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15-Hydroxygermacranolides as Sources of Structural Diversity. Synthesis of Sesquiterpene Lactones by Cyclization and Rearrangement Reactions. Experimental and DFT Study

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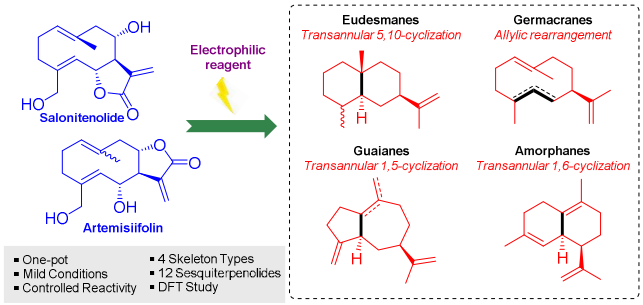


ABSTRACT: A study on the electrophile-induced rearrangement of two 15-hydroxygermacranolides, salonitenolide and artemisiifolin, was carried out. These compounds underwent electrophilic intramolecular cyclizations or acid-mediated rearrangements to give sesquiterpene lactones with different skeletons such as eudesmanolides, guaianolides, amorphanolides or other germacranolides. The cyclization that gives guaianolides can be considered as a biomimetic route to this type of sesquiterpene lactones. The use of acetone as solvent changes the reactivity of the two starting germacranolides to the acid catalysts, with a 4,15-diol acetonide being the main product obtained. The δ-amorphenolide obtained by intramolecular cyclization of this acetonide is a valuable intermediate for accessing the antimalarials artemisinin and its derivatives. Mechanistic proposals for the transformations are raised, and to provide support them, quantum chemical calculations [DFT B3LYP/6-31+G(d,p) level] were undertaken.

INTRODUCTION

Sesquiterpene lactones are a large group of plant metabolites mainly isolated from numerous genera of the family Asteraceae (Compositae) that possess a broad spectrum of biological activities such as anti-inflammatory, antibacterial, antifungal, phytotoxic, cytotoxic, and anticancer.[1] In recent years, the anticancer properties shown by sesquiterpene lactones have attracted a great deal of interest, and extensive research has been carried out to elucidate their

molecular mechanism of action as well as their potential use as chemopreventive and chemotherapeutic agents.[2] Some sesquiterpene lactones with anticancer potential are parthenolide (germacranolide isolated from *Tanacetum parthenium*),[3] thapsigargin (guaianolide isolated from *Thapsia garganica*),[4] artemisinin (endoperoxide, mainly known for its antimalarial activity, isolated from *Artemisia annua*),[5] helenalin (pseudoguaianolide isolated from *Psilostrophe cooperi*),[6] arglabin (guaianolide isolated from *Artemisia myriantha*),[7] or alantolactone (eudesmanolide isolated from *Inula helenium*).[8]

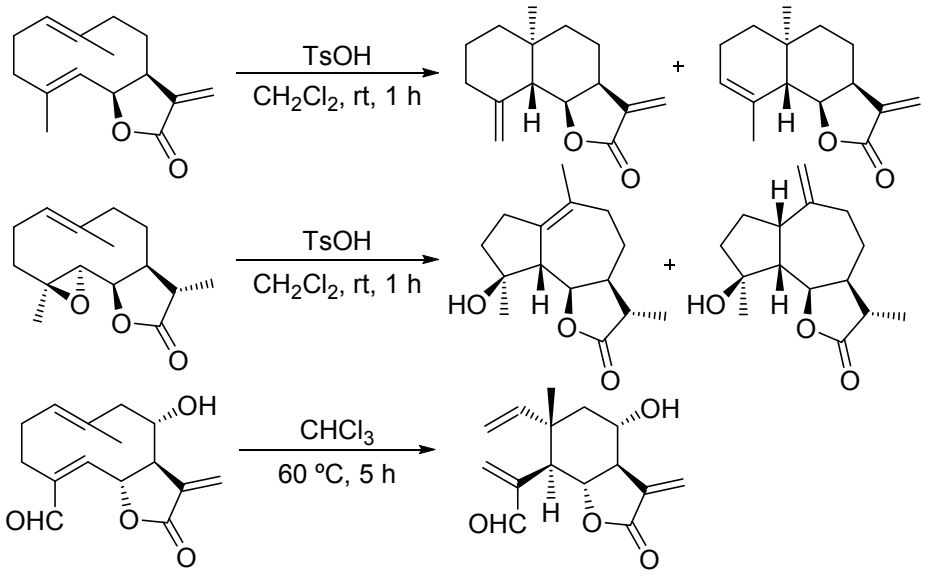
Germacranolides are an abundant subset within sesquiterpene lactones which are considered key biosynthetic precursors for other sesquiterpene skeletons such as elemanolides, guaianolides and eudesmanolides.[9] The major structural feature of this type of sesquiterpene lactones is the *trans*,*trans* ring skeleton, *trans*,*trans*-cyclodeca-1(10),4-diene, which is well known for its ability to undergo conformational changes that have been the subject to theoretical studies.[10] This conformational flexibility plays an important role in the reactivity of these compounds, particularly in thermal, photochemical and acidic transannular cyclizations,[11] since the spatial arrangement of the different conformers determines the outcome of the reactions.[9b,12]

Taking into account their biosynthetic interest, numerous germacranolides have been used as models for synthesizing different skeletal types of sesquiterpenolides (Scheme 1a).[13] These reactions can be considered as a biomimetic synthesis of this type of secondary metabolites and have been used by our group to propose a route for the biogenesis of sesquiterpenolides produced by plants of the Umbelliferae family.[13b] Most of the works on the mechanism of cyclization are based on establishing the relationships between the conformation of the initial germacranolide and the stereochemistry of the reaction products, but very few ones provide reliable evidences of the mechanisms that lead to these products. In our efforts to develop new

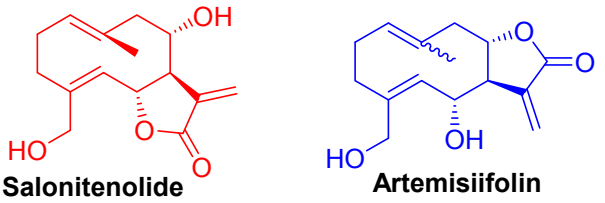
synthetic applications of germacranolides via transannular cyclization and provide proofs about the mechanisms, we herein present the biomimetic synthesis of several sesquiterpene lactones starting from the 15-hydroxygermacranolides salonitenolide and artemisiifolin (Scheme 1b). A computational study with DFT at B3LYP/6-31+G(d,p) level was conducted to justify the formation of compounds described.

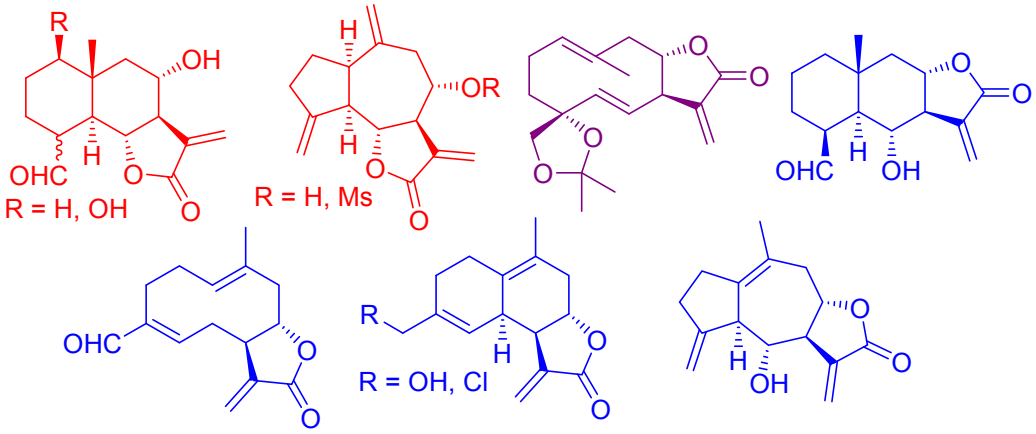
Scheme 1. Reactivity of Germacranolides

a) Reported reactivity of germacranolides



b) This work





RESULTS AND DISCUSSION

The presence of an oxygenated function at C15 confers a characteristic reactivity to the germacranolides and makes them valuable starting materials for the hemisynthesis of different skeletons of sesquiterpene lactones.[13a,13c,13d]

With the purpose of increasing the potentiality of these compounds and their derivatives to create structural diversity, we decided to explore their chemical behavior against different acids and other electrophilic reagents. For this purpose, we selected as starting materials salonitenolide (**2**)[14] and artemisiifolin (**3**),[15] two 15-hydroxygermacranolides which can be obtained in good yield from cnicin (**1**),[13a,13c] a germacranolide easily accessible from species of *Centaurea* genus,[16] (Figure 1). Both compounds have been prepared from cnicin (**1**) although slight modifications of the reported methods have been introduced. Additionally artemisiifolin (**3**) has been isolated from *Staehelina dubia* (see Experimental Section).[10b]

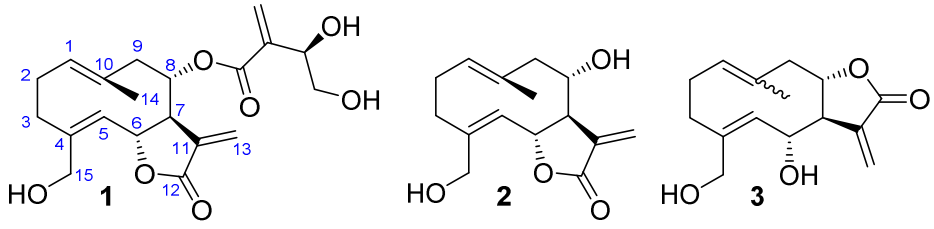
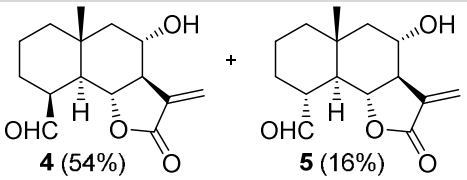
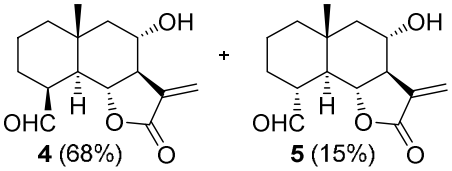
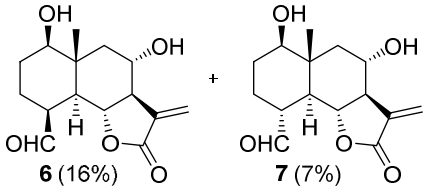
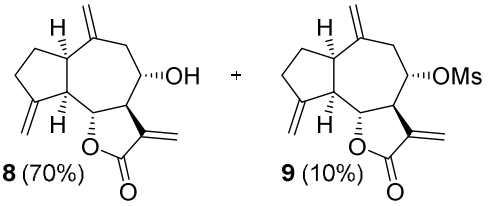
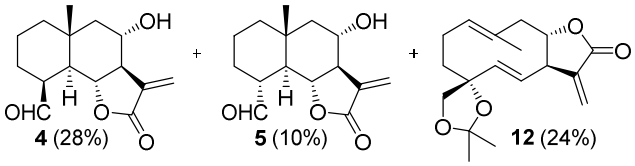
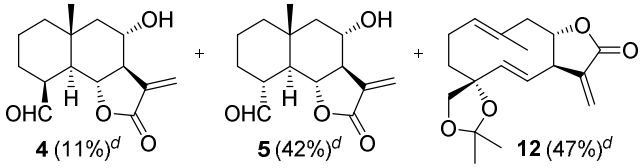


Figure 1. Cnicin (**1**), salonitenolide (**2**), and artemisiifolin (**3**).

The transannular cyclizations were initiated with the treatment of salonitenolide (**2**) with silica sulfuric acid (SSA) (Table 1, entry 1), a nontoxic heterogeneous solid acid catalyst that presents great chemical versatility.[17] The recent reported effectiveness of SSA to promote three-component condensation reactions[18] encouraged us for studying the reactivity of this heterogeneous protic acid with germacranolides. Treatment of **2** with SSA in $CHCl_3$ led to the formation of stoebenolide (**4**) and its C4 epimer, **5**, in only 15 min (Table 1, entry 1). Stoebenolide (**4**) has been isolated from *Centaurea stoebe*,[19] and synthesized by transannular

cyclization of **2** promoted by palladium(II).[13d] Both compounds were also obtained when **2** was treated with *p*-toluenesulfonic acid (TsOH) in $CHCl_3$ for 1 h (Table 1, entry 2), demonstrating the great catalytic activity of the heterogeneous protic system.

Table 1. Reactivity of Salonitenolide (2)

entry	electrophilic reagent	solvent	time	products(%)[a]
1	SSA (1.0 equiv)	$CHCl_3$	15 min	 **4** (54%) + **5** (16%)
2	$TsOH·H_2O$ (1.0 equiv)	$CHCl_3$	1 h	 **4** (68%) + **5** (15%)
3[b]	MCPBA (1.0 equiv)	CH_2Cl_2	1.5 h	 **6** (16%) + **7** (7%)
4[c]	MsCl (2.0 equiv)	CH_2Cl_2	2 d	 **8** (70%) + **9** (10%)
5	SSA (0.9 equiv)	Acetone	3 d	 **4** (28%) + **5** (10%) + **12** (24%)
6	$TsOH·H_2O$ (1.0 equiv)	Acetone	6 d	 **4** (11%)[d] + **5** (42%)[d] + **12** (47%)[d]

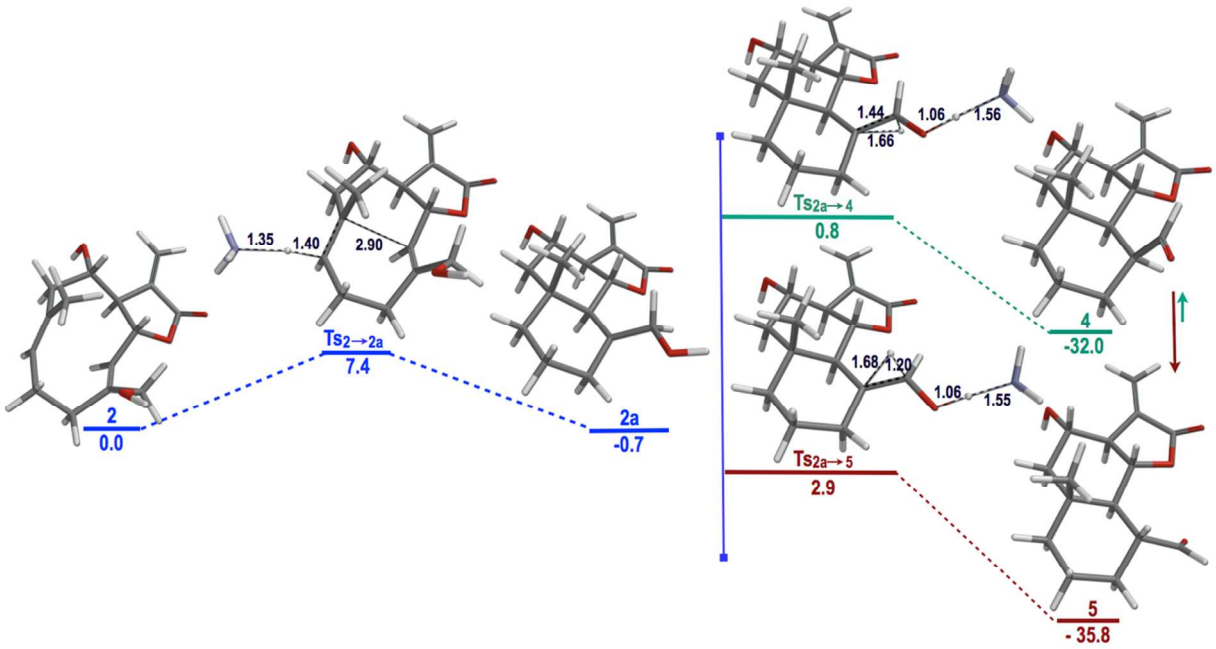
[a]Isolated yield. [b]K_2CO_3 (3.7 equiv) used as base. [c]Et_3N (6.0 equiv) used as base. [d]The relative ratio was established from ^1H NMR (500 MHz) analysis of reaction crude.

Treatment of **2** with MCPBA in the presence of anhydrous K_2CO_3, to minimize *m*-chlorobenzoic acid generated during the reaction, gave the eudesmanolides **6** and its C4

epimer, **7**, (Table 1, entry 3). 8α-Hydroxy-4-*epi*-sonchucarpolide (**6**) is an antifungal compound that has been isolated from different *Centaurea* species.[20] The epimeric compound, **7**, has been found in *Centaurea zuccariniana*[20c] and *Onopordum cynarocephalum*,[21] and has not been previously synthesized. Eudesmanolide **7** induces apoptotic cell death in the A375 human melanoma cell line and a high DNA fragmentation correlated to a significant increase of the caspase-3 enzyme activity.[21] The same type of cyclization to give aldehydes has been described for other 1,10-epoxy-15-hydroxygermacranolides.[13a,22]

Formation of **4** can be derived from the UU[23] conformation of **2** through C1-C10 double bond protonation, cyclodecadiene cyclization, and hydride shift (Scheme 2). Aldehyde **5** should come from slow epimerization at C4 via enol, promoted by the acidic medium. This fact was confirmed by transformation of aldehyde **4** to the epimer **5** by its treatment with SSA in CH_2Cl_2 (see Experimental Section).

Scheme 2. Proposed Mechanism for the Formation of Aldehydes 4 and 5*



* NH_4^+ and NH_3 have been considered in calculations to emulate catalytic effects of the different acids used and their conjugated bases generated during the reaction. Free energies relative to **2**+NH_4^++NH_3 [B3LYP/6-31+G(d,p) scrf=(smd, solvent=chloroform)//B3LYP/6-31+g(d,p)] in kcal/mol in blue, green and red. Selected distances in TSs are shown in Å. To clarify the image, NH_3 and NH_4^+ of reagent, intermediate and products included in the calculation have been deleted from the image.

To justify this finding a computational study was undertaken. A conjugate base moiety and the solvent effect (chloroform) have been considered in the calculations by a single point energy calculations using the SMD continuum model.[24] The geometries and binding energies for the carbocation-ammonia complex analyzed by the B3LYP/6-31+G* method gave satisfactory results.[25] Compound **5**, with the aldehyde group in equatorial disposition, turns out to be 3.8 kcal/mol more stable than **4**, which seems to disagree with the formation of a larger ratio of **4**.

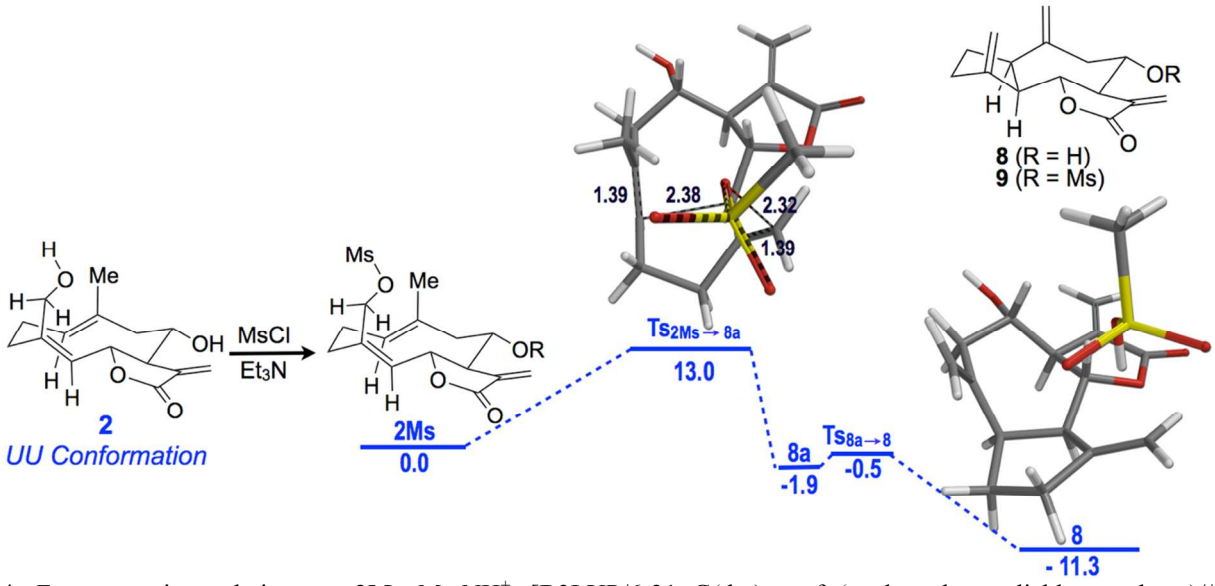
This prompted us to study the formation path of both compounds, the results of which are shown in Scheme 2. The process is initiated by the protonation of the C1-C10 double bond of the conformer with lower energy (UU).[23] As a result, the carbocation at C10 triggers the

cyclization until the carbocation is stabilized on C4, producing the eudesmanolide cation intermediate, **2a** (See C.1.1 in Supporting Information). Subsequent 1,2-hydride shift across both faces of the C4-C15 bond provides **4** and **5** after deprotonation catalyzed by the conjugate base formed during the reaction. To overcome the last step, carbocation **2a** must rotate the C4-C15 bond to achieve an orthogonal arrangement for each of the methylene hydrogens that will lead in each case to compounds **4** and **5**. The interconversion barrier of carbocation **2a** through the 1,2-suprafacial shift conducting to **5** is more than 2 kcal/mol higher than its alternative, which is consistent with compound **4** being formed in higher ratio (See C.1.2 and C.1.3 in Supporting Information).

In a similar manner, compound **6** comes from the transient and non-isolable C1-C10 epoxide (See Scheme S2 in Supporting Information). The reaction is initiated by the protonation of the oxirane ring followed by an intramolecular cyclization that leads to the **2c** intermediate carbocation in a concerted manner through a 12.2 kcal/mol barrier (See C.2.1 in Supporting Information). As we have described for the formation of **4** and **5**, intermediate **2c** evolves to **6** and **7** by a hydrogen shift over both sides of the C4-C15 bond followed by deprotonation. The barrier for the formation of **7** results to be 1.1 kcal/mol higher than the one leading to **6**, which would justify the higher formation ratio of **6** with respect to **7** (See C.2.2 and C.2.3 in Supporting Information).

In order to explore the behavior of germacranolides which carry a C15 leaving group, salonitenolide (**2**) was treated with mesyl chloride. In these conditions the cyclization occurs spontaneously and goes in the opposite direction to that described above, to give the unexpected natural guaianolide deacylsubexpinnatin (**8**)[26] in 70% yield, and the mesylate **9** as a minor product (Table 1, entry 4). The formation of the guaianolides comes from the conformation UU of **2**, through the cyclization shown in Scheme 3.

Scheme 3. Cyclization of Salonitenolide (2) to Give Guaianolides*



* Free energies relative to **2Ms**+Me_3NH^+ [B3LYP/6-31+G(d,p) scrf=(smd, solvent=dichloromethane)// B3LYP/6-31+g(d,p)] in kcal/mol in blue. Selected distances in TSs are shown in Å. Me_3N included in the calculations has been eliminated for simplification of the picture. (For complete results of calculations see Supporting Information: C.3.1 and C.3.2).

The catalytic role of amine present in the medium significantly lowers the transition state barriers. IRC calculations indicate that the beginning of mesylate oxygen-C15 bond breaking is favored by the approximation of the basic amine hydrogen to another mesylate oxygen surmounting a first barrier of 13 kcal/mol. This enables-the carbocation to swiftly move, after overcoming a second small barrier of 1.4 kcal/mol, through 1,5-cyclization until the carbocation is located at C10. Simultaneously, the elimination of H14 takes place through its trapping by the mesylate anion, thus completing the reaction (See C.3.1 and C.3.2 in Supporting Information). When the dgdzvp2 basis set is used instead off 6-31+g(d,p), an asynchronous concerted process is observed with only one saddle point between **2Ms** and **8**.

Simultaneous presence of guaianolides and 15-hydroxygermacranolides in plants of the Compositae and Magnoliaceae families[1g,27] might be explained through this type of cyclization. Noteworthy is the isolation of picriside B (**10**) from *Saussurea lappa*, a plant on which dehydrocostuslactone (**11**) is the main component (Figure 2).[28] Therefore, these

transformations can be considered as an alternative way to guaianolide biosynthesis. González et al. described a similar transformation of the germacranolide gallicin to give guaianolides.[29]

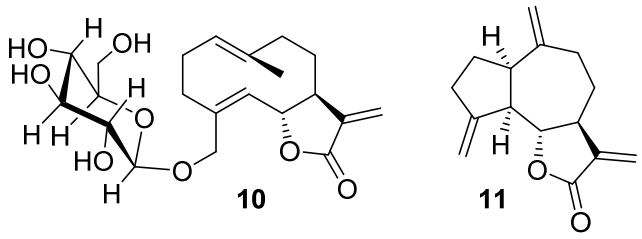


Figure 2. Picriside B (**10**) and dehydrocostuslactone (**11**).

The influence of solvents over conformational equilibria is well known.[30] For this reason, we decided to study the electrophilic cyclizations of salonitenolide (**2**) using acetone as solvent. The reaction with SSA or TsOH in this solvent (Table 1, entries 5 and 6), in addition to the formation of acetonide **12**, an evolution/inversion in the ratio **4**/**5** can be observed, which would be in accordance with the results of the computational studies shown in Scheme 2, since a longer time required for the consumption of starting material would imply a greater evolution in the equilibrium of aldehyde **4** towards the thermodynamically more stable **5**.

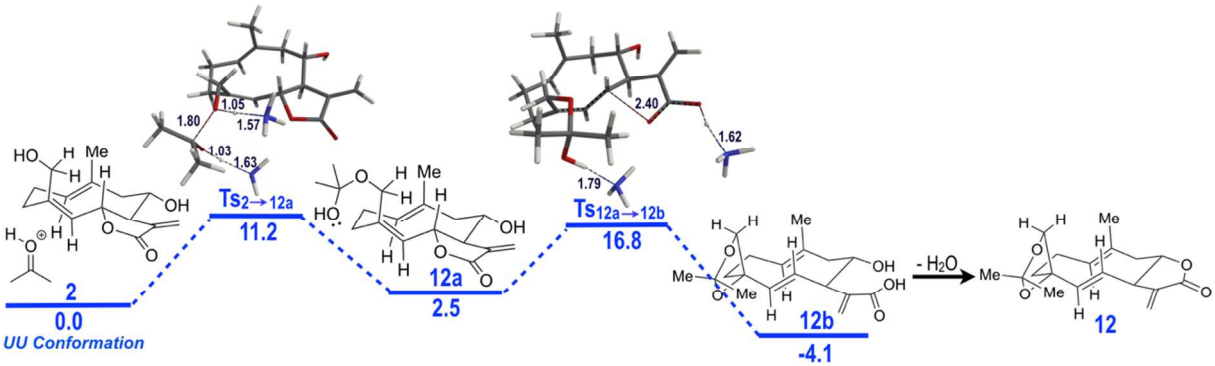
^{1}H NMR (500 MHz) spectrum in C_6D_6 of **12** at rt shows the presence of three interconverting conformers with ratio 74:22:3 (See Supporting Information). These conformational equilibria were corroborated by NOESY-1D since irradiating the proton signals of the major conformer, the saturation of the frequency was transferred to the corresponding proton signals of the other two conformers by the exchange process (see Supporting Information). This phenomenon has also been observed by Faraldos et al.,[31] who have used it as a very useful tool to assign the conformers of (+)-germacrene A in solution. The major conformer and the intermediate one of **12** exhibit parallel UU orientation wherein the conformational movement occurs at C2/C3, adopting chair-chair and boat-chair conformations, respectively. On the other hand, the minor conformer presents crossed DU orientation adopting boat-chair

conformation. Germacrene D, a sesquiterpene with germacra-1(10),5-diene core also shows in solution this conformational movement around C2/C3,[32] and the corresponding conformers have been previously predicted by computational calculations.[33] Similar behavior have been revealed for germacra-1(10),5-dien-4-ols by molecular mechanic calculations,[34] or reported for other described sesquiterpenes[35] and, even the natural diterpene obscuronatin.[36] To better understand the complexity of the conformational equilibrium observed for compound **12** in NMR studies, a total conformational search with Molecular Mechanics force field MMFF (Merck Pharmaceuticals) was carried out using the Mixed torsional/Low-mode sampling method.[37] 1000 conformations were generated, and those presenting up to 10 kcal/mol above the overall minimum were selected. Subsequently, an optimization at B3LYP/6-31+G(d,p) level was performed with the lower energy conformers. Finally, the four lower energy conformers were selected (See C.4 in Supporting Information) and optimized considering benzene as solvent using the SMD continuum model to better reproduce experimental conditions. In agreement with experimental NMR observations, very small energy differences have been found between the three lower energy conformers (less than 0.5 kcal/mol) while the fourth turns out to be more than 3 kcal/mol less stable. The three lower energy conformers found in the conformational search correspond perfectly to those derived from NMR studies including NOE experiments.

The unexpected formation of **12** from salonitenolide (**2**) implies relactonization from C6 to C8 via allylic rearrangement that must be promoted by acetone since, in the absence of this solvent this transformation does not take place. The reaction starts (Scheme 4) with the formation of the hemiacetal **12a** through a barrier of 11.2 kcal/mol (See C.5.1 in Supporting Information). Subsequently, in a concerted process, the formation of acetonide moiety of intermediate **12b** is produced via allylic rearrangement and nucleophilic opening of the

lactone ring, favored by protonation of the lactone carbonyl (See C.5.2 in Supporting Information). Similar allylic rearrangement along with the formation of an acid has been reported in diterpenes.[36] Finally, relactonization affords acetonide **12**.

Scheme 4. Proposed Mechanism for the Formation of Acetonide 12*



* NH_4^+ and NH_3 have been considered in calculations to emulate catalytic effects of the different acids used and their conjugated bases during the reaction. Free energies relative to **2**+Me_2CO+NH_4^++NH_3 [B3LYP/6-31+G(d,p) scrf=(smd, solvent=acetone)//B3LYP/6-31+g(d,p)] in kcal/mol in blue. Selected distances in TSs are shown in Å.

When acetonide **12** was subjected to acid treatment with TsOH in chloroform, cadalane **13** (Figure 3) was obtained in 69% yield. The configuration at C6 was inferred from NOE experiments (See Supporting Information). The key NOE between H6 and H7 indicates that both hydrogens are in *cis* disposition over the alpha side of the molecule, and therefore the skeleton of the compound **13** corresponds to that of a δ-amorphene.

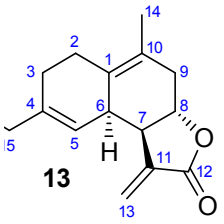
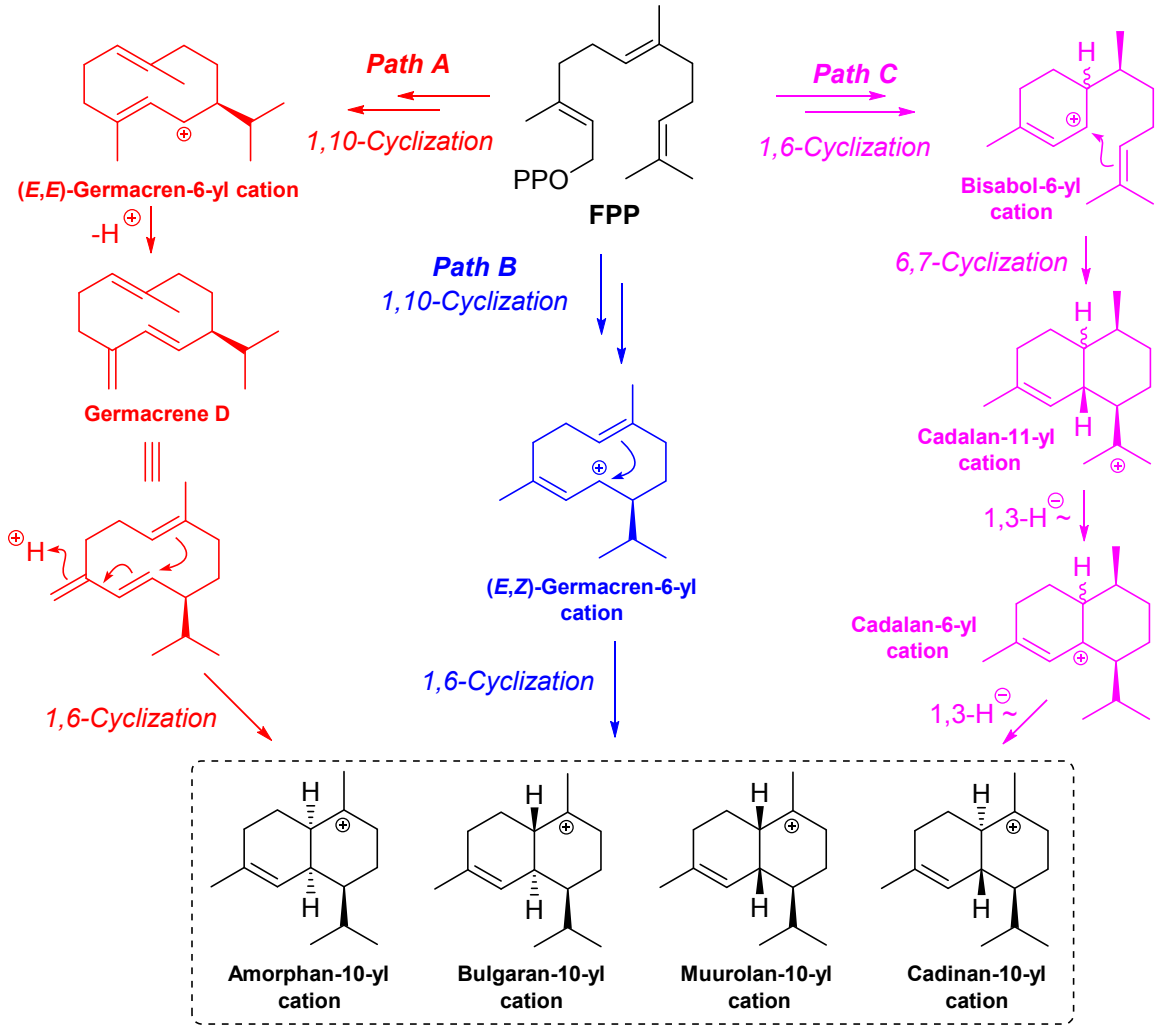


Figure 3. Amorphene **13**.

Amorphanes (relative configuration, H1α,H6α,H7α) are a sesquiterpene subgroup belonging to the family of cadalanes, which have been isolated from different biological sources.[38] The

mechanism for the biosynthesis of amorphanes, and their other possible diasteromers (bulgaranes, H1β,H6α,H7α; cadinanes, H1α,H6β,H7α; and muurolanes, H1β,H6β,H7α), from farnesyl pyrophosphate (FPP) catalyzed by sesquiterpene cyclases is still unclear.[39] Three possible mechanistic routes are proposed for the biosynthesis (Scheme 5). Path A implies the (*E*,*E*)-germacren-6-yl cation, derived from 1,10-cyclization of FPP, which is converted into germacrene D followed by transannular 1,6-cyclization to afford the different cadalane cations. Route B differs from the above in that the (*E*,*Z*)-germacren-6-yl cation intermediate has a structure suitable for undergoing direct transannular 1,6-cyclization to cadalenes. The third path is based on the formation of the bisabol-6-yl cation by 1,6-cyclization followed by 6,7-cyclization to give the cadalan-11-yl cation. Successive 1,3-hydride shifts lead to the corresponding skeletons of cadalanes.

Scheme 5. Mechanistic Routes Proposed for the Biosynthesis of Cadalanes from FPP Catalyzed by Sesquiterpene Cyclases



Subsequently, mechanistic insights about the formation of amorphadiene and amorphenes have been obtained using density functional calculations.[40] The routes via bisabolyl and (*E*,*Z*)-germacrenyl cations (paths B and C, Scheme 5) were examined, concluding that the first one is the most accessible energetically, although both paths converge as a result of a low energy 1,5-hydride transfer involving a non-classical carbocation.

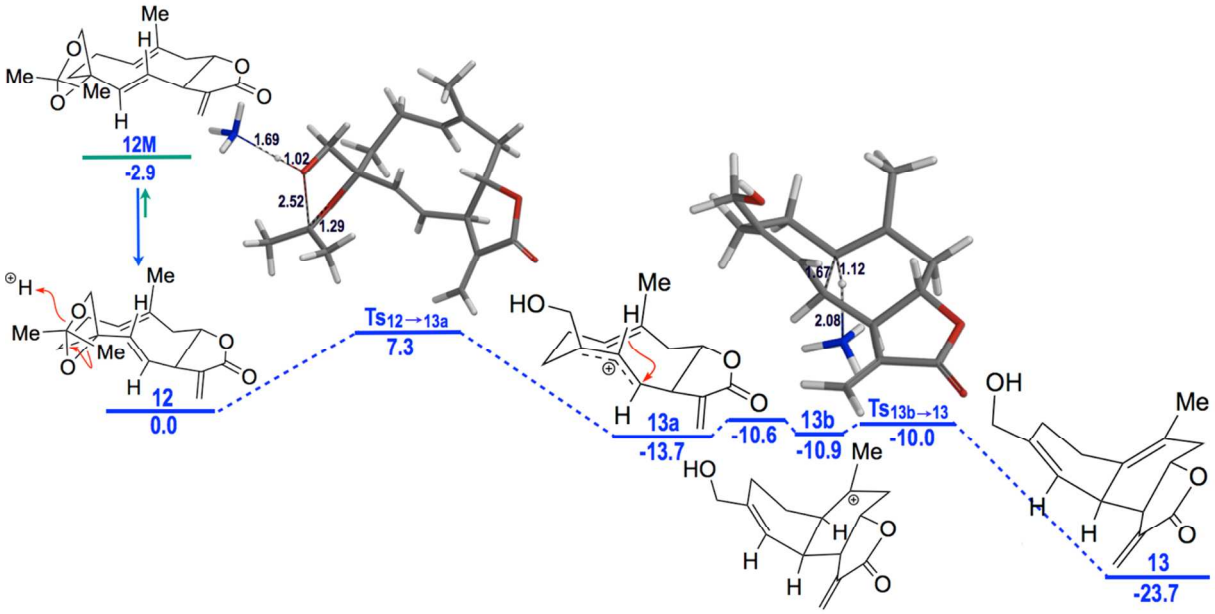
While transannular 1,6-cyclizations of germacrene D to cadalanes have been investigated,[32] such cyclization studies for other germacrenes are scarce. (–)-Germacrene D or (–)-

isogermacrene D under acidic conditions produced different sesquiterpenes among which cadalanes of the cadinane, muurolane and amorphane types were found.[32] Treatment of (1*E*,4*S*,5*E*,7*R*)-4,11-dihydroxygermacra-1(10),5-diene with protic acids only produced cadinanes,[41] whereas treatment of 15-deoxy-8-*epi*-salonitenolide acetate with methanolic potassium followed by acidification afforded a bulgarane skeleton.[42] A mixture of δ-amorphene and δ-cadinene in 2:3 ratio was isolated by heating 14-acetoxy-15-deoxyartemisiifolin in the presence of acid traces.[43]

Theoretical calculations of the acid-catalyzed cyclization of germacrene D have established that relative ratios of cadinane and muurolane sesquiterpenoids found in essential oil compositions as well as the experimental cyclization of germacrene D, reflect the energetic differences of the sesquiterpenoids and their carbocation precursors.[44]

Taking into account the above precedents, a computational study was undertaken to clarify the mechanism of formation of δ-amorphene **13** (Scheme 6). After a detailed study of the different spatial arrangements of acetonide **12**, the only productive conformation capable of evolving towards δ-amorphene **13** is the UU conformation in which the olefinic H6 is in alpha orientation. This conformation is 2.9 kcal/mol less stable than the minimum energy conformation (**12M**) due to the eclipsed disposition of H6 and H7. The acidic medium triggers the cleavage of the acetonide moiety giving the allylic carbocation **13a** (See C.6.1 in Supporting Information). Transannular 1,6-cyclization affords the amorphane skeleton that evolves to the δ-amorphene **13** by deprotonation across low energy barriers (See C.6.2 and C.6.3 in Supporting Information).

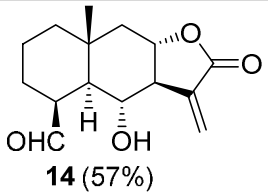
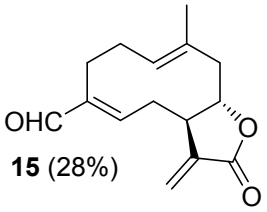
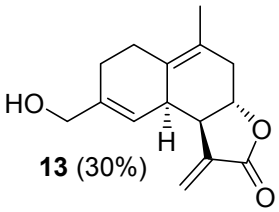
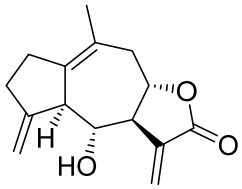
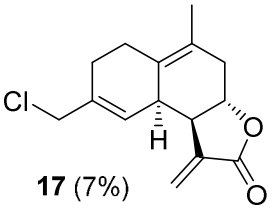
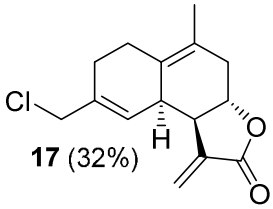
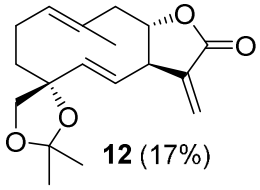
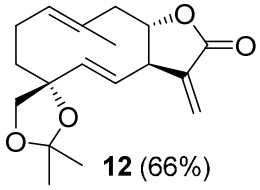
Scheme 6. Proposed Mechanism for the Formation of δ-Amorphene Lactone 13*



* NH_4^+ and NH_3 have been considered in calculations to emulate catalytic effects of used TsOH and its conjugated base generated during the reaction. Free energies relative to **12**+NH_4^+ [B3LYP/6-31+G(d,p)] in kcal/mol in blue. Selected distances in TSs are shown in Å.

Artemisiifolin (**3**) (Figure 1), the C8-lactonized isomer of salonitenolide (**2**), exists as a mixture of four slowly interconverting conformers with different ratios of conformers (UD:UU:DU:DD) in $CDCl_3$ (60:15:14:11) and Me_2CO-d_6 (29:30:27:14).[10b] Due to the fact that this flexibility could play a fundamental role in reactivity, we decided to explore the chemical behavior of artemisiifolin (**3**) in transannular cyclizations (Table 2), by subjecting this compound to the reactions described above for salonitenolide (**2**) (Table 1).

Table 2. Reactivity of Artemisiifolin (3)

entry	electrophilic reagent	solvent	time	products(%)[a]
1	SSA (1.1 equiv)	$CHCl_3$	2 h	 **14** (57%)
2	$TsOH·H_2O$ (1.0 equiv)	$CHCl_3$	2 d	 **15** (28%) +  **13** (30%)
3[b]	MsCl (1.0 equiv)	CH_2Cl_2	24 h[c]	 **16** (3%) +  **17** (7%)
4[d]	MsCl (2.4 equiv)	CH_2Cl_2	24 h[c]	 **17** (32%)
5	SSA (1.2 equiv)	Acetone	2.5 d	 **12** (17%)
6	$TsOH·H_2O$ (1.0 equiv)	Acetone	3 d	 **12** (66%)

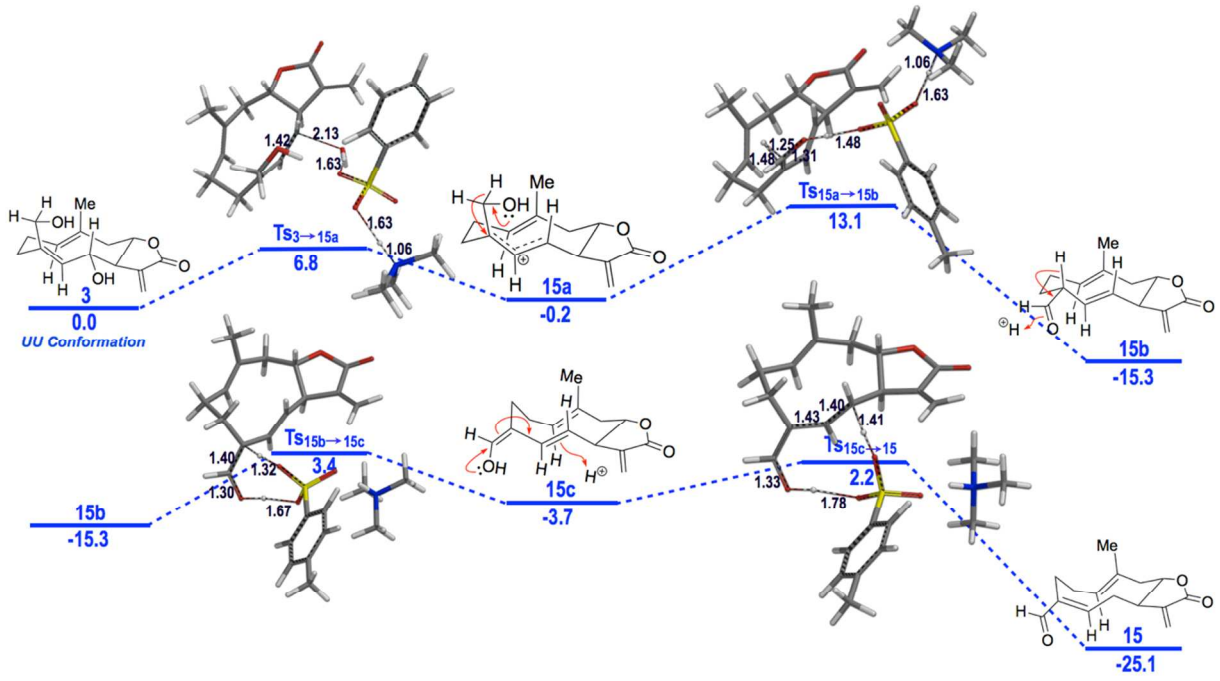
[a]Isolated yield. [b]Et_3N (1.3 equiv) used as base. [c]Additionally, the reaction crude was solved in $CDCl_3$ and kept for 3 d at rt. [d]Et_3N (6.4 equiv) used as base.

When **3** was treated with SSA in chloroform, aldehyde **14** was the only compound detected (Table 2, entry 1). It seems evident that the reaction proceeds through the UU conformation in a similar way to the cyclization of salonitenolide (**2**) (Table 1, entry 1). However, the reaction

of **3** with TsOH in the same halogenated solvent was slower, 2 days, from which the amorphene lactone **13** and the natural heliangolide liabinolide (**15**)[45] were obtained (Table 2, entry 2).

The formation of heliangolide **15** (Scheme 7) involves the formation of the allylic cation **15a** (See C.7.1 in Supporting Information), and a 1,2-hydride shift favored by the presence of the tosylate anion in the medium, which takes the proton of the alcohol at C15 giving the unsaturated β,γ-aldehyde intermediate **15b** with the aldehyde in equatorial disposition (See C.7.2 in Supporting Information). This step, across a barrier of 13.3 kcal/mol, is thermodynamically favorable by more than 15 kcal/mol. In addition, *p*-toluenesulfonic acid catalyzes a keto-enol tautomerism to give the **15c** intermediate (See C.7.3 in Supporting Information). The acid-promoted isomerization of but-2-en-1,4-diol units into α,β-unsaturated aldehydes has already been reported in the literature.[46] Finally, catalyzed once again by *p*-toluenesulfonic acid, the enol **15c** evolves to give an α,β-unsaturated aldehyde by protonation at C6, thus giving heliangolide **15** (See C.7.4 in Supporting Information). As can be seen in the diagram, the overall process is thermodynamically favorable by 25 kcal/mol, and only the enolization from **15b** to **15c** shows a barrier that, although high, is surmountable and could be the cause of the slowness of the process since it takes place in 2 days. The production of heliangolide **15** as the only diasteromer would be supported by the fact that germacranolides, bearing an aldehyde group at C15, under acidic conditions, change from *trans* to *cis* the configuration of the C4-C5 double bond.[10a,13c]

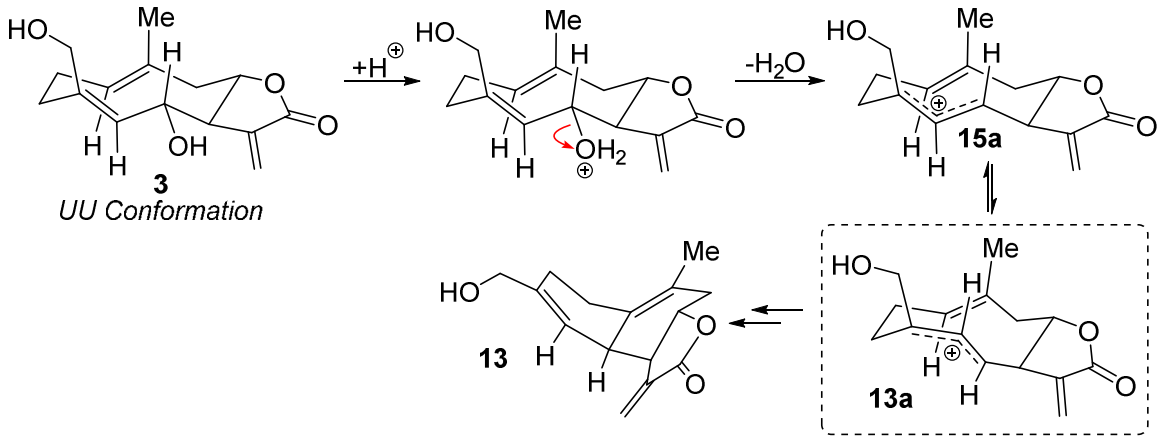
Scheme 7. Proposed Mechanism for the Formation of Heliangolide 15*



* In accordance with experimental conditions, TsOH has been considered in the calculation. Me_3NH^+ has also been considered. Free energies relative to **3**+TsOH+Me_3NH^+ [B3LYP/6-31+G(d,p), scrf=(smd, solvent=chloroform)//B3LYP/6-31+g(d,p)] in kcal/mol in blue. Selected distances in TSs are shown in Å.

Obtaining δ-amorphene **13** by acid treatment of both artemisiifolin (**3**) and acetonide **12** suggests the formation of a common intermediate during both transformations. In the case of artemisiifolin, the reaction mechanism (Scheme 8) begins with the loss of water, giving the allylic carbocation **15a** (also involved in the formation of heliangolide **15**), that, after a conformational change over the partial double bond C5-C6, evolves to the common key intermediate **13a**. Transannular 1,6-cyclization and deprotonation give the final product **13**. This mechanism is supported by the computational results described in Schemes 6 and 7.

Scheme 8. Proposed Mechanism for the Formation of δ-Amorphene 13



The differences in reactivity and reaction times observed in the treatments of artemisiifolin (**3**) with SSA and TsOH in $CHCl_3$ (Table 2, entries 1 and 2), demonstrate the importance of the heterogeneous nature of the catalyst.

Cyclization via epoxidation of artemisiifolin (**3**) has been previously described by Bruno et al.[13a] Of the two epoxides obtained by these authors, only the compound with UU conformation experienced cyclization in acid medium to give guaianolides (Figure 4). This can be explained taking into account that the spatial arrangement of the C1-C10 double bond and the epoxide is the "crossed" one which is the appropriate for the cyclization.[10f,12b,47]

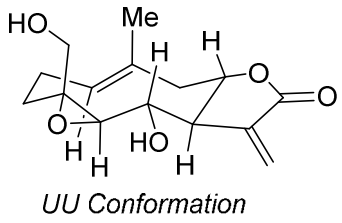


Figure 4. (4*R*,5*S*)-Epoxyartemisiifolin.

In order to explore if the reaction with sulfonyl chlorides to give guaianolides is a common behaviour of 15-hydroxygermacranolides, artemisiifolin (**3**) was treated with 1.0 equiv of mesyl chloride (Table 2, entry 3). The ^{1}H NMR spectrum of the reaction crude in $CDCl_3$ showed the presence of different mesylated compounds. With the aim of leaving these labile

species to evolve, the reaction crude was kept in the deuterated solvent for 3 d at rt. After chromatographic separation, guaianolide **16** and cadalane **17** were obtained in low yields.

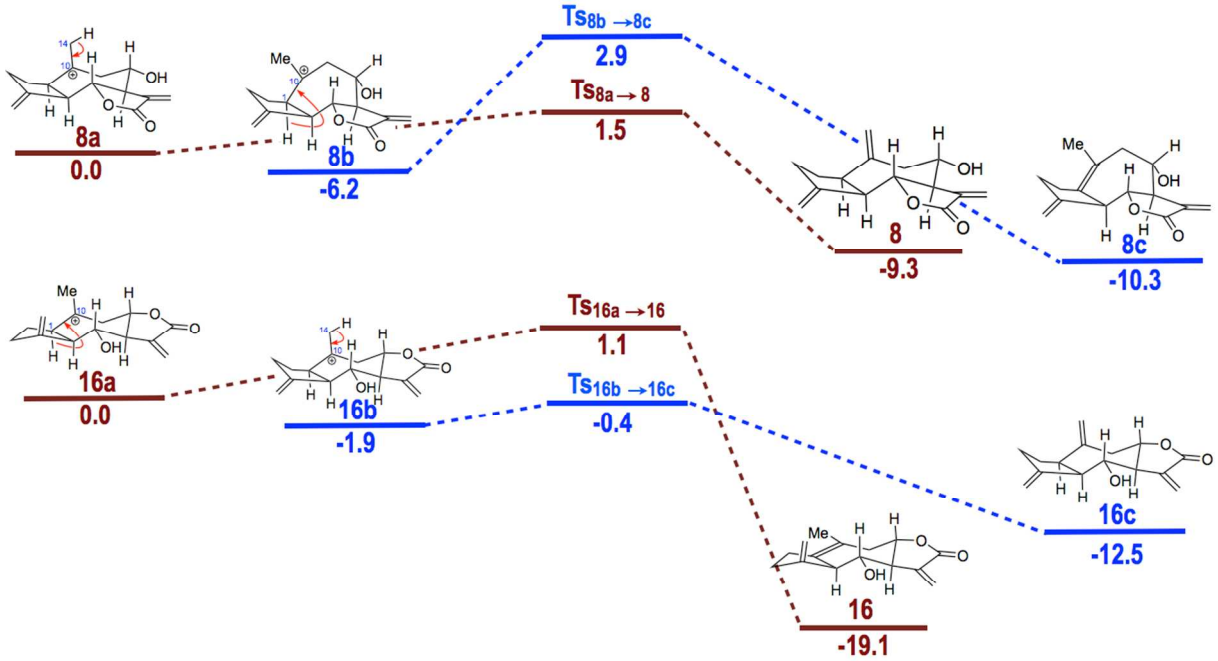
Compound **16** is an example of C8-lactonized guaianolide that has not been reported before. The absolute configuration of C5 was perfectly established by ^{1}H NMR wherein the spatial disposition *anti* between the protons H5 and H6 with J = 8.7 Hz was observed. NOE experiments by irradiating H5, H6, H7 and H8 corroborated the absolute configuration of guaianolide **16**.

The initial step in the formation of compound **16** from the UU conformation of 15-mesylartemisiifolin, through 1,5-cyclization until the carbocation is located at C10 (See C.8.1 in Supporting Information), takes place in the same way as the formation of guaianolide **8** described above in Scheme 3. However, the deprotonation leading to the final product takes place at C1 in this case (See C.8.2 in Supporting Information), rather than in C14 as occurs in the formation of compound **8**. This deprotonation is a consequence of the approximation of the mesylate anion generated during the reaction by the alpha face of the sesquiterpenoid instead of approximation by beta face which yields **8**. These finding clearly indicate that the global reaction is not a concerted process, as corroborated by the computational studies carried out for guaianolide **8** (See C.3 in Supporting Information).

In order to justify the regioselective deprotonation that leads to guaianolides **8** and **16**, additional computational studies were undertaken (Scheme 9). The deprotonation at C14 that gives **8** is clearly favored respect to the elimination of H1 that would yield a hypothetical guaianolide with an endocyclic double bond. In fact, the barrier for the former is more than 7 kcal/mol lower (See C.3.2 and C.3.3 in Supporting Information and Scheme 9), while both compounds exhibit similar thermodynamic stability (See C.3.2.2 and C.3.3.3 in Supporting

Information). For the formation of guaianolide **16** and its hypothetical isomer with an exocyclic double bond derived from deprotonation at C14, both deprotonation barriers are very low (about 1 kcal/mol) (See C.8.2 and C.8.3 in Supporting Information); however, compound **16** is 6.6 kcal/mol more stable than the other isomer and its reverse barrier is high (19.1 kcal/mol) (See C.8.2.3 and C.8.3.3 in Supporting Information and Scheme 9).

Scheme 9. Potential Energy Profiles for Rationalizing the Observed Regioselectivity for Compounds 8 and 16*



* Free energies relative to **8a** or **16a** [B3LYP/6-31+G(d,p), scrf=(smd, solvent=dichloromethane)//B3LYP/6-31+g(d,p)] in kcal/mol.

The ^{1}H NMR spectrum of cadalane **17** is very similar to that of amorphane **13** with the main differences being the deshielding of 0.11 ppm of H5 and the shape of the proton signal at C15 (See Figures S1B and S1C in Supporting Information). This fact, together with the similarity of NOEs indicate that **17** is also a δ-amorphene. The diastereotopic nature of the protons at C15, the great shielding of this carbon in ^{13}C NMR ($\Delta\delta$ = –17.4 ppm) and the different state of aggregation of this compounds (white solid) made us think of a possible chlorinated δ-

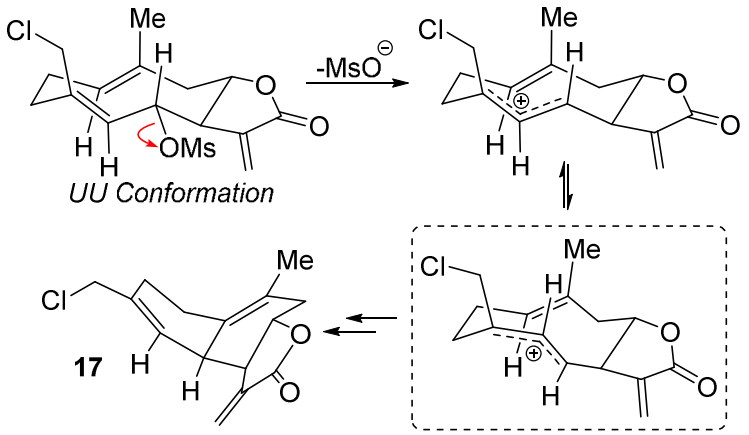
amorphene. This possibility was corroborated by the appearance in HRMS of the molecular ions $[M+H]^+$ 265.0995 and 267.0970 with ratio 3:1.

When the amount of mesyl chloride was increased to 2.4 equiv (Table 2, entry 4), ^{1}H NMR spectrum of reaction showed mainly a major product and the chlorinated amorphane **17** in 4:1 ratio (See Figure S1A in Supporting Information). When this same sample was kept in the NMR tube for 3 d, only the δ-amorphene **17** was observed, practically pure (See Figure S1B in Supporting Information). This result evidences that this chlorinated cadalane derives from the initial major product whose structure is assigned to a possible 15-chloro-6-mesyloxygermacranolide by the presence of two vinyl protons at 5.00 ppm (bd, J = 10.3 Hz, H1) and 4.88 (d, J = 10.9 Hz, H5), one deshielded proton at 5.12 ppm (t, J = 10.5 Hz, H6), and one chloromethylene group at 4.18 and 3.94 ppm as doublets with J = 11.6 Hz.

The high tendency of the mesyloxy group at C15 to undergo nucleophilic substitution S_N2 by chloride instead of transannular cyclization to give guaianolides, as in the case of salonitenolide (**2**) (Table 1, entry 4), could be explained considering that artemisiifolin (**3**) in solution exists as a mixture of four slowly interconverting conformers, UD being the major conformer that cannot undergo transannular cyclization. Transformations of primary allylic alcohols to chlorinated derivatives using the MsCl/Et_3N system have been reported in the literature.[48]

A proposal for the formation of chlorinated δ-amorphene **17** is depicted in Scheme 10. The mechanism is the same to that proposed for the formation of hydroxylated δ-amorphene **13** from artemisiifolin (**3**) (Scheme 8) but starting from 15-chloro-6-mesyloxygermacranolide. The involvement of the same carbocation intermediate is again key for transannular 1,6-cyclization to afford the amorphane skeleton.

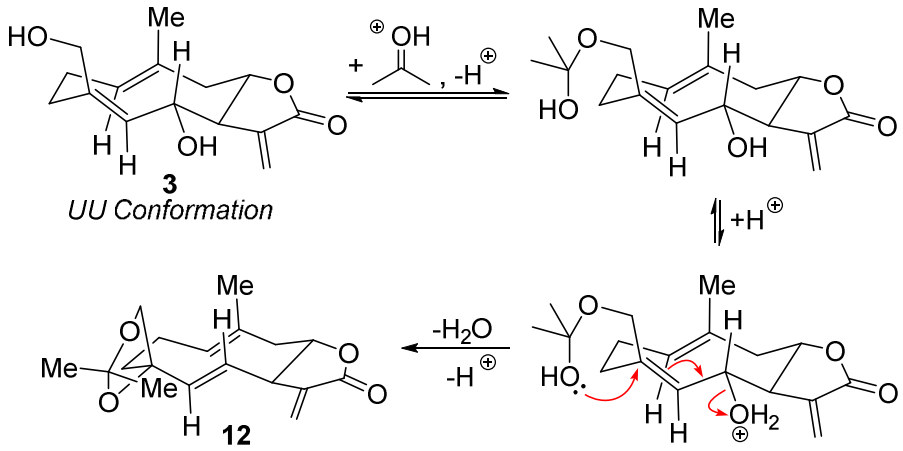
Scheme 10. Proposed Mechanism for the Formation of Chlorinated δ-Amorphene 17



Finally, as with salonitenolide (**2**), the assays of artemisiifolin (**3**) against the above catalysts (SSA or TsOH) were carried out in acetone, giving in all cases the acetonide **12** as the only product in 17% and 66% yields, respectively (Table 2, entries 5 and 6). In principle, starting from but-2-en-1,4-diol unit, the formation of a seven-membered acetonide is expected, but nevertheless a 1,3-dioxolane is produced. This same reactivity has also been reported for but-2-en-1,4-diols by using $BF_3 \cdot Et_2O$ as Lewis acid in acetone,[46c] however the authors achieved the synthesis of the seven-membered acetonide operating at –78 ºC. Recently, transformations of but-2-en-1,4-diols into 1,3-dioxolanes have been reported by using aldehydes as condensing agent in the presence of a gold(I) catalyst.[49]

A plausible mechanism for the formation of acetonide **12** from artemisiifolin (**3**) in acetone is depicted in Scheme 11. The transformation begins with the nucleophilic attack of the hydroxyl group at C15 to the protonated carbonyl of acetone to afford a hemiketal intermediate which evolves to acetonide **12** by intramolecular ring-closing reaction, allylic transposition and the loss of water, in tandem. Generation of carbocation at C6, derived from the loss of water, could also be considered.

Scheme 11. Proposed Mechanism for the Formation of Acetonide 12 from Artemisiifolin (3) in Acetone



The structural relationship of amorphane **13** with some of the intermediates of the synthesis of artemisinin and its derivatives is evident.[50] Since artemisiifolin (**3**) can be obtained at multigram scale from *Staehelina dubia*, and, in turn, the latter leads to **13** in two steps in good yield, we have found a valuable intermediate to access these antimalarial compounds.

CONCLUSIONS

The presence of a hydroxyl group at C15 in germacranolides gives to these metabolites a particular reactivity in the cyclization reactions that allows obtaining different sesquiterpenolides. Under acid catalysis, this hydroxyl contributes to give 15-oxoeudesmanolides. Instead, when this hydroxyl is transformed in a good leaving group the cyclization goes in the opposite direction to produce guaianolides. This last reaction can be considered as a biomimetic synthesis of guaianolides.

The nature of the solvent has great influence on the outcome of the reaction. Thus, when acetone is used as solvent, the main reactions observed instead of the cyclization, were the rearrangement concomitant with C8-relactonization of salonitenolide (**2**), or the allylic transposition of artemisiifolin (**3**) to give the acetonide **12**.

It is worth noting that cyclization of **12** gives a lactone with the skeleton of δ-amorphene in good yield. The stereo-structural relationship of the amorphene **13** with some of the intermediates of the synthesis of artemisinin and its derivatives, and its ready availability from artemisiifolin (**3**), make it a valuable intermediate to access this antimalarial compounds.

All the mechanistic proposals in this paper have been evaluated by computational studies.

EXPERIMENTAL SECTION

General Information. Reagents and solvents were purchased from commercial suppliers and were used as received. All experiments were carried out under air atmosphere, unless otherwise indicated. Reactions were monitored through TLC on commercial silica gel plates precoated with silica gel F254. Visualization of the developed plate was performed by fluorescence quenching and *p*-anisaldehyde stain. Column chromatography was performed on silica gel (60, particle size 40–63 μm) as the stationary phase and the solvents employed were of analytical grade, and reaction crudes were added by wet-loading method due to sensitivity of products against silica gel acidity. Deactivated silica gel was prepared by addition of deionized water (15% w/w) and homogenization. NMR spectra were recorded on 400 or 500 MHz spectrometers using standard pulse sequences. ^{1}H NMR chemical shifts (δ) are expressed in ppm referenced internally to residual solvent signal ($CHCl_3$, δ = 7.26 ppm; acetone, δ = 2.05 ppm; benzene, δ = 7.16 ppm). ^{13}C NMR chemical shifts (δ) are expressed in ppm relative to the central resonance of deuterated solvent ($CDCl_3$, δ = 77.0 ppm; acetone-d_6, δ = 29.9 ppm; C_6D_6, δ = 128.4 ppm). Coupling constant (*J*) are given in Hz. Signal splitting were designated as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), doublet of doublet of doublets (ddd), multiplet (m), broad singlet (bs). Two dimensional NMR spectroscopy (gCOSY, gHSQC, gHMBC, NOESY-2D) and NOESY-

1D were used to assist the assignment of signal in the ^{1}H and ^{13}C NMR spectra. Melting points were measured on a melting point apparatus and are uncorrected. Optical rotations were obtained at 20 ºC in $CHCl_3$ and calibrated with pure solvent as a blank. Fourier transform infrared spectroscopy (FTIR) spectra were recorded using NaCl plates, and data are reported in cm^{-1}. Mass spectra were recorded on a UPLC-QTOF mass spectrometer. Silica sulfuric acid (SSA) was prepared according to the literature.[51]

Isolation of (6*R*,7*R*,8*S*,1''*R*)-8-[(1'',2''-dihydroxyethyl)acryloyl]-15-hydroxygermacra-1(10),4,11(13)-trien-6,12-olide (cnicin, 1). *Centaurea calcitrapa* L. was collected in June 2013 at Torre del Puerco, Chiclana de la Frontera (Cádiz), Spain. The dry aerial part (890 g) was submitted to 40 h maceration in CH_2Cl_2 (3.5 L). The solid residues were removed by filtration and the solvent was evaporated under reduced pressure to afford a greenish viscous extract (16 g). The above extract was supported on deactivated silica gel, and was purified by deactivated silica column chromatography (EtOAc:Hexane = 1:2, 1:1, 2:1 to 1:0) to afford, after crystallization from EtOAc, cnicin (**1**) as white amorphous solid (1.7 g, 0.2% yield from dry plant). ^{1}H and ^{13}C NMR spectra are in accordance with the literature.[52]

Preparation of (6*R*,7*R*,8*S*)-8,15-dihydroxygermacra-1(10),4,11(13)-trien-6,12-olide (salonitenolide, 2). Due to instability problems shown by salonitenolide (**2**) in the cyclization reactions, its obtention from cnicin (**1**) was modified with respect to those previously reported methods. In these cases salonitenolide (**2**) was used immediately in the cyclization reactions and yields were calculated from cnicin (**1**). *General procedure:* An aqueous 0.25 M Na_2CO_3 solution (1.2 equiv) was dropped to a solution of cnicin (**1**) (0.1 mmol) in 2:3 dioxane/water (2 mL). The mixture was stirred for 15 min at rt and was poured into a vigorously stirred mixture of EtOAc (15 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The biphasic system was stirred for 10 min, the organic phase was separated and the aqueous

phase was extracted with EtOAc (10 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The reaction crude, whose ^1H and ^{13}C NMR spectra are in accordance with the literature,[52] was used immediately without purification.

Isolation of (6*R*,7*S*,8*S*)-6,15-dihydroxygermacra-1(10),4,11(13)-trien-8,12-olide (artemisiifolin, 3). *Staehelina dubia* L. was collected in June 2014 at Benamahoma (Cádiz), Spain. The dry aerial part (108 g) was submitted to 3 d maceration in acetone (700 mL). The solid residues were removed by filtration and the solvent was evaporated under reduced pressure to afford a brownish viscous extract (8.2 g). The above extract was subjected to deactivated silica column chromatography (EtOAc:Hexane = 1:9, 2:3, 3:2 to 1:0) to yield, after crystallization from acetone, artemisiifolin (**3**) as colorless crystalline solid (1.83 g, 2% yield from dry plant) whose ^1H and ^{13}C NMR spectra are in accordance with the literature.[10b]

Preparation of (6*R*,7*S*,8*S*)-6,15-dihydroxygermacra-1(10),4,11(13)-trien-8,12-olide (artemisiifolin, 3). *General procedure:* An aqueous 1 M NaOH solution (1.5 mL, 1.5 mmol, 5.0 equiv) was dropped to a solution of cnicin (**1**) (99 mg, 0.3 mmol) in 2:3 dioxane/water (5.8 mL). The mixture was stirred for 1 h at rt and was poured into a vigorously stirred mixture of EtOAc (60 mL) and aqueous 0.1 M HCl (60 mL). The biphasic system was stirred for 5 min. The organic phase was separated and the aqueous phase was extracted with EtOAc (60 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (60 mL) and brine (60 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The reaction crude, whose ^1H and ^{13}C NMR spectra are in accordance with the literature,[10b] was used immediately without purification and yields were calculated from cnicin (**1**).

General Procedure for Acid Treatment of Germacranolides. The corresponding protic acid (1.0 equiv) was added to a solution of germacranolide (0.1–0.2 mmol) in the appropriated

organic solvent. The reaction was stirred at rt until TLC indicated complete consumption of starting material. Then, the mixture was poured into a vigorously stirred mixture of EtOAc (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The biphasic system was stirred for 10 min. The organic phase was separated and the aqueous phase was extracted with EtOAc (2×20 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The reaction crude was purified by silica column chromatography.

*Treatment of salonitenolide (**2**) with SSA in $CHCl_3$.* SSA (38 mg, 2.6 mmol H^+/g, 0.1 mmol, 1.0 equiv) was added to a solution of **2** (37 mg cnicin, 0.1 mmol) in $CHCl_3$ (2 mL), and the reaction was stirred for 15 min at rt. The reaction crude was purified by silica column chromatography (EtOAc:Hexane = 1:2) to afford stoebenolide (**4**) as colourless oil (14 mg, 54% yield from cnicin) whose ^{1}H and ^{13}C NMR spectra are in accordance with the literature;[13d,19] and 4-*epi*-stoebenolide (**5**) as colourless oil (4 mg, 16% yield from cnicin): $[\alpha]_D^{20}$ +66.51 (*c* 0.62, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (d, *J* = 4.1 Hz, 1H), 6.15 (d, *J* = 3.2 Hz, 1H), 5.94 (d, *J* = 3.0 Hz, 1H), 4.13 (td, *J* = 10.5, 4.3 Hz, 1H), 3.79 (t, *J* = 11.2 Hz, 1H), 2.59 (tt, *J* = 10.6, 3.0 Hz, 1H), 2.47 (tt, *J* = 11.9, 4.0 Hz, 1H), 1.91 (dd, *J* = 13.0, 4.5 Hz, 1H), 1.87 (t, *J* = 11.6 Hz, 1H), 1.75–1.67 (m, 2H), 1.62 (qt, *J* = 13.4, 4.0 Hz, 1H), 1.53 (dtd, *J* =13.1, 3.1, 1.3 Hz, 1H), 1.43 (qd, *J* = 12.8, 4.9 Hz, 1H), 1.38 (dd, *J* = 11.9, 10.9 Hz, 1H), 1.33 (td, *J* = 13.1, 4.5 Hz, 1H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.0, 169.2, 137.1, 120.4, 79.4, 67.3, 56.0, 51.5, 48.8, 48.6, 40.5, 35.5, 26.2, 19.4; IR (film) ν_{max} 3468, 3407, 2929, 2853, 1769, 1720, 1251, 1124, 1048, 963, 732, 620 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{21}O_4$ $[M+H]^+$ 265.1440, found 265.1438.

*Treatment of salonitenolide (**2**) with TsOH in $CHCl_3$.* *p*-Toluenesulfonic acid monohydrate (39 mg, 0.2 mmol, 1.0 equiv) was added to a solution of **2** (76 mg cnicin, 0.2 mmol) in $CHCl_3$ (2 mL), and the reaction was stirred for 1 h at rt. The reaction crude was purified by silica column chromatography (EtOAc:Hexane = 1:2) to afford the eudesmanolides **4** (36 mg, 68% yield from cnicin) and **5** (8 mg, 15% yield from cnicin).

*Treatment of salonitenolide (**2**) with SSA in acetone.* SSA (140 mg, 2.6 mmol H^+/g, 0.36 mmol, 0.9 equiv) was added to a solution of **2** (149 mg cnicin, 0.39 mmol) in acetone (8 mL), and the reaction was stirred for 3 d at rt. The reaction crude was purified by silica column chromatography (EtOAc:Hexane = 7:3) to afford (4*R*,7*R*,8*S*)-4,15-dimethylmethylenedioxygermacra-1(10),5,11(13)-trien-8,12-olide (**12**) as colourless oil (29 mg, 24% yield from cnicin): $[\alpha]_D^{20}$ –207.69 (*c* 0.13, $CHCl_3$); mixture of three conformers with a ratio of 74:22:3 in NMR: *major conformer* (**12M**) ^{1}H NMR (500 MHz, C_6D_6) δ 6.04 (d, *J* = 3.3 Hz, 1H), 5.45 (d, *J* = 16.5 Hz, 1H), 5.00 (d, *J* = 3.0 Hz, 1H), 4.85 (dd, *J* = 9.5, 3.4 Hz, 1H), 4.58 (dd, *J* = 16.5, 8.9 Hz, 1H), 3.95 (d, *J* = 8.4 Hz, 1H), 3.57 (d, *J* = 8.4 Hz, 1H), 3.42 (ddd, *J* = 11.9, 9.6, 2.8 Hz, 1H), 2.93 (tt, *J* = 9.3, 3.2 Hz, 1H), 2.48 (d, *J* = 11.6 Hz, 1H), 2.24 (t, *J* = 11.8 Hz, 1H), 1.93 (dq, *J* = 15.3, 5.5 Hz, 1H), 1.87 (ttd, *J* = 14.3, 9.9, 3.6 Hz, 1H), 1.60 (ddd, *J* = 18.1, 9.7, 3.9 Hz, 1H), 1.52 (ddd, *J* = 13.4, 7.2, 3.8 Hz, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.1, 145.4, 140.8, 132.5, 127.8, 123.3, 119.9, 110.0, 83.3, 76.5, 70.3, 55.7, 45.4, 38.9, 28.1, 27.4, 24.6, 17.7; *intermediate conformer* (**12i**) ^{1}H NMR (500 MHz, C_6D_6) δ 6.11 (d, *J* = 3.4 Hz, 1H), 5.77 (d, *J* = 16.9 Hz, 1H), 5.03 (d, *J* = 2.9 Hz, 1H), 4.64 (bd, *J* = 11.3 Hz, 1H), 4.51 (dd, *J* = 16.9, 8.9 Hz, 1H), 3.85 (d, *J* = 8.1 Hz, 1H), 3.80 (ddd, *J* = 11.1, 8.9, 6.1 Hz, 1H), 3.61 (d, *J* = 8.1 Hz, 1H), 2.94 (d, *J* = 13.9 Hz, 1H), 2.81 (tt, *J* = 8.7, 3.3 Hz, 1H), 2.48 (q, *J* = 12.4 Hz, 1H), 1.85–1.80 (m, 1H), 1.79 (dd, *J* =

13.2, 6.9 Hz, 1H), 1.60 (t, *J* = 13.4 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 6H), 1.21 (t, *J* = 12.1 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.0, 143.4, 140.4, 133.2, 128.2, 126.9, 121.4, 110.2, 84.1, 80.3, 75.3, 51.6, 42.2, 40.3, 27.8, 27.4, 24.4, 21.9; *minor conformer* (**12m**) ^{1}H NMR (500 MHz, C_6D_6) δ 6.04–6.03 (overlapped signal, 1H), 5.96 (dd, *J* = 16.6, 8.5 Hz, 1H), 5.04–5.02 (overlapped signal, 1H), 4.84 (d, *J* = 16.6 Hz, 1H), 4.69 (bd, *J* = 12.1 Hz, 1H), 4.06 (td, *J* = 10.9, 5.7 Hz, 1H), 3.55 (d, *J* = 7.9 Hz, 1H), 3.50 (d, *J* = 8.2 Hz, 1H), 2.86 (dd, *J* = 13.0, 5.5 Hz, 1H), 2.55 (tt, *J* = 8.7, 3.3 Hz, 1H), 1.53 (t, *J* = 12.5 Hz, 1H), 1.51–1.45 (overlapped signal, 1H), 1.48 (d, *J* = 15.5 Hz, 1H), 1.43–1.37 (overlapped signal, 1H), 1.40 (overlapped signal, 3H), 1.33 (s, 6H), 0.99 (td, *J* = 13.2, 2.9 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.1–169.0 (overlapped signal), 142.3, 139.0, 130.6, 128.4, 122.0, 119.3, 110.4, 85.8, 83.8, 74.9, 47.2, 40.5, 36.9, 28.2, 27.0, 24.3, 21.8; IR (film) ν_{max} 2963, 2926, 2856, 1770, 1370, 1263, 1140, 1061, 1000, 864, 807 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{25}O_4$ $[M+H]^+$ 305.1753, found 305.1732; the eudesmanolide **4** (29 mg, 28% yield from cnicin) and the eudesmanolide **5** (10 mg, 10% yield from cnicin).

*Treatment of salonitenolide (**2**) with TsOH in acetone.* *p*-Toluenesulfonic acid monohydrate (19 mg, 0.1 mmol, 1.0 equiv) was added to a solution of **2** (35 mg cnicin, 0.1 mmol) in acetone (2 mL), and the reaction was stirred for 6 d at rt. The reaction crude analyzed by ^{1}H NMR (500 MHz, $CDCl_3$) showed a mixture of **12**, **4** and **5** with 47:11:42 ratio.

*Treatment of artemisiifolin (**3**) with SSA in $CHCl_3$.* SSA (79 mg, 2.6 mmol H^+/g, 0.21 mmol, 1.1 equiv) was added to a suspension of **3** (51 mg, 0.19 mmol) in $CHCl_3$ (2 mL), and the reaction was stirred for 2 h at rt. The reaction crude was purified by silica column chromatography (EtOAc:Hexane = 2:3) to afford (4*S*,5*S*,6*R*,7*S*,8*S*,10*R*)-6-hydroxy-15-oxo-eudesm-11(13)-en-8,12-olide (**14**) as colourless oil (29 mg, 57% yield): $[\alpha]_D^{20}$ –105.72 (*c* 0.57,

$CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 1H), 6.15 (d, *J* = 3.1 Hz, 1H), 5.98 (d, *J* = 2.9 Hz, 1H), 4.22 (t, *J* = 10.3 Hz, 1H), 3.99 (td, *J* = 11.8, 3.6 Hz, 1H), 2.91 (bt, *J* = 5.0 Hz, 1H), 2.55 (tt, *J* = 10.8, 2.9 Hz, 1H), 2.35 (ddq, *J* = 13.9, 4.1, 2.2 Hz, 1H), 1.95 (dd, *J* = 11.8, 3.8 Hz, 1H), 1.72 (qt, *J* = 13.9, 3.9 Hz, 1H), 1.69 (dd, *J* = 10.1, 5.1 Hz, 1H), 1.65–1.58 (m, 2H), 1.51 (t, *J* = 12.0 Hz, 1H), 1.50 (qt, *J* = 13.9, 5.0 Hz, 1H), 1.31 (td, *J* = 13.3, 4.2 Hz, 1H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.3, 170.4, 137.5, 120.1, 76.5, 68.0, 56.1, 55.4, 45.1, 43.3, 40.7, 35.8, 25.5, 21.3, 18.1; IR (film) ν_{max} 3459, 2937, 2867, 1769, 1713, 1403, 1263, 1127, 1050, 1003, 954, 733 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{21}O_4$ $[M+H]^+$ 265.1440, found 265.1443.

*Treatment of artemisiifolin (**3**) with TsOH in $CHCl_3$.* *p*-Toluenesulfonic acid monohydrate (37 mg, 0.2 mmol, 1.0 equiv) was added to a suspension of **3** (50 mg, 0.2 mmol) in $CHCl_3$ (5 mL), and the reaction was stirred for 2 d at rt. The reaction crude was purified by deactivated silica column chromatography (EtOAc:Hexane = 1:4 to 1:2) to afford liabinolide (**15**) as colourless oil (13 mg, 28% yield) whose ^1H NMR spectrum is in accordance with the literature;[45] and (6*R*,7*R*,8*S*)-15-hydroxyamorpha-1(10),4,11(13)-trien-8,12-olide (**13**) as colourless oil (14 mg, 30% yield): $[\alpha]_D^{20}$ +59.99 (*c* 0.08, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, *J* = 3.6 Hz, 1H), 5.74 (bq, *J* = 1.6 Hz, 1H), 5.52 (d, *J* = 3.3 Hz, 1H), 3.97–3.96 (m, 2H), 3.96 (ddd, *J* = 11.3, 9.1, 6.5 Hz, 1H), 3.38–3.34 (m, 1H), 2.89 (ddt, *J* = 11.3, 6.5, 3.4 Hz, 1H), 2.82 (ddd, *J* = 12.6, 10.9, 5.3 Hz, 1H), 2.44–2.41 (m, 2H), 2.31 (dq, *J* = 10.4, 2.0 Hz, 1H), 2.14–2.10 (m, 2H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 140.7, 135.7, 132.1, 121.3, 120.4, 120.2, 76.1, 66.3, 47.5, 37.6, 37.2, 29.3, 27.7, 19.2; IR (film) ν_{max} 3431, 2961, 2924, 2854, 1771, 1462, 1262, 1091, 1021, 865, 805, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1334, found 247.1339.

*Treatment of artemisiifolin (**3**) with SSA in acetone.* SSA (500 mg, 2.6 mmol H^+/g, 1.3 mmol, 1.2 equiv) was added to a solution of **3** (294 mg, 1.1 mmol) in acetone (30 mL), and the reaction was stirred for 2.5 d at rt. The reaction crude was purified by deactivated silica column chromatography (EtOAc:Hexane = 1:4) to afford the acetonide **12** (58 mg, 17% yield).

*Treatment of artemisiifolin (**3**) with TsOH in acetone. p*-Toluenesulfonic acid monohydrate (38 mg, 0.2 mmol, 1.0 equiv) was added to a solution of **3** (50 mg, 0.2 mmol) in acetone (5 mL), and the reaction was stirred for 3 d at rt. The reaction crude was purified by silica column chromatography (EtOAc:Hexane = 1:5) to afford the acetonide **12** (38 mg, 66% yield).

*Treatment of the acetonide **12** with TsOH in $CHCl_3$. p*-Toluenesulfonic acid monohydrate (15 mg, 0.1 mmol, 1.0 equiv) was added to a solution of **12** (27 mg, 0.1 mmol) in $CHCl_3$ (2 mL), and the reaction was stirred for 24 h at rt. The δ-amorphene **13** (15 mg, 69% yield) was obtained practically pure without purification.

Treatment of salonitenolide (2) with MCPBA. MCPBA (77%, 66 mg, 0.3 mmol, 1.0 equiv) was added to a mixture of **2** (100 mg cnicin, 0.3 mmol) and anhydrous K_2CO_3 (149 mg, 1.1 mmol, 3.7 equiv) in CH_2Cl_2 (10 mL), and the reaction was stirred for 1.5 h at rt. The mixture was poured into a vigorously stirred mixture of EtOAc (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL). The biphasic system was stirred for 30 min. The organic phase was separated and the aqueous phase was extracted with EtOAc (2×10 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (2×10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The reaction crude was purified by deactivated silica column chromatography (EtOAc:Hexane = 1:9, 1:1, 7:3 to 1:0) to afford 8α-hydroxy-4-*epi*-sonchucarpolide (**6**) as colourless oil (12 mg, 16% yield from

cnicin) whose ^{1}H and ^{13}C NMR spectra are in accordance with the literature;[53] and 8α-hydroxysonchucarpolide (**7**) as colourless oil (5 mg, 7% yield from cnicin) whose ^{1}H and ^{13}C NMR spectra are in accordance with the literature.[20c]

Mesylation of salonitenolide (2). Mesyl chloride (45 μL, 0.6 mmol, 2.0 equiv) was added to a solution of **2** (67 mg, 0.3 mmol), obtained according to reported method,[13c] and Et_3N (0.25 mL, 1.8 mmol, 6.0 equiv) in dry CH_2Cl_2 (5 mL). The mixture was stirred for 2 d at rt. The reaction was quenched by addition of water (10 mL), and was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The reaction crude was purified by deactivated silica column chromatography (EtOAc:Hexane = 3:7) to afford *O*-mesyldeacylsubexpinnatin (**9**) as yellowish oil (6 mg, 10% yield): $[\alpha]_D^{20}$ +46.90 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (d, *J* = 3.4 Hz, 1H), 6.07 (d, *J* = 3.0 Hz, 1H), 5.29 (qd, *J* = 2.6, 0.8 Hz, 1H), 5.13 (bs, 1H), 5.11 (qd, *J* = 2.0, 0.9 Hz, 1H), 5.07 (dt, *J* = 1.5, 0.7 Hz, 1H), 4.95 (dt, *J* = 9.6, 4.8 Hz, 1H), 4.00 (dd, *J* = 10.6, 8.9 Hz, 1H), 3.14 (tt, *J* = 9.2, 3.2 Hz, 1H), 3.13 (s, 3H), 3.00 (q, *J* = 8.1 Hz, 1H), 2.81 (dddt, *J* = 10.9, 9.3, 2.3, 1.2 Hz, 1H), 2.75 (t, *J* = 5.3 Hz, 2H), 2.55 (dtq, *J* = 12.7, 8.6, 2.2 Hz, 1H), 2.45 (dtt, *J* = 17.3, 8.8, 2.2 Hz, 1H), 1.92–1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 149.3, 141.5, 136.1, 124.1, 118.1, 111.7, 80.6, 77.7, 53.1, 49.1, 47.9, 39.7, 38.8, 31.8, 30.1; IR (film) ν_{max} 3477, 2925, 1759, 1348, 1173, 927, 757 cm^{-1}; HRMS (ASAP) calcd. for $C_{16}H_{21}O_5S$ $[M+H]^+$ 325.1110, found 325.1118; and deacylsubexpinnatin (**8**) as colourless oil (43 mg, 70% yield) whose ^{1}H NMR spectrum is in accordance with the literature.[26e]

Mesylation (1.0 equiv MsCl) of artemisiifolin (3). Mesyl chloride (25 μL, 0.3 mmol, 1.0 equiv) was dropped to a cooled solution of **3** (99 mg cnicin, 0.3 mmol) and Et_3N (60 μL, 0.4

mmol, 1.3 equiv) in dry CH_2Cl_2 (5.8 mL) at –20 ºC. The mixture was stirred for 2 h at –20 ºC followed by 22 h at rt. The reaction was poured into a vigorously stirred mixture of EtOAc (20 mL), and saturated aqueous $NaHCO_3$ (20 mL). The biphasic system was stirred for 30 min. The organic phase was separated and the aqueous phase was extracted with EtOAc (2×20 mL). The combined organic phases were washed with aqueous 1 M HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The reaction crude was solved in $CDCl_3$ (0.8 mL) and kept for 3 d at rt. The solvent was evaporated under reduced pressure and the reaction crude was purified by silica column chromatography (EtOAc:Hexane = 1:9 to 1:4) to afford (6*R*,7*R*,8*S*)-15-chloroamorpha-1(10),4,11(13)-trien-8,12-olide (**17**) as white solid (5 mg, 7% yield from cnicin): mp 120–123 ºC; $[\alpha]_D^{20}$ +169.15 (*c* 0.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, *J* = 3.6 Hz, 1H), 5.85 (bs, 1H), 5.52 (d, *J* = 3.3 Hz, 1H), 3.96 (d, *J* = 11.3 Hz, 1H), 3.93 (ddd, *J* = 11.3, 9.8, 5.7 Hz, 1H), 3.91 (d, *J* = 11.1 Hz, 1H), 3.38–3.35 (m, 1H), 2.90 (ddt, *J* = 11.3, 6.6, 3.3 Hz, 1H), 2.83 (ddd, *J* = 12.4, 11.1, 6.2 Hz, 1H), 2.47–2.38 (m, 3H), 2.21–2.10 (m, 2H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 137.5, 135.6, 131.2, 125.7, 121.2, 120.3, 76.0, 48.9, 47.3, 37.8, 37.2, 29.7, 27.5, 19.2; IR (film) ν_{max} 2918, 2856, 1771, 1441, 1386, 1262, 1224, 1124, 1021, 943, 817 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{18}O_2{}^{35}Cl$ $[M+H]^+$ 265.0995, found 265.0998; HRMS (ESI) calcd. for $C_{15}H_{18}O_2{}^{37}Cl$ $[M+H]^+$ 267.0966, found 267.0970; and (5*S*,6*R*,7*S*,8*S*)-6-hydroxyguaia-1(10),4(15),11(13)-trien-8,12-olide (**16**) as colourless oil (2 mg, 3% yield from cnicin): $[\alpha]_D^{20}$ –60.56 (*c* 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 2.9, 1.0 Hz, 1H), 6.19 (dd, *J* = 3.2, 1.0 Hz, 1H), 5.18 (s, 1H), 5.02 (s, 1H), 3.79 (td, *J* = 10.6, 1.8 Hz, 1H), 3.37 (t, *J* = 9.5 Hz, 1H), 2.99 (bd, *J* = 9.8 Hz, 1H), 2.86 (tt, *J* = 10.0, 3.1 Hz, 1H), 2.64 (bt, *J* = 12.5 Hz, 1H), 2.52 (dd,

J = 14.1, 1.8 Hz, 1H), 2.48 (bdd, *J* = 14.8, 3.6 Hz, 1H), 2.41–2.30 (m, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 151.7, 138.5, 136.5, 127.3, 122.1, 110.7, 77.8, 68.3, 57.9, 57.3, 38.8, 32.4, 31.6, 22.3; IR (film) ν_{max} 3481, 2919, 2853, 1766, 1660, 1262, 1149, 1066, 1011, 970, 905, 819 cm^{-1}; HRMS (APGC) calcd. for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1334, found 247.1344.

Mesylation (2.4 equiv MsCl) of artemisiifolin (3). Mesyl chloride (90 μL, 1.2 mmol, 2.4 equiv) was dropped to a cooled solution of **3** (203 mg cnicin, 0.5 mmol) and Et_3N (440 μL, 3.2 mmol, 6.4 equiv) in dry CH_2Cl_2 (11.6 mL) at 0 ºC. The mixture was stirred for 10 min at 0 ºC followed by 24 h at rt. The reaction was poured into a vigorously stirred mixture of EtOAc (30 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The biphasic system was stirred for 30 min. The organic phase was separated and the aqueous phase was extracted with EtOAc (2×20 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The reaction crude was solved in $CDCl_3$ (0.8 mL) and kept for 3 d at rt. The solvent was evaporated under reduced pressure and the reaction crude was purified by silica column chromatography (EtOAc:Hexane = 3:97, 5:95 to 1:9) to afford chloroamorphene **17** (45 mg, 32% yield from cnicin).

Epimerization of aldehyde 4 to 5. SSA (11 mg, 2.6 mmol H^+/g, 0.03 mmol, 1.5 equiv) was added to a solution of **4** (4 mg, 0.02 mmol) in CH_2Cl_2 (1 mL), and the reaction was stirred for 5 d at rt. The mixture was poured into a vigorously stirred mixture of EtOAc (10 mL), brine (5 mL), and saturated aqueous $NaHCO_3$ (5 mL). The biphasic system was stirred for 30 min. The organic phase was separated and the aqueous phase was extracted with EtOAc (10 mL). The combined organic phases were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to afford aldehyde **5** (2 mg, 50% yield).

Computational Chemistry Methodology. Conformational search with Molecular Mechanics (MMFF94) was carried out with Macromodel Package.[37] Geometry optimizations and energy calculations were performed with Gaussian09-revD16[54] using DFT[55] at the B3LYP/6-31+G(d,p)[56] level of theory. To simulate the solvent effect used in the experimental reactions (acetone, benzene, chloroform, dichloromethane), a single point calculation was performed at the same level described before, using the SMD continuum model.[24] Intermediates and products and the saddle points of the reactions were located by using the SCW[57] and 2PSHS[58] algorithms included in the GRRM[59] (Global Reaction Route Mapping) package. Transition state structures were optimized as saddle points at the same level of calculation with the routine SADDLE implemented also in GRRM. A vibrational analysis was performed at the same level of theory in order to determine the zero-point vibrational energy and to characterize each stationary point as a minimum or transition state structure. Transition states were identified by the presence of a single imaginary frequency that corresponds to the expected motion along the reaction coordinate. To verify that the TSs correspond to the expected reactant and product wells, intrinsic reaction coordinate (IRC)[60] calculations were performed at the same level B3LYP/6-31+G(d,p). The reported energies in the schemes are expressed in kcal/mol and correspond to relative free energies, while those that appear in the IRC plot, expressed also in kcal/mol, correspond to relative electronic energies and do not include zero-point energy corrections. Structural drawings were produced with Spartan08.[61]

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Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting information

The Supporting Information is available free of charge on the ACS Publications website at DOI: **XXXXX**.

Proton and carbon assignations for all products, NMR spectra for all compounds and IRC plots, coordinates and energies for computed structures. (PDF).

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