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Partial Synthesis of Germacranolides with Pyran and Furan-Type Rings

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Abstract: Pathways to synthesize germacranolides with ether bridges between C_1 and C_5 or C_3 and C_{10} were described. A joint precursor was prepared using a readily available and inexpensive compound as starting material. The key step in the preparation of dihydropyranone-germacranolides proved to be a one-pot procedure involving several transformations, induced by the iodotrimethylsilane/acetonitrile system.

Several germacrane-skeleton sesquiterpene lactones with ether bridges linking different parts of the molecule have been isolated from natural sources.[1] Oxygen atoms has been observed linking C_1 and C_4, C_1 and C_5, C_2 and C_5, C_3 and C_{10}, and C_5 and C_{10}. Elsewhere[2] we have reported the intramolecular cyclization of a suitable hydroxygermacradiene to give Chapliatrin-type germacrenes[3] containing an ether bridge between C_5 and C_{10} (Fig. 1).

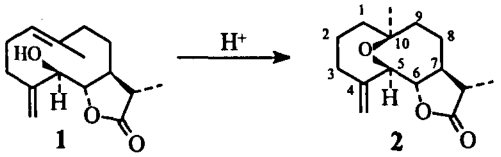
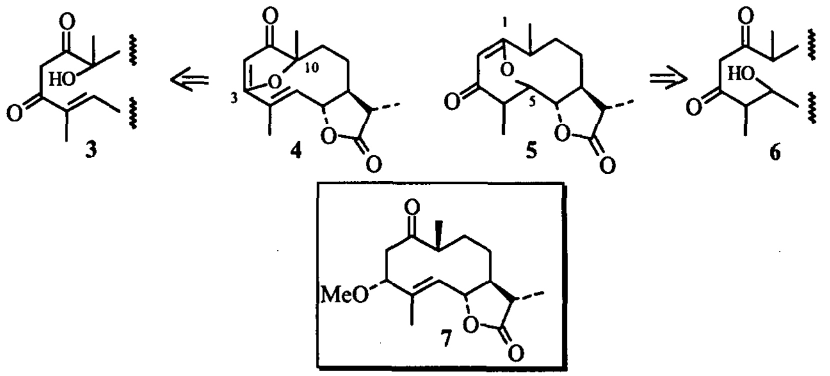


Fig. 1

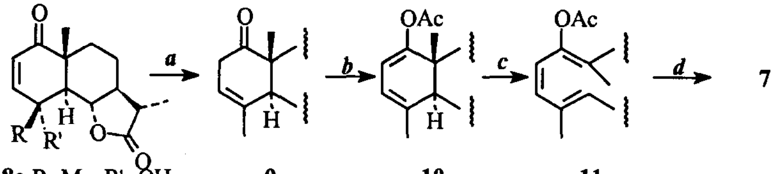
This paper deals with the synthesis of germacrenes containing furan (4) and pyran (5) rings. A number of sesquiterpenes lactones are germacranolides with a furan ring in their framework,[4] and although fewer have a pyran ring, nonetheless this type of compound does occur.[5] Both types of compound are very interesting from the chemotaxonomical point of view.



Scheme 1

Our approach to the synthesis was based on the idea that naturally-occurring compounds of this class can be formed *in vivo,* via the intramolecular hemiketalization of appropriate hydroxidiketones such as **3** and **6** (Scheme 1), followed in some cases by dehydration. We envisioned **7** as the precursor for both series of compounds, since it has the functional groups at C_1 and C_3, and the C_5 oxygen atom required for **6** to be synthesized, can easily be introduced if the double bond already present is epoxidized.

The synthesis of **7** was as set out in Scheme 2. Vulgarin **8a**, an eudesmanolide isolated on a multigram scale from the abundant endemic Canary Island plant, *Artemisia canariensis Lee,*[6] was transformed in two steps to the enol acetate **10** (67% yield) ;**10** was irradiated at -30ºC under argon atmosphere (253 nm, MeOH, 9h),[7] and, after quenching with KOH-MeOH at -30ºC and purification, gave **7** in 38% yield, together with **8a** + **8b** (27%) and **8c** (14%).



8a R=Me; R'=OH
8b R=OH; R'=Me
8c R=H; R'=Me

9

10

11

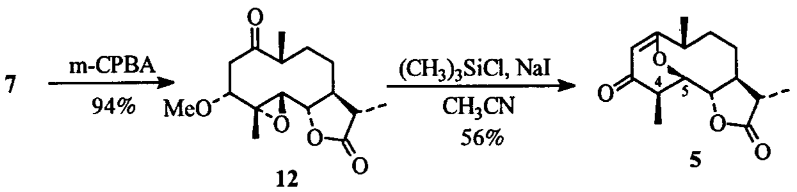
Scheme 2

Reagents: a) Zn, AcOH, Δ (85%); *b)* Isopropenyl acetate, p-TsOH (95%); *c)* hν, -30ºC, MeOH; *d)* KOH, MeOH, -30ºC to RT (38% **7** , 2 steps).

The structure of **7** was established from its spectroscopic data,[8] and is consistent with a Michael addition of methanol to the dienone obtained when the enol acetate **11** was saponified. The stereochemistry at C_3 was assigned as depicted by NOE studies and is in good agreement with molecular mechanics calculations,[9] which show that the α is the less hindered face of the intermediate dienone in the lowest energy conformation.

To obtain germacrenes with an ether bridge between C_1 and C_5, **7** must be transformed into the intermediate hydroxydiketone **6** by introduction of a hydroxyl group at C_5 and demethylation of the C_3 methoxy group, followed by oxidation to a ketone. It is known that iodotrimethylsilane produces mild dealkylation of methyl ethers,[10] and causes epoxide opening,[11] and so it was decided to see if these two transformations could be carried out in a one-pot process. Epoxidation of **7** with m-chloroperbenzoic acid, yielded **12** (94%), in which the epoxide was formed from the most accessible side of the double bond, in the most stable conformer in accordance with molecular mechanics. Compound **12** was then subjected to the action of the iodotrimethylsilane generated in acetonitrile *in situ* .[12] After two hours, the reaction was stopped and purified by column chromatography, affording **5** as the major product (56%). To our surprise, not only did the two expected transformations take place, but also several other processes, leading at once to the target compound. This set of transformations can be attributed to the electrophilic nature of the iodotrimethylsilane/acetonitrile complex,[12] which acts as a Lewis acid, opening the epoxide in a Markovnikov sense, followed by (or simultaneous with) a [1,2]-hydride shift and demethylation to give an hydroxidiketone, which undergoes hemiketalization and dehydration in the acidic media, resulting in the formation of **5** (Scheme 3).

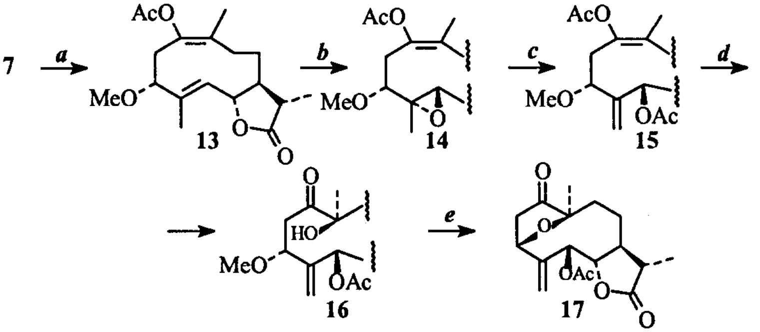
The structure of **5** was deduced from its spectroscopic data,[13] and the configuration at C_4 was assigned as shown on the basis of the coupling constant value $J_{4,5}$ =1.2Hz, which is in good agreement with that of the coupling constant on the lowest energy conformer for this structure according to molecular mechanics (0.7Hz). The corresponding value for the most stable conformer on the C_4 α epimer is 5.8 Hz, and clearly indicates that epimerization to the more stable β isomer took place during the reaction.



Scheme 3

This five-step process, using a very abundant and inexpensive product as starting material, constitutes a very simple way to gain access to this class of compounds, and can be extended to the preparation of products with similar functional groups.

For a germacrene skeleton with a C_3/C_{10} oxygen bridge, an oxygen atom was needed at C_{10}, and the strategy followed was to introduce this atom by epoxidation of the enol acetate **13** prepared from **7** (Scheme 4). To avoid undesired side reactions arising from the Δ^4 double bond in the later stages of the synthesis, compound **13** was selectively epoxidized and the epoxide transformed into an allylic alcohol which was acetylated to give **15**. The stereochemistry of the enol acetate group was established as E through a ROESY experiment on **13** which showed a *cis* relationship between the C_{10} methyl and the acetate group. The disposition of the groups on the lowest energy conformer of **15** as predicted by molecular mechanics, allowed selective epoxidation of the enol acetate to take place through the *re,si* face, and after treatment with HCl, the hydroxyketone **16** was obtained in an 86% yield.



Scheme 4

Reagents: *a*) Ac_2O, p-TsOH, Δ, (70%); *b*) m-CPBA, CH_2Cl_2 (76%); *c*) i: TMSCl, NaI, CH_3CN, (48%); ii: Ac_2O, Py (98%); *d*) i: m-CPBA, CH_2Cl_2 (86%) ; ii: $HCl_{(g)}$, MeOH, (87%); *e*) TMSCl, NaI, CH_3CN, Δ,(40%) or Ph_3CBF_4,(76%).

The subsequent steps involved the demethylation of the C_3 methoxy group on **16** and oxidation to a hydroxydiketone. To achieve this, **16** was treated with iodotrimethylsilane under the conditions described above. After several hours at room temperature, no change was observed but after refluxing for 2.5 hours, **17** was obtained in low yield (40%).[14] As no demethylated product had been obtained, we decided to carry out a direct oxidation of the methoxy group, using triphenylcarbenium tetrafluoroborate to remove the hydride.[15] However, after treatment of **16** with this reagent, only **17** was obtained in an acceptable yield (76%). The formation of this compound can be explained if it is accepted that both, iodotrimethylsilane/acetonitrile and triphenylcarbenium tetrafluoroborate, act as Lewis acids, favouring the attack of the C_{10} hydroxyl on C_3, while the C_3 methoxy act as leaving group, forming the furan ring. The transformation of this skeleton into known natural products of interest is currently under way.

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13. ^1H-NMR data for **5**, (δ, $CDCl_3$, 200 MHz): 5.51 (s, 1H, H_2), 4.89 (dd, J=6.5 and 1.2 Hz, 1H, H_5), 4.41 (dd, J=10.2 and 6.4 Hz, 1H, H_6), 1.38 (d, J=7.5 Hz, 3H, C_4-Me), 1.16 (d, J=6.7 Hz, 3H, C_{10}-Me), 1.13 (d, J=6.9 Hz, 3H, C_{11}-Me).
14. ^1H-NMR data for **17**, (δ, C_6D_6, 400 MHz): 5.49 (d, J=8.5 Hz, 1H, H_5), 4.98 (s, 1H, H_{15}), 4.93 (t, J=8.8 Hz, 1H, H_6), 4.69 (X part of ABX system, J_{AX}=1.3, J_{BX}8.8 Hz, 1H, H_3), 4.57 (d, J=1.7 Hz, 1H, $H_{15'}$), 2.20 (AB part of ABX system, J_{AB}=18.4 Hz, J_{AX}=1.8 Hz, J_{BX}= 8.8 Hz, 2H, H_2 and $H_{2'}$), 1.75 (s, 3H, OAc), 1.62 (c, 1H, H_{11}), 1.11 (s, 3H, C_{10}-Me), 0.95 (d, J=7.1 Hz, 3H, C_{11}-Me).
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