ORGANIC LETTERS

2002
Vol. 4, No. 20
3363−3366

Synthesis of the Hydroazulene Portion of Guanacastepene A from the Cyclopentannelation Reaction

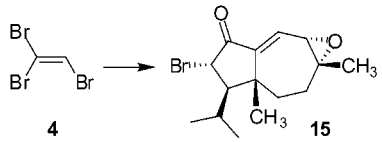
Atsuo Nakazaki, Utpal Sharma, and Marcus A. Tius*

Department of Chemistry, 2545 The Mall, University of Hawaii, Honolulu, Hawaii 96822, and The Cancer Research Center of Hawaii, 1236 Lauhala Street, Honolulu, Hawaii 96813

tius@gold.chem.hawaii.edu

Received June 26, 2002

ABSTRACT



Commercially available tribromoethylene has been converted to ketoepoxide 15, an advanced intermediate in the total synthesis of guanacastepene A.

Guanacastepene A (Figure 1) was isolated from cultures of an endophytic fungus from a Costa Rican tree in 2000 by Clardy and co-workers.[1] In 2001 the structures of a series of congeners were disclosed by the same group.[2] Guanacastepene A is active against vancomycin-resistant *Enterococcus faecalis* (VREF) and against methicillin-resistant *Staphylococcus aureus* (MRSA). For example, against MRSA guanacastepene A and vancomycin produce 11- and 17-mm zones of inhibition, respectively, at 100 μg/mL. At 100 μg/mL guanacastepene A produces a 9-mm zone of inhibition against VREF, whereas vancomycin is completely ineffective.[3] Nevertheless, guanacastepene A is not likely to be developed into a useful therapeutic agent because it also lyses red blood cells efficiently. It is an interesting target for total synthesis because it represents a new carbon skeleton. Several approaches to guanacastepene A have been disclosed,[4] as well as a total synthesis by Danishefsky.[5]

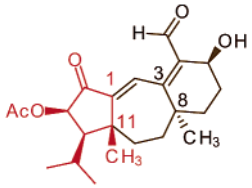


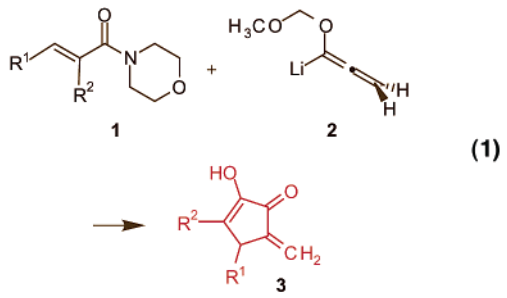
Figure 1. Guanacastepene A.

Although guanacastepene A is a rather simple structure, there are challenges associated with the construction of the two stereogenic quaternary carbon atoms at C11 and C8. The close homology between the five-membered ring portion of the natural product and the general structure of the cyclopentenones that are accessible from the allenyllithium/

(1) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116.
(2) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900.
(3) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256.
(4) (a) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569. (b) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399. (c) Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063. (d) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947. (e) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789. (f) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123. (g) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063. (h) Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033.
(5) (a) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Ang. Chem., Int. Ed.* **2002**, *41*, 2188. (b) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Ang. Chem., Int. Ed.* **2002**, *41*, 2185.

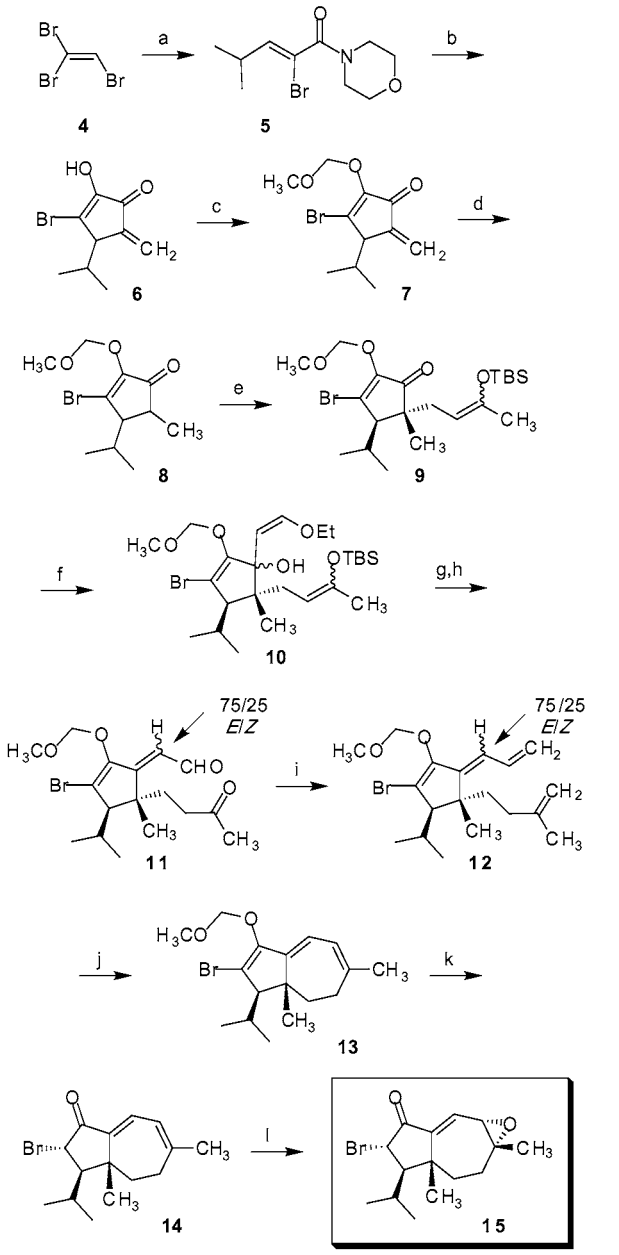
10.1021/ol026428f CCC: $22.00
Published on Web 08/31/2002

vinyl amide cyclopentannelation reaction (eq 1) suggested that an α,β-unsaturated morpholino amide such as **1** could serve as the starting material for the synthesis.[6] We recognized several possibilities for the construction of the "left-hand" portion of guanacastepene A by means of the reaction of eq 1. In this Letter we describe the successful implementation of one of these strategies for the synthesis of the fully functionalized hydroazulene portion of the natural product.



The synthesis is summarized in Scheme 1. The preparation of α-bromoamide **5** was accomplished in a single operation from tribromoethylene **4**. Exposure of **4** to 2 equiv of lithium morpholinamide led initially to dehydrobromination to generate dibromoacetylene. A second equivalent of lithium morpholinamide, acting as a nucleophile, displaced one of the bromine atoms from dibromoacetylene, presumably though an addition−elimination process, to give 1-bromo-2-morpholinoacetylene.[7] Addition of a small excess of isobutyraldehyde led to amide **5** in good yield as a single *Z* geometrical isomer. Amide **5** is an excellent substrate for the allenylithium/vinyl amide cyclopentannelation reaction. Treatment of **5** with a modest excess of allenyllithium species **2** at −78 °C in THF, followed by quenching with acidic ethanol led to cyclopentenone **6** in 75% yield. Our goal was to use the isopropyl group in **6** to control stereochemistry at C11 (guanacastepene numbering). Accordingly, the free hydroxyl group in **6** was first protected as the methoxymethyl ether (91% yield) to produce **7**. The exocyclic methylene group in **7** could be saturated cleanly under 1 atm of hydrogen gas in the presence of catalytic 5% Rh on alumina.[8] Under these conditions enone **8** was isolated in 81% yield as a 95/5 mixture of diastereomers. The choice of catalyst appears to be important for the success of this reaction. All attempts to use Pd on carbon led to hydrogenolytic cleavage of the carbon−bromine bond in addition to the desired reaction. The liberated strong acid led to ethanolysis of the methoxymethyl enol ether.

Scheme 1[a]



[a] Reaction conditions: (a) 2 equiv of Li-morpholinamide, THF, −78 °C, 1 h; add 1.3 equiv of isobutyraldehyde; reflux in THF, 1 h; 71−73%; (b) 1.7 equiv of **2**, THF, −78 °C, 2.5 h; add HCl in EtOH, warm to 0 °C; 75%; (c) 1.7 equif of MOM-Cl, 2.0 equif of $(i\text{Pr})_2\text{NEt}$, CH_2Cl_2, 0 °C, 1.5 h; 91%; (d) 5% Rh on Al_2O_3, EtOH, 1 atm H_2, rt, 1.5 h; 81%; (e) (1) THF, 1.6 equiv of LDA, add **8** at −78 °C, warm to 0 °C, cool to −78 °C, 45 min; (2) add 1.5 equiv of MVK, warm to −40 °C, 15 min; cool to −78 °C; (3) add 1.5 equiv of TBSOTf; 62%; (f) 4.5 equif of 2-ethoxyvinyllithium, THF, −78 to −30 °C, 30 min; (g) 1 equiv of TBAF, THF, 0 °C, 5 min; (h) Cl_3CCO_2H, wet CH_2Cl_2, 0 °C, 5 min; 75% (*E* + *Z*) overall for the three steps from **9**; (i) 7.0 equiv of $Ph_3P{=}CH_2$, THF, −78 to 0 °C, 30 min; 71%; (j) second generation Grubbs catalyst, 0.01 M in CH_2Cl_2, 45 °C, 21 h; 82% from *E*-**12**; (k) Cl_3CCO_2H, wet CH_2Cl_2, 0 °C, 45 min; 80%; (l) CH_2Cl_2, satd aq $NaHCO_3$, 0 °C, add 5 equiv of *m*-CPBA, warm to room temperature, 1.5 h; 81%.

(6) For some examples of the cyclopentannelation, see: (a) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509. (b) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219. (c) Tius, M. A.; Hu, H.; Kawakami, J. K.; Busch-Petersen, J. *J. Org. Chem.* **1998**, *63*, 5971.

(7) (a) Movassaghi, M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2456. (b) Balsells, J.; Vazquez, J.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2000**, *65*, 7291. (c) Himbert G.; Nasshan, H.; Gerulat, O. *Synthesis* **1997**, 293. (d) Berger, D.; Bartolme, A.; Neuwenschwander, M. *Helv. Chim. Acta* **1996**, *79*, 179. (e) Sato, Y.; Kobayashi, Y.; Sugiura, M.; Shirai, H. *J. Org. Chem.* **1978**, *43*, 199.

(8) Heathcock, C. H.; DelMar, E. G.; Graham, S. L. *J. Am. Chem. Soc.* **1982**, *104*, 1907.

We chose a Michael addition to methyl vinyl ketone (MVK) for the stereochemistry-determining step. The enolate derived from **8**, which was prepared by treatment with LDA at −78 °C, was trapped with a small excess of MVK. Addition of *tert*-butyldimethylsilyl triflate to the reaction mixture before quenching led to **9** in 62% yield. Cyclopentenone **9** was formed as a mixture of *E* and *Z* isomers. The relative stereochemistry was tentatively assigned as shown in **9** (see Scheme 1). 2-Ethoxyvinyllithium[9] added cleanly to **9** to produce **10**, an intermediate with three enol ether functions. Immediate treatment of **10** with tetra-*n*-butylammonium fluoride (TBAF) followed by exposure of the reaction product to wet trichloroacetic acid in dichloromethane led to keto aldehyde **11** as a 75/25 mixture of geometrical isomers in 75% overall yield for the three steps from **9**. The major geometrical isomer at the exocyclic double bond was assigned on the basis of the positive NOE between the vinylic proton and the methylene of the methoxymethyl protecting group. Exposure of **11** to an excess of methylenetriphenylphosphorane in THF at −78 °C, followed by warming to 0 °C over 30 min, led to tetraene **12** in 71% yield. The seven-membered ring was closed by treating a 0.01 M solution of **12** (*E* + *Z*) in dichloromethane with the second-generation Grubbs catalyst (Figure 2) at 45 °C for 21 h.[10]

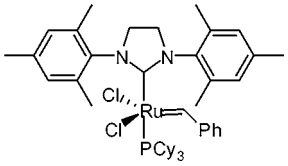


Figure 2. The second generation Grubbs catalyst.

The isolated yield of bromotriene **13** was 82% from *E*-**12**. The next task to be performed was the hydrolysis of the enol ether function in **13**. This was accomplished by exposure of **13** to wet trichloroacetic acid in dichloromethane at 0 °C to produce α-bromoketone **14** as a single isomer in 80% yield. The stereochemical assignment was verified by means of the nOe experiments on **14** that are summarized in Figure 3. Selective epoxidation of the *γ*,*δ*-double bond in **14** took place in a two-phase system of aqueous $NaHCO_3$ and *m*-CPBA in dichloromethane. Epoxide **15** was formed as a single isomer in 81% yield. The assignment of epoxide

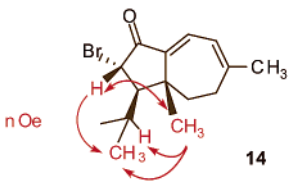
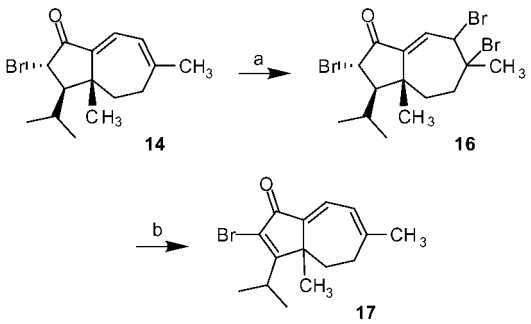


Figure 3. Nuclear Overhauser enhancements for hydroazulene **14**.

Scheme 2[a]



[a] Reaction conditions: (a) Br_2, CH_2Cl_2, 0 °C; 98%; (b) DBU, CH_2Cl_2, −78 °C; 69%.

stereochemistry in **15** is based on NOE correlations and should be considered tentative at this time. It is conceivable that the angular C11 methyl group in **14** directs the epoxidation to take place on the α surface of the diene. The overall yield of **15** from commercially available tribromoethylene is ca. 5.2% over the 12 steps.

Some features of this synthesis require comment. The 75/25 ratio of geometrical isomers of keto aldehyde **11** from the hydrolysis of **10** is apparently determined kinetically. Exposure of the isomeric mixture to phenyl disulfide and light (500 W incandescent bulb) led to a product that was highly enriched in the undesired *Z* isomer. The same preference for the *Z* isomer of the exocyclic alkene was observed during the isomerization of **12**. The isomeric ratio in both cases presumably reflects the balance between a smaller unfavorable $A^{1,3}$ interaction with the (methoxy)methoxy group on one hand and a larger steric effect imposed by the adjacent quaternary carbon atom on the other. It is therefore quite puzzling that addition of lithium ethoxyacetylide to **9**, followed by hydrolysis and isomerization, led preferentially to the *E*-α,*β*-unsaturated ethyl ester.

Several unsuccessful attempts to functionalize C3 (guanacastepene numbering) of **14** were made before settling on epoxide **15**. For example, exposure of **14** to bromine in dichloromethane led to tribromide **16** (Scheme 2). Surpris-

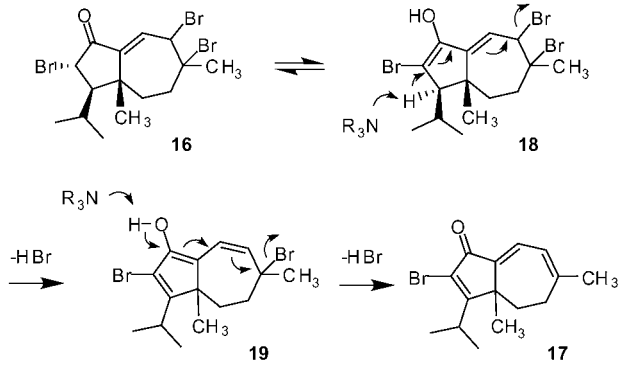


Figure 4. Postulated mechanism for the cine elimination that leads to **17**.

ingly, dehydrohalogenation of **16** with an excess of DBU in dichloromethane at −78 °C led cleanly to bromotriene **17**. This appears to be an unusual example of a cine elimination that may take place according to the mechanism shown in Figure 4.

In conclusion, the allenyllithium/vinyl amide cyclopentannelation reaction has been used to prepare the fully functionalized guanacastepene intermediate **15**. Elaboration of the remaining carbon atoms of the natural product can be accomplished through selective ring opening of the allylic epoxide function, whereas the bromine atom can be exchanged for oxygen in several ways.

Acknowledgment. We thank the National Institutes of Health (GM57873) for generous support and Callery Chemical Co. for a gift of potassium *tert*-butoxide. A.N. acknowledges support from the NSF through the ERC Program under Award EEC-9731725.

Supporting Information Available: Detailed experimental procedures and full characterization for compounds **6**, **13**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026428F

(9) Schlosser, M. In *Organometallics in Synthesis*; Schlosser, M., Ed.; John Wiley & Sons: Chichester, 1994; p 126.

(10) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. For a related example of a RCM reaction, see: Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742.