Synthetic Studies toward the Guanacastepenes

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ABSTRACT





The guanacastepenes are a family of structurally diverse diterpenes isolated from an unidentified endophytic fungus found in the Guanacaste Conservation Area of Costa Rica (Figure 1).¹ Some members, such as guanacastepene A, display potent antibiotic activity against drug-resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis*. In light of their reported hemolytic activity, however, the potential of the guanacastepenes as lead compounds for drug development remains to be seen.

Architecturally, the natural products are marked by a highly unsaturated and oxygenated lower rim and a nonpolar upper half. Their common carbocyclic [6-7-5] core contains two quaternary stereocenters in a 1,4-relationship and is often fused to additional heterocycles.

Since the disclosure of their structures by Clardy et al., numerous synthetic approaches to the guanacastepenes have surfaced in the literature.² In 2002, Danishefsky reported the total synthesis of racemic guanacastepene A^{2h,i} using a synthetic route that was subsequently intercepted at a late stage by Snider.^{2c} Alternative approaches have been reported by the groups of Magnus,^{2d,e} Mehta,^{2j-/} Sorensen,²ⁿ Lee,^{2o,p} Tius,^{2q} Hanna,^{2r} and Kwon.^{2s} The asymmetric total synthesis of a guanacastepene, however, has not yet been disclosed.

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Our synthetic strategy calls for the combination of two enantiomerically pure building blocks, **1** and **2**, representing the six- and five-membered rings of the guanacastepenes. Subsequently, the central seven-membered ring would be closed along the bond indicated in Scheme 1. Cyclopentenone **2** has been previously obtained in racemic form through ring-closing metathesis.^{2m,3} We now report the asymmetric synthesis of furanocyclohexanol **1** and describe our first forays into the formation of the seven-membered ring.

The synthesis starts with known 2,3-diiodofuran (**3**, Scheme 2).⁴ Monolithiation of this compound at low temperature⁵ followed by addition of the organolithium species



Figure 1. Selected guanacastepenes.

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to (E)-4-methylhex-4-enal⁶ and oxidation furnished furyl ketone **4**.^{2m} Enantioselective reduction of this material was achieved by using (–)-*B*-chlorodiisopino-campheylborane (DIP-Cl) in 94% ee. The absolute configuration was assigned by analogy with literature precedence.⁷

The six-membered ring was formed via intramolecular Heck reaction,⁸ using the method described by Jeffery.⁹ Under optimized conditions, alcohol **5** cyclized to give an inseparable 5.1:1 mixture of **1** and its diastereomer **6** in good yield. Protection of the secondary alcohol followed by hydroboration/oxidation gave a mixture of diastereomeric primary alcohols from which the major isomer **8** could be separated by column chromatography.¹⁰

The relative configuration of alcohol **7** was elucidated via extensive NMR studies as well as an X-ray structure of diol **8** (Figure 2), formed by desilylation of **7**.

The favorable diastereoselectivity of the intramolecular Heck reaction was found to be dependent on the presence

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(10) The 9-BBN adduct was also found to readily engage in Suzuki couplings.



^{*a*} Reagents and conditions: (a) *n*-BuLi, Et₂O, -78 °C, then (*E*)-4-methylhex-4-enal, 62%; (b) DMP, CH₂Cl₂, rt, 88%; (c) (–)-DIP-Cl, THF, -20 °C, 75%; (d) Pd(OAc)₂, Et₃N, (*n*-Bu)₄NBr, MeCN, H₂O, 75 °C, 83%; (e) TBDPSCl, imid., DMAP, CH₂Cl₂, 0 °C, 98%; (f) (1) 9-BBN, THF, reflx., (2) EtOH, NaOH, H₂O₂, rt, 81%; (g) HF•pyr., pyr., THF, rt, 54%.

of the free secondary hydroxy group in **5**. Protected versions of **5** cyclized with decreased or inverted selectivity (Scheme 3). Similar observations concerning the directing effect of a nearby functional group have been made by Overman in the context of a total synthesis of gelsemine.¹¹

Several methods can be envisaged to unravel the furan and form the central seven-membered ring. A particularly attractive one involving the rhodium-catalyzed decomposition of a furyl diazo ester is shown in Scheme 4.

The reaction between carbenoids derived from diazocarbonyl compounds and furans provides rapid entry into 2,4diene-1,6-dicarbonyl systems. Intramolecular versions have been described by Wenkert, Padwa, and Davies.¹² To the best of our knowledge, applications of this chemistry in the synthesis of complex natural products have not yet been described.



Figure 2. X-ray structure of compound 8.

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^{*a*} Reagents and conditions: (a) TBSCl, imid., DMAP, CH_2Cl_2 , rt, 98%; (b) (1) NaH, THF, 0 °C, (2) MeI, 72%; (c) Pd(OAc)₂, Et₃N, (*n*-Bu)₄NBr, MeCN, H₂O, 75 °C.

In our model study for a synthesis of guanacastepene A, alcohol 7^{13} was converted into homologated aldehyde 11 with use of a standard sequence of steps. The DBU-catalyzed addition of ethyl diazoacetate to this aldehyde then afforded 12.¹⁴ Since direct oxidation of 12 to diazoester 13 was met with difficulties, the compound was first treated with rhodium acetate to give the corresponding β -ketoester. Diazo transfer with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) then furnished 13. Finally, exposure of 13 to rhodium acetate led to formation of aldehyde 15 in 50% unoptimized yield. This reaction presumably proceeds through intermediate 14, which could exist as a cyclopropane derivative or as a zwitterionic structure.^{12g} Note that the product 15 includes the entire unsaturated lower half of the guanacastepenes and the fully substituted cyclohexene ring.

In summary, we have demonstrated that the central sevenmembered ring of the guanacastepenes can be established through intramolecular reaction between a carbenoid and a furan. Though the synthesis of diazoester 13 could certainly be streamlined, the focus of future investigations will lie in the procurement of enantiomerically pure enone 2 and the

(13) For the sake of convenience and cost, racemic material wa elaborated in the subsequent steps.



^{*a*} Reagents and conditions: (a) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, 91%; (b) MePPh₃Br, *n*-BuLi, THF, 0 °C, 95%; (c) (1) 9-BBN, THF, rt, (2) EtOH, NaOH, H₂O₂, rt, 92%; (d) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C; (e) ethyl diazoacetate, DBU (cat.), MeCN, rt, 76% (two steps); (f) Rh₂(OAc)₄, CH₂Cl₂, rt, 95%; (g) *p*-ABSA, Et₃N, MeCN, rt, 92%; (h) Rh₂(OAc)₄, CH₂Cl₂ (0.002 M), rt, 50%.

efficient linkage of the two segments. Total syntheses of enantiomerically pure guanacastepenes are well underway in our laboratories and will be reported in due course.

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Supporting Information Available: Spectroscopic and analytical data for compounds 1, 3–7, 11–13, and 15, as well as X-ray structural data of compound 8 (CCDC-219930). This material is available free of charge via the Internet at http://pubs.acs.org.

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