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# Didemnilactone and Neodidemnilactone, Two New Fatty Acid Metabolites Possessing a 10-Membered Lactone from the Tunicate *Didemnum moseleyi* (Herdman)

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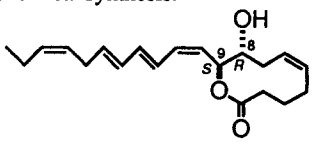
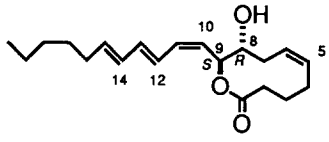
**Abstract:** Didemnilactone (**1**) and neodidemnilactone (**2**), two new fatty acid metabolites possessing a 10-membered lactone were isolated from the colonial tunicate *Didemnum moseleyi* (Herdman). Their structures including absolute stereochemistry were determined on the basis of spectral studies and the enantioselective synthesis of the antipode of **2**.

We have examined the constituents of the colonial tunicate *Didemnum moseleyi* (Herdman) collected at Hinata Island of Toba City, Japan and isolated two new fatty acid metabolites, designated as didemnilactone (**1**) and neodidemnilactone (**2**). We wish to report herein the structural elucidation of these metabolites on the basis of spectral data and chemical synthesis.



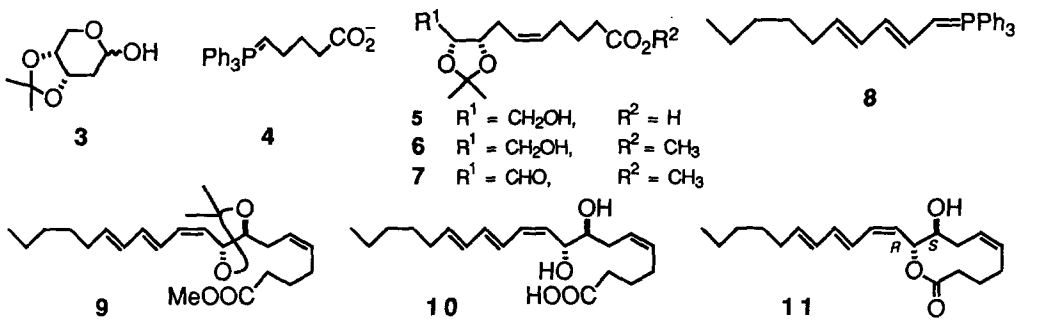

**1** didemnilactone




**2** neodidemnilactone

The EtOAc-soluble material obtained from the MeOH extract of the tunicate was partitioned between hexane and MeOH–$H_2O$ (9:1 v/v). The MeOH–$H_2O$-soluble material was further partitioned between $CH_2Cl_2$ and MeOH–$H_2O$ (3:1). The hexane- and $CH_2Cl_2$-soluble materials were subjected to repeated column chromatography on silica gel and alumina followed by reversed-phase HPLC [ODS, $CH_3CN$–$H_2O$ (70:30)] to give didemnilactone (**1**)[1] (colorless oil; 5.7 x $10^{-5}$% wet weight) and neodidemnilactone (**2**)[2] (colorless oil; 2.5 x $10^{-5}$% wet weight). The extensive studies of their $^1H$ and $^{13}C$ NMR, mass, IR, and UV spectra revealed the structures of didemnilactone and neodidemnilactone to be as depicted in formula **1** and **2** (or the antipode), respectively.

In order to establish the absolute stereostructure of didemnilactone (**1**) and neodidemnilactone (**2**) unambiguously, the synthesis of (8*S*,9*R*)-neodidemnilactone (**11**) was performed. Wittig reaction of 3,4-*O*-isopropylidene-2-deoxy-D-ribose (**3**)[3] with ylide **4** prepared by reaction of (4-carboxybutyl)triphenylphosphonium bromide with $NaN(SiMe_3)_2$, in toluene at –78 °C → –20 °C afforded selectively (*Z*)-olefinic acid **5**,[4] which was converted into methyl ester **6** with $CH_2N_2$ (58% overall). Swern oxidation of **6** gave aldehyde **7** (95%). Wittig reaction of **7** with ylide **8** prepared by reaction of (*E*,*E*)-(2,4-decadienyl)triphenylphosphonium chloride[5] with $NaN(SiMe_3)_2$, in toluene at –78 °C provided selectively (5*Z*,10*Z*,12*E*,14*E*)-tetraene **9** (62%). Acidic hydrolysis (AcOH–$H_2O$) of the acetonide group in **9** and subsequent basic hydrolysis (LiOH, MeOH–$H_2O$) of the ester group yielded diol acid **10** (34% overall). Lactonization of **10** by means of the Yamaguchi's method[6] furnished dextrorotatory (8*S*,9*R*)-neodidemnilactone (**11**) [$[\alpha]_D^{18}$ +218° (*c* 0.054, MeOH), 28%], whose spectral properties except for the sign of the specific rotation were identical with those of natural,




levorotatory (8*R*,9*S*)-neodidemnilactone (**2**) [$[\alpha]_D^{22}$ −200° (*c* 0.17, MeOH)]. Thus, the absolute stereochemistry of neodidemnilactone (**2**) is established to be 8*R*,9*S*. Further, the absolute stereochemistry of didemnilactone (**1**) may be concluded to be 8*R*,9*S* from the similarity of the chiroptical properties of **1** and **2**.[7]

Didemnilactone (**1**), neodidemnilactone (**2**), and the corresponding diol acids obtained by hydrolysis of **1** and **2** exhibit week binding activity ($IC_{50}$ 50 ~ 100 μM) to leukotriene $B_4$ receptors of human polymorphonuclear leukocyte membrane fractions.

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## Notes and References

1. **1**: $C_{20}H_{28}O_3$ [*m/z* 316.2048 ($M^+$), Δ +0.9 mmu]; $[\alpha]_D^{22}$ −190° (*c* 0.18, MeOH); IR ($CHCl_3$) 3590, 3450, 1730 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ 261 (ε 24,600), 271 (30,500), 279 nm (25,400); EIMS *m/z* (relative intensity) 316 ($M^+$, 42), 298 (14), 177 (12), 160 (100), 139 (42); $^1H$ NMR ($C_6D_6$, 270 MHz) δ 0.88 (3 H, t, *J* = 7.6 Hz), 1.32 (1 H, m), 1.63 (1 H, m), 1.95 (2 H, m), 1.85-2.10 (4 H, m), 2.19 (1 H, m), 2.62 (1 H, m), 2.69 (2 H, dt, *J* = 1.0, 6.6 Hz), 3.65 (1 H, ddd, *J* = 9.1, 3.9, 3.9 Hz), 5.22 (1 H, dd, *J* = 11.5, 9.1 Hz), 5.36 (1 H, m), 5.35-5.40 (1 H, m), 5.41 (1 H, m), 5.57 (1 H, dt, *J* = 14.7, 6.6 Hz), 5.75 (1 H, m), 5.75 (1 H, dd, *J* = 9.1, 9.1 Hz), 6.02 (1 H, ddt, *J* = 14.7, 11.2, 1.0 Hz), 6.17 (1 H, dd, *J* = 11.5, 11.5 Hz), 6.18 (1 H, dd, *J* = 14.7, 11.2 Hz), 7.03 (1 H, dd, *J* = 14.7, 11.5 Hz); $^{13}C$ NMR ($C_6D_6$, 67.8 MHz) δ 14.3 (q), 20.8 (t), 25.4 (t), 26.3 (t), 30.8 (t), 32.6 (t), 34.7 (t), 72.4 (d), 72.6 (d), 125.4 (d), 126.3 (d), 126.7 (d), 127.0 (d) 131.2 (d), 131.7 (d), 132.9 (d), 134.6 (d), 134.9 (d), 136.5 (d), 172.5 (s).
2. **2**: $C_{20}H_{30}O_3$ [*m/z* 318.2191 ($M^+$), Δ −0.3 mmu]; $[\alpha]_D^{22}$ −200° (*c* 0.17, MeOH); IR ($CHCl_3$) 3570, 3450, 1730 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ 261 (ε 22,900), 271 (29,100), 279 nm (24,000); EIMS *m/z* (relative intensity) 318 ($M^+$, 49), 300 (12), 179 (33), 162 (100), 139 (67); $^1H$ NMR ($C_6D_6$, 270 MHz) δ 0.86 (3 H, t, *J* = 7.6 Hz), 1.10-1.40 (7 H, m), 1.63 (1 H, m), 1.85-2.10 (6 H, m), 2.20 (1 H, m), 2.62 (1 H, m), 3.65 (1 H, ddd, *J* = 9.1, 3.9, 3.9 Hz), 5.22 (1 H, dd, *J* = 11.5, 9.1 Hz), 5.37 (1 H, m), 5.62 (1 H, dt, *J* = 14.7, 6.6 Hz), 5.74 (1 H, dd, *J* = 9.1, 9.1 Hz), 5.77 (1 H, m), 5.99 (1 H, ddt, *J* = 14.7, 11.2, 1.0 Hz), 6.19 (1 H, dd, *J* = 11.5, 11.5 Hz), 6.20 (1 H, dd, *J* = 14.7, 11.2 Hz), 7.03 (1 H, dd, *J* = 14.7, 11.5 Hz); $^{13}C$ NMR ($C_6D_6$, 67.8 MHz) δ 14.2 (q), 22.8 (t), 25.4 (t), 26.3 (t), 29.2 (t), 31.7 (t), 32.7 (t), 33.0 (t), 34.7 (t), 72.4 (d), 72.6 (d), 125.5 (d), 126.3 (d), 126.8 (d), 131.1 (d), 131.7 (d), 135.0 (d), 136.7 (d), 136.8 (d), 172.4 (s).
3. Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. *J. Am. Chem. Soc.* **1980**, *102*, 7984.
4. Satisfactory spectral and analytical data were obtained for all new compounds. All yields refer to materials purified by column chromatography on silica gel.
5. This phosphonium salt was prepared from (*E,E*)-2,4-decadien-1-ol by reaction with $Ph_3P$ (1 equiv) and HCl (1 equiv) in MeOH at room temperature (65%); cf. Rüegg, R; Schwieter, U; Ryser, G; Schudel, P.; Isler, O. *Helv. Chim. Acta* **1961**, *44*, 985.
6. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. The isomeric 9-membered lactone was not detected.
7. A recent paper reports the occurrence of the related compounds having a 9-membered lactone and a triene; Lindquist , N.; Fenical, W. *Tetrahedron Lett.* **1989**, *30*, 2735.

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