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Formal Synthesis of (±)-Guanacastepene A: A Tandem Ring-Closing Metathesis Approach

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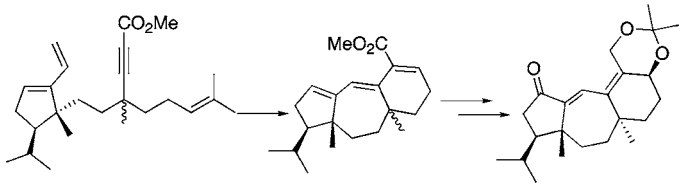
ABSTRACT



A concise route to a key intermediate in the total synthesis of guanacastepene A is described. The main features include the simultaneous construction of the seven- and six-membered rings, using a tandem ring-closing metathesis and a stereoselective introduction of the oxygenated function at the C5 position.

Guanacastepene A (**1**) is a novel 5,7,6-ring fused diterpene, originally isolated from a fungus collected in the Guanacaste Conservation Area in Costa Rica. It exhibits excellent activity against both methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*.[1] Further biological studies indicated that **1** has moderate activity against gram-positive bacteria, poor activity against gram-negative bacteria, and hemolytic activity against human red blood cells.[2] Despite these drawbacks, guanacastepene could be considered as a potential lead compound in the development of new antibacterial agents. The biological activity and the novel carbon skeleton of this product have made it a synthetic target for a number of groups.[3−13] Challenges in the total synthesis of **1** include construction of the tricyclic carbon skeleton with its dense array of oxygen functionality and introduction of the two stereogenic quaternary carbon centers

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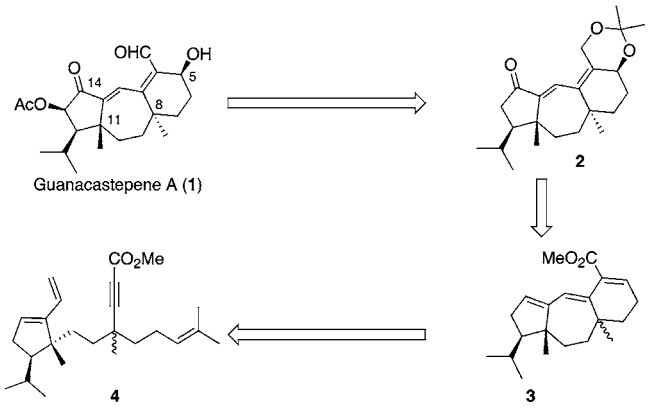
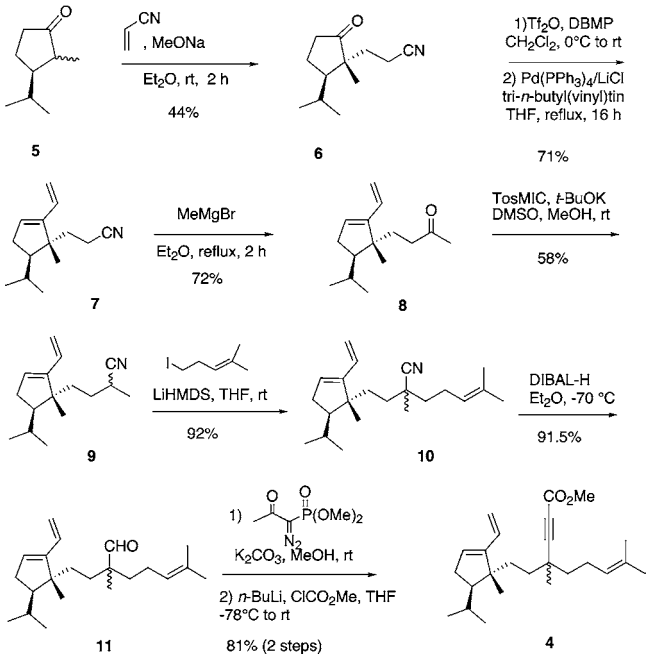
Scheme 1



Scheme 2



at C11 and C8. The first total synthesis of guanacastepene was reported by Danishefsky and co-workers[4c,d] in 2002, and shortly after Snider's group disclosed a formal total synthesis.[3c] Both of these approaches involve a strategy that begins with formation of a hydroazulene core, followed by the introduction of the six-membered ring onto the existing seven-membered ring, i.e., an A→ AB → ABC approach. Our route entails constructing the seven- and six-membered rings simultaneously through a tandem ring-closing metathesis (RCM) approach,[14,15] i.e., A→ ABC (Scheme 1). Previous results from our laboratory established the feasibility of such a strategy and described construction of a functionalized tricyclic ring system related to guanacastepene.[16]

However, this structure, in which the stereocenter at the 7−6 ring-junction bears an oxygen rather than a methyl substituent, is not adaptable for the synthesis of the natural product. We now describe a short formal synthesis of **1** in which the key C8 methyl group was set up before the tandem RCM reaction.

As in our previous work, the synthesis began with the readily available 3-isopropyl-2-methylcyclopentanone **5**.[17] Treatment of **5** with a catalytic amount of sodium methoxide in diethyl ether followed by the addition of acrylonitrile afforded ketone **6** as a single diastereomer and generated the quaternary center at C11 of the target (Scheme 2). The stereochemical outcome of the alkylation reaction was controlled by the steric influence of the β-isopropyl group, and can be assigned by analogy to similar reactions.[4a,18] Cyclopentanone **6** was converted to diene **7** via the corresponding enol triflate, using the Stille coupling reaction with tri-*n*-butyl(vinyl)tin in 71% overall yield. Addition of methylmagnesium bromide to nitrile **7** furnished ketone **8** in 72% yield. One-carbon homologation was efficiently achieved by treatment of **8** with tosylmethyl isocyanide (TosMIC) according to van Leusen's procedure,[19] to afford nitrile **9** in 58% yield. To set up the quaternary center at C8, alkylation of **9** was next considered.[20] After considerable experimentation, it has been found that the best results were obtained when a solution of lithium hexamethyldisilazane (LiHMDS) was added to a mixture of **9** and homoprenyl iodide[21] in THF at room temperature. Under these conditions, compound **10** was obtained with high reproducibility in 92% yield as a 1:1 mixture of diastereomers. To introduce the alkyne moiety, aldehyde **11**, prepared by reduction of **10**, was treated with dimethyl 1-diazo-2-oxopropylphosphonate (the Ohira reagent)[22] in the presence of K_2CO_3 in MeOH and the resulting acetylenic derivative was converted to the RCM precursor **4** in the usual way in 81% yield from **11**. Treatment of trienyne **4** with 12% of the Grubbs catalyst **12**[23] in refluxing

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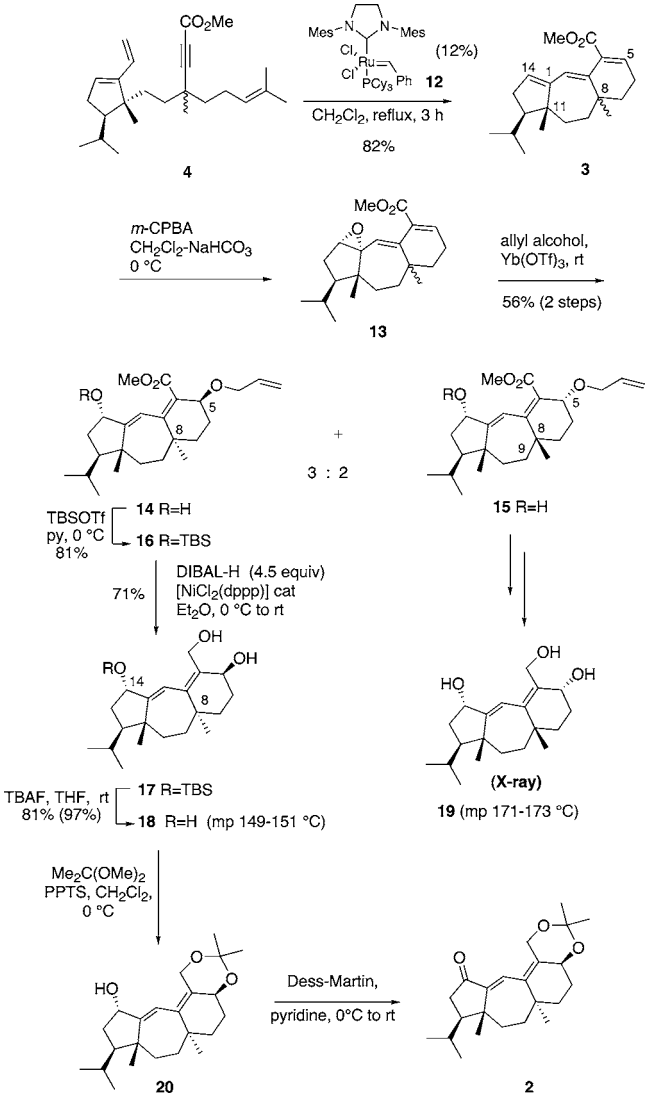
(23) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 953.

Scheme 3



CH_2Cl_2 for 3 h provided the RCM product **3** in 82% yield as a 1:1 mixture of C8 epimers (Scheme 3).

With the desired tricyclic frame in hand, we next undertook the introduction of the oxygen functionalities at C5 and C14. Oxidation of **3** with *m*-CPBA at 0 °C in CH_2Cl_2 and saturated aqueous $NaHCO_3$ was found to be chemo- and stereoselective producing a mixture of two diastereomeric epoxides **13.** The stereochemical outcome of this reaction was controlled by the angular methyl group at C11, which blocks the β-face at C1.[24] Although these isomers could be separated by flash column chromatography, the next step was carried out on the crude mixture. On the basis of our previous work, we anticipated that treatment of epoxydiene **13** with an alcohol in the presence of a Lewis acid, i.e., $CeCl_3 \cdot 7H_2O$, should lead to opening the epoxide ring concomitant with introduction of an ether group at C5.[16] After a brief survey of reaction conditions, we found that stirring **13** in allyl alcohol using catalytic ytterbium triflate [$(Yb(OTf)_3$] for 1 h at room temperature produced a 3:2 separable mixture of alcohols **14** and **15** in 56% overall yield from **3**.[25,26] These structures were deduced from the spectroscopic data and were confirmed later in the synthesis. In particular, while NMR spectra of **15** showed sharp signals for hydrogen and carbon atoms, compound **14** gave complex spectra difficult to interpret. This anomaly, first observed by Clardy and coworkers with the natural product, results from the presence of two conformers in a dynamic equilibrium at room temperature, which reflects the flexibility in the C9−C8 region of the central cycloheptane ring.[1a] These observations suggest that the relative configuration of the methyl group at C8 in **14** is the same as that of guanacastepene A. The stereochemistry at C5 was deduced from the assumption that nucleophilic attack of the alcohol, which probably proceeded via an S_N2'-type mechanism, took place on the opposite face to the angular methyl at C8.[27] This nucleophilic addition may also be assisted by the electron-withdrawing ester group.

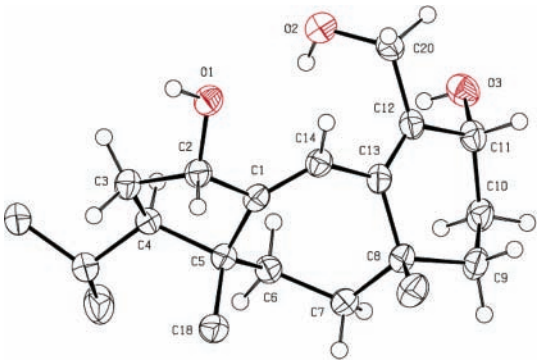


Figure 1. ORTEP drawing of **19**. Hydrogen atoms of the isopropyl and methyl groups are omitted for clarity and the numbering does not refer to the corresponding centers of guanacastepene.

With the required relative configuration of the methyl at C8 in hand, we turned to the next phase of the synthesis: conversion of **14** to ketone **2**, a late intermediate in Danishefsky's total synthesis[4d] and Snider's formal synthesis.[3c] To this end, alcohol **14** was protected as its OTBS ether and then submitted to nickel(0)-catalyzed hydroalumination, using complex $Cl_2Ni(dppp)$[28] in the presence of an excess of DIBAL-H. Under these conditions, direct cleavage of the allyl ether occurred concomitant with reduction of the ester group affording **17** in 71% yield. Cleavage of the silyl ether (TBAF, THF, rt, 6 days) furnished triol **18** (81%) as a crystalline compound (mp 149−151 °C). It is noteworthy that treatment of **14** under nickel(0)-catalyzed hydroalumination−elimination conditions led to direct formation of **18** albeit in low yield (20%).[29] In the same way isomer **15** was converted into the crystalline triol **19** (mp 171−173 °C) whose structure was confirmed by X-ray analysis (Figure 1).[30] Diastereomers **18** and **19** exhibit differences not only in their mp but more strikingly in their ^{13}C NMR spectra. As we mentioned for compounds **14** and **15**, while triol **19** showed sharp signals for all carbon atoms, many of its

(24) The stereochemical assignment at C14 was also based on extensive literature precedent (see for example refs 3a and 3c).

diastereomers were broad or hardly observed. This result strongly suggests that the syn relationship between methyl groups at C8 and C11 forces the seven-membered ring of **19** to adopt only one stable conformation at room temperature.

Protection of **18** as the acetonide gave **20**, which was oxidized with Dess−Martin's periodinane reagent[31] in the presence of pyridine furnishing ketone **2**. The ^{1}H and ^{13}C NMR spectra of **18**, **20**, and **2** are identical with those described by Snider and co-workers.[32]

In summary, we have developed a concise route to the key intermediate **2** in the total synthesis of guanacastepene A. The main features include the simultaneous construction of the seven- and six-membered rings by using a tandem ring-closing metathesis and a stereoselective introduction of the oxygenated function at C5 by S_N2' reaction on the epoxidiene **13**.

Supporting Information Available: Experimental procedures and characterization data for compounds **3**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) First attempts with $CeCl_3$ (anhydrous or heptahydrate) or $InCl_3$ gave lower yields.

(26) The loss of isomer **15** with respect to **14** is probably due to the instability of the corresponding epoxide.

(27) Although the S_N2' displacement by organocopper reagents is well documented, to our knowledge the ring-opening of vinyl oxiranes by alcohols in the presence of Lewis acid according to such a process is unprecedented.

(28) Taniguchi T. T.; Ogasawara, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 1136.

(29) Attempts to achieve direct palladium- or rhodium-mediated allylic cleavage were unsuccessful. Details will be given in the full account of this work.

(30) The full description of the X-ray structure of **19** has been deposited with the Cambridge Crystallographic Data Centre, UK.

(31) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

(32) The spectra of **18**, **20**, and **2** were compared with the copies of NMR spectra published as Supporting Information by Snider and co-workers (ref 3c).