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A synthetic approach to the functionalized hydroazulene core of guanacastepenes and heptemerenes

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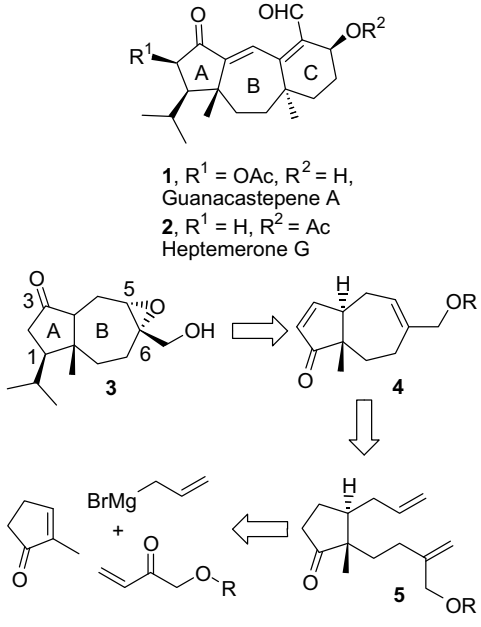
ABSTRACT

A functionalized hydroazulene derivative has been synthesized efficiently from 2-methylcyclopent-2-en-1-one as a part of a study oriented toward the total synthesis of diterpenoids of biological significance, guanacastepenes, and heptemerones.

Fungal microorganisms colonizing inside a healthy plant may contribute to protection of the host by generating metabolites that are active against nematodes, mammal or insect herbivores, or fungal pathogens.[1] Study on the fungi–plant relationship has contributed significantly to the development of new drugs and crop protection products.[2] A great deal of attention has recently been devoted to a family of diterpenes produced by an endophilic fungus CR115 growing in branches of a *Daphnopsis americana* tree in the Guanacastepene rainforest of Costa Rica. The extract of the fungus, as well as the isolated parent member of the group, guanacastepene A (**1**, Scheme 1), shows high antibiotic activity against drug-resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis* in preliminary tests.[3] However, further development of guanacastepene A as an antibacterial agent is limited by its hemolytic activity against human red blood cells.[4] Fourteen other guanacastepenes (B-O) have been isolated from cultures of CR115 grown in potato dextrose broth. One of them (guanacastepene I) showed pronounced activity against *S. aureus*.[5] Structurally closely related diterpenes named heptemerones were isolated from the broth of the submerged culture *Coprinus heptemerus*.[6,7] Among the biological activities of these metabolites, the inhibition of fungal germination was most potent along with moderate cytostatic activity. Heptemerone G (**2**) was found to be the most biologically active representative of this sub-group.

A combination of five-, seven-, and six-membered rings with the highly polar 'northern' rim of the molecule and two quaternary carbon atoms and the isopropyl group in the 'southern' rim presents a challenge for the total synthesis. Within the few years since their isolation, guanacastepenes have become a testing field for terpenoid-oriented synthetic methodology.



Scheme 1. Structures of the target compounds and an overview of the synthetic strategy.

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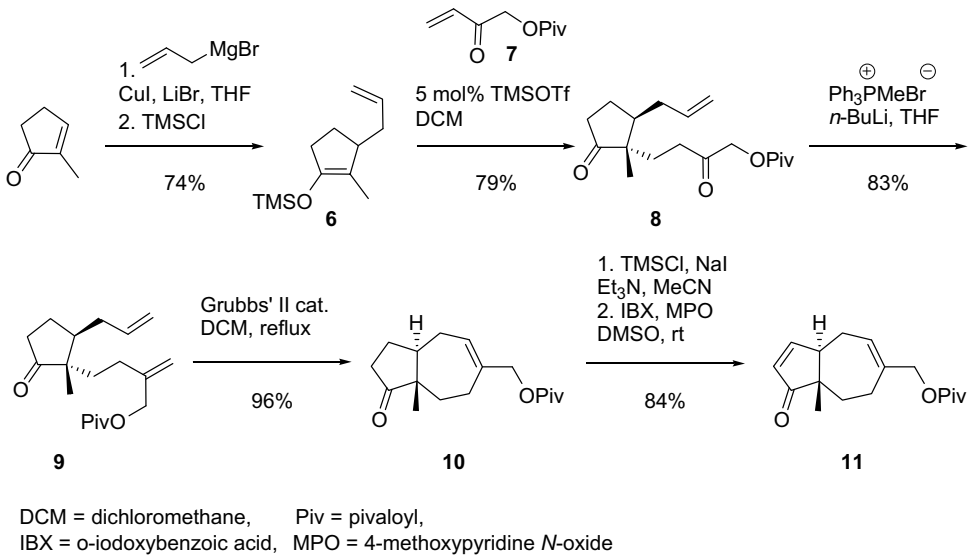


Scheme 2.

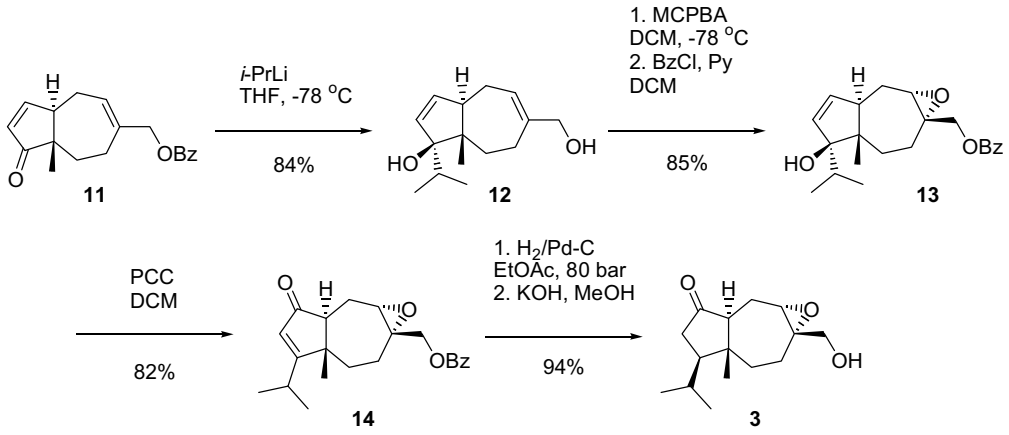
The first synthesis of racemic and then natural guanacastepene A was achieved by Danishefsky and co-workers.[8–10] The enantioselective synthesis of guanacastepene A has also been accomplished by Shipe and Sorensen,[11] and formal total syntheses of guanacastepene A were reported by Hanna,[12] Snider,[13] and Mehta[14] and their respective co-workers. Guanacastepene C was synthesized by Mehta,[14] guanacastepene N by Overman,[15] and guanacastepene E, and heptemerone B by Trauner.[16] Several approaches to advanced intermediates for guanacastepenes or their structural analogues have been developed.[13,16–23] We chose the *trans*-hydroazulene derivative **3** (Scheme 1) as the key intermediate for guanacastepene and heptemerone synthesis. The five-membered ring in **3** matches the heptemerone G ring A, and is well suited for the introduction of an acetoxy group at C-2 at the appropriate stage of guanacastepene A synthesis. The hydroxy epoxide moiety in **3** will provide a handle for installing the tertiary carbon center at C-6 and for further annulation. It was thought that **3** would be accessible by regioselective transformations of dienone **4**. A short sequence to **4** from 2-methylcyclopent-2-en-1-one via 1,8-diene **5** (Scheme 2) was projected on the grounds of our previous experience with cyclopenta-cyclooctane synthesis.[24,25] Now, we report an efficient and scalable method for the synthesis of functionalized hydroazulene **3**.

Copper-catalyzed addition of allylmagnesium bromide to 2-methylcyclopent-2-en-1-one, and trapping of the resulting enolate with the trimethylsilyl chloride was performed by analogy to the reported procedure[26] (Scheme 2) giving **6** in a 74% yield after distillation. It is noteworthy that the indium chloride–trimethylsilyl chloride-catalyzed Hosomi–Sakurai addition of allyl silane[27,28] to 2-methylcyclopent-2-enone afforded 3-allyl-2-methylcyclopentanone in an excellent yield. However, all our attempts to obtain the trimethylsilyl enol ether **6** by this route failed.

The Mukaiyama–Michael addition of **6** to pivaloyloxymethyl vinyl ketone **7**[29] was carried out conveniently in the presence of 10 mol % of trimethylsilyl triflate[30] to provide the adduct **8** in 79% yield. The reagent **7** was prepared from easily accessible but-3-en-1,2-diol[31] by selective acylation of the primary hydroxy group with pivaloyl chloride,[32] followed by oxidation of the secondary hydroxyl group with Jones' reagent.

The dione **8** was treated with methylidenetriphenylphosphorane generated in situ from methyltriphenylphosphonium bromide and *n*-butyllithium (THF, −78 to −20 °C) to afford the product **9** of regioselective olefination in 83% yield.

Diene **9** was subjected to ring-closing metathesis (RCM) using the Grubbs' second generation catalyst to afford **10** in an almost quantitative yield.



Scheme 3.

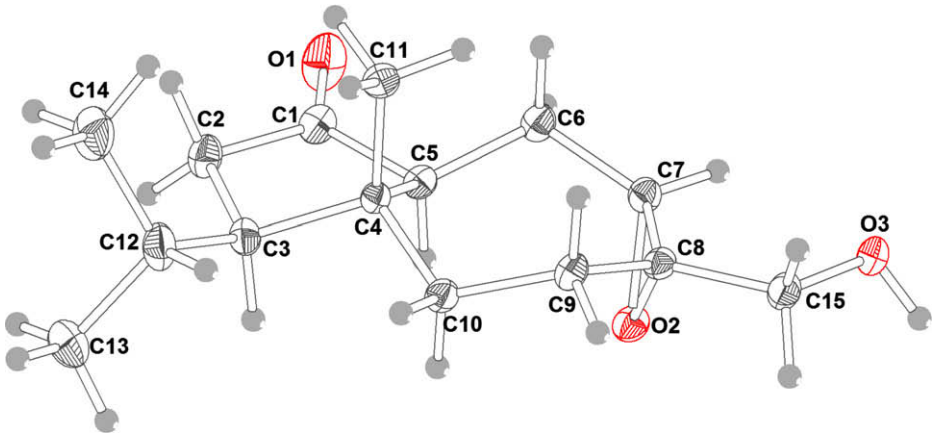


Figure 1. ORTEP plot of the single crystal X-ray structure of compound **3** (arbitrary numbering).

Dehydrogenation of **10** via the respective trimethylsilyl ether with *o*-iodoxybenzoic acid (IBX) and 4-methoxypyridine *N*-oxide (MPO)[33] gave **11** in 84% yield.

Ketone **11** in THF at −78 °C was treated with freshly prepared isopropyllithium in hexanes to afford **12** in 84% yield (Scheme 3). The two allyl alcohol moieties in compound **12** differ significantly with respect to steric shielding. Indeed, reaction of **12** with 3-chloroperoxybenzoic acid (3 equiv) in dichloromethane at −78 to 0 °C gave the corresponding monoepoxide, selectively. Since this product was sparingly soluble in common solvents, it was converted into benzoate **13** without isolation (85% yield in two steps).

The allylic alcohol **13** was oxidized with pyridinium chlorochromate (PCC) in dichloromethane to form α,β-unsaturated ketone **14** with the oxygen function transposed[34–36] (82% yield).

Finally, the double bond in **14** was hydrogenated at 80 bar over 10% palladium-on-carbon in ethyl acetate, and then the benzoate protecting group was removed to give alcohol **3**. The structure of this intermediate was confirmed by single crystal X-ray analysis (Fig. 1).[37]

In conclusion, a method for the diastereoselective synthesis of the functionalized hydroazulene derivative **3** from 2-methylcyclopent-2-en-1-one involving eight isolated intermediates and providing the product in 22% overall yield was developed. The method is well suited to preparation of **3** on a multigram scale.

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37. Alcohol **3**: mp 65–68 °C (Et_2O–hexanes) (370 mg, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) 3.61 (dd, J = 12.1, 4.8 Hz, 1H), 3.53 (d, J = 12.1, 7.9 Hz, 1H), 3.26 (d, J = 5.4 Hz, 1H), 2.60 (ddd, J = 16.2, 5.4, 2.7 Hz, 1H), 2.45 (ddd, J = 19.7, 8.6, 1.3 Hz, 1H), 2.25–2.19 (m, 1H), 2.09–1.89 (m, 4H), 1.81–1.55 (m, 5H), 1.04 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.69 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 217.1, 66.3, 63.9, 57.9, 57.4, 51.1, 44.5, 40.0, 35.3, 28.9, 24.2, 23.7, 22.2, 21.7, 11.7; HRMS calcd for $C_{15}H_{24}O_3$ (M^+) 252.1725, found: 252.1723. Crystallographic data for compound **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 697539. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or email:deposit@ccdc.cam.ac). The structure was solved by direct methods and refined using SHELXL. The refinement was based on F^2 for all reflections except those with very negative F^2. Weighted R factors wR and all goodness-of-fit S values are based on F^2. Conventional R factors are based on F with F set to zero for negative F^2. The $F_o^2 > 2\sigma(F_o^2)$ criterion was used only for calculating R factors, and is not relevant to the choice of reflections for the refinement. The R factors based on F^2 are about twice as large as those based on F. All hydrogen atoms were located geometrically, and their position and temperature factors were refined.