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New Pathways in Transannular Cyclization of Germacrone [Germacra-1(10),4,7(11)-trien-8-one]: Evidence Regarding a Concerted Mechanism

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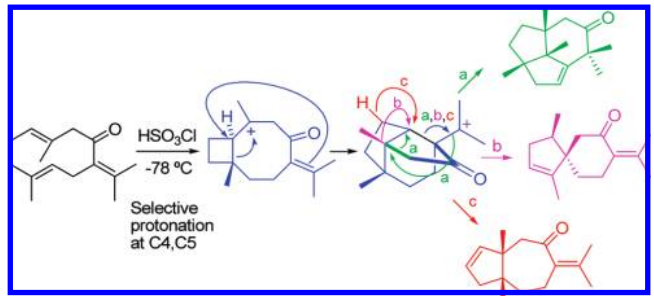
ABSTRACT



The transannular cyclization of germacrone with HSO_3Cl at −78 °C by means of a concerted and regioselective mechanism gives rise to a bicyclo[6.2.0]decan-2-ylium intermediate ion, which evolves to unusual skeletons through subsequent cyclization and Wagner−Meerwein rearrangements. This novel germacra-1(10),4-diene cyclization could suggest the existence of a new biosynthetic pathway to sesquiterpenes.

Germacra-1(10),4-dienes are considered key intermediates in the biosynthesis of numerous skeletons of cyclic sesquiterpenes.[1] Owing to their biosynthetic involvement, various natural germacra-1(10),4-dienes and their corresponding monoepoxides have been used to study transannular cyclizations and to develop biomimetic syntheses that give rise mostly to eudesmanes or guaianes.[2] In all of these cyclizations, it is generally accepted that the regio- and stereochemical course of the process depends upon the spatial arrangement of the cyclodecadiene derivative.[3]

Germacrone (**1**) is a sesquiterpene found widely in plants[4] with applications for the perfume industry.[4b] The concept of diversity-oriented and biomimetic organic synthesis[5] and the functionality present in **1** indicate that this molecule may be a suitable source of a wide variety of more complex molecules. Despite the range of possibilities, its chemistry has not been thoroughly studied.[6] We therefore decided to

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explore the chemical behavior of germacrone (**1**) in transannular cyclizations.

Before the reactions were performed, an exhaustive characterization of the conformation of germacrone **1** was carried out. In doing this, a conformational analysis performed by molecular mechanics (MMFF94s) revealed the existence of four low-energy conformations that were completely optimized by density functional calculation at the B3LYP 6-31+G* level[7] (Figure 1). **1a** (C/β,β/N)[8] is the most

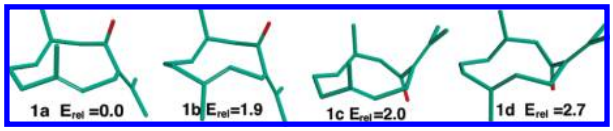


Figure 1. Low-energy conformations of **1** (relative energies in kcal/mol).

stable conformation. The conformational analysis in solution by ^{1}H and ^{13}C NMR at variable temperature allows us to distinguish only two sets of differentiated signals that by means of NOE effects demonstrate the coexistence of conformers **1a** and **1b** at a ratio of 12:1 at room temperature.

A remarkable characteristic of this natural product is the spatial proximity observed between C1 and C4, both in the model obtained by X-ray diffraction[9] (2.780 Å) and in the minimum-energy conformation **1a** of the theoretical model (2.823 Å). Surprisingly, this distance is smaller than the sum of the van der Waals radii. The HOMO-1 molecular orbital of this model (Figure 2) clearly shows some bonding

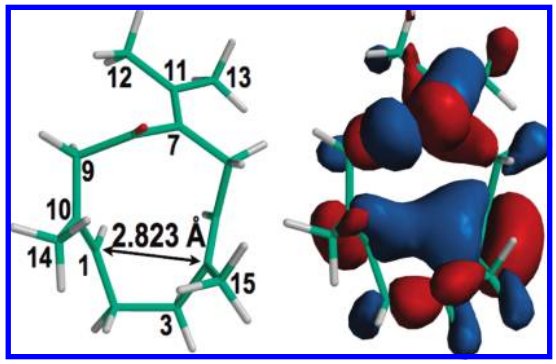
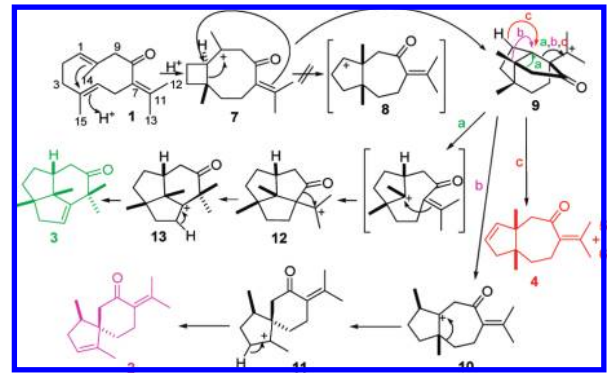


Figure 2. Compound **1**: global minimum conformation and HOMO-1 molecular orbital.

between the two endocyclic double bonds, which explains the short distance observed between C1 and C4 as mentioned above. It likewise indicates a preorganization in **1** that must facilitate some transannular cyclization reactions induced by electrophiles.

These observations led us to consider the possibility of establishing a suitable choice for the experimental cyclization conditions to control the selectivity of the process toward double bond 4,5. To test this hypothesis we used chlorosulfonic acid in 1-nitropropane, a medium that has produced good results in cyclizations of acyclic[10] and cyclic[11] polyprenoids, which allowed lowering the temperature to −78 °C owing to the good solubility of the reaction mixture. The addition of 4 equiv of acid to 1 equiv of germacrone (**1**) gave **2** (24%), **3** (35%), **4** (8%), **5** (2%), and **6** (1%) (Scheme 1) with 30% of starting product remaining noncyclized after

Scheme 1. Postulated Mechanism for Obtaining Products **2**−**6**



10 min. Over a period of 60 min **2** (27%), **3** (39%), **4** (9%), **5** (4%) and **6** (1%) were obtained and only 20% of **1** remained noncyclized. Compounds **2**−**6** have new sesquiterpenoid skeletons whose structures were elucidated from detailed interpretation of their spectroscopic data (see Supporting Information). Eudesmane formation was not detected, although these are the only compounds found in previously reported acid cyclizations of **1** at room temperature.[6c]

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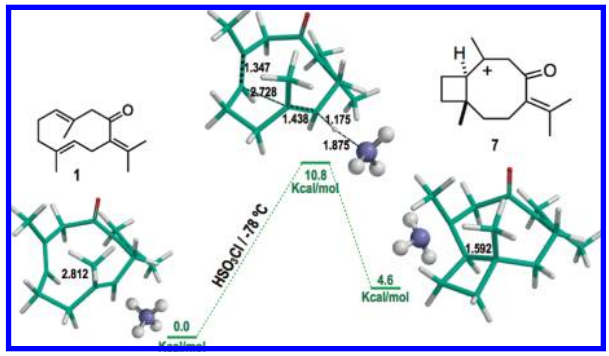
Similar results are obtained by doubling the concentration of chlorosulphonic acid, but greater proportions of products **5**−**6** (21% and 15%, respectively) are obtained. If the temperature is raised under these conditions, noteworthy product decomposition occurs, making results inconclusive. If, in contrast, only 2 equiv of acid is used, there is no cyclization and only partial isomerization take place at endocyclic double bonds.

A summary of the formation mechanism of novel compounds **2**−**6** is found in Schemes 1 and 3. These products are the result of the protonation of the 4,5 double bond from **1** and a transannular cyclization with the 1,10 double bond, followed by other cyclizations, Wagner−Meerwein rearrangements, and electrophilic additions. Recently, theoretical studies have provided important insights into the mechanisms of sesquiterpene-forming reactions.[12] DFT calculations with B3LYP/6-31+G* in a SM8 solvated model[13] allow for the characterization of transition states and the intermediates, products, and diagram of the reaction (Schemes 2 and 4).

Scheme 2. $TS_{1,7}$[a]



[a] Calculation performed with a conjugate base; DFT/B3LYP/6-31+G* in SM8 solvated model; distances in Å.

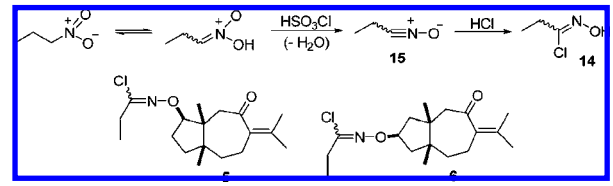
The election of the DFT method with the B3LYP/6-31+G* basis set is justified by the good results obtained in previous cyclization or rearrangement studies.[14] To reproduce experimental conditions of this reaction, ethanol has been considered as solvent in the calculations. In these diagrams, the transition states present appropriate spatial geometries for a suitable overlap of the orbitals facilitating the corresponding reaction of **1** with protonic acids. Moreover, the stereochemistries of the intermediates corroborate the relative configurations assigned by NMR spectroscopy.

Intermediate **7** comes from **1** in a concerted way as can be deduced from the examination of the imaginary frequency of $TS_{1,7}$ and confirmed by calculating the intrinsic reaction coordinate that links **1** and **7** when a conjugate base is considered. Geometries and binding energies for a carbocation−ammonia complex analyzed by the B3LYP/6-31+G* method gave satisfactory results.[15] The IRC profile of $TS_{1,7}$ involves a concerted proton transfer from NH_4 to C-5. The distance C1−C4 in the $TS_{1,7}$ (2.728 Å) is between that of **1** (2.812 Å) and **7** (1.592 Å). Thus, the activation energy of $TS_{1,7}$ was 10.8 kcal/mol.

Tricyclic system **9** being formed in the following step would involve an interesting rearrangement of the bicycle tertiary carbocation **7** to the tricycle tertiary carbocation **9** thus avoiding the intermediate of the less stable secondary cyclopentyl carbocation **8** with a positive charge at C-1. In fact, this secondary carbocation, which would relieve the strain of the four-membered ring, was not located as a minimum on the potential surface during the computational calculations. This would be analogous to the proposed concerted ring expansion of ring C and to the formation of ring D in the cyclization of squalene to lanosterol[16] and consistent with the results published for other sesquiterpene pathways.[17] Carbocation **9** is a common intermediate and evolves easily to **4**, **10**, and **12** following routes a, b or c as can be seen in the Scheme 1.

Following route c, deprotonation of **9** at position 2 gives rise to compound **4**, which reacts by electrophilic addition with **14** (Scheme 3). The latter is the compound resulting from the solvent's reaction with the acid yielding **5** and **6**. For its part, **9** evolves through the other two routes (a and b) set out in Schemes 1 and 4 giving rise to **10** and **12**. Route a entails a concerted aperture of the cyclohexane ring, alkyl rearrangement, and cyclization with an energetic barrier of 18.1 kcal/mol. Recalculation of this barrier at −78 °C results in a further decrease of 2 kcal/mol on the free energy, due to a decrease in the unfavorable entropy contribution to the overall energy, probably associated with the highly rigid nature of **9** when compared to the ring-breaking transition state (see $G°$ in Supporting Information).

Scheme 3. Formation of the Side Chain in Compounds **5** and **6**



Scheme 4 shows that the energy barrier is close to 1 kcal/mol, which is more favorable toward **12** than **10** and a little more favorable still to deprotonation leading to **4**. This explains the greater proportion of compound **3** compared to **2** and **4** in all of the reactions. Once **12** has been formed (route a), it evolves by surmounting a very small barrier

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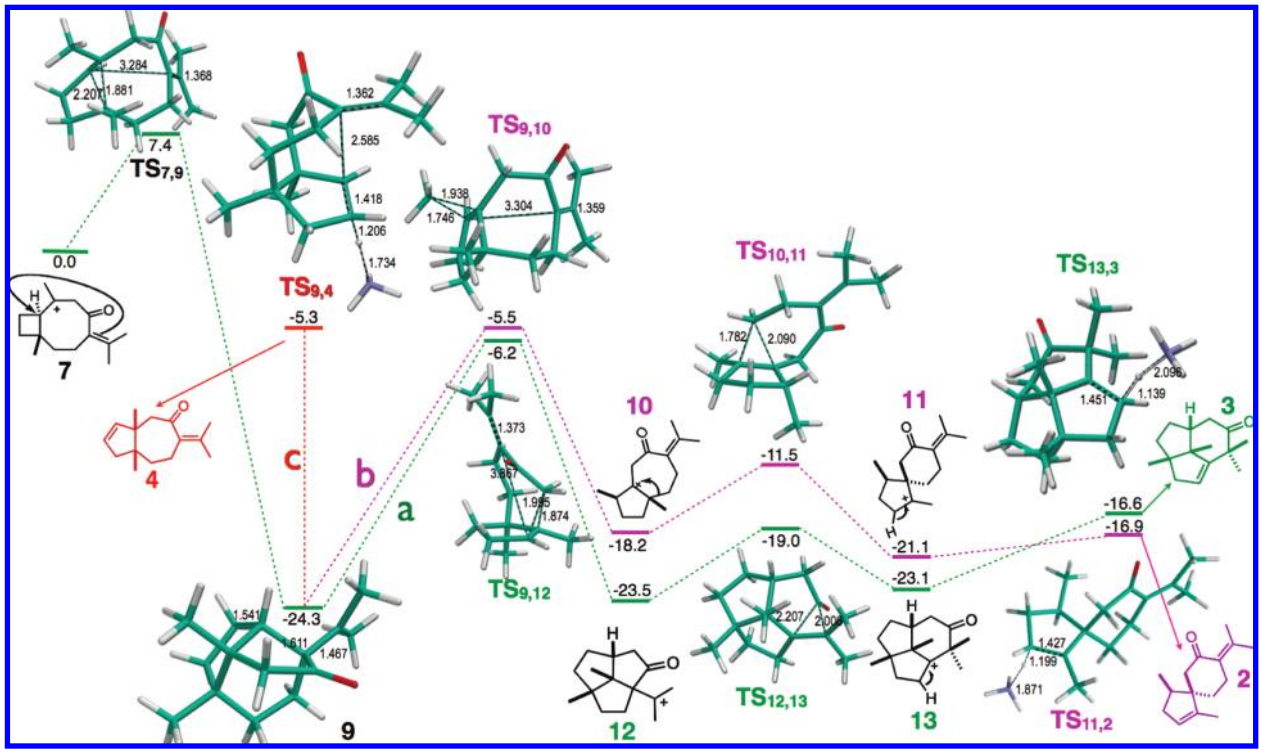
Scheme 4. Progress of the Reaction Diagram[a]



[a] Energies in kcal/mol relative to that of **7** for intermediates. Energies for products **2**, **3** and **4** relative to germacrone **1a** are −28.1, −33.2, and −17.5 kcal/mol respectively. Distances are expressed in Å.

toward carbocation **13**, the precursor of compound **3**, also in accordance with the greater proportion of the latter. In route b leading to the formation of **2**, the barrier that **9** has to surmount is caused by the migration of methyl from C10 to C1, which is slightly lower than that in route c such that the deprotonation of **9** gives **4**. To calculate the barriers of deprotonation of **9**, **11**, and **13**, ammonia has been considered as a base due to the satisfactory results obtained in similar theoretical studies.[17b] With **11** and **13**, *exo* and *endo* deprotonation were explored and differ by less than 0.2 kcal/mol.

In conclusion, the existence of some bonding between endocyclic double bonds in the most stable conformation **1a** gives rise to a new type of transannular cyclization reaction in germacrone (**1**). Germacrene B, the hydrocarbon related to **1**, is a well-known intermediate in the sesquiterpene biosynthesis starting from farnesyl pyrophosphate to eudesmanes, guaianes,[1] etc. Its major conformation is similar to that of **1a**[1c] and it could react in a similar fashion. Consequently the C4−C5 double bond protonation of germacrene B and subsequent cyclizations and rearrangements could constitute a new biosynthetic way toward sesquiterpenes with unusual skeletons. Recent reports on the isolation of jasomontanone from the Asteracea *Jasonia montana*,[18] which contains the bicyclo[5.3.0]decane skeleton present in **4**−**6**, support this hypothesis.

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Supporting Information Available: Experimental procedures and spectroscopic data of new compounds, ^{1}H NMR and ^{13}C NMR spectra of new compounds and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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