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A Four-Step Synthesis of the Hydroazulene Core of Guanacastepene

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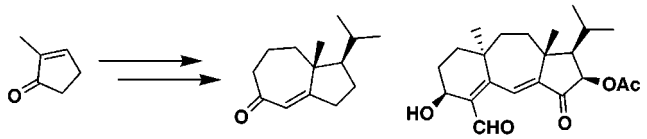
ABSTRACT



(2) guanacastepene (1)

A concise, four-step conversion of 2-methylcyclopentenone to hydroazulene 2 is described. An alternative approach that led to an unexpected [5,5]-bicyclic carbon framework is also discussed.

Guanacastepene (**1**, Figure 1), a diterpene with a heretofore unknown carbon skeleton, was recently isolated by Clardy and co-workers from an unidentified endophytic fungus collected in the Guanacaste Conservation Area in Costa Rica.[1] Guanacastepene's activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis* makes it of interest as a potential lead compound in the development of new antibacterial agents. Unfortunately, guanacastepene also exhibits hemolytic activity against human red blood cells.[1b] This side property could undercut its therapeutic value. Thus, analogues of guanacastepene offer the best prospects for capitalizing on the promising antibiotic activity of this system.

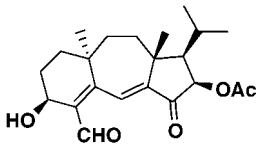


Figure 1. Structure of guanacastepene (**1**).

In light of the inherent interest generated by a novel carbon skeleton, and with a long-term hope of synthesizing congeneric structures, guanacastepene has been identified as an appropriate target for total synthesis. The first approach to the hydroazulene ring system of guanacastepene was reported by Snider and Hawryluk.[2] Herein we report a rapid and efficient synthesis of hydroazulene **2**. This chemistry provides a framework on which future efforts can be mounted.

We initially envisioned preparing **2** via an intramolecular Horner−Wadsworth−Emmons reaction.[3] With this strategy in mind, synthetic efforts commenced as outlined in Scheme 1. Thus, copper-catalyzed conjugate addition of isopropyl Grignard to **3**, promoted by Me_3SiCl−HMPA, proceeded as described previously by Piers.[4] Alkylation of the resulting silyl enol ether (**4**), via the corresponding lithium enolate,[5]

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

(2) Snider and Hawryluk prepared a system closely related to **2**, with an additional site of oxidation on the cyclopentane ring. See: Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569.

(3) For a review, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

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

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

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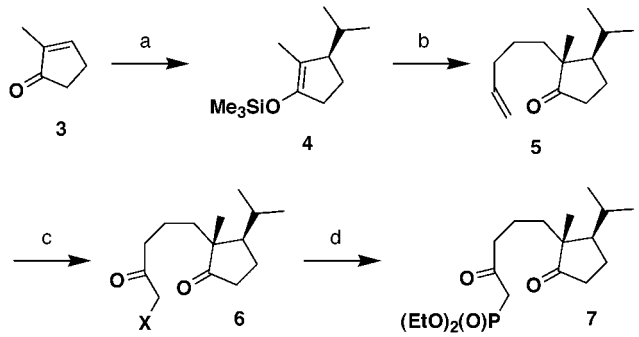
Scheme 1[a]



[a] Key: (a) ref 4, 94%; (b) MeLi, THF, 0 °C, 1 h, then 2.5 equiv of 5-iodo-1-pentene, HMPA, −78 °C to rt, 63−72%; (c) Chloramine-T, water, H_2SO_4, acetone, 50 °C, 30 min, then Jones, rt, 30 min, 54−63% (X = Cl); (d) (i) NaI, acetone, 15 min; (ii) $(EtO)_3P$, PhH, reflux, 5 h, 70−74%.

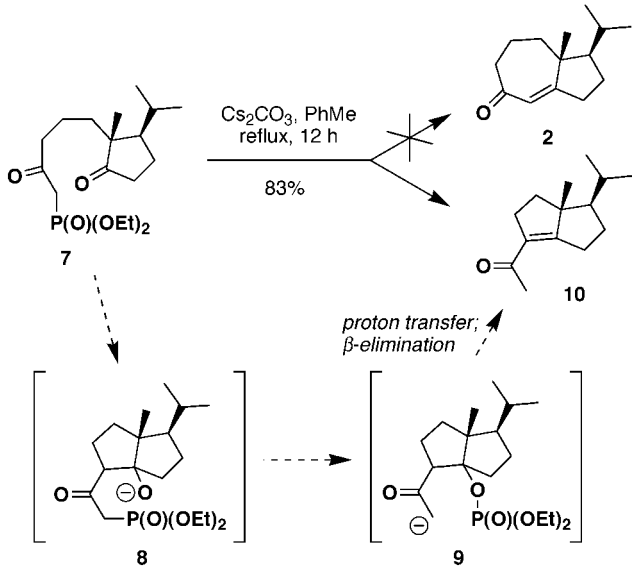
provided ketone **5** and generated one of the quaternary centers of the target.[6] The stereochemical outcome of the alkylation reaction is controlled by the steric influence of the β-isopropyl group, and can be assigned with confidence by analogy to similar reactions of **4**[4,7] and by comparison with the data previously reported for **5**.[8]

Hydroxy-chlorination[9] of **5**, followed immediately by Jones oxidation of the presumed chlorohydrin intermediate, yielded ketone **6** (X = Cl) in a one-pot sequence. The Arbuzov reaction[10] on the corresponding iodide[11] afforded the requisite β-ketophosphonate (**7**) in acceptable overall yield.

The stage was set for the intramolecular olefination reaction. The cyclization of phosphonate **7** (or the analogous dimethylphosphonate and diphenylphosphine oxide) was examined using conditions that were successful in forming other seven-membered rings (e.g., NaH, PhMe;[12] DBU, MeCN[13]). The desired product (**2**) was not observed. *When treated with 5.0 equiv of Cs_2CO_3 in refluxing toluene, however, **7** was converted to a single product, identified as the unexpected five-membered ring product **10**.*

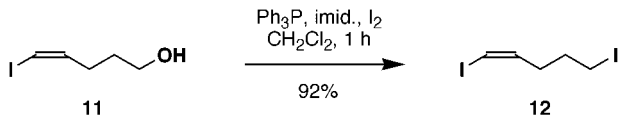
A proposal to account for the formation of **10** is outlined in Scheme 2. Presumably, entropic or steric barriers disfavor the hoped for Horner−Wadsworth−Emmons cyclization step, thus allowing the competing aldol pathway to predominate. Transfer of the phosphono group to the newly formed hydroxyl activates the oxygen for β-elimination, thereby

Scheme 2



generating the α,β-unsaturated ketone (**10**).[14] This unanticipated result led us to consider alternative strategies for the preparation of the hydroazulene core.

We next investigated the applicability of a recently disclosed cycloheptenone annulation strategy[15] to the problem at hand. Diiodide **12**, identified as an attractive alkylating agent for an enolate derived from silyl enol ether **4**, was easily prepared from the known alcohol **11**[16] in good yield.



As outlined in Scheme 3, alkylation of **4** with iodide **12** proceeded smoothly, without any noticeable base-induced elimination of the *Z*-vinyl iodide, to afford **13**. Although the use of 2.5 equiv of **12** was found to be necessary for complete consumption of the enolate, the excess iodide can be recovered by chromatographic separation on silica gel.

With the alkylation product (**13**) in hand, exploration into the critical reductive cyclization commenced.[17] The vinyllithium intermediate, generated in situ by halogen−metal exchange, reacts by competing pathways that lead to significant amounts of two distinct products.[15] The undesired

(6) 5-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.

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

(8) This compound, prepared by a different route, is an intermediate to Snider and Hawryluk's hydroazulene ring system (ref 2).

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

(10) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.

(11) α-Chloro ketones are susceptible to the Perkow reaction; see ref 10 and Lichtenthaler, F. W. *Chem. Rev.* **1961**, *61*, 607.

(12) Mikolajczyk, M.; Mikina, M. *J. Org. Chem.* **1994**, *59*, 6760.

(13) Kim, D.; Shin, K. J.; Kim, I. Y.; Park, S. W. *Tetrahedron Lett.* **1994**, *35*, 7957.

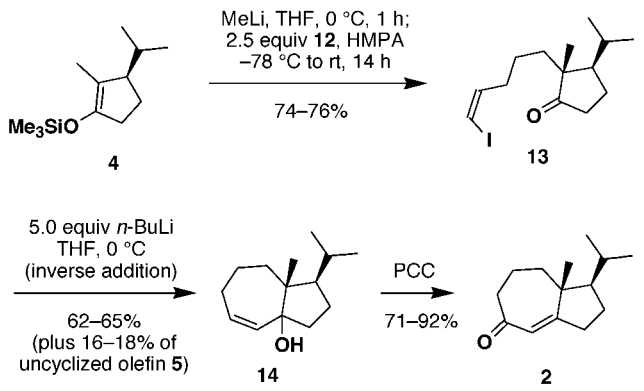
(14) Compound **10** was also observed following treatment of the methyl ketone corresponding to **6** (X = H) with base. A similar finding was reported by Snider and Hawryluk (ref 2).

(15) Piers, E.; Walker, S. D.; Armbrust, R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 635.

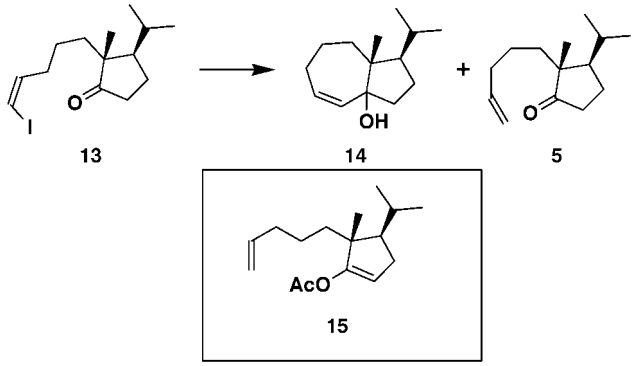
(16) Obtained by diimide reduction of the iodoalkyne derived from 4-pentynol using a modification of the literature procedure; see: Yenjai, C.; Isobe, M. *Tetrahedron* **1998**, *54*, 2509. In our hands, the desired *Z*-iodide (**11**) thus prepared was contaminated with varying amounts of 5-iodopentanol from overreduction of **11**. Therefore, the crude product mixture was treated with potassium phthalimide (DMF, 50 °C, 1 h) to consume this unwanted impurity and facilitate isolation of pure **11**.

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

Scheme 3



Scheme 4



product, deiodinated olefin **5**, presumably arises by protonolysis of the vinyllithium intermediate. Under optimal conditions, cyclization onto the ketone predominates, providing the bicyclic allylic alcohol **14**.[18] Oxidative rearrangement[19] of **14** occurs upon treatment with PCC (powdered sieves, CH_2Cl_2, rt) to afford the hydroazulene core of guanacastepene in only four steps from 2-methylcyclopentenone (**3**).

Maximization of the amount of reductively cyclized product **14** relative to uncyclized olefin **5** was critical to the usefulness of this approach. As expected for an intramolecular reaction such as the desired cyclization, dilute reaction mixtures imparted better yields of **14**. In this case, the ratio of **14** to **5** increases with decreasing concentration. This suggests that the undesired protonolysis of the intermediate vinyllithium occurs, at least to some extent, via intermolecular means.

We speculate that the enolizable cyclopentanone itself serves as the proton source. The resulting enolate would yield **5** upon aqueous workup. In fact, no deuterium-for-iodine exchange was observed upon quenching the reaction with D_2O, indicating that the vinyllithium derivative of **13** was quenched internally and was not present at the end of the reaction.[20] Proton transfer from the solvent can be excluded, because a reaction conducted in THF-d_8 failed to result either in deuterium incorporation in **5** or in alteration of the ratio of **14**:**5**. Finally, treatment of the reaction mixture with acetic anhydride for 30 min prior to workup allowed us to isolate **15** (the enol acetate of **5**), providing evidence in support of the presumed enolate intermediate (Scheme 4).

The influence of solvent and temperature on the course of the reaction is summarized in Table 1. A comparison of reactions conducted at 0 °C vs room temperature (entries 1, 2) indicates a slight advantage for the room-temperature experiment.[21,22] Including a polar, coordinating cosolvent (HMPA, entry 3) had a negligible effect on the reaction outcome, but switching to ether disfavored the cyclization pathway (entry 5). Addition of vinyl iodide **13** to a solution of *n*-butyllithium in THF at 0 °C (an "inverse addition", entry 6) provided the highest ratio of **14**:**5** that we have thus far observed, and this protocol is currently in favor for our preparative work.

Table 1. Effect of Reaction Conditions on the Reductive Cyclization of Vinyl Iodide **13**[a]

entry	*n*-BuLi, equiv	temp	solvent	ratio (**14**:**5**)[b]
1	2.2	0 °C	THF	1.6:1[c]
2	2.2	rt	THF	2.0:1[c]
3	2.2	rt	THF + HMPA	1.9:1[c]
4	3.0	50 °C	THF	2.0:1
5	3.5	rt	Et_2O	<0.1:1
6	3.5 (inverse addition)	0 °C	THF	3.5:1[c]

[a] Reactions described in entries 1−5 were carried out by rapid addition of *n*-butyllithium in hexanes to a 0.015 M solution of **13** in THF and stirring the resulting solution for 30−45 min. The reaction described in entry 6 was carried out by adding a solution of **13** in THF over 15 min to a freshly prepared mixture of *n*-butyllithium in hexanes and THF and stirring the resulting solution (0.015 M in **13**) for 30 min. [b] Estimated by ^{1}H NMR analysis of the crude product mixture. [c] Unreacted **13** also observed in the crude product mixture.

In summary, we have developed a concise and efficient synthesis of hydroazulene **2** via a reductive cyclization strategy. With this versatile intermediate in hand, we have begun efforts to build up the remaining quaternary center and to install the six-membered ring required to complete the carbon skeleton of guanacastepene (**1**). The results of these efforts will be reported in due course.

(18) Alcohol **14** is apparently produced as a single diastereomer; however, the relative stereochemistry of the tertiary alcohol was not determined.

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

(20) The extent of deuterium incorporation α to the ketone (from quenching of the presumed enolate intermediate) could not be quantified by ^{1}H NMR, because the relevant signals were not well resolved. Furthermore, isotopic scrambling of deuterated ketone **5** during the quench, workup, or purification cannot be rigorously excluded.

(21) Although this temperature effect is subtle, it is consistent with a competition between *intra*molecular cyclization and *inter*molecular proton transfer. Recalling that $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$, one expects that the formation of **5** via intermolecular processes would be suppressed by conducting the reaction at higher temperatures. Intramolecular proton transfer probably also contributes to the formation of **5**, and this pathway would be more difficult to inhibit.

(22) In practice, this observation must be balanced against the instability of alkyllithium reagents in warm ethereal solvents; see: Stanetty, P.; Mihovilovic, M. D. *J. Org. Chem.* **1997**, *62*, 1514.

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Supporting Information Available: Experimental procedures and characterization data for compounds **5**−**7**, **10**, **12**−**14**, and **2**. This material is available free of charge via the Internet as http://pubs.acs.org.

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