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Synthesis of the 5-7-6 Core of Guanacastepenes. Construction of C8 Quaternary Carbon via the Inversion of Stereochemistry

Truc M. Nguyen, Robert J. Seifert, Dale R. Mowrey, and Daesung Lee*

*Department of Chemistry, University of Wisconsin−Madison,
Madison, Wisconsin 53706*

dlee@chem.wisc.edu

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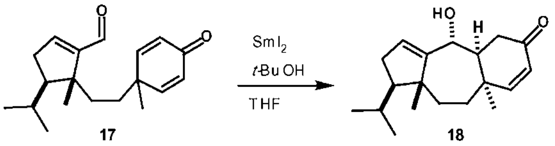
ABSTRACT



An efficient and unique route to the 5-7-6 core of guanacatepene A (1) is described. The installation of the desired stereochemistry at the C8 position was achieved via the desymmetrization of the cyclohexadienone by reductive ring closure of the seven-membered ring. That the closure of the seven-membered ring produced only the desired isomer is hypothesized to be a result of the more stable trans relationship between the C8 and C11 methyl groups.

Guanacastepene A (**1**) is a new class of diterpene natural product isolated from the extracts of endophytic fungus living on the branch of a *Daphnopsis americana* tree in the Guanacaste Conservation Area in Costa Rica (Figure 1).[1] In the screening for antibiotic activity against drug-resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis*, guanacastepene A has initially shown an excellent activity against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *E. faecalis* (VREF), which are two of the most problematic drug-resistant pathogens.[2] Subsequent study indicates that **1** exerts its biological effect by nonspecific membrane lysis, causing hemolysis in human red blood cells.[1c] The initially observed promising biological profile and the challenges associated with the construction of a previously unreported guanacastane skeleton have invited much attention from synthetic chemists. The challenges in the total synthesis of **1** include two ring-junction quaternary methyl groups and a new 5-7-6 tricyclic carbon skeleton having a dense array of oxygen and unsaturated functionalities. While many groups disclosing approaches to the synthesis of **1**,[3] including Danishefsky's recent total synthesis,[3f,g] propose formation of a hydroazulene core,

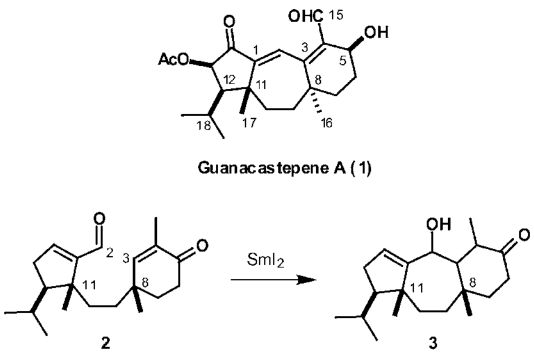


Figure 1. A reductive ring closure for the construction of the 5-7-6 tricyclic core of 8-*epi*-guanacastane.

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[1] (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116. (b) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900. (c) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J. *J. Antibiot.* **2000**, *53*, 256.

[2] Swartz, M. N. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 2420.

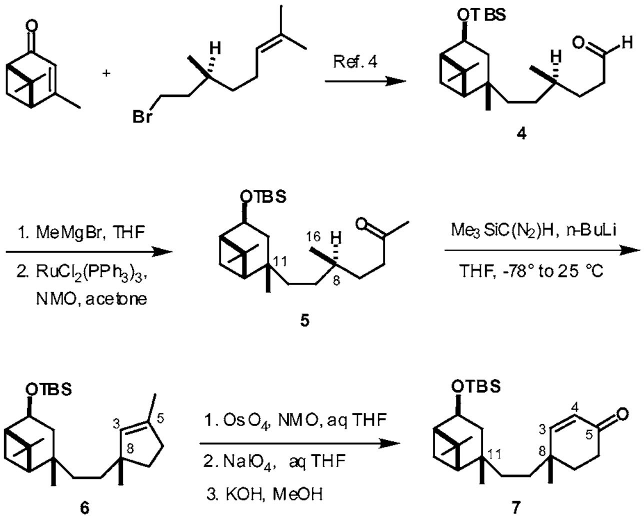
10.1021/ol026820t CCC: $22.00

followed by the introduction of the six-membered ring onto the existing seven-membered ring.[3a−g] Our route entails closure of the seven-membered ring with the existing five- and six-membered rings connected at C8 and C11 by a C9−C10 two-carbon linker, forming the complete tricyclic skeleton (Figure 1).[4]

As an initial effort for the total synthesis of **1**, we have demonstrated that a reductive ring closure of **2** afforded the 8-*epi*-guanacastane **3** in moderate yield. As noted in our previous communication,[4] we have used (*S*)-citronellyl bromide to generate **2** due to the higher cost of (*R*)-isomer,[5] which would give the opposite stereochemistry of the C8 quaternary carbon compared to that of guanacastepene A upon carbene insertion. The decision necessitates the inversion of stereochemistry at C8. We had hypothesized that this seemingly difficult task could be accomplished by repositioning the double bond from C3−C4 to C6−C7 on a compound that contains a psuedosymmetry plane that bisects the C8 and C5 carbons of the C ring.

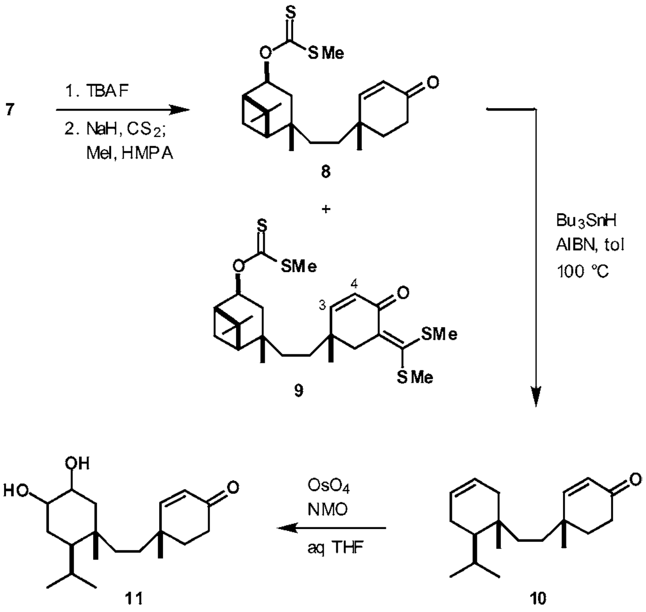
Herein we report two procedures to fix the stereochemistry at C8 via indirect inversion. To explore the inversion at C8, aldehyde **4** was selected as a branching point and constructed in high yield based on procedures analogous to the ethyl series of the previous communication.[4] Addition of methylmagnesium bromide to **4** followed by oxidation of the secondary carbinols (5 mol % $RuCl_2(PPh_3)_3$, 2.5 equiv of NMO, acetone, 25 °C, 3 h)[6] gave a good yield of the corresponding methyl ketone **5**. Treatment of ketone **5** with lithium(trimethylsilyl)diazomethane (Me_3SiCHN_2, *n*-BuLi, THF, −78 to 25 °C) smoothly generated the cyclopentene **6** in 92%,[7] which was oxidatively cleaved by a two-step protocol (OsO_4, NMO, THF−H_2O; $NaIO_4$) to the corresponding keto aldehyde. Direct treatment of this unstable keto aldehyde with KOH in MeOH at room temperature delivered the expected cyclohexenone derivative **7** without any complication (76% in three steps). Removal of the TBS group from **7** (Bu_4NF, THF, 25 °C, 98%) followed by xanthate formation[8] under our modified conditions (NaH, THF, CS_2; MeI, HMPA)[9] gave the desired xanthate **8** along with **9** (Scheme 1). The formation of **9** is the consequence of competing enolization of the carbonyl group followed by reaction of the enolate with CS_2 and two molecules of MeI.[10]

Scheme 1



Subsequent treatment of this inseparable mixture of xanthates **8** and **9** with tributylstannane (Bu_3SnH, AIBN, toluene, 100 °C) yielded the desired cyclobutane ring-opened product **10** in moderate yield (45−50%, 2 steps). Osmylation of the more electron-rich double bond of **10** then smoothly afforded a 5:1 diastereometic mixture of the diols **11** (Scheme 2).

Scheme 2



The indirect inversion process of the C8 stereochemistry was initiated by protection of the diol **11** as its acetonide (73% from **10**) (Scheme 3). With the diol protected, introduction of a carboethoxy group at the C6 position (LDA,

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(3) (a) Dudley, G. B.; Danishefsky, S. *Org. Lett.* **2001**, *3*, 2399. (b) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. *Tetrahedron Lett.* **2001**, *42*, 6789. (c) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569. (d) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947. (e) Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063. (f) Tan, D. S.; Dudley, G. B.; Danishefsky, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185. (g) Lin, S.; Dudley, G. B.; Tan D. S.; Danishefsky, S. *Angew. Chem., Int. Ed.* **2002**, *42*, 2188. (h) Gradl, S. N.; Kennedy-Smith, J. J.; Kim, J.; Trauner, D. *Synlett* **2002**, *3*, 411. (i) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063. (j) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363.

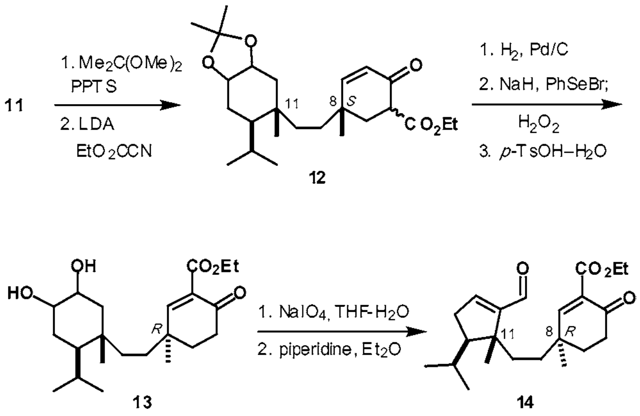
(4) Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033.

(5) (*S*)-Citronellyl bromide is ca. 3.5 times less expensive than (*R*)-citronellyl bromide. Aldrich: (*S*)-citronellyl bromide $31.70/5 g, (*R*)-citronellyl bromide $108.70/5 g.

(6) Baker, R.; Brimble, M. *Tetrahedron Lett.* **1986**, *27*, 3311.

(7) (a) Ohira, S.; Ishi, S.; Shinohara, K.; Nozaki, H. *Tetrahedron Lett.* **1990**, *31*, 1039. (b) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc. Chem. Commun.* **1992**, 721. (c) Taber, D. F.; Walter, R.; Meagley, R. P. *J. Org. Chem.* **1994**, *59*, 6014. (d) Ohira, S.; Sawamoto, T.; Yamato, M. *Tetrahedron Lett.* **1995**, *36*, 1537. (e) Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723. (f) Taber, D. F.; Yu, H.; Incarvito, C. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 13285. (g) Taber, D. F.; Christos, T. E.; Neubert, T. D.; Batra, D. *J. Org. Chem.* **1999**, *64*, 9673. (h) Mapitse, R.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 3541.

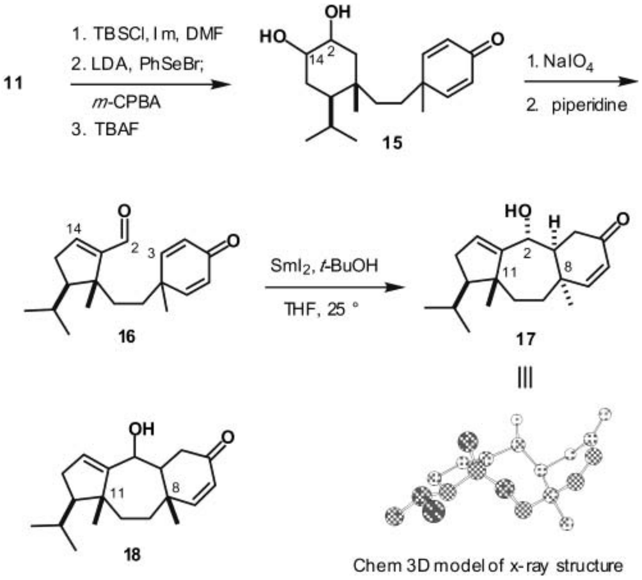
Scheme 3



THF, EtO_2CCN) afforded a diastereomeric mixture of **12**.[11] Subsequent removal of the double bond at the C2−C4 position (H_2, Pd/C, EtOAc) followed by subjection of the β-dicarbonyl compound to the known dehydrogenation conditions developed by Reich and co-workers[12] delivered the desired unsaturated enone diol **13** after removal of the acetonide (33%, 5 steps). The overall consequence of this five-step transformation is the inversion of the C8 methyl stereochemistry and the introduction of the C20 carbon at the C4 position as a form of carboethoxy group. The carboethoxy group at C4 is critical for the post-cyclization functionalization because the more sterically congested nature of the C4 carbon compared to C6 hinders the introduction of unsaturation between C3 and C4 after the formation of the tricyclic skeleton. Oxidative cleavage of diol **13** ($NaIO_4$, THF−H_2O) and immediate treatment of the resultant dialdehyde with excess piperidine in ether at room temperature produced the enal **14** (67%, 2 steps) together with its regioisomer in varying ratios (5:1 to 2:1).[13] The intramolecular reductive cyclization of **14** (SmI_2, THF, *t*-BuOH, 25 °C) proceeded poorly. The major product formed was a mixture of inseparable compounds, the characterization of which was not actively pursued, albeit traces of the desired tricycle were observed in the crude ^1H NMR.

The lengthy steps for the preparation of **14** and its reduced efficiency for the seven-membered-ring closure brought our attention to a rather bold hypothesis that compounds like **16** could self-differentiate the diastereotopic C3−C4 and C6−C7 double bond during the cyclization by forming the C2−C3 bond to generate the guanacastane tricycle with the desired trans stereochemical relationship between the C16 and C17 methyl groups. This hypothesis is not unreasonable because the sterically more favorable trans relationship between the C16 and C17 angular methyl groups in the natural guanacastanes is assumed to be the consequence of a thermodynamically driven process. To test this hypothesis, the above route was branched at enone **11**. This compound was converted to the cyclohexadienone **15**, whereby the stereogenic C8 carbon becomes nonstereogenic and the two double bonds at C3−C4 and C6−C7 become identical (43%, 3 steps). Diol cleavage of **15** ($NaIO_4$, THF−H_2O) followed by intermolecular aldol condensation (piperidine, Et_2O, 25 °C) delivered aldehyde **16** (45%, 2 steps) and the corresponding regioisomer in a maximum 5:1 ratio. Treatment of **16** under SmI_2-mediated reductive cyclization conditions[14] delivered a single isomer of the tricyclic core of guanacastane **17** (70% yield). The structure of **17** was unambiguously assigned by the spectroscopic and X-ray crystallographic analysis.[15] The tricycle **18** with the β-methyl stereochemistry at C8 was not observed, confirming our hypothesis that the trans stereochemical arrangement of the C16 and C17 angular methyl groups is more favorable.

Scheme 4



With this successful route to the tricycle complete, the formation of xanthates **8** and **9** was revisited. To eliminate the formation of undesired xanthate **9**, the C6−C7 double bond was introduced on compound **8**, thereby blocking the unwanted enolization (Scheme 5). Removal of the TBS group from this compound and subsequent xanthate formation proceeded as expected, producing only the xanthate **19** (39%

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(8) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Crich, D.; Beckwith, A. L. J.; Chen, C.; Yao, Q.; Davison, I. G. E.; Longmore, R. W.; De Parrodi, C. A.; Quintero-Cortes, L.; Sandoval-Ramirez, J. *J. Am. Chem. Soc.* **1995**, *117*, 8757. (c) Kanie, K.; Tanaka, Y.; Suzuki, K.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 471.

(9) Without HMPA, no xanthate formation was observed.

(10) Dieter, R. K. *J. Org. Chem.* **1981**, *46*, 5031. On a closely related compound **9** bearing a methyl group at the C4 position, this reaction did not occur.

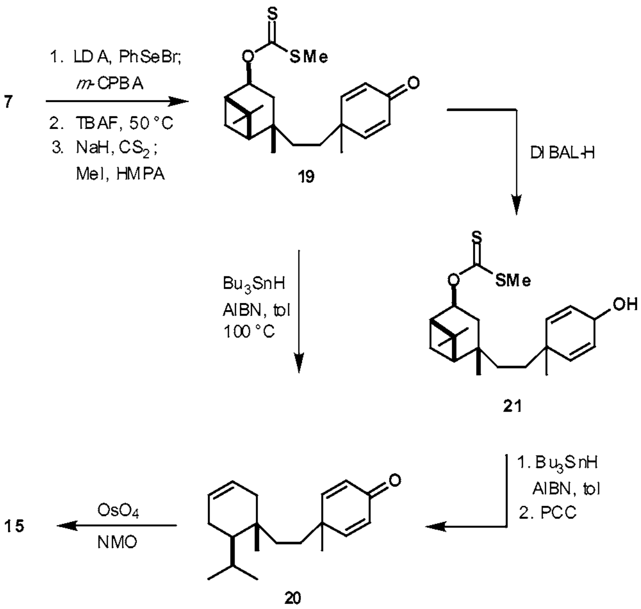
(11) Mander, L. N.; Sethi, P. *Tetrahedron Lett.* **1983**, *24*, 5425.

(12) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Org. Chem.* **1974**, *39*, 2133.

(13) (a) DeCamp, A. E.; Mills, S. G.; Kawaguchi, A. T.; Desmond, R.; Reamer, R. A.; DiMichele, L.; Volante, R. P. *J. Org. Chem.* **1991**, *56*, 3564. (b) Takazawa, O.; Kogami, K.; Hayashi, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2427.

(14) (a) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064. (b) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236. For review, see: (c) Molannder, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

Scheme 5



yield, 3 steps). However, the attempts to generate **20** directly from **19** by the cyclobutane ring opening were capricious due to the instability of the cyclohexadienone under the reaction conditions. To alleviate this problem, the carbonyl group of **19** was reduced (DIBAL-H, CH_2Cl_2, −78 °C, 77%) to a bisallylic alcohol **21** prior to treatment with tributylstannane. Compound **21** underwent reductive cyclobutane ring-opening cleanly under high dilution conditions, resulting in the desired compound **20** after oxidation of the bisallylic alcohol (PCC, 3 Å MS, CH_2Cl_2, 64%, 2 steps). Osmylation (OsO_4, NMO, acetone−H_2O, 73%) of **20** to the diol **15** completes an alternative route to an advanced intermediate tricycle **17**, eliminating problems associated with the formation of xanthate **9** in Scheme 2. Via this route **17** is produced in 18 steps and an overall 1.2% yield from commercially available starting materials.

In summary, we have disclosed two variations of an inversion strategy for the synthesis of quaternary carbons and used one of them for the synthesis of an advanced tricyclic core intermediate of the guanacastanes. The final reductive ring closure of this utilized route not only proves efficient (70% yield) but also provides only a single diasteromer. Further progress on the total synthesis of guanacastepene A (**1**) by using the current approach will be reported in due course.

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Supporting Information Available: Experimental details, characterization data for key new compounds, and X-ray crystallographic information for compound **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Spectroscopic information for **17**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.49 (dd, $J = 10$, 2 Hz, 1H), 6.00 (dd, $J = 10$, 1 Hz, 1H), 5.72 (br s, 1H), 3.91 (br d, $J = 10$ Hz, 1H), 3.08 (br d, $J = 17$ Hz, 1H), 2.69 (dd, $J = 17$, 5 Hz, 1H), 2.37 (ddd, $J = 16$, 8, 3 Hz, 1H), 1.96 (ddt, $J = 16$, 10, 2 Hz, 1H), 1.90−1.40 (m, 8H), 1.25 (s, 3H), 1.70 (dd, $J = 15$, 10 Hz, 1H), 0.97 (d, $J = 6$ Hz, 3H), 0.91 (s, 3H), 0.90 (d, $J = 6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 199.35, 158.08, 157.00, 128.57, 121.91, 166.20, 66.59, 54.07, 53.31, 48.78, 39.28, 37.36, 36.17, 35.57, 33.17, 29.63, 28.76, 22.95, 20.27. Crystallographic information for **17**: monoclinic crystal system (size = $0.40 \times 0.30 \times 0.30$ mm^3), space group $P2_1$, unit cell constants $a = 6.3772(6)$ Å, $b = 8.5780(7)$ Å, $c = 15.5692(14)$ Å, $\alpha = 90°$, $\beta = 91.385(2)°$, $\gamma = 90°$, $V = 851.44(13)$ Å^3, $Z = 2$, density = 1.125 Mg/m^3. The crystal evaluation and data collection were performed on a Bruker CCD-1000 diffractometer with Mo Kα ($\lambda = 0.71073$ Å) radiation in a stream of cold nitrogen at 100(2) K. A total of 44 reflections was obtained. The reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from a set of 4515 strong reflections from the actual data collection. A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The final least-squares refinement of 195 parameters against 3416 data resulted in residuals R (based on F^2 for $I \geq 2$) and wR (based on F^2 for all data) of 0.0433 and 0.1089, respectively.