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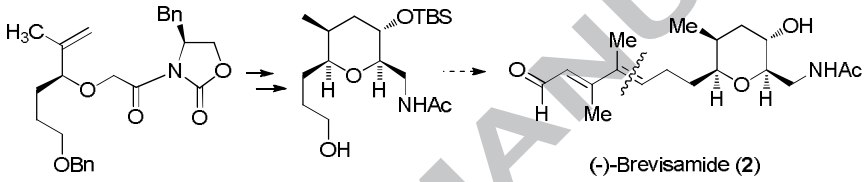
Graphic Abstract



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Abstract

A formal total synthesis of (–)-brevisamide, a monocyclic ether amide with architecturally unique structural features, has been achieved. The tetrahydropyran core part of the target was synthesized by the aldol reaction followed by ring-closing metathesis using the Grubbs second generation catalyst. After the stereochemistry at the carbon center bearing the hydroxy group was adjusted, the carbon-carbon double bond was stereoselectively reduced by catalytic hydrogenation. Finally, introduction of the amino group was followed by acetylation, which provided the desired advanced intermediate.

Keywords: Brevisamide, Asymmetric synthesis, Natural products, Aldol reaction, Ring-closing metathesis

Ladder-frame polyethers secreted by dinoflagellates have been the subject of much interest in recent years. Marine toxins such as brevetoxins, which belong to the polyether class of natural products, are responsible for the mass death of fishes and marine animals in the Florida Coast and Gulf of Mexico. Brevetoxin B, the first member of a new class of unique marine natural products with a ladder-like molecular architecture, binds to the voltage-sensitive sodium channels in neurons. A simpler polyether, brevenal (**1**), which is actually an antagonist of brevetoxins, has been isolated from the marine dinoflagellate *Karenia brevis*. In 2008, Wright and co-workers discovered a new alkaloid, (–)-brevisamide (**2**),[1] from the same dinoflagellate. Based on the structure of these two compounds, **2** has been assumed to be the biosynthetic precursor to **1** (Fig 1).[2,3] (–)-Brevisamide (**2**), a monocyclic ether amide, contains a characteristic tetrahydropyran ring substituted with a 3,4-dimethylhepta-2,4-dienal side

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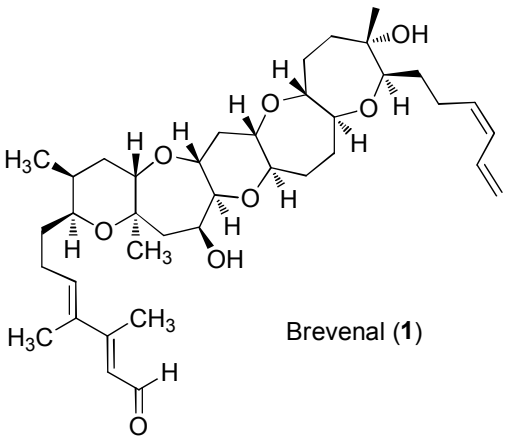
chain. Ever since the first total synthesis of **2** was reported by Satake, Tachibana, and co-workers,[4a] it has attracted increasing attention from synthetic chemists. Many research groups have reported the total synthesis[4] as well as formal total synthesis[5] of **2**.



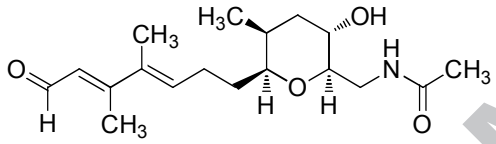
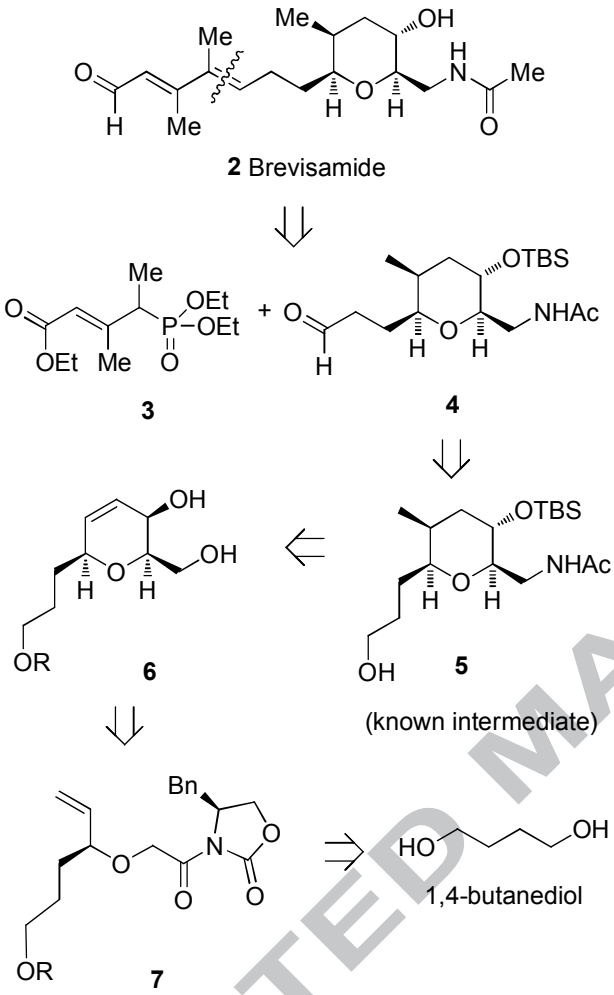


Figure 1. Brevenal (**1**) and brevisamide (**2**).

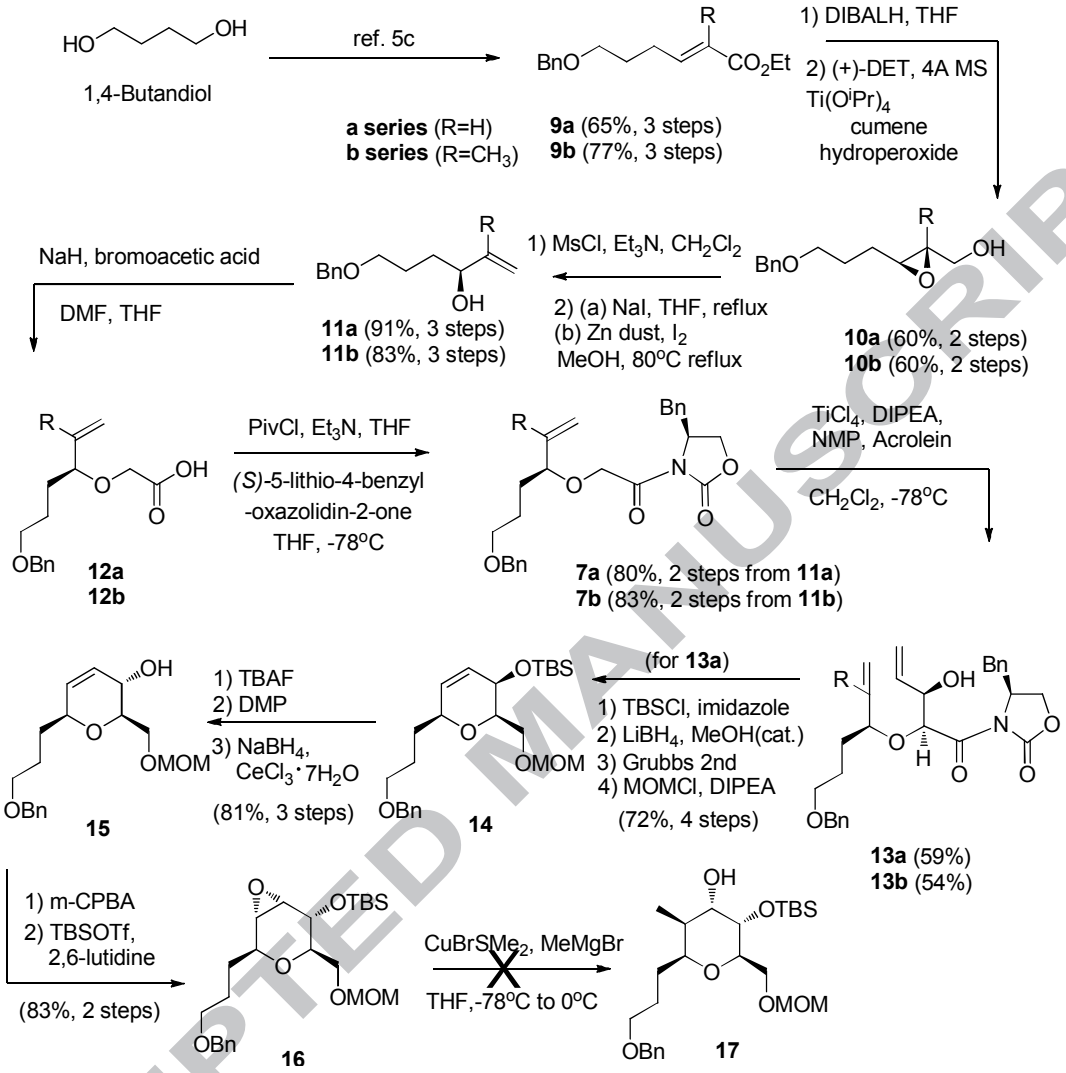
We have been interested in the synthesis of **2** because of its unique tetrahydropyran core structure with multiple stereocenters. The synthesis of **2** may also provide an efficient synthetic route to oxacyclic natural products.

Retrosynthetic analysis of the target is shown in Scheme 1. The synthesis of brevisamide (**2**) could be achieved by coupling the side chain part **3** with the tetrahydropyran ring part **4**, which, in turn, could be derived from the known intermediate **5**. The tetrahydropyran core part **5** could be synthesized from **6**. The compound **6** then could be derived from **7** by aldol reaction followed by ring-closing metathesis (RCM), which is eventually synthesized from 1,4-butanediol. Because the protected substituted tetrahydropyran core **5** has been known as a synthetic intermediate for the target **2**,[4b] successful synthesis of **5** could complete a formal total synthesis of **2**.



Scheme 1. Retrosynthetic analysis of brevisamide (**2**).

The synthetic sequence to the key precursor **13** for the cyclization is shown in Scheme 2. Our synthesis commenced with 1,4-butanediol, which was first converted to α,β-unsaturated ester **9a** via a three-step sequence (**a** series) as reported in the literature.[5c]



Scheme 2. Synthesis of **13** and attempt to prepare functionalized tetrahydropyran **17**.

After reduction of the ester group, the resulting allylic alcohol was subjected to Sharpless asymmetric epoxidation to afford the optically pure epoxy alcohol **10a.** Next, mesylation of **10b** followed by the reaction with NaI provided the corresponding iodide, which was treated with Zn dust, successfully afforded the optically active allylic alcohol **11a** in good yield. For synthesizing the substituted tetrahydropyran ring, we decided to adopt the strategy developed by the Crimmins' group.[6] Thus, glycolic acid was first attached to the alcohol **11a** by the reaction with bromoacetic acid in order to prepare the substrate for the aldol reaction. The resulting carboxylic acid **12a** was then activated with pivaloyl chloride to attach the Evans' oxazolidinone chiral auxiliary to prepare the desired aldol substrate **7a**. The asymmetric aldol reaction of **7a** with acrolein was then

successively accomplished via enolate generation with $TiCl_4$ in the presence of a base.[7] In this way, the desired aldol product **13a** was prepared in reasonable yield. The TBS-protection of hydroxy group followed by removal of the Evans' chiral auxiliary ($LiBH_4$ reduction) afforded the desired diene for cyclization to form the tetrahydropyran core. RCM using the Grubbs second generation catalyst,[8] which was succeeded by a MOM protection of the resulting hydroxy group, led to the dihydropyran **14**, thus proving the utility of the aldol-RCM strategy. Next, for introducing a methyl group stereoselectively, we decided to use the stereoselective nucleophilic opening of an epoxide. Thus, deprotection of the TBS group followed by a DMP oxidation afforded the corresponding ketone, which was then subjected to Luche reduction ($NaBH_4$, $CeCl_3$).[9] The hydride attack exclusively produced the desired allylic alcohol **15** with an inverted stereochemistry of the carbon bearing the hydroxy group. In this case, an excellent selectivity (ca. 20:1 (^{1}H NMR)) was achieved, compared with the $NaBH_4$ reduction of a similar ketone substrate that only afforded an 1:1 mixture of products.[4e] The subsequent epoxidation was expected to be controlled by the hydroxy group. In fact, after protection of the hydroxy group with TBS, epoxide **16** could be successfully prepared, where the oxygen was delivered from the same side as that of the hydroxy group. We expected at this stage that a cuprate ($CuBr{\cdot}SMe_2$, MeMgBr) attack would enable the nucleophilic ring opening of the epoxide. Unfortunately, the reaction failed, presumably due to the existence of a substituent at the carbon adjacent to the epoxide ring. This forced us to modify the synthetic route.

We decided to introduce the methyl group before the RCM reaction, assuming that the steric hindrance caused by an additional methyl group would be tolerated in the RCM reaction. The synthetic sequence corresponding to this strategy is also summarized in Scheme 2 (**b** series). The desired 2-methyl-substituted α,β-unsaturated ester **9b** was prepared according to the procedure reported in the literature.[5c] Reduction of **9b** followed by Sharpless asymmetric epoxidation afforded the epoxy alcohol **10b** (92% ee, determined by chiral HPLC). Then, allylic alcohol **11b** was prepared by the previously mentioned three-step sequence [(1) Et_3N, MsCl, (2) NaI, THF, reflux, (3) Zn dust, I_2, MeOH, reflux]. Introduction of the glycolic acid followed by attachment of the Evans' chiral auxiliary secured the substrate **7b** for the asymmetric aldol-RCM protocol. Asymmetric aldol reaction was successfully performed in acceptable yield to provide **13b** (dr 12:1 determened by ^{1}H NMR analysis of **6b** (vide infra)).

The synthesis of the key intermediate **5** from **13b** is summarized in Scheme 3. Removal of the chiral auxiliary by reduction now set the stage for the critical RCM reaction. The RCM reaction of the resulting diol using the Grubbs second generation

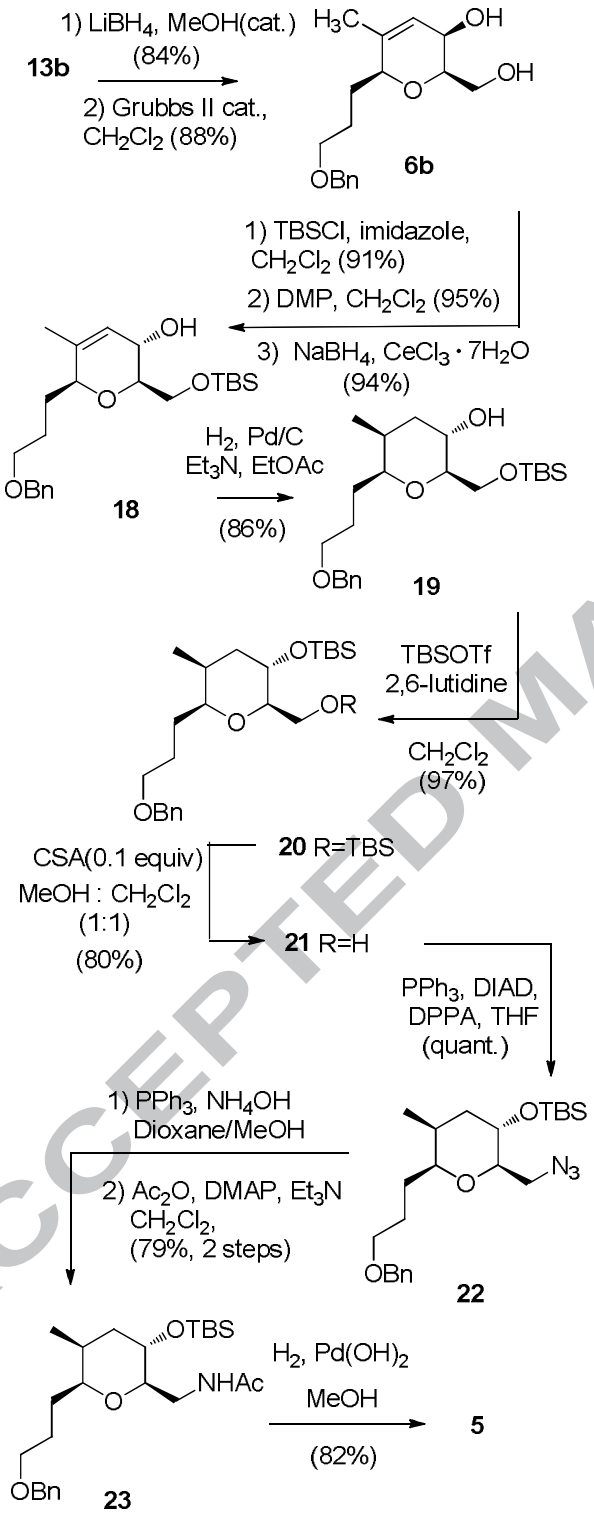
catalyst indeed smoothly afforded the cyclic product **6b**. After protection of the primary hydroxy group of **6b** with TBS, inversion of the carbon stereochemistry bearing secondary hydroxy group by an oxidation-reduction sequence exclusively gave the desired six-membered cyclic allylic alcohol **18** (with >20:1 selectivity (^{1}H NMR)) with a methyl group in good overall yield.

With the desired intermediate **18** in hand, selective reduction of the double bond of **18** was needed, through which the hydrogen atom would come from the same side of the hydroxy group to afford the tetrahydropyran ring with the methyl group *trans* to the hydroxy group. Catalytic hydrogenation of **18** under normal reaction conditions (Pd/C, RT) in EtOAc provided the hydrogenated product with concomitant debenzylation. The product with benzyl group that remained intact could not be obtained. A solvent change from EtOAc to MeOH did not solve the problem. The use of PtO_2, as the hydrogenation catalyst, afforded the desired product in low yield with concomitant debenzylation.

Finally, to our delight, the selective hydrogenation of **18** without debenzylation was achieved by adding Et_3N to the reaction mixture.[10] The desired product **19** was obtained in good yield (86%). After the hydroxy group of **19** was protected (TBSOTf, 2,6-lutidine), the primary hydroxy group of **20** was deprotected under the acidic condition (CSA) to provide alcohol **21**. An azido group was successfully introduced using the Mitsunobu procedure to afford **22**. Next, the azido group was reduced to an amine, which was then acetylated to give **23**. This acetamide **23** is previously known in the literature as an advanced intermediate for the total synthesis of **2**. The spectral data (^{1}H and ^{13}C NMR) of **23** was consistent with those reported in the literature.[4b] Finally, the benzyl group of **23** was removed under the standard conditions, to afford alcohol **5**. The spectral data and the optical rotation value of **5** were in agreement with those reported in the literature.[4b] Because a five-step conversion of **5** to **2** has been reported in the literature,[4b] the synthesis of **5** completes a formal total synthesis of **2**.

In conclusion, a formal total synthesis of (–)-brevisamide, a monocyclic ether amide, was achieved. We successfully synthesized the advanced intermediate **5**, the dihydropyran core of (–)-brevisamide with an overall yield of 4.5% in 23 steps starting from 1,4-butanediol. This was performed by the asymmetric aldol and RCM reaction as the key combination of reactions to construct the desired tetrahydropyran ring with multiple stereocenters. Generation of the dihydropyran ring with a trisubstituted carbon-carbon double bond was achieved by RCM efficiently. Selective hydrogenation was also successfully conducted in the presence of the labile benzyl group, which resulted in the effective installation of the required stereochemistry of the carbon bearing a methyl group on the tetrahydropyran ring as well as the elimination of an additional protection

step for the hydroxy group.



Scheme 3. Completion of the formal total synthesis of brevisamide (**2**) (Synthesis of **5**).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the on line version at _____.

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