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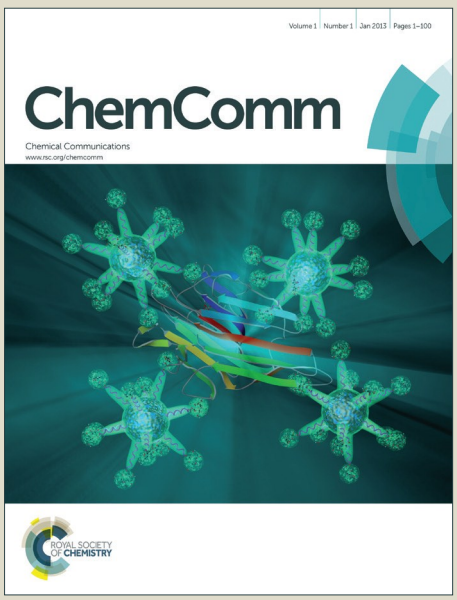

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Divergent pathways to furosesquiterpenes. First total syntheses of (+)-Zedoarol and (*Rac*)-Gweicurculactone†

Elissavet E. Anagnostaki, Vera P. Demertzidou and Alexandros L. Zografos*

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A non-natural hydroxy-elemane was found amenable to divergent transformations producing either polyunsaturated guaianes under basic oxygen free conditions or oxidized furogermacranes when anionic oxy-Cope reaction quenched by an oxidant is employed. Based on these findings the first total syntheses of zedoarol and gweicurculactone is reported.

Sesquiterpene lactones are among the highest cytotoxic compounds found in nature.[1] In contrast to their impressive biological properties as anticancer and anti-inflammatory agents as documented from the increased clinical trials[2] the development of reliable synthetic protocols for constructing their rich molecular diversity is not yet an effortless task.[3] A variety of challenges have to be addressed during their synthesis and/or isolation which are grounded to their usual thermal and acidic instability and their notoriously oxidizable carbocyclic character.

Moved by our longstanding interest in terpene chemistry, we initiated a program focused on the divergent synthesis of furosesquiterpenes as a convenient first step entry to the biological intriguing sesquiterpene lactone motif. Recently, we have reported an efficient synthesis of the 10-member macrocycle furanogermenone (**2**), based on the thermal oxy-Cope reaction of the non-natural elemane **1** (Figure 1).[4] Due to its cost efficient accessibility from (*R*)-carvone and to its easily scaled up to several grams protocol, compound **1** was recognized as an ideal common scaffold[5] for accessing the rich diversity presented in furosesquiterpenes.

Wishing to explore further the ability of **1** to create different sesquiterpene motifs, we tested its reaction under basic conditions in logic of optimizing our reported furanogermenone synthesis through its milder anionic oxy-Cope variant. To our delight, when KHMDS in deoxygenated THF at 75 °C conditions were applied, the desired 10-

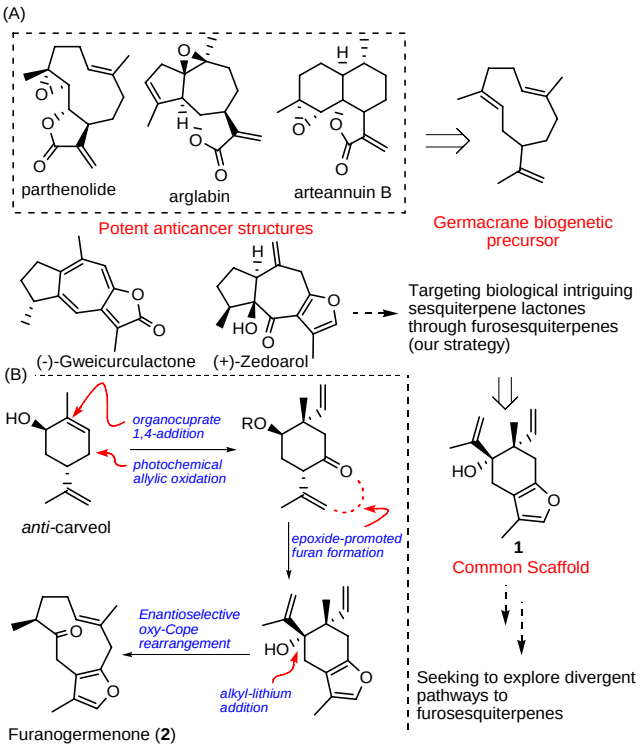
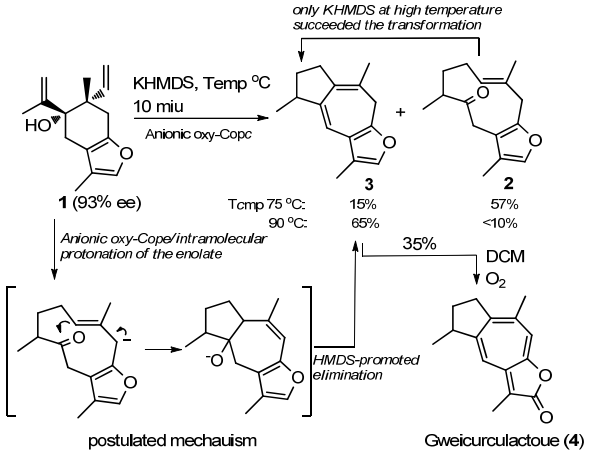
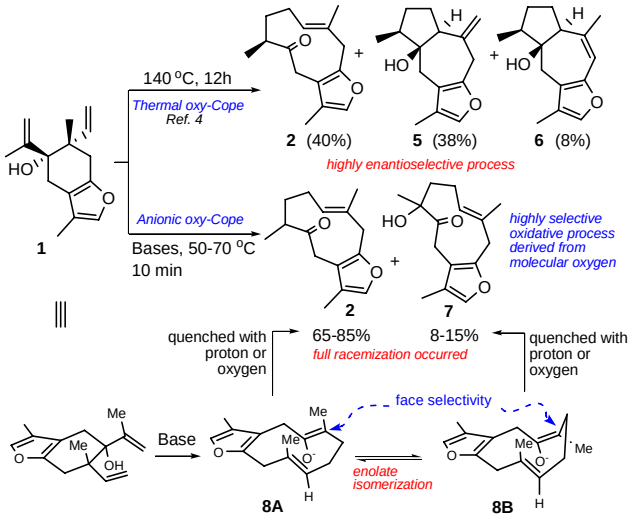


Figure 1 (A) Some important sesquiterpene lactones and their biogenetic precursor; (B) Our previous reported method to access furanogermenone (**2**).

member macrocycle **2** was observed by TLC after 10 min reaction, along with a new less polar spot (Scheme 1). NMR spectroscopy of the crude reaction mixture indicated furanogermenone **2** and an unknown guaiane compound in an almost 5:1 ratio.



Scheme 1 Synthesis of Guaiane **3** and Completion of the Total Synthesis of Gweicurculactone (**4**).



Scheme 2 Thermal vs. Anionic oxy-Cope reaction of **1**

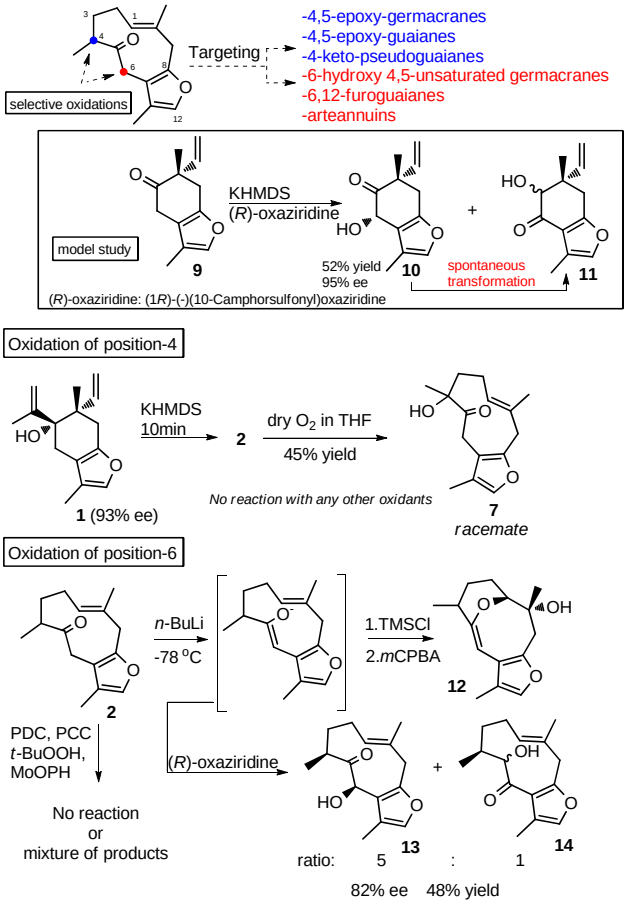
Further optimization of reaction conditions to 90 °C led to the isolation and characterization of racemic guaiane diene **3** in 65% yield after chromatographic purification with only traces of furanogermenone (**2**) which also obtained as racemate. Spontaneous aerobic oxidation of guaiane **3** in DCM completed the first total synthesis of racemic gweicurculactone (**4**) in 35% yield.[6] Interestingly, different bases even at the same or higher temperatures led only to the expected anionic oxy-Cope to provide compound **2** in high yields. What is more, when purified furanogermenone (**2**) was tested for its ability to be transformed to guaiane **3**, under basic conditions, only KHMDS at high temperatures, succeeded to make the conversion, revealing the notorious character of the macrocycle in different reaction conditions. Although still under investigation, this transformation is believed to invoke an initial generation of an anion at the double activated allylic-benzylic position, through intramolecular protonation of the formed enolate, followed by an intramolecular attack to the carbonyl to provide the guaiane core (Scheme 1). Tertiary alcohol activation by HMDS probably offers the conditions for elimination to the final product.

On the other hand, anionic oxy-Cope reaction of **1** with several bases (KH/65 °C, DBU/65 °C, Et_3N/65 °C, etc.) provided high yields (65-85%) of racemic furanogermenone (**2**). In most of these cases, a more polar spot was observed by TLC indicating the spontaneous oxidation on the furogermacrane core under the applied conditions. In sharp contrast, thermal oxy-Cope reaction did not provide oxidation products but instead under prolonged heating conditions the reaction proceeded to an ene-reaction on the germacrane core providing the expected guaiane analogues **5** and **6** (Scheme 2).[4]

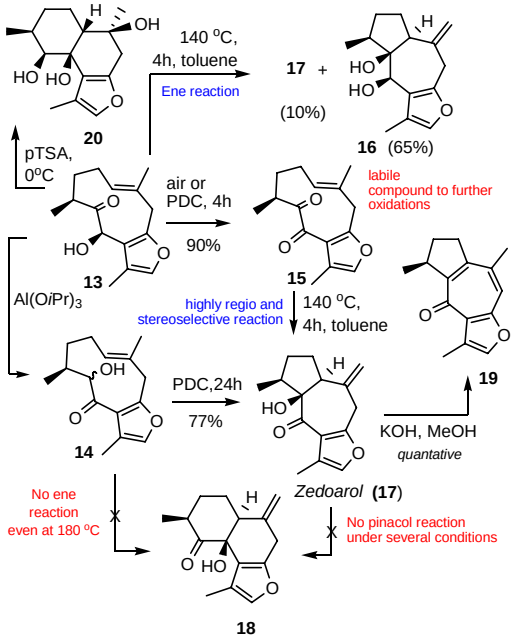
Although low in yield, these spontaneous oxidations observed during anionic oxy-Cope pathway are highlighting the ability of germacrane core to be oxidized providing more complex sesquiterpenoids. Wishing to explore further this possibility, the reaction mixture was carefully purified and analyzed. Confirming our predictions anionic oxy-Cope reaction provided selectively 8-15% of compound **7** representing the direct addition of molecular oxygen to the formed enolate **8A** (Scheme 2). Unfortunately, both compound **7** and synthetic furanogermenone (**2**) were lacking of optical activity. This drawback of anionic oxy-Cope protocol can be rationalized by the isomerization of the enolate olefin (**8A**-**8B**) rather than the direct rotation of the opposed alkene inside the macrocycle (Scheme 2). Barriault and his colleagues witnessed the same behavior when specific macrocycles were involved in anionic oxy-Cope/ene reaction.[7] Although, different bases seems to contribute in the extend of the racemization process none of the tested bases were able to produce high enantioselectivities. Besides this weakness, anionic oxy-Cope provided not only a high yielding entry into the germacrane core of furanogermenone but also a regioselective access into its oxidized congener **7**. Based on these results, extended experimentation was initiated to achieve selective oxidations on both sides of the carbonyl group of **2** aiming to the construction of its maximum diversity (Scheme 3).

Optimized conditions to achieve tertiary hydroxylation was achieved by running anionic oxy-Cope reaction in the presence of oxygen to provide finally 45% yield of the desired product **7**.[8] However, hydroxylation positioned α-to the furan was proved to be much more challenging. Early work on the cyclohexane model **9** has revealed that introduction of hydroxy group α-to the furan (**10**) results spontaneous tautomerization providing both β-hydroxy isomers of the α-keto compound **11** in 1:1 ratio (Scheme 3).[9]

Having this in mind, we initiated our survey by neutral or mild acidic oxidants to achieve our goal. Several of these oxidants (PDC, PCC, t-BuOOH) failed to provide clean transformations due to the parallel oxidations of the furan ring and/or allylic oxidations. Moreover, reaction of **2** under Rubottom oxidation condition[10] resulted the formation of compound **12** from the intramolecular attack of enol moiety to the distal epoxide. On the other hand, basic conditions as KHMDS and LiHMDS at -50 °C quenched by oxaziridines or MoOPH provided only traces of the desired product.[11] On the contrary, kinetic control of the enolate by utilizing *n*-BuLi at -78 °C quenched by (*R*)-oxaziridine provided compounds **13** and **14** in a ratio of 5:1 and 82-85% ee for compound **13** (Scheme 3).[12] Although, compound **13** was found much more stable to isomerization than our model compound **10**, resulting at much less extend diastereoisomers **14**, it was prone to further oxidations providing labile diketone compound **15**, even upon



Scheme 3 Selective Oxidations of Furanogermenone (**2**).



Scheme 4 Total Synthesis of Zedoarol (**17**), Analogues **16** and **19** and cadinane **20**.

standing. Compound **13** finally, can be also cleanly transformed to diastereomeric mixture of compounds **14** upon treatment with Al(O*i*Pr)$_3$ in high yield (Scheme 4).

With the oxidized derivatives of furanogermanone **13**-**15** in hands, we tested their ability to further transform into natural substances of furosesquiterpenes. Thus, when compound **13** was heated at 140 °C in toluene, compound **16** was isolated along with minor amounds of the natural product zedoarol (**17**)[13] (Scheme 4). On the other hand, diketone **15** under the same heating conditions afforded zedoarol (**17**) in 80% yield, in an entirely regioselective and stereoselective reaction. Although, diastereoisomers of **14** failed to react even at higher temperatures (>180 °C) in an analogous six member ene-type reaction, in order to produce cadinane **18**, it can also be transformed to zedoarol (**17**) under mild conditions by applying PDC oxidation conditions at room temperature. Attempts to isomerize zedoarol (**17**) to cadinane **18**, in a pinacol-type reaction, failed under several acidic or basic conditions but instead provided only compound **19** when KOH in methanol was applied.

In sharp contrast to these attempts, compound **13** was found amenable to further transformations when acidic conditions were applied. Thus, allowing **13** to react with p-toluenesulfonic acid (pTSA) resulted the formation of cadinane compound **20**, resembling the core of arteannuin B, in high yield.

Conclusions

In conclusion, the first total syntheses of zedoarol (**17**) and gweicurculactone (**4**) have been achieved through common intermediate **1**, by utilizing highly selective oxidative transformations. Interestingly, novel access to cadinane core **20** has been elaborated by the use of the oxidized germacrane **13**. Further studies following these directions are underway in our laboratory in order to reveal missing biosynthetic links correlating different furosesquiterpene cores and will be communicated in due course.

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Notes and references

Aristotle University of Thessaloniki, Department of Chemistry, Laboratory of Organic Chemistry, University Campus, 54124 Thessaloniki, Greece.

† Electronic Supplementary Information (ESI) available: Experimental details, ^{1}H, ^{13}C and 2D NMR spectra along with comparison of natural and synthetic substances. See DOI: 10.1039/c000000x/

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