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# Total Synthesis of (+)-Vibsanin A

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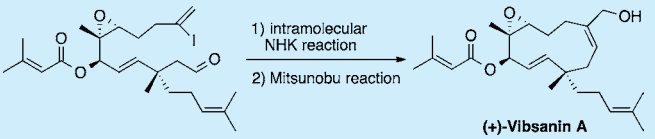
Supporting Information

**ABSTRACT:** The first total synthesis of (+)-vibsanin A, an 11-membered vibsane diterpenoid, was achieved, unambiguously establishing its relative and absolute stereochemistry. Highlights of the synthesis include the stereoselective formation of an all-carbon quaternary stereocenter by a zinc-mediated Barbier-type allylation in an aqueous medium, and the efficient construction of an 11-membered ring skeleton by a combination of an intramolecular Nozaki–Hiyama–Kishi (NHK) reaction and a Mitsunobu reaction.




Vibsane diterpenoids occur in only *Viburnum* species, and more than 80 compounds have been found so far.[1] Vibsanins A–F, **1**–**6**, were first isolated by Kawazu in 1980 from the leaves of *Viburnum awabuki*, which was previously used in Japan as a fish poison for fishing.[2] Only vibsanin A **1** showed piscicidal activity against *Oryzias latipes* (killifish). These diterpenoids can be divided into 11-membered ring compounds **1**, **2**, and **6** and 7-membered ring compounds **3**, **4**, and **5**. Representative vibsane diterpenoid **1** possesses a unique 11-membered ring skeleton that contains an epoxy ring, two unsaturated double bonds, and four stereogenic centers including an all-carbon quaternary center. In the original characterization, the stereochemistry of **5** was determined by single-crystal X-ray diffraction analysis.[3] Later, the absolute structures of **2**, **3**, and **6** were established by Fukuyama and co-workers through X-ray analysis of a derivative of **2**, chemical conversion of **2** into **3**, and synthesis of the unnatural diastereomer (6-*epi*-isomer) of **6**.[4] On the basis of these structural studies, the assumed stereochemistry of **1** is shown in Figure 1. Fukuyama and co-workers isolated rearranged vibsane diterpenoids (neovibsanins) from the same plant and observed their neurite outgrowth-promoting activity.[5] Recently, vibsane diterpenoids have attracted the attention of synthetic chemists, and the total syntheses of 7-membered ring and rearranged visbane diterpenoids have been reported.[6] However, the total synthesis of 11-membered ring vibsane diterpenoids has not yet been reported. Vibsanin A **1** is a synthetically challenging target due to its highly functionalized 11-membered ring skeleton, and it is an attractive target due to the broad bioactivity of vibsane diterpenoids.[1] Here we describe the first total synthesis of **1** and thereby unambiguously establish the relative and absolute stereochemistry of natural (+)-vibsanin A.

The development of novel and efficient methods for the synthesis of 11-membered carbocycles is an important challenge in synthetic organic chemistry. A number of methods have been reported for synthesizing natural products based on 11-membered skeletons.[7] For example, Corey and co-workers succeeded in the total synthesis of humulene by using a Ni-mediated ring closure.[7a] Yamamoto and co-workers used a Tsuji–Trost reaction for achieving the highly stereoselective synthesis of humulene.[7b] Also in Fukuyama's synthesis of the diastereomer (6-*epi*-isomer) of vibsanin F **6**, a Tsuji–Trost reaction was employed to form the 11-membered ring.[4b] However, the newly formed trisubstituted olefin (C2–C3 double bond) had the *Z*-configuration, which had to be converted to the *E*-configuration. Accordingly, the development of new synthetic methods for 11-membered vibsane diterpenoids is needed. Our retrosynthetic analysis of (+)-vibsanin A **1** is shown in Scheme 1. The design of our synthetic plan relied on the combination of an intramolecular

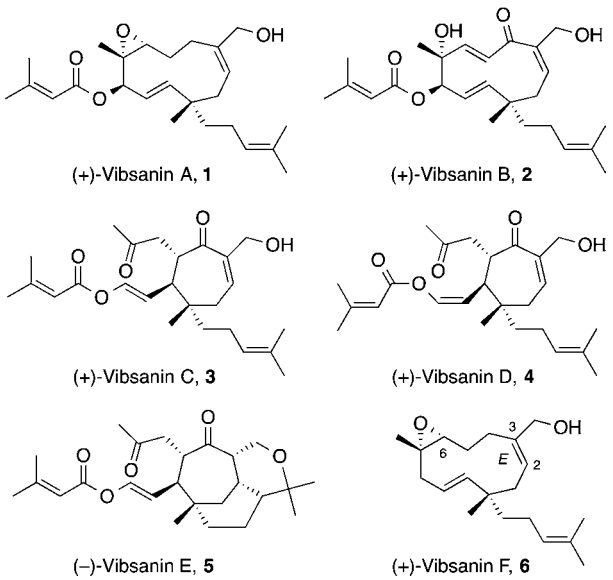



**Figure 1.** Structures of vibsanins A–F, **1**–**6**.

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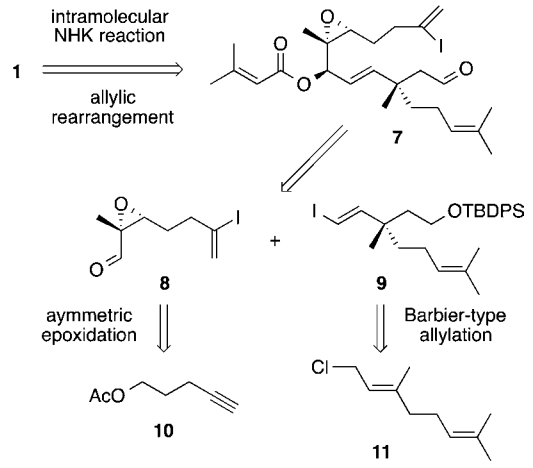
**Scheme 1. Retrosynthetic Analysis of (+)-Vibsanin A 1**

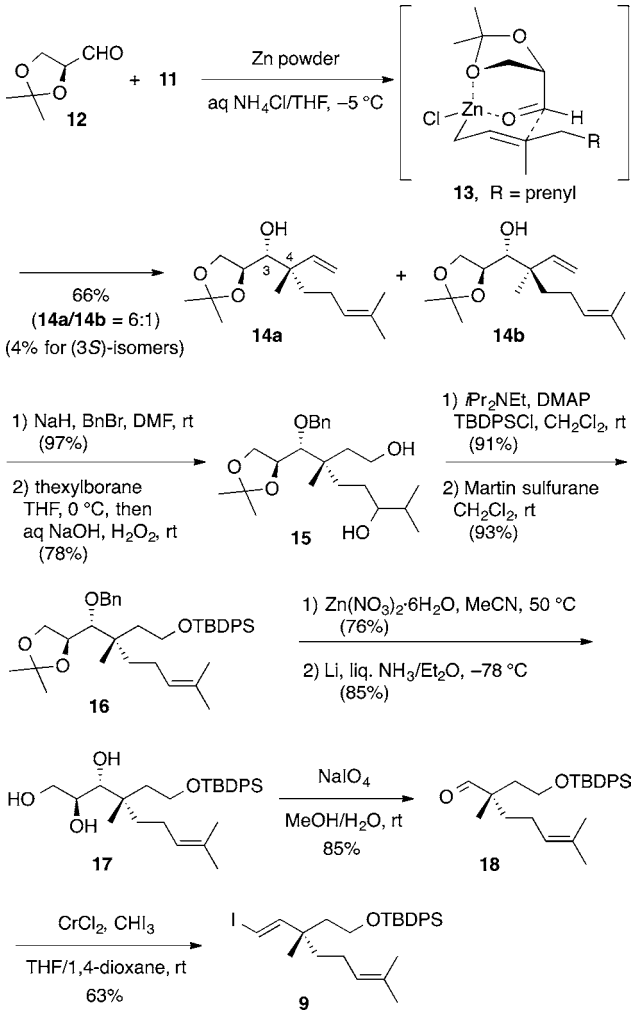



Nozaki–Hiyama–Kishi (NHK) reaction and an allylic rearrangement to assemble the 11-membered ring. The intramolecular NHK reaction is a powerful cyclization method that has given good results in some difficult cases.[8,9] We expected that the NHK reaction would enable the efficient formation of the 11-membered ring skeleton of **1**. Substrate **7** for the key NHK reaction would be obtained by coupling fragments **8** and **9**, both containing an alkenyl iodide moiety. This convergent strategy could potentially streamline the synthetic route. We envisaged that upper fragment **8** would arise from commercially available 4-pentynyl acetate **10** through an asymmetric epoxidation, whereas lower fragment **9** would be derived from geranyl chloride **11** using our previously established procedure involving a Barbier-type allylation.[10]

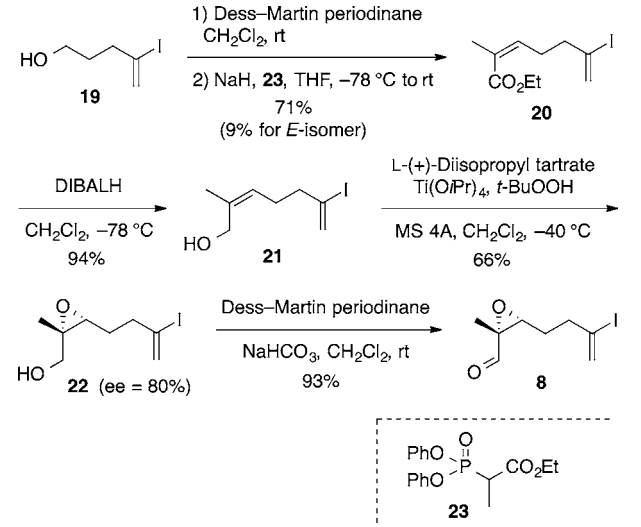
The synthesis of lower fragment **9** began with the construction of the all-carbon quaternary stereocenter (Scheme 2). Quaternary stereocenters are a particular challenge for stereoselective synthesis.[11] This stereocenter was formed by a zinc-mediated Barbier-type allylation in an aqueous medium[10] of L-glyceraldehyde acetonide **12**[12] with geranyl chloride **11** to generate a 6:1 mixture of diastereomers favoring desired (4*S*)-isomer **14a**.[13] In this reaction, readily available L-ascorbic acid-derived **12** was employed as a chiral source. The stereochemical outcome obtained from the reaction can be explained using the *β*-chelation/6-membered model **13**.[14] Benzylation of **14ab** followed by hydroboration with thexylborane and an oxidative workup provided diol **15** with high regioselectivity.[15] Before hydroboration, protection of the C3-OH of **14ab** was required to ensure the desired regioselectivity. The minor diastereomer derived from **14b** was removed at this stage. The primary alcohol was selectively protected as a *tert*-butyldiphenylsilyl (TBDPS) ether, and treatment of the resulting secondary alcohol with Martin sulfurane ($Ph_2S[OC(CF_3)_2Ph]_2$)[16] regenerated the trisubstituted olefin to furnish **16** as a single isomer.[17] Selective hydrolysis of the isopropylidene acetal[18] in **16** and deprotection of the benzyl group under Birch conditions afforded triol **17**. Oxidative cleavage of **17** provided aldehyde **18**, which was subjected to Takai olefination[19] to provide enantiomerically pure fragment **9**.

Upper fragment **8** was prepared from known iodo olefin–alcohol **19**, which can be obtained from 4-pentynyl acetate **10** in two steps (Scheme 3).[20] Alcohol **19** was oxidized with Dess–Martin reagent[21] to an aldehyde, which was treated with Ando reagent **23**[22] to give unsaturated ester **20** with good *Z*

**Scheme 2. Synthesis of Lower Fragment 9**




**Scheme 3. Synthesis of Upper Fragment 8**




selectivity. Reduction of **20** with DIBALH provided allylic alcohol **21**, and then asymmetric epoxidation of **21** was examined. Although moderate enantioselectivity (70% ee) was observed for the Sharpless asymmetric epoxidation under catalytic conditions, stoichiometric conditions improved the



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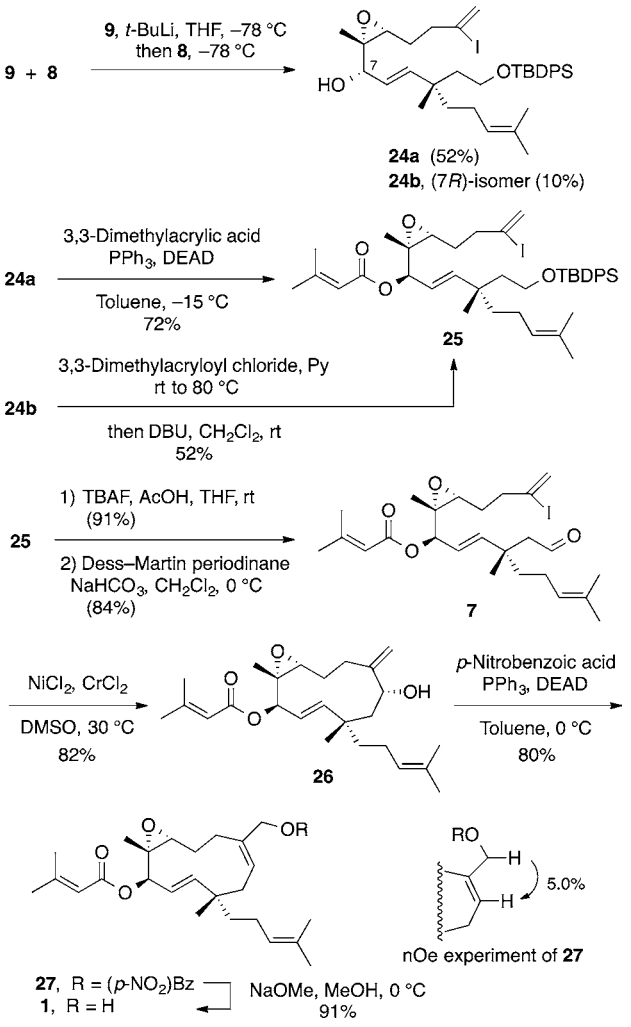
enantioselectivity to provide epoxide **22** in 80% ee.[23,24] Finally, oxidation of **22** to an aldehyde afforded desired upper fragment **8** in an enantioenriched form.

The upper and lower fragments were coupled by converting alkenyl iodide **9** into the alkenyl lithium intermediate using *t*-BuLi and the subsequent addition of 2 equiv of aldehyde **8** (Scheme 4).[25] The coupled products **24a** and **24b** were

**Scheme 4. Completion of the Total Synthesis of (+)-Vibsanin A 1**




obtained in 52% and 10% yields, respectively, and unreacted **8** was recovered with good mass balance. In this case, the lithium–halogen exchange of **8** was not observed. Because the newly formed stereogenic center in major isomer **24a** possessed the opposite configuration to the synthetic target,[26] esterification of **24a** under Mitsunobu conditions was explored.[27] Although 3,3-dimethylacrylic acid was not a strong acid, the Mitsunobu reaction with **24a** proceeded smoothly in toluene at −15 °C,[28] giving desired ester **25** with configurational inversion. Unexpectedly, acylation of the minor isomer **24b** proved to be problematic. Direct acylation using 3,3-dimethylacrylic acid or 3,3-dimethylacryloyl chloride under standard conditions caused the double-bond isomerization of the 3,3-dimethylacryloyl moiety to give an inseparable mixture of **25** and the $\beta,\gamma$-unsaturated isomer.[29] However, the $\beta,\gamma$-unsaturated isomer was converted to **25** by treatment with a base.[30] Removal of the TBDPS group from **25**, followed by oxidation of the resulting primary alcohol, furnished aldehyde **7**.

With iodo olefin–aldehyde **7** in hand, we then turned our attention to the intramolecular NHK reaction. To our delight, treatment of dilute solution of **7** (0.005 M) in DMSO with $CrCl_2$ and catalytic $NiCl_2$ effected formation of the 11-membered ring and provided the cyclized product **26** as a single isomer.[31] At this stage, the diastereomer derived from the minor enantiomer of **8** was separated by column chromatography, allowing the isolation of diastereomerically pure **26**. As expected, the allylic rearrangement of **26** to **27** was achieved by the Mitsunobu reaction using *p*-nitrobenzoic acid.[32] The newly formed trisubstituted olefin in **27** was determined to have the *E*-configuration by an NOE experiment, as shown in Scheme 4. Consequently, the intramolecular NHK reaction followed by the Mitsunobu reaction allowed us to construct the challenging 11-membered ring skeleton of vibsanin A with the correct stereochemistry. Chemoselective methanolysis of diester **27** finally afforded (+)-vibsanin A **1**. The spectroscopic data ($^1H$ and $^{13}C$ NMR) of natural **1** and synthetic **1** matched well.[33] The optical rotation of synthetic **1** was consistent with that reported for the natural product.[2]

In summary, we have achieved the total synthesis of (+)-vibsanin A **1**. To our knowledge, this is the first successful synthesis of a natural 11-membered vibsane diterpenoid. The key features of the synthesis are a zinc-mediated Barbier-type allylation of chiral aldehyde **12** with geranyl chloride **11** to form the all-carbon quaternary stereocenter, and the combination of an intramolecular NHK reaction and a Mitsunobu reaction to construct the functionalized 11-membered ring skeleton. This work has unambiguously established the absolute structure of natural (+)-vibsanin A. Further application of the methodology to the synthesis of other 11-membered vibsane diterpenoids is currently in progress and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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(32) For examples of the Mitsunobu reaction involving an allylic rearrangement, see ref 27b.
(33) For the spectroscopic comparison of natural and synthetic **1** ($^{1}$H and $^{13}$C NMR), see the Supporting Information.



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