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ASYMMETRIC SYNTHESIS OF (1S)-(-)-TRYPARGINE

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(1S)-(-)-Trypargine (1a) was synthesized from (1S,3R)-(-)-2-benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-1-propionic acid (3a), prepared by the asymmetric Pictet-Spengler reaction of N_b-benzyl-(D)-tryptophan methyl ester (2) with α-ketoglutaric acid. The absolute configuration of natural trypargine (1a) at the C_1 position was determined to be the S-configuration.

KEYWORDS ———— (1S)-(-)-trypargine; asymmetric synthesis; absolute configuration; Pictet-Spengler reaction; X-ray crystallographic analysis; N_b-benzyl-(D)-tryptophan methyl ester; α-ketoglutaric acid

Trypargine (1a)[1] is a toxic component (LD_{50}=16.9 mg/kg, intravenous administration to mice[2]) isolated from the skin of African rachophorid frog, Kassina senegalensis.

In the course of synthetic studies of trypargine (1a),[3] we developed a method for the chiral synthesis of 1a or 1b. In earlier studies,[4] we carried out a model experiment, and found that 3c as a synthetic intermediate could be converted to (±)-trypargine (1). The present paper reports a new route for the total synthesis of 1a based on a model experiment using the asymmetric Pictet-Spengler reaction, and elucidates the absolute configuration at the asymmetric center of 1a.

The condensation of N_b-benzyl-(D)-tryptophan methyl ester (2) with α-ketoglutaric acid in a mixture of dry benzene - dry dioxane (1:1) for 8 h under reflux with water removal by a Dean-Stark trap[5a,b] yielded a diastereoisomeric mixture of 3a and 3b (6-7:1) in a 75.6% yield [3a: a main product; mp 174-176°C; $[\alpha]_D$ -18.0° ($CHCl_3$); ^{1}H-NMR[6] δ: 3.09 (1H, dd, J=16.2, 5.3Hz, C_4-H), 3.15 (1H, dd, J=16.2, 8.9Hz, C_4-H), 4.00-4.08 (2H, m, C_1- and C_3-H)], and two isomeric 6-oxocanthine derivatives (4a and 4b) [4a: 5.5% yield; mp 167.5-168.5°C; $[\alpha]_D$ +37.0° ($CHCl_3$); ^{1}H-NMR δ: 3.91 (1H, dd, J=1.9, 6.8Hz, C_3-H), 4.50-4.60 (1H, m, C_1-H). 4b: 3.3% yield; mp 166-167°C; $[\alpha]_D$ +5.3° ($CHCl_3$); ^{1}H-NMR δ: 3.99 (1H, dd, J=9.1, 5.1Hz, C_3-H), 4.05-4.20 (1H, m, C_1-H)]. The mixture of 3a and 3b in CH_2Cl_2 - MeOH (3:1) was treated with ethereal diazomethane to give the dimethyl esters (5a and 5b) [5a: 78.6% yield; mp 150-151°C; $[\alpha]_D$ -38.0° ($CHCl_3$); ^{1}H-NMR δ: 3.50 and 3.75 (each 3H, s, CO_2CH_3), 3.87-3.96 (1H, m, C_1-H), 3.98 (1H, dd, J=8.8, 5.3Hz, C_3-H); ^{13}C-NMR δ: 53.4 (t,

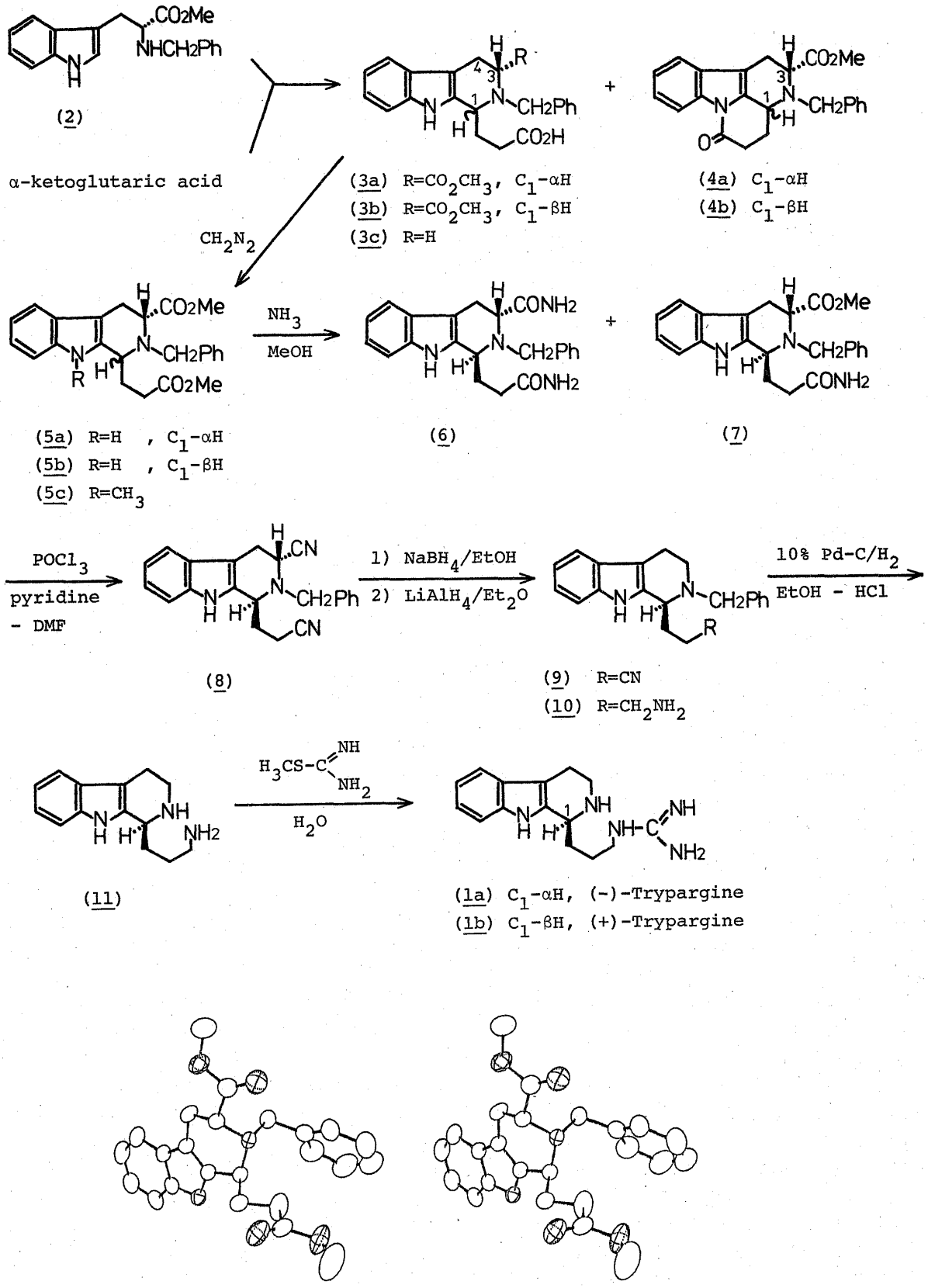

Fig-1 Stereoscopic View of 5a

$\underline{CH_2}Ph$), 54.7 (d, C_1), 56.7 (d, C_3). 5b as an amorphous compound: 7.5% yield; $[\alpha]_D$ -1.3° ($CHCl_3$); ^{1}H-NMR δ: 2.98 (1H, dd, J=15.8, 6.3Hz, C_4-H), 3.23 (1H, dd, J=15.8, 3.6Hz, C_4-H), 3.55 and 3.60 (each 3H, s, CO_2CH_3), 3.81-3.91 (2H, m, C_1- and C_3-H); ^{13}C-NMR δ: 56.2 and 58.7 (each d, C_1 and C_3), 59.4 (t, $\underline{CH_2}Ph$)] after purification by repeated column chromatography on silica gel. The major isomer (5a) on treatment with methanol saturated with ammonia for 20 d at room temperature afforded the diamide [6: 86.4% yield; mp 244-246°C (dec.); $[\alpha]_D$ -94.4° (MeOH); IR ν_{max}^{KBr} cm^{-1}: 1680, 1670; ^{1}H-NMR δ: 3.65-3.75 (1H, m, C_1-H), 3.97 (1H, dd, J=10.5, 5.6Hz, C_3-H)] and the monoamide [7: 11.9% yield; mp 226-227°C; $[\alpha]_D$ -33.2° ($CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 1740, 1665]. The MS spectrum exhibited the base ion peak at m/z 319 indicating the structure of 7 having a C_3-methoxycarbonyl group.

The absolute configuration of the above-mentioned compounds was determined as follows. Cyclization of 3a under the above Pictet-Spengler conditions gave only one isomer (4a). Ammonolysis of both 5a and 4a gave rise to a mixture of 6 and 7. The assignment of the stereochemistry by ^{13}C-NMR[5c] was limited by the complexity of the steric interactions in 1,2,3-trisubstituted groups because the N_b-benzyl substituent was a bulky group. It became clear from X-ray analysis that the N_b-benzyl group in 5a occupied the axial position as will be described later. The C_1-proton in 4a is approximately 0.4 ppm downfield relative to that in 4b. This reveals by examination of the coupling constants and molecular model that both C_3-methoxycarbonyl group and C_1-proton in 4a exist in the α, axial orientation. Thus, the chemical and spectroscopic evidence suggests that the compounds (3a, 4a, 5a, 6 and 7) have the 1,3-trans configuration. On the other hand, it is known that the racemic 1,3-trans-N_a-methyl isomer (5c) can be isomerized into the 1,3-cis isomer by alkaline hydrolysis followed by methylation.[7] Therefore, to attempt the above isomerization, optically active trans isomer (5a) was methylated with $NaNH_2$ in liquid ammonia and MeI[8] to afford optically active 5c. The ^{1}H- and ^{13}C-NMR spectra indicate that 5c [δ: 3.83 and 3.46 (each 3H, s, CO_2CH_3), 3.63 (3H, s, N-CH_3), 4.08 (1H, dd, J=10.5, 5.6Hz, C_3-H); 52.9 (t, $\underline{CH_2}Ph$), 53.4 (d, C_1) 56.2 (d, C_3)] has the same stereochemistry as 5a. However, alkaline hydrolysis of optically active trans-5c provided the corresponding trans-diacid, which was converted back to the original trans isomer (5c) with diazomethane. Definitive evidence for the stereochemistry of 5a was obtained by X-ray crystallographic analysis.[9] The structure of 5a was unambiguously established as (1S,3R)-(-)-methyl 2-benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-1-propionate as shown in Fig-1, since (R)-tryptophan was the precursor to 5a.

Dehydration of 6 was carried out using 2.5 eq of $POCl_3$ in pyridine and DMF at 0°C to afford the dinitrile [8: mp 125-130°C; $[\alpha]_D$ +3.0° ($CHCl_3$); MS m/z: 340 (M^+)] in a 92.1% yield. The ^{13}C-NMR spectrum of 8 showed two nitrile carbons, at 117.4 and 119.8 ppm. The dinitrile (8) was subjected to reductive decyanation[10] with $NaBH_4$ in EtOH at 60°C to give the unstable product [9: 69.4% yield; MS m/z: 315 (M^+)] after rapid purification by column chromatography on silica gel. The labile nitrile (9) was first reduced with $LiAlH_4$ to afford 10 [a viscous oil; MS m/z: 319 (M^+)], and then without purification, reductive debenzylation of 10 with 10% palladium on charcoal in EtOH and concd. HCl gave the debenzylated amine (11) as a hydrochloride [mp 240-242°C (dec.); $[\alpha]_D$ -40.0° (MeOH)] in a 95.3% yield from 9. The IR (KBr), MS and ^{13}C-NMR (CD_3OD) spectra of the hydrochloride of 11 were virtually identical with those of the hydrochloride of the racemic authectic sample.[3] The

mixture of the free base of 11 and S-methylisothiourea sulfate in water was heated at 50°C to yield synthetic trypargine (1a) as a sulfate, which was converted to the corresponding hydrochloride of 1a [60% yield; mp 211-213°C; $[\alpha]_D$ -37.5° (MeOH)] according to the procedure as described in the previous paper.[3] The synthetic trypargine hydrochloride was completely identified with the natural trypargine hydrochloride in mixture melting point test and by comparison of their IR (KBr) and ^{13}C-NMR (CD_3OD) spectra, and optical ratations.

To obtain 1b with the opposite configuration, the same sequence of above-mentioned reactions was carried out with N_b-benzyl-(L)-tryptophan methyl ester as a starting material to give the synthetic 1b [hydrochloride mp 212-214°C; $[\alpha]_D$ +37.0° (MeOH)].[3]

It is considered that no epimerization occurs at C_1 position during the present synthetic route, and the stereochemistry of 5a which is the main isomer obtained by the condensation of 2 with α-ketoglutaric acid in an aprotic solvent followed by methylation with diazomethane was unequivocally proven to be the (1S,3R)-trans configuration. Therefore, the absolute configuration at the asymmetric center of natural trypargine (1a) was determined to be the S-configuration.

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