(*S*)-2-METHYL-1,5-BIS(1,3-DIMETHYL-6-LUMAZINYL)-1,5-PENTANEDIONE FROM THE MARINE POLYCHAETE, *ODONTOSYLLIS UNDECIMDONTA*

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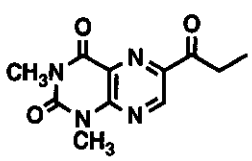
Abstract - (*S*)-2-Methyl-1,5-bis(1,3-dimethyl-6-lumazinyl)-1,5-pentanedione (**3**), a new metabolite of the dimeric form of 1,3-dimethyl-6-acyllumazine derivatives, was isolated from the swimming polychaete, *Odontosyllis undecimdonta*.

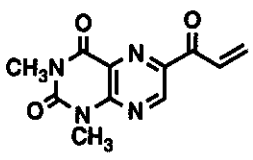
The marine swimming polychaete, *Odontosyllis undecimdonta*, was found to contain considerable amounts of 6-acyllumazines and related compounds.[1] During further examination of the constituents of this polychaete, a new metabolite of the dimeric form of 1,3-dimethyl-6-acyllumazine derivatives was isolated. This compound was extracted from the swimming worm as follows: Freeze dried worms (10 g, *ca.* 5000 individuals),[2] after being ground, emitted bright luminescence when placed in 200 ml of water. The suspended worms were repeatedly ground and squeezed until luminescence ceased to be detectable in the dark and the system was then evaporated to dryness *in vacuo*. The contents obtained were extracted with MeOH, and the MeOH extracts were taken up in MeOH-CH_2Cl_2 (1:1). Separation of the soluble portion (1.67 g) in CH_2Cl_2-MeOH (1:2) through silica gel column using MeOH-CH_2Cl_2 (1:5) afforded three fractions. Successive tlc purification of the first fraction (370 mg) using i) MeOH-CH_2Cl_2 (3:97), ii) AcOEt-benzene (2:3), and iii) AcOEt-hexane- H_2O (10:10:1) gave pure compound (**3**) (2.2 mg).[3]

The empirical formula of the metabolite was established as $C_{22}H_{22}N_8O_6$ based on its high resolution mass spectrum [*m/z* 494.1578 (M^+), calcd 494.1661]. This formula corresponds to that of 1,3-dimethyl-6-propionyllumazine ($C_{11}H_{12}N_4O_3$) (**1**)[1] with $C_{11}H_{10}N_4O_3$ (**2**),[4] equivalent to the dehydro form of **1**. Uv absorption data of the compound were consistent with those of 1,3-dimethyl-6-acyllumazine chromophore with no bathochromic shift in basic medium.[5] The ^1H nmr spectrum showed signals of two aromatic protons [δ 9.25

(1H, s) and 9.30 (1H, s)], four *N*-methyl protons [δ 3.50 (3H, s), 3.51 (3H, s), 3.75 (3H, s), and 3.78 (3H, s)], and four other coupled proton signals which indicated the presence of a disubstituted C_4 chain [-CH(CH_3)-CH_2-CH_2-] as confirmed by a ^{1}H-^{1}H COSY experiment. Based on these data, the structure of this compound was concluded to be the dimeric structure of 1,3-dimethyl-6-acyllumazines (**1**+**2**) as shown in **3**. The stereochemistry of the chiral center in **3**, as determined by the following asymmetric synthesis starting from (+)-β-citronellene (**4**),[6] indicated it to have the (*S*)-configuration.



1



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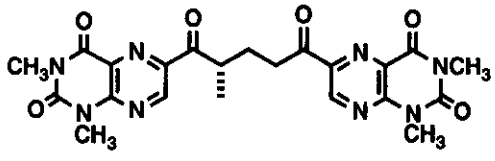
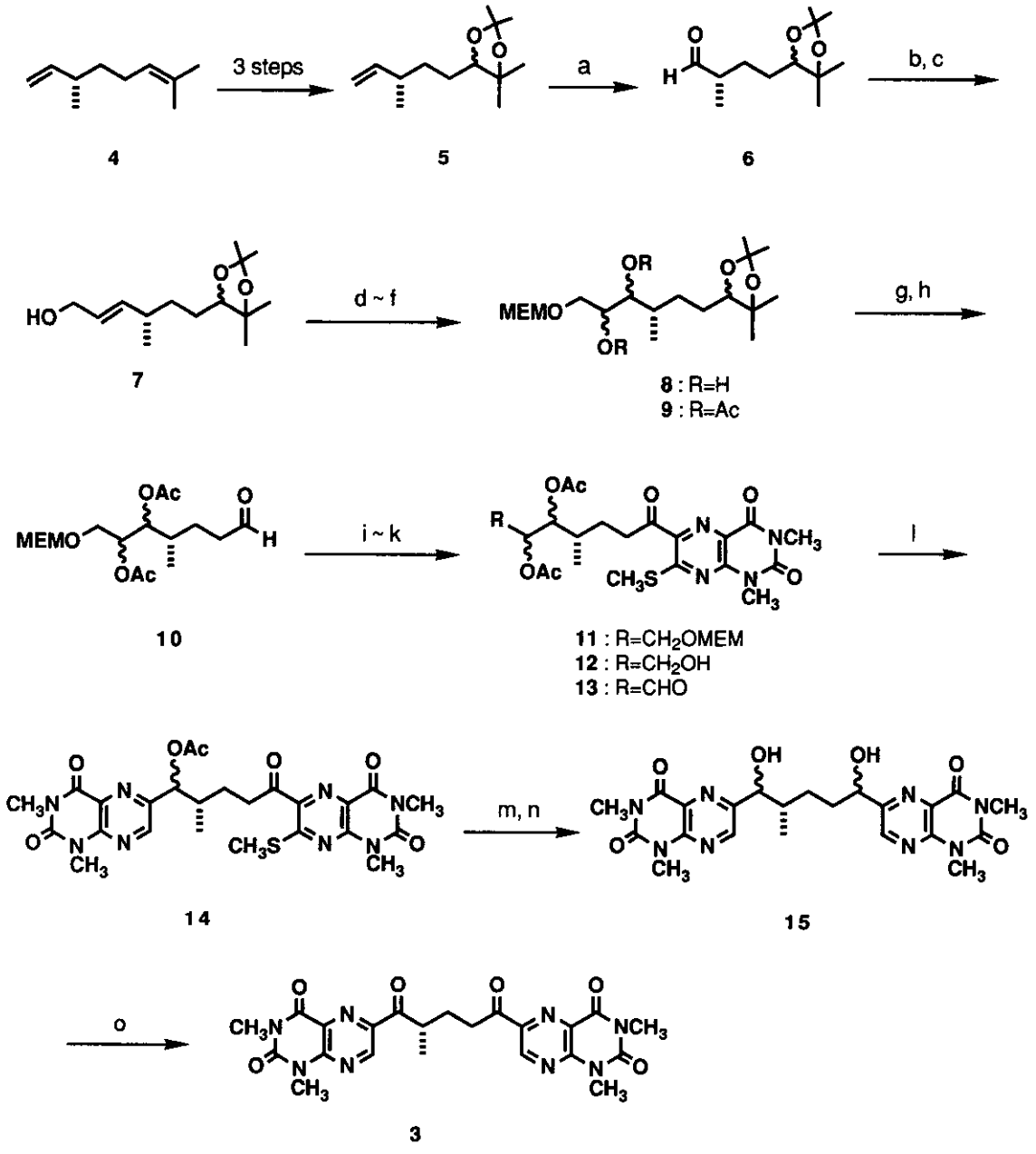


3

Acetonide (**5**)[7] obtained from **4** was converted quantitatively into aldehyde (**6**)[8] by the usual ozonolysis which in turn underwent conversion to (*E*)-allylic alcohol (**7**) in 67% yield by Horner-Emmons olefination [diisopropyl(ethoxycarbonylmethyl)phosphonate, *t*-BuOK/THF][9] followed by diisobutylaluminum hydride reduction. After protection of the hydroxyl group in **7** with 2-methoxyethoxymethyl chloride (MEMCl), the MEM ether thus obtained was treated with a catalytic amount of osmium tetroxide in the presence of 4-methylmorpholine *N*-oxide in aqueous acetone to give diol (**8**) from which diacetate (**9**) was obtained in 87% yield from **7**. Diacetate (**9**) obtained as a mixture of inseparable diastereomers was converted into aldehyde (**10**) in two steps: i) removal of the isopropylidene protective group with 80% AcOH at 65 °C and ii) oxidative cleavage of the diol with HIO_4 at 0 °C. Minisci reaction of aldehyde (**10**) with 1,3-dimethyl-7-methylthiolumazine/ferrous sulfate/*t*-butyl hydroperoxide (TBHP) in aqueous AcOH at room temperature for 1 h afforded 6-acyllumazine derivative (**11**),[5,10] which subsequently underwent conversion to aldehyde (**13**) *via* alcohol (**12**) by deprotection of the MEM group with trimethylsilyl chloride in the presence of sodium iodide in MeCN[11] followed by Dess-Martin oxidation.[12] Reaction of the phenylhydrazone of **13** with 5,6-diamino-1,3-dimethyluracil in the presence of sodium acetate and sodium hydrosulfite in aqueous MeOH followed by oxidation with iodine resulted in ring closure to give the desired bislumazine derivative (**14**) in 45% yield.[13] Compound (**14**) was desulfurized with Raney Ni in EtOH-acetone (1:1), and then treated with 5% NH_4OH in MeOH to give diol (**15**) in 44% overall yield. Finally, the oxidation of **15** with pyridinium chlorochromate (PCC) in CH_2Cl_2 gave dimeric acyllumazine (**3**) {$[\alpha]_D^{25}$ - 86.2° (*c* 0.42, $CHCl_3$)} in 88% yield. A synthetic product (**3**) thus obtained was identical with the natural product in all respects (uv, ir, ^{1}H nmr , ms, tlc, and



a) i) O_3, CH_2Cl_2, -78 °C; ii) Ph_3P, CH_2Cl_2, room temperature, 2 h; **b**) (i-PrO)$_2$P(O)CH_2COOEt, t-BuOK, THF (0 °C to room temperature, 1 h), -78 °C, 30 min; **c**) DIBAL-H, CH_2Cl_2-hexane, -78 °C, 40 min; **d**) MEMCl, DIPEA, CH_2Cl_2, 0 °C to room temperature, 3.5 h; **e**) OsO_4, 4-methylmorpholine N-oxide, aq. acetone, room temperature, 3 days; **f**) Ac_2O, pyridine, room temperature, 6 h; **g**) 80% AcOH, 65 °C, 4 h; **h**) HIO_4, THF-Et_2O, 0 °C, 15 min; **i**) 1,3-dimethyl-7-methylthiolumazine, 78% TBHP, $FeSO_4$, aq. AcOH, room temperature, 1 h; **j**) TMSCl, NaI, MeCN, -15 °C, 1h; **k**) Dess-Martin triacetoxyperiodinane, CH_2Cl_2, room temperature, 30 min; **l**) i) $PhNHNH_2$, cat. AcOH, MeOH, room temperature, 1 h; ii) 5,6-diamino-1,3-dimethyluracil, AcONa, $Na_2S_2O_4$, aq. MeOH, 40 °C, 20 h; iii) I_2, aq. MeOH, room temperature, 30 min; **m**) Raney Ni, EtOH-acetone (1:1), room temperature, 30 min; **n**) c.NH_4OH, MeOH, 50 °C, 1 h; **o**) PCC, CH_2Cl_2, room temperature, 4 h.

specific rotation). The stereochemistry was thus concluded to demonstrate the (*S*)-configuration for the chiral center of the natural product (**3**).

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2. This swimming worms appeared at the surface of the water only once a year for about four weeks from the end of September to the end of October at Toyama Bay in Japan and the surfaced worms were collected by using a fine mesh net.
3. Natural product (**3**): colorless solid; mp 114-115 °C; uv (MeOH) λ_{max} 252 (log ε 4.35), 282 (4.32), 332 (4.23) nm; $[\alpha]_D^{25}$ -61.9° (*c* 0.21, $CHCl_3$); ir (KBr) ν_{max} 1720, 1670, 1540, 1500, 1450, 1280 cm^{-}; ^1H nmr (400 MHz, $CDCl_3$) δ 1.30 (3H, d, J=6.8 Hz), 2.06 (1H, m), 2.23 (1H, m), 3.20 (1H, m), 3.39 (1H, m), 3.50 (3H, s), 3.51 (3H, s), 3.75 (3H, s), 3.78 (3H, s), 4,21 (1H, m), 9.25 (1H, s), 9.30 (1H, s); ms (EI) *m/z* (%) 494 (M^+, 45), 275 (41), 260 (100), 219 (82), 191 (98); HRms (EI) found: *m/z* 494.1578 (M^+), calcd for $C_{22}H_{22}N_8O_6$ 494.1661.
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6. (+)-β-Citronellene (**4**) ($[\alpha]_D^{20}$ +10.4°) was purchased from Fluka Chemie AG.
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8. Aldehyde (**6**): $[\alpha]_D^{25}$ +5.8° (*c* 2.28, $CHCl_3$); *cf.* Nguyen Cong Hao, M. V. Mavrov, and E. P. Serebryakov, *Zh. Org. Khim.*, 1987, **23**, 1649 (*Chem. Abstr.*, 1988, **109**, 22678y).
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Received, 28th March, 1995