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A Concise Asymmetric Total Synthesis of (+)-Brevisamide

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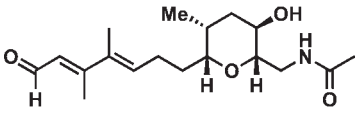
ABSTRACT



(+)-brevisamide

A new protecting-group-free synthesis of the marine monocyclic ether (+)-brevisamide is reported. The enantioselective synthesis utilizes a key asymmetric Henry reaction and an Achmatowicz rearrangement for the formation of the tetrahydropyran ring. A penultimate Stille cross-coupling allows for an efficient installation of the conjugated (*E*,*E*)-diene side chain ultimately delivering (+)-brevisamide.

The art and science of natural product total synthesis has become increasingly more associated with the various priniciples of the "economies" of synthesis.[1,2] Evaluation of protecting group use serves as one metric of synthetic efficiency and can provide a framework for developing a synthesis plan. Among various classes of natural products prepared by total synthesis without the use of protecting groups, examples featuring polyketides or cyclic ethers are scarce.[2,3] Herein, we report a concise, enantioselective, protecting-group-free total synthesis of the diversely functionalized cyclic ether natural product brevisamide.

Brevisamide is a metabolite from *Karenia brevis* comprised of a complex functionalized tetrahydropyran core containing a conjugated 3,4-dimethylhepta-2,4-dienal and acetylated terminal amine subunits. The tetrahydropyran ring also contains methyl and hydroxyl substituents. Brevisamide has been a target of total synthesis for multiple research groups since its recent isolation by Wright and co-workers.[4] By completion of the first total synthesis, the groups of Satake, Tachibana, and Wright provided conclusive evidence for the absolute and relative stereochemistry of brevisamide.[5] Their synthesis is characterized by a stepwise construction of the pyran ring followed by a Suzuki–Miyaura coupling to assemble the dienal fragment. This synthesis required 21 steps in the longest linear sequence, 28 steps total, with an overall yield of 2.0%. In a subsequent paper, Satake and co-workers improved their overall synthetic yield to 8.6%.[5c] Lindsley and co-workers completed the second total synthesis using a different route in which the tetrahydropyran ring was formed by a reductive cyclization with samarium(II) iodide.[6] A Horner–Wadsworth–Emmons reaction was recruited to install the diene fragment. This synthesis was accomplished in 18 steps (longest linear sequence, 21 total) and 6.3% overall yield. Shortly after Lindsley's synthesis, Ghosh and co-workers described an alternative route using an asymmetric hetero-Diels–Alder reaction to form the tetrahydropyran ring of brevisamide. This synthesis provided brevisamide in higher enantiopurity than the prior two and required 23 steps total with the longest linear sequence of 19 steps and a ca. 1.5% overall yield from commercially available starting materials.[7] The last reported total synthesis of brevisamide is described by Panek and Lee. A [4 + 2]

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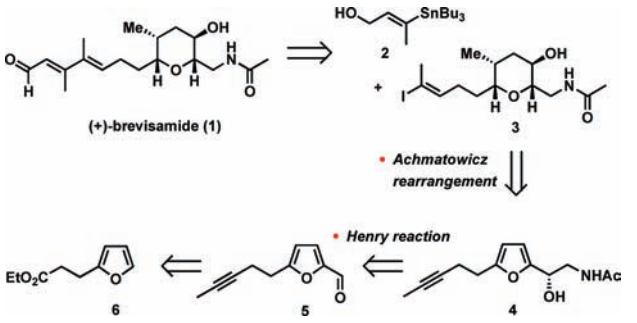
annulation approach utilizing a (*Z*)-crotylsilane was used as a strategic basis for the synthesis. This route provided brevisamide in a 0.8% overall yield in 30 total steps, with the longest linear sequence of 27 steps from commercially available starting materials.[8] Since this latest completed total synthesis, two formal syntheses have been accomplished by the groups of Smith and Sabitha.[9]

In devising our own approach, we became intrigued by the challenge of developing a concise, enantioselective, and protecting-group-free construction of the diversely functionalized tetrahydropyran ring in brevisamide. A synthesis plan based on the combination of a catalytic asymmetric Henry reaction and an Achmatowicz rearrangement,[10] outlined in Scheme 1, proved to be successful in meeting this challenge. The final operation in the synthesis was envisioned to employ a Stille-cross-coupling reaction to install the conjugated (*E,E*)-dieneal.

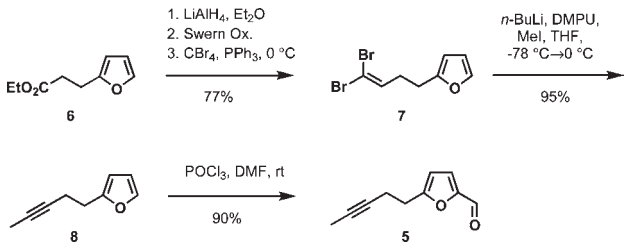
Scheme 1. Synthesis Plan for Brevisamide (**1**)



The synthesis of the aldehyde **5**, shown in Scheme 2, begins from commercially available ethyl 3-(furan-2-yl)-propionate **6**, which was treated with $LiAlH_4$ to afford the corresponding primary alcohol. After oxidation, the resultant aldehyde was immediately submitted to the Corey–Fuchs reaction yielding dibromoalkene **7**,[11] which was treated with *n*-butyllithium and iodomethane to form the desired alkyne **8**, along with a furan methylation byproduct. Addition of DMPU prior to the addition of iodomethane resulted in the isolation of only the desired methylated alkyne **8** in high yield. Aldehyde **5** was prepared directly from **8** by a Vilsmeier–Haack reaction in 90% yield.[12]

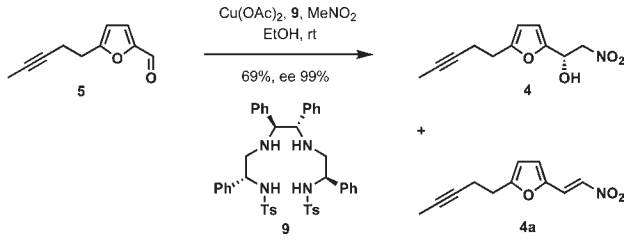
With aldehyde **5** in hand, the key enantioselective Henry reaction was investigated. Although a variety of methods are available for this transformation, we focused on a

Scheme 2. Synthesis of Aldehyde **5**



procedure developed by Wan and co-workers.[13] This method has been reported to provide products in high enantioselectivity, under practical reaction conditions at room temperature and within reasonable reaction times. The method employs a catalytic system derived from readily available $Cu(OAc)_2 \cdot H_2O$ and ligand **9** in ethanol as the solvent. Much to our delight, when **5** was exposed to these conditions, the product **4** was isolated with a 99% ee. Extended reaction times resulted in accumulation of the nitroalkene **4a** as a byproduct resulting from dehydration of the initially formed nitro-alcohol **4** (Scheme 3). To minimize this problem, the reaction was terminated after 40 h at room temperature and the products were separated to provide the requisite Henry addition product **4** (57% yield, 99% ee), the starting material (33% yield), and the nitroalkene **4a** (10% yield). The starting material was then resubmitted to the reaction conditions to afford **4** in a 69% combined yield and 99% ee after one recycle.

Scheme 3. Asymmetric Henry Reaction



After the development of the enantioselective Henry reaction, the synthesis was advanced as illustrated in Scheme 4. The nitro group in **4** was reduced to the corresponding amine with $LiAlH_4$ under carefully controlled reaction conditions. Lithium aluminum hydride was preferred to other commonly used reagents for reduction of nitro compounds such as H_2 and Pd/C, Raney-Nickel, and SmI_2, due to incompatibility of these reagents with the alkyne group present in the substrate.[13,14] After assessment of a variety of reaction conditions, it was determined that a dropwise addition of a solution of the nitro compound **4** into a precooled solution of $LiAlH_4$ in THF (−15 °C) limited the retro-Henry process leading to the formation of an

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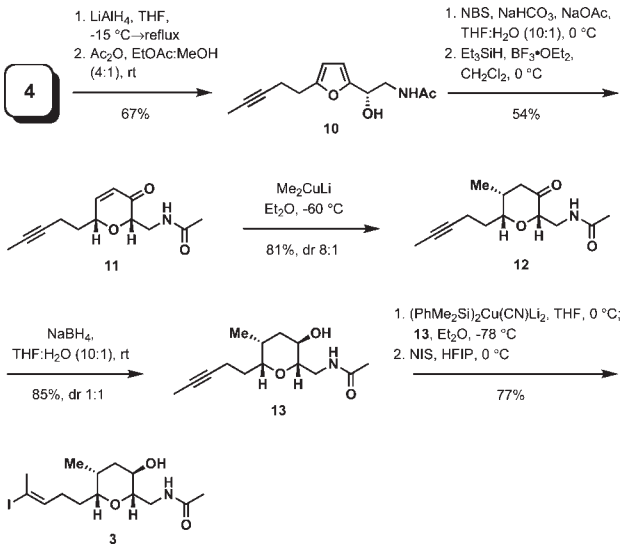
undesired primary alcohol. The reaction was then heated to reflux, which delivered the primary amine in optimized yields. The primary amine was then chemoselectively acetylated with acetic anhydride in ethyl acetate–methanol (4:1), giving amide **10** in 67% yield over the two steps.

Scheme 4. Synthesis of the Tetrahydropyran Core

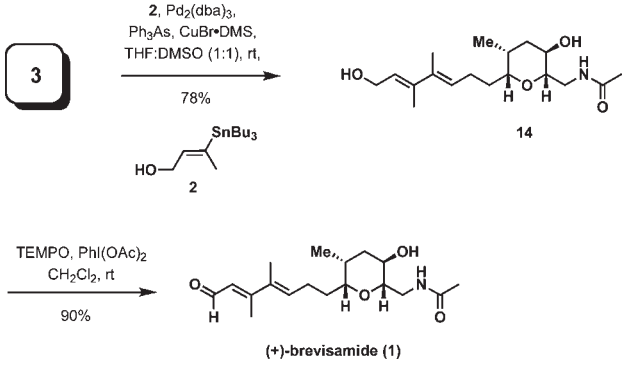


According to our synthesis plan, acetamide **10** was now properly functionalized for the ensuing key Achmatowicz rearrangement. Furan **10** underwent oxidative ring expansion in the presence of NBS to form the cyclic hemiketal, which was then treated with $BF_3 \cdot OEt_2$ and Et_3SiH to produce intermediate **11** in a satisfactory 54% yield.[15] Installation of the methyl group was achieved by conjugate addition of lithium dimethylcuprate directly to enone **11** (81% yield, 8:1 dr).[16]

Our next goal was reduction of **12** under thermodynamic conditions to generate the more stable diastereomer **13** that has the desired configuration at the newly generated stereocenter. Our initial attempts centered on various versions of the Meerwein–Pondorf–Verley (MPV) reaction using Al(OPr-*i*)$_3$ and Sm(OPr-*i*)$_3$ reagents. With the aluminum-based reagent, the desired diastereomer **13** was formed exclusively at high temepratures (100 °C), however, at low yields. An unidentified byproduct was formed in significant quantitites apparently resulting from reactivity of the acetamide. At lower temperatures (75 °C), an equimolar mixture of diastereomeric alcohols was produced. Similar outcomes were observed with the samarium-based reagent. Reduction with sodium borohydride under standard conditions in methanol produced the undesired axial alcohol exclusively. On the other hand, reduction with $NaBH_4$ in aqueous THF substantially increased the fraction of the desired equatorial alcohol, giving a 1:1 mixture of separable products in 85% isolated yield.[17] The undersired isomer could be separated and recycled through an additional oxidation–reduction sequence.

Installation of vinyl iodide proceeded in high regioselectivity and yield employing the silylcupration-iododesylilation protocol.[18,19] Silylcupration took place with complete stereoselectivity and high regioselectivity (~13:1). Subsequent iododesilyation with *N*-iodosuccinimide (NIS) in hexafluoroisopropanol (HFIP) successfully delivered the (*E*)-iodoalkene **3** in high yield and with complete retention of the double bond geometry.[18,20]

Scheme 5. Completetion of Brevisamide (**1**) Synthesis



Known vinyltin reagent **2** (prepared by hydrostannylation of 2-butyn-1-ol)[21] was used in a Stille cross-coupling reaction with **3** to forge the conjugated diene (Scheme 5). Sasaki and co-workers previously reported a similar Stille

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coupling in the total synthesis of brevenal.[20] In our work, copper(I) thiophene-2-carboxylate was replaced with the copper(I) bromide dimethylsulfide complex (CuBr•DMS) without any detrimental effect on the $Pd_2(dba)_3/Ph_3As$-catalyzed cross-coupling process, furnishing **14** in 78% yield. Completion of the synthesis was achieved with a chemoselective oxidation of the allylic alcohol using TEMPO in the presence of $PhI(OAc)_2$ in CH_2Cl_2 at room temperature, yielding (+)-brevisamide (**1**) in 90% yield.[7]

In summary, the total synthesis of (+)-brevisamide (**1**) has been completed in 16 steps (longest linear sequence) and an overall yield of 2.5% starting from the commercially available ethyl 3-(furan-2-yl)propionate **6**. The strategy was developed based on a notion of concise enantioselective assembly of the properly functionalized tetrahydropyran ring without the use of protecting groups. A catalytic asymmetric Henry reaction and then an Achmatowicz rearrangement were enlisted to successfully achieve this goal.

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Supporting Information Available. General experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for compounds **1**–**14**. This material is available free of charge via the Internet at http://pubs.acs.org.