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Synthesis of Montiporynes A and B

Traci Jenelle Speed
Colby College

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Synthesis of Montiporynes A and B

Traci Jenelle Speed

A thesis submitted to the Chemistry Department at Colby
College, Waterville, ME in partial fulfillment of the
requirements for graduation

with

HONORS IN CHEMISTRY

May 24, 2003

A handwritten signature in black ink, appearing to read 'Dasan', written over a horizontal line.

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Assistant Professor of Chemistry

A handwritten signature in black ink, appearing to read 'Jeffrey L. Katz', written over a horizontal line.

Jeffrey L. Katz, Ph.D.
Assistant Professor of Chemistry

The development of organic synthesis during a period of a little over one hundred years has afforded efficient industrial methods for the preparation of paints and dyes, pharmaceuticals and vitamins, insecticides and herbicides, which increase our harvests, plastics and textile fibers, which clothe humanity. Organic synthesis has contributed to the high standards of living and health and the longevity enjoyed at least in the Western world.

--Salo Gronowitz

The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them.

--Sir William Bragg

In loving memory of Gram
for all the love you gave me
and dedicated to Mom, Dad, and Brent
for teaching me how to reach for the stars.

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I thank my parents, William and Sharon Speed, for their unconditional love and support. They continuously offer me strength, guidance, wisdom, and the encouragement to strive for success. I could not have come this far without the morals and principles they have instilled in me. I also thank my brother, Brenton Speed, for his love and support and for always having the ability to make me laugh. I feel so blessed to have such an extraordinarily intelligent and talented brother.

I also thank the faculty and staff of the Colby College Chemistry department. Just as Keyes has become my second home, they have become my second family. They have challenged me, encouraged me, and prepared me well to further my educational career. I am very fortunate to have had Tom Shattuck, Brad Mundy, Julie Millard, and Das Thamattoor as my professors. In particular, my research advisor, Das Thamattoor has truly made my experience at Colby College unforgettable. Working with him in the organic chemistry laboratory has been deeply rewarding. His passion for teaching has inspired me and provided me with the determination to succeed. I am eternally grateful for his time, motivation, and especially, his friendship and honesty.

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VITAE

Traci Jenelle Speed was born in Hartford, CT on December 29, 1981 to William and Sharon Speed. Five and one half years later she was blessed with her younger brother, Brenton Speed. Raised in Rocky Hill, CT, she fondly remembers lazy summer afternoons watching television and making arts and crafts with her Gram. She graduated from Rocky Hill High School as captain of the girl's varsity tennis team and President and Valedictorian of the Class of 1999.

She entered Colby College in September 1999 eager to pursue a major in Chemistry. Exuding her passion for organic chemistry, she began research with Dr. Dasan Thamattoor during the summer after her sophomore year. With her hard work and dedication she has managed to convince others that she is a capable chemist. During her four years at Colby College she realized that she wants to provide others with a better quality of life and continue to conduct research in the laboratory. She will graduate from Colby College on May 25, 2003 with a B.A. in Chemistry with a concentration in Cellular and Molecular Biology/Biochemistry, a mouthful for her parents. In August 2003 she will begin the M.D./Ph.D. program at Johns Hopkins Medical School with aspirations to one day practice pediatric oncology and run her own research laboratory.

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Abstract

This thesis reports the first complete synthesis of montiporynes A and B, isomeric diacetylenes that bear α,β -unsaturated ketone functionalities. Recently isolated from the stony coral *Montipora* sp. these compounds are reported to possess *in vitro* cytotoxic activity against several human solid tumor cells. We have synthesized both isomers in three simple steps. In the first step, 1-iodononyne was prepared by reacting 1-nonyne with *N*-iodosuccinimide and a catalytic amount of silver nitrate. This iodoalkyne was then coupled with propargyl alcohol using copper iodide as the catalyst to give 2,4-dodecadiynyl alcohol. Finally, the diacetylenic alcohol was subjected to the Swern oxidation and the resulting aldehyde trapped via a Wittig reaction with 1-triphenylphosphoranylidene-2-propanone to afford montiporyne A. Upon standing at room temperature for a few hours, montiporyne A partially isomerized to its isomer, montiporyne B. The two isomers were separated by flash chromatography and characterized by NMR, IR, and GC-MS. The “one-pot” conversion of a primary alcohol to an α,β -unsaturated ketone, using the Swern and Wittig reactions, proved to be an efficient procedure in the synthesis of montiporynes A and B. While a number of protocols have been developed to convert alcohols to α,β -unsaturated esters via oxidation followed by an *in situ* Wittig olefination, not much is known about the utility of this “one-pot”, two-step process to prepare α,β -unsaturated ketones. Thus a number of structurally diverse primary alcohols were subjected to the Swern/Wittig sequence to investigate the scope and limitations of the method. Although preliminary results are promising much work still remains to be done to optimize the yields of products.

Introduction

Organic chemistry remains one of the leading fields in science as researchers continually discover novel carbon compounds. About ten percent of these compounds have been isolated from natural organisms including animals, plants, fungi, and microorganisms. Since the beginning of time, humans have known that many of these compounds have medicinal purposes against a vast array of human illnesses. From the Egyptians of 1500 B.C., who have recorded over 850 plant medicines, to Hippocrates of 460 B.C., and the Shakers of the 1850s, humans have continuously used medicinal plants to remedy illnesses and diseases.¹

By the end of the eighteenth century scientists began to isolate compounds from natural sources such as plants and animals. Until the first quarter of the nineteenth century, scientists believed in the *vital force*, the theory that compounds in living organisms had properties and laws that distinguished them from compounds of inanimate objects, and prevented humans from reproducing them in lab. However, in 1828 the German scientist Friedrich Wöhler accidentally discovered that urea could be synthesized from ammonium cyanate. Wöhler's demonstration that not all organic compounds had to be isolated from natural products sparked new confidence in organic chemists and encouraged them to synthesize further compounds.

Since the 1920s synthetic organic compounds have replaced plant-derived compounds as the most widely used source of drugs. Nevertheless, scientists continue to elucidate the structures of natural compounds in order to pursue their medicinal potentials and to derive useful analogs from them. In 1928, Alexander Fleming accidentally

discovered penicillin. Two decades later, in the midst of World War II, Dorothy Crowfoot determined its structure. Pharmaceutical companies have since been able to derive thousands of possible drugs based on penicillin's structure that will increase efficacy, lower cost, and reduce toxicities.²

Cancer, a malignant disease caused by the uncontrolled proliferation of cells, kills over six million people per year.³ As this disease is the second largest cause of death in the U.S.,⁴ scientists are eagerly searching for improved chemotherapeutic agents. Just before World War II, it was found that nitrogen mustard (mechlorethamine) isolated from the mustard seed, possessed high cytotoxicity against various cancers.⁵ Unfortunately, nitrogen mustard and other current antitumor treatments have poor selectivity, killing all rapidly dividing cells in patients including normal and neoplastic cells. Currently, scientists are searching for other natural products with greater selectivity to cancer cells to eliminate the undesirable side effects caused by current treatments. While marine natural products, such as microorganisms, algae, sponges, and mollusks, have been a source of interest for bioactive natural products, it has only been within the last decade that natural product chemists have looked at compounds from stony (hard) corals for biologically active compounds.⁶

Literature data, while limited, suggest that stony corals do indeed produce interesting natural products with bioactive properties. Examples of secondary metabolites isolated from stony corals include anthraquinoid derivatives, tubastrine, tubastrine, aplysinopsin, and acetylenic compounds.⁷ Bae and coworkers reported the isolation and characterization of six novel acetylenic compounds (1-6) isolated from the stony coral *Montipora* sp. isolated from Korean waters in 2000.⁸ The biological

evaluation of these compounds suggests that some have *in vitro* cytotoxicities against various human solid tumor cells comparable to that of cisplatin, an inorganic platinum-coordinating cross-linking agent currently used as a chemotherapeutic agent (Table 1).⁹

Figure 1. Structure of diacetylenic compounds isolated from the hard coral *Montipora* sp.

Table 1.¹⁰ *In vitro* cytotoxicities (ED₅₀, µg/mL) of montiporynes A and B against Human Solid Tumor Cells^a

compound	A549	SK-OV-3	SK-MEL-2	XF498	HCT15
1	>50	3.2	1.4	1.9	3.7
3	>50	2.5	1.5	3.2	5.2
5	>50	>50	>50	>50	>50
cisplatin	0.8	1.2	1.5	0.7	1.5
2	>50	25.9	42.6	>50	>50
4	>50	45.1	43.1	>50	>50
6	>50	29.2	36.7	31.3	45.1
cisplatin	0.6	0.9	0.7	0.6	0.6

^aA549: human lung cancer; SK-OV-3: human ovarian cancer; SK-MEL-2: human skin cancer; XF498: human CNS cancer; HCT15: human colon cancer. Compounds were assayed in two separate batches.

We in Dr. Dasan Thamattoor's lab became interested in the synthesis of montiporynes A and B, 1 and 2, respectively, which are only available in minute quantities from the corals. Montiporyne A, with its *trans* disubstituted olefin is more

abundant in nature and has a greater cytotoxicity than its *cis* isomer, montiporyne B. Of the six acetylenic compounds, **1** and **2** have the simplest structure, featuring an extensively conjugated system that includes an α,β -unsaturated ketone functionality. Indeed, we were successfully able to prepare both **1** and **2** and test the effectiveness of the former against murine hepatoma cells. In the course of our synthetic work we were also able to make progress in designing a general, mild, and "one-pot" method for the efficient conversion of primary alcohols to α,β -unsaturated ketones.

Results and Discussion

Synthetic strategy: The retrosynthetic analysis that guided our approach to prepare **1** and **2** is shown in figure 2.

Figure 2. Retrosynthetic analysis of montiporynes A and B.

Thus, we decided to start with the commercially available 1-nonyne (**7**) and convert it into 1-iodononyne (**8**). Subsequent coupling of **8** with propargyl alcohol was expected to furnish the diacetylenic primary alcohol **9**. Oxidation of this alcohol to the aldehyde **10**, followed by a Wittig reaction, should give **1/2**.

Step 1: Our route to the diacetylenic ketones **1** and **2** began with the iodination of 1-nonyne (**7**) to 1-iodononyne (**8**). Haloacetylenes are important and commonly used intermediates in organic synthesis. They are often prepared by reacting the terminal alkyne with a base and a halogen.¹¹ These reactions are successful because of the acidity of the terminal acetylenes. Generally, it is difficult for a base to remove a hydrogen from

a hydrocarbon, which creates a carbanion with a pair of nonbonding electrons. However, terminal acetylenes are relatively strong proton donors ($\text{pK}_a \approx 25$) compared to other hydrocarbons. It is believed that the hybridization of the carbon losing the proton accounts for the differences in acidity of hydrocarbons. For instance, whereas the lone pair electrons of a methyl anion reside in a sp^3 hybrid orbital only having 25% s character, those of a vinyl anion exist in a sp^2 hybrid orbital with 33% s character. The lone pair electrons of an acetylide anion reside in orbitals with the greatest s character at 50% because the orbital is sp hybridized. Since an s orbital is lower in energy than a p orbital, the electrons in the acetylide ion orbital have the lowest energy and are therefore more stable.¹² (figure 3).

Figure 3. Orbital structures of carbanions.

In order to synthesize **8** we used ethylmagnesium bromide as the base and solid iodine to obtain the product in a 49% yield.¹³ An alternative and equally effective procedure was to iodinate the terminal alkyne using n-butyllithium and iodine as reported by Mowery et al.¹⁴

Figure 4. Iodination of 1-nonyne (method A).

However, Dr. Nancy Goroff of SUNY, StonyBrook later informed us that iodinations of terminal acetylenes with *N*-iodosuccinimide (NIS) and a catalytic amount of AgNO₃ in acetone is another effective and simple way to synthesize iodoacetylenes. This method proved to be more efficient and convenient than the Grignard reaction producing **8** in a quantitative yield.

Figure 5. Iodination of 1-nonyne (method B).

The conversion of trimethylsilylacetylenes into haloacetylenes has also become a desirable method because of its mildness and convenience, but we found that the conversion of **7** into **8** worked extremely well without first converting **7** to a trimethylsilylacetylene.¹⁵ While the actual mechanism of this reaction is unknown, we speculate that it involves the interaction of Ag⁺ with the terminal acetylene. When silver (I) coordinates with the π bonds of the alkynes, the terminal C-H bond is polarized and subsequently weakened.¹⁶ **8** can then form through the exchange of the acidic terminal H for I from **8**.

Figure 6. Proposed mechanism of step 1. sp C-H bond weakening due to π bond coordination with Ag^+ .

Step II: Barbu has previously shown that diacetylenes can be easily synthesized by coupling propargyl alcohol to 1-iodoacetylenes.¹⁷ Therefore, we knew that once we prepared the iodoacetylene we could continue with our synthetic scheme to produce the diacetylenic precursor to **1** and **2**. An abundance of di- and poly-acetylenic compounds have been isolated from natural sources. The biological importance and the electronic and optical properties of these compounds have generated much synthetic interest in them. In 1869, Carl Glaser discovered the first homocoupling reaction of acetylenes when he exposed phenylacetylide (**12**) to air to afford diphenyldiacetylene (**13**).¹⁸

Figure 7. First acetylenic coupling discovered by Glaser.

While the Glaser reaction is still commonly used, many methods have since been developed with the more recent focus on acetylenic heterocoupling. The Cadiot-Chodkiewicz coupling of 1-haloacetylenes with terminal acetylenes in the presence of copper (I) salt and an aliphatic amine is a common method to synthesize unsymmetrically disubstituted diacetylenes. However, unless the diacetylene is directly attached to an aromatic ring, this synthetic method is often irreproducible and tends to afford poor

yields.¹⁹ The Cadiot-Chodkiewicz coupling is also less successful with iodoalkynes than with bromoalkynes.²⁰ It has also been reported that the coupling reaction can be carried out in the presence of 1-haloalkynes and a water-soluble palladium catalyst. However, we employed the simple and mild method reported by Alami and Ferri, which does not require a palladium catalyst, to synthesize the unsymmetrical diyne, **9**. While the mechanism of this method is unknown, it is believed to be a radical reaction initiated by the copper ion.

Figure 8. Heterocoupling of 1-iodononyne in presence of propargyl alcohol.

The experiment proved facile to conduct. We determined through various TLC trials that a 2:8 ratio of ethyl acetate:hexanes would yield the best separation of our product from other side-products. After silica gel chromatography we obtained **9** in 89% yield.

Step III: In the final step of the synthesis we decided to attempt a “one-pot”, two-step process by using the Swern oxidation to convert **9** to the aldehyde **10**, which was subsequently trapped with a keto bearing stabilized ylid via an *in situ* Wittig reaction to afford **1**.

Figure 9. Oxidation via the Swern Oxidation followed by elimination using an *in situ* Wittig reaction.

The Swern oxidation, which employs oxalyl chloride as the oxidizing agent, is a common and high yielding reaction that converts primary alcohols to aldehydes. As seen in Figure 10 the Swern oxidation is a multistep process in which dimethyl sulfoxide (DMSO) attacks the electrophilic oxalyl chloride to form an electrophilic sulfur complex. The chloride ion then attacks the sulfur complex forming the chlorosulfonium ion, CO_2 , CO , and another Cl^- . This reaction is favored by the increase in entropy. Now the alcohol is introduced to the system. Its nucleophilic hydroxyl group attacks the chlorosulfonium ion. The resulting sulfonium salt is deprotonated by base, in this case, triethylamine, leading to a rearrangement of the complex in which an aldehyde and dimethylsulfide are formed.

Figure 10. Mechanism of Swern Oxidation.

Without isolating **10** we proceeded with the Wittig reaction, eliminating the need to purify **10**. The Wittig reaction is one of the most widely used methods to synthesize alkenes from aldehydes and ketones. Positively charged phosphorus ions as seen in figure 11 increase the acidity of protons on the α carbon. Phosphonium salts can be deprotonated by a strong base to create ylids, species that carry positive and negative charges on adjacent atoms. Ylids can also be represented as phosphoranes.

Figure 11. Representation of ylid and phosphorane species in Wittig reaction.

Ylids are nucleophiles that attack the carbonyl groups of ketones and aldehydes forming oxaphosphetanes, four-membered unstable rings that undergo elimination affording an alkene and triphenylphosphine oxide as depicted in figure 12. The resulting strong double bond between oxygen and phosphorus drives the reaction forward.

Figure 12. Mechanism of the Wittig Reaction.

Ylids can be stabilized or unstabilized. Stabilized ylids are so named because the ylid's negative charge is stabilized by the positively charged phosphorus atom and the adjacent carbonyl group. This resonance allows for the formation of an enolate as shown in figure 13. Ylids that are not stabilized by an adjacent functional group are called unstabilized ylids.

Figure 13. Stabilized ylid (red) and unstabilized ylid (blue).

Unstabilized ylids are selective for the *Z* isomer as depicted in figure 14 because of the kinetically controlled stereoselective formation of the oxaphosphetane ring. Two diastereomers of the oxaphosphetane ring can form from the addition of an aldehyde or ketone to the ylid. The oxaphosphetane ring that normally forms with unstabilized ylids is the *Z* diastereomer. It is presumed that the ylid and carbonyl compound approach each other perpendicularly in order to form the oxaphosphetane ring in one step. The oxaphosphetane ring has *Z* stereochemistry in order to keep large substituents apart.

Figure 14. Formation of *Z* oxaphosphetane ring followed by stereospecific *Z* elimination during Wittig reaction.

Next, the elimination step occurs in a stereospecific *syn-periplanar* transition state forming the *Z* isomer. Since formation of the oxaphosphetane ring is irreversible when using unstabilized ylids, the stereospecificity of the latter elimination reaction reflects the kinetically controlled stereoselectivity of the former addition step.

To synthesize **1** and **2**, we use the stabilized ylid, 1-triphenylphosphoranylidene-2-propanone, which favors formation of **1**, the *E* isomer. Stabilized ylids confer *E* selectivity because formation of the oxaphosphetane ring is reversible and therefore the initial addition step is thermodynamically controlled. The *Z*- and *E*-oxaphosphetane ring diastereomers have enough time to equilibrate before the alkene is formed. The ratio of the *E*:*Z* diastereomers will favor the *E*-oxaphosphetane ring because it is more stable to have the bulky side groups on the opposite sides of the ring. The *E*-oxaphosphetane ring then undergoes stereospecific elimination faster than its *Z* isomer because it has less steric hindrance. Therefore the *E*-alkene is the dominant product when stabilized ylids are used.²¹

Figure 15. Reversible formation of the oxaphosphetane ring and followed by elimination to form the *E* and *Z* isomers during the Wittig reaction.

We were able to obtain high yields of **1** and **2** because the two isomers are able to interconvert between themselves at room temperature due to the resonance stabilization of the α,β -unsaturated ketone as depicted in Figure 15. The most challenging aspect of this synthesis proved to be separating **1** and **2** because they isomerize so readily. After performing flash chromatography over silica gel with hexanes/ether (90:10), hexanes/ether (98:2), hexanes/ether (99:1), and hexanes as various eluents, we found that the most effective solvent system was hexanes/ether (99.5:0.5) to afford **1** and **2** in 58%

and 19% yields, respectively. We were able to obtain such a high yield of **2** by leaving our samples containing a mixture of **1** and **2** at room temperature overnight, in which case **1** readily isomerized to **2**. The ratio of **1**:**2** at equilibrium appears to be approximately 3:1 in favor of the *trans* isomer.²²

Characterization of 1 and 2: We were able to characterize **1** and **2** through NMR, GC/MS, and IR spectra. Comparing our spectral data to that taken from the naturally occurring compounds indicates that our compounds are the same. The ¹H NMR of **1** shows the expected singlet at δ 2.27 ppm, representing the methyl group α to the carbonyl. The hydrocarbon tail is represented by the peaks in the δ 0.91 to 2.40 ppm region. The olefinic protons are each represented by a doublet. The α and β protons appear at δ 6.57 and 6.73 ppm respectively. Upon first glance one might expect the α proton to be more downfield since it is closer to the carbonyl group, but the β proton is actually more electropositive due to resonance contributions. (Figure 16).

Figure 16. Resonance structures of 1.

NMR data of **2** is very similar to that of **1**. The ¹H NMR of **2** a multiplet at δ 2.4-0-2.45 ppm representing the methyl group α to the carbonyl. The peaks from δ 0.93-1.59 ppm represent the hydrocarbon tail. The α and β olefinic protons are indicated by doublets at δ 6.31 and 6.48 ppm, respectively. The two isomers are differentiated by the splitting pattern of the olefinic protons. The *trans* compound displayed a larger coupling constant ($J = 16$ Hz) than the *cis* isomer ($J = 12$ Hz). LRMS

of **1** and **2** also display the expected mass of 216. (M^+). HRMS of **1** provided a more specific mass of 216.1515.

Biological testing: Our synthetically derived **1** has been tested for its potency as an inducer of quinone reductase, a phase 2 enzyme, in murine hepatoma cells in Dr. Paul Talalay's laboratory at Johns Hopkins Medical Institute. His lab studies ways to induce phase 2 enzymes, which are believed to serve as chemopreventive agents by converting xenobiotics and potential toxins to water-soluble compounds that can be excreted out of the body. His laboratory has determined that compounds with the α,β -unsaturated ketones are one of the nine known functional groups that can activate phase 2 enzymes. Unfortunately, **1** was only weakly active with a CD of 75 μM . This compares to oltipraz, a phase 2 enzyme inducer currently undergoing clinical trials to prevent breast cancer, which has a CD of 20 μM . However, knowledge about the practical applications of α,β -unsaturated ketones proves why developing a method to synthesize them is so important.

Method development: The last step of our synthesis of **1** and **2** employed the Swern oxidation followed by an *in situ* Wittig reaction to convert a primary alcohol to an α,β -unsaturated ketone. While researching synthetic routes to **1** and **2** we discovered that while this one-pot, two-step process has been employed to synthesize α,β -unsaturated esters from primary alcohols, little is known about the convenience of this process to prepare α,β -unsaturated aldehydes and ketones.²³ Given the practical application of this oxidation/olefination method, we chose to explore the scope and limitations of this method. We have since been investigating the conversion of primary alcohols to α,β -unsaturated ketones by employing the Swern oxidation and trapping the resulting aldehyde with a keto bearing stabilized ylid in an *in situ* Wittig reaction. The primary

alcohols used in this method development include benzyl alcohol (**14a**), cinnamyl alcohol (**14b**), octanol (**14c**), pentanol (**14d**), isobutanol (**14e**), and 2,4-hexadiyn-1,6-diol (**14f**).

Figure 17. Primary alcohols that we attempted to convert into α,β -unsaturated ketones. Synthesis used oxalyl chloride, DMSO, Et_3N , and 1-Triphenylphosphoranylidene-2-propanone in CH_2Cl_2 at -68°C .

Each experiment was run under the same reaction conditions except for varying reaction times as seen in table 2. To purify our synthesized α,β -unsaturated ketones we

first dissolved them in hexanes. Triphenylphosphine oxide, the byproduct of the Wittig reaction, which results from the formation and opening of the oxaphosphetane ring, is a highly polar molecule and therefore is insoluble in the nonpolar hexanes. After filtration we removed the solvent *in vacuo* and further purified the products by running them through a pipet filled with silica gel using hexanes and ether as the eluents. In some cases this last step needed to be repeated to remove all impurities.

Table 2. Reaction conditions and results in the development of the Swern oxidation and *in situ* Wittig reaction method.

compound	Reaction Time	Final Mass, (Percent Yield)
15a	3 h	0.69 g (100 %)
15b	24 h	Needs to be optimized
15c	3 h	Needs to be optimized
15d	24 h	0.22 g (33%)
15e	24 h	Needs to be optimized
15f	3 h	0 %

While we have had some success with this procedure, we have not found the optimal method to purify our products. Even after repetitive runs through silica gel, our products have still been contaminated with triphenylphosphine oxide and other impurities. The complete purification of **15a** and **15d** yielded a yellow liquid. While it is more time-consuming, column chromatography may be a more effective method to purify the products; especially in the case of **15b**, where in the second step of the “one-pot” method all of the aldehyde was not trapped by the keto bearing Wittig reagent affording a

3:1 ratio of the ketone:aldehyde. NMR data shows the *E* isomer predominated in most reactions, but just as in the case of **1** and **2** some *Z* isomer was obtained as well.

Conclusions

We have successfully completed the total synthesis of montiporynes A and B making available several hundred milligrams of these marine secondary metabolites, which are presently only found in small quantities from coral. In the first step we converted 1-nonyne into 1-iodononyne by means of NIS and a catalytic amount of AgNO_3 affording a quantitative yield. We then coupled the haloalkyne with propargyl alcohol using copper iodide to furnish dodeca-2,4-diyn-1-ol in a 89% yield. The diacetylenic alcohol underwent the Swern oxidation and the resulting aldehyde was trapped by 1-triphenylphosphoranylidene-2-propanone via a Wittig reaction to give montiporyne A in a 58% yield. Upon resting at room temperature this diacetylenic α,β -unsaturated ketone partially isomerized to montiporyne B. We found that the *E* isomer was preferred over the *Z* isomer in a 3:1 ratio. The two isomers can be distinguished by measuring the splitting pattern of the olefinic protons, which showed a larger coupling constant ($J = 16 \text{ Hz}$) for the *trans* product than for its *cis* isomer ($J = 12 \text{ Hz}$). The potency of montiporyne A has been tested against murine hepatoma cells at Johns Hopkins Medical Institute. Our synthetically derived compound was only weakly active relative to other drugs currently in clinical trials.

The "one-pot", two-step conversion of the primary alcohol to the α,β -unsaturated ketone via the Swern and Wittig reactions proved to be a successful means to prepare α,β -unsaturated ketones. While methods have been developed to convert alcohols to α,β -unsaturated esters, little is known about the utility of the Swern oxidation and *in situ* Wittig reaction to convert primary alcohols to α,β -unsaturated ketones. We have had some success demonstrating that the procedure works on a variety of primary alcohols.

Future work should focus on optimizing the reaction conditions and purification techniques for the oxidation/olefination method by the Swern oxidation and Wittig reaction. An optimized procedure may also help increase yields in the future synthesis of other α,β -unsaturated ketones isolated from the stony coral *Montipora* sp.

Experimental

All GC/MS data were obtained on either a Varian CP-3800 Gas Chromatograph/Saturn 2000 MS, or a Hewlett-Packard 5890 Gas Chromatograph/5891 mass selective detector. The former employed a Chromapac CP Sil 8 CB capillary column measuring 30 m x 0.25 mm and the latter used a Supelco 2-4028 SPB-1 fused silica column measuring 30 m x 0.25 mm. All ^1H and ^{13}C NMR data were taken at 400 MHz and 100 MHz, respectively, using a Bruker Avance 400 spectrometer. IR spectra were obtained on a Mattson 4020 Galaxy Series FT-IR. High Resolution Mass Spectrometry was provided courtesy of Professor Robert Pascal using a Kratos MS 50.

Column chromatography was performed using a Biotage Flash Column system and with locally prepared columns using 60-200 mesh silica gel. All reactions were run under anhydrous conditions under nitrogen and with oven-dried equipment.

1-Iodononyne (4): Method A. EtMgBr (40 mL, 306 mmol) was added to an oven-dried 3-neck round-bottom flask, under nitrogen. 1-nonyne (16.5 mL, 75.6 mmol) and ether (50 mL) were added dropwise through an addition funnel over 1 h under reflux. I_2 (2.73 g, 103 mmol) was poured down reflux condenser over 45 min period and rinsed with ether (15 mL) producing a pale reddish-brown solution. The reaction mixture was added to water (300 mL) and acidified with glacial acetic acid (50 mL). The aqueous layer was separated and extracted twice with ether (50 mL each). The organic layers were washed with 10% $\text{Na}_2\text{S}_2\text{O}_3$ solution (x4) and water, and dried over anhydrous Na_2SO_4 . The solvent was evaporated *in vacuo*. The residue was purified by distillation *in vacuo* to give 14.93 g (60%) of a pale yellow liquid. The yield was 69% based on consumed 1-nonyne.

1-Iodononyne (4): Method B. 1-nonyne (0.50 g, 40.3 mmol) and AgNO_3 (0.37 g, 2.0 mmol) were stirred in acetone (25 mL) under nitrogen in an oven-dried round-bottom flask. *N*-iodosuccinimide (NIS) (10.99 g, 48.3 mmol) was added to the solution and the solution continued stirring for 3 h with aluminum foil wrapped around the flask. The solution was cooled to 3°C in an ice bath producing a yellow solution, which was vacuum filtered. Water (50 mL) was added. The aqueous layer was extracted thrice with ether (50 mL) and the organic phases were washed twice with water (50 mL), thrice with saturated NaCl solution (50 mL), and once with saturated NH_4Cl solution (50 mL) and dried over anhydrous Na_2SO_4 . The solvent was evaporated *in vacuo* and the residue was distilled to give a pale yellow liquid (10.07 g, 100% yield). ^1H NMR (CDCl_3) δ 0.89 (t, J = 6.0 Hz, 3H), 1.24-1.40 (m, 8H), 1.54 (q, J = 7.0 Hz, 2H), 2.36 (t, J = 6.8 Hz, 2H). ^{13}C NMR (CDCl_3) δ 14.97, 21.22, 23.03, 28.90, 29.16, 32.10, 95.26, 109.98. LRMS (EI) 250 (M^+).

Dodeca-2,4-diyn-1-ol (5). In a 50-mL 2-neck oven-dried round-bottom flask under nitrogen, **4** (2.50 g, 9.9 mmol) and propargyl alcohol (1.2 mL, 20.3 mmol) were stirred in pyrrolidine (15 mL). CuI (0.20 g, 1.1 mmol) was added and the orange-brown solution stirred for 45 min. The flask felt warm to touch. Saturated NH_4Cl solution (25 mL) was added. The aqueous layer was extracted with ether thrice (25 mL) and washed with saturated NH_4Cl (25 mL), water (25 mL), and saturated NaCl (25 mL), and dried over anhydrous MgSO_4 yielding a green solution, which turned orange over a 12 h period at 4°C. The solvent was evaporated *in vacuo*. The residue was filtered through silica gel (elution hexanes: ethyl acetate, 8:2) *in vacuo* and the solvent was evaporated *in vacuo*

affording brown crystals (1.5 g, 89% yield). ^1H NMR (CDCl_3) δ 0.82 (t, J = 6.6 Hz, 3H), 1.15-1.35 (m, 4H), 1.46 (q, J = 6.6 Hz, 6H), 2.21 (t, J = 7.0 Hz, 2H), 4.30 (s, 2H). ^{13}C NMR (CDCl_3) δ 13.08, 18.21, 21.57, 27.09, 27.70, 30.63, 50.52, 63.31, 69.76, 72.52, 80.87. LRMS (EI) 178 (M^+).

(*E*)-Pentadec-3-ene-5,7-diyn-2-one (1). In a 50-mL 3-neck oven-dried round-bottom flask under nitrogen, oxalyl chloride (0.36 mL, 4.1 mmol) in CH_2Cl_2 (14 mL) was cooled to -68°C in a dry ice/acetone bath and stirred for 5 min. Anhydrous dimethyl sulfoxide (DMSO) (0.4 mL, 5.6 mmol) was added and stirring continued. **5** (0.50 g, 2.8 mmol) was dissolved in anhydrous CH_2Cl_2 :DMSO solution (1:1, 1.4 mL) and added to the solution which stirred for another 15 min. Triethylamine (Et_3N) (1.7 mL, 12.2 mmol) was added dropwise making sure that the temperature did not go above -50°C and stirred for an additional 5 min. The solution was warmed up to 0°C and was cooled back down to -60°C . 1-Triphenylphosphoranylidene-2-propanone (1.42 g, 4.5 mmol) in anhydrous CH_2Cl_2 (7 mL) was added to the solution, which was stirred for 10 min. The solution was then warmed to room temperature and hydrolyzed with saturated NH_4Cl solution and extracted three times with CH_2Cl_2 . The organic phases were combined, washed with 10 mL each of HCl, saturated NaHCO_3 solution, water, and saturated NaCl solution, and dried over anhydrous MgSO_4 . The solvent was evaporated *in vacuo* and the residue was chromatographed using flash chromatography over silica gel (elution hexanes:ether, 99.5:0.5) to give **1** as a yellow liquid (0.35 g) in a yield of 58%. ^1H NMR (CD_3OD) δ 0.91 (t, J = 7.0 Hz, 3H), 1.25-1.44 (m, 8H), 1.57 (q, J = 6.8 Hz, 2H), 2.27 (s, 2H), 2.40 (t, J = 6.9, 2H), 6.57 (d, J = 16 Hz, 1H), 6.73 (d, J = 16 Hz, 1H). ^{13}C NMR (CD_3OD) δ 20.58,

24.05, 27.87, 27.88, 29.58, 30.23, 30.27, 33.24, 65.96, 73.04, 85.35, 90.88, 124.57, 141.59, 199.39. IR (neat) 2929, 2857, 1677, 1590, 1360, 1248, 1172, 957. HRMS (EI) calculated for $C_{15}H_{20}O$ 216.1515: found 216.1515.

(Z)-Pentadec-3-ene-5,7-diyn-2-one (2). **2** was synthesized as according to the same procedure as **1**. In order to increase the yield of **2**, **1** was allowed to isomerize at room temperature and the mixture of **1** and **2** was chromatographed using flash chromatography over silica gel (elution hexanes: ether, 99.5:0.5) to give **2** as a yellow liquid (0.11 g) in a yield of 19%. 1H NMR (CD_3OD) δ 0.93 (t, $J=4.0$ Hz, 3H), 1.28-1.48 (m, 4H), 1.59 (q, $J=7.2$ Hz, 1H), 2.40-2.45 (m, 2H), 6.31 (d, $J=11.9$ Hz, 1H), 6.48 (d, $J=11.8$ Hz, 1H). ^{13}C NMR (CD_3OD) δ 14.59, 20.42, 23.84, 29.39, 30.03, 30.09, 30.30, 33.04, 65.84, 72.87, 87.50, 91.34, 120.99, 140.80, 199.10. IR (neat) 2929, 2857, 2225, 1670, 1582, 1175. LRMS (EI) 216 (M^+).

General Procedure for conversion of primary alcohols to α,β -unsaturated ketones.

In a 50 mL 3-neck round bottom flask, equipped with magnetic stir bar and thermometer under nitrogen, oxalyl chloride (1.43 eq) was added to CH_2Cl_2 (20 mL). The flask was cooled to $-65^\circ C$ with a dry ice/acetone bath. DMSO (2.4 eq) was added and the reaction stirred for 5 min. The primary alcohol (0.5 g, 1 eq) was then added and the reaction stirred for 15 min. Et_3N (4.26 eq) was added and the reaction stirred for an additional 5 min. The flask was then allowed to warm up to $5^\circ C$ and stirred at this temperature for 5 min. The flask was then re-cooled to $-65^\circ C$. 1-Triphenylphosphoranylidene-2-propanone (1.3 eq) was dissolved in CH_2Cl_2 (10 mL) and added to the reaction, which stirred at $-60^\circ C$ for 10 min. The flask was allowed to warm up to room temperature and

stirred for 3 h often producing a creamy tan solution. Saturated NH_4Cl solution (25 mL) was then added to the reaction and the aqueous layer was extracted with CH_2Cl_2 (25 mL) twice. The organic layers were combined and washed with 10 mL each of HCl, saturated NaHCO_3 solution, water, and saturated NaCl solution, and dried over Na_2SO_4 , which was then filtered off. The solvent was then removed *in vacuo* often affording a yellow liquid. The product was dissolved in hexanes and stirred. The solid was filtered off and the solvent was removed *in vacuo*. The compound was further purified by running it through a pipet of silica gel using hexanes and ether repeatedly if necessary.

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Speed, Traci J. and Dasan M. Thamattoor, "Synthesis of Montiporynes A and B", *Tetrahedron Letters* 43, 2002, 367-369

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1-iodononyne
C13CPD

Current Data Parameters
NAME tjspeed0718iodo
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters

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Time 16.31
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DS 2
SWH 25125.629 Hz
FIDRES 0.383387 Hz
AQ 1.3042164 sec
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DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

===== CHANNEL f1 =====

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PL1 0.00 dB
SF01 100.6237959 MHz

===== CHANNEL f2 =====

CPDPRG2 waltz16
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PCPD2 80.00 usec
PL2 4.00 dB
PL12 23.47 dB
PL13 120.00 dB
SF02 400.1316005 MHz

F2 - Processing parameters

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GB 0
PC 1.40

1D NMR plot parameters

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CY 12.50 cm
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F1 21631.74 Hz
F2P -5.000 ppm
F2 -503.06 Hz
PPNCH 11.00000 ppm/cm
HZCM 1106.73999 Hz/cm

File : C:\HPCHEM\1\DATA\TSB0712D.D
Operator : Traci
Acquired : 12 Jul 101 7:24 pm using AcqMethod DAS
Instrument : 5970B
Sample Name: 1-iodononye
Misc Info :
Vial Number: 1

diynol
PROTON

diynol
C13CPD

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Instrument : 5970B
Sample Name: acetylenic compound
Misc Info :
Vial Number: 1

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Acquired : 16 Jul 101 9:02 pm using AcqMethod DAS
Instrument : 5970B
Sample Name: Montiporyne A
Misc Info : rack 1 fraction #72
Vial Number: 1

Montiporyne A (CD3OD, 400 MHz)
PROTON

Montiporyne A (CD3OD, 100 MHz)
C13CPD

File : C:\HPCHEM\1\DATA\TSB0716D.D
Operator : Traci
Acquired : 16 Jul 101 8:28 pm using AcqMethod DAS
Instrument : 5970B
Sample Name: Montiporyne B
Misc Info : rack 2 fraction #59
Vial Number: 1

Montiporyne B (CD3OD, 400 MHz)
PROTON

Montiporyne B (CD3OD, 100 MHz)
C13CPD

Montiporyne B

B4

4-phenyl-3-en-2-butanone
PROTON

Current Data Parameters

NAME tjsphenyl
EXPNO 30
PROCNO 1

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TE 300.0 K
D1 1.00000000 sec

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F2 - Processing parameters

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LB 0.30 Hz
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PC 1.00

1D NMR plot parameters

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F2P -4.189 ppm
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HZCM 413.90726 Hz/cm

pentanol ketone
PROTON

Current Data Parameters
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EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
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TE 300.0 K
D1 1.00000000 sec

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LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
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F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
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HZCM 240.07800 Hz/cm