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Asymmetric Total Synthesis of Bacillariolide III, a Marine Oxylipin

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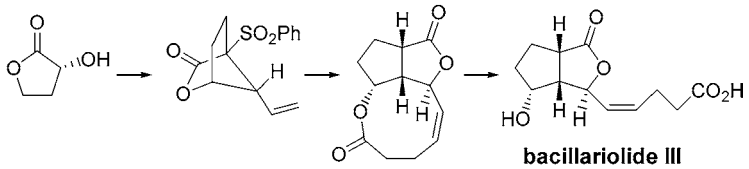
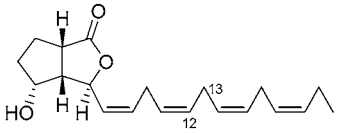
ABSTRACT



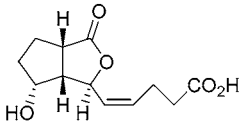
bacillariolide III

The asymmetric total synthesis of bacillariolide III has been achieved via 15 linear steps in 14.6% overall yield. The key feature of this synthetic route involves the highly stereoselective construction of the vinyl-substituted bicyclic lactone by an intramolecular Pd(0)-catalyzed allylic alkylation and its facile conversion to the hydroxy bicyclic lactone skeleton of bacillariolide III, induced by stereoselective vinylcerium addition to the aldehyde. In addition, the (*Z*)-pentenoic acid was efficiently introduced by the internal hydroxy group tethered ring-closing metathesis (RCM).

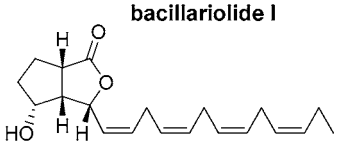
Bacillariolides I and II, which are new carbocyclic oxylipins,[1] were isolated from the marine diatom *Pseudonitzschia multiseries*, a causative organism of amnesic shellfish poisoning, by Shimizu and Wang.[2] The detailed structure and absolute configurations of bacillariolide I, possessing significant inhibitory activity against phospholipase A_2 (PLA_2), have been established based on extensive spectroscopic analyses in conjunction with the X-ray crystallographic analysis of the (−)-camphanic acid derivative. On the other hand, bacillariolide III, which was isolated from the culture medium of the same marine diatom, was proposed to be an extracellular metabolite derived from bacillariolide I by oxidative cleavage of the polyene side chain, especially at C-12 and C-13.[3]



bacillariolide I



bacillariolide III (1)



bacillariolide II

Although the biological function of this extracellular metabolite is still under investigation, the novel structural features of bacillariolide III (**1**), involving the highly functionalized cyclopentanol framework with four contiguous stereocenters and the potential biological activity derived from its structural resemblance to the well-known biologically important prostaglandins and jasmonates,[4] led us to undertake the total synthesis of bacillariolide III. We herein report the asymmetric total synthesis of bacillariolide III, which previously was reported only by Yamada and coworkers.[5]

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[§] Center for Bioactive Hybrids.
[‡] Chungbuk National University.

(1) (a) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685. (b) Gerwick, W. H. *Chem. Rev.* **1993**, *93*, 1807. (c) Shimizu, Y. *Annu. Rev. Microbiol.* **1996**, *50*, 431.

(2) (a) Wang, R.; Shimizu, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 413. (b) Wang, R.; Shimizu, Y.; Steiner, J. R.; Clardy, J. *J. Chem. Soc., Chem. Commun.* **1993**, 379.

(3) Zheng, N.; Shimizu, Y. *Chem. Commun.* **1997**, 399.

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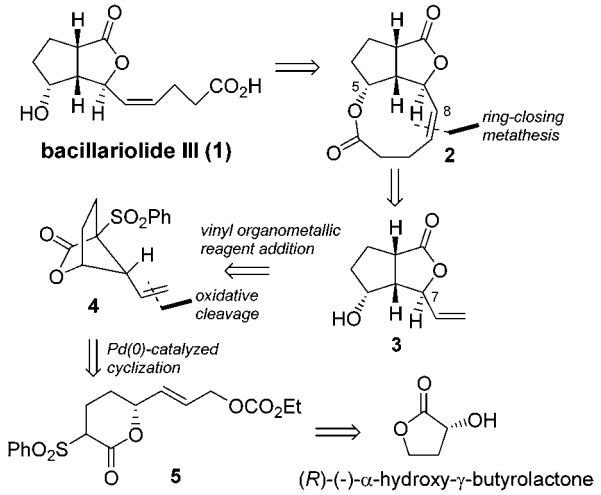
Our retrosynthetic analysis for bacillariolide III (**1**) is illustrated in Scheme 1. In contemplating the synthesis of

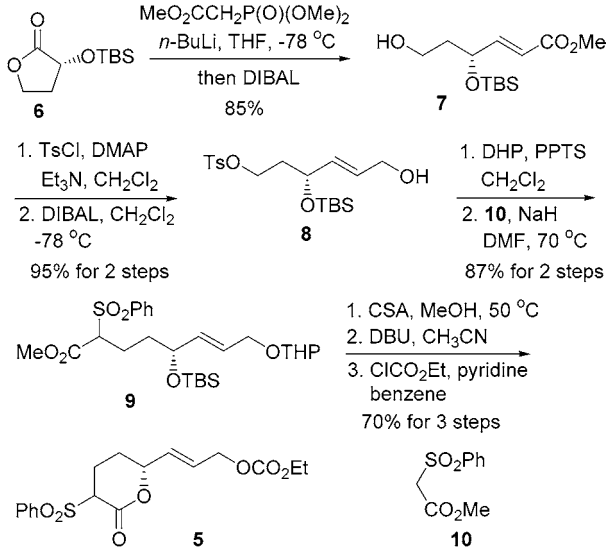
Scheme 1. Retrosynthesis of Bacillariolide III



bacillariolide III, it was envisioned that the (*Z*)-pentenoic acid side chain could be installed by the C5 hydroxy group tethered ring-closing metathesis (RCM)[6] from **3** and the subsequent hydrolysis of the nine-membered lactone **2**. The crucial C7 stereochemistry of the hydroxy bicyclic lactone **3** would be established with stereoselective addition of a vinyl organometallic reagent to the aldehyde, prepared by oxidative cleavage of the vinyl substituent of the bicyclic lactone **4**. The initial vinyl addition product was expected to spontaneously isomerize to the hydroxy bicyclic lactone **3**. On the basis of the stereoselective Pd(0)-catalyzed cyclization of allylic carbonate recently developed in our laboratory,[7] the requisite bicyclic lactone **4**, corresponding to the hydroxy-cyclopentane skeleton of the bacillariolide series, would be efficiently prepared from the allylic carbonate **5**. The cyclization precursor **5** can be conveniently derived from the known (*R*)-(−)-α-hydroxy-γ-butyrolactone. This transformation involves a two-carbon homologation and the introduction of benzenesulfonyl acetate, followed by δ-lactone formation.

Our synthesis commenced with the preparation of the requisite allylic carbonate **5** for the key Pd(0)-catalyzed cyclization, as shown in Scheme 2. Thus, the α,β-unsaturated

Scheme 2



ester **7** was prepared from the known TBS-protected (*R*)-(−)-α-hydroxy-γ-butyrolactone **6**[8] in 85% yield by a convenient one-pot procedure, involving a DIBAL reduction followed by a Horner−Wadsworth−Emmons reaction.[9] Tosylation of the primary alcohol **7** and then DIBAL reduction of the ester furnished the allylic alcohol **8** in 95% overall yield. THP protection of the allylic alcohol **8** and subsequent alkylation of the tosylate with benzenesulfonyl acetate **10** provided the alkylation product **9**. Concurrent removal of both the TBS and THP protecting groups with CSA and lactonization of the resulting hydroxy ester in the presence of DBU afforded the δ-valerolactone, which was subjected to ethoxycarbonylation to provide the allylic carbonate **5**.

With the requisite cyclization precursor **5** in hand, we carried out a survey of diastereoselective Pd(0)-catalyzed cyclizations under a variety of reaction conditions, including different ligands and solvents as summarized in Table 1. Initial treatment of **5** with 10 mol % of $Pd(dppe)_2$ in THF afforded the cyclization product as a mixture of **4** and **4′** in 78% yield, with a disappointingly low stereoselectivity (entry 1). Fortunately, the poor diastereoselectivity was solved by the use of $Pd(PPh_3)_4$. The cyclization of **5** in the presence of 5 mol % of $Pd(PPh_3)_4$ in CH_2Cl_2 (entry 4) resulted in the exclusive formation of the desired isomer **4**, along with a trace amount of the minor isomer **4′** (30:1), in 88% yield. Interestingly, the cyclization in the presence of $Pd(dba)_2$ (entry 7) showed the opposite diastereoselectivity, although

(4) For recent reviews related to prostaglandins and jasmonates, see: (a) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185. (b) *Prostaglandins, Leukotrienes and Other Eicosanoids. From Biogenesis to Clinical Applications*; Marks, F., Furstenberger, G., Eds.; Wiley-VCH: Weinheim, Germany, 1999. (c) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533. (d) Cheong, J.-J.; Choi, Y. D. *Trends Genet.* **2003**, *19*, 409. (e) Liechti, R.; Farmer, E. E. *Science* **2002**, *296*, 1649 and references therein.

(5) (a) Miyaoka, H.; Tamura, M.; Yamada, Y. *Tetrahedron Lett.* **1998**, *39*, 621. (b) Miyaoka, H.; Tamura, M.; Yamada, Y. *Tetrahedron* **2000**, *56*, 8083.

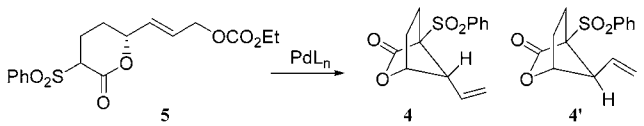
(6) For recent reviews concerning RCM reactions, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 371. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013.

(7) (a) Suh, Y.-G.; Jung, J.-K.; Kim, S.-A.; Shin, D.-Y.; Min, K.-H. *Tetrahedron Lett.* **1997**, *38*, 3911. (b) Suh, Y.-G.; Jung, J.-K.; Suh, B.-C.; Lee, Y.-C.; Kim, S.-A. *Tetrahedron Lett.* **1998**, *39*, 5377. (c) Suh, Y.-G.; Seo, S.-Y.; Jung, J.-K.; Park, O.-H.; Jeon, R.-O. *Tetrahedron Lett.* **2001**, *42*, 1691. (d) Suh, Y.-G.; Jung, J.-K.; Seo, S.-Y.; Min, K.-H.; Shin, D.-Y.; Lee Y.-S.; Kim, S.-H.; Park, H.-J. *J. Org. Chem.* **2002**, *67*, 4127.

(8) (a) Shiuey, S. J.; Partridge, J. J.; Uskokovic, M. R. *J. Org. Chem.* **1988**, *53*, 1040. (b) Mulzer, J.; Mantoulidis, A.; Ohler, E. *J. Org. Chem.* **2000**, *65*, 7456.

(9) Takacs, J. M.; Helle, M. A.; Seely, F. L. *Tetrahedron Lett.* **1986**, *27*, 1257.

Table 1. Pd(0)-Catalyzed Cyclization of Allylic Carbonate **5**[a]



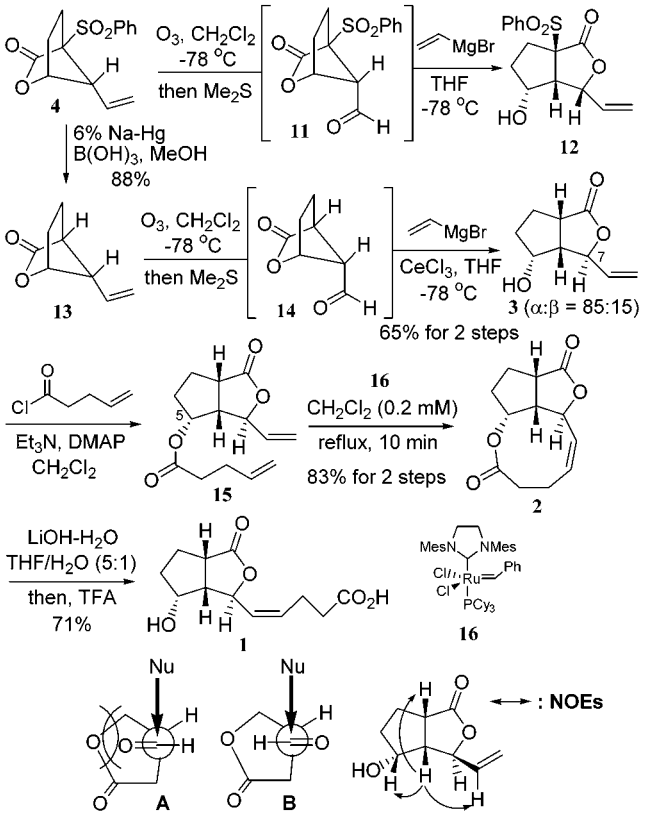
entry	catalyst	solvent	yield (%)[b]	ratio[c] (**4**:**4′**)
1	$Pd(dppe)_2$	THF	78	2:1
2	$Pd(dppe)_2$	DMSO	33	1:1
3	$Pd(PPh_3)_4$	THF	65	5:1
4	$Pd(PPh_3)_4$	CH_2Cl_2	88	30:1
5	$Pd(PPh_3)_4$	DMSO	57	10:1
6	$Pd(PPh_3)_4$	CH_3CN	59	1.1:1
7	$Pd(dba)_2$	DMSO	27	1:2.4
8	$Pd(dba)_2$	THF	*d*	

[a] Reactions were conducted with 10 mol % of Pd catalyst at 80 °C for 2 h except for the reaction of entry 4 performed with 5 mol % of Pd catalyst under reflux for 1 h. [b] Isolated yields. [c] Determined by 300-MHz ^{1}H NMR spectra of the crude diastereomeric mixtures. [d] Not determined.

the yield was quite low. Notably, our methodology provides the bicyclic lactone **4** as an excellent equivalent of the thermodynamically less favorable *cis*-2,3-disubstituted-cyclopentanol system, which is not easily accessible by the conventional cyclization methods.[10]

Having successfully addressed the synthesis of the bicyclic lactone **4**, we turned our attention to the facile transformation of **4** into the bicyclic lactone **3**, as well as to the stereoselective introduction of the C7 vinyl substituent, which is essential for the projected RCM (Scheme 3). We initially attempted to add the vinyl group to the aldehyde **11** possessing the benzenesulfonyl group. Thus, ozonolysis (O_3, CH_2Cl_2, then Me_2S) of the cyclization adduct **4** and the immediate subjection of the unstable aldehyde **11** to the vinylation conditions ($CH_2CHMgBr$, THF, −78 °C) gave the transposed lactone **12** as a single diastereomer in low yield (~25%). This low yield seems to be due to the inherent lability of the strained β-alkoxyaldehyde, which induces the formation of the elimination and/or epimerization product. Furthermore, the structural assignment of **12** by extensive NOE studies revealed that the C7 stereochemistry is opposite to the desired one. Other methods for stereoselective vinylation were also investigated, with little success.[11] In light of the fact that the cerium reagents react with the readily enolizable carbonyl group,[12] we considered the use of an organocerium reagent for the pivotal vinylation of the desulfonylated aldehyde. Thus, desulfonylation (6% Na−Hg, $B(OH)_3$, MeOH) of **4** without ring opening of the bicyclic lactone[7d] and then direct vinylcerium addition to the

Scheme 3



crude aldehyde **14**, which was prepared by ozonolysis of **13**, afforded the desired bicyclic intermediate **3** (65%) along with a small amount of the undesired isomer (10%). The stereoselectivity of vinylcerium addition to the aldehyde is not readily explainable. However, this selectivity is likely due to the preferred anti relationship of the polar groups, as shown in conformation **B**, which minimizes the electronic repulsion.[13] The structure of **3**, as well as the stereochemistries of its stereogenic centers, was confirmed by an intensive analysis of the spectral data, including NOE studies.

To complete the synthesis of bacillariolide III, the C-5 hydroxy group of the vinylated bicyclic lactone **3** was acylated with pentenoyl chloride to give the ester **15** as an internal hydroxy group tethered RCM precursor.[14] To our delight, the ring-closing metathesis of diene **15** with the second-generation Grubbs' catalyst **16** proceeded smoothly, to give the nine-membered lactone **2** with the desired (*Z*)-geometry of the pentenoic side chain.[15] It is noteworthy that the ring-closing metathesis of the diene **15** under highly diluted conditions (0.2 mM) was completed in 10 min, and afforded the nine-membered lactone **2** along with little dimerization product.

Finally, hydrolysis of the nine-membered lactone **2**, followed by trifluoroacetic acid treatment, provided bacil-

(10) (a) Trost, B. M.; Lee, P. H. *J. Am. Chem. Soc.* **1991**, *113*, 5076. (b) Reference 6a and references therein.

(11) All attempts for the direct installation of the (*Z*)-pentenoic acid side chain, however, were unsatisfactory.

(12) For reviews concerning organocerium compounds, see: (a) Liu, H.-J.; Shia, K. S.; Shang, X.; Zhu, B.-Y. *Tetrahedron* **1999**, *55*, 3803. (b) Takeda, N.; Imamoto, T. *Org. Synth.* **1999**, *76*, 228. (c) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: London, UK, 1994; p 80. (d) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (e) Imamoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 1, p 231.

(13) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1986**, *27*, 4011 and references therein.

(14) For recent examples of tethered ring-closing metathesis, see: (a) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702. (b) Van de Weghe, P.; Aoun, D.; Boiteau, J.-G.; Eustache, J. *Org. Lett.* **2002**, *4*, 4105 and references therein.

lariolide III (**1**) in 71% yield. The synthetic bacillariolide III was identical with the natural product in all aspects, including optical rotation.[3,5b]

In summary, we have achieved the asymmetric total synthesis of bacillariolide III in 15 linear steps, with a 14.6% overall yield. The key feature of this synthetic route involves (1) the highly stereoselective construction of the *cis*-2,3-disubstituted hydroxy-cyclopentane intermediate **4** via Pd(0)-catalyzed allylic cyclization, (2) the stereoselective vinylcerium addition, which induces its facile transformation into the bicyclic lactone skeleton of bacillariolide III, and (3) the efficient introduction of the (*Z*)-pentenoic acid side chain by RCM. Our synthetic procedure is quite versatile and expected to be widely utilized for the synthesis of oxylipins and their structural analogues.

(15) For an example of the nine-membered lactone formation using RCM, see: (a) Takemoto, Y.; Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T. *Tetrahedron Lett*. **2000**, *41*, 3653. For selected examples of the synthesis of nine-membered carbo- and heterocycles, see: (b) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548. (c) Delgado, M.; Martin, J. D. *Tetrahedron Lett*. **1997**, *38*, 6299. (d) Bond, S.; Perlmutter, P. *Tetrahedron* **2002**, *58*, 1779. (e) Bamford, S. J.; Goubitz, K.; van Lingen, H. L.; Luker, T.; Schenk, H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 345. (f) Harris, P. W. R.; Brimble, M. A.; Gluckman, P. D. *Org. Lett*. **2003**, *5*, 1847. (g) Clark, J. S.; Marlin, F.; Nay, B.; Wilson, C. *Org. Lett*. **2003**, *5*, 89.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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