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Synthesis and Absolute Configuration of (+)-Gonyauline: A Modulating Substance of Bioluminescent Circadian Rhythm in the Unicellular Alga *Gonyaulax polyedra*

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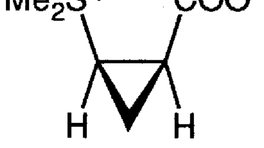
Key words: Gonyauline; Period-shortening substance, Bioluminescent circadian rhythm; *Gonyaulax polyedra*; Dinoflagellate

***Abstract:** Gonyauline,* cis*-2-(dimethylsulfonio)cyclopropanecarboxylate, an endogenous period-shortening substance of bioluminescent circadian rhythm of the dinoflagellate* Gonyaulax polyedra *was synthesized from (+)-2-methylthio-1,2-*trans*-cyclopropanedicarboxylic acid (3a) and the absolute configuration was established as* 1R, 2R.

Gonyauline (**1**) is a unique cyclopropane derivative containing a novel zwitter ion structure composed of carboxylate and dimethylsulfonium functionalities and has recently been identified as an endogenous principle which shortens the period of bioluminescent circadian rhythm in the cultured marine dinoflagellate *Gonyaulax polyedra.*1) The structure and biological activity of gonyauline (**1**) were established by the synthesis of racemic gonyauline.2) Here we would like to report the synthesis of (+) (**1a**) and (-)-gonyauline (**1b**) as well as the absolute configuration of natural (+)-gonyauline (**1a**), which would enable us to investigate biological role of gonyauline in the dinoflagellate.



1a
Natural (+)-gonyauline

2 : (±)-R=COOEt
3a : (+)-R=COOH
4a : (+)-R=CH$_2$OH
5a : (+)-R=CHO
E
6a : (+)-R=-CH=CH-COOMe
7a : (+)-R=COO-(-)-Menthyl

A (±)-*trans*-dicarboxylic acid (**3**) obtained by alkaline hydrolysis of the readily available (±)-ethyl ester (**2**) was resolved with the aid of optically active alkaloids. Among them resolution with brucine gave optically active acids (**3a** and **3b**) with large values of optical rotation, $[\alpha]_D$ +100° and -96.0° (*c* 0.5, H_2O), respectively.[3] (+)-Acid (**3a**) was derivatized to (+)-gonyauline by two steps, *i.e.*, methylation with methyl p-toluenesulfonate followed by acidic decarboxylation in 2-methyl-2-propanol. After purification on a DEAE and a Sephadex G-10 column chromatographies, the synthetic (+)-gonyauline showed $[\alpha]_D$ value of +139° (*c* 1.0, MeOH) which corresponds to 65% of that of natural gonyauline, $[\alpha]_D$ +214° . By the same sequence of reactions the enantiomeric (-)-dicarboxylic acid (**3b**) furnished (-)-gonyauline, $[\alpha]_D$ -130°.

The absolute configuration of gonyauline (**1a**) was determined by exciton chirality method.[4] Reduction of the acid **3a** with BH_3 yielded a diol (**4a**) (57 % yield), which was oxidized with PDC to give a dialdehyde (**5a**, 16 % yield). Upon treatment with methyl (triphenylphosphoranylidene)acetate in benzene at room temperature, **5a** furnished bis-α,β-unsaturated ester (**6a**,[5] 53 % yield). A CD spectrum of the ester (**6a**) in EtOH showed ellipticity maxima at 260 (Δε +3.2), 230 (Δε +6.2) and 207 nm (Δε -6.1), suggesting the absolute configuration of the ester as illustrated in the structure (**6a**). Thus the absolute configuration of natural (+)-gonyauline (**1a**) should be represented as 1*R*, 2*R*.

Among various ester derivatives of **3**, bis-menthyl ester (**7**) prepared from dicarboxylic acid (**3**) and (-)-menthol (DCC and 4-pyrrolidinopyridine) was easily separated by a silica gel HPLC to yield **7a** from its diasteromer. (+)-Menthyl ester (**7a**) with a shorter retention time, $[\alpha]_D$ +31° (*c* 1.5, $CHCl_3$), was hydrolyzed (LiOH-MeOH-THF) to furnish (+)-dicarboxylic acid (55% yield), $[\alpha]_D$ + 161°, which was derivatized to enantiomerically pure (+)-gonyauline (**1a**) with $[\alpha]_D$ +210°, securing 100% optical purity of natural gonyauline.

Studies on biogenesis, metabolisms, and the biological role of gonyauline in the dinoflagellate with use of labelled substances prepared by this method are in progress at our laboratory.

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2. Nakamura, H., *J. Chem. Soc. Perkin Trans 1*, **1990**, 3219.
3. All new compounds exhibited satisfactory spectroscopic properties including HREIMS.
4. Harada, N. and Nakanishi, K.,. Circular Dichroic Spectroscopy - Exciton Coupling in Organic Stereochemistry; University Science Books: Mill Valley, CA, 1983.
5. Data for **6a**: $[\alpha]_D$ +202° (*c* 0.1, $CHCl_3$); UV (EtOH) λmax 203 (ε 16400), 236 nm (18500); HREIMS *m/z* 256.0755 (δM -1.4mamu); ^1H NMR ($CDCl_3$) δ1.52 (1H, dd, *J*= 6, 5 Hz), 1.63 (1H, dd, *J*=10, 5 Hz), 2.03 (3H, s), 2.12 (1H, td, *J*=10, 6 Hz), 3.74 (3H, s), 3.75 (3H, s), 6.03 (1H, d, *J*=16 Hz), 6.21 (1H, d, *J*=15 Hz), 6.51 (1H, d, *J*=15 Hz,), 6.98 (1H, dd, *J*=16, 10 Hz).

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