VOLUME 70, NUMBER 26

JOC Articles

DECEMBER 23, 2005

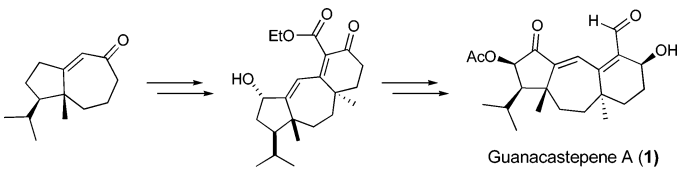
Total Synthesis of Guanacastepene A: A Route to Enantiomeric Control

Mihirbaran Mandal,[†] Heedong Yun,[‡] Gregory B. Dudley,[§] Songnian Lin,[∥] Derek S. Tan,[⊥] and Samuel J. Danishefsky*[,†,‡]

Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, Box 106, New York, New York 10021, Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027

s-danishefsky@mskcc.org

Received July 15, 2005



Guanacastepene A (**1**)

The goal of the total synthesis of guanacastepene A served as a focus to bring together several chemical inquiries. One involved the synthesis of fused 5,7-hydrazulenones (see structure **20**). Another issue had to do with the mechanistic intermediates in reductive cyclizations (see **17** to **18** and **19**). The total synthesis required a mastery of an intramolecular Knoevenagel condensation of a β,γ-unsaturated ketone (see compound **41**). Actually, cyclization was best accomplished when the terminal double bond of **41** was first converted to an epoxide. Further issues related to the stereochemistry at C_5 and, rather surprisingly, the propensity for β-face acetoxylation at C_{13}. Crystallographic verification of the assigned β-stereochemistry at C_{13} is provided. Finally, a route to optically active material is provided (see compound **20**). A key element in this construction was an enantioselective addition of isopropenyl cuprate to 2-methylcyclopentenone (see compound **99**).

Introduction

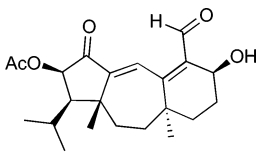
Guanacastepene A was first identified and isolated as part of a program to evaluate Endophytic fungi as sources of potential antibiotics.[1] In particular, the focus of the search was directed to the identification and isolation of compounds that display activity against organisms (cf. *Staphylococcus aureus* and *Enterococcus faecalis*) that are resistant to agents such as methicillin and vancomycin. The structure of guanacastepene A, a diterpenoid which registered positive in this screening context, was solved by Clardy and colleagues. As is often the case with complex isolates, the assignments of gross structural connectivity and stereostructures were first attempted using spectroscopic criteria, including NMR (^{1}H and ^{13}C) and high-resolution mass spectroscopy as well as infrared and ultraviolet measurements. In the end, it remained for single-crystal X-ray diffraction to clarify the structure of guanacastepene A (**1**, Figure 1).[1]

The combination of the novel structure and promising screening genealogy of guanacastepene A converged to prompt significant interest in the community of chemists as to its total synthesis. The privileged target status of

[†] Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research.
[‡] Department of Chemistry, Columbia University.
[§] Present address: Department of Chemistry and Biochemistry, The Florida State University.
[∥] Present address: Department of Medicinal Chemistry, Merck Research Laboratories.
[⊥] Present address: Tri-Institutional Research Program and Molecular Pharmacology & Chemistry Program, Memorial Sloan-Kettering Cancer Center.

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

10.1021/jo051470k CCC: $30.25
Published on Web 09/20/2005



Guanacastepene A (**1**)

FIGURE 1. Structure of guanacastepene A.

1 at the chemistry level survived some otherwise adverse information with respect to its likely emergence as a valuable resistance-breaking antibiotic agent. Thus, guanacastepene A exhibits hemolytic activity against human red blood cells.[1b] Clearly, for the guanacastepene A structure to survive as a platform for discovering new antibiotics of value in treating infectious diseases, it would be necessary to differentiate antibiotic from hemolytic selectivity.[2] Certainly, the best opportunity for accomplishing this goal would lie in gaining access to a range of congeners of guanacastepene A. A careful survey of the biological properties of such a focused compendium of guanacastepene-related compounds may provide suggestions as to directions to be followed for decoupling antibiotic and hemolytic prospects in this series. This potentially serious complication at the translational level notwithstanding, guanacastepene still maintains its standing as a stimulating target for chemical total synthesis. It was in such a chemistry-dominated context that our laboratory pursued this goal. Below, we record the realization of the goal of the total synthesis of guanacastepene A.[3,4] It will be seen that the synthesis was accomplished in the setting of a series of complications—many of them unexpected.

Given the extensive record of involvement of our laboratory in the synthesis of steroids and biogenetically related polyisoprenoids,[5] it was not surprising that we sought to translate the guanacastepene synthesis problem to that of a variation of the synthetic logic describable under the term "Robinson annulation," which can be encompassed in the expression **2** → **3** (Figure 2). While the short-term goal of the Robinson annulation itself is well understood by practitioners of synthesis, its conceptual reach is broad and powerful, encompassing a diverse range of methodological platforms. [6,7]

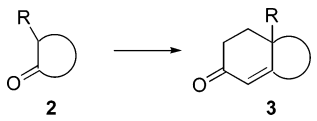


FIGURE 2. Robinson annulation.

An evaluation of the logic of the Robinson annulation for the purposes of assembling guanacastepene A leads to the formalized hypothetical progression **4** → **5** → **6** → **1** (Scheme 1). A wealth of methods, protocols, and reagents have been fashioned and coordinated to facilitate the core transformation of **2** → **3**. Given the extensive research that has been directed to cover countless permutations of the central theme captured in this expression,[8] it is perhaps inevitable that the literature contains seemingly redundant solutions to this problem. However, closer consideration of the precise issues in a particular synthetic approach may well oblige the chemist to draw from a specialized subset of the overall Robinson annulation methodology. Thus, the existence of a range of protocols and underlying thought processes, which can be grouped under the rubric of "Robinson annulation," adds much to its value.

Even a cursory inspection of the guanacastepene case at hand soon reveals the need for improvisation in that the sequence to be employed (**4** → **5**) must, ultimately, give rise to a cycloheptenone rather than to the usual cyclohexenone (cf. **2** → **3**). Moreover, in moving toward **1**, the cycloheptenone must emerge such that its substituents at carbons 8 and 11 translate, in the end, to the required C_8–C_{11} *anti* backbone relationship. Well in advance of dealing with the C_8–C_{11} *anti* correlation, there would be a need to provide for the *syn* C_{11}–C_{12} connectivity.

Results/Discussion

We set, as our first goal, the synthesis of compound **5** (R^1 = H) starting from 2-methylcyclopentenone **4**. Our thought to reach **5** envisioned *C*-alkylation of the kinetically generated enolate **7**,[9] fashioned from **4** using methodology demonstrated by Piers,[10] with an agent, RX (Scheme 2). Such a sequence would be expected to secure the future C_{11}–C_{12} *anti* relationship. RX would be chosen so that, in due course, there would be generated a β-ketophosphonate, **12**. It was assumed that intramolecular Horner–Wadsworth–Emmons[11] (HWE) reaction would lead to the homo-Robinson annulation product **5**. We initially took recourse to 5-iodo-1-pentene (**8**)[12] as RX.[3a]

In pursuing the synthesis as discussed below, we were operating in the racemic series. As will be described, after

(2) For an explanation of the selectivity of membrane-lysing peptide antibiotics, see: Zasloff, M. *Nature* **2002**, *415*, 389.

(3) (a) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399. (b) Dudley, G. B.; Danishefsky, S. J.; Sukenick, G. *Tetrahedron Lett.* **2002**, *43*, 5605. (c) Mandal, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2004**, *45*, 3827. (d) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789. (e) Mandal, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2004**, *45*, 3831. (f) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185. (g) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188. (h) Yun, H.; Danishefsky, S. J. *Tetrahedron Lett.* **2005**, *46*, 3879.

(4) For other syntheses of structures which connected with late compounds described herein, thus constituting formal syntheses, see: (a) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030. (b) Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817. For other stimulating work in the guanacastepene series, cf. inter alia: (c) Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. *Org. Lett.* **2002**, *4*, 3959. (d) Du, X.; Chu, H. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923. (e) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063. (f) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113. (g) Sarpong, R.; Su, J. T.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 13624.

(5) Danishefsky, S. J. *Tetrahedron* **1997**, *53*, 8689.

(6) Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285.

(7) Reviews: (a) Gawley, R. E. *Synthesis* **1976**, 777. (b) Jung, M. E. *Tetrahedron* **1976**, *32*, 3.

(8) Cf. inter alia: (a) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152. (b) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682. (c) Scanio, C. J. V.; Starrett, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1539. (d) Zoretic, P. A.; Golen, J. A.; Saltzman, M. D. *J. Org. Chem.* **1981**, *46*, 3554. (e) Heathcock, C. H.; Ellis, J. E.; McMurry, J. E.; Coppolino, A. *Tetrahedron Lett.* **1971**, *12*, 4995.

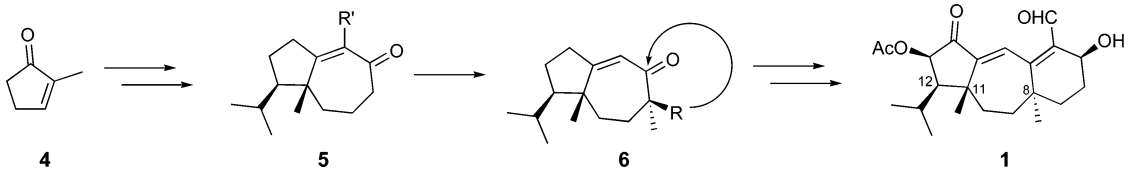
(9) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.

(10) Piers, E.; Renaud, J.; Rettig, S. J. *Synthesis* **1998**, 590.

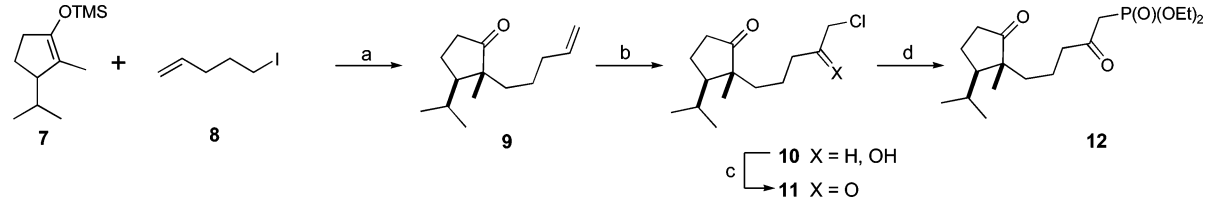
(11) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(12) Iodo-1-pentene was prepared by treatment of 5-bromo-1-pentene with 3.0 equiv of NaI in refluxing acetone for 6 h as described previously: Padwa, A.; Kamigata, N. *J. Am. Chem. Soc.* **1977**, *99*, 1871.

SCHEME 1. Synthetic Strategy toward Guanacastepene A

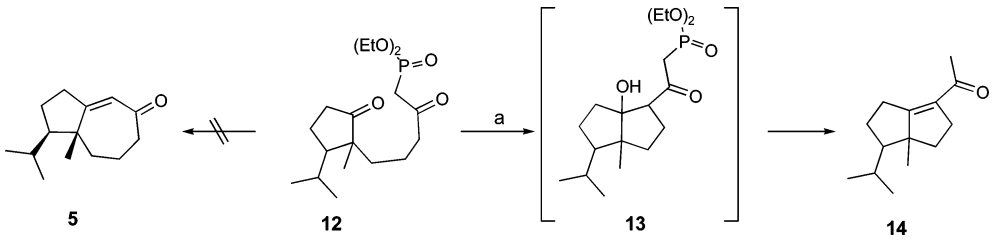


SCHEME 2. Synthesis of Horner–Wadsworth–Emmons Precursor 12[a]



[a] Key: (a) MeLi, THF, 0 °C, 1 h, then 2.5 equiv of **8**, HMPA, −78 °C to rt, 63−72%; (b) Chloramine-T, H_2O, H_2SO_4, acetone, 50 °C, 30 min; (c) Jones' reagent, rt, 30 min, 54−63% for two steps; (d) (i) NaI, acetone, 15 min; (ii) $(EtO)_3P$, PhH, reflux, 5 h, 70−74%.

SCHEME 3. Unsuccessful Horner–Wadsworth–Emmons Cyclization[a]



[a] Key: (a) Cs_2CO_3, PhMe, reflux, 12 h, 83% (**14**).

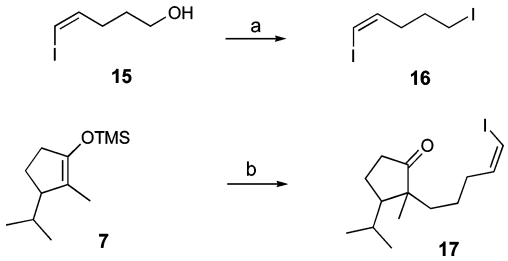
the total synthesis of guanacastepene was accomplished, we turned our attentions to charting a path that would lead to enantiohomogeneous guanacastepene. Here, again, we were successful.

Alkylation of enolate **7** with **8** generated **9** in approximately 65−70% yield. According to plan, **9** lent itself to transformation to **12** via ketone **11**, in turn fashioned from **10** via Jones oxidation. Compound **10** arose following oxidation of the terminal olefin linkage of **9** with Chloramine T.[13] Unfortunately, several attempts to reach compound **5** via HWE cyclization of **12** were unsuccessful (Scheme 3). While we did not follow up in detail on every failed attempt to synthesize **5**, the case of the reaction of **12** with cesium carbonate was particularly telling. The product was **14** rather than the anticipated **5**. Presumably, **14** arose from cyclized product **13**, following the general pathway shown.[14]

Apparently, in the case of **12**, internal aldolization using a 5-*exo*-initiated pathway is kinetically favored over the 7-*endo* bond closure, notwithstanding the enhanced acidity of the β-ketophosphonate network. Indeed, this setback underscores a key issue of directionality that would have to be solved if transformations of the genus **4** → **5** were to be realizable by direct aldolization as its ring-closing step. We shall revisit this question after the total synthesis of the racemate is described.

Anxious to focus on the guanacastepene problem, we set aside our preference to realize the homo-Robinson annulation by direct aldolization. Rather, another possibility to accomplish the consequences, if not the hoped-for direct intramolecular style, of the homo-Robinson annulation presented itself. As will be seen, this method, while solving the **4** → **5** transformation, was not without its own complications. It started on a promising note. Thus, alkylation of enolate **7** with diiodide **16**, prepared as shown from the known **15**,[15] gave rise to **17** in ca. 75% yield (Scheme 4).[3a]

SCHEME 4. Preparation of Vinyl Iodide 17[a]



[a] Key: (a) PPh_3, imid, I_2, CH_2Cl_2, 1 h, 92%; (b) MeLi, THF, 0 °C, 1 h, then 2.5 equiv of **16**, HMPA, −78 °C to rt, 74−76%.

At this stage, our hope was to accomplish reductive cyclization of **17** with concomitant formation of **18**.[16,17] In the event, lithiation of **17** with *n*-butyllithium in hexanes afforded a 1.6:1 mixture of **18**:**19** (Scheme 5). For obvious reasons, we term the former as the product of reductive cyclization, while **19** is referred to as the

(13) For the hydroxy-chlorination of olefins with chloramine-T, see: Damin, B.; Garapon, J.; Sillion, B. *Synthesis* **1981**, 362.

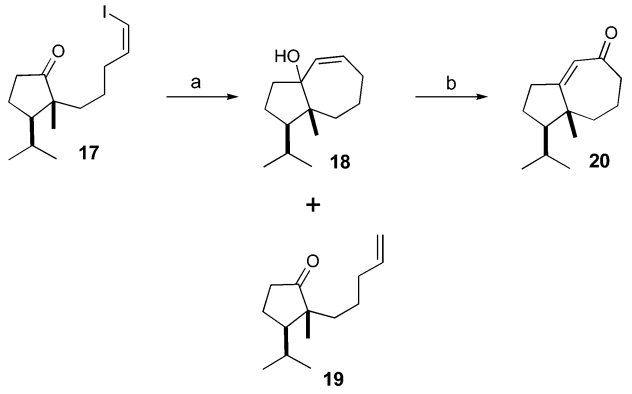
(14) Snider and Hawryluk also observed only formation of a 5,5-fused ring system in their attempts to perform a direct aldol with a similar substrate. See ref 4a.

(15) Yenjai, C.; Isobe, M. *Tetrahedron* **1998**, *54*, 2509.

(16) For a seminal report on this general cyclization strategy, see: Corey, E. J.; Kuwajima, I. *J. Am. Chem. Soc.* **1970**, *92*, 395.

(17) Piers, E.; Walker, S. D.; Armbrust, R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 633.

SCHEME 5. Reductive Cyclization of 17[a]

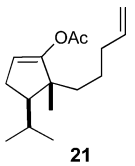


[a] Key: (a) 2.2 equiv of *n*-BuLi, THF, 0 °C, 30 min, 1.6:1 **18**:**19**; (b) PCC, powdered sieves, CH_2Cl_2, ca. 70%.

reduction product. Upon treatment with PCC, compound **18** undergoes a precedented oxidative rearrangement[18] to give rise to enone **20**.

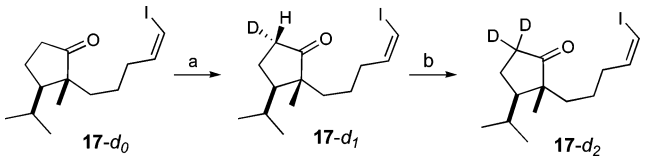
In an effort to improve the yield of **18**, we examined the effects of concentration on the ratio of formation of **18** relative to **19**. Indeed, we found that, upon dilution of the reaction mixture, the bias toward formation of the desired intramolecular cyclization product, **18**, could be further encouraged. Under optimal conditions, the ratio of **18**:**19** could be increased to 3.5:1. Since decreasing concentration favors intramolecular reaction pathways, these results suggest that the undesired reduction product, **19**, proceeds, at least partially, through an intermolecular protonolysis pathway. However, as a practical matter, we were already operating in a dilute setting and we could not hope to solve our problem by adjustments of the concentrations.

A propos of the problem of competitive noncyclizing reduction, we sought to identify the source of the hypothesized proton transfer. We were able to rule out transfer from solvent by conducting the reaction in THF-d_8. No deuterium incorporation in **19** and no change in the ratio of products was observed. Furthermore, workup of the reaction mixture with D_2O resulted in no exchange of iodine for deuterium in **17**, indicating that at the time of the quenching of the reaction, there was no remaining viable vinyllithium species. Postulating that the enolizable cyclopentanone may actually serve as the proton source, we treated the reaction mixture with acetic anhydride for 30 min prior to workup. Indeed, following this sequence, one could isolate significant but variable amounts of enol acetate **21**. This outcome indicates the existence of an enolate intermediate in the reaction mixture.



If, as the evidence suggests, the enolizable protons α to the keto group are serving as proton sources in the reduction pathway, suppression of cyclopentanone proton transfer should result in a corresponding attenuation of formation of **19**. Thus, we surmised that if the α-protons were replaced with less "kinetically acidic" deuterium atoms, the product distribution should shift in a direction favoring cyclization over reduction.[19] In practice, deuteration of starting material **17** was accomplished with DBU in deuterated methanol (Scheme 6). Interestingly, the use of a weaker base, such as triethylamine, gave rise only to monodeuterated intermediate. We note that deuteration had occurred with selectivity, as shown, at the α-face (**17**-d_1).[3b]

SCHEME 6. Preparation of Dideuterated Vinyl Iodide 17-d_2[a]



[a] Key: (a) Et_3N, CD_3OD, rt, 20 h, 94% of **17**-d_1; (b) DBU, CD_3OD, rt, 4 h, 91% of **17**-d_2.

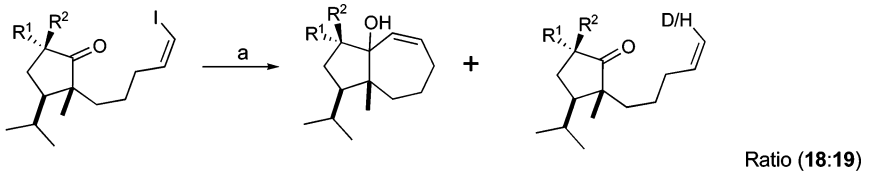
Each substrate (**17**-d_0, **17**-d_1, and **17**-d_2) was subjected to standard cyclization conditions, and the ratio of formation of cycloadduct (**18**) to reduction product (**19**) was evaluated (Scheme 7). As shown below, although incorporation of deuterium did not entirely eliminate the formation of **19**, it did significantly shift the product ratio in favor of **18**. These results implicate enolization of the cyclopentanone as the major proton source in the reduction pathway. Interestingly, although deuterium isotopes are frequently employed as valuable tools in probing reaction mechanisms, they are only rarely considered as a means to overcome problems in synthetic chemistry.

To probe the mechanism of the protonolysis still further, we examined the origins of formation of **19**-d_2, the noncyclized reduction product of the dideutero substrate (Scheme 8).[3c] Upon quenching the reaction mixture with H_2O, we found that only 30% of the total uncyclized product incorporated deuterium at the vinylic position (cf. **22**:**23**). This interesting result seems to teach that in the dideutero case, the major proton source in the much suppressed reduction pathway is no longer the enolizable cyclopentanone. When the mixture was quenched with D_2O, minimal change in the ratio of **22** to **23** was observed. It was thus deemed unlikely that significant amounts of vinyllithium species remained, preworkup. Furthermore, the solvent was seen to be a highly improbable source of proton transfer, as conduct of the reaction in THF-d_8 did not result in deuterium incorporation at the vinylic position. Accordingly, we are left with the possibility that the "*n*-butyl" group may be a minor contributing proton source in the quenching of the vinyllithium intermediate. For instance, perhaps, iodobutane, which is formed in the initial metal−halogen

(18) For an early example of a similar oxidative transposition, see: Büchi, G.; Egger, B. *J. Org. Chem.* **1971**, *36*, 2021.

(19) For a general discussion of isotope effects, see: Lowry, T. H.; Richardson, K. S. Isotope effects. In *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper Collins: New York, 1987; p 232. For related applications to synthesis, see: (a) Laplaza, C. E.; Davis, W. M.; Cummins, C. C. *Organometallics* **1995**, *14*, 577. (b) Schrock, R. R.; Baumann, R.; Reid, S. M.; Goodman, J. T.; Stumpf, R.; Davis, W. M. *Organometallics* **1999**, *18*, 3649. (c) Vedejs, E.; Little, J. *J. Am. Chem. Soc.* **2002**, *124*, 748.

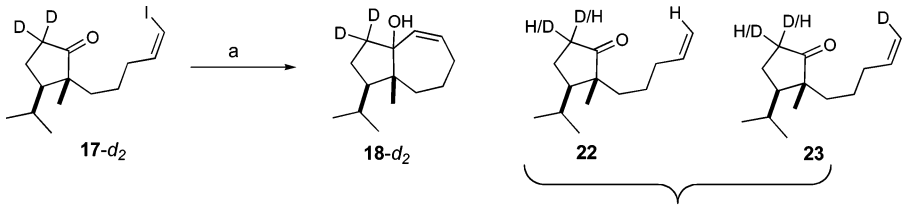
SCHEME 7. Improving the Cyclization of 17 through a Kinetic Isotope Effect[a]



			Ratio (**18**:**19**)
17-d_0 $R^1 = R^2 = H$	**18**-d_0 65%	**19**-d_0 18%	78 : 22
17-d_1 $R^1 = D, R^2 = H$	**18**-d_1 71%	**19**-d_1 9.3%	88 : 12
17-d_2 $R^1 = R^2 = D$	**18**-d_2 84%	**19**-d_2 8.6%	91 : 9

[a] Key: (a) 5.0 equiv of *n*-BuLi (inverse addition), THF, 0 °C, 30 min.

SCHEME 8. Investigating the Mechanism of the Noncyclizing Reduction[a]

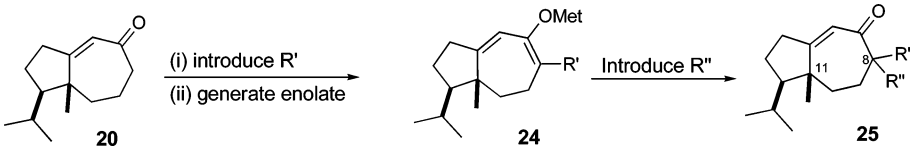


17-d_2 **18**-d_2 **22** **23**

H_2O workup	84%	8.6%	**22**:**23** = 7 : 3
D_2O workup	84%	8.6%	**22**:**23** = 6 : 4

[a] Key: (a) 5.0 equiv of *n*-BuLi (inverse addition), THF, 0 °C, 30 min.

SCHEME 9. Strategy for Formation of 25 through Dialkylation



20 **24** **25**

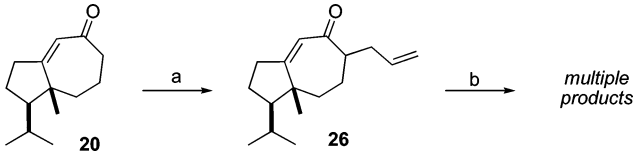
exhange of *n*BuLi and **17**, may undergo E2 elimination, generating a source for protonolysis of the vinyllithium species.

In summary, the main lesson of this detour is that, in the nondeutero pathway described earlier, the main proton source in the undesired reduction is the enolizable cyclopentanone of **17**. Replacing the enolizable protons of **17** with less kinetically acidic deuterium isotopes significantly suppresses the noncyclizing reduction pathway. The minimal amount (<9%) of reduction product, which is still observed in the dideutero case, is perhaps attributable to an E2 elimination of the *n*-butyl iodide species generated in the lithium−halogen exchange.

We return to the guanacastepene A total synthesis problem. With compound **20** in hand, we directed our attention to system **6**. At this stage of our deliberations, much design and experimentation would be necessary before defining the optimal nature of the R function at C_8. As in the case of the building of the seven-membered B ring, the paradigm of Robinson annulation—broadly construed—served to help organize our thinking. In other words, R at C_8 must, at an appropriate stage undergo cyclization (presumably by some variation of the aldol condensation).

However, before addressing the all-critical specifics of such a prospectus, it was necessary to establish the sort of latitude open to us in terms of the interfacing of the configurations at C_8 and C_{11}. Not surprisingly, our earliest thoughts were to introduce the methyl group and the future R group (albeit undefined in its specifics) at

SCHEME 10. Unsuccessful Dialkylation of 20[a]



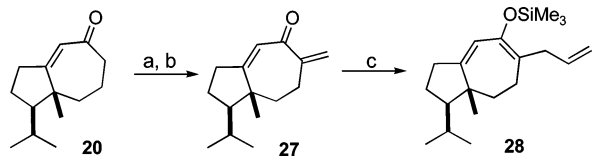
20 **26**

[a] Key: (a) LiHMDS, allyl iodide; (b) LiHMDS (MeI or TMSCl).

C_8 in a sequential fashion. To do this in a sensible way, it would be necessary to know the likely outcome, at the stereochemical level, of the transformation of **20** to **25** (Scheme 9). In particular, we wanted to gain an assessment as to whether the last group introduced in the alkylation event would enter *syn* or *anti* to the resident methyl function at C_{11}. In principle, specific schemes could be proposed to deal with either stereochemical eventuality. While a priori it might be assumed that the group introduced in the last alkylation event would enter *anti* to the resident C_{11} methyl function, this issue had to be studied, particularly as to the sorts of selectivity margins to be anticipated.

We initially sought to accomplish dialkylation of **20** through sequential installation of the allyl and methyl substituents.[3d] Accordingly, **20** was deprotonated and treated with allyl iodide to give rise to **26** (Scheme 10). We were pleased to find that allylation had proceeded with high stereoselectivity (although the relative configuration of the allyl group had not been determined at this stage). Unfortunately, our attempts to install the

SCHEME 11. Preparation of Silyl Enol Ether 28[a]



[a] Key: (a) 1.5 equiv of LiHMDS, THF, −78 °C, 1 h, then 3.0 equiv of Eschenmoser's salt, THF, −78 °C to rt, 20 min; (b) *m*-CPBA, CH_2Cl_2/$NaHCO_3$ (aq) (2:1), 60−70% over two steps; (c) 3.0 equiv of vinyl-MgBr, 1.5 equiv of CuI, 4.5 equiv of HMPA, 4.5 equiv of TMSCl, THF, −78 °C, 20 min, 77%.

methyl group in a following step were hampered by the difficulty of generating the α-enolate (i.e., C_8) of **26**. Clearly, our original direct dialkylation strategy would have to be reconsidered. Nonetheless, the success of the first alkylation (cf. **20** → **26**) did provide us with some valuable encouragement as to the feasibility of achieving stereoselective alkylation at C_8 of a cycloheptenone system of the type **20**.

A revised strategy was designed to circumvent the problematic enolate regeneration step. We postulated that an *exo*-methylene group, such as found in **27**, could be of value in a modified route (Scheme 11). To synthesize **27**, we revisited chemistry that had been developed in our own laboratory some years ago. Thus, cyclopentenone **20** was subjected to enolization, as shown, and the presumed enolate was treated with Eschenmoser's salt[20] to produce the dimethylaminomethylene Mannich base product.[21] Upon exposure of this material to *m*-CPBA, elimination occurred readily to afford **27**. Vinyl cuprate addition to **27** in the presence of TMSCl[22] provided our target compound, **28**, in which the enolate had been trapped as a silyl enol ether.

The lithium enolate was then generated from **28** as shown (Scheme 12). Exposure of this enolate to the action of methyl iodide provided exclusively **29** (vide infra for structural arguments in support of this stereochemical assignment). *Importantly, no other diastereomer was observed following this reaction.*[23] At this point, the ketonic function of **29** was protected as a dioxolane ketal with concurrent olefin migration,[24] and the terminal olefin was taken through a hydroboration-oxidation protocol to afford **30**.[25] Following concomitant ketal deprotection and Jones oxidation,[26] the target compound **31** was in hand. We note, parenthetically, that in the deprotection of the ketal precursor to **31**, reconjugation of the enone had not occurred.

For comparative purposes, we sought to reverse the order of introduction of the methyl and allyl groups at the quaternary carbon center. It was assumed that inverting the sequence of the two alkylation events would lead to the C_8 epimer of **29**. The synthesis of this target commenced with 1,4-hydride addition to **27** (Scheme 13).[27] This step was followed by addition of allyl iodide. Importantly, the formation of **29** was not observed from this reaction sequence. Rather, a new product, isomeric with **29**, was obtained. This compound was formulated as **32**. Thus, an important finding had been made. The stereochemistry at C_8 is indeed dictated by the order in which the substituents are introduced, with the second alkylation occurring *anti* to the C_{11} methyl group.

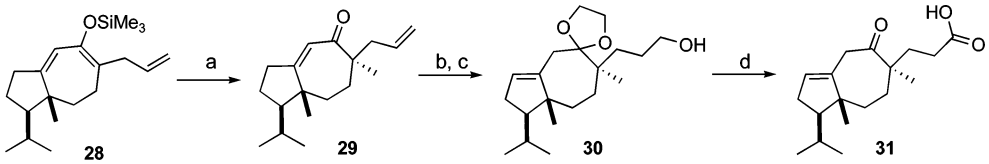
The relative stereochemistries of **29** and **32** were first assigned through extensive NMR analysis (Figure 3). In summary, ^1H and ^{13}C resonances were assigned from J-resolve, COSY, NOESY, DEPT, HMQC, and HMBC data. In analogy to the modeling studies of guanacastepene by Clardy and co-workers,[1a] two possible gauche butane-conformers about the C_9-C_{10} bond of **29** were identified using the MM2 force field. NOE interactions involving $C_{12}-H$, $C_{17}-H_3$, and $C_{19}-H_3$ supported assignment as the pseudo-chair conformation shown below. The C_8 stereochemical configuration could then be assigned based upon NOE interactions between $C_{16}-H_3$ and both C_9-H_α and $C_{10}-H_\alpha$. The NMR analysis of **32** was complicated by overlapping ^1H signals; however, the C_7-H_2 NOE interactions are consistent with the pseudo-chair conformation and C_8 conformation shown.

Although we had foreseen some level of selectivity for introduction of the C_8 methyl group *anti* to the resident C_{11} methyl substituent (cf. **28** → **29**), we had not anticipated apparently exclusive methylation from the α-face. Needless to say, we were very pleased with this favorable outcome, which would prove to be of great value in the completion of the synthesis of guanacastepene A. Though we have not pursued the generality of the finding, this result may underscore the underappreciated stereoselectivity margins that can be attained in the alkylation of appropriately substituted cycloheptenone systems.

We return to compound **31**. Our plan envisioned utilization of a Turner−Fujimoto logic,[28] wherein the carbonyl group of an intermediate enol lactone (cf. **33**) would be attacked with generalized nucleophile **34**, with the expectation of reaching **35**.[3f] Indeed, the desired enol lactone **33** was prepared as shown (Scheme 14).[29] We examined its reactions with methyl (**34**, Y = H) and ethyl (**34**, Y = Me) nucleophiles. However, in practice, we were unable to isolate or even identify any of the hoped-for **35** or its fully conjugated dienone isomer. Instead complex mixtures of products were obtained. We note that, unlike the situation in the Turner−Fujimoto reaction, the carbonyl group in **33** is present in the context of a dienol lactone. Thus, hypothetical attack by **34** leads to dienolate **36**. By analogy to the textbook dehydro case, the sequence **36** → **37** → **38** → **35** would be necessary. In the case at hand, somewhere in this projected sequence, the

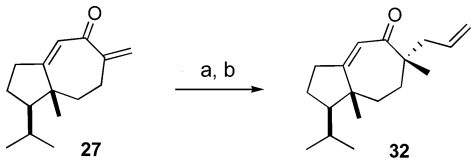
(20) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330.
(21) (a) Danishefsky, S. J.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715. (b) Piers, E.; Marais, P. C. *J. Chem. Soc., Chem. Commun.* **1989**, 122.
(22) For a discussion of the role of TMSCl in cuprate additions, with leading references, see: Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288.
(23) For an example of another stereoselective cycloheptenone alkylation, see: Pearson, A. J.; Bansal, H. S. *Tetrahedron Lett.* **1986**, *27*, 287.
(24) (a) Stork, G.; Uyeo, S.; Wakamatsu, T.; Grieco, P.; Labovitz, J. *J. Am. Chem. Soc.* **1971**, *93*, 4945. (b) (a) Daignault, R. A.; Eliel, E. L. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 303. (b) De Leeuw, J. W.; De Waard, E. R.; Beetz, T.; Huisman, H. O. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 1047.
(25) Brown, H. C.; Chen, J. C. *J. Org. Chem.* **1981**, *46*, 3978.
(26) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.
(27) Ojima, I.; Kogure, T. *Tetrahedron Lett.* **1972**, *13*, 5035.
(28) (a) Turner, R. B. *J. Am. Chem.* Soc. **1950**, *72*, 579. (b) Fujimoto, G. I. *J. Am. Chem. Soc.* **1951**, *73*, 1856.
(29) Barkley, L. G.; Knowles, W. S.; Raffelson, H.; Thompson, Q. E. *J. Am. Chem. Soc.* **1956**, *78*, 4111.

SCHEME 12. Preparation of Acid 31[a]



[a] Key: (a) 1.5 equiv of MeLi, THF, 0 °C, 10 min, then 5.0 equiv of HMPA, 5.0 equiv of MeI, −78 °C to rt, 15 min, 96%; (b) $(CH_2OH)_2$, *p*-TsOH, PhH, reflux, 11 h, 88%; (c) 9-BBN, THF, rt, 1 h, then 3 M NaOH, 30% H_2O_2, rt, 3 h, 71%; (d) Jones' reagent, acetone, 2 h, 77%.

SCHEME 13. Preparation of the Opposite Diastereomer, 32[a]



[a] Key: (a) $PhMe_2SiH$, Wilkinson's catalyst ($[Ph_3P]_3RhCl$; 1%), benzene, reflux, 20 min; (b) MeLi, THF, 0 °C, 10 min, then allyl iodide, −78 °C to rt, 30 min, 69% over two steps.

analogy with the usual Turner−Fujimoto progression[28] breaks down.

Of course, our original purpose in trying to realize the sequence **33** → **36** → **35** was the hope that, in the end, Y in **35** would correspond to a group (cf. inter alia C≡N, CO_2R, CHO) that would facilitate building the olefinic hydroxyaldehyde functionality embracing carbons 15, 4, and 5. With the breakdown of this initiative, alternatives directed to the same subgoal were pursued.

In particular, we returned to compound **30**.[3f] Oxidation of the latter under controlled conditions afforded ketal aldehyde **39** (Scheme 15).[30] As was anticipatable by precedent, the aldehyde function reacted smoothly with ethyldiazoacetate in the presence of $SnCl_2$.[31] In this way, compound **40**, equipped with a β-ketoester on the side chain, was in hand. Finally, deprotection of the ketal linkage led to **41**, wherein the β,γ-unsaturated keto arrangement in the future B,C sector had withstood potential conjugation.[32]

With compound **41** in hand, it seemed that there was now a clear path to be followed to reach the tricyclic core structure of guanacastepene A. It was expected that an intramolecular Knoevenagel condensation would complete construction of the ring system (Scheme 16).[33] We recognized that such a reaction could produce either the fully conjugated dienyl ring structure **43** or, conceivably, the partially conjugated dienone, **42**. In either case, we could imagine programs that would be feasible for introduction of the required oxygen at C_{14} and, thence, the acetoxy function at C_{13}.

It was, therefore, surprising to find that under a variety of attempted conditions to achieve intramolecular Knoevenagel condensation we could not obtain either compound **42** or **43**. The major product was actually the ester, **44**, arising from formal retro-Claisen cleavage of the β-ketoester ensemble in the side chain of **41**. In addition, in the absence of provisions to rigorously exclude all possible contamination from oxygen, two other products, **45** and **46**, were identified, albeit in low yields and with poor reproducibility. These two compounds were separated and their NMR spectra studied. It was promising to find that each of these tricyclic core structures exhibited conformational mobility, as judged by the coalescence of otherwise complex spectra following heating. Similar conformational behavior had been described for guanacastepene A.[1a]

We first focused on understanding the nature of the retro-Claisen cleavage step, which clearly had occurred in preference to the expected formation of compound **42**. Needless to say, such a retro-Claisen reaction on an enolizable β-ketoester, particularly one bearing two highly enolizable α−protons, had not been expected, certainly under the relatively mild conditions (ethanol, 60 °C) used in this experiment. In an orienting experiment, we studied the possibility of executing a deliberate retro-Claisen reaction on ketal **47** (Scheme 17). Interestingly, even under conditions identical to those used on **41**, compound **48** was not observed. Thus, the ethoxide-mediated degradative excision of the carboxymethyl group is dependent on the existence of a carbonyl group at the future C_3 of guanacastepene A.

We took this finding to suggest that the retrograde Claisen step is driven by attack of the cycloheptanone ketonic oxygen (either as its dienolate **49** or as its ethoxide addition product, **50**) on the β-ketone of the β-ketoester side chain (Scheme 18). In either case, further unraveling of the system leads to the observed major product, **44**.

Furthermore, it was of interest that no adventitious oxidation products were noted in the attempted retrograde Claisen reaction. Conversely, in the early stages of the study, we could not obtain Knoevenagel products (cf. **42** or **43**) independent of oxidation.

We could envision two possible pathways that would account for the products observed from the Knoevenagel-like cyclization reaction. In one, adventitious oxidation occurs on starting material **41**. The oxidized intermediates thus produced would be quite prone to cyclization, affording **45** and **46**. Failure to find products **42** and **43** might suggest that cyclization in the absence of prior oxidation does not occur. Alternatively, it is conceivable that such a cyclization does occur, but under the conditions of our experiment, adventitious oxygenation of the product gives rise to the observed **45** and **46**.

We tested this second possibility by conducting the cyclization reaction in deuterated solvent, in an anaerobic setting in a gastight NMR tube, involving repeated freeze−thawing and evacuation (Scheme 19). Under

(30) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(31) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.

(32) Hagiwara, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1351.

(33) We were encouraged by literature precedent involving cyclization of a similar β-keto ester side chain onto a cycloheptanone system with an adjacent quaternary center: van der Baan, J. L.; Barnick, J. W. F. K.; van Beek, G.; Bickelhaupt, F.; Spek, A. L. *Tetrahedron* **1992**, *48*, 2773.

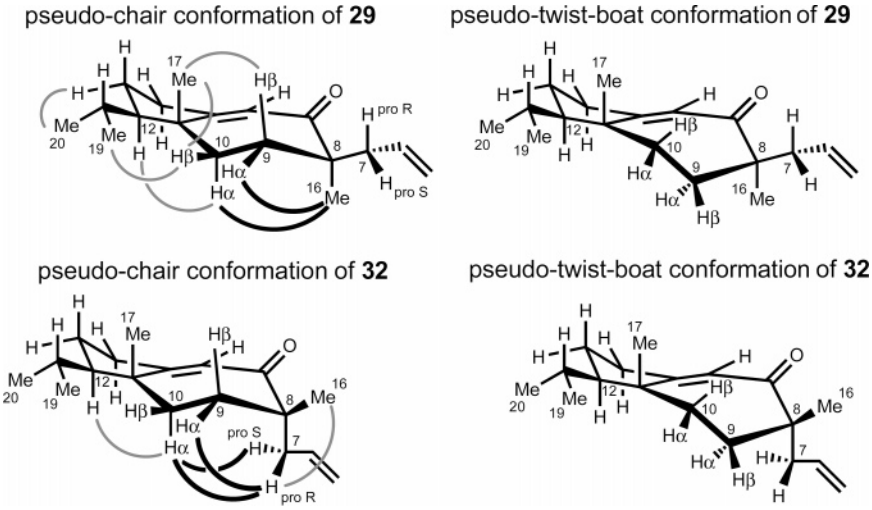
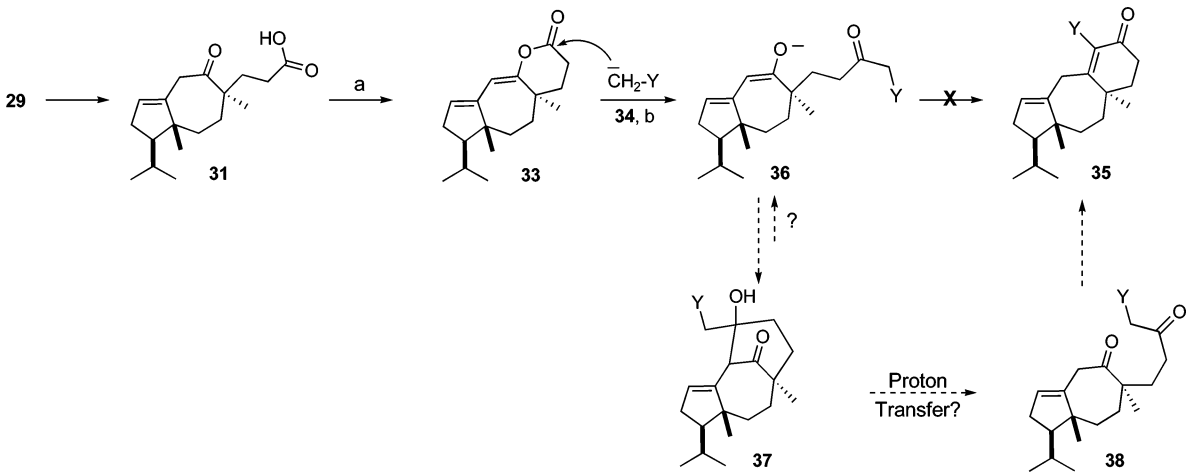


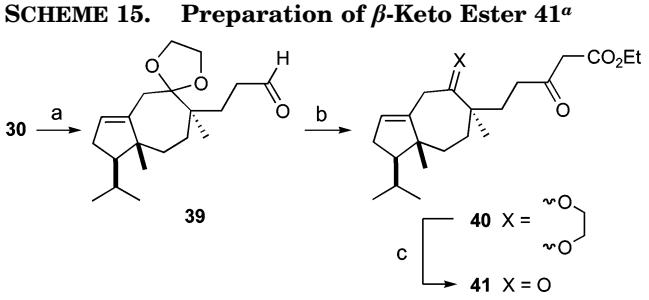
FIGURE 3. Pseudo-chair and pseudo-twist-boat conformations of **29** and **32** with selected strong NOE interactions. Interactions used to assign the C8 stereochemical configuration are shown in bold.

SCHEME 14. Unsuccessful Attempts at Turner–Fujimoto Cyclization[a]



[a] Key: (a) NaOAc, Ac_2O, 140 °C, 80 min, 59%; (b) MeLi or EtMgBr.

SCHEME 15. Preparation of β-Keto Ester 41[a]

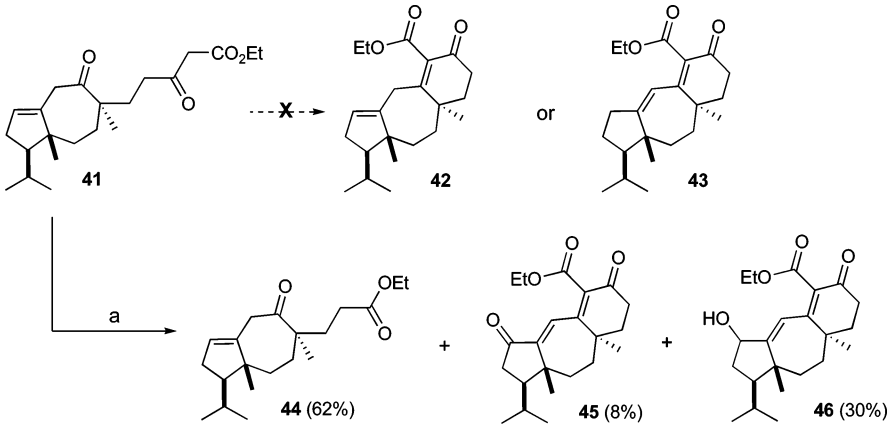


[a] Key: (a) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h, 83%; (b) ethyl diazoacetate ($N_2CHCOOEt$), $SnCl_2$, CH_2Cl_2, rt, 3.5 h; (c) TsOH, H_2O in acetone (5%), 70 °C, 90 min, 80% over two steps.

these conditions, the tetradeuterated tricyclic system **51** was detected by mass spectrometric analysis. Furthermore, when this compound was exposed to air, it gave rise to an ϵ-hydroxylated trideuterated compound, assigned as **52**. Thus, under conditions of rigorous oxygen exclusion, a non-oxidative adduct can apparently be produced. A model for late-stage ω-oxidation had presented itself, though by happenstance.

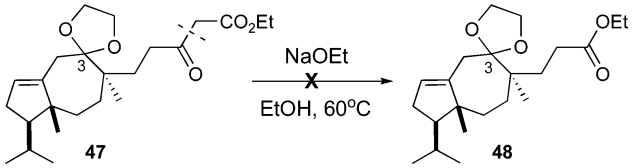
While we were gaining some confidence in our understanding of the variously competitive pathways operating in our system, we had not yet realized a protocol by which we could obtain ω-oxidized products of the type **45** or **46** in serviceable yields. Accordingly, we examined the purposeful introduction of an oxygen atom into our bicyclic substrate prior to attempted intramolecular Knoevenagel condensation. Toward this end, we revisited β-ketoester **41** and studied its reaction with *m*-CPBA (Scheme 20). In the event, despite the presence of a potentially competing β-ketoester linkage in this molecule, epoxidation of the future C_1–C_{14} bond occurred to give rise to **53**. The stereochemistry of the epoxide linkage was formulated as α. This assignment was validated on the basis of subsequent events. In particular, treatment of this compound with sodium ethoxide in ethanol at room temperature led to the formation of the 14-hydroxylated bicyclic structure **54**. Indeed, when **54** was subjected to the action of sodium ethoxide/ethanol at 50 °C, a 74% yield of the much desired compound **55** was obtained. By the same token, treatment of compound **53** under the more forcing sodium ethoxide/ethanol, 50 °C conditions also led to compound **55** in acceptable yield.

SCHEME 16. Attempted Intramolecular Knoevenagel Condensation of 41[a]



[a] Key: (a) NaOEt, EtOH, 60 °C, 19 h.

SCHEME 17. Control Study: Attempted Retrograde Claisen Condensation of 47



At last, a serviceable route to the construction of the tricyclic core structure had been realized. The key was to oxidize (via epoxidation) the C_1-C_{14} olefin prior to Knoevenagel cyclization.

Our next area of focus would be that of dealing with the novel α,β-unsaturated aldehyde embracing carbons 3, 4, and 15, as well as the allylic alcohol encompassing carbons 3, 4, and 5. It seemed prudent to protect the C_{14} alcohol before generating hydroxy functionality at C_5 or C_{15}. Accordingly, compound **55** was subjected to the action of triethylsilyl triflate under the conditions shown, thereby affording **56** (Scheme 21).

In planning concurrent reduction of both the ester and keto functions, we were concerned that the ylidene β-ketoester function would be subject to facile conjugate reduction.[3g] In actuality, this was not a significant problem. Treatment of **56** with DIBAL-H led to smooth reduction of the ester and ketonic functions with preservation of the diene system. A separable mixture of two diol products was obtained, reflecting diastereomers at C_5 (vide infra).[34] The use of other reducing agents was explored in an attempt to render the reaction more stereospecific. However, recourse to other reducing agents, such as $LiAlH_4$, $Li(OtBu)_3AlH$,[35] 9-BBN,[36] and $NaBH_4/CeCl_3$,[37] in fact led to reduced stereoselectivities.

We theorized that the minor reduction product corresponds to structure **57**, bearing the required β-configuration at C_5. The major compound was correspondingly formulated as **58**, in which inversion at C_5 would be necessary to reach the required (5β) guanacastepene stereochemistry. The notion was that the principal trajectory of hydride delivery by a hindered reducing agent had occurred from the β-face, thereby leading to the α-alcohol at C_5. Our formulation was based on the supposition that hydride delivery would occur from the β-face *anti* to the angular methyl at C_8. In conformational analysis terms, the guanacastepene stereochemistry at C_5 would correspond to formation of an equatorial alcohol by means of axial delivery.[38] With this bias influencing our tentative assignments, the major compound was subjected to Mitsunobu inversion.[39] Compound **58** was converted to its dibenzoate, **59**, as shown. Hydrolysis of the dibenzoate, in turn, produced the original minor product, **57**. Each diol, **57** and **58**, could be converted to its cyclic acetonide derivative, formulated as **60** and **61**, respectively. It was possible to sustain the cyclic acetonide protecting group through the protocol which accomplished desilylation at C_{14}. The resultant product, when subjected to Dess–Martin oxidation,[30] gave rise to the C_{14} ketone in each of the two epimeric C_5 acetonides (**62** and **63**).

At this point, we faced the issue of introduction of the C_{13} acetoxy function. We first studied the problem in the major diol series, which we construed to have the 5-*epi*-guanacastepene stereochemistry, in the context of its acetonide (**63**). Subsequently, we undertook to study the acetoxylation of the ketone in the minor (C_5-β) series (**62**), which now became readily available through the Mitsunobu protocols described above. The thought was that as we came closer to reaching guanacastepene itself, it would be possible to rigorously distinguish between the two late-stage diastereomers, **57** and **58**.

Our initial approach to the installation of the C_{13} acetoxy function involved formation of a $C_{13}-C_{14}$ enol derivative (cf. **64**, Scheme 22).[40] We anticipated that epoxidation of the enol would occur from the α-face, anti to the resident C_{12}-isopropyl and C_{11}-methyl functionalities. Two stereochemically divergent pathways can then

(34) For a discussion of the general preference for axial hydride delivery to cyclohexenones, with leading references, see: Davis, A. P. In *Methods in Organic Chemistry (Houben-Weyl) Stereoselective Synthesis*, Workbench Edition E21; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: New York, 1996; Vol. 7, 4034.

(35) For a review of reductions using lithium trialkoxyaluminum hydrides, see: Málek, J. *Org. React.* **1985**, *34*, 1.

(36) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197.

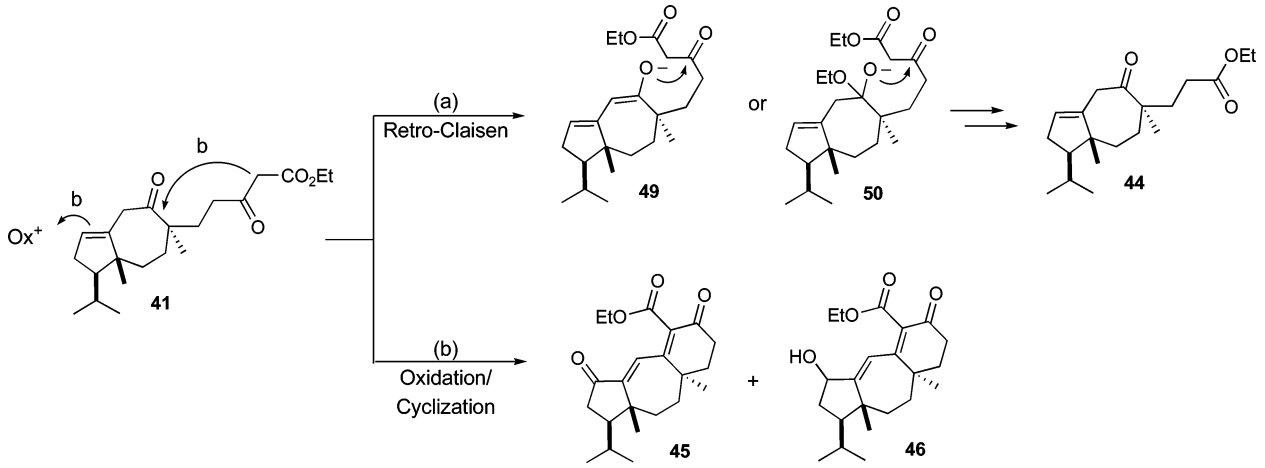
(37) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(38) Wu, Y.-D.; Houk, K N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560.

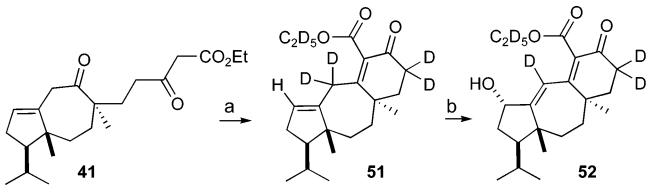
(39) For a review of the Mitsunobu reaction, see: Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(40) Brevet, J.-L.; Fournet, G.; Gore, J. *Synth. Commun.* **1996**, *26*, 4185.

SCHEME 18. Proposed Pathway of Formation of 44

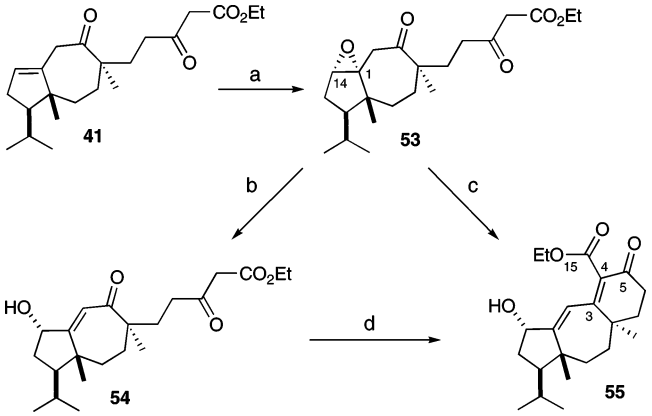


SCHEME 19. Mechanistic Studies on the Serendipitous Oxidation[a]



[a] Key: (a) NaOEt-d_5, EtOH-d_6, 60 °C, 17 h; (b) exposure to air, rt, <4 h.

SCHEME 20. Synthesis of Oxidatively Functionalized Gunacastane Skeleton 55[a]



[a] Key: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 2 h, 89%; (b) NaOEt, EtOH, rt, 30 min, 82%; (c) NaOEt, EtOH, 50 °C, 6 h, 74%; (d) NaOEt, EtOH, 50 °C, 6 h, 80%.

be envisioned from epoxide **65**. Under a solvolytic pathway (path *a*), the C_{14}−O epoxide bond is cleaved to afford α-hydroxyketone **66**, with retention of stereochemistry at C_{13}. By contrast, a thermolytic pathway (path *b*) triggering strictly intramolecular bond reorganization events would entail transfer of the intact acetoxy function from C_{14} to C_{13}, resulting in an overall inversion of stereochemistry at C_{13}.[41] Given our initial expectation that epoxidation would occur from the seemingly less congested α-face, we anticipated that the thermolytic pathway would be the one which would lead to the guanacastepene (C_{13}-β) stereochemistry from the presumed **65**.

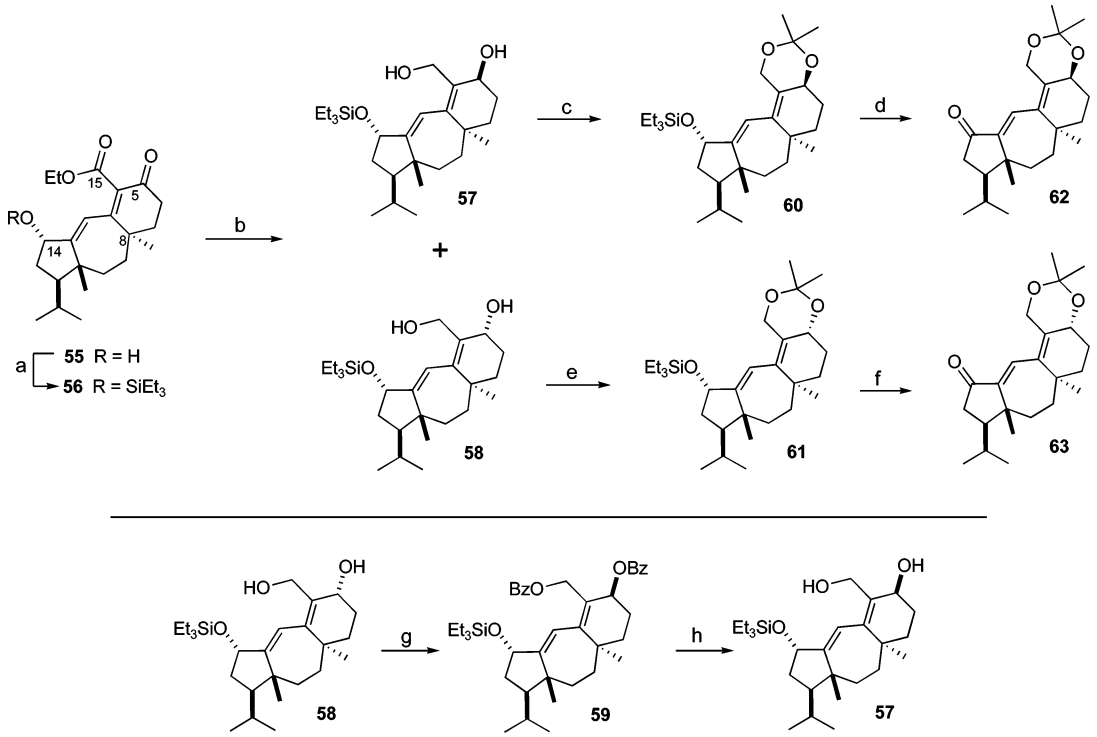
We now digress briefly to explain our paradigm for analysis of the stereochemistry of the C_{13}-acetoxylated compounds. In the precursor ketone, **63**, the C_{13} geminal protons are coupled to the C_{12} α-proton with distinct coupling constants (13.2 and 7.6 Hz). Based on analogy to guanacastepene A ($J_{(13-H\alpha,12-H\alpha)} \approx 7$ Hz), we could tentatively assign the 13.2 Hz coupling constant to $13H_\beta$−$12H_\alpha$ and the 7.6 Hz coupling constant to $13H_\alpha$−$12H_\alpha$. This assignment was supported by observed NOE interactions. In this way, we looked forward to assigning the stereochemistry of the C_{13}-acetoxylated products **69** and **70** by evaluating the $J_{(13-H,12-H\alpha)}$ coupling constants in the context discussed above.

In the event, ketone **63** was converted to epoxide **68** as shown (Scheme 23). The stereochemistry of the epoxide was not determined at this stage. The epoxide was then subjected to acidic conditions, which should favor the solvolysis pathway, with retention of the epoxide stereochemistry. As discussed above, we had expected this pathway to yield α-acetoxy ketone (cf. **70**), and were thus surprised to find **69** as the major product. As discussed above, the assignment of the stereochemistry of **69** at C_{13} was based on an evaluation of the vicinal 13-H/12-H coupling constant (6.7 Hz), which correlates to the coupling constant observed for the natural product (7.5 Hz), in the $13H_\alpha$-$12H_\alpha$ series.[1a]

By contrast, when **68** was subjected to pyrolysis conditions, expected to result in overall inversion of stereochemistry, a ca. 1:1 mixture of **69** and **70** was observed. Again, we turned to an analysis of the 13-H/12-H coupling constant to assign the C_{13} stereochemistry for compound **70**. As expected for a structure with a trans relationship between 13-H and 12-H, the observed $J_{(13-H\beta,12-H\alpha)}$ was 12.8 Hz. The product obtained from the solvolytic pathway led us to conclude that epoxidation (cf. **63** → **68**) must have occurred from the seemingly more hindered β-face of the enol acetate. However, the surprising lack of product stereoselectivity resulting from

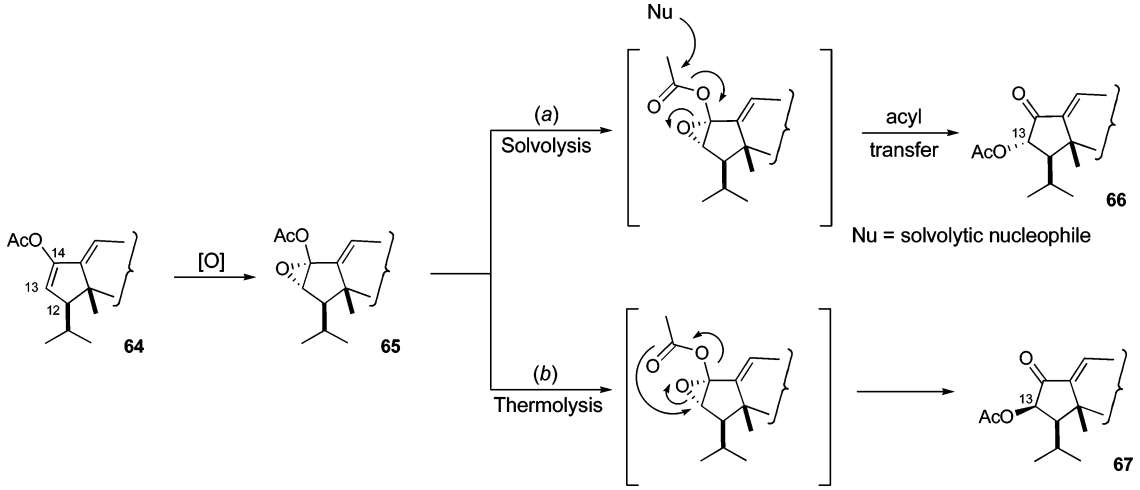
(41) For acid catalyzed and thermal rearrangements of enol ether epoxides, cf. inter alia: (a) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818. (b) Williamson, K. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1961**, *83*, 4563. (c) Soloway, A. H.; Considine, W. J.; Fukushima, D. K.; Gallagher, T. F. *J. Am. Chem. Soc.* **1954**, *76*, 2941. (d) Heathcock, C. H.; Smith, S. C. *J. Org. Chem.* **1994**, *59*, 6828. (e) Hernández, R.; Velázquez, S. M.; Suárez, E. *J. Org. Chem.* **1994**, *59*, 6395.

SCHEME 21. Preparation of the Diastereomeric Keto-Acetonides 62 and 63[a]



[a] Key: (a) Et_3SiOTf, pyridine, CH_2Cl_2, 0 °C, 80−85%; (b) DIBAL-H, CH_2Cl_2, −78 to 0 °C (**58**/**57** 80:20); (c) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 0 °C, 67% (from **56**); (d) TBAF, THF, 0 °C, 91−98%, then Dess−Martin periodinane, pyridine, CH_2Cl_2, 90%; (e) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 0 °C, 86% (from **56**); (f) HF·pyridine, pyridine, THF, then Dess−Martin periodinane, CH_2Cl_2, 77−85%; (g) PPh_3, benzoic acid, DIAD, THF, −78 °C to rt; (h) DIBAL-H, CH_2Cl_2, −78 to 0 °C.

SCHEME 22. Proposed Oxidation of C_{13} via Solvolytic and Thermolytic Pathways

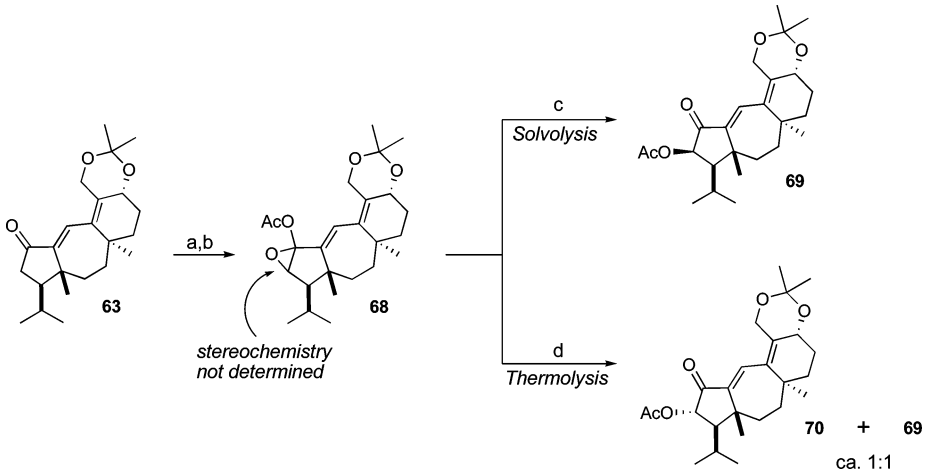


the thermolytic pathway in any case merited further scrutiny.

We sought to examine the origins of the nonhomogeneity of the thermolysis pathway. Upon subjection of **68** (ratio of β- to α-epoxide ≈ 90:10) to thermolytic conditions (150 °C for 18 min), a ca. 2:1 mixture of **70** and **69** was observed (Scheme 24).[3e] In addition to these two acetoxyketone diastereomers, a hydroxyketone intermediate, **72**, was identified. This intermediate was very predominantly of the 13-β configuration (ca. 40:1). Acetylation of **72** and combination of this product with the acetoxyketones afforded an overall 1:1 mixture of **70** and **69**.[42] These results serve to illuminate the course of the thermolytic reaction pathway. Normally, one would expect this reaction to produce acetoxyketone **70**, with inversion of stereochemistry from epoxide **68**-β. In this case, the results indicate the existence of a competing C_{14}-oxido heterolytic pathway, perhaps a consequence of the allylic relationship of the epoxide to the C_1-C_2 olefin.

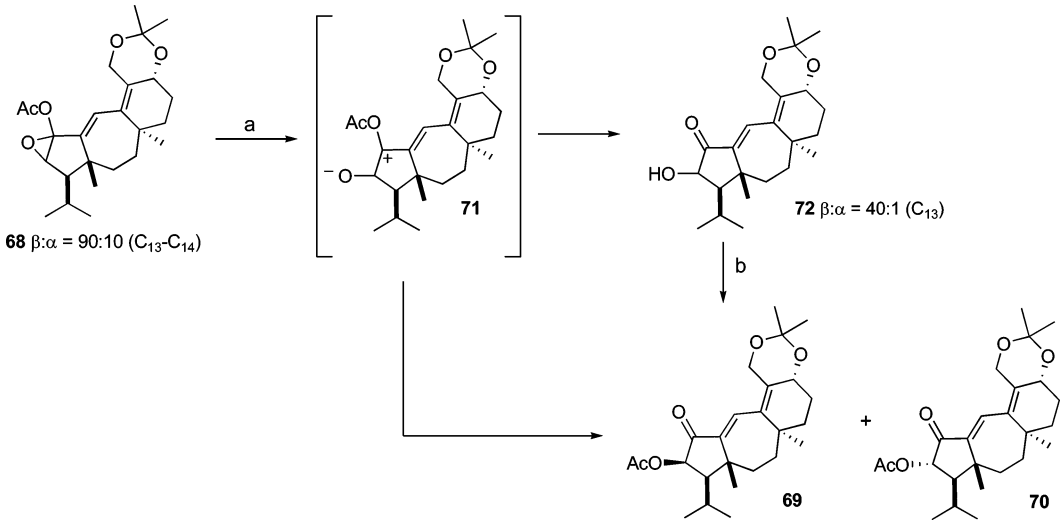
(42) The thermolysis study described above for the 5-α series has been separately performed on the equivalent substrate in the 5-β series (see **62**), which corresponds to the guanacastepene stereochemistry. In studies with this substrate, there appears to be a preference for formation of the 13-β acetoxy product (**74**) over the 13-α acetoxy product (13-*epi*-**74**). The ratio of **74** to 13-*epi*-**74** was approximately 2.3: 1.

SCHEME 23. Studies on the Stereoselective Oxidation of 63[a]



[a] Key: (a) Et_3N, DMAP, AcCl, Ac_2O, 100 °C, 90%; (b) DMDO/acetone, CH_2Cl_2, −78 to 0 °C; (c) *p*-TsOH, $MeNO_2$, then Ac_2O, pyridine, DMAP, 60% from **63**; (d) 150 °C (neat), then Ac_2O, pyridine, DMAP, 65% from **63** (**69/70** ca. 1:1).

SCHEME 24. Investigations on the Lack of Stereoselectivity in the Thermolysis of 68[a]



[a] Key: (a) DMDO/acetone, CH_2Cl_2, 150 °C, then Me_2S, 80%; (b) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 80%.

Thus, compound **68** could undergo heterolytic cleavage to generate intermediate **71**, which could be converted to either acetoxyketone or hydroxyketone. In either event, product generated under this pathway would be formed with retention of the epoxide stereochemistry, thus eroding the overall selectivity for the inversion product, **70**.

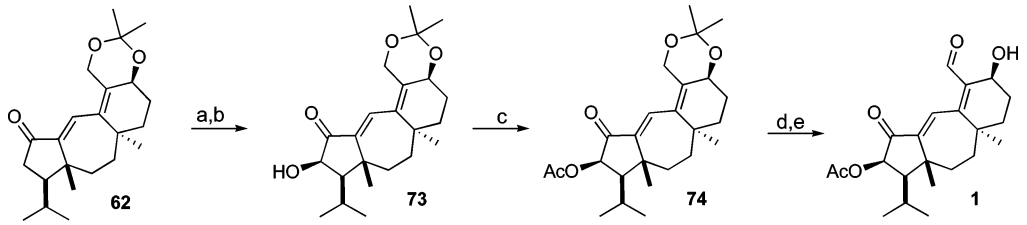
Having thus identified the origin of the lack of stereoselectivity in the thermolysis route, we returned to the task of installing the guanacastepene C_{13} β-acetoxy functionality. Clearly, the solvolytic pathway described above would be a viable means of accomplishing this goal. However, given that the intermediate epoxide formed, albeit surprisingly was actually of the β-configuration, we opted to install the acetoxy group via the more straightforward Rubottom oxidation protocol.[43] Thus, conversion of compound **62** to its silyl enol ether, followed by exposure to DMDO, gave rise to hydroxyketone **73** (ca. 10:1 β:α), which was subsequently acetylated to afford **74** (Scheme 25). An X-ray structure was obtained for **73**, and the stereochemical nature of this late stage intermediate was confirmed as corresponding to that of guanacastepene A (Figure 4).[44]

We digress briefly to note that, although we had inferred the stereochemistry of the intermediate epoxide to be β, based on its conversion to the acetoxyketone **74**, an alternate mechanism has been proposed by Magnus and Ollivier.[45] According to the Magnus hypothesis, epoxidation may occur from the α-face of the silyl enol

(43) (a) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319. (b) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; DiGrandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843. (c) Rubottom, G. M.; Gruber, J. M.; Boeckman, R. K., Jr.; Ramaiah, M.; Medwid, J. B. *Tetrahedron Lett.* **1978**, 4603.

(44) The X-ray shows that, while the first carbon of the isopropyl group is, indeed, β, the geminal dimethyls are α-disposed. Therefore, in addition to confirming the stereochemical assignment described above, the X-ray also rationalizes why attack of oxidizing agents occurs primarily from the β-face of the molecule. We and others continue to investigate this matter.

SCHEME 25. Completion of the Synthesis of Guanacastepene A[a]



[a] Key: (a) Et_3SiOTf, Et_3N, CH_2Cl_2; (b) DMDO/acetone, CH_2Cl_2, −78 °C, then Me_2S, 82−90% over two steps; (c) Ac_2O, pyridine, DMAP, CH_2Cl_2, 96%; (d) PPTS, MeOH, 70 °C; (e) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 59−65% over two steps.

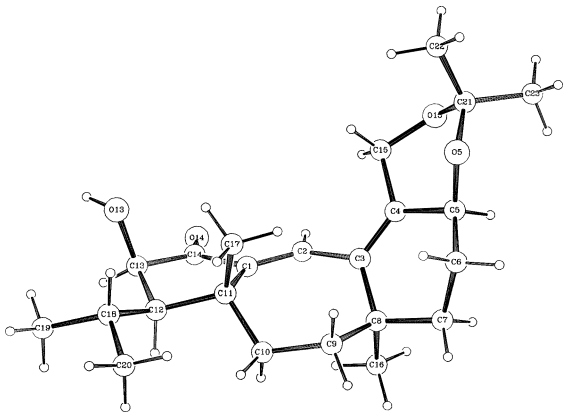
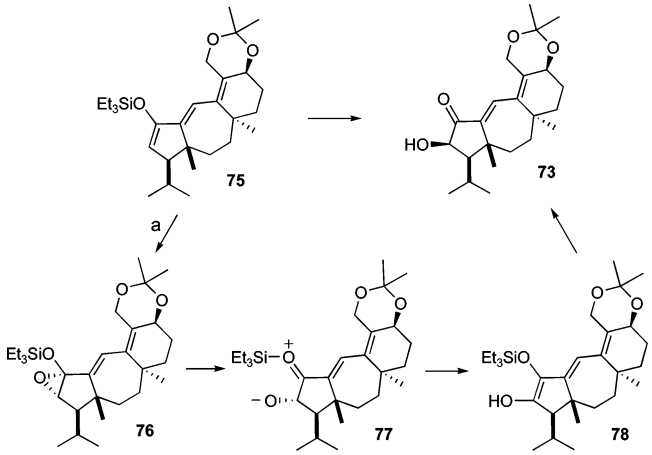


FIGURE 4. X-ray structure of **73**.

SCHEME 26. Proposed Alternate Mechanism for Formation of 73[a]



[a] Key: (a) DMDO/acetone, CH_2Cl_2, −78 °C, then Me_2S.

ether **75**, affording **76**, which could plausibly rearrange to the C_{13}-β-hydroxyketone, **73**, as shown (Scheme 26).

To test the applicability of the proposed Magnus mechanism to our own case, we prepared the C_{13}-dideuterated compound **79**, which was then enolized to afford deuterated silyl enol ether **80** (C_{13}-D/C_{13}-H = 85:15) (Scheme 27). The latter was subjected to the Rubottom conditions described above, followed by acetoxylation. The ratio of deuterated acetoxy compound **81** to nondeuterated **69** was again 85:15, thus confirming that significant deprotonation at C_{13} had not occurred. Given these results, it is highly unlikely that an inversion pathway, such as that suggested by Magnus, is responsible for the observed C_{13} stereochemistry. The reader will note that this mechanistic evaluation was performed in the C_5-α series. As indicated above, our studies have demonstrated that the nature of the remote C_5 stereocenter does not impact the stereochemistry of epoxidation at C_{13}.

We return to the completion of the synthesis of guanacastepene A. Hydrolysis of the acetonide of **74** followed by TEMPO-catalyzed oxidation[46] of the resultant primary alcohol afforded guanacastepene A (**1**), whose spectral data (^{1}H NMR at 25 °C and −50 °C, ^{13}C NMR at 25 °C and −50 °C, IR, and mass spectra) were found to be in complete accord with those obtained for the natural material (Scheme 25).[47,48] Due to the instability of guanacastepene, it would not be possible to obtain a sample of the natural product. Given the crystallographic determination on compound **74**, we could be very confident of the correctness of our assignment.

Indeed, prior to obtaining verification from the crystallographic determination, we had prepared and evaluated the remaining three diastereomers of **1**, with respect to C_5 and C_{13}, to demonstrate that the guanacastepene epimers can be differentiated by ^{1}H NMR. Indeed, the epimeric C_{13}-acetoxy functionalities were shown to exhibit markedly different coupling constants. In addition, the epimeric C_5-hydroxy groups exhibited differential effects on the peak shape of the C_{15} aldehyde. This evidence is thus overwhelming, in the absence of a direct comparison of samples, that the total synthesis of racemic guanacastepene had, indeed, been accomplished.

We now sought to adapt our program to allow us to gain access to fully synthetic optically active natural product. In this context, we identified intermediate **20** from our racemic route as a key target compound for our modified asymmetric synthesis. With enantioenriched **20** in hand, the route to optically active guanacastepene A

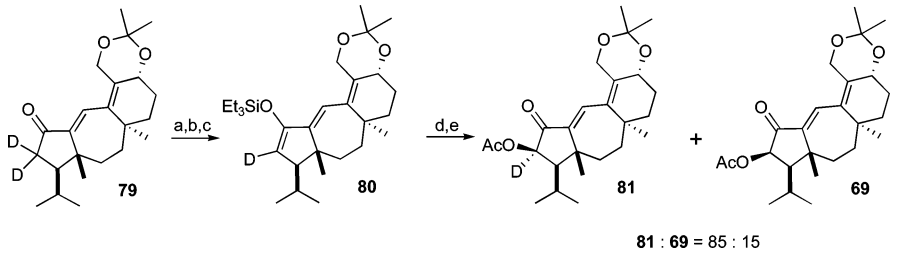
(45) Magnus, P.; Ollivier, C. *Tetrahedron Lett.* **2002**, *43*, 9605.

(46) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

(47) An authentic sample is no longer available for comparison (J. Clardy, personal communication). In fact, at the present time chemical synthesis is the only source of this compound.

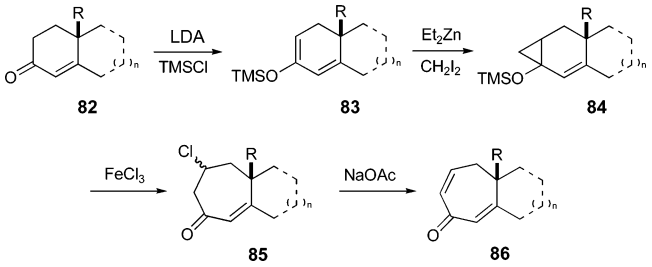
(48) ^{1}H NMR for synthetic guanacastepene at 25 °C (acetone-d_6, 400 MHz): δ 9.91 (br s, 1H), 7.45 (d, J = 1.1 Hz, 1H), 5.48 (d, J = 6.5 Hz, 1H), 4.62 (m, 1H), 3.97 (br s, 1H, OH), 2.08 (s, 3H), 1.99 (m), 1.90 (m), 1.79 (m), 1.63 (m), 1.40 (m), 1.27 (s, 3H), 1.12 (d, J = 6.6 Hz, 3H), 1.09 (s, 3H), 0.93 (d, J = 6.4 Hz, 3H). ^{1}H NMR for synthetic guanacastepene at −50 °C (acetone-d_6, 500 MHz, key signals): major δ 9.96 (s), 7.42 (s), 5.45 (d, J = 5.6 Hz), 4.64 (m), 4.59 (d, J = 5.4 Hz) (OH), 2.10 (s); minor δ 9.72 (s), 7.49 (s), 5.53 (d, J = 7.1 Hz), 4.52 (m), 4.48 (d, J = 4.1 Hz, OH), 2.11 (s). These data match the data obtained directly from the ^{1}H NMR spectra of the natural product. We are grateful to Prof. Jon Clardy and Dr. Sean F. Brady for providing detailed NMR spectra of natural guanacastepene A.

SCHEME 27. Evaluation of the Applicability of the Magnus Mechanism to Guanacastepene A[a]

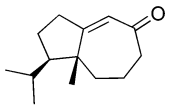


[a] Key: (a) Et_3N, CD_3OD, rt, 20 h, 90%; (b) DBU, CD_3OD, rt, 4 h, 95%; (c) Et_3SiOTf, Et_3N, CH_2Cl_2, 79%; (d) DMDO/acetone, CH_2Cl_2, −78 °C, then Me_2S; (e) Ac_2O, pyridine, DMAP, CH_2Cl_2, ca. 60%.

SCHEME 28. Proposed Homo-Robinson Annulation Strategy



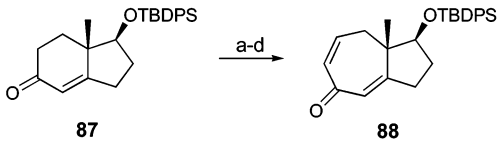
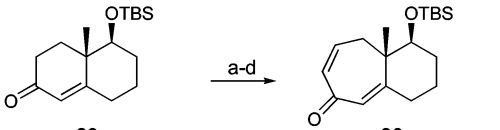
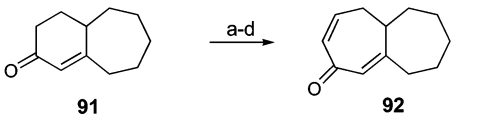
would converge with our established synthesis in the racemic series. In this context, we revisited a general strategy that had been considered early in the project: that of using a homo-Robinson annulation to assemble a structure such as **20**. Our early efforts to assemble the B,C-system through a Robinson annulation strategy had been unsuccessful due to the preferential formation of a five-membered ring in lieu of the requisite seven-membered ring (see Scheme 3). We were hopeful that an alternate approach might allow us to circumvent this problem.



In a revised early phase strategy, we would draw from the previously reported work of Saegusa,[49] involving oxidative cleavage of silyloxycyclopropanes to generate ring-expanded α,β-unsaturated ketones. We proposed to extend the Saegusa teaching to produce ring-expanded cross-conjugated dienones. Thus, our proposed route would commence with a standard Robinson annulation to generate a fused cyclohexenone of the type **82** (Scheme 28). The latter would be converted to the cyclopropane **84** via the cross-conjugated silyloxydiene **83**. On the basis of both independent chemical reasoning and precedent, we anticipated that treatment of **84** with $FeCl_3$ would induce oxidative cleavage of the interior cyclopropane bond, giving rise to chloroketone **85**. Following β-elimination, the cross-conjugated dienone **86** would be in hand.

As recently described,[3h] we first demonstrated the cyclopropanation route to homo-Robinson annulation products in the context of racemates. Several examples are summarized below (Table 1). Starting materials **87**[50] and **89**[51] were prepared from the Hajos−Parrish[52] and Weiland−Meischer[53] ketones, respectively. Known compound **91** was prepared by a direct Robinson annulation-annular decarboxylation protocol.[54] Importantly, the route from cyclohexenone (cf. **82**) to cycloheptadienone (cf. **86**) can be conducted without purification of any of the intermediates. The yields reported below are overall yields from the four-step procedure.

TABLE 1. Successful Ring Expansion of Robinson Annulated Substrates

Substrate	Product	Yield (4 steps)[a]
		45%
		40%
		43%

[a] Key: (a) $(i\text{-Pr})_2NH$ (2.5 equiv), *n*-BuLi (2.8 equiv), TMSCl (2.0 equiv), THF, −78 °C; (b) Et_2Zn (1.5 equiv), CH_2I_2 (1.1 equiv), Et_2O, 0 °C; (c) $FeCl_3$ (2.5 equiv), 0 °C; (d) NaOAc, reflux.

Having established this homo-Robinson equivalent protocol as a viable means to generate fused cycloheptadienone structures, we returned to our goal of reaching bicyclic compound **20**. Our program commenced with silyl enol ether **7** (Scheme 29). Michael addition of **7** to methyl vinyl ketone, under Mukayama conditions,[55] gave rise to intermediate **93**, which, following aldol cyclization, yielded the fused cyclohexenone intermediate **94**. This compound was subjected to the four-step ring-expansion sequence

(49) Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073.

(50) Caine, D.; Kotian, P. L.; McGuiness, M. D. *J. Org. Chem.* **1991**, *56*, 6307.

(51) Kim, M.; Kawada, K.; Watt, D. S. *Synth. Commun.* **1989**, *19*, 2017.

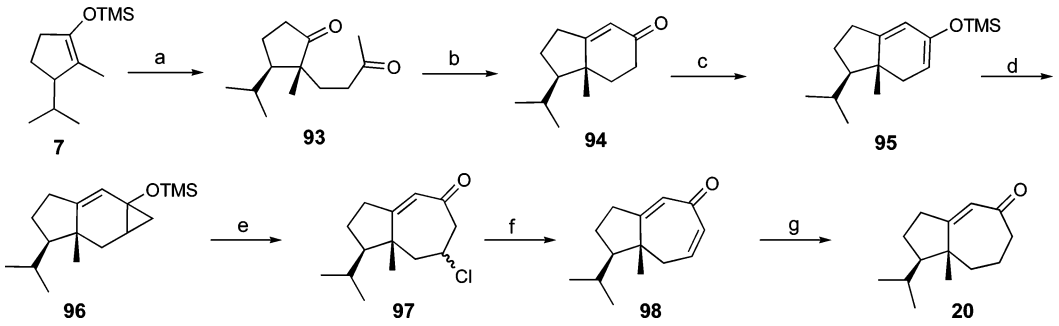
(52) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975,** *40*, 675.

(53) Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215.

(54) Ozaki, Y.; Kubo, A.; Kim, S. W. *Chem. Lett.* **1993**, *6*, 993.

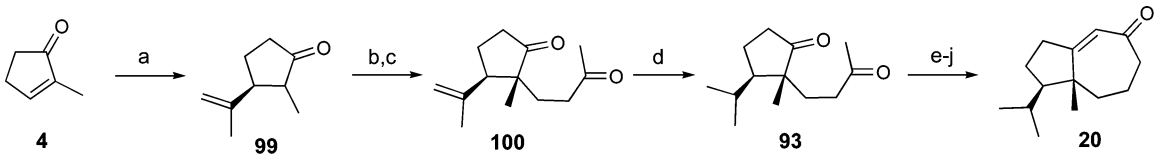
(55) Duhamel, P.; Dujardin, G.; Hennequin, L.; Poirier, J. M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 387.

SCHEME 29. Application of Homo-Robinson Annulation Strategy to Guanacastepene A[a]



[a] Key: (a) MVK, AcOH, $BF_3{\cdot}Et_2O$, −20 °C, 97%; (b) NaOMe, 98%; (c) $(i\text{-Pr})_2NH$, *n*-BuLi, TMSCl, THF, −78 °C; (d) Et_2Zn, CH_2I_2, Et_2O, 0 °C; (e) $FeCl_3$, 0 °C; (f) NaOAc, reflux, 40% yield for four steps; (g) Wilkinson's catalyst, H_2, 83%.

SCHEME 30. Formal Enantioselective Total Synthesis of Guanacastepene A[a]



$[\alpha]_D$ -44.8 (*c* 0.1, $CHCl_3$)

[a] Key: (a) CuSCN, isopropenyllithium, (*S*)-2-methoxymethylpyrrolidine, 4 Å MS, −100 °C, 96%, 90% ee; (b) TBSOTf, TEA, 90%; (c) MVK, AcOH, $BF_3{\cdot}Et_2O$, −20 °C, 90%; (d) H_2, Pd/C, 92%; (e) NaOMe, 98%; (f) $(i\text{-Pr})_2NH$, *n*-BuLi, TMSCl, THF, −78 °C; (g) Et_2Zn, CH_2I_2, Et_2O, 0 °C; (h) $FeCl_3$, 0 °C; (i) NaOAc, reflux, 40% yield over four steps; (j) Wilkinson's catalyst, H_2, 83%

as described above, to afford ultimately cycloheptadienone **98** in 40% overall yield from **94**. Finally, selective Wilkinson reduction[56] of **98** was easily executed, giving rise to **20** in racemic form.

At this point, there remained only the adaptation of this route to allow for the enantioselective preparation of key intermediate **20**. To accomplish this goal, we made use of an enantioselective conjugate addition described by Quinkert and colleagues.[57] Thus, as described by the German workers, addition of isopropenyl cuprate to methyl cyclopentenone **4** afforded **99** in 90% ee (Scheme 30). It is only appropriate to note that the Quinkert protocol, however impressive in its outcome, does apparently require the use of substantial excesses of chiral additive. Thus, from the perspective of convenience, there is certainly room for new technology to be brought to bear on the problem. Nonetheless, we moved forward. Thus, silyl enol ether formation on **99**, followed by Michael addition to methylvinyl ketone, gave rise to **100**. The isopropenyl group of the latter was hydrogenated to afford highly enantioenriched **93**. When subjected to the conditions described above for the racemic protocol, compound **93** was smoothly converted to optically enriched **20**. This novel reaction protocol constitutes the basis of an enantioselective formal synthesis of guanacastepene A. Following the routes documented above in the racemic series, compound **20** could be converted to enantioenriched or possibly enantiopure guanacastepene A (depending on full purification through crystallization), though we have not in practice done so at this writing.

(56) Bhattacharyya, S.; Karpha, T. K.; Mukherjee, D. *Synth. Commun.* **1989**, *19*, 673.

(57) Quinkert, G.; Müller, T.; Königer, A.; Schultheis, O.; Sickenberger, B.; Dürner, G. *Tetrahedron Lett.* **1992**, *33*, 3469.

Conclusions

In summary, the main goals of the guanacastepene A project have been met. A total synthesis of the racemate has been accomplished. A route to enter the appropriate enantiomeric series has been fashioned and documented for use. The route to guanacastepene involved a multifaceted travelogue, which led us along several fascinating excursions. First, we would cite the issue of reductive cyclization relative to reduction (see compounds **18** and **19**) and the way in which deuterated compounds were used both to influence yield distributions and to teach mechanistic pathways. The solution to the control of stereochemistry at C_8 was critical to the success of the program. The sorting out of the issues of how to conduct intramolecular Knoevenagel condensation (see precursor **53**) turned into an unexpected challenge. The solution to the problem of stereoselective acetoxylation at C_{13} was solved only after recognizing that attack of the $C_{12}-C_{13}$ enol was occurring from the β-face (see **62** → **73**). Finally, it was the lure of guanacastepene which led us to study means for accomplishing the equivalent of the homo-Robinson annulation.[3h] With the benefit of a valuable enabling contribution from Quinkert,[57] we could exploit our chemistry to enable the enantiocontrolled synthesis of guanacastepene itself. Inevitably, some of our findings provoke questions that have not been fully answered. Indeed, the journey to guanacastepene had carried with it many interesting teachings and stimulating questions in chemistry, well worth continuing attention.

Experimental Section

8β-(4′-Carbethoxy-3′-ketobutyl)-8α,11β-dimethyl-12β-isopropyl-1,14-oxiranylhydroazulen-3-one 53. In a 25 mL conical flask, the β,ζ-diketo ester **41** (96 mg, 265 μmol, 1.0 equiv) was dissolved in 5 mL of CH_2Cl_2 and cooled to 0 °C.

m-CPBA (57−86%, 420 mg, 1.39−2.09 mmol, 5.3−8.0 equiv) was added in three portions over 1 h. After an additional 2 h, 5 mL of 1 M $Na_2S_2O_3$ was added and the reaction removed from the bath and allowed to warm to rt. The mixture was partitioned between 15 mL of Et_2O and 5 mL of satd $NaHCO_3$. The organic phase was washed 1× with brine, dried ($MgSO_4$), filtered, and evaporated to yield the crude product. Purification by silica flash chromatography (4:1 hexanes/EtOAc, then 2:1 hexanes/EtOAc) yielded the epoxide **53** as a colorless oil (89 mg, 89%). TLC: R_f 0.31 (2:1 hexanes/EtOAc), R_f 0.50 (1:1 hexanes/EtOAc). IR (film): 2945, 1745 (C=O), 1716 (C=O), 1698 (C=O), 1646, 1473, 1367, 1317, 1238, 1174, 1084, 1033, 942. ^{1}H NMR (500 MHz, $CDCl_3$, 81:19 keto/enol form): (keto form) δ 4.19 (q, 2H, J = 7.1 Hz, C25−H_2), 3.47 (AB d, 1H, J = 15.5 Hz, C4−H_a), 3.42 (AB d, 1H, J = 15.5 Hz, C4−H_b), 3.24 (app s, 1H, C14−H), 3.23 (obsc d, 1H, J = 15.8 Hz, C2−H_a), 2.58 (ddd, 1H, J = 17.3, 10.1, 5.5 Hz, C6−H_a), 2.49 (ddd, 1H, J = 17.3, 10.0, 5.5 Hz, C6−H_b), 2.32 (d, 1H, J = 15.8 Hz, C2−H_b), 2.12 (dd, 1H, J = 14.2, 6.9 Hz, C13−H_a), 1.95−1.78 (obsc m, 3H, C3−H_a, C4−H_2), 1.84 (obsc m, 1H, C7−H_a), 1.75 (ddd, 1H, J = 14.0, 10.0, 5.5 Hz, C7−H_b), 1.51 (m, 1H, C18−H), 1.43 (obsc m, 1H, C9−H_b), 1.39 (ddd, 1H, J = 13.9, 10.6, 0.9 Hz, C13−H_b), 1.28 (obsc t, 3H, J = 7.1 Hz, C26−H_3), 1.26 (obsc s, 3H, C16−H_3), 1.20 (td, 1H, J = 10.0, 7.0 Hz, C12−H), 0.92 (d, 3H, J = 6.5 Hz, C19−H_3), 0.91 (s, 3H, C17−H_3), 0.85 (d, 3H, J = 6.6 Hz, C20−H_3), (enol form, diagnostic peaks) δ 12.11 (s, 1H, C5−OH), 4.99 (s, 1H, C4−H). ^{13}C NMR (100 MHz, $CDCl_3$): (keto form) δ 212.6 (C3), 202.7 (C5), 167.2 (C15), 66.85 (C1), 62.88 (C14), 61.32 (C25), 51.07 (C12), 49.90 (C8), 49.22 (C4), 44.68 (C2), 44.18 (C11), 38.38 (C6), 34.62 (C7), 32.98 (C9), 32.24 (C10), 32.05 (C13), 29.02 (C18), 23.13 (C19), 22.66 (C20), 20.00 (C16), 14.60 (C17), 14.08 (C26), (enol form, additional nonoverlapping peaks, partially assigned) δ 178.7 (C4/5), 172.8 (C4/5), 66.92, 62.93, 59.92 (C25), 51.13, 50.10, 44.85, 38.07, 32.38, 30.20, 20.33, 14.68, 14.24. ESI-MS *m/z* (rel int): (pos) 401.2 ([M + Na]$^+$, 100); (neg) 413.0 ([M + Cl]$^-$, 100), 376.9 ([M − H]$^-$, 40). HRMS (EI): *m/z* 401.2311 (M + Na$^+$), calcd for $C_{22}H_{34}O_5$ 378.2406.

8β-(4′-Carbethoxy-3′-ketobutyl)-8α,11β-dimethyl-12β-isopropyl-14α-hydroxy-($\Delta^{1,2}$)-hydroazulen-3-one 54. In a 25 mL conical flask, the epoxide **53** (54.7 mg, 145 μmol, 1.0 equiv) was azeotroped 1× from PhH, and then NaOEt (0.1 N in anhyd EtOH, prepared from Na^0, 1.6 mL, 159 μmol, 1.1 equiv) was added via syringe and the solution was stirred at rt. After 15 min, the reaction mixture was poured into satd aq NH_4Cl and extracted 3× with EtOAc. The combined organic extracts were washed 1× with H_2O and 1× with brine, dried ($MgSO_4$), filtered, and evaporated to yield the crude product as a clear oil (53.4 mg). Purification by silica flash chromatography (2:1 hexanes/EtOAc) yielded the γ-hydroxyhydroazulenone **54** as a clear oil (44.6 mg, 82%). TLC: R_f 0.23 (1:1 hexanes/EtOAc). IR (film): 3456 (br, O-H), 2961, 1742 (C=O), 1716 (C=O), 1652 (enone C=O), 1150, 1450, 1368, 1316, 1233, 1178, 1095, 1032, 874. ^{1}H NMR (500 MHz, $CDCl_3$, 92:8 keto/enol form): (keto form) δ 5.88 (d, 1H, J = 1.3 Hz, C2−H), 4.51 (br s, 1H, C14−H), 4.20 (q, 2H, J = 7.1 Hz, C25−H_2), 3.47 (app s, 2H, C4−H_2), 2.61 (app ddd, 2H, J = 9.3, 6.3, 3.1 Hz, C6−H_2), 2.02 (obsc m, 1H, C9−H_α), 1.98 (obsc m, 2H, C10−H_2), 1.89 (obsc m, 1H, C13−H_a), 1.87 (obsc m, 1H, C7−H_a), 1.83−1.75 (m, 4H, C13−H_b, C14−OH, C7−H_b, C12−H), 1.64 (app sxt, 1H, J = 6.7 Hz, C18−H), 1.50 (dd, 1H, J = 13.2, 7.0 Hz, C9−H_β), 1.28 (t, 3H, J = 7.1 Hz, C26−H_3), 1.17 (s, 3H, C16−H_3), 1.00 (d, 3H, J = 6.7 Hz, C19−H_3), 0.95 (s, 3H, C17−H_3), 0.92 (d, 3H, J = 6.6 Hz, C20−H_3), (enol form, diagnostic peaks) δ 12.13 (s, 1H, C5−OH), 5.04 (s, 1H, C4−H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7 (C3), 202.9 (C5), 167.3 (C15), 166.8 (C1), 123.8 (C2), 73.2 (C14), 61.3 (C25), 53.9 (C12), 49.7 (C8), 49.2 (C4), 48.6 (C11), 38.6 (C6), 36.5 (C13), 34.3 (C10), 32.5 (C7), 32.3 (C9), 28.2 (C18), 24.1 (C16), 23.7 (C19), 22.1 (C20), 20.9 (C17), 14.1 (C26). ESI-MS *m/z* (rel int): (pos) 401.4 ([M + Na]$^+$, 100); (neg) 413.0 ([M + Cl]$^-$, 65), 377.0 ([M − H]$^-$, 100).

Knoevenagel Cyclization of γ-Hydroxyenone 54 to Tricyclic Alcohol 55. A solution of freshly prepared sodium ethoxide (0.1 M in ethanol, 0.26 mL, 0.026 mmol, 1.1 equiv) was added to a solution of γ-hydroxyenone **54** (9.1 mg, 0.024 mmol, 1.0 equiv) in 0.74 mL of ethanol in a resealable vial. The vial was closed with a Teflon-lined cap and heated at 50 °C for 6 h. The reaction mixture was cooled to room temperature, diluted with 10 mL of ether, and washed with two 3-mL portions of water and then with 3 mL of saturated sodium chloride solution. The combined aqueous layers were extracted with 5 mL of ether, and the combined organic layers concentrated at reduced pressure, diluted with 10 mL of ether, washed with 3 mL of saturated sodium chloride solution, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. Purification by flash column chromatography on 4 g of silica gel (elution with 30% ethyl acetate/hexanes) provided 6.4 mg (74%) of tricyclic alcohol **55**. The tricyclic alcohol (**55**) synthesized in this way has the exact NMR characteristics of compound **46**. In this way, it confirms the stereochemistry of the C14-hydroxy to be α.

4-Carbethoxy-8α,11β-dimethyl-12β-isopropyl-14α-triethylsilyloxy-(Δ,$^{1,2}\Delta^{3,4}$)-tricycle 56. A solution of alcohol **55** (66 mg, 0.18 mmol, 1.0 equiv) and pyridine (89 μL, 1.1 mmol, 6.0 equiv) in 9 mL of CH_2Cl_2 in a 25-mL round-bottomed flask was stirred at 0 °C under argon, and triethylsilyl triflate (0.13 mL, 0.55 mmol, 3.0 equiv) was added rapidly dropwise. After 5 min, the reaction mixture was diluted with 27 mL of ether, washed successively with 9-mL portions of water, 1.0 M aqueous HCl, and a 1:1 mixture of saturated sodium bicarbonate and saturated sodium chloride solutions, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The crude material was purified by flash column chromatography on 9 g of silica gel (gradient elution with 10−30% ethyl acetate/hexanes) to provide 74 mg (85%) of **56** as a colorless oil. TLC: R_f 0.34 (8:2 hexanes/EtOAc). IR (film): 2956.2, 2874.7, 1735.2, 1674.3, 1456.5, 1366.6, 1226.6. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.02 (d, 1H, J = 1.6 Hz), 4.45 (br s, 1H), 4.16−4.31 (m, 2H), 2.50−2.60 (m, 2H), 1.85−2.13 (m, 2H), 1.59−1.85 (m, 8H), 1.27 (t, 3H, J = 7.1 Hz), 1.23 (s, 3H), 0.90−1.00 (m, 15H), 0.89 (d, 3H, J = 6.6 Hz), 0.56−0.63 (m, 6H). HRMS (EI): *m/z* 497.3056 (M + Na$^+$), calcd for $C_{28}H_{46}O_4Si$ 474.3165.

8α,11β-Dimethyl-5α-hydroxy-4-hydroxymethyl-12β-isopropyl-14α-triethylsilyloxy-(Δ,$^{1,2}\Delta^{3,4}$)-tricycle 58. A solution of keto-ester **56** (79 mg, 0.166 mmol, 1.0 equiv) in 16.5 mL of CH_2Cl_2 in a 50 mL round-bottomed flask under argon was immersed deeply in a −78 °C-cooling bath. A solution of DIBAL-H (1.0 M in CH_2Cl_2, 1.6 mL, 1.6 mmol, 10 equiv) was added slowly down the side of the flask, and the resulting mixture was stirred for 30 min at −78 °C and then for 30 min at 0 °C. The reaction mixture was quenched (carefully at first) with ethyl acetate (10 mL). The resulting solution was washed with 1:1 mixture of 1.0 M aqueous HCl/saturated sodium chloride solution (2 × 10 mL) and then with 1:1 mixture of saturated sodium bicarbonate/saturated sodium chloride solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated at reduced pressure to afford a mixture, which was ca. 4:1 mixture (α:β) of C5 diastereomers. The diastereomers were separated carefully by preparative TLC (25% ethyl acetate in hexanes) to obtain 0.039 g of major α-epimer in 54% yield and minor β-epimer in 8% yield (6 mg). α-Epimer of **58**. TLC: R_f 0.25 (3:1 hexanes/EtOAc). IR (film): 3282.2, 2953.3, 2934.1, 2874.3, 1456.0, 1239.3, 1049.9, 1013.4, 987.6. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.01 (s, 1H), 4.31−4.44 (m, 3H), 4.11 (br d, 1H, J = 9.4 Hz), 2.29−2.33 (b, 2H), 1.51−2.00 (m, 9H), 1.36−1.49 (m, 2H), 1.21−1.30 (m, 1H), 1.08 (s, 3H), 0.94−0.99 (m, 12H), 0.87 (d, 3H, J = 6.6 Hz), 0.79 (s, 3H), 0.56−0.60 (m, 6H). ESI-MS *m/z* (rel int): (pos) 457.3 ([M + Na]$^+$, 100); (neg) 469.0 ([M + Cl]$^-$, 55).

8α,11β-Dimethyl-5β-benzoyloxy-4-benzoyloxymethyl-12β-isopropyl-14α-triethylsilyloxy-(Δ,$^{1,2}\Delta^{3,4}$)-tricycle 59. A mixture of diol **58** (40 mg, 0.092 mmol, 1.0 equiv), Ph_3P (120 mg, 0.46 mmol, 5.0 equiv), and benzoic acid (56 mg, 0.46 mmol,

5.0 equiv) in 9 mL of THF in a 25-mL round-bottomed flask was cooled at −78 °C under argon. DIAD (90 μL, 0.46 mmol, 5.0 equiv) was added dropwise and the resulting yellow solution stirred overnight with gradual warming to room temperature. After 15 h, the reaction mixture was diluted with 27 mL of ether, washed with 9 mL of half-saturated sodium bicarbonate and 9 mL of saturated sodium chloride, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Partial purification was accomplished by flash column chromatography on silica gel (elution with 5% ethyl acetate/hexanes) to 55 mg (92% yield) of **59**. TLC: R_f 0.82 (2:1 hexanes/EtOAc). IR (film): 2966.0, 1718.6, 1452.5, 1314.2, 1269.7, 1175.6, 1109.6, 1067.9, 1025.8, 968.4, 709.7. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03−7.96 (m, 4H), 7.56−7.50 (m, 2H), 7.42−7.35 (m, 4H), 6.14 (app s, 1H), 5.81 (m, 1H), 4.96 (d, J = 12. 3 Hz, 1H), 4.79 (d, J = 12.4 Hz, 1H), 4.45 (m, 1H), 2.14−1.98 (m, 2H), 1.95−1.45 (m, 10H), 1.13 (s, 3H), 1.02−0.92 (m, 18H), 0.65−0.59 (m, 6H). HRMS (EI): *m/z* 665.3652 (M + Na^+), calcd for $C_{40}H_{54}O_5$ 642.3741.

8α,11β-Dimethyl-5β-hydroxy-4-hydroxymethyl-12β-isopropyl-14α-triethylsilyloxy-(Δ,^{1,2}Δ^{3,4})-tricycle 57. A solution of dibenzoate **59** (55 mg, 0.085 mmol) in 9 mL of CH_2Cl_2 in a 25-mL round-bottomed flask was cooled at −78 °C under argon, and a solution of DIBAL-H (1.0 M in CH_2Cl_2, 0.85 mL, 0.85 mmol, 0 equiv) was added dropwise down the sides of the flask. The resulting colorless solution was stirred for 30 min at −78 °C and 30 min at 0 °C and then quenched with 27 mL of ethyl acetate (carefully at first). The reaction mixture was washed with two 9-mL portions of a 1:1 mixture of 1.0 M aqueous HCl/saturated sodium chloride solution and one 9-mL portion of a 1:1 mixture of saturated sodium bicarbonate/saturated sodium chloride solutions. The organic layer was dried with $MgSO_4$, filtered, and concentrated at reduced pressure. Partial purification by flash column chromatography on 4 g of silica gel (gradient elution with 30−50% ethyl acetate/hexanes) provided 35 mg of a colorless oil **57** in 67% yield. TLC: R_f 0.24 (2:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93 (s, 1H, C2-H), 4.37 (br m, 2H, C5-H, C14-H), 4.33 (d, 1H, J = 12.4 Hz, C15-H), 4.21 (br d, 1H, J = 12.0 Hz, C15−H), 2.43 (br s, 1H), 2.14 (br s, 1H), 1.91 (m, 1H), 1.83−1.70 (m, 6H), 1.64 (m, 2H), 1.60 (hept, 1H, J = 6.8 Hz, C18-H), 1.39 (br m, 2H), 1.00 (s, 3H, C16/17-H_3), 0.97 (t, 9H, J = 7.9 Hz, C28-H_3), 0.95 (d, 3H, J = 6.0 Hz, C19/20-H_3), 0.89 (s, 3H, C16/17-H_3), 0.88 (d, 3H, J = 6.5 Hz, C19/20-H_3), 0.60 (q, 6H, C27-H_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 142.0, 129.5, 121.0, 77.2, 73.8, 72.7, 71.3, 68.7, 63.1, 4.5, 38.0, 37.1, 36.9, 36.6, 32.7, 28.2, 27.3, 25.5, 23.8, 22.4, 6.9, 5.0. ESI-MS *m/z* (rel int): (pos) 457.3 ([M + $Na]^+$, 100); (neg) 469.3 ([M + $Cl]^-$, 100). HRMS (EI): *m/z* 457.2985 (M + Na^+), calcd for $C_{26}H_{46}O_3Si$ 434.3216

8α,11β-Dimethyl-12β-isopropyl-5β,15-isopropylidenedioxy-14α-triethylsilyloxy-(Δ,^{1,2}Δ^{3,4})-tricycle 60. In a 100 mL round-bottom flask, the 14-TES-5β,15-diol **57** (ca. 35 mg, 0.08 mmol, 1.0 equiv) was dissolved in 12 mL of CH_2Cl_2 and cooled to 0 °C. PPTS (7.6 mg) and DMP (0.196 mL, 1.6 mmol, 20 equiv) were added in sequence, and the reaction mixture was stirred for 30 min at 0 °C before quenching with K_2CO_3. The resulting solution was stirred for 10 min, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography (hex/EtOAc = 10/1 followed by 4/1) to yield the 14-TES-5,15-acetonide **60** (31 mg, 81% yield, as white solids. TLC: R_f 0.74 (4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (s, 1H, C2-H), 4.35 (dd, 2H, J = 8.4, 6.4 Hz, C14-H/C5-H), 4.27 (d, 1H, J = 4.4 Hz, C5-H/14-H), 4.26 (d, 1H, J = 15.2 Hz, C15-H), 4.11 (d, 1H, J = 15.3 Hz, C15-H), 2.23 (br m, 1H), 1.84 (m, 1H), 1.81−1.69 (m, 4H), 1.61 (hept, 1H, J = 6.8 Hz, C18-H), 1.54 (dd, 2H, J = 10.1, 3.1 Hz), 1.44 (s, 3H, C40-H_3), 1.41 (m, 1H), 1.37 (s, 3H, C40-H_3), 1.26 (m, 2H), 1.00 (s, 3H, C16/17-H_3), 0.97 (d, 3H, J = 6.5 Hz, C19/20-H_3), 0.95 (t, 9H, J = 7.9 Hz, C28-H_3), 0.87 (d, 3H, J = 6.5 Hz, C19/20-H_3), 0.84 (s, 3H, C16/17-H_3), 0.58 (q, 6H, J = 7.9 Hz, C27−H_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 134.8, 132.1, 120.8, 99.5, 77.2, 74.4, 67.7, 60.5, 54.6, 46.1, 38.2, 38.0, 37.6, 35.8, 34.1, 27.9, 26.4, 25.3, 25.2, 23.9, 23.6, 22.5, 17.2, 6.9, 5.1. ESI-MS *m/z* (rel int): (pos) 497.3 ([M + $Na]^+$, 100). HRMS (EI): *m/z* 497.3449 (M + Na^+), calcd for $C_{29}H_{50}O_3Si$ 474.3529.

8α,11β-Dimethyl-12β-isopropyl-5α,15-isopropylidenedioxy-14α-triethylsilyloxy-(Δ,^{1,2}Δ^{3,4})-tricycle 61. Compound **61** was prepared from **58** in 91% yield following the similar procedure that has been used to prepare **60**. TLC: R_f 0.92 (2.3: 1 hexanes/ethyl acetate). IR (film): 2954, 2912, 2874, 1455, 1413, 1377, 1223, 1198, 1089, 1060. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65 (app s, 1H), 4.32−4.22 (m, 3H), 4.06 (d, J = 14 Hz, 1H), 1.79−1.60 (m, 5H), 1.56−1.46 (m, 4H), 1.43−1.35 (m, 5H), 1.34−1.29 (m, 4H), 0.98 (s, 3H), 0.91−0.0.84 (m, 12H), 0.80 (s, d, J = 7 Hz, 3H), 0.76 (s, 3H), 0.55−0.0.48 (m, 6H). ESI-MS *m/z* 497.3 [M + $Na]^+$, calcd for $C_{29}H_{50}O_3Si$ 474.3. HRMS (EI): *m/z* 497.3425 (M + Na^+), calcd for $C_{29}H_{50}O_3Si$ 474.3529.

8α,11β-Dimethyl-12β-isopropyl-5β,15-isopropylidenedioxy-14-keto-(Δ,^{1,2}Δ^{3,4})-tricycle 62. A solution of triethylsilyl ether **60** (31 mg, ca. 0.065 mmol) in 0.75 mL of THF in a 15-mL round-bottomed flask was cooled at 0 °C under argon, and HF−pyridine (80 μL) was added. The mixture was stirred at 0 °C for 5 min and warmed to room temperature. After being stirred at room temperature for 1 h, the reaction mixture was quenched with TMSOMe (1 mL) and stirred for 30 min, evaporated under reduced pressure, and purified by preparative TLC (20% ethyl acetate in hexanes) to afford TES-deprotected alcohol in 85% yield. TLC: R_f 0.2 (4:1 hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (s, 1H), 4.31−4.41 (m, 2H), 4.26 (d, 1H, J = 14.8 Hz), 4.11 (d, 1H, J = 15.4 Hz), 2.25 (br t, 1H, J = 13.7 Hz), 1.44−1.89 (m, 13H), 1.38 (s, 3H), 1.22−1.34 (m, 2H), 0.98−1.05 (m, 6H), 0.91 (d, 3H, J = 6.6 Hz), 0.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 134.4, 133.8, 122.0, 100.0, 75.0, 68.0, 60.7, 55.4, 47.0, 38.5, 37.8, 36.9, 36.0, 34.8, 28.5, 26.9, 25.6, 25.4, 24.3, 24.0, 22.9, 17.4. HRMS (EI): *m/z* 383.2570 (M + Na^+), calcd for $C_{23}H_{36}O_3$ 360.2664. A solution of Dess−Martin periodinane (72 mg, 0.17 mmol, 1.3 equiv) and pyridine (41 μL, 0.51 mmol, 3.8 equiv) in 7 mL of CH_2Cl_2 was prepared under argon. At the same time, a solution of TES-deprotected alcohol (48 mg, 0.13 mmol, 1.0 equiv) in 7 mL of CH_2Cl_2 was prepared in a 50-mL round-bottomed flask under argon. 5.2 mL of the Dess−Martin solution was added dropwise to the alcohol solution, and after 10 min, the remaining 1.8 mL was added. After an additional 10 min, the reaction mixture was purified directly by flash column chromatography on 10 g of silica gel (gradient elution with 10−20% ethyl acetate/hexanes) to provide 43 mg (90%) of the keto-acetonide **62** as a colorless oil. TLC: R_f 0.36 (4:1 hexanes/EtOAc). IR (film): 2937, 2870, 1715, 1620, 1453, 1378, 1221, 1175, 1149, 1022, 903, 866. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (s, 1H), 4.32−4.39 (m, 2H), 4.07 (dd, 1H, J = 17.8, 1.8 Hz), 2.49 (dd, 1H, J = 18.1, 7.5 Hz), 2.37 (br t, 1H, J = 12 Hz), 2.10−2.19 (m, 1H), 1.82−1.98 (m, 2H), 1.56−1.82 (m, 7H), 1.43 (s, 3H), 1.38 (s, 3H), 1.04 (d, 3H, J = 6.6 Hz), 1.01 (s, 3H), 0.95 (s, 3H), 0.93 (d, 3H, J = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.5, 146.4, 138.8, 133.1, 129.5, 100.1, 67.6, 60.1, 51.4, 46.0, 41.2, 38.2, 36.9, 36.4, 33.8, 28.5, 26.9, 25.0, 24.5, 24.2, 23.9, 22.3, 17.9. ESI-MS *m/z* (rel int): (pos) 381.1 ([M + $Na]^+$, 100), (neg) 393.0 ([M + $Cl]^-$, 33), 357.2 ([M − $H]^-$, 100).

8α,11β-Dimethyl-12β-isopropyl-5α,15-isopropylidenedioxy-14-keto-(Δ,^{1,2}Δ^{3,4})-tricycle 63. A solution of triethylsilyl ether **61** (31 mg, ca. 0.065 mmol) in 0.75 mL of THF in a 15-mL round-bottomed flask was cooled at 0 °C under argon, and HF−pyridine (80 μL) was added. The mixture was stirred at 0 °C for 5 min and warmed to room temperature. After being stirred at room temperature for 1 h, the reaction mixture was quenched with TMSOMe (1 mL) and stirred for 30 min, evaporated under reduced pressure, purified by preparative TLC (20% ethyl acetate in hexanes) to afford TES-deprotected alcohol in 86% yield. TLC: R_f 0.17 (4:1 hexanes/EtOAc); IR (film): 3440 (br), 2940, 2869.0, 1450, 1377, 1223, 1198, 1087, 1025, 864. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (br-s, 1H), 4.39−

4.27 (m, 3H), 4.09 (d, J = 14.4 Hz, 1H), 1.87−1.71 (m, 6H), 1.61−1.40 (m, 8H), 1.36−1.32 (m, 4H), 1.01 (s, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.0 Hz, 3H), 0.82 (s, 3H). ESI-MS m/z 383.1 $[M + Na]^+$, calcd for $C_{23}H_{36}O_3$ 360.2. HRMS (EI): m/z 383.2561 ($M + Na^+$), calcd for $C_{23}H_{36}O_3$ 360.2664. A solution of Dess−Martin periodinane (72 mg, 0.17 mmol, 1.3 equiv) and pyridine (41 μL, 0.51 mmol, 3.8 equiv) in 7 mL of CH_2Cl_2 was prepared under argon. At the same time, a solution of TES-deprotected alcohol (48 mg, 0.13 mmol, 1.0 equiv) in 7 mL of CH_2Cl_2 was prepared in a 50-mL round-bottomed flask under argon. A 5.2 mL portion of the Dess−Martin solution was added dropwise to the alcohol solution, and after 10 min, the remaining 1.8 mL was added. After an additional 10 min, the reaction mixture was purified directly by flash column chromatography on 10 g of silica gel (gradient elution with 10−20% ethyl acetate/hexanes) to provide 43 mg (90%) of the keto-acetonide **63** as a colorless oil. TLC: R_f 0.36 (4:1 hexanes/EtOAc). IR (film): 2956, 2870, 1716, 1626, 1450, 1377, 1266, 1174, 1092. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.67 (br-s, 1H), 4.50 (br-d, J = 15 Hz, 1H), 4.30 (m, 1H), 4.10 (d, J = 16 Hz, 1H), 2.41 (dd, J = 18.5 Hz, J = 7.5 Hz, 1H), 2.09 (dd, J = 18 Hz, J = 13 Hz, 1H), 1.90 (m, 1H), 1.83−1.73 (m, 3H), 1.72−1.66 (m, 1H), 1.61−1.51 (m, 2H), 1.48−1.40 (m, 2H), 1.38−1.33 (m, 4H), 1.30 (s, 3H), 0.977−0.92 (m, 9H), 0.86 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.2, 147.2, 141.4, 132.8, 127.7, 99.8, 67.4, 60.7, 51.6, 46.9, 41.3, 39.3, 37.6, 37.0, 34.7, 28.7, 25.2, 25.0, 24.3, 24.0, 22.5, 19.5. HRMS (EI): m/z 381.2408 ($M + Na^+$), calcd for $C_{23}H_{34}O_3$ 358.2508.

8α,11β-Dimethyl-13β-hydroxy-12β-isopropyl-5β,15-isopropylidenedioxy-14-keto-(Δ^{1,2}Δ^{3,4})-tricycle 73. In a 10 mL pear-shaped flask, the keto-acetonide **62** (8.5 mg, 0.024 mmol, 1.0 equiv) was dissolved in 1 mL of CH_2Cl_2 under argon. Et_3N (33 μL, 0.24 mmol, 10 equiv) and then Et_3SiOTf (27 μL, 0.12 mmol, 5 equiv) were added via syringe. The reaction mixture was stirred for 10 min and then diluted with 5 mL of ethyl acetate, washed with 1 mL of saturated sodium bicarbonate solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. This oil was azeotropically dried with toluene, dissolved in 2.4 mL of CH_2Cl_2 in a 10-mL pear-shaped flask, and cooled at −78 °C under argon. A solution of DMDO (0.52 mL, 0.036 mmol, 1.5 equiv) was added dropwise down the sides of the flask. The resulting solution was stirred for 15 min at −78 °C, and then Me_2S (27 μL, 0.37 mmol, 15 equiv) was added to quench excess DMDO. The quenched reaction solution was stirred for 5 min at −78 °C, and then the cooling bath was removed and after an additional 15 min the solution was concentrated under reduced pressure. Purification by flash column chromatography (gradient elution with 5−20% ethyl acetate/hexanes) provided 7.3 mg (82%) of hydroxy-ketone **73** as a colorless oil. In a separate run, 13 mg of **73** was dissolved in 0.34 mL of ethyl acetate (0.1 M solution) in a small (4-mL) vial, which was left uncapped and placed in a larger vial containing an excess amount of hexanes. The larger vial was sealed, and the hydroxy-ketone (**73**) was allowed to crystallize by vapor-diffusion over the course of 2 days to provide white needles (mp 184.6−186.4 °C). TLC: R_f 0.28 (4:1 hexanes/EtOAc). IR (film): 3422.0, 2938.8, 1710.1, 1614.2, 1455.2, 1379.5, 1223.4, 1088.7. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (s, 1H), 4.32−4.40 (m, 2H), 4.05−4.12 (m, 2H), 2.12−2.34 (m, 3H), 1.95−2.06 (m, 1H), 1.83−1.95 (m, 1H), 1.51−1.75 (m, 4H), 1.45 (s, 3H), 1.30−1.43 (m, 1H), 1.36 (s, 3H, partially obscured), 1.22 (s, 3H), 1.07−1.13 (m, 6H), 0.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9,145.7, 140.6, 133.3, 117.8, 100.4, 74.7, 67.8, 60.3, 56.3, 45.9, 38.3, 36.9, 36.5, 34.4, 27.2, 25.2, 24.8, 24.6, 24.2, 23.7, 23.4, 19.5. ESI-MS m/z (rel int): (pos) 397.2 ($[M + Na]^+$, 100), 379.2 ($[M + H]^+$, 80); (neg) 409.2 ($[M + Cl]^-$, 40).

13β-Acetoxy-8α,11β-dimethyl-12β-isopropyl-5β,15-isopropylidenedioxy-14-keto-(Δ^{1,2}Δ^{3,4})-tricycle 74. In a 10-mL, pear-shaped flask, hydroxy ketone **73** (7.3 mg, 0.019 mmol, 1.0 equiv) was dissolved in 0.9 mL of CH_2Cl_2 under argon. Pyridine (31 μL, 0.38 mmol, 20 equiv) and DMAP (0.5 mg, 0.004 mmol, 0.2 equiv) were added, followed by Ac_2O (18 μL, 0.19 mmol, 10 equiv). The reaction mixture was stirred for 3 h, diluted with 5 mL of toluene, and concentrated under reduced pressure. Purification by column chromatography on ca. 1 g of silica gel (gradient elution with 5−10% ethyl acetate/hexanes) provided 7.9 mg (97%) of acetate **74** as an oil. TLC: R_f 4.6 (5% ethyl acetate in CH_2Cl_2). IR (film): 2938.0, 2872.9, 1750.8, 1721.3, 1613.5, 1371.5, 1216.3, 1089.8, 1018.7. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (s, 1H), 5.37 (d, 1H, J = 6.5 Hz), 4.29 (m. 2H), 4.03 (d, 1H, J = 16.5 Hz), 2.21 (dt, 1H, J = 12 Hz, J = 2 Hz), 2.03 (s, 3H), 2.0−1.8 (m, 3H), 1.68−1.48 (m, 5H), 1.37 (s, 3H), 1.30−1.25 (m, 4H), 1.13 (s, 3H), 1.02 (d, 3H, J = 7 Hz), 0.863 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.7, 169.5, 145.1, 140.6, 133.5, 133.0, 100.1, 74.3, 67.6, 60.1, 55.2, 45.6, 38.0, 36.8, 36.3, 34.0, 27.0, 25.0, 24.8, 24.6, 23.7, 23.3, 23.0, 20.9, 18.8. HRMS (EI) m/z 439.2462 ($M + Na^+$), calcd for $C_{25}H_{36}O_5$ 416.2563.

Enol Acetate 64. In a 5 mL vial containing keto-acetonide **63** (17 mg, 0.047 mmol) in 1.6 mL of acetic anhydride was added freshly distilled triethylamine (0.825 mL) and then DMAP (8.7 mg). The resulting solution was cooled to 0 °C, and acetyl chloride (165 μL) was added slowly via syringe. The reaction mixture was stirred for 30 min with slowly warmed to room temperature and then was heated at 100 °C. After 12 h, the reaction mixture was cooled to room temperature and filtered through a bed of Celite, and the filtrate was concentrated to yield the crude product, which was purified by preparative TLC (using 20% ethyl acetate in hexanes) to afford **64** in 89% yield. TLC: R_f 0.4 (8:2 = hexanes\ethyl acetate). IR (film): 2937.3, 2869.8, 1769.6, 1453.6, 1371.8, 1223.0, 1199.0, 1091.8. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (d, J = 2.0 Hz, 1H), 5.47 (s, 1H), 4.36 (d, J = 14.5 Hz, 1H), 4.30 (m, 1H), 4.09 (d, J = 15.5 Hz, 1H), 2.13 (s, 3H), 1.87−1.48 (m, 7H), 1.42 (m, 1H), 1.39 (s, 3H), 1.32 (m, 4H), 0.98 (m, 6H), 0.927 (d, J = 7 Hz, 3H), 0.90 (d, J = 6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 150.5, 147.9, 134.0, 133.6, 122.6, 112.0, 99.6, 67.8, 60.9, 59.5, 46.9, 40.3, 38.1, 37.6, 34.6, 27.6, 26.1, 25.8, 25.4, 24.3, 23.5, 22.8, 21.5. ESI-MS: m/z 423.2 ($[M + Na]^+$, calcd for $C_{25}H_{36}O_4$ 400.26.

C13β-Acetate 69. To a solution of enol acetate **64** (2 mg, 0.0048 mmol) in 0.5 mL of CH_2Cl_2 was added slowly a solution of DMDO in acetone (0.07 M in acetone, 68 μL, 1 equiv) at − 50 °C, and the resulting solution was stirred for 40 min at − 50 °C and then 20 min at 0 °C. Dimethyl sulfide (1 μL) was added, and the resulting mixture was warmed to room temperature and evaporated to dryness. This crude epoxide was dissolved in $MeNO_2$ (0.5 mL), and p-TSA (10 mol %) was added. The resulting solution was stirred for 20 min at rt. Saturated $NaHCO_3$ (1 mL) was added and the reaction mixture diluted with water and extracted with EtOAc. The organic layers were dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude product. To this crude product in CH_2Cl_2 (0.5 mL) were added a catalytic amount of DMAP, 80 μL of pyridine, and 40 μL of acetic anhydride. The resulting solution was stirred for 3 h (or until the reaction was complete). The reaction mixture was evaporated to dryness and purification using preparative TLC (using 3% ethyl acetate/chloroform) afforded **69** as the major isomer in 60% yield. TLC: R_f 0.23 (8:2) hexanes\ethyl acetate). IR (film): 2938.1, 1750.1, 1718.6, 1613.3, 1372.1, 1216.2, 1093.7. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.8, 5.41 (d, 1H, J = 6.5 Hz), 4.49 (d, 1H, J = 16.5 Hz), 4.31 (m, 1H), 4.14 (d, 1H, J = 16.5 Hz), 2.03 (s, 3H), 1.91 (m, 1H), 1.84−1.71 (m, 3H), 1.63−1.44 (m, 6H), 1.37 (s, 3H), 1.31 (s, 3H), 1.14 (s, 3H), 1.02 (d, 3H, J = 7.5 Hz), 0.93 (s, 3H), 0.86 (d, 3H, J = 7.0 Hz). ESI-MS: m/z 439.3 ($[M + Na]^+$, calcd for $C_{25}H_{36}O_5$ 416.25.

Preparation of C13β Acetate 69 and C13α Acetates 70 by Thermolysis of the Epoxy Acetate Derived from 64. To a solution of enol acetate **64** (7 mg, 0.017 mmol) in 0.5 mL of CH_2Cl_2 was added slowly a solution of DMDO in acetone (0.07 M in acetone, 249 μL, 1 equiv) at − 50 °C, and the resulting solution was stirred for 40 min at −50 °C and then

20 min at 0 °C. Dimethyl sulfide (1 μL) was added, and the resulting mixture was warmed to room temperature and evaporated to dryness. The crude epoxy acetate was heated neat at 150 °C for 18 min. The reaction mixture was cooled to room temperature and was dissolved in 1 mL of CH_2Cl_2. Pyridine (80 μL), a catalytic amount of DMAP, and acetic anhydride (40 μL) were added, and the mixture was stirred for 12 h. Evaporation provided crude product, which was purified by preparative TLC (3% ethyl acetate in chloroform) to afford the acetates in 1:1 de ratio. The C13-β acetate **69** was obtained in 31% yield (2.2 mg) and also C13-α acetate **70** was obtained in 31% yield (2.2 mg). C13-α Acetate **70**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79 (br-s, 1H), 5.44 (d, 1H, J = 12.0 Hz), 4.48 (br-d, 1H, J = 16.0 Hz), 4.30 (m, 1H), 4.08 (d, 1H, J = 16.0 Hz), 2.10 (s, 3H), 1.93−1.72 (m, 6H), 1.62−1.44 (m, 3H), 1.41−1.35 (m, 4H), 1.31 (s, 3H), 1.02 (s, 3H), 0.97 (d, J = 7 Hz, 3H), 0.93 (s, 3H), 0.91 (d, J = 7.5 Hz, 3H). ESI-MS: *m/z* 439.3 ($[M + Na]^+$, calcd for $C_{25}H_{36}O_5$ 416.25.

Guanacastepene A (1). A 10-mL, round-bottomed flask equipped with a reflux condenser and an argon inlet was charged with a solution of acetonide **74** (7.9 mg, 0.019 mmol, 1.0 equiv) and PPTS (0.95 mg, 0.0038 mmol, 0.2 equiv) in 1.9 mL of methanol under argon and heated at 70 °C for 30 min. The reaction mixture was allowed to cool to room temperature and then was concentrated under reduced pressure (at room temperature). Purification by column chromatography on ca. 1 g of silica gel (elution with ethyl acetate) followed by azeotropic drying with benzene at room temperature provided diol, which was not stable to storage and used immediately in the next step. The freshly prepared diol from the previous step was dissolved in 1.6 mL of CH_2Cl_2 in a 10-mL, pear-shaped flask under argon, and $PhI(OAc)_2$ (12.3 mg, 0.038 mmol, 2.0 equiv) was added. A solution of TEMPO (0.30 mg, 0.0019 mmol, 0.1 equiv) in 0.3 mL of CH_2Cl_2 was added, and the resulting solution was stirred for 3 h at room temperature and concentrated under reduced pressure (at room temperature). Purification by column chromatography on ca. 1 g of silica gel (gradient elution with 20−30% ethyl acetate/hexanes) provided 4.2 mg (59%) of guanacastepene A (**1**) as an amorphous white solid. TLC: R_f 0.73 (1:3 hexanes/EtOAc). IR (film): 3433 (br), 1750, 1371, 1219, 1020. ^{1}H NMR (400 MHz, acetone-d_6, 25 °C): δ 9.91 (br s, 1H, C15−H), 7.45 (d, 1H, J = 1.1 Hz, C2−H), 5.48 (d, 1H, J = 6.5 Hz, C13−H), 4.62 (m, 1H, C5−H), 3.97 (br s, 1H, OH), 2.08 (s, 3H, OAc), 1.99 (m), 1.90 (m), 1.79 (m), 1.63 (m), 1.40 (m), 1.27 (s, 3H, C16/17-H_3), 1.12 (d, 3H, J = 6.6 Hz, C19/20-H_3), 1.09 (s, 3H, C16/17-H_3), 0.93 (d, 3H, J = 6.4 Hz, C19/20-H_3). ^{1}H NMR (500 MHz, acetone-d_6, −50 °C, key signals): major δ 9.96 (s, C15-H), 7.42 (s, C2-H), 5.45 (d, J = 5.6 Hz, C13-H), 4.64 (m, C5-H), 4.59 (d, J = 5.4 Hz, OH), 2.10 (s, OAc); minor 9.72 (s, C15-H), 7.49 (s, C2-H), 5.53 (d, J = 7.1 Hz, C13-H), 4.52 (m, C5−H), 4.48 (d, J = 4.1 Hz, OH), 2.11 (s, OAc). ^{13}C NMR (125 MHz, acetone-d_6, −50 °C, observed signals): δ 201.1, 200.4, 193.3, 192.6, 170.4, 170.2, 161.6, 158.2, 149.34, 149.29, 140.1, 138.6, 133.3, 131.7, 74.6, 73.5, 62.5, 59.3, 59.2, 54.8, 50.4, 47.7, 46.4, 41.9, 38.7, 38.5, 35.5, 35.4, 27.7, 25.9, 25.6, 23.7, 23.5, 21.0. 20.2. ESI-MS *m/z* (rel int): (pos) 397.2 ($[M + Na]^+$, 100); (neg) 409.1 ($[M + Cl]^-$, 100).

Acknowledgment. This work was supported by a grant from the National Institutes of Health (CA-28824). G.B.D. was an NIH Postdoctoral Fellow (1 F32 NS11150-01). H.Y. is grateful for a Predoctoral Fellowship from Eli Lilly & Company. D.S.T. was a Damon Runyon Cancer Research Foundation Postdoctoral Fellow (DRG-1641). S.L. was a US Army Breast Cancer Research Program Postdoctoral Fellow (DAMD-17-99-1-9373). We thank Dr. George Sukenick, Sylvi Rusli, Anna Dudkina, and Hui Fang (NMR Core Facility, CA-02848) for mass spectral analysis and Dr. Louis Todaro (Hunter College) for X-ray crystallographic analysis.

Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR spectral data, optical rotations, HRMS, and additional information on key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051470K