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An Electrochemical Approach to the Guanacastepenes

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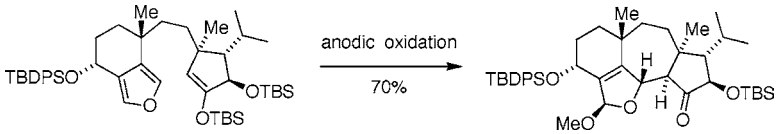
ABSTRACT



An asymmetric approach toward the [6–7–5] ring system of the guanacastepenes is described.

The guanacastepenes are a family of diterpenes sharing a common carbon skeleton that has been modified through various oxidations. Their simpler members, for instance, guanacastepene A and C, feature a tricyclic ring system with a highly oxidized "lower" and an unfunctionalized "upper rim" (Figure 1). Several more complex congeners, such as guanacastepenes E, I, K, and L, have been isolated that contain additional dihydrofuran or furanone moieties.

Guanacastepene A has received considerable attention by the synthetic community due to its interesting antibiotic activity and attractive molecular structure. In addition to Danishefsky's total synthesis, more than 10 distinct synthetic approaches toward the molecule have been reported, including two formal syntheses.[1] However, the asymmetric total synthesis of a guanacastepene has not yet been disclosed.

In previous communications, we have outlined a convergent synthetic strategy that hinges on the closure of the central seven-membered ring at a late stage (Scheme 1).[2] It also calls for the combination of two enantiomerically pure

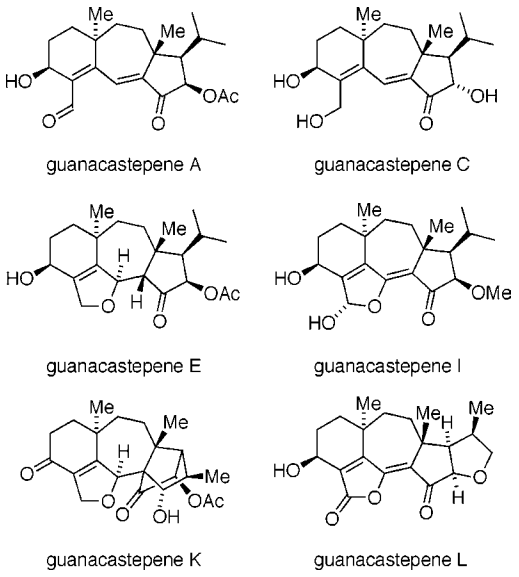


Figure 1. Selected guanacastepenes.

(1) (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) Mandal, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2004**, *45*, 3827. (k) Mandal, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2004**, *45*, 3831. (l) Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063. (m) Mehta, G.; Umarye, J. D.; Gagliardini, V. *Tetrahedron Lett.* **2002**, *43*, 6975. (n) Mehta, G.; Umarye, J. D.; Srinivas, K. *Tetrahedron Lett.* **2003**, *44*, 4233. (o) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063. (p) Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033. (q) Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. *Org. Lett.* **2002**, *4*, 3959. (r) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363. (s) Boyer, F.-D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469. (t) Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817. (u) Du, X.; Chu, H. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923. (v) Du, X.; Chu, H. V.; Kwon, O. *Tetrahedron Lett.* **2004**, *45*, 8843. (w) Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491. (x) Srikrishna, A.; Dethe, D. H. *Org. Lett.* **2004**, *6*, 165. (y) Chiu, P.; Li, S. *Org. Lett.* **2004**, *6*, 613.

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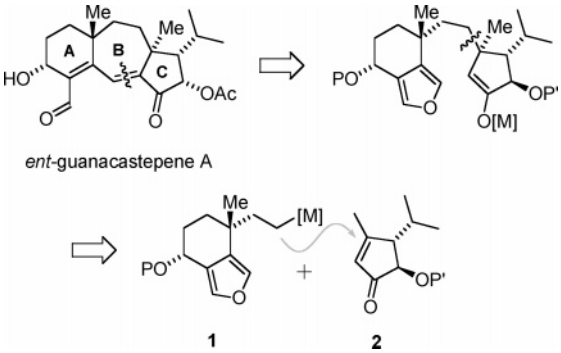
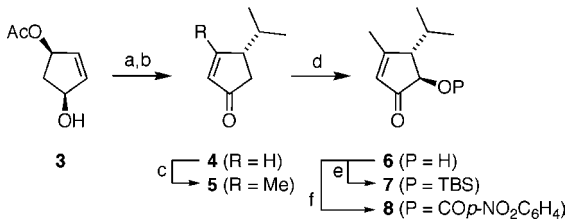
Scheme 1. Retrosynthetic Analysis of *ent*-Guanacastepene A



building blocks, **1** and **2**, representing the A and C rings of the guanacastepenes. Following a diastereoselective conjugate addition of organometallic compound **1** to cyclopentenone **2**, the central B ring would be closed along the bond indicated in Scheme 1. While the initially envisioned rhodium-based ring closure has not yet transpired (see below), the remarkable synthetic versatility of the furan moiety allowed us to forge the guanacastepene skeleton in another way. Concomitantly, the focus of our program has shifted toward the more complex tetracyclic guanacastepenes, such as guanacastepenes E and I. We now wish to report the synthesis of an advanced precursor of these targets, which contains the entire carbon skeleton of the guanacastepenes. For practical reasons, this study was conducted in the nonnatural enantiomeric series.

Starting with enantiopure alcohol **3**, a multigram synthesis of a chiral cyclopentenone corresponding to **2** was developed in our laboratories (Scheme 2). This alcohol, readily obtained

Scheme 2[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 94%; (b) (1) *i*-PrMgBr, CuBr·DMS, HMPA, TMSCl, THF, −78 °C → −40 °C, (2) CSA, H_2O, CH_2Cl_2, reflx., 63%; (c) (1) Me_2CuLi, TMSCl, Et_2O, −40 °C, (2) $Pd(OAc)_2$, MeCN, rt, 70%; (d) LDA, THF, −78 °C, then (1*R*)-(−)-(10-camphorsulfonyl)-oxaziridine, −30 °C, 85%; (e) TBSCl, imid., DMF, rt, 93%; (f) *p*-$NO_2C_6H_4COCl$, Et_3N, DMAP, CH_2Cl_2, reflx., 79%.

from the achiral diacetate using an electric eel acetylcholineesterase (EEAC),[3] was first oxidized to the cyclopentenone. Conjugate addition of isopropyl-magnesium bromide in the presence of catalytic amounts of copper(I) then yielded a single diastereomer,[4] which upon treatment with acid underwent elimination to furnish compound **4** in 90% ee. Presumably, this loss in enantiomeric purity results from the reversible acid-catalyzed isomerization of the cyclopentenone to the achiral β,γ-unsaturated ketone.

Cyclopentenone **4** was subsequently treated with Me_2CuLi in the presence of chlorotrimethylsilane (TMSCl), and the resulting enol ether was subjected to Saegusa oxidation to form **5** in good overall yield.[5] Reaction of the lithium enolate with the camphor-based oxaziridine developed by Davis gave acyloin **6**.[6,7] Notably, both enantiomers of the oxaziridine produced, exclusively, the trans diastereomer, indicating that the diastereoselectivity of the process is entirely controlled by the substrate. Finally, protection of the secondary alcohol furnished silyl ether **7**.

The trans configuration of the chiral cyclopentenone was confirmed with an X-ray crystal structure of compound **8** (Figure 2), formed via acylation of the free alcohol with *p*-nitrobenzoyl chloride.

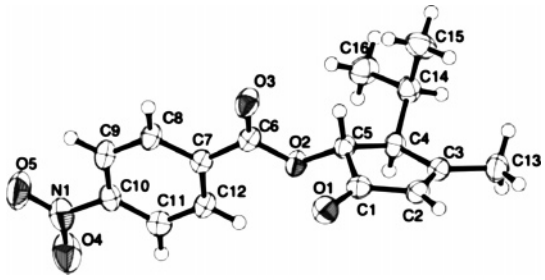


Figure 2. X-ray structure of compound **8**.

A synthetic route to the "left-hand" fragment (**1**), which we have described previously,[2] begins with 2,3-diiodofuran (**9**, Scheme 3).[8] Addition of the lithiated furan to aldehyde **10**[9] and oxidation furnished the furyl ketone. Enantioselective reduction of this material was achieved using (+)-*B*-chlorodiisopinocampheylborane (DIP-Cl) to give **11** in 94% ee. The six-membered ring was then formed via intra-

(2) (a) Gradl, S. N.; Kennedy-Smith, J. J.; Kim, J.; Trauner, D. *Synlett* **2002**, 411. (b) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113.

(3) (a) Deardorff, D. R.; Myles, D. C. *Organic Syntheses*; Wiley & Sons: New York, 1993; Collect. Vol. 8, p 13. (b) Deardorff, D. R.; Windham, C. Q.; Craney, C. L. *Organic Syntheses*; Wiley & Sons: New York, 1998; Collect. Vol. 9, p 487.

(4) (a) Patterson, J. W., Jr.; Fried, J. H. *J. Org. Chem.* **1974**, *39*, 2506. (b) Suzuki, M.; Kawagishi, T.; Yanagisawa, A.; Suzuki, T.; Okamura, N.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1299.

(5) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

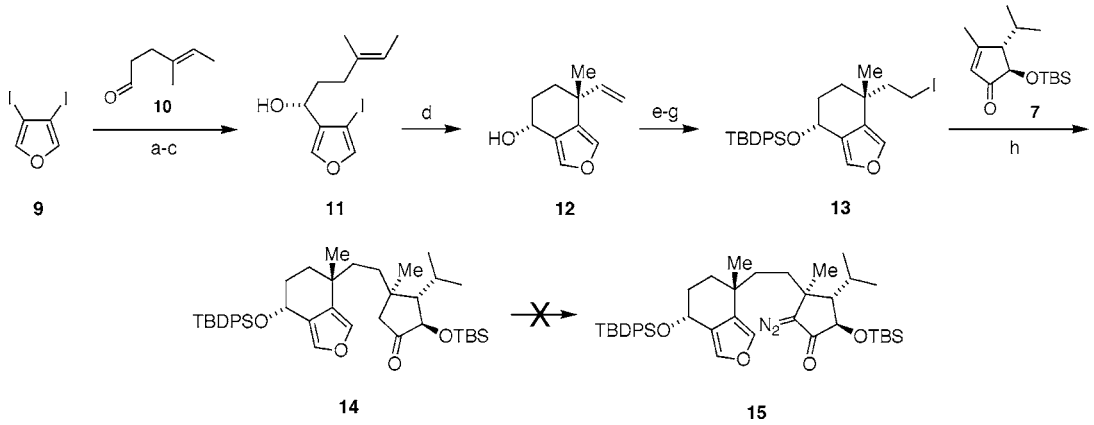
(6) (a) Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986**, *51*, 4083. (b) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carrol, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477.

(7) None of the desired material was obtained upon reacting the enolate with 2-(phenylsulfonyl)-3-phenyloxaziridine, described in (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. A known side product of this reaction, which we observed as well, is formed from addition of the enolate to the sulfonimine. See: (b) Davis, F. A.; Wei, J.; Sheppard, A. C.; Guberick, S. *Tetrahedron Lett.* **1987**, *28*, 5115. (c) Smith, A. B., III; Dorsey, B. D.; Ohba, M.; Lupo, A. T., Jr.; Malamas, M. S. *J. Org. Chem.* **1988**, *53*, 4314.

(8) Kraus, G. A.; Wang, X. *Synth. Commun.* **1998**, *28*, 1093.

(9) Ho, N.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 2018.

Scheme 3[a]



[a] Reagents and conditions: (a) *n*-BuLi, Et_2O, −78 °C, then **10**, 62%; (b) Dess−Martin periodinane, CH_2Cl_2, rt, 88%; (c) (+)-DIP-Cl, THF, −20 °C, 75%; (d) $Pd(OAc)_2$, Et_3N, $(n\text{-}Bu)_4NBr$, MeCN, H_2O, 75 °C, 75%; (e) TBDPSCl, imid., DMAP, CH_2Cl_2, 0 °C, 98%; (f) (1) 9-BBN, THF, reflx., (2) EtOH, NaOH, H_2O_2, rt, 81%; (g) I_2, PPh_3, imid., THF, 0 °C → rt, 90%; (h) *t*-BuLi, Et_2O, −78 °C, then (2-thienyl)Cu(CN)Li, THF, then **7**, $BF_3{\cdot}OEt_2$, −40 °C, 50%.

molecular Heck reaction to yield a 5.1:1 mixture of diastereomers.[10] Finally, in three steps, the major diastereomer **12** was further elaborated to iodide **13**.

The two fragments were then coupled through a challenging cuprate conjugate addition (see Scheme 3).[11] In this event, lithiation of iodide **13** was followed by treatment with lithium 2-thienylcyanocuprate.[12] The resulting mixed, higher-order heterocuprate was treated with cyclopentenone **7** in the presence of boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) to furnish **14**. Similar yields were achieved with the Gilman cuprate derived from copper(I) iodide and 3,3-dimethylbutyne as the dummy ligand.[13] Again, the use of $BF_3{\cdot}OEt_2$ was indispensable for efficient addition of this cuprate to the hindered cyclopentenone. Unfortunately, the additive precluded interception of the enolate as the silyl enol ether.

Encouraged by previous model studies, we next sought to unravel the furan in **14** and form the central seven-membered ring via a rhodium-catalyzed cyclopropanation/rearrangement reaction.[14] Our efforts toward the elaboration of **14** to the required diazo ketone **15**, however, were met with little success.[15] Using various sulfonyl azides as diazo transfer reagents, we were unable to effect the desired transformation either directly[16] or with several α-acylated derivatives of **14**. The reaction suffers, presumably, from the steric congestion afforded by the adjacent quaternary carbon center.

The difficulty associated with making diazo compound **15** led us to consider alternatives for forming the central seven-membered ring. We realized that coupling of the nucleophilic furan to the enol form of the cyclopentanone moiety would require some form of "umpolung", most easily achieved by oxidation of one of these components to the corresponding radical cation. To this end, we turned our attention toward the electrooxidative coupling of silyl enol ethers and furans. This methodology, developed by the groups of Moeller[17a,b] and Wright,[17c−e] has been used in the preparation of several annulated furans, including a key intermediate in the synthesis of the natural product (−)-alliacol A.[17b] Very recently, Wright showed that a *gem*-dialkyl effect is required for the efficient formation of seven-membered rings,[18] rendering our system ideal for the implementation of this methodology.

Formation of the kinetic enolate of ketone **14** in the presence of *tert*-butyldimethylsilyl triflate (TBSOTf) cleanly gave silyl enol ether **16** (Scheme 4). This material was then dissolved in a dichloromethane/methanol mixture and sub-

(10) (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. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: Weinheim, Germany, 1998; Chapter 6, p 231.

(11) Ibuka, T.; Yamamoto, Y. *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; Chapter 7, p 143.

(12) (a) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945. (b) Lipshutz, B. H. *Synthesis* **1987**, 325.

(13) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

(14) (a) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1986**, *51*, 5036. (b) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1989**, *54*, 299. (c) Wenkert, E.; Guo, M.; Pizzo, F.; Ramachandran, K. *Helv. Chim. Acta* **1987**, *70*, 1429. (d) Wenkert, E.; Decorzant, R.; Näf, F. *Helv. Chim. Acta* **1989**, *72*, 756. (e) Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J.-H. *J. Org. Chem.* **1990**, *55*, 6203. (f) Davies, H. M. L.; McAfee, M. J.; Oldenburg, C. E. M. *J. Org. Chem.* **1989**, *54*, 930. (g) Davies, H. M. L.; Calvo, R. L. *Tetrahedron Lett.* **1997**, *38*, 5623.

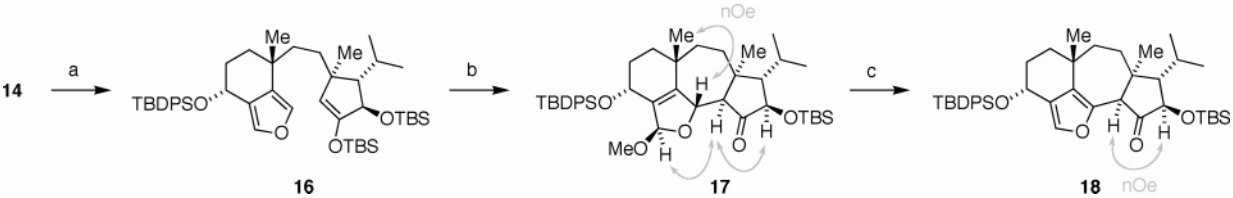
(15) (a) Regitz, M. *Synthesis* **1972**, 351. (b) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: Orlando, FL, 1986; Chapter 13, p 326. (c) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998; Chapter 1, p 1.

(16) For example, see: Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

(17) (a) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 36. (b) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 9106. (c) Wright, D. L.; Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Frey, D. A. *Org. Lett.* **1999**, *1*, 1535. (d) Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Wright, D. L. *Org. Lett.* **2002**, *4*, 3763. (e) Sperry, J. B.; Whitehead, C. R.; Ghiviriga, I.; Walczak, R. M.; Wright, D. L. *J. Org. Chem.* **2004**, *69*, 3726. For a review of anodic electrochemistry, see: (f) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527.

(18) Sperry, J. B.; Wright, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 8034.

Scheme 4[a]



[a] Reagents and conditions: (a) LDA, TBSOTf, THF, HMPA −78 °C, 93%; (b) RVC anode (0.2 mA), 2,6-lutidine, 0.06 M $LiClO_4$, 20% MeOH in CH_2Cl_2, rt, 17 h, 2.44 F/mol, 70%; (c) HCl, H_2O, THF, rt, 85%.

jected to anodic oxidation at constant current using a reticulated vitreous carbon (RVC) anode and a platinum cathode. Under these carefully optimized conditions, acetal **17** was formed in good yield and as a single diastereomer. Note that **17**, whose stereochemistry was fully assigned by detailed nOe measurements, corresponds to guanacastepenes E and I. Acetal **17**, which was stable to silica gel chromatography, could be further reacted with aqueous acid to form the corresponding furan **18**. The relative stereochemistry of this advanced intermediate was also confirmed by 2D NOESY experiments, as a strong correlation was observed between the α and α′ protons of the C ring (see Scheme 4).

In summary, we have procured the tricyclic framework found in the guanacastepene family of natural products using an electric eel esterase-catalyzed saponification, several conjugate additions, and an electrochemical oxidation as key steps. Current work in our laboratories is devoted to the elaboration of either acetal **17** or furan **18** to one of the guanacastepenes and the development of other cyclopentenone building blocks corresponding to **2**. Alternative methods of installing the α-diazo group onto ketone **14**, and so accessing other members of the guanacastepene family via rhodium-catalyzed cyclopropanation/rearrangement, are also being explored.

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Supporting Information Available: Spectroscopic and analytical data for compounds **4**−**7**, **13**, **14**, **16**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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