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A formal stereoselective synthesis of (−)-brevisamide

J. S. Yadav [a,*], A. Raju [a,b], K. Ravindar [a], B. V. Subba Reddy [a]

[a] Natural Product Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 607, India
[b] University of Hyderabad, Hyderabad 500 046, India

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ABSTRACT

An efficient stereoselective formal synthesis of marine derived monocyclic ether (−)-brevisamide is reported. The key steps involved in this synthesis are *syn*-Aldol reaction, Sharpless asymmetric epoxidation, and stereoselective construction of tetrahydropyran ring by 6-*endo*-cyclization of suitably substituted hydroxy styrylepoxide.

The isolation and structural elucidation of brevisamide (**1**), a marine derived monocyclic ether was reported in 2008 by Satake et al., (Fig. 1).[1] It was isolated from *Karenia brevis* (Red tide dinoflagellate) which is a well known species to produce various cyclic polyether toxins such as brevetoxins A and B, ciguatoxins, and maitotoxins. The absolute and relative stereochemistry of brevisamide was determined by various research groups through its stereoselective total synthesis employing Brown's crotylation, Curtius rearrangement, and Suzuki–Miyaura cross coupling as key transformations.[2] Very interesting structural features such as tetrahydropyran core coupled with dienal side chain and terminal amide subunit of brevisamide (**1**) have attracted the attention of many synthetic research groups for the last four years.[3]

In light of interesting structural features of brevisamide (**1**) and in continuation of our interest in total synthesis of oxygen containing heterocyclic natural products,[4] most recently, we have demonstrated a stereoselective formal synthesis of (−)-brevisamide (**1**) by means of an unprecedented redox reaction of palladium hydroxide ($Pd(OH)_2$) catalyzed isomerization of primary allylic alcohol to the corresponding aldehyde and intramolecular oxa-Michael strategy (IMOM) for the construction of a key tetrahydropyran core unit.[5] Herein, we report an efficient formal synthesis of (−)-brevisamide (**1**) employing *syn*-Aldol reaction, Sharpless asymmetric epoxidation and stereoselective construction of tetrahydropyran moiety via 6-*endo*-cyclization of hydroxy styrylepoxide.

Taking into consideration Lindsley's protocol and our own reported synthetic strategy,[3a,5] we envisioned the retrosynthetic

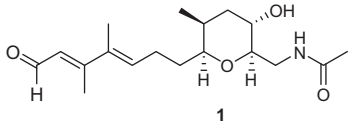

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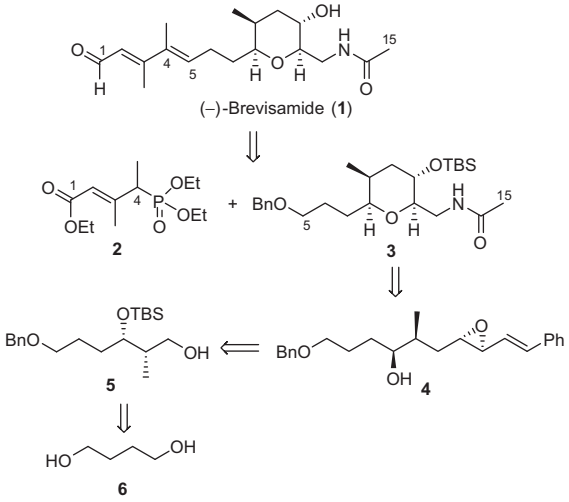
Fig. 1. (−)-Brevisamide (**1**).



Scheme 1. Retrosynthetic analysis of (−)-brevisamide (**1**).

analysis of (−)-brevisamide (**1**) as depicted in Scheme 1. (−)-Brevisamide (**1**) could easily be synthesized via the Horner–

* Corresponding author. Fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (J.S. Yadav).

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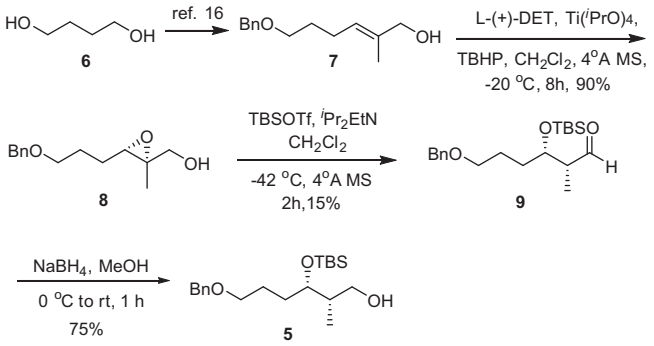
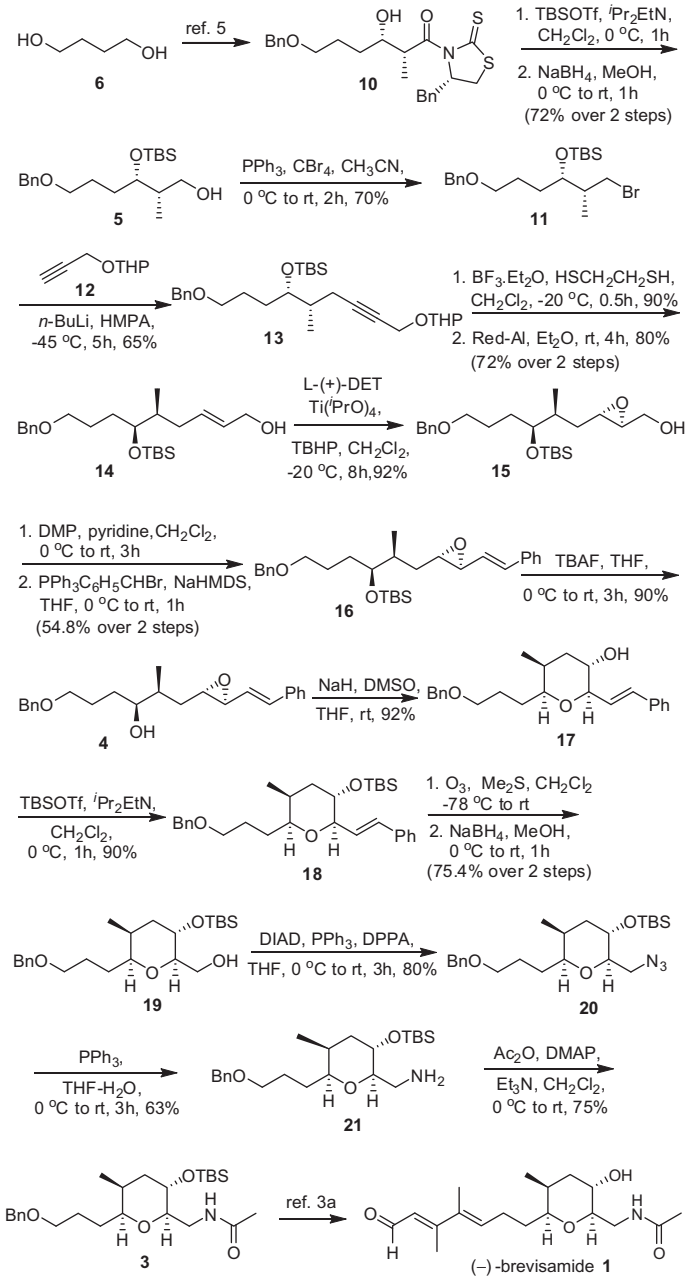


Scheme 2.

Wadsworth–Emmons (HWE) reaction between two coupling partners of C1–C4 side chain **2** and C5–C15 tetrahydropyran core **3** (by the use of corresponding C5 aldehyde intermediate). Tetrahydropyran segment (C5–C15 fragment) **3** can be achieved via the base induced 6-*endo*-cyclization of hydroxy styrylepoxide **4**, which could in turn be prepared from a commercially available 1,4-butanediol **6** via *syn*-stereo-diad **5** employing asymmetric *syn*-Aldol reaction, Sharpless asymmetric epoxidation, and Wittig olefination sequence.

Initially, we planned the synthesis of stereo-diad **5** from the *syn*-Aldol intermediate **9** via a nonaldol strategy using *t*-butyldimethylsilyltrifluoromethanesulfonate (TBSOTf) and Hunig's base mediated intramolecular epoxide opening reaction (Jung's protocol)[6] from chiral epoxy alcohol **8**. Accordingly, allylalcohol **7** was readily prepared from 1,4-butanediol **6** using well precedented literature procedures, which was then subjected to Sharpless asymmetric



Scheme 3.

epoxidation[7] using *t*-BuOOH, L-(+)-diethyl tartrate, and $Ti(^iOPr)_4$ to afford the epoxy alcohol **8** in 90% yield with excellent enantioselectivity (95% ee, determined by chiral HPLC), which was then treated with TBSOTf and Hunig's base in order to accomplish the TBS protected *syn*-Aldol product **9**. Unfortunately, the desired aldol product **9** was obtained only in 15% yield which could be due to the interference of the C6–OBn group as has been reported by others.[8] Aldehyde **9** was reduced using $NaBH_4$ in MeOH to get the desired stereo-diad **5** in 75% yield (Scheme 2).

Unsatisfied with the above result, we adopted a well precedented asymmetric Aldol addition strategy for the synthesis of stereo-diad **5** via thiazolidinethione ester **10**, as we have reported in our previous synthetic approach to breviasmide.[5] TBS protection of secondary alcohol **10** and subsequent reductive cleavage of chiral auxiliary furnished primary alcohol **5**,[9] which was then converted into the corresponding bromide derivative **11** in 70% yield using triphenylphosphine (TPP) and CBr_4 in anhydrous acetonitrile.[10] The bromo compound **11** was then coupled with lithiated 1-(tetrahydropyranyloxy)-2-propyne **12** to obtain propargyl ether **13**. Deprotection of THP group of **13** followed by chemoselective reduction of alkyne moiety with Red-Al gave the allyl alcohol **14** in 80% yield.[11] Sharpless asymmetric epoxidation[7] of the allyl alcohol **14** using L-(+)-diethyl tartrate, $Ti(^iOPr)_4$, and *t*-BuOOH in anhydrous CH_2Cl_2 gave the epoxy alcohol **15** in 92% yield. Dess–Martin periodinane oxidation[12] followed by Wittig olefination[13] of the epoxy alcohol **15** gave styrylepoxide **16** in 63% yield with 9:1 *E*/*Z* ratio (Scheme 3).

Next we intended to attempt the 6-*endo*-cyclization of hydroxy styrylepoxide **4** to access the tetrahydropyran **17**. Accordingly, compound **16** was treated with *tetra*-*n*-butylammonium fluoride (TBAF) in anhydrous THF to provide the hydroxy styrylepoxide **4** in 90% yield. NaH induced 6-*endo*-cyclization of styryl epoxide **4** (Tadashi Nakata protocol)[14] gave the desired tetrahydropyranyl ether **17** in 90% yield with the requisite stereochemistry. Secondary hydroxyl group of tetrahydropyran **17** was protected as its TBS ether **18** using *t*-butyldimethylsilyltrifluoromethanesulfonate (TBSOTf), diisopropylethylamine in CH_2Cl_2 in 90% yield. Ozonolysis[13,15] of olefin **18** followed by the reduction of the resulting aldehyde with $NaBH_4$ afforded the primary alcohol **19** in 82% yield. Next, alcohol **19** was converted[3c] into the primary azide **20** using Diisopropyl azodicarboxylate (DIAD), triphenylphosphine (TPP), and diphenylphosphoryl azide (DPPA), which was then reduced to the corresponding amine **21** using triphenylphosphine (TPP) in THF/H_2O system.[3c] Acylation of the primary amine **21** with Ac_2O, TEA in CH_2Cl_2 gave the desired C1–C15 fragment **3** of (−)-brevisamide in 75% yield (Scheme 3). This route provided fragment **3** in a 1.35% overall yield in the longest linear sequence of 20 steps from commercially available starting material. The spectral data and optical rotation values of this advanced intermediate **3** (C1–C15 fragment) were in agreement with a known compound reported in the literature.[3a,5]

In conclusion, the formal synthesis of (−)-brevisamide has been accomplished by constructing the tetrahydropyran core unit (C1–C15 fragment of brevisamide). The base induced epoxide rearrangement strategy has been used to achieve *syn*-Aldol reaction. The synthesis involves simple and straightforward reactions such as the Sharpless asymmetric epoxidation and base induced 6-*endo*-cyclization of hydroxy styrylepoxide.

Uncited references

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.134.

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