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Structural Diversity from the Transannular Cyclizations of Natural Germacrone and Epoxy Derivatives: A Theoretical–Experimental Study

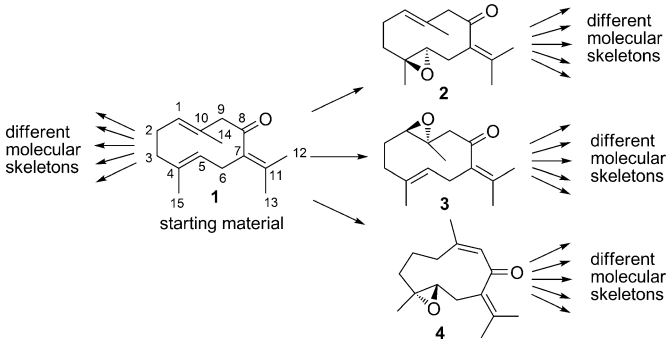
M. Carmen Pérez Morales,[a] Julieta V. Catalán,[a] Victoriano Domingo,[a] Martín Jaraíz,[b] M. Mar Herrador,[a] José F. Quílez del Moral,[a] José-Luis López-Pérez,*[c] and Alejandro F. Barrero*[a]

Abstract: Treatment of germacrone (**1**) with different electrophiles, and of its epoxy derivatives germacrone-4,5-epoxide (**2**), germacrone-1,10-epoxide (**3**) and isogermacrone-4,5-epoxide (**4**) with Brönsted/Lewis acids and Ti^{III}, gives rise to a great structural diversity. Thus, by using a maximum of two steps, the production of more than 40 compounds corresponding to 14 skeletons is described. Computational calculations rationalizing the structural divergence produced are also described. Finally, since some of the compounds generated are bioactive natural sesquiterpenes, the mechanisms of formation of these substances will provide new insights in their biosynthesis.

Keywords: biosynthesis · conformational analysis · density functional calculations · ring closure · terpenes

Introduction

Biologically active small molecules have always attracted great interest due to their capability to modulate the functions of macromolecules in living systems.[1] In this sense, the efficient generation of a library of compounds possessing a high degree of structural and functional diversity entails a major challenge.[2] Since Schreiber's seminal works in the early 2000s,[3] the use of diversity-oriented synthesis (DOS, defined as the deliberate, simultaneous and efficient synthesis of more than one target compound in a diversity-driven approach) is increasing in number and sophistication.[4] Outstanding studies very recently reported by Winssinger and Baran[5] prove the current relevance of this strategy. The biosynthesis of natural products, especially that of terpenes (from which an amazing number of skeletons are produced from simple substrates), in some ways parallels the key principles of the diversity-oriented synthesis. Thus, germacradienes, are postulated to be biosynthetic intermediates of an extensive group of different sesquiterpenic structures.[6] With the final aim of developing a synthetic strategy allowing the efficient generation of many structurally diverse compounds, we conceived that natural germacrone (**1**)[7] could well be used in a reagent-based approach to produce the targeted scaffold diversity (Scheme 1).



Scheme 1. Germacrone-based approach to skeleton diversity.

Germacrone can be isolated on a multigram scale from the essential oils of *Bacharis latifolia*[8] and *Geranium macrorrhizum*.[9] To assure the availability of this starting material, we are optimizing *Geranium macrorrhizum* cultures for the sustainable production of germacrone.[10] Some transannular cyclization reactions of **1** mediated by different electrophiles have also been described, leading fundamentally to bicyclic compounds with eudesmane and occasionally guaiane and cadinane structures.[11] In this regard, we have recently reported the first results showing a new type of transannular cyclization of germacrone mediated by HSO_3Cl at low temperature.[12] Easily available from germacrone,[13] epoxides **2**–**4** also possess a latent reactivity that gives these molecules the potential to be converted into different molecular skeletons only by varying the reagents used. Epoxides **2**–**4** are also natural products isolated mainly from the rhizomes of different species of *Curcuma*.[14] Some examples of the reactivity of epoxides **2**–**4** against different acid media were also described. Thus, epoxide **2** was reported to lead mainly to guaianes, whereas eudesmanes were the major products resulting from the transannular cyclizations of **3** and **4**.[7,15]

The present study intends to prove the usefulness of **1**–**4** as a source of structural diversity and also as starting materials in natural product synthesis. Thus, we report here the cyclization reactions of **1** mediated by electrophiles, such as Brønsted and Lewis acids, and those of epoxides **2**–**4**, triggered either by Lewis acids or $[TiCl(Cp)_2]$ (Cp = cyclopentadienyl). In the event, these studies will also permit us to

[a] M. C. Pérez Morales, Dr. J. V. Catalán, Dr. V. Domingo, Dr. M. M. Herrador, Dr. J. F. Quílez del Moral, Prof. A. F. Barrero
Department of Organic Chemistry
Institute of Biotechnology, University of Granada
Avda. Fuente Nueva, s/n, 18071 Granada (Spain)
Fax: (+34) 958243318
E-mail: afbarre@ugr.es

[b] Prof. M. Jaraíz
Department of Electronics, ETSIT, University of Valladolid
Paseo de Belén 15, 47011 Valladolid (Spain)

[c] Prof. J.-L. López-Pérez
Department of Pharmaceutical Chemistry
Faculty of Pharmacy, University of Salamanca
Avda. Campo Charro, s/n, 37007 Salamanca (Spain)
E-mail: lopez@usal.es

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compare the behavior of the corresponding radical intermediates with that of their cationic equivalents.

Additionally, we have performed theoretical studies,[16–19] not only to rationalize the formation of the sesquiterpenic structures generated, but also to provide new insights in the mechanisms of formation of these sesquiterpenes. In this sense, theoretical studies providing relevant insights into the mechanisms of sesquiterpene-forming reactions have been reviewed very recently.[20]

Results and Discussion

Cyclizations of germacrone: Transannular cyclization reactions from medium-sized cycles are usually governed by the geometry of the most stable conformation or conformations.[21] The adopted conformation capable of undergoing a transannular interaction accounts for the regio- and stereospecificity of this reaction. In this sense, germacrone (**1**) presents two major conformations in solution as can be found in variable-temperature NMR spectra confirmed by DFT calculations by using the B3LYP 6-31+G* method (Figure 1).[12,22]

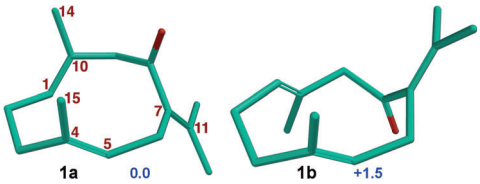


Figure 1. Major (**1a**) and minor (**1b**) solution conformations of germacrone (**1**). Relative energies [kcal mol^{-1}, uB3LYP/6-31G(d)] in blue. The IUPAC numbering is in black.

In the predominant conformation (**1a**) the distance between C-1 and C-4 is quite short (2.80 Å), which favors a transannular cyclization processes.[12] Theoretical comparative calculations at the DFT level have been carried out on the activation and reaction energies from the major conformer **1a** to the bicyclic carbocationic intermediates **II** and **III**, resulting from the initial protonation–cyclization of the double bonds 1,10 and 4,5, respectively (Figure 2). These studies have shown that the formation of cation **III** is concerted, whereas that of eudesmanic carbocation **II**, originated through 1,10 protonation, is not a concerted process, involving the initial production of carbocation **I**, which subsequently cyclizes to **II**.[23] This two-step transformation has an activation energy of 3.3 kcal mol^{-1}, higher than the 2.2 kcal mol^{-1} leading to the cyclobutanic derivative carbocation **III**. Moreover, **II** is considerably more stable than **III** (12.0 kcal mol^{-1}) (Figure 2).

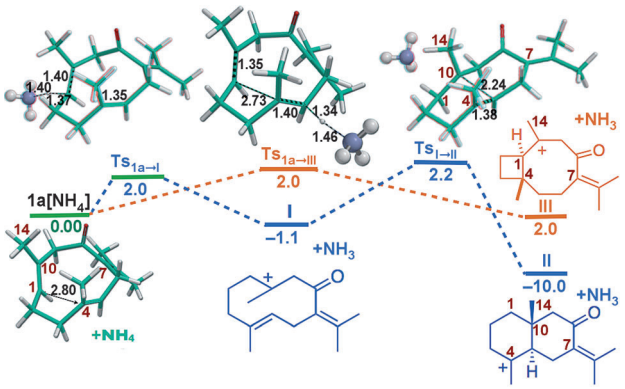
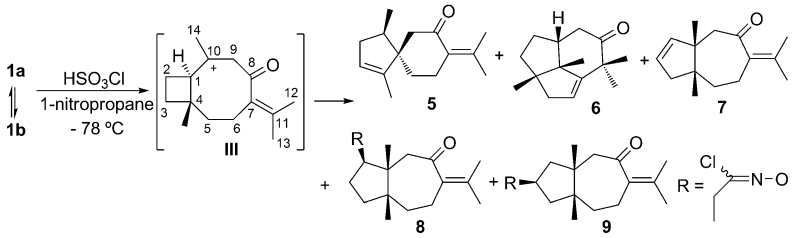


Figure 2. Energy diagram for the formation of carbocations **I**–**III** (ammonium ion was included in the calculation to emulate the acidic medium in the experimental conditions, see ref. [23]). Relative energies [kcal mol^{-1}, UB3LYP/6-31G(d)]. Selected distances in Å. The IUPAC numbering is in magenta.

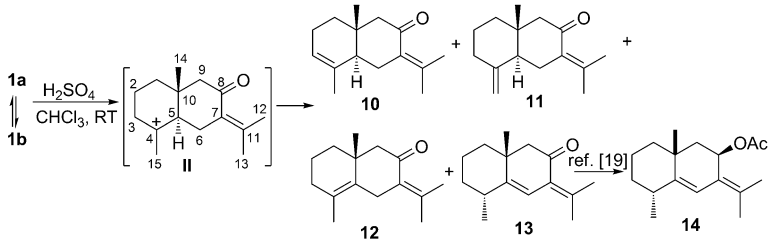
These results led us to study the possibility of selecting the experimental conditions that would lead with a certain degree of selectivity over one cyclization type to another.[11] Thus, as we recently reported,[12] when germacrone **1** was treated with chlorosulphonic acid (4 equiv) in nitropropane at low temperatures (−78 °C) for 10 min, only products derived from intermediate **III** are obtained, namely spirane **5** (24 %), together with the tricyclic compound **6** (35 %), the bicyclic compound **7** (8 %), and minor compounds **8** (2 %) and **9** (1 %) (Scheme 2). Compounds **5**–**9** possess new sesquiterpenoid skeletons.

On the other hand, when the reaction was carried out with chlorosulphonic acid at room temperature, we observed a rapid decomposition of the products, which prevented a conclusive analysis of the results. Nevertheless, when sulphuric acid in $CHCl_3$ was used at room temperature, eudesmanes **10**–**13**, produced through intermediate **II**, were obtained (Scheme 3).



Scheme 2. Formation of compounds **5**–**9** from **1**.

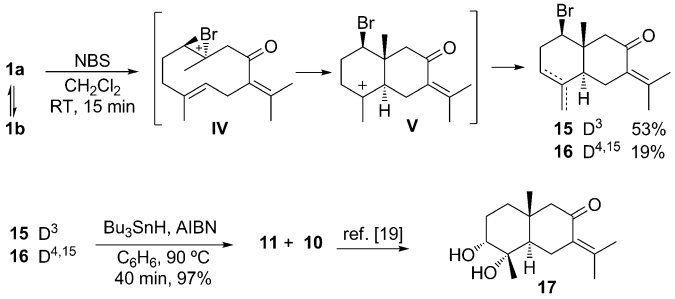
When the cyclization of **1** was stopped after 60 min, 94 % of the more stable eudesmane **13**[24] was obtained. If the reaction was stopped at shorter times, the proportion of **13** fell and that of **10**–**12** increased. Consequently, compound **13** should be formed after acid-mediated isomerization of compound **12** through stereoselective protonation of the 4,5-double bond by the convex face. For eudesmanes **10** and **11**,



Scheme 3. Formation of compounds **10**–**14** from **1**.

which possess a known structure,[25,26] the stereochemistry of interannular junction is *trans* as a result of the participation of the major conformation **1a** in the cyclization process. In all these cases, only 1,10 double bond protonation products were obtained. Compound **13** can be easily transformed into the natural product coralloidin A (**14**).[24]

By following our reagent-based skeletal diversity approach, the behavior of **1** versus softer electrophiles, such as *N*-bromosuccinimide (NBS), PhSeCl, and *N*-chlorosuccinimide (NCS) was also examined. Initially, compound **1** was reacted with NBS (1.1 equiv) in CH_2Cl_2 at room temperature. After 15 min the reaction was complete, yielding 78% of a mixture of eudesmanes **15** and **16** (Scheme 4) in a 3:1

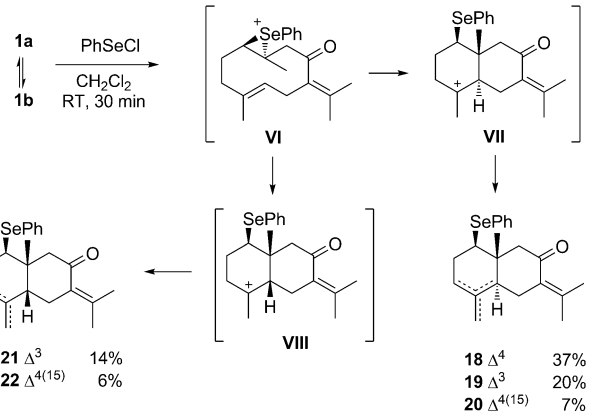


Scheme 4. Mechanism for the preparation of compounds **15**–**17** from **1**.

ratio. *Trans*-decaline structures of **15** and **16** were confirmed through radical reduction with Bu_3SnH/azobisisobutyronitrile (AIBN) to the above mentioned compounds **10** and **11**. This regioselective and stereospecific cyclization started by interaction of NBS with the double bond 1,10 present in the major conformation **1a**. This interaction originated the bromonium ion **IV**[27] on the α face of the double bond. The transannular cyclization gave rise to the bicyclic carbocation **V**, which after deprotonation, yielded the bromine derivatives **15** and **16** (Scheme 4).

The preparation of compound **10** in two steps from **1** constitutes a formal synthesis of natural cuauhtemone (**17**; Scheme 4).[28]

The result of the cyclization of **1** with PhSeCl in CH_2Cl_2 at room temperature was similar to the previous one, and eudesmanic-phenylseleno derivatives **18**–**22** (Scheme 5) were formed exclusively after 30 min with yields of 37, 20, 7, 14, and 6%, respectively. The relative stereochemistry of **19** and **20** was demonstrated by reducing them to **10** and **11** in identical conditions to those employed for **15** and **16**. On the other hand, compounds **21** and **22** showed eudesmane properties in the NMR spectrum. The

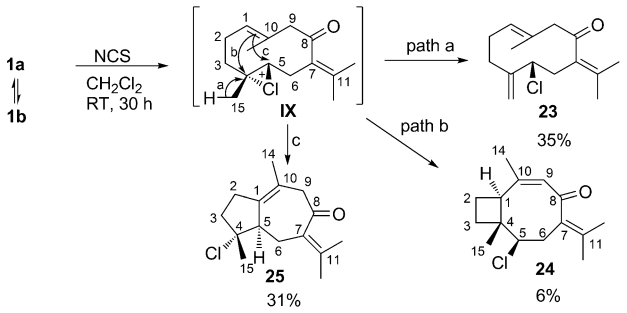


Scheme 5. Mechanism for the preparation of compounds **18**–**22** from **1**.

cis interannular junction was determined from the observed nuclear Overhauser effect (NOE) between Me14 and H5. In this case, the reaction mechanism involves the formation of both the *trans*- and *cis*-eudesmane carbocations **VII** and **VIII**, resulting from the participation of the conformers **1a** and **1b** in the process (Scheme 5). The formation of *cis*-eudesmanes constitutes an outstanding novelty on germacra-1(10),4-diene cyclizations, since they derived from transannular cyclizations involving the minor conformer **1b**.

The treatment of **1** with NCS (1.1 equiv) in CH_2Cl_2 at room temperature led, after 30 h, to the formation of the unstable allyl chloride **23** as the major product, together with guaiane **25** and the bicyclic compound **24**. All these products resulted from the initial reaction of NCS with the 4,5 double bond, yielding the chloronium ion **IX**,[27] with the last two compounds being formed as a result of different transannular cyclizations from **IX** (Scheme 6).

The structural elucidation of compound **24** was carried out by an exhaustive analysis of its 1D and 2D NMR spectra. The molecular formula $C_{15}H_{21}ClO$, established by HRMS, confirmed the presence of chlorine as well as five degrees of unsaturation. Combined analysis of its COSY and HMBC spectra allowed the presence of the connectivities shown in Figure 3 to be determined. Study of the long-range correlations in its HMBC spectrum led us to the structure of this compound. The relative stereochemistry was determined on the basis of the NOE-difference experiments (Figure 3), with the NOE effects observed between Me15 and H2β, H6β, and between H1α and H5, H2α confirming



Scheme 6. Synthesis and mechanism for the preparation of compounds **23**–**25** stemming from **1**.

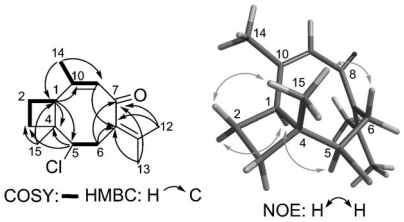


Figure 3. Key COSY and HMBC correlations, and NOE effects of **24**.

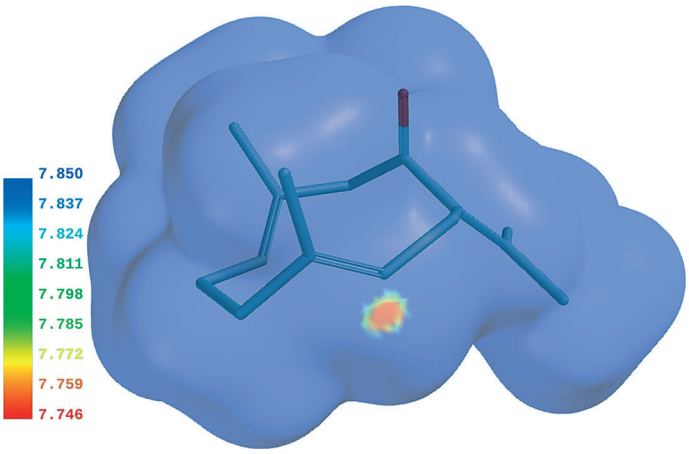


Figure 4. Local ionization potential (LIP) mapped onto the electron density surface. The red spot (lowest LIP value) over the 4,5 double bond corresponds to the most favorable site for an electrophilic attack. The representation was obtained with Spartan '08.[29]

the *trans* interannular junction and the *syn* relationship between Me15 and the chlorine atom. Finally, the *trans* interannular junction is in agreement with the participation of the major conformation **1a** in the cyclization process.

The above results on the reaction of **1** with the softer electrophilic reagents, NBS and PhSeCl at room temperature, follow the general guideline for germacra-1(10),4-dienes and led only to eudesmanes, again as a consequence of the large difference in stability of the bicyclic intermediates. Only NCS, due to its lower reactivity as an electrophile (since chlorine hardly accommodates a positive charge), could react selectively with the more reactive 4,5 double bond, leading to the cyclobutadiene derivative **24** and guaiane **25** as products of the transannular cyclization. The higher reactivity of the 4,5 double bond towards an electrophilic attack stems from its low local ionization potential, as shown in Figure 4.

Up to now, we have shown how germacrone can be converted through transannular cyclizations into more than 20 different products with different molecular skeletons through the variation of reagents and conditions and, quite remarkably, after only one chemical step.

Cyclizations of epoxides of germacrone and isogermacrone: Once we had confirmed the diversity of skeletons available from germacrone, we focused our efforts on analyzing the Lewis acid and/or Ti^{III}-mediated radical cyclization of epoxides of germacrone and isogermacrone, with the ultimate goal of further widening the variety of structures derived from germacrone. As with germacrone **1**, an exhaustive conformational study of germacrone-4,5-epoxide (**2**), germacrone-1,10-epoxide (**3**), and isogermacrone-4-epoxide (**4**) was carried out, and the energies of the different conformations were calculated in vacuum (Figure 5).

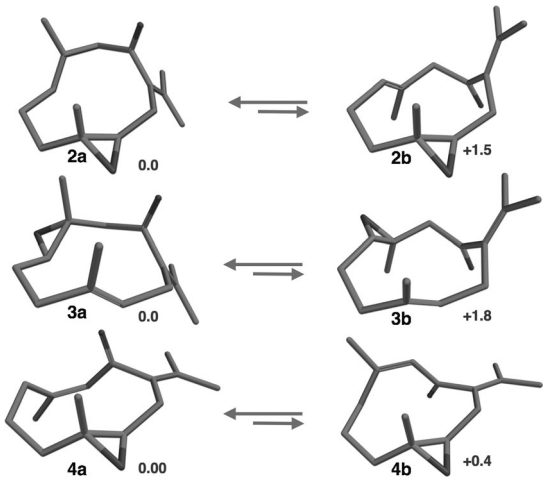


Figure 5. Main conformations of epoxigermacrones **2** and **3** and epoxyisogermacrone **4**. The relative energies (kcal mol^{-1}, UB3LYP/6-31G(d)) are given.

Epoxygermacrones can adopt eight low-energy conformers; four diastereomers and their respective enantiomers (see the Supporting Information and Figure 1). The two major conformers of the three products are represented in Figure 5. These results are in agreement with the NMR spectroscopic studies performed for some germacranolides showing the existence of different conformer ratios depending on the solvent.[30] To test the solvent effect, the calculations were performed also by applying the polarizable continuum model (PCM),[31] to reproduce the experimental conditions. In this sense, THF was considered as a solvent. The results obtained with solvent were almost identical to those

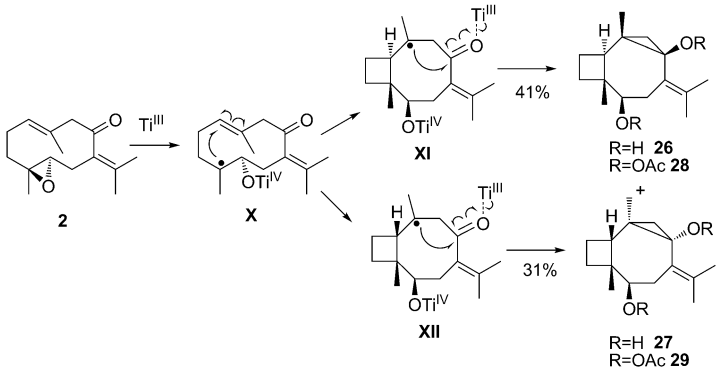
in vacuum. Consequently, the rest of the calculations performed in this study were carried out only in the gas phase.

We began our study by treating germacrone-4,5-epoxide (**2**) with $[Ti^{III}Cl(Cp)_2]$, a mild and highly chemoselective single-electron transfer (SET) reagent that has been used in the radical cyclization of epoxides.[32] In the event, two main tricyclic compounds possessing a new sesquiterpenic skeleton, **26** and **27**, were obtained after a cascade cyclization that could be rationalized by considering the intermediacy of radicals **X–XII** (Scheme 7). No eudesmane or guaiane formation was detected, although these are the main compounds found in previously reported acid or basic cyclizations of **2**.[15]

Table 1. ^{1}H (400 for **24** and 500 MHz for **28**) and ^{13}C NMR (100 for **24** and 125 MHz for **28**) data (δ, ppm) of compounds **24** and **28**.

24 ^{1}H NMR	**28** ^{1}H NMR	**24** ^{13}C NMR	**28** ^{13}C NMR
3.48 (br t, $J=9.7$ Hz, H_1)	1.39–1.35 (m, H_1)	44.8 (C_1)	48.4 (C_1)
2.17 (q, $J=10.5$ Hz, $H_{2\beta}$)	2.16–2.08 (m, H_{2b})	19.8 (C_2)	21.7 (C_2)
2.02–1.94 (m, $H_{2\alpha}$)	1.77–1.72 (m, H_{2a})		
1.82–1.78 (m, $H_{3\beta}$)	1.62–1.57 (m, H_{3b})	31.8 (C_3)	33.3 (C_3)
1.73 (dt, $J=11.3$, 1.7 Hz, $H_{3\alpha}$)	1.50–1.45 (m, H_{3a})		
–	–	47.2 (C_4)	46.5 (C_4)
4.14 (dd, $J=12.3$, 4.0 Hz, H_5)	4.42 (dd, $J=11.6$, 3.1 Hz, H_5)	70.9 (C_5)	81.8 (C_5)
2.86 (dd, $J=14.0$, 3.9 Hz, $H_{6\beta}$)	2.78 (t, $J=12.5$ Hz, H_{6b})	33.4 (C_6)	33.8 (C_6)
2.29 (dd, $J=14.0$, 12.6 Hz, $H_{6\alpha}$)	2.42 (dd, $J=13.2$, 3.1 Hz, H_{6a})		
–	–	133.5 (C_7)	127.5 (C_7)
–	–	201.4 (C_8)	66.8 (C_8)
6.01 (br s, H_9)	0.93 (d, $J=5.9$ Hz, 1H, H_{9b})	129.0 (C_9)	32.5 (C_9)
	0.91 (d, $J=5.8$ Hz, 1H, H_{9a})		
–	–	156.8 (C_{10})	25.3 (C_{10})
–	–	133.8 (C_{11})	140.2 (C_{11})
1.62 (s, H_{12})	1.95 (s, H_{12})[a]	21.8 (C_{12})	21.2 (C_{12})[a]
1.82 (s, H_{13})	1.79 (s, H_{13})[a]	20.1 (C_{13})	22.5 (C_{13})[a]
1.92 (s, H_{14})	1.19 (s, H_{14})	25.4 (C_{14})	16.5 (C_{14})
1.06 (s, H_{15})	1.41 (s, H_{15})	13.7 (C_{15})	14.9 (C_{15})

[a] Interchangeable assignments.



Scheme 7. Radical cyclization of **2** leading to **26–27**.

Due to the marked instability of compounds **26** and **27**,[33] their structures were elucidated through extensive studies of the spectroscopic data of their corresponding diacetate derivatives, **28** and **29**. Thus, compound **28** possesses the molecular formula $C_{19}H_{28}O_4$ (HRFABMS). Taking into account the presence of the two acetoxy groups and only one double bond, the molecule must possess a tricyclic skeleton. Comparison of its ^{1}H and ^{13}C NMR spectroscopic data with those of compound **24** (Table 1) showed a similarity in many of the signals, with the two main differences found in the moiety C8–C10, apart from the change of the substituent at C5, which is Cl in **24** and AcO in **28**. The presence of a cyclopropane ring located at C8–C9–C10 was deduced from the shielded AB system corresponding to the two C9 protons (H9a, $\delta=0.91$ ppm, d, $J=5.8$ Hz; H9b, $\delta=0.93$ ppm, d, $J=5.8$ Hz).

The connectivities deduced from its COSY spectrum together with some of the long-range correlations observed in the HMBC spectrum (Figure 6) confirmed the proposed

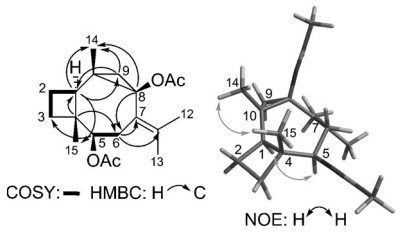


Figure 6. Key COSY and HMBC correlations, and NOE effects of **28**.

structure for **28**. Finally, the correlations found in its NOESY spectrum between H5 and H1 and between Me15 and Me14 established the relative stereochemistry. Compound **29** was assigned to be a diastereomer of diacetate **28** (see the Supporting Information), in which the existence of NOE effects between H5 and Me14 and between H1 and Me15 determined its relative stereochemistry.

Theoretical calculations let us propose the pathway for the formation of these compounds, shown in Figure 7. We began these calculations without reagent, but the energy barriers of transition states were very high and the latest cyclization in both cases did not converge with the B3LYP method recommended for this type of calculation.[20] We therefore performed these calculations considering $TiCl_3$ as the electron-transfer reagent for the transannular cyclizations of both low-energy conformations (**2a** and **2b**) of germacrone-4,5-epoxide **2**.[34] In the presence of this reagent, germacrone adopts preferred conformations with the substituents at C7 and C8 disposed in a planar disposition,

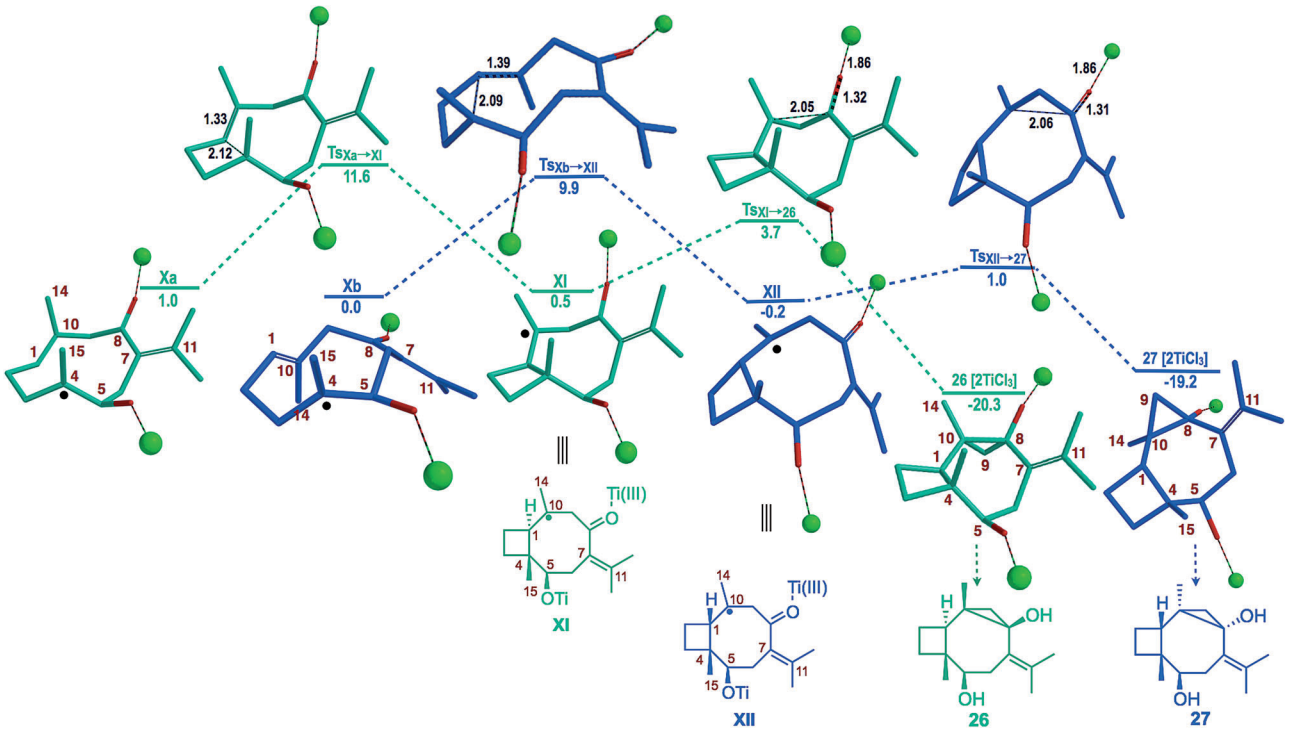


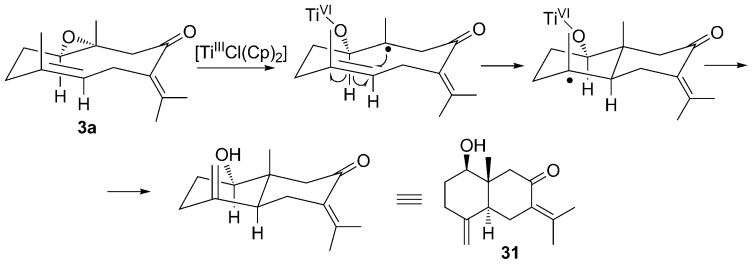
Figure 7. Mechanism proposed for the radical-mediated formation of tricycles **26** and **27**. The relative energies (kcal mol^{-1}, UB3LYP/6-31G(d)). Selected distances in TSs are shown in Å. The IUPAC numbering is in magenta.

which facilitates the second cyclization step in both cases. The transition states were verified by IRC calculations. The potential energy surface is a little more favorable for **26**-[**2**$\mathbf{TiCl_3}$] than for **27**[**2**$\mathbf{TiCl_3}$], which is in agreement with the ratio of compounds **28** and **29** found in the experimental conditions. The radicals resulting from the epoxide opening, **Xa** and **Xb** (both derived from the two lower energy conformations **2a** and **2b** of germacrone-4,5-epoxide, respectively), underwent a 4,1-closure to yield [4+8]-bicyclic-ring systems (radicals **XI** and **XII**). These processes were predicted to be exothermic by only 0.5 and 0.2 kcal mol^{-1}, respectively, and with activation barriers of about 10 kcal mol^{-1}. At this point, the proximity between C10 and the carbonyl carbon atom C8 (2.44 Å in **XI**, and 2.40 Å in **XII**) together with their appropriate spatial arrangement, allows a second cyclization process to take place with a low barrier in both cases (3.2 and 1.2 kcal mol^{-1}, respectively). The data are consistent with the fact that minor geometric changes are required for this attack to occur. The tricyclic intermediates **26**[**2**$\mathbf{TiCl_3}$] and **27**[**2**$\mathbf{TiCl_3}$] are thus generated, and their formation predicted to be exothermic by 21.3 and 19.2 kcal mol^{-1}.

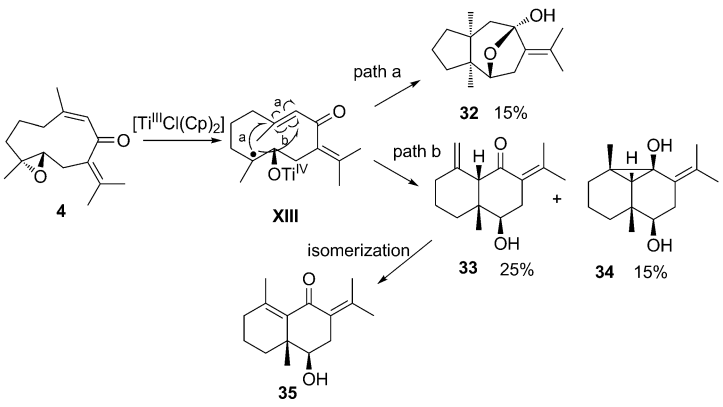
It should be noted that compounds **26** and **27** were formed as a result of a radical 4-*exo*-trig,3-*exo*-trig domino process. Individual 3-*exo*-trig[35] or 4-*exo*-trig[36] cyclizations have been reported, but as far as we know, there are no precedents for a transformation involving the consecutive generation of a four- and then a three-membered cycle.

We continued our study by treating germacrone-1,10-epoxide (**3**) with the same [$Ti^{III}Cl(Cp)_2$] reagent. In this case, only one eudesmane alcohol was obtained (**31**) in an excellent (89%) yield. The stereochemistry of **31** is rationalized by considering that the most stable conformation of epoxide **3**, that is **3a**, is the reactive conformer (Scheme 8). Compound **31** was previously reported,[15c] together with its Δ^3-regioisomer, as a product of the reaction of epoxide **3** with BF_3 in ether (27% yield).

We concluded these radical-triggered cyclizations of epoxy-derivatives of germacrone by treating isogermacrone-4,5-epoxide (**4**) with [$Ti^{III}Cl(Cp)_2$]. In the event, three main structures were produced after the homolytic opening of the epoxide present in **4**, namely **32**–**34** (Scheme 9).



Scheme 8. Radical cyclization of **3** leading to **31**.



Scheme 9. Radical cyclization of **4** leading to **32**–**34**.

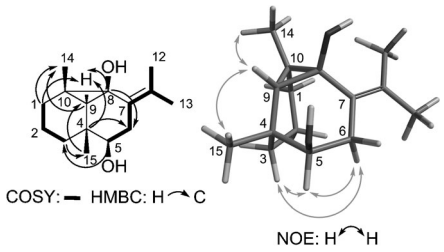


Figure 8. Key COSY and HMBC correlations, and NOE effects of **34**.

The 5+7 skeleton present in compound **32** was originated after the addition of the initially formed tertiary radical **XIII** to the C10 carbon atom (Scheme 9, pathway a). The same bicyclic scaffold was already found in **7**, a compound produced in the low-temperature protic-induced cyclization of germacrone; however, to our knowledge, natural hederacines A and B[37] and jasomontanone[38] were the only natural precedents reported to possess this skeleton. The structure assigned to compound **33** (Scheme 9, pathway b) was confirmed by the basic isomerization of **33** into its known tetrasubstituted isomer **35**.[39] The structural elucidation of compound **34** was carried out by an exhaustive analysis of its 1D and 2D NMR spectra and by comparison of its spectroscopic data with those of **33**. In Table 2, significant changes were observed in the signals corresponding to C8–C9–C10, in which the presence of a cyclopropane ring is inferred from the chemical shifts of H9 and C9 (Table 2). The selected bidimensional correlations shown in Figure 8 confirmed the tricyclic core for compound **34**. The existence of NOE effects between H9 and Me14 and Me15 indicated their *syn* relative stereochemistry (Figure 8). Furthermore, after noticing on the one hand the geometric requirements of the cyclopropane ring fused to the decalin, and on the other the NOE effects observed between H5 and H3β and H6β, the relative stereochemistries at C8 and C5 were also unambiguously assigned.

Theoretical studies were carried out to find a plausible mechanism for the formation of **33** and **34** (Figure 9). Accordingly, the homolytic opening of isogermacrone-4,5-epoxide (**4**) leads to radical **XIII**, with **XIIIa** as the most stable conformation for this intermediate—a conformation that differs from the most stable one found for the starting epoxide **4**. Intermediate **XIIIa** then evolves to conformation **XIIIb**, which is less stable by 1.9 kcal mol^{-1}, but the only one able to cyclize to eudesmane **33** through the bicyclic radical **XIV**. This radical evolved through a 3-*exo* cyclization to the tricyclic compound **34**. The formation of this structure was the result of a new domino 6-*endo*-trig, 3-*exo*-trig process, the calculated activation energies of which were predicted to be only 3.0 and 2.2 kcal mol^{-1}, as can be seen in the computed pathway for compounds **33** and **34** in Figure 9. The global process was predicted to be exothermic by 36.8 kcal mol^{-1}.

Being aware of the recent papers reporting promising results on the In^{III}-promoted cyclization of epoxyalkenes,[40] as well as the use of Et_2AlCl by Corey et al. to trigger cascade cyclizations of monoepoxypolyprenes,[41] we decided to treat the three epoxides deriving from germacrone with these Lewis acids. With these experiments we aimed not only to compare the behavior of these epoxides under radical and cationic conditions, but also we anticipated that new structural variety could emerge from these experiences. Thus, treatment of germacrone-4,5-epoxide (**2**) with $InBr_3$ resulted in the gen-

Table 2. ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) data (δ, ppm) of compounds **33** and **34**.

33 ^{1}H NMR	**34** ^{1}H NMR	**33** ^{13}C NMR	**34** ^{13}C NMR
2.17–2.11 (m, H_{1a}) 2.27–2.19 (m, H_{1b})	1.27–1.21 (m, H_{1a}) 1.47–1.41 (m, H_{1b})	33.8 (C_1)	29.6 (C_1)
1.66–1.60 (m, H_{2a}) 1.74–1.68 (m, H_{2b}),	1.14–1.09 (m, H_{2b}, H_{2a}),	22.1 (C_2)	20.7 (C_2)
1.26–1.17 (m, H_{3a}) 1.66–1.60 (m, H_{3b})	0.89–0.83 (m, H_{3a}) 0.98–0.94 (m, H_{3b})	33.3 (C_3)	33.4 (C_3)
		41.8 (C_4)	32.1 (C_4)
3.94 (t, J=6.0 Hz, H_5),	3.50 (br s, H_5)	70.5 (C_5)	75.0 (C_5)
2.59 (dd, J=15.8, 6.6 Hz, H_{6a}) 2.87 (br d, J=15.6 Hz, H_{6b})	2.38 (d, J=18.3 Hz, H_{6a}) 2.47 (br d, J=17.5 Hz, H_{6b})	34.0 (C_6)	35.9 (C_6)
		128.4 (C_7)	126.4 (C_7)
		203.1 (C_8)	58.5 (C_8)
2.93 (s, H_9)	0.38 (s, H_9)	62.5 (C_9)	31.5 (C_9)
		145.0 (C_{10})	25.2 (C_{10})
		145.9 (C_{11})	133.3 (C_{11})
2.03 (s, H_{12})	1.78 (s, H_{12})[a]	23.3 (C_{12})	19.9 (C_{12})[a]
1.83 (s, 3H, H_{13})	1.59 (s, H_{13})[a]	22.6 (C_{13})	22.2 (C_{13})[a]
4.50 (s, 1H, H_{14a}) 4.92 (s, 1H, H_{14b})	1.28 (s, H_{14})[b]	112.0 (C_{14})	23.1 (C_{14})
1.03 (s, 3H, H_{15})	1.17 (s, H_{15})[b]	20.8 (C_{15})	23.1 (C_{15})

[a] and [b] Interchangeable assignments.

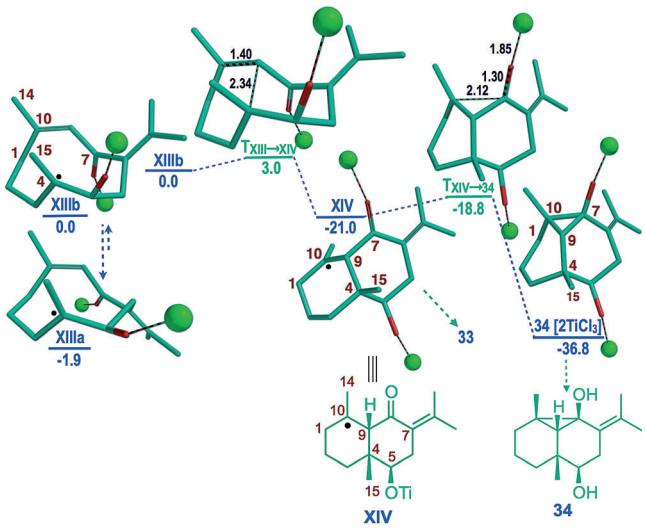
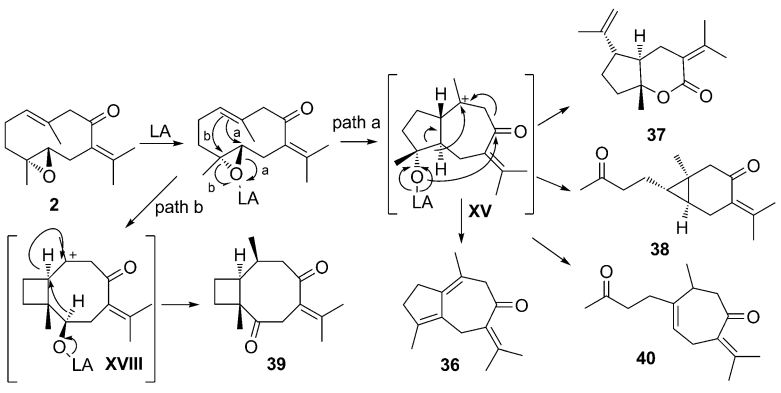


Figure 9. Mechanism proposed for the radical-mediated formation of tricycle **34**. The relative energies (kcal mol^{-1}, UB3LYP/6-31G(d)) are in blue for intermediates and in green for TS. Selected distances in TSs are shown in Å. The IUPAC numbering is in magenta.

eration of two main structures, **37** (30%) and **38** (35%), together with minor guaiane **36** (8%) (Scheme 10). When the same epoxide **2** was exposed to Et_2AlCl, **36**–**38** were again obtained (4, 31, and 22%, respectively), although now accompanied by two new diketones, **39** (11%) and **40** (18%). A reasonable mechanistic proposal for the formation of these compounds is shown in Scheme 10. Thus, the type a cyclization leads to **36**–**38** and **40** through guaiane carbocation **XV**, whereas the opening of the epoxide through path b produces **39** through intermediate **XVIII**.

Compound **37** possesses identical spectroscopic data to those reported for gajutsulactone A, which, together with its epimer at C1, possesses a unique *seco*-guaiane-type skeleton isolated from the rhizome of *Curcuma zeodaria*.[42] Gajutsulactone A was found to inhibit nitric oxide (NO) production in lipopolysaccharide (LPS)-activated mouse peritoneal macrophages.[43] Compound **38** was identified as curcumenone, again as a result of a domino process. This compound



Scheme 10. Treatment of **2** with Lewis acids (LA).

was reported to be produced by biotransformation of germacrone-4,5-epoxide with *Cichorium intybus*,[15b] although in the same work it was claimed that conversion of **2** into **38** appeared to be an uncatalyzed process. Curcumenone is a bioactive cyclopropane-sesquiterpene with hepatoprotective effects, antidiabetes activity,[44] and was also found to inhibit nitric oxide production.[42] Diketone **39** is a new compound. Only one precedent of a natural compound possessing the [4+8] bicyclic skeleton present in **39** has been reported.[45] Remarkably, the interannular junction of the natural compound was reported to be *cis*, contrary to that reported for **39**. This stereochemical dissimilarity constituted another example of the capability of these Lewis acid mediated cyclizations to generate diversity. Compound **40** showed the spectroscopic features of the natural product curcumadione. This *seco*-guaiane derivative has been isolated from different *Curcuma* species.[46]

Quantum mechanics calculations were undertaken to reveal the role played by the Lewis acid species in the whole process. Lewis acids were included in the calculations to emulate experimental conditions. The proposed pathways from 4,5-epoxygermacrone (**2**) to gajutsulactone A (**37**) and curcumenone carbocation **XVII** are shown in Figure 10.[47] It was then observed that the interaction of epoxide **2** with the Lewis acid caused this germacrone derivative to adopt a productive conformer **2e**[$AlBr_3$], in which the methyl groups are disposed *anti*, contrary to their disposition in the most stable conformer of the starting epoxide **2a**. This productive conformer also presented a planar disposition for both carbonyl and isopropilidene so as to overcome the transition-state barrier (7.0 kcal mol^{-1}) of the transannular cyclization leading to intermediate **XV**. Interestingly, the generation of **XV** involves a concerted asynchronous rearrangement reaction in which the portion of the reaction coordinate that precedes the transition structure shows a substantial degree of synchrony between the opening of the epoxy group and the approximation of the generated carbocation to the double bond, whereas the portion of the reaction coordinate following the transition-state structure shows that the epoxide is already fully opened, whereas the C5−C1 bond-formation is still under progress.[48] At this point, it should be noted that a mechanistic proposal for compound **37** was reported and this involved the attack of the oxygen atom derived from the epoxide opening to the carbonyl carbon atom.[43] However, this proposal seems unlikely since a secondary carbocation would be generated as an intermediate.[49,20] Apart from this, the axial H at C5 would prevent the approach of the oxygen to the carbonyl group.

Theoretical calculations on the intermediate guaiane carbo-

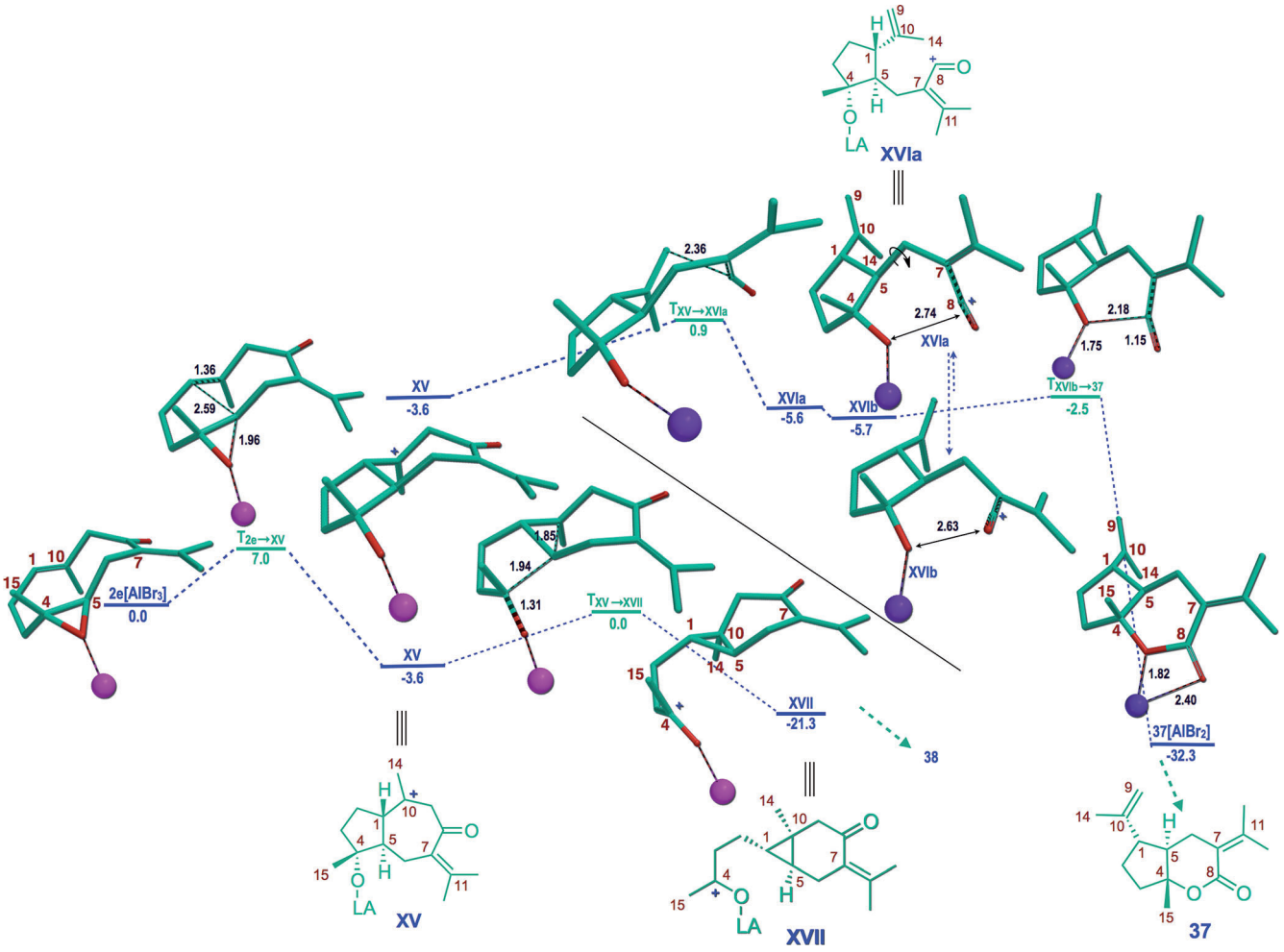


Figure 10. Mechanism proposed for the formation of **37** and **38**. The relative energies (kcal mol^{-1}, UB3LYP/6-31G(d)) are in blue for intermediates and in green for TS. Selected distances in TSs are shown in Å. The IUPAC numbering is in magenta.

cation **XV** revealed an elongation of the C8–C9 bond (1.66 Å), which should be caused by a hyperconjugative effect since the carbocation is located at an allylic position. This elongation facilitated the cycle opening through a transition state $\mathbf{T_{XV\rightarrow XVI}}$, which presents a distance between C8–C9 of 2.36 Å. The opening of the cycle leads to intermediate **XVIa**, which, by rotation of the C5,6 bond, originates a new rotamer (**XVIb**) that is 0.1 kcal mol^{-1} more stable. In this intermediate, an approximation between the oxygen deriving from the epoxide opening to the carbonyl carbon atom takes place. Finally, the nucleophilic attack to the carbonyl group (through a barrier of 3.2 kcal mol^{-1}) produces compound **37** through a clearly exothermic process.

On the other hand, the rearrangement step leading to the formation of curcumene carbocation **XVII** from **XV** involves a second concerted asynchronous rearrangement reaction with a low barrier of only 3.6 kcal mol^{-1}. This second concerted process evolves just as the opposite of the generation of **XV**: the portion of the reaction coordinate that precedes the transition structure takes place asynchronously, with the closure of the three-membered ring; whereas the portion of the reaction coordinate following the transition state structure shows a high degree of synchrony.

The formation of compound **39** could be rationalized by considering an acid-mediated concerted cyclization process of the germacrone-4,5-epoxide leading to a 4+8 bicyclic intermediate **XVIII**, which would progress to **39** through a transannular 1,4 hydride-transfer process from **XVIII** to **XX**.[50] Nevertheless, our computational studies showed that the very high activation energy for this 1,4-hydride transfer (40.5 kcal mol^{-1}) can be alternatively avoided through two sequential hydride-transfer reactions, 1,2- and 1,3-hydride from **XVIII** to **XIX** and from **XIX** to **XX**, respectively. The calculated activation energies for these processes are 12.6 and 8.4 kcal mol^{-1}, which are substantially lower than the corresponding 1,4-hydride transfer (Figure 11). It should be pointed that although compound **39** could not be detected when $InBr_3$ was used as a Lewis acid, this compound appears in the reaction of **2** with the harder Lewis acid Et_2AlCl.[51] This fact indicates that the coordination of this Lewis acid with **2** somehow also provokes the formation of the carbocationic intermediate **XVIII** instead of only **XV**. In

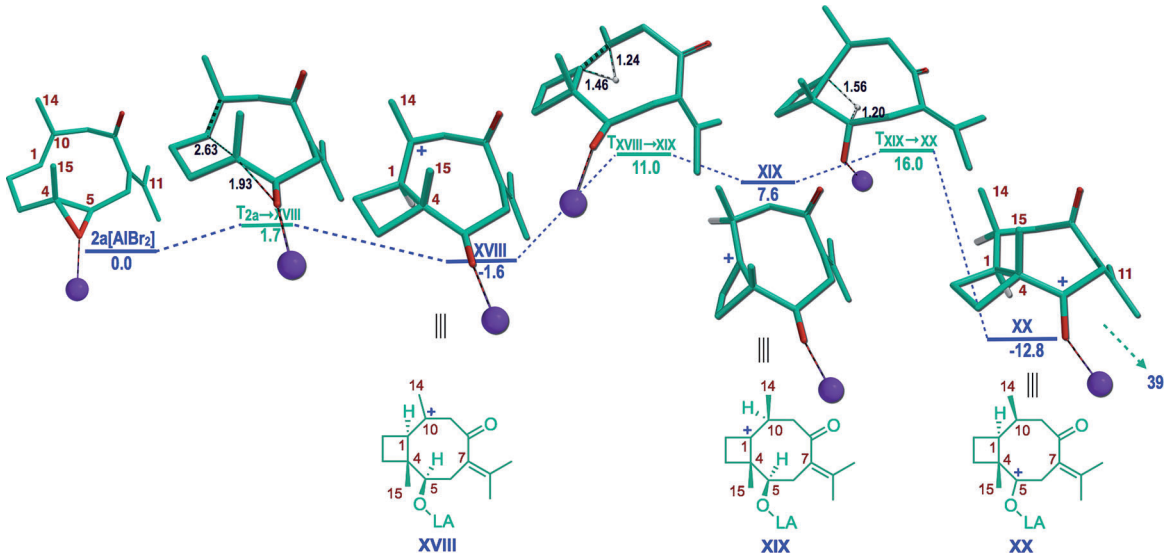
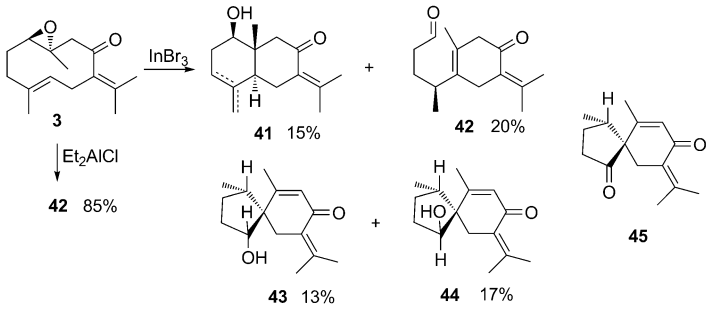


Figure 11. Mechanism proposed for the formation of **39**. The relative energies (kcal mol^{-1}, UB3LYP/6-31G(d)) are in blue for intermediates and in green for TS. Selected distances in TSs are shown in Å. The IUPAC numbering is in magenta.

this sense, theoretical calculations emulating the experimental procedure by using $AlBr_3$ as a Lewis acid show that the oxyrane opening and subsequent formation of **39** is not possible. However, when the harder $AlBr_2$ species is included in the computational studies, the formation of **39** turned into a straightforward process.

We continued our study by analyzing the behavior of germacrone-1,10-epoxide (**3**) under the presence of In^{III} and Al^{III} species (Scheme 11).



Scheme 11. Treatment of **3** with Lewis acids.

When $InBr_3$ was used as Lewis acid, we obtained the mixture of eudesmanes **41**, aldehyde **42**, and alcohols **43** and **44** (a pair of epimers found to possess a rare spiro[4.5]decane carbon framework), which constituted a new proof of the singular role of these Lewis acids. On the other hand, the use of Et_2AlCl led to the formation of aldehyde **42** as a major compound.

Eudesmanes **41** were previously reported to be obtained after treating **3** with BF_3 etherate.[15c] With respect to aldehyde **42**, no natural compound possessing this skeleton has been previously reported to our knowledge, whereas the two spiro derivatives **43** and **44** were also new sesquiterpenic compounds. In fact, we found only two precedents of natural compounds presenting this skeleton, namely spirojatamol, a sesquiterpene alcohol of *Nardostachys jatamansi*,[52] and spirolepechinene, from *Lepechinia bullata*.[53] The obtention of diketone **45** after Dess–Martin oxidation of a mixture of **43** and **44** confirmed that these two compounds are epimers at C1. As we did with many of the compounds obtained, we studied theoretically the mechanistic aspects of their formation. Computational studies led us to propose the formation of aldehyde **42** and spirojatamanes **43** (Figure 12). In these calculations, $AlBr_3/AlBr_2$ were considered to emulate experimental conditions. In the presence of the Lewis acid $AlBr_3$, the preferred conformation of the starting epoxide coincides with that found when the acid is not considered. The computations gave an activation energy of 14.3 kcal mol^{-1} to lead to the *trans*-eudesmanyl intermediate **XXI**, an exothermic cyclization by 10.3 kcal mol^{-1}. After the ring closure, the process continues with a typical hydride-shift step from C5 to C4 to produce species **XXII**, a process that is predicted to be exothermic by 1.4 kcal mol^{-1}. The opening of the cycle, an unusual process favored by the stability of the resulting carbonyl group, led to monocycle **XXIIIa** and its lower energy rotamer **XXIIIb**, which are direct precursors of aldehyde **42**. However, intermediates **XXIIIa** and **XXIIIb** can further evolve, with remarkably low energetic barriers of 2.8 and 1.8 kcal mol^{-1}, through an intramolecular Prins reaction[54] to intermediates **XXIV** and **XXV**, which are direct precursors of compounds **43** and **44**. In this sense, the physical basis for the rearrangement of the eudesm-5-yl carbocation leading to the spirojatamane skeleton (Scheme 12 path a), among others, was reported very recently.[55] It should be noted that the herein-described mechanism for the formation of spirojatames **43** and **44** involves an alternative route to these sesquiterpenes (Scheme 12, path b). With

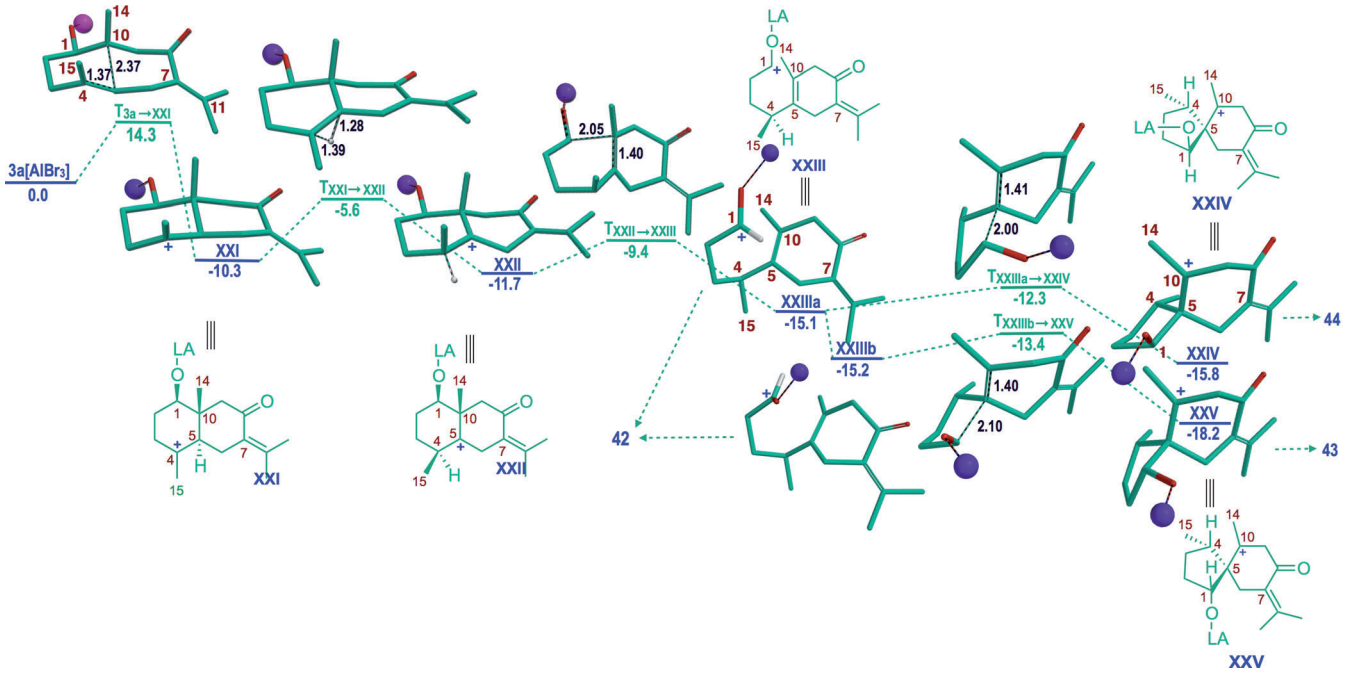
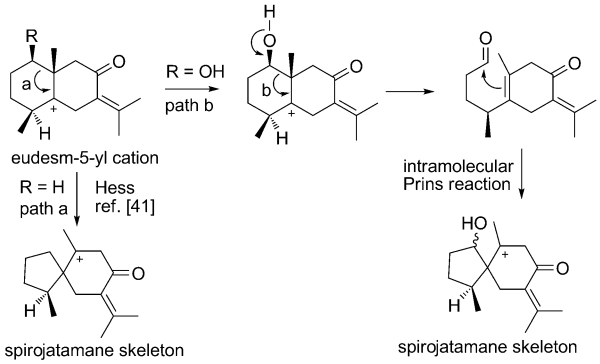
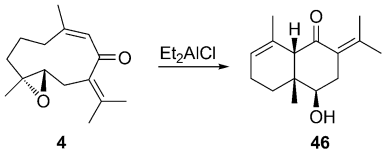


Figure 12. Mechanism proposed for the formation of **42**, **43**, and **44**. The energies (kcal mol^{-1}, relative to **3a**, UB3LYP/6-31G(d)) are shown in blue for intermediates and in green for TS. The selected distances in the TSs are shown in Å in black. The IUPAC numbering is in magenta.



Scheme 12. Different pathways towards the spirojatamane skeleton from eudesm-5-yl cation.



Scheme 13. Treatment of **4** with Et_2AlCl.

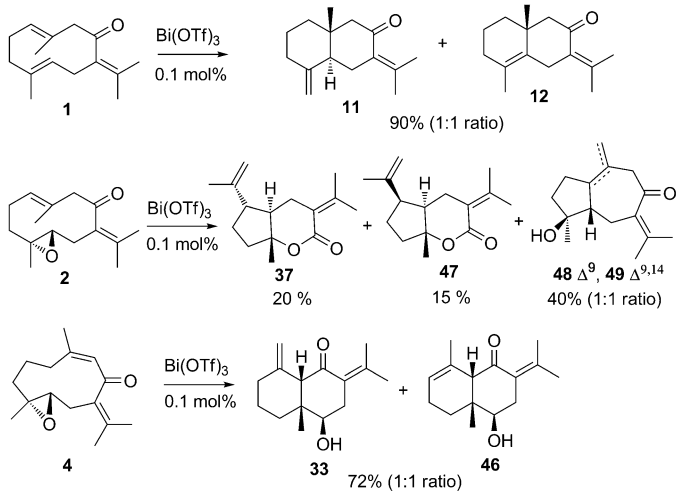
a view to contributing to gain more insights into the biosynthesis of these sesquiterpenes, we performed new theoretical calculations, which on the one hand, confirmed that the non-functionalized eudesm-5-yl cation evolves directly to the spirojatame skeleton as described by Hess.[55] On the other hand, they also revealed that this direct pathway could not be found when an extra hydroxyl group is incorporated in the parent eudesm-5-yl cation. Consequently, the herein-described mechanism should not be ruled out a priori when addressing the biosynthetic origin of new natural products showing this skeleton.

We continued our study by analyzing the behavior of isogermacrone epoxide **4** in the presence of Lewis acids. In the event, treatment of **4** with Et_2AlCl led mainly to the *cis*-eudesmane **46** (Scheme 13). It should be noted that the stereochemistry of **46** reveals that this product is derived from the cyclization of the less-stable conformation of **4**, that is, from **4b**, which indicates that the coordination of the Lewis acid alters the energies of the corresponding conformers.

Since no redox changes can be inferred from these cyclization processes, we devoted our final efforts to studying the feasibility of achieving these transformations catalytically. In this sense, some examples of cyclizations of polyprenes or epoxypolyprenes catalyzed by metallic triflates can be found in the literature.[56] Thus, our preliminary studies revealed that the cyclization of not only germacrone (**1**) but also of its epoxy derivatives **2** and **4** can be very efficiently catalyzed by using bismuth triflate ($Bi(OTf)_3$, 0.1 mol%) at room temperature (Scheme 14).

Conclusion

In the reactions of germacrone (**1**) with electrophiles, the type of electrophile and the reaction conditions used in each case allow the selection of the trisubstituted double bond to start the reaction, and subsequently the type of transannular cyclization. Furthermore, the processes of the opening of



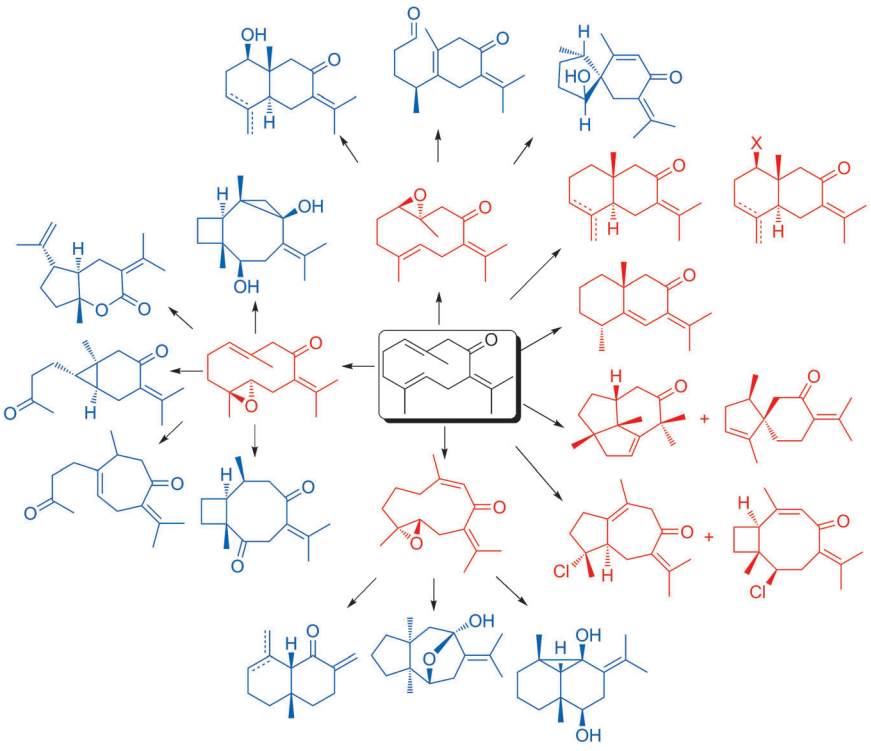
Scheme 14. Treatment of compounds **1**, **2**, and **4** with $Bi(OTf)_3$ (0.1 mol%).

the three monoepoxy derivatives of germacrone (**2**–**4**), either homo- or heterolytic, turned out to be complexity-generating reactions. Thus, selective transformations have been achieved to originate a set of products showing a broad structural diversity, including several compounds that possess new mono-, bi-, and tricyclic sesquiterpene skeletons (Scheme 15). This fact should be highlighted since the existing correlation between skeletal variations and biorelevant diversity is widely accepted.[57] Furthermore, this diversity is not only limited to the presence of different skeletons, but also includes functional and stereochemical variations, covering thus the main types of structural diversity.[58] In this sense, it should be mentioned that these compounds contain peripheral functional groups, which further increases the possibilities of diversification. For instance, the structures generated could incorporate (by using branching reaction sequences) well-established privileged substructures[59] or other molecular features that aid the conversion of the molecule into a therapeutic agent. It is also remarkable that this diversity has been reached only after a minimum number of steps (1–2), which should facilitate the large-scale preparation of these compounds.

We are aware that the ultimate goal of a DOS is the discovery of biologically active molecules. In this regard, the fact that some of the compounds obtained are natural products already proven to possess biological activity could be considered a good starting point in this research.

Regarding the mechanistic studies, it can be concluded that the initial conformation of the starting materials can be modified by their interaction with the electrophilic reagents, thus justifying the structural diversity found. We have also found that the acid-mediated cyclizations of germacrone epoxides are all concerted processes. In our opinion, this conformational alteration caused by the reagents resembles somehow the action of the enzymes in the biosynthesis of terpenes.[49a]

Finally, we have also performed preliminary tests in which nontoxic and readily available $Bi(OTf)_3$ (0.1 mol%) proved to catalyze the cyclizations of germacrone and derivatives with high efficiency.



Scheme 15. Summary of compounds obtained from germacrone. Compounds in red were obtained after only one step. Compounds in blue were obtained after two steps.

Acknowledgements

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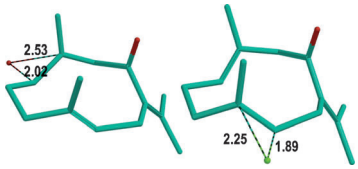

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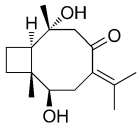

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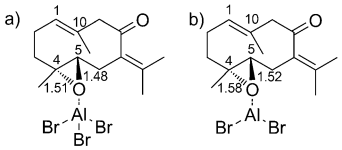

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