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Synthesis of the [5–7–6] Tricyclic Core of Guanacastepene A via an Intramolecular Mukaiyama Aldol Reaction

Xiaohui Du, Hiufung V. Chu, and Ohyun Kwon*

Department of Chemistry & Biochemistry, University of California, Los Angeles, 607 Charles E. Young Drive East, Los Angeles, California 90095-1569

ohyun@chem.ucla.edu

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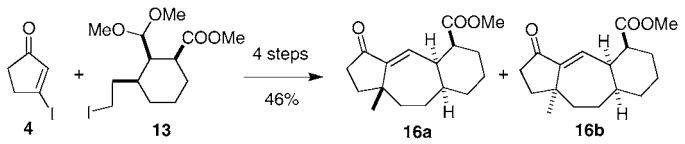
ABSTRACT



A synthesis of the tricyclic [5–7–6] skeleton of guanacastepene A is described. The six-membered ring of guanacastepene A was constructed by a Diels–Alder reaction. After several functional group transformations, it was coupled to β-iodocyclopentenone. Lithium dimethylcuprate conjugate addition followed by an intramolecular Mukaiyama aldol reaction furnished the desired [5–7–6] tricyclic ring system.

For the past two decades, vancomycin has been the antibiotic of last resort for treating infections caused by resistant strains of bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA). Consequently, the emergence of vancomycin-resistant *Enterococcus faecalis* (VREF) has posed a potential threat to human health.[1] Guanacastepene A (**1**), isolated by Clardy and his colleagues from a fungus collected in the Guanacaste Conservation Area in Costa Rica in 2000, showed antibiotic activity against both MRSA and VREF.[2] The promising biological profile of guanacastepene A renders it a potential lead compound in the development of novel antibiotics combating multidrug-resistance. The X-ray crystal structure of guanacastepene A displays a roughly rectangular tricyclic [5−7−6] diterpenoid skeleton with a highly oxidized northern face and a hydrophobic southern part. The biological activity of guanacastepene A combined with its previously unknown carbon skeleton has attracted much attention from the synthetic community,[3] including the first total synthesis reported by Danishefsky and co-workers.[3h−i]

Most of the groups, including Snider,[3a−c] Magnus,[3d,e] Danishefsky,[3f−i] Mehta,[3j,k] and Tius,[3p] adopted nonconvergent approaches. They have in common the formation of a hydroazulene core, followed by the introduction of the six-membered ring onto the existing seven-membered ring. Lee's approach[3n,o] differs from those of the aforementioned groups by starting from a five-membered ring equivalent, introducing the six-membered ring and then the seven-membered ring. Sorensen's[3m] is the only convergent approach so far in which

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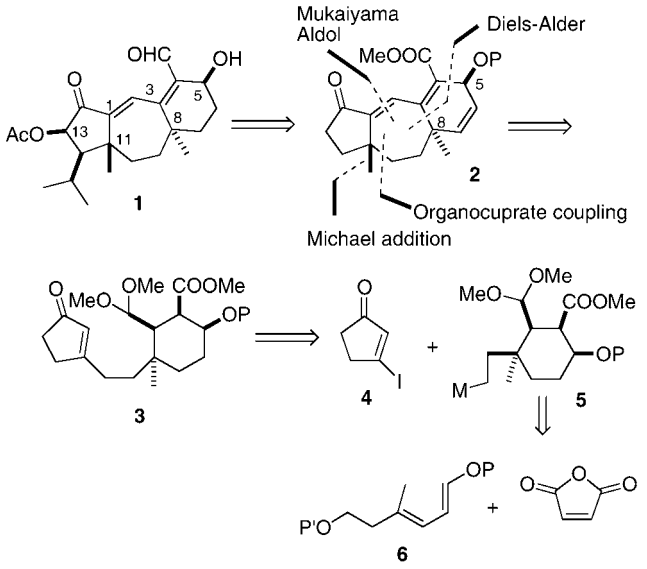
Scheme 1. Retrosynthetic Analysis

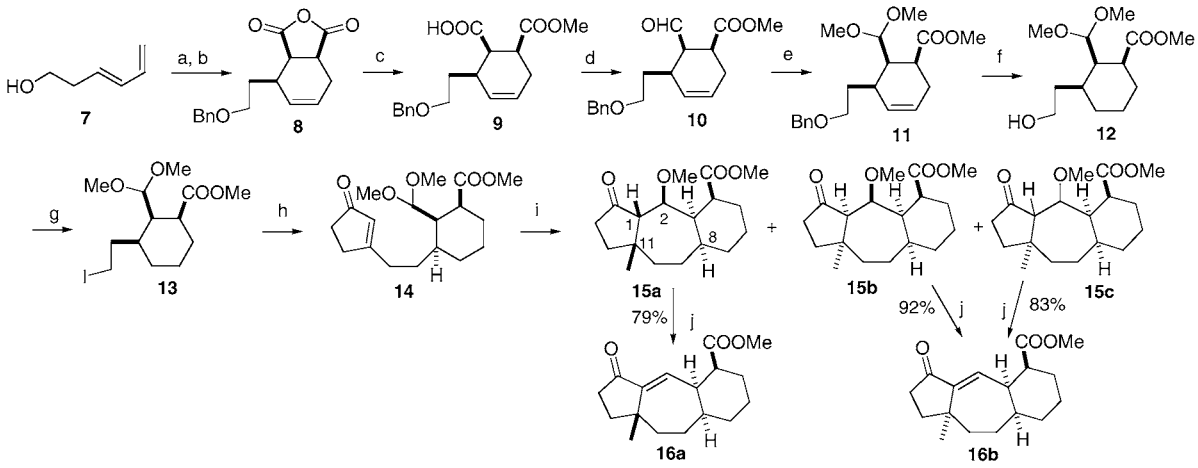


the five-membered ring and the six-membered ring were conjoined to form the middle seven-membered ring through a [2 + 2] photocycloaddition and ring fragmentation. Our group has been interested in developing a convergent synthesis of guanacastepene A that will enable us to generate its analogues. Herein, we report an efficient way of constructing the [5−7−6] carbocyclic core of guanacastepene A through a sequential conjugate addition/intramolecular Mukaiyama aldol reaction.

Our retrosynthetic plan is shown in Scheme 1.[4] The functional groups on the five-membered ring can be introduced at a later stage from intermediate **2**. The C11 methyl and the C1−C2 bond in the seven-membered ring can be constructed via a sequential Michael addition/intramolecular Mukaiyama aldol reaction from intermediate **3**. Intermediate **3** can be obtained by coupling *β*-iodocyclopentenone (**4**) with a highly functionalized six-membered ring moiety **5** through an organocuprate addition followed by an iodide elimination. Compound **5** with the desired relative stereochemistry at C5 and C8 can be constructed through a Diels−Alder reaction of diene **6** with maleic anhydride. One of the challenges in our plan is to set the trans relationship between the C11 and C8 methyl groups. On the other hand, various guanacastepene analogues can be generated through this route by altering the five-membered ring and the six-membered ring portions. As guanacastepene A demonstrates hemolytic activity as well as activity against MRSA and VREF, the generation of its analogues will be of great importance.

A simple diene lacking the C8-methyl and C5-oxygenation in guanacastepene A was chosen to serve as a readily accessible starting point to validate our strategy to build the [5−7−6] core structure of guanacastepene A. Diene **7** was conveniently prepared in large scale by known procedures (Scheme 2).[5,6] After benzyl protection of the free hydroxy group in **7**, Diels−Alder reaction with maleic anhydride furnished exclusively the *endo* adduct **8** where all three substituent groups are on the same side of the six-membered ring. Regioselective methanolysis of the anhydride group in **8** resulted in **9** as a sole product with the carboxylic acid moiety at the more hindered position of the six-membered ring.[7] The acid functional group in **9** was converted to an aldehyde group through a three-step sequence. Following Kokotos' method,[8] carboxylic acid **9** was first converted to

Scheme 2[a]



[a] Reagents and conditions: (a) NaH, THF, BnBr, 18 h, 99.5%. (b) Maleic anhydride, 105 °C, 16 h, 79%. (c) MeOH, reflux, 16 h, 89%. (d) (i) ClCOOEt, NMM, THF, 10 min; (ii) $NaBH_4$ (1 equiv), THF/MeOH = 1:1.3, 25 min; (iii) oxalyl chloride, DMSO, Et_3N, −60 °C, 30 min, 57% over three steps. (e) Bu_4NBr_3 (0.01 equiv), MeOH, $CH(OMe)_3$, 3 h, 71%. (f) H_2, 10% Pd on carbon (0.1 equiv), 95% EtOH, 1 h, 88%. (g) PPh_3, I_2, imidazole, Et_2O/CH_3CN = 3:1, 0 °C to room temperature, 1 h, 90%. (h) Activated zinc, 40 °C, 17 h, CuCN·2LiCl, −10 °C, 10 min then *β*-iodocyclopentenone (**4**), 0 °C to room temperature, 2 h, 89%. (i) (i) Me_2CuLi, TMSCl, Et_3N, HMPA, −10 °C to room temperature, 77%; (ii) $TiCl_4$ (2 equiv), 4 Å MS, CH_2Cl_2, −78 °C, 1 h, 79% (**15a**: 39%; **15b**: 30%; **15c**: 11%). (j) TsOH·H_2O, benzene, 95 °C.

its mixed anhydride with ethyl chloroformate. After fast filtration on a short silica gel pad to remove the *N*-methyl morpholinium salt, the pure anhydride was reduced with sodium borohydride to the corresponding alcohol. Since the alcohol was not stable and closed onto the methyl ester functional group to form a lactone, it was immediately subjected to Swern oxidation to provide aldehyde **10**. The aldehyde **10** was transformed to acetal **11** by applying Patel's procedure[9] with a catalytic amount of *N*-tetrabutylammonium tribromide. Saturation of the double bond and deprotection of the benzyl group in acetal **11** to form alcohol **12** were achieved simultaneously by hydrogenation with 10% palladium on carbon. Alcohol **12** was converted to iodide **13** by following a modified procedure of Corey.[10] Iodide **13** was first converted to the alkylzinc iodide by insertion using activated zinc. The zinc species was then converted to the highly functionalized copper reagent by transmetalation with the soluble CuCN·2LiCl salt.[11] This organocuprate intermediate was efficiently coupled to β-iodocyclopentenone (**4**)[12] to form compound **14** in 88% yield, regenerating the double bond by elimination of the β-iodide.

Formation of the [5−7−6] tricyclic ring system began with the conjugate addition of a methyl group to the β-position of cyclopentenone with lithium dimethylcuprate followed by in situ formation of the TMS enol ether with chlorotrimethylsilane.[13] The intramolecular Mukaiyama aldol reaction of the TMS enol ether with the acetal was mediated by titanium tetrachloride.[14] It generated the [5−7−6] tricyclic products **15a**−**c** in an overall yield of 79%.[15] Elimination of the C2 methoxy group from **15a**−**c** was facilitated by treatment with a catalytic amount of *p*-toluenesulfonic acid to furnish **16a** and **16b**. The successful formation of the [5−7−6] tricyclic skeleton in **15a** and **15b** as well as the *endo* selectivity of the Diels−Alder reaction were corroborated by the X-ray structures of isomers **15a** and **15b** (Figure 1). Isomer **15c** is an oil, and its X-ray structure is not available. However, the fact that isomer **15c** generated the same elimination product (**16b**) as isomer **15b** established that it has the same cis stereochemistry between the C11-methyl and the C8-hydrogen as isomer **15b**. The C11-methyl group in **15a** has the opposite stereochemistry of **15b** and **15c**. The ratio between the amount of **15a** and the sum of **15b** and **15c** is about 1:1, indicating that the addition of lithium dimethylcuprate to compound **14** was not stereoselective. In the future, if the conjugate addition is not stereoselective with the fully

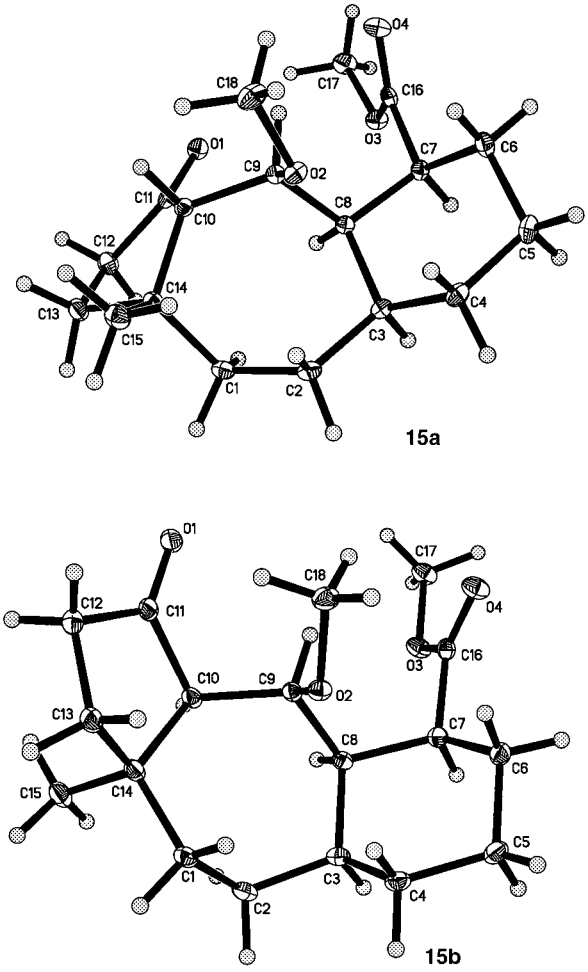
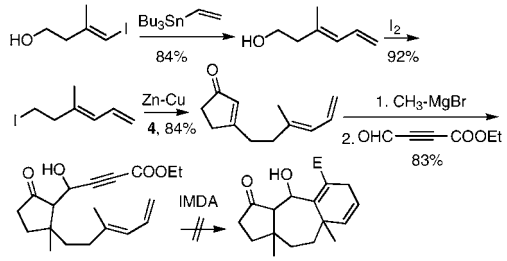


Figure 1. X-ray (ORTEP) structures of **15a** and **15b**.

(4) Similar to Hanna's approach (ref 3q) to construct seven- and six-membered rings simultaneously through ring-closing metathesis, our initial strategy was to generate the seven- and six-membered ring of guanacastepene A at the same time as shown below:



Starting from the (*E*)-vinyl iodide known in the literature, the skeletal framework of guanacastepene A was assembled rapidly in four steps. However, the intramolecular Diels−Alder reaction (IMDA) to generate the [5−7−6] core structure of guanacastepene A did not take place even with various modifications on either the diene or the dienophile moiety. Nonetheless, the design of our current synthetic plan benefited greatly from our initial approach because the same reaction tools such as organocuprate coupling, Diels−Alder reaction, and tandem conjugate addition/aldol reaction are maintained.

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(15) Other Lewis acids such as TMSOTf, BF_3·Et_2O, and $SnCl_4$ were not as efficient as $TiCl_4$ in the Mukaiyama aldol reaction.

functionalized six-membered ring, both five- and six-membered rings will be prepared in enantiomerically pure forms to be engaged in a more convergent synthesis.

To summarize, we have synthesized the [5−7−6] tricyclic skeleton of guanacastepene A through a tandem conjugate addition/intramolecular Mukaiyama aldol reaction. Future work will focus on constructing a fully functionalized six-membered ring and on completing the total synthesis of guanacastepene A through the strategy shown in this letter.

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Supporting Information Available: Experimental procedures and characterization data for compounds **8**−**16** and crystallographic data for compounds **15a** and **15b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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