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Progress towards the total synthesis of guanacastepene A. Approaches to the construction of quaternary carbons and the 5-7-6 tricyclic carbon skeleton

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Abstract—The construction of the 5-7-6 tricyclic skeleton of guanacastepene A, including the quaternary carbons, has been achieved. The C-11 and C-8 quaternary carbons were constructed by cuprate addition and carbene insertion, respectively. The 5-7-6 tricyclic core was generated by a selective aldol and SmI_2-induced intramolecular aldehyde–alkene coupling.

Guanacastepene A (**1**) is a diterpene antibiotic isolated by Clardy and co-workers in 2000 from the extracts of fungus living on the branch of a *Daphnopsis americana* tree (Fig. 1).[1] In the screening for antibiotic activity against drug-resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis*, guanacastepene A was discovered and has shown excellent activity against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *E. faecalis* (VREF), which are two of the most problematic drug-resistant pathogens. This promising biological profile and the challenges associated with the construction of a previously unreported guanacastane skeleton have drawn much attention from synthetic chemists. The challenges in the total synthesis of **1** include two ring-junction quaternary methyl groups and a 5-7-6 tricyclic carbon skeleton having a dense array of oxygen functionalities and double bonds only on the northern hemisphere of the molecule. Several groups, including Danishefsky,[2] Snider,[3] Magnus,[4] and Mehta,[5] have disclosed approaches to the synthesis of guanacastepene A, but the total synthesis has not been achieved. These approaches have in common the formation of a hydroazulene core, followed by the introduction of the six-membered ring onto the existing seven-membered ring.

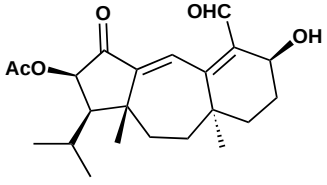

Figure 1. Structure of guanacastepene A (**1**).

Our approach towards the total synthesis of guanacastepene A (**1**) involves a conceptually different strategy whereby the seven-membered ring would be formed at the later stage of the synthesis from an elaborated A and C ring-containing precursor. More specifically, the α,β-unsaturated ketoaldehyde **3**, possessing the necessary C-8 and C-11 quaternary carbons and the C-12 isopropyl group in their correct stereochemical relationship, would serve as a pivotal substrate for the formation of the seven-membered ring via the C-2 and C-3 bond formation to generate a complete 5-7-6 carbocyclic core **2** of guanacastepene A (Scheme 1). Ketoaldehyde **3** would be derived from cyclopentene **4**, which in turn was envisioned to be constructed from two readily available building blocks, verbenone **6** and citronellyl bromide **7** via the intermediacy of **5**. For the installation of the C-11 quaternary carbon, a conjugate addition of a suitable carbon nucleophile to the facially-biased homochiral verbenone was chosen, while the C-8 quaternary carbon was planned to be created by a stereospecific carbene insertion reaction from a precursor having the strategically positioned C-16 methyl group.[6,7]

In practice, we used (*S*)-citronellyl bromide to generate **8** due to the higher cost of (*R*)-isomer **7**,[8] which would give the opposite stereochemistry of the C-8 quaternary

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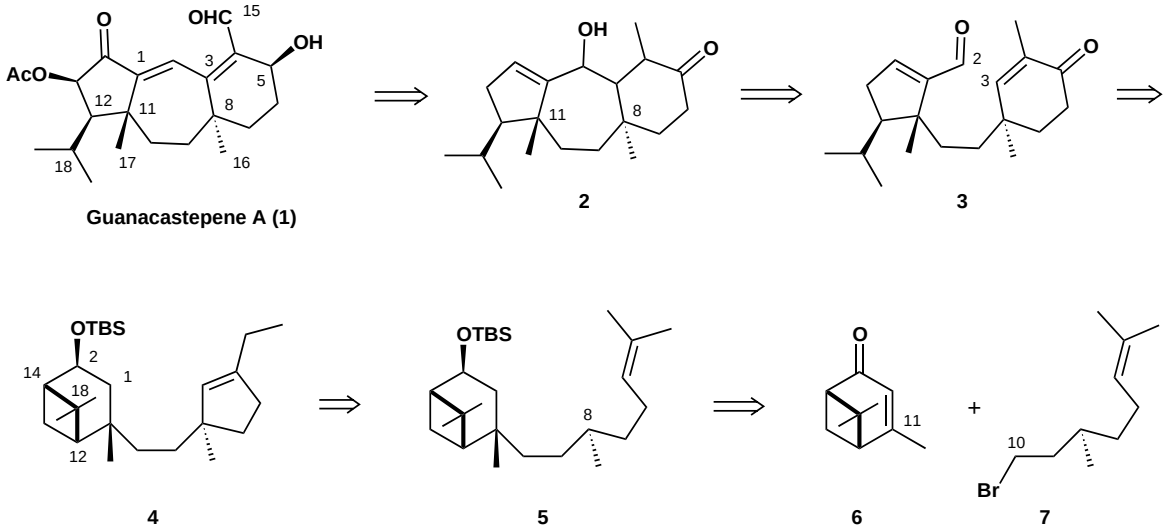
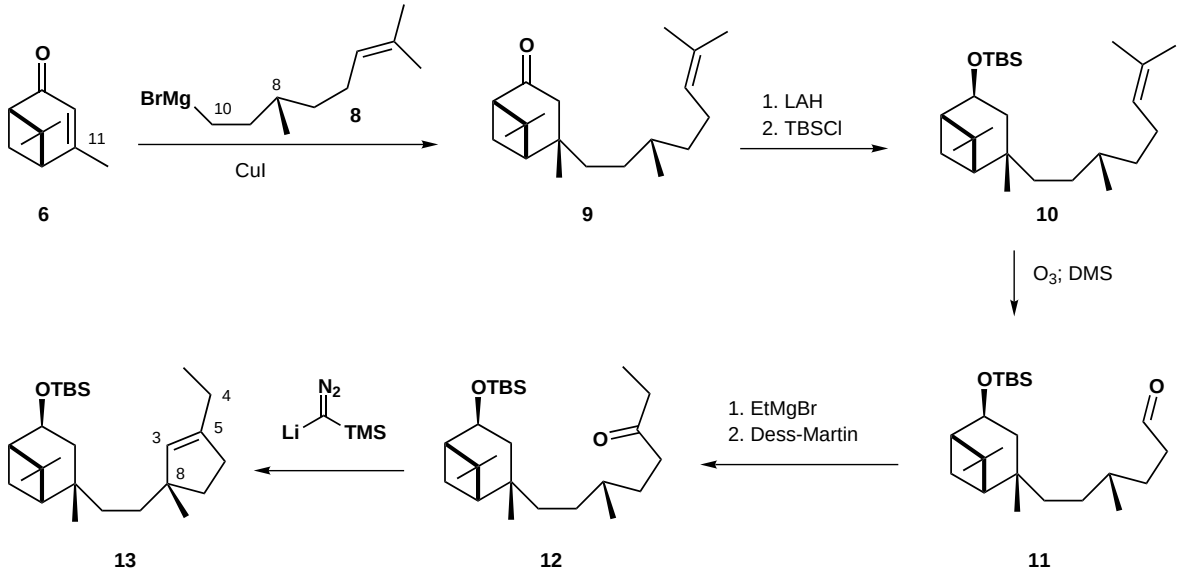


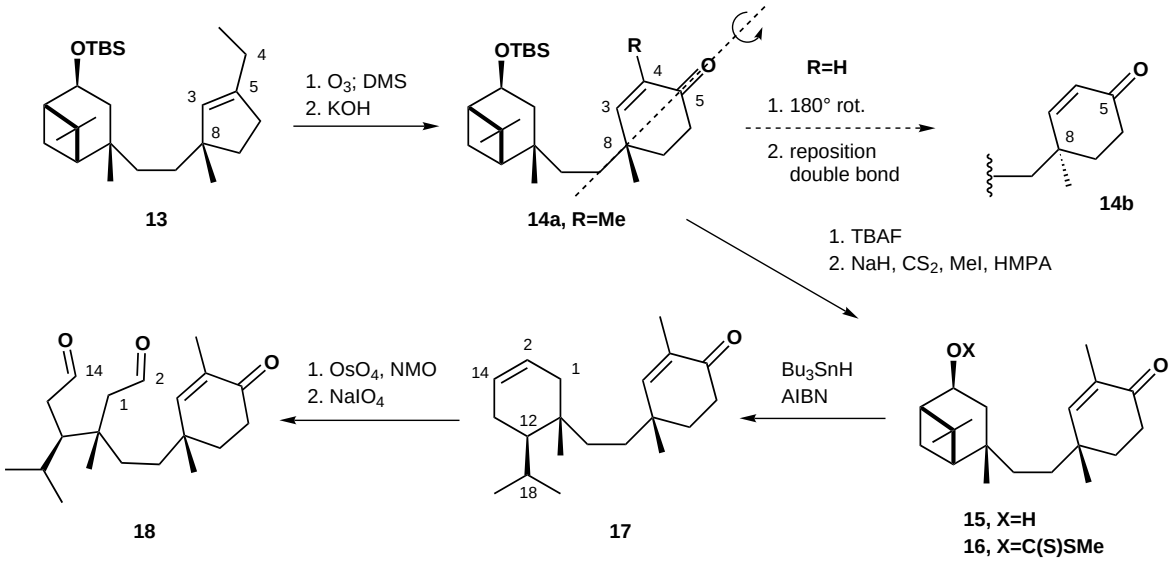
Scheme 1. Retrosynthetic analysis of guanacastepene A (**1**).

carbon compared to that of guanacastepene A upon carbene insertion. The decision entails the inversion of stereochemistry at C-8. This seemingly difficult task would be realized rather easily by repositioning the double bond from C-3 and C-4 to C-6 and C-7 position on a compound like **14b** (R = H) that has a freely rotating bond between C-8 and C-9 position. Having set the inversion strategy for C-8 quaternary center, the most urgent agenda to be addressed in our current synthesis plan for guanacastepene A is the formation of C–C bond between C-2 and C-3 with substrate similar to **3**. In order to test the viability of this bond-forming process at the earliest possible stage, we decided to construct C-8 epimer **19**.

The copper-catalyzed addition of Grignard reagent **8**, derived from (*S*)-citronellyl bromide, to (1*S*)-verbenone **6** led to the formation of 1,4-adduct **9** in 85% yield (Scheme 2).[9] Reduction of the carbonyl group ($LiAlH_4$, THF, −78°C) and TBS protection of the corresponding secondary alcohol (TBSCl, imidazole, DMF) gave the TBS ether **10** as a single diastereomer (95% for two steps). Ozonolysis and reductive workup (O_3, CH_2Cl_2, −78°C; Me_2S) afforded the unstable aldehyde **11** (60%), which was directly reacted with ethyl Grignard reagent to give the ethyl carbinol (85%). The epimeric mixture of the secondary alcohols was oxidized with Dess–Martin periodinane, producing the ethyl ketone **12** (56%), which was treated with lithium(trimethylsilyl)diazomethane (Me_3SiCHN_2, *n*-BuLi, THF, −78°C) to smoothly generate the cyclopentene **13** (93%).[7] Oxidative cleavage of cyclopentene **13** (O_3, CH_2Cl_2, −78°C; Me_2S) followed by immediate treatment of the ketoaldehyde with KOH in MeOH led to the formation of cyclohexenone **14** in 81% yield (Scheme 3).[7a,b] Deprotection of the TBS ether (Bu_4NF, THF, 70°C, 8 h) produced the secondary alcohol **15**, which occurred under relatively harsh conditions, presumably due to



Scheme 2. Generation of C-11 and C-8 quaternary carbons.

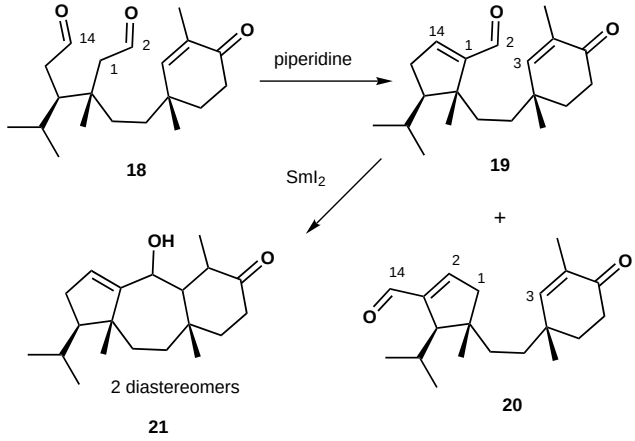


Scheme 3. Generation of C-12 isopropyl group and preparation for formation of 5-7-6 tricyclic carbon skeleton.

the steric nature of the dimethylmethano-bridge of the bicyclic system. Optimization of reaction conditions for the deprotection was achieved by using *p*-toluenesulfonic acid in MeOH at 25°C for 3 h to afford the alcohol in 90% yield. Formation of the xanthate **16** (NaH, CS_2, THF/HMPA; MeI, 70°C, 86%)[10] followed by subsequent treatment with tributyltin hydride (Bu_3SnH, AIBN, toluene, 110°C) led to the cyclobutane ring-opened alkene **17** (68%) together with varying amounts of the simple reduction product. Selective cleavage of the more electron-rich double bond of **17** via the standard two-step protocol (OsO_4, NMO, THF/H_2O; $NaIO_4$) produced the bis-aldehydes **18**.[11]

At this juncture, it was not obvious which aldol formation would be favored under what reaction conditions. Pleasingly, reaction of the bis-aldehydes **18** with excess piperidine in diethyl ether at room temperature led to the selective formation of α,β-unsaturated aldehyde **19** (52% from **17**) over the other possible aldol reaction product **20** in a ca. 5:1 ratio (Scheme 4).[12] Interestingly, a careful monitoring of the conversion of **18** to **19** showed the classical Curtin–Hammett kinetic behavior. It was observed that at the early stage of the reaction the undesired regioisomeric aldol product formed predominantly, but it did not undergo rapid water elimination to give **20**. Instead, the reversible retroaldol process slowly drained the undesired aldol to **19** via the faster water elimination from the desired minor aldol intermediate. Securing the synthesis of aldehyde **19** has set the stage for exploring a number of cyclization reactions to form the seven-membered ring. Initially, we have tried those cyclization reactions that will maintain the unsaturation on the six-membered ring after the cyclization, such as ene reaction,[13] nitrile oxide-mediated cycloaddition,[14] and the thiazolium-catalyzed Stetter reaction.[15] But none of these reactions provided the desired tricyclic structure. Instead, under these reaction conditions either the substrate decomposed or no reaction occurred. At this point we decided to do reductive coupling between enal and enone although one of the double bonds would be lost during the coupling. Pleasingly, treatment of aldehyde **19** with SmI_2 in THF in the presence of *t*-BuOH provided the 5-7-6 tricyclic core **21** of guanacastepene A (**1**) as two diastereomers (45%) (Scheme 4).[16] Extensive NMR spectroscopic studies and mass spectrometry have confirmed the connectivity of the tricyclic carbon skeleton. However, the assignment of stereochemistry of the newly generated stereogenic centers was inconclusive based on NOESY experiments.

In summary, we have delineated a unique and viable approach to the synthesis of the quaternary carbons and the 5-7-6 tricyclic carbon skeleton of guanacastepene A (**1**). The C-11 quaternary carbon can be synthesized in a highly stereoselective manner by cuprate addition to verbenone while the C-8 quaternary carbon can be generated stereospecifically by alkylidene insertion chemistry. Further progress on the total synthesis of guanacastepene A (**1**) by using the current approach will be reported in due course.



Scheme 4. Generation of the 5-7-6 tricyclic carbon skeleton of guanacastepene A.

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