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Exploring an Expedient IMDA Reaction Approach to Construct the Guanacastepene Core

Chuang-Chuang Li,[†] Shuang Liang,[†] Xin-Hao Zhang,[‡] Zhi-Xiang Xie,[†] Jia-Hua Chen,*[,†] Yun-Dong Wu,*[,†,‡] and Zhen Yang*[,†,§]

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Science, and Laboratory of Chemical Genomics, Shenzhen Graduate School, Peking University, Beijing, 100871, Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China, and VivoQuest, Inc., 711 Executive Boulevard, Valley Cottage, New York 10989

zyang@pku.edu.cn

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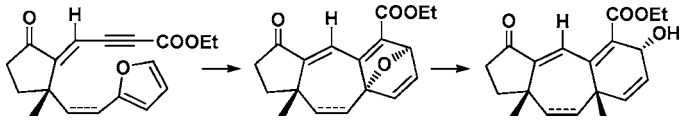
ABSTRACT



Construction of the [5-7-6] tricyclic core of guanacastepenes was attempted by using the intramolecular Diels–Alder (IMDA) reaction and Me_3Al-mediated ring opening of the oxabridge as key synthetic steps. The illustrated chemistry demonstrated a synthetic feasibility to build up the framework of guanacastepenes by the IMDA reaction.

Guanacastepenes are a novel class of richly functionalized diterpenoids isolated by Clardy and co-workers in 2000 (see selected examples **1**−**6** in Figure 1).[1] Some of the family members (such as guanacastepene A) are known to be active against methicillin-resistant strains of *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VREF).[2] However, their hemolytic activity against human red blood cells prevents them from being directly used as therapeutic agents.

Because of their novel structural features and important biological activities, guanacastepenes have attracted the interest of synthetic laboratories around the world since they were initially isolated,[3] culminating in the total syntheses of guanacastepene A by the laboratory of Danishefsky in 2002[4a] and two formal total syntheses by the laboratories of Snider[4b] in 2003 and Hanna[4c] in 2004.

Drug resistance[5] of bacteria poses a serious public health threat and demands effective countermeasures.[6] Given the potential of guanacastepenes as leads to find new

[†] Peking University.
[‡] The Hong Kong University of Science and Technology.
[§] VivoQuest, Inc.

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antibacterial agents, development of efficient approaches to rapidly access a variety of functionalized guanacastepene derivatives is imperative.

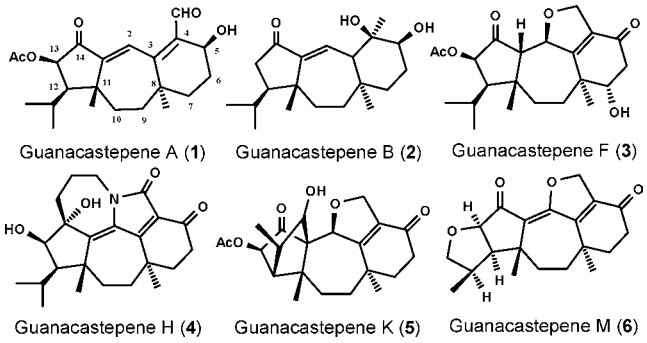
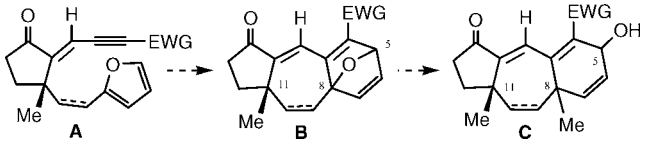


Figure 1. Naturally occurring guanacastepenes.

Inspired by the increasing number of seven-membered-ring-containing natural products being identified and their interest to the academic and pharmaceutical communities,[7] we started our synthetic study of guanacastepenes in early 2001. We expected that our developed synthetic approach would be efficient in synthesizing the [5-7-6] tricyclic core of guanacastepenes, as well as other [*n*-7-6] tricyclic ring systems. We report herein our study on the development of an IMDA reaction approach to construct the guanacastepenes framework, which allows us to effectively and conveniently construct structurally diverse compounds having the [5-7-6] tricyclic framework similar to the guanacastepenes.

Structurally, guanacastepenes share a common [5-7-6] tricyclic core decorated with a variety of functional groups. This feature inspired us to stereoselectively construct the tricyclic core **B** from the furan-tethered[8] dieneophile **A** through the IMDA reaction[9] by taking advantage of the conformationally preorganized feature of substrate **A** (see Scheme 1).[10] We also expected that the Lewis acid-assisted methylation of **B** could provide **C** with a quaternary carbon

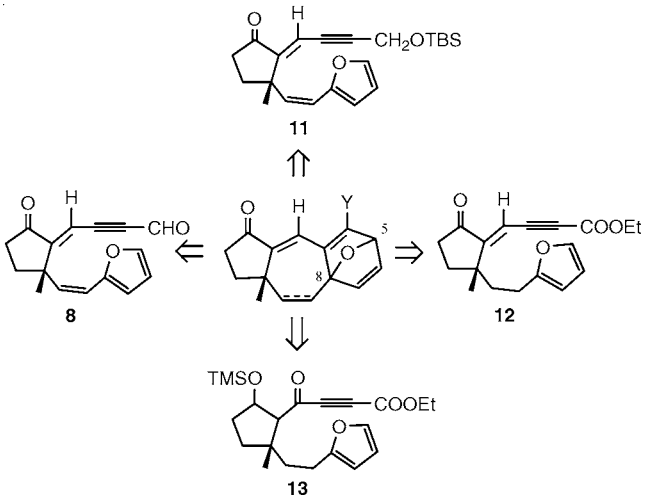
Scheme 1. Construction of [5-7-6] Tricyclic Core by IMDA



at C8, ideally in a stereoselective manner. A search of the primary literature yielded no relevant study in this aspect, which encouraged us to initiate our program.[11]

To put the proposed synthetic transformation into practice, **8**, **11**, **12**, and **13** (Scheme 2) were selected as substrates to test the cyclization tendency of their IMDA reactions.

Scheme 2. Designed Precursors for IMDA Reaction



Scheme 3 illustrates the synthesis of **8** and **11** and their IMDA reactions to form the tricyclic products **20** and **21**. The synthesis started with furan-2-aldehyde **14**, which was first converted to *cis*-vinyl bromide **15** in 92% yield first by Corey−Fuchs reaction[12] in 90% yield, followed by debromination with $Pd(PPh_3)_4/Bu_3SnH$.[13] Compound **15** was then utilized to synthesize **18** by a modification of Noyori's tandem reaction procedure.[14] In the event, compound **15** was first treated with *t*-BuLi in Et_2O at −94 °C to form the vinyllithium and then treated with CuI and Bu_3P; the resultant cuprate reagent was then coupled with 3-methyl cyclopentenone **16** in the presence of $BF_3{\cdot}Et_2O$ at −78 °C for 1 h, followed by reaction with aldehyde **17**[15] to give the desired product **18** in 67% overall yield.

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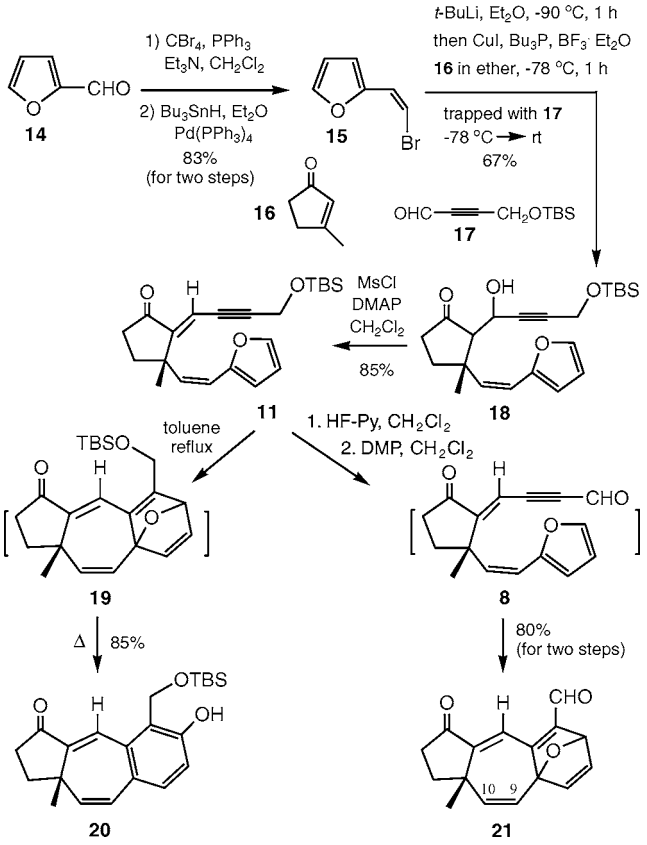
Scheme 3. Synthesis of Compounds **8** and **11**



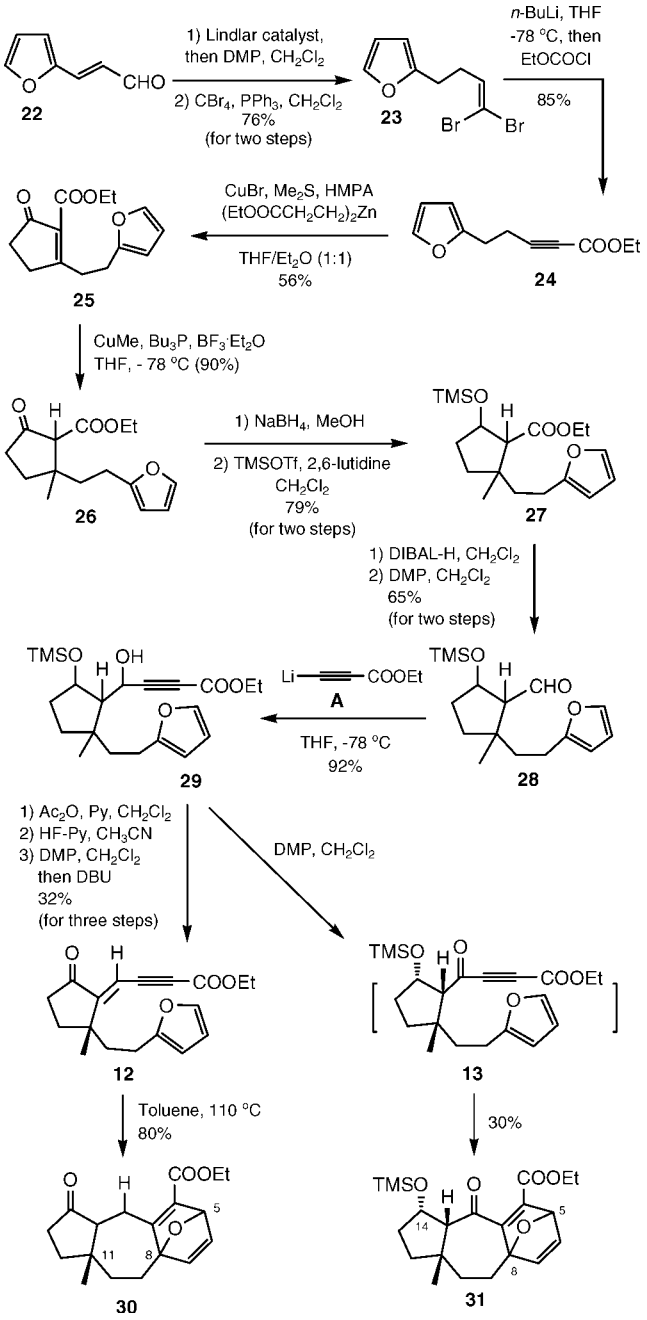
With **18** in hand, we first tested its synthetic feasibility for constructing the [5-7-6] tricyclic core of guanacastepenes by IMDA reaction, but no desired cyclization products were obtained under a variety of reaction conditions. Thus, we were led to explore the substrates with electron-deficient dieneophiles such as enyne **11** and envisioned that the cyclization would happen more readily. To this end, compound **18** was first converted to its mesylate, followed by elimination to give enyne **11** in 85% yield. The stereochemistry of the double bond in compound **11** was established by the NMR analysis developed by Johnson.[16]

Interestingly, when **11** was heated in refluxing THF or benzene, the expected IMDA reaction did not occur. However, under more forcing conditions (refluxing in toluene), phenol **20** was obtained in 85% yield, presumably through intermediate **19**.

We next turned our attention to synthesizing the even more active substrate **8**, which has a ketone and an aldehyde as double activating groups. Thus, following desilylation of compound **11**, the newly derived alcohol was then oxidized to aldehyde **8** with Dess−Martin periodinane (DMP). To our delight, the IMDA reaction of **8** could occur at 25 °C, and the cyclized product **21** was obtained in 80% yield in two steps.

Encouraged by these results, we then started to synthesize compounds **12** and **13**. Although **12** and **13** could potentially be made from **18** by selective hydrogenation to remove the double bond between C9 and C10, the synthetic transformation encountered a difficulty due to the presence of the triple bond. Thus, an alternative approach was employed to make **12** and **13** as detailed in Scheme 4.

Scheme 4. Synthesis of Compounds **12** and **13**



Accordingly, aldehyde **22** was subjected to sequential hydrogenation and oxidation, followed by Corey−Fuchs reaction, to give bromide **23** in 76% overall yield. Subsequent treatment with *n*-BuLi at −78 °C, followed by reaction with ClCOOEt, generated **24** in 85% yield, which was then reacted with $(EtOOCCH_2CH_2)_2Zn$ in the presence of CuBr, Me_2S,

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and HMPA to produce cyclopentenone **25** in 56% yield by Crimmins' procedure.[17]

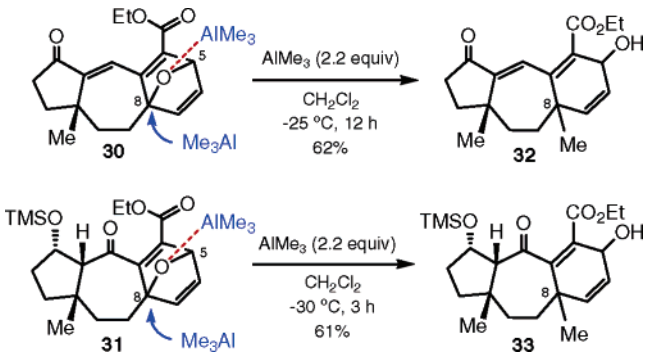
As shown in Scheme 4, when compound **25** was treated with MeCu in the presence of Bu_3P and $BF_3{\cdot}Et_2O$, the ketoester **26** was generated as a mixture of diastereoisomers in 90% yield. $NaBH_4$ reduction of the mixture **26** produced a secondary alcohol, which was subsequently protected as its TMS ether **27** in 79% yield for the two steps. Further reduction of the ester **27** with DIBAL-H gave a primary alcohol, which upon oxidation by DMP yielded **28** in 65% overall yield. Thus, aldehyde **28** was easily converted to alcohol **29** via lithium acetylide **A** in 92% yield.

To make **12**, **29** was first reacted with acetic anhydride in the presence of pyridine to convert its secondary alcohol into the acetate. Subsequent desilylation with HF-Py afforded another secondary alcohol, which was then subjected to oxidation with DMP and elimination with DBU to give **12** in 32% overall yield. As a result, the expected product **30** was formed in 80% yield when compound **12** was refluxed in toluene for 2 h.

To get substrate **13**, **29** (a mixture of diastereoisomers) was oxidized to the corresponding ketones by DMP. Fortunately, one of the diastereoisomers **13** was directly cyclized to **31** in 30% yield at room temperature.

To complete the proposed synthetic transformation listed in Scheme 1, we carried out the methylation of **30** and **31** to install the quaternary methyl group at C8 by $AlMe_3$-mediated ring opening of the oxabridge.[18] To do so, **30** and **31** were separately treated with $AlMe_3$ (2.2 equiv) in CH_2Cl_2; as expected, **32** and **33** were obtained stereoselectively in 62 and 61% yields, respectively (Scheme 5).

Scheme 5. Me_3Al-Mediated Stereoselective Methylation



We reasoned that the complex formation between $AlMe_3$ and substrates **30** or **31** is critical for this stereoselective outcome. Theoretical calculations[19] indicated that when one molecule of $AlMe_3$ coordinates with the bridging oxygen, the C8−O bond becomes over 0.01 Å longer than the C5−O bond, and the former is considerably better activated. Therefore, the methylation reaction is expected to be a Lewis acid-assisted S_N2 reaction to generate the desired regio- and stereochemistry. It should be noted that our effort to methylate **21** failed, presumably due to the presence of the double bond in the seven-membered ring; thus, the cleavage of the C8−O bond by a Lewis acid leads to aromatization.

At this stage, one of the remaining issues is how to establish the stereochemistry of **32** and **33**. At the beginning, we attempted to use crystallography to determine their relative stereochemistry, but we failed to get good quality crystals for X-ray study. We then decided to use two-dimensional NMR for the structure determination. To this end, we eventually identified the benzyl ester **34** as the sample for two-dimensional NMR study (see Supporting Information for detail).

Unfortunately, the relative stereochemistry at C5 and C8 in **34** was the opposite of the stereochemistry of desired compound **35** (Figure 2). We therefore decided to conduct a

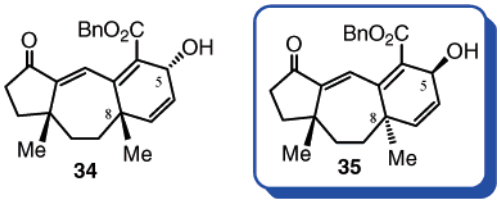


Figure 2. Two-dimensional NMR study results for compound **34**.

computational study and analyze the key factors that potentially influence the cyclization tendency. A detailed discussion regarding this aspect of the study will be reported in due course.

In summary, we have systematically evaluated the furan-based IMDA reaction to construct the framework of guanacastepenes, and their stereochemistry was determined by two-dimensional NMR. Although the furan-based IMDA reaction approach gave the undesired stereochemistry of the cyclized products, the generated information eventually led us to work out a new IMDA reaction approach to build up the framework of guanacastepenes, and the total synthesis of the guanacastepenes is currently underway in our laboratory.

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Supporting Information Available: Experimental procedure and ^1H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) All quantum mechanics calculations were performed using the Gaussian 98 program. Geometries were fully optimized with the density functional method of B3LYP using the 6-31G* basis set, which has been shown to be reliable for the study of Diels−Alder reactions. Vibration frequency was determined for each structure to confirm the structure to be a local minimum or transition state and to derive thermodynamic properties.