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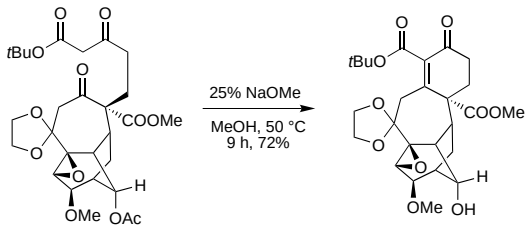

[21] For experimental and structure determination details of **20**, **21**, and **22**, see Supporting Information.
[22] The unconjugated tricycle [D_9]**19** could not be unambiguously detected by ^{1}H NMR spectroscopic analysis because of deuterium exchange at C2 and a solvent signal that obscured the vinylic C14-H region.
[23] Assigned by analogy to C14-H for **21** in $CDCl_3$ at room temperature ($\delta = 4.34$, br d, $J = 5.31$ Hz).
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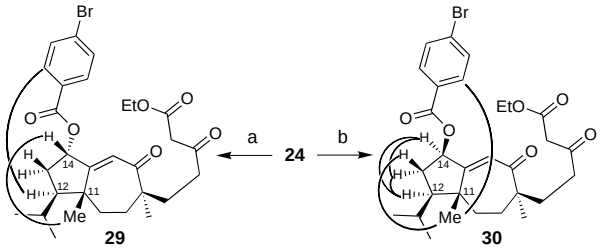

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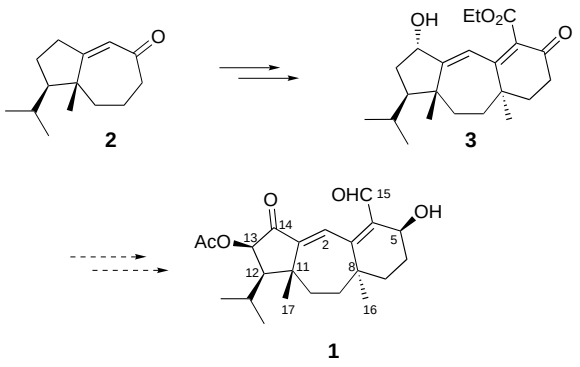
A Stereoselective Route to Guanacastepene A through a Surprising Epoxidation**

Songnian Lin, Gregory B. Dudley, Derek S. Tan, and Samuel J. Danishefsky*

In the preceding paper we reported the preparation of compound **3** (Scheme 1),[1] which bears much of the functionality required, in principle, to reach guanacastepene A (**1**).[2, 3]



Scheme 1. Overview of the synthetic strategy towards **1**.

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[**] This work was supported by the National Institutes of Health (CA-28824). S.L. is a US Army breast cancer research program postdoctoral fellow (DAMD-17-99-1-9373). G.B.D. is an NIH postdoctoral fellow (1 F32 NS11150-01). D.S.T. is a Damon Runyon Cancer Research Foundation postdoctoral fellow (DRG-1641). We thank Dr. George Sukenick and Sylvi Rusli (NMR Core Facility, CA-02848) for mass spectral analyses.

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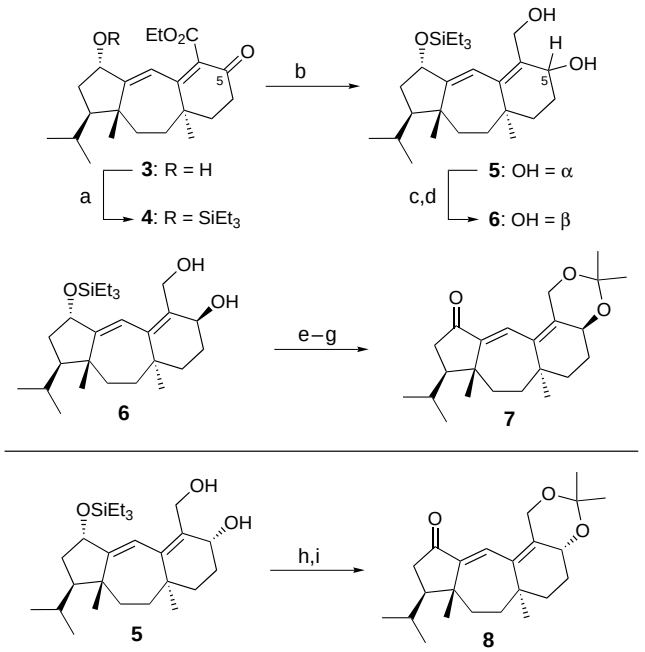
To complete the synthesis,[4] it would be necessary to reproduce, through chemical synthesis, the densely packed and varied functionality between C13 and C5. Of particular interest were the two stereogenic centers yet to be formed. Oxidation at C13, ultimately in the form of a β-acetoxy substituent, had to be properly orchestrated with oxidation at C14 and overall two-electron reductions at C5 and C15.

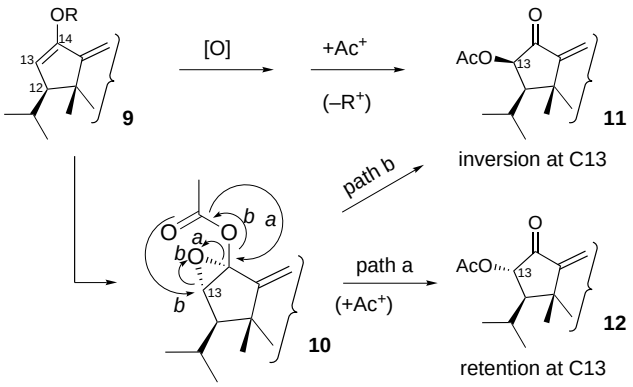
Introduction of the stereogenic center C5 is described in Scheme 2. The sequence was initiated by protection of the free hydroxy group of **3** as its triethylsilyl ether to give **4**.



Scheme 2. Preparation of the keto acetonides. a) Et_3SiOTf, pyridine, CH_2Cl_2, 0 °C, 80–85 %; b) DIBAL-H, CH_2Cl_2, −78 → 0 °C (**5**/**6** 80:20); c) Ph_3P, benzoic acid, DIAD, THF, −78 °C → RT; d) DIBAL-H, CH_2Cl_2, −78 → 0 °C; e) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 0 °C, 67 % from **4**; f) TBAF, THF, 0 °C, 91–98 %; g) Dess–Martin periodinane, pyridine, CH_2Cl_2, 90 %; h) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 0 °C, 86 %; i) HF · pyridine, pyridine, THF, then Dess–Martin periodinane, CH_2Cl_2, 77–85 %. Tf = triflate = trifluoromethanesulfonyl, DIBAL-H = diisobutylaluminum hydride, DIAD = diisopropyl azodicarboxylate, PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetrabutylammonium fluoride.

Reduction of the latter with DIBAL-H in CH_2Cl_2 provided a mixture of C5 diastereomers (**5**/**6** 80:20).[5, 6] Use of various alternative reducing agents, including $LiAlH_4$, Li-(tBuO)$_3$AlH,[7] 9-BBN,[8] and $NaBH_4 \cdot CeCl_3$,[9] led to less favorable diastereomeric ratios. The diastereomers **5** and **6** can be separated by careful purification on silica gel.[10] The α epimer (**5**, major) was subjected to a Mitsunobu[11] inversion sequence via an intermediate dibenzoate. Protection of diol **6** as its acetonide, cleavage of the silyl ether, and Dess–Martin oxidation[12] in the presence of pyridine[13] provided ketone **7**. In initial experiments prior to optimization of the Mitsunobu inversion, diol **5** was advanced to ketone **8** by a sequence analogous to the transformation of **6** to **7**.

For the stereoselective installation of the C13-acetoxy substituent, we envisioned the creation of the C13–C14 enol derivative **9**, for the moment unspecified (Scheme 3). The



Scheme 3. Overview of the acetoxy installation strategy.

conversion **9** → **11** is intended to show, in formal terms, oxidation at C13. At this stage, the nature of the step to introduce the acetyl function is also not specified. For instance, there might be a sequential hydroxylation at C13 and acetylation. Alternatively, the delivery of the "acetyl" and "hydroxenium" components of the overall C13-acetoxy group might be coordinated. At this stage, it was expected that oxidants attacking C13 would do so from the α-face, that is, *anti* to the β C12-isopropyl and C11-methyl groups. This presumption led to a more specific proposal.

Enol acetylation of a C14-ketone would give **9** (R = Ac). Following the bias discussed above, epoxidation might well lead to **10**. Two stereochemically diverging pathways are possible in advancing from epoxide type **10** to an acetoxy ketone. In path a, we emphasize the vulnerability of the C14–O bond of the epoxide. This bond cleavage could lead to loss of $MeCO^+$ to adventitious external nucleophiles and formation of a non-acetylated C13-hydroxy function. Alternatively, but still within the confines of path a, the acylium function may be transferred internally to the emerging C13-hydroxy group. In either case, path a leads to an acetoxy ketone (see **12**) in which the stereochemistry at C13 is the same as that of the epoxide. In contrast, in path b one contemplates transfer of an intact acetoxy function from C14 to C13. Here, clearly, the stereochemistry of C13 will reflect the inversion during the migration of the acetoxy group (see **10** → **11**).[14]

Since we first obtained the keto acetonide **8** (Scheme 2), we proceeded to test our strategy in this series. Before relating our results, we should describe our method of analysis even before reaching guanacastepene A. In ketone **8**, two vicinal coupling constants (13.2 Hz and 7.6 Hz) relate the geminal protons at C13 with the α-proton at C12. Noting that $J_{(13\text{-H}\alpha,12\text{-H}\alpha)} \approx 7$ Hz in the natural product,[21] we could assign the 13.2-Hz coupling constant to 13-Hβ–12-Hα, whereas J = 7.6 Hz is a result of the coupling between α-H and 12-Hα. This assignment was substantiated by the observation of the indicated NOE interactions (Scheme 4). We hoped to assign the stereochemistry of the C13-acetoxylated product by measuring $J_{(13\text{-H},12\text{-H})}$ in the context discussed above.

In the event, ketone **8** was converted into enol acetate **13** (Scheme 4).[15] Epoxidation with DMDO led to the formation of a single observable epoxide. The stereochemistry of the oxido linkage (see **13a** or **13b**) was not known at this stage. We

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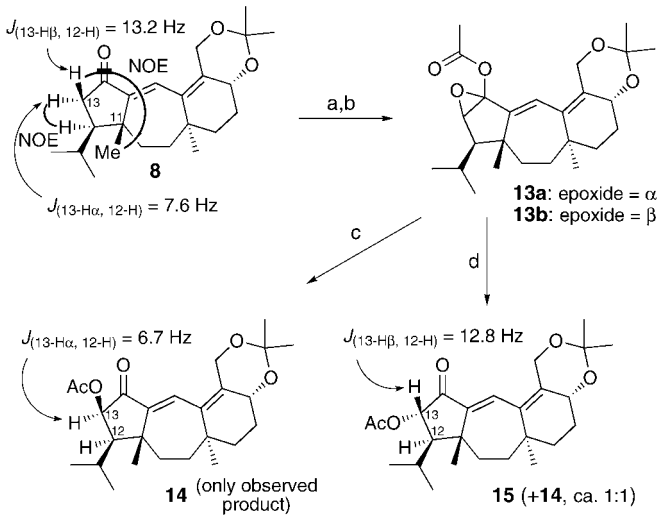
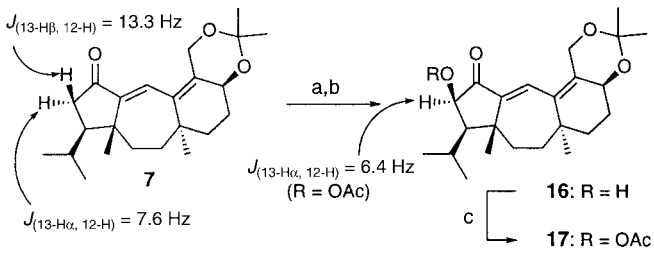


Scheme 4. Investigations into the stereoselective installation of the C13-acetoxy functionality. a) Et_3N, DMAP, AcCl, Ac_2O, 100 °C, 90 %; b) DMDO/acetone, CH_2Cl_2, −78 → 0 °C; c) *p*-TsOH, $MeNO_2$, then Ac_2O, pyridine, DMAP, ≈60 % from **8**; d) 150 °C (neat), then Ac_2O, pyridine, DMAP, ≈65 % from **8** (**14**/**15** ≈ 1:1). DMAP = 4-(dimethylamino)pyridine, DMDO = dimethyldioxirane.

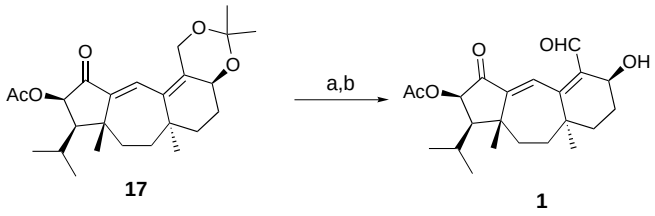
were surprised to find that when the compound was subjected to acidic conditions, which favor path a, followed by acetylation as shown, compound **14** was obtained; the coupling constant for the vicinal 13-H/12-H was similar to that of guanacastepene A. In contrast, pyrolysis of the epoxy acetate under conditions that we hoped would favor path b (inversion) ultimately led to two compounds.[16] One was the acetoxy ketone corresponding to the previously encountered **14**. The other was a new acetoxy ketone **15**, which gave a coupling constant that suggests a *trans* relationship between 12-H and 13-H. Assuming that the assignments at C13 in **14** and **15** are correct, these data can only be rationalized by the surprising conclusion that epoxidation of the enol acetate of **8** had occurred from the β-face (see **13b**).

From this newly gained insight, it was opportune to direct efforts toward the synthesis of guanacastepene A itself. For this purpose we commenced with keto acetonide **7** (Scheme 5). Since retention of the stereochemistry at C13 was desired, it was advantageous to employ a Rubottom-type protocol.[17] Conversion of **7** into its silyl enol ether was followed by exposure of the latter to DMDO, thereby providing hydroxy ketone **16** (ca. 94:6 dr, major isomer shown). Acetylation gave **17**. As before, the diagnostic



Scheme 5. Rubottom-type oxidation strategy. a) Et_3SiOTf, Et_3N, CH_2Cl_2; b) DMDO/acetone, CH_2Cl_2, −78 °C, then Me_2S, 82–90 % overall yield; c) Ac_2O, pyridine, DMAP, CH_2Cl_2, 96 %.

coupling constants demonstrated that acetoxylation had occurred *syn* to the isopropyl and methyl substituents. As the rearrangement associated with the Rubottom protocol can be safely assumed to occur by retention,[18] we must conclude that epoxidation had again occurred from the β face. The assignment of the stereochemistry of **17** was confirmed by its ultimate transformation into guanacastepene A (Scheme 6).



Scheme 6. Synthesis of **1**. a) PPTS, MeOH, 70 °C; b) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 59–65 % overall yield. TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical.

Hydrolysis of the acetonide of **17** provided an unstable diol, which was purified quickly by chromatography on silica gel and used immediately. TEMPO-catalyzed oxidation of the primary alcohol[19] to the aldehyde left the secondary alcohol undisturbed. The spectral data recorded from this product (^{1}H NMR at 25 °C and at −50 °C, ^{13}C NMR at 25 °C and at −50 °C, IR, and mass spectra) were in complete accord with those of guanacastepene A.[20, 21]

We were at this point quite confident that we had completed the total synthesis of racemic guanacastepene A. However, in the absence of an authentic sample of the natural product, we sought to demonstrate rigorously that various epimers of guanacastepene A were indeed distinguishable by NMR spectroscopy. In this spirit, we prepared the remaining three diastereomers with respect to C5 and C13 (**1a**, **1b**, and **1c**).[22] A selection of the diagnostic ^{1}H NMR data of the various diastereomers is shown in Scheme 7. In short, the C13 protons in the epimeric 13-acetoxy compounds exhibit drastically different coupling constants. Interestingly, the epimeric 5-hydroxy groups affect the peak shape of the aldehyde signal. This may reflect different, configurationally sensitive, proclivities of the C5 hydroxy groups for hydrogen bonding to the proximal formyl oxygen atom.

In light of the observed β-face oxidation of ketone **7**, it was appropriate to reexamine our original thinking about the steric biases of this system. Calculations with the MM2 force field[23] provided energy-minimized conformers of silyl enol ether **18** (derived from **7**), one of which is shown in Scheme 8. Based on these calculations, it appears that the pseudo-equatorial isopropyl group may not exert a dominant steric influence on facial selectivity. Furthermore, C17 and C10 are approximately equidistant from the locus of the C13–C14 double bond. By the same token, the modeling exercise did not reveal a convincing steric bias to rationalize the highly selective β-face epoxidation observed above.[24]

In summary, the total synthesis of the naturally occurring guanacastepene A has been completed. As we did not have a sample of the natural product for comparison, we could only

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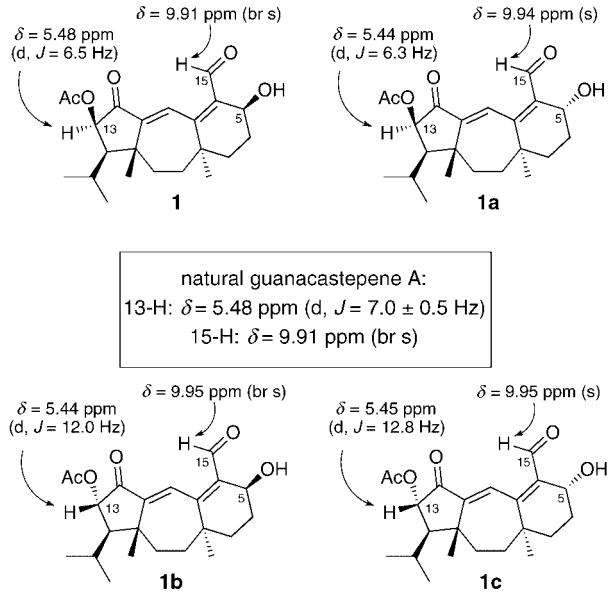
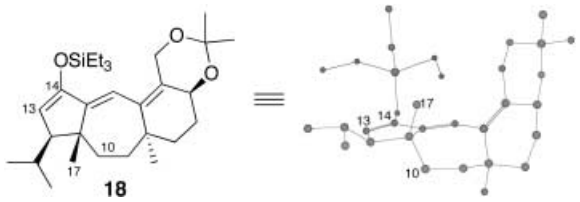


Scheme 7. Structures and illustrative NMR data of the four guanacastepene diastereomers.



Scheme 8. Silyl enol ether **18**, and an energy-minimized representation of its three-dimensional structure.

be confident about this result after synthesizing the four guanacastepene isomers with the possible permutations of the stereogenic centers at C5 and C13. Our findings on the remarkably uniform sense of the epoxidation reactions should serve to underscore the subtlety of biases that control stereochemical outcomes. Full details of the total synthesis and a fuller consideration of this fascinating epoxidation tendency will be described shortly.

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[4] For earlier accounts of our studies, see: a) G. B. Dudley, S. J. Danishefsky, *Org. Lett.* **2001**, *3*, 2399 – 2402; b) G. B. Dudley, D. S. Tan, G. Kim, J. M. Tanski, S. J. Danishefsky, *Tetrahedron Lett.* **2001**, *42*, 6789 – 6791.

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[6] Based on extensive literature precedent (see ref. [5]), this reduction was assumed to proceed as indicated in Scheme 2; confirmation of this tentative assignment was obtained upon conversion into the natural product.

[7] For a review of reductions with lithium trialkoxyaluminum hydrides, see: J. Málek, *Org. React.* **1985**, *34*, 1 – 317.

[8] S. Krishnamurthy, H. C. Brown, *J. Org. Chem.* **1977**, *42*, 1197 – 1201. 9-BBN = 9-borabicyclo[3.3.1]nonane.

[9] A. L. Gemal, J.-L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454 – 5459.

[10] The minor product **6** could be used without further manipulation; thus **5** and **6** are stereoconvergent.

[11] For a review of the Mitsunobu reaction, see: D. L. Hughes, *Org. React.* **1992**, *42*, 335 – 656.

[12] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155 – 4156; b) R. E. Ireland, L. Liu, *J. Org. Chem.* **1993**, *58*, 2899.

[13] The yield for this oxidation step increases from 50% to 90% in the presence of pyridine (3 equiv relative to Dess – Martin periodinane).

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[19] A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974 – 6977.

[20] An authentic sample is no longer available for comparison (J. Clardy, personal communication). In fact, chemical synthesis is currently the only source of this compound.

[21] Synthetic guanacastepene ([D$_6$]acetone, 400 MHz, 25 °C): $\delta = 9.91$ (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 ppm (d, $J = 6.4$ Hz, 3H); ([D$_6$]acetone, 500 MHz, -50 °C, key signals): major isomer: $\delta = 9.96$ (s), 7.42 (s), 5.45 (d, $J = 5.6$ Hz), 4.64 (m), 4.59 (d, $J = 5.4$ Hz) (OH), 2.10 ppm (s); minor isomer: $\delta = 9.72$ (s), 7.49 (s), 5.53 (d, $J = 7.1$ Hz), 4.52 (m), 4.48 (d, $J = 4.1$ Hz, OH), 2.11 ppm (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.

[22] **1a** and **1c** were prepared from **14** and **15**, respectively, by analogy to the conversion **17** → **1** (Scheme 6); **1b** was derived similarly from the minor diastereomer obtained in the Rubottom-type oxidation of **7** (Scheme 5).

[23] *MacroModel* version 5.5, Department of Chemistry, Columbia University.

[24] The possibility that the silyl group orientates itself preferentially on the α-face, thus blocking the epoxidation from below, was also considered; however, the MM2 calculations suggest little energy difference with respect to various silyl group orientations, disfavoring this hypothesis.