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SYNTHESIS OF CYCLOPENTANE-CONTAINING MARINE EICOSANOID BACILLARIOLIDE II

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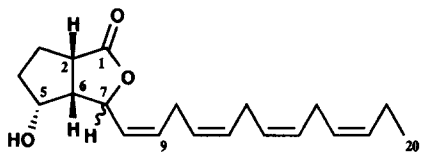
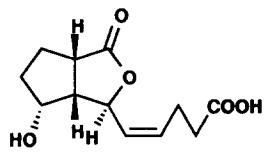
Abstract: Marine eicosanoid bacillariolide II was synthesized from (*R*)-malic acid, involving the diastereoselective one-pot formation of chiral cyclopentane derivative **12** from the anion of allyl phenyl sulfone and chiral epoxymesylate **11** as the key step.

Marine eicosanoids are of interest owing to their unique structures, peculiar biosynthetic pathways and various biological activities.[1] Bacillariolides I, II (**1**) and III, isolated from the marine diatom, *Pseudo-nitzschia multiseries*,[2] a causative organism of so-called amnesic shellfish poisoning (ASP),[3c] are cyclopentane-containing structurally unique eicosanoids.[3] Bacillariolide I is known to possess significant inhibitory activity against phospholipase A_2,[4] while the biological activity of either bacillariolides II or III has get to be reported. The relative configurations of bacillariolides I-III were determined based on spectroscopic analysis[3a,c] and the absolute configuration of bacillariolide I was determined by X-ray crystallography of the camphor derivative.[3b] The absolute configurations of bacillariolides II and III were surmised based on an apparent biosynthetic relationship of bacillariolides II and III with bacillariolide I.



7α-H : bacillariolide I
7β-H : bacillariolide II (1)



bacillariolide III

Previously, the synthesis of the chiral cyclopropane derivative using the anion of allyl phenyl sulfone and chiral epoxide was reported and the stereocontrolled synthesis of cylopropane-containinig marine eicosanoid constanolactone E was carried out by this reaction.[5] To explore potential applications of the

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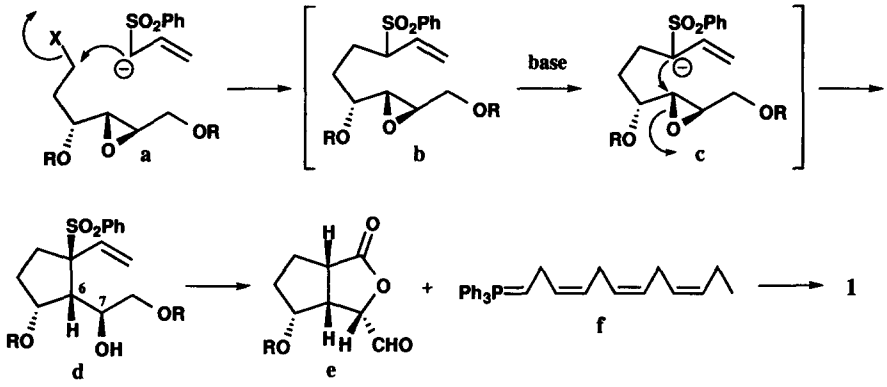
method of cyclopentane formation, [6] a new method for the synthesis of the chiral cyclopentane derivative was developed and used to synthesize bacillariolide II.

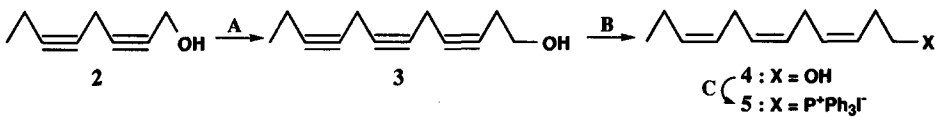
The synthetic strategy for bacillariolide II (**1**) involves the one-pot cyclopentane formation, which is as follows: 1) an anion of allyl phenyl sulfone is reacted with chiral epoxide **a** to give epoxysulfone **b**, 2) deprotonation of **b** *in situ* generates an anion of epoxysulfone **c** and 3) intramolecular cyclization gives chiral cyclopentane derivative **d** having the requisite chiral centers at C-6 and C-7,[7] and coupling reaction of aldehyde **e** obtained from **d**, with Wittig reagent **f** corresponding to C-9~20 segment (Figure 1).

Figure 1



Phosphonium salt **5** corresponding to the C-9~20 segment was prepared from 2,5-octadiyn-1-ol (**2**) (Scheme 1). 2,5-Octadiyn-1-ol (**2**)[8] was converted to 1-bromo-2,5-octadiyne by treatment with carbon tetrabromide and triphenylphosphine. The treatment of 1-bromo-2,5-octadiyne with 3-butyn-1-ol, in the presence of CuI, K_2CO_3 and NaI in DMF[9] gave 3,6,9-dodecatriyn-1-ol (**3**). The stereoselective partial reduction of the obtained triynol **3** was efficiently carried out to give (*Z,Z,Z*)-trienol **4**. (*Z,Z,Z*)-Trienol **4** was converted to phosphonium salt **5** in three steps: 1) tosylation of hydroxyl group, 2) treatment with NaI in acetone and 3) treatment with triphenylphosphine in benzene.

Scheme 1

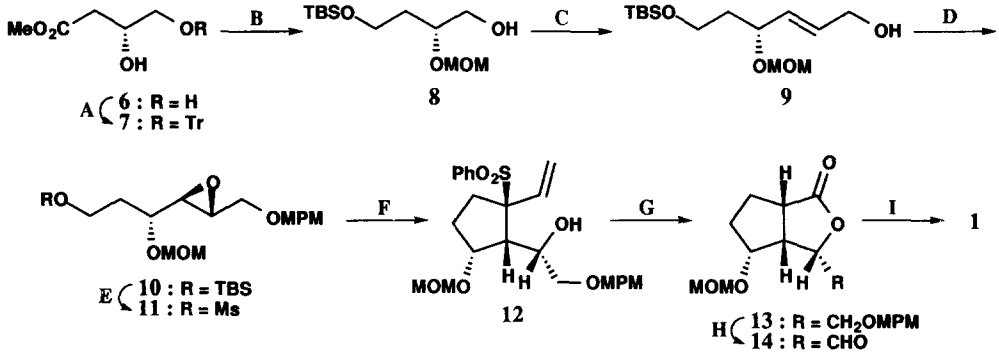


Reagents and conditions : A. i) CBr_4, Ph_3P, CH_2ClCH_2Cl, 0°C, ii) 3-butyn-1-ol, K_2CO_3, CuI, NaI, DMF, r.t., 80% (2 steps); **B**. H_2, Pd-$BaSO_4$, quinoline, MeOH, r.t., 75%; C.i) TsCl, Py, $CHCl_3$, r.t., quant., ii) NaI, acetone, r.t., 71%, iii) Ph_3P, benzene, reflux, 75%.

Stereoselective synthesis of bacillariolide II involving formation of the chiral cyclopentane derivative was carried out as shown in Scheme 2. The primary hydroxyl group of methyl (*R*)-3,4-dihydroxybutanoate (**6**),[10] prepared from (*R*)-malic acid, was protected as triphenylmethyl (trityl) ether to give **7**.[11] Trityl ether **7** was converted to alcohol **8** in four steps: 1) protection of hydroxyl group as MOM ether, 2) reduction of the ester with $LiAlH_4$, 3) protection of the hydroxyl group as TBS ether, and 4) deprotection of trityl ether. The hydroxyl group of **8** was oxidized by Swern procedure followed by Horner-Emmons reaction to give α,β-

unsaturated ester, which was then reduced with DIBAL-H to give allylic alcohol **9**. The stereoselective epoxydation of allylic alcohol **9** according to the procedure of Sharpless[12] was carried out followed by protection of hydroxyl group as MPM ether **10**. Compound **10** was converted to epoxymesylate **11** *via* deprotection of TBS ether and mesylation. Reaction of the lithio derivative of allyl phenyl sulfone (2.4 equiv.) with epoxymesylate **11** (1.0 equiv.) in THF at -78°C to room temperature over 12 h, gave cyclopentane **12**[13,14] as the sole product in 99% yield. The terminal olefin in **12** was oxidized by OsO_4-$NaIO_4$ to give hemiacetal, which was then oxidized with Jonens reagent, and the phenylsulfonyl group was removed by treatment with Na-Hg to give lactone **13** bearing the requisite chiral centers at C-2, C-5, C-6 and C-7 corresponding to the C-1~8 segment. Deprotection of MPM ether in **13** afforded an alcohol, which was oxidized by the Swern procedure to give the aldehyde **14**. Coupling reaction of the aldehyde **14** with Wittig reagent, prepared using phosphonium salt **5**, corresponding to the C-9~20 segment, afforded the (8Z,11Z,14Z,17Z)-tetraene as the sole product. Finally, deprotection of MOM ether completed the synthesis of bacillariolide II (**1**), $[\alpha]_D^{24}$ -58.5° (*c* 0.33, MeOH).[15] The spectral data of **1** and natural bacillariolide II, $[\alpha]_D^{23}$ -59.2° (*c* 0.33, MeOH),[3a] as well as the sign of optical rotation were identical. This paper presents the first total synthesis of bacillariolide II and the absolute configuration of bacillariolide II was confirmed as **1**.

Scheme 2



Reagents and conditions : **A**. TrCl, Et_3N, DMAP, DMF, 65°C, 87%; **B**. i) MOMCl, $^iPr_2NEt$, $CHCl_3$, 40°C, ii) $LiAlH_4$, Et_2O, 0°C, iii) TBSCl, imidazole, DMF, r.t., iv) Na, liq. NH_3-THF, -34°C, 94% (4 steps); **C**. i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C, ii) $(^iPrO)_2P(O)CH_2CO_2Et$, ^tBuOK, THF, -42°C, 96% (2 steps), iii) DIBAL-H, toluene, -78°C, 88%; **D**. i) TBHP, (-)-DET, $(^iPrO)_4Ti$, 4ÅMS, CH_2Cl_2, -20°C, 90%, ii) MPMBr, NaH, THF-DMF, 0°C, 88%; **E**. i) Bu_4NF, THF, r.t., ii) MsCl, DMAP, CH_2Cl_2, 0°C~r.t., quant. (2 steps); **F**. allyl phenyl sulfone, BuLi, THF, -78°C~r.t., 99%; **G**. i) OsO_4, $NaIO_4$, dioxane-H_2O, r.t., ii) Jones ox., acetone, 0°C, 82% (2 steps), iii) Na-Hg, Na_2HPO_4, MeOH, r.t., 85%; **H**. i) CAN, CH_3CN, r.t., 88%, ii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C, quant.; **I**. i) **5**, BuLi, THF-HMPA, -78°C, 66%, ii) AcOH-conc.HCl (50:1), 40°C, 83%.

The present work indicates a new method for the stereocontrolled synthesis of chiral cycopentane derivative, which should also be applicable to the synthesis of other cyclopentane-containing natural products. The synthesis of bacillariolides I and III is now in progress.

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References and Notes

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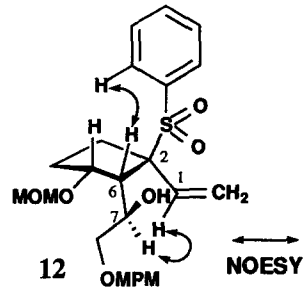
13. **12**: $[\alpha]_D^{22}$ -74.4° (*c* 1.0, $CHCl_3$); EIMS m/z 476 (M^+), 444, 431, 121; IR (neat) 3494, 2935, 1612, 1514, 1295, 1142 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.84 (1H, m), 1.93 (1H, m), 2.25 (1H, ddd, *J* = 14.1, 11.8, 6.8 Hz), 2.36 (1H, ddd, *J* = 14.1, 7.4, 2.2 Hz), 3.15 (1H, dd, *J* = 4.6, 3.6 Hz), 3.28 (3H, s), 3.60 (2H, d, *J* = 6.0 Hz), 3.81 (3H, s), 4.05 (1H, m), 4.47 (1H, d, *J* = 11.5 Hz), 4.50 (1H, d, *J* = 6.9 Hz), 4.56 (1H, d, *J* = 6.9 Hz), 4.57 (1H, d, *J* = 11.5 Hz), 4.59 (1H, m), 5.11 (1H, d, *J* = 17.3 Hz), 5.37 (1H, d, *J* = 10.7 Hz), 6.42 (1H, dd, *J* = 17.3, 10.7 Hz), 6.90 (2H, m), 7.31 (2H, m), 7.45 (2H, m), 7.61 (1H, m), 7.81 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.0, 30.3, 48.5, 55.1, 56.0, 69.3, 72.6, 72.9, 74.5, 82.2, 95.1, 113.6, 120.0, 128.2, 129.4, 130.1, 130.7, 133.5, 134.4, 135.2, 159.0.
14. Relative configuration at C-2 position in **12** was determined by NOESY correlations between H-1 (δ_H 6.42) and H-7 (δ_H 4.05) and H-6 (δ_H 3.15) and phenyl protons (δ_H 7.81).



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15. **1**: $[\alpha]_D^{24}$ -58.5° (*c* 0.33, CH_3OH); EIMS m/z 316 (M^+), 298; HREIMS: Calcd for $C_{20}H_{28}O_3$ (M^+) 316.2038: Found 316.2034; IR ($CHCl_3$) 3528, 1763 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.97 (3H, t, *J* = 7.5 Hz), 1.65 (1H, m), 1.82 (1H, m), 2.0-2.2 (4H, m), 2.77 (1H, ddd, *J* = 9.3, 6.0, 3.5 Hz), 2.83, (2H, t, *J* = 5.8 Hz), 2.88 (2H, t, *J* = 5.7 Hz), 2.95 (2H, m), 3.19 (1H, dt, *J* = 5.1, 9.5 Hz), 4.21 (1H, t, *J* = 3.0 Hz), 5.25-5.35 (6H, m), 5.50 (1H, m), 5.64 (1H, ddt, *J* = 11.0, 1.4, 7.6 Hz), 6.05 (1H, ddt, *J* = 11.0, 8.3, 1.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 14.7, 21.5, 25.5, 26.4, 26.5, 27.0, 36.9, 45.3, 52.6, 73.4, 77.7, 127.5, 128.1, 128.4, 128.8, 129.6, 129.9, 132.9, 133.1, 183.6.