The Absolute Configuration of Bacillariolides I and II, a New Type of Cyclopentane Icosanoids from a Marine Diatom

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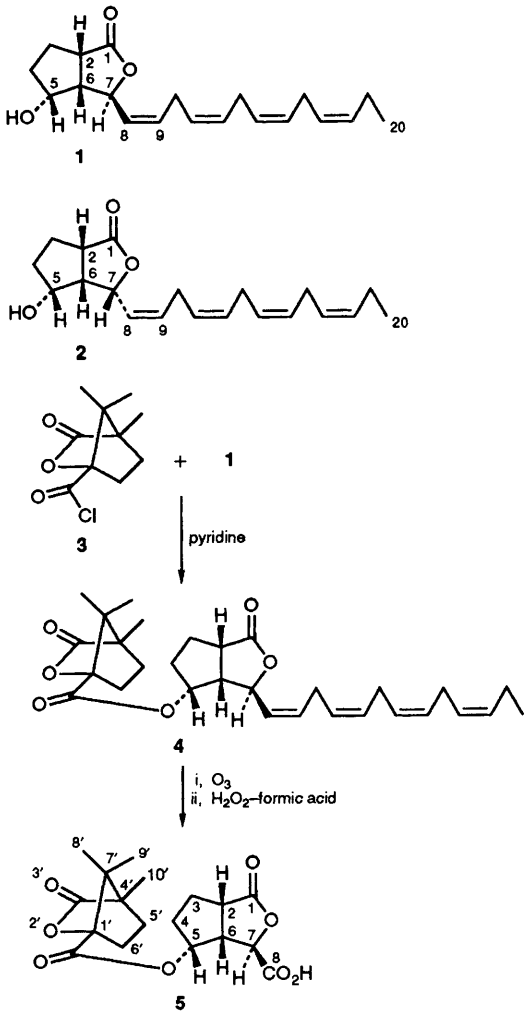
The structures of a new type of cyclopentane icosanoids from the marine diatom, *Nitzschia pungens* f. *multiseries*, have been confirmed by X-ray crystallography, and their absolute configurations determined.

In 1990, we reported the isolation of two new cyclopentane-containing icosanoids, bacillariolide I **1** and bacillariolide II **2** from the diatom, *Nitzschia pungens* f. *multiseries*, and mussels, which caused amnesic shellfish poisoning (ASP).[1–3] The structures of these compounds were proposed on the basis of spectroscopic evidence, especially ^{1}H and ^{13}C NMR data.[4] The stereochemistry of the compounds was assigned on the basis of their NOE spectra. However, probably owing to the unpredictable conformations of the two *cis*-fused five-membered rings, the spin–spin coupling constants of some proton



crystallography. As the internal reference, we chose (−)-camphanic acid, which was derived from (1*R*)-(+)-camphor.[5]

The esterification of bacillariolide **1** (17 mg) with (1*S*)-(−)-camphanic chloride **3**, $[\alpha]_D$ − 18.8 (*c* 2.06, CCl_4), in pyridine gave the oily camphanate ester **4**, δ in CD_2Cl_2: 5.22 (m, H-5), 2.40 (d,d,d, *J* 4.1, 10.6, 10.3, H-6), 5.62 (d, t, *J* 7.6, 10.7, H-9), 2.05 (m, H-19), 0.96 (t, *J* 7.5, H-20), 0.94, 1.01, 1.10 (all s, CH_3-8′,9′,10′). The ester **4** was ozonized in CH_2Cl_2 at −40 °C, and the ozonide was treated with a mixture of 30% H_2O_2 and 90% formic acid (1 : 2) at room temperature. Purification of the reaction product by silica gel chromatography and recrystallization from H_2O afforded the carboxylic acid **5** (7 mg), m.p. >300 °C, $[\alpha]_D$ − 16.3 (*c* 0.096, MeOH), δ in CD_3OD: 3.22 (m, H-2), 4.75 (m, H-5), 2.48, (m, H-6), 5.51 (m, H-7), 0.92, 1.04, 1.08 (all s, CH_3-8′,9′,10′).†

Fig. 1 shows a computer-generated perspective of the camphanate m lecule **5**. It confirms the proposed structure and relative stereochemistry of bacillariolide I **1**. However, since the camphanate used in this experiment has the absolute configuration (1′*S*, 4′*R*) as depicted, the absolute configurations of **1** should be (2*S*,5*R*,6*S*,7*S*). Bacillariolide II **2** is known to be the 7-epimer of **1**. Therefore, it should have the configuration (2*S*,5*R*,6*S*,7*R*).

These absolute configurations of bacillariolides are opposite to those predicted in the previous report on the basis of a hypothetical biosynthetic pathway.[4] In the hypothesis, it was assumed that the biosynthesis of bacillariolides is initiated by (5*S*)-perhydroxylation of icosapentaenoic acid (IPA), rearrangement of the hydroperoxy derivative (5-HPEPE) to the hydroxy epoxide, and carbon ring closure by anionic opening of the epoxide ring. Generally, 5-lipoxygenases are known to introduce (5*S*)-hydroperoxides.[6] The finding of the opposite absolute configuration in bacillariolides may necessitate the reconsideration of this biosynthetic scheme. However, it is also possible that the 5-lipoxygenase in the diatom has the opposite stereospecificity, leading to the antipodal absolute configuration (Scheme 1). Further studies are requried to clarify this point.

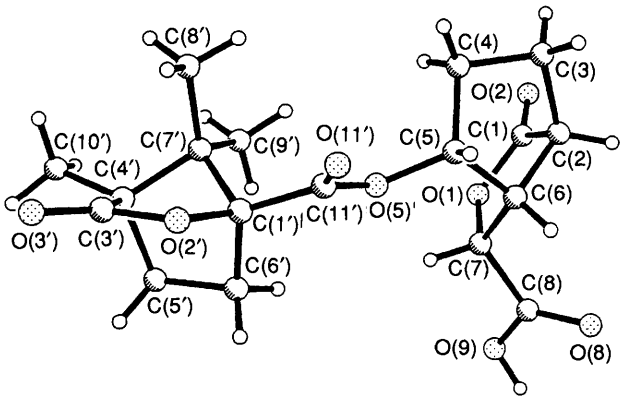
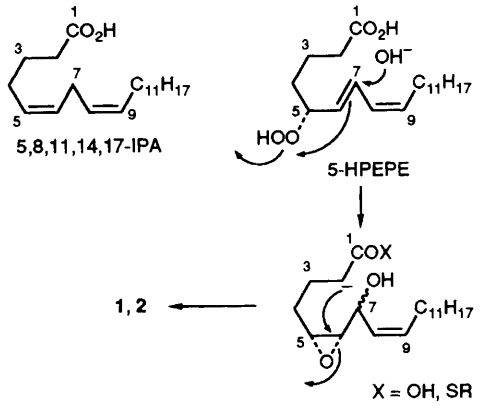


Fig. 1 Computer-generated perspective view of **5**.



Scheme 1 Hypothetical biosynthetic route to bacillariolides

signals in the NMR spectra are not easily correlated with the proposed stereochemistry. Therefore, we decided to establish the structures unequivocally and also to determine the absolute configuration. We are particularly interested in the absolute configuration of this new type of compound, which seem to be closely related to the physiologically important icosanoids such as prostanoids and leucotrienes.

The strategy adopted was to prepare a crystalline derivative of **1**, which had an internal reference chiral centre for X-ray

† *Crystal data*, compound **5**, monoclinic, space group $P2_1$, a = 6.387(4), b = 20.59(3), c = 6.619(5) Å, β = 104.05(5)°, one molecule of composition $C_{18}H_{22}O_8$ forming the asymmetric unit. All unique diffraction data with $2\theta \leq 116°$ were collected using variable-speed 2θ–θ scans and graphite-monochromated Cu-K$\bar{\alpha}$ radiation. After data work-up, 2075 (95%) were judged observed [$|F_o| \geq 4.0\sigma(F_o)$]. A phasing model was determined by direct methods and full-matrix least-squares refinement with anisotropic nonhydrogen atoms and riding hydrogens converted to a standard crystallographic residual of R = 4.23%. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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