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Synthesis of the Hydroazulene Ring System of Guanacastepene

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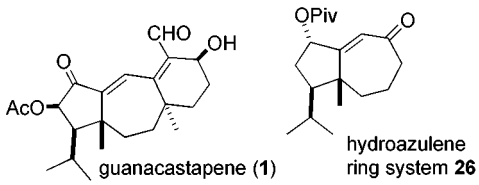
ABSTRACT

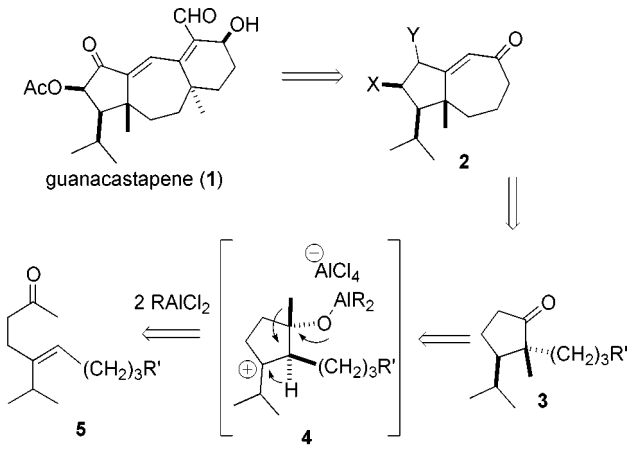


A 12-step synthesis of 26, the functionalized hydroazulenone ring of guanacastepene (1), has been completed using the $EtAlCl_2$-initiated cyclization of γ,δ-unsaturated ketone 13 to construct 2,2,3-trisubstituted cyclopentanone 14, the palladium-catalyzed coupling of vinylmagnesium bromide with enol triflate 17 to prepare triene 21, and olefin metathesis of triene 21 to form the key hydroazulene 20.

The novel, diterpene antibiotic guanacastepene (**1**), which was isolated from an unidentified fungus growing on the tree *Daphnopsis americana*, shows excellent activity toward methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.[1] Further biological studies indicated that **1** has moderate activity against Gram-positive bacteria, poor activity against Gram-negative bacteria, and hemolytic activity against human red blood cells.[2] The structure of **1** was determined by X-ray crystallography by Clardy and co-workers.[1] The NMR spectrum indicates that the cycloheptene ring of **1** exists as a mixture of two slowly equilibrating conformers.

Retrosynthetic analysis suggested that the cyclohexene ring of guanacastepene (**1**) could be synthesized from hydroazulenone **2** by methylation and Robinson annulation. The order of steps will have to be determined experimentally because of the conformational flexibility of the cycloheptene ring of **1** and, presumably, **2** as well. Elaboration of the functionality on the cyclohexane and cyclopentane rings will then complete the synthesis. A variety of sequences can be envisioned to construct the cycloheptenone of hydrazulenone **2** from cyclopentanone **3**.

Scheme 1



We thought that cyclopentanone **3** could be prepared stereospecifically by the $EtAlCl_2$-initiated cyclization of γ,δ-unsaturated ketone **5**. Several years ago we reported a new method for cyclopentanone annulation by treatment of γ,δ-

(1) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116−2117.
(2) 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.
(3) (a) Snider, B. B.; Kirk, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2364−2368. (b) Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984**, *49*, 153−157.

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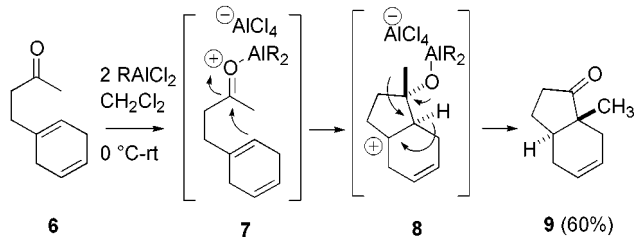
unsaturated ketones with excess $RAlCl_2$.[3] For instance, treatment of dienone **6** with 2 equiv of $RAlCl_2$ generated the very electrophilic complex **7**, which cyclized to give zwitterion **8** with the bulky R_2AlO group cis to the ring fusion hydrogen. Concerted 1,2-hydride and methyl shifts afforded 60% of trans-fused hydrindenone **9**, which was elaborated to an 11-oxosteroid intermediate (see Scheme 2).

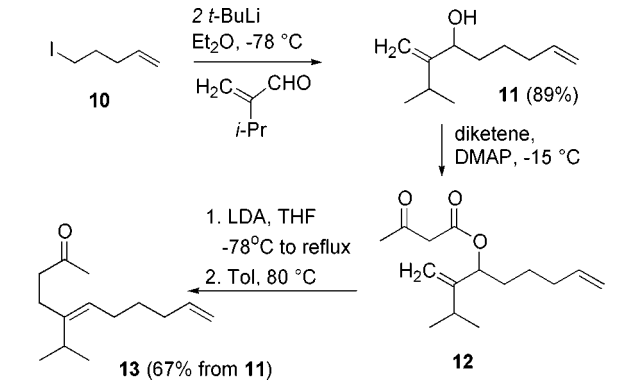
Scheme 2



This method has been used mainly to make fused ring systems but also should be suitable for the construction of 2,2,3-trialkylcyclopentanone **3** by cyclization of γ,δ-unsaturated ketone **5** to give zwitterion **4**, which should undergo concerted 1,2-hydride and methyl shifts to give **3** stereospecifically. We chose to carry out this reaction on **13** with a side chain containing a synthetically versatile terminal double bond since the successful cyclization of **6** indicated that isolated double bonds are compatible with the acidic conditions required for this cyclization.[4−6]

4-Pentenyllithium, prepared by halogen−metal exchange[7] of 5-iodo-1-pentene (**10**)[8] with 2 equiv of *t*-BuLi in THF at −78 °C, was added to 2-isopropylacrolein[9] to afford 89% of allylic alcohol **11**. Reaction of **11** with diketene and DMAP provided acetoacetate **12** (see Scheme 3). Enolate

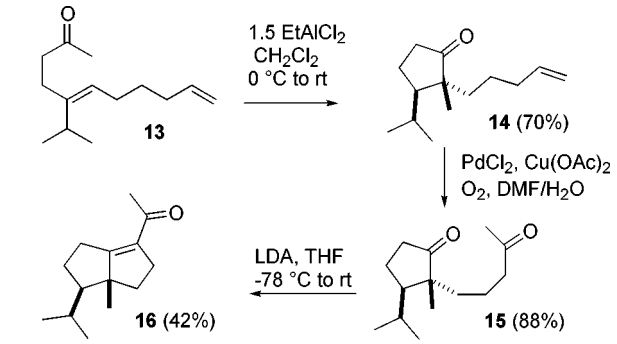
Scheme 3



accelerated Carroll rearrangement by the procedure of Wilson[10] was effected by treating **12** with 2 equiv of LDA in THF at −78 °C and heating at reflux to give the β-keto acid. Decarboxylation by heating in toluene at 80 °C provided dienone **13** in 67% yield from alcohol **11**.

We were delighted to find that treatment of γ,δ-unsaturated ketone **13** with 1.5 equiv of $EtAlCl_2$ in CH_2Cl_2 at 0 °C with gradual warming to room temperature over 24 h gave 70% of cyclopentanone **14** as the only cyclic product (see Scheme 4). The stereochemistry of **14** was established by NOE

Scheme 4



studies on the cyclopentenone prepared by phenylselenylation, oxidation, and elimination. The allylic methine hydrogen adjacent to the isopropyl group at δ 2.45 showed an NOE to the methylene protons on the side chain at δ 1.51−1.34 but not to the methyl singlet at δ 1.04.[11]

Initially, we planned to form the cycloheptenone by an intramolecular aldol reaction, which has been used successfully to form related hydroazulenones.[12] Diketone **15** was prepared in 88% yield by Wacker oxidation of **14** with $PdCl_2$, $Cu(OAc)_2{\cdot}H_2O$ and O_2 (1 atm) in DMF.[13] Unfortunately, no reaction occurred on treatment of diketone **15** with pyrrolidine at 80 °C[12a] or KOH in MeOH.[12b] Aldol reaction was eventually achieved by reaction of diketone **15** with LDA in THF at −78 to 0 °C to give 42% of acetylhydropentalene **16** rather than the desired hydrazulenone.

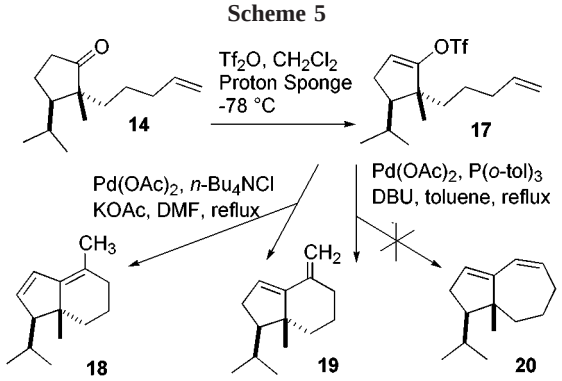
We then unsuccessfully explored sequences involving nucleophilic addition to the carbonyl group of cyclopentanone **14**. Enolization was the only reaction even with unhindered nucleophiles such as *n*-BuLi and $CeCl_3$. The carbonyl group is very hindered by the three adjacent

(4) Related cyclopentanones have been prepared by trapping the enolate formed by addition of an isopropylcuprate to 2-methyl-2-cyclopentenone with MVK[5] or allylic halides.[6] This approach is unlikely to be successful with less reactive alkyl halides.

(5) Duhamel, P.; Dujardin, G.; Hennequin, L.; Poirier, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 387−396.
(6) Piers, E.; Renaud, J.; Rettig, S. J. *Synthesis* **1998**, 590−602.
(7) Negishi, E.-i.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406−5409.
(8) Prepared in 96% yield by reaction of 5-bromo-1-pentene with NaI in acetone at reflux for 2 h. Only 59% of **11** was obtained from halogen−metal exchange with 5-bromo-1-pentene.
(9) Riehs, G.; Urban, E. *Tetrahedron* **1996**, *52*, 1221−1230.
(10) (a) Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722−725. (b) Snider, B. B.; Beal, R. B. *J. Org. Chem.* **1988**, *53*, 4508−4515.
(11) The NOE study was carried out in the analogous series prepared by addition of *n*-BuLi rather than 4-pentenyllithium to isopropylacrolein.
(12) (a) Ravi Kumar, V. T.; Swaminathan, S.; Rajagopalan, K. *J. Org. Chem.* **1985**, *50*, 5867−5869. (b) Money, T.; Wong, M. K. C. *Tetrahedron* **1996**, *52*, 6307−6324.
(13) Smith, A. B., III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765−8768.

substituents, whereas the α-position is unhindered. We decided to take advantage of the facile enolization of **14** by exploring Pd-insertion reactions of enol triflate **17** (see Scheme 5).

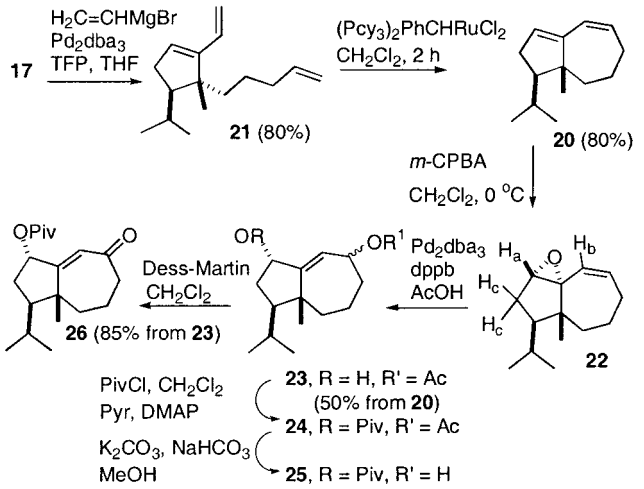
Scheme 5



Reaction of cyclopentanone **14** with Tf_2O and Proton Sponge afforded enol triflate **17** in 86% yield. A Heck reaction on enol triflate **17** with $Pd(OAc)_2$, P(*o*-tol)$_3$, and DBU in toluene at reflux gave only the 6-exo product **19** and none of the desired 7-endo product hydroazulene **20**. Rigby has reported endo-selective intramolecular Heck reactions using Jeffery phosphine-free conditions: $Pd(OAc)_2$, *n*-Bu_4NCl, and KOAc in DMF.[14] Using these conditions we obtained a mixture of **19** and the isomerized diene **18**. Endo selective intramolecular Heck reactions have also been described by Genêt using TPPTS (*m*-sulfonated triphenylphosphine) in aqueous solution.[15] However, treatment of triflate **17** with $Pd(OAc)_2$ and TPPTS in water and CH_3CN gave only the 6-exo product **19**.

We then decided to prepare hydroazulene **20** by olefin metathesis of triene **21**. Formation of triene **21** proved to be quite challenging as a result of the facility of the intramolecular 6-exo Heck reaction that formed **19**. For instance, treatment of triflate **17** with 5 equiv of tributylvinyltin, Pd_2dba_3 (0.02 equiv), and tri-2-furylphosphine (TFP) (0.04 equiv) in THF gave a 9:1 mixture of Heck product **19** and triene **21** even though these conditions have been reported to accelerate Stille coupling.[16] We then tried to prepare triene **21** without competing Heck reaction by Cu-catalyzed coupling of vinylmagnesium bromide with triflate **17**.[17] Unfortunately, we obtained only traces of triene **21**, in agreement with previous reports that cuprate coupling with enol triflates can be problematic.[18] Finally, we concluded that Pd-catalyzed coupling of vinylmagnesium bromide with enol triflate **17** should be faster than the intramolecular Heck reaction (see Scheme 6).[19]

Scheme 6



We were pleased to find that treatment of triflate **17** with vinylmagnesium bromide and $Pd(Ph_3P)_4$ in THF at reflux gave a 9:1 mixture of triene **21** and Heck product **19**. The formation of the Heck product can be completely suppressed using catalyst conditions optimized for Stille coupling.[16] Treatment of **17** with vinylmagnesium bromide (5 equiv), Pd_2dba_3 (0.02 equiv), and TFP (0.08 equiv) in THF at room temperature gave triene **21** in 80% yield. Olefin metathesis[20] of triene **21** with bis(tricyclohexylphosphine)benzylidine-ruthenium dichloride (Grubbs' catalyst, 2 × 0.1 equiv) in CH_2Cl_2 for 2 h cleanly afforded the desired hydroazulene **20** in 80% yield. The use of CH_2Cl_2, rather than benzene, as solvent was crucial for the success of this reaction. Starting material was still present and significant amounts of byproducts had formed after reaction for 2 d in benzene.

Treatment of hydroazulene **20** with *m*-CPBA at 0 °C in CH_2Cl_2 and saturated aqueous $NaHCO_3$ gave epoxide **22** as a single stereoisomer. A 1D NOESY spectrum of epoxide **22** with irradiation of the epoxide hydrogen H_a at δ 3.26 shows a larger cross peak to the alkene hydrogen H_b at δ 5.50 than to the cyclopentane methylene hydrogens H_c at δ 2.06 and 1.33. The distances calculated by conformational searching with MM2 minimization in **22** are $H_a-H_b = 2.80$ Å and $H_a-H_c = 2.62$ and 2.69 Å. The calculated distances in the stereoisomer in which epoxidation occurred from the more hindered β-face are $H_a-H_b = 3.37$ Å and $H_a-H_c = 2.54$ and 2.83 Å. In this isomer the NOE between the epoxide hydrogen H_a and the alkene hydrogen H_b should be much smaller than those to the cyclopentane methylene hydrogens H_c.

(14) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834−7835.
(15) (a) Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genêt, J.-P. *Tetrahedron Lett.* **1996**, *37*, 2003−2006. (b) Bombrun, A.; Sageot, O. *Tetrahedron Lett.* **1997**, *38*, 1057−1060.
(16) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.
(17) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313−4316.
(18) (a) Lipshutz, B. H.; Vivian, R. W. *Tetrahedron Lett.* **1999**, *40*, 2871−2874. (b) Lipshutz, B. H.; Elworthy, T. R. *J. Org. Chem.* **1990**, *55*, 1695−1696. (c) Hirama, M.; Nakamine, T.; Itô, S. *Tetrahedron Lett.* **1988**, *29*, 1197−1198.
(19) Murahashi, S.-I.; Yamamura, M.; Yanagisawa, K.-i.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408−2417.
(20) (a) Schneider, M. F.; Junga, H.; Blechert, S. *Tetrahedron* **1995**, *51*, 13003−13014. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (c) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007.

Treatment of epoxide **22** under Deardorff's conditions,[21] $(Ph_3P)_4Pd$ and AcOH in THF at 65 °C, afforded 30% of acetoxy alcohol **23** as 1:1 mixture of acetate stereoisomers. The yield increased to 50% with Pd_2dba_3, dppb, and AcOH in THF at 65 °C.[22] We were unable to open the vinyl epoxide with triphenylsilanol by the Trost procedure.[21] Deardorff reported the exclusive formation of the cis acetoxy alcohol from cyclopentadiene monoepoxide.[20] It is not clear why there was a loss of stereocontrol with epoxide **22**, but this is of no concern since this stereocenter is lost on oxidation to the enone.

Acetoxy alcohol **23** was elaborated to hydroazulenone **26** in 85% overall yield by protection of the alcohol with pivaloyl chloride, DMAP, and pyridine in CH_2Cl_2 to give pivaloate **24**, selective hydrolysis of the acetate using K_2CO_3 and $NaHCO_3$ in MeOH to give alcohol **25**, and oxidation with the Dess−Martin reagent to give hydroazulenone **26**.

In conclusion, we have completed the synthesis of the functionalized hydroazulenone ring system of guanacastepene in 12 steps using the $EtAlCl_2$-initiated cyclization of γ,δ-unsaturated ketone **13** for the preparation of 2,2,3-trisubstituted cyclopentanone **14**, the palladium-catalyzed coupling of vinylmagnesium bromide with enol triflate **17** to prepare triene **21**, and olefin metathesis of triene **21** to form the key hydroazulene **20**. We are currently exploring methods to elaborate the cyclohexene ring and modify the functionality in the cyclopentane ring to complete the synthesis of guanacastepene.

Acknowledgment. We are grateful to the National Institutes of Health (GM-50151) for generous financial support.

Supporting Information Available: Full experimental procedures for the sequence leading to **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) (a) Deardorff, D. R.; Myles, D. C.; MacFerrin, K. D. *Tetrahedron Lett.* **1985**, *26*, 5615−5618. (b) Deardorff, D. R.; Myles, D. C. *Organic Synthesis, Collective Volume 8*; Wiley & Sons: New York, 1993; pp 13−19.

(22) Trost, B. M.; Ito, N.; Greenspan. P. D. *Tetrahedron Lett.* **1993**, *34*, 1421−1424.