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Stereoselective total synthesis of (−)-brevisamide

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ABSTRACT

The stereoselective total synthesis of (−)-brevisamide, a novel marine cyclic ether alkaloid isolated from dinoflagellate *karenia brevis* is described. The key steps involved in this synthesis are the Sharpless asymmetric epoxidation and regioselective ring opening of chiral epoxide by Gilman's reagent. The tetrahydropyran core has been constructed by an intramolecular S_N2 cyclisation.

1. Introduction

The dinoflagellate *Karenia brevis* produces polycyclic ethers, such as brevetoxins and brevenal.[1–4] The brevetoxins are found to exhibit potent neurotoxicity, which causes massive killing of fish and marine animals, such as dolphins and manatees in the Florida coast. The brevenals display antagonist activity against the brevetoxins.[1,5] (−)-Brevisamide[6] (**1**) is one of such brevenals, which was isolated by Wright's group from dinoflagellate *karenia brevis*. Considering its interesting biological activity, five research groups have independently reported the total synthesis of brevisamide.[7] Our group recently published a formal synthesis of brevisamide.[8] As part of our ongoing program towards the total synthesis of biologically active complex natural products,[9] we herein, disclose a stereoselective total synthesis of (−)-brevisamide (Fig. 1).

Scheme 1 describes retrosynthetic analysis of (−)-brevisamide (**1**) following a convergent synthetic strategy. The functionalized tetrahydropyran ring moiety (**3**) could be constructed from compound **4a** via intramolecular S_N2 cyclisation. The phosphonate ester **6** could be obtained from acetoin. The target molecule might be achieved by the coupling of compounds **3** and **6** using a Horner–Wadsworth–Emmons reaction.

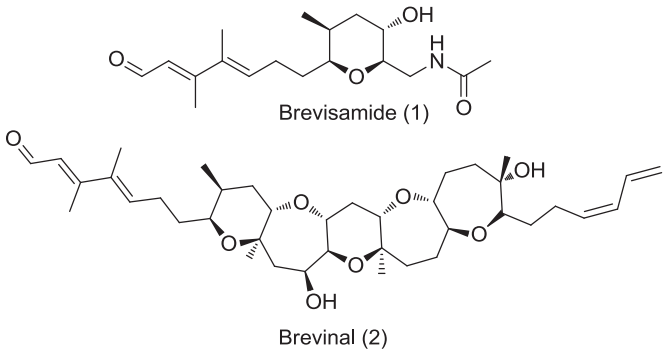

Fig. 1. Structures of brevisamide (**1**) and brevenal (**2**).

2. Results and discussion

The synthesis of tetrahydropyran moiety **3** began with (*R*)-2,3-*O*-isopropylidene glyceraldehyde **5**. Treatment of the aldehyde **5** with allyl bromide in the presence of zinc dust and aqueous NH_4Cl solution in THF at 0 °C afforded the corresponding homoallyl alcohol **7** as a major diastereomer favouring *anti*-isomer (*anti*/*syn* 96:4, from ^1H NMR spectrum).[10] Protection of free hydroxyl group as its benzyl ether using BnBr in the presence of NaH in THF gave the compound **8** in 92% yield. Ozonolysis of the olefin **8** followed by Wittig olefination with a stable ylide, i.e., (ethoxycarbonylmethylene)triphenylphosphorane in CH_2Cl_2 gave the α,β-unsaturated ester **9** in 78% yield.

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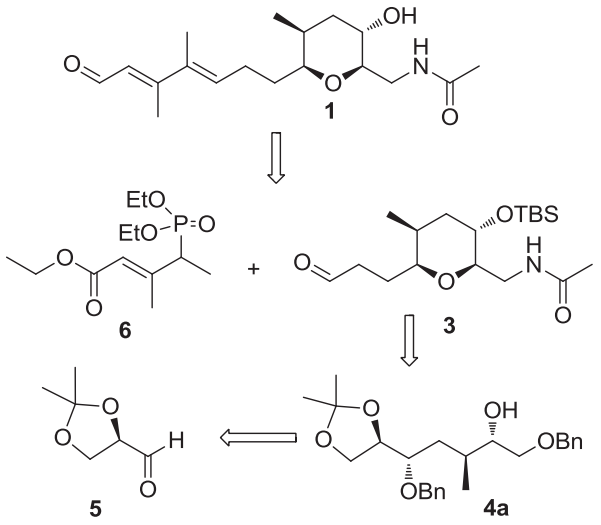
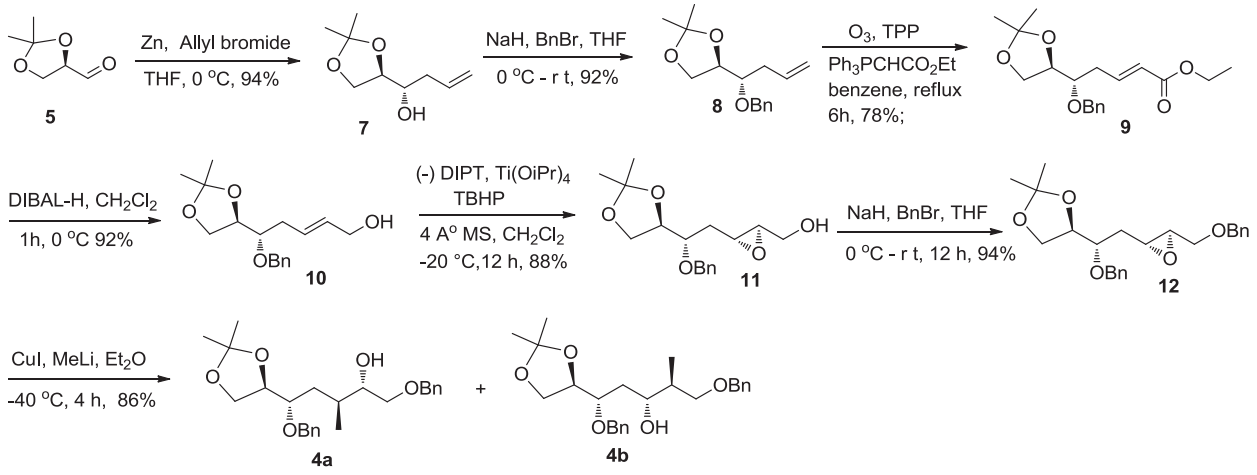


Scheme 1. Retrosynthesis of brevisamide.

Reduction of the α,β-unsaturated ester **9** with DIBAL-H in CH_2Cl_2 afforded the allylic alcohol **10** in 92% yield. The Sharpless asymmetric epoxidation of allylic alcohol **10** using (−)-DIPT, $Ti(O^iPr)_4$ and TBHP in CH_2Cl_2 furnished the epoxide **11** in 88% yield. Protection of epoxy alcohol **11** as its benzyl ether with BnBr in the presence of NaH in THF afforded the compound **12** in 94% yield. Regioselective ring opening of the chiral epoxide **12** with Gilman's reagent, i.e., lithium dimethylcuprate in ether at −40 °C gave the 7:1 mixture of positional isomers **4a** and **4b**, respectively, in 86% yield,[11] which could be easily separated by column chromatography (Scheme 2).



Scheme 2.

Mesylation of secondary hydroxyl group in **4a** using MsCl, TEA in CH_2Cl_2 followed by removal of acetonide using *p*-TSA in MeOH gave the diol **14**. An intramolecular S_N2 cyclisation of compound **14** in the presence of NaH in THF afforded a key intermediate, tetrahydropyran moiety **15** in 75% yield over three steps.[12] Protection of the primary hydroxyl group of compound **15** as its TBS ether using TBSOTf and 2,6-lutidine in CH_2Cl_2 gave the compound **16** in 96% yield. Removal of both benzyl groups in compound **16** using Li/naphthalene in THF afforded the diol **17** in 93% yield.[13] Chemoselective oxidation of the primary alcohol from diol **17** with TEMPO-BAIB in CH_2Cl_2 followed by Wittig olefination with a stable ylide, i.e., (ethoxycarbonylmethylene)triphenylphosphorane gave the α,β-unsaturated ester **18** in 86% yield in a single step.[14] Reduction of the double bond in ester **18** with PtO_2 in EtOAc followed by protection of secondary hydroxyl group as TBS ether using TBSOTf and 2,6-lutidine in CH_2Cl_2 afforded the compound **20** in 96% yield over two steps. Selective removal of the TBS group from compound **20** with cat. CSA in CH_2Cl_2/MeOH (4:1) gave the primary alcohol **21** in 90% yield.[15] Further treatment of compound **21** with TPP, DPPA, and DIAD in THF under Mistunobu conditions gave the azide **22** in 82% yield.[16] Reduction of the azide in the presence of Pd/C in MeOH/THF followed by acetylation of the primary amine with Ac_2O in the presence of $NaHCO_3$ gave the acetyl amide **23** in 97% yield over two steps. Reduction of the ester **23** with DIBAL-H in CH_2Cl_2 at −100 °C afforded the aldehyde **3** in 80% yield (Scheme 3).

The phosphonate **6** was obtained from acetoin[7d] by using simple chemical modifications. Wittig olefination followed by bromination of action **24** produced bromoester **25**. Reaction of bromoester with triethyl phosphate afforded phosphonate ester **6** in 95% yield. Finally, having the two fragments **3** and **6** in hand, we followed the Lindsley approach to achieve the total synthesis of brevisamide[7d] (Scheme 4). The physical and spectroscopic data of brevisamide were in good agreement with the data reported to the natural brevisamide and previously prepared synthetic brevisamide.

3. Conclusion

In summary, we have accomplished the total synthesis of brevisamide from (*R*)-2,3-*O*-isopropylideneglyceraldehyde. The Sharpless asymmetric epoxidation of allylic alcohol, the regioselective ring opening of chiral epoxide with Gilman's reagent to introduce methyl group, the formation of tetrahydropyran ring via S_N2 cyclisation, one-pot TEMPO-BIAB oxidation followed by Wittig olefination and the stereoselective formation of *E*-olefin by Horner–Wadsworth–Emmons reaction are employed as key steps in this synthesis. The present synthesis will provide access to a variety of structural analogues for further studies.

4. Experimental section

4.1. General

All reactions were performed under inert atmosphere, if argon mentioned. All glassware apparatus used for reactions are perfectly