Organic LETTERS

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Substrate-Controlled Asymmetric Total Synthesis and Structure Revision of (−)-Bisezakyne A

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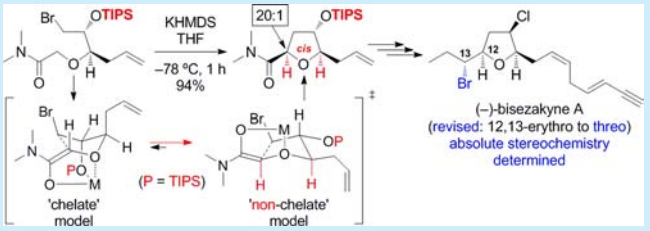
Supporting Information

ABSTRACT: The first asymmetric total synthesis and subsequent structure revision of (−)-bisezakyne A, a Laurencia C_{15} acetogenin from *Alpysia oculifera*, has been accomplished. Our substrate-controlled synthesis of this oxolane natural product features a highly stereoselective "protecting-group-dependent" intramolecular amide enolate alkylation strategy for the synthesis of the key 9,10-*trans*-9,12-*cis*-10-hydroxytetrahydrofuran intermediate through "nonchelate" control. In addition, our synthesis determined the absolute configuration of the halogenated marine natural product.



(−)-Bisezakyne A, a halogenated C_{15} acetogenin, was isolated from an undescribed species of the red algal genus *Laurencia* collected from Japan by Suzuki and co-workers in 1999 (Figure 1).[1] The relative stereochemistry of the trisubstituted tetrahydrofuran core of (−)-bisezakyne A (**1a**) was established by extensive spectroscopic studies. In particular, NOE interactions between the protons on C(9) and C(12) and between the protons on C(10) and C(12) were supportive of the assigned all-*cis* relative stereochemistry of the tetrahydrofuran ring. The positions of the bromine and chlorine atoms were established by the halogen-induced ^{13}C isotope shifts in the ^{13}C NMR spectrum. The C(12)/C(13) *erythro* configuration was tentatively assigned by the biogenetic considerations that **1a** might be derived from (3*E*,12*E*)-laurediol.[1] However, the absolute stereochemistry of this oxolane marine natural product was not assigned yet. To date, the total synthesis of this *Laurencia* marine natural product has not been reported.

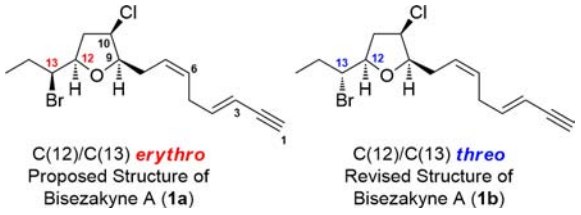
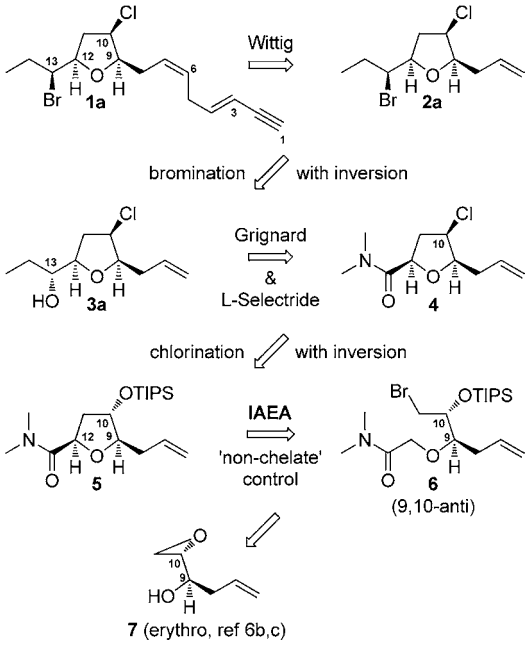


Figure 1. Proposed (**1a**) and revised (**1b**) structures of bisezakyne A.

Herein we describe the first asymmetric total synthesis and structure revision of (−)-bisezakyne A by a highly stereoselective "protecting-group-dependent" intramolecular amide enolate alkylation (IAEA) methodology for the construction of the trisubstituted tetrahydrofuran core in the natural product.[2−4]

We arbitrarily opted to synthesize bisezakyne A with 9*R*,10*R*,12*R* absolute stereochemistry, as depicted in our retrosynthetic plan (Scheme 1), among the two proposed enantiomeric structures for the natural product. We envisioned that the 3,6-dien-1-yne side-chain appendage at C(9) in **1a** could be incorporated through a stereoselective Wittig reaction from **2a**. We further envisioned that the C(13)-bromine function in **2a** could be introduced from alcohol **3a** with inversion of configuration, which in turn could be elaborated from

Scheme 1. Retrosynthetic Plan for Bisezakyne A (1a)



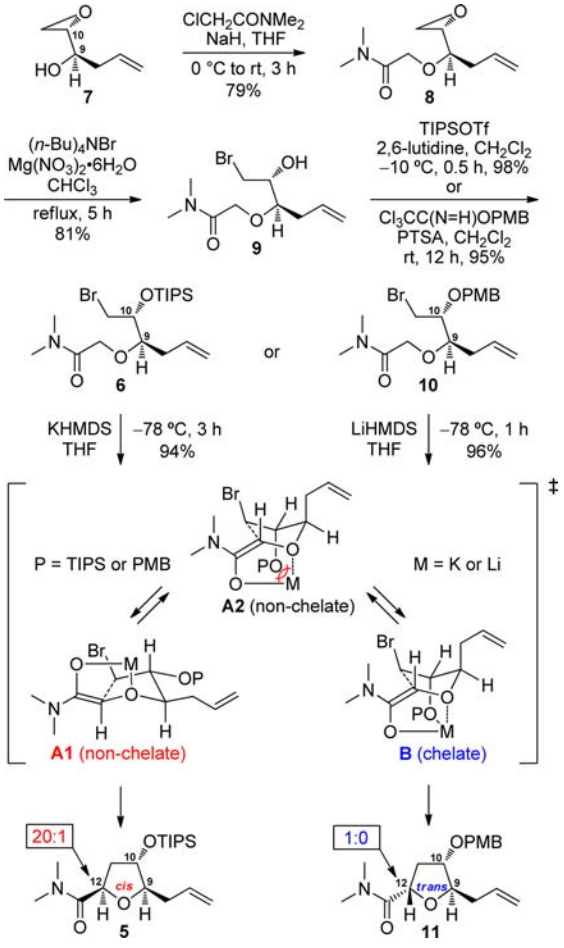
Received: July 30, 2016
Published: August 23, 2016

DOI: 10.1021/acs.orglett.6b02239
Org. Lett. 2016, 18, 4420−4423

tetrahydrofuranyl α-alkoxy dimethylamide **4** by application of a direct ketone synthesis/L-Selectride reduction protocol.[5] The premise that the C(10)-chlorine would be incorporated through chlorination of the corresponding hydroxyl with inversion of configuration necessitates the synthesis of the key 9,10-*trans*-9,12-*cis*-10-hydroxy-THF intermediate **5**. In this regard, we were confident that the crucial trisubstituted THF **5** would be accessible by IAEA of TIPS-protected ω-bromo-α-alkoxyamide **6** through "nonchelate" control (see below). Further analysis indicated that IAEA substrate **6** with 9,10-*anti* relative stereochemistry could be readily accessible from known *erythro*-epoxy alcohol **7** patterned after a three-step sequence formulated in our previous study[2] in a concise and efficient manner.

Our synthesis of key 9,10-*trans*-9,12-*cis*-THF intermediate **5** commenced with *O*-alkylation of known *erythro*-epoxide **7**,[6] prepared by use of the Sharpless kinetic resolution protocol,[6a] with *N*,*N*-dimethylchloroacetamide to afford the corresponding epoxy α-alkoxyamide **8** (Scheme 2). Regioselective opening of

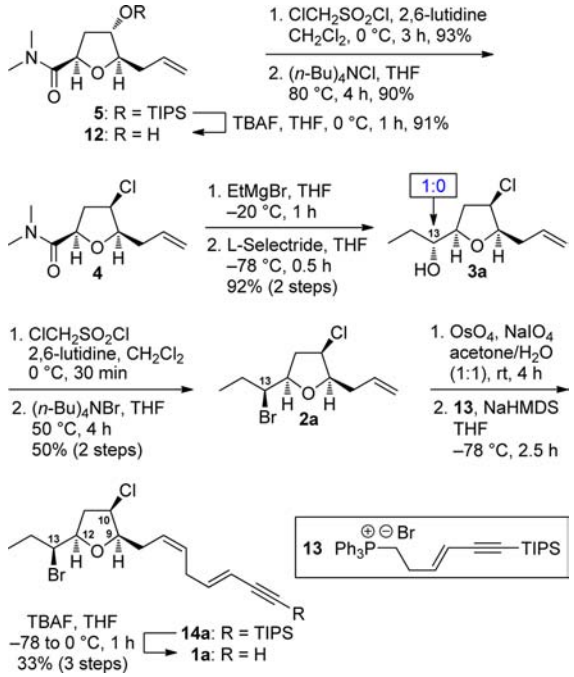
Scheme 2. "Protecting-Group-Dependent" Intramolecular Amide Enolate Alkylation for Key Intermediate 5



terminal epoxide **8** by exposure to $(n\text{-Bu})_4\text{NBr}$ in the presence of $Mg(NO_3)_2{\cdot}6H_2O$[7] followed by protection of the hydroxyl group in the resultant bromohydrin **9** as the TIPS ether[8] afforded key IAEA substrate **6** in good yield and set up the stage for the key intramolecular amide enolate alkylation. Very recently, we demonstrated that each of the four possible diastereomeric 2,5-disubstituted-3-oxygenated tetrahydrofurans could be synthesized by the IAEA strategy in a highly stereoselective fashion through chelate or nonchelate control by a judicious choice of the protecting group of the C(3)-hydroxyl function.[2] As anticipated and happily, treatment of 9,10-*anti*-bromo α-alkoxyamide **6** bearing a TIPS-protected alkoxy group at C(10), which is known to be a poor coordinating group for steric and electronic reasons,[2,9] with KHMDS in THF at −78 °C for 1 h delivered the desired 9,10-*trans*-9,12-*cis*-THF **5** in high yield (94%) and diastereoselectivity (dr = 20:1), presumably via nonchelated transition state geometry **A1**.[10] In addition, the IAEA reaction of PMB-protected bromo amide **10** by treatment with LiHMDS in THF afforded 9,10-*trans*-9,12-*trans*-THF **11** as a single stereoisomer via chelated transition state geometry **B** in excellent yield (96%).

With the key 9,10-*trans*-9,12-*cis*-10-hydroxytetrahydrofuran **5** in hand, we embarked upon the final stage of the synthesis of **1a** as summarized in Scheme 3. To this end, removal of the TIPS

Scheme 3. Synthesis of the Proposed Structure 1a



group in **5** followed by chlorination of the resultant alcohol **12** with inversion of configuration under the modified conditions of Nakata's two-step chloromethanesulfonate-mediated halogenation protocol[11] furnished the desired chloro amide **4** in 76% overall yield for the three steps from **5**. Next, application of the direct ketone synthesis protocol to α-alkoxy dimethylamide **4** with EtMgBr followed by Felkin−Anh L-Selectride reduction of the resultant ketone[12] provided the requisite (13*R*)-alcohol **3a** as a single stereoisomer in 92% yield over two steps. The stereochemistry of C(13) in **3a** was confirmed unambiguously utilizing Kakisawa's extension of Mosher ester analysis.[13] Introduction of a bromine function at C(13) of alcohol **3a** with inversion was effected in a manner analogous to the above-described chlorination of **12** to furnish (13*S*)-bromide **2a** in 50% yield over two steps.

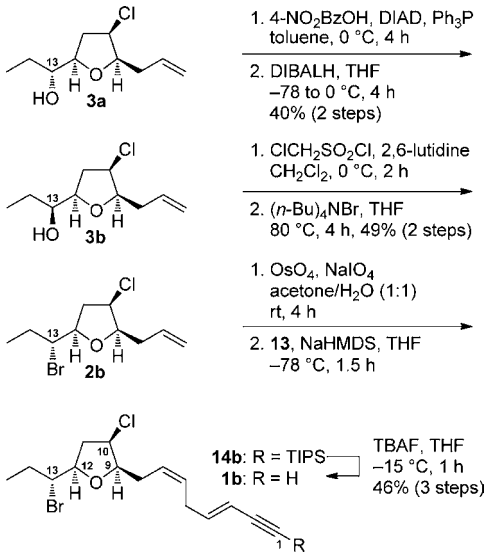
With both halogen atoms installed successfully, the remaining task was the assembly of the unsaturated C(9) 3,6-dien-1-yne side-chain appendage. Thus, incorporation of the 3,6-dien-1-yne side-chain appendage by Lemieux−Johnson oxidation[14] of terminal olefin **2a** followed by stereoselective Wittig olefination

DOI: 10.1021/acs.orglett.6b02239
Org. Lett. 2016, 18, 4420−4423

of the resulting aldehyde with **13**[15] by treatment with NaHMDS in THF at −78 °C for 2.5 h gave rise to (6*Z*)-TIPS-enyne **14a**. Removal of the TIPS group in enyne **14a** by exposure to TBAF produced bisezakyne A (**1a**) in 33% overall yield for the three steps from **2a**. Unfortunately, the ^{1}H NMR spectrum of synthetic **1a** did not match that of natural bisezakyne A.

Careful examination of NMR data, coupled with biogenetic considerations (see below), led to the possibility that bisezakyne A might possess a (13*R*) configuration. On the basis of this assumption, we set out to synthesize the C(13) epimer of **1a**, as shown in Scheme 4. In the event, Mitsunobu reaction[16] of (13*R*)-

Scheme 4. Asymmetric Total Synthesis and Structure Revision of (−)-Bisezakyne A



alcohol **3a** with *p*-nitrobenzoic acid followed by reductive removal of the PNB group in the resulting Mitsunobu product furnished 13(*S*)-alcohol **3b**. Finally, **3b** was converted into **1b**, the (C13) epimer of the proposed structure of bisezakyne (**1a**), by a five-step sequence analogous to that employed for the synthesis of **1a** described in Scheme 3. The spectral data of our synthetic **1b** were in good agreement with those reported for natural (−)-bisezakyne A (Figure 2).

On the basis of the synthesis, the relative structure of natural (−)-bisezakyne A should be revised to **1b** shown in Scheme 4. Moreover, the value of the optical rotation of synthetic **1b** (*c* 0.14, $[\alpha]_D^{23}$ −5.56) was also in accordance with that of the natural product (*c* 0.33, $[\alpha]_D^{22}$ −7.13), thus determining the absolute configurations of C(9), C(10), C(12), and C(13) of (−)-bisezakyne A as *R*, *R*, *R*, and *R*.

Our asymmetric total synthesis of (−)-bisezakyne A (**1b**) with the determination of its relative and absolute stereochemistry suggests a plausible biosynthetic pathway[11d,17] for the C_{15} *Laurencia* natural product involving (3*E*,12*Z*,9*R*,10*S*)-laurepoxide (**15**) in contrast to the originally proposed (3*E*,12*E*)-laurediol (Scheme 5). It is of note that these biogenetic precursors might be present in nature as an unequal mixtures of (3*E*/*Z*,12*E*/*Z*) stereoisomers.[18] Regioselective opening of laurepoxide **15** at C(10) followed by the action of bromide and a bromoperoxidase (BPO) on the resultant chlorohydrin[19] would lead to bromonium ion intermediate **C**, which would undergo cyclization in a 5-*exo* fashion to give the natural product. An alternative biogenetic pathway might involve a concerted

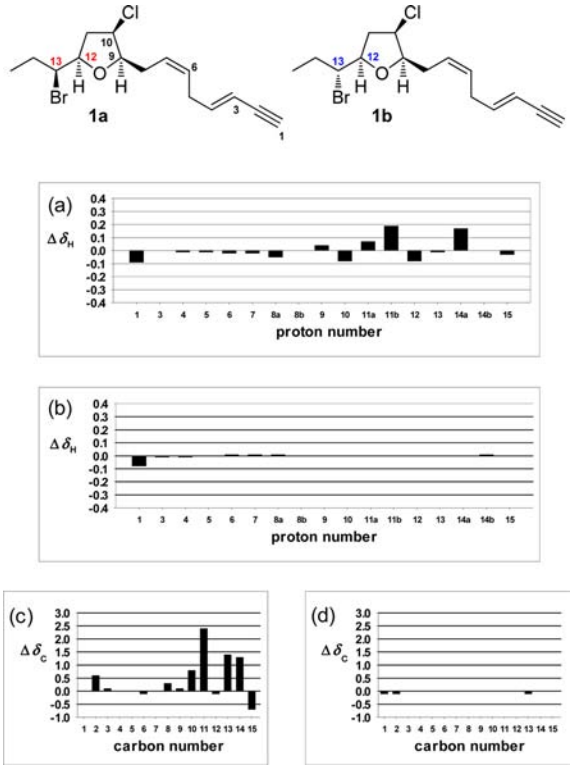
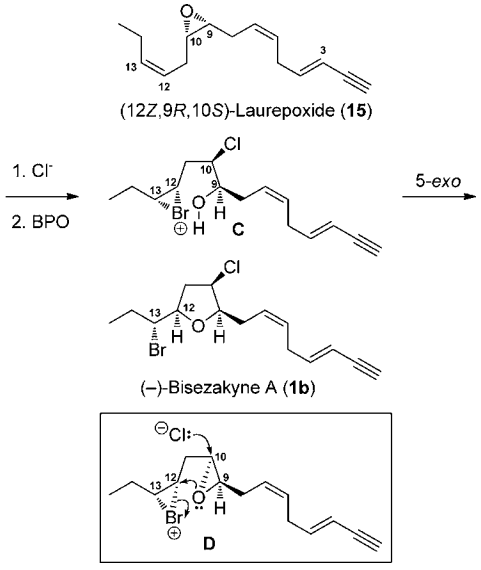


Figure 2. Chemical shift differences between the synthetic compound (**1a** or **1b**) and the natural product (NP). The *x* axis represents the proton or carbon number, and the *y* axis shows the chemical shift differences in ppm. (a) $\Delta\delta_H$ = **1a** − NP. (b) $\Delta\delta_H$ = **1b** − NP. (c) $\Delta\delta_C$ = **1a** − NP. (d) $\Delta\delta_C$ = **1b** − NP.

Scheme 5. Plausible Biogenetic Pathway to 1b



process via a bromonium ion-assisted epoxide opening with concurrent attack by chloride as an external nucleophile as depicted in **D**, as postulated recently by Braddock and co-workers.[20]

In summary, we have accomplished the first asymmetric total synthesis and structure revision of (−)-bisezakyne A (**1b**) featuring a highly stereoselctive intramolecular amide enolate alkylation of TIPS-protected 2,3-*anti*-bromo α-alkoxyamide **6** to construct key 9,10-*trans*-9,12-*cis*-tetrahydrofuran intermediate **5**

DOI: 10.1021/acs.orglett.6b02239
Org. Lett. 2016, 18, 4420−4423

through nonchelate control and efficient construction of C(12) bromopropyl and C(9) (3*Z*,6*E*)-dien-1-yne appendages. In addition, our synthesis determined the absolute configuration of the natural (−)-bisezakyne A.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02239.

Experimental procedures, spectroscopic and analytical data, and copies of ^{1}H and ^{13}NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (NRF-2014R1A1A2056603).

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