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Remarkable stereoselectivity in the alkylation of a hydroazulenone: progress towards the total synthesis of guanacastepene

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Abstract—*exo*-Methylene ketone **6** serves as a vehicle for elaboration of the C8 quaternary center en route to guanacastepene via a conjugate addition–alkylation sequence. Methylation of the cycloheptadienolate derived from **7** is highly selective for the desired relative stereochemistry, as determined by NMR and crystallographic analysis. © 2001 Published by Elsevier Science Ltd.

Guanacastepene (**1**, Fig. 1),[1,2] a recently disclosed antibacterial diterpenoid natural product with a novel carbon skeleton, has attracted interest from the synthetic community, as witnessed by the disclosure of several approaches to its hydroazulene core.[3–5] The incorporation of quaternary stereogenic centers at remote ends of the cycloheptene ring posses one of the inherent challenges for the synthesis of guanacastepene. In this letter, we report the remarkably efficient relay of stereochemical information from C11 to C8 of hydroazulene **4** (guanacastepene numbering).

Direct dialkylation of hydroazulene **4** was frustrated by difficulties generating the α′-enolate of **5** (Scheme 1). However, we observed that the conversion of **4** to **5** (stereochemistry not determined) was highly stereoselective.

Based on these results, we identified *exo*-methylene ketone **6** as a potentially versatile intermediate (Scheme 2).[6,7] Cuprate addition[8] to **6** provided silyl enol ether **7**, which upon treatment with methyllithium revealed the lithium enolate[9] that could not be generated cleanly by direct deprotonation of **5**. Reaction of this enolate with methyl iodide gave rise to **8** *as the only observed diastereomer*.

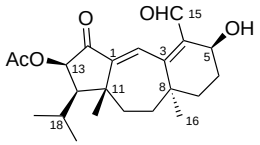
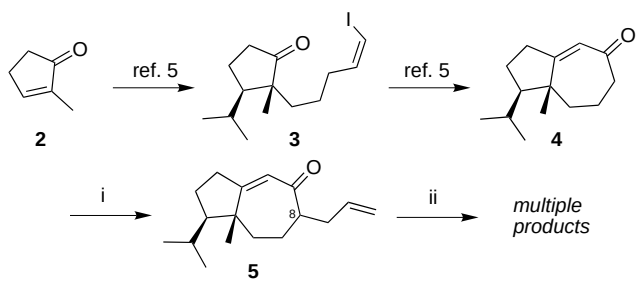


Figure 1. Structure of guanacastepene (**1**).

To facilitate the structure determination of **8**, at that stage the C8 epimer (**9**) was prepared in low yield (Scheme 3, not optimized).[10,11] Notably, **8** apparently was not produced in this reaction.

Though some instances of stereoselective cycloheptenone alkylations have been reported previously,[12] the exceptional selectivity imparted by the present system had not been anticipated. Preliminary assignment of the relative stereochemistry in **8** was made by extensive



Scheme 1. (i) LiHMDS, allyl iodide; (ii) LiHMDS, (MeI or TMSCl).

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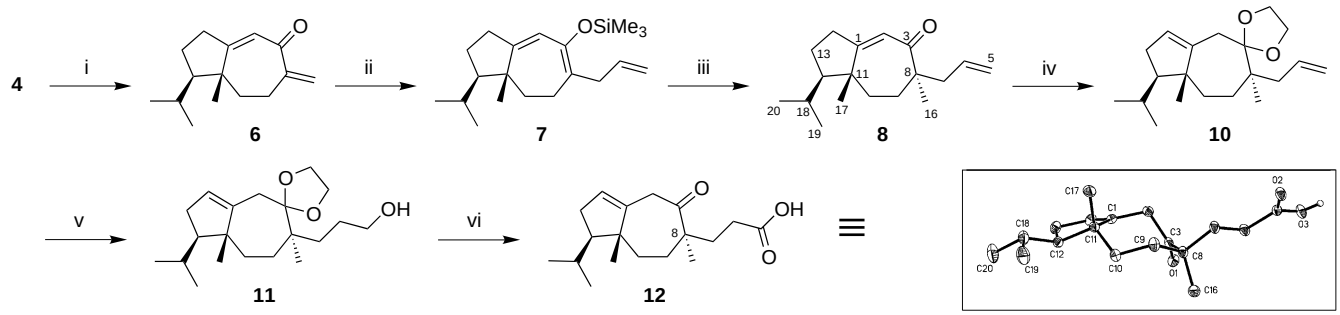
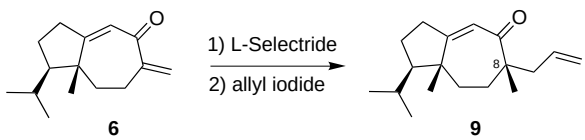


Scheme 2. *Reagents and conditions*: (i) (a) 1.5 equiv. LiHMDS, THF, −78°C, 1 h, then add to 3.0 equiv. Eschenmoser's salt, THF, −78°C to rt, 20 min; (b) 1.5–2.3 equiv. *m*-CPBA, $CH_2Cl_2/NaHCO_3$ (aq.) (2:1), 60–70%; (ii) 3.0 equiv. vinyl-MgBr, 1.5 equiv. CuI, 4.5 equiv. HMPA, 4.5 equiv. TMSCl, THF, −78°C, 20 min, 77%; (iii) 1.5 equiv. MeLi, THF, 0°C, 10 min, then 5.0 equiv. HMPA, 5.0 equiv. MeI, −78°C to rt, 15 min, 96%; (iv) $(CH_2OH)_2$, *p*-TsOH, PhH, reflux ($-H_2O$), 11 h, 88%; (v) (a) 9-BBN, THF, rt, 1 h; (b) 3 M NaOH, 30% H_2O_2, rt, 3 h, 71%; (vi) Jones reagent, acetone, 2 h, 77%. (Inset) ORTEP plot of X-ray crystal structure of **12**.



Scheme 3.

NMR analysis.[13] In summary, ^1H and ^{13}C resonances were assigned from J-resolve, COSY, NOESY, DEPT, HMQC, and HMBC data. In analogy to the modeling studies of guanacastepene by Clardy and co-workers,[1] two *gauche* butane-conformers about the C9–C10 bond of **8** were identified using the MM2 force field.[14] NOE interactions involving C12–H, C17–H_3, and C19–H_3 supported the pseudo-chair conformation as depicted (Fig. 2). The C8 configuration could then be assigned based upon NOE interactions between C16–H_3 and both C9–H_α and C10–H_α. The NMR analysis of **9** was complicated by overlapping ^1H signals; however, the C7–H_2 NOE interactions indicated in Fig. 2 are consistent with the pseudo-chair conformation and C8 configuration shown.

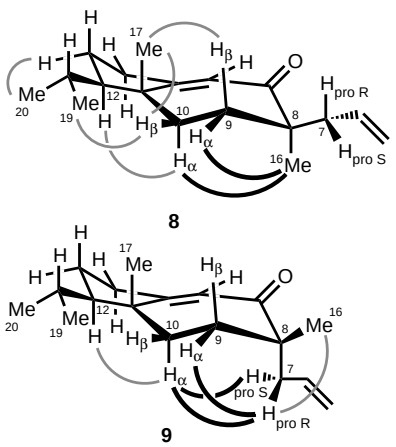


Figure 2. Pseudo-chair conformations of **8** and **9** with selected strong NOE interactions. Bold lines indicate NOE interactions used to assign relative stereochemistry at C8.

With the relative stereochemistry confidently established, further elaboration of **8** proceeded as described in Scheme 2 to yield carboxylic acid **12**.[15] Crystallization of **12** from ethyl acetate–hexanes provided crystals (mp 135.7–137.3°C) suitable for X-ray analysis (Scheme 2 inset), which provided decisive structural confirmation.[16]

In conclusion, we have assembled the C8 quaternary center of guanacastepene with remarkably high diastereoselectivity by substrate-controlled elaboration of hydroazulene **4**. This finding is obviously of interest for synthetic efforts toward guanacastepene, but on a broader plane exemplifies the perhaps underappreciated degree of selectivity imparted during alkylation of certain substituted cycloheptenones. The accessibility of *exo*-methylene ketone **6**, a critical intermediate for our approach, allows us to apply a variety of nucleophiles towards the synthesis of the carbon skeleton of guanacastepene. Efforts to elaborate **6** and **12** to totally synthetic goal structures including guanacastepene are ongoing, and the outcome of these efforts will be reported in due course.

Acknowledgements

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