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A facile construction of the tricyclic 5-7-6 scaffold of fungi-derived diterpenoids. The first total synthesis of (±)-heptemerone G and a new approach to Danishefsky's intermediate for a guanacastepene A synthesis

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ABSTRACT

The first total synthesis of (±)-heptemerone G, a diterpenoid metabolite of a submerged culture *Coprinus heptemerus*, and a new approach to an advanced intermediate for a synthesis of guanacastepene A are reported.

Fungi-derived and microbial terpenoids, distinctive by the presence of medium rings in their structures, are important synthetic targets.[1] Recently, the attention of several groups has focused on guanacastepenes, a family of diterpenoids isolated from endophilic fungi growing on the branches of the *Daphnopsis americana* tree (Guanacaste Conservation Area, Costa Rica).[2] The first identified representative of this family, guanacastepene A (**1**, Fig. 1), has a tricyclic structure with linearly fused five-, seven- and six-membered rings. The 'northern' region of this molecule is highly polar while the opposite side is hydrophobic and bears two quaternary carbon atoms, and an isopropyl group. More recently, structurally closely related terpenoids named heptemerones, including heptemerone G (**2**) were isolated from a broth of a submerged culture of *Coprinus heptemerus*.[3]

Interest in guanacastepene and heptemerone synthesis has been stimulated by their fascinating structures and biological activity. The crude fermentation extracts of fungi from *Daphnopsis* as well as isolated guanacastepene A were found to be highly active against certain malicious antibiotic-resistant bacteria.[2b] Although the biological activity profile of guanacastepene A is encumbered with a detrimental side effect (lysis of human red blood cells), a new class of structures has been revealed for chemical and pharmacological exploration.

The first total synthesis of guanacastepene A (**1**) was reported by Danishefsky and co-workers.[4] The synthesis of **1** has also been accomplished by Shipe and Sorensen[5] and formal total syntheses were reported by Hanna,[6] Snider,[7] and Mehta et al.[8] Guanacastepene C was synthesized by Mehta et al.,[8] guanacastepene N by Overman and co-workers,[9] and guanacastepene E by Trauner and co-workers.[10] To date, only one representative of the heptemerone family, heptemerone B, has been synthesized.[10] Several approaches to advanced intermediates for guanacastepene synthesis have also been developed.[11,12]

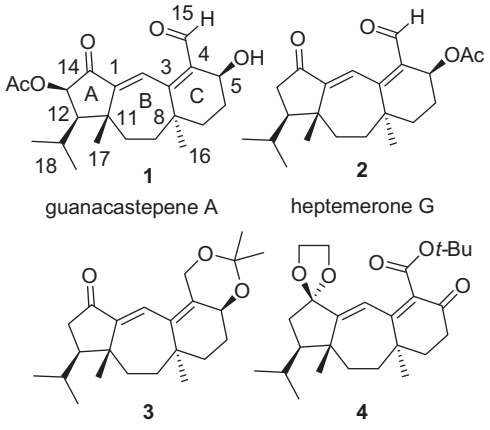

Figure 1. Structures of guanacastepene A, heptemerone G and the key synthetic intermediates.

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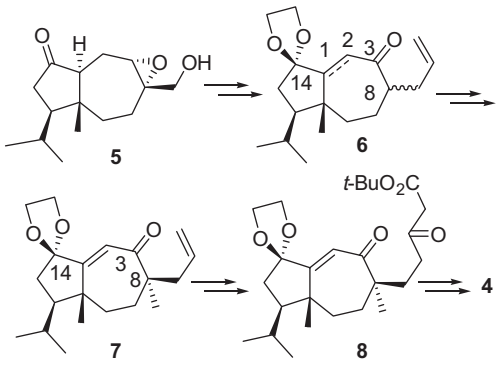
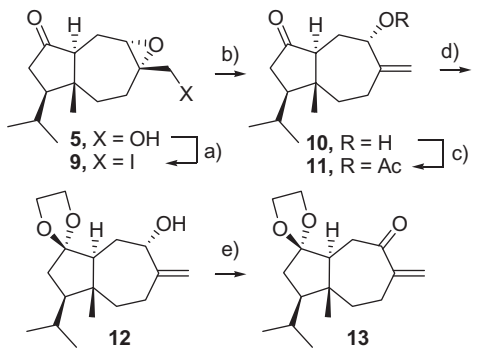


Scheme 1. Highlights of the proposed scheme for the synthesis of **4**.

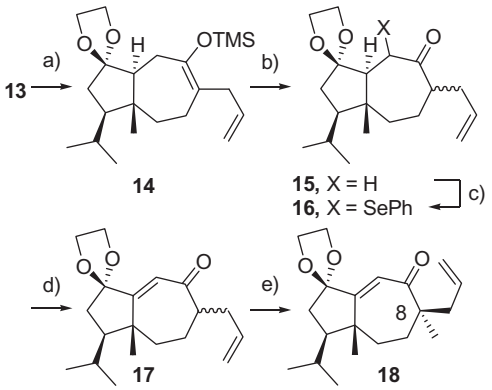
We now report the first total synthesis of heptemerone G (**2**) and, en route, a new synthetic approach to compound **3** (which is a guanacastepene A precursor in the Danishefsky synthesis), via the versatile tricyclic intermediate **4**.

The main features of the proposed synthetic route to **4** are shown in Scheme 1. The bicyclic intermediate **5**, readily prepared from 2-methylcyclopent-2-en-1-one, allylmagnesium bromide, and pivaloyloxymethyl vinyl ketone was the connection point to our earlier work.[13] It was envisioned that the hydroxy-epoxide function in **5** will be used, after protection of the oxo group at C-14, to install the oxo group at C-3 and the allyl group at C-8. The intermediate **6** would then be dehydrogenated and the product subjected to methylation to afford **7**. Danishefsky[4b,d] and Mehta[14] have shown that methylation of similar α,β-unsaturated ketones introduces the methyl group in a *trans*-orientation with respect to the angular methyl group. The allyl and oxo groups in the intermediate **7** were designed to serve as bridgeheads for forming ring C via the keto-ester **8**. Further transformations of **4** into **2** and **3** will require diastereoselective reduction of the keto group (C-5) and other functional group interconversions.

The alcohol **5**,[13a] on treatment with *p*-tosyl chloride in pyridine, gave the corresponding tosylate which, without purification, was subjected to Finkelstein exchange and the resulting unstable iodide **9** (Scheme 2) was reduced immediately with zinc in absolute ethanol[15] to give alkene **10**. Careful acetylation of **10** with acetic anhydride and DMAP in dichloromethane gave the acetate **11** contaminated with (presumably) its *cis*-azulene epimer (10% by ^{1}H NMR). All attempts to protect the keto group in **10** or **11** by reaction with ethylene glycol under standard conditions (acid catalyst, benzene, reflux with water removal) led to the formation of mixtures of products. After considerable experimentation, we found that treatment of a suspension of **11** in ethylene glycol with



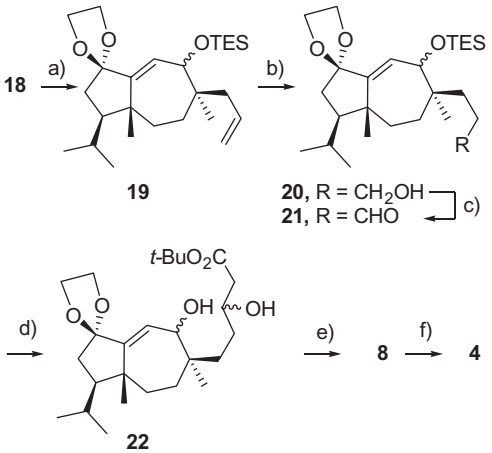
Scheme 2. Synthesis of methylidene ketone **13**. Reagents and conditions: (a) (1) *p*-TsCl, pyridine, 0 °C, 6 h, (2) NaI, acetone, reflux, 20 min; (b) Zn, absolute EtOH, reflux, 1 h, 92% from **5**; (c) Ac_2O, DMAP cat., CH_2Cl_2, rt, 89%; (d) (1) ethylene glycol, *p*-TsOH cat., $(MeO)_3CH$, rt; (2) KOH, MeOH, 96%; (e) MnO_2, Et_2O, rt, 84%.



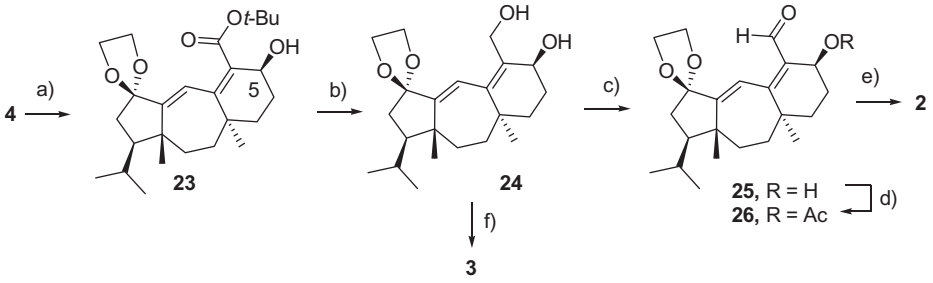
Scheme 3. Construction of the required stereogenic center at C-8. Reagents and conditions: (a) CH_2=CHMgBr, CuI, HMPA, TMSCl, THF, −78 °C to rt, 30 min; (b) $Bu_4NF{\cdot}3H_2O$, THF, rt, 15 min, 92% from **13**; (c) (1) LDA, THF, hexanes, −78 °C then Me_3SiCl, −78 °C to rt, (2) PhSeCl, CH_2Cl_2, Py, −78 °C to rt, 73%; (d) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, −78 °C, 30 min and then Et_3N, satd aq Na_2SO_3, rt, 20 h, 89%; (e) LHMDS, THF, 0 °C, 2 h and then HMPA, MeI, −20 °C, 1 h, 98%.

p-toluenesulfonic acid as the catalyst and methyl orthoformate as the water scavenger, at room temperature, afforded the corresponding ethylene ketal. Hydrolysis of the crude ester then gave the hydroxy-ketal **12**. Manganese dioxide oxidation[16] of **12** furnished the methylidene ketone **13** and the latter was used immediately in the next step.

Copper-assisted conjugate addition of vinylmagnesium bromide to enone **13** (Scheme 3) in the presence of TMSCl[4d,17] gave the silyl enol ether **14** which was subsequently treated with tetrabutylammonium fluoride to afford ketone **15** as a single epimer (the configuration at C-8 is of no consequence for the synthesis). The 'kinetic' lithium enolate was then generated from **15** using LDA and trapped with TMSCl. The trimethylsilyl derivative was then transformed[18] into the phenylselenide **16** and subsequently into the enone **17**. The lithium enolate generated from **17** and LHMDS was treated with an excess of methyl iodide in the presence of HMPA. A single product was obtained in 98% yield, which was at least 99% pure by HPLC. The structure **18** was assigned to this product.[4d,7,14] Computational studies on the stereochemistry of the methylation of **17** and its 1,2-dihydro-analog have been reported previously.[19]



Scheme 4. Synthesis of the tricyclic intermediate **4**. Reagents and conditions: (a) (1) $NaBH_4$–$CeCl_3{\cdot}7H_2O$, MeOH, (2) Et_3SiCl, imidazole, DMAP, CH_2Cl_2, 16 h, 90% from **18**; (b) 9-BBN, THF, 0 °C to rt and then aq NaOH, H_2O_2, 0 °C to rt, 97%; (c) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 95%; (d) (1) CH_3CO_2t-Bu, LDA, THF, hexanes, −78 °C to rt, (2) $Bu_4NF{\cdot}3H_2O$, THF, rt, 0.5 h, 91% from **21**; (e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 15 min and then Na_2SO_3; (f) EtONa, EtOH, rt, 2.5 h, 80% from **22**.



Scheme 5. Transformations of the core carbocyclic systems. Reagents and conditions: (a) $LiAlH_4$, THF, −93 °C, chromatography, 77%; (b) $LiAlH_4$, THF, rt, 0.5 h; (c) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, rt, 60–70% from **23**; (d) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt; 94%; (e) acetone, PPTS (cat.), rt, 94%; (f) acetone, *p*-TSA, rt, 95%.

Ketone **18** was reduced applying the Luche protocol,[20] and the resulting alcohol was protected as its triethylsilyl ether to give **19** (Scheme 4). The terminal double bond in **19** was then subjected to hydroboration–oxidation to afford alcohol **20**. Oxidation of **20** with tetra-*n*-propylammonium perruthenate (TPAP)–NMO[21] gave the aldehyde **21**. Addition of lithium *tert*-butyl acetate[22] (generated from *tert*-butyl acetate and LDA in THF at −78 °C) to **21** afforded an adduct that was desilylated without purification. The mixture of diols **22** so obtained was oxidized with freshly prepared Dess–Martin periodinane[23] to give dione **8** that decomposed on attempted isolation. However, when crude **8** was treated with sodium ethoxide in absolute ethanol, the tricyclic derivative **4** was formed smoothly (80% yield from diol **22**). It was pleasing to obtain this intermediate as beautiful crystals (mp 145–146 °C, hexane), after struggling through several stages with unstable oily intermediates.

The keto group in keto-ester **4** could be reduced selectively using several reducing agents to afford a readily separable mixture of alcohol **23** (Scheme 5) and its 5α-epimer. Lithium aluminum hydride in THF at -93 °C was the most favorable providing **23** in 77% yield (6.5:1 isomer ratio).

The hydroxy ester **23** was further reduced with $LiAlH_4$ at room temperature into the diol **24** which was oxidized selectively with $PhI(OAc)_2$-TEMPO (2,2,6,6-tetramethyl-1-pyridinyloxyl) following the procedure developed by Danishefsky et al. for a related diol.[4d,24] The hydroxy-aldehyde **25** obtained in 60–70% yield was acetylated with acetic anhydride in the presence of DMAP and triethylamine to give acetate **26**. Finally, removal of the ketal protecting group afforded heptemerone G (**2**). The HRMS, ^1H NMR (500 MHz, $CDCl_3$), IR and UV spectra confirmed the structure. The ^1H NMR spectrum (500 MHz) in DMSO-d_6 at 100 °C showed signals in full agreement with the reported data for heptemerone G.[3a] Interestingly, the synthetic material showed well-resolved signals in the ^1H NMR spectrum at room temperature.[25] However, broadening of some signals was observed in its ^{13}C NMR spectrum, presumably due to the conformational flexibility of this compound.[2a,3a] No spectrum of the natural compound was available for a direct comparison.

To complete the formal synthesis of guanacastepene A (**1**), diol **24** was dissolved in acetone and treated with a catalytic amount of *p*-toluenesulfonic acid. Compound **3** was obtained (crystalline solid, 95% yield) showing the expected HRMS spectrum and ^1H, and ^{13}C NMR spectra (500 and 125 MHz, respectively) in agreement with the reported spectra.[4d]

In summary, a versatile intermediate **4** for the synthesis of tricyclic 5-7-6 diterpenoids has been synthesized from 2-methylcyclopent-2-en-1-one in thirty three steps and in a 5.2% overall yield. This intermediate was employed in the first total synthesis of (±)-heptemerone G (**2**) and in a synthesis of the (±)-guanacastepene precursor **3**. Key features of the synthesis include an efficient new synthetic sequence for annulation of the 2-methylcyclopent-2-en-1-one fragment, an early introduction of the keto group at C-14, a Wharton-type reduction of hydroxy-epoxide **5** into the allylic alcohol **10**, protection of enolizable ketone **11** under mild conditions and a diastereoselective alkylation of the 'kinetic' enolate generated from **17**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.064.

References and notes

1. (a) Brase, S.; Encinas, A.; Keck, J.; Nising, C. F. *Chem. Rev.* **2009**, *109*, 3903–3990; (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3007; (c) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757–5821.
2. (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, S. *J. Am. Chem. Soc.* **2000**, *122*, 2116–2117; (b) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256–261.
3. (a) Valdivia, C.; Kettering, M.; Anke, H.; Thines, E.; Sterner, O. *Tetrahedron* **2005**, *61*, 9527–9532; (b) Kettering, M.; Valdivia, C.; Sterner, O.; Anke, H.; Thines, E. *J. Antibiot.* **2005**, *58*, 390–396.
4. (a) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399–2402; (b) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185–2188; (c) Lin, S. N.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188–2191; (d) Mandal, M.; Yun, H. D.; Dudley, G. B.; Lin, S. N.; Tan, D. S.; Danishefsky, S. J. *J. Org. Chem.* **2005**, *70*, 10619–10637.
5. Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025–7035.
6. Boyer, F. D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469–7472.
7. Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030–1042.
8. Mehta, G.; Pallavi, K.; Umarye, J. D. *Chem. Commun.* **2005**, 4456–4458.
9. Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, *128*, 13095–13101.
10. Miller, A. K.; Hughes, C. C.; Kennedy-Smith, J. J.; Gradl, S. N.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 17057–17062.
11. (a) Fang, X. J.; Tong, X. F. *Tetrahedron Lett.* **2010**, *51*, 317–320; (b) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 6614–6617; (c) Malik, C. K.; Ghosh, S. *Org. Lett.* **2007**, *9*, 2537–2540; (d) McGowan, C. A.; Schmieder, A. K.; Roberts, L.; Greaney, M. F. *Org. Biomol. Chem.* **2007**, *5*, 1522–1524.
12. Maifeld, S. V.; Lee, D. *Synlett* **2006**, 1623–1644.
13. (a) Michalak, K.; Michalak, M.; Wicha, J. *Tetrahedron Lett.* **2008**, *49*, 6807–6809; (b) Michalak, K.; Michalak, M.; Wicha, J. *Molecules* **2005**, *10*, 1084–1100.
14. Mehta, G.; Umarye, J. D.; Srinivas, K. *Tetrahedron Lett.* **2003**, *44*, 4233–4237.
15. (a) Logusch, E. W. *Tetrahedron Lett.* **1979**, *20*, 3365–3366; (b) Oikawa, Y.; Nishi, T.; Yonemitsu, O. *J. Chem. Soc., Perkin Trans. 1* **1985**, 7–17.
16. Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094–1111.
17. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019–6022.
18. (a) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137–6139; (b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447; (c) Ryu, I.; Murai, S.; Niwa, I.; Sonda, N. *Synthesis* **1977**, 874–876.
19. Wang, H.; Michalak, K.; Michalak, M.; Jiménez-Osés, G.; Wicha, J.; Houk, K. N. *J. Org. Chem.* **2010**, *75*, 762–766.
20. Luche, J.-L.; Rodriguez-Hahn, L.; Crabbe, P. *Chem. Commun.* **1978**, 601–602.
21. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
22. Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318–2320.
23. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
24. De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977.
25. The spectra of compounds **2**, **3**, **4** and **23** are included in the Supplementary data.