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A Convergent Synthesis of the Tricyclic Architecture of the Guanacastepenes Featuring a Selective Ring Fragmentation

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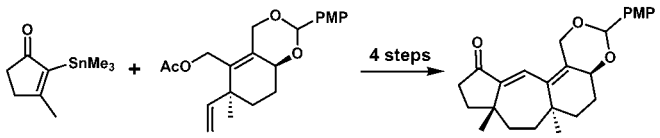
ABSTRACT



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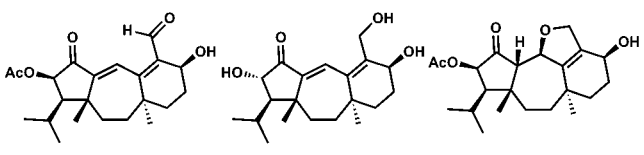
This Letter describes a concise, diastereoselective synthesis of the tricyclic carbon framework of the guanacastepene family of natural products. An intermolecular Diels–Alder reaction established a remote stereochemical relationship and facilitated a synthesis of allylic acetate 3, which was subsequently joined with vinylstananne 9 via a Stille coupling. An intramolecular [2 + 2] photocycloaddition then afforded complex cyclobutyl ketone 19, which underwent a stereoelectronically controlled fragmentation to the guanacastepene architecture on treatment with samarium diiodide.

Clardy and co-workers recently discovered the structurally diverse guanacastepene family of secondary metabolites during an investigation of the endophytic fungus CR115 found in the Guanacaste Conservation Area in Costa Rica.[1,2] These diterpenes possess novel carbon skeletons, and several members have shown promising antibiotic activity against drug-resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis*.[2,3] As a result, there has been great interest in the chemical problems posed by the guanacastepenes, and approaches toward the synthesis of guanacastepene A (**1a**) have already been described by the groups of Snider, Magnus, Danishefsky, Mehta, and Trauner.[4]



1a: guanacastepene A 1c: guanacastepene C 1e: guanacastepene E

In this Letter, we describe a convergent synthesis of the [5-7-6] tricyclic ring system of the guanacastepenes based on the design shown in Scheme 1. We envisioned that a union of appropriately functionalized five- and six-membered rings, such as **2** and **3** (P, P′ = unspecified protecting groups), could furnish enone **4** and set the stage for an intramolecular [2 + 2] photocycloaddition.[5] If successful, the latter process would afford a complex tetracyclo[7.5.0.0.^{1,11}0^{3,8}]tetradecane

(1) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116−2117.
(2) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900−9901.
(3) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256−261.
(4) (a) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569−572. (b) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947−4950. (c) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399−2402. (d) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789−6791. (e) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123−9126. (f) Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063−1066. (g) Gradl, S. N.; Kennedy-Smith, J. J.; Kim, J.; Trauner, D. *Synlett* **2002**, *3*, 411−414.

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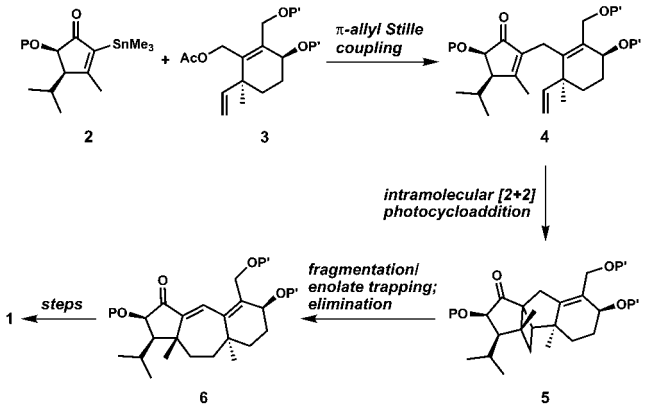
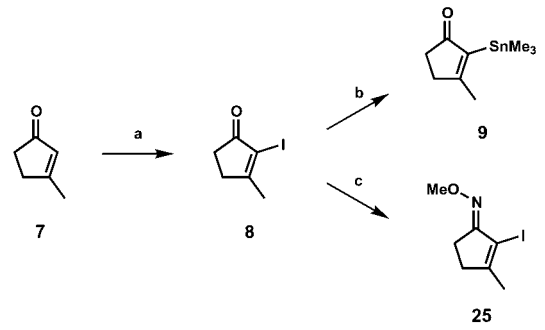
Scheme 1



ring system **5** wherein one of the bonds of the cyclobutane ring is more conjugated with the ketone carbonyl than the other. On this basis, we hoped that a transient cyclobutylcarbinyl radical produced by a one-electron reduction of the keto group of **5** would undergo a selective, stereoelectronically favored ring fragmentation to the guanacastepene [5-7-6] ring framework.[6] Rearrangements of cyclobutylcarbinyl radicals were described in some of the earliest reports of radical fragmentations[7] and have a broad utility in synthesis.[8] An analysis of molecular models of **5** suggested that the cyclobutane bond that is exocyclic to the five-membered ring should be predisposed to fragment owing to its nearly parallel relationship to the p-orbital of the putative ketyl radical anion. This expectation is substantiated by several literature reports.[9,10] A noteworthy feature of this type of ring fragmentation is that it would leave in its wake a regiodefined enolate ion that could conceivably permit the controlled introduction of an alkene into the central seven-membered ring. Should α-deoxygenation prove troublesome in the one-electron reduction step, the convergent synthetic design permits easy omission of an α-oxy substituent.

A five-membered ring lacking the isopropyl group and α-oxygenation found in guanacastepene A (**1a**) was chosen to serve as a readily accessible setting in which to test the proposed photocycloaddition/fragmentation chemistry (Scheme 2). Cyclopentenone **7** was converted to α-iodoenone **8**

Scheme 2[a]



[a] Reagents: (a) I_2, pyridine, CH_2Cl_2, 0 °C → rt, 18 h, 77%. (b) $Me_3SnSnMe_3$, $Pd(PPh_3)_4$ (0.05 equiv), PhH, 80 °C, 3 d, 90%. (c) $H_2NOMe{\cdot}HCl$, pyridine, MeOH, rt, 12 h, 83%.

following the procedure of Johnson.[11] A palladium-catalyzed reaction of **8** with hexamethylditin under the conditions shown then furnished **9** in good yield.[12]

Construction of the six-membered ring of the guanacastepenes began from commercially available cyclohexenone **10** (Scheme 3). Formation of the kinetic enolate of **10**, followed by enolate trapping with TMSCl, gave diene **11**.[13] Diels−Alder reaction of **11** with dimethylacetylenedicarboxylate cleanly gave the bridged bicyclic ketone **12** after acidic hydrolysis of the silyl enol ether. Subsequent Baeyer−Villiger oxidation was regiospecific and provided lactone **13** as a white solid. This three-step sequence afforded large quantities of a substance having the appropriate stereochemical relationship and useful functionality for a synthesis of key intermediate **3**.

Acid-catalyzed methanolysis of the bridged lactone was achieved in quantitative yield, and the resulting hydroxytriester was protected in the form of PMB ether **14**. A complete reduction of the three methyl ester groups with lithium aluminum hydride produced a triol that was selectively converted to a mixture of diastereomeric benzylidene acetals shown as **15**. The alkene side chain of **16** was installed by reaction of the *o*-nitrophenylselenide derived from alcohol **15** with hydrogen peroxide.[14] The diol produced by acid-catalyzed methanolysis of the benzylidene acetal in **16** was

(5) For a comprehensive review of enone olefin [2 + 2] photochemical cycloadditions, see: Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297−588.

(6) For pioneering studies of reductive ring openings of conjugated cyclopropyl ketones, see: (a) Norin, T. *Acta Chem. Scand.* **1965**, *19*, 1289−1292. (b) Dauben, W. G.; Deviny, E. J. *J. Org. Chem.* **1966**, *31*, 3794−3798. (c) Dauben, W. G.; Schutte, L.; Wolf, R. E.; Deviny, E. J. *J. Org. Chem.* **1969**, *34*, 2512−2517.

(7) (a) Oldroyd, D. M.; Fisher, G. S.; Goldblatt, L. A. *J. Am. Chem. Soc.* **1950**, *72*, 2407−2410. (b) Dupont, G.; Dulou, R.; Clément, G. *Bull. Soc. Chim. Fr.* **1950**, 1056−1057. (c) Dupont, G.; Dulou, R.; Clément, G. *Bull. Soc. Chim. Fr.* **1950**, 1115−1120.

(8) (a) Beckwith, A. L. J. *Spec. Publ. Chem. Soc.* **1970**, *24*, 239−269. (b) Yet, L. *Tetrahedron* **1999**, *55*, 9349−9403.

(9) For examples of selective cyclobutyl bond cleavages, see: (a) Crimmins, M. T.; Mascarella, S. W. *Tetrahedron Lett.* **1987**, *28*, 5063−5066. (b) Ziegler, F. E.; Zheng, Z. *J. Org. Chem.* **1990**, *55*, 1416−1418. (c) Cossy, J.; Aclinou, P.; Bellosta, V.; Furet, N.; Baranne-Lafont, J.; Sparfel, D.; Souchaud, C. *Tetrahedron Lett.* **1991**, *32*, 1315−1316. (d) Crimmins, M. T.; Dudek, C. M.; Cheung, A. W.-H. *Tetrahedron Lett.* **1992**, *33*, 181−184. (e) Crimmins, M. T.; Wang, Z.; McKerlie, L. A. *Tetrahedron Lett.* **1996**, *37*, 8703−8706. (f) Ziegler, F. E.; Kover, R. X.; Yee, N. N. K. *Tetrahedron Lett.* **2000**, *41*, 5155−5159.

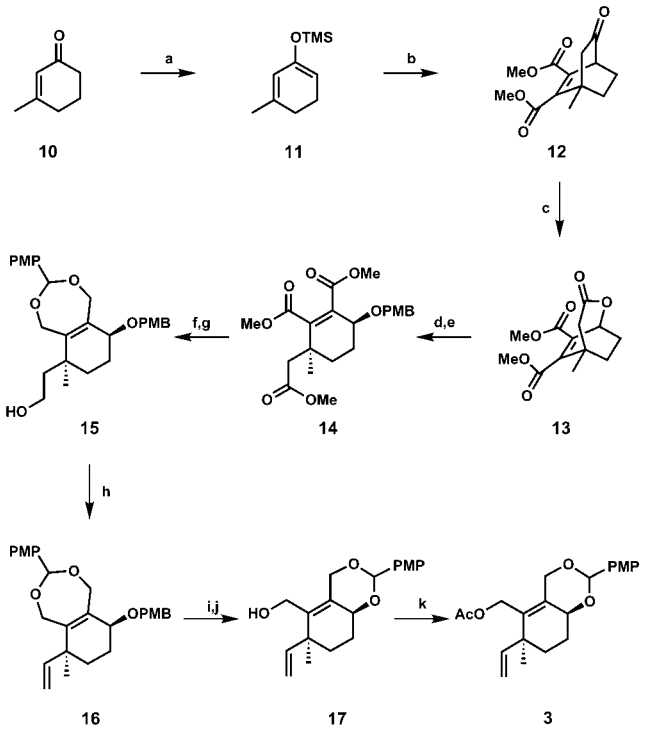
(10) For examples of selective cyclopropyl bond cleavages, see: (a) Stork, G.; Uyeo, S.; Wakamatsu, T.; Grieco, P.; Labovitz, J. *J. Am. Chem. Soc.* **1971**, *93*, 4945−4947. (b) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 6429−6431. (c) Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett.* **1991**, *32*, 6649−6652. (d) Kirschberg, T.; Mattay, J. *Tetrahedron Lett.* **1994**, *35*, 7217−7220. (e) Ziegler, F. E.; Zheng, Z. *J. Org. Chem.* **1990**, *55*, 1416−1418.

(11) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917−918.

(12) (a) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277−279. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040.

(13) Rubottom, G. M.; Gruber, J. M.; Juve, H. D., Jr.; Charleson, D. A. *Org. Synth.* **1986**, *64*, 118−126.

Scheme 3[a]

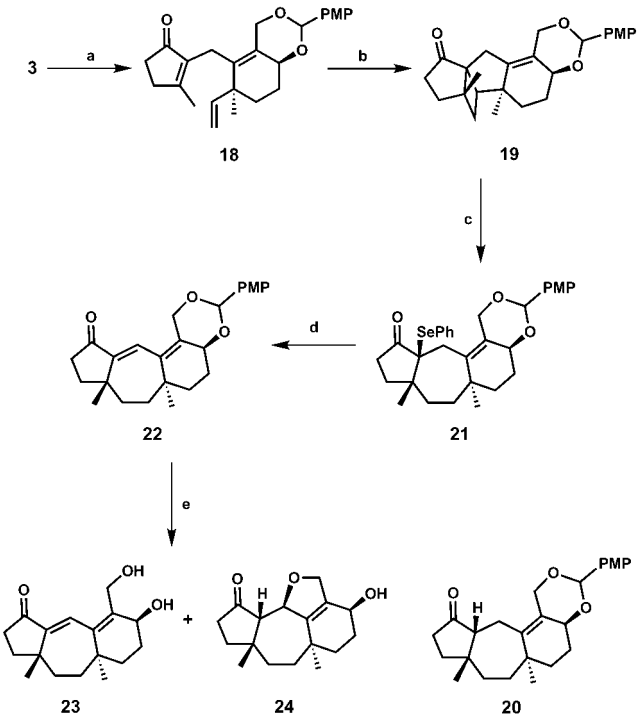


[a] Reagents: (a) LDA, TMSCl, THF, −15 °C → rt, 12 h, 98%. (b) Dimethylacetylenedicarboxylate, THF, 0 °C → rt; then 1 N aq HCl, 0 °C → rt, 12 h, 99%. (c) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt, 16 h, 96%. (d) CSA (0.07 equiv), MeOH, reflux, 12 h, 100%. (e) *p*-Methoxybenzyl trichloroacetimidate, CSA (0.1 equiv), CH_2Cl_2, rt, 15 h. (f) $LiAlH_4$, Et_2O, 0 °C → rt, 1 h, 87% (over 2 steps). (g) Anisaldehyde dimethyl acetal, PPTS (0.1 equiv), CH_2Cl_2, rt, 90 min, 80%. (h) *o*-Nitrophenylselenocyanate, *n*-Bu_3P, THF, 30 min, 0 °C → rt; then 30% aq H_2O_2, *i*-Pr_2EtN, 0 → 45 °C, 3 h, 71%. (i) PPTS (0.25 equiv), MeOH, rt, 3 h, 85%. (j) DDQ, CH_2Cl_2, rt, 30 min, 69% and 9% starting material. (k) Ac_2O, DMAP, pyridine, rt, 10 min, 100%. TMS = $SiMe_3$; PMP = *p*-$MeOC_6H_4$; PMB = $CH_2C_6H_4$-*p*OMe.

differentiated in the course of an oxidation with DDQ.[15] Finally, allylic acetate **3** was obtained in quantitative yield by treatment of alcohol **17** with acetic anhydride and a catalytic amount of DMAP in pyridine.

Palladium-catalyzed π-allyl Stille coupling[16] of stannane **9** and allylic acetate **3** proceeded efficiently, furnishing cycloaddition substrate **18** in 87% yield (Scheme 4). Irradiation of **18** with a 450-W Hanovia medium-pressure mercury vapor lamp effected the desired intramolecular enone-olefin [2 + 2] cycloaddition and provided cyclobutyl ketone **19** in 76% yield.[17]

Scheme 4[a]



[a] Reagents: (a) **9**, LiCl, Pd_2dba_3 (0.2 equiv), NMP, 50 °C, 16 h, 87%. (b) *hν*, diisopropylethylamine (0.25 equiv), Et_2O, 3 h, 76%. (c) SmI_2 (2.1 equiv), HMPA, THF, rt, 5 min; then PhSeBr, rt, 5 min, 44%. (d) *m*CPBA, CH_2Cl_2, −78 °C, 5 min, 84%. (e) PPTS (0.25 equiv), CH_3CN, H_2O, rt, 7 h, 49% of **23** and 45% of **24**. PMP = *p*-$MeOC_6H_4$.

Having accomplished the desired photocycloaddition, we were in a position to address the crucial cyclobutane fragmentation. The reduction of ketone **19** with SmI_2[18] in THF containing HMPA as a cosolvent was attended by the desired cyclobutane fragmentation and resulted in the formation of **20** in 72% yield after an aqueous quench. This favorable outcome invited the possibility of trapping the putative, regiodefined samarium(III) enolate with a suitable electrophile[10a,c] that could facilitate the goal of introducing a needed alkene into the seven-membered ring. When the reaction mixture for the samarium-mediated reduction of **19** was treated with phenylselenenyl bromide at room temperature, compound **21** was obtained in 44% yield. Exposure of **21** to *m*CPBA smoothly afforded **22**, a substance embodying the tricyclic dienone system of the guanacastepenes. To our knowledge, this is the first reported example of the use of this type of fragmentation to create the hydroazulene substructure.[19] Acidic hydrolysis of the benzylidene acetal produced diol **23**, which bears much structural similarity to guanacastepene C (**1c**). Compound **23** slowly isomerizes to

(14) (a) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485−1486. (b) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947−949.

(15) Oikawa, Y.; Yoshioka, T.; Yonemitsu, U. *Tetrahedron Lett.* **1982**, *23*, 889−892.

(16) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

(17) The benzylidene acetal of **18** was found to be rather labile to the photochemical conditions, but this problem was overcome by the addition of 0.25 equiv of diisopropylethylamine to the reaction mixture prior to irradiation. Compound **19** was the only diastereomer observed.

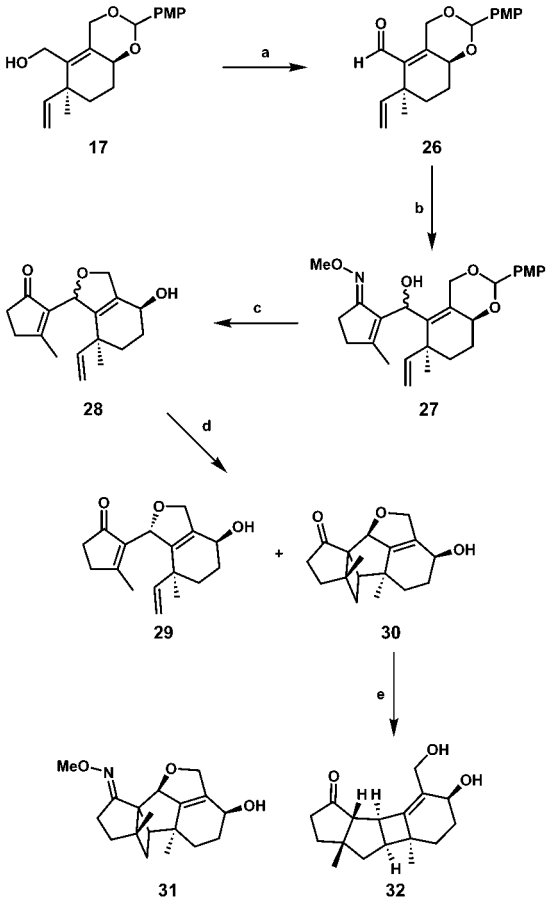
(18) For an excellent review, see: Molander, G. A. *Org. React.* **1994**, *46*, 211−367.

(19) For application of the intramolecular de Mayo reaction to the synthesis of the hydroazulene skeleton, see: (a) Begley, M. J.; Mellor, M. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1905−1912. (b) Seto, H.; Sakaguchi, M.; Fujimoto, Y.; Tatsuno, T.; Yoshioka, H. *Chem. Pharm. Bull.* **1985**, *33*, 412−415.

dihydrofuran **24**, a close relative of guanacastepene E (**1e**), and this process is accelerated by silica gel.[20]

In an effort to form the hydroazulenone substructure of the guanacastepenes directly in the course of the reductive fragmentation, we performed the chemistry shown in Scheme 5. Oxidation of alcohol **17** with Dess−Martin periodinane

Scheme 5[a]



[a] Reagents: (a) Dess−Martin periodinane, CH_2Cl_2, 0 °C → rt, 20 min, 100%. (b) **25**, *t*-BuLi, Et_2O, −70 °C, 30 min, 78%. (c) 1 N aq HCl, CH_3CN, 30 min, 84%. (d) *hν*, acetone, 2 h, 48% of **29**, 25% of **30**. (e) SmI_2 (3.0 equiv), THF, rt, 20 min, ~25%. PMP = *p*-$MeOC_6H_4$.

afforded aldehyde **26**, which was to serve the role of electrophile in a carbonyl addition reaction with the organolithium reagent derived from iodomethoxime **25** (Scheme 2). In the event, sequential addition of *tert*-butyllithium and aldehyde **26** to a solution of **25** in ether at −70 °C resulted in the formation of a ca. 2:1 mixture of diastereoisomeric alcohols shown as **27** in 78% yield.[21] The methoxime function was resistant to cleavage but could be hydrolyzed with 1 N HCl. Interestingly, these conditions gave not the expected epimeric triols resulting from benzylidene acetal cleavage but rather dihydrofurans **28**. When this mixture was irradiated, one of the dihydrofuran epimers underwent [2 + 2] cycloaddition to pentacycle **30** in 25% yield; the other dihydrofuran diastereomer was recovered unchanged in 48% yield.[22] This product distribution reflects the ratio of stereoisomers formed in the carbonyl addition step. The constitution and relative stereochemistry of **30** was confirmed by an X-ray crystallographic analysis of the crystalline derivative methoxime **31**.

Reasoning that compound **30**, a cyclobutyl ketone with a heteroatom in the β-position, could conceivably undergo a tandem ring fragmentation/β-elimination sequence in the presence of reducing metals, we treated it with samarium diiodide. This reaction, which afforded the interesting tetracycle **32** as the only isolable product, caused three changes: a selective, reductive fragmentation of the strained ring, the desired β-elimination, and a transannular conjugate addition. This outcome suggests that the desired enone system exists only transiently in this process.

In this Letter, we described a convergent approach to the tricyclic architecture of the guanacastepenes featuring an efficient Stille cross-coupling, a diastereoselective [2 + 2] photocycloaddition, and a selective fragmentation of a putative cyclobutylcarbinyl radical. From two five- and six-membered ring building blocks, this approach can furnish guanacastepene systems in four steps. Efforts are currently underway to employ fully functionalized cyclopentenone derivatives in this chemistry and to accomplish enantioselective syntheses of these intriguing, biologically active diterpenes.

Acknowledgment. We thank Dr. R. Chadha for the X-ray crystallographic analysis of **31** and Drs. D.-H. Huang and L. B. Pasternack for NMR spectroscopic assistance. Our work was supported by The Skaggs Institute for Chemical Biology at TSRI, Merck Research Laboratories, an Eli Lilly Award, a Beckman Young Investigator Award, an AstraZeneca Excellence in Chemistry Award, a Camille-Dreyfus Teacher-Scholar Award, and a predoctoral fellowship from the Skaggs Institute (W.D.S.).

Supporting Information Available: Characterization data and experimental procedures for **3**, **9**, **13**, **17**−**24**, **26**, and **32**; ORTEP drawing of X-ray structure of **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Thus, flash chromatographic purification of the hydrolysis reaction yielded both products **23** and **24**. Stirring a solution of **23** in Et_2O with silica gel results in the formation of **24**. The structure of **24** is supported by gHMBC, gHSQC, gdqCOSY, and ROESY experiments.

(21) Attempts to add the dioxolane-protected cyclopentenyllithium to **26** using various protocols were unsuccessful.

(22) Examination of molecular models indicates that **29** is not conformationally inclined to undergo [2 + 2] photocycloaddition. However, the epimer giving rise to **30** can easily access the necessary alignment for cycloaddition.