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Stereodivergent Approach to the Asymmetric Synthesis of Bacillariolides: A Formal Synthesis of *ent*-Bacillariolide II

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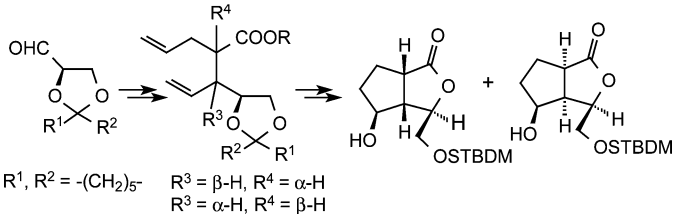
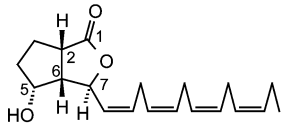
ABSTRACT

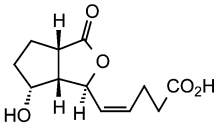


Asymmetric synthesis of densely functionalized bicyclic frameworks for entry into bacillariolides I/III and *ent*-bacillariolide II is reported. The key features are ring-closing metathesis of a pair of diastereomerically related dienes obtained through a stereodivergent route from a *R*-(+)-glyceraldehyde derivative, transformation of a nonstereoselective cyclopentene ester enolate alkylation process to a completely stereoselective one through alkylation of a bulky ester enolate with a bulky electrophile, and a remote silyloxymethyl group directed epoxidation.

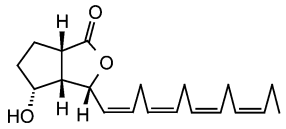
Bacillariolides I and II are oxylipins isolated from the marine diatom *Pseudonitzschia multiseries*, a causative diatom of amnesic shellfish poisoning, by Shimizu and Wang.[1] Subsequently, bacillariolide III, believed to be derived from bacillariolide I by oxidative cleavage of the polyene side chain, was isolated[2] from the culture broth of the same marine diatom. Marine oxylipins[3] are of considerable interest for diverse biological activities. Although the biological function of bacillariolides II and III are yet to be established, bacillariolide I has been found to possess[4] significant inhibitory activity against phospholipase A_2. Our interest in the synthesis of bacillariolides was piqued by their densely functionalized cyclopentanol framework with four contiguous



bacillariolide I



bacillariolide III



bacillariolide II

stereocenters coupled with their potent biological activities specially to those of the hitherto unknown *ent*-series. Synthesis of bacillariolides have been accomplished by two groups.[5] One[5a] of them describes the synthesis of bacillariolide III, while the other[5b,c] reports the synthesis of bacillariolide II and its diastereomerically related bacillariolides I and III through epimerization of a key intermediate. We herein report a stereocontrolled approach to the asymmetric synthesis of the fully functionalized bicyclic frameworks,

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(1) (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.
(2) Zheng, N.; Shimizu, Y. *Chem. Commun.* **1997**, 399.
(3) (a) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685. (b) Gerwick, W. H. *Chem. Rev.* **1993**, *93*, 1807.
(4) Shimizu, Y. *Annu. Rev. Microbiol.* **1996**, *50*, 431.

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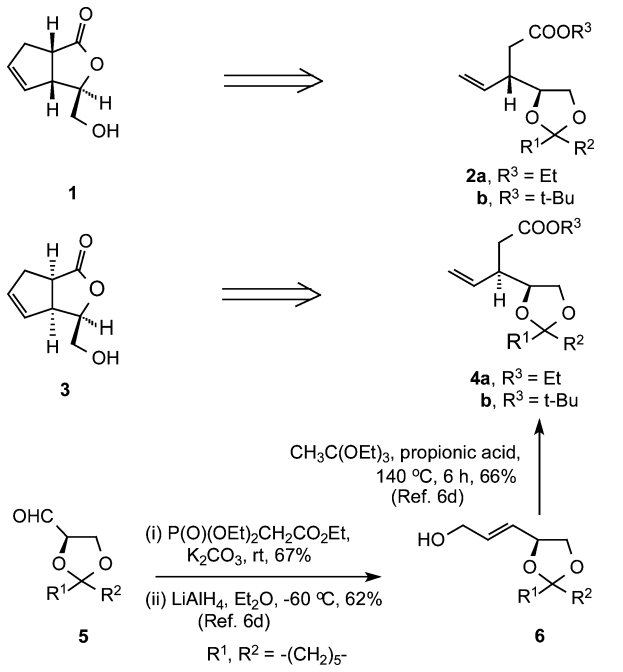
one of which allows access to bacillariolides I and III, while the other provides access to bacillariolide II.

The unique feature of our strategy lies in the stereodivergency that allows access to both the diastereomeric series from a common precursor. Retrosynthetically, bacillariolide I/III may be obtained through hydroxylation of the cyclopentene **1**, which in turn would be available from the unsaturated ester **2** (Scheme 1). The unsaturated ester **2** is

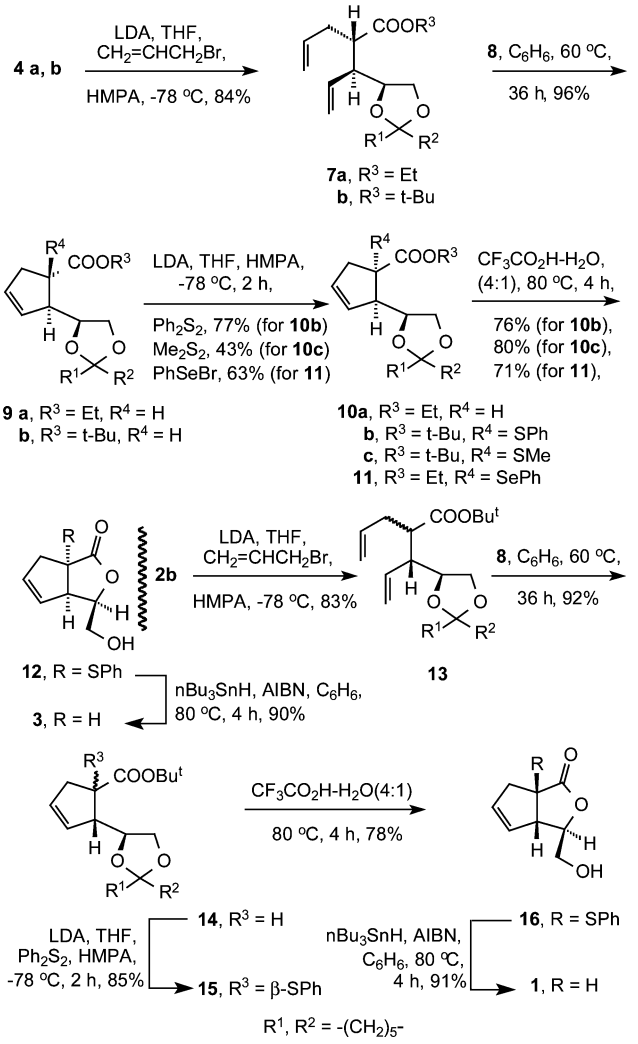
Scheme 1



appropriately functionalized to deliver the lactone ring at one side and the cyclopentene ring on the other side, with the desired anti stereochemistry between the hydrogens at C-6 and C-7. A similar consideration depicts that the unsaturated ester **4** will be required for the construction of the diastereomeric bicyclic lactone **3** for entry into bacillariolide II. An ortho ester Claisen rearrangement of the allyl alcohol **6** derived from the *R*-(+)-glyceraldehyde derivative **5**[6] will give rise to the stereodivergency, providing the required diastereomeric unsaturated esters **2** and **4**.

Initially we focused our attention on the construction of the bicyclic lactones **1** and **3** from the unsaturated esters **2** and **4**, respectively. The unsaturated esters **2** and **4** were prepared according to our previously published procedure.[6d] We needed to construct the cyclopentene derivative, for example, **10** (Scheme 2), in which the ketal unit is *cis* to the

Scheme 2



ester group so as to facilitate lactone formation. However, earlier we have observed[6d] that alkylation of the enolate of the ester **4a** with allyl bromide, followed by ring-closing metathesis (RCM)[7] of the resulting mixture of the diene **7a** and its syn isomer with Grubbs' catalyst $(PCy_3)_2Cl_2Ru{=}CHPh$ **8**, led to a mixture of the cyclopentene **9a** and its *cis*-isomer in 3:1 ratio. Thus, it is necessary to convert the *trans*-cyclopentene derivative **9** to the *cis*-cyclopentene **10a**. On the basis of Houk's model[8] for addition of electrophiles to C=C double bonds having a α-chiral center, we anticipated that alkylation of the enolate derived from the cyclopentene ester **9** with an electrophile would take place from the side of the smallest group (H atom in the present case) of the chiral center to produce the *cis*-analogue **10** ($R^4 \neq H$). Subsequent lactone formation and removal of the group (R^4) would provide the desired bicyclic framework of bacillariolides. To this end, alkylation of the enolate of the ester **9a** with PhSeBr led to reversal of the *cis*/*trans* ratio from 1:3 to 2.5:1 with the *cis*-isomer **11a** being the major product.

(5) (a) Seo, S. Y.; Jung, J. K.; Paek, S. M.; Lee, Y. S.; Kim, S. H.; Lee, K. O.; Suh, Y. G. *Org. Lett*. **2004**, *6*, 429. (b) Miyaoka, H.; Tamura, M.; Yamada, Y. *Tetrahedron Lett*. **1998**, *39*, 621. (c) Miyaoka, H.; Tamura, M.; Yamada, Y. *Tetrahedron* **2000**, *56*, 8083.

(6) (a) For a review on the application of *R*-(+)-glyceraldehyde derivative in synthesis, see: Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447. For our own work in this area, see: (b) Nayek, A.; Banerjee, S.; Sinha, S.; Ghosh, S. *Tetrahedron Lett*. **2004**, *45*, 6457. (c) Sarkar, N.; Nayek, A.; Ghosh, S. *Org. Lett*. **2004**, *6*, 1903. (d) Banerjee, S.; Ghosh, S.; Sinha, S.; Ghosh, S. *J. Org. Chem*. **2005**, *70*, 4199.

(7) For a recent review on the RCM reaction, see: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed*. **2005**, *44*, 4490.

(8) Mengel, A.; Reiser, O. *Chem. Rev*. **1999**, *99*, 1191.

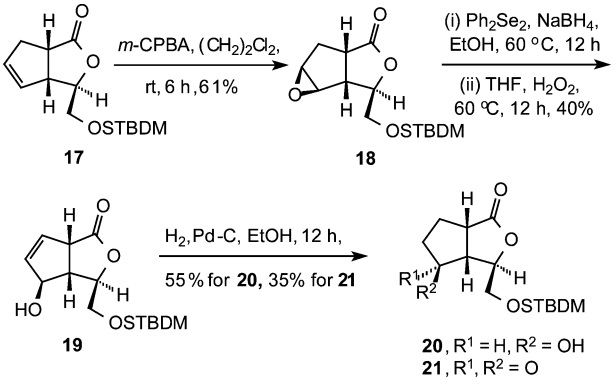
After considerable experimentation, the desired *cis*-disubstituted cyclopentene derivative could be formed exclusively by using a combination of a bulky ester and a bulky electrophile.

Thus, the ethyl ester **4a** was converted to the *tert*-butyl ester **4b**. Allylation of its lithium enolate, followed by RCM of the crude resulting diene mixture, led to the cyclopentene **9b** and its *cis*-analogue in 1:1 ratio. Alkylation of the lithium enolate of **9b** with Ph_2S_2 gave exclusively the *cis*-disubstituted cyclopentene **10b** in excellent yield. Interestingly, when dimethyl disulfide was used as the alkylating agent, the reaction was totally nonstereoselective, producing a 1:1 mixture of the cyclopentene derivative **10c** and its corresponding *trans*-isomer. Treatment of the cyclopentene **10b** with TFA effected ester hydrolysis with concomitant deketalization and lactonization to afford the lactone **12** in 76% yield, confirming the *cis*-stereochemical assignment of the vicinal substituents in the cyclopentene **10b**. Reductive removal of the SPh group with tributyltin hydride (TBTH) gave the bicyclic lactone in excellent yield. The lactone **3** represents the carbocyclic core with *cis*-stereochemistry between C-6 and C-7 Hs required for bacillariolide II.

In a similar fashion, the *tert*-butyl ester **2b** prepared from the ethyl ester **2a** was alkylated with allyl bromide. The resulting diene mixture **13** was treated with Grubbs' catalyst **8** to produce the cyclopentene derivatives **14** as a 1:1 mixture of *cis*- and *trans*-isomers. The lithium enolate generated from **14** was alkylated with Ph_2S_2 to form exclusively the *cis*-alkylated product **15** in 85% yield. When the ketal-ester **15** was treated with TFA, the lactone **16** was formed in 78% yield. Reductive removal of the SPh group from **16** with TBTH afforded the lactone **1** in 91% yield.

With the lactones **1** and **3** ready in hand, we first chose the lactone **1** for introduction of the OH group at C-5. The hydroxyl group in **1** was protected to give the silyl ether **17**. Epoxidation of **17** with *m*-CPBA afforded a mixture of the epoxide **18** along with its other diastereoisomer (7:1) in 88% yield (Scheme 3). The assignment of stereochemistry to the

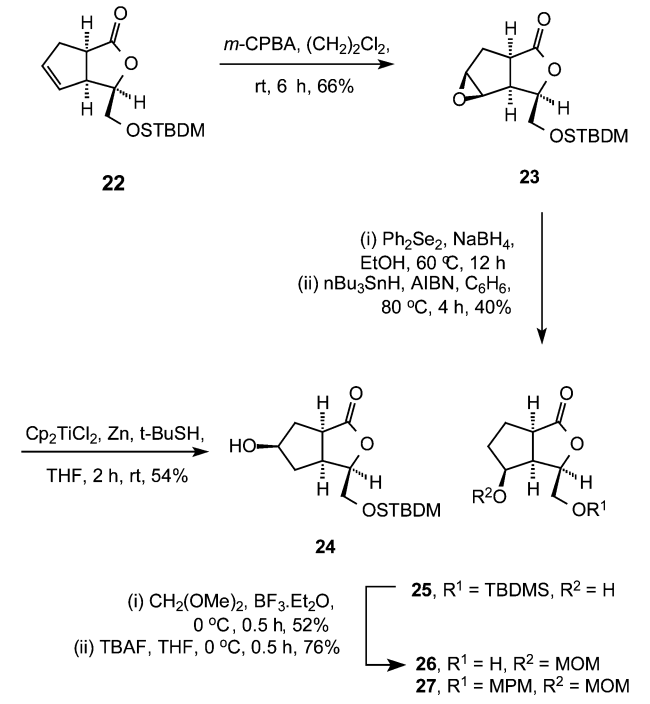
Scheme 3



epoxide **18** followed from its conversion to the allylic alcohol **19** in 40% yield, following the procedure of Sharpless and Lauer.[9] The characteristic feature that led to this structural assignment is the presence of two olefinic protons at δ 5.86 as a broad singlet in ^{1}H NMR and two olefinic methine carbons at δ 129.6 and 136.2 in ^{13}C NMR spectra. The stereochemical assignment of the C-5 OH group was based on NOE (2.2%) between C-5 and C-7 Hs. This also established that the epoxidation of **17** occurred from the β-face. Although this might have resulted from a preference for addition to the less-hindered face of the alkene, further observations (vide infra) indicate that epoxidation is directed by the silyloxymethyl group in **17**. Hydrogenation of the cyclopentene **19** with 10% Pd−C led to a mixture of the cyclopentanol **20** (55%) and the cyclopentanone **21** (35%). The latter probably arises through the corresponding enol arising through isomerization of the double bond in the presence of the Pd catalyst. Reduction of the cyclopentanone **21** with $NaBH_4$ in MeOH gave back the cyclopentanol **20** in 83% yield. The cyclopentanol **20** represents the completely functionalized, C-5 *epi*-bicyclic framework of bacillariolides I and III.

For entry into the *ent*-series, the hydroxyl group in the lactone **3** was protected to give the silyl ether **22**. Epoxidation of the cyclopentene **22** with *m*-CPBA gave a mixture of the epoxide **23** and its diastereoisomer (7:1) in 84% yield (Scheme 4). The stereochemical assignment to the epoxide

Scheme 4



23 could not be made at this stage. Attempted opening of the epoxy ring using the procedure of Sharpless' and Lauer to convert it into allyl alcohol, as in the previous example, did not proceed well. We thought that reduction of the

(9) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

epoxide **23** might proceed from the less-substituted site to give the OH group at C-5. To our dismay, when the reduction was carried out with Cp_2TiCl,[10] the undesired regioisomeric cyclopentanol **24** was obtained as a crystalline solid, mp 118−120 °C in 54% yield. The regio- and stereochemistry of the cyclopentanol derivative was established through single-crystal X-ray structure (Figure 1).[11] It may be noted

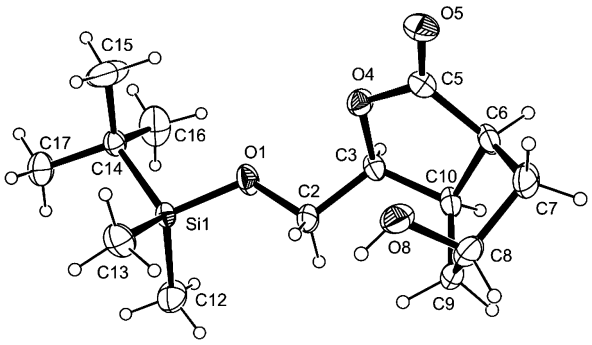


Figure 1. ORTEP plot of compound **24**.

that epoxidation in this case also occurred preferentially from the sterically congested β-face, confirming the directing effect of the silyloxymethyl group. It is believed that reduction of epoxide with Cp_2TiCl proceeds through a radical intermediate.[10] Thus, it is probably the stability of the radical formed at C-5 next to the C-6 tertiary carbon that directed opening of the epoxide to give the alcohol **24**. Finally, treatment of the epoxide **24** with PhSeNa (generated in situ from Ph_2Se_2 with $NaBH_4$), followed by reductive removal of the SePh group with TBTH from the organoselenium intermediate, afforded the desired cyclopentanol **25** in 40% yield.[12]

Protection of the hydroxyl group as MOM ether, followed by desilylation, afforded the bicyclic lactone **26**: mp 112−113 °C; $[\alpha]^{25}_D$ 1.20 (*c* 1.00, $CHCl_3$) [lit.[5c] (for its enantiomer) mp 115−117 °C; $[\alpha]^{25}_D$ −1.1 (*c* 1.00, $CHCl_3$)]. The spectral data (IR and ^1H and ^{13}C NMR) of the lactone obtained as above are closely comparable with those reported in the literature[5c] for its enantiomer. The enantiomer of the lactone **26** has already been converted[5b,c] to bacillariolide II through Wittig olefination of the aldehyde derived from it, followed by removal of the MOM group. Thus, with the synthesis of the lactone **26**, a formal synthesis of *ent*-bacillariolide II is achieved. Further, the MPM-protected analogue **27** has also been converted[5c] to bacillariolide I and III. Thus, the lactone **26** obtained as above provides access to the *ent*-bacillariolides I and III, also.

In summary, we have achieved asymmetric synthesis of a fully functionalized bicyclic framework for entry into bacillariolide I and III and a formal synthesis of *ent*-bacillariolide II. The key features of this approach are RCM of dienes obtained from a *R*-(+)-glyceraldehyde derivative to *trans*-vicinally disubstituted cyclopentanes and their isomerization to the *cis*-disubstituted cyclopentenes through enolate alkylation of *tert*-butyl ester with a removable electrophile (SPh). A silyloxy group directed epoxidation, followed by epoxide opening, furnished the bicyclic core structures of bacillariolides. Synthetic protocol developed by us is simple, efficient, and expected to provide structural analogues.

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Supporting Information Available: Experimental procedures with spectroscopic data, X-ray crystal data for compound **24**, and ^1H and ^{13}C NMR spectra of compounds **1**, **3**, **18**−**20**, **23**, **25**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061377Y

(10) Rajanbabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.*, **1994**, *116*, 986.

(11) Crystallographic data for compound **24** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 602703. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.. Fax: +44-1233-336033. E-mail: deposit@ccdc.cam.ac.uk.

(12) The regioisomeric cyclopentanol **24** was also isolated in about the same yield from this reaction.