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Asymmetric Synthesis and Absolute Configuration of (−)-Trypargine[1)]

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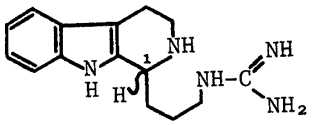
An asymmetric synthesis of (1*S*)-(−)-trypargine (**1a**) was accomplished. The Pictet–Spengler condensation of (+)-N_b-benzyl-D-tryptophan methyl ester ((+)-**3**) with α-ketoglutaric acid, followed by methylation of the resulting monocarboxylic acid ((−)-**4a**), provided (1*S*,3*R*)-(−)-methyl 2-benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate ((−)-**6a**), which was converted into (−)-trypargine (**1a**). The absolute configuration of natural trypargine (**1a**) at the C-1 position was determined to be *S*.

Keywords——(1*S*)-(−)-trypargine; asymmetric synthesis; Pictet–Spengler reaction; (1*S*,3*R*)-(−)-methyl 2-benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate; X-ray crystallographic analysis; absolute configuration; stereochemistry

(−)-Trypargine (**1a**)[2)] is an optically active and unique 1-substituted tetrahydro-β-carboline derivative isolated from African rhacophorid frog, *Kassina senegalensis*, and is a toxic skin component (LD_{50} 16.9 mg/kg, intravenous administration to mice) with several biological activities.[3)]

In previous papers,[4a,b)] we reported the synthesis of (±)-trypargine (**1**) through two different routes, one of which might be applicable to an asymmetric synthesis of (−)-**1a**,[4b)] and a levorotatory enantiomer (**1a**) was prepared by the optical resolution of **1**. The stereochemistry of (−)-**1a** has been presumed to be *S* on the basis of circular dichroism (CD) and optical rotatory dispersion (ORD) spectral analysis.

We wish to report in the present paper a new route for the total synthesis of (−)-trypargine (**1a**) using an asymmetric Pictet–Spengler reaction, and determination of the absolute configuration at the chiral center of (−)-**1a**.



1a: (−)-trypargine C_1-αH
1b: (+)-trypargine C_1-βH

Chart 1

The most significant problem is how to introduce a chiral center at the C-1 position with the same chirality as that of the natural product ((−)-**1a**). In general, the Pictet–Spengler reaction of optically active tryptophan as a chiral synthon with aldehydes or its congeners has been extensively employed for construction of the optically active tetrahydro-β-carboline nucleus by 1,3-asymmetric induction.[5)] Moreover, Cook *et al.* recently reported[6)] that the

condensation of N_b-benzyltryptophan methyl ester with some aldehydes proceeds in a stereospecific fashion to provide the 1,3-*trans* disubstituted tetrahydro-β-carbolines.

In our synthetic plan, (−)-**4a** was chosen as a chiral intermediate for the synthesis of (−)-**1a**. In the expectation of predominant formation of the 1,3-*trans* isomer in the asymmetric Pictet–Spengler reaction, N_b-benzyl-D-tryptophan methyl ester ((+)-**3**) was employed since it has been presumed that (−)-**1a** has the *S*-configuration at the asymmetric carbon-1.

The reaction of D-tryptophan methyl ester ((−)-**2**)[7] with benzaldehyde in dry benzene at room temperature gave N_b-benzylidenetryptophan methyl ester as a viscous oil, which was reduced with $NaBH_4$ in MeOH to furnish N_b-benzyltryptophan methyl ester ((+)-**3**) in 81.5% yield from (−)-**2**. The N_b-benzyl ester ((+)-**3**) was independently obtained by catalytic hydrogenation (2.5—3.0 kg/cm^2) over 10% palladium on charcoal from a mixture of (−)-**2** and benzaldehyde in EtOH.

The N_b-benzyl ester ((+)-**3**) when reacted with α-ketoglutaric acid under conditions similar to those previously reported[4b] (toluene–dioxane (1 : 1), reflux, 4—5 h) gave **4a**, **b** and **5a**, **b** in a ratio of *ca.* 4 : 1 in about 60% yield, while the Pictet–Spengler condensation of (+)-**3** with α-ketoglutaric acid in a mixture of dry benzene–dry dioxane (1 : 1) for 8 h under reflux with azeotropic removal of water by means of a Dean-Stark trap afforded a diastereoisomeric mixture of (−)-**4a** and **4b** (*ca.* 6—7 : 1, as determined by high-performance liquid chromatography (HPLC) in 75.6% yield, and two isomeric oxocanthine derivatives (+)-**5a** and (+)-**5b** in yields of 5.5 and 3.3%, respectively. The mass spectrum (MS) of (−)-**4a**, which was separated in a pure crystalline form by crystallization from the mixture of (−)-**4a** and **4b**, showed the molecular ion (M^+) at *m/z* 392 and its ultraviolet (UV) absorption spectrum was characteristic of the indole chromophore. The less polar (+)-**5a** and the more polar (+)-**5b** exhibited the same M^+ at *m/z* 374 in the MS and the same UV absorption common to the N_a-acylindole. The planar structures of (−)-**4a**, (+)-**5a** and (+)-**5b** were clearly assigned on the basis of the above-mentioned and other spectral data. The stereochemistry of these compounds will be discussed later.

It has been reported by Cook and co-workers[8] that heating of (±)-**3** and α-ketoglutaric acid at reflux in a solution of toluene–dioxane (1 : 1) or benzene–dioxane (2 : 1) gave **4** and **5** in a ratio of *ca.* 6 : 4 or *ca.* 3 : 7, respectively, but they did not mention the stereochemistry or the presence of diastereoisomers of these compounds (**4** and **5**). In our experiments, the major products were always the tetrahydro-β-carbolines (**4a**, **b**), the ratio of **4a**, **b** : **5a**, **b** being *ca.* 4 : 1—9 : 1. The difference between Cook's work and our own in the ratio of the products may be explained as being due to the prolonged reaction time used to permit subsequent lactamization of monocarboxylic acid (**4**) in Cook's case.

The mixture of (−)-**4a** and its diastereoisomer (**4b**) in CH_2Cl_2–MeOH was treated with ethereal diazomethane to furnish the dimethyl ester ((−)-**6a**) as a crystalline compound and its diastereoisomer ((−)-**6b**) as an amorphous substance after separation by careful column chromatography. The ^1H nuclear magnetic resonance (NMR) spectra of both compounds ((−)-**6a** and (−)-**6b**) show two sets of 3H singlets (δ 3.50 and 3.75 in (−)-**6a** and δ 3.55 and 3.60 in (−)-**6b**, respectively) due to two methoxycarbonyl groups. The major isomer ((−)-**6a**) on treatment with MeOH saturated with ammonia for 20 d provided the diamide ((−)-**7**) and the monoamide ((−)-**8**) in yields of 86.4 and 11.9%, respectively. The infrared (IR) spectrum of (−)-**7** showed bands due to two amide carbonyl groups at 1680 and 1670 cm^{-1}. The MS of (−)-**8** displayed M^+ at *m/z* 391 and a base peak at *m/z* 319 ($M^+ - CH_2CH_2CONH_2$) thus indicating the structure of (−)-**8** to be as illustrated in Chart 2.

The stereochemistry, including the absolute configuration of the foregoing compounds, (−)-**4a**, (+)-**5a**, (+)-**5b**, (−)-**6a**, (−)-**6b**, (−)-**7** and (−)-**8**, was deduced as follows. Under the above-mentioned Pictet–Spengler conditions, the major product ((−)-**4a**) was cyclized to only one diastereoisomer ((+)-**5a**), ammonolysis of which afforded a mixture of (−)-**7** and (−)-**8**.

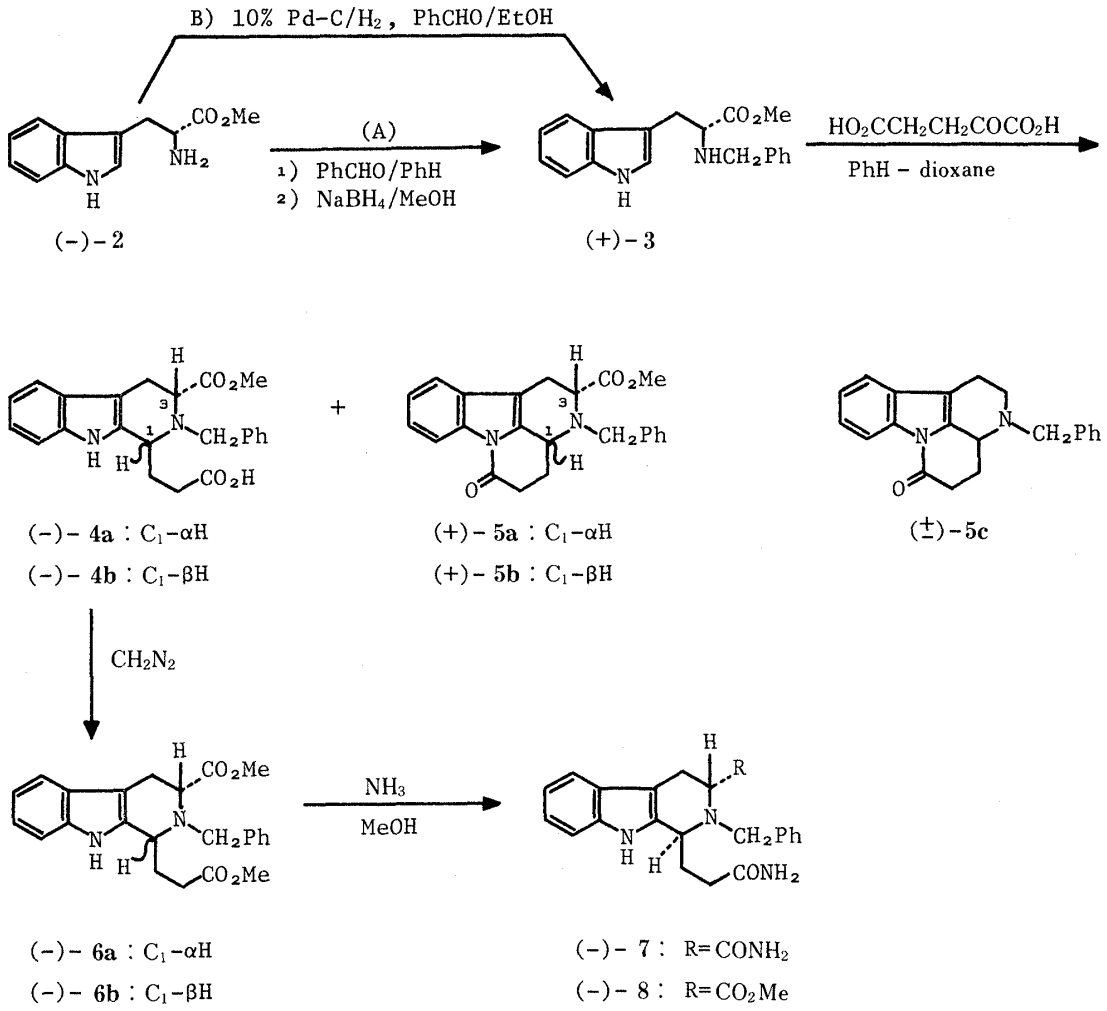
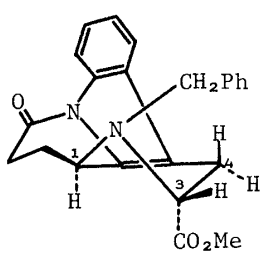


Chart 2

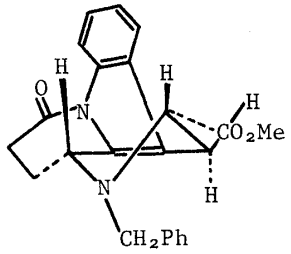
It is clear by examination of the molecular models that both δ-lactams ((+)-**5a** and (+)-**5b**) have the 1-substituted group in the equatorial position. In the ^{1}H-NMR spectrum of (+)-**5a**, the C_1-proton at δ 4.50—4.60 (m) is approximately 0.4 or 1.0 ppm downfield relative to that in (+)-**5b** or (±)-**5c**[4b] (devoid of the C_3-methoxycarbonyl moiety), respectively. These observations reveal that the C_1-proton and C_3-methoxycarbonyl functional group in (+)-**5a** exist in the diaxial relationship, while no steric interaction between the C_1-proton and C_3-methoxycarbonyl group is present in the case of (+)-**5b**, as shown in Chart 3. Thus, it is considered that the δ-lactam ((+)-**5a**) has the 1,3-*trans* configuration, and the compounds ((–)-**4a**, (–)-**6a**, (–)-**7** and (–)-**8**) which are chemically related to (+)-**5a** have the same configuration.

On the other hand, it has been reported that the *trans*-(±)-N_a-methyl dimethyl ester **9a** whose stereochemistry had already been proved by Yoneda's original work[9] can be isomerized into the corresponding *cis* isomer (**9b**) by treatment with NaOH followed by methylation (Chart 4). To obtain a chemical correlation with *trans*-**9a** or *cis*-**9b**, the optically active isomer ((–)-**6a**) was alkylated with MeI in liquid ammonia in the presence of $NaNH_2$ to give the optically active N_a-methylated compound ((–)-**9**) as an amorphous substance in a yield of 77.7%. Under the same conditions, the diastereoisomer ((–)-**6b**), however, furnished only a complex mixture of products. In the ^{13}C-NMR spectra (Table IV), fairly good agreement was observed in the chemical shifts of the carbon atoms between (–)-**9** [δ: 53.4 (C_1), 56.2 (C_3), 20.3 (C_4), 52.9 (C_{14})] and (–)-**6a** [δ: 54.7 (C_1), 56.7 (C_3), 21.3 (C_4), 53.4 (C_{14})]

and (−)-**6b** [δ: 56.2 and 58.7 (C_1 and C_3), 19.8 (C_4), 59.4 (C_{14})]. Moreover, the shape of the CD curve of (−)-**9** closely resembled that of (−)-**6a**. Thus, it is considered that the N_a-methylation reaction of (−)-**6a** proceeds with retention of configuration. Hydrolysis of the N_a-methylated compound ((−)-**9**) with NaOH afforded the dicarboxylic acid ((−)-**10**), which was converted to the original dimethyl ester ((−)-**9**) by treatment with diazomethane (Chart 4). This chemical reactivity indicates that (−)-**9** is the *cis* isomer (**9b**).

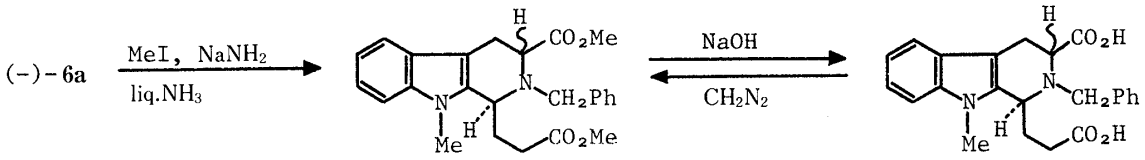


(+)-**5a**



(+)-**5b**

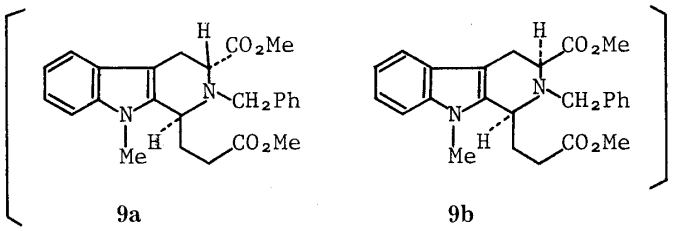
Chart 3



(−)-**6a**

(−)-**9**

(−)-**10**



9a **9b**

Chart 4

From the above results, we could not obtain definitive evidence for the stereochemistry of (−)-**6a**. Therefore, X-ray crystallographic analysis was performed in order to confirm the stereochemistry of (−)-**6a**.

The dimethyl ester ((−)-**6a**) crystallized in the monoclinic space group $P2_1$ with $a=$ 11.180 (2), $b=15.184$ (2), $c=6.433$ (2) Å, $\beta=99.97$ (2)° and $z=2$. We measured 3114 unique reflections having $Fo>3\sigma$ (Fo) on a Rigaku AFC-5 diffractometer using graphite-monochromated Mo$K\alpha$ radiation. The scanning was done by the ω-2θ scanning method at a speed of 2°/min in 2θ in the range up to $2\theta=65°$.

The structure was solved by the direct method using the structure determination program package based on MULTAN[10] provided with the diffractometer. The structure was refined by block-diagonal least-squares methods to an R value of 0.079.

The ORTEP drawing of the solved structure of (−)-**6a** is shown in Figs. 1 and 2,[11] and the stereochemistry of (−)-**6a** was unambiguously confirmed to be the (1*S*, 3*R*)-*trans* since D-tryptophan of known absolute configuration (*R*) was the precursor to (−)-**6a**. The absolute configurations of 1,2,3-trisubstituted tetrahydro-β-carbolines ((−)-**4a**, (+)-**5a**, (+)-**5b**, (−)-

TABLE I. Final Atomic Parameters ($\times 10^4$)

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	2757 (5)	884 (4)	3472 (9)	54 (4)	35 (3)	190 (13)	2 (3)	18 (6)	2 (5)
N(2)	2553 (4)	1717 (3)	4453 (7)	51 (3)	35 (2)	179 (10)	−1 (2)	14 (4)	7 (4)
C(3)	1317 (5)	1759 (4)	5008 (8)	59 (4)	35 (2)	171 (11)	4 (3)	29 (5)	−4 (5)
C(4)	273 (5)	1773 (5)	3042 (9)	57 (4)	53 (3)	194 (13)	13 (3)	12 (6)	−25 (6)
C(4A)	574 (5)	1073 (4)	1574 (9)	58 (4)	38 (3)	197 (13)	4 (3)	22 (6)	−11 (5)
C(4B)	−148 (5)	722 (4)	−269 (9)	60 (4)	42 (3)	179 (13)	−2 (3)	25 (6)	1 (5)
C(5)	−1346 (6)	889 (6)	−1360 (10)	63 (5)	64 (4)	230 (16)	−6 (4)	9 (7)	−1 (7)
C(6)	−1757 (6)	401 (6)	−3187 (11)	74 (5)	82 (6)	253 (18)	−16 (5)	2 (8)	−22 (8)
C(7)	−1016 (6)	−253 (6)	−3948 (11)	96 (6)	61 (4)	230 (17)	−21 (4)	25 (8)	−17 (7)
C(8)	159 (6)	−436 (5)	−2886 (9)	92 (6)	46 (3)	198 (14)	−20 (4)	35 (7)	−16 (6)
C(8A)	565 (5)	64 (4)	−1069 (8)	69 (4)	38 (3)	166 (12)	−10 (3)	38 (6)	3 (5)
N(9)	1681 (4)	35 (4)	268 (7)	61 (3)	41 (2)	189 (11)	0 (3)	32 (5)	−6 (5)
C(9A)	1679 (5)	664 (4)	1827 (8)	60 (4)	37 (3)	185 (13)	1 (3)	28 (6)	1 (5)
C(10)	3107 (5)	152 (5)	5112 (10)	67 (4)	39 (3)	272 (17)	9 (3)	21 (7)	16 (6)
C(11)	4353 (6)	409 (6)	6421 (13)	74 (6)	84 (6)	341 (22)	−12 (5)	−40 (9)	82 (10)
C(12)	4674 (5)	−76 (5)	8448 (10)	68 (5)	46 (4)	264 (17)	17 (4)	7 (7)	8 (6)
C(15)	6368 (8)	−409 (10)	11142 (17)	100 (8)	149 (10)	512 (35)	−9 (8)	−80 (14)	149 (17)
C(16)	2848 (5)	2485 (4)	3214 (9)	63 (3)	42 (3)	220 (14)	−3 (3)	23 (6)	28 (6)
C(17)	4214 (6)	2545 (5)	3399 (11)	88 (5)	33 (3)	342 (20)	−5 (3)	74 (9)	26 (7)
C(18)	4924 (7)	2735 (6)	5355 (12)	87 (6)	53 (4)	353 (23)	−12 (4)	13 (9)	3 (9)
C(19)	6225 (8)	2745 (7)	5580 (17)	111 (9)	67 (6)	640 (40)	−25 (6)	−8 (14)	59 (14)
C(20)	6753 (8)	2536 (7)	3853 (21)	94 (8)	67 (6)	969 (58)	2 (6)	141 (18)	67 (16)
C(21)	6038 (8)	2338 (8)	1845 (19)	119 (9)	87 (7)	743 (47)	12 (7)	178 (18)	53 (15)
C(22)	4737 (8)	2345 (7)	1589 (15)	133 (9)	68 (5)	508 (32)	0 (6)	172 (15)	40 (11)
C(23)	1231 (6)	2510 (5)	6525 (9)	84 (5)	44 (3)	167 (12)	4 (3)	31 (6)	6 (5)
C(26)	−160 (8)	3401 (6)	8038 (11)	131 (8)	60 (5)	259 (19)	13 (5)	82 (10)	−35 (8)
O(13)	4025 (4)	−450 (4)	9461 (8)	79 (4)	80 (4)	323 (15)	13 (3)	53 (6)	40 (7)
O(14)	5878 (4)	2 (5)	9139 (9)	62 (4)	98 (4)	385 (16)	−2 (3)	−6 (6)	75 (7)
O(24)	2062 (5)	2837 (4)	7669 (8)	104 (5)	82 (4)	314 (15)	−3 (4)	30 (7)	−75 (7)
O(25)	85 (4)	2740 (4)	6511 (7)	83 (4)	61 (3)	257 (12)	11 (3)	38 (5)	−36 (5)

Temperature factors are of the form: $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$.

TABLE II. Bond Lengths in Å Unit

Atom 1	Atom 2	Length (STD)	Atom 1	Atom 2	Length (STD)
C(1) –	N(2)	1.450 (8)	C(11) –	C(12)	1.488 (12)
N(2) –	C(3)	1.487 (10)	C(12) –	O(13)	1.200 (12)
C(3) –	C(4)	1.567 (20)	C(12) –	O(14)	1.347 (11)
C(4) –	C(4A)	1.500 (10)	O(14) –	C(15)	1.452 (16)
C(4A) –	C(9A)	1.367 (8)	N(2) –	C(16)	1.483 (9)
C(9A) –	C(1)	1.499 (18)	C(16) –	C(17)	1.514 (9)
C(4A) –	C(4B)	1.419 (16)	C(17) –	C(18)	1.398 (17)
C(4B) –	C(8A)	1.428 (11)	C(18) –	C(19)	1.437 (12)
C(8A) –	N(9)	1.388 (17)	C(19) –	C(20)	1.383 (20)
N(9) –	C(9A)	1.387 (8)	C(20) –	C(21)	1.430 (22)
C(4B) –	C(5)	1.424 (15)	C(21) –	C(22)	1.435 (13)
C(5) –	C(6)	1.400 (13)	C(22) –	C(17)	1.425 (16)
C(6) –	C(7)	1.433 (13)	C(3) –	C(23)	1.516 (9)
C(7) –	C(8)	1.400 (16)	C(23) –	O(24)	1.190 (14)
C(8) –	C(8A)	1.404 (11)	C(23) –	O(25)	1.327 (8)
C(1) –	C(10)	1.537 (10)	O(25) –	C(26)	1.464 (10)
C(10) –	C(11)	1.548 (18)			

TABLE III. Bond Angles in Degrees

Atom			Angle (STD)	Atom			Angle (STD)
1	2	3		1	2	3	
N(2)	C(1)	C(9A)	109.5 (14)	C(4)	C(3)	C(23)	112.9 (6)
N(2)	C(1)	C(10)	111.8 (5)	C(3)	C(23)	O(24)	125.7 (7)
C(9A)	C(1)	C(10)	113.7 (7)	C(3)	C(23)	O(25)	111.2 (9)
C(1)	C(10)	C(11)	106.8 (9)	O(24)	C(23)	O(25)	122.9 (8)
C(10)	C(11)	C(12)	114.3 (10)	C(23)	O(25)	C(26)	117.9 (9)
C(11)	C(12)	O(13)	129.4 (8)	C(3)	C(4)	C(4A)	106.4 (5)
C(11)	C(12)	O(14)	108.8 (11)	C(4)	C(4A)	C(4B)	129.5 (5)
O(13)	C(12)	O(14)	121.7 (8)	C(4)	C(4A)	C(9A)	123.0 (9)
C(12)	O(14)	C(15)	117.3 (11)	C(4B)	C(4A)	C(9A)	107.5 (9)
C(1)	N(2)	C(3)	111.4 (6)	C(1)	C(9A)	C(4A)	125.7 (7)
C(1)	N(2)	C(16)	112.6 (6)	C(1)	C(9A)	N(9)	124.4 (6)
C(3)	N(2)	C(16)	113.5 (7)	C(4A)	C(9A)	N(9)	109.9 (9)
N(2)	C(16)	C(17)	108.7 (8)	C(4A)	C(4B)	C(5)	134.1 (9)
C(16)	C(17)	C(18)	119.4 (11)	C(4A)	C(4B)	C(8A)	107.0 (6)
C(16)	C(17)	C(22)	118.3 (11)	C(5)	C(4B)	C(8A)	118.9 (6)
C(18)	C(17)	C(22)	122.1 (7)	C(4B)	C(5)	C(6)	117.7 (10)
C(17)	C(18)	C(19)	120.0 (12)	C(5)	C(6)	C(7)	122.0 (8)
C(18)	C(19)	C(20)	118.8 (12)	C(6)	C(7)	C(8)	121.3 (7)
C(19)	C(20)	C(21)	121.8 (8)	C(7)	C(8)	C(8A)	116.2 (10)
C(20)	C(21)	C(22)	119.9 (14)	C(4B)	C(8A)	C(8)	124.0 (7)
C(21)	C(22)	C(17)	117.3 (12)	C(4B)	C(8A)	N(9)	107.2 (5)
N(2)	C(3)	C(4)	113.6 (7)	C(8)	C(8A)	N(9)	128.8 (9)
N(2)	C(3)	C(23)	110.6 (8)	C(8A)	N(9)	C(9A)	108.3 (7)

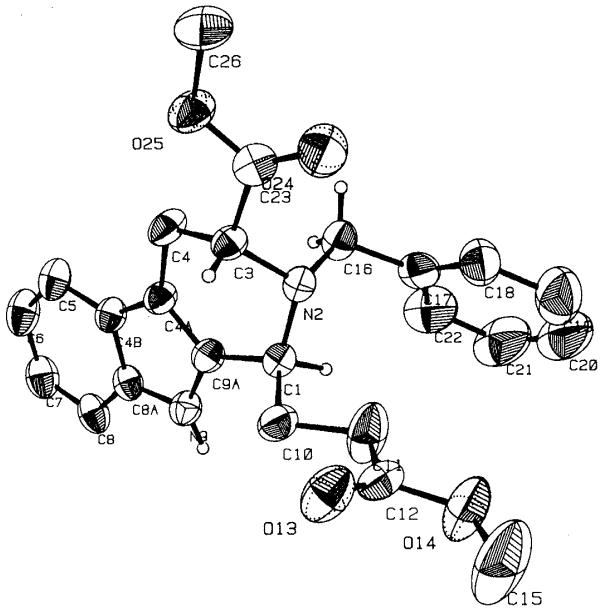


Fig. 1. An ORTEP Drawing of (−)-**6a**

6b, (−)-**7** and (−)-**8**) were also determined to be as depicted in Chart 2.

Now the stereochemistry of the N_a-methylated compound ((−)-**9**) derived from *trans*-(−)-**6a** comes in question. The compound ((−)-**9**) was suggested to be the 1,3-*cis* isomer based on the chemical reactivity, as pointed out in the literature.[9] This finding indicates that epimerization occurs during the N_a-methylation of *trans*-(−)-**6a**, and it is difficult to explain

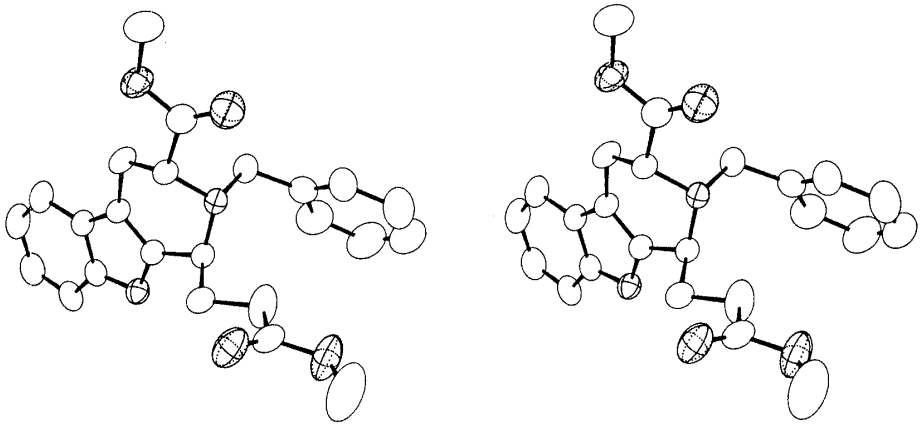


Fig. 2. Stereoscopic View of (−)-**6a**

the similarity of the NMR spectra of *trans*-(−)-**6a** and (−)-**9**. Therefore, additional experiments were required to verify the stereochemistry of (−)-**9**.[12]

The diamide ((−)-**7**) was dehydrated using $POCl_3$ in a mixture of dimethylformamide (DMF) and pyridine to provide the dinitrile ((+)-**11**) in 92.1% yield. The ^{13}C-NMR spectrum of (+)-**11** showed the signals due to two nitrile carbons at δ 117.4 and 119.8 ppm. The α-aminonitrile ((+)-**11**) was subjected to reductive decyanation with $NaBH_4$ in EtOH to furnish the labile decyanized product (**12**) in a yield of 69.4% accompanied with the unreacted dinitrile ((+)-**11**) in 14.2% yield. The unstable mononitrile (**12**) was subjected to reduction with $LiAlH_4$ in dry Et_2O to afford the amine (**13**), and then without purification, reductive debenzylation of **13** over 10% palladium on charcoal in EtOH and conc. HCl proceeded readily to give the debenzylated amine ((−)-**14**) as a hydrochloride in 95.3% yield from **12**; the structure was corroborated by the identity of the IR (KBr), mass and ^{13}C-NMR spectra with those of the racemic authentic specimen (**14**).[4a,b] The free base of (−)-**14** was reacted with *S*-methylisothiourea in H_2O at 50 °C to yield the desired trypargine ((−)-**1a**) as a sulfate, which was converted to the corresponding hydrochloride of (−)-**1a** [mp 211—213 °C, $[\alpha]_D$ −37.5° (MeOH)][4a] in 55.2% yield. The synthetic trypargine hydrochloride was identical with the natural trypargine hydrochloride.

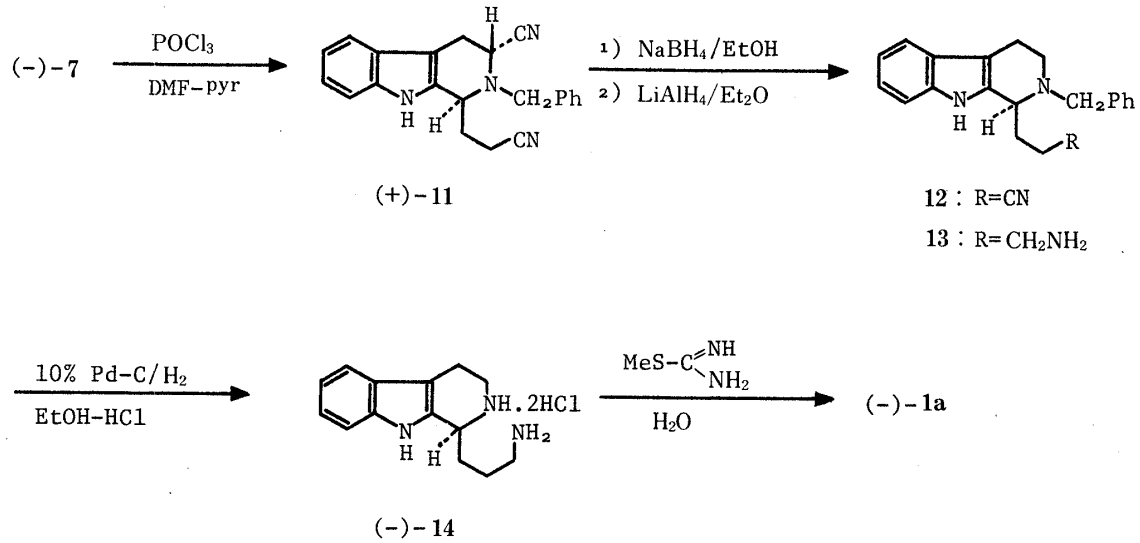
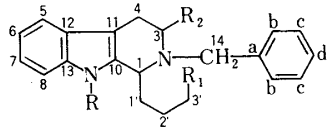


Chart 5

TABLE IV. Carbon-13 Chemical Shifts[a]

	(−)-**4a**[b]	(+)-**5a**[b]	(+)-**5b**[b]	(−)-**6a**[b]	(−)-**6b**[b]	(−)-**7**[b]	(−)-**8**[b]	(−)-**9**[b]	(−)-**10**[c]	(+)-**11**[b]	(−)-**14**[d]	(−)-**1a**[d]
C(1)	55.6[e]	52.2	56.4	54.7	56.2[e]	55.7	55.3	53.4	55.1	54.7	54.0	54.3
C(3)	56.5[e]	57.6	62.8	56.7	58.7[e]	57.5	57.2	56.2	56.8	48.3	42.8	42.8
C(4)	21.2	24.1	22.9	21.3	19.8	18.1	21.0	20.3	20.0	24.9	19.3	19.3
C(5)	118.3	118.0	118.1	118.1	118.2	118.3	118.1	118.2	118.5	118.2	119.0	118.9
C(6)	119.7	123.9[e]	124.0[e]	119.5	119.4	119.5	119.4	119.2	119.6	120.1	120.6	120.5
C(7)	122.1	124.5[e]	124.6[e]	121.7	121.7	121.9	121.8	121.4	121.9	122.7	123.5	123.4
C(8)	111.0	116.2	116.2	110.9	110.9	111.0	111.1	108.9	109.2	111.3	112.4	112.3
C(10)	133.0	134.8[f]	133.8[f]	134.2	133.4	133.5	134.1	135.7	134.3	130.7	129.3	129.5
C(11)	107.5	111.0	111.6	107.4	106.3	107.5	107.2	106.4	106.8	107.8	107.5	107.3
C(12)	126.8	129.2	129.0	126.95	127.0	127.0	126.8	126.6	126.6	126.5	127.2	127.2
C(13)	136.4	135.1[f]	134.9[f]	136.3	136.2	136.4	136.3	137.5	137.5	136.5[e]	138.2	138.1
C(14)	53.5	54.9	53.4	53.4	59.4	52.3	53.5	52.9	56.8	55.5		
C(14a)	137.9	139.2	139.5	139.3	139.0	138.8	139.8	139.3	138.0	136.7[e]		
C(14b)	129.5[f]	128.5[g]	128.4[g]	129.1[e]	129.0[f]	129.3[e]	129.5[e]	129.3[e]	129.8[e]	129.1[f]		
C(14c)	128.5[f]	128.3[g]	128.1[g]	128.2[e]	128.3[f]	128.5[e]	128.3[e]	128.2[e]	128.7[e]	128.8[f]		
C(14d)	127.6	127.3	127.1	127.04	127.3	128.2	127.2	127.0	128.0	128.2		
C(1′)	28.3	28.3	27.8	28.9	29.3[g]	29.6	29.7	28.0	28.0	27.9	30.1	30.3
C(2′)	31.3	33.1	33.5	29.8	30.4[g]	32.9	31.9	29.6	31.4	11.4	24.3	25.6
C(3′)											41.9	41.9
	52.1	51.5	52.1	51.4	51.5	175.6	52.0	29.6	29.8	117.4		158.5
	($CO_2\underline{C}H_3$)	($CO_2\underline{C}H_3$)	($CO_2\underline{C}H_3$)	51.8	51.8	175.8	($CO_2\underline{C}H_3$)	($N\text{–}CH_3$)	($N\text{–}CH_3$)	119.8		(NH–C$\begin{matrix}\nearrow NH\\ \searrow NH_2\end{matrix}$)
	172.6	168.2	167.9	($CO_2\underline{C}H_3$)	($CO_2\underline{C}H_3$)	($CONH_2$)	173.3	51.3	174.2	(CN)		
	($\underline{C}O_2CH_3$)	(=N–CO)	(=N–CO)	173.3	173.9		($\underline{C}O_2CH_3$)	52.0	176.7			
	177.3	173.0	172.8	174.3	174.6		175.6	($CO_2\underline{C}H_3$)	(CO_2H)			
	(CO_2H)	($\underline{C}O_2CH_3$)	($\underline{C}O_2CH_3$)	($\underline{C}O_2CH_3$)	($\underline{C}O_2CH_3$)		($CONH_2$)	173.4				
								173.9				
								($\underline{C}O_2CH_3$)				

a) The δ values are in ppm downfield from tetramethylsilane. *b*) In $CDCl_3$ solution. *c*) In $CDCl_3+CD_3OD$ solution. *d*) In CD_3OD solution. *e, f, g*) Signals in any column may be reversed. *h*) For convenience the numbering for tetrahydro-β-carbolines is employed, as shown below.



The absolute configuration of the chiral intermediate ((−)-**6a**) was unequivocally proved to be (1*S*, 3*R*) by the X-ray crystallographic analysis, and it was considered that no epimerization occurred at C-1 position of (−)-**6a** in the present synthetic routes. Therefore, the absolute configuration at the chiral center of natural trypargine (**1a**) was determined to be *S*. This result is in accord with that based on the CD and ORD spectral analysis[4a] of (−)-**1a**.

In order to obtain the enantiomer ((+)-**1b**) of (−)-**1a**, the chiral synthesis was accomplished using L-tryptophan as a starting material to yield synthetic (+)-**1b** [hydrochloride, mp 212—214 °C, $[\alpha]_D$ +37.0° (MeOH)].[4a] The IR (KBr) spectrum of (+)-**1b** (hydrochloride) was virtually identical with that of (−)-**1a** (hydrochloride).

Experimental

All melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Ultraviolet (UV) spectra were determined 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. ^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 as an internal standard. Abbreviations used are: singlet = s: doublet = d; triplet = t; quartet = q, multiplet = m; broad = br; aromatic = arom. Chromatography was performed on SiO_2 (Kieselgel 60, 35—70 mesh, Merck) unless otherwise indicated. HPLC was carried out in the reverse phase [μ-Bondapak C_{18} (3.9 mm × 30 cm) and 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). The CD curves were measured with a JASCO J-20 recording spectropolarimeter and the optical rotations were measured with a JASCO DIP-140 polarimeter.

D-Tryptophan Methyl Ester ((−)-2)——D-Tryptophan methyl ester was synthesized according to the method described for L-tryptophan methyl ester by Boissonnas *et al.*[7]

D-Tryptophan (20.0 g, 0.098 mol) was added in one portion to a stirred solution of MeOH (200 ml) containing $SOCl_2$ (24.0 g, 0.202 mol) at −10 °C. The mixture was stirred at −10 °C for 2 h and then at room temperature for 2 d. Et_2O (800 ml) was added to the reaction mixture and the resulting crystals were filtered off and washed sufficiently with Et_2O to afford the crude hydrochloride of (−)-**2** (23.6 g, 94.8% yield). On work-up as usual, the free base of (−)-**2** was obtained, and was crystallized from Et_2O to provide colorless prisms. mp 91—92 °C. $[\alpha]_D^{12}$ −37.0° (c = 1.0, MeOH). MS m/z (%): 218 (M^+, 5.1), 130 (100). IR ν_{max}^{KBr} cm^{-1}: 1730 (ester). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.11; H, 6.45; N, 12.92.

N_b-Benzyl-D-tryptophan Methyl Ester ((+)-3)——[Method 1]: Benzaldehyde (4.88 g, 0.046 mol) was added to a stirred solution of D-tryptophan methyl ester ((−)-**2**, 8.29 g, 0.038 mol) in dry benzene (200 ml), and the solution was stirred at room temperature under an atmosphere of nitrogen gas. After stirring for 5 h, anhydrous sodium sulfate (40 g) was added and the mixture was stirred for an additional 5 h. The organic layer was separated from the sodium sulfate and concentrated under reduced pressure to give a pale orange viscous oil (12.74 g, 0.042 mol). The reaction product was dissolved in absolute MeOH (50 ml) and reduced with $NaBH_4$ (0.985 g, 0.026 mol) for 4 h at room temperature. After evaporation of the solvent, the residue was mixed with H_2O (400 ml) and extracted with AcOEt (4 × 250 ml). The combined AcOEt extract was dried over anhydrous sodium sulfate and concentrated. The residual oil (11.98 g) was purified by chromatography on silica gel (180 g) using a mixture of *n*-hexane–AcOEt (4 : 1; v/v) to afford a colorless solid (9.54 g, 81.5% yield from (−)-**2**), which was recrystallized from Et_2O–*n*-hexane to give (+)-**3** as colorless needles. mp 108—109 °C. [(±)-**3**: mp 85—87 °C (Et_2O–*n*-hexane, needles)]. $[\alpha]_D^{12}$ +8.6° (c = 1.0, MeOH). MS m/z (%): 308 (M^+, 3.6), 249 (5.3), 178 (25.5), 130 (100), 91 (84.3). IR ν_{max}^{KBr} cm^{-1}: 1745 (ester). ^1H-NMR ($CDCl_3$) δ: 1.99 (1H, br s, NH), 3.15 (1H, dd, J = 6.9 and 14.0 Hz, CH_2CH), 3.19 (1H, dd, J = 6.6 and 14.0 Hz, CH_2CH), 3.62 (3H, s, CO_2CH_3), 3.67 (1H, dd, J = 6.6 and 6.9 Hz, CH_2CH), 3.67 and 3.82 (2H, AB-q, J = 13.2 Hz, CH_2Ph), 7.00 (1H, d, J = 2.3 Hz, NH = CH–), 7.05—7.36 (8H, m, arom H), 7.56 (1H, d, J = 7.6 Hz, arom H), 8.07 (1H, br s, indole NH). *Anal.* Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 73.93; H, 6.47; N, 8.96.

[Method 2]: D-Tryptophan methyl ester ((−)-**2**, 1.97 g, 0.009 mol) and benzaldehyde (1.43 g, 1.5 eq) were dissolved in EtOH (10 ml) and the mixture was subjected to catalytic hydrogenation (2.5—3.0 kg/cm²) over 10% palladium on charcoal (0.20 g) for 5 h. The catalyst was filtered off and the solvent was removed under reduced pressure. Column chromatography of the residue (3.26 g) on silica gel (65 g) with a mixture of *n*-hexane–AcOEt (2 : 1; v/v) as an eluent gave colorless crystals of (+)-**3** (2.28 g, 82.1% yield).

(1*S*, 3*R*)-(−)-2-Benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (4a), (1*S*, 3*R*)-(+)-Methyl 3-Benzyl-1,2,3,3a,4,5-hexahydro-6-oxocanthine-2-carboxylate (5a) and (1*R*, 3*R*)-(+)-Methyl 3-Benzyl-1,2,3,3a,4,5-hexahydro-6-oxocanthine-2-carboxylate (5b)——N_b-Benzyl-D-tryptophan methyl ester ((+)-**3**, 6.16 g, 0.02 mol) was dissolved in dry benzene–dry dioxane (1 : 1; v/v; 200 ml), and α-ketoglutaric acid (3.50 g, 0.024 mol) was added in one portion to the stirred solution at room temperature. The mixture was refluxed for 8 h

with water removal by means of a Dean-Stark trap. After removal of the solvent, the residue (9.96 g) was chromatographed on silica gel (120 g). Elution with *n*-hexane–AcOEt (4 : 1; v/v) gave a diastereoisomeric mixture of (+)-**5a** and (+)-**5b** (0.76 g) as a viscous oil. Elution with *n*-hexane–AcOEt (2 : 1—1 : 1; v/v) yielded a mixture of (−)-**4a** and its diastereoisomer (**4b**) (5.93 g, 75.6% total yield) as a colorless solid, which was recrystallized from AcOEt–*n*-hexane to provide only one diastereoisomer ((−)-**4a**) as colorless prisms. A mixture of (−)-**4a** and **4b** was used for the following reaction without separation. (−)-**4a**: mp 174—176 °C. [(±)-**4a**: mp 213—215 °C (dec.) (MeOH–CH_2Cl_2, prisms)]. $[\alpha]_D^{17}$ −18.0° (*c* = 1.0, $CHCl_3$). MS *m/z* (%): 392 (M^+, 4.7), 333 (5.9), 319 (43.1), 315 (15.7), 301 (5.9), 283 (33.3), 225 (10.8), 198 (12.7), 184 (5.9), 170 (15.7), 169 (14.7), 168 (17.6), 156 (8.8), 154 (5.9), 130 (3.1), 129 (3.1), 128 (3.1), 115 (4.9), 91 (100). IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1730 (ester), 1710 (acid). UV λ_{max}^{MeOH} nm (log ε): 225 (4.60), 275 (shoulder, 3.90), 282 (3.91), 290 (3.82). ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.08 (2H, m, H–$C_{1'}$ and H–$C_{2'}$), 2.10—2.24 (1H, m, H–$C_{2'}$), 2.34—2.48 (1H, m, H–$C_{1'}$), 3.04—3.20 (2H, m, H_2–C_4), 3.63 and 3.98 (2H, AB-q, *J* = 12.9 Hz, CH_2Ph), 3.76 (3H, s, CO_2CH_3), 4.00—4.08 (2H, m, H–C_1 and H–C_3), 7.08—7.40 (8H, m, arom H), 7.53 (1H, dd, *J* = 1.3 and 6.9 Hz, arom H), 8.01 (1H, s, NH). *Anal.* Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.28; H, 6.19; N, 7.09.

A mixture of diastereoisomers ((+)-**5a** and (+)-**5b**, 0.76 g) was separated by re-chromatography on silica gel (30 g). Elution with a mixture of *n*-hexane–AcOEt (10 : 1; v/v) gave (+)-**5a** (408 mg, 5.5% yield) as a pale greenish solid, which was recrystallized from MeOH–AcOEt (1 : 1; v/v) to provide colorless prisms. Elution with *n*-hexane–AcOEt (9 : 1; v/v) gave (+)-**5b** (244 mg, 3.3% yield) as pale yellow crystals. Recrystallization from MeOH–AcOEt furnished colorless scales.

(+)-**5a**: mp 167.5—168.5 °C. [(±)-**5a**: mp 183—184 °C (MeOH, prisms)]. $[\alpha]_D^{16}$ +37.0° (*c* = 1.0, $CHCl_3$). MS *m/z* (%): 374 (M^+, 21.6), 315 (19.6), 283 (76.5), 223 (17.6), 198 (19.6), 197 (17.6), 184 (9.8), 170 (2.9), 169 (11.8), 168 (22.5), 156 (2.0), 154 (7.8), 130 (1.0), 129 (2.0), 128 (2.9), 115 (3.9), 91 (100). IR ν_{max}^{KBr} cm^{-1}: 1740 (ester), 1715 (lactam). UV λ_{max}^{MeOH} nm (log ε): 240.5 (4.30), 265 (4.02), 271 (shoulder, 3.99), 293 (3.62), 301 (3.61). ^{1}H-NMR ($CDCl_3$) δ: 1.70—1.90 (1H, m, H–$C_{1'}$), 2.39—2.49 (1H, m, H–$C_{1'}$), 2.73—2.90 (2H, m, H_2–$C_{2'}$), 3.01 (1H, ddd, *J* = 2.9, 6.8 and 16.5 Hz, H–C_4), 3.10 (1H, dt, *J* = 1.9 and 16.5 Hz, H–C_4), 3.91 (1H, dd, *J* = 1.9 and 6.8 Hz, H–C_3), 3.98 and 4.26 (2H, AB-q, *J* = 14.4 Hz, CH_2Ph), 4.50—4.60 (1H, m, H–C_1), 7.23—7.45 (8H, m, arom H), 8.35—8.40 (1H, m, arom H). *Anal.* Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.65; H, 5.94; N, 7.49.

(+)-**5b**: mp 166—167 °C. [(±)-**5b**: mp 154—156 °C (MeOH–AcOEt, prisms)]. $[\alpha]_d^{15}$ +5.3° (*c* = 1.0, $CHCl_3$). MS *m/z* (%): 374 (M^+, 13.7), 315 (84.3), 283 (11.8), 223 (7.8), 198 (29.4), 197 (37.3), 184 (15.7), 170 (3.9), 169 (11.8), 168 (20.6), 156 (2.0), 154 (5.9), 130 (1.0), 129 (1.6), 128 (2.0), 115 (2.0), 91 (100). IR ν_{max}^{KBr} cm^{-1}: 1740 (ester), 1700 (lactam). UV λ_{max}^{MeOH} nm (log ε): 240.5 (4.31), 265 (4.04), 271 (shoulder, 4.01), 293 (3.65), 301 (3.63). ^{1}H-NMR ($CDCl_3$) δ: 1.79—1.95 (1H, m, H–$C_{1'}$), 2.00—2.11 (1H, m, H–$C_{1'}$), 2.54—2.78 (2H, m, H_2–$C_{2'}$), 2.98 (1H, ddd, *J* = 2.5, 5.1 and 16.2 Hz, H–C_4), 3.13 (1H, ddd, *J* = 2.5, 9.1 and 16.2 Hz, H–C_4), 3.69 (3H, s, CO_2CH_3), 3.88 (2H, s, CH_2Ph), 3.99 (1H, dd, *J* = 5.1 and 9.1 Hz, H–C_3), 4.08—4.18 (1H, m, H–C_1), 7.20—7.50 (8H, m, arom H), 8.32—8.40 (1H, m, arom H). *Anal.* Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.56; H, 5.87; N, 7.40.

Transformation of *trans*-(−)-4a into *trans*-(+)-5a——The *trans* monomethyl ester ((−)-**4a**, 100 mg) in dry benzene–dry dioxane (1 : 1; v/v; 25 ml) was heated under reflux for 4 d. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (5 g) eluted with *n*-hexane–AcOEt (10 : 1; v/v), affording (+)-**5a** (6 mg). The IR (KBr) and mass spectra of (+)-**5a** were identical with those of *trans*-(+)-**5a** described above. Elution with AcOEt gave the starting material ((−)-**4a**, 75 mg).

(1*S*,3*R*)-(−)-Methyl 2-Benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (6a) and (1*R*,3*R*)-(−)-Methyl 2-Benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (6b)——An excess of ethereal diazomethane was added to a stirred solution of a diastereoisomeric mixture of (−)-**4a** and **4b** (6.50 g, 0.0166 mol) in CH_2Cl_2–MeOH (3 : 1; v/v; 120 ml) over a 30 min period at room temperature. The mixture was stirred for an additional 1 h. After removal of the solvent, the residual oil (6.62 g) was carefully chromatographed on silica gel (Wakogel C-200, 165 g) with a mixture of *n*-hexane–AcOEt (10 : 1; v/v) as an eluent.

The *trans* dimethyl ester ((−)-**6a**, 5.29 g, 78.6% yield) was eluted from the column first, and then the *cis* isomer ((−)-**6b**, 0.50 g, 7.5% yield) was obtained. The less polar isomer ((−)-**6a**) was crystallized from MeOH to give colorless prisms. Attempts to crystallize (−)-**6b** were unsuccessful.

(−)-**6a**: mp 150—151 °C. [(±)-**6a**: mp 129—130 °C (MeOH, prisms)]. $[\alpha]_D^{15}$ −38.0° (*c* = 1.0, $CHCl_3$). MS *m/z* (%): 406 (M^+, 9.3), 347 (10.8), 319 (100), 315 (20.6), 259 (6.9), 170 (5.9), 169 (19.6), 168 (10.8), 156 (11.8), 154 (3.9), 130 (3.1), 129 (3.9), 128 (3.1), 115 (4.9), 91 (84.3). IR ν_{max}^{KBr} cm^{-1}: 3310 (NH), 1745 and 1720 (ester). UV λ_{max}^{MeOH} nm (log ε): 225 (4.60), 275 (shoulder, 3.90), 282 (3.92), 290 (3.83). ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.15 (2H, m, H_2–$C_{1'}$), 2.20—2.50 (2H, m, H_2–$C_{2'}$), 3.03 (1H, dd, *J* = 5.3 and 15.8 Hz, H–C_4), 3.12 (1H, dd, *J* = 8.8 and 15.8 Hz, H–C_4), 3.50 and 3.75 (each 3H, s, CO_2CH_3), 3.58 and 3.84 (2H, AB-q, *J* = 13.6 Hz, CH_2Ph), 3.87—3.96 (1H, m, H–C_1), 3.98 (1H, dd, *J* = 5.3 and 8.8 Hz, H–C_3), 7.05—7.38 (8H, m, arom H), 7.52 (1H, dd, *J* = 1.3 and 6.9 Hz, arom H), 8.03 (1H, br s, NH). *Anal.* Calcd for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.89; H, 6.47; N, 6.90. CD (*c* = 0.00025, MeOH) $\Delta\varepsilon^{25}$ (nm): 0 (300); −1.08 (280); 0 (250); +0.60 (237); 0 (234); −15.54 (220); 0 (205).

(−)-**6b**: $[\alpha]_D^{17}$ −1.3° (*c* = 1.0, $CHCl_3$). MS *m/z* (%): 406 (M^+, 4.9), 347 (6.1), 319 (100), 315 (5.9), 259 (5.9), 170 (5.9), 169 (17.6), 168 (7.8), 156 (7.8), 154 (3.9), 130 (3.9), 129 (2.9), 128 (2.0), 115 (3.9), 91 (68.6). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470

(NH), 1730 (ester). ^{1}H-NMR ($CDCl_3$) δ: 1.72—1.88 (1H, m, H–$C_{1'}$), 1.88—2.05 (1H, m, H–$C_{1'}$), 2.42—2.62 (2H, m, H_2–$C_{2'}$), 2.99 (1H, dd, J=6.3 and 15.8 Hz, H–C_4), 3.22 (1H, dd, J=3.6 and 15.8 Hz, H–C_4), 3.55 and 3.66 (each 3H, s, CO_2CH_3), 3.76—3.94 (2H, m, H–C_1 and H–C_3), 3.82 and 3.89 (2H, AB-q, J=14.0 Hz, C$\underline{H}_2$Ph), 7.02—7.44 (8H, m, arom H), 7.52 (1H, d, J=6.9 Hz, arom H), 8.13 (1H, br s, NH).

Ammonolysis of (−)-6a and (+)-5a: (1*S*, 3*R*)-(−)-2-Benzyl-3-(amide)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionamide (7) and (1*S*, 3*R*)-(−)-2-Benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionamide (8)——[1] An ice-cooled solution of (−)-**6a** (5.52 g, 0.0136 mol) in MeOH (200 ml) was saturated with ammonia gas. The mixture was allowed to stand in a closed bottle at room temperature for 20 d. The solvent was evaporated off under reduced pressure to afford a crystalline residue (5.15 g), which was chromatographed on silica gel (160 g). Elution with AcOEt provided the monoamide ((−)-**8**, 0.63 g, 11.9% yield) as colorless crystals, which were recrystallized from MeOH to give colorless needles. mp 226—227 °C. $[\alpha]_D^{16}$ −33.2° (c=1.0, $CHCl_3$). MS m/z (%): 391 (M^+, 3.1), 319 (100), 300 (52.9), 283 (15.7), 259 (7.8), 223 (7.8), 170 (8.8), 169 (26.5), 168 (10.8), 156 (9.8), 154 (4.9), 130 (3.9), 129 (3.5), 128 (2.9), 115 (3.9), 91 (88.2). IR ν_{max}^{KBr} cm^{-1}: 3480 and 3380 (NH), 1740 (ester), 1670 (amide). UV λ_{max}^{MeOH} nm (log ε): 225 (4.60), 275 (shoulder, 3.91), 282 (3.92), 290 (3.83). ^{1}H-NMR ($CDCl_3$) δ: 1.82—1.98 (1H, m, H–$C_{1'}$), 2.04—2.18 (2H, m, H–$C_{1'}$ and H–$C_{2'}$), 2.18—2.34 (1H, m, H–$C_{2'}$), 3.06 (1H, dd, J=5.3 and 16.0 Hz, H–C_4), 3.13 (1H, dd, J=9.2 and 16.0 Hz, H–C_4), 3.52 and 3.86 (2H, AB-q, J=13.7 Hz, C$\underline{H}_2$Ph), 3.79 (3H, s, CO_2CH_3), 3.77—3.86 (1H, m, H–C_1), 4.02 (1H, dd, J=5.3 and 9.2 Hz, H–C_3), 7.08—7.42 (8H, m, arom H), 7.53 (1H, d, J=7.3 Hz, arom H), 8.51 (1H, br s, NH). *Anal.* Calcd for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.74. Found: C, 70.30; H, 6.45; N, 10.47.

Elution with 5% MeOH–AcOEt gave a crystalline solid ((−)-**7**, 4.42 g, 86.4% yield). Recrystallization from MeOH yielded colorless prisms, mp 244—246 °C (dec.) and recrystallization from MeOH–Et_2O afforded colorless needles, mp 138—141 °C. $[\alpha]_D^{14}$ −94.4° (c=1.0, MeOH). MS m/z (%): 376 (M^+, 7.3), 332 (20.6), 315 (5.9), 304 (22.5), 285 (54.9), 268 (18.6), 259 (16.7), 223 (17.6), 170 (13.7), 169 (54.9), 168 (13.7), 156 (10.8), 154 (5.9), 130 (3.9), 129 (3.9), 128 (3.8), 115 (5.9), 91 (100). IR ν_{max}^{KBr} cm^{-1}: 3500, 3470, 3380 and 3300 (NH), 1680 and 1665 (amide). UV λ_{max}^{MeOH} nm (log ε): 225.5 (4.62), 275 (shoulder, 3.90), 282 (3.92), 290 (3.83). ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.25 (4H, m, H_2–$C_{1'}$ and H_2–$C_{2'}$), 3.04 (1H, dd, J=5.6 and 16.3 Hz, H–C_4), 3.09 (1H, dd, J=10.8 and 16.3 Hz, H–C_4), 3.42 and 3.72 (2H, AB-q, J=13.4 Hz, C$\underline{H}_2$Ph), 3.65—3.75 (1H, m, H–C_1), 3.97 (1H, dd, J=5.6 and 10.8 Hz, H–C_3), 7.05—7.35 (8H, m, arom H), 7.54 (1H, dd, J=1.5 and 5.8 Hz, arom H), 8.55 (1H, br s, NH). *Anal.* Calcd for $C_{22}H_{24}N_4O_2$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.04; H, 6.43; N, 14.85.

[2] Treatment of the *trans* lactam ((+)-**5a**, 150 mg, 0.4 mmol) with methanolic ammonia under the same conditions as described above afforded the monoamide ((−)-**8**, 10 mg, 6.4% yield) and the diamide ((−)-**7**, 139 mg, 92.1% yield) after purification by column chromatography on silica gel (6 g).

(−)-Methyl 2-Benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (9)——The *trans* dimethyl ester ((−)-**6a**, 1.015 g, 2.5 mmol) suspended in dry Et_2O (20 ml) was added to a stirred dark-blue solution of liquid ammonia containing $Fe(NO_3)_3 \cdot 9H_2O$ (8.4 mg) and metallic Na (138 mg). After 30 min, MeI (0.994 g, 7 mmol) was added in four portions over 1 h, and the mixture was stirred for an additional 30 min. The solvent was evaporated off *in vacuo*, and the resulting viscous oil was suspended in H_2O (50 ml) and extracted with 5% MeOH–$CHCl_3$ (4×70 ml). The organic layer was washed with brine, dried and concentrated *in vacuo*. The residue (1.607 g) was purified by column chromatography over silica gel (48 g) using a mixture of *n*-hexane–AcOEt (9 : 1; v/v) as an eluent to furnish the N_a-methylated compound ((−)-**9**, 0.816 g, 77.7% yield) in an amorphous state. $[\alpha]_D^{21}$ −56.3° (c=2.7, $CHCl_3$). MS m/z (%): 420 (M^+, 6.7), 361 (5.9), 333 (100), 273 (3.9), 243 (1.6), 184 (13.7), 182 (5.5), 170 (5.9), 169 (2.4), 168 (5.7), 91 (39.2). UV λ_{max}^{MeOH} nm: 228, 278, 284, 292. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (ester). ^{1}H-NMR ($CDCl_3$) δ: 1.72—2.04 (2H, m, H_2–$C_{1'}$), 2.36 (1H, dt, J=5.3 and 17.5 Hz, H–$C_{2'}$), 2.57 (1H, ddd, J=5.6, 9.3 and 17.5 Hz, H–$C_{2'}$), 3.05 (1H, dd, J=5.4 and 15.8 Hz, H–C_4), 3.12 (1H, dd, J=10.5 and 15.8 Hz, H–C_4), 3.35 (1H, A part of AB-q, J=13.2 Hz, C$\underline{H}_2$Ph), 3.45 and 3.81 (each 3H, s, CO_2CH_3), 3.61 (3H, s, N–CH_3), 3.74—3.84 (2H, m, H–C_1 and C$\underline{H}_2$Ph), 4.05 (1H, dd, J=5.4 and 10.5 Hz, H–C_3), 7.06—7.36 (8H, m, arom H), 7.54 (1H, d, J=7.6 Hz, arom H). CD (c=0.00026, MeOH) $\Delta\varepsilon^{25}$ (nm): 0 (303); −1.61 (275); −1.03 (261); −3.16 (240); −13.80 (224); 0 (212.5); +6.33 (205).

Hydrolysis of the N_a-Methyl Dimethyl Ester ((−)-9): (−)-2-Benzyl-3-carboxy-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (10)——A mixture of (−)-**9** (436 mg, 1.04 mmol), NaOH (116 mg, 4.15 mmol), MeOH (13 ml) and H_2O (2 ml) was heated under reflux for 80 h in an atmosphere of nitrogen gas. The solution was concentrated *in vacuo*, and the residue was diluted with H_2O (50 ml), acidified with 2 N HCl and extracted with 10% MeOH–$CHCl_3$ (4×70 ml). The combined organic layer was washed with H_2O, dried and concentrated *in vacuo* to afford a crystalline product ((−)-**10**, 390 mg, 95.7% yield), which was recrystallized from benzene–MeOH to provide colorless needles. mp 207—208 °C (dec.). $[\alpha]_D^{23}$ −38.7° (c=1.0, MeOH). IR ν_{max}^{KBr} cm^{-1}: 1760 and 1700 (acid). MS m/z (%): 392 (M^+, 0.3), 374 (5.6), 319 (47.8), 273 (11.1), 184 (8.9), 183 (22.2), 182 (13.3), 170 (9.4), 168 (12.2), 91 (100). ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 1.85—2.13 (2H, m, H_2–$C_{1'}$), 2.20—2.56 (2H, m, H_2–$C_{2'}$), 3.13—3.23 (2H, m, H_2–C_4), 3.47 and 4.07 (2H, AB-q, J=13.0 Hz, C$\underline{H}_2$Ph), 3.57 (3H, s, N–CH_3), 3.83—3.93 (1H, m, H–C_1), 4.20—4.30 (1H, H–C_3, overlapped with H_2O), 7.10—7.40 (8H, m, arom H), 7.58 (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, 70.47; H, 6.15; N, 7.00.

Esterification of the Dicarboxylic Acid ((−)-10) with Diazomethane——An excess of ethereal diazomethane was added to a stirred solution of the dicarboxylic acid ((−)-**10**, 78.4 mg, 0.2 mmol) in MeOH–CH_2Cl_2 (1 : 1; v/v; 5 ml). After 1 h, the solvent was evaporated off *in vacuo* and the residue was purified by column chromatography on silica gel (10 g). Elution with *n*-hexane–AcOEt (10 : 1; v/v) gave the dimethyl ester ((−)-**9**, 83 mg) as an amorphous compound. $[\alpha]_D^{22}$ −54.2° (c = 1.2, $CHCl_3$). This was identical with (−)-**9** obtained above in terms of the IR ($CHCl_3$), mass, ^{1}H-NMR and ^{13}C-NMR spectra.

(1*S*, 3*R*)-(+)-2-Benzyl-3-cyano-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionitrile (11)——Phosphorus oxychloride (3.297 g, 21.5 mmol) was added dropwise to a stirred solution of the diamide ((−)-**7**, 3.234 g, 8.6 mmol) in dry pyridine (6.804 g, 86 mmol) and dry DMF (60 ml) below 0 °C. The mixture was stirred for an additional 1 h, diluted with $CHCl_3$ (200 ml) and ice-water (200 ml), and then basified with 10% aqueous sodium carbonate. The $CHCl_3$ layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 200 ml). The combined $CHCl_3$ phase was washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue (3.843 g) was chromatographed on silica gel (115 g) using a mixture of *n*-hexane–AcOEt (4 : 1; v/v) to yield the dinitrile ((+)-**11**, 2.694 g, 92.1% yield) as a colorless solid. Recrystallization from MeOH provided colorless prisms. mp 125—130 °C. $[\alpha]_D^{15}$ +3.0° (c = 1.0, $CHCl_3$). MS m/z (%): 340 (M^+, 0.6), 313 (4.9), 286 (3.1), 259 (64.7), 168 (9.8), 91 (100). IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 2250 and 2225 (CN). UV λ_{max}^{MeOH} nm (log ε): 222.5 (4.59), 270 (shoulder, 3.89), 273 (3.90), 279 (3.89), 282 (shoulder, 3.88), 290 (3.79). ^{1}H-NMR ($CDCl_3$) δ: 1.82—1.98 (1H, m, H–$C_{2'}$), 2.02—2.18 (1H, m, H–$C_{1'}$), 2.28—2.46 (2H, m, H–$C_{1'}$ and H–$C_{2'}$), 2.97 (1H, ddd, J = 1.6, 5.4 and 16.2 Hz, H–C_4), 3.01 (1H, ddd, J = 1.6, 3.6 and 16.2 Hz, H–C_4), 3.64 and 4.08 (2H, AB-q, J = 13.9 Hz, CH_2Ph), 4.00—4.08 (2H, m, H–C_1 and H–C_3), 7.10—7.50 (9H, m, arom H), 8.04 (1H, br s, NH). *Anal.* Calcd for $C_{22}H_{20}N_4 \cdot 1/2CH_3OH$: C, 75.82; H, 6.22; N, 15.72. Found: C, 75.62; H, 6.27; N, 15.75.

(1*S*)-(−)-1,2,3,4-Tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propylamine (14)——A stirred solution of the dinitrile ((+)-**11**, 2.056 g, 6.05 mmol) in EtOH (100 ml) was treated with $NaBH_4$ (2.288 g, 6.05 mmol). The mixture was stirred at 60 °C for 10 h. Further $NaBH_4$ (1.144 g) was added to the mixture, and stirring was continued at 60 °C for 14 h. After evaporation of the solvent, the residue was diluted with brine (300 ml) and extracted with Et_2O (4 × 250 ml). The Et_2O layer was washed with brine, dried over anhydrous potassium carbonate, and concentrated under reduced pressure. The resulting viscous oil was purified by column chromatography over silica gel (52 g) using a mixture of *n*-hexane–AcOEt (9 : 1; v/v) to afford the mononitrile (**12**, 1.322 g, 69.4% yield) as a viscous oil. MS m/z (%): 315 (M^+, 6.9), 261 (100), 170 (3.9), 169 (11.8), 156 (13.7), 154 (3.9), 130 (2.9), 129 (2.9), 128 (2.9), 115 (3.9), 91 (54.9).

Elution with *n*-hexane–AcOEt (3 : 1; v/v) gave the starting material ((+)-**11**, 0.294 g, 14.2% recovery).

A solution of the mononitrile (**12**, 1.034 g, 3.3 mmol) in dry Et_2O (120 ml) was added to a stirred suspension of $LiAlH_4$ (0.624 g, 16.4 mmol) in dry Et_2O (80 ml) over a period of 20—30 min at room temperature. The mixture was refluxed for 3 h, and then worked up in the usual manner to furnish **13** (0.967 g) as a pale yellow viscous oil. MS m/z (%): 319 (M^+, 3.7), 261 (100), 228 (62.7), 200 (7.8), 198 (10.0), 170 (9.8), 169 (17.6), 156 (5.6), 154 (3.9), 130 (6.9), 129 (3.5), 128 (3.5), 115 (4.9), 91 (90.2).

The amino compound (**13**, 0.967 g) in EtOH (45 ml) containing conc. HCl (1.0 ml) was catalytically hydrogenated over 10% palladium charcoal (194 mg) at 30 °C for 10 h under atmospheric pressure. The catalyst was separated by filtration through Celite. The filtrate was concentrated *in vacuo* to give the crude hydrochloride of (−)-**14** (0.950 g, 95.3% yield from **12**), which was recrystallized from MeOH–Et_2O to afford colorless needles. mp 240—242 °C (dec.). $[\alpha]_D^{15}$ −40.0° (c = 1.0, MeOH). MS m/z (%): 229 (M^+, 34.5), 211 (19.6), 199 (7.1), 198 (7.8), 197 (6.3), 184 (11.0), 171 (100), 156 (8.0), 154 (8.0), 146 (10.9), 130 (8.4), 115 (6.3). *Anal.* Calcd for $C_{14}H_{19}N_3 \cdot 2HCl \cdot 1/4H_2O$: C, 54.82; H, 7.06; N, 13.70. Found: C, 54.98; H, 7.02; N, 13.77.

The IR (KBr), mass and ^{13}C-NMR spectra of (−)-**14** (hydrochloride) were virtually identical with those of the racemate of **14** (hydrochloride) obtained in an earlier experiment.[4a,b]

(1*S*)-(−)-Trypargine (1a)——A mixture of the free base of (−)-**14** (202 mg, 0.88 mmol) and *S*-methylisothiourea sulfate (135 mg, 0.97 mmol) in H_2O (8 ml) was stirred at 50 °C for 12 h and then at room temperature for 12 h. The solvent was evaporated off under reduced pressure to give the sulfate of **1a** (230 mg). This sulfate was converted to the corresponding diformate by the method reported in our previous papers.[4a,b] The hydrochloride of **1a** was obtained by treatment of the diformate with 10% w/v HCl–EtOH and was recrystallized from MeOH–Et_2O to provide colorless needles (167 mg, 55.2% yield). mp 211—213 °C. $[\alpha]_D^{17}$ −37.5° (c = 1.0, MeOH). *Anal.* Calcd for $C_{15}H_{21}N_5 \cdot 2HCl \cdot 1/4H_2O$: C, 51.65; H, 6.79; N, 20.08. Found: C, 51.89; H, 6.61; N, 20.10.

The synthetic trypargine hydrochloride (**1a**) was identical with the natural trypargine hydrochloride (**1a**) on the basis of the mixture melting point test and comparisons of their IR (KBr), ^{1}H-NMR and ^{13}C-NMR spectra, and optical rotations.

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