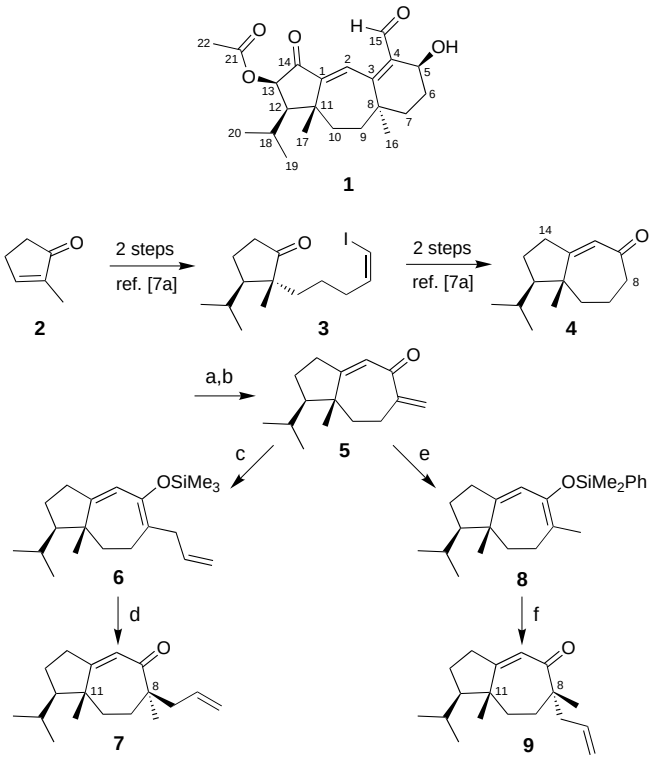
Synthesis of the Functionalized Tricyclic Skeleton of Guanacastepene A: A Tandem Epoxide-Opening β-Elimination/Knoevenagel Cyclization**

Derek S. Tan, Gregory B. Dudley, and Samuel J. Danishefsky*

Guanacastepene A (**1**, Scheme 1) is the parent member of a family of diterpene natural products produced by an unclassified endophytic fungus from the Guanacaste Conservation Area in Costa Rica.[1] Initial interest in this compound arose from its activity against antibiotic-resistant bacteria. However, subsequent experiments in *E. coli imp* and observed hemolytic activity against human red blood cells supported nonspecific membrane lysis as its mode of action.[1b] Despite the discouraging implications for its usefulness as an antibiotic,[2] guanacastepene A remains a synthetic target of current interest owing to its novel structure and the possibility of exploring the activity of this family in other biological assays.[1c] Interestingly, the cultured fungus no longer produces guanacastepene A.[3] To date, synthetic studies have been reported by a number of other groups[4–6,28] as well as by our group.[7]



Scheme 1. Structure of guanacastepene A (**1**) and synthesis of epimeric allyl methyl hydroazulenones **7** and **9**. a) LiHMDS, THF, $-78\,^{\circ}C$, 1 h, then add to Eschenmoser's salt (Me_2NCH_2I), THF, $-78\,^{\circ}C \rightarrow RT$, 20 min; b) MCPBA, CH_2Cl_2/aqueous $NaHCO_3$ (2:1), 86% over two steps; c) $CH_2{=}CHMgBr$, CuI, HMPA, TMSCl, THF, $-78\,^{\circ}C$, 25 min; d) MeLi, THF, $0\,^{\circ}C$, 10 min, then MeI, HMPA, $-78\,^{\circ}C \rightarrow RT$, 20 min, 77% over two steps; e) $PhMe_2SiH$, Wilkinson's catalyst ($[Ph_3P]_3RhCl$; 1%), benzene, reflux, 20 min; f) MeLi, THF, $0\,^{\circ}C$, 10 min, then allyl iodide, $-78\,^{\circ}C \rightarrow RT$, 30 min, 69% over two steps. HMDS = hexamethyldisilazane, MCPBA = *m*-chloroperoxybenzoic acid, HMPA = hexamethyl phosporamide, TMS = trimethylsilyl.

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Our next goal was that of constructing the novel tricyclic core of guanacastepene A from the suitably configured hydroazulenone **7**. Naively, we thought this would be a straightforward matter following traditional methods of steroid and terpenoid annulation. As we show herein, the pathway from **7** to the core system was beset by several unanticipated difficulties. Fortunately, the solution devised to solve these problems carried us closer to the total synthesis goal than would have been the case through the envisioned sequence.

The early phase of our approach to guanacastepene A, outlined in Scheme 1, exploited successive β,α-dialkylation to fashion vinyl iodide **3**. Reductive cyclization followed by oxidative rearrangement led to **4**.[7a] Upon α-methylenation of **4** by means of the Eschenmoser salt[8a] Mannich protocol,[8b,c] compound **5** was available.[7b] As previously reported and amplified in Scheme 1, the stereochemistry at C8 (guanacastepene A numbering) can be controlled by stepwise introduction of two alkyl groups with due attention to proper sequencing. In the case of geminal allyl and methyl groups, the group introduced second enters from the face of C8 that is *anti* to the angular methyl group attached to C11 (i.e., α as shown). Correspondingly, the resident group emerges in the β configuration in **7** and **9**.

Elaboration of 8β-allyl-8α-methyl hydroazulenone **7** proceeded in analogy to literature precedent (Scheme 2).[9] Protection of the enone as a dioxolane (**10**) with concurrent double-bond migration[10] allowed efficient hydroboration and oxidation to yield alcohol **11**.[11] Jones oxidation[12] simultaneously installed the side-chain carboxylate and removed the dioxolane protecting group to generate keto acid **12**. Notably, reconjugation of the enone did not occur under these conditions. Cyclization of **12** afforded dienol lactone **13** in moderate yield.[13]

At this stage, we attempted to employ a Turner–Fujimoto protocol to generate tricycles **15a** and **15b**.[14] Unfortunately, after the addition of either methyllithium or ethylmagnesium bromide, we obtained complex mixtures of products that were not resolved by equilibration in refluxing methanolic potassium hydroxide.[15] Although the reasons for the failure of these reactions were unclear at the time, subsequent experiments suggest that complications involving C2 may thwart the desired cyclizations.

In light of the complexities of the multistep Turner–Fujimoto sequence,[15] we elected to pursue an alternative route to the tricyclic core through direct Knoevenagel cyclization of

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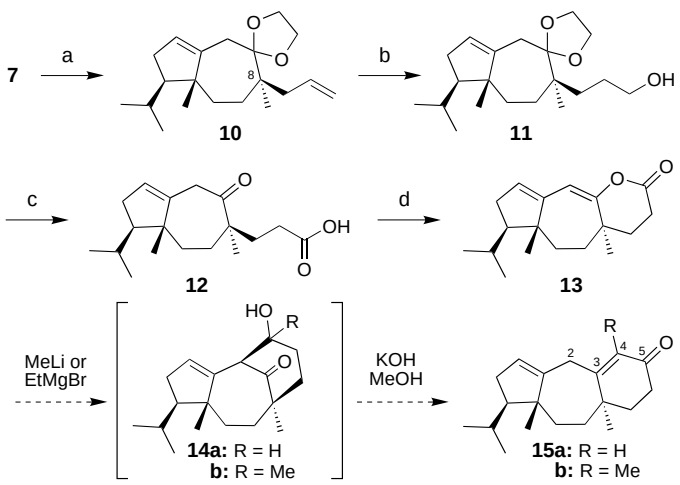
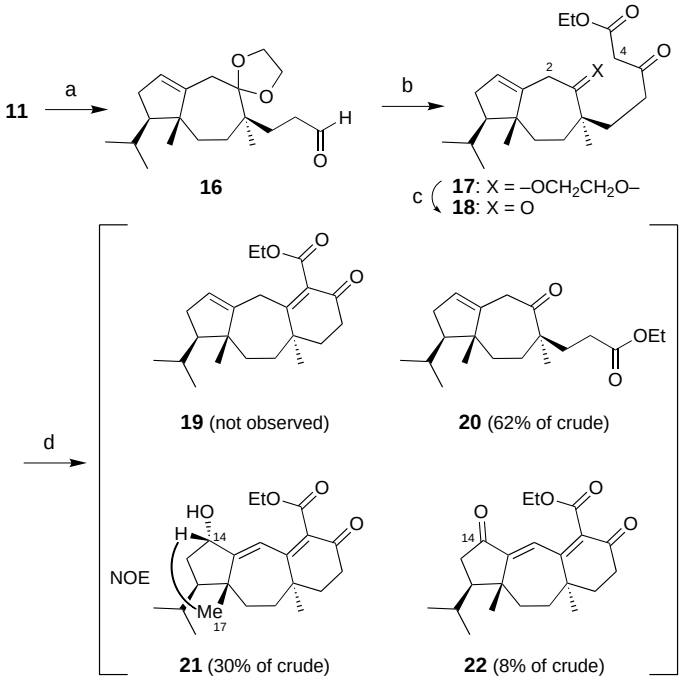


Scheme 2. Synthesis of dienol lactone **13** and attempted Turner–Fujimoto reactions. a) Ethylene glycol, TsOH, benzene, reflux, [$-H_2O$], 36 h, 89%; b) 1) 9-BBN, THF, 0 °C→RT, 3.5 h; 2) NaOH (aqueous, 3 N), H_2O_2 (aqueous, 30%), room temperature, 1.5 h, 98%; c) CrO_3, H_2SO_4, acetone, room temperature, 2 h, 62%; d) NaOAc, Ac_2O, 140 °C, 80 min, 59%. TsOH = *p*-toluene sulfonic acid, 9-BBN = 9-borabicyclo[3.3.1]nonane.

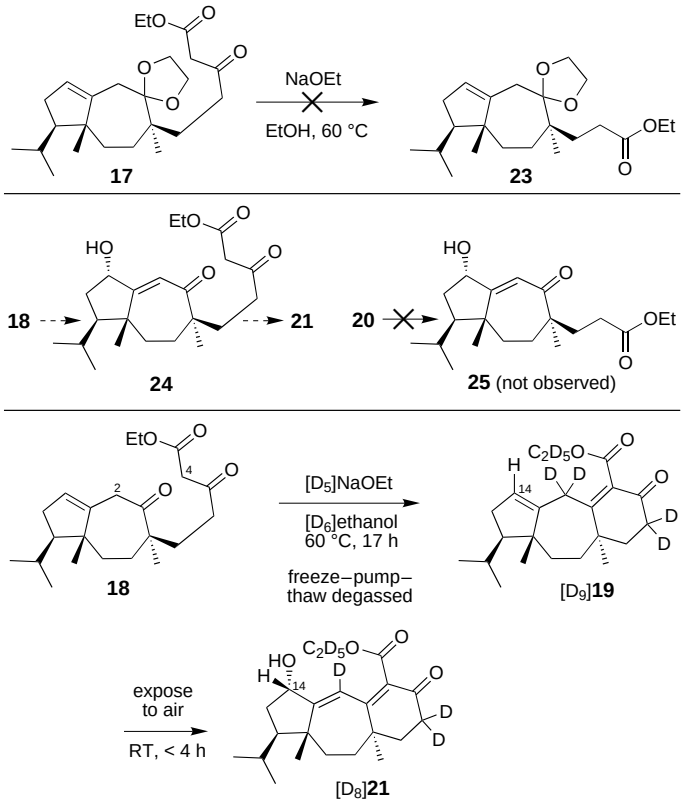
the discrete β-keto ester precursor **18** (Scheme 3). We recognized that the ethyl ester in **18** could also serve as a suitable precursor to the required C15 aldehyde in guanacastepene A (**1**). Toward this end, alcohol **11** was oxidized[16] to give aldehyde **16**, which was then converted directly into β-keto ester **17** by using ethyl diazoacetate and tin(II) chloride.[17] Deprotection of the dioxolane[18] afforded β,ζ-diketo ester **18**.[19]



Scheme 3. Conversion of alcohol **11** into β,ζ-diketo ester **18** and attempted Knoevenagel cyclization. a) Dess–Martin periodinane, CH_2Cl_2, room temperature, 2 h, 83%; b) ethyl diazoacetate ($N_2CHCOOEt$), $SnCl_2$, CH_2Cl_2, room temperature, 3.5 h; c) TsOH, H_2O in acetone (5%), 70 °C, 90 min, 80% over two steps; d) NaOEt, EtOH, 60 °C, 19 h.

With the desired substrate in hand, we were poised to attempt the key Knoevenagel cyclization.[20] Exposure of **18** to sodium ethoxide in ethanol at 60 °C resulted in slow conversion into a mixture of products.[21] Surprisingly, the expected cyclization product **19** was not observed. Instead, the major product was the "truncated" ethyl ester **20**. Additionally, two minor products were identified as tricyclic alcohol **21** and tricyclic diketone **22**. The configuration at C14 in **21** was assigned tentatively based upon NOESY correlation between 14-H and the angular C17 methyl group. Both cyclized products exist at room temperature as two slowly interconverting conformers whose NMR resonances coalesce upon heating. Similar conformational behavior has been reported for guanacastepene A.[1a]

A number of further studies were conducted to investigate the pathways leading from **18** to **20** and **21** (Scheme 4). First, exposure of the dioxolane-protected β-keto ester **17** to the Knoevenagel cyclization conditions did not result in the



Scheme 4. Experimental probes for the mechanisms of formation of **20** and **21**.

formation of the corresponding truncated ester **23**. This clearly suggests a role of the ζ-keto group of **18** in the formation of **20**. Next, we considered the order of the oxidation and cyclization steps to form **21**. A pathway that involves initial oxidation to **24** followed by cyclization to **21** is not supported since the corresponding oxidation product **25** of the truncated ester **20** was not observed in the cyclization reaction. Finally, when the cyclization reaction was carried out with rigorous exclusion of air in deuterated solvent (gas-tight NMR tube, freeze–pump–thaw degassed five cycles), the

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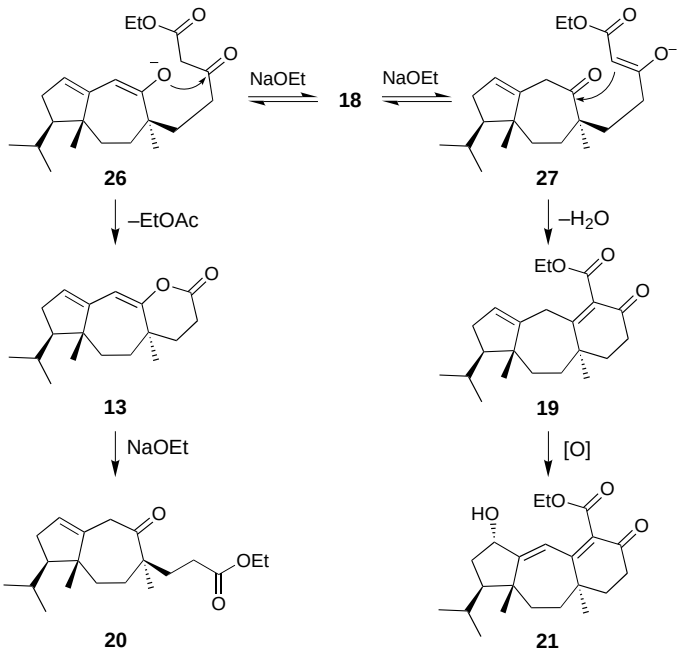
originally expected cyclization product [D_9]**19** could be detected by mass spectrometric analysis of the crude reaction mixture.[22] Furthermore, the ^{1}H NMR resonance of the C14 methine proton of [D_8]**21** ([D_6]ethanol, RT, $\delta = 4.38$ ppm, m)[23] appeared only after the reaction mixture was exposed to air.

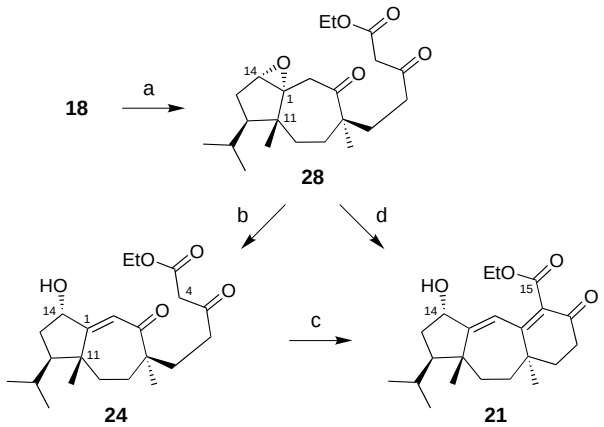
We therefore hypothesize that the truncated ester **20** and the oxidized tricycle **21** are formed from **18** by two competing reaction pathways (Scheme 5). Compound **18** is distinguished from typical Knoevenagel cyclization substrates by the



Scheme 5. Proposed mechanisms for the formation of **20** and **21** during attempted Knoevenagel cyclization of **18**. Enhanced acidity at the α-carbon of the unconjugated hydroazulenone (**18** → **26**) allows a retro-Claisen condensation to form dienol lactone **13**, which undergoes ethanolysis to give "truncated" ester **20**. This reaction competes with the desired α-deprotonation of the β-keto ester (**18** → **27**), which forms the putative unconjugated tricycle **19**. Unless oxygen is rigorously excluded from the reaction, this compound undergoes oxidation to the conjugated hydroxy tricycle **21**.

enhanced acidity of the unconjugated enone α-protons at C2. Thus, under the reaction conditions, formation of the hydroazulenone enolate **26** could set the stage for reaching dienol lactone **13** through a retrograde Claisen condensation, which would be followed by ethanolysis to **20**. The corresponding dioxolane **17**, which lacks the feature of a participating ζ-enolate, does not undergo fragmentation to **23**. Concurrently, formation of the β-keto ester enolate **27** likely does, in fact, lead to the expected unconjugated tricycle **19**. However, this compound apparently undergoes rapid oxidation (see **21** and **22**) unless oxygen is rigorously excluded from the reaction.

One cannot help but notice that tricycles **21** and **22**, although formed in low yield, possess potentially useful oxygen functionalities at C14. Accordingly, we next undertook to introduce this oxygen group *purposefully*. Thus, **18** was converted into epoxide **28** (Scheme 6). Epoxide-opening β-elimination at room temperature provided conjugated



Scheme 6. Epoxidation of unconjugated hydroazulenone **18** and stepwise or tandem epoxide-opening β-elimination/Knoevenagel cyclization to form tricycle **21**. a) MCPBA, CH_2Cl_2, 0 °C, 2 h, 89 %; b) NaOEt, EtOH, room temperature, 30 min; 82 %; c) NaOEt, EtOH, 50 °C, 6 h; 74 %; d) NaOEt, EtOH, 50 °C, 6 h, 80 %.

γ-hydroxy hydroazulenone **24**.[24, 25] We were gratified to find that this substrate underwent facile Knoevenagel cyclization at elevated temperature to produce tricycle **21**. Apparently, the reactivity of **24** is sufficiently altered relative to that of the unconjugated substrate **18**, that the desired cyclization reaction is favored. Notably, the corresponding truncated ester **25** was not observed in the crude product. Moreover, the yield of the reaction sequence could be further increased by converting **28** directly into **21** by means of a tandem epoxide-opening β-elimination/Knoevenagel cyclization reaction.[26]

In summary, difficulties in synthesizing the tricyclic dienone core of guanacastepene A when using the Turner–Fujimoto reaction led us to develop a novel and efficient tandem epoxide-opening β-elimination/Knoevenagel cyclization reaction. Importantly, our route has the added benefit of installing desirable oxygen functionalities at C14 and C15 of tricycle **21**. As a result, we had in hand a far more mature precursor of guanacastepene A than the initially projected target **15**. Seemingly, a clear route to **1** was in place. However, as described in the following paper, some major surprises awaited us in completing this goal.[27]

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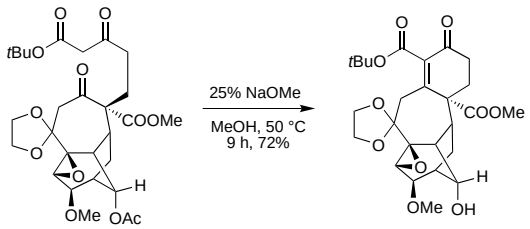

[21] For experimental and structure determination details of **20**, **21**, and **22**, see Supporting Information.
[22] The unconjugated tricycle [D_9]**19** could not be unambiguously detected by ^{1}H NMR spectroscopic analysis because of deuterium exchange at C2 and a solvent signal that obscured the vinylic C14-H region.
[23] Assigned by analogy to C14-H for **21** in $CDCl_3$ at room temperature ($\delta = 4.34$, br d, $J = 5.31$ Hz).
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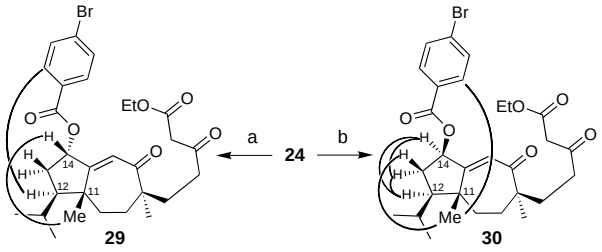
[25] Confirmation of the stereochemical assignment at C14 of **24** (and indirectly at C14 of **21** and **28**) was made by multidimensional NMR spectroscopic analysis of the *p*-bromobenzoate derivative **29** and its C14 epimer **30**. Notably, whereas the angular methyl group at C11 apparently blocks the β-face at C1 to promote epoxidation on the α-face of the C1–C14 olefin of **18**, successful Mitsunobu inversion at C14 of **24** indicates that the C11 methyl group does not overridingly block the β-face at that remote site. The significance of these observations with respect to the introduction of the C13 acetoxy group will be described in the following paper.[27] a) *p*-BrBzCl, DMAP, Et_3N, CH_2Cl_2, room temperature, 1 h, 27% (not optimized); b) *p*-BrBzOH, DIAD, PPh_3, THF, 0 °C → RT, 1 h, 55% (not optimized). DMAP = 4-(dimethylamino)pyridine, DIAD = diisopropyl azodicarboxylate. NOE interactions (——).



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[28] Note added in proof: since the acceptance of this paper, new studies toward the synthesis of guanacastepene A have been published; see a) S. N. Gradl, J. J. Kennedy-Smith, J. Kim, D. Trauner, *Synlett* **2002**, *3*, 411 – 414; b) T. M. Nguyen, D. Lee, *Tetrahedron Lett.*, article in press, available on the WWW 1 May 2002; c) W. D. Shipe, E. J. Sorenson, *Org. Lett.*, in press, ASAP article, available on the WWW 16 May 2002.

A Stereoselective Route to Guanacastepene A through a Surprising Epoxidation**

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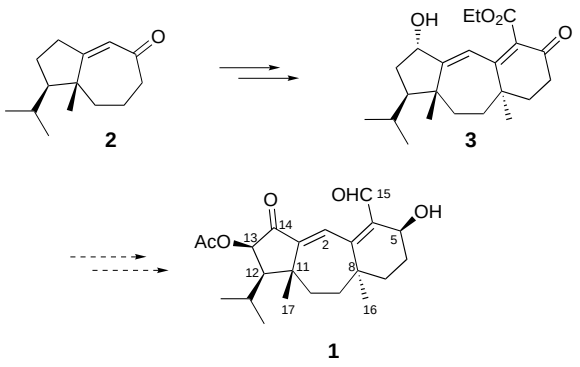
In the preceding paper we reported the preparation of compound **3** (Scheme 1),[1] which bears much of the functionality required, in principle, to reach guanacastepene A (**1**).[2, 3]



Scheme 1. Overview of the synthetic strategy towards **1**.

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