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# Non-natural Elemane as the "Stepping Stone" for the Synthesis of Germacrane and Guaiane Sesquiterpenes

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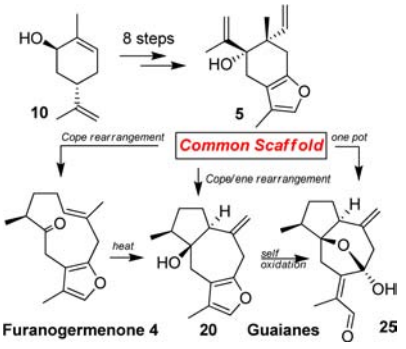
## ABSTRACT




**The synthesis of hydroxyelemane 5 from (*R*)-carvone and its utilization as a common synthetic scaffold to produce structurally diverse germacrane and guaiane sesquiterpenes are described. A highly enantio- and stereoselective biomimetic tandem oxy-Cope/ene rearrangement was used as the key reaction to access the 10-membered macrocyclic core of germacranes and the condensed 5−7 carbocycles of guaiane sesquiterpenes. Additionally, reactions of furanoguaianes under acidic or oxidizing reagents have been investigated, and preliminary results of these conversions are presented.**

Sesquiterpenes are plant-derived compounds often used in traditional medicine[1] against inflammation and cancer.[2] Comprising more than 5000 members,[3] sesquiterpene subfamilies provide an infinite synthetic challenge for organic chemists because of their complex molecular diversity[4] and rich biological profile.[5] Sesquiterpenoid-derived drugs from thapsigargin (**1**),[6] parthenolide (**2**),[7] and artemisinin (**3**)[8] (Figure 1) are now in clinical trials for an array of tumor cell lines. More specifically, parthenolide (**2**), a 6,12-germacranolide, was found to selectively reduce the growth of tumor cells[7] by its potent ability to inhibit an NF-$\kappa$B signaling pathway.[2] Yet, despite the promising array of biochemical behavior, the true clinical potential for these compounds and especially their isomeric 8,12-sesquiterpene analogues has barely been tapped. Taxonomically,

(1) Merfort, I. *Curr. Drug Targets* **2011**, *12*, 1560–1573.
(2) Hehner, S. P.; Heinrich, M.; Bork, P. M.; Vogt, M.; Ratter, F.; Lehmann, V.; Schulze-Osthoff, K.; Dröge, W.; Lienhard Schmitz, M. *J. Biol. Chem.* **1998**, *273*, 1288–1297.
(3) Schmidt, T. J. *Stud. Nat. Prod. Chem.* **2006**, *33*, 309–392.
(4) Series of Annual Reviews by: Fraga, B. M. *Nat. Prod. Rep.* **2011**, *28*, 1580–1610.
(5) (a) Ghantous, A.; Gali-Muhtasib, H.; Vuorela, H.; Saliba, N. A.; Darwiche, N. *Drug Discov. Today* **2010**, *15*, 668–678. (b) Picman, A. K. *Biochem. Syst. Ecol.* **1986**, *14*, 255–281.
(6) Christensen, S. B.; Skytte, D. M.; Denmeade, S. R.; Dionne, C.; Moller, J. V.; Nissen, P.; Isaacs, J. T. *Anticancer Agents Med. Chem.* **2009**, *9*, 276–294.
(7) Pajak, B.; Orzechowski, A.; Gajkowska, B. *Folia Histochem. Cytobiol.* **2008**, *46*, 129–135.
(8) Efferth, T. *Curr. Drug Targets* **2006**, *7*, 407–421.
(9) (a) Shibuya, H.; Ohashi, K.; Kawashima, K.; Hori, K.; Murakami, N.; Kitagawa, I. *Chem. Lett.* **1986**, 85–86. (b) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fukazawa, Y.; Okajima, T.; Fujise, Y. *Tetrahedron* **1987**, *43*, 5499–5520.
(10) (a) Schall, A.; Reiser, O. *Eur. J. Org. Chem.* **2008**, 2353–2364. (b) Andrews, S. P.; Ball, M.; Wierschem, F.; Cleator, E.; Oliver, S.; Hogenauer, K.; Simic, O.; Antonello, A.; Hunger, U.; Smith, M. D; Ley, S. V. *Chem.—Eur. J.* **2007**, *13*, 5688–5712. (c) Sun, L.; Shah, F.; Helal, M. A.; Wu, Y.; Pedduri, Y.; Chittiboyina, A. G.; Gut, J.; Rosenthal, P. J.; Avery., M. A. *J. Med. Chem.* **2010**, *53*, 7864–7868. (d) Yang, H.; Qiao, X.; Li, F.; Ma, H.; Xie, L.; Xu, X. *Tetrahedron Lett.* **2009**, *50*, 1110–1112. (e) Lee, E.; Lim, J. W.; Yoon, C. H; Sung, Y. S.; Kim, Y. K.; Yun, M.; Kim, S. *J. Am. Chem. Soc.* **1997**, *119*, 8391–8392.

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8,12-members represent half of the components isolated from Nature. Although numerous synthetic strategies exist in order to access the carbocyclic cores of 6,12-germacranolides[9] and 6,12-guaianolides,[10] rather few references appear in the literature for the synthesis of isomeric 8,12-germacranolides and 8,12-guaianolides,[11] and even fewer study their biological profile.

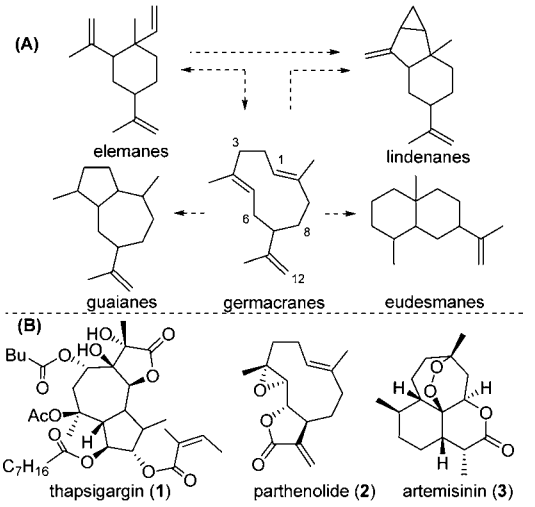



**Figure 1.** (A) Biosynthetic correlation of sesquiterpenoids and (B) selected examples of biological active sesquiterpenoids.

Intrigued by the structural infinity and the possible biological activity of these sesquiterpenes, our group initiated a research effort to discover a novel and efficient synthetic route to 8,12-sesquiterpene motifs. The rich diversity of this class is well delineated by the existence of germacrane, guaiane, pseudoguaiane, elemane, eudesmane, and lindenane subfamilies (Figure 1).[4] In a hypothetical carbocyclic sesquiterpene biosynthetic pyramid, germacranes lay on top accounting for all the presented diversity. However, the exact nature and sequence of these biosynthetic steps are currently unknown, and their investigation remains a challenging task.[12] On the basis of this biosynthetic hypothesis, furanogermenone (**4**)[13] was envisioned as an ideal common synthetic scaffold to access the rich diversity of the 8,12-subfamily. Retrosynthesis of **4** was designed through an nonreversible oxy-Cope rearrangement of the non-natural elemane compound **5**, avoiding the known equilibration between germacrane and elemane pair which predominantly produces the elemane component.[14] Elemane **5** could then be disconnected to carveol **8** utilizing an array of sequential oxidation and alkyl addition steps (Figure 2).

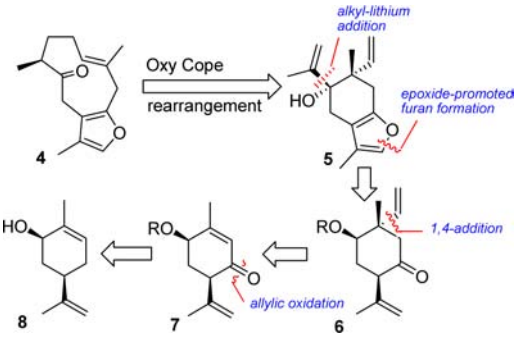



**Figure 2.** Initial retrosynthetic plan for the synthesis of furanogermenone (**4**).

Despite the direct accessibility to the *syn*-carveol **8**,[15] its oxidation to the ketone **7** was perceived to be rather problematic. Thus, when it was allowed to be oxidized under a number of reported conditions (chromium pyrazole,[16] TEMPO,[17] PCC,[18] PDC,[18b] *t*-BuOOH in the presence of metals,[19] etc.), an inconsistent, inseparable mixture of oxidized products was observed in very low yields (5−12%). After extended experimentation, it was found that when *anti*-carveol **10**[20] was used instead of **8** in reaction under singlet oxygen conditions,[21] a 2:1 diastereoisomeric mixture of α- and *β*-hydroxylated products was obtained, which after selective protection of secondary alcohols with pivaloyl group and chromatographic purification led to the desired compound **11** in 39% overall yield (Scheme 1). Hydroxyl migration of the unprotected tertiary alcohol followed by direct oxidation with PCC[22] afforded the α,*β*-unsaturated ketone **12**. 1,4-Conjugated addition of vinyl group, promoted by copper iodide,[23] produced the alkylated product **13** in high diastereoselectivity (ratio 12:1) favoring the *syn*-orientation between the methyl and the

(11) (a) Tanis, S. P.; Robinson, E. D.; McMills, M. C.; Watt, W. *J. Am. Chem. Soc.* **1992**, *114*, 8349–8362. (b) Valot, G.; Garcia, J.; Duplan, V.; Serba, C.; Barluenga, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 5391–5394.

(12) Miller, D. J.; Allemann, R. K. *Nat. Prod. Rep.* **2012**, *29*, 60–71.

(13) Shibuya, H.; Yamamoto, Y.; Miura, I.; Kitagawa, I. *Heterocycles* **1982**, *17*, 215–218.

(14) (a) Jain, T. C.; Banks, C. M.; McCloskey, J. E. *Tetrahedron Lett.* **1970**, *11*, 841–844. (b) Rosselli, S.; Maggio, A.; Raccuglia, R. A.; Bruno, M. *Eur. J. Org. Chem.* **2003**, 2690–2694.

(15) Garver, L.; Van Eikeren, P. *J. Org. Chem.* **1976**, *41*, 2273–2274.

(16) Sakagami, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1393–1398.

(17) (a) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *Org. Lett.* **2008**, *10*, 4715–4718. (b) Vatele, J.-M. *Tetrahedron* **2010**, *66*, 904–912.

(18) (a) Kuroda, C.; Nakamura, T.; Hirota, H.; Enomoto, K.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 146–151. (b) Fousteris, M. A.; Koutsourea, A. I.; Nikolaropoulos, S. S.; Riahi, A.; Muzart, J. *J. Mol. Catal. A-Chem.* **2006**, *250*, 70–74. (c) Dauben, W. G; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587–3592. (d) Nakayama, M.; Shinke, S.; Matsushita, Y.; Ohira, S.; Hayashi, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 184–185.

(19) (a) Zhao, Y.; Yueng, Y.-Y. *Org. Lett.* **2010**, *12*, 2128–2131. (b) Catir, M.; Kilic, H. *Synlett* **2010**, *9*, 1319–1322. (c) Yang, M.; Peng, Q.-R; Lan, J.-B.; Song, G.-F.; Xie, R.-G. *Synlett* **2006**, 2617–2620. (d) Salvator, J. A. R.; Silvestre, S. M. *Tetrahedron Lett.* **2005**, *46*, 2581–2584. (e) Miller, A. R.; Li, W.; Hymphrey, R. G. *Tetrahedron Lett.* **1996**, *37*, 3429–3432. (f) Shing, T. K. M.; Yeung, Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149–3151.

(20) (a) Salvador, J. A. R.; Leitão, A. J.; L.Sa e Melo, L.; Hanson, J. R. *Tetrahedron Lett.* **2005**, *46*, 1067–1070. (b) The enantiomeric excess of compound **10** was calculated to be 72%. This material was chirally resolved to 93% ee.

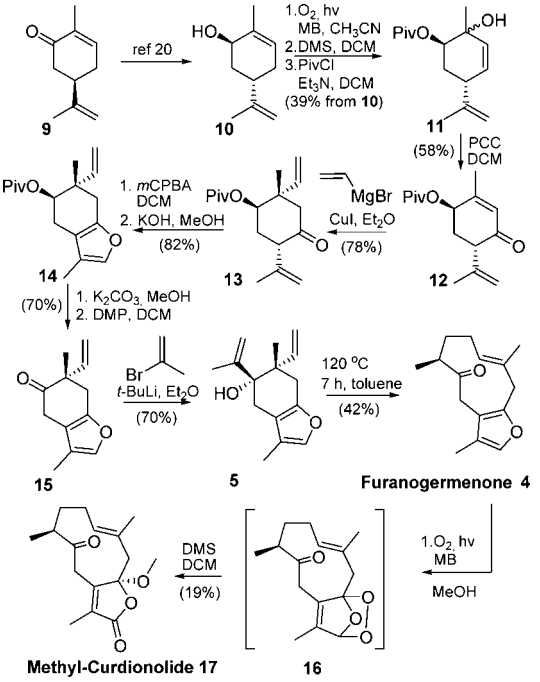
(21) Alberti, M. N.; Orfanopoulos, M. *Synlett* **2010**, 999–1026.

(22) Fernández-Mateos, A.; Ramos Silvo, A. I. R.; Rubio González, R.; Simmonds, M. S. J. *Tetrahedron* **2006**, *62*, 7809–7816.

(23) Lipshutz, B. H. Organocopper Chemistry. In *Organometallics in Synthesis: A Manual*, 2nd ed.; Schlosser, M., Eds.; Wiley & Sons Ltd.: West Sussex, 2002; p 762.

pivaloate group. Epoxidation with the strict use of one equivalent of *m*-CPBA,[24] followed by subsequent epoxide cleavage in methanolic KOH, provided furan compound **14**.[25] Deprotection of pivaloyl group under basic conditions led to the free alcohol which was readily oxidized by DMP to the respective ketone **15**.[26] Finally, nucleophilic addition of 2-propene to the ketone was accomplished by using 2-bromopropene with *t*-BuLi[27] providing diastereoselectively (dr = 20:1) isomer **5** in 70% yield.

**Scheme 1.** Total Syntheses of Furanogermenone (**4**) and Its Oxidized Congener **17**




When compound **5** was heated to 120 °C, a thermal oxy-Cope reaction initiated accomplishing, to our delight, the first total synthesis of furanogermenone **4** in 42% yield and high enantioselectivity (87% ee)[28] along with unreacted starting material **5**. Furanogermenone **4** was readily oxidized under singlet oxygen conditions to provide the methylated congener of curdionolide A[29] (**17**) albeit in low yield. Interestingly, when **4** was insistently heated to 140 °C for 12 h in toluene, a highly stereoselective ene-type reaction was observed affording furan−guaiane **20** as a single isomer in 58% yield along with 8% of compound **22** (Figure 3 and Scheme 2).

Inspired by the elegant work of Barriault and his group on tandem oxy-Cope/ene reactions,[30] we aimed to explore the ability of elemane **5** to serve as a common synthetic scaffold to the synthesis of diverse guaiane structures. Thus, when **5** was heated to the higher temperature of 140 °C for prolonged reaction times the same products **20** and **22** were observed in 40% and 8% yields, respectively.

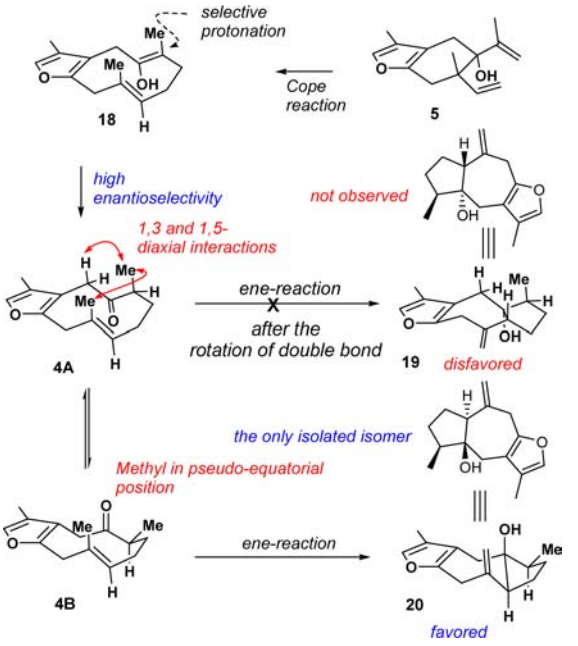



**Figure 3.** Transition states in tandem oxy-Cope/ene reaction.

Comparison of the absolute and relative stereochemistry of the two newly formed stereocenters in **20** and **22** with those present in natural guaiane components shows their perfect matching, pointing out a potential discovery of a biomimetic transformation. The high enantio- and diastereoselectivity observed in oxy-Cope and ene reaction can be rationalized through the transition states shown in Figure 3.

Specifically, heating compound **5** rearranges the six-membered ring to the 10-membered enol carbocycle **18**. The macrocycle exists exclusively in conformation **18** due to the energetically demanding rotation of tetrasubstituted enol moiety inside the macrocycle (Figure 3).[27] Selective protonation from the least hindered face of **18** delivers **4A** in high enantioselectivity compared to the starting carveol **10**. The initially formed conformer **4A** directs the methyl group axially, leading to disfavored 1,3- and 1,5-diaxial interactions. In order for the ene reaction to proceed, the

(24) Fuchs, S.; Zinn, S.; Beck, T.; Mosandl, Á. *J. Agric. Food Chem.* **1999**, *47*, 4100–4105.

(25) Furan moieties incorporated in these systems were found to be prone to uncontrollable oxidations thus, special care was given that all molecules bearing furan functionality to be handled in the absence of light and oxygen.

(26) Yick, C.-Y.; Wong, H. N. C. *Tetrahedron* **2001**, *57*, 6935–6940.

(27) Sauer, E. L. O.; Hooper, J.; Woo, T.; Barriault, L. *J. Am. Chem. Soc.* **2007**, *129*, 2112–2119.

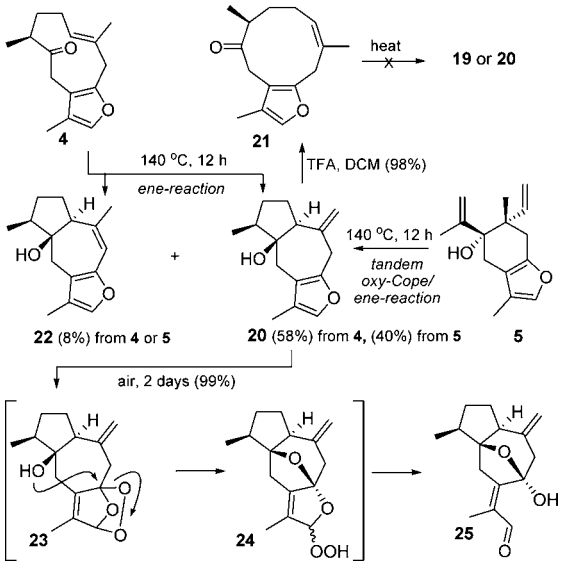
(28) The enantiomeric excess was calculated based on the optical rotation of the natural component. The enantiomeric excess was further supported by the observed $^1$H NMR diasteromeric ratio of the SAMP hydrazone of compound **25**.

(29) Lou, Y.; Zhao, F.; Wu, Z.; Peng, K.-F.; Wei, X.-C.; Chen, L.-X.; Qiu, F. *Helv. Chim. Acta* **2009**, *92*, 1665–1672.

(30) For excellent studies on the topic: (a) Sauer, E. L. O.; Barriault, L. *J. Am. Chem. Soc.* **2004**, *126*, 8569–8575. (b) Barriault, L.; Deon, D. H. *Org. Lett.* **2001**, *3*, 1925–1927. (c) Arns, S.; Lebrum, M.-E.; Grisé, C. M.; Denissova, I.; Barriault, L. *J. Org. Chem.* **2007**, *72*, 9314–9322. (d) Arns, S.; Barriault, L. *Chem. Commun.* **2007**, 2211–2221. (e) Hooper, J.; Sauer, E. L. O.; Arns, S.; Woo, T. K.; Barriault, L. *Chem.—Eur. J.* **2010**, *16*, 14124–14130.

methyl group should be positioned favorly axial against the keto group either by rotating the double bond or through conformer **4B**. Both of them can undergo an ene-type reaction. Reaction through rotation of the double bond still directs the methyl group to an axial orientation, whereas in **4B** the methyl group is positioned in a pseudoequatorial position, thus favoring **20** over **19**.

**Scheme 2.** Elemane **5** as a Common Scaffold To Access Diverse Sesquiterpenoids




Compound **20** can serve in its own right as an excellent precursor for the synthesis of natural-like sesquiterpene scaffolds. Thus, when it was directly treated with TFA, a retro-ene reaction led selectively to the formation of melambolide core producing compound **21** in quantative yield (Scheme 2). Following our mechanistic hypothesis for the ene-reaction, the structurally locked melambolide **21** is not expected to permit the favorable orientation between the ketone and the methyl group for the initiation of the reaction. Indeed, when compound **21** was heated between 140 and 200 °C, no formation of guaiane **19** or **20** was observed even after prolonged reaction times.

Furanoguaiane **20** was also found to be extremely sensitive upon standing. Thus, leaving a sample of **20** in deuteriurated chloroform for 2 days at 5 °C led to the selective formation of lactole product **25** through its spontaneous oxidation (Scheme 2). Attempts to rationalize this transformation revealed a direct correlation of the free tertiary alcohol and the ability of guaiane to be oxidized. This oxidation was found to be accelerated on silica gel while it is prohibited in the complete absence of molecular oxygen. Based on these facts, we assumed that a hydroxyl promoted delivery of molecular oxygen initiates the reaction on the furan ring producing intermediate **23**. Decomposition of the endoperoxide to hydroperoxide with subsequent intramolecular trap of the α-position of the furan by the secondary alcohol leads to intermediate **24** and finally to compound **25**.

In conclusion, there is a high demand for reaction sequences that lead to diverse structures of biologically interesting scaffolds. The present study illustrates a highly efficient route to the synthesis of divergent germacrane, guaiane and furomelampolide natural core structures emerging from the different cyclization modes of the common non-natural elemane scaffold **5**. The syntheses of the three distinct classes of sesquiterpenes described above have been evolved relying either on the development of a highly enantioselective oxy-Cope reaction for the construction of germacranes or its advancement to the complete diastereoselective oxy-Cope/ene reaction cascade to access guaiane structural motifs. Reactions that direct guaiane **20** either to furomelampolide **21** through an acidic retro-ene reaction or to the congested **25** by its spontaneous oxidation have also been explored shedding light upon potential existing biosynthetic transformations. The common non-natural elemane scaffold **5** is expected to be proven applicable in the synthesis of other diverge members of the sesquiterpene family such as lindenanes, eudesmanes, pseudoguaianes, etc., providing a reliable entry to prevalidated libraries of sesquiterpenoids. Further studies on these directions are currently in progress and will be communicated in due course.

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**Supporting Information Available.** Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.