(*S*)-6-(1-HYDROXYPROPYL)LUMAZINE DERIVATIVES FROM THE MARINE POLYCHAETE, *ODONTOSYLLIS UNDECIMDONTA*

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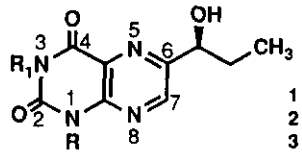
Abstract - (*S*)-6-(1-Hydroxypropyl)-3-methyllumazine (**1**) and (*S*)-6-(1-hydroxypropyl)-1,3-dimethyllumazine (**3**) were isolated from the swimming polychaete, *Odontosyllis undecimdonta*.

In 1981, Cardellina and Meinwald[1] isolated a minor metabolite of 6-substituted lumazine derivative from the marine calcareous sponge *Leucetta microraphis* and named it leucettidine. Its structure was proposed as 6-(1-hydroxypropyl)-3-methyllumazine (**1**) on the basis of various spectral data. The absolute configuration of the hydroxypropyl substituent placed at C-6 in **1** was proposed as the (*S*)-configuration on the basis of comparison of optical rotation of **1** with those of other pteridines and related model compounds bearing the chiral alcoholic methine center. However, in 1984 Pfleiderer[2] revised the structure of leucettidine to 6-(1-hydroxypropyl)-1-methyllumazine (**2**) by identification of the natural product with a racemic authentic sample prepared by an ambiguous synthesis.



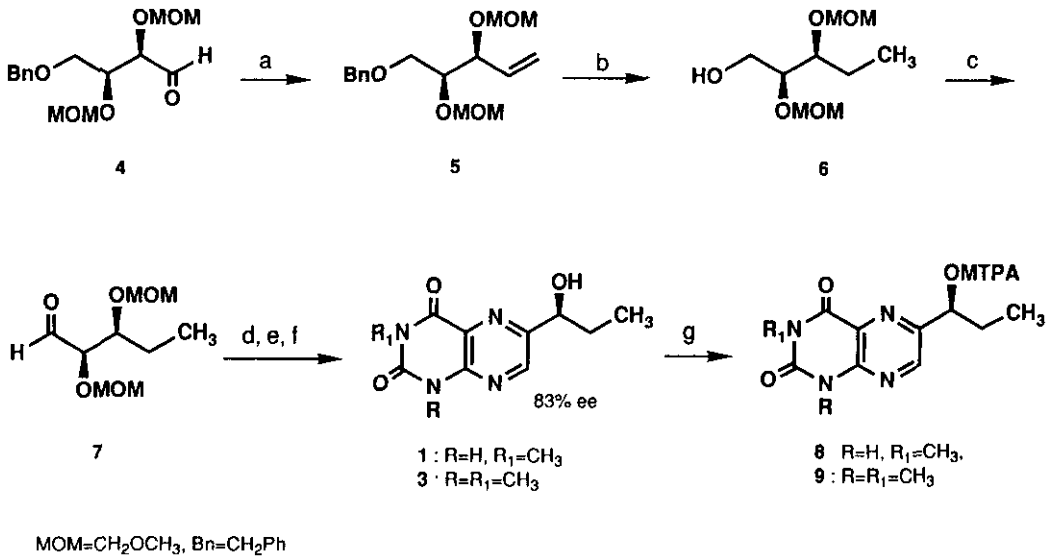
1 R=H, R_1=CH_3
2 R=CH_3, R_1=H
3 : R=R_1=CH_3

Recently, we reported the isolation of nine 6-substituted lumazine derivatives from the luminescent marine polychaete, *Odontosyllis undecimdonta*, collected at Toyama-Bay in Japan.[3]

In subsequent studies to isolate related lumazine derivatives, two additional metabolites having the 1-hydroxypropyl side chain were isolated from the same polychaete. The structure of one of them was found to be 6-(1-hydroxypropyl)-3-methyllumazine (**1**),[4] an isomer of leucettidine and the other one was deduced as its 1,3-dimethyl derivative (**3**). This paper describes the structures and stereochemistries of these natural products.

Crude methanol extracts of freeze-dried worms (11 g, *ca.* 5500 individuals) reported previously,[3a,b] were chromatographed on a silica gel column using a CH_2Cl_2/MeOH (10:1) solvent system into three fractions. The first fraction was further chromatographed on a silica gel column developed with CH_2Cl_2/MeOH (97:3) and then with CH_2Cl_2/MeOH (10:1). The blue fluorescent fraction eluted with CH_2Cl_2/MeOH (10:1) was purified by successive silica gel tlc using CH_2Cl_2/MeOH (10:1) and AcOEt/benzene (2:1) to afford 3-methyl derivative (**1**)[4] (*ca.* 0.1 mg). The less polar fraction eluted with CH_2Cl_2/MeOH (97:3) was separated twice by silica gel tlc [CH_2Cl_2/MeOH (20:1) and AcOEt/benzene (2:1)] to give 1,3-dimethyl derivative (**3**)[5] (*ca.* 0.1 mg).

The empirical formulae of the metabolites were established to be $C_{10}H_{12}N_4O_3$ and $C_{11}H_{14}N_4O_3$ by high resolution mass spectra [*m/z* 236.0931 (M^+), calcd 236.0909 and *m/z* 250.1064 (M^+), calcd 250.1066] and the structures of **1** and **3** were confirmed as 6-(1-hydroxypropyl)-3-methyllumazine (**1**) and 6-(1-hydroxypropyl)-1,3-dimethyllumazine (**3**) by comparison of their spectral data (uv and ^{1}H nmr) with those of racemic samples prepared from the corresponding 6-propionyllumazines.[3a] The stereochemistry of the two metabolites was determined as the (*S*)-configuration by synthesis of optically active (**1**) and (**3**) starting from 4-*O*-benzyl-2,3-*O*-bis(methoxymethyl)-L-threose (**4**)[6] by the following experiments. Treatment of **4** with a mixture of methylene iodide, zinc, and trimethylaluminum in THF at 0 °C for 2 h under a nitrogen atmosphere gave 4-benzyloxy-1-pentene (**5**) in 86% yield.[7] Hydrogenation of **5** with 10% palladium-charcoal in AcOH/MeOH (1:1) at room temperature for 5 h gave pentanol (**6**) as a 12:1 inseparable mixture of the threo/erythro isomeres, which was converted to the aldehyde (**7**)[8] by Swern oxidation (oxalyl chloride/DMSO/triethylamine). The condensation of 5,6-diaminopyrimidine derivatives with pentose phenylhydrazone followed by oxidation was reported to give the 6-substituted pteridine derivatives.[9] Application of this procedure to the synthesis of 6-(1-hydroxypropyl)lumazines was successful. Thus, heating of the phenylhydrazone of **7** with the hydrochloride of 5,6-diamino-3-methyluracil[10] in aqueous MeOH containing 4N H_2SO_4 followed by oxidation with $K_3[Fe(CN)_6]$ in the presence of potassium iodide gave (*S*)-6-(1-hydroxypropyl)-3-methyllumazine (**1**) {21%, $[\alpha]_D^{25}$ -76.0° (c 0.938, MeOH)}.[11] Similarly, (*S*)-6-(1-hydroxypropyl)-1,3-dimethyllumazine (**3**) {mp 173-174 °C, $[\alpha]_D^{25}$ -59.6° (c 1.079, MeOH)} was also prepared from **7** and 5,6-diamino-1,3-dimethyluracil in 22% yield. The optical purities of **1** (83% ee) and **3** (83% ee) were conventionally determined by ^{1}H nmr analysis of the corresponding (+)-MTPA esters (**8**)[12] and (**9**).[13]



MOM=CH_2OCH_3, Bn=CH_2Ph

a) CH_2I_2, Zn, Me_3Al,THF; b) H_2, 10% Pd-C, 50% AcOH-MeOH; c) i) DMSO, $(COCl)_2$, CH_2Cl_2; ii) Et_3N; d) $PhNHNH_2$, AcOH, MeOH; e) 5,6-diamino-3-methyluracil hydrochloride (or 5,6-diamino-1,3-dimethyluracil), 4N H_2SO_4, aq MeOH; f) $K_3[Fe(CN)_6]$, KI, 35% H_2O_2; g) (+)-MTPA-Cl, pyridine.

Since the *Rf* values on tlc (*Rf*=0.30 for **8**, isopropyl ether/MeOH=100:3; *Rf*=0.58 for **9**, AcOEt/benzene=1:2) and ^1H nmr spectra of the (+)-MTPA esters of natural products (**8**) and (**9**) were in accord with those of the synthetic (+)-MTPA esters of (*S*)-6-(1-hydroxypropyl)-3-methyllumazine and (*S*)-6-(1-hydroxypropyl)-1,3-dimethyllumazine, respectively, the stereochemistry of the chiral centers of both natural products (**1**) and (**3**) was concluded to be the (*S*)-configuration.

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4. Compound (**1**): uv (MeOH) λ_{max} nm 236, 332; uv (MeOH-NaOH) λ_{max} nm 249, 277, 373; ^1H nmr (400 MHz, $CDCl_3$) δ 1.01 (3H, t, J=7.3 Hz), 1.85 (1H, m), 1.98 (1H, m), 3.52 (3H, s), 4.92 (1H, dd, J=7.2,

4.3 Hz), 8.34 (1H, br s, NH), 8.70 (1H, s); HRms (EI) found: *m/z* 236.0931, calcd for $C_{10}H_{12}N_4O_3$: 236.0909.

5. Compound (**3**): uv (MeOH) λmax nm 240, 336; uv (MeOH-NaOH) λmax nm 240, 336; ^{1}H nmr (400 MHz, $CDCl_3$) δ 1.01 (3H, t, J=7.5 Hz), 1.85 (1H, m), 1.98 (1H, m), 3.55 (3H, s), 3.73 (3H, s), 4.93 (1H, dd, J=7.3, 4.8 Hz), 8.75 (1H, s); HRms (EI) found: *m/z* 250.1064, calcd for $C_{11}H_{14}N_4O_3$: 250.1066.
6. a) H. Iida, N. Yamazaki, and C. Kibayashi, *Tetrahedron Lett.*, 1985, **26**, 3255. b) H. Iida, N. Yamazaki, and C. Kibayashi, *J. Org. Chem.*, 1986, **51**, 1069.
7. K. Takai, Y. Hotta, K. Oshima, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1698.
8. Compound (**7**): ^{1}H nmr (270 MHz, $CDCl_3$) δ 0.96 (3H, t, J=7.4 Hz), 1.73 (2H, m), 3.35 (3H, s), 3.45 (3H, s), 3.90 (1H, ddd, J=6.7, 6.7, 3.4 Hz), 4.06 (1H, dd, J=3.4, 1.0 Hz), 4.63 and 4.70 (2H, d of AB, J=7.1 Hz), 4.75 and 4.81 (2H, d of AB, J=7.1 Hz), 9.76 (1H, d, J=1.0 Hz); HRms (FAB) found: *m/z* 207.1216 $(M+H)^+$, calcd for $C_9H_{19}O_5$: 207.1232.
9. T. Sugimoto and S. Matsuura, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 3767.
10. W. Pfleiderer, *Chem. Ber.*, 1957, **90**, 2272.
11. In this reaction, the MOM ether of **1** (8%) was obtained and it was hydrolysed to **1** (96%) by treatment with 1N HCl-MeOH at 50 °C for 2 h.
12. Compound (**8**): ^{1}H nmr (270 MHz, $CDCl_3$) δ 0.98 (3H, t, J=7.4 Hz), 2.11 (2H, m), 3.52 (3H, s), 3.57 (3H, m), 6.14 (1H, t, J=6.4 Hz), 7.35-7.55 (5H, m), 8.39 (1H, s), 9.61 (1H, br s, NH); tlc: *Rf*=0.30 (Merck, silica gel 60 F254, 0.25 mm; isopropyl ether/MeOH=100:3). (*R*)-Isomer of **8**: ^{1}H nmr (270 MHz, $CDCl_3$) δ 0.90 (3H, t, J=7.4 Hz), 2.11 (2H, m), 3.53 (3H, s), 3.57 (3H, m), 6.07 (1H, dd, J=7.7, 5.7 Hz), 7.35-7.60 (5H, m), 8.58 (1H, s), 9.70 (1H, br s, NH); tlc: *Rf*=0.34 (Merck, silica gel 60 F254, 0.25 mm; isopropyl ether/MeOH=100:3).
13. Compound (**9**): ^{1}H nmr (270 MHz, $CDCl_3$) δ 0.98 (3H, t, J=7.4 Hz), 2.12 (2H, m), 3.54 (3H, s), 3.57 (3H, m), 3.71 (3H, s), 6.16 (1H, t, J=6.4 Hz), 7.35-7.55 (5H, m), 8.43 (1H, s); tlc: *Rf*=0.58 (Merck, silica gel 60 F254, 0.25 mm; AcOEt/benzene=1:2). (*R*)-Isomer of **9**: ^{1}H nmr (270 MHz, $CDCl_3$) δ 0.89 (3H, t, J=7.4 Hz), 2.11 (2H, m), 3.55 (6H, br s), 3.72 (3H, s), 6.09 (1H, dd, J=7.4, 5.7 Hz), 7.35-7.65 (5H, m), 8.63 (1H, s); tlc: *Rf*=0.64 (Merck, silica gel 60 F254, 0.25 mm; AcOEt/benzene=1:2).

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