

# Synthetic Studies toward the Guanacastepenes

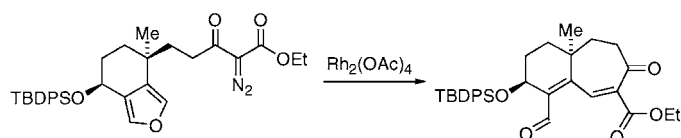
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## ABSTRACT



An asymmetric approach toward the [6–7] ring system of the guanacastepenes is described.

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).<sup>1</sup> 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.<sup>2</sup> In 2002, Danishefsky reported the total synthesis of racemic guanacastepene A<sup>2h,i</sup> using a synthetic route that was subsequently intercepted at a late stage by Snider.<sup>2c</sup> Alternative approaches have been reported by the groups of Magnus,<sup>2d,e</sup> Mehta,<sup>2j–l</sup> Sorensen,<sup>2n</sup> Lee,<sup>2o,p</sup> Tius,<sup>2q</sup> Hanna,<sup>2r</sup> and Kwon.<sup>2s</sup> The asymmetric total synthesis of a guanacastepene, however, has not yet been disclosed.

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.<sup>2m,3</sup> 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).<sup>4</sup> Monolithiation of this compound at low temperature<sup>5</sup> followed by addition of the organolithium species

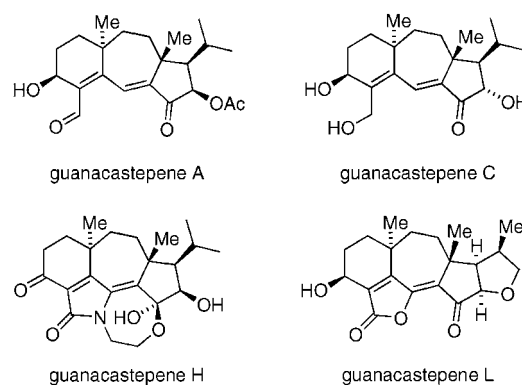
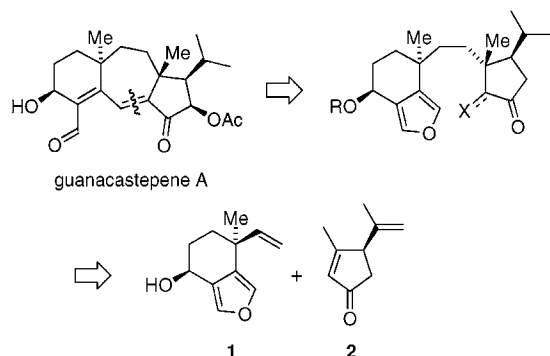


Figure 1. Selected guanacastepenes.

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**Scheme 1.** Retrosynthetic Analysis of Guanacastepene A



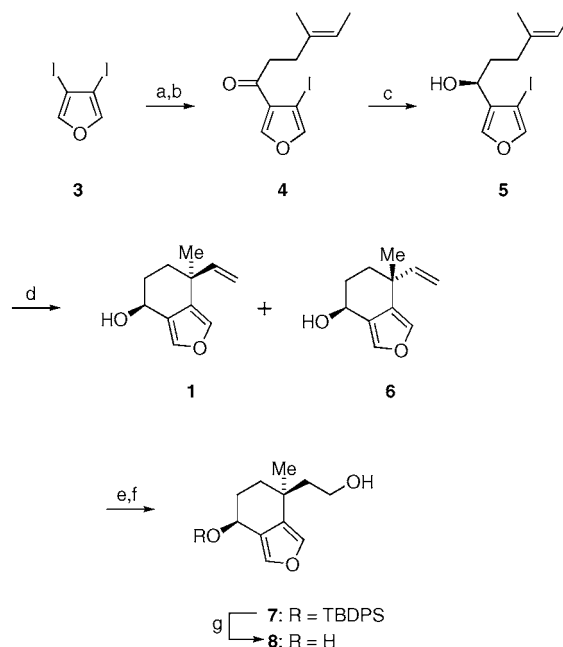
to (*E*)-4-methylhex-4-enal<sup>6</sup> and oxidation furnished furyl ketone **4**.<sup>2m</sup> Enantioselective reduction of this material was achieved by using (–)-*B*-chlorodiisopinocampheylborane (DIP-Cl) in 94% ee. The absolute configuration was assigned by analogy with literature precedence.<sup>7</sup>

The six-membered ring was formed via intramolecular Heck reaction,<sup>8</sup> using the method described by Jeffery.<sup>9</sup> 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.<sup>10</sup>

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

**Scheme 2<sup>a</sup>**



<sup>a</sup> Reagents and conditions: (a) *n*-BuLi, Et<sub>2</sub>O, –78 °C, then (*E*)-4-methylhex-4-enal, 62%; (b) DMP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 88%; (c) (–)-DIP-Cl, THF, –20 °C, 75%; (d) Pd(OAc)<sub>2</sub>, Et<sub>3</sub>N, (*n*-Bu)<sub>4</sub>NBr, MeCN, H<sub>2</sub>O, 75 °C, 83%; (e) TBDPSCI, imid., DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 98%; (f) (1) 9-BBN, THF, refl., (2) EtOH, NaOH, H<sub>2</sub>O<sub>2</sub>, 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.<sup>11</sup>

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 2,4-diene-1,6-dicarbonyl systems. Intramolecular versions have been described by Wenkert, Padwa, and Davies.<sup>12</sup> To the best of our knowledge, applications of this chemistry in the synthesis of complex natural products have not yet been described.

- (2) (a) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123. (b) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569. (c) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030. (d) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947. (e) Magnus, P.; Ollivier, C. *Tetrahedron Lett.* **2002**, *43*, 9605. (f) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399. (g) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789. (h) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185. (i) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188. (j) Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063. (k) Mehta, G.; Umarye, J. D.; Gagliardini, V. *Tetrahedron Lett.* **2002**, *43*, 6975. (l) Mehta, G.; Umarye, J. D.; Srinivas, K. *Tetrahedron Lett.* **2003**, *44*, 4233. (m) Gradl, S. N.; Kennedy-Smith, J. J.; Kim, J.; Trauner, D. *Synlett* **2002**, 411. (n) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063. (o) Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033. (p) Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. *Org. Lett.* **2002**, *4*, 3959. (q) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363. (r) Boyer, F.-D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469. (s) Du, X.; Chu, H. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923.

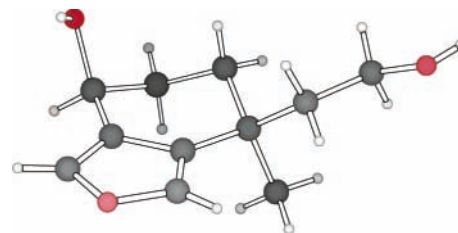
(3) Efforts to render the RCM *enantiotopos*-selective have thus far met with limited success.

- (4) Kraus, G. A.; Wang, X. *Synth. Commun.* **1998**, *28*, 1093. (5) Gorzynski, M.; Rewicki, D. *Liebigs Ann. Chem.* **1986**, 625. (6) Ho, N.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 2018. (7) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.

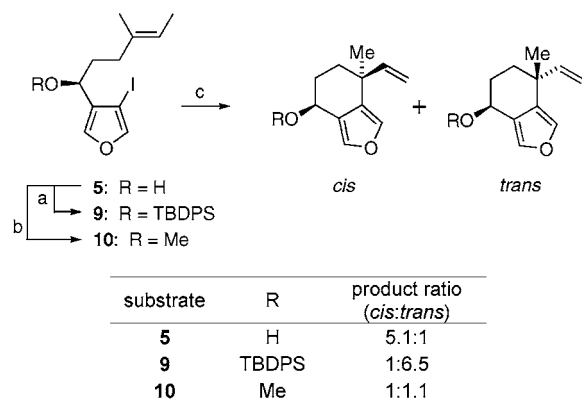
(8) (a) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1880. For reviews, see: (b) Link, J. T.; Overman, L. E. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: Weinheim, Germany, 1998; Chapter 6, pp 231–269. (c) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.

(9) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

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



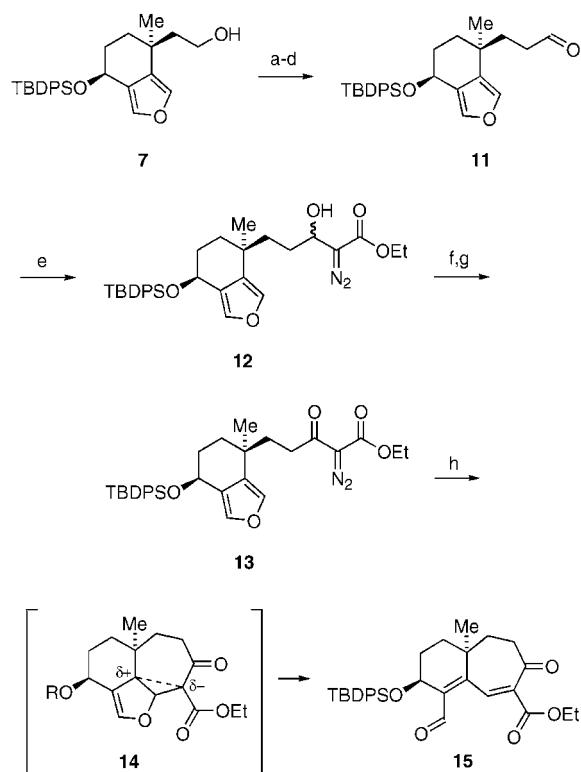
**Figure 2.** X-ray structure of compound **8**.

Scheme 3<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) TBSCl, imid., DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 98%; (b) (1) NaH, THF, 0 °C, (2) MeI, 72%; (c) Pd(OAc)<sub>2</sub>, Et<sub>3</sub>N, (*n*-Bu)<sub>4</sub>NBr, MeCN, H<sub>2</sub>O, 75 °C.

In our model study for a synthesis of guanacastepene A, alcohol **7**<sup>13</sup> 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**.<sup>14</sup> Since direct oxidation of **12** to diazoester **13** was met with difficulties, the compound was first treated with rhodium acetate to give the corresponding  $\beta$ -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.<sup>12g</sup> 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 seven-membered 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

Scheme 4<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 91%; (b) MePPh<sub>3</sub>Br, *n*-BuLi, THF, 0 °C, 95%; (c) (1) 9-BBN, THF, rt, (2) EtOH, NaOH, H<sub>2</sub>O<sub>2</sub>, rt, 92%; (d) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (e) ethyl diazoacetate, DBU (cat.), MeCN, rt, 76% (two steps); (f) Rh<sub>2</sub>(OAc)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 95%; (g) *p*-ABSA, Et<sub>3</sub>N, MeCN, rt, 92%; (h) Rh<sub>2</sub>(OAc)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub> (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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