) and methyl 3-formylpropionate (1.508 g, 0.013 mol) in H_2O–MeOH (1 : 1; v/v; 50 ml) was heated to reflux for 40 h under nitrogen. The resultant crystals were separated and washed with a small volume of cold MeOH to afford a mixture of **3a** and **5a** (2.430 g). The mixture was separated by column chromatography on silica gel (60 g). Elution with a mixture of *n*-hexane–AcOEt (9 : 1; v/v) gave the *trans*-dimethyl ester (**3a**: 2.14 g, 51.0% yield) as colorless crystals. Recrystallization from MeOH furnished colorless plates. mp 145—146 °C [lit.,[3,9] mp 137—140 °C]. IR ν_{max}^{KBr} cm^{-1}: 1730 (ester). MS *m/z* (%): 420 (M^+, 9.2), 389 (1.3), 361 (7.1), 333 (100), 273 (6.1), 243 (4.6), 184 (16.3), 183 (6.1), 182 (4.6), 170 (7.7), 169 (4.1), 168 (7.7), 99 (31.6). ^1H-NMR ($CDCl_3$) δ: 1.76—2.07 (2H, m, H_2–$C_{1'}$), 2.39 (1H, dt, J = 5.6 and 17.5 Hz, H–$C_{2'}$), 2.59 (1H, ddd, J = 5.6, 9.6 and 17.5 Hz, H–$C_{2'}$), 3.06 (1H, dd, J = 5.3 and 15.8 Hz, H–C_4), 3.13 (1H, dd, J = 10.5 and 15.8 Hz, H–C_4), 3.38 and 3.81 (2H, ABq, J = 13.2 Hz, CH_2Ph), 3.47 and 3.38 (each 3H, s, CO_2CH_3), 3.64 (3H, s, N–CH_3), 3.76—3.88 (1H, m, H–C_1), 4.09 (1H, dd, J = 5.3 and 10.5 Hz, H–C_3), 7.09—7.37 (8H, m, arom H), 7.56 (1H, d, J = 7.9 Hz, arom H). *Anal.* Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.50; H, 6.69; N, 6.68.

Elution with *n*-hexane–AcOEt (4 : 1—1 : 1, v/v) afforded the *trans*-monomethyl ester (**5a**: 137 mg). Moreover, the mother liquor of the reaction mixture was concentrated in a small volume, adjusted to pH 7.0 with AcOH and extracted with $CHCl_3$ (3 × 70 ml). The combined $CHCl_3$ layer was washed, dried and concentrated *in vacuo* to give 1.79 g of the residue. This residue was purified by column chromatography over silica gel (72 g) with AcOEt to provide a colorless solid (**5a**: 230 mg), which was recrystallized from MeOH to afford colorless prisms. The total yield of **5a** was 9.0%. mp 199—201 °C (dec.) [lit.,[3,9] mp 197—199 °C]. IR ν_{max}^{KBr} cm^{-1}: 1730 and 1710 (ester and acid). MS *m/z* (%): 406 (M^+, 9.5), 347 (9.1), 333 (100), 273 (6.6), 242 (5.8), 184 (5.0), 183 (17.4), 182 (6.6), 170 (9.9), 169 (4.5),

168 (9.1), 91 (41.3). ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.02 (2H, m, H_2–$C_{1'}$), 2.35 (1H, dt, J=6.0 and 17.3 Hz, H–$C_{2'}$), 2.56 (1H, dt, J=6.8 and 17.3 Hz, H–$C_{2'}$), 3.08—3.22 (2H, m, H_2–C_4), 3.43 and 3.94 (2H, ABq, J=12.9 Hz, CH_2Ph), 3.59 (3H, s, N–CH_3), 3.83 (3H, s, CO_2CH_3), 3.82—3.90 (1H, m, H–C_1), 4.12 (1H, d, H–C_3), 7.10—7.40 (8H, m, arom H), 7.58 (1H, d, J=7.1 Hz, arom H). *Anal.* Calcd for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.95; H, 6.48; N, 6.91.

Esterification of the *trans*-Monomethyl Ester (5a) with Diazomethane——An excess of ethereal diazomethane was added to a stirred solution of **5a** (40.6 mg, 0.1 mmol) in a mixture of MeOH–CH_2Cl_2 (1:1; v/v; 2 ml) at room temperature, and then the mixture was stirred for an additional 1 h. After removal of the solvent, the residue was crystallized from MeOH to yield the *trans*-dimethyl ester (**3a**: 40.6 mg, 96.7% yield) as colorless plates (mp 145—146 °C). This product was identical (mp, MS, IR, ^{1}H and ^{13}C-NMR spectra) with the foregoing *trans*-dimethyl ester (**3a**).

Synthesis of the *trans*-Monomethyl Ester (5a) by an Alternative Method——A mixture of N_a-methyl- N_b-benzyltryptophan methyl ester (**4b**: free base, 4.750 g, 0.0148 mol) and α-ketoglutaric acid (2.585 g, 0.0177 mol) in dry benzene–dry dioxane (2:1; v/v; 120 ml) was refluxed for 10 or 20 h with water removal by a Dean–Stark trap. After evaporation of the solvent, the yellowish residue was chromatographed on silica gel (117 g) with a mixture of *n*-hexane–AcOEt (2:1, v/v) to afford a mixture of the *trans*-monomethyl ester (**5a**) and its diastereoisomer (**5b**) (5.333 g, 89.1% total yield), which was crystallized from MeOH–benzene (8:1; v/v) to give only one isomer (**5a**: 1.931 g) as colorless prisms.

Methyl *cis*-2-Benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (3b) and *trans*-3a——N_b-Benzyl ester (**4b**: free base, 5.50 g, 0.017 mol) and methyl 3-formylpropionate (4.50 g, 0.039 mol) were dissolved in dry benzene (125 ml), and then the solution was refluxed for 23 h. Water was removed by means of a Dean–Stark trap. The solvent was concentrated under reduced pressure to provide a viscous oil (9.23 g), which was chromatographed on silica gel (140 g). Elution with *n*-hexane–AcOEt (10:1—8:1; v/v) gave a mixture of *trans*-**3a** and *cis*-**3b** (5.34 g, 74.8% yield).

The above mixture was re-chromatographed over silica gel (Wakogel C-200, 120 g) using a mixture of *n*-hexane–AcOEt (12:1; v/v). The less polar *trans*-**3a** (2.99 g) was eluted first as colorless crystals, and the more polar *cis*-**3b** (1.37 g) was obtained next as an amorphous compound.

cis-**3b**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (ester). MS *m/z* (%): 420 (M^+, 5.3), 389 (0.8), 361 (4.2), 333 (100), 273 (5.9), 243 (2.0), 184 (3.9), 183 (17.6), 182 (5.9), 170 (5.9), 169 (2.9), 168 (7.8), 91 (43.1). ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.56 (1H, m, H–$C_{1'}$), 1.86—2.00 (1H, m, H–$C_{1'}$), 2.52 (1H, dt, J=5.5 and 17.3 Hz, H–$C_{2'}$), 2.80 (1H, ddd, J=5.9, 9.2 and 17.3 Hz, H–$C_{2'}$), 3.02 (1H, dd, J=6.1 and 16.2 Hz, H–C_4), 3.32 (1H, dd, J=2.0 and 16.2 Hz, H–C_4), 3.52, 3.63 and 3.65 (each 3H, s, CO_2CH_3 and N–CH_3), 3.73 and 3.87 (2H, ABq, J=13.4 Hz, CH_2Ph), 3.82—3.94 (2H, m, H–C_1 and H–C_3), 7.08—7.44 (8H, m, arom H), 7.55 (1H, d, J=7.6 Hz, arom H).

N_a-Methylation of Methyl *trans*-2-Benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (2a); Synthesis of *trans*-3a——Metallic Na (138 mg) was added in small pieces to a stirred solution of liquid ammonia (*ca.* 20 ml) containing $Fe(NO_3)_3 \cdot 9H_2O$ (8.4 mg). When metallic Na was completely dissolved, *trans*-**2a** (1.015 g, 2.5 mmol) suspended in dry Et_2O (20 ml) was added to the stirred mixture. After 30 min, MeI (0.994 g, 7 mmol) was added in four portions over 1 h, and then the mixture was stirred for an additional 30 min. After evaporation of the solvent, the residue was suspended in H_2O (40 ml) and brine (30 ml), and extracted with 5% MeOH–$CHCl_3$ (4×70 ml). The combined organic phase was washed with brine (100 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residual oil (1.132 g) by column chromatography over silica gel (45 g) with a mixture of *n*-hexane–AcOEt (9:1; v/v) as the eluent produced the crystalline *trans*-N_a-methylated compound (**3a**: 0.874 g, 83.2% yield), which was recrystallized from MeOH to give colorless plates. This product was identical with *trans*-**3a** (mp, IR, MS, ^{1}H and ^{13}C-NMR spectra) prepared by the Pictet–Spengler reaction of **4a** or **4b** with methyl 3-formylpropionate.

Treatment of *trans*-2a with $NaNH_2$ in Liquid Ammonia in the Absence of MeI——A suspension of *trans*-**2a** (1.015 g, 2.5 mmol) in dry Et_2O (20 ml) was added to a solution of liquid ammonia (*ca.* 20 ml) containing $Fe(NO_3)_3 \cdot 9H_2O$ (8.4 mg) and metallic Na (138 mg). The mixture was stirred for 30 min, then NH_4Cl (321 mg, 6 mmol) was added and the stirring was continued for an additional 1.5 h. The work-up was identical with that described above. The residue was crystallized from MeOH to give *trans*-**2a** (746 mg, 73.5% recovery) as colorless prisms. This product was identical with the starting material (**2a**)[10]

Hydrolysis of *trans*-3a and *trans*-(−)-2a with Sodium Hydroxide Followed by Esterification of the Resultant Diacid (7a and 8a) with Diazomethane: [A] *trans*-2-Benzyl-3-carboxy-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (7a)——A mixture of *trans*-**3a** (420 mg, 1 mmol), NaOH (164 mg, 4 mmol), MeOH (13 ml) and H_2O (2 ml) was refluxed for 80 h under nitrogen. After removal of MeOH by evaporation, the residue was diluted with H_2O (50 ml), acidified with 2 N HCl and extracted with 10% MeOH–$CHCl_3$ (4×50 ml). The organic layer was washed with brine, dried and concentrated to provide a solid (397 mg), which was recrystallized from benzene to afford the *trans*-diacid (**7a**: 371 mg, 94.6% yield) as colorless prisms. mp 190—195 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1710 (acid). MS *m/z* (%): 392 (M^+, 11.7), 319 (100), 273 (17.5), 184 (9.7), 183 (21.4), 182 (9.7), 170 (11.7), 169 (7.8), 168 (11.7), 91 (62.1). ^{1}H-NMR ($CDCl_3$) δ: 1.72—1.86 (1H, m, H–$C_{1'}$), 2.00—2.13 (1H, m, H–$C_{2'}$), 2.20—2.38 (1H, m, H–$C_{1'}$), 2.42—2.52

(1H, m, H–$C_{2'}$), 3.11 (1H, dd, J=12.2 and 15.7 Hz, H–C_4), 3.35 and 4.14 (2H, ABq, J=12.5 Hz, CH_2Ph), 3.30—3.40 (2H, H–C_4, overlapped with CH_2Ph), 3.54 (3H, s, N–CH_3), 3.60—3.70 (1H, m, H–C_1), 4.52 (1H, dd, J=4.8 and 12.2 Hz, H–C_3), 7.22—7.50 (8H, m, arom H), 7.60 (1H, d, J=7.6 Hz, arom H). *Anal.* Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.63; H, 6.17; N, 7.04.

An excess of ethereal diazomethane was added to a stirred solution of the above diacid (**7a**: 118 mg, 3 mmol) in MeOH (5 ml). The mixture was stirred for 1 h at room temperature. After evaporation of the solvent, the residue was crystallized from MeOH to afford the dimethyl ester (**3a**: 114 mg, 90.5% yield), which was identical with *trans*-**3a** on the basis of the mixed melting point test and the IR (KBr), ^{1}H and ^{13}C-NMR spectra.

[B] (1*S*, 3*R*)-(−)-2-Benzyl-3-carboxy-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (8a)——Optically active *trans*-(−)-**2a** ($[\alpha]_D^{15}$ −38.0° (c=1.0, $CHCl_3$)) was hydrolyzed with NaOH under the same conditions as in the case of *trans*-**3a**, and the product (**8a**: 97.6% yield) was obtained as colorless needles from benzene–MeOH. mp 205—207 °C (dec.). $[\alpha]_D^{23}$ −6.0° (c=1.0, MeOH). MS m/z (%): 378 (M^+, 7.9), 360 (2.5), 333 (4.0), 305 (100), 287 (4.2), 259 (6.5), 205 (8.6), 170 (9.7), 169 (11.4), 168 (8.4), 91 (74.8). ^{1}H-NMR ($CDCl_3+CD_3OD$) δ: 2.04—2.26 (3H, m, H–$C_{1'}$ and H_2–$C_{2'}$), 2.38—2.56 (1H, m, H–$C_{1'}$), 3.19 (1H, dd, J=10.8 and 16.2 Hz, H–C_4), 3.74 and 4.42 (2H, ABq, J=12.7 Hz, CH_2Ph), 4.22—4.30 (2H, m, H–C_1 and H–C_3), 7.08—7.50 (8H, m, arom H), 7.56 (1H, d, J=7.3 Hz, arom H). *Anal.* Calcd for $C_{22}H_{22}N_2O_4 \cdot 1/2C_6H_6$: C, 71.93; H, 6.04; N, 6.71. Found: C, 71.97; H, 6.06; N, 6.66.

The above diacid (**8a**: 253 mg) was methylated with ethereal diazomethane at room temperature for 1 h to give the dimethyl ester (**2a**: 204 mg). Recrystallization from MeOH afforded colorless prisms. mp 150—151 °C. $[\alpha]_D^{20}$ −33.6° (c=1.0, $CHCl_3$). This product was identical with the starting material (**2a**).

Epimerization of *cis*-3b with Sodium Hydroxide——A mixture of *cis*-**3b** (408 mg, 0.97 mmol), NaOH (156 mg, 4 eq), MeOH (13 ml) and H_2O (2 ml) was refluxed for 80 h, then worked up as described for *trans*-**3a** to afford a residual oil (379 mg). Without purification, the foregoing product (379 mg) was treated with an excess of ethereal diazomethane. After evaporation of the solvent, the residue was purified by silica gel (Wakogel C-200, 13 g) column chromatography using a mixture of *n*-hexane–AcOEt (12 : 1; v/v) as the eluent. The *trans*-dimethyl ester (**3a**: 255 mg, 62.6% yield) was eluted from the column first, and then the *cis*-dimethyl ester (**3b**: 94 mg, 22.6% yield) was recovered.

Dieckmann Cyclization of *trans*-3a: Methyl 5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloocta[*b*]indole-8-carboxylate (9)——A solution of *trans*-**3a** (3.36 g, 0.008 mol) in anhydrous toluene (16 ml) was added dropwise to a stirred suspension of NaH (50% oil dispersion, 1.06 g, 0.022 mol, previously washed three times with *n*-hexane) in anhydrous toluene (16 ml). The mixture was brought to reflux followed by the dropwise addition of a mixture of MeOH (0.32 ml, 0.008 mol) and anhydrous toluene (2.88 ml) over a period of 1 h. The reaction mixture was refluxed for an additional 2 h and then stirred at room temperature overnight. AcOH (2 ml) was added cautiously to the reaction mixture, then the mixture was basified with saturated $NaHCO_3$ solution and extracted with benzene (4×120 ml). The benzene layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated to afford a brownish viscous oil (3.46 g), which was solidified by addition of MeOH (20 ml) to give the β-ketoester (**9**: 2.26 g, 83.8% yield). Recrystallization from MeOH–AcOEt provided **9** as colorless prisms. mp 151—153 °C. IR ν_{max}^{KBr} cm^{-1}: 1670 and 1625 (enol form of β-ketoester). MS m/z (%): 388 (M^+, 73.5), 356 (41.2), 328 (14.7), 297 (5.9), 273 (99.0), 265 (41.2), 184 (11.8), 183 (35.3), 182 (24.5), 170 (10.8), 169 (11.8), 168 (24.5), 91 (100). ^{1}H-NMR ($CDCl_3$) δ: 2.29 (1H, d, J=15.3 Hz), 2.86 (1H, dd, J=5.5 and 15.3 Hz), 2.93 (1H, d, J=15.7 Hz), 3.17 (1H, dd, J=5.5 and 15.7 Hz), 3.58 and 3.66 (each 3H, s, N–CH_3 and CO_2CH_3), 3.70 and 3.80 (2H, ABq, J=13.4 Hz, CH_2Ph), 3.76 (1H, d, J=5.5 Hz), 4.08 (1H, d, J=5.5 Hz), 7.04—7.40 (8H, m, arom H), 7.50 (1H, d, J=7.9 Hz, arom H), 11.98 (1H, s, –C=C–OH). *Anal.* Calcd for $C_{24}H_{24}N_2O_3$: C, 74.20; H, 6.23; N, 7.21. Found: C, 73.85; H, 6.29; N, 7.19.

Dieckmann Reaction of *cis*-3b: Epimerization of *cis*-3b to *trans*-3a——The reaction was carried out under the same conditions as described above using *cis*-**3b** (970 mg, 2.3 mmol). The reaction mixture was worked up as above to afford a viscous oil (874 mg), which was purified by silica gel (35 g) column chromatography using a mixture of *n*-hexane–AcOEt (10 : 1; v/v) to provide the dimethyl ester (**3a**: 777 mg, 80.1% yield) as colorless plates. This product was identical with *trans*-**3a** obtained above.

References and Notes

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9) Although compunds **3** and **5** were also synthesized by Cook *et al.*,[3] the stereochemistry was not discussed. Compounds **3** and **5** reported by Cook *et al.* appear to correspond well to our *trans*-**3a** and *trans*-**5a**, respectively, by comparison with their physical constants and spectral data.
10) Racemic *trans*-**2a** was prepared under conditions analogous to those described in our previous paper.[1] (±)-**2a**: mp 129—130 °C. IR ν_{max}^{KBr} cm^{-1}: 1740 and 1720 (ester). *Anal.* Calcd for $C_{23}H_{22}N_2O_4$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.65; H, 5.89; N, 7.42.