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Progress toward the Total Synthesis of Bielschowskysin: A Stereoselective [2 + 2] Photocycloaddition

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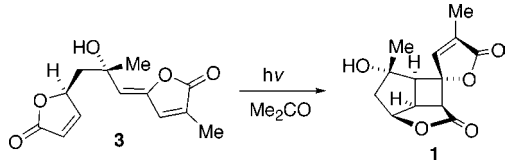
ABSTRACT



The tetracyclic core of the diterpene bielschowskysin has been prepared as a single enantiomer via a stereoselective intramolecular [2 + 2] photocycloaddition of 5-alkylidene-2(5*H*)-furanone 3.

Gorgonian octacorals are the most plentiful source of octacorals in the West Indies. With over 190 documented species in this family, these marine organisms have proven to be an excellent source of biologically active metabolites.[1] Recently, there has been interest in the reef-dwelling sea plume *Pseudopterogorgia kallos* as it has been shown to produce a wide range of structurally interesting diterpenes displaying a broad spectrum of bioactivities.[2]

Rodriguez and co-workers have reported the isolation of the novel diterpene bielschowskysin (Figure 1) from *P. kallos* collected near Old Providence Island off the coast of Columbia.[3] Bielschowskysin is a highly oxygenated hexacyclic diterpene that incorporates 11 stereocenters (seven contiguous) and a novel [9.3.0.0^{2,10}] tetradecane ring system.

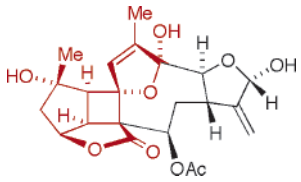


Figure 1. Structure of bielschowskysin.

While the relative configuration has been established via X-ray crystal analysis, the absolute configuration has yet to be assigned.

Bielschowskysin demonstrated strong in vitro cytotoxicity against small cell lung cancer and renal cancer cells.[3] Furthermore, it exhibits antiplasmodial activity against *Plasmodium falciparum* with an $IC_{50} = 10\ \mu g/mL$. Owing to its intriguing architecture and our interest in the design of synthetic strategies for the purpose of investigating biological properties of natural products, we are currently exploring a route toward the synthesis of this diterpene and

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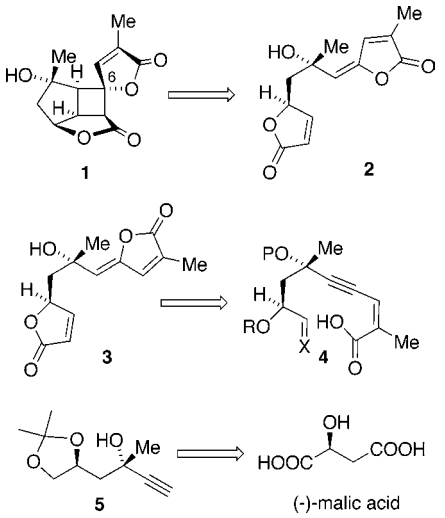
herein report the preparation of the tetracyclic core (**1**) of bielschowskysin employing a stereoselective intramolecular [2 + 2] photocycloaddition.

We reasoned that the congested tetracyclic intermediate **1** would be a good candidate for construction via an intramolecular [2 + 2] photocycloaddition of the appropriate 5-alkylidene-2(5*H*)-furanone **2** (Scheme 1). Here, a key issue

Scheme 1

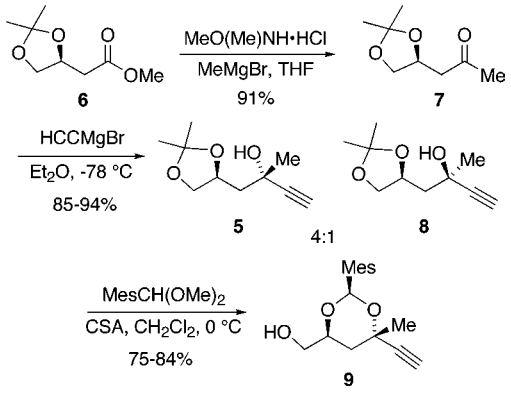


to be addressed was the stereoselectivity of the photocycloaddition and its dependence on the starting double bond geometry (vis à vis **2** and **3**). In the forward sense, the *Z*-olefin **3** would be readily accessed by a silver-catalyzed cycloisomerization of eneyne **4**. Irradiation of **3** was anticipated to rapidly lead to a mixture of double bond isomers **2** and **3**.[4] The overall stereoselectivity of the cycloaddition, particularly the configuration of the C6 quaternary carbon (cf. **1**), would need to be determined by experimentation. The carboxylic acid **4** was anticipated to be generated from alkynyl alcohol **5**, which itself may be prepared from (−)-malic acid.

The ester **6** has been prepared previously starting from malic acid and served as the starting point for the synthesis.[5] It was converted directly to the methyl ketone **7** via in situ formation of the Weinreb amide and reaction with methylmagnesium bromide.[6] Chelation-controlled addition of ethynylmagnesium bromide to ketone **7** was achieved in good yield and selectivity to provide a 4:1 mixture of alcohols **5** and **8** (Scheme 2).

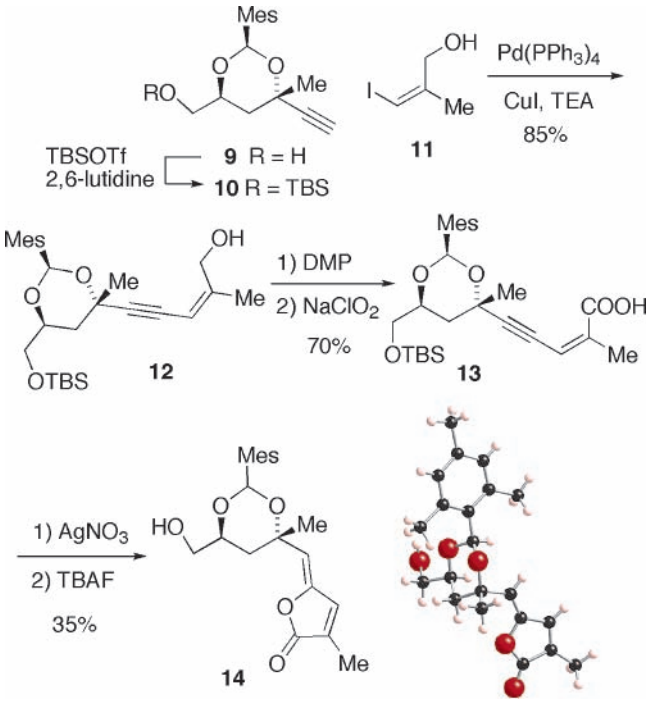
As our synthetic strategy developed, we required protection of the tertiary and secondary alcohols of **5** and unique differentiation of the remaining primary alcohol. Meyers and co-workers reported that treatment of an acetonide-protected triol, related to **5**, with mesitaldehyde dimethyl acetal under acidic conditions led to exchange of the acetonide group for a 1,3-dioxane leaving the primary alcohol uprotected.[7] Indeed, treatment of **5** with camphorsulfonic acid and mesitaldehyde dimethyl acetal affected exchange of the five-membered acetonide ring for 1,3-dioxane acetal to give alcohol **9** with the desired protecting group pattern.

Scheme 2



Silyl protection of the primary alcohol **9** was undertaken in order to examine elaboration of the terminal acetylene to the γ-alkylidene butenolide moiety. This was to be followed by release of the primary alcohol and construction of the second butenolide ring (cf. **3**, Scheme 1). To this end, Sonogashira coupling with *Z*-vinyl iodide **11**[8] was followed by a standard two-step oxidation leading to carboxylic acid **13** (Scheme 3). Silver-catalyzed cyclization yielded γ-alky-

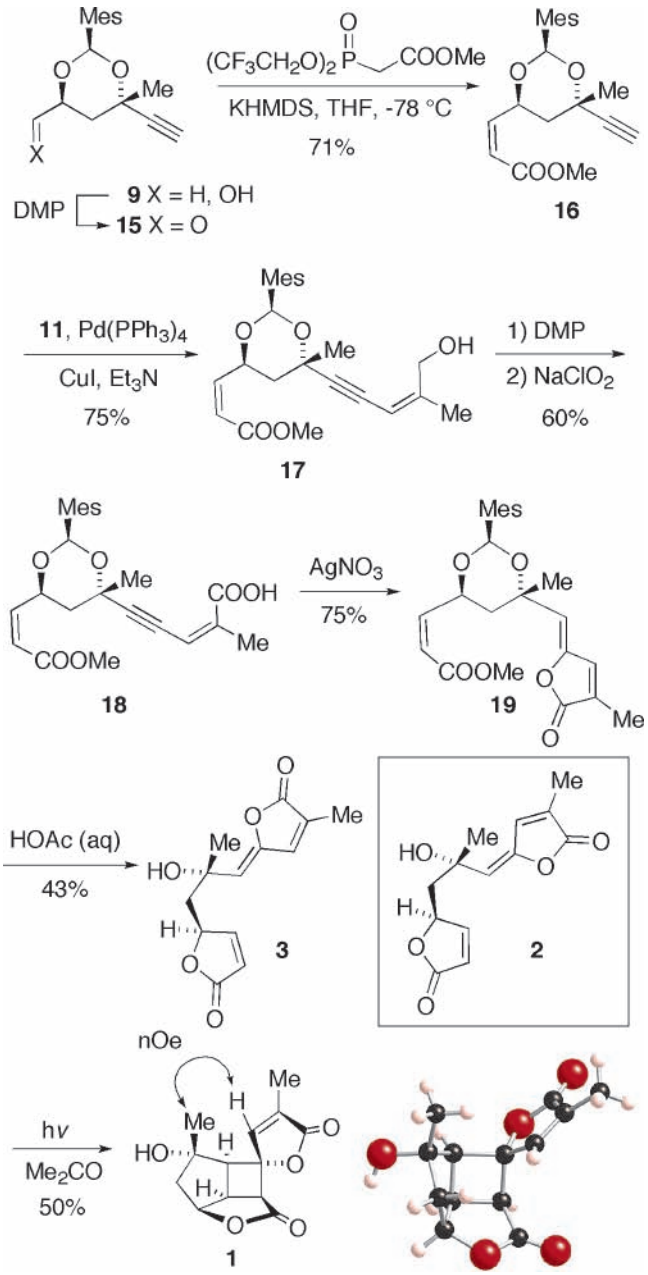
Scheme 3



lidene buteneolide **14** as a crystalline solid.[9] X-ray analysis of this product confirmed the assigned configuration of the stereocenter resulting from the alkyne addition to ketone **7** as well as the double-bond geometry of the γ-alkylidene butenolide produced from the cycloisomerization of **13**. Unfortunately, elaboration of alcohol **14** to butenolide **3** proved to be difficult, and this approach to **3** was abandoned.

A second approach to bis-butenolide **3** that circumvents difficulties encountered in our first reaction sequence is shown in Scheme 4. Experience demonstrated that early

Scheme 4



Still−Gennari olefination[10] resulted in higher yields and stereoselectivity when compared to olefination reactions *after* construction of the γ-alkylidene butenolide (vide supra). Also, delayed completion of the butenolide avoided undesired Michael addition of the tertiary alcohol to the neighboring butenolide. Therefore, *Z*-enoate **16** was directly subjected to Sonogashira coupling conditions to yield allylic alcohol **17**. Consecutive oxidations afforded the carboxylic acid **18** in acceptable overall yield. Silver nitrate catalyzed cyclization under Negeshi's conditions afforded alkylidene buteneolide **19** as a single geometric isomer. Finally, treatment of mesityl-

ene acetal **19** with aqueous acetic acid at room temperature led to butenolide formation and completion of **3**.

Irradiation of a chloroform solution of **3** with a sun lamp for 2 h led to an approximately 3.6:1 mixture of geometric isomers **3** and **2** as determined by ^{1}H NMR analysis. Continued irradiation of a chloroform solution of **3** and **2** resulted in consumption of both isomers and production of a complex mixture of products. Upon replacing chloroform with acetone, a similar equilibration−cyclization sequence was observed on irradiation with a sun lamp; however, in this case far fewer side products were observed. Moreover, a 5:1 mixture of [2 + 2] photoadducts was isolated in 50% yield with the major product assigned the structure of the desired photoadduct **1**. Initially, the stereochemical assignment of **1**, and most significantly the C6 sterecenter, rested on an observed NOE between the β hydrogen of the butenolide and the endo-oriented methyl group. The assignment of **1** was later confirmed by single-crystal X-ray analysis (Scheme 4).

The intramolecular [2 + 2] photocycloaddition of butenolides **2** and **3** likely follows the so-called rule of five leading to intermediate 1,4-biradicals **2a** and **3a** (Figure 2), respec-

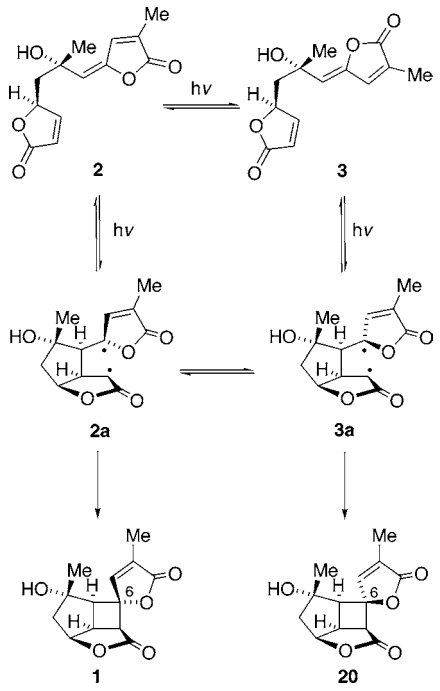


Figure 2. Model for observed diastereoselectivity of [2 + 2] photocycloaddition.

tively.[11] Weedon and Maradyn, who trapped triplet 1,4-biradicals using hydrogen selenide, provided evidence for the intermediacy of 1,4-biradicals and the appropriateness of the rule of five in intramolecular photocycloadditions.[12] Extending this model to substrates **2** and **3**, triplet 1,4-

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biradicals **2a** and **3a** could interchange by one of two mechanisms. First, simple bond rotation could lead to rapid interconversion of triplet biradicals **2a** and **3a**. A second pathway involves simple reversion of **2a** and **3a** to starting γ-alkylidene butenolides **2** and **3**, respectively, which our photochemical experiments showed interchange by simple photoisomerization. By either of these two mechanisms the favored production of photoadduct **1** by closure of **2a** may be explained by the development of unfavorable dipole and/or electrostatic interactions in the alternative closure of 1,4-biradical **3a** to **20**.[13]

In conclusion, we have described a concise and stereocontrolled assembly of the tetracyclic core (**1**) of the marine diterpene bielschowskysin. Current efforts are directed toward completion of the total synthesis of bielschowskysin using the reported photocycloaddition as a key step.

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Supporting Information Available: Full characterization data and experimental procedures for **1**, **3**, **5**, **9**, and **15**−**19**. X-ray data for compounds **1** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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